Dear Editor:

The topic “diabetes mellitus and renal transplantation” can be viewed from 2 aspects: renal transplant in diabetic patients and new-onset diabetes after renal transplant.

The prevalence of diabetes mellitus is steadily increasing worldwide. It is estimated that 330 million people will have diabetes mellitus in 2030. Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in Western societies and accounts for approximately 40% to 45% of cases of ESRD in the United States. Diabetic nephropathy was the cause of ESRD in approximately 23% of patients who received kidney transplants in the United States in 2008.1

Patients with type 1 diabetes and ESRD have 3 therapeutic options apart from dialysis: (1) living-donor renal transplant, preferably preemptive;2 although patients with diabetes are less likely to receive preemptive kidney transplant,3 (2) pancreas transplant, either simultaneously or sequentially after renal transplant, and (3) being placed on a wait list for deceased-donor renal transplant. Pancreas transplant is often not an option for patients with type 2 diabetes; therefore, they have to undergo a living- or deceased-donor renal transplant.

For type 1 diabetic patients, life expectancy after simultaneous pancreas-kidney transplant is 23.4 years; after living-donor renal transplant, life expectancy is 20.9 years and 12.6 years after deceased-donor renal transplant, which is somewhat less but definitely more than life expectancy on dialysis.4 Transplant and patient survival rates seem to be optimal after a simultaneous pancreas-kidney transplant. The outcomes regarding patient survival with simultaneous pancreas-kidney transplant versus living-donor renal transplant are similar, with the former having a greater early mortality risk and the latter having a greater late mortality risk.5 However, it seems that recipients of simultaneous pancreas-kidney transplant who have a functioning pancreas have significantly better outcomes.6 Using a novel statistics methodology on the outcomes of about 12,000 patients with type 1 diabetes mellitus, Sung and associates demonstrated that simultaneous pancreas-kidney transplant is associated with statistically but not clinically significant increases in graft (0.18 years) and patient survival (0.17 years).7 However, even if there is no substantial advantage regarding patient survival, we have to take into consideration the improvement on the quality of life that simultaneous pancreas-kidney transplant offers.

For patients with type 2 diabetes mellitus who receive a living- or deceased-donor renal transplant, a marked decrease in mortality risk is evident, independently of the age of the recipient. The seminal study of Wolfe and associates8 showed that renal transplant provided a clear survival advantage for patients with diabetes and ESRD and reduced mortality by 73% compared with patients who remained on wait lists. Furthermore, patient and graft survival rates seem to be similar in patients with type 2 diabetes mellitus and matched9 or unmatched10 patients without diabetes. Although simultaneous pancreas-kidney transplant is not generally an option for patients with type 2 diabetes mellitus, more recent studies have suggested that it could be applied in well-selected patients. The most recent of these studies11 concluded that simultaneous pancreas-kidney transplant is a safe procedure with
excellent pancreas and kidney graft outcomes and that it should be offered to more uremic patients with labile type 2 diabetes mellitus as it restores euglycemia and freedom from insulin and dialysis. Diabetes presents particular challenges both during the pretransplant evaluation and after transplant. These challenges are related to the high incidence of cardiovascular disease among diabetic patients and the increased risk of bacterial and fungal infections compared with transplant recipients without diabetes. In addition, glycemic control is more difficult after transplant.

All patients with diabetes should be evaluated for the presence of coronary heart disease before transplant with a noninvasive test, preferably dobutamine-induced stress echocardiography. If there are symptoms or signs consistent with coronary heart disease or a positive noninvasive test, they should undergo cardiac catheterization. Some centers have suggested a more aggressive pretransplant approach in high-risk patients. However, Patel and associates have challenged this approach, reporting that aggressive pretransplant testing and coronary interventions did not translate into better outcomes after transplant in high-risk patients.

Diabetes and subdiabetic hyperglycemia occur in a substantial number of patients after renal transplant. New-onset diabetes after transplant is associated with increased mortality and morbidity as well as decreased long-term allograft survival.

The incidence of new-onset diabetes after transplant is variable, ranging from 7% to 46% in different studies. Studies that use up-to-date criteria for diagnosis have suggested that up to one-third of kidney transplant recipients who do not have diabetes develop persistently impaired glucose metabolism by 6 months after transplant. The incidence of new-onset diabetes after transplant is higher among transplant recipients than the incidence of new-onset diabetes among dialysis patients. Risk factors include increased age, obesity, African American race/ethnicity, Hispanic ethnicity, and family history of diabetes or gestational diabetes. Furthermore, there are transplant-specific risk factors such as medications (glucocorticoids, tacrolimus, sirolimus) and presence of hepatitis C and cytomegalovirus infections, hypomagnesemia, and polycystic kidney disease.

Care includes regular monitoring of all patients, consideration of immunosuppressant therapy, modification, and therapy of diabetes mellitus.

References


Transplant Patients With Failing Renal Allografts

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Abstract

Progress in patient care and immunosuppressive medications has resulted in improved allograft survival in the early posttransplant period; however, substantial graft loss continues in the long term. Therefore, the number of dialysis patients with failed allografts is increasing progressively. These patients have a worse prognosis than naive dialysis patients. Cardiovascular causes are the leading cause of death, followed by infections and malignancies. Delay in return to dialysis, a chronic inflammatory state, infections, and cancer are contributing factors to mortality, whereas type of dialysis modality does not have a significant effect on outcomes. Graft nephrectomy is a risky operation; therefore, it should not be a routine procedure and rather should be performed only when indicated. Overall, most grafts are left in place, whereas graft nephrectomy is performed in patients with graft intolerance syndrome. Management of immunosuppressive drugs after graft failure is controversial. In the case of maintaining immunosuppression, there is increased risk of infections, cardiovascular diseases, and malignancies and also steroid-related adverse effects. On the other hand, discontinuation of immunosuppressants may result in loss of residual allograft function and also acute graft inflammation. Together, immunosuppressive drugs are almost always discontinued in these patients because of their inherent adverse effects. Considering the sequence of cessation, first antiproliferative drugs are stopped, followed by calcineurin inhibitors, and finally steroids. Because many studies show a clear survival benefit, every attempt should be made for a retransplant in patients with failed renal allografts.

Key words: Failed transplant, Rejected allografts, Weaning immunosuppression

Introduction

Progress in patient care and immunosuppression has resulted in an improvement in graft survival in the early posttransplant period; however, there is a substantial graft loss afterward. Not surprisingly, nearly 40% of all patients lose their grafts within 10 years, and the number of patients returning to dialysis with a failed allograft has increased every year. In the United States, in 2010, more than 5500 patients returned to dialysis after transplant failure.

Outcomes of Patients With Failed Renal Allografts

No randomized controlled trial has yet been conducted to study the prognosis of patients with failed allografts. Most of the few controversial reports on this topic are retrospective, single-center reviews; therefore, registry reports are of major importance. Gill and associates analyzed the United States Renal Data System (USRDS) data in patients who were started on dialysis from 1995 to 2003 and were subsequently placed on kidney transplant wait lists. The authors studied death rates in diabetic and nondiabetic patients during waiting time on transplant wait lists (89000 patients), during the time after transplant (stable phase; 47433 patients), and during the second dialysis period after allograft failure (5461 patients) over a 3-year period. Death rates were determined in 3-month intervals during the stable phase and over 2-week intervals during transitions for a period of 3 months. When the 3 study periods were compared, the lowest death rate was found during transplant function, whereas the highest mortality was noted during the second dialysis period after allograft failure. Mortality rates were higher during periods of transition from wait list to transplant (8.2/100 patient-years) and during the
reinitiation of dialysis after transplant failure (17.9/100 patient-years). In each period of transplant care, patients with diabetes had higher mortality rates than patients without diabetes. In this analysis, causes of death were classified as septic, cardiovascular, and other/unknown. During the wait list period, cardiovascular causes of death were more frequent, especially in patients with diabetes. Other causes, including malignancies, were more common in other periods. The proportion of death due to sepsis was greatest (16.8%) after allograft failure versus during the wait list period (14.0%) and during allograft function (12.7%). Death rates (per 100 patient-years) due to cancer were 0.18 (95% confidence interval [CI], 0.16-0.20) during the wait list period, 0.11 (95% CI, 0.09-0.13) during allograft function, and 0.25 (95% CI, 0.16-0.39) after allograft failure.

Several factors can be responsible for this unfavorable outcome. First, there can be a delay in return to dialysis; thus, uremic complications such as hyperkalemia, volume overloading, and metabolic acidosis may contribute to mortality. Second, a rejected allograft can result in a chronic inflammatory state, which can trigger malnutrition and hypoalbuminemia. Furthermore, elevated serum ghrelin levels and inflammation might decrease appetite and contribute to malnutrition. Third, increased cardiovascular risks due to inflammation and secondary to other uremia-related factors, such as bone mineral disorders, increased sympathetic activity, anemia, oxidative stress, and endothelial dysfunction, may contribute to increased risk. Fourth, immunosuppression sustains even when immunosuppressive drugs are discontinued, and these patients are susceptible to malignancies and to many conventional and unconventional infections. Changes in psychologic/emotional states may also influence patient health.

In a USRDS analysis, which included 5077 incident patients restarting hemodialysis after allograft failure, associations between various factors and mortality were studied. In a Cox regression analysis, risk of mortality increased with lack of arteriovenous fistula at initiation of dialysis, albumin < 3.5 g/dL, and being underweight. Interestingly, a glomerular filtration rate (GFR) of < 10 mL/minutes at time of dialysis initiation was associated with reduced mortality. The authors hypothesized that patients with worse clinical conditions were restarted on dialysis earlier at a higher GFR; hence, a selection bias in this surprising finding was possible.

**Timing of Return to Dialysis**

When dialysis is restarted, the effects of GFR level on patient outcomes are controversial. Arias and associates presented several possibilities on this subject. In their retrospective analysis of outcomes of 192 patients from 1995 to 2000, 70 patients returned to dialysis after a failed graft, whereas 122 patients began de novo dialysis. When laboratory results were compared, patients with failed grafts had significantly higher levels of urea, lower levels of creatinine clearance, and were more anemic at the time of initiation of dialysis. Patient morbidity, which was defined as the need for hospitalization within the first year of dialysis, was significantly higher in patients with failed grafts. One-year mortality rate of patients with failed grafts was high (27%). Interestingly, patients who died were characterized by a lower GFR at the reintroduction of dialysis. The reasons for the late return are obscure; there may have been problems in accepting irreversible graft failure and difficulty in assessing kidney function in transplanted patients. Serum creatinine levels, which are quite low in these patients due to reduced muscle mass, may have overestimated the correct kidney function. Equations used for calculating GFR in the general chronic kidney disease population have not been validated in transplant recipients and may overestimate GFR due to low creatinine values.

To summarize, optimal levels of GFR for return to dialysis in patients with a failing transplant are not clear. The decision should be individualized and should consider several factors, including, but not limited to, cause and timing of graft failure, immunosuppressive therapy before graft failure, complications during graft function, and presence of comorbidities or heavy proteinuria.

**Selecting Dialysis Modality**

Patients needing dialysis may have both hemodialysis and peritoneal dialysis (PD). However, there is concern that return to PD after transplant failure may be risky because sustaining immunosuppression may predispose patients to peritonitis.

A retrospective analysis of 34 PD patients with a failed renal transplant compared outcomes with 82 PD patients who had never received a kidney transplant. The groups were similar regarding
demography, residual renal function, and dialysis adequacy (Kt/V). Patients with failed transplants had a higher number of peritonitis episodes per patient than those who did not receive a transplant (2.42 ± 0.41 vs 1.61 ± 0.15 episodes/patient; P = .013). In the failed transplant group, time to the first episode of peritonitis was also shorter than in nontransplanted patients. However, 1-, 3-, and 5-year patient and technique survival rates did not differ significantly between the 2 groups. The authors concluded that PD appears to be a good option for patients with transplant failure and a previous renal transplant does not adversely affect patient survival with regard to technique, although the somewhat higher infection risk is of some concern.15

The largest study to address this issue was conducted in the United States by Mujais and Story.16 The authors compared outcomes of patients who started PD after a failed renal allograft with outcomes of new PD patients and patients who had been transferred from hemodialysis and then started PD between 2000 and 2003. The patients were followed until 2005. There were nearly 500 patients in each group. Patients were matched by age, sex, presence of diabetes mellitus, and PD submodality (continuous ambulatory PD vs automated PD). Infection rates and other complications (eg, dialysis adequacy, ultrafiltration failure, catheter problems) were not significantly different across the groups. Overall, patient and technique survival rates were similar, and the authors concluded that the high success of PD in patients with failed allografts suggested that this modality should be used more frequently than the current practice.16

To the best of our knowledge, only one study has made a head-to-head comparison between hemodialysis and PD after a failed transplant. In a retrospective analysis of 60 patients with failed transplants, 21 patients were started on PD and 39 were started on hemodialysis.17 For each group of patients, data were collected until death, retransplant, or transfer to hemodialysis or PD. The study found no significant differences in regard to demographics, time on renal replacement therapy, and serum albumin and C-reactive protein levels at baseline. Furthermore, the baseline comorbidity was similar in both groups. During follow-up, patients in the hemodialysis group tended to accumulate more new comorbidities. Furthermore, the PD group tended to have higher patient survival and retransplant rates; however, these differences did not reach to statistical significance.17

All of these studies suggest that dialysis modality does not have a significant effect on the outcome of patients with failed transplants.

Immunosuppressive Therapy Considerations

In patients without transplant nephrectomy, immunosuppression can be maintained or discontinued. Both options have advantages and drawbacks3,18-29 (Table 1), and some clinical and laboratory data may be helpful in deciding which option is better3 (Figure 1).

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintaining residual kidney function18,19</td>
<td>Increased risk of:</td>
</tr>
<tr>
<td>Prevention of allosensitization20-22</td>
<td>• Infections21,17</td>
</tr>
<tr>
<td>Prevention of graft intolerance syndrome23,24</td>
<td>• Cardiovascular problems26</td>
</tr>
<tr>
<td>Avoiding transplantectomy23,24</td>
<td>• Metabolic complications28</td>
</tr>
<tr>
<td>Prevention of steroid withdrawal symptoms25</td>
<td>• Malignancies28,29</td>
</tr>
<tr>
<td></td>
<td>Adverse effects of steroids3</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
</tr>
</tbody>
</table>

Figure 1. Algorithm Describing How to Handle Immunosuppressants in Patients With Transplant Failure

Briefly, if there is a probability of a living donor, immunosuppressants may be continued at a low dose. If there is no such chance, then urine output should be considered. If there is no urine, then immunosuppressants should be stopped. If there is a significant amount of urine, complication risks should be considered. If there is a high risk of complications, immunosuppressants should be stopped immediately. However, if the patient has no apparent risks, then immunosuppressants may be continued at a low dose.
Regarding weaning of immunosuppressants, there is no consensus yet on how to taper and stop these drugs. They can be stopped either instantly or after a gradual taper. For this decision, duration of allograft function is usually considered. For patients with early allograft failure (defined as less than 1 year of function), immunosuppressants are usually discontinued immediately, which is mostly followed by preemptive nephrectomy. However, for patients with late allograft failure, discontinuation can be done slowly over weeks or even months. In this case, most authors have suggested first stopping the antiproliferative drugs (azathioprine, mycophenolate mofetil/sodium or mammalian target of rapamycin inhibitor), which is followed by stopping the calcineurin inhibitor after a rapid taper; steroids should be withheld last and by a protocol of slow taper. If possible, all immunosuppressants should be discontinued by postoperative month 6.

Graft Nephrectomy
Chronic inflammation caused by rejected grafts can be a risk factor for an unfavorable outcome. Lopez-Gomez and associates studied this issue prospectively. The authors followed 43 patients for 6 months who started dialysis after graft failure; 29 of these patients were symptomatic and had general and/or local symptoms of graft inflammation. Their inflammatory parameters (such as erythropoietin resistance index, obtained simply by dividing the total weekly erythropoietin dose first by the patient’s weight [in kg] and then by the patient’s hemoglobin level [in g/dL], expressed as U/week per kg per g/dL) were compared with 121 patients who never received a transplant. At the beginning, erythropoietin resistance and C-reactive protein levels were greater and serum albumin was lower than for nontransplanted patients. After patients received nephrectomy and 6 months after nephrectomy, inflammatory parameters of the study group became similar to those of the nontransplanted patients. The authors concluded that maintaining a failed graft represents a chronic inflammatory state, and transplant nephrectomy should be considered for patients with failed grafts, especially if there are signs and symptoms of inflammation. Advantages and drawbacks of transplant nephrectomy are summarized in Table 2.

Regarding current practice, most grafts are left in place. Johnston and associates analyzed the USRDS database between 1995 and 2003 and found that more than 19,000 patients had failed grafts. Among these, graft survival was shorter than 1 year in 3701 patients (which can be referred to as early graft failure). Nephrectomy rate was 56% in this group, and almost 90% of nephrectomies were performed within the first year. On the other hand, in the 15,406 patients with longer graft survival, nephrectomy rate was 27%.

Another more recent USRDS database study analyzed effects of transplant nephrectomy on patient survival. This study included more than 10,000 patients who returned to dialysis after transplant failure. Of these, 3451 (31.5%) received an allograft nephrectomy. Overall, 3785 of total study patients died during follow-up. It was noted that transplanteectomy was associated with a 32% lower relative risk of mortality (after adjustment for sociodemographic factors, comorbidities, donor features, and other variables). Patients with nephrectomy also had significantly increased chance of retransplant.

Retransplant
An important issue in the care of patients after transplant failure is retransplant. Many studies have shown a clear survival benefit of retransplant compared with patients who remain on dialysis. In an analysis of the Canadian Organ Replacement Registry, more than 3000 patients who began dialysis between 1981 and 1998 were studied. These patients had received a renal transplant and had graft failure, with 1163 patients later retransplanted. Retransplanted patients had a higher risk of death only during the first month posttransplant and experienced significantly reduced mortality thereafter compared with patients on dialysis. Overall, retransplant was associated with a 50% reduction in

Table 2. Advantages and Drawbacks of Transplant Nephrectomy in Dialysis Patients With Transplant Failure

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoiding chronic inflammatory state</td>
<td>Increase in serum levels of preformed cytotoxic antibodies</td>
</tr>
<tr>
<td>Avoiding acute symptomatic rejection</td>
<td>Adverse effects on prognosis of a future transplant</td>
</tr>
<tr>
<td></td>
<td>More stringent fluid restriction</td>
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<td></td>
<td>Surgery-related morbidity and mortality</td>
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</table>
mortality compared with mortality in patients who remained on dialysis. However, only 15% of patients had received another transplant.

Conclusions

Outcomes of patients with failed grafts are unfavorable. There are many uncertainties, which include, but are not limited to, timing of reinitiation of dialysis, dialysis modalities to be applied, handling of immunosuppressive agents, indications for graft nephrectomy, and many others. Well-designed studies are needed to clarify these issues. Nephrologists and surgeons should collaborate to offer the best care to transplant patients with failing renal allografts.

References

Preoperative Echocardiographic Differences and Transplant Outcomes Among Patients Receiving Simultaneous Liver-Kidney Versus Liver Transplant Alone

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Abstract

Objectives: Liver transplant and simultaneous liver-kidney transplant are major surgeries performed on high-risk individuals with end-stage liver disease and end-stage renal disease. We sought to examine the relationship between pretransplant echocardiographic parameters and outcomes in our simultaneous liver-kidney transplant and liver transplant-alone populations.

Materials and Methods: In our retrospective analysis, we included adult patients who underwent index transplant from January 1, 2010 to December 31, 2015 at Johns Hopkins Comprehensive Transplant Center.

Results: Our study included 312 patients, 266 who underwent liver transplant alone and 46 who underwent simultaneous liver-kidney transplant. Baseline population demographics were similar in both groups of patients. Primary diagnosis at transplant was similar in both groups except that patients undergoing liver transplant were more likely to have a diagnosis of hepatocellular carcinoma, whereas those undergoing simultaneous liver-kidney transplant were more likely to have polycystic kidney disease. Within the liver transplant-alone group, the strongest demographic predictor of poor outcome was age at transplant. The strongest echocardiographic predictors were related to elevated left ventricular ejection fraction and right ventricular systolic pressure.

Conclusions: In our investigation regarding whether the pretransplant cardiovascular evaluation predicted outcomes for patients undergoing liver transplant alone and patients undergoing simultaneous liver-kidney transplant, we found that elevations in right ventricular systolic pressure and left ventricular ejection fraction may be associated with poor outcomes in the posttransplant period.

Key words: Cardiac echocardiography, Left ventricular ejection fraction, Right ventricular systolic pressure

Introduction

Liver transplant is a major surgery performed on high-risk individuals for the treatment of end-stage liver disease. Simultaneous liver-kidney transplant (SLK) is offered to such patients who also present with end-stage renal disease. Preoperative assessment of both types of surgeries includes a thorough cardiac evaluation comprising diagnostics that identify potentially modifiable conditions that should be optimized before surgery and physiologic states that preclude safe transplant.

This evaluation often results in indeterminate test results of unclear significance. For instance, in liver transplant recipients, Bushyhead and associates described the associations between mildly elevated preoperative right ventricular systolic pressure (RVSP) and posttransplant mortality, myocardial infarction, and heart failure.1 In their analysis, they also noted a relationship between preoperative left ventricular ejection fraction (LVEF) greater than 65% and increased rate of posttransplant chronic kidney disease. Two other groups also examined this relationship and found that mildly elevated pre-operative RVSP was a top predictor of posttransplant mortality and graft failure.2,3 Model for End-Stage Liver Disease (MELD) score itself has also been correlated with RVSP.4 The cause of this increased mortality posttransplant is unclear as most other
Echocardiographic alterations are thought to be reversed after transplant. In patients on chronic hemodialysis, an increasing intradialytic period and corresponding volume changes are known to be associated with elevated RVSP. Other studies have seen some suggestion that elevated RVSP may be a cardiovascular risk factor after kidney transplant. Notably, most of these RVSP measurements found are modest and by definition of the study populations did not preclude transplant. Given the unclear generalizability of these prior results, we sought to first verify this relationship in our liver transplant population and then to expand this exploration to our SLK transplant patients.

Materials and Methods

In this retrospective analysis, we included adult patients who underwent index transplant from January 1, 2010 to December 31, 2015 at Johns Hopkins Comprehensive Transplant Center. We excluded patients who were under the age of 18 years, those who were transplanted for acute liver failure, and those who were to receive living-donor liver grafts. All patients were evaluated with a preoperative transthoracic echocardiogram with assessment of LVEF, presence and severity of right ventricular and right atrial dilation, qualitative assessment of right ventricular performance, and calculated RVSP by tricuspid jet if present. Some patients also underwent right heart catheterization (RHC) based on contemporary clinician judgment. Patient demographic and follow-up data were abstracted from the hospital electronic medical records after Internal Review Board approval was obtained.

Outcomes

Our composite primary outcome was time to death or graft failure. Time at risk for survival analysis was defined as time from date of transplant to outcome. Time at risk was censored at last known follow-up. The follow-up period was ended at the beginning of this study’s data collection (January 28, 2016).

Statistical analyses

Statistical analyses were performed using R statistical software (R studio version 0.98.501). We used t tests, chi-square tests, and Kruskal-Wallis rank sum test as applicable for between-group comparisons. Cox proportional hazards modeling was performed using the survival package in R. Multivariable models were compared using analysis of variance to judge goodness of fit. Model building was step-wise and screened with $P = .2$ in univariate modeling to be considered for the full model.

Results

Our study included 312 patients, 266 who underwent liver transplant alone and 46 who underwent SLK. Baseline population demographics were similar in both groups of patients (Table 1). Patients were mostly male, white, and in their early 50s (years) at time of transplant. Both populations were transplanted in similar patterns across the study period, and both populations received similar amounts of posttransplant follow-up prior to censoring or outcome (approximately 2 years). Model for End-Stage Liver Disease score at transplant in SLK patients was higher (28.7 vs 21.8; $P < .001$) but as expected based on incorporation of creatinine and/or the use of dialysis, a component of the MELD score calculation. Primary diagnosis at transplant was similar in both groups except that patients undergoing liver transplant were more likely to have a diagnosis of hepatocellular carcinoma than those undergoing SLK who were more likely to have polycystic kidney disease (Table 2).

| Table 1. Patient Demographics by Transplant Type |
|-----------------|-----------------|-----------------|
| Transplant Group | Liver Alone | SLK | $P$ Value |
| No. of patients | 266 | 46 | 985 |
| Race, No. (%) | White 184 (69) | 32 (69.6) | 985 |
| | Black 54 (20) | 9 (19.6) | 952 |
| | Other 27 (10) | 5 (10.9) | 956 |
| Mean age (SD), years | 54.1 (11.0) | 51.8 (13.1) | 209 |
| Mean BMI (SD), kg/m2 | 28.1 (5.1) | 29.2 (7.0) | 243 |
| Mean MELD (SD) | 21.8 (10.0) | 28.7 (8.2) | <0.001 |
| Days of follow-up (SD) | 755.6 (573.6) | 741.7 (605.4) | 881 |
| Year of transplant, No. (%) | 2010 25 (9.4) | 5 (10.9) | 973 |
| | 2011 29 (10.9) | 4 (8.7) | 973 |
| | 2012 29 (10.9) | 4 (8.7) | 973 |
| | 2013 19 (5.9) | 0 (0.0) | 973 |
| | 2014 60 (22.6) | 11 (23.9) | 973 |
| | 2015 64 (24.1) | 13 (28.3) | 973 |

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease; SD, standard deviation; SLK, simultaneous liver-kidney transplant

All patients were evaluated with preoperative echocardiography (Table 3). There was no difference in LVEF. Patients who had SLK had a higher RVSP.
pretransplant than patients who had liver transplant alone (39 vs 32 mm Hg; \( P < .001 \)). Right heart catheterization was significantly more prevalent in the SLK group (6 RHC among 46 SLK recipients [13%] vs 13 RHC among 266 liver transplant alone recipients [5%]); however, this effect was directly correlated with RVSP rather than the organ transplant group itself (odds ratio of pretransplant RHC per 5 mm Hg RVSP was 2.6; 95% confidence interval [CI], 1.8-4.0; \( P > .001 \)).

**Table 2. Diagnosis**

<table>
<thead>
<tr>
<th>Transplant Group, % of patients</th>
<th>Liver Alone</th>
<th>SLK</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>266</td>
<td>46</td>
<td>.93</td>
</tr>
<tr>
<td>HCV</td>
<td>50%</td>
<td>37%</td>
<td>.08</td>
</tr>
<tr>
<td>HBV</td>
<td>6%</td>
<td>0%</td>
<td>.78</td>
</tr>
<tr>
<td>ETOH</td>
<td>20%</td>
<td>15%</td>
<td>.42</td>
</tr>
<tr>
<td>NASH</td>
<td>7%</td>
<td>11%</td>
<td>.38</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>2%</td>
<td>4%</td>
<td>.40</td>
</tr>
<tr>
<td>HCC</td>
<td>40%</td>
<td>7%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PBC</td>
<td>2%</td>
<td>0%</td>
<td>.40</td>
</tr>
<tr>
<td>PKD</td>
<td>0%</td>
<td>13%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PSC</td>
<td>7%</td>
<td>2%</td>
<td>.23</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
<td>17%</td>
<td>.03</td>
</tr>
</tbody>
</table>

**Abbreviations:** ETOH, alcoholic cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PKD, polycystic kidney disease; PSC, primary sclerosing cholangitis; SLK, simultaneous liver-kidney transplant

**Table 3. Pretransplant Evaluation Stratified by Transplant Type**

<table>
<thead>
<tr>
<th>Echocardiogram</th>
<th>Liver Alone</th>
<th>SLK</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>266</td>
<td>46</td>
<td>.71</td>
</tr>
<tr>
<td>Mean LVEF (SD), %</td>
<td>62.05 (5.94)</td>
<td>62.39 (5.24)</td>
<td>.71</td>
</tr>
<tr>
<td>RVSP &gt; 60%, No. (%)</td>
<td>155 (58.3)</td>
<td>27 (58.7)</td>
<td>.70</td>
</tr>
<tr>
<td>Mean RVSP (SD), mm Hg</td>
<td>32.84 (8.71)</td>
<td>39.22 (9.90)</td>
<td>.00</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>31</td>
<td>37</td>
<td>.02</td>
</tr>
<tr>
<td>No. of patients</td>
<td>13</td>
<td>6</td>
<td>.20</td>
</tr>
<tr>
<td>Mean RA (SD), mm Hg</td>
<td>8.46 (4.29)</td>
<td>13.00 (11.06)</td>
<td>.01</td>
</tr>
<tr>
<td>Mean RVSP (SD), mm Hg</td>
<td>39.85 (9.55)</td>
<td>42.33 (12.69)</td>
<td>.64</td>
</tr>
<tr>
<td>Mean pulmonary artery</td>
<td>36.54 (10.98)</td>
<td>39.33 (12.16)</td>
<td>.62</td>
</tr>
<tr>
<td>Systolic pressure (SD), mm Hg</td>
<td>36.54 (10.98)</td>
<td>39.33 (12.16)</td>
<td>.62</td>
</tr>
<tr>
<td>Mean mPAP (SD), mm Hg</td>
<td>23.31 (7.47)</td>
<td>27.17 (9.30)</td>
<td>.34</td>
</tr>
<tr>
<td>Mean PCWP (SD), mm Hg</td>
<td>14.00 (4.02)</td>
<td>19.50 (12.42)</td>
<td>.15</td>
</tr>
<tr>
<td>Mean PVRI (SD)</td>
<td>203.54 (191.7)</td>
<td>159.33 (136.67)</td>
<td>.61</td>
</tr>
</tbody>
</table>

**Abbreviations:** LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RVSP, right ventricular systolic pressure; SD, standard deviation; SLK, simultaneous liver-kidney transplant

**Posttransplant outcomes**

We found no statistically significant increased risk death or retransplant in the SLK group compared to liver transplant-alone group (hazard ratio [HR] of 1.7; \( P = .18 \)) on unadjusted analysis. Within the liver transplant-alone group, the strongest demographic predictor of poor outcome was age at transplant (unadjusted HR of 1.04, 95% CI, 0.999-1.08; \( P = .053 \)) (Table 4). The strongest clinical predictors were related to LVEF and RVSP on echocardiogram. Specifically, patients with an elevated pretransplant LVEF above the median (ie, greater than 60%) were at increased risk of death or retransplant (unadjusted HR of 2.91, 95% CI, 1.40-6.06; \( P < .005 \)) (Table 4). There was also a dose response-type relationship seen at each increasing level of calculated RVSP compared with the baseline of “no tricuspid regurgitation” seen (Table 4), which seemed to plateau around 35 mm Hg.

**Within the SLK group, there were no strong demographic or echocardiographic predictors of outcome. However, point estimates from this analysis seem to suggest a similar association between poor outcomes and both hyperdynamic LVEF and elevated RVSP (Table 4).**

Based on the predetermined \( P \) value cutoff of .2 for univariate inclusion into multivariate modeling, an adjusted analysis was only performed on the liver transplant data. As shown in Table 5, the adjusted HR analysis for multivariate modeling shows results for age, LVEF category, and RVSP category. In this adjusted model, the outcome was associated with moderately elevated RVSP (HR of 3.42, 95% CI 1.31-8.93; \( P = .01 \)) as well as LVEF greater than 60% (HR 2.92, 95% CI, 1.37-6.25; \( P = .006 \)).
In this study, we sought to determine whether an association existed between preoperative cardiac parameters and posttransplant outcomes in liver transplant-alone recipients versus SLK recipients. Here, we demonstrated the relationship between elevated LVEF and RVSP and increased mortality and retransplant in the posttransplant period. Interestingly, in our stratified analysis, this relationship between RVSP and LVEF seemed most pronounced in patients who had liver transplant alone, with only a trend toward this conclusion in SLK patients. Unfortunately, given the relative rarity of this dual-organ transplant, this signal may have been lost due to type II error.

The exact cause of this excess mortality is unclear. We offer 3 potential explanations for this finding. The first is that these physiologic abnormalities directly affect mortality. With regard to elevated LVEF, this could be a sign of nonsystolic heart failure in the setting of end-stage liver disease. Pulmonary hypertension is a well-known risk factor for poor outcomes in liver transplant, and perhaps elevated RVSP measurements more likely belie undiagnosed elevated pulmonary arterial pressure. This would be consistent with the dose-response relationship seen, as well as the abrupt drop off at an RVSP of 35 mm Hg, as this is the typical threshold for RHC at our institution.

A second potential explanation for this finding is that these findings do not directly cause mortality but are simply markers of diastolic heart failure and volume overload. A hyperdynamic state with low systemic resistance is the classical physiologic phenotype of the patient with cirrhosis. An elevated LVEF in our study may be a marker of end-stage liver disease, which is more advanced and thus portends a riskier postoperative course. It is also possible that prolonged hyperdynamic physiology could cause increased left ventricular hypertrophy and result in a relative increase in ejection fraction. Likewise, increased volume overload is known to cause increased mean pulmonary artery pressure and RVSP. The postoperative risks to uncorrected volume overload are well known. This could be consistent with the elevations in RVSP seen between the SLK and the liver transplant-alone groups along with the increased gross mortality seen in the SLK group on univariate analysis, as renal failure is an independent risk factor for elevated RVSP.

A final explanation of this relationship is that this is simply an artifactual finding of an epidemiologic retrospective study. If true, this would have to be
intrinsically related to undergoing a transplant and doing poorly without involving the more typical covariates examined in this study (including MELD, body mass index, race, and sex). Although we cannot refute this possibility in our study or the other retrospective analyses done on this topic, it remains a possibility.

A limitation of our study is that we only have data of patients who underwent transplant. Clearly, there are many patients who had significantly abnormal cardiac workups and were not listed for transplant. This could also explain why the HR is the highest at only mildly elevated RVSP, as patients with markedly elevated RVSP may be removed from transplant consideration early on.

In summary, we set out to determine to what extent pretransplant cardiovascular evaluation predicted outcomes in both liver transplant-alone and SLK transplant patients. We found suggestions that elevations in RVSP and LVEF may portend poor outcomes in the posttransplant period. These findings have been seen in multiple retrospective studies and should be investigated in a systematic, prospective manner. Also of note is that the SLK recipients are more prone to receive an RHC during the pretransplant evaluation period.

References

Abstract

During pediatric kidney transplant, surgical challenges occasionally occur. In particular, vascular anastomosis should be considered for children with small body weight < 12 kg, multiple renal arteries, vascular anomaly, and inferior vena cava occlusion. In pediatric patients, a living-donor renal graft is usually donated from a parent. Therefore, the renal artery and vein are too large to be anastomosed with the recipient’s internal iliac artery and external iliac vein. In children who are > 12 kg, the renal artery and vein could be anastomosed with the external iliac artery and the external iliac vein. In children who are < 10 kg, the renal artery and vein should be anastomosed directly with the aorta and inferior vena cava. A pediatric transplant surgeon should consider arterial and venous anastomosis sites before transplant surgery. In small children with partial or total inferior vena cava occlusion, the venous anastomosis site should be evaluated. If the graft is placed on the left side, a venous graft must be used as a bridge between the renal vein and inferior vena cava. In 13 kidney transplants in children with inferior vena cava occlusion, 7 were on the left and 6 were on the right side. A patent segment of the inferior vena cava, the left original renal vein, an ascending lumbar vein, an azygos vein, the first graft renal vein, and a portal vein were used for venous anastomosis in 6, 2, 2, 1, 1 and 1 recipient, respectively. One child had graft loss due to renal vein thrombosis and one died of hemorrhage immediately posttransplant. Three had grafts with relatively long-term function, but these were lost due to chronic allograft nephropathy 100, 122, and 137 months posttransplant. However, the other 8 recipients have so far maintained graft function from 6 to 138 months since transplant.

Key words: Living-donor renal transplant, Small body weight, Vascular anastomosis

Introduction

For kidney transplant, young children usually receive a living-related transplant from a parent donor. However, this adult renal allograft is transplanted in a small space in young children. In small children who are less than 10 kg body weight, we usually make a paramedian incision and the intraperitoneal approach is preferred, although recently the extraperitoneal approach has been also used in children who are less than 10 kg body weight.1

When a renal allograft has double arteries, a conjoined and end-to-side anastomoses to one orifice are performed. Procedure times for multiple anastomoses are lengthy, leading to long ischemic time in the lower extremities and pelvic organs. In addition, a multiple arterial anastomosis to a direct aorta increases the risk of massive bleeding.

In children with a thrombosed inferior vena cava (IVC), a pretransplant evaluation with three-dimensional computed tomographic (3D-CT) venography is important.2-4 This procedure can allow clear discussion of the venous anastomosis site5-14 and the necessity of a venous graft5-12,13 before transplant surgery.

In this report, we outline our pretransplant evaluation of the donor’s renal artery and vein and the recipient’s vascular system, including the aorta and the IVC, for vascular anastomosis in small children. We also outline the vascular surgical techniques that we use in small children with compromised arteries and veins, including thrombosed IVC. Previously, kidney transplants for small children with thrombosed IVC were not performed and were
contraindicated because the vascular anastomosis was difficult and complicated. However, a successful kidney transplant promises no dialysis, normal growth, and normal child life. The benefits of transplant outweigh the challenges of vascular surgery in small children.

Incision and Approach
In our center, we prefer the hockey stick incision; occasionally, the incision is extended to the subcostal area in children who are more than 12 kg. In children who are less than 10 kg, we make a paramedian incision. Usually, the right side is chosen because venous anastomosis with IVC is much easier than a left-side procedure.

The extraperitoneal approach is used for children who are more than 12 kg, and the intraperitoneal approach is preferred for children who are less than 12 kg. Exposure of an operative field is better with vascular anastomosis in the intraperitoneal approach than in the extraperitoneal approach. However, an ileus due to bowel adhesion may occasionally occur posttransplant with the intraperitoneal approach. With the intraperitoneal approach, the graft, including the renal pedicle, should be surrounded by retroperitoneum as much as possible. A ureter also should be placed in the retroperitoneal space.

Presence of Double Renal Arteries

Double renal arteries of the same size
The conjoined ex vivo method is preferred for joining double renal arteries to one orifice. This is a lengthy method and a risk to children when anastomosis of each renal artery with each aorta is needed.

Upper renal artery is larger than the lower artery
When there is a short distance between the upper and lower arteries, the lower artery is anastomosed with the upper artery end-to-side to join double renal arteries to one orifice (Figure 1). When there is a long distance between these arteries, the upper artery is anastomosed with the aorta or the common iliac artery and the lower artery is anastomosed with the external or internal iliac artery.

Upper renal artery is smaller than the lower artery
When there is a short distance between the upper and lower arteries, the upper artery is anastomosed with the lower artery end-to-side to join the double renal arteries into one orifice. When there is a long distance between these arteries, the graft is placed upside down and the lower artery is anastomosed with the aorta or common iliac artery and the upper artery is anastomosed with the external or internal iliac artery. A ureter should be placed with reversed U shape to avoid a sharp bend (Figure 2).

Occlusion of Inferior Vena Cava

Some children with Wilms tumor, neuroblastoma, hepatoblastoma, or previous transplant procedures have partially or totally thrombosed IVC. The venous anastomosis site of an allograft renal vein should be evaluated by reviewing 3D-CT venography image results. In 13 pediatric kidney transplants in children with occlusion of IVC at our center, 7 grafts were placed on the left and 6 grafts were placed on the right side. A patent segment of IVC, the left original renal vein, an ascending lumbar vein, an azygos vein, the first graft renal vein, and a portal vein were used.
for venous anastomosis in 6, 2, 2, 1, 1, and 1 recipient, respectively (Table 1). One child had graft loss due to renal vein thrombosis, and one child died of hemorrhage immediately posttransplant. Three children had long-term graft function, but grafts were lost due to chronic allograft nephropathy 100, 122, and 137 months posttransplant. However, 8 recipients have shown graft function for 6 to 138 months since transplant (Table 2).

Table 1. Kidney Transplant in Children with Inferior Vena Cava Occlusion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Donor Graft Transplant, y</th>
<th>Donor</th>
<th>Arterial Anastomosis</th>
<th>Venous Anastomosis</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.4</td>
<td>Living Right Ao</td>
<td>Patent segment of IVC</td>
<td>Left renal vein</td>
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<tr>
<td>2</td>
<td>2.8</td>
<td>Living Right Ao</td>
<td>Patent segment of IVC</td>
<td>Left renal vein</td>
<td></td>
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<tr>
<td>3 (2-2)</td>
<td>6.4</td>
<td>Deceased Left Ao</td>
<td>Patent segment of IVC</td>
<td>Patent segment of IVC</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.7</td>
<td>Living Right Ao</td>
<td>Left Ao</td>
<td>Left renal vein</td>
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<tr>
<td>5 (4-2)</td>
<td>14.9</td>
<td>Deceased Left Ao</td>
<td>Patent segment of IVC</td>
<td>Patent segment of IVC</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.5</td>
<td>Deceased Right Ao</td>
<td>Azygos vein</td>
<td>Patent segment of IVC</td>
<td></td>
</tr>
<tr>
<td>7 (6-2)</td>
<td>15.9</td>
<td>Living Right Ao</td>
<td>First graft vein</td>
<td>Patent segment of IVC</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6.8</td>
<td>Living Right Ao</td>
<td>Patent segment of IVC</td>
<td>Patent segment of IVC</td>
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<tr>
<td>9</td>
<td>10.3</td>
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<td>Ascending lumbar vein</td>
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<td>10</td>
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<td>Ascending lumbar vein</td>
<td>Patent segment of IVC</td>
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<tr>
<td>11</td>
<td>4.9</td>
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<td>Patent segment of IVC</td>
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<tr>
<td>12</td>
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<td>Patent segment of IVC</td>
<td>Patent segment of IVC</td>
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<tr>
<td>13</td>
<td>5.9</td>
<td>Living Left Ao</td>
<td>Patent segment of IVC</td>
<td>Portal vein</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Ao, aorta; IVC, inferior vena cava

Table 2. Outcomes of Kidney Transplant in Children with Inferior Vena Cava Occlusion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum Creatinine (3 mo), mg/dL</th>
<th>Serum Creatinine (1 y), mg/dL</th>
<th>CCr, mL/min/1.73 m²</th>
<th>Outcome</th>
<th>Posttransplant, mo</th>
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<tbody>
<tr>
<td>1</td>
<td>0.56</td>
<td>0.7</td>
<td>77</td>
<td>Graft loss</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>ND</td>
<td></td>
<td></td>
<td>Graft loss</td>
<td>0</td>
</tr>
<tr>
<td>3 (2-2)</td>
<td>0.65</td>
<td>0.78</td>
<td>72.2</td>
<td>Graft survival</td>
<td>138</td>
</tr>
<tr>
<td>4</td>
<td>0.54</td>
<td>0.58</td>
<td>107.7</td>
<td>Graft loss</td>
<td>122</td>
</tr>
<tr>
<td>5 (4-2)</td>
<td>1.55</td>
<td>1.76</td>
<td>56.5</td>
<td>Graft survival</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>0.98</td>
<td>0.92</td>
<td>64.2</td>
<td>Graft loss</td>
<td>137</td>
</tr>
<tr>
<td>7 (6-2)</td>
<td>ND</td>
<td></td>
<td></td>
<td>Graft survival</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>ND</td>
<td></td>
<td></td>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0.84</td>
<td>1.27</td>
<td>55.4</td>
<td>Graft survival</td>
<td>78</td>
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<tr>
<td>10</td>
<td>0.57</td>
<td>0.84</td>
<td>71.6</td>
<td>Graft survival</td>
<td>60</td>
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<tr>
<td>11</td>
<td>0.62</td>
<td>0.57</td>
<td>94.2</td>
<td>Graft survival</td>
<td>28</td>
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<tr>
<td>12</td>
<td>0.37</td>
<td>0.61</td>
<td></td>
<td>Graft survival</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>0.12</td>
<td></td>
<td></td>
<td>Graft survival</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: CCr, creatinine clearance; ND, not determined

Case Presentation

Case A
Case A was an 11-year-old boy (patient 12; Table 1) who had previous kidney transplant twice in the right side of the pelvic space. The second graft had been replaced using an intra-abdominal approach after the first graft was removed; however, this graft showed primary graft nonfunction and was removed 9 days after transplant. Before a third kidney transplant was planned, a 3D-CT angiography showed absence of the right common, external, and internal iliac arteries. In addition, the IVC was mostly occluded, although partial patentcy was shown around the junction of the left original renal vein to the IVC (Figure 3). Therefore, we decided that a third graft could be placed in the left side with a transverse incision and intraperitoneal approach. The renal vein was extended so that it could be anastomosed with the junction of the left original renal vein using the venous graft, which was modified by the donor’s left ovarian and right saphenous veins (Figure 4). The renal artery was anastomosed with the aorta. Blood flow was observed at 3 months posttransplant from the renal vein to the central IVC through the venous graft, which crossed over the aorta (Figure 5).
Case B
Case B was a 5-year-old girl (patient 13; Table 1) in whom the IVC was mostly occluded because of congenital nephrotic syndrome. A small part of the IVC in the central area was patent; however, it was not an appropriate anastomosis site (Figure 6). Other veins such as the left original renal vein, ascending lumbar vein, and azygos vein were also too small to anastomose. We implemented a transverse incision with intraperitoneal approach in the upper abdomen. The graft was placed upside down in the left renal fossa after left nephrectomy. The renal vein was extended by the venous graft, which consisted of the donor’s retrieved left ovarian and left saphenous veins. The venous graft was anastomosed with the portal vein as a bypass from the graft renal vein (Figure 7, left). The renal artery was anastomosed with the aorta. Renal venous flow was observed 3 months posttransplant from the renal vein to the portal vein through the venous graft, which crossed over the aorta (Figure 7, right).

Case C
Case C was a 10-year-old boy (patient 9; Table 1) in whom the IVC was totally occluded after hepatoblastoma surgery (Figure 8, left). The donor’s ovarian vein was retrieved, replacing the upper site of the graft renal vein with side-to-end anastomosis (Figure 8, right; Figure 9, left). The ovarian vein graft was anastomosed with the splenic vein after splenectomy (Figure 9, left). The renal vein was anastomosed with the junction of the left original renal vein to the left testicular vein (Figure 8, right; Figure 7, right).
Figure 9, left). The renal artery was anastomosed with the aorta. Blood flow was observed at 3 months posttransplant from the renal vein to the portal vein through the ovarian vein graft and the splenic vein, as shown by 3D-CT venography (Figure 9, right).

**Figure 9.** Ovarian Vein Used as Venous Graft Between the Renal Vein and the Splenic Vein in Case C

(Left) Ovarian vein used as venous graft between the renal vein and the splenic vein. This figure was modified from Shishido and associates. (Right) 3-dimension computed tomographic venography at 3 months posttransplant. The ovarian vein was used as a bypass between the renal vein and the splenic vein.

**Discussion**

An intraperitoneal approach is the easier operative procedure to expose the operating field and perform vascular anastomosis than the extraperitoneal approach. However, an adhesive intestinal ileus occasionally occurs in the intraperitoneal approach. The extraperitoneal approach is preferred in children who are more than 12 kg body weight. Heap and associates demonstrated that between days 2 and 14 postoperatively, an extraperitoneal renal transplant in patients less than 6 years of age resulted in a transient improvement in early graft function; however, there were no significant differences in the number of complications between intra- and extraperitoneal approaches.

In children with renal double arteries, the conjoined method or end-to-side anastomosis between the small artery and the main artery is preferred. The preferred choice is dependent on the size and position of the double arteries. It is necessary to avoid multiple anastomoses between the renal arteries and aorta. Multiple anastomoses with aortas increase the risk of long ischemic time in the pelvic organs and legs and can result in massive bleeding.

Intravenous blood pressure should be below 25 mm Hg, otherwise, renal vein thrombosis frequently occurs. A venous anastomosis should be considered for small children with a defect of the IVC. If the IVC cannot be used for venous anastomosis, the native renal vein, the gonadal vein, or the ascending lumbar vein could be options. When these veins are too small to keep venous flow and to avoid high venous pressure, a splenic vein after splenectomy, an inferior mesenteric vein, a superior mesenteric vein, or a portal vein can be anastomosed with the renal vein.

A pediatric kidney transplant surgeon should master good vascular surgical techniques; however, it is also important to identify the suitable arterial and venous anastomosis sites. Particularly for children with thrombosed IVC, the inferior and the superior mesenteric veins, the splenic vein, or the portal vein could be indicated for venous anastomosis with a renal vein.

Kidney transplant in children with thrombosed IVC was previously not performed because of difficulty with vascular anastomosis. However, successful kidney transplant can result in no dialysis, normal growth, and normal child life. To achieve good quality of life for children with end-stage renal disease, a pediatric transplant surgeon should master vascular anastomosis techniques to allow these children a chance for transplant. Despite the surgical challenges in children with a compromised vascular system, kidney transplant is beneficial.

**References**


Surgical Challenge in Pediatric Kidney Transplant: Lower Urinary Tract Abnormality

Atsushi Aikawa1, Masaki Muramatsu1, Yusuke Takahashi2, Yuko Hamasaki2, Junya Hashimoto2, Mai Kubota2, Youji Hyoudou1, Yoshihiro Itabashi1, Takeshi Kawamura1, Seiichiro Shishido1,2

Abstract

Lower urinary tract abnormalities are difficult to resolve in pediatric kidney transplant patients. Measurement of residual urine, voiding cystourethrography, retrograde urethrogram, cystometry, electromyography of urethral external sphincter muscle, urethrometry, and uroflowmetry are the primary methods for evaluation of lower urinary tract abnormalities. Endoscopic resection or ablation of urethral valves is required in children with posterior urethral valve to treat obstruction, but bladder function does not always recover and may deteriorate to end-stage renal failure even after the obstruction is released. This bladder dysfunction in posterior urethral valve defines valve bladder syndrome. Vesicoureteral reflux caused by high vesical pressure can cause even worse renal graft function posttransplant. In our patient group, urinary diversion occurred with Mitrofanoff conduit using an appendix in 6 children, a Yang-Monti channel conduit using ileum in 1 patient, with cystostomy in 3 children, and with augmented cystoplasty in 9 children before or simultaneously with kidney transplant. These procedures should be selected based on the type of lower urinary tract abnormality including bladder function. Recently, we have preferred a continent diversion for self-catheterization in children with lower urinary tract abnormalities. A continent diversion is preferred to a simple diversion for kidney transplant. It is easy for a parent or a child to manage the clean intermittent catheterization (CIC) required with the Mitrofanoff conduit. The Mitrofanoff conduit is advantageous for children because it can be kept dry and a urine storage bag is not required.

Key words: Bladder function, Preoperative evaluation, Urinary diversion

Introduction

Lower urinary tract abnormalities (LUTAs) can be divided into 2 groups: neurogenic bladders and lower urinary tract anomalies. A neurogenic bladder is caused by spina bifida,1 anal atresia,2 spiral cord injury or tumor, or cerebral palsy. Prune belly syndrome,3 persistent cloaca,4 and posterior or anterior urethral valve5-7 all involve lower urinary tract anomalies. Pretransplant evaluations of LUTAs are important, particularly for children with neurogenic bladders and those unable to void through a native urethra. In this situation, a diversion or a conduit should be considered.

The Mitrofanoff conduit using an appendix is preferred to a simple diversion for kidney transplant.8,9 It is easy for a parent or a child to manage the clean intermittent catheterization (CIC) required with the Mitrofanoff conduit. The Mitrofanoff conduit is advantageous for children because it can be kept dry and a urine storage bag is not required.

An augmentation cystoplasty for a neurogenic bladder with high pressure and small capacity is a good option for children with LUTA.10 A ureterocystostomy with an antireflux submucosal tunnel can be created easily in an augmented colon in which a submucosal layer is thicker than the ileum.

Here, we describe the challenging surgical techniques and skills required for children with LUTAs during kidney transplant and their kidney transplant outcomes.
Mitrofanoff Conduit

In our reported patient group, the Mitrofanoff conduit was used during kidney transplant in 7 children with LUTA from our department and from the Tokyo Metropolitan Children’s Hospital (Table 1). An appendix and a contralateral ureter were used as a conduit in 6 and 1 children, respectively (Figure 1 and Figure 2). As shown in Figure 1, the appendix was mobilized and separated from the cecum and placed in the retroperitoneal space, preserving the vascular pedicle. The one end of an appendix is introduced through a bladder submucosal tunnel and anastomosed with a bladder in an antireflux method to act as a continence mechanism (Figure 1 and Figure 2). The other end is passed through an opening in the umbilicus, and a catheter can pass to empty the bladder 4 to 6 times per day (Figure 3).

Case Presentations

Case 1

Case 1 was a 5-year-old boy who had a posterior urethral valve. At birth, he required a cystostomy for megalocystis and bilateral grade 5 reflux. At 3 months, a posterior urethral valve was diagnosed, and transurethral incision and resection of valves were performed (Figure 4).

His renal function gradually deteriorated; at 2 years of age, his serum creatinine value was 1.42 mg/dL. The Mitrofanoff conduit using an appendix was indicated, and the Mitrofanoff conduit and a living-donor kidney transplant were simultaneously performed. So far, the patient has had stable renal function with catheterization 6 to 7 times daily.

Case 2

Case 2 was a 6-year-old boy with anal atresia, hypoplastic kidneys, and a neurogenic bladder. A

Table 1. Surgical Treatment in Children with Lower Urinary Tract Abnormalities for Kidney Transplant (Toho University Omori Medical Center and Tokyo Metropolitan Children's Hospital)

<table>
<thead>
<tr>
<th>Surgical Cystoplasty</th>
<th>Mitrofanoff</th>
<th>Diversion</th>
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<tbody>
<tr>
<td>Treatment: Own Bladder Used</td>
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<tr>
<td>Posterior urethral valve</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Urethral hypoplasia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Meningocele</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Anal atresia, neurogenic bladder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Persistent cloaca</td>
<td>1</td>
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</table>

Figure 1. Mitrofanoff Conduit Procedure Using an Appendix

Figure 2. Mobilization of Appendix, Preserving the Vascular Pedicle (Left) and Anastomosis Between Appendix and Bladder Using Antireflux Method, Creating a Submucosal Tunnel (Right)

Figure 3. Catheterization Into the Mitrofanoff Conduit

The Mitrofanoff conduit keeps clean and dry due to a continent diversion.

Figure 4. Voiding Cystourethrography Showing Posterior Urethral Valves and Dilated Posterior Urethra (Left). With Urethroscopy Showing Transurethral Incision and Remnants of Valves After Transurethral Resection (Right)
Mitrofanoff conduit was indicated for his neurogenic bladder. A right native ureter after right nephrectomy was used as a conduit (Figure 5). One end was anastomosed with the bladder using the antireflux method. The other end was placed in the skin orifice (Figure 5). Renal function has so far been stable with catheterization 2 to 4 times daily.

**Figure 5.** Mitrofanoff Conduit Using the Right Native Ureter (Left) and Catheterization Into Ureterocutaneostomy (Right)

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**Case 3**

Case 3 was a 6-year-old boy with posterior urethral valve. A Mitrofanoff conduit was indicated for a neurogenic bladder. A 2- to 2.5-cm segment of the ileum with a strip of mesentery was isolated from the distal ileum to serve as a conduit (the Spiral Yang-Monti channel; Figure 6). The conduit was anastomosed with the bladder using the antireflux method, and an orifice of the conduit was made in the lower abdomen. Renal function has so far been stable with catheterization at 4 to 5 times per day.

**Figure 6.** A Mitrofanoff Conduit Indicated For a Neurogenic Bladder

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**Augmentation Cystoplasty**

We treated 9 recipients with neurogenic bladders with augmentation cystoplasty. A cystoplasty using a sigmoid colon was performed in 5 kidney transplant recipients with meningocoele, in 1 recipient with posterior urethral valve, in 1 recipient with spina bifida, and in 1 recipient with persistent cloaca (Table 1). A 30-cm-long segment of the colon was mobilized, preserving the mesentery (Figure 7). A seromuscular end-to-end anastomosis was made between the remaining oral and anal sides of the colon stump (Figure 7). The posterior wall of the colon pouch was created by side-to-side anastomosis of the opposed margins (Figure 7).

**Figure 7.** Cystoplasty Using a Colon

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One patient with an anal atresia and a neurogenic bladder underwent an augmentation cystoplasty using an ileum. A 45-cm-long segment of an ileum cystostomy was mobilized, preserving the mesentery, and a seromuscular end-to-end anastomosis was made between the remaining oral and anal sides of the ileum stump (Figure 8). The longer ileum segments were sutured in a “W-shaped” configuration to each other to create an ileum pouch (Figure 8). The bladder was opened transversally to create an anastomosis site with a colon or an ileum pouch (Figure 9). A colon or an ileum pouch was sutured to the bladder remnant (Figure 9).

**Figure 8.** Procedure of an Ileum Pouch for Cystoplasty

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(Left) Isolating an ileum segment with a strip of mesentery; (B) creating a conduit with double layer suture over a 12-14 Fr catheter; (C) modifying an ileum segment with a strip of mesentery to a conduit (Yang-Monti channel)

(Left) Excluding a 30-cm-long segment from a sigmoid colon (modified from Reference 14). (Middle) End-to-end anastomosis of a colon and incision of the tenia (modified from Reference 14). (Right) Side-to-side anastomosis of the opposed margins to create a colon pouch (modified from Reference 14).

(Left) Mobilizing a 45-cm-long segment and opening the ileum for augmentation. (Middle) Suturing an ileum segment in a “W-shaped” configuration to each other. (Right) Creating an ileum pouch.
Outcomes
We conducted cystoplasty procedures in 9 children, Mitrofanoff in 7 children, and diversion (cystostomy) in 3 children from Kiyose Tokyo Metropolitan Children’s Hospital from 1975 to 2009 and Toho University Omori Medical Center from 2005 to 2016. Seventeen children retained their own bladder during kidney transplant, despite presence of LUTA (Table 1), and CIC was performed from 2 to 6 times daily. Graft survival rates in children with LUTA (n = 36) and those without LUTA (n = 85) were 100% and 97% at 1 year, 98% and 97% at 5 years, and 98% and 92% at 10 years posttransplant, respectively (Figure 10), in our centers.

Discussion
In the 2010 North American Pediatric Renal Trials and Collaborative Studies annual transplant report, causes of end-stage renal disease were classified into hypo/dysplastic kidney (15.8%), obstructive uropathy (15.3%), focal segmental glomerular sclerosis (11.7%), reflux nephropathy (5.2%), and others (52%). An obstructive uropathy and reflux nephropathy including LUTA and renal hypo/dysplastic kidney were accompanied by LUTA. Adams and associates reported that malformations of the lower urinary tract were the reasons for end-stage renal failure in 66 children (18.6%) among 349 pediatric kidney transplant patients. Lower urinary tract abnormalities also included neurogenic bladders due to meningocoele.

Valve bladder syndrome is defined as persistent or progressive severe hydrourteronephrosis without residual or recurrent obstruction in patients with posterior urethral valve. Renal function can occasionally deteriorate even after ablation of posterior valves. A bladder overdistention due to a combination of polyuria, impaired bladder sensation, and residual urine volume can develop hydroureteronephrosis and impair renal function. Therefore, a conduit or diversion with CIC is indicated to keep the bladder emptying in kidney transplant for children with the valve bladder syndrome. The Mitrofanoff conduit is an excellent surgical procedure and has an advantage as a continent diversion. It is also easy to introduce CIC posttransplant. We mainly used an appendix as a conduit; however, we used an ileum with the spiral Yang-Monti channel method in one child. Intravesical pressure should be controlled below approximately 35 to 40 cmH₂O under administration of anticholinergic drugs and catheterization. An augmentation cystoplasty is indicated for children with small bladder capacity, low bladder compliance, and high intravesical pressure. An augmentation cystoplasty is a safe and effective option for children with end-stage renal disease undergoing kidney transplant. Recurrent urinary tract infection can occur posttransplant in children with an augmentation cystoplasty. It can also increase the risk of deterioration of renal graft function. Clean intermittent catheterization and antibiotic prophylaxis are important treatments to prevent urinary tract infection.

Reabsorption of ammonium chloride and ammonia and secretion of bicarbonate by the bowel can create an acid-base disturbance with augmentation cystoplasty, resulting in hyperchloremic metabolic acidosis. Most patients who have augmentation cystoplasty require bicarbonate, resulting in a longer follow-up. Chronic metabolic acidosis could lead to depletion of calcium carbonate from bone, which may cause growth retardation in children.
There is no significant increased risk of bladder cancer after bladder augmentation for a dysfunctional bladder.\textsuperscript{24} However, patients with spina bifida are at risk for cancer regardless of whether augmentation is performed.

The graft survival rate of children with LUTA in our centers was 98\% at 5 and 10 years posttransplant. Adams and associates reported that the graft survival rates in children with posterior urethral valve, Prune belly syndrome/VATER association, neurogenic bladder, and vesicoureteral reflux were 62.9\%, 71.4\%, 50\%, and 78.5\% at 5 years posttransplant, respectively.\textsuperscript{16} Kamal and associates reported that 5-year graft survival rate in living-donor kidney transplant in children with posterior urethral valve was 81\%.\textsuperscript{6} Hatch and associates reported that 5- and 10-year graft survival rate in kidney transplant for 31 children with augmentation or diversion was 60\%.\textsuperscript{23} Our 5- and 10-year graft survival rates in kidney transplant for children with LUTA of 98\% may be because we conduct pretransplant evaluations of LUTA, use appropriate indications for diversion including the Mitrofanoff conduit, and use augmentation cystoplasty and effective surgical skills.

Surgical challenges are present in pediatric kidney transplant patients with LUTA. The Mitrofanoff conduit, Yang-Monti channel, and augmentation cystoplasty are complicated urologic surgical techniques. A pediatric transplant surgeon should train and master the surgical skills necessary for LUTA. Proper care and successful surgery may promise better long-term outcomes of kidney transplant for children with LUTA.

References

Abstract

Solid-organ transplant recipients are at higher risk of developing Kaposi sarcoma, which is a multicentric vascular neoplasm of lymphatic endothelium-derived cells. Reducing doses of immunosuppressive drugs and switching from calcineurin inhibitors to the mammalian target of rapamycin inhibitor rapamycin have been suggested as an effective first-line treatment modality in most patients. Herein, we report a 64-year-old renal transplant recipient who developed multiple cutaneous and visceral Kaposi sarcoma lesions 2 months after transplant. The patient showed no improvement, with progression of the disease until month 15 of the suggested therapy of rapamycin.

Key words: mTOR inhibitor, Renal transplant recipient, Solid-organ transplant recipient

Introduction

Kaposi sarcoma is a low-grade angioproliferative tumor associated with human herpes virus 8.1 Solid-organ transplant recipients are more susceptible to having Kaposi sarcoma, which affects 0.2% to 11% of renal transplant recipients.2 The risk increases with recipient age at transplant and peaks in the first 2 years after the operation.3 The average time between transplant and occurrence of the sarcoma has been reported to be 20 months (2 months to 18 years).3,4 Kaposi sarcoma carries a variable clinical course in renal transplant recipients, ranging from minimal mucocutaneous disease to extensive internal organ involvement.5 Mucocutaneous lesions occur in more than 90% of the cases, whereas internal organs are involved in less than 50% of cases. Lesions mainly localize on the lower limbs and generally associate with a preceding leg edema.6

The cornerstone in the treatment of Kaposi sarcoma in this patient population has been suggested as tapering down the doses of immunosuppressive drugs in addition to conversion to the mammalian target of rapamycin (mTOR) inhibitor rapamycin if the previous protocol included a calcineurin inhibitor (namely, cyclosporine and tacrolimus).5,7 However, this management strategy does not end with successful results in all cases.8

Case Report

A 64-year-old female patient was referred to our clinic for the presence of purple painless lesions on her extremities that had been present for 1 month. She had undergone renal transplant 3 months previously and was on maintenance immunosuppression with prednisolone (20 mg/day), tacrolimus (2 mg/day), and mycophenolate mofetil (720 mg/day). Dermatologic examination disclosed multiple violaceous indurated plaques of 1 to 3 cm in diameter located on her forearms but especially on the lower legs, favoring the left side (Figure 1A). However, her physical examination was unremarkable.

Histopathology revealed ectatic irregularly shaped round capillaries, slit-like endothelium lined vascular spaces, and spindle-shaped cells. Human herpes virus 8 antigens were detected by immunohistochemistry, but the patient was seronegative for human immunodeficiency virus. Endoscopic examination disclosed multiple violaceous indurated plaques of 1 to 3 cm in diameter located on her forearms but especially on the lower legs, favoring the left side (Figure 1A). However, her physical examination was unremarkable.

Histopathology revealed ectatic irregularly shaped round capillaries, slit-like endothelium lined vascular spaces, and spindle-shaped cells. Human herpes virus 8 antigens were detected by immunohistochemistry, but the patient was seronegative for human immunodeficiency virus. Endoscopic examination of the gastrointestinal system revealed involvement of the sigmoid colon and gastric mucosa; however, lymph node ultrasonography, chest radiography, and chest and abdomen computed tomography scans showed no abnormal findings. Consequently, the
diagnosis was established as Kaposi sarcoma with cutaneous and visceral involvement, corresponding to stage 3 disease.

Although reduction of prednisolone (10 mg/day) and switch from tacrolimus to rapamycin were performed immediately, new cutaneous lesions formed in clusters on her lower legs accompanied by leg edema (Figure 1B). Moreover, a new lesion developed on her left ala nasi within the following 4 months. She also received follow-up clinical examination every month and radiologic investigation quarterly.

Because previous lesions got bigger and new ones continued to form (Figure 1C), prednisolone dose was reduced again (5 mg/day). However, satellite-like papules and exophytic nodules (Figure 1D) developed and enlarged over time, causing difficulty in walking. Cryotherapy was performed for these polypoid lesions, resulting in improvement after 2 sessions. She received 2 more endoscopic examinations that revealed stable lesions. Regression of lesions finally started after month 15 (Figure 1E). At 4-year follow-up, 80% of the cutaneous lesions had cleared, leaving postinflammatory hyperpigmentation (Figure 1F).

The patient continues to have bilateral leg edema. Her maintenance immunosuppressive therapy includes prednisolone (5 mg/day), rapamycin (1 mg/every other day), and mycophenolate mofetil (720 mg/day); her renal functions have remained under good control.

Discussion

Therapeutic options for Kaposi sarcoma are mainly based on the distribution and extent of the lesions, stage of the disease, and immune status of the patient. Visceral involvement is usually associated with poor prognosis, especially when it is extensive and progressive. For treatment of Kaposi sarcoma in solid-organ transplant recipients, the ultimate aim should not necessarily be complete regression of the lesions. Instead, one should accept a few stable, largely asymptomatic lesions.9 Because there is a strong relationship between the level of immunosuppression and the occurrence of Kaposi sarcoma, reduction of immunosuppressive drugs is the treatment of choice. Hence, they should be tapered down to the lowest level possible while keeping the risk of rejection of the transplanted organ in mind.9

Rapamycin is a potent immunosuppressive agent that is an mTOR inhibitor.10 Unlike other conventional immunosuppressants, it possesses antineoplastic and antiangiogenic properties. The antineoplastic effect has been suggested to depend on the blockage of cell cycle progression from G1 to S phase by mTOR inhibition.11 Concerning the antiangiogenic effect, it has been proposed that activation of vascular endothelial growth factor receptors plays a possible role in the development of Kaposi sarcoma, and rapamycin induces the regression of the lesions via impairing the production of vascular endothelial growth factor.7 Therefore, a switch from calcineurin inhibitors to mTOR inhibitors is strongly advised as soon as the diagnosis is established.7,9

There are several articles in the literature revealing the efficacy of rapamycin in posttransplant Kaposi sarcoma and also in several other skin and visceral cancers.7,10 However, there are also some case reports regarding its ineffectiveness in treatment or development of Kaposi sarcoma under rapamycin-based immunosuppression.12,13 In 2006, a study of 14 patients demonstrated that, although switching to rapamycin from calcineurin inhibitors is usually useful, it was ineffective or transiently effective in some patients.8 In the literature, the mean time for the regression of the lesions has been reported to be 8 months. However, in some rare
cases, this period has extended to 18 months. In our patient, the period was 15 months before we observed an improvement of the cutaneous lesions.

In case of treatment failure with rapamycin, conventional treatments are advised. Cryotherapy, laser therapy, surgery, intralesional chemotherapy, and topical imiquimod are not good options when the lesions are numerous and widespread as occurred in our patient.\(^6,14\) Furthermore, radiotherapy is not recommended in this patient population because it increases the risk of developing cutaneous neoplasms that have already an increased prevalence in solid-organ transplant recipients.\(^6,9\)

Regarding systemic chemotherapy, it is generally reserved in cases of symptomatic progressive visceral involvement; otherwise, this form of treatment is not preferred as it would lead to more severe immunosuppression in solid-organ transplant recipients.\(^6,9,14\)

Regarding the lymphedema, our patient had no leg edema when Kaposi sarcoma first developed on her extremities. After 3 months, it appeared on the left leg first, with both legs swelling at 6 months. It is well known that Kaposi sarcoma is frequently associated with a preceding leg edema; however, it is also known that lymphedema is a complication of rapamycin treatment, although it is rarely observed. Thus, rapamycin had probably a role in inducing leg swelling in our patient, especially on the right leg, which always had just a few lesions.

In conclusion, posttransplant Kaposi sarcoma can still be a therapeutic challenge in some solid-organ transplant recipients, since tapering down the immunosuppressive drugs to the lowest possible level in conjunction with a switch to rapamycin from calcineurin inhibitors do not always lead to a stable asymptomatic disease status or a long time may be necessary to achieve an improvement.

References

Quality of Life Through Gender Role Perspective in Candidate Renal Transplant Recipients: A Report From Başkent University Using the Short Form 36 Health Survey

Aydan Akyüz Özdemir,1 Cihat Burak Sayın,2 Rengin Erdal,1 Cihangir Özcan,1 Mehmet Haberal3

Abstract

Objectives: The aim of the study was to evaluate the quality of life of patients with end-stage renal disease through a “gender role perspective.” Patients were on hemodialysis treatment and on a wait list for transplant.

Materials and Methods: This study was conducted at the Başkent University Adana, Ankara, and Istanbul hemodialysis centers. Patients completed Short Form 36 Health Survey questionnaires voluntarily to evaluate quality of life. The questions were answered independently by patients while they were undergoing hemodialysis treatment.

Results: The mean age of participants was 54 ± 16.5 years. Quality of life was found to be higher in men (44.7 ± 19.2), and there was a negative correlation between quality of life and age in both sexes, as well as marriage age, number of pregnancies, and age of patient at the first live birth in women (P < .05). We found statistically significant differences between men and women regarding physical health and mental health dimensions. Quality of life scores increased with level of education (P < .001). In addition, patients in Ankara had the highest quality of life compared with Istanbul and Adana (P < .01). Average time on hemodialysis treatment, the number of weekly hemodialysis sessions, mean time of the disease, and mean duration of abandoning hemodialysis sessions were negatively associated with all components of quality of life (P < .05).

Conclusions: We found that sex, education level, social status, and home city of patients had a high impact on quality of life. Thus, it is essential to educate both male and female patients regarding sex/gender and health issues before transplant to increase the recipient’s physical and mental health dimensions.

Key words: Candidate renal transplant recipients, End-stage renal disease, Mental health, Physical health

Introduction

Patients with end-stage renal disease (ESRD) have to face negative impacts associated with being dependent on devices and people in physical, psychological, and social life dimensions. This dependence can negatively affect quality of life (QOL). Quality of life can be defined as the well-being of an individual in psychological, physical, and economic aspects by satisfying all needs, having good interactions with other individuals, having social competence, and having leisure time.1 Quality of life is a discrete concept; hence, the exact measurement of it is not easy. It has both objective and subjective components where both need to be measured separately. The objective components include the physical indicators of well-being, such as the ability to perform physical activities, functional capability, working status, and symptoms of illness. The subjective components include mainly the psychological aspects, such as emotional well-being, life satisfaction, and efficacy.1

Patients with ESRD can only survive with either hemodialysis or peritoneal dialysis treatment. Hemodialysis can especially result in patients being more dependent. The obligation of going to dialysis centers every week, possibly 2 or 3 times per week, introduces more problems. In addition to physical and psychological problems due to hemodialysis treatment, the economic power of the patient may also change because of necessary changes in work schedule and increased medical costs. Depression,
limitation of sex life, and the challenges of the illness can also result in decreased QOL.2-10

There is a difference between women and men in the adaptation process to hemodialysis.3,5-8,11-13 The expectations and attitudes of women are different from men. Although women expect more emotional and psychological support, men want more medical attention related to their sex life.3,6,8,14-16

A person’s sex and gender are 2 different concepts. Sex is defined as all of the biological features, whereas gender reflects the expectations of the population based on the defined roles. Although there are some dissimilarities based on anatomic structure of women versus men that can affect treatment, there is a huge gap created by the population under the term “gender” that directly affects health status.17-19 It is reported that women have more stress and illnesses than men in some communities. The longer life expectancy of women can be a disadvantage because of the burden of chronic diseases that they have to face.17-25 In addition, facts such as economic dependency of women, having lower education, and delayed health care can lower the QOL of women.2,17-24

Treatments for women may not be as successful as for men because of not only the physiologic differences but also because of challenges dictated by gender roles, which can negatively affect treatment success.10,14,20,21,26-28 The responsibilities designated by gender roles and sex discrimination could result in lower QOL at all stages of life and illness.

This study was designed to find the possible effects of gender on patients with ESRD. The aim is to evaluate their quality of life through a “gender role perspective.” All study participants were undergoing hemodialysis treatment and on wait lists for transplant.

Materials and Methods

This study was conducted at the Başkent University Adana, Ankara, and Istanbul hemodialysis centers. Our study included 378 patient participants (female/male = 190/188). Patients answered the Short Form 36 (SF-36) Health Survey questionnaire voluntarily to evaluate quality of life. All components (Physical Functioning, Psychological Functioning, General Health, and Global) of the SF-36 questionnaire were analyzed separately, and its scales and dimensions were scored as a number between 0 and 100. To perform the SF-36 measurements in our patients, we used the Turkish questionnaire, which was formatted by Pinar and associates in 1995.29 All participating patients were able to answer the SF-36 questions independently within 10 to 30 minutes while undergoing hemodialysis treatment. In addition, all social and educational life dimensions were analyzed with another questionnaire form.

Results

The distribution of the participating patients in the study from hemodialysis centers of Başkent University is shown in Table 1. The Istanbul hemodialysis center had the highest participation with 70%, while Ankara had 54% and Adana had 41%. In the 190 female and 188 male patients who participated in the study, the mean age was 54 ± 16.5 years.

We observed significant differences between the sex of the participant and the SF-36 components (Table 2). The QOL score for men (44.7 ± 19.2) was higher than for women (36.1 ± 7). Among all SF-36 components, men had higher QOL scores than women. As shown in Table 2, education affected the QOL score. The SF-36 scores of patients versus level of education were significantly different among all components. As level of education increased, so did the QOL of the patient.

The QOL scores versus location of the hemodialysis center were also significantly different (Table 2). Patients participating from Ankara (50.3 ± 20) had higher SF-36 scores than others (P < .001). When scores were ranked, Istanbul followed Ankara with a score of 39.5 ± 17.2, whereas Adana had the lowest SF-36 score of 34.3 ± 15.9.

We analyzed the effects of treatment on QOL by using the number of weekly hemodialysis sessions, the frequency of hemodialysis sessions abandoned, the average time on hemodialysis treatment, the
duration of the disease, and the patient’s first visit to a medical center (Table 2). The number of weekly hemodialysis sessions was significantly associated with SF-36 score ($P < .001$). Quality of life decreased with increased number of hemodialysis sessions that a patient received. Patients with 1 hemodialysis session per week had a score of 70.6 ± 14 in the SF-36 survey, and those with 4 sessions per week had a score of 21.3 ± 8.3. As shown in Table 2, every added session drops the QOL score gradually.

Patients who did not abandon hemodialysis sessions had higher SF-36 scores than those who either frequently or sometimes abandoned sessions (Table 2). The frequency of abandoning sessions was significantly associated with the Physical Functioning component ($P < .001$). There was also a significant negative correlation between abandoning sessions and QOL scores ($P < .05$). Age, average time on hemodialysis treatment, mean period of the disease, and the mean duration of the disease to the first visit to the medical center (Table 2) were also negatively associated with the components of the SF-36 ($P < .05$).

With regard to the family member who supported the patient at home as a caregiver (Table 3), most of the patients had a female caregiver (90.66%). The sex of the family member supporting the patient (Table 3) significantly influenced SF-36 scores. Patients with female caregivers had the highest SF-36 scores, whereas the lowest scores were shown in patients supported by their son or daughter-in-law ($P < .001$).

When we compared the educational levels of the cities (Table 4), Ankara had the highest percentage of patients with high education level (31.5% with university degree), whereas Adana had the lowest (3%) ($P < .001$). The QOL components increased with
increases in level of education ($P < .001$). A history of renal transplant did not show any influence on SF-36 scores.

**Discussion**

End-stage renal disease and gender discrimination are listed as global public health problems. The primary issues of chronic diseases are the challenges of psychological, physiological, and social problems that occur because of a lifelong illness. This is especially shown in those who depend on a treatment such as hemodialysis. A hemodialysis patient can feel hopeless, and QOL is negatively affected. In addition, issues due to illness, gender discrimination, and gender roles can also decrease patient QOL.\textsuperscript{2,12,25,30-40} Nephrology departments, who treat one of the most dependent patient groups, are giving close concern to QOL. For its evaluation, SF-36 is the preferred method of evaluation.\textsuperscript{29,38,40,41} In this study, SF-36 was used to show the QOL of male versus female patients on hemodialysis.

At dialysis centers, the QOL of participants has been found to be average or below average.\textsuperscript{41-44} Our results between male and female patients have been supported by other studies showing significant differences between men, who have higher QOL, versus women.\textsuperscript{41-49} Evans and associates\textsuperscript{50} and Wolcott and colleagues\textsuperscript{51} showed that women have higher QOL on functional and psychological components, whereas Suet-Ching and associates\textsuperscript{48} stated that men had higher QOL than women.

Although some studies could not show a significant association between age and QOL,\textsuperscript{42,43,52,53} others\textsuperscript{44,46,47,54-58} confirmed this association. In this study, we found a significant negative association between age and QOL, with QOL decreasing with increasing age. Although most QOL components were significantly associated, psychological functioning showed no association with age. This is an expected result since getting old brings many physical restrictions and QOL decreases.\textsuperscript{41,44,51,58}

Education has a positive and significant relation with QOL. It has been found that higher education brings an increase in all components of the SF-36. This same result has been reported in several

### Table 3. Distribution and Correlation of Short Form 36 Scores According to Presence of Caregiver and Correlation With Sex of Caregiver

<table>
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<th>Component</th>
<th>n</th>
<th>General Health, $\bar{x} \pm SD$</th>
<th>Physical Functioning, $\bar{x} \pm SD$</th>
<th>Psychological Functioning, $\bar{x} \pm SD$</th>
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<tr>
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<td>29.37 ± 12.83</td>
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**Abbreviations:** $\bar{x}$, mean; SD, standard deviation

### Table 4. Distribution of Level of Education According to Sex and Hemodialysis Center

<table>
<thead>
<tr>
<th>Hemodialysis Center and Sex</th>
<th>Level of Education</th>
<th>F (n = 190)</th>
<th>M (n = 188)</th>
<th>P Value</th>
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<td>Patient Sex</td>
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<tr>
<td>Adana (n = 165)</td>
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<tr>
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<td>.168</td>
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<tr>
<td>F (n = 83)</td>
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<td>M (n = 82)</td>
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<td>16.2</td>
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**Abbreviations:** F, female; M, male
studies, An increase in general health with higher level of education is an expected result. People with higher levels of education will take responsibility for their living style, have more information about the symptoms, and be more successful in managing comorbidities. As a result, their QOL will be higher.

The cities where patients live and thus where their hemodialysis treatment center is located was also significantly associated with QOL scores. Ankara had the highest SF-36 score, and Adana had the lowest. This difference was significant. Because all hemodialysis centers of Başkent University are providing standard service due to ISO-9000 quality standards, the reason for this difference can be explained by the city’s living conditions. A city’s QOL is a combination of the physical, social, and economic environment. The physical environment consists of the amount of green zone, transportation types and network, public transportation, infrastructure, municipal services, communication, and type and quality of residences. Because of the nature of hemodialysis treatment, the type of transportation available is important. Patients are required to go to the hospital or hemodialysis center 2 or 3 times per week. The city’s transportation network and public transportation services become vital for ESRD patients and have a direct effect on patient QOL.

The QOL index of cities, which was formed by using 281 different variables, supports the importance of living conditions on a person’s QOL. This city index indicates that Istanbul, Ankara, and Izmir have the highest QOL in Turkey and the highest rank regarding living conditions, whereas Adana has the second level of QOL. This index and its ranking are supported by the results of our study and could unveil the reason for Adana’s lowest SF-36 scores.

Early marriages can be seen worldwide but have high incidence in developing or less developed countries. All marriages that occur below the age of 18 years are considered as early-age or child marriages. Today, in general, every 1 marriage of 4 is a child marriage in Turkey. There are many reasons for these marriages. Neighborhood pressure, lack of education, religious and cultural misinformation, domestic violence, economic distress, and possession can be listed as reasons. Early marriages decrease QOL, and most child brides are reported to be domestic violence victims.

Early marriages also result in early-age pregnancies and the high number of labors, which can also negatively affect QOL. Early-age pregnancies can result in chronic diseases, which are caused by complications. The number of labors may also result in additional physical problems to women, such as the health problems caused by short intervals between pregnancies.

Women who marry at an early age and become pregnant afterward either resulting in live birth or not have lower QOL. Among all women participants, the ones who married and gave birth at an early age had lower SF-36 scores in our study. As the results indicated, there was a positive correlation between the QOL and the age of marriage and the age of first live birth. In addition, the number of pregnancies had a negative association with SF-36 scores.

The duration of the illness and frequency of hemodialysis sessions were found to affect QOL. Participants with higher ESRD duration and hemodialysis frequency had lower SF-36 scores. Many studies support this result, suggesting that there is a negative relation between duration of illness and frequency of hemodialysis. As duration of illness increases, hopelessness and depression of the patient also rise. Length of the illness is directly linked to hemodialysis frequency. Starting from day 1, the day of ESRD diagnosis, the patient must face restrictions of the treatment and problems occurring from illness. Patients become more hopeless and agitated, with possibility of necrophobia, resulting in lower QOL.

Hemodialysis treatments should be regularly applied at a needed amount to increase the QOL of ESRD patients. A lack of hemodialysis treatment will bring deadly complications as a result of an imbalance in liquid electrolytes and increase in level of urea. Although patients are aware of the results, they may abandon hemodialysis sessions because of psychological or socioeconomic problems. Having irregular hemodialysis treatments and abandoning sessions result in lowered QOL, as shown in our study. Patients who received regular hemodialysis treatments and did not abandon sessions had higher scores in all SF-36 components versus those who attended hemodialysis sessions irregularly and then abandoned them. There was a significant negative correlation between QOL and leaving sessions. As frequency of abandoning sessions increased, SF-36 scores decreased at the same ratio.
Although the presence of a caregiver did not significantly affect QOL, the sex of the caregiver did. Having a female caregiver was significantly associated with SF-36 scores, although patients who had a son or daughter-in-law as the caregiver had the lowest QOL score. Although almost 50% of the participants were female patients, most of the caregivers were women. In short, it can be suggested that women were primary caregivers of patients with chronic illness. Regarding gender roles, women tend to be more care-giving and patient as a result of motherhood. Therefore, it is an expected result to have these scores for patients with women caregivers. The lower scores of patients having daughter-in-laws as caregivers can be explained by the difference of concern. The concern of a patient’s own daughter will be much more intense than an in law.

Conclusions

In addition to level of education, social status, and residing city, gender role and sex also had high impacts on QOL. The effects of sex/gender discrimination and gender roles were shown in the study results. Most of the caregivers were women, and female patients had the lowest SF-36 scores. It is essential to educate women and men with ESRD on these scores for patients with women caregivers. The concern of a patient’s own daughter will be much more intense than an in law.

References

Liver Biopsy Results in Potential Donor Evaluation in Living Related Liver Transplant

Ebru H. Ayvazoglu Soy,1 Fatih Boyvat,2 B. Handan Ozdemir,3 Nihan Haberal,3 Fatih Hilmioglu,4 Mehmet Haberal1

Abstract

Objectives: The number of living-donor liver transplants has been increasing due to the growing discrepancy between the number of patients on wait lists for liver transplant and the availability of deceased donations. Evaluations of potential liver donors should ensure the safety of the surgical procedure for both the donor and recipient. Liver biopsy is the criterion standard for selecting optimal donors. In this study, we evaluated the importance of preoperative liver biopsy in selecting donor candidates.

Materials and Methods: We evaluated the data of 612 living-related liver donor candidates who received liver biopsies between January 2001 and June 2017 at our center.

Results: In the 612 liver donor candidates (328 male, 284 female; age range, 18-69 years), 416 liver biopsies (68%) were reported as normal and 196 liver biopsies (32%) had pathologic findings. Of 196 donors with pathologic findings, 86 (44%) had fatty changes and 24 (12%) had portal inflammation.

Conclusions: The high rate of pathologic findings in liver biopsy of healthy-appearing donor candidates indicated the importance of liver biopsy in the preoperative evaluation of donors.

Key words: Liver pathology, Preoperative evaluation, Wait list

Introduction

Living-donor liver transplant (LDLT) has become a life-saving surgery for patients with liver failure due to the growing discrepancy between the number of patients waiting for liver transplant and the availability of organs from deceased donors.1 The overriding goals in the LDLT setting are to guarantee donor safety and to optimize recipient outcome.2 Any abnormality in graft liver will reduce the functional hepatic mass, affect the donor fragment, and increase the risk of primary nonfunction of the recipient allograft. Therefore, accurate quantitative assessment of the liver graft is crucial.

Although various biochemical, anthropometric, and radiologic methods have been extensively evaluated, despite its invasiveness, percutaneous liver biopsy remains the criterion standard for determining graft pathology.3 In addition, liver donor biopsy provides a unique source of normal liver tissue and the opportunity to study the prevalence of preclinical liver disease. At our center, percutaneous liver biopsy is a standard protocol of living donor evaluation. In this study, we aimed to evaluate the importance of liver biopsy in selecting donor candidates for LDLT and to identify the histopathologic abnormalities of liver biopsies of apparently healthy donors as a representative figure of our population.

Materials and Methods

The potential donor evaluation protocol at Baskent University consists of 4 steps. In the first step, a thorough clinical evaluation and physical examination are done. Blood group typing and serologic tests for viral hepatitis are checked. The second step consists of a computed tomography evaluation of the donor and measurement of graft volume. The third step includes detailed cardiac and pulmonary evaluations and biochemical and serologic testing. The last step is a percutaneous liver biopsy. We evaluated the demographic data of 612 living-related liver donor candidates who received liver biopsies between January 2001 and June 2017 at our center.
candidates who received liver biopsies between January 2001 and June 2017. All donors were first-, second-, or third-degree relatives of the recipients.

Body mass index (BMI) ratio was assessed to predict the degree of histologically determined steatosis. All histologic specimens were obtained from donor candidates with an 18-gauge biopsy needle. Specimens were formalin fixed, paraffin embedded, and sectioned at 3 or 4 μm. Hematoxylin and eosin stain, Masson trichrome stain, Gomori reticulin stain, and Perls stain were routinely prepared. The biopsies were examined by an experienced pathologist, blinded to the radiologic and surgical findings. Liver pathologies such as fatty changes of the liver, steatohepatitis, granulomatous reaction, fibrosis, portal tract inflammation, iron deposition, and focal hepatocellular necrosis were reported. The degree of steatosis was quantified on a percent scale, which estimated the amount of liver parenchyma that is replaced by steatosis droplets. Steatosis was graded as mild (0%-30%), moderate (30%-60%), or severe (> 60%).

Results

Between January 2001 and June 2017, we performed 612 liver biopsies for donor candidates of 315 LDLT procedures. Liver biopsies from 328 male (53.5%) and 284 female (46.5%) donor candidates were evaluated (age range, 18-69 years). Of 612 biopsies, 416 (68%) were reported as normal liver tissue and 196 (32%) were reported as having various pathologic findings. The most common pathologic finding was steatosis with different degrees; in total, 86 cases of steatoses (44%) were detected. In 110 donor candidates (56%), histologic findings other than steatosis included 24 cases of portal inflammation (12%), 18 cases of hepatocellular swelling (10%), 16 cases of focal spotty necrosis, and 8 cases of fibrosis (4%). “Other” findings (30%) included hepatitis, granulomatous reactions, lipofuscin pigment deposition, and necrosis. For those with histologic findings other than steatosis, no cause was found. Of the 86 patients with steatoses, 60 (70%) were mild, 14 (16%) were moderate, and 12 (14%) were severe. Of total patients, steatosis was seen in 25% of male and 15% of female donor candidates. The BMI of donors with steatosis was greater than that of donors with normal biopsy findings (29.7 ± 3.6 vs 24.8 ± 4.2 kg/m²; P < .001). The mean age of donors with steatosis seen on pathology was higher than the mean age of donors with normal findings (45.8 ± 10.2 vs 37.3 ± 10.4 years; P < .001).

Discussion

In LDLT, donor morbidity and mortality should be minimum, whereas graft and recipient survival must be maximum. Good liver quality is essential for both donor and recipient safety. Accurate preoperative assessment of degree of steatosis is essential for transplant. In deceased donor grafts, steatosis > 30% is reported to increase the risk of primary nonfunction of grafts compared with grafts without steatosis (13% vs 2.5%). In another study, patients who received deceased donor grafts with high-grade steatosis showed higher graft loss and mortality rates than patients who received grafts with moderate to mild steatosis. Severe steatosis in LDLT donors is associated with a greater risk of primary nonfunction. Moderate steatosis in grafts is found to decrease hepatocyte regeneration and increase graft dysfunction, nonfunction, and ischemic injury. Steatosis greater than 30% is therefore considered as a relative risk factor for liver dysfunction, and steatosis greater than 60% is considered an absolute risk factor for liver dysfunction. Because data are scarce regarding noninvasive tests being sufficiently accurate to detect and measure hepatic steatosis, many experts advise performing liver biopsy in donor candidates.
the last step of the evaluation, we perform liver biopsy in donors with normal noninvasive test results. Despite those normal test results, 32% of healthy-appearing potential donors showed findings in liver pathology, including granulomatous reactions, fibrosis, and hepatitis of unknown origin. This indicates the necessity of liver biopsy in all liver donors. The significant negative effect of unexpected donor deaths or significant complications because of preexisting and undetected donor disease can be used to justify routine biopsy sampling.

The predictive value of BMI on hepatic steatosis has also been reported. Body mass index is reported as a reliable predictor of hepatic steatosis. It is suggested that donors with high BMI should undergo liver biopsy because noninvasive tests are not reliable to diagnose steatosis. In our study, we found that BMI of donor candidates with steatosis is higher than that of donors with normal liver pathology.

A thorough evaluation of donor candidates is essential to assess graft function and for the safety of both the donor and recipient. This is especially true for cases of extended liver resection. Our data showed that, to detect liver pathology in healthy-appearing potential donors, liver biopsy is needed.

References

Complications of Liver Transplant in Adult Patients With the Hepatic Form of Wilson Disease

Ruhsen Öcal,¹ Serkan Öcal,² Mahir Kırnap,³ Gökhan Moray,³ Mehmet Haberal³

Abstract

Objectives: Wilson disease is an autosomal, recessive, inherited disorder of copper metabolism that results in the accumulation of copper in many organs and tissues. This disease is mainly characterized by dysfunction due to copper accumulation in the liver, kidney, brain, cornea, bone, heart, and blood cells. The clinical spectrum is broad in Wilson disease. Asymptomatic Wilson disease may be present, but findings related to the involvement of an individual organ or multiple organ failure can be seen. These findings can include neurologic and neuropsychiatric complications. Our aim here was to examine the neurologic complications and our clinical experience in patients who underwent liver transplant for Wilson disease in our clinic.

Materials and Methods: We retrospectively reviewed the medical records of transplant patients with Wilson disease who were seen at Baskent University Faculty of Medicine Transplantation Science between 2005 and 2017. Patient demographics, neurologic complaints, findings from neurologic examinations, and imaging findings were recorded. We also recorded the presence of the Kayser-Fleischer ring, serum ceruloplasmin, 24-hour copper urine levels, and levels of dry copper in liver in each patient.

Results: Our study included 19 patients who ranged in age range from 18 to 44 years (mean age of 26 years). Seven of 19 patients (36.8%) had neurologic symptoms, including epileptic seizures in 2 patients (10.5%), encephalopathy in 1 patient (5.2%), tremor in 3 patients (15.7%), and headache in 1 patient (5.2%). The cause of these long-term neurologic complications was the immunosuppressive drugs. Patients with epileptic seizures were provided with seizure control medication (levetiracetam). Tremor did not need treatment.

Conclusions: In Wilson disease, neurologic complications can be severe. The most common complication seen in our patients was tremor. Early diagnosis and treatment may slow down neurologic disability.

Key words: Immunosuppressive agent, Seizure, Tremor

Introduction

Wilson disease (WD) is an autosomal recessive disorder caused by mutations in the ATP seven B gene. The gene responsible for WD was mapped to chromosome 13. This gene is only found in hepatocytes. The mutation reduces the hepatobiliary system excretion of copper and reduces the synthesis of the ceruloplasmin. Copper cannot be excreted through bile, and it accumulates in many organs, mainly in the liver and brain. The clinical spectrum is broad in WD. Hepatic involvement is common during the first 2 decades of life. Neurologic findings are dominant in the third and fourth decades.¹

Apolipoprotein E (apoE) and prion protein have been proposed as potential candidates that could modify the phenotype and age of disease onset. A genetic variation in apoE is the causative factor of neurologic symptoms. Hence, no neurologic symptoms occur in people carrying the APOE3 variant, whereas people carrying the APOE1 and APOE2 variants may have neurologic symptoms.²

For diagnosis, copper in 24-hour urine, dry copper weight in liver, and typical histologic liver biopsy findings were used. Diagnosis is difficult and involves blood tests, urine tests, and liver biopsy. Genetic testing may be used to screen family members of patients.³

Treatment includes reduction of copper uptake by diet, reduction of copper absorption, methods to increase copper excretion, and liver transplant when neurologic symptoms develop. Future treatment...
may also involve gene therapy. Indications for liver transplant in patients with WD include acute liver failure or end-stage liver failure not treatable by medical therapy and neurologic deterioration despite medical therapy.4

Here, we describe the long-term neurologic symptoms and complications in patients who underwent liver transplant for WD in our clinic.

Materials and Methods

We retrospectively reviewed the medical records of transplant patients with WD who were treated at the Department of Transplantation Science at Baskent University Faculty of Medicine between 2005 and 2017. We recorded patient demographics, neurologic complaints, findings from neurologic examinations, and imaging findings from patient medical records. We also recorded presence of Kayser-Fleischer ring, serum ceruloplasmin level, copper levels in 24-hour urine tests, and liver dry copper levels in each patient. Patients with neurologic symptoms in the preoperative period were excluded from the study. This study was approved by the ethics committee of Baskent University Medical Faculty.

Statistical analyses

Statistical analyses were performed with SPSS software (version 16.0 for Windows, SPSS, Inc, Chicago, IL, USA). Data are expressed as number and percentages for categorical variables.

Results

This study included 19 adult patients with WD who underwent liver transplant at our center (14 males and 5 females; average of 26 years) (Table 1). Neurologic complications were seen in 7 patients (36.8%) (Table 2): 1 patient had encephalopathy, 2 patients had seizures, 3 patients had tremor, and 1 patient had headache.

The 2 patients with seizures had a generalized tonic clonic seizure due to immunosuppressant agent. Seizure was controlled by reduction of the immunosuppressant dose and levetiracetam administration. The encephalopathy seen in 1 patient was due to the immunosuppressant agent. Adjustment of immunosuppressant agent dose was sufficient for treatment of encephalopathy. In the 3 patients with tremor, no motion disorders had been shown preoperatively, and brain magnetic resonance imaging results were normal. Cause of tremors was also due to the immunosuppressant agent. Immunosuppressive therapy for tremor affecting activities of daily living was not changed. In the patient with headache, brain magnetic resonance imaging scan was normal. This patient was diagnosed with tension-type headache, with cause attributed to depression, which was improved with antidepressant treatment.

Discussion

Indications for liver transplant in patients with WD include acute liver failure or end-stage liver failure not treatable by medical therapy and neurologic deterioration despite medical therapy. Liver transplant prolongs survival and improves quality of life in patients with WD and liver failure.5

Wilson disease may present with neurologic findings. Therefore, in our study, we excluded patients with neurologic symptoms in the preoperative period. We found no other studies that investigated the frequency of neurologic complications after liver transplant, especially in adult patients with WD. The frequency of neurologic complications after liver transplant can vary from study to study. This may be due to a lack of a common neurologic symptom (Table 3).

Tremor was the most common long-term complication in our study (3 patients, 15.7%). Gungor and associates6 investigated early-term and late-term neurologic complications posttransplant and found tremor in 2.4% of their patients. This tremor rate is less than found in our study. However, in a study from Dehghani and associates, tremor was the most

| Table 1. Male and Female Distribution of Transplant Recipients With Wilson Disease |
|-----------------------------|-----------------------------|-----------------------------|
|                           | Male | Female | Total   |
| Wilson disease liver transplant (mean age of 26 years) | 14 (73.6%) | 5 (26.4%) | 19 (100%) |

| Table 2. Incidence of Neurologic Complications After Liver Transplant With Wilson Disease |
|-------------------------------------|-----------------------------|-----------------------------|
| Neurologic Complication | Number of Patients (%) | Cause                      |
| Seizure                  | 2 (10.5%)                  | Immunosuppressive agent     |
| Tremor                   | 3 (15.7%)                  | Immunosuppressive agent     |
| Encephalopathy           | 1 (5.2%)                   | Immunosuppressive agent     |
| Headache                 | 1 (5.2%)                   | Tension-type headache (stress) |
| Total                    | 7 (36.8%)                  |                             |
frequent neurologic complication at 16.7%, which is similar to our study. In our study, similar to other studies, immunosuppressive agents were held responsible for tremor (Table 4).

In our study, seizures (generalized tonic clonic convulsions) were seen in 2 patients (10.5%), which were due to the immunosuppressive agents. Without altering the drug level, levetiracetam was given at 1000 mg/day for seizure control. Gungor and associates reported a seizure rate of 11.5%, with Dehghani reporting a rate of 16.7% in their patients. Immunosuppressive agents were responsible for seizures in these studies (Table 4).

In our study, encephalopathy was detected in 1 patient (5.2%). Encephalopathy was found to be low in our study and was caused by the immunosuppressive agent. Symptoms improved when medication was reduced (Table 4).

In our study, 1 patient (5.2%) reported having a headache, which is a higher rate than that shown by Gungor and associates (2.4%) but lower than that reported by Dehghani and associates (10.4%). Our patient had a normal brain magnetic resonance imaging scan and was diagnosed with a tension-type headache. The patient recovered with antidepressant treatment (Table 4).

Conclusions

Neurologic complications after liver transplant for patients with WD at our center included encephalopathy, seizures, tremor, and headache. Immunosuppressive agents were responsible for most of the neurologic complications in these patients. A possible way to reduce long-term complications after solid-organ transplant is careful use of immunosuppressive agents.

References

Abstract

Objectives: Transplant vasculopathy is a significant predictor of poor outcome. We investigated whether age or pretransplant renal arterial vasculopathy of grafted kidneys affected allograft survival.

Materials and Methods: This study included 148 recipients and their donors. All donors underwent pretransplant renal arterial biopsy, with renal artery vascular score determined for each artery. Chronic rejection and graft loss were noted for all patients.

Results: Variable grades of pretransplant renal arterial lesions were noted in 103 donors (69.6%). A positive correlation was found between donor age and renal artery score ($r = 0.650$, $P < .001$), and chronic rejection and graft loss were found to increase with increasing score ($P < .001$). Recipient and donor age was significantly associated with graft loss and chronic rejection. With either younger or older donors, recipients had similar and best results regarding chronic rejection and graft loss if donors had renal artery scores of 0 or 1, but worse effects if donors had scores of 2 or 3. Five-year allograft survival rates for scores of 0, 1, 2, and 3 were 91%, 68%, 46%, and 33%. Univariate analyses showed that acute rejection episode (relative risk: 2.729, 95% confidence interval, 1.496-4.977; $P = .001$), older (≥ 50 y) donor age (relative risk: 1.970, 95% confidence interval, 1.038-3.736; $P = .04$), and donor renal artery score (relative risk: 2.466, 95% confidence interval, 1.382-4.401; $P = .002$) were associated with decreased allograft survival. Multivariate Cox analysis showed that only acute rejection episode (relative risk: 3.585, 95% confidence interval, 1.781-7.217; $P < .001$) and renal artery score (relative risk: 2.642; 95% confidence interval, 1.355-5.150; $P = .004$) were independent predictors of allograft survival.

Conclusions: Pretransplant vasculopathy in donor renal artery implies a poor prognosis for renal allograft survival and is independent of other risk factors. Pretransplant renal artery biopsy is recommended for both deceased and living donors, and therapeutic interventions to modify transplant vasculopathy progression should start early posttransplant in recipients with affected renal arteries.

Key words: Arteriosclerosis, Chronic rejection, Donor age, Kidney transplant, Renal artery, Transplant vasculopathy

Introduction

End-stage renal disease affects a high percentage of the population, and the number of patients with end-stage renal disease requiring renal replacement therapy continues to multiply.1,2 Because of the shortfall in available organs from deceased donors for transplant, the upper age limit for accepting deceased donors has been raised to increase the organ pool and to reduce wait list time for kidney transplant. Studies on kidney viability from older donors have demonstrated higher incidences of delayed graft function and poor graft outcomes in kidneys from older donors, with cumulative graft survival found to decrease with increasing donor age.1-5

There are several reasons for the inferior results with organs from older donors. Among these are physiologic changes, leading to loss of renal function in aging kidneys, increased arteriosclerosis with increased susceptibility to ischemic damage, and decreased total functioning mass.1,5-7 Therefore, it is essential to consider objective
criteria when evaluating future allograft function and prognosis. In addition, whether differences in donor versus recipient age influences graft survival needs to be investigated.

The aim of this study was twofold. First, we aimed to evaluate the donor-related arteriosclerotic changes in the renal artery at the time of transplant and to clarify the impact of these findings on renal allograft outcome. Second, we aimed to determine the influence of donor age and age differences between donor and recipient on graft survival.

Materials and Methods

Our study included 148 recipients with a mean age of 29.1 ± 11.9 years (range, 12-63 y). Of 148 recipients, 89 were male and 39 were female patients. Mean time on dialysis was 18.1 ± 15.2 months. Regarding donor type, 32 received kidneys from deceased donors and 96 received kidneys from living donors. The mean age of the 148 donors (male/female ratio, 54/74) was 39.8 ± 15.3 years (range, 10-75 y). The mean cold ischemic time was 9.4 ± 2.3 hours, and the mean number of HLA mismatches was 3 ± 1.3. All recipients received a triple-drug immunosuppressive protocol (corticosteroids, calcineurin inhibitors, and azathioprine or mycophenolate mofetil).

Several parameters of recipients and donors underwent univariate and multivariate analyses. In addition to age, sex, and time on dialysis, other parameters for recipients that underwent univariate and multivariate analyses are shown in Table 1. To evaluate the influence of donor and recipient age, we separated donors and recipients into 2 groups: a younger group (donors and recipients with age lower than 50 y) and an older group (donors and recipients with age equal or higher than 50 y).

A scoring system for renal artery vascular status was applied to renal artery biopsies obtained during operation at the exact time of renal arterial anastomosis. Before end-to-end anastomosis, to increase the coherence between donor and recipient renal arteries, a small full-thickness patch of arterial sample was removed from both the donor and recipient arteries. These renal arterial samples were fixed in 10% buffered formaldehyde and embedded in paraffin. Sections of about 3 μm were stained by hematoxylin and eosin, Mason trichrome, and Van Gieson elastic stain (Dako autostainer, Agilent Technologies, Palo Alto, CA, USA).

Each biopsy was evaluated and graded for the presence of intimal hyperplasia (Table 2). The presence of calcification and the degeneration of membrana elastica interna were also evaluated and graded (Table 2). Each parameter was assessed according to its relative importance for an arteriosclerotic change, and the sum of these graded and weighted parameters constituted the renal artery (RA) vascular status score (RA0 status = 0 score, RA1 = 3-5, RA2 = 6-8, and RA3 ≥ 9).

Recipients were followed for 86.4 ± 38.8 months after transplant, and all recipients were evaluated for the development of chronic rejection (CR) and graft loss during 5 years after transplant.

Table 1. Recipient Clinical and Pathologic Characteristics

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<td>Amyloidosis</td>
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<td>Diabetes</td>
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<td>Polycystic kidney</td>
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<td>Urolithiasis</td>
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<tr>
<td>Alport</td>
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<td>Secondary to steroid</td>
<td>11</td>
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<td>Hypertension Present</td>
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<tr>
<td>Coronary artery disease Present</td>
<td>17</td>
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<tr>
<td>Hyperlipidemia Present</td>
<td>84</td>
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<tr>
<td>Chonic liver disease Present</td>
<td>32</td>
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<tr>
<td>Acute rejection Present</td>
<td>77</td>
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</tbody>
</table>

Table 2. Renal Artery Status Score Based on Scoring of 3 Parameters, Weighted and Summed to a Single Parameter

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<thead>
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<td>3x a</td>
<td>a</td>
</tr>
<tr>
<td>Calcification 0 (no calcification), 1 (calcification on arterial wall)</td>
<td>1x b</td>
<td>b</td>
</tr>
<tr>
<td>MEI degeneration 0 (no change), 1 (mild), 2 (moderate), 3 (severe)</td>
<td>1x c</td>
<td>c</td>
</tr>
<tr>
<td>RA score = a + b + c</td>
<td>RA0 = 0, RA1 = 3-5, RA2 = 6-8, RA3 ≥ 9</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MEI, membrana elastica interna; RA, renal artery

Statistical analyses

Descriptive data are expressed as means and standard deviations. The chi-square test was used to analyze categorical variables; the t test or the Mann-Whitney test was used to compare between the 2 groups. We used analysis of variance or the Kruskal-Wallis test for comparisons among multiple groups. Spearman rank correlation test was used for detection of correlations between groups. Univariate and multivariate Cox regression analyses were developed to assess risk factors independently.
associated with graft loss. We performed Kaplan-Meier tests for graft survival analyses. Statistical significance was assigned to events with $P < .05$.

**Results**

Variable grades of pretransplant renal arterial lesions were noted in 103 donors (69.6%) (Table 3). As shown, 41 donors (27.7%) had mild RA scores, whereas 26 donors (17.6%) had moderate and 36 donors (24.3%) had severe RA scores. Although a significant positive correlation was found between donor age and RA score ($r = 0.650$, $P < .001$), no association was noted between donor sex and RA score ($r = 0.038$, $P = .651$). The risk of development of CR and graft loss of recipients at 5 years posttransplant was found to increase with increasing degree of donor RA score (Table 3). In addition, mean time to development of recipient CR and graft loss was found to decrease with increasing degree of donor RA score (Table 3).

Recipient age was significantly associated with graft loss and development of CR, with recipient age showing a significant negative correlation with both graft loss time ($r = -0.513$, $P < 0.001$) and time to development of CR ($r = -0.506$, $P < .001$).

Of 148 donors, only 41 (27.7%) were 50 years of age or older (older donors). As shown in Table 4, RA scores were higher in older donors ($\geq 50$ y) than in younger donors ($P < .001$). Incidence of graft loss and development of CR was significantly higher in recipients of kidneys from older donors than in recipients of kidneys from younger donors (Table 3). Compared with recipients who had donations from younger donors, the mean time to development of CR and graft loss occurred sooner when recipients had an older donor ($P < .001$). Donor age showed a significant negative correlation with both mean time to graft loss ($r = -0.511$, $P < .001$) and mean time to development of CR ($r = -0.510$, $P < .001$).

To understand the influence of RA score independent of donor age, we separated donors into 4 groups as shown in Table 3. Having a donor with an RA status of RA0 or RA1, regardless of age, resulted in better outcomes for recipients regarding time to development of CR and graft loss. Similarly, having a donor with RA2 or RA3 status, regardless of age, resulted in worse outcomes for recipients (Table 3).

<table>
<thead>
<tr>
<th>Table 3. Influence of Prognostic Parameters on Graft Loss and Development of Chronic Rejection</th>
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<tbody>
<tr>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>RA0</td>
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<tr>
<td>RA1</td>
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<tr>
<td>RA2</td>
</tr>
<tr>
<td>RA3</td>
</tr>
</tbody>
</table>

| **Donor age** | **n** | **%** | **RA0, n (%)** | **RA1, n (%)** | **RA2, n (%)** | **RA3, n (%)** |
|---|
| < 50 y | 107 | 72.3 | 35 (32.7) | 19 (17.8) | 10 (9.3) | < .001 |
| ≥ 50 y | 41 | 27.7 | 6 (14.6) | 7 (17) | 26 (63.4) | < .001 |

| **Younger R-younger D** | **n** | **%** | **RA0, n (%)** | **RA1, n (%)** | **RA2, n (%)** | **RA3, n (%)** |
|---|
| 100 | 67.6 | 33 (33) | 16 (16) | 8 (8) | 25 (62.5) | < .001 |
| Younger R-older D | 40 | 27 | 5 (12.5) | 8 (20) | 25 (62.5) | < .001 |

| **Older R-younger D** | **n** | **%** | **RA0, n (%)** | **RA1, n (%)** | **RA2, n (%)** | **RA3, n (%)** |
|---|
| 5 | 3 | 0 | 2 (40) | 0 | 3 (60) |

| **Older R-older D** | **n** | **%** | **RA0, n (%)** | **RA1, n (%)** | **RA2, n (%)** | **RA3, n (%)** |
|---|
| 77 | 52 | 22 (28.6) | 28 (36.4) | 12 (15.6) | 15 (19.5) | NS |

**Abbreviations:** AR, acute rejection; CR, chronic rejection; D, donor; NS, not significant; R, Recipient; RA, renal artery

<table>
<thead>
<tr>
<th>Table 4. Correlation of Renal Artery Score With Donor Age Group and Recipient-Donor Combination Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Donor age &lt; 50 y</td>
</tr>
<tr>
<td>Donor age ≥ 50 y</td>
</tr>
</tbody>
</table>

| **Younger R-younger D** | **n** | **%** | **RA0, n (%)** | **RA1, n (%)** | **RA2, n (%)** | **RA3, n (%)** |
|---|
| 100 | 67.6 | 43 (43) | 33 (33) | 16 (16) | 8 (8) | < .001 |
| Younger R-older D | 40 | 27 | 2 (5) | 5 (12.5) | 8 (20) | 25 (62.5) | < .001 |

| **Older R-younger D** | **n** | **%** | **RA0, n (%)** | **RA1, n (%)** | **RA2, n (%)** | **RA3, n (%)** |
|---|
| 5 | 3 | 0 | 2 (40) | 0 | 3 (60) |

| **Older R-older D** | **n** | **%** | **RA0, n (%)** | **RA1, n (%)** | **RA2, n (%)** | **RA3, n (%)** |
|---|
| 77 | 52 | 22 (28.6) | 28 (36.4) | 12 (15.6) | 15 (19.5) | NS |

**Abbreviations:** AR, acute rejection; D, donor; NS, not significant; R, Recipient; RA, renal artery
Among these 4 RA status groups, recipients of older grafts with RA2 or RA3 score had the worst outcomes regarding mean time to development of CR and graft loss (17.3 ± 10 and 18.9 ± 11.6 mo, respectively). In contrast, recipients of grafts from younger donors with RA0 or RA1 score showed mean time to development of CR and graft loss of 37.5 ± 8.4 and 40.3 ± 9.5 months, respectively (Table 3).

When we analyzed various donor-recipient age combinations, we found that incidence of development of CR and graft loss was lowest in the combination group of younger recipient-younger donor, whereas it was highest in the combination group of older recipient-older donor. We also noted that the combination of younger recipient-older donor had better results than a older recipient-younger donor combination (Table 3). A significant correlation was found between these 4 combination groups and donor RA score (Table 4).

Among the 148 recipients, 71 (48%) developed at least 1 episode of acute rejection (AR) at a mean time of 8.5 ± 1.5 months. The mean AR episode of 71 recipients was 0.77 ± 0.1 (range, 0-5).

The risk of graft loss and development of CR was higher in recipients with AR than in patients without an AR episode \( (P = .008) \). However, no differences were found between recipients with and without AR with regard to mean time to graft loss and mean time to development of CR. No significant correlations were found between donor RA score and the presence or absence of AR. The mean AR episode was 0.6 ± 0.1 and 1 ± 0.12 for recipients with and without CR development during 5 years, respectively \( (P = .015) \). Mean AR episode was 0.6 ± 0.1 and 1.04 ± 0.13 for recipients with and without graft loss, respectively \( (P = .012) \).

We observed no correlations between graft loss/development of CR during the 5 years after transplant and primary disease, presence of cytomegalovirus, hepatitis C virus, diabetes mellitus, hypertension, coronary artery disease, hyperlipidemia, chronic liver disease, HLA mismatch, ischemia time, and time on dialysis.

Overall, the 5-year allograft survival rate of recipients with score of RA0, RA1, RA2, RA3 was 91%, 68%, 46% and 33%, respectively (Figure 1), with significant differences found between donor RA scores \( (P < .001) \). Overall, the 5-year allograft survival was significantly lower in recipients with older \( (≥ 50 \text{ y}) \) donors than in recipients with younger \( (< 50 \text{ y}) \) donors \( (49% \text{ vs } 68%; \ P = .004; \text{ Figure 2}) \). Similarly, 5-year survival was significantly lower in older \( (≥ 50 \text{ y}) \) recipients than in younger \( (< 50 \text{ y}) \) recipients \( (30.8% \text{ vs } 66%; \ P < .001; \text{ Figure 3}) \).
In univariate analysis, the presence of AR episode (relative risk [RR] of 2.729, 95% confidence interval [CI], 1.496-4.977; \( P = .001 \)), older donor age (RR of 1.970, 95% CI, 1.038-3.736; \( P = .04 \)), and donor RA score (RR of 2.466, 95% CI, 1.382-4.401; \( P = .002 \)) were associated with decreased allograft survival. Multivariate Cox analysis showed that only the presence of AR episode (RR of 3.585, 95% CI, 1.781-7.217; \( P < .001 \)) and donor RA score (RR of 2.642, 95% CI, 1.355-5.150; \( P = .004 \)) were independent predictors of allograft survival.

**Discussion**

The influences of donor and recipient age on renal allograft outcomes have been investigated in numerous studies. The fact remains true that survival of elderly patients who undergo transplant is significantly higher than in those who stay on dialysis treatment. Previous studies have shown that patient survival after renal transplant is mainly dependent on recipient age and comorbid conditions. In studies that considered the bias of “age-matching,” in which elderly kidneys are transplanted into elderly recipients, it is clear that patient survival is primarily influenced by recipient age rather than by donor age. Our findings also support this, with older recipients having lower overall 5-year graft survival (30.8%) than younger recipients (66%). We also noted that, when recipients and donors were matched according to the age-matching system, elderly recipients had the lowest graft survival with either a younger or older donor. Furthermore, better graft survival was shown in younger recipients who had received grafts from older donors versus older recipients who received grafts from younger donors. The best results were shown in a younger recipient-younger donor combination.

In an analysis of more than 30,000 kidney transplants from deceased donors, 2-year graft survival rates were significantly different when stratified by age of donors, with rate of 90% with donors from 0 to 15 years old, 91% with donors from 16 to 45 years, 88% with donors from 46 to 55 years, and 87% with donors > 55 years. Another report that studied 31,000 renal allograft recipients reported similar results, with recipients of kidney donors who were between 20 and 24 years of age having the best allograft survival rate (78%). Kidneys from donors at both extremes of age had the lowest renal allograft survival rates, with 60% in donors from 0 to 4 years, 66% in donors from 5 to 9 years, 59% in donors from 60 to 64 years, and 58% in donors > 65 years. Other reports have presented similar results. Our study confirmed these results, with donor age showing a significant negative correlation with both mean time to development of CR and graft loss. Mean time to development of CR and graft loss decreased with increasing donor age.

Although our study and others have shown that donor age is an important variable for the prediction of renal allograft survival, recipient age is a more critical factor. In fact, regarding whether differences in age between donor and recipient influence graft survival, we showed that recipient age was critical in age-matched groups, with lower survival in older recipients compared with younger recipients, even when the kidney was from a younger donor. This finding also underlines the importance of recipient age.

In addition to age, vascular status can have predictive value for determining the risk of graft loss and development of CR. Previous reports have analyzed renal biopsies at transplant and at 1 month posttransplant to evaluate allograft function. Gaber and associates found significant correlations between extent of glomerulosclerosis (≥ 20%) and donor age, delayed graft function, primary nonfunction, mean serum creatinine at 12 months after transplant, and 1-year graft survival. Minakawa and associates used a vasculopathy score, a scale for evaluation of arteriosclerotic changes of donor origin by grading the severity of glomerulosclerosis and arterial and arteriolar changes in the renal allograft at 1 month posttransplant. In their study, they found that this score was valuable in predicting short-term graft function and graft survival. Confirming their results, we also found a significant association between our renal artery vascular status scoring system (RA score) and short-term and long-term graft survival. Our RA scores increased with increasing donor age, with the RA scoring system showing a close association with donor-recipient age combination groups. A younger recipient-younger donor combination showed the lowest RA scores, whereas older recipient-older donor and younger recipient-older donor combinations had the highest RA scores.

The superiority of our study to other studies was the examination of the renal artery itself before transplant before any possible influences of the
recipient. All findings in the evaluation of the RA score were purely attributed to the donor. Furthermore, our univariate and multivariate analyses showed that the RA vascular status scoring system was an independent predictor of renal allograft survival.

In conclusion, the presence of renal arterial vasculopathy before transplant significantly negatively affected renal allograft survival, with recipients who had donors with a high degree of RA score showing reduced graft survival. The prognostic impact of RA scoring is independent of other risk factors. Pretransplant biopsy of the renal artery should be part of the procedure in both deceased and living donors, and therapeutic interventions to modify the progression of transplant vasculopathy should start in recipients with affected renal arteries soon after transplant.

References

Frequency of Finding Family Donors: A Single Center Experience

Mutlu Kasar,1 Mahmut Yeral,1 Soner Solmaz,1 Nurhilal Büyükkurt,1 Suheyl Asma,2 Çiğdem Gereklioğlu,2 Can Boğa,1 Hakan Özdoğu,1 Bilkay Baştürk3

Abstract

Objectives: Allogeneic hematopoietic stem cell transplant is a curative treatment option for many hematologic diseases. The existence of a fully compatible donor for recipients is the first condition for minimized transplant-related mortality and morbidity. The best donor for hematopoietic stem cell transplant is an HLA-matched sibling donor. The possibility of finding an HLA-matched sibling is less than 30% worldwide. Hematopoietic stem cell transplant is needed for an increasing number of patients every year, but the ability to find a fully compatible donor has limited its use.

Materials and Methods: From August 2012 to May 2017, we screened 412 adult patients who required AHSCT and their families for HLA tissue groups who were seen at our center (Baskent University Adana Dr. Turgut Noyan Research and Medical Center Hematology Unit). To screen tissue groups at our center, we perform low-resolution typing for HLA-A, -B, -C, -DRB1, and –DQB. If an HLA genotype cannot be identified, verification typing is done using high-resolution testing.

Results: We found matched family donors in 227 (55%) of 412 patients screened at our center. The ratio of HLA-matched related donors was 83% for 279 patients who received allogeneic stem cell transplant.

Conclusions: The likelihood of finding eligible unrelated donors has been gradually increasing, in part due to the development of the National Bone Marrow Bank. However, a careful screening for related donors is still important. Our findings indicate the importance of careful examination of family genealogy and of careful family screening in our region.

Key words: Allogeneic stem cell transplant, Genealogy, National Bone Marrow Bank, Related donor, Screening

Introduction

Allogeneic hematopoietic stem cell transplant (AHSCT) is a curative treatment option for a variety of malignant diseases of the hematopoietic system and certain life-threatening nonmalignant conditions. Results after AHSCT are affected by many factors. Among these factors, polymorphism of the classical human leukocyte antigen (HLA) genes represents the most important barrier.1 The degree of HLA matching between donor and recipient is important. A 10/10 matched donor (HLA-A, -B, -C, -DRB1, -DQB1) is considered the ideal match.2,3 The best donor for AHSCT is an HLA-matched sibling donor. When an HLA-compatible related donor is not found, an HLA-matched unrelated donor, a haploidentical related donor, and umbilical cord blood stem cell products are 3 alternative options.4,5

The number of patients needing hematopoietic stem cell transplants has been increasing every year; however, the ability to find a fully compatible donor has limited its use. The likelihood of finding an HLA-matched sibling has been reported to be less than 30% worldwide.5,6 Although these rates can be altered by extended family screenings, a shrinking family structure, especially in Western societies, does not always make this possible. In Western communities, the rate of finding a donor match has increased with the help of donor banks. However, in areas without this option, a careful screening for related donors remains important.

Due to cultural characteristics and religious beliefs of ethnic groups, consanguineous marriages are frequent in the Çukurova Region of Turkey. In addition, families are generally larger. Here, we report the frequency of finding an HLA-matched...
related donor for this patient group who were preparing for AHSCT.

**Materials and Methods**

We screened 412 adult patients who required AHSCT and their families for HLA tissue groups who were seen at our center (Baskent University Adana Dr. Turgut Noyan Research and Medical Center Hematology Unit) between 2012 and 2017.

To screen tissue groups at our center, we perform low-resolution typing for HLA-A, -B, -C, -DRB1, and -DQB1 using sequence-specific primers and/or sequence-specific oligonucleotides. Before transplant, typing is verified once the donors are selected. If an HLA genotype cannot be identified, verification typing is done using high-resolution testing. High-resolution verification typing is also conducted for recipients who are not HLA identical siblings and potential related donors.

First-degree relatives were primarily screened for donor matching to allogeneic transplant patients. If a donor was not available, the family genealogy was examined and an extended family screening was conducted. Screening of patients and siblings was done in pairs or triples of groups. When a donor was found, tissue typing screening was immediately terminated. We do not screen donors who are not eligible because of age or because of clinical exclusions or other comorbidities.

**Results**

At our center, eligible related donors could be found for 227 patients (55%) of 412 adult patients who were scheduled for AHSCT between 2012 and 2017. Among these donors, 213 were siblings, 4 were mothers, 3 were fathers, 1 was a daughter, 1 was a son, 2 were cousins, and 3 were nephews (Table 1).

The rate of having an HLA-matched related donor was 83% for 279 patients who received AHSCT at our center between 2004 and 2017. The rate of having an HLA-matched unrelated donor was 7.8% (22 patients), and the rate of having a haploidentical related donor was 8.9% (25 patients).

Between 2012 and 2017, our center performed 131 AHSCT procedures from fully matched related donors. Among these donors, 124 were siblings, 2 were mothers, 2 were fathers, 1 was a daughter, 1 was a son, and 1 was a nephew.

**Discussion**

The first step for patients requiring AHSCT is finding an appropriate donor. Allele-level matching for HLA-A, -B, -C, -DRB1, and -DQB1 loci is considered as the criterion standard. An HLA-matched sibling is the ideal donor. Approximately 30% of patients have HLA-matched sibling donors. However, this rate is only 20% in the United States because of smaller average family size.7

The rate of finding an HLA-matched related donor in the communities where consanguineous marriages are frequent, such as Arabic communities and Pakistan, is reported to range from 60% to 80%.8-10 In a recent study in our country, matched related donors were identified for 44% of patients, with a significantly higher rate in pediatric patients (52%) than in adult patients (41%).11

According to our results, at our center, the rate of finding an HLA matched related donor was 55% (51% siblings, 3% nonsiblings) for patients waiting for AHSCT. Because of cultural characteristics and religious beliefs of ethnic groups in our region, consanguineous marriages are frequent. Therefore, these ethnic groups have a relatively homogeneous structure within themselves. A careful screening for nonsibling related donors is important.

At our center, 83% of HSCDs were performed from fully matched related donors. This rate is around 30% in Western societies. According to the data from the US Department of Health and Human Services, between 2010 and 2014, the proportion of HLA matched sibling donors among AHSCDs was 32% in the United States (https://bloodcell.transplant.hrsa.gov).12 According to data from the European Group for Blood and Marrow Transplantation, the proportion of HLA-matched related donors among AHSCDs was 36% in 2014.13

<table>
<thead>
<tr>
<th>Table 1. Donor Distribution</th>
<th>Number (%)</th>
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</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>412</td>
</tr>
<tr>
<td>Patients with donor</td>
<td>227 (55%)</td>
</tr>
<tr>
<td>Donor distribution</td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>213</td>
</tr>
<tr>
<td>Mother</td>
<td>4</td>
</tr>
<tr>
<td>Father</td>
<td>3</td>
</tr>
<tr>
<td>Son</td>
<td>1</td>
</tr>
<tr>
<td>Daughter</td>
<td>1</td>
</tr>
<tr>
<td>Cousin</td>
<td>2</td>
</tr>
<tr>
<td>Nephew</td>
<td>3</td>
</tr>
</tbody>
</table>
The use of alternative graft sources such as unrelated donors, haploidentical donors, and cord blood is increasing in parallel with advances in conditioning regimens and graft-versus-host disease prophylaxis. However, use of these alternative graft sources depends on the individual experience of centers.

Over 27 million donors are registered in the international database (www.bmdw.org), and the probability of identifying a 10/10 HLA-matched voluntary unrelated donor is estimated at 1 per 1 million donors. However, the possibility of reaching matched unrelated donors is very different for communities. The likelihood of finding an 8/8 matched unrelated donor is approximately 75% for White individuals, 35% for Hispanic individuals, and 18% for Black individuals. Between 2000 and 2011, the use of unrelated donors in our country has been reported to be 9% and 22% for 2015. At our center, the proportion of HLA-matched sibling donors among AHSCs was 7.8%. Fortunately, in our country, the likelihood of finding eligible unrelated donors is gradually increasing together with the development of the National Bone Marrow Bank.

HLA class I and II genes are the most polymorphic genes of the human genome. As of November 2017, over 17,000 HLA alleles have been recognized by the World Health Organization Nomenclature Committee on Factors of the HLA System (http://hlaalleles.org). HLA frequencies in the population for transplant, haplotype frequencies, and compliance or incompatibility of certain HLA alleles are being investigated with regard to graft-versus-host disease, graft failure, and survival. HLA-DRB1*11 has a reported role in the development of transplant-associated thrombotic microangiopathy. Du and associates reported that HLA-DRB1*09 was associated with increased incidence of cytomegalovirus infection and disease after AHSC. Oral health risks have also been associated with certain HLA types in patients who underwent AHSC. In a previously reported study from our center, we found that the most frequent class I alleles were HLA-A*02, HLA-B*35, and HLA-C*04 and the most frequent class II alleles were HLA-DRB1*11 and HLA-DQB1*03. It is also known that HLA antigens are associated with certain diseases (such as HLA-B27 with ankylosing spondylitis and HLA-DQB1*02 with celiac disease) and associated with certain transplant complications. For this reason, it is important to know the distribution and frequency of HLA antigens in our region.

Conclusions

An HLA-matched donor is important for successful engraftment and to protect against posttransplant graft-versus-host disease in AHSC. The rate of finding an HLA-matched related donor is high in our country and especially in our region. These data indicate the importance of a careful examination of family genealogy and family screening in our region.

References

37. Petersdorf EW. The World Marrow Donor Association: 20 years of international collaboration for the support of unrelated donor and cord blood hematopoietic cell transplantation. Bone Marrow Transplant. 2010;45(5):807-810.
The Effect of Standardized Interviews on Organ Donation

Pelin Corman Dincer,1 Deniz Birtan,2 Mustafa Kemal Arslantas,1 Gulbin Tore Altun,3 Hilmi Omer Ayanoglu1

Abstract

Objectives: Organ donation is the most important stage for organ transplant. Studies reveal that attitudes of families of brain-dead patients toward donation play a significant role in their decision. We hypothesized that supporting family awareness about the meaning of organ donation, including saving lives while losing a loved one, combined with being informed about brain death and the donation process must be maintained by intensive care unit physicians through standardized interviews and questionnaires to increase the donation rate.

Materials and Methods: We retrospectively evaluated the final decisions of families of 52 brain-dead donors treated at our institution between 2014 and 2017. Data underwent descriptive analyses. The standard interview content was generated after literature search results were reviewed by the authors. Previously, we examined the impact of standardized interviews done by intensive care unit physicians with relatives of potential brain-dead donors regarding decisions to donate or reasons for refusing organ donation. After termination of that study, interviews were done according to the intensivist's orientation, resulting in significantly decreased donation rates. Standardized interviews were then started again, resulting in increased donation rates.

Results: Of 17 families who participated in standardized interviews, 5 families (29.4%) agreed to donate organs of their brain-dead relatives. In the other group of families, intensivists governed informing the families of donation without standardized interviews. In this group of 35 families, 5 families (14.3%) approved organ donation. The decision regarding whether to agree to organ donation was statistically different between the 2 family groups (P < .05).

Conclusions: Conducting a standard interview between relatives of brain-dead donors and the intensivists, facilitating visits between relatives and the brain-dead patients, and informing relatives about the donation process resulted in an increased rate of organ donation compared with routine protocols.

Key words: Attitudes and beliefs, Family discussion, Intensive care physician, Potential brain-dead donor

Introduction

Transplant is the therapy of choice for end-stage organ failure. Better results due to improvements in surgical techniques and pharmacologic and immunologic approaches have enabled improved patient survival. Unfortunately, the increase in the number of patients on transplant wait lists is not met by the number of organ donations.

In developed countries, transplant procedures are done mostly from deceased donors, whereas in our country it is the opposite. According to the International Registry on Organ Donation and Transplantation in 2015, Turkey showed the highest rate of living organ donation in the world, ie, 45.4 donors per million population (pmp), with only 6.3 donors pmp for actual deceased organ recovery.1 After creation of a system for organ donation (“Organizacion Nacional de Trasplantes”) and its promotion, Spain has become the world leader in deceased organ donations with 40 donors pmp. Matesanz and associates concluded that, by a healthcare system making adaptations according to recommendations of organ donation organizations...
and using these novel strategies to deal with the challenges in organ donation, organ donation and transplant rates can be increased.²

In our previous study, we investigated how intensivists affect the decision-making process during interviews with family members of potential donors and the reasons for not giving consent to donate.³ After the termination of that study, the rate of donation declined significantly. We subsequently restarted the standardized interviews again, which eventually increased the donation rate. In this current study, we compared the time periods and analyzed the best method to enhance organ donation approval.

Materials and Methods

In this retrospective study, the final decisions of families of brain-dead donors who were treated at the Marmara University Pendik Training and Research Hospital Intensive Care Units between May 2014 and March 2017 were evaluated. The study was conducted after authorization from the institution and approval by the Ethics in Clinical Research Committee of Marmara University School of Medicine (09.2017.308).

In our previous study, we examined the impact of standardized interviews done by intensivists with relatives of brain-dead potential donors regarding the decision to donate or the reason to refuse organ donation.³ After termination of that study, interviews with families were done according to the individual intensivist. During this 18-month period, donation rates declined significantly. After that, standardized interviews were again started, resulting in increased donation rates. We divided the families into 2 groups: group S represented the group who received standardized interviews and group NS represented those who received information from the intensivists without direction.

A standard interview content (which included a potential donor questionnaire, family notification, brain death criteria fulfillment, and organ donation conversation questionnaires) was generated in the previous study after literature results were reviewed by the authors³ (Table 1). The questionnaires were used by intensivists during the interviews with families of the potential donors. Data had undergone descriptive analyses.

Results

The families of 52 intubated potential organ donor patients were included in the study. Of 17 families who received the standardized interview, 5 families (29.4%) agreed to donate organs of their brain-dead relatives. In this group (group S), families of relatives with Glasgow coma scale < 5 were approached and interviewed 3 times daily. The first interviews, which were done after brain death diagnosis, lasted 16.1 ± 6 minutes (range, 10-30 min); second interviews were done with the hesitant families and lasted 10 ± 4 minutes (range, 5-15 min). During this period, families were able to see their relatives 2 to 5 times per day.

In the second group (group NS), the intensivists governed informing the families and interviews were not standardized. During this period, families were approached and interviewed once or twice per day and could see their relatives once per day. The approximate interview duration was 10 to 15 minutes. Of 35 families in the NS group, 5 families (14.3%) approved organ donation.

The decision regarding whether to donate was significantly different between the groups (P < .05; Figure 1).

Table 1. The Standardized Interview

<table>
<thead>
<tr>
<th>Headlines</th>
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<tbody>
<tr>
<td>1 An intensivist must do the interview.</td>
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<tr>
<td>2 The information must be given to spouse, parents, siblings, children, cousin, etc.</td>
</tr>
<tr>
<td>3 When GCS is &lt; 5, detailed information about the patient’s condition must be given by the intensivist twice daily, either at bedside or at the doctor’s office.</td>
</tr>
<tr>
<td>4 Relatives of brain-dead donors must be permitted to visit the potential donor whenever they want as long as the intensive care unit conditions are appropriate.</td>
</tr>
<tr>
<td>5 The frequency with which a patient’s relatives are informed by the same doctor every day and the visiting frequency must be recorded.</td>
</tr>
<tr>
<td>6 When brain death is considered (GCS = 3), the intensivist must say to the family members, “Your patient’s situation is critical; if brain death occurs, there is no hope for your patient to recover. Brain death is irreversible loss of clinical function of the brain including the brain stem. A specialist doctor from the Neurosurgery, Intensive Care or Anaesthesia and Reanimation Departments will examine your patient and run some tests to assess your patient’s situation.” The content and results of the examination and tests must be explained to the family members before and after tests.</td>
</tr>
<tr>
<td>7 If brain death is diagnosed, it must be declared to the family members by the intensivist as “Brain death, including the brain stem, is the irreversible loss of the clinical function of the brain; it is a precise death in medical and legal sense.”</td>
</tr>
<tr>
<td>8 The organ transplant coordinator must be included in the process from the beginning and must be informed about the decision of the family.</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow coma scale
Discussion

To raise the rate of donations from deceased donors, early detection and diagnosis of brain death should be done. Donations after brain death and after cardiac death are the sources of deceased donations. Campaigns to raise awareness of the importance of donation and to encourage people to donate should be implemented. Awareness about donation is especially important as is early diagnosis of brain death.

Similar to the Spanish model, in Turkey, intensivists are responsible for disseminating information as they are the doctors in charge of potential donors. Intensivists diagnose brain death, inform the relatives about the situation, prepare families for the expected course during the donation process, and inform the organ donation coordinator. Because intensivists have a prominent role in the process, they are trained about donation, transplant, death, and mourning. All health personnel are trained on communication techniques, how to give bad news, how to approach minorities, and how to work within cultural differences. The decision to donate might be influenced by the attending doctor’s approach and the doctor’s communication skills, confidence, and knowledge; therefore, simulation-based communication training sessions may be helpful and should be included in clinician education programs.

Organ donation coordinators are the ones that ask for the family’s permission of donation after a diagnosis of brain death is made. Having the coordinators involved early in the process is beneficial for families and their understanding of the donation process, which can lead to increased donation rates; therefore, early diagnosis is essential.

Donation rates are different between regions and hospitals and even within hospitals during different time phases. The reasons for these differences should be understood as they could allow improvements in donation rates.

In our current practice, even if the person who has died has provided consent for donation, we seek consent from the next of kin before proceeding with organ retrieval. In Turkey, we do not have a standard protocol or path for discussing donation with families and obtaining consent; the process differs depending on the circumstances.

The attitude of families toward donation plays an important role; therefore, to increase the donation rate, we must know which families are more likely to give consent. Families of young, white, male donors who have died from trauma are more likely to give consent for donation. In Australia among the non-English-speaking families, the rate of consent is low (12.5%). It is important that good communication (verbal and nonverbal) is established between intensivists and families.

Intensivists should be aware of the religious and cultural background of the donors and their families. Because the interviews done with families play a significant role in decisions to donate, differences in religious and cultural background should be considered. Culture models the perception of health and illness and the behavior and beliefs of people; therefore, giving information and bad news should be tailored according to the individual.

Environmental variables within hospitals, intensivists’ sociodemographic characteristics, and their attitudes toward organ donation do not affect consent rates; however, their comfort level in answering questions from families about donation has been shown to be significantly associated with organ donation. When information is given by the same intensivist who has detailed knowledge about the intensive care unit course of the patient, a bond with relatives could develop.

In a study of factors influencing consent of families for transplant, 55% of the families had made
their decision on the first interview, with 56.7% in favor of donation, 25.5% not in favor of donation, and 16.9% undecided. In our group S, 23.5% of the families had agreed to donation on the first interview, 23.5% (4 families) were undecided, and 1 family gave consent after the second interview.

The frequency of talking frankly about the patient’s condition and providing information is important. The donation rate was low when families were surprised to be asked about donation; having frequent interviews that are started before the donation request are associated with favorable outcomes. In the standardized interview that we conducted, the frequency and duration of the interviews done with the families were recorded as they are extremely important; interviews should be done frequently and thoroughly to explain the condition of their relative, and unlimited visits with their relative should be allowed if the intensive care unit conditions are appropriate. We recommend that a first interview should be done when the Glasgow coma scale is < 5. Interactions with families of potential donors should be done properly, not only to ask for consent but also to allow families to accept the imminent loss of their loved ones.

The place and timing of providing information to families are also important. A location where relatives can express their feelings and thoughts freely is optimal. Interviews must not be done in the doctors’ or nurses’ rooms but rather in designated areas. Information must be given frankly without using medical terms and should be provided in a nonemotional manner. Although the truth must not be hidden, discussing brain death should not be presented abruptly; as with other terminally ill patients, it should be done gradually step by step. When brain death is considered, relatives must be informed before tests are initiated. This will give time for relatives to accept the idea of losing someone who they love. The declaration of brain death should be done by the same intensivist who is in charge of the patient, and then the organ donation coordinator must be introduced to the relatives.

Conclusions

Intensivists who followed a standardized information interview combined with allowing relatives to have frequent visits with the potential brain-dead donor led to improved donation rates in our institution.

References

Nursing Care After Kidney Transplant: Case Report

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Abstract

Kidney transplant is the leading treatment method for patients with recent renal failure in terms of quality of life, cost, and survival. After transplant, rejection, infection, cardiovascular diseases, malignancies, immunosuppressive therapy failure, and psychologic problems may occur. Posttransplant nursing care is as important as pretransplant nursing care in terms of enhancing quality of life, preventing complications, and providing necessary changes to treatment. In this report, we presented ways to increase quality of care after transplant and outlined standardized nursing care to reduce work and time loads by ensuring integrative and systematic approaches of nurses.

Key words: Posttransplant care, Quality of life, Renal failure

Introduction

A worldwide public health problem is chronic kidney disease, presenting alarming epidemiologic data.¹ According to the National Nephrology, Dialysis, and Transplant Registry System Report from Turkey in 2016, the prevalence of end-stage renal disease (ESRD) has increased every year in Turkey. In 1995, the number of patients with ESRD in Turkey was 78 per million population; however, this number has reached 491 per million population in 2005 and 933 per million population in 2016, increasing more than 10 times in a 20-year period (http://www.tsn.org.tr/folders/file/2016_REGISTR Y.pdf, Access date: January 04, 2018).

In this report, we aimed to help nurses who care for patients posttransplant at kidney transplant centers.

Case Report

Recipient

The recipient was a female patient who was born in 1993. At 18 years of age, she presented to the hospital for examination and was diagnosed with right agenetic kidney and hydronephrosis in the left kidney. She was monitored due to chronic renal failure and received medical treatment for 5 years. In 2016, she gave preterm birth at 32 weeks of pregnancy due to preeclampsia during pregnancy. Because the patient developed ESRD and had renal replacement therapy is needed for the survival of patients with ESRD. Treatment options include hemodialysis, peritoneal dialysis, and kidney transplant (www.tkhk.gov.tr, Access date: October 04, 2017). In terms of survival, health care costs, and quality of life, the criterion standard treatment for ESRD is kidney transplant.²³ The first living-donor kidney transplant in Turkey was carried out by Haberal and associates in 1975 with a kidney donated to a 12-year-old child (http://www.tond.org.tr, Access date: October 04, 2017). The first deceased-donor kidney transplant in Turkey was also carried out by Haberal and associates in 1978 with a kidney supplied by the Eurotransplant Foundation (http://www.tond.org.tr, Access date: October 04, 2017).

Kidney transplant remains the preferred treatment for ESRD.⁴ According to Turkey’s National Nephrology, Dialysis and Transplant Registry System Report, the number of patients who had a kidney transplant was 215 in 1995; this number has generally increased every year, reaching 3416 in 2016 (http://www.tsn.org.tr/folders/file/2016_REGISTR Y.pdf, Access date: January 04, 2018).

In this report, we aimed to help nurses who care for patients posttransplant at kidney transplant centers.
continuous increase of serum creatinine levels since giving birth, renal replacement therapy was needed. Her mother volunteered to be the living donor, and both the patient and mother underwent examination at Akdeniz University Hospital Tuncer Karpuzoğlu Transplantation Center.

The patient underwent blood group testing, tissue group testing, blood tests, C-reactive protein level measurements, complete urine analysis, urine culture tests, stool spread parasite, Hb/hidden blood in the stool, hepatitis and human immunodeficiency tests in gaita, and tests for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis infections. Results of urinary system ultrasonography, chest radiography, pulmonary function test, echocardiography, and female pelvic, renal, and upper abdominal ultrasonography and voiding were recorded and evaluated by the physicians. In addition, urology, mental health and other diseases, and cardiology consultations were completed. Blood pressure, pulse, and height and weight were measured and recorded. The multidisciplinary team determined that there were no medical or ethical obstacles for the transplant of the recipient from her mother, and a kidney transplant was conducted.

**Donor**

The 48-year-old female donor underwent blood group testing, tissue group testing, blood tests, C-reactive protein level measurements, complete urine analysis, urine culture, gaita spread parasite, Hb/hidden blood in the stool, hepatitis and human immunodeficiency tests in gaita, and tests for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis infections. Results of urinary system ultrasonography, chest radiography, pulmonary function test, echocardiography, abdominal computed tomography, computed tomography angiography, electrocardiogram, dynamic kidney scintigraphy, and female pelvic, renal, and upper abdominal ultrasonography and voiding were recorded and evaluated by the physicians. In addition, urology, mental health and other diseases, and cardiology consultations were completed. Blood pressure, pulse, height, and weight were measured and recorded. After council approval, the donor underwent a left nephrectomy operation for kidney transplant to her daughter.

**Pretransplant preparation**

The recipient and donor were admitted to the clinic 1 day before transplant. Medical history and physical examinations were conducted and checked versus patient files. Preoperative training was planned for the recipient and donor, which was handled in 3 parts: briefing, psychosocial support, and skill development. The briefing included topics such as clinic location and presentation, date and time of surgery, visit hours, nutrition before transplant and preoperative fasting times, bowel preparation, skin preparation, anesthesia type, information on postoperative collection unit and transfer to clinic, presence of drains, drug and fluid treatment to be administered, diet and nutrition posttransplant, pain control, and wound site and dressing. It was observed that worries and fears of the donor and recipient decreased with the briefings from the clinic nurse. In addition, both were encouraged to ask questions concerning the perioperative process, and appropriate answers were given to the questions. Deep respiration and coughing exercises, use of spirometer, postoperative posture and body movements, and the ability to protect the operation site were taught, and patients were asked to repeat them. One day before the surgery (in the evening and in the morning of the surgery), immunosuppressive treatment was started for the recipient (tacrolimus and mycophenolic acid). Intravenous fluid support was started in the donor at midnight with 80% cm³/hour with 0.9% NaCl and in the recipient at 6 AM with 40 cm³/h with 0.9% NaCl until surgery. An appropriate and silent atmosphere was provided so that the patients could sleep sufficiently and comfortably. On the day of the surgery, before the donor and recipient left the clinic, the first part of the Safe Surgical Checklist was completed, and both patients became ready for surgery. Patients were safely transferred to the operating room. Surgical procedures conducted in the recipient and donor were carried out under general anesthesia. No complications occurred during the surgery or in the recovery area.

**Discussion**

After transplant, the recipient was admitted to the Organ Transplantation Clinic. The postoperative care plan was divided into complications and issues that needed to be evaluated by a health care team and existing and possible problems to be cared for by the nursing team.
Postoperative day 0 vital signs
The recipient’s vital signs were as follows: blood pressure from 124/75 mm Hg to 90/50 mm Hg, pulse from 110 beats/min to 89 beats/min, breathing rate from 20 breaths/min to 23 breaths/min, body temperature from 36°C to 36.5°C, and oxygen saturation from 96% to 100%.

Treatment on postoperative day 0
Medications included the following: ceftriaxone 1 g intravenously at 2 times per day, tacrolimus 5 mg orally at 2 time per day, mycophenolate mofetil 500 mg orally at 2 times per day, metoclopramide HCl 10 mg/2 mL intravenously at 4 times per day, asetisistein 300 mg/3 mL intravenously at 2 times per day, tramadol HCl 100 mg/2 mL intravenously at 2 times per day, methylprednisolone sodium succinate 250 mg intravenously at 1 time per day, with 500 mg administered in the operating room, omeprazol 40 mg intravenously at 2 times per day, nystatin oral suspension at 4 times per day 20 mL (gargle), and Lasix 20 mg/2 mL intravenously at 1 time per day.

After kidney transplant, patients can have a number of issues diagnosed by the nursing staff, and appropriate nursing procedures must be made. These are outlined below.

Bleeding risk (common diagnosis/possible problem)
Bleeding is the most common early surgical complication after kidney transplant. Postoperative bleeding may occur from the anastomotic sites, the graft itself, or the dissection site. Postoperative bleeding significantly threatens patient survival, and it requires surgical reexamination and hemostasis. Bleeding complications that require surgical procedures increase the risk of loss of the transplanted kidney.

Postoperative bleeding due to kidney transplant surgery usually occurs on postoperative days 0 and 1 and may also be caused by the presence of drain. The expected goals for patients include no more bleeding signs and having normal platelet counts, coagulation time, and hemoglobin and hematocrit values. The patient is expected to know ways to protect from further trauma.

Nursing care for postoperative bleeding includes monitoring patient vital signs, monitoring ingestion and egestion every 8 hours, monitoring the incision site and drain, monitoring laboratory findings, monitoring bleeding, monitoring consciousness, and supporting return to daily life activities. The patient is also observed for shock signs, constipation is prevented, and the patient is protected against trauma.

In our donor and recipients, no bleeding symptoms or signs were observed postoperatively.

Acute pain (existing problem)
Pain may occur as a result of bladder distension and abdominal distension due to Foley catheter blockage to the surgical wound after kidney transplant. For pain control, the most reliable criterion to indicate pain intensity is the Numerical Pain Scale (visual and verbal classification of pain with a scale from 0-10).

Causes of pain include abdominal surgery, surgical incision site, presence of drains, and secondary immobility. Pain can occur during the early postoperative period. The goal for the patient is for pain to diminish or to have no pain and for patients to know the reason for pain and the increasing and reducing factors of pain. In addition, the goal is for pain to have a numerical pain score of less than 2 and for the patient to have no facial expression altered by pain. Patients should be able to perform activities appropriate to day and time in the postoperative period (for example, coughing and respiration exercise, mobilization). Vital signs should be normal.

Nursing care for pain includes evaluation by using the Visual Analog Scale (0 = no pain, 10 = intolerably strong). Vital signs should be monitored, and analgesic medicine should be administered according to the physician’s request. Patients should be encouraged to ask questions to lower stress, anxiety, and fear that occur due to the pain, express their worries, and participate in pain management. A detailed pain diagnosis should be given for the pain management, which should include decreasing and/or increasing situations to reduce pain; measuring quality, severity, duration, and place of pain; and evaluating and monitoring the effect of pain on daily life activities. Nonpharmacologic methods for pain care should be included (talking, listening to music, respiration practices). Patients should be positioned in a pain-reducing position.

In our recipient, the Visual Analog Scale pain score was 7 on postoperative day 0. The recipient received intravenous analgesics (tramadol HCl 100 mg/2 mL intravenously 2 times per day). Nonpharmacologic methods were also used to
reduce pain (providing mobilization, appropriate positioning, breathing exercises, preparing a peaceful atmosphere without noise, talking). Pain was controlled in our patient on postoperative day 2 (pain score = 2), and analgesics were administered when necessary (postoperative day 4). Vital signs and pain scores of the patient were monitored throughout the postoperative period.

**Risk of inefficiency in respiratory functions (possible problem)**
In general in organ transplant patients, the defense systems become less adequate, making them more sensitive to respiratory tract infections due to their primary disease, having major surgery, and the use of immunosuppressive drugs. In addition, factors such as surgical procedures lasting more than 3 hours, incision site, preoperative respiratory problems, extended bed rest, aspiration, dehydration, and immunosuppression are risk factors for respiratory complications.

Causes of respiratory problems include noneffective spirometer usage on incision site due to the pain, noneffective coughing, and insufficient mobilization. The goal for patients is to have respiratory rates and depth and oxygen saturation to be at normal values and for patients to have effective and easy respiration.

Nursing care includes ensuring an open respiratory way, teaching deep respiration and coughing exercises, evaluating sounds from the lungs, ensuring pain control, and teaching the use of a spirometer and monitoring its practice. Oxygen saturation and respiratory rates should also be monitored; if necessary, oxygen support should be provided. Patients should also be placed in an appropriate position. Skin, nail, and mucous membranes should be monitored, and mobilization at the earliest period should be implemented.

In our patient, mobilization and pain control were implemented at the earliest period. On postoperative day 0, spirometer use was supported during deep respiration and coughing exercises. The patient was continuously monitored on other days. The respiratory rate was 18 to 20 breaths/min and oxygen saturation was from 97% to 100%.

**Infection risks (possible problem)**
Due to the immunosuppressive treatment, patients who have kidney transplant are more susceptible to various viral, fungal, and other opportunistic infections than individuals who are immunocompetent. Kidney transplant recipients have various risk factors (eg, diabetes mellitus) that increase their sensitivity to infection in addition to the effects of immunosuppression. Bacterial wound infections are commonly observed. Wound infections are more common in kidney transplant recipients who are obese and have diabetes. Viral infections especially derive from human herpes virus infections, and these are important problems during the first 6 months after transplant. The most common fungal infection is urinary tract infection.

Causes of infection include invasive procedures, incision site, presence of catheter and drains, and immunosuppressive treatment.

The goals for the patient include knowing risk factors for infection and taking relevant precautions to protect from infections, protecting against hospital infections during hospitalization, having no redness, heat increases, fluxion, pain, swelling, or edema in the incision site, and protecting against urinary tract infection. Patients should be monitored for symptoms of pneumonia (fever, fatigue, chills, sore throat, cough, secretion removal), with the aim of protecting against this.

Nursing care should include monitoring body temperature; evaluating the incision site in terms of bleeding, fluxion, redness, edema, pain, local fever, and appearance; evaluating laboratory results; applying aseptic techniques to patients during procedures; evaluating the central catheter entry site daily for symptoms and signs of infection; and administering antibiotic treatment according to the physician’s request. Symptoms and signs of pneumonia should be monitored, and deep respiration and coughing exercises should be practiced. The color, smell, and density of urine should be monitored. Visitors should be restricted to prevent infections (eg, mask usage, hand hygiene). Patients and relatives should be informed about the importance of handwashing, symptoms of infections, ventilation of the room at certain times, and body hygiene. Teeth should be brushed after all meals and before sleeping. Oral care should also include mouthwash done with nystatin oral suspension as per the physician.

Our patient was monitored in terms of symptoms of infection, and no symptom of infection was observed during care in the transplant unit.
Laboratory values and body temperature were within normal values.

**Risk of rejection (common diagnosis/possible problem)**

Organ rejection can occur as the result of immune response by the recipient against the transplanted organ. Hyperacute rejection occurs within minutes or in the first 2 or 3 days after transplant. Acute cellular rejection may develop in 5 or more days after transplant but is more likely to develop within the first 3 months. Chronic rejection is caused by slow progressive graft destruction, fibrosis, and arteriosclerosis, and its cause is unknown. General causes of rejection can also include the surgical procedure (kidney transplant). Goals for the patient are being sure that rejection will not occur.

Nursing care should include effectively and accurately administering immunosuppressive treatment supporting patient compliance and participation in immunosuppressive treatment. Nurses should also monitor therapeutic side effects and whether therapeutic agents are negatively interacting. Nurses should monitor for rejection symptoms and signs (pain and sensitivity at graft site, fever, anomaly in drainage, increase in weight, sudden decrease in urine amount). Patients should be made aware of these symptoms, and the patient should be informed to follow-up immediately with a health facility when these symptoms are observed.

Our patient was observed for rejection symptoms, and acute rejection did not occur during stay in the transplant unit.

**Risk of deterioration in liquid-electrolyte balance (possible problem)**

Acute tubular necrosis, rejection, and fluid electrolyte imbalance depending on bleeding in the surgical incision site may develop due to polyuria, dehydration, congestive heart failure, pulmonary edema, hypokalemia, hyperkalemia, hyperglycemia, hyponatremia, hypernatremia, hemorrhage, and fluid therapy.

Causes of electrolyte balance deterioration can include the long transplant procedure and the inability of the kidney to function completely.

The goal for the patient is for vital signs to be at normal limits. In addition, mucous membranes should not be dry, skin color should not be pale, and skin turgor should not be reduced. Ingestion and egestion should be balanced, and electrolyte laboratory values should be within normal limits.

Nursing care should include monitoring patient vital signs, monitoring dehydration symptoms daily, monitoring ingestion-egestion every 8 hours, checking laboratory values daily, providing, according to physician request, 0.9% NaCl fluid as an infusion, and monitoring weight daily.

In our patient, vital signs were within normal limits. In addition, 24-hour surveillance of ingestion-egestion monitoring was balanced. System diagnosis was normal, and there were no abnormal laboratory values.

**Interruption in breastfeeding (existing problem)**

Nursing procedures do not treat interruption in breastfeeding, but they treat the effects of this situation. The defining characteristic of this nursing diagnosis is to be sure that the baby is adequately breastfed. Causes for interruption include mother and baby separation. The goal for patients is to allow lactation to be carried out by the patient as optimally necessary.

Nursing care should include providing enough breast milk to the baby through mother lactation and breast pump. Training regarding lactation should be provided. To prevent cracks, infection, and pain at the nipples, breast care should be performed and taught to the patient.

In our patient, training was provided to the patient about lactation and milk pumps, and procedures were observed during practice. To prevent potential problems, care methods were taught and daily breast examinations were conducted.

**Risk of deterioration in parent-baby attachment (possible problem)**

Risks to parent-baby attachment include deteriorating support, nutrition, and protective and dynamic interactions between baby and parents. Environment, lack of information, anxiety, and health of the baby or parents are the main factors affecting this relationship. The nurse should focus on improving the relationship between the baby and the parents and avoiding destructive parenting patterns to avoid the possible risk to become a long-term problem.

Reasons for detachment between parent and baby include hospitalization of the parents for kidney transplant surgery. The goals for the patient include parents showing behaviors such as hugging, smiling,
talking, and having eye contact with the baby. Parents should also begin verbally expressing positive feelings about the baby. Parents should engage in the baby’s care after being discharged from the hospital.

Nursing care goals should include having the mother express her feelings verbally and nurses being good listeners. Nurses should avoid behaviors that will annoy the mother, and positive feedback should be given to the mother. The mother should be provided photographs of the baby and be encouraged to view them. The mother should be encouraged to participate in the baby’s care after discharge from the hospital. Training should also be given to other members of the family to support mother-baby relationship.

Our patient was allowed to express her feelings. She became knowledgeable about baby care and was encouraged to participate in baby care after discharge from the hospital. The patient was allowed to see her baby everyday through video calls. She was observed to show her baby’s photo to the health care workers. Other family members were trained.

**Discharge training**

Discharge training begins with the patient’s hospitalization, and this process provides the patient the ability to carry out postdischarge care. The trainings should include short, medium, and long sessions of home care training activities for the specific illness or health problems. The training activities should include the patient, their family, and their relatives.12

**Training subjects for patients, families, and relatives**

Training should include information on emergency situations after kidney transplant, information on polyclinic follow-up, information on continued treatment, information on drugs and drug interactions, rejection symptoms, wound care and dressing, pain management, information on meeting self-care needs, information on oral care, breastfeeding/lactation education, infection control, nutrition after kidney transplant, breathing exercises, physical activity and exercises, alcohol and cigarettes after kidney transplant, sexual life, driving, and travel and sun protection.

A multidisciplinary approach is essential in organ transplant. The nurse has a central role in the team approach to patient care. Observations, training and shadowing, and evaluation of organ transplant nurses are of vital importance as nurses can realize and prevent complications early, increasing survival rates and getting optimal recovery. Our presentation aimed to contribute to aiding professional nursing care after kidney transplant.

**References**

Abstract

Obesity, which has become an increasing problem worldwide, poses a risk for kidney transplant recipients both before and after surgery. In this literature review, we studied the effects of obesity before and after kidney transplant. There are numerous studies and different opinions on the effects of obesity on graft function before and after transplant. Obesity prolongs surgery time and the ischemic process. A large cohort study of 11,836 recipients noted a close association between body mass index and delayed renal transplant and delayed graft function. However, another study found that being overweight or obese before transplant did not have any effects over the medium and long term. A 20-year follow-up study indicated that the first-year body mass index in recipients after renal transplant had a greater effect on graft function and survival than body mass index before transplant. Still, another study found that body mass index had no effects on graft function and survival. In the study, 3-year graft function and mortality rates of morbidly obese people without diabetes, the functional status without dialysis, and living-donor transplant were reported to be much lower than in those with normal weight. In conclusion, there is no consensus on the effects of obesity before and after transplant, and it has been pointed out that more research should be done on this subject.

Key words: Body mass index, Diabetes mellitus, Graft function, Survival

Introduction

It is known that body mass index (BMI) of kidney transplant recipients has been increasing steadily. Obesity is an ongoing problem that is increasing throughout the world. The World Health Organization (WHO) stated that 1.9 billion adults were overweight, whereas 650 million adults were obese. Obesity and its related consequences create a great risk for patients before and after kidney transplant. It is known that pretransplant obesity is a predisposing factor in delayed graft function after transplant. Obesity also adversely affects the process of choosing candidates. It has been indicated that obesity compromises prognosis while affecting graft and long-term results negatively after transplant. In this literature review, we studied the effects and importance of obesity during the pretransplant and posttransplant process in kidney transplant recipients.

Materials and Methods

We used the following key words in a search of Ebscohost, PubMed, Google Scholar, and Cinahl database: obesity and kidney/renal transplant, body mass index, and pretransplant/posttransplant weight.

Results and Discussion

Obesity causes increased sympathetic nervous activity, vasoconstriction, and damage to renal perfusion. However, there are several disagreements on the effects of obesity on renal function during the preoperative and postoperative process.

Postoperative obesity has been reported to cause delayed graft function by extending the duration of surgery and the ischemic process. A meta-analysis stated that high body mass index (BMI) of recipients before transplant is associated with a high mortality rate. However, in a retrospective study by Gill and associates that involved 702,456 patients with chronic kidney disease, women with high BMI had a lower rate of transplant. In another study, Molnar and...
associates found that, in 11,836 recipients, there was a close association between pretransplant BMI and posttransplant delayed graft function. In a retrospective monocentric analysis from 2012, BMI of both donors and recipients in deceased-donor renal transplant was clearly the most important factor affecting delayed graft function.

Body mass index may increase surgical complications in the early posttransplant process, although graft function is reversible affected. A meta-analysis that compared obese versus other patients posttransplant found that patients with obesity had worse results. In this respect, it was highlighted that candidates with BMI > 35 kg/m² and comorbidity and those with BMI > 40 kg/m² must be evaluated carefully before transplant.

Hoogeveen and associates reported that BMI of recipients during the first year after renal transplant had a greater effect on graft function and recovery (survival) rates than pretransplant BMI. Other studies are available that reveal this relationship. In a meta-analysis, low BMI was noted to decrease posttransplant mortality rates while having a positive effect on graft survival. In a retrospective study from Veasey and associates, BMI and functional outcome of patients had no effect on posttransplant complications separately. However, there was a significant increase in surgical complications when 2 of them existed at once.

Furriel and associates stated that being overweight or obese before transplant had no long-term or medium-term effects after transplant. In a retrospective study that evaluated the effects of morbidity on 42,787 renal transplant recipients, patients with morbidity obesity had longer duration of hospital stay, although results between groups were not statistically significant. In a study from Pieloch and associates of 30,132 patients, BMI had no effect on graft function and survival.

Survival rates of patients who received long-term dialysis treatment before transplant and who had high BMI have been reported to be higher than in other patients. In addition, 3-year graft function and mortality rates in patients without diabetes, not receiving dialysis, having positive functional status, who were morbidly obese, and who received transplants from living donors were reported to be much lower than in normal-weight individuals. Another study by Tremblay and associates emphasized that BMI ≥ 40 kg/m² significantly affected graft function and survival rates compared with low BMI. This positive effect is called the “obesity paradox” in the literature.

Studies on the effects of obesity before and after renal transplant have had varied results. There is no clear consensus on the use of BMI in the selection of recipients. The European Renal Best Practice suggested in a guideline published in 2013 that patients with BMI > 30 kg/m² should lose weight before transplant. The guideline also agreed that evidence on the issue is insufficient. In another guideline from 2011, obesity was stated to not be a contraindication for transplant; however, candidates with obesity should be evaluated in detail in terms of pretransplant and posttransplant cardiovascular disease.

Conclusions

There is no consensus regarding the effects of obesity on patients before and after kidney transplant. Comorbid conditions should be considered along with BMI during the process of patient evaluation before and after transplant. Obesity-related studies, which have had different views on the subject, reveal the necessity of further research.

References

Factors Predisposing to the Use of Complementary Therapies in Patients With Chronic Renal Failure

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Abstract

Objectives: Our aim was to gather information about complementary medicine applications used by chronic renal failure patients and their relation to demographic factors.

Materials and Methods: Of 1750 chronic renal disease patients who were undergoing hemodialysis, only 450 patients attended in the study. Among 450 patients, 388 gave consent and were interviewed using a previously tested questionnaire. Questions about complementary and alternative medicine use, a list of commonly used methods, and the sources of knowledge about these were asked of all patients.

Results: We observed a significant difference in the patients who were using complementary and alternative medicines before and after diagnosis of chronic renal disease (P < .001). We noted that 87% of the patients used complementary and alternative medicines before diagnosis and 49.8% used these after diagnosis. Among the patients who used complementary and alternative medicines, 76% had faith in these therapies. Of patients who used complementary and alternative medicines, 95% believed that the remedies or processes used were beneficial to their health. Furthermore, 71% of users had great confidence in these therapies and had no belief that these could be harmful. Of those who used complementary and alternative therapies, 51% had no idea whether these therapies were harmful. The source of knowledge was mass media tools (47%), social life (friends, relatives, neighbors, colleagues; 45%), and other patients with chronic renal disease (8%).

Conclusions: Complementary and alternative medicine therapies have a significant impact on patients with chronic renal disease. Doctors can warn patients about possible dangers of complementary and alternative medicine remedies and treatments.

Key words: Chronic renal disease, Complementary and alternative medicine, Hemodialysis

Introduction

End-stage renal disease (ESRD) is a progressive chronic disease, and there is no cure. Medical technologies such as hemodialysis, peritoneal dialysis, and renal transplant are prolonging lives; however, many patients still die from the disease. The adaptation of these patients to illness and accepting life changes with ESRD are not always straightforward. Chronic hemodialysis requires significant alterations in lifestyle, and there are many potential problems, which can be grouped as physiologic, psychosocial, and economic.1-4 During the early phases of hemodialysis, patients are especially vulnerable to anxiety, depression, and demoralization due to feelings of restriction emerging from hemodialysis treatment.1,9 Although religious beliefs could be an important factor in a patient’s ability to cope, patients have been reported to try other various complementary and alternative medicines (CAM) throughout their illness and dialysis process.10-13

There are no clear and consistent definitions of alternative or complementary medicines. Because CAM practices involve many components, some definitions have been found to be incomplete, whereas others have been found to be unclear. In 1995, the Panel on Definition and Description announced the following definition at a National Institutes of Health research methodology conference: “Complementary and alternative medicine (CAM) is a broad domain of resources that encompasses health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the dominant health system of a
particular society or culture in a given historical period. CAM includes such resources perceived by their users as associated with positive health outcomes. Boundaries within CAM and between the CAM domain and the domain of the dominant system are not always sharp or fixed.14

Complementary and alternative medicines have been available for centuries. The Ebers papyrus, which was written in 1536 BC and accepted as the first textbook on medicine, has over 900 recipes for almost every health problem.15 Because of the lack of modern medical supplies, CAM applications were the only approaches to heal the sick. Until the 19th and 20th centuries, CAM applications were used by caregivers. With the technological developments of the Industrial Revolution, the instruments of the health caregivers have evolved and everything changed. First, cells were identified, then the germ theory was articulated, and, throughout the modernization process, plant extracts were taken to create modern medicine.16,17

During the past 2 decades, CAM use has increased to reach almost 80% in the world.18,19 Increased life expectancy have also increased the number of individuals with chronic diseases, which has increased CAM use. Although some herbal remedies result in organ deficiencies, users are unconvinced of potential dangers, perhaps as a result of mass media and the Internet.19-23 Today, natural and other alternative approaches that complement conventional medicine include dietary supplements, megadose vitamins, herbal preparations, fruit teas, acupuncture, massage therapy, magnet therapy, spiritual healing, and meditation.

Patients with ESRD use CAM as a way out of hopelessness. Patients may use every possible means to find a miracle, but these may lead to complications. Understanding and caring for these complications can be a challenge to medical teams since they may not know what the patient is using.

We conducted this study to gather information about CAM applications used by chronic renal failure patients and their relation to demographic factors.

Materials and Methods

All patients had ESRD and were receiving hemodialysis treatment. Data were collected from different cultural regions of Turkey. Hemodialysis patients at the Başkent University Ankara, Adana, Alanya, and İskenderun Dialysis Centers (1700 total hemodialysis patients) were asked to participate in the study. Patients who were at least 18 years old and who verbally consented were included in the study. Among 1750 patients, 450 agreed to participate, with 388 of 450 patients giving their consent. The patients were interviewed by using a pretested questionnaire. The questionnaire included 21 questions with subsets that were clustered under 4 different subjects. The first subject group involved patient demographic characteristics. The second group included questions on CAM use (whether they were currently using CAM or had used CAM in the past before ESRD diagnosis; their perceptions of its efficacy, that is, whether CAM had worsened their condition, made no difference, helped somewhat, or helped substantially; and whether they used CAM occasionally or regularly). The third subject group included a list of commonly used methods (alternative medical systems, mind-body interventions, biologic-based therapies, manipulative and body-based methods, and energy therapies). The final subject group included questions regarding the patient’s knowledge about CAM and the source of their knowledge.

Results

Of 388 hemodialysis patients included in the study, there were 204 men (52.6%) and 184 women (47.4%) with a mean age of 48.9 ± 15.9 years (range, 18-85 years) (Table 1).

Our results showed that 225 participants (58%) used at least one CAM application. Among these users, most had lower levels of education and believed that these applications were beneficial for their disease ($P < .001$). The socio-demographic characteristics of the 225 patients who used at least one type of CAM for their condition are shown in Table 2. As shown, there were no significant associations between CAM use versus sex and age. However, we did observe a significant correlation between use of CAM and level of education ($P < .05$).

The geographical area of patients was also significantly associated with CAM use (Table 3). Patients who lived in Alanya and Iskenderun had the highest percentage of CAM use.

There was a significant difference in CAM use before and after diagnosis (Figure 1). Before diagnosis, 87% of patients used CAM; however, after diagnosis,
49.8% started to use CAM ($P < .001$). Only 12.9% of patients did not use CAM before diagnosis, whereas 50.2% did not use CAM after diagnosis. Among patients who used CAM, 76% had faith in these therapies and 71% reported having a great level of confidence in these treatments that they disregarded that these could be harmful (Figure 2). In users of CAM therapies, 51% had no idea whether CAM was harmful. In addition, 95% also believed that CAM treatments were beneficial to their health.

Figure 1. Complementary and Alternative Medicines Before and After Diagnosis

Table 1. Socio-Demographic Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic (N = 388 Patients)</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-36 years</td>
<td>107</td>
<td>27.6</td>
</tr>
<tr>
<td>37-50 years</td>
<td>90</td>
<td>23.2</td>
</tr>
<tr>
<td>51-61 years</td>
<td>100</td>
<td>25.7</td>
</tr>
<tr>
<td>62-85 years</td>
<td>91</td>
<td>23.5</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>267</td>
<td>68.9</td>
</tr>
<tr>
<td>Single</td>
<td>74</td>
<td>19.0</td>
</tr>
<tr>
<td>Divorced</td>
<td>18</td>
<td>4.6</td>
</tr>
<tr>
<td>Widowed</td>
<td>29</td>
<td>7.5</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not literate</td>
<td>75</td>
<td>19.4</td>
</tr>
<tr>
<td>Literate</td>
<td>28</td>
<td>7.2</td>
</tr>
<tr>
<td>Primary school graduate</td>
<td>150</td>
<td>38.7</td>
</tr>
<tr>
<td>Secondary school graduate</td>
<td>45</td>
<td>11.5</td>
</tr>
<tr>
<td>High school graduate</td>
<td>49</td>
<td>12.7</td>
</tr>
<tr>
<td>University graduate</td>
<td>41</td>
<td>10.5</td>
</tr>
<tr>
<td>Working status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>50</td>
<td>12.9</td>
</tr>
<tr>
<td>Not working</td>
<td>338</td>
<td>87.1</td>
</tr>
</tbody>
</table>

*P > .05; ‡P < .05; ‡‡P < .001.

Table 2. Patient Socio-demographic Characteristics According to Use of Complementary and Alternative Medicines

<table>
<thead>
<tr>
<th>Patients Who Use CAM</th>
<th>Patients Who Never Used CAM</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>118</td>
<td>57.8</td>
</tr>
<tr>
<td>Female</td>
<td>107</td>
<td>58.2</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-36</td>
<td>59</td>
<td>55.1</td>
</tr>
<tr>
<td>37-50</td>
<td>53</td>
<td>58.9</td>
</tr>
<tr>
<td>51-61</td>
<td>57</td>
<td>57.0</td>
</tr>
<tr>
<td>62-85</td>
<td>56</td>
<td>61.5</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>51</td>
<td>22.7</td>
</tr>
<tr>
<td>Literate</td>
<td>16</td>
<td>7.1</td>
</tr>
<tr>
<td>Primary school graduate</td>
<td>116</td>
<td>51.6</td>
</tr>
<tr>
<td>High school graduate</td>
<td>21</td>
<td>9.3</td>
</tr>
<tr>
<td>University graduate</td>
<td>21</td>
<td>9.3</td>
</tr>
<tr>
<td>Total expenses for complementary treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No money</td>
<td>84</td>
<td>37.3</td>
</tr>
<tr>
<td>$&lt; 330</td>
<td>124</td>
<td>55.1</td>
</tr>
<tr>
<td>$30 to $100</td>
<td>16</td>
<td>7.1</td>
</tr>
<tr>
<td>$100 to $350</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt; $800</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*P < .001.

Table 3. Relation Between Use of Complementary and Alternative Medicine and the Hemodialysis Treatment Center

<table>
<thead>
<tr>
<th>Hemodialysis Treatment Center</th>
<th>CAM Use</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Ankara</td>
<td>48</td>
<td>43.2</td>
</tr>
<tr>
<td>Adana</td>
<td>67</td>
<td>57.3</td>
</tr>
<tr>
<td>Alanya</td>
<td>48</td>
<td>71.6</td>
</tr>
<tr>
<td>Işıkderenur</td>
<td>62</td>
<td>66.7</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>58.0</td>
</tr>
</tbody>
</table>

*P < .001.

Complementary and alternative medicines can be divided into 3 groups: herbal remedies, religious-based applications, and other CAM therapies based on patient choices. As shown in Table 4, most patients used herbal mixtures (43.1%) among the herbal remedy group. These mixtures were followed by fruit teas (30.2%) and seed or fruit consumption (20%). Among religious-based CAM therapies (Table 5), Zamzam water (24.2%) had the highest percentage, whereas thermal therapy (42.5%) was the leading choice in the “other” CAM types (Table 6).
Regarding source of information, most patients who used CAM applications received information from mass media (47%) or relatives and friends (45%) (P < .001). The most popular CAM applications were the ones related to their religion (82.1%).

**Discussion**

Type 2 diabetes mellitus and hypertension are the leading causes of ESRD; both of these conditions have increased in frequency with the rise in life expectancy in the population. Although ESRD is mostly seen in older people in developed countries, in Turkey, it can be seen in every age group. This can be explained by the population distribution of Turkey, as Turkey has a higher percentage of younger people than developed countries.

Most research on CAM has shown statistical differences in use between the sexes, marital status, and working status. Our study showed no significant differences in CAM use among these factors. This can be explained by the cultural structure of Turkey. Although ESRD is one of the most desperate chronic diseases and involves a restricted life, the nature of the Turkish culture has a big effect on the person itself. No matter the level of education, Turkish people will listen to the advice of friends and relatives. Our study supports this contention as friends and family were an important source of information (45%), which was nearly equal with mass media as the source (47%).

Studies in the United States have shown a positive correlation between CAM use and level of education, with a higher level of education equaling a higher use of CAM.24,25 However, our study showed the opposite. We found that most CAM users had either a primary school education or none. This result can be explained by the effects of culture and faith in traditional treatments in Turkey. The effects of culture and tradition in developing countries have been reported by the World Health Organization. That study indicated that, especially in developing or underdeveloped countries, most illnesses are treated with traditional methods. The influence of culture-oriented region was shown in our study. Regarding distribution of CAM users among the hemodialysis centers included in our study, patients treated and living in the southern part of Turkey had the highest percentages of CAM users (Alanya with 71.6% and İskenderun with 66.7%).

Knowledge on CAM therapies and applications was not significantly associated with use. Patients tended to use CAM modalities even if they did not have any idea of their purpose. The reason for this behavior can be explained by the hopelessness of ESRD patients, who are diagnosed with a chronic disease that will be life long and will require a treatment that restricts their life. These factors can create a desperate person looking for a miracle. The high CAM use with less knowledge can also be explained by the educational status of our study patients. Because most of the users had low levels of education, the information sources were limited.

We observed significant associations between use of CAM and belief of CAM therapies. Among 338 patients, 162 patients had faith in CAM therapies, with 75.9% of these patients using at least one CAM therapy or application. This result is not surprising. However, it is surprising that 45% of users had no faith in the CAM treatment, perhaps using CAM as a coping mechanism. To cope with comorbidities, patients may try new things to comfort themselves even if they do not believe in them.

The percentage of users among those who believed that CAM therapies were not harmful was 71%. The percentage of users who thought that CAM can be harmful and still used them was 45%; among those who had no idea about its harm, use was

<table>
<thead>
<tr>
<th>Table 5. Religious-Based Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Religious-Based Modalities</td>
</tr>
<tr>
<td>Zamzam water</td>
</tr>
<tr>
<td>Making offering</td>
</tr>
<tr>
<td>Evil eye bead</td>
</tr>
<tr>
<td>Charm, amulet</td>
</tr>
<tr>
<td>Cevşen</td>
</tr>
<tr>
<td>Entombed saint</td>
</tr>
<tr>
<td>Hodja</td>
</tr>
<tr>
<td>Prayed meal or drink</td>
</tr>
<tr>
<td>Praying</td>
</tr>
<tr>
<td>Healer</td>
</tr>
<tr>
<td>Pool of Abraham (Lake of Fish)</td>
</tr>
<tr>
<td>Rosary</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Total is higher than the patient number because patients used more than 1 application/therapy.

<table>
<thead>
<tr>
<th>Table 6. Other Complementary and Alternative Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Type</td>
</tr>
<tr>
<td>Thermal therapy</td>
</tr>
<tr>
<td>Massage</td>
</tr>
<tr>
<td>Acupuncture</td>
</tr>
<tr>
<td>Heated stone</td>
</tr>
<tr>
<td>Healing stone</td>
</tr>
<tr>
<td>Yoga</td>
</tr>
<tr>
<td>Leech</td>
</tr>
<tr>
<td>Reiki</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
53.2%. The use of CAM modalities among those who believe that they are not harmful is an expected result. Nevertheless, use among patients who believe that CAM modalities are harmful can only be explained by the progressive nature of the illness. Although this study did not study quality of life, it is a known fact that quality of life of hemodialysis patients decreases. Therefore, hemodialysis patients will do anything to improve quality of life because they believe they have nothing to lose. In addition, the placebo effect of these therapies is an undeniable factor of the continuum. All of these determinants can be the underlying factors of this result. Those who have nothing to lose may try anything, even if they believe it is harmful.

The use of CAM before and after diagnosis was significantly different. We found that CAM use was higher before diagnosis. The reason for continued CAM use after diagnosis may be explained by the belief of patients in these remedies. They may not believe that they are harmful and may not believe that there could be a relation between the herbal remedy used and the progress of the illness. After patients are diagnosed with a chronic disease, they may more fully believe and hold on to their belief in CAM therapies.

Complementary and alternative therapies and applications can be grouped into 3 groups. The first group, which includes herbal remedies and herbal mixtures, was the most frequently used. Ingredients included stinging nettle, apple peel, cinnamon, lemon zest, dried tea, white wine, flaxseed, garlic, ginger, cherry stem, fennel, senna, sage, rosehip, linden, molasses, sesame oil, flaxseed oil, and grape seed. Frequency of use ranged from daily to 2 or 3 times per week. The herbs listed here are different from those used in Europe and the United States. This result can be explained by vegetation differences between countries. Studies have shown that herbal mixtures are often considered safe by patients, leading to their preferred use.

The second group includes religious-based applications. When patients are diagnosed with a chronic disease, they may take refuge in religion. Because ESRD is accompanied by restrictive treatment and no cure, religious activities and belief in God for a miracle may occur. We also observed this pattern in our study. The ESRD diagnosis itself led to the patient relying more on religious applications, with most stating use of Zamzam water (24.2%) followed by making offerings (16.9%). As shown in Table 5, although there is no scientific evidence of healing powers, patients prefer to wear evil eye beads, charms, and cevsen. This belief in their healing powers could be attributed to comfort in religion. Despite turning to use of religious-based modalities, patients did not necessarily seek advice from religious leaders.

The third group of CAM therapies included thermal therapy (42.5% use), massage (30.97% use), and acupuncture (7.96% use). Because Turkey has many thermal therapy sites, resulting in a lesser cost, patients often used this CAM modality.

Conclusions and suggestions
Complementary and alternative therapies have a significant effect on ESRD patients, who gather knowledge on these modalities from either mass media or social engagements. There is a positive correlation between CAM use and education. Geographic origin also plays a significant role in CAM use. Doctors should alert ESRD patients about the possible dangers of CAM remedies and therapies. Mass media can also be used to inform ESRD patients and their families about the pros and cons of CAM use. A similar study in patients after transplant could be helpful to see the effects of CAM therapies.

References


Causes of Hemoptysis in Renal Transplant Patients

Irem Serifoglu, Balam Er Dedekarginoglu, Ebru Hatice Ayvazoglu Soy, Gaye Ulubay, Mehmet Haberal

Abstract

Objectives: Hemoptysis is a symptom that can be caused by airway disease, pulmonary parenchymal disease, or pulmonary vascular disease, or it can be idiopathic. Infection is the most common cause of hemoptysis, accounting for 60% to 70% of cases. Hemoptysis is also an initial symptom of diffuse alveolar hemorrhage syndrome, although it may be absent at presentation in one-third of patients. Diffuse alveolar hemorrhage is characterized by disruption of the alveolar-capillary basement membranes because of either injury or inflammation of the arterioles, venules, or capillaries, resulting in bleeding in alveolar spaces. To date, no study in the literature has investigated the cause of hemoptysis in renal transplant patients. In this retrospective study, we aimed to investigate the causes of hemoptysis in renal recipients.

Materials and Methods: The data included in this study were obtained from 352 renal transplant patients who were consulted by the pulmonology department regarding hemoptysis between 2011 and 2017 at Baskent University. Patient medical records were reviewed for demographic, clinical, radiographic, bronchoscopic features, and microbiology data. Immunosuppressive drugs and clinical outcome data were also noted.

Results: This study included 352 renal transplant patients (139 male patients with mean age of 34.9 ± 7 years and 113 female patients with mean age of 31.1 ± 5 years). Hemoptysis was detected in 17 patients (4.8%), with 3 (0.85%) having massive hemoptysis as a result of diffuse alveolar hemorrhage syndrome. Fourteen of our patient group (4%) had pneumonia, and Aspergillus species was detected in 5 patients (1.4%). The only reason for diffuse alveolar hemorrhage was immunosuppressive agents, including sirolimus and mycophenolate mofetil.

Conclusions: Hemoptysis is an important respiratory symptom in renal transplant patients. Although community- or hospital-acquired pneumonia may result in hemoptysis, drug-induced diffuse alveolar hemorrhage and Aspergillus infection should be considered for causes in renal transplant patients.

Key words: Diagnosis, Hemoptysis, Transplantation

Introduction

Hemoptysis, expectoration of blood from the tracheobronchial tree, is associated with numerous diseases. The causes of hemoptysis are categorized under airway diseases, pulmonary parenchymal diseases, vascular diseases, coagulation disorders, iatrogenic injuries, and miscellaneous. It is important to evaluate the amount of hemoptysis and to identify the underlying causes. Expectorated volume of blood over a 24-hour period is used to classify hemoptysis as massive or nonmassive bleeding. Massive hemoptysis, a life-threatening condition in which bleeding cannot be cleared from the dead space, has also been defined as more than 600 mL of blood expectorated over 1 day. Nonmassive hemoptysis is defined as less than 200 mL of blood expectorated during a 24-hour period.

Anemia, alveolar infiltrates, decreased hemoglobin levels, and respiratory failure can be found clinically according to amount of hemoptysis. Impaired platelet function in patients with renal failure results in increased risk of bleeding, including gastrointestinal bleeding, retinal hemorrhage, hemoptyis, gingival bleeding, subdural hematoma, hemorrhathosis, and petechial. A hospital-based study found that the risk of bleeding is increased 2-fold in patients with renal failure. The pathophysiologic basis for the increased risk of bleeding in patients with renal
failure and how much this risk of bleeding decreases after renal transplant are unclear. Hemoptysis, a serious clinical condition, has not been investigated for its cause in renal transplant patients as far as we know. In this retrospective study, we investigated the causes of hemoptysis in renal transplant patients.

**Materials and Methods**

We collected data from medical records of 352 renal transplant patients who were seen at the pulmonology department regarding hemoptysis between 2011 and 2017 at Baskent University. All patients with hemoptysis had been assessed by the consulting pulmonologist at the time of hospital admission; therefore, pseudo-hemoptysis had been already excluded by the consulting doctor. Patient demographic, clinical, laboratory, and microbiology data and radiographic and bronchoscopic features were obtained from the medical records. Immunosuppressive drugs and clinical outcome data were also noted. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 21.0, IBM Corporation, Armonk, NY, USA). Descriptive statistics are presented as means and standard deviation, median (minimum to maximum), frequency distribution, and percent.

**Results**

The study included 352 renal transplantation patients (139 male and 113 female) with mean age of 33.9 ± 7 years. We found 17 renal transplantation patients (4.8%) who developed hemoptysis from follow-up data. Pneumonia was the leading cause of hemoptysis, with 4% (14 patients) in the study group. The microbiologic agent was Aspergillus species in 5/14 patients (35.7%), whereas any causative agent was not obtained in the other 9 patients (64%). The other causes of hemoptysis included drug-induced diffuse alveolar hemorrhage (DAH) caused by sirolimus and mycophenolate mofetil (MMF) in 3 patients (0.85%) (Table 1). Massive hemoptysis was detected in 3 patients: 2 with drug-induced DAH and 1 with invasive pulmonary aspergillosis. The 4 patient deaths in our study group were attributed to pneumonia.

Characteristics of renal transplant patients with hemoptysis are presented in Table 2. There were 12 male and 5 female patients with mean age of 33 ± 5 years. Regarding smoking, 10 of 17 patients were never-smokers, 5 patients had smoked more than 10 packs/year, and 2 patients reported a history of less than 10 packs/year. The causes of renal failure were vesicoureteral reflux, hypertension, unknown cause, pyelonephritis, systemic lupus erythematosus, membranoproliferative glomerulonephritis, diabetes mellitus, Alport syndrome, and Buerger disease.

**Discussion**

Hemoptysis is an important symptom, creating anxiety for both the clinician and the patient based on the amount of hemoptysis found clinically. Fortunately, it is self-limiting in most cases, with less than 5% of patients having severe or massive bleeding. The blood supply of the lung originates from the pulmonary and bronchial arterial system. Small vessels usually cause focal or diffuse hemorrhage due to immunologic, vasculitic, cardiovascular, and coagulation-related causes, whereas hemoptysis originating from large vessels is due to infection, cardiovascular, congenital, neoplastic, and vasculitic diseases.

Diffuse alveolar hemorrhage is characterized by hemoptysis, anemia, and diffuse pulmonary infiltrates.
on radiologic examination. In solid-organ transplant patients, DAH may occur secondary to infection or drug reaction. Infection is the most common cause of hemoptysis, found in nearly 60% to 70% of all cases. Hemoptysis is mostly associated with lung abscess, fungal pneumonia, necrotizing pneumonia, and tuberculous and nontuberculous mycobacterial diseases.

In our study, we found 14 renal transplant patients who developed hemoptysis secondary to infection. We documented that pneumonia found in 5 of 14 patients was caused by Aspergillus infection. Aspergillus fumigatus was the most common isolated pathogen in our study group. Invasive pulmonary aspergillosis has been reported to occur in approximately 0.7% and in up to 4% of renal transplant patients. The difference between the literature and our study population could be explained by differences in environmental exposure in the patients.

Invasive pulmonary aspergillosis causes massive and life-threatening hemoptysis in 40% to 60% of patients. In our study, all pneumonia patients, except for one who had invasive pulmonary aspergillosis, developed nonmassive and self-limiting hemoptysis. Fiberoptic bronchoscopy (FB) was performed within the first 48 hours in these patients, and antifungal agents were administered empirically after the procedure. We suggest that an early decision to perform FB and empiric treatment initiation for fungus could decrease the poor effects of invasive pulmonary aspergillosis on bronchial arterial vessels.

Fiberoptic bronchoscopy was performed in 8 (57%) of the 14 renal transplant patients with pneumonia. One study suggested that, when an initial episode of nonmassive hemoptysis occurs, the presence of an infiltrate combined with signs and symptoms consistent with pneumonia may require only antibiotics and repeated radiography to ensure resolution of the infiltrate and no evaluation by FB. On the basis of this perspective, FB should be considered when it is necessary to obtain the causative pathogen of infection. To our knowledges, with high-resolution computed tomography, the appearance of pulmonary hemorrhage is variable and not specific for a particular cause. In addition, the amount of hemoptysis may not reflect the actual bleeding in some cases. However, despite early imaging features, hemoptysis is a life-threatening clinical condition that should be treated without delay. For these reasons, we believe that FB and bronchoalveolar lavage should both be performed to detect the side of bleeding and to allow discovery of the underlying cause in all renal transplant patients with hemoptysis.

Diffuse alveolar hemorrhage has been described to be related to viruses (including cytomegalovirus, human immunodeficiency, Epstein-Barr, and type 1 human T-cell lymphotrophic infections), Mycoplasma species, fungi (invasive pulmonary aspergillosis, Candida species, and Pneumocystis jiroveci), bacterial pneumonia (Legionella pneumonieae, Stenotrophomonas maltophilia), and mycobacteria (Mycobacterium tuberculosis) in immunosuppressed patients. Early sputum and bronchoalveolar lavage of patients who had these tests did not yield the causative pathogens other than Aspergillus. This result could be attributed to FB not performed in all of the 14 patients in our study. The diagnostic yield of bronchoscopy ranges from 30% to 72% and is highest when performed for pulmonary opacities within the first 6 months of transplant.

The history of the patient frequently guides the clinician to investigate other causes of hemoptysis besides infection. The diagnosis of pulmonary drug toxicity begins with suspicion in transplant patients who have new or progressive respiratory symptoms, including hemoptysis and dyspnea. Certain immunosuppressive drugs used to prevent organ rejection have been described to lead to DAH. We found 3 patients had drug-induced DAH, 1 who received sirolimus and 2 who received MMF for maintenance of immunosuppression. Withdrawal of these drugs resulted in improvement of hemoptysis and pulmonary infiltrates in a few months. Sirolimus, an inhibitor of the mammalian target of rapamycin, was reported previously as cause for DAH in a renal transplant patient. Mycophenolate mofetil, a newly developed immunosuppressive agent that inhibits T-cell and B-cell proliferation by blocking the production of guanosine nucleotides, was described in the literature as a cause of hemoptysis and pulmonary infiltrates on postoperative day 1 of a renal transplant recipient. There are some reports regarding mammalian targets of rapamycin being associated with drug-induced interstitial pneumonitis, fibrosing alveolitis, and pulmonary hemorrhage after renal transplant, and mechanisms are not clear whether this association is a direct or immuno-mediated toxicity. The literature is scarce about the pulmonary effects of MMF, including its role in...
DAH. It remains unclear whether MMF-induced pulmonary pathology lay along with its better known side effects or is a unique condition that occurs itself.

Some reports have suggested that the adverse effects of sirolimus are dose dependent; however, a few patients who had sirolimus trough concentrations lower than previously shown toxic levels still developed pulmonary toxicity. Therapeutic MMF monitoring in renal transplant has not yet been clarified. Dose reduction and discontinuation of the drug are major treatment recommendations for drug-induced DAH. We preferred an immunosuppressive drug change in our patients who had drug-induced hemoptysis. We need to share our experiences more about the pulmonary adverse effects of these immunosuppressive drugs.

A tendency to bleed has been reported in patients with chronic renal failure. Insufficient platelet function related to composition of α-granules, impaired binding of platelets to the vessel wall, and drug interactions between platelets and uremic toxins resulting in a reduced adhesion and aggregation of platelets can increase the risk of bleeding in patients with chronic renal failure. Nine patients in our study group had organ rejection and required hemodialysis again. We could not deny enhanced impairment of renal function as the cause of increased bleeding risk and dysfunctional hemostasis in our patients; however, hemodialysis has been shown to improve platelet abnormality due to removal of uremic toxins.

Conclusions

When renal transplant patients present with hemoptysis and pulmonary infiltrates, clinicians should consider infectious and noninfectious causes, mainly pneumonia, including pulmonary aspergillosis, and drug-induced DAH. We suggest that FB and bronchoalveolar lavage should be performed to differentiate the underlying cause and to avoid delayed treatment.

References


Hand-Grip Strength Is Associated With Serum Testosterone and Albumin Levels in Male Kidney Transplant Recipients

Bahar Gürlek Demirci,1 Siren Sezer,1 Emre Tütal,1 Turan Çolak,1 Saliha Uyanık,2 Mehmet Haberal3

Abstract

Objectives: In kidney transplant recipients, reduced muscle mass and hand-grip strength are associated with impaired nutritional status. Serum testosterone is highly associated with muscle strength in the general population. Here, we aimed to determine the associations among serum testosterone, hand-grip strength, and nutritional and inflammatory parameters, as well as graft function.

Materials and Methods: Our study included 144 stable male kidney transplant recipients from our renal transplant outpatient clinic. All patients were evaluated for clinical parameters (age, duration of hemodialysis, and posttransplant time), biochemical parameters (calcium, phosphorus, parathyroid hormone, C-reactive protein, albumin, creatinine), and serum testosterone levels. Body composition was analyzed with the bioimpedance spectroscopy analysis technique using a body composition monitor that estimates body mass index and percent fat. Hand-grip strength was analyzed by using a dynamometer (ProHealthCareProducts.com, Park City, UT, USA). We calculated estimated glomerular filtration rate using the Modification of Diet in Renal Disease-4 equation.

Results: Demographic characteristics, duration of dialysis before transplant, biochemical parameters, and estimated glomerular filtration rates were similar among study patients. Mean (standard deviation) serum testosterone was 588.0 (55.5) ng/dL, mean body mass index was 26.8 (0.6) kg/m², and mean hand-grip strength was 42.2 (1.7) mm². Serum testosterone levels were positively correlated with hand-grip strength ($r = 0.445; P = .033$) and serum albumin ($r = 0.399; P = .05$) and negatively correlated with serum C-reactive protein ($r = -0.454; P = .05$) and age. In linear multiple regression analysis, serum albumin ($P = .033$) and testosterone levels ($P = .038$) were shown to be predictors of hand-grip strength. However, we could not show a significant correlation between graft function and testosterone.

Conclusions: Serum testosterone level is correlated with hand-grip strength and C-reactive protein and albumin levels, which may indicate that testosterone affects nutritional status and inflammation in male renal transplant recipients.

Key words: C-reactive protein, Muscle weakness, Renal transplantation

Introduction

Muscle weakness is a common problem in patients who are on maintenance hemodialysis. Although kidney transplantation is the criterion standard for patients with end-stage kidney disease, muscle weakness may continue, especially in the early posttransplant period. Muscle weakness is associated with several factors, including increased catabolism driven by inflammation, lack of physical activity, depression, prolonged hospitalization, secondary hyperparathyroidism, anemia, and steroid myopathy.1

Serum testosterone, which decreases in patients with end-stage renal disease, is highly associated with muscle strength. It is well known that hypothalamic-pituitary and testicular dysfunction may recover after successful renal transplant; however, the extent of recovery is controversial.2 The use of hand-grip strength to assess muscle strength has been reported to be reliable in dialysis patients and is correlated with lean body mass. In kidney transplant recipients, reduced muscle mass and hand-grip strength are associated with impaired nutritional status.

Reports on muscle weakness and hormonal dysfunction are scarce in kidney transplant recipients. In this study, we aimed to determine the associations among serum testosterone, hand-grip strength, and
nutritional and inflammatory parameters as well as graft function in stable kidney transplant recipients.

**Materials and Methods**

This study included renal transplant recipients who were regularly followed in the Nephrology Department of Baskent University Medical Faculty Ankara Hospital. Exclusion criteria included patients with gynecomastia, galactorrhea, testicular atrophy, acute graft rejection, graft failure (glomerular filtration rate of < 30 mL/min), posttransplant diabetes mellitus, and congestive heart failure. Patients who were using drugs that affected sex hormones (H2 receptor blockers, spironolactone, ketoconazole, benzodiazepines, tricyclic antidepressants, and opiates) were also excluded. Patients without regular follow-up data and those who had malignant disease, had rheumatologic or chronic inflammatory diseases of unknown origin, or had systemic vasculitis history and presence of active infection were also excluded. Our study included 144 stable male renal transplant recipients from our renal transplant outpatient clinic. The study was approved by the Ethical Review Committee of the Baskent University Faculty of Medicine. All of the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all participants.

We evaluated clinical parameters (age, duration of hemodialysis, posttransplant time), biochemical parameters (calcium, phosphorus, parathyroid hormone, C-reactive protein [CRP], albumin, creatinine), and serum testosterone levels of all study patients. Patient body composition was analyzed with the bioimpedance spectroscopy analysis technique using a body composition monitor (Fresenius Medical Care Deutschland GmbH, Germany), which estimates body mass index (BMI) and percent fat. Hand-grip strength was analyzed with a dynamometer (ProHealthcareProducts.com, Park City, UT, USA). We calculated the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease-4 equation.3

**Anthropometric measurements**

For bioimpedance spectroscopy analysis, 4 electrodes were placed on the hand in the metacarpophalangeal articulations and in the corpus, respectively, 5 cm apart. The electrode pair on the foot was located in the metatarsophalangeal and in the articulation, 6 cm apart. Dry weight, fat mass, fat-free mass, BMI, and muscle mass were analyzed.

**Hand-grip strength**

Hand-grip strength was evaluated using a Takei TKK 5401 digital hand-grip dynamometer (Takei Scientific Instruments Co., Ltd, Niigata, Japan). Maximum strength of the dominant hand was measured 3 times, and the highest recorded value was considered maximal grip strength.

**Statistical analyses**

Statistical analyses were performed with SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc., Chicago, IL, USA). Normality of data was analyzed by using the Kolmogorov-Smirnov test. All numerical variables with normal distribution are expressed as means and standard deviation, whereas variables with skew distribution are expressed as medians and interquartile range. Categorical variables are expressed as percentages and compared by chi-square test. Normally distributed numeric variables were analyzed by independent sample t tests or one-way analysis of variance (post hoc Tukey test). Skew-distributed numeric variables were compared using the Mann-Whitney U test and the Kruskal-Wallis tests. Spearman and Pearson correlation tests were used for correlation analyses. A P value < .05 was considered statistically significant.

**Results**

Demographic characteristics, duration of dialysis before transplant, biochemical parameters (serum calcium, phosphorus, lipid profile), and eGFR levels are shown in Table 1. Mean (SD) serum testosterone level was 588.0 (55.5) ng/mL, mean (SD) BMI was 26.8 (0.6) kg/m², and mean (SD) hand-grip strength was 42.2 (1.7) mm².

Serum testosterone levels were positively correlated with hand-grip strength (r = 0.445; P = .033) (Figure 1) and serum albumin (r = 0.399; P = .05) (Figure 2) and negatively correlated with serum CRP levels (r = -0.454; P = .05) and age (Table 2 and Figure 3).
In linear multiple regression analysis, serum albumin \( (P = .033) \) and testosterone levels \( (P = .038) \) were shown to be predictors of hand-grip strength. However, we could not demonstrate a significant correlation between graft function and testosterone.

### Table 1. Demographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>Age (SD), years</td>
<td>39.8 (10.5)</td>
</tr>
<tr>
<td>Time after transplant (SD), years</td>
<td>6.5 (4.9)</td>
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<td>Cause of renal disease; No</td>
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</tr>
<tr>
<td>Glomerulonephritis</td>
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<tr>
<td>Hypertension</td>
<td>22</td>
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<tr>
<td>Urologic factors</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Nephrolithias</td>
<td>5</td>
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<tr>
<td>Genetic cause</td>
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<tr>
<td>Familial Mediterranean fever</td>
<td>2</td>
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<tr>
<td>Pyelonephritis</td>
<td>1</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Unknown and other</td>
<td>26</td>
</tr>
<tr>
<td>BMI (SD), kg/m²</td>
<td>25.9 (3.8)</td>
</tr>
<tr>
<td>Serum albumin (SD), g/dL</td>
<td>4.2 (0.4)</td>
</tr>
<tr>
<td>Serum creatinine (SD), mg/dL</td>
<td>1.4 (0.5)</td>
</tr>
<tr>
<td>eGFR (SD), mL/min</td>
<td>68.5 (21.2)</td>
</tr>
<tr>
<td>Serum testosterone (SD), ng/dL</td>
<td>479.8 (259.3)</td>
</tr>
<tr>
<td>Serum CRP (SD) (minimum-maximum), U/L</td>
<td>2.6 (2.5) [0.1-11.0]</td>
</tr>
<tr>
<td>Hand-grip strength (SD), kg</td>
<td>37.4 (9.2)</td>
</tr>
<tr>
<td>Fat mass (SD), kg</td>
<td>15.9 (7.3)</td>
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<tr>
<td>Fat-free mass (SD), kg</td>
<td>59.7 (8.1)</td>
</tr>
<tr>
<td>Muscle mass (SD), kg</td>
<td>56.9 (7.5)</td>
</tr>
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</table>

### Table 2. Results of Linear Regression Analysis of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>r Value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>-0.354</td>
<td>.047</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.2</td>
<td>.913</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>0.433</td>
<td>.03</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>0.124</td>
<td>.53</td>
</tr>
<tr>
<td>CRP, U/L</td>
<td>-0.565</td>
<td>.001</td>
</tr>
<tr>
<td>Hand-grip strength</td>
<td>0.412</td>
<td>.019</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>0.105</td>
<td>.58</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FFM, fat-free mass; GFR, glomerular filtration rate

### Figure 1. Serum Testosterone Levels Are Positively Correlated With Hand-Grip Strength

### Abbreviations: HGS, hand-grip strength

### Figure 2. Serum Testosterone Levels Are Positively Correlated With Serum Albumin

### Abbreviations: HGS, hand-grip strength

### Figure 3. Serum Testosterone Levels Are Negatively Correlated With Age

### Abbreviations: HGS, hand-grip strength
Our present study is the first to reveal the associations among serum testosterone, hand-grip strength, and inflammation, which may indicate that testosterone can affect nutritional status and inflammation in male renal transplant recipients.

The high prevalence of hypogonadism and inflammation in patients who are on maintenance hemodialysis has been reported in previous studies. Although successful renal transplant leads to improved testosterone levels, immunosuppression and underlying comorbidities may contribute to impaired gonadal function compared with healthy individuals. On the other hand, similar to the chicken or the egg phenomenon, nutritional status and inflammation also result in impaired testosterone in male renal transplant recipients. In our study, we only included patients who were receiving the same immunosuppressive protocol (prednisolone, mycophenolate mofetil, and calcineurin inhibitors), which have negligible effects on the hypothalamic-pituitary-gonadal axis. We excluded patients who were receiving sirolimus because of its possible negative effect on serum testosterone.

It is well-known that restoration of kidney function by renal transplant improves CRP, a common finding with chronic inflammation. In the present study, serum testosterone levels were all within normal ranges and positively correlated with CRP in male renal transplant recipients. A previous study that compared renal replacement therapies reported improved gonadal function and CRP levels in recipients, similar to our present study. In addition, a previous study showed a negative association between testosterone concentration and serum inflammation that was independent of age in patients with end-stage renal disease. Also in support, Malkin and associates demonstrated that testosterone replacement in hypogonadal men with diabetes or coronary disease shifts the cytokine balance to a state of reduced inflammation. Moreover, previous trials have also shown improved testosterone levels after resolution of inflammation.

Another finding of our study was the significant positive association between serum testosterone and albumin, which may be both related to inflammation and nutrition. Our results supported a previous study that showed reduced inflammatory cytokines and increased albumin levels after normalization of testosterone levels.

It is well documented that testosterone actively induces muscle protein synthesis and has anabolic effects. Although measurements of the muscle compartment are difficult by traditional methods, hand-grip strength has been shown to be useful for assessment of the functional status of general muscles. Previous studies detected a positive correlation between testosterone and hand-grip strength in healthy elderly men and male nonrenal patients. Gungor and associates demonstrated that the association between endogenous testosterone and mortality was the result of aging in patients who were on hemodialysis. However, a recent study found that serum total testosterone was an independent determinant of muscle mass in men undergoing hemodialysis. To our knowledge, our present study is the first to show the associations among testosterone, muscle strength, and inflammation in male renal transplant recipients. We believe that the underlying disease of end-stage renal disease, social isolation, immunosuppression with steroid treatment, and inadequate physical activity may result in decreased muscle mass or muscle atrophy in male renal transplant recipients compared with healthy men.

Reports showing an association between serum testosterone and graft function are scarce. A heart transplant study detected the relation between low testosterone and allograft vasculopathy. A retrospective study identified a cohort of men with low testosterone levels at the time of transplant who had significantly reduced graft survival in the early posttransplant period. In our present study, we could not demonstrate an association between testosterone and graft function. This may due to the untimed collection of blood samples, as most serum testosterone levels improve early after transplant.

There are several limitations of the study. First is its cross-sectional design, with inherent lack of pretransplant data and small sample size. Second, samples were not collected on the same day after transplant; therefore, results may be affected by the diurnal variations of testosterone. In addition, we did not evaluate proteinuria, which can affect graft function and survival.

In conclusion, we showed that the serum testosterone level is positively correlated with hand-grip strength and with albumin and negatively correlated with CRP, indicating that testosterone may...
affect nutritional status and inflammation in male kidney transplant recipients. Larger studies starting from the pretransplant period should be designed to obtain more information on inflammation, skeletal muscle strength, and gonadal function.

References

Abstract

Objectives: Endomyocardial biopsy sampling is used to check acute rejection after cardiac transplant. However, it may lead to tricuspid valve injury and cardiac perforation; therefore, less invasive tools may be useful. Right heart catheterization provides valuable information about cardiac hemodynamics. Herein, we aimed to determine the correlation of right heart catheterization parameters with acute rejection and death during cardiac transplant follow-up.

Materials and Methods: We retrospectively evaluated follow-up right heart catheterization and endomyocardial biopsy results from 47 adult patients who underwent cardiac transplant at Başkent University Faculty of Medicine between 2004 and 2016. Right heart catheterization parameters were compared between deceased and surviving patients and were correlated with acute cellular and humoral rejection. Averaged right heart catheterization parameters were correlated with death. We used Cox regression analysis to determine risk of death and acute cellular rejection and Kaplan-Meier survival analysis to determine any survival differences associated with pulmonary hypertension.

Results: There were 47 patients (38 males, 9 females) with a mean age of 44 ±10 years at transplant. In our patient group, 18 patients (38.3%) died at a median time of 11.2 months. Ninety endomyocardial biopsy samples (22.1%) showed cellular rejection, and 61 samples (4.5%) showed humoral rejection. The deceased patients had significantly greater mean and systolic pulmonary artery pressures, which were significantly correlated with acute cellular rejection. Death was significantly correlated with averaged values of mean and systolic pulmonary artery pressures. Our Cox regression analysis revealed that pulmonary hypertension was significantly associated with risk of death and acute cellular rejection. A Kaplan-Meier survival analysis revealed that pulmonary hypertension was associated with a significantly lower median survival.

Conclusions: Pulmonary artery pressures are significantly correlated with acute cellular rejection and death after cardiac transplant. Pulmonary hypertension significantly increases the risk of death and shortens survival after cardiac transplant.

Key words: Cardiac transplantation, Cellular rejection, Pulmonary artery pressure, Right heart catheterization, Survival

Introduction

Cardiac transplant is a life-saving procedure in patients with end-stage heart failure due to various causes, including ischemic cardiomyopathy, dilated cardiomyopathy, fulminant myocarditis, and various other cardiomyopathy types. Acute rejection is a major problem after cardiac transplant that increases mortality. Currently, acute cardiac allograft rejection is detected by the endomyocardial biopsy (EMB) procedure, which is an invasive procedure in which biopsy samples are taken from the right ventricular endocardium. However, the EMB procedure may result in short- and long-term complications, namely, myocardial perforation and tamponade, arrhythmias, heart block, pneumothorax, pulmonary embolization, nerve block or injury, hematoma formation, tricuspid valve injury, arteriovenous fistula development, and deep venous thrombosis, with a rate of incidence of between 1% and 6%. Furthermore, inflammation is usually of patchy nature, causing biopsy to miss focal rejection. In addition, the pathologic appearance of a rejection...
Episode is a delayed phenomenon, and myocardium may have been already damaged at the time of biopsy specimen assessment and when the necessary treatment has started. Therefore, other noninvasive or semi-invasive methods are needed to detect or predict rejection among cardiac transplant recipients.

Right heart catheterization (RHC) provides valuable information regarding cardiac hemodynamics. Acute rejection episodes cause myocardial injury, which may theoretically increase left ventricular end-diastolic pressure (LVEDP), pulmonary capillary wedge pressure (PCWP), and pulmonary artery pressure (PAP). It is unknown whether RHC parameters, particularly pulmonary pressures, are correlated with acute rejection episodes and death during follow-up of cardiac transplant recipients. In this study, we aimed to determine whether RHC can be used to obtain information about acute rejection and death during cardiac transplant follow-up and whether it can possibly guide the timing of EMB sampling.

Materials and Methods

This retrospective study was approved by the local ethics committee of our university and conducted according to the terms of the Helsinki Declaration. We retrospectively reviewed the digital and written medical records of 47 adult patients who underwent orthotopic cardiac transplant with the bicaval anastomosis method at Başkent University Faculty of Medicine, Department of Cardiovascular Surgery, between 2004 and 2016. All patients underwent serial EMB and RHC procedures on the basis of a predetermined schedule and whenever acute rejection was suspected. We collected demographic and clinical properties, including age at transplant, patient sex, cause of heart failure, comorbidities, smoking and alcohol use, the number and percentage of deceased patients, and time to death from transplant. We also collected EMB follow-up characteristics of the study cohort, namely, the number of EMB procedures, the number of EMB procedures per patient, and the total number of acute cellular and humoral rejections.

Routine diagnostic EMBs were done at weeks 1, 2, 6, 10, 22, 34, and 52, which were then followed by annual EMB procedures. Endomyocardial biopsy procedures were also performed whenever acute rejection was suspected. Endomyocardial biopsy procedures were carried out using a specialized cardiac biopente via right femoral vein under fluoroscopic guidance. A minimum of 3 and preferably 4 or more evaluable specimens of endomyocardial tissue were obtained from the right ventricular septum and submitted for pathologic assessment. Cellular rejection was diagnosed according to the International Society for Heart and Lung Transplant standardized cardiac biopsy grading system. Humoral rejection was also evaluated at each biopsy sampling.

All RHC procedures were performed at the time of EMB procedures. The right femoral vein was used as the entry site inferior vena cava to reach the right heart chambers. All RHC measurements were obtained with a Cournand catheter and a pressure transducer to record intracardiac and pulmonary pressures. The RHC parameters analyzed were mean and systolic PAP, mean PCWP, systolic and end-diastolic right ventricular pressure, mean right atrial pressure, and transpulmonary gradient (TPG). The latter was calculated by subtracting mean PCWP from mean PAP.

All statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 20, IBM Corporation, Armonk, NY, USA). Data distribution was analyzed using the Kolmogorov-Smirnov test. Descriptive data included mean and standard deviation for normally distributed quantitative variables, median and interquartile range (IQR) for nonnormally distributed quantitative variables, and number and percent for categorical variables. The study population was grouped into deceased and surviving patient groups, and RHC parameters averaged by the number of procedures were compared between deceased and surviving patients. The normally distributed quantitative variables were compared using the independent sample t-test, nonnormally distributed quantitative variables using the Mann-Whitney U-test, and the categorical variables using the chi-square test. Correlation analyses between the humoral and cellular rejection episodes were performed using the Pearson and Spearman correlation analyses, depending on the type (quantitative vs qualitative) and normality of distribution of the variables.

Right heart catheterization parameters at each procedure were correlated to cellular and humoral rejection data of the same procedure. Right heart catheterization parameters were averaged by the number of procedures, and the average value of each
parameter was correlated to death during follow-up. A Cox regression analysis was performed to determine whether pulmonary hypertension during follow-up (mean PAP ≥ 25 mm Hg) was associated with acute cellular rejection and death. A Kaplan-Meier survival analysis was performed to determine the survival difference by the presence of pulmonary hypertension during follow-up.

Results

The study population was composed of 47 adult patients (mean age of 44 ± 10 years), of whom 38 were men (80.9%) and 9 were women (19.1%). The demographic characteristics of the study population are presented in Table 1. Table 2 summarizes the acute rejection and survival status of the study population. In our patient group, 18 patients (38.3%) died, with a median time to death of 11.2 months. A total of 420 EMB procedures were performed, with a median number of EMB procedures per patient of 9 (range, 3-20). A total of 408 EMB samples were sent for evaluation of cellular rejection, of which 90 (22.1%) showed cellular rejection and 4 (0.9%) revealed a suspicious result. Of the 420 EMB samples evaluated for humoral rejection, 61 (4.5%) showed humoral rejection and 42 (10.0%) showed a suspicious result. The comparison of the deceased and surviving patients with respect to the RHC parameters revealed that the deceased patients had significantly greater mean PAP, TPG, systolic PAP, and end-diastolic right ventricular pressure, and mean PCWP (Table 3). There were significant correlations between mean values of PAP, systolic PAP, PCWP, and right ventricular systolic pressure and acute cellular rejection but not humoral rejection during follow-up (Table 4).

The average mean PAP was also significantly correlated with the number of acute cellular rejections of any degree (r = 0.353, P < .05). However, TPG was not correlated with either the presence or the number of acute cellular rejections. Death during follow-up was significantly correlated with mean values of PAP, systolic PAP, PCWP, TPG, and end-diastolic right ventricular pressure (Table 5). A total of 5 patients had pulmonary hypertension (mean PAP > 25 mm Hg) during follow-up. A Cox regression analysis revealed that having pulmonary hypertension during follow-up was significantly associated with death (odds ratio

<table>
<thead>
<tr>
<th>Table 1. Demographic Properties of the Study Population (N = 47)</th>
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<tbody>
<tr>
<td>Demographic</td>
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<tr>
<td>Sex (male)</td>
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<tr>
<td>Mean age at transplant, years</td>
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<tr>
<td>Cause of heart failure</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
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<tr>
<td>Diabetic mellitus</td>
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<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Chronic renal disease</td>
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<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Lung disease (obstructive/restrictive)</td>
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<td>History of cerebrovascular events</td>
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<table>
<thead>
<tr>
<th>Table 2. Acute Rejection and Survival Characteristics of the Study Population</th>
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<tbody>
<tr>
<td>Acute Rejection and Survival Characteristic</td>
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<tr>
<td>Total number of follow-up EMB procedures</td>
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<td>Median follow-up EMB procedure per patient (range)</td>
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<tr>
<td>Total number of EMB samples sent for cellular rejection</td>
</tr>
<tr>
<td>Total number of EMB samples sent for humoral rejection</td>
</tr>
<tr>
<td>Cellular rejection results</td>
</tr>
<tr>
<td>No cellular rejection</td>
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<tr>
<td>Grade 1R cellular rejection</td>
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<tr>
<td>Grade 2R cellular rejection</td>
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<tr>
<td>Grade 3R cellular rejection</td>
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<td>Suspected cellular rejection</td>
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<tr>
<td>Humoral rejection results</td>
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<tr>
<td>Acute humoral rejection</td>
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<td>Suspected humoral rejection</td>
</tr>
<tr>
<td>Deceased</td>
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<td>Median time to death, months (minimum to maximum)</td>
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Abbreviations: EMB, endomyocardial biopsy

<table>
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<tr>
<th>Table 3. Comparison of Mean Follow-Up Right Heart Catheterization Parameters by Survival Status (Deceased Versus Surviving)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Median TPG (IQR), mm Hg</td>
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<tr>
<td>Mean PAP (SD), mm Hg</td>
</tr>
<tr>
<td>Mean systolic PAP (SD), mm Hg</td>
</tr>
<tr>
<td>Mean PCWP (SD), mm Hg</td>
</tr>
<tr>
<td>Mean RVSP (SD), mm Hg</td>
</tr>
<tr>
<td>Mean RVEDP (IQR), mm Hg</td>
</tr>
<tr>
<td>Mean RAP (SD), mm Hg</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; NS, not significant; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RVSP, right ventricular systolic pressure; TPG, transpulmonary gradient

<table>
<thead>
<tr>
<th>Table 4. Correlation Between Right Heart Catheterization Parameters and Cellular Rejection During Follow-Up</th>
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<tbody>
<tr>
<td>Right Heart Catheterization Parameter</td>
</tr>
<tr>
<td>Mean PAP</td>
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<tr>
<td>Systolic PAP</td>
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<tr>
<td>TPG</td>
</tr>
<tr>
<td>Mean PCWP</td>
</tr>
<tr>
<td>RVSP</td>
</tr>
<tr>
<td>RVEDP</td>
</tr>
<tr>
<td>Mean RAP</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RVSP, right ventricular systolic pressure; TPG, transpulmonary gradient
of 3.63; 95% confidence interval, 1.16-11.38; \( P < .05 \) and acute cellular rejection (odds ratio of 1.86; 95% confidence interval, 1.04-3.33; \( P < .05 \)). A Kaplan-Meier survival analysis revealed that those having pulmonary hypertension during follow-up had a significantly lower median survival than those who did not (median 32.6 vs 5.8 months; \( P < .05 \)) (Figure 1).

**Table 5. Correlation Between Mean Pulmonary Pressures and Death During Follow-Up**

<table>
<thead>
<tr>
<th>Right Heart Catheterization Parameter</th>
<th>( r ) (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP</td>
<td>0.340 (&lt; .05)</td>
</tr>
<tr>
<td>Systolic PAP</td>
<td>0.347 (&lt; .05)</td>
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<tr>
<td>TPG</td>
<td>0.298 (&lt; .05)</td>
</tr>
<tr>
<td>Mean PCWP</td>
<td>0.322 (&lt; .05)</td>
</tr>
<tr>
<td>RVSP</td>
<td>0.197 (NS)</td>
</tr>
<tr>
<td>RVEDP</td>
<td>0.323 (&lt; .05)</td>
</tr>
<tr>
<td>Mean RAP</td>
<td>0.250 (NS)</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RVSP, right ventricular systolic pressure; TPG, transpulmonary gradient

**Figure 1.** Kaplan-Meier Survival Analysis With Respect to Presence of Pulmonary Hypertension (Mean Pulmonary Artery Pressure > 25 mm Hg) During Follow-Up

**Discussion**

Increased PAP results, and in turn right ventricular and right atrial pressures, increase the risk of death among cardiac transplant recipients. Studies in the literature have suggested that increased pulmonary pressures before transplant increase the risk of right ventricular failure and death. However, there are limited numbers of studies investigating RHC parameters after cardiac transplant. Greenberg and associates performed a single RHC in 19 patients at 13 ± 3 months after cardiac transplant, with a second procedure in 5 patients at mean restudy time of 24 ± 4 months after transplant. The investigators demonstrated significantly increased systolic pressure, diastolic pressure, and mean PAP, as well as the LVEDP. They also demonstrated increased mean PAP (defined as > 21 mm Hg) in 3 of 19 patients (16.6%) and increased LVEDP; in other words PCWP (defined as > 15 mm Hg), in 6 of 19 patients (33.3%). At the second RHC, 4 of 5 patients (80%) showed reduced mean PAP and LVEDP; the patient with increased mean PAP also had increased LVEDP. No significant difference in mean LVEDP was demonstrated between the groups by the number of episodes of rejection.

Lundgren and associates investigated the effects of postoperative pulmonary hypertension on death in the first year after cardiac transplant in 89 recipients. They found that patients with pulmonary hypertension (mean PAP > 25 mm Hg) showed rates of acute cellular rejection that were no different from those who did not have pulmonary hypertension. Conversely, patients with pulmonary hypertension at 2 or more consecutive RHCs had significantly worse survival than those without. Pulmonary hypertension found at repeated measurements was associated with a higher risk of death (hazard ratio of 4.4; 95% confidence interval, 2.0-9.8) than those with no or 1 measurement of pulmonary hypertension. The authors concluded that persistent pulmonary hypertension after cardiac transplant may adversely influence outcomes, with early and repeated catheterizations after cardiac transplant prognostically important by identifying patients with persistent pulmonary hypertension with adverse survival.

Our study is the first to demonstrate that mean and systolic PAP measurements, as well as right ventricular systolic pressure and PCWP, were significantly correlated with any acute cellular rejection and acute cellular rejections equal or greater than grade 2R. We also showed that mean PAP was significantly correlated with the number of acute cellular rejections of any degree. These results suggest a relation between the existence and the number of acute cellular rejections and increased PAPs, which may occur through repetitive left ventricular injury and fibrosis leading to increased LVEDP and, in turn, a passively increased mean PCWP. Indeed, TPG was not correlated with the presence or number of acute cellular rejections,
suggesting that acute cellular rejection episodes may not necessarily lead to intrinsic pulmonary vascular disease but may be passive transmission of increased LVEDP, possibly because acute rejection episodes are aggressively and rapidly treated and there exists no sustained injury on pulmonary vasculature or because they are of episodic nature. Soderlund and associates showed that acute cellular rejections are correlated with worsened survival among cardiac transplant recipients. According to our results, this survival disadvantage may be due to increased PAPs and its hypothetic negative impact.

Although TPG was not significantly correlated with acute cellular rejection episodes, it was nonetheless significantly increased among deceased patients and significantly correlated with death during follow-up. In accordance, increased PAPs along with right ventricular systolic and end-diastolic pressures were correlated with mortality, with mean PAP increasing the mortality by more than 3 times and shortening survival duration by approximately 80%, further emphasizing the importance of pulmonary hypertension and intrinsic pulmonary vascular disease for patient survival among cardiac transplant recipients.

Our study had some limitations. First, this was a retrospective study with relatively small sample size. Second, the effects of graft vasculopathy, hypertension, and antihypertensive and other cardiac and immunosuppressive medications on PCWP, PAP, and death were not assessed. Third, because consecutive patients undergoing cardiac transplant between preset dates were enrolled, the number of EMB and RHC procedures and duration of follow-up were not uniform among study participants. Fourth, we lacked histopathologic data to show whether pulmonary hypertension resulted from pulmonary intrinsic vasculopathy or a simple increase in PCWP. Finally, we did not ascertain the cause of death in the deceased patients and could not identify pulmonary hypertension as the true culprit of death.

In conclusion, this study demonstrated that mean PAP and systolic PAP are significantly correlated with acute cellular rejection but not humoral rejection. The average mean and systolic PAPs were also correlated with death during cardiac transplant follow-up. Presence of pulmonary hypertension significantly increased the risk of death of any cause and significantly shortened survival after cardiac transplant. The association between acute cellular rejection and increased PAPs should be further investigated in future studies.

References

Prevalence and Angiographic Characteristics of Coronary Vasospasm Detected at Surveillance Coronary Angiograms Among Patients With Heart Transplants

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Abstract

Objectives: Coronary vasospasm in heart transplant recipients occurs through various mechanisms. It has been linked to allograft rejection and coronary vasculopathy, which can result in mortality during follow-up. Here, we investigated the prevalence of coronary vasospasm among heart transplant recipients undergoing surveillance coronary angiography procedures.

Materials and Methods: This study was prospectively performed at Başkent University Faculty of Medicine by retrospectively analyzing medical information of patients who underwent bicaval heart transplant between 2003 and 2016 and subsequently had coronary angiography to rule out allograft vasculopathy. We analyzed prevalence of coronary vasospasm, affected vessels, underlying vessel properties, and treatment modalities. Coronary vasospasm was defined as transient diffuse or localized luminal narrowing, either spontaneously or catheter-induced, relieved spontaneously or with nitroglycerine.

Results: Forty-one coronary angiography procedures were performed using the standard Judkins technique. Among these, 5 patients showed coronary vasospasm a mean of 2 years after cardiac transplant. All vasospasm episodes involved the left anterior descending artery, with 2 also involving the circumflex artery and 1 involving the right coronary artery. The degree of luminal narrowing ranged from mild to severe. Episodes that involved the left anterior descending artery more often diffusely involved most of the vessel. In 3 patients, vasospasms were recurrent. Three patients had underlying coronary artery disease, which was relieved in 2 patients who progressed by stent implant. Neither ischemic events nor reduction of ejection fraction was observed during follow-up. There were also no occurrences of cellular or humoral rejection or death in any of the patients with vasospasm.

Conclusions: Coronary vasospasm is common in heart transplant recipients. It may be diffuse or localized and occur spontaneously or because of underlying coronary artery disease. Factors, including allograft vasculopathy, associated with coronary vasospasm remain to be determined, and further related research is needed.

Key words: Allograft vasculopathy, Cardiac allograft vasculopathy, Coronary artery disease, Left anterior descending artery

Introduction

Physicians have been attempting to treat organ failure with transplant for centuries. Heart transplant remains the criterion standard therapy for refractory dilated cardiomyopathy in adult patients. Organ transplant carries a risk of serious complications. Although long-term survival after heart transplant has improved, there is a need for evidence-based strategies that reduce long-term mortality. During recovery, heart transplant patients face the possibility of organ rejection and graft failure. Early complications include primary graft failure, right ventricular dysfunction, rejection, and infections. Late complications include cardiac allograft vasculopathy (CAV) and neoplasms.

Cardiac allograft vasculopathy is among the primary causes of death the first year after heart transplant, and it is the most important limiting factor of long-term survival, along with neoplasms, with an incidence of 8% during the first year, 30% at 5 years, and 50% at 10 years.¹
Coronary angiography is the criterion standard for CAV diagnosis in most transplant centers and in our center. The pathophysiology of CAV is still unknown. Coronary artery spasm and thrombosis are some rare manifestations accompanying this entity. Coronary artery spasm has been reported to occur in 4.9% of adult heart transplant recipients during a follow-up coronary angiography.2

Herein, we aimed to determine the prevalence of coronary artery spasm and its association with rejection and development of coronary artery disease among heart transplant recipients undergoing surveillance coronary angiography procedures at our institution.

Materials and Methods

In our center, coronary angiography is performed yearly in all heart transplant recipients. This study was performed at Baskent University Faculty of Medicine, Department of Cardiology, by retrospectively analyzing medical information of patients who underwent bicaval heart transplant between 2003 and 2016 and subsequently coronary angiography to rule out allograft vasculopathy as part of our heart transplant surveillance program while electrocardiograph and Holter monitoring did not show ischemic changes.

Coronary angiography was performed using the standard Judkins technique in all patients. All procedures included left-sided/right-sided heart catheterization and selective coronary angiography of the right and left coronary arteries using the femoral arterial and venous approach, with endomyocardial biopsy samples taken from the septal surface and apical area of the right ventricle during the same procedure. We injected 3 cm³ of contrast agent for each coronary artery. At least 3 or 4 views were obtained for the right and left coronary arteries. Coronary artery spasm was diagnosed by 2 skilled operators when a localized or diffused and reversible narrowing of the coronary artery lumen was identified. When a coronary vasospasm was shown, intracoronary nitroglycerin was administered at a dose between 100 and 150 μg according to the patient’s blood pressure.

We calculated the prevalence of coronary artery spasm, the affected vessels, underlying vessel properties, and treatment modalities used. All patients received clinical and angiographic follow-up. In those who required further studies, the development of coronary artery disease was assessed.

Results

During the study period, 41 coronary angiography procedures were performed. Among these, 5 patients (12.1%) showed coronary vasospasms a mean of 3.3 years after cardiac transplant. Our study cohort consisted of 3 male and 2 female patients (mean age of 43 years; range, 23-58 y) (Table 1). Left ventricular ejection fraction was normal in all patients (Table 1).

All vasospasm episodes involved the left anterior descending artery with 2 vasospasm episodes involving the circumflex artery and 1 involving the right coronary artery. Coronary artery spasm appeared as a tubular concentric stenosis in all patients and was more discrete in 2 patients (Figures 1-3).

The degree of luminal narrowing ranged from mild to an almost complete occlusion. Left anterior descending artery vasospasm episodes especially diffusely involved most of the vessel. In 3 patients, vasospasms were recurrent. Three patients had underlying coronary artery disease, which progressed in 2 patients and required stent implantation at subsequent coronary angiography procedures.

Two patients were prescribed oral nitrates, and 3 patients were prescribed calcium antagonist at long-term therapy. Neither ischemic events nor reduction of ejection fraction was observed during follow-up. There were also no occurrences of cellular or

Table 1. Patient Characteristics, Date of Transplant, Coronary Artery Spasm, Angiographic Presentation, and Follow-Up Therapy

<table>
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<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Time After Tx, mo</th>
<th>Coronary Induction</th>
<th>Coronary Resolution</th>
<th>Coronary Morphology</th>
<th>CAD Location</th>
<th>EF</th>
<th>Rejection</th>
<th>Long-term Therapy</th>
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<td>F</td>
<td>44</td>
<td>33</td>
<td>LAD, CX</td>
<td>Spontan</td>
<td>Nitrates</td>
<td>CX</td>
<td>60</td>
<td>No</td>
<td>Oral nitrates</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>54</td>
<td>24</td>
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<td>Spontan</td>
<td>Nitrates</td>
<td>Tubular, discrete</td>
<td>54</td>
<td>No</td>
<td>CCB</td>
</tr>
<tr>
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<td>53</td>
<td>24</td>
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<tr>
<td>4</td>
<td>M</td>
<td>58</td>
<td>47</td>
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<td>Nitrates</td>
<td>Tubular, discrete</td>
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<td>36</td>
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<td>59</td>
<td>No</td>
<td>CCB</td>
</tr>
</tbody>
</table>

Abbreviations: CCB, calcium channel blocker; CX, circumflex artery; EF, ejection fraction; F, female; LAD, left anterior descending artery; M, male; RCA, right coronary artery; Spontan, spontaneous; Tx, transplant
Coronary vasospasm can present in patients with or without vasculopathy, and it can be superimposed on organic lesions. The angiographic appearance of coronary vasculopathy has been described in heart transplant recipients. A type A lesion is discrete and can have tubular or multiple stenosis, a type B1 lesion shows distal concentric narrowing and obliterated vessels, a type B2 lesion shows concentric tapering with the distal portion having sonic residual lumen, and a type C lesion shows narrowed irregular distal branches with termination that are often nontapered and squared off, ending abruptly.3

Cardiac allograft vasculopathy cannot be diagnosed based on typical symptoms of angina pectoris. When CAV becomes symptomatic, it is usually at an end stage, and myocardial dysfunction is irreversible. Because of this, it is important to perform screening measures to improve early diagnosis. Coronary angiography is used to establish the diagnosis of CAV in most transplant centers such as ours.

Development of CAV represents the major determinant of long-term survival in patients after heart transplant. Diagnosing coronary vasospasm in transplant patients is important because its prognosis is poor and can be an early sign of CAV. Because CAV is the predominant form of chronic rejection in transplanted hearts and coronary artery spasm can be an early sign of CAV, we retrospectively analyzed the presence of coronary artery spasm in heart transplant recipients at our center. The most common presentation of coronary artery spasm was a symmetric, smooth narrowing of the lumen of a major coronary artery or of its secondary branch, ranging in length from discrete to long and tubular. These features are different from those usually observed in organic arteriopathy of the graft; therefore, diagnosis of coronary artery vasospasm is usually achievable.3

Nitroglycerin has been widely used in the treatment of coronary artery disease in adults; its vascular effects are endothelium independent and are mediated at the cellular level by nitric oxide.4,5 The diagnosis is certain only if the sublingual or intracoronary administration of nitrates induces the prompt resolution of the coronary narrowing. The routine use of intracoronary nitroglycerin to prevent coronary artery spasm in heart transplant patients is not recommended because it can be masked, and other potentially useful therapies are not taken into consideration.
In our series, coronary artery spasm was observed in 12.1% of the heart transplant recipients (5/41 patients). The progression to coronary artery disease was observed in 60% of the cases. Coronary vasospasm prevalence is higher in this study than in previous reports. In one patient, coronary artery spasm was superimposed on an angiographically serious organic vasculopathy, which was relieved by stent implantation. During follow-up, none of our patients showed allograft vasculopathy.

The presence of coronary artery spasm after heart transplant in our study was not associated with the presence of malignant arrhythmias, acute myocardial infarction, acute ischemic events, or sudden death.

Conclusions

The prevalence of coronary artery spasm was more frequent in our study than commonly believed in heart transplant recipients. In our institutional practice, we do not routinely use intracoronary nitroglycerin. We prescribed oral nitrates and calcium antagonists to all transplant patients with coronary artery spasm. The angiographic diagnosis of coronary artery spasm can be inadvertently interpreted as an organic arteriopathy, especially when it presents as a discrete lesion. Further studies are needed to determine whether coronary artery spasm is an early manifestation of CAV or to understand its prognostic significance.

References

Abstract

Objectives: At the National Scientific Center of Surgery named A. Syzganova, more than 100 liver transplants have been conducted from 2012 to November 2017. Survival and quality of life of patients in the posttransplant period largely depend on the compliance of patients, monitoring of complications, cause of liver disease, the severity of the condition of patients in the pretransplant period, and the technical features of the operation. The aims of the study were to analyze the results of liver biopsy in patients after liver transplant and to evaluate the value of morphologic studies of the liver for the diagnosis of complications in the posttransplant period.

Materials and Methods: Liver transplant recipients undergoing liver biopsy between 2012 and 2017 were analyzed. Our study included 40 liver biopsies in 29 patients after orthotopic liver transplant who fulfilled the inclusion criteria.

Results: In 51.7% of cases in patients (that is, in 15 of 29 patients), biopsy data revealed changes characteristic of rejection. Biliary complications were found in 10.34% of patients, recurrent liver diseases were confirmed in 17.24% of patients, 3.45% of patients had confirmed cholangitis, and 6.90% of patients were diagnosed with liver steatosis.

Conclusions: Histopathology assessment of allograft liver biopsies plays an important role in the differential diagnosis of posttransplant complications and in identifying the cause of graft damage; having this information can lead to the appropriate therapeutic intervention.

Key words: Liver biopsy, Liver cirrhosis, Posttransplant complication, Recurrent hepatitis, Rejection

Introduction

In the management of terminal liver diseases worldwide, liver transplant has been shown to be the most effective method for treatment of liver cirrhosis and hepatocellular carcinoma. Survival and quality of life of patients in the posttransplant period largely depend on the compliance of patients, monitoring of complications, cause of liver disease, the severity of the condition of patients in the pretransplant period, and the technical features of the operation.

An important group of disorders after orthotopic liver transplant (OLT) might be classified as “primary hepatic complications.” These complications manifest with graft dysfunction and can be caused by the following factors: immunologic (acute and chronic rejection, chronic hepatitis, de novo or recurrent autoimmune disease), viral (recurrent hepatitis B virus [HBV] and/or hepatitis C virus [HCV], de novo cytomegalovirus, and other virus-related hepatitis), toxic (usually drug-related), and ischemic (late effects of ischemic and reperfusion injury, manifesting within few days from OLT).1,2 Graft loss can manifest as chronic ductopenic rejection, which typically affects the graft between 6 weeks to 6 months after transplant and occurs in up to 17% of patients,3 and as recurrent disease occurring mainly because of HCV recurrence. Primary hepatic complications can be a co-manifestation of vascular or biliary complications (eg, multiple biliary strictures in recurrent sclerosing cholangitis).

Clinical manifestations of complications 1 year after liver transplant require careful analysis and an integrated approach. With early manifestations of complications in most cases, there is a change in the biochemical parameters of the blood, shown as elevation of transaminases, gamma-glutamate
transpeptidase, alkaline phosphatase, and/or bilirubin. The cause of changes in laboratory indicators can be a crisis of rejection and recurrent liver disease and/or biliary complications and liver diseases that have occurred de novo.

The aims of our study were to analyze the results of liver biopsy in patients after liver transplant in our center and to evaluate the value of morphologic studies of the liver for diagnosis of complications in the post transplant period.

**Materials and Methods**

From 2012 to November 2017, the National Scientific Center of Surgery named A.N. Syzganova of the Health Ministry of the Republic of Kazakhstan conducted 106 liver transplants, which included 89 from living donors and 17 from deceased donors. Eighteen transplants were conducted in pediatric patients.

Figure 1 shows the causes of liver diseases. Causes included progression of liver cirrhosis and hepatocellular cancer, with 30% having HBV and hepatitis D virus (HDV). The second most frequent pathology was primary biliary cholangitis (primary biliary cirrhosis; 19% of patients), and the third most frequent was chronic HBV (monoinfection).

There were a total of 40 liver biopsies in 29 patients after OLT who fulfilled the inclusion criteria. The biopsies were classified according to the main histologic diagnosis. All biopsies were clinically indicated. Of the 29 patients, 20 were female patients and 9 were male patients, including one 6-year-old child (girl). The causes of terminal liver disease in these patients was HDV in 34.5%, primary biliary cirrhosis in 24.1%, HBV in 17.24%, HCV in 13.8%, and autoimmune hepatitis in 10.34%. Table 1 presents the patient demographic characteristics and transplant data, including indications for OLT in the study cohort.

**Results and Discussion**

Histologic assessments continue to play an important role in the diagnosis and management of liver allograft rejection. Since 1997, with the introduction of the Banff classification of liver allograft rejection, most centers have assumed a unified approach to the diagnosis and grading of acute cellular rejection. Although the prevalence of acute rejection has been declining, 20% to 40% of patients still have one or more episode requiring treatment with additional immunosuppression. These episodes usually occur during the first 3 months after transplant, and the diagnosis at this time is generally easy. The updated Banff schema published in 2000 is also widely used for the diagnosis and staging of chronic rejection.

Table 2 presents the histologic diagnoses of 29 liver biopsies obtained > 3 months after transplant during the 5.5-year study period (2011-2017). Most
patients were treated with a triple therapy, and only 3.6% (1/28) received monotherapy. One patient with severe rejection had autoimmune hepatitis overlapping with primary biliary cirrhosis. The patient was refractory to methylprednisolone. Simultaneously with the rejection, the patient developed end-stage renal failure. A second incident of severe acute cellular rejection developed in a patient with recurrent HBV infection. The patients with rejection activity index of 3 or 4 did not receive pulse therapy (methylprednisolone) because they had biliary and septic complications. One patient with severe rejection (rejection activity index of 8) stopped immunosuppressive therapy for 1.5 months at 1.5 years after liver transplant. He had cirrhosis due to HBV and HDV and biliary stricture 6 months after liver transplant (Figure 2, A and B).

**Recurrence of hepatitis C virus**

For diagnosis of recurrent HCV (excluding other causes of graft dysfunction), liver biopsies are used to assess disease severity and progression. Histologic abnormalities are often present in protocol biopsies from HCV-positive patients who are clinically healthy, with apparently normal graft function. The changes seen in these specimens may have implications for prognosis and treatment. For example, the presence and severity of fibrosis at 1 year have been shown to be predictive of subsequent progression to cirrhosis and graft failure. This information may help identify patients who are most likely to benefit from antiviral therapy.

Recurrent HCV was found in a patient with genotype 1b. This patient received pegylated interferon and other direct-acting antiviral drugs. The reason for recurrent HBV was the interruption of antiviral therapy 9 months after liver transplant (Figure 3).

**Recurrence of hepatitis B virus**

According to the recommendations of the International Liver Transplantation Society (2016), patients who undergo liver transplant in connection with terminal liver disease from HBV are classified into 3 categories: (1) patients with low risk of recurrent HBV infection, (2) patients with a high risk of recurrent HBV infection, and (3) patients with limited therapeutic options for specific prevention of recurrent HBV infection.

The first category includes patients with undetectable levels of HBV DNA during the pretransplant period and during liver transplantation, patients with viral load less than 1000 IU/mL, and patients with fulminating HBV with absence of HDV coinfection. Patients with a viral load of more than 1000 IU/mL, patients with chronic liver failure, and patients with HBeAg-positive HBV belong to the second category. The third category includes patients with HDV coinfection, patients with a high risk of recurrent viral hepatitis, patients with enhanced
resistance to nucleotide analogs, and patients with human immunodeficiency virus coinfection.

In our center, patients with cirrhosis because of HBV and HDV receive nucleoside analogs of entecavir or tenofovir during the pretransplant and posttransplant periods for prevention of recurrent hepatitis (n = 20). Twelve patients, in addition to nucleoside analogs, received specific hepatitis B immunoglobulin during transplant.

A patient with the recurrent HDV infection received entecavir at 0.5 mg per day. The patient had positive HBsAg, negative results of polymerase chain reaction HBV DNA analysis, and positive results of polymerase chain reaction HDV RNA analysis at 72 weeks after liver transplant. However, 3 months later, results of polymerase chain reaction HDV analysis were negative and results of HBsAg were positive. In the liver tissue (Figure 4), moderate inflammatory infiltrates were seen spreading to the hepatic lobes, forming step necroses. In periportal fields, an increase in the content of connective tissue is visible, with the spread of fibrosis in most portal tracts with single short fibrotic septa.

**Recurrent primary biliary cirrhosis**

Four patients transplanted for primary biliary cirrhosis were followed for up to 3.5 years. At about 1.5 years after surgery, 3 patients experienced elevations of alanine aminotransferase and alkaline phosphatase, with liver biopsy indicating graft dysfunction. Two patients had diabetes, and 1 patient had biliary stricture 2 years after transplant. Titers of antimitochondrial antibodies fell to undetectable levels shortly after transplant in all recipients; however, values similar to or higher than those before transplant were observed over time. Biopsies revealed portal inflammation, lymphoid aggregates, granulomas, bile duct injury, and ductopenia. The histology was not suggestive of chronic rejection (Figure 5).

**Nonalcoholic fatty liver disease**

The distinction between recurrent and de novo nonalcoholic fatty liver disease (NAFLD) is often difficult. Liver transplant patients are at risk for developing a number of features of metabolic syndrome, such as diabetes mellitus, weight gain, hypertension, and hyperlipidemia and are thus predisposed to the development of NAFLD. Steatosis in the donor liver has also been identified as a risk factor for the development of steatosis in late posttransplant biopsies, although the mechanism for this is uncertain. Cases of NAFLD have been identified that appear to have arisen de novo after
liver transplant. However, some of these have occurred in patients who were transplanted for cryptogenic cirrhosis and/or had risk factors for metabolic syndrome before transplant and could thus be regarded as having recurrent rather than de novo disease. Interactions between HCV infection, insulin resistance, and NAFLD also appear to be important in the pathogenesis of recurrent HCV and de novo NAFLD.

In the 2 cases of NAFLD, the cause in 1 patient was metabolic changes that occurred de novo. The second patient was a 6-year-old child. The most likely cause in this case was steatosis of the donor liver. In this pediatric patient, indications for liver biopsy were high rates of transaminases throughout the posttransplant period (1 year and 3 months) (Figures 6 and 7).

Morphologic results showed that most patients, that is, in 15/29 patients (51.7%), were diagnosed with acute and chronic rejection. Biliary complications were found in 10.34% of cases. Recurrent liver diseases were confirmed in 17.24% of patients after liver transplant. Studies have shown the frequency of recurrent liver disease to vary from 13.2% to 20%. Among our patients, 3.45% had confirmed cholangitis and 6.90% were diagnosed with liver steatosis.

An evaluation of allograft liver biopsies at our center revealed that, although acute and chronic rejection episodes were major factors in liver dysfunction, all cases of acute rejection were promptly diagnosed and successfully treated as a result of close cooperation between clinicians and pathologists. The overall occurrence of chronic rejection was 3.6%.
Conclusions

Liver histology remains the criterion standard test for diagnosis of allograft dysfunction, rejection of the transplant,\textsuperscript{17} NAFLD,\textsuperscript{18,19} and recurrence of viral hepatitis. Therefore, histopathologic assessments of allograft liver biopsies play an important role in treatment of liver transplant patients.

Many common posttransplant complications cannot be differentiated by clinical, paraclinical, and imaging studies; in many situations, more than 1 cause contributes to graft dysfunction. Therefore, histopathologic assessment of allograft liver biopsies plays an important role in the differential diagnosis of posttransplant complications, allowing identification of cause of graft damage and subsequently the initiation of appropriate therapeutic intervention.

References

Nonmelanoma Skin Cancers in Solid-Organ Transplant Recipients: A Single Center Experience

Abbas Albayati,1 Burak Ozkan,1 Atilla Adnan Eyuboglu,1 Ahmet Cagri Uysal,1 Nilgun Markal Ertas,1 Mehmet Haberal2

Abstract

Objectives: Skin cancers are one of the most common malignancies in solid-organ transplant recipients. Increased age and immunosuppressive drug use are risk factors for posttransplant skin malignancies. We evaluated nonmelanocytic skin cancer incidence and development time in transplant patients.

Materials and Methods: We reviewed 1833 patients who received kidney, liver, and heart grafts between 1996 and 2016 at Baskent University. We excluded melanocytic skin cancers, premalignant lesions, and benign skin tumors.

Results: Of 1833 patients, 1253 were male (68.4%) and 580 were female (31.6%), composed of 1133 kidney (61.8%), 512 liver (27.9%), and 120 heart recipients (6.5%). Of these, 22 patients (18 kidney/3 liver/1 heart) developed 23 different types of skin cancer. Prevalence of skin cancer was 1.20%. Mean age at presentation was 55.8 years (range, 37-71 y). Average time from transplant to skin malignancy was 6.1 years (range, 1-13 y), with the most common being basal cell carcinoma (43%, 10 cases), followed by squamous cell carcinoma (39%, 9 cases) and Kaposi sarcoma (13%, 3 cases). Tumor sites included head and neck (15 case), trunk (2 cases), lower extremity (2 cases), and upper extremity (2 cases). Neither local recurrence nor distant metastasis was shown.

Conclusions: Skin cancer risk is increased in solid-organ transplant recipients versus the general population. Although squamous cell carcinoma is the most common tumor in this patient population, followed by basal cell carcinoma, we found this reversed in our patients. The low prevalence of skin malignancy (1.20%) may be associated with close clinical follow-up to detect premalignant skin lesions and the low-dose immunosuppressive drug regimen. We believe that local recurrence and distant metastasis were absent because we use a wide surgical margin of excision and provide strict follow-up. Routine dermatologic follow-up visits of transplant recipients are recommended to detect and treat early skin cancer and premalignant lesions and thus lower morbidity and mortality.

Key words: Basal cell carcinoma, Immunosuppression, Squamous cell carcinoma, Transplantation

Introduction

Organ transplant is a life-altering event for thousands of patients around the world. The success of long-term survival of the graft depends mainly on suppressing the host’s immune system with immunosuppressive therapies. The new advances in treatment, however, are leading to a variety of medical complications that limit the success of immunosuppressive agents. Among these problems are infectious complications, cardiovascular diseases, and malignancies. Neoplasm represents an important disease entity for mortality after organ transplant. The most common cancers after transplant are cutaneous malignancies, with 95% of cases being nonmelanocytic skin cancers (NMSC), such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).1 Reported incidence of skin cancer following organ transplant varies widely according to series across countries. An incidence of 40% of premalignant lesions and nonmelanoma skin cancer is observed within the first 5 years after transplant.2 This incidence is increased proportionally to the duration of immunosuppression, reaching up to 60% after 20 years.3 According to the literature, the most common type of skin cancer in the general population is BCC followed by SCC. The predilection for the development of SCC in immunosuppressed patients favors
a reversed ratio (SCC > BCC) of skin cancers in solid-organ transplant recipients (SOTRs), reflecting a different pathogenic mechanism in the development of these skin malignancies.

In addition to NMSC, other skin cancers, although relatively rare, are also increased in transplant patients. Cutaneous Kaposi sarcoma (KS), a malignant vascular tumor, is seldom encountered in healthy individuals; however, its frequency is increased 400- to 500-fold in transplant recipients, and it is associated largely with reactivation of human herpesvirus-8.4,5 Merkel cell carcinoma and malignant melanoma are among other rare skin cancers reported frequently in SOTR, with more aggressive tumor behavior and higher mortality rate.

The clinical aspect of skin cancers in transplant patients is unusual, compared with the general population; these may be highly aggressive, may develop in a short time, and, in the case of SCC, may metastasize early.

The most prevalent factor to affect the development of skin cancer after transplant is immunosuppressive therapy, which is used to prevent graft rejection; nevertheless, it leads to dysfunction of antiviral and antitumoral properties of the immune system. The skin is a mechanical barrier protecting the body, and it acts as a true peripheral immunologic organ. The skin immune system contains most of the cell types present in lymphoid organs, including dendritic cells, natural killer cells, macrophages, T cells, and Langerhans cells. All immunosuppressive drugs suppress the skin immune system by impairing dendritic cells, leading to an increased incidence of skin cancers.6 The intensity and duration of immunotherapies are greater for heart graft recipients; therefore, incidence of cancer after heart transplant is higher than that shown in kidney transplant.

The prolonged use of immunosuppression enhances the potential effects of ultraviolet B radiation on DNA and exposes the patient to potentially oncogenic viral infections. E6 and E7 oncoproteins derived from human papillomavirus have an active role in the pathogenesis of SCC,7 which is confirmed by the presence of human papillomavirus DNA in skin cancers of these patients.8 Some immunosuppressive drugs, for example, cyclosporine, have a direct effect on neoplasms and may promote cancer progression.9 A lower dose of cyclosporine is reported to be associated with lower cancer incidence without any evidence of deterioration of graft function or survival.10

Another risk factor for skin cancer development in transplant patients is ultraviolet radiation exposure. Ultraviolet B induces DNA gene mutation, as well as direct depression of the skin immune system.6 Its effect is well-established in geographical locations of high altitude, where the incidence of skin cancer is markedly increased.11

Other risk factors include age of the patient at transplant, sex of the patient, fair skin complexion (Fitzpatrick skin type I to III), and a history of skin cancer before transplant. Older age at transplant increases cancer risk.12 Patients older than 50 years of age tend to have a steady increase in the incidence of skin cancers, especially in the first 2 years after transplant.13 Male sex appears to have a higher risk for NMSC.12 Skin type is found to be a predictor of NMSC in transplant recipients.12 White people living in Australia have the highest rates of NMSC in the world.14 Patients with a history of actinic keratosis or skin cancer before transplant also have a higher risk of skin cancer after transplant.12

Skin biopsy is an important diagnostic tool for early detection of cancerous lesions. Precancerous lesions can be treated by topical retinoid, 5-flurouracil, photodynamic therapy, and topical immune modulators such as imiquimod. Selected cases of less aggressive forms of NMSC can be treated by destructive techniques, including electrodesiccation and curettage, as well as cryosurgery. However, the mainstay of treatment is by Mohs micrographic surgery or surgical excision with margin assessment. The risk of local recurrence and distant metastasis is higher than that observed in immunocompetent patients. However, the mortality rate of skin cancers is lower than that of other malignancies in SOTR patients, due to early detection and relatively slow progression.

Materials and Methods

We retrospectively evaluated 1833 transplant recipients who were operated on between 1996 and 2016, in terms of age, sex, the histopathologic findings, time to development of cancer, and immunosuppressive medications. Patients were followed for at least 1 year after organ transplant. Patients with melanocytic skin cancers and premalignant lesions were excluded from the study.
The study was approved by the ethics committee of the institute. All protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all participants.

Results

The total numbers and relative percentages of our transplant cases were as follows: 1133 kidney (61.8%), 512 liver (27.9%), and 120 heart (6.5%). Among these patients, 1253 were male (68.3%) and 580 were female (31.7%). The mean age of patients at time of transplant was 55.8 years (range, 37-71 y); follow-up ranged from 12 to 60 months (median, 39 mo). The elapsed median time between transplant and the appearance of skin cancer was 6.1 years (range, 1-13 y) (Table 1).

There were 22 patients (18 kidney, 3 liver, and 1 heart recipient) who developed 23 different skin cancers. Of these patients, 17 were male (77.2%) and 5 were female (22.7%). The mean age at presentation was 58.7 years (range, 44-71 y). The prevalence of NMSC in transplant patients in general was 1.20%. Among these patients, 10 were diagnosed with BCC (43%), 9 with SCC (39%), and 3 with KS (%13). One patient (4.5%) of the 22 SOTRs had BCC twice at 1 year apart. The skin cancer sites were in the head and neck region (15 cases), lower limb (2 cases), upper limb (2 cases), and trunk (2 cases). Of the 11 BCC cases, 9 were in a sun-exposed area, and 2 were in a sun-protected part. For the SCC cases, 8 occurred in a sun-exposed area, and 1 was in a sun-protected part; all of the KS cases were in sun-protected parts of the lower limb (Table 2).

All tumors appeared within the first 2 years after transplant (median of 18 months). The mean time to develop SCC (6.1 years) was similar to that for BCC (6.3 years). All patients diagnosed with SCC were investigated by ultrasonography for the evaluation of regional lymphadenopathy. Local recurrence and metastasis were not detected in our patients.

Discussion

Skin malignancies are a growing problem and still a main issue in SOTR patients due to the higher incidence, aggressive behavior, and higher potential for mortality and morbidity. The increased risk is well-known in SOTRs.

In our study, most transplant patients with skin cancer were male patients, similar to previous studies, and the proportion of NMSC in sun-exposed parts was higher (Table 2).14,15 We found a significantly higher frequency of skin cancer for recipients older than 50 years (81.8%). The head and neck region accounted for 68.8% of skin cancers. Ramsay and associates showed that more than 80% of lesions were found in the head and neck region of patients.16 Our findings are consistent with data from the literature. Our study confirmed that age and male sex were associated with development of skin cancer.

Transplant-specific differences in skin cancer incidence have also been noted. The incidence of skin cancer in our liver transplant patients was less than that for kidney transplant patients because of lower immunosuppression (13.6%, 3 cases). Euvrard and associates found a twofold increase in incidence of cutaneous neoplasm in heart transplant patients.

### Table 1. Demographic Characteristics of Patients With Skin Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at transplant, y</td>
<td>55.8 (range, 37-71)</td>
</tr>
<tr>
<td>Sex of patient, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (77.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Type of graft, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>18 (81.8%)</td>
</tr>
<tr>
<td>Liver</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>Heart</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Type of tumor, No. (%)</td>
<td></td>
</tr>
<tr>
<td>BCC</td>
<td>10 (43%)</td>
</tr>
<tr>
<td>SCC</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>KS</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Location of skin cancer, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>15 (68.1%)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Trunk</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Mean time from transplant to tumor diagnosis, y</td>
<td>6.1 (range, 1-13)</td>
</tr>
<tr>
<td>Immunosuppressive therapy, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus + Pred + MMF</td>
<td>8 (36.3%)</td>
</tr>
<tr>
<td>Tacrolimus + Pred</td>
<td>4 (18.1%)</td>
</tr>
<tr>
<td>Tacrolimus + CSA + Pred</td>
<td>4 (18.1%)</td>
</tr>
<tr>
<td>CSA + MMF + Pred</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>Sirolimus + Pred</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Sirolimus + Pred + MMF</td>
<td>1 (4.5%)</td>
</tr>
</tbody>
</table>

### Table 2. Distribution of Skin Cancer in Solid-Organ Transplant Patients

<table>
<thead>
<tr>
<th>Type of Skin Cancer</th>
<th>Sex of Patient</th>
<th>No. of Cases in Sun-Exposed Area</th>
<th>No. of Cases in Sun-Protected Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>1 F, 8 M</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>BCC</td>
<td>3 F, 7 M</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>KS</td>
<td>1 F, 2 M</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>All tumors</td>
<td>5 F, 17 M</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

**Abbreviations:** BCC, basal cell carcinoma; CsA, cyclosporine; KS, Kaposi sarcoma; MMF, mycophenolate mofetil; Pred, prednisone; SCC, squamous cell carcinoma.
compared with kidney transplant recipients.\textsuperscript{17} In our study, 1 incidence of SCC was detected in a heart transplant recipient (4.5%).

Organ transplant is also associated with increased risk of certain cutaneous cancers that are uncommon in the general population. Kaposi sarcoma is one such cancer. In our study, all cases of KS occurred in patients with kidney transplants; no liver transplant recipient developed KS. This may be explained by the higher level of virus activation due to higher state of immunosuppression in kidney recipients, as reported by Andreoni and associates.\textsuperscript{18}

In contrast to most studies regarding the BCC/SCC ratio, the most common type of skin cancer encountered in our patients was BCC rather than SCC. Some studies have reported similar findings. A prospective study by Fuente and associates involving 174 kidney transplant recipients showed a BCC/SCC ratio of 1.4:1.\textsuperscript{19} Another study by an Italian group showed a BCC/SCC ratio of 2.1:1.\textsuperscript{20} In a Spanish study, Ferrandiz and associates reported the ratio of BCC/SCC as 3.1:1.\textsuperscript{21} We have no explanation for this high incidence of BCC and lower incidence of SCC in our patients.

The low prevalence of skin cancers (1.20%) in our SOTR patients contrasts with other series reported from different transplant centers.\textsuperscript{16,22-24} We believe this finding is due to pretransplant education of patients about risk of developing skin cancers and the low-dose immunotherapy regimens that patients received.

It is well-known that the longer duration of immunosuppression, the greater the incidence of skin cancer. Incidence rates differ according to geographical location. In The Netherlands, a cumulative incidence of 2\% after 3 years is increased to 40\% after 10 years.\textsuperscript{25} In Italy, it has been reported as 7.5\% to 28.6\% versus the higher rates observed in Australia (45\% after 11 years and 70\% after 20 years).\textsuperscript{14,20} Our study did not confirm previous studies on the cumulative incidence of skin cancer in SOTR. The overall incidence dropped with time elapsed since time of transplant from 5.4 per 1000 persons/year within the first 3 years after transplant to 4.5 per 1000 persons/year in the period of 4 to 10 years, and to 2.1 per 1000 persons/year after more than 10 years posttransplant. Nevertheless, our overall finding was in line with that reported by the Northern Ireland Cancer Registry in terms of cumulative incidence.\textsuperscript{26}

All tumors were treated with surgical excision that involved at least 5 mm of surgical margins and coverage of the resultant tissue defect with suitable reconstructive option, through either local skin flaps or skin grafts. All cases of SCC were examined thoroughly and investigated by ultrasonography for regional lymphadenopathy. The local recurrence rate of SCC in kidney transplant recipients is reported to be approximately 13\%, and the risk of metastases in SCC is approximately 8\%.\textsuperscript{27,28} However, neither recurrence nor distant metastasis was seen in our cases. We believe that this is due to our treatment strategy involving wide margins of tumor excision and close follow-up of patients. Findings from the University of Cincinnati Health Transplant program (Cincinnati, OH, USA) revealed that 5\% of transplant patients died of their skin malignancies.\textsuperscript{29} No cases of death from complication related to skin cancers were shown in our study.

The longer transplant survival and potent immunosuppressive agents may lead to an increased incidence of skin cancer in the following years. Low level of immunosuppression, use of immunosuppressive drugs with antitumoral properties, and regular screening are essential to reduce tumor risk while improving graft survival. Revision of immunosuppression therapy is another method of reducing the risk of posttransplant malignancies. Changing the immunosuppressive regimen or reducing the dose of the current drugs is the initial step in a revised treatment regimen, taking into account the risk of graft rejection. The antineoplastic characteristics of mTOR (ie, “mammalian target of rapamycin”) inhibitors sirolimus and everolimus have been proven in several animal studies and prospective trials.\textsuperscript{30-32} A study by Salgo and associates showed a significant reduction in NMSC in transplant recipients switched to sirolimus compared with those maintaining the initial immunosuppressive therapies.\textsuperscript{33} Another study conducted by Euvrard and associates revealed a 44\% reduction of secondary SCC after conversion to sirolimus 12 years after kidney transplant.\textsuperscript{34} Patients receiving mycophenolate mofetil appear to have lower risk than those treated with azathioprine.\textsuperscript{35} However, Bouwes Bavinck and colleagues concluded that the increased risk of skin cancer is independent of the agent and is a result of the immunosuppression per se.\textsuperscript{14} Different combinations of immunotherapies were given to our SOTRs. All patients received
corticosteroids. Most of our patients had tacrolimus-based immunotherapy (Table 1). We found that patients treated with tacrolimus-based immunotherapy had an increased risk versus patients who received sirolimus alone or in combination with mycophenolate mofetil.

Reducing sunlight exposure is an essential measure to prevent skin cancers in transplant patients. Because transplant recipients are well known for their low compliance on sunscreen use, these patients should be offered full information on the potential risk of sun exposure. Patients should be encouraged to use effective sunscreens with an effectively high sun protection factor on a daily basis and to wear long-sleeved shirts, a hat, and sunglasses when outdoors.

All patients diagnosed with skin cancer should be followed regularly and strictly by an experienced dermatologist for early detection and monitoring of skin tumors. An interval of 3 to 6 months of clinical follow-up is recommended for patients diagnosed with NMSC. Transplant patients should be educated for the recognition of new skin lesions. Frequent self-examination is also encouraged in patients diagnosed with SCC for early detection of similar skin lesions and regional lymphadenopathy.

Conclusions

In SOTRs, NMSC is still a substantial problem. Older patients and those with prolonged graft survival have a greater risk of developing skin cancers. The incidence of skin cancer in our patients was associated with immunosuppression treatment and other risk factors that are in accordance with the literature. The incidence of NMSC in SOTR patients at Baskent University Hospital is lower than that described elsewhere. At our center, the most common type of skin cancer differs from that shown in international studies. Transplant recipients should be offered full information on the potential risk of sun exposure. Any suspicious lesion should be biopsied and treated according to histologic analyses. Transplant patients should be followed regularly for early detection and treatment of evolving skin cancers. This necessitates a multidisciplinary approach involving dermatologist, plastic surgeon, surgical oncologist, pathologist, and the transplant team.

References

Descemet Membrane Endothelial Keratoplasty: Outcomes in the First Year of Experience

Dilek D. Altınörs, Leyla Asena

Abstract

Objectives: We aimed to report the clinical outcomes of Descemet membrane endothelial keratoplasty in our first year of experience.

Materials and Methods: Patients who underwent Descemet membrane endothelial keratoplasty at the Baskent University Faculty of Medicine, Department of Ophthalmology, between 2015 and 2016 were included in the study. Patient demographics, cause of endothelial dysfunction, best-corrected visual acuity, central corneal thickness, graft survival, follow-up duration, and intraoperative and postoperative complications were recorded.

Results: Five eyes of 5 patients (4 female, 1 male) with a mean age of 53.4 ± 12.7 years were included. Cause of endothelial dysfunction included corneal endothelial dystrophy in 3 patients, pseudophakic bullous keratopathy in 1 patient, and endothelial graft failure after previous penetrating keratoplasty in 1 patient. Pre-stripped Descemet membranes obtained from the Ankara State Hospital Eye Bank were used. Mean duration of postoperative follow-up was 7.4 ± 3.7 months. Mean preoperative Snellen best-corrected visual acuity and central corneal thickness were 0.24 ± 0.15 and 625.5 ± 97.4 μm. Mean best-corrected visual acuity increased to 0.67 ± 0.26 (P = .02) in the first month and to 0.84 ± 0.11 (P < .01) at the end of follow-up. Mean central corneal thickness decreased to 546.6 ± 28.4 μm (P = .03). Graft detachment was observed in 1 patient on the first postoperative day, and it was reattached successfully by injection of air into the anterior chamber. There were no intraoperative complications. All corneas were clear at the end of follow-up.

Conclusions: Descemet membrane endothelial keratoplasty provides a new and exciting option for endothelial transplant and has the potential to become the primary procedure for surgical management of Fuchs endothelial dystrophy and corneal endothelial disease. Rapid visual rehabilitation with few and manageable complications and good visual outcomes are the major advantages of this procedure.

Key words: Corneal endothelial dystrophy, Endothelial dysfunction, Endothelial keratoplasty, Visual acuity

Introduction

Lamellar keratoplasty techniques have significantly evolved over the past decade, and endothelial keratoplasty has become the preferred technique in patients with corneal endothelial dysfunction. Selectively replacing damaged endothelial cells leads to a more rapid visual recovery, better refractive outcome, and superior tectonic integrity compared with traditional full-thickness or penetrating keratoplasty.1-3 Over the years, endothelial keratoplasty techniques have also evolved to be more selective in the layers of corneal replacement. In deep lamellar endothelial keratoplasty, a stromal layer is transplanted in addition to the Descemet membrane and the endothelium.3 In Descemet stripping endothelial keratoplasty, the transplanted stromal layer is thinner than with deep lamellar endothelial keratoplasty, and, in Descemet membrane endothelial keratoplasty (DMEK), only the endothelium and Descemet membrane are replaced. Descemet membrane endothelial keratoplasty is a relatively new partial-thickness cornea transplant procedure. It was first described by Melles and associates, and the same group published a case of a patient who achieved 20/20 visual acuity at week 1 with DMEK in 2006.4 Descemet membrane endothelial keratoplasty offers the most rapid visual rehabilitation of any keratoplasty technique to date.5
can be outstanding due to minimal optical interface effects. Because less tissue is transplanted, there is lower risk of allograft rejection and less long-term reliance on topical steroids than other types of keratoplasty. Indications for DMEK include corneal endothelial dystrophies (such as Fuchs corneal dystrophy and posterior polymorphous corneal dystrophy), pseudophakic bullous keratopathy, and other causes of corneal endothelial dysfunction.

Challenges in performing DMEK remain because it is technically more difficult to perform and has a steeper learning curve. Successful and reliable retrieval of the donor graft, intraocular placement and positioning of the graft, and postoperative management to ensure successful attachment of the graft to the recipient cornea are all challenging steps, even for an experienced corneal transplant surgeon. The aim of this study was to report the clinical outcomes of DMEK in our first year of experience.

Materials and Methods

Patients who underwent DMEK at Baskent University Faculty of Medicine, Department of Ophthalmology, between 2015 and 2016 were included in this retrospective chart review. The study was approved by the Ethical Board of Baskent University Faculty of Medicine. All surgeries were performed by the same experienced corneal transplant surgeon (DDA). The standardized “no-touch” DMEK surgery technique was used.7 Informed consent was obtained from all patients. Patient demographics, cause of endothelial dysfunction, pre- and postoperative best-corrected visual acuity (BCVA), central corneal thickness (CCT), graft survival, duration of follow-up, and intraoperative and postoperative complications were recorded.

Results

Five eyes of 5 patients (4 female, 1 male) with a mean age of 53.4 ± 12.7 years were included. Cause of endothelial dysfunction included corneal endothelial dystrophy in 3 patients, pseudophakic bullous keratopathy in 1 patient, and endothelial graft failure after previous penetrating keratoplasty in 1 patient. Pre-stripped Descemet membranes obtained from the Ankara State Hospital Eye Bank were used. Mean duration of postoperative follow-up was 7.4 ± 3.7 months. Mean preoperative Snellen BCVA and CCT were 0.24 ± 0.15 and 625.5 ± 97.4 μm. Mean BCVA increased to 0.67 ± 0.26 (P = .02) in the first month and to 0.84 ± 0.11 (P < .01) at the end of follow up. The visual acuity increased in 4 eyes (80%) and remained unchanged in 1 eye (20%). Mean CCT decreased to 546.6 ± 28.4 μm (P = .03) at the end of follow-up. Graft detachment was observed in 1 case on the first postoperative day, and it was reattached successfully by injection of air into the anterior chamber. There were no intraoperative complications. All corneas were clear at the end of follow-up. Figure 1 shows pre- and postoperative anterior segment photographs of a patient with an endothelial graft failure after previous penetrating keratoplasty who underwent a successful DMEK surgery. The cornea was clear at month 6 of follow-up, and the Snellen BCVA increased from 0.1 to 0.9 at month 6.

Discussion

In our retrospective study, we evaluated the 6-month clinical outcomes of the first 5 DMEK procedures performed by an experienced corneal transplant surgeon. Our report suggests that good visual
outcomes and clear grafts can be obtained with current DMEK technique(s), even during the first stages of the learning curve. Descemet membrane endothelial keratoplasty surgery techniques have significantly evolved since the first case reported in 2006. In a recent study reporting the 6-month clinical outcomes of a large cohort of DMEK eyes operated by 55 starting or experienced surgeons, BCVA improved in 90.5% of eyes, remained unchanged in 4.6%, and deteriorated in 4.9%. Similarly, in our study, visual acuity increased in 4 eyes (80%) and remained unchanged in 1 eye (20%).

It has been reported that graft detachment (partial or complete) remains the most common complication of DMEK surgery, which is most commonly observed in the early postoperative period, with incidence decreasing with increased experience of the surgeon. Partial detachment was also the most common, as well as the only, complication in our study. This complication was treated successfully with a single air injection into the anterior chamber to facilitate visual recovery. The reported rates of partial detachment of DMEK tissues that required air injection range from 9% to 82%. Often, small detachment at the periphery does not affect final visual acuity and could reattach spontaneously. The air injection rate in our study, which was 20%, is also within the published range.

We evaluated the CCT as an indicator of corneal endothelial function. In our study, CCT significantly decreased from 625.5 ± 97.4 μm preoperatively to 546.6 ± 28.4 μm at postoperative month 6. There was roughly a 13% decrease in CCT at month 6. In a recent study, which evaluated the clinical outcomes of 500 consecutive cases up to 2 years after DMEK, a 20 ± 11% decrease in CCT was observed at 6 months postoperatively and CCT remained stable thereafter. In another study, which reported the results of the first 40 consecutive cases of the same surgeon, mean CCT decreased from 624 ± 40 μm preoperatively to 513 ± 34 μm postoperatively, which is similar to our results.

As a result, DMEK provides a new and exciting option for endothelial transplant and has the potential to become the primary procedure for surgical management of Fuchs endothelial dystrophy and corneal endothelial disease. Rapid visual rehabilitation with few and manageable complications and good visual outcomes are the major advantages of this procedure.

References
Experience With Cardiac Implantable Electrical Device Explantation After Cardiac Transplantation: A Report of 16 Cases From a Single Center in a Period of 5 Years

Orçun Çiftci,1 Kerem Can Yılmaz,1 Atilla Sezgin,2 Mehmet Bülent Özün,1 İbrahim Haldun Müderrisoğlu,İ Mehmet Haberal3

Abstract

Objectives: Cardiac implantable electrical devices are widely used for patients with advanced heart failure and are usually explanted during orthotopic heart transplant. However, lead fragments and the pulse generator are sometimes left after the procedure. Given the concerns of infectious and thromboembolic complications, their removal is recommended. Herein, we report our experience with cardiac implantable electrical device explantation after orthotopic heart transplant.

Materials and Methods: We included recipients of heart transplants performed at Başkent University Faculty of Medicine, Department of Cardiovascular Surgery, who underwent lead and pulse generator explantation by manual traction between January 2012 and June 2017. We analyzed patient demographic, clinical, biochemical, and treatment properties.

Results: Sixteen patients (11 males, 5 females) with a median age of 45 years (range, 18-52 y) were included. Two patients (12.5%) died during follow-up but not secondary to device explantation. All patients were using immunosuppressives and 50% were receiving antiplatelet/anticoagulant agents. All pulse generators were located at the left prepectoral area, with tips of lead fragments in the superior vena cava or left subclavian vein. No procedural complications were observed. Aspirin was continued uninterrupted perioperatively, warfarin was stopped 2 days before the procedure, and low-molecular-weight heparins were skipped on the morning and evening of the procedure. One patient (6.3%) complained of postoperative pain, and another (6.3%) developed a pocket hematoma, which was treated conservatively. No patient developed fever, clinical infection, or major bleeding. Preoperative and postoperative levels of hemoglobin, white blood cells, and C-reactive protein were similar. No demographic, procedural, or biochemical variable was significantly correlated with postprocedural complications.

Conclusions: In our cohort, explantation of lead fragments and pulse generators of cardiac implantable electrical devices was safe after heart transplant. It appears that neither antiplatelet/anticoagulant agents nor immunosuppressives seem to put patients at increased risk of postoperative complications.

Key words: Explantation, Implantable electrical device, Orthotopic heart transplantation

Introduction

Cardiac transplant is a life-saving procedure in patients with end-stage heart failure due to various causes, including ischemic cardiomyopathy, dilated cardiomyopathy, fulminant myocarditis, and various other cardiomyopathy types. Cardiac transplant candidates usually undergo cardiac electrical device implantation before transplant. Most of these devices are implantable cardioverter defibrillators (ICD) and biventricular pacemakers with dual defibrillation coils in the right ventricular apex and the superior vena cava. After cardiac transplant, these devices become obsolete, and the implanted device is usually removed together with the leads during orthotopic heart transplant. In as many as 39% of patients, however, pacemaker and ICD leads are transected at the level of the superior vena cava and subclavian veins and left in situ. Although challenged by recent data, these fragments are usually seen as a source of thromboembolism, infection, and sepsis. Furthermore, these fragments...
and pulse generators, when they are not magnetic resonance imaging (MRI)-conditional, may preclude use of MRIs. Therefore, it is usually recommended to explant these fragments as soon as possible after cardiac transplant. Lead fragment explantation can be accomplished by manual traction or special lead extraction systems. Lead fragment extraction can be sometimes quite problematic, even leading to serious complications. Data on the complications and postoperative course of cardiac implantable electrical device (CIED) fragment explantation after orthotopic heart transplant are limited. Here, we report our experience with CIED explantation in patients who received heart transplants at our institution.

Materials and Methods

This study was approved by the local ethics committee of our university and conducted in accordance with the Helsinki Declaration. We retrospectively reviewed the medical records of cardiac transplant patients who underwent manual explantation of CIEDs under local anesthesia at the cardiac angiography laboratory between January 2012 and June 2017. We recorded the demographic properties and anticoagulants and immunosuppressives used at the time of device explantation as well as survival status, time from cardiac transplant to device explantation, time from cardiac device implantation to explantation, complications of device explantation, retained lead parts after explantation, preoperative and postoperative hemoglobin levels, C-reactive protein (CRP) levels, white blood cell and platelet counts, preoperative creatinine levels, and international normalized ratio.

Postoperative complications included bleeding at the site of pulse-generator pocket or any vascular bleeding; pain, inflammation, or infection at the pacemaker pocket site; sepsis; vascular or cardiac injury or perforation; pneumo/hemothorax, and methemoglobinemia due to local anesthetic. Major bleeding was defined as any intracranial bleeding, clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL or a ≥ 15% absolute decrease in hematocrit, or fatal bleeding (bleeding that directly results in death within 7 d). Minor bleeding was defined as clinically overt bleeding (including imaging) resulting in hemoglobin drop of 3 to < 5 g/dL or ≥ 10% decrease in hematocrit, no observed blood loss, and ≥ 4 g/dL decrease in the hemoglobin concentration or ≥ 12% decrease in hematocrit. Minor bleeding also included any overt sign of hemorrhage that did not meet criteria for a major or minor bleeding event, as defined above, but that required intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) and that led to hospitalization or prolonged hospitalization or that prompted evaluation (leading to an unscheduled visit to a health care professional and diagnostic testing, either laboratory or imaging). Minimal bleeding was defined as any overt bleeding event that did not meet the criteria above and in which no clinically overt signs of hemorrhage (including with imaging) were shown and that was associated with a < 3 g/dL decrease in hemoglobin concentration or < 9% decrease in hematocrit.

Descriptive results of demographic, procedural, or biochemical variables are shown as median and interquartile range for continuous variables or number (percent) for categoric variables. The demographic, procedural, or biochemical variables were correlated with the rate of postprocedural complications. We compared preoperative and postoperative 24-hour hemoglobin levels, CRP levels, white blood cell count, and body temperature with each other using the Wilcoxon test.

Results

Our study group included 16 patients with a median age of 45 years (18-52 y). Of these, 5 (31.2%) were female and 11 (68.8%) were male. Two patients (12.5%) died during follow-up, although death was not secondary to device explantation. Most patients (81.3%) had nonischemic dilated cardiomyopathy before transplant. All patients were using immunosuppressives, and all but 2 were receiving steroids at the time of the procedure (Table 1).

All pulse generators were located at the left prepectoral area, with tips of lead fragments remaining in the superior vena cava or left subclavian vein (Figure 1). All pulse generators were reached through a surgical incision at the left prepectoral area, and retained lead fragments were extracted by simple manual traction. No special lead extraction system was used. No procedural complications of device
explantation and no deaths were observed. No device part was retained after the procedure.

Regarding antiplatelet and anticoagulant agents, 5 patients (31.3%) were using aspirin, 1 patient (6.3%) was using warfarin, and 2 patients (12.5%) were using low-molecular-weight heparin (LMWH) before the procedure. All patients on aspirin continued that medication uninterrupted perioperatively. The patient taking warfarin stopped the drug 2 days before and entered the procedure with an international normalized ratio of 1.96 and experienced no bleeding complication. Those taking LMWH skipped their injections on the morning and evening of the procedure and resumed the next morning. At the postoperative period, 1 patient (6.3%) complained of pain, which responded to paracetamol, and another patient (6.3%) who was taking LMWH developed pocket hematoma at the pacemaker pocket site, which was conservatively treated.

No patients developed fever or clinical infection, and no patients experienced major bleeding that necessitated red blood cell transfusion after the procedure. The median hemoglobin drop was 0.5 g/dL (0.0-1.0 g/dL), and the median white blood cell increase was 3.1 × 10^3/μL (0.2-3.9 × 10^3/μL). The median CRP increase was 1.65 mg/dL (-68 to 59 mg/dL) among 4 patients for whom preoperative and postoperative CRP values were obtained. There were no significant differences between preoperative and postoperative hemoglobin, white blood cell, and CRP levels (Table 2). No demographic, procedural, or biochemical parameters were correlated with procedural complications. Use of anticoagulant, antiplatelet agent, or immunosuppressives was not found to confer any significant risk for postoperative bleeding or infection.

**Discussion**

Cardiac implantable electrical devices, particularly biventricular pacemakers and ICDs, which are implanted in patients with end-stage heart failure destined to undergo orthotopic heart transplant, are usually explanted at the time of the transplant procedure. Nevertheless, some leads are left in situ in central veins, namely, the superior vena cava and subclavian vein. The superior vena cava shock coils of the ICD leads are particularly prone to fibrous ingrowth and adherence to vessel wall, resulting in surgeons leaving them in place. Although recently challenged by some studies, we and others explant CIEDs as soon as possible after heart transplant due

---

**Table 1. General Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
<th>Median (minimum to maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men)</td>
<td>11 (68.8%)</td>
<td></td>
</tr>
<tr>
<td>Age at CIED explantation, years</td>
<td>40 (18-44)</td>
<td></td>
</tr>
<tr>
<td>Device type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual-coil ICD</td>
<td>14 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Biventricular pacemaker</td>
<td>2 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Time from CIED implantation to</td>
<td>13 (8-36)</td>
<td></td>
</tr>
<tr>
<td>explantation, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surviving patients</td>
<td>14 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Cause of heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart failure</td>
<td>14 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
<td>2 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Smoking (active or former)</td>
<td>7 (43.8%)</td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>4 (25%)</td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>1 (6.25%)</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>13 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>MMF</td>
<td>15 (93.7%)</td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>14 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>5 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>2 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>NOAC</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Comparison of Preoperative and Postoperative Hemoglobin, Leucocyte, and C-Reactive Protein Levels**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median Preoperative Level (IQR)</th>
<th>Median Postoperative Level (IQR)</th>
<th>P Value (Wilcoxon test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12 (2)</td>
<td>11.7 (1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Leucocyte count, × 10^5</td>
<td>8.6 (2.9)</td>
<td>11.1 (3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>CRP mg/dL</td>
<td>5.0 (160.6)</td>
<td>23.5 (147.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASA, acetylsalicylic acid; CIED, cardiac implantable electrical device; CVA, cerebrovascular accident; ICD, implantable cardioverter defibrillator; LMWH, low-molecular-weight heparin; MMF, mycophenolate mofetil; NOAC, novel oral anticoagulants (thrombin or factor X inhibitors); UFH, unfractionated heparin

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**Figure 1.** Chest Radiography Before and After Device Extraction Showing Successful Cardiac Implantable Electrical Device Extraction Procedure and No Retained Fragment in Central Venous System
to the traditional concerns about intravascular or endocardial infection or thrombosis. Moreover, the theoretical need of heart transplant recipients to undergo MRIs for a variety of indications makes the explantation of most non-MRI conditional generators and lead fragments necessary.

In our study group, we applied manual traction and used no special extraction systems for the intravascular parts of the lead fragments. We observed no major complication of the explantation of pulse generators and retained lead fragments of previously implanted CIEDs. Although a drop in hemoglobin and increase in white blood cell count and CRP levels occurred, these levels were not statistically significant. Furthermore, no biochemical, clinical, or procedural variables were associated with postoperative complications. Our results suggest that manual extraction of lead fragments can be safely accomplished, with no parts retained in the vasculature.

Previous studies of CIED explantation using both manual extraction and percutaneous extraction systems have also indicated a low complication risk, with adverse events being mostly located in the pulse-generator pocket and occurring at a rate of 0 to 3.4%. We also observed no increase in the rate of infectious complications despite the fact that all patients were using immunosuppressives. This suggests that, once foreign bodies are explanted, the risk of infection is negligible. We also observed only one pacemaker pocket hematoma, which required no surgical evacuation and was treated conservatively and in a patient who required anticoagulants with LMWH, which was stopped on the morning of the procedure. However, we suggest that risks of pocket hematoma are related to inadequate procedural hemostasis rather than anticoagulants. Therefore, we meticulously check for vascular bleeding during the procedure and use cauterization liberally to avoid any bleeding once the procedure is over.

Our study has some limitations. First, it was retrospective study with a small sample size. Second, we did not apply special percutaneous lead extraction systems but extracted all lead fragments and other CIED parts manually. Therefore, we could not convey any experience with percutaneous lead extraction systems.

In conclusion, explantation of the remnants of CIEDs after heart transplant was a safe procedure with low morbidity and mortality risk in our cohort. It appears that, when antiplatelet agents and anticoagulants are managed appropriately, they cause no excess bleeding. Taking immunosuppressives or steroids do not seem to put patients at risk of postoperative infective complications.

References

The Economics of Organ Transplantation

Nur Altnörs,1 Mehmet Haberal2

Abstract

To determine the cost effectiveness of transplantation, we analyzed the financial economics of the organ and tissue transplant process. We compared the cost of this process with traditional modalities for treating end-stage liver and kidney disease. Medical, surgical, legal, social, ethical, and religious issues are important in organ transplant procedures. Government, health insurance companies, and uninsured individuals are affected by the financial economics of organ transplantation. The distribution of financial burden differs among countries and is dependent on the unique circumstances of each country.

Key words: Economy, Finance, Hemodialysis, Kidney transplant, Liver transplant

Introduction

The gap between supply and demand is a universal problem for organ and tissue transplantation. In some countries, transplant access is further hampered by financial obstacles. Financial costs include transplant evaluation and testing, organ procurement, transplant surgery, recipient postoperative medical care and immunosuppressive therapy, and those related to donation. In the United States (US), elderly patients > 65 years of age represent more than 25% of all transplant recipients. Kidney transplant in the elderly is associated with a marked increase in the incidence of perioperative complications and extended length of stay, which incur extra costs.1

Discussion

Health service financing systems differ among countries. In the US, insurance status and personal ability to pay significantly affect access to transplant because these procedures are expensive and the United States lacks universal health insurance for all citizens.2 Decreasing financial barriers to organ transplant may increase the number of transplantable organs from donors.3

Rodrique and associates4 conducted a multicenter prospective study, known as the Kidney Donor Outcomes Cohort Study, in which they collected cost data for 12 months following donation from 182 living kidney donors (LKDs). Most LKDs (n = 167 or 92%) incurred 1 or more direct cost following donation, including ground transportation (86%), health care (41%), meals (53%), medications (36%), lodging (23%), and air transportation (12%). Living kidney donors missed 33 072 total work hours, 40% of which were unpaid, resulting in $302 175 in lost wages (mean $1660). Caregivers lost $68 655 in wages (mean $377). Although some donors received financial assistance, 89% had a net financial loss over the 12-month period, with 33% reporting a loss exceeding $2500. Financial burden was greater for those with farther distance traveled to the transplant center, lower household income, and more unpaid work hours missed.

A study in the US reported the estimated costs of various organ transplants as of 2017. These were $414 800 for kidney and $812500 for liver transplants. Cornea transplants were the least expensive, costing $30 200, while heart transplants were the most expensive at $1 382 400.5 In comparison, the cost for 1 transplant patient in Serbia over a 10-year period is €48 949 (about $40 089).6

It has been estimated that, based on a mean wait time for a kidney transplant of 49 months, private payers spend $250 000 to $400 000 on end-stage renal
disease care over the first 33 months. When Medicare is the second insurer, Medicare spends nearly $100,000 for the additional 16 months during which it is the primary payer. In the US, the direct costs of dialysis exceed $73,000 per year per patient under the Medicare system, whereas private payments can be nearly double that amount.

A study from Japan that analyzed the cost of transplant reported that living-donor liver transplant was the most expensive transplant procedure at a total cost of ¥4,950 million or nearly $40,000. The cost of deceased-donor renal transplant was higher than the cost of living-donor renal transplant procedures: ¥3,690 million versus ¥3,550 million or $32,654 versus $31,416, respectively. The study also found that recipients of auto-pancreatic blood stem cell transplant complicated by graft-versus-host disease, urinary tract infection, sepsis, or pneumonia had a significantly higher average total cost during the month of transplant and the 2 following months than patients without, in addition to statistically more total treatment days.

Total additional costs of ancillary transplant activities were determined by comparing the cost of kidney transplant from living donors versus deceased donors in France. Additional transplant costs varied from €13,835 to €20,050 for a deceased donor compared with €13,601 for a living donor.9

Turri and associates10 evaluated the total cost of a patient on a wait list for liver transplant and the main resources related to higher costs. They found that patients on wait lists for liver transplant were subjected to many complications and incurrences that led to hospitalization and procedures that increased costs. They concluded that the patient’s wait list cost for liver transplant increased as the patient’s severity increased. Procedures related to treatment of hepatocellular carcinoma, the use of blood components, and hospitalization were the main cost drivers.

Rancic and associates11 performed a literature review to analyze the economic feasibility of pharmacogenetic testing in renal transplant patients. Sources from the US reported that the total cost per renal transplant was $343,300 in 2014. The authors concluded that a specific suggestion could not be made regarding use of therapeutic drug monitoring due to a lack of sufficient cost-effectiveness studies on this subject. In England, treatment of chronic renal disease comprises 1.3% of health care-related expenses.

Regardless of the source (ie, deceased, living-related, living-unrelated, or altruistic donor), the supply of kidneys does not meet the demand. It is estimated that 6.3% of kidney transplant candidates die while on a wait list.12 Patient survival and graft survival are inversely related to length of time on dialysis.13-15 The annual death rate for all patients on dialysis was 16.1%. The relative risk of death during the first 2 weeks after transplant was 2.8 times greater than that for patients on dialysis with similar follow-up time since wait list placement.16

In many countries, organs are being bought and sold illegally. To prevent uncontrolled trade of organs and to increase the frequency of transplant activities, it has been proposed that a regulated system of kidney sales, with a fixed price for vendors, would reduce the mortality rate of patients on wait lists. Matas and associates17 determined the most cost-effective payment amount for society and what costs would be saved by removing a patient from a wait list using a paid donor-vendor: a living-unrelated donor transplant saved $94,579, and 3.5 quality-adjusted life-years (QALY) were gained. In the illegal organ markets, kidney transplants (including certified organs) would cost about $20,000.18

Iran started a compensated and regulated living-unrelated kidney donation program in 1988 with considerable success. More than 59% of patients with end-stage kidney disease in Iran are living with a functioning graft.19 Despite being exemplary for some time, the Iranian model has serious ethical problems and it is no longer regarded as a sustainable and ethically justified system.19,20

The idea of a regulated paid organ system has been criticized. Kahn and Delmonico21 reported that the ethics of organ sales should precede any analysis of the economic and practical value. They also suggested that development of a regulated system in the Western world would encourage the development elsewhere of unregulated systems without protection for vendors. The authors also expressed their concern regarding harm to the doctor-patient relationship.

In 2014, 120,000 organs were transplanted throughout the world, with 10% performed illegally. Two-thirds of these illegal transplants were kidney, followed by liver, heart, lung, and pancreas. Illicit organ trafficking is estimated to generate $840 million to $1.7 billion annually. Most vendors are young individuals from developing or underdeveloped countries.22

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regions, whereas the recipients are middle-aged patients with mid-to-high income from developed countries. Worldwide, 21 people die every day on average due to not being able to find a donor.\textsuperscript{22}

Organ sales are strictly forbidden by law in Turkey. Organ commerce advertisers, organ buyers, and organ sellers and brokers are punished by 9 years of imprisonment. In the case of organized crime, the penalty is 15 years of imprisonment. Turkish legislation permits living-related donors up to fourth-degree blood relatives. Unrelated-living donor candidate files are brought to the city ethics committee for a final decision.

In Turkey, the Social Security Association (Sosyal Güvenlik Kurumu; SGK) covers all employees working in state and private sectors. The system covers most of the population; individuals under the SGK umbrella have the right to free transplant procedures. No extra payment can be requested, even by private hospitals and private universities. Under defined conditions for transplant, SGK has authorized some departments to refer patients abroad for transplant to 3 centers for lung, 13 centers for heart, 30 centers for liver, 6 centers for intestine, 3 centers for pancreas, 16 centers for pediatric bone marrow, and 32 centers for adult bone marrow transplant procedures. The Başkent University Ankara and Adana hospitals are authorized to make referrals abroad for kidney, liver, and adult bone marrow transplant. Istanbul hospital is authorized for abroad kidney referral only.\textsuperscript{23}

In Turkey, 3423 kidneys, 1396 livers, 69 hearts, 22 lungs, 6 pancreases, and 5 ileums were transplanted in 2016. Payments made by national health care for various transplants are shown in Table 1. In Turkey, it is estimated that 71 000 individuals have end-stage renal disease, and 60 000 of these patients receive hemodialysis treatment. Hemodialysis constitutes 79\% of all the chronic treatment modalities for chronic renal disease. The number of patients on kidney transplant wait lists is over 23 000. Hemodialysis expenses per patient are approximately $25 000 each year, and the total cost of hemodialysis treatment is $1 billion annually.

Yiğit and Erdem\textsuperscript{24} researched the cost-effectiveness of hemodialysis, peritoneal dialysis, and kidney transplant. The SGK budget for these treatment modality costs, life-years, and QALY were calculated using a Markov model. They found that the costs were ₺29.592 for hemodialysis, ₺29.061 for peritoneal dialysis, and ₺51.279 in the first year after transplant and ₺8.654 in the second and subsequent years. A transplant is cost-effective compared with both hemodialysis and peritoneal dialyses. The cost of these 3 treatment methods was ₺2.047.633.644 in 2012 in Turkey. In fact, 4.64\% of the SGK’s total health expenditure is estimated to be spent on hemodialysis, peritoneal dialysis, and transplant treatment.

### Table 1. Payments Made by the Turkish Social Security Association for Different Types of Organ Transplants

<table>
<thead>
<tr>
<th>Organ Transplanted</th>
<th>Turkish Lira ($)</th>
<th>US Dollar ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>132079.32</td>
<td>36888</td>
</tr>
<tr>
<td>Heart and lung</td>
<td>155817.88</td>
<td>43282</td>
</tr>
<tr>
<td>Lung, global</td>
<td>155817.88</td>
<td>43282</td>
</tr>
<tr>
<td>Liver</td>
<td>129848.23</td>
<td>36068</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23709.95</td>
<td>6585</td>
</tr>
<tr>
<td>Kidney</td>
<td>52276.56</td>
<td>14521</td>
</tr>
<tr>
<td>Cornea</td>
<td>2443.89</td>
<td>678</td>
</tr>
<tr>
<td>Extremity, single</td>
<td>64924.11</td>
<td>18034</td>
</tr>
<tr>
<td>Face</td>
<td>70826</td>
<td>19673</td>
</tr>
<tr>
<td>Umbilical blood</td>
<td>151132.65</td>
<td>41981</td>
</tr>
<tr>
<td>Hematopoietic cell, related donor, HLA compatible</td>
<td>77585.44</td>
<td>21551</td>
</tr>
<tr>
<td>Hematopoietic cell, non-related donor, HLA compatible</td>
<td>151132.65</td>
<td>42106</td>
</tr>
</tbody>
</table>

Abbreviations: HLA, human leukocyte antigen, US, United States

Nations allocate an important portion of their budget to health care. Nationwide studies are needed to compare the cost-effectiveness of organ transplant compared with conservative treatment during the transplant waiting period. Major complications that lengthen hospital stay, and consequently increase the cost, should be analyzed. In countries without national health insurance, access to transplant procedures is highly limited, creating ethical issues. As financial barriers to organ transplant are reduced, an increase in transplantable organs is expected.\textsuperscript{3} Living-donor transplant shortens dialysis exposure and increases the number of kidney transplants and is cost-effective due to the lower cost per life gained by kidney transplant.

### References


Influence of Social, Economic, Familial, Marital Status, and Disease Adaptation on the Physical and Mental Health Dimensions of Patients Who Are Candidates for Renal Transplant

Aydan Akyüz Özdemir, Cihat Burak Sayın, Rengin Erdal, Cihangir Özcan, Mehmet Haberal

Abstract

Objectives: End-stage renal disease is a disease with a long duration, requiring patients to live with the limitations imposed by their condition. Stressors associated with this disease are demanding, with patients dependent on support from their social environment. Here, we aimed to show the influences of familial, social, economic, and marital status on quality of life in patients with end-stage renal disease.

Materials and Methods: Patients (190 women/188 men) who were under hemodialysis treatment and on transplant wait lists were included in the study. To evaluate the quality of life, patients completed the Short Form 36 health survey questionnaire voluntarily while undergoing hemodialysis treatment. All Short Form 36 questionnaire components were analyzed separately, and all social, economic, and business life dimensions were examined with another questionnaire.

Results: Significant differences were observed between single and married patients regarding physical and mental health dimensions ($P < .001$), with quality of life higher in single patients than in married. Patients who lived in villages had lower health quality than patients who resided in cities or towns ($P < .01$). Patients who were home owners and who had a job had higher degrees of health quality than those who did not ($P < .01$). The lowest Short Form 36 scores were in housewives and farmers ($P < .001$). Comparisons between patients who went home after hemodialysis versus those who went to work showed better Short Form 36 scores in working patients ($P < .001$). Patients with private insurance and family support had better Short Form 36 scores ($P < .001$). Patients who did not comply with their doctor and dietician showed the lowest health quality ($P < .05$). Regular or irregular drug use did not affect scores.

Conclusions: Familial, social, economic, and marital statuses, in addition to the influence of disease adaptation, independently affected the well-being of patients with end-stage renal disease.

Key words: End-stage renal disease, Hemodialysis, Quality of life, Social life, Working status

Introduction

End-stage renal disease (ESRD) is a disease with a long duration in which patients are required to live with limitations imposed by their condition. The only treatment, hemodialysis, restricts the life of the patient and brings physical, psychological, social, and economic problems.1-9 While patients adapt to this new life, challenges occur.1,5,9-12 The primary problem is the hemodialysis treatment itself. The unquestionable frequency of the therapy, diet obligations, and having to go to the hospital or hemodialysis center 2 or 3 times per week are obstacles for the patient.9,12-14 Sexual dysfunction, job and financial losses, continual illness, insomnia, and dependency on health care personnel increase patient stress.9,12-21 When these factors are added, the adaptation process of the patient is damaged, resulting in decreased quality of life (QOL).1,8,10,12,16,17

Over the course of ESRD, psychiatric problems can occur in patients. The most common mental problems include depression, anxiety, dissonance, insomnia, suicidal behaviors, psychosis, and difficulty of rehabilitation. Psychological issues combined with restricted life dimensions may lead patients to not follow diet requirements, not
communicate with doctors, not follow drug use
guidelines, abandon hemodialysis sessions, and lash
out verbally or physically toward health care
personnel. The degree of these behaviors may change
according to the patient’s premorbid character, the
level of support from family and friends, and the
features of underlying illness.8,9,12,13,15-21

Starting from the day a patient receives the
diagnosis, the QOL is affected by stressors associated
with ESRD.22,23 For QOL to be obtained in patients
with chronic illness at reasonable levels, both
psychological support and social support are needed.
Family support is especially vital because of the
compulsive nature of the illness and treatment. In this
study, we aimed to show the influences of familial,
social, economic, and marital status on quality of life
in ESRD patients.

Materials and Methods

The study was conducted at the Başkent University
Ankara, Istanbul, and Adana hemodialysis centers. All
patients completed the Short Form 36 (SF-36) health
survey questionnaire voluntarily while undergoing
hemodialysis treatment to evaluate quality of life.
Patients completed the questionnaire at minute 45 of
hemodialysis under the advice of nephrologists.
Because hemodialysis is a treatment that achieves the
extracorporeal removal of waste products, such as
creatinine and urea and free water from the blood, the
patient’s psychological and physical condition does
not allow answering the questionnaire forms. After 30
minutes of hemodialysis, the emotional mood of the
patient becomes much more regular and more
energetic. With the completion of questionnaires at the
same time, at minute 45, we suggest that errors could
be minimized.

All components (Physical Functioning, Psychological Functioning, General Health, Global) of the SF-36 questionnaire were analyzed separately, and its scales and dimensions were scored as a number between 0 and 100. All social, economic, and business life dimensions were examined with another questionnaire.

Results

We included 378 patients (190 females/188 males,
50.26% and 49.74%, respectively) who were under-
going hemodialysis treatment and on transplant wait

<table>
<thead>
<tr>
<th>Table 1. Distribution of Patients According to Level of Education, Marital Status, and Working Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of education (P &lt; .001)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Literate/primary school</td>
</tr>
<tr>
<td>Secondary school</td>
</tr>
<tr>
<td>High school</td>
</tr>
<tr>
<td>University</td>
</tr>
<tr>
<td>Marital status (P &lt; .001)</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Widowed</td>
</tr>
<tr>
<td>Working status (P &lt; .001)</td>
</tr>
<tr>
<td>Working</td>
</tr>
<tr>
<td>Not working</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Quality of Life Scores of Participating Study Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Physical Functioning</td>
</tr>
<tr>
<td>Psychological Functioning</td>
</tr>
<tr>
<td>General Health</td>
</tr>
<tr>
<td>Global Health</td>
</tr>
</tbody>
</table>
(32.2 ± 15.6) or dieticians (37.4 ± 18.9) had low QOL scores ($P < .05$; Table 4). Regular or irregular drug use of patients did not show any influence on SF-36 scores.

**Table 3. Quality of Life Scores According to Marital Status, Family Type, Working Status, Type and Place of Residence, and Occupation of the Patient**

<table>
<thead>
<tr>
<th>Marital status</th>
<th>n</th>
<th>General Health, mean ± SD</th>
<th>Physical Functioning, mean ± SD</th>
<th>Psychological Functioning, mean ± SD</th>
<th>Global Health Quality, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married</td>
<td>240</td>
<td>38.5 ± 22</td>
<td>34.6 ± 21.3</td>
<td>43.4 ± 21</td>
<td>40.4 ± 18.6</td>
</tr>
<tr>
<td>Single</td>
<td>65</td>
<td>45.5 ± 20</td>
<td>45.6 ± 24.1</td>
<td>44.1 ± 21</td>
<td>43 ± 17.8</td>
</tr>
<tr>
<td>Widowed</td>
<td>73</td>
<td>36.3 ± 22.4</td>
<td>36 ± 17.4</td>
<td>36.9 ± 21.5</td>
<td>35.4 ± 19.2</td>
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<table>
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<tr>
<th>Working status</th>
<th>n</th>
<th>General Health, mean ± SD</th>
<th>Physical Functioning, mean ± SD</th>
<th>Psychological Functioning, mean ± SD</th>
<th>Global Health Quality, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working</td>
<td>85</td>
<td>48.1 ± 21.4</td>
<td>42.7 ± 24.6</td>
<td>46.4 ± 22.8</td>
<td>44.5 ± 20.5</td>
</tr>
<tr>
<td>Not working</td>
<td>293</td>
<td>37.5 ± 21.3</td>
<td>34.2 ± 21.3</td>
<td>41.0 ± 20.5</td>
<td>39.2 ± 17.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of residence</th>
<th>n</th>
<th>General Health, mean ± SD</th>
<th>Physical Functioning, mean ± SD</th>
<th>Psychological Functioning, mean ± SD</th>
<th>Global Health Quality, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Own house</td>
<td>163</td>
<td>40.0 ± 22.6</td>
<td>35.6 ± 22.5</td>
<td>42.9 ± 23.7</td>
<td>40.9 ± 20.7</td>
</tr>
<tr>
<td>Family house</td>
<td>136</td>
<td>36.3 ± 20.5</td>
<td>33.2 ± 21.5</td>
<td>37.9 ± 17.3</td>
<td>36.6 ± 15.7</td>
</tr>
<tr>
<td>Rental</td>
<td>79</td>
<td>45.6 ± 21.2</td>
<td>42.4 ± 22.3</td>
<td>48.4 ± 20.1</td>
<td>45.7 ± 17.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupation</th>
<th>n</th>
<th>General Health, mean ± SD</th>
<th>Physical Functioning, mean ± SD</th>
<th>Psychological Functioning, mean ± SD</th>
<th>Global Health Quality, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No occupation</td>
<td>17</td>
<td>48.6 ± 20.4</td>
<td>51.8 ± 29.3</td>
<td>49.0 ± 27.7</td>
<td>46.7 ± 24.2</td>
</tr>
<tr>
<td>Farmer</td>
<td>17</td>
<td>33.8 ± 24.7</td>
<td>27.8 ± 20.3</td>
<td>37.1 ± 22.3</td>
<td>34.6 ± 22.6</td>
</tr>
<tr>
<td>Teacher</td>
<td>17</td>
<td>42.3 ± 20.1</td>
<td>43.9 ± 22.6</td>
<td>45.3 ± 21.0</td>
<td>44.5 ± 20.7</td>
</tr>
</tbody>
</table>

**Table 4. Quality of Life Scores According to Activities After Hemodialysis, Family Support, Existence of Private Insurance, and Complying With Proposals From Health Care Provider**

<table>
<thead>
<tr>
<th>Activities after hemodialysis</th>
<th>n</th>
<th>General Health, mean ± SD</th>
<th>Physical Functioning, mean ± SD</th>
<th>Psychological Functioning, mean ± SD</th>
<th>Global Health Quality, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Going to work</td>
<td>41</td>
<td>53.4 ± 20.2</td>
<td>53.9 ± 24</td>
<td>56.2 ± 23</td>
<td>53.6 ± 20</td>
</tr>
<tr>
<td>Going home</td>
<td>337</td>
<td>38.2 ± 21.4</td>
<td>33.9 ± 21.1</td>
<td>40.6 ± 20.4</td>
<td>38.7 ± 17.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family support</th>
<th>n</th>
<th>General Health, mean ± SD</th>
<th>Physical Functioning, mean ± SD</th>
<th>Psychological Functioning, mean ± SD</th>
<th>Global Health Quality, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exist</td>
<td>333</td>
<td>40.1 ± 21.5</td>
<td>36 ± 21.6</td>
<td>42.3 ± 21.1</td>
<td>40.5 ± 18.6</td>
</tr>
<tr>
<td>Do not exist</td>
<td>45</td>
<td>38.9 ± 23.6</td>
<td>36.5 ± 27.1</td>
<td>41.7 ± 21.5</td>
<td>39.6 ± 19.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health insurance type</th>
<th>n</th>
<th>General Health, mean ± SD</th>
<th>Physical Functioning, mean ± SD</th>
<th>Psychological Functioning, mean ± SD</th>
<th>Global Health Quality, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social insurance</td>
<td>375</td>
<td>39.6 ± 21.6</td>
<td>35.8 ± 22.2</td>
<td>42.1 ± 21.1</td>
<td>40.2 ± 18.6</td>
</tr>
<tr>
<td>Private insurance</td>
<td>3</td>
<td>74.1 ± 10.9</td>
<td>70.2 ± 17.5</td>
<td>60.2 ± 13.6</td>
<td>60.6 ± 12.9</td>
</tr>
</tbody>
</table>

**Discussion**

Restrictions on lifestyle occur after a chronic illness diagnosis. Life becomes harder in patients diagnosed with ESRD. When the nature of the illness and hemodialysis treatment are added, these can result in a challenging and dependent life. To sustain quality of life in ESRD patients, social support is as necessary as medical care. Although the QOL of ESRD patients has been previously studied, there is a lack of studies on social aspects influencing QOL of the ESRD patients.

The effects of marital status on QOL of HD patients have been previously reported and have stated that further studies are required. Although an opposite result is expected, similar to previous studies, we also found that single patients had higher QOL scores than married ones. Higher QOL of single patients may be explained by lack of family responsibilities. In the married patient, dependency due to illness and treatment colliding with liabilities of a spouse and children may lower QOL. The autonomy of single patients in the self-care process should also be considered.

The place where the patient lives has an undeniable affect on QOL. Having a hemodialysis center within a close distance is a must and the obligation of going to hospitals 2 or 3 times per week brings the importance of public transportation. The QOL of participants of this study confirmed this with the changing results of SF-36 scores. Patients living in cities or towns have significantly lower SF-36 scores than those living in cities or towns. This is not a surprising result due to the obligations of ESRD patients undergoing hemodialysis. Because there is no scientific evidence regarding the meaning of these results, we suggest that the absence of hemodialysis centers and health facilities in villages may have caused more problems during treatment, resulting in decreased QOL. Further studies should be done to address the effects of living conditions on QOL of patients undergoing hemodialysis.

An unexpected result concerned the type of residence of the patient, that is, whether patients lived in their own house or lived in a rented home. The expected result was higher QOL scores in ESRD patients living at an owned home or living with their family. In contrast, patients living in rented houses had significantly higher SF-36 scores. Further studies...
should be designed to find reasons determining this result.

Quality of life in working patients was significantly higher than in other patients. As an expected result, it can be suggested that working patients are not focusing on their illnesses because of being busy and distracted at work. Because working patients are spending most of their time with colleagues, talking about work, or having social activities such as lunch and meetings, their ability to cope with depression becomes easier. In addition, having economic power may be one of the facts that affects QOL positively.

Regarding the type of occupation, the SF-36 scores of housewives and farmers were significantly lower than others. The reason for this result may be suggested as having a sedentary life with physical function-required duties. Most of the daily routines of farmers and housewives require physical capabilities and living in a specific environment because of the nature of the occupation. The side effects of hemodialysis treatment affecting physical functioning include malaise, hypotension, and muscle cramps. These side effects are challenging for both farmers and housewives to fulfill their duties, thus lowering SF-36 scores. As shown in Table 3, the lowest score of SF-36 components of housewives and farmers was indeed physical function.

Activities to cope with side effects of hemodialysis treatment after each session are essential for patient QOL. The relation between activities after hemodialysis and QOL was statistically significant. Scores were higher in working patients than in those who went home after the hemodialysis sessions. Although the expectation was for QOL scores to be higher in resting patients, having a job and work-related duties seemed to distract the patient’s focus on the illness, thereby increasing QOL.

Patients with ESRD require as much social support as they can get because of the challenges of the illness and treatment. The importance of family support on patients with ESRD was shown in our study. Although no significant association was shown between family support and QOL, the existence of family support increased SF-36 scores. In addition, having private insurance was not significant but increased QOL scores. It can be suggested that, in general, since higher educated people have private insurance, the impact of education also affected the SF-36 scores.

To ease the restricted life that results from an ESRD diagnosis, complying with orders and proposals from doctors and dieticians has an undeniable impact. Some studies have shown that complying to these proposals increases QOL. In our study, although we showed no significant difference between the complying factor and most of the SF-36 components, patients who complied with doctors and dieticians had higher SF-36 scores. The Global Health component of SF-36 was significantly associated with QOL.

Conclusions

Familial, social, economic, and marital status independently affected the well-being of ESRD patients, in addition to the influences of disease adaptation.

References

Abstract

Information technology and the Internet are rapidly becoming effective tools for teaching. Self-management skills are important for adaptation and long-term survival in kidney recipients. Web-based training may help patients develop self-management skills through information access. This literature review aimed to determine the effects of Web-based educational intervention on self-management in kidney recipients. The Internet supports effective health education intervention strategies by providing a learning environment that is always available. Medicine management, routine follow-up, awareness of the signs and symptoms of rejection, infection prevention, self-monitoring, physical activity, and nutrition are important during the posttransplant period. Another important component of achievement in related matters is the competence of individuals with their own self-management. Web-based training is beneficial for appointment follow-up, nutritional adaptation, and treatment of anxiety and depression. Web-based training allows kidney recipients to access information at any time and place; this information promotes proper self-management.

Key words: Renal transplant, Self-management, Web-based health education

Introduction

Communications, information technology, and Internet use are increasing rapidly worldwide, and Turkey is no exception. Web-based educational systems that allow Internet surfing are among the most effective. Kidney recipients who reside in regions without easy access to health care professionals require the availability of Web-based training.

Self-management is defined as being capable of participating actively in one’s own care, including the use of behavioral and psychologic strategies and treatments. It is known that education is important for the acquisition of self-management. This literature review aimed to highlight the effects of Web-based educational intervention on self-management in kidney recipients.

Materials and Methods

Google Scholar, PubMed, and EBSCOhost were searched in both English and Turkish, using the keywords “web-based education,” “kidney/renal transplantation,” “distance education,” and “kidney transplant.” Relevant studies are discussed.

Results and Discussion

According to the 2016 report on Information and Communication Technology by the Turkish Statistical Institute, overall Internet usage reached 93.7% and household Internet usage reached 76.3%. These data show that Internet use has become prevalent. Therefore, individuals may prefer online training materials for health education. The content of online training materials must be comprehensible and appropriate for the educational status of specific individuals.

Individuals with chronic diseases need support for the disease, treatment options, social support, decision-making, diet, exercise, and behavioral change. Computer-based programs can be used for online support, decision-making on health-related issues, evaluating behavioral change, and meeting the needs of individuals. It is known that patients...
with chronic renal failure lack knowledge that may be life-threatening. Information is essential for self-management in patients with chronic disease. Online tools enable patients worldwide to communicate with each other through synchronous or asynchronous networks. Web-based training is also important for social support. Internet-based educational support can also be downloaded and printed to share with patients.7

Kidney transplant is a treatment that positively affects quality of life. However, challenges in adapting to immunosuppressive treatment increase the need for recipient and caregiver information.4 The increased need for information and responsibility cause patients and their families to have difficulty adapting and maintaining treatment regimens.8 Patient decisions and behaviors affect their health status during the pre- and posttransplant process.9 Accordingly, communication technologies can improve health care.10

The Internet provides affordable, effective health interventions regardless of physical access to a health care provider. Medical status and adaptability may decrease participation in Web-based interventions; however, reminder e-mails may motivate patients during the educational intervention process.11 A computer-based system allows for both self-learning and instructor-led e-learning, either individually or in a group, via synchronous or asynchronous communication. E-learning can employ blended learning methods that include both a specific training environment and distance learning.12 Web-based learning is accepted as an effective tool for information sharing.13

Patients must take medication(s) at the same time every day, have regular follow-up, be aware of rejection signals,9 monitor side effects, prevent infections, self-monitor, and engage in physical activity and nutritional self-management after transplant.14,15 After transplant, patients may experience setbacks due to mental health, quality of life, and medication management; these are important issues for individuals without easy access to transplant care providers. Web-based training is useful for follow-up appointments and nutritional adaptation. Internet-based training has positive effects on patients and caregivers with anxiety and depression.16 Web-based training is preferred because of its ubiquitous availability, independent of time and location. It can reach many patients at once and is cost-effective.17

Conclusions

Information and training have not been sufficient for kidney recipients in in-home care or those required to remain at home because of postdischarge requirements. Web-based training for kidney recipients can allow recovering patients to access health care information at will and can be useful for self-management.

References

Abstract

Urinary tract infection is the most common complication after kidney transplant and often is associated with graft loss and mortality. Ultrasonography is the most widely applied imaging modality for diagnosis of complications after kidney transplant. Here, we report a case of a 52-year-old male patient who underwent renal transplant 1 month earlier and who presented with fever, leukocytosis, and leukocyturia. Klebsiella pneumoniae was found in the urine and blood cultures. Ultrasonography revealed multiple, ill-defined margined, hypoechoic areas and cysts within the cortex. Both clinical findings and ultrasonography findings were resolved after antimicrobial therapy. One month later, the patient presented again with fatigue, leukocytosis, and leukocyturia. Blood and urine culture results were consistent with Klebsiella pneumoniae. Ultrasonography revealed large hypoechoic mass, including multiple cysts in the upper pole of the transplanted kidney. Doppler ultrasonography showed increased vascularity within the hypoechoic mass and surrounding parenchyma. Renal parenchymal echogenicity was also increased in the upper pole. Ultrasonography-guided percutaneous drainage was performed. Clinical, laboratory, and ultrasonography findings were resolved after antimicrobial therapy. Ultrasonography plays an important role in the diagnosis and evaluation of the treatment response of urinary tract infections after kidney transplant.

Key words: Graft loss, Klebsiella pneumoniae, Parenchymal abscess, Renal transplantation

Introduction

Urinary tract infections may result in morbidity, mortality, and graft loss after kidney transplant. Immunosuppressive therapy and comorbidities such as diabetes mellitus and vesicoureteral reflux may increase the risk of infections. Early diagnosis of infections decreases morbidity and mortality. Ultrasonography is considered to be the most preferable modality for diagnosis. Ultrasonography may provide information about the kidney parenchyma, collecting system, ureter, peritransplant collections, and vascular structure. Here, we report ultrasonography findings in a patient with multiple parenchymal abscesses and parenchymal infection following kidney transplant.

Case Report

A 52-year-old man, who underwent kidney transplant 1 month earlier, was presented with fever, leukocytosis, and leukocyturia. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae bacteria were found in the blood, urine, and drain cultures. Ultrasonography revealed multiple, ill-defined margined, hypoechoic areas and cysts within the cortex, especially in the lower pole of the kidney (Figure 1). The vascularity decreased in the surrounding parenchyma of the cysts and hypoechoic areas, and low peak systolic velocity values were noted within the interlobar and segmental arteries in the lower pole. Resistive index values were normal. Clinical, laboratory, and ultrasonography findings were resolved after antimicrobial therapy. One month later, the patient presented again with fever, nausea, fatigue, leukocytosis, and leukocyturia. Blood and urine culture results were consistent with Klebsiella pneumoniae. Multiple cysts and collection within the large hypoechoic-heterogeneous mass were found in
the upper pole of the kidney in ultrasonography examination (Figure 2). Doppler ultrasonography showed increased vascularity within the hypoechoic mass and surrounding parenchyma (Figure 2). We observed high resistive index values, which ranged from 0.77 to 0.8 in the interlobar and segmental arteries. Increased parenchymal echogenicity was seen in the upper pole. Ultrasonography-guided percutaneous drainage was performed. Clinical and laboratory findings, including blood and urine cultures and ultrasonography findings, regressed after antimicrobial therapy.

Discussion

Urinary tract infection is a common disease after kidney transplant. The prevalence of urinary tract infection ranges from 6% to 89%, with a slight female predominance.3 Bacterial infections including Klebsiella pneumoniae and Escherichia coli are the most common causes of urinary infections. Fungal and viral infections are less commonly seen.3 In addition to clinical and laboratory examinations, imaging modalities such as ultrasonography, computerized tomography, and magnetic resonance imaging have potential roles in the diagnosis of complications after kidney transplant. Ultrasonography is considered to be the primary imaging technique in the evaluation of kidney transplant. Ultrasonography is a safe, noninvasive, and cost-effective modality and allows serial examinations, which may be applied during intraoperative, early postoperative, and early and late follow-up examinations. The sonographic appearance of urinary infections can vary considerably. Focal and diffuse areas of increased or decreased parenchymal echogenicity with surrounding edema are the most common findings. Mucosal thickening or focal echogenicity in the pelvicaliceal system may be suggestive of pyonephrosis or infections of the collecting system.4 Gas within the parenchyma is associated with emphysematous pyelonephritis. Abscesses may be

Figure 1. Ultrasonography Results at First Hospital Visit

(a) Ultrasonography revealed multiple, ill-defined margined, hypoechoic areas (open arrows). (b) Ultrasonography showed cysts within the cortex and increased echogenicity in the surrounding parenchyma (arrows).

Figure 2. Ultrasonography Results at Second Hospital Visit

(a) Ultrasonography revealed large hypoechoic mass, including multiple cysts in the upper pole (arrows). (b) Vascularity was increased in the hypoechoic mass (arrow) and surrounding tissue. (c) Ultrasonography showed the collection within the hypoechoic mass (arrow).
seen in severe cases; these are characterized by fluid-filled complex cysts within the parenchyma and resolve after ultrasonography-guided drainage and antimicrobial therapy.4,5

Ultrasonography is the most preferred imaging modality for the diagnosis of complications, evaluation of kidney vascularity, and follow-up after kidney transplant due to advantages such as being safe and inexpensive and being available for serial examinations over the intraoperative and postoperative periods. However, sonographic characteristics are nonspecific, and rejection or malignity may mimic infections, which may result in misdiagnoses.

References

Abstract

Objectives: Pulmonary infections are a significant cause of morbidity and mortality in solid-organ transplant recipients despite enhanced facilities for perioperative care. The aim of this study was to evaluate the demographic characteristics, clinical course, and outcomes of renal transplant recipients with pneumonia.

Materials and Methods: The medical records of all renal transplant recipients from January 2010 to December 2014 were retrospectively reviewed, and patients diagnosed with pneumonia according to Centers for Disease Control and Prevention criteria were evaluated. Pneumonia was classified as community acquired or nosocomial. Patient demographics, microbiologic findings, need for intensive care/mechanical ventilation over the course of treatment, and information about clinical follow-up and mortality were all recorded.

Results: Eighteen (13.4%) of 134 renal transplant recipients had 25 pneumonia episodes within the study period. More than half (56%) of the pneumonia episodes developed within the first 6 months of transplant, whereas 44% developed after 6 months (all > 1 year). Eight cases (32%) were considered nosocomial pneumonia, and 17 (68%) were considered community-acquired pneumonia. Bacteria were the most common cause of pneumonia (28%), and fungi ranked second (8%). No viral or mycobacterial agents were detected. No patients required prolonged mechanical ventilation. No statistically significant difference was found in the need for intensive care or regarding mortality between patients with nosocomial and community-acquired pneumonia.

Two patients (11%) died, and all remaining patients recovered.

Conclusions: The present study confirmed that pneumonia after renal transplant is not a rare complication but a significant cause of morbidity. Long-term and close follow-up for pneumonia is necessary after renal transplant.

Key words: Complications, Outcome, Renal transplantation

Introduction

The incidence of pulmonary infection after solid-organ transplant (SOT) has decreased with the development of effective prophylactic strategies and improved immunosuppressive treatment regimens. Nevertheless, lower respiratory tract infection remains a life-threatening complication. Approximately two-thirds of pulmonary infiltrations in this group are infectious.1,2 The incidence of pneumonia in renal transplant recipients reportedly ranges from 8.8% to 20.0%.3-6 The mortality rate in this group ranges from 10% to 30% depending on the type of transplant and study duration.7

Infectious complications vary according to the individual patient’s degree of immunosuppression and epidemiologic exposure. Opportunistic infections usually do not occur in the first month after transplant because not all effects of immunosuppression have manifested. Patients waiting for transplant may be colonized with nosocomial microorganisms due to frequent hospital stays, and pulmonary infections in the first month after transplant usually appear as nosocomial pneumonia caused by these microorganisms. Opportunistic pulmonary infections are predominant in the interim period from the first to the sixth month after transplant. Pneumonia that occurs in the late posttransplant period (ie, the sixth month) is usually community acquired.8,9
In the present study, we aimed to identify pneumonia episodes in renal transplant recipients followed in our center to determine the prevalence, risk factors, cause, and prognosis of pneumonia in this patient population.

**Materials and Methods**

The medical records of all renal transplant recipients from January 2010 to December 2014 were retrospectively reviewed. Pneumonia was defined according to Centers for Disease Control and Prevention criteria. Transplant recipients who presented to the hospital with relevant symptoms after transplantation, such as fever, cough, sputum production, chest pain, shortness of breath, and respiratory failure; those with new-onset or progressed pulmonary infiltration on chest radiography accompanied by a physical examination; and those with similar symptoms and signs that occurred during the hospital stay were considered to have pneumonia. Pneumonia was categorized as either nosocomial or community acquired. This study was approved by the Baskent University Institutional Review Board (project No. KA16/186) and supported by the Baskent University Research Fund.

The following data were obtained from medical records: patient age; sex; pretransplant risk factors; serology for hepatitis C virus, hepatitis B virus, and cytomegalovirus (CMV); postoperative complications; need for reoperation or dialysis; acute rejection episodes; induction therapies; immunosuppressive treatment regimens; time of pneumonia episodes; isolated microorganisms; need for intensive care and/or mechanical ventilation over the course of the treatment period; complications such as renal failure and acute rejection; clinical outcomes; and mortality. According to the perioperative prophylaxis protocol of our center, cefazolin was administered for 2 days before the procedure. All transplant recipients received trimethoprim/sulfamethoxazole as prophylaxis for *Pneumocystis jiroveci* and valganciclovir as prophylaxis for CMV.

Statistical analysis was performed using the statistical software package SPSS (version 17.0; SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables are presented as the mean ± standard deviation (P < .05 in Kolmogorov-Smirnov test or Shapiro-Wilk test; n < 30), and nonnormally distributed continuous variables are presented as the median. Categorical variables between the 2 groups were analyzed with the chi-square test or the Fisher exact test. Values of P < .05 were considered statistically significant.

**Results**

Of the 134 transplant recipients, 94 (70.1%) were male and 40 (29.9%) were female. The median age was 47 years (range, 18-69 y). Eighteen patients had 25 pneumonia episodes, with a cumulative incidence of 13.4%. Of the 18 patients with pneumonia, 16 (88.8%) were male, the mean age was 42.6 ± 13.6 years, and the mean follow-up was 992 ± 445 days. Demographic characteristics, comorbidities, viral serologic status, immunosuppressive therapy regimens, and posttransplant complications of the patients are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Patients with Pneumonia (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Mean age, years</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Mean follow-up, days</td>
</tr>
<tr>
<td>Comorbidities and risk factors</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>CMV donor (+)/recipient (−)</td>
</tr>
<tr>
<td>Pretransplant HCV-positive</td>
</tr>
<tr>
<td>Immunosuppressive therapy regimen</td>
</tr>
<tr>
<td>Calcineurin inhibitor + MMF + Deltacortril</td>
</tr>
<tr>
<td>Calcineurin inhibitor + mTOR + Deltacortril</td>
</tr>
<tr>
<td>MMF + mTOR</td>
</tr>
<tr>
<td>Induction therapy</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Basiliximab</td>
</tr>
<tr>
<td>ATG + rituximab</td>
</tr>
<tr>
<td>ATG + methylprednisolone</td>
</tr>
<tr>
<td>ATG</td>
</tr>
<tr>
<td>Posttransplant complication</td>
</tr>
<tr>
<td>Acute rejection</td>
</tr>
<tr>
<td>Reoperation</td>
</tr>
<tr>
<td>Need for dialysis</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

**Abbreviations:** ATG, antithymocyte globulin; CMV, cytomegalovirus; HCV, hepatitis C virus; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin

Results are mean ± standard deviation or No. (%).

More than half (56%) of the pneumonia episodes occurred within the first 6 months after transplant. Those that occurred after 6 months (44%) were diagnosed at or after 1 year. The characteristics of pneumonia episodes in our patients are shown in Table 2. Whereas 68% of pneumonia cases were community acquired, 32% were nosocomial. Bacterial pneumonia was the most prevalent type (28%), followed by fungal pneumonia (8%). Viral or mycobacterial agents were not detected in any of the
patients. No microorganism could be isolated in 64% of pneumonia episodes.

The distribution of microorganisms isolated from the patients is shown in Table 3. Polymicrobial cause was not found in any of the patients. In 2 patients who had fungal pneumonia, *Aspergillus* was determined to be the causative agent based on *A. fumigatus* growth in sputum culture, galactomannan positivity, and relevant radiologic findings. Both patients responded to antifungal therapy.

We compared the characteristics of pneumonia episodes between patients with nosocomial pneumonia and those with community-acquired pneumonia. The patients were evaluated for infectious agents, complications, the need for intensive care and mechanical ventilation, and mortality. None of the patients required prolonged mechanical ventilation.

Two patients (11%) died, and the remaining patients achieved complete remission (Table 4).

**Discussion**

The risk of infection in SOT recipients is largely associated with immunosuppressive therapies. Although antimicrobial prophylaxis has changed the evolution of infectious complications, lower respiratory tract infections remain a significant source of morbidity. In the present study, the incidence of pneumonia in renal transplant recipients was 13.4%, which is consistent with the literature.

Nosocomial and opportunistic infections in SOT recipients are most frequently seen within the first 6 months after transplant. Although late infections are less frequently seen more than 6 months after transplant, they are as serious as those in the early period. High-risk groups for infection include recipients who develop chronic graft malfunction, develop infection in the first 6 months after transplant, or undergo graft-related reoperation. A recent study reported that late infections are not rare complications and that close clinical monitoring of risky patients would be beneficial. The present study determined that 44% of pneumonia episodes occurred 6 months or more after transplant. Evaluation of patients with late pneumonia (> 1 year) demonstrated that 10 community-acquired pneumonia episodes occurred in 7 patients (40%). Nosocomial pneumonia developed in the late period in 1 patient. This patient had been included in a chronic dialysis program because of loss of graft function, which occurred 1 year after receiving induction therapy comprising posttransplant antithymocyte globulin and pulse methylprednisolone.

Although community-acquired pneumonia is more benign in SOT recipients, higher mortality rates have been reported for nosocomial infections. In the present study, complete recovery was observed in all patients except 2 (11%), who died. Comparison of nosocomial pneumonia and community-acquired pneumonia in terms of prognosis and mortality revealed no statistically significant differences between the 2 groups; this finding was attributed to the small number of patients.

The prevalence of tuberculosis is 20 to 74 times higher in SOT recipients than in the general population. Whereas the prevalence of tuberculosis is 0.5% to 6.4% in low-endemic regions, it is
reportedly 15.2% in high-endemic regions. Active tuberculosis after transplant may occur in association with various factors, such as latent infection in the recipient, latent infection in the donor, contact with patients with active tuberculosis after transplant, or the need for urgent transplant in a patient with active tuberculosis. The degree of immunosuppression and age are also significant factors that enhance the lifetime cumulative risk of infection. Other factors that are likely to influence the incidence, particularly in renal transplant recipients, include baseline use of antithymocyte globulin, chronic renal failure, and the need for hemodialysis. Randomized controlled studies indicate that chemoprophylaxis with isoniazid reduces the risk of tuberculosis by 60% to 90% in immunosuppressed individuals. No patients in the present study were diagnosed with tuberculosis. Although the study was conducted in a region endemic for tuberculosis, this result is likely primarily associated with the small number of patients because no patient had a history of tuberculosis or close contact with tuberculosis and all patients received isoniazid chemoprophylaxis except living renal donor recipients.

The incidence of CMV infections is low in renal transplant recipients because of routine prophylaxis for CMV (<1%). Prophylaxis with co-trimoxazole reduces the risk of P. jiroveci-associated pneumonia by more than 90%. Neither P. jiroveci nor CMV was found in any of the present cases. We believe that the prophylaxis was beneficial.

Limitations of the present study include the small number of both overall patients and microorganisms isolated. The small number of agents isolated may be because fiberoptic bronchoscopy, which has a 56.2% diagnostic yield in immunosuppressed patients, was performed in only 2 cases. The number of bronchoscopy procedures was low because clinical and radiologic improvements were achieved within 2 to 3 days of treatment in all patients except the 2 who died.

In conclusion, nosocomial or community-acquired pneumonia is not a rare complication in renal transplant recipients. Community-acquired pneumonia is more prevalent. There was no statistically significant difference in prognosis or mortality between these 2 groups. Although bacteria are the most common cause of pneumonia, exclusion of other pathogens and close, long-term monitoring are needed because the spectrum of likely pathogens differs between immunosuppressed and immunocompetent patients.

References

Renal Allograft With Calcium Oxalate Deposition: Association with Urinary Tract Infection and Development of Interstitial Fibrosis

B. Handan Özdemir,1 Şebnem Ayva,1 Gökçe Özdemir,1 Alev Ok Atilgan,1 Eda Akçay,1 F. Nurhan Özdemir,1 Mehmet Haberal2

Abstract

Objectives: The interaction between calcium oxalate deposition and urinary tract infection is not well established. We aimed to identify the association between these and to determine the role of calcium oxalate deposition on interstitial fibrosis development.

Materials and Methods: Renal allograft biopsies of 967 patients were reviewed to identify those with calcium oxalate deposition in the renal allograft, with 27 (2.8%) identified. Follow-up biopsies were conducted to reevaluate for calcium oxalate presence and interstitial fibrosis development. At time of biopsy, presence of urinary tract infection and oxaluria was also examined from medical records.

Results: Mean time for development of calcium oxalate deposition in renal allografts was 1.7 ± 0.4 and 32.7 ± 21.6 months in patients with primary and secondary oxalosis, respectively (P < .001). Of 27 patients with calcium oxalate deposition, 7 (25.9%) showed tubulointerstitial nephritis, with 2 also having urinary tract infection. Four patients (14.8%) had only urinary tract infection. Causes of tubulointerstitial nephritis were secondary to bacterial infection in 2 and secondary to viral infection in 5 patients (2 polyomaviruses, 2 cytomegaloviruses, 1 adenovirus). Time until development of interstitial fibrosis after calcium oxalate deposition was 3.5 ± 2.1 and 10.3 ± 4.1 months in patients with primary and secondary oxalosis, respectively (P = .01). Time until graft loss after calcium oxalate deposition was 9.3 ± 7.8 and 21.8 ± 12 months in those with primary and secondary oxalosis (P < .001), with 1-, 3-, and 5-year kidney graft survival of 43%, 28%, and 0% and 100%, 100%, and 67% in those with primary and secondary oxalosis, respectively.

Conclusions: Calcium oxalate deposits increased the risk of urinary tract infection and tubulointerstitial nephritis, with bacteria inducing increased presence of calcium oxalate deposition in a renal allograft. Calcium oxalate deposition had a significant influence on interstitial fibrosis development, therefore negatively affecting graft survival.

Key words: Calcium oxalate crystal, Cytomegalovirus, Escherichia coli, Polyomavirus, Tubulointerstitial nephritis

Introduction

Previous studies reported that nonacute rejection events can affect graft survival. Because oxalosis is one cause of rapid renal allograft failure immediately after transplant, it is essential to find possible preventative parameters in recipients who have the potential risk of developing calcium oxalate (CaOx) deposits.

Primary oxalosis is a genetic disorder of glyoxylate metabolism that leads to systemic overproduction of oxalate. However, the origins of CaOx deposits in renal transplant are unclear. Both primary oxalosis (PO) and secondary oxalosis (SO) are significant causes of renal failure.1-4 Greater than 50% of renal allograft biopsies performed within 3 months after transplant can show CaOx crystals in renal tubules.3 Although their presence can be benign, when present in moderate to high intensity, these crystals contribute to increased incidence of acute tubular necrosis and poor allograft survival.1,5

Studies regarding the presence of CaOx deposition in renal allografts of recipients after transplant without primary hyperoxaluria are scarce. Secondary oxalosis affecting the renal allograft is an uncommon cause of acute kidney injury. To the best
of our knowledge, only a few case reports mention CaOx deposition in renal allografts with post-transplant acute renal failure and consider CaOx as an additional cause for tubular cell injury. The correlation of CaOx deposits with acute renal failure and renal allograft survival is a matter of interest.

Recently, it was reported that children with idiopathic hypercalciuria have increased rates of urinary tract infections (UTIs). Balestracci and associates reported that idiopathic hypercalciuria prevalence in children with UTIs was high (20%), with no differences observed between patients with and without vesicoureteral reflux. On the other hand, the identification of bacteria in CaOx kidney stones raises the possibility of a close association between UTI and CaOx deposition. Recently, it was shown that 4 of 5 (80%) kidney stones were positive for Enterobacteriaceae that may be associated with pediatric kidney stones.

With this in mind, it is possible that the presence of CaOx deposits in tubules of the kidney is a sign of the UTI and/or tubulointerstitial nephritis (TIN) in renal allograft recipients. The interaction between CaOx deposition both with UTI and TIN has not been established in renal allografts. Here, we aimed to understand whether there was a relation between CaOx deposits and UTI and/or TIN. We evaluated all follow-up allograft biopsies to analyze the effects of CaOx deposits on development of renal fibrosis and on graft survival.

Materials and Methods

Renal allograft biopsies of 967 patients were retrospectively reviewed to identify those with CaOx deposition. Calcium oxalate deposits were identified under polarized light, and only cases with significant tubular or interstitial CaOx deposits were included in the study. Biopsies with isolated tubular CaOx deposits were not included in the study. Biopsies with isolated tubular CaOx deposits were not included in the study. After the reevaluation of all biopsies, only 27 recipients (2.8%) showed moderate to severe CaOx deposition in renal allografts. These 27 recipients (21 men and 6 women; mean age of 27.2 ± 13.2 years; range, 2-52 years) were enrolled in this study. Seven of 27 patients (26%) were under 18 years old. Regarding donor type, 14 patients (52%) received grafts from living related donors and 13 (48%) received grafts from deceased donors. The maintenance immunosuppressive medications in all recipients with CaOx deposition were cyclosporine or tacrolimus, mycophenolate mofetil (MMF), and prednisone.

Medical records of study patients were reviewed, with particular attention to conditions that could be associated with UTI. An infection was confirmed if the single microorganism had a count > 10⁵ colony-forming units/mL with urinary tract inflammatory reaction (> 10 leukocytes/field) in a midstream urine sample collection. Follow-up and further indication biopsies for presence of CaOx deposition were reevaluated for development of interstitial fibrosis in all patients.

Statistical analyses

Descriptive data are expressed as mean ± standard deviation. Comparisons of continuous variables were performed with t test or the Mann-Whitney U test where appropriate, and the chi-square or Fisher exact tests were used to compare categorical variables. Kaplan-Meier analysis was used to calculate allograft and patient survival rates, and the log-rank test was used to compare allograft survival curves. Statistical significance was assumed for P values of less than 0.05.

Table 1. Clinicopathologic Characteristics of 27 Patients with Calcium Oxalate Deposition

<table>
<thead>
<tr>
<th></th>
<th>All Cases</th>
<th>PO Cases</th>
<th>SO Cases</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>21/6</td>
<td>6/1</td>
<td>15/5</td>
<td>NS</td>
</tr>
<tr>
<td>Recipient age, years</td>
<td>27.2 ± 13.2</td>
<td>18.2 ± 7.8</td>
<td>30.4 ± 13.4</td>
<td>.03</td>
</tr>
<tr>
<td>Donor age, years</td>
<td>41 ± 8.9</td>
<td>40.2 ± 6.1</td>
<td>41.3 ± 9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine at biopsy, mg/dL</td>
<td>2.7 ± 1.3</td>
<td>2.2 ± 0.8</td>
<td>3.3 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic GN</td>
<td>13 (48.1%)</td>
<td>13 (48.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMM amyloidosis</td>
<td>4 (14.8%)</td>
<td>4 (14.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary oxalosis</td>
<td>7 (26%)</td>
<td>7 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesicoureteral reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time on dialysis, mo</td>
<td>26.4 ± 11.9</td>
<td>35 ± 9</td>
<td>23.4 ± 11.4</td>
<td>.025</td>
</tr>
<tr>
<td>Acute rejection, mean no.</td>
<td>0.7 ± 0.4</td>
<td>0</td>
<td>0.7 ± 0.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>UTI, mo</td>
<td>35 ± 18.5</td>
<td>35 ± 18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIN, mo</td>
<td>35.6 ± 17.4</td>
<td>1.3 ± 0.7</td>
<td>52.8 ± 24.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Time until CaOx deposition, mo</td>
<td>21.6 ± 13.7</td>
<td>1.7 ± 0.4</td>
<td>52.7 ± 21.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CaOx deposition, mo</td>
<td>8.8 ± 4.9</td>
<td>3.5 ± 2.1</td>
<td>103 ± 41</td>
<td>.01</td>
</tr>
<tr>
<td>Graft loss, mo</td>
<td>163 ± 12.7</td>
<td>93.7 ± 7.8</td>
<td>218 ± 12</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

Abbreviations: CaOx, calcium oxalate; FMM, Familial Mediterranean fever; GN, glomerulonephritis; IF, interstitial fibrosis; NS, not significant; PO, primary oxalosis; SO, secondary oxalosis; TIN, tubulointerstitial nephritis; UTI, urinary tract infection
Results

Mean follow-up time was 89.2 ± 33.7 months for the 27 patients with CaOx deposition. All patients had oxaluria. As shown in Table 1, significant differences were found between patients with PO and SO with regard to recipient age and time on dialysis. Recipients with PO were younger than those with SO (P = .03). Time on dialysis was longer in recipients with PO than in patients with SO (P = .025). Patients with PO showed no episodes of acute rejection, whereas patients with SO had a mean number of 0.7 ± 04 episodes of acute rejection.

The mean time to development of CaOx deposits in renal allografts was 1.7 ± 0.4 months and 32.7 ± 21.6 months in patients with PO and SO, respectively (Table 1), with significant differences found between the groups (P < .001). Seven of the 27 patients with CaOx deposits (25.9%) also showed TIN at the same biopsy (Table 2). Two of these patients also had UTI at the same period. Four patients (14.8%) had only UTI. None of the patients with PO had UTIs, with UTIs only observed in recipients with SO (Table 2).

Discussion

Oxalate is a simple dicarboxylic acid produced as a by-product of some metabolic pathways and is excreted by the kidney.11,12 Oxalate is freely filtered at the glomerulus and undergoes both reabsorption and secretion in the proximal tubules.11 Removal of oxalate in the kidney is facilitated by a variety of transport systems at the apical and basolateral surfaces of both proximal and distal tubular cells. Although oxalate accumulation in tubular cells is usually benign, oxalate can alter the activity of some enzymes. Oxalate exposure has been shown to increase the production of free radicals in tubular cells, with this increase in free radical production suggested to be responsible for oxalate toxicity.11-14 Calcium oxalate can directly injure tubular cells by causing obstructive damage as a result of luminal deposition. Calcium oxalate seems to have a biphasic effect on tubular cells, which is toxic at high levels but acts as a mitogen at lower concentrations.11,12,15

The time to development of interstitial fibrosis after CaOx deposition in renal allograft was 3.5 ± 2.1 months and 10.3 ± 4.1 months in patients with PO and SO, respectively (P = .01). Graft loss after CaOx deposition was 9.3 ± 7.8 months in those with PO and 21.8 ± 12 months in those with SO (P < .001). Among patients with PO, 1-, 3-, and 5-year kidney graft survival rates were 43%, 28%, and 0%. In patients with SO, 1-, 3-, and 5-year kidney graft survival rates were 100%, 100%, and 67%.

Table 2. Distribution of Patients With Tubulointerstitial Nephritis and Urinary Tract Infection

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y</th>
<th>Primary Disease</th>
<th>TIN</th>
<th>UTI Infection Time, months</th>
<th>IF Time, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>FMF, CMV</td>
<td>No</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>GN, CMV</td>
<td>No</td>
<td>9</td>
<td>Yes 15</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Primary oxalosis, PVN</td>
<td>No</td>
<td>3</td>
<td>Yes 1</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>Primary oxalosis, PVN</td>
<td>No</td>
<td>2</td>
<td>Yes 2</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>GN, Adenovirus</td>
<td>No</td>
<td>21</td>
<td>Yes 6</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>FMF, Granulomatous, E. coli</td>
<td>58</td>
<td>Yes 16</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>GN, Acute, E. coli</td>
<td>16</td>
<td>Yes 10</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>GN, E. coli</td>
<td>36</td>
<td>Yes 15</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>GN, E. coli</td>
<td>15</td>
<td>Yes 11</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>VUR, None</td>
<td>5</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>VUR, None</td>
<td>10</td>
<td>Yes 12</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; FMF, Familial Mediterranean fever; GN, glomerulonephritis; IF, interstitial fibrosis; PVN, polyomavirus nephropathy; TIN, tubulointerstitial nephritis; UTI, urinary tract infection; VUR, vesicoureteral reflux

The cause of TIN was secondary to bacterial infection in 2 cases and secondary to viral infection in 5 cases. Among 5 patients with viral TIN, 2 patients had polyomavirus nephropathy, 2 had cytomegalovirus (CMV), and 1 had an adenoviral infection (Table 2). *Escherichia coli* was identified in urine culture of all recipients with UTIs. Patients with UTI tended to show an increasing amount of CaOx depositions in their follow-up biopsies compared with initial biopsies.

The cause of TIN was secondary to bacterial infection in 2 cases and secondary to viral infection in 5 cases. Among 5 patients with viral TIN, 2 patients had polyomavirus nephropathy, 2 had cytomegalovirus (CMV), and 1 had an adenoviral infection (Table 2). *Escherichia coli* was identified in urine culture of all recipients with UTIs. Patients with UTI tended to show an increasing amount of CaOx depositions in their follow-up biopsies compared with initial biopsies.
The underlying mechanism leading to UTI and TIN in recipients with hyperoxaluria and/or renal CaOx deposition may be explained by the impairment mechanisms of the tubular and bladder epithelium with CaOx microcrystals. Both the uroepithelium and tubular epithelium have significant roles in the host defense, such as bactericidal activity and the continuity of the inflammatory response. To initiate the antibacterial response, close contact is required between the bacteria and epithelial cell surface. Calcium oxalate crystals slow down the defense mechanism by blocking bacteria and epithelial cell surface contact, disrupting the continuity of the barrier that prevents infection. 

Previous reports have shown that patients with hyperoxaluria tended to show a higher incidence of recurrent and persistent UTIs. In one study of 124 children with idiopathic hyperoxaluria, 50 patients (40%) showed UTI, with 39 (78%) having recurrent UTI. After treatment of idiopathic hyperoxaluria, no recurrence of UTI was observed in 24 of 29 patients (83%) with follow-up of 6 years.

In the present study, we found that 7 of 27 patients (25.9%) with renal CaOx deposition showed TIN at the same biopsy, with 2 of these 7 patients also having UTI during the same period. Among 27 recipients, four patients (14.8%) had only UTI. The cause of TIN was secondary to bacterial infection in 2 patients and secondary to viral infection in 5 patients. The most interesting finding in our study was that viral TIN among the 5 patients was secondary to polyomavirus (n = 2), CMV (n = 2), and adenovirus (n = 1). Although previous studies have reported a close association between bacterial infection and oxalosis, no association between viral infection and oxalosis has been shown.

Escherichia coli was identified in urine culture of all of our recipients with UTI. Patients who had UTI tended to show an increasing amount of CaOx deposits in their follow-up biopsies compared with initial biopsies. The high incidence of bacterial and viral TIN in these cases may be explained by the mechanisms discussed above that CaOx crystals slow down the defense mechanism by blocking microorganism and tubular cell surface contact, disrupting the continuity of the barrier that prevents infection.

It has been shown that CaOx crystals induce an inflammatory response through dendritic cell secretion of interleukin 1β, inflammasomes involved in kidney stone pathogenesis, and increased urine interleukin 6 levels in patients with kidney stones. From this point of view, we hypothesized that the increased secretion of inflammatory cytokines, such as interleukin 1β and interleukin 6, contributes to CaOx-induced tissue inflammation in both UTI and TIN.

Reports have suggested that increases in growth factors, including mitogen-activated protein kinases and extracellular matrix regulators, involve CaOx in the pathogenesis of interstitial fibrosis in the kidney. In this sense, the presence of intraluminal CaOx crystals may induce tubular cells to secrete profibrotic factors and promote renal interstitial fibrosis. Confirming this suggestion, we showed that patients with CaOx deposition in renal allografts tended to show early development of interstitial fibrosis after CaOx deposition appeared in the allograft.

Isolated tubular deposits of CaOx crystals are not an uncommon finding in renal allografts. Although it was proposed that isolated CaOx crystals do not imply renal damage, we suggest that CaOx crystals in renal allografts have a negative influence on long-term renal function. In addition, moderate or severe tubular or interstitial deposits of CaOx are highly suggestive of a hyperoxaluric condition in the kidney.

The most common cause of SO is enteric dysfunction. In a typical situation, enteric calcium binds to oxalates and is excreted as CaOx in the stool, thereby limiting the absorption of the enteric oxalates. In situations that affect the absorption physiology of the bowel, such as with malabsorption and steatorrhea, the enteric calcium chelates with fatty acids and is not biochemically available to bind with oxalates, thereby increasing systemic absorption. Immunosuppressed patients, including renal transplant recipients, tend to show a higher incidence of bacterial or viral enteric infections (eg, Escherichia coli, CMV) and bacterial overgrowth syndromes. Confirming these findings, our 2 patients with CMV TIN and 1 patient with adenovirus TIN also had diarrhea during the same period. Furthermore, most renal allograft recipients were taking MMF therapy. It has been reported that intestinal epithelial cells are partially dependent on the de novo purine synthesis pathway for replication and regeneration, which is inhibited by MMF. Therefore, MMF can lead to malabsorption and
diarrhea, which could be a precipitating factor for SO. Our results also support this suggestion, as recipients with renal CaOx deposition were on MMF as part of their immunosuppressive regimen.

In conclusion, we demonstrated a significant association between CaOx deposition and graft loss, mainly due to the susceptibility of the renal allograft to infection and/or due to the early development of interstitial fibrosis.

References

De Novo Thrombotic Microangiopathy in Renal Transplant Patients

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Abstract

Objectives: Thrombotic microangiopathy is a form of renal capillary injury possibly associated with calcineurin inhibitor toxicity, acute humoral rejection, infections, and recurrent diseases. Here, we examined its incidence in patients diagnosed with acute and chronic active humoral rejection, polyomavirus nephropathy, acute cellular rejection, and immunoglobulin A recurrence.

Materials and Methods: In total, 272 renal allograft recipients who met the inclusion criteria were reevaluated for presence of renal thrombotic microangiopathy. Thrombotic microangiopathy diagnosis was established by clinical, laboratory, and histologic features. C4d expression in peritubular capillaries was determined. Clinical data were collected from medical records.

Results: Of 272 patients (mean age of 42.8 ± 12.7 years), only 74 patients (27.2%) had de novo thrombotic microangiopathy, which was found in 30/90 patients (33.3%) with acute humoral rejection, 9/51 (17.6%) with acute cellular rejection, 22/53 (41.5%) with chronic active humoral rejection, 10/55 (18.2%) with polyomavirus nephropathy, and 3/23 (13%) with immunoglobulin A nephropathy. Significant differences were shown between therapy type and thrombotic microangiopathy development ($P = .02$). Patients who received cyclosporine (38.5%) tended to show higher incidence of thrombotic microangiopathy than patients who received tacrolimus (20.7%) or sirolimus (7.7%). Patients with C4d-positive acute humoral (97.6% vs 2.4%) or sirolimus (7.7%). Patients with C4d-positive acute humoral than patients who received C4d-negative acute and chronic active humoral rejection (68.2% vs 31.8%) had greater incidence of thrombotic microangiopathy versus those who were C4d-negative. Graft loss was significantly higher in C4d-positive than in C4d-negative thrombotic microangiopathy groups ($P < .001$). Overall 1-, 3-, and 5-year graft survival was 94%, 85%, and 85% versus 83%, 51%, and 51% in thrombotic microangiopathy-negative versus thrombotic microangiopathy-positive patients ($P < .001$).

Conclusions: Acute humoral rejection and chronic active humoral rejection were the most common and therefore most important causes of de novo thrombotic microangiopathy in renal transplant patients. Its presence in the renal allograft biopsy should arouse suspicion for underlying acute or chronic active humoral rejection.

Key words: Acute cellular rejection, Acute humoral rejection, C4d expression, Chronic active humoral rejection, IgA nephropathy, Polyomavirus nephropathy, Renal allograft biopsy

Introduction

Thrombotic microangiopathy (TMA) describes a pathologic lesion in which abnormalities in the vessel wall of arterioles and capillaries lead to microvascular thrombosis. The clinical features of TMA result from the obstruction of the microcirculation and ultimately depend on the distribution of involved vascular beds. Microangiopathic hemolysis is the hallmark feature of this obstructed microcirculation. Thrombotic microangiopathy is a pathologic diagnosis, but its presence is commonly inferred from observations of thrombocytopenia and microangiopathic hemolysis in the appropriate clinical setting.1-4

Posttransplant TMA has shown incidence ranging from 3% to 14%.1-4 Several TMA syndromes have been described, of which transplant-associated TMA differed from other TMA syndromes with its mechanism, clinical presentation, and management.1-3 The accurate diagnosis of TMA in solid-organ transplant is often difficult to establish. Patients with this disease frequently have multiple potential causes for

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renal dysfunction and fever. Persistent anemia or thrombocytopenia may be mistakenly ascribed to underlying disease rather than to consumption.

Thrombotic microangiopathy in the transplanted kidney is a form of renal vascular injury that may be associated with many disorders, including calcineurin inhibitor toxicity, antibody-mediated rejection (AMR), viral infections, ischemia-reperfusion injury, and recurrent diseases.1-7 The presentation of TMA is highly heterogeneous, ranging from asymptomatic, low-level red blood cell fragmentation to systematic signs of hemolytic uremic syndrome.1,2,7 The histopathologic features of TMA in the transplanted kidney include occlusion or narrowing of the capillaries, subendothelial amorphous material accumulation in glomeruli, and fibrinoid changes in the intima of small arteries.2,4,8

The risk for development of TMA is highest in the first 3 months after transplant, and presence of de novo TMA is much less common than recurrent hemolytic uremic syndrome.1-3,7,9,10 Because of its distinct characteristics and clinical courses, it has been suggested to classify posttransplant TMA into localized and systemic forms. Systemic-form TMA is associated with thrombocytopenia and microangiopathic hemolysis. Patients with systemic TMA have a higher rate of graft loss.3-6,11,12 A subgroup of TMA (approximately 30%-40%) is localized only to the graft, and patients do not show the classic signs of a hemolytic uremic syndrome, such as hemolytic anemia, peripheral schistocytes, thrombocytopenia, and rapid deterioration of renal function.3,6,11,12

Detection of C4d expression in renal allograft biopsies is an essential tool, particularly for diagnosis of AMR.13,14 The incidence of TMA in recipients with AMR has been reported to range from 4% to 46%, with the highest frequency shown in the early posttransplant period.1-6,7,10,15 Glomerular and arteriolar thrombi in renal transplant biopsies with the diagnosis of AMR and chronic antibody-mediated rejection are frequently reported, whereas reports of presence of peritubular capillary (PTC) thrombi are scarce.2,6,8,15,16

This study examined the incidence of renal TMA in patients with acute humoral rejection (AHR), chronic active humoral rejection (CAHR), polyomavirus nephropathy (PVN), acute cellular rejection (ACR), and immunoglobulin A (IgA) recurrence.

Materials and Methods

Our retrospective analysis showed 272 renal allograft recipients with the diagnosis of PVN, IgA nephropathy, ACR, AHR, and CAHR. These patients were reevaluated for final diagnosis and presence of renal TMA. The study was approved by the Ethical Review Committee of the Institute. All of the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration. Diagnosis of TMA was established by clinical, laboratory, and histologic features. The histologic diagnosis of TMA was given if patients had occlusive fibrin thrombi in at least one glomerulus or one arteriole with or without other TMA findings. Other TMA findings included endothelial swelling and detachment, glomerular basement membrane double contour formation, mesangiolysis with microhemorrhage, luminal occlusion with mural myxoid or fibrinoid change with or without erythrocytolysis, and mucointimal proliferation of small-caliber arteries in the absence of C4d deposits along PTCs.6

All renal allograft biopsies were routinely stained for C4d. C4d staining status was defined as extent of the involvement of PTC by linear deposition of C4d. Focal expression of C4d was defined as < 50% staining of the PTC network of cortex and medulla. Diffuse expression of C4d was defined as ≥ 50% staining of the PTC network of cortex and medulla. The most common immunosuppressive maintenance regimen consisted of tacrolimus (150 patients) or cyclosporine (109 patients), mycophenolate mofetil, and prednisone. A few patients (n = 13) received sirolimus. Clinical data were collected from medical records of all patients. Clinical records were evaluated to exclude other possible causes of allograft TMA, including malignant hypertension, hepatitis C infection, lupus anticoagulants, and primary or recurrent hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.

Statistical analyses

Descriptive data are expressed as mean ± standard deviation. The chi-square test was used to analyze categorical variables. We used t test or the Mann-Whitney test to compare between 2 groups of patients. Comparisons between multiple groups were handled by analysis of variance or the Kruskal-Wallis test. We used the Kaplan-Meier method with the log-rank comparison for survival analyses.
Statistical significance was assumed for \( P \) values of .05 or less.

**Results**

Renal allograft biopsies of 272 patients (mean age of 42.8 ± 12.7 years) were reevaluated for presence of TMA. Of 272 patients 90 patients had pure AHR, 51 had pure ACR, 53 had CAHR, and 23 had IgA nephropathy. As shown in Table 1, 15 patients with other pathologies also had AHR; therefore, the total number of both pure and mixed AHR was 105 patients. Similarly, in addition to 51 patients with pure ACR, 47 patients also showed other pathologies accompanying ACR (Table 1); therefore, the total number of both pure and mixed ACR was 98 patients.

Among 90 patients with diagnosis of pure AHR, 35 (38.9%) showed focally and 38 (42.2%) showed diffuse C4d-positive staining, whereas 17 patients (18.9%) did not show C4d expression on PTCs (Table 2). Of 105 patients with mixed or pure AHR, 89 patients (84.8%) showed positive C4d expression and 16 patients (15.2%) showed negative C4d expression on PTCs. In 53 patients with CAHR, positive C4d expression on PTCs was found in 28 patients (52.8%). Table 2 shows the distribution of the PTC C4d expression among patients with pure AHR, CAHR, PVN, and IgA nephropathy. The incidence of diffuse C4d expression on PTC was 42.2%, 24.5%, 16.4%, and 8.7% in patients diagnosed with pure AHR, CAHR, PVN, and IgA nephropathy, respectively. Incidence of focal C4d expression on PTCs was 38.9%, 28.3%, 7.2%, and 0% in patients diagnosed with pure AHR, CAHR, PVN, and IgA nephropathy, respectively.

Only 74 of 272 patients (27.2%) had de novo TMA: 30/90 patients (33.3%) with pure AHR, 9/51 patients (17.6%) with ACR, 22/53 patients (41.5%) with CAHR, 10/55 patients (18.2%) with PVN, and 3/23 patients (13%) with IgA nephropathy recurrence (Table 2). The rate of TMA was higher in C4d-positive AHR (97.6%) and CAHR (68.2%) patients than in C4d-negative AHR (2.4%) and CAHR (31.8%) patients (\( P = .002 \) for AHR and \( P < .05 \) for CAHR; data not shown).

All PVN and IgA nephropathy patients who demonstrated C4d-positive expression on PTCs had AHR at the same time (Table 1). Patients with PVN and IgA nephropathy who also had AHR at biopsy tended to show a higher incidence of TMA than patients with PVN and IgA nephropathy alone (\( P < .001 \)). In addition, the rate of TMA was higher in PVN and IgA nephropathy patients who also had AHR than in patients with pure AHR (\( P < .01 \); Table 1 and Table 2).

---

**Table 1. Distribution of Second Pathology in Patients with Acute Cellular and Acute Humoral Rejection: Correlation With C4d Expression and Thrombotic Microangiopathy**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>%</th>
<th>Concomitant Pathology, No. (%)</th>
<th>C4d-Negative, No. (%)</th>
<th>Focal C4d-Positive, No. (%)</th>
<th>Diffuse C4d-Positive, No. (%)</th>
<th>TMA-Negative, No. (%)</th>
<th>TMA-Positive, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR No</td>
<td>174</td>
<td>64</td>
<td>89 (51.1)</td>
<td>44 (25.3)</td>
<td>41 (23.6)</td>
<td>144 (82.8)</td>
<td>30 (17.2%)</td>
<td></td>
</tr>
<tr>
<td>ACR Yes</td>
<td>98</td>
<td>36</td>
<td>Pure: 51 (52)</td>
<td>1 (5.9)</td>
<td>6 (33.3)</td>
<td>31 (58.8)</td>
<td>17 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHR: 17 (17.3)</td>
<td>1 (5.9)</td>
<td>6 (33.3)</td>
<td>31 (58.8)</td>
<td>17 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAHR: 20 (20.4)</td>
<td>1 (5.9)</td>
<td>6 (33.3)</td>
<td>31 (58.8)</td>
<td>17 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PVN: 4 (4.2)</td>
<td>0</td>
<td>4 (100)</td>
<td>0</td>
<td>4 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgA: 6 (6.1)</td>
<td>4 (66.7)</td>
<td>0</td>
<td>2 (33.3)</td>
<td>4 (66.7)</td>
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</tr>
<tr>
<td>AHR No</td>
<td>167</td>
<td>61.4</td>
<td>139 (83.2)</td>
<td>15 (9)*</td>
<td>13 (7.8)*</td>
<td>134 (80.2)</td>
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</tr>
<tr>
<td>AHR Yes</td>
<td>105</td>
<td>38.6</td>
<td>Pure: 90 (85.7)</td>
<td>17 (18.9)</td>
<td>35 (38.9)</td>
<td>38 (42.2)</td>
<td>60 (66.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAHR: 20 (20.4)</td>
<td>1 (5.9)</td>
<td>6 (33.3)</td>
<td>31 (58.8)</td>
<td>22 (41.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PVN: 13 (12.4)</td>
<td>0</td>
<td>4 (30.8)</td>
<td>9 (69.2)</td>
<td>4 (30.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgA: 2 (1.9)</td>
<td>0</td>
<td>2 (100)</td>
<td>0</td>
<td>2 (100)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACR, acute cellular rejection; AHR, acute humoral rejection; CAHR, chronic active humoral rejection; IgA, immunoglobulin A; PVN, polyomavirus nephropathy; TMA, thrombotic microangiopathy

*Focal and diffuse C4d-positive biopsies in this group were diagnosed as CAHR.

**Table 2. Summary of Results of Thrombotic Microangiopathy and C4d Expression**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>%</th>
<th>C4d-Negative, No. (%)</th>
<th>Focal C4d-Positive, No. (%)</th>
<th>Diffuse C4d-Positive, No. (%)</th>
<th>TMA-Negative, No. (%)</th>
<th>TMA-Positive, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>51</td>
<td>18.8</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
<td>42 (82.4)</td>
<td>9 (17.6)</td>
</tr>
<tr>
<td>AHR pure</td>
<td>90</td>
<td>33</td>
<td>17 (18.9)</td>
<td>35 (38.9)</td>
<td>38 (42.2)</td>
<td>60 (66.7)</td>
<td>30 (33.3)</td>
</tr>
<tr>
<td>CAHR</td>
<td>53</td>
<td>19.5</td>
<td>25 (47.2)</td>
<td>15 (28.3)</td>
<td>13 (24.5)</td>
<td>31 (58.5)</td>
<td>22 (41.5)</td>
</tr>
<tr>
<td>PVN</td>
<td>55</td>
<td>20.2</td>
<td>42 (76.4)</td>
<td>4 (7.2)</td>
<td>9 (16.4)</td>
<td>45 (81.8)</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td>IgA</td>
<td>23</td>
<td>8.5</td>
<td>21 (91.3)</td>
<td>0</td>
<td>2 (8.7)</td>
<td>20 (87)</td>
<td>3 (13)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACR, acute cellular rejection; AHR, acute humoral rejection; CAHR, chronic active humoral rejection; IgA, immunoglobulin A; PVN, polyomavirus nephropathy; TMA, thrombotic microangiopathy
As shown in Table 1, in 98 patients with ACR, 17 patients (17.3%) also had AHR, 20 patients (20.4%) also had CAHR, 4 patients (4.2%) also had PVN, and 6 patients (6.1%) also had IgA nephropathy at biopsy. Patients who had other pathologies accompanying ACR had the highest rates of TMA development in the renal allograft biopsy (Table 1). The type of the ACR also had a significant impact on the development of TMA; patients with type III and type II ACR (vascular rejection) tended to show a higher incidence of TMA development than patients with type I rejection ($P = .007$; Table 3).

As shown in Table 3, the incidence of TMA was higher in patients with focal and diffuse positive C4d expression on PTCs than in patients with negative C4d expression on PTCs ($P < .001$). In 109 patients who received cyclosporine, 150 who received tacrolimus, and 13 patients who received sirolimus (Table 3), significant differences were found between type of immunosuppressive therapy and development of TMA ($P = .02$). Patients who received cyclosporine (38.5%) tended to show a higher incidence of TMA than patients who received tacrolimus (20.7%) or sirolimus (7.7%) (Table 3).

Graft loss was found to be significantly higher in C4d-positive and TMA-positive patients ($P < .001$; Table 3). Rate of graft loss was also significantly higher in C4d-positive TMA patients (30/54 patients, 55.6%) than in C4d-negative TMA patients (6/20 patients, 30%; $P = .04$). Overall 1-, 3-, and 5-year graft survival rates were 94%, 85%, and 85% for TMA-negative patients and 83%, 51%, and 51% for TMA-positive patients ($P < .001$).

**Discussion**

Thrombotic microangiopathy is a well-recognized complication after renal transplant. However, there are important differences between TMA in native and transplanted kidneys. In a renal allograft, TMA can either be recurrent or de novo. Recurrent TMA is mostly related to genetic abnormalities and autoimmune diseases. However, de novo TMA is commonly related as a result of immunosuppression, renal allograft rejection, infections like cytomegalovirus, and other causes such as recurrent glomerulonephritis. The reported rates of de novo TMA vary from 1.1% to 14%. As we observed, the incidence of Escherichia coli-associated typical hemolytic uremic syndrome is significantly low in renal transplant patients. Renal transplant patients with TMA usually do not have systemic signs of hemolytic uremic syndrome. The diagnosis of TMA in renal allografts is made with renal allograft biopsy analyses. De novo TMA often occurs in the early posttransplant period (first 6 months), but it may also develop later.

It has been well documented that chronic administration of cyclosporine or tacrolimus is associated with microvascular disease, with calcineurin inhibitor toxicity reported to be the most common cause of posttransplant de novo TMA. A recent experimental study showed that cyclosporine induces increased endothelial release of complement-activating microparticles, suggesting that blocking complement activation may help to alleviate the condition. Carmona and associates found that cyclosporine alone and the combination of tacrolimus and sirolimus had an increased proinflammatory effect on endothelial cells; however, only cyclosporine showed additional prothrombotic effects.

The incidence of de novo TMA was recently shown to be 3% in renal allografts without evidence of AHR; however, all of the study patients were receiving tacrolimus and none were using...
mammalian target of rapamycin inhibitors. In another study of patients receiving a combination of sirolimus and cyclosporine with steroid avoidance, the incidence of de novo TMA was 3.6% in biopsies without evidence of AHR. In our study, we found that patients who were under cyclosporine therapy (38.5%) tended to show a higher incidence of TMA than patients receiving tacrolimus (20.7%) or sirolimus (7.7%).

Donor-specific antibody-mediated endothelial injury has been shown to be associated with TMA. Supporting these previous reports, we also demonstrated the importance of AHR-associated de novo TMA in renal transplant patients. We found that the rate of TMA was higher in patients with AHR and CAHR. We also found that presence of TMA in renal allografts was significantly higher in patients with AHR and CAHR who had C4d-positive biopsies versus AHR and CAHR patients with C4d-negative biopsies. Satoskar and associates reported results similar to ours, finding that presence of TMA among patients with C4d-positive biopsies was 4 times higher than patients with C4d-negative biopsies.

We also observed that recipients with pathologies combined with AHR or CAHR had higher incidences of TMA than patients with only one pathologic diagnosis, such as PVN, IgA nephropathy, or ACR. Patients with PVN and IgA who also had AHR at the same biopsy tended to show a higher incidence of TMA.

The rate of TMA was also higher in patients with PVN and IgA nephropathy who also had AHR versus patients who only had pure AHR. Of note, patients who had other pathologies combined with ACR had the highest rates of TMA in the renal allograft biopsy, with type of ACR having a significant impact on the development of TMA. Patients with type III and II ACR (vascular rejection) tended to show a higher incidence of TMA development than patients with type I rejection. All patients with type II and type III ACR who had TMA were C4d positive, indicating the possible influence of AHR on the development of TMA.

We suggest that AHR and CAHR are the most common and therefore important causes of de novo TMA in renal transplant patients. Therefore, the presence of TMA in the renal allograft biopsy should arouse suspicion for an underlying AHR or CAHR.

References

FGF23, NGAL, and Endostatin: the Predictors of Allograft Function in Renal Transplant Recipients

Bahar Gürlek Demirci, 1Siren Sezer,1 Salıha Ulyanı Yıldırım,2 Meltem Kaynar Erdoğan,2 Emre Tutal,1 Özlem Özdemir,3 Gani Orazbayev,1 Mehmet Haberal4

Abstract

Objectives: Increased circulating levels of fibroblast growth factor 23, neutrophil gelatinase-associated lipocalin, and endostatin are independent risk factors for cardiovascular disease. Here, we evaluated correlations among these parameters and graft dysfunction and their relation with arterial stiffness.

Materials and Methods: This prospective study included 73 maintenance kidney transplant patients with stable allograft function who had received the transplant at least 36 months previously. We calculated the estimated glomerular filtration rate (eGFR). Pulse-wave velocity was determined. Serum levels of fibroblast growth factor 23, neutrophil gelatinase-associated lipocalin, and endostatin were measured by enzyme-linked immunosorbent assay.

Results: Demographic characteristics and pulse-wave velocity values were similar in groups 1 and 2 (GFR < 60 and > 60 mL/min, respectively). Mean levels of fibroblast growth factor 23 (P = .036), neutrophil gelatinase-associated lipocalin (P = .018), and endostatin were significantly higher in group 1. Fibroblast growth factor 23 was negatively correlated with eGFR (r = -0.267, P = .023) and positively correlated with neutrophil gelatinase-associated lipocalin (r = 0.258, P = .036) and endostatin (r = 0.321, P = .006). Serum endostatin levels were positively correlated with pulse-wave velocity (r = 0.276, P = .019). In linear regression analysis, eGFR was detected as the unique predictor of neutrophil gelatinase-associated lipocalin (P = .001). In addition, each 1 mL/min decrease in eGFR resulted in a 0.281 pg/mL increase in fibroblast growth factor 23 (P = .023) and a 0.04 ng/mL increase in neutrophil gelatinase-associated lipocalin (P = .007); each 1 cm/s increase in pulse-wave velocity resulted in a 3648.7 U/L increase of endostatin (P = .019).

Conclusions: All 3 parameters were associated with loss of graft function in kidney transplant recipients. Moreover, endostatin can be used as an independent predictor for cardiovascular morbidity in this population.

Key words: Glomerular filtration rate, Kidney transplant, Pulse-wave velocity

Introduction

Renal transplantation is the ideal method for renal replacement therapy in patients with end-stage renal disease. Although cardiovascular risk decreases after renal transplant compared with patients with chronic kidney disease (CKD), these patients have still higher risk compared with the general population. The increased cardiovascular risk in patients with CKD can be explained by higher prevalence of traditional risk factors and presence of some risk factors specific to the CKD population, which include abnormal calcium-phosphorus metabolism, inflammation, oxidative stress, hyperhomocysteinemia, and microalbuminuria. Recently, increased circulating levels of fibroblast growth factor 23 (FGF23), neutrophil gelatinase-associated lipocalin (NGAL), and endostatin were also shown to be independent risk factors for mortality, cardiovascular disease, and progression of disease in CKD patients.

Fibroblast growth factor 23 is a phosphaturic hormone synthesized from osteocytes, and its level increases progressively from the early stages of CKD.1 An increased FGF23 level in CKD is associated with left ventricular hypertrophy,2 myocardial damage,3 increased cardiovascular events,4 progression of CKD,4,5 and mortality.6,7
Neutrophil gelatinase-associated lipocalin is a small glycoprotein that binds and transports different molecules and is secreted by many different tissue cells. Increased levels of NGAL can be determined after acute kidney injury. Recently, plasma NGAL levels in CKD patients were demonstrated to predict cardiovascular events and progression of CKD.

Endostatin is the 20-kDa C-terminal fragment of collagen XVIII and is an endothelial cell-specific angiogenesis inhibitor. Elevated plasma endostatin is associated with progression of CKD, cardiovascular events, and mortality.

Although increased FGF23, NGAL, and endostatin are each independent risk factors for cardiovascular and renal morbidity in CKD patients, studies of these markers in renal transplant recipients are limited and have shown conflicting results.

The aim of this study is to evaluate the relationship among FGF23, NGAL, endostatin, and graft dysfunction and to identify their relation with arterial stiffness.

Materials and Methods

This study included renal transplant recipients who were regularly followed in the Nephrology Department of Baskent University Faculty of Medicine Ankara Hospital. Patients < 18 years and > 65 years of age, patients who had an acute rejection episode during follow-up, or patients who had been followed for less than 36 months were excluded. Our study included 73 patients. All patients gave written informed consent for this study, which was approved by the ethics committee of Baskent University School of Medicine.

Age, sex, posttransplant duration, serum creatinine, parathyroid hormone, C-reactive protein, and lipid levels were recorded.

Values for estimated glomerular filtration rate (eGFR) were calculated using the Modification of Diet in Renal Disease 4-variable equation. Pulse-wave velocity (PWv) was determined from pressure tracing over carotid and femoral arteries using the SphygmoCor system (AtCor Medical, Itasca, IL, USA). Serum FGF23, NGAL, and endostatin levels were measured by enzyme-linked immunosorbent assay. Systolic and diastolic blood pressures of the participants were measured after 5 minutes of resting in supine position. Two measurements were performed for each patient, and the average values of the measurements were recorded.

Patients were divided into 2 groups according to the GFR. The patients with GFR less than 60 mL/min were categorized as group 1, and the patients with GFR equal or greater than 60 mL/min were categorized as group 2.

Statistical analyses were performed with SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). The distribution of variables was evaluated with the Kolmogorov-Smirnov test. Continuous variables were described as means and standard deviation or median (minimum to maximum) and evaluated with analysis of variance or the Kruskal-Wallis test. Categorical variables were described as number or percentage and evaluated with the chi-square test. The Pearson correlation coefficient was used for continuous variables with normal distribution, and the Spearman correlation coefficient was used for continuous variables that are not normally distributed. When correlations between variables were seen, multivariate regression analyses were performed. P < .05 was considered to be statistically significant.

Results

The study included 73 patients (22 females, 51 males). Mean age of the patients was 40.4 ± 10.6 years, and median transplant duration was 72 months (range, 12-324 mo).

Demographic characteristics, basic laboratory values, systolic-diastolic blood pressures, and PWv values were similar between group 1 (patients with GFR < 60 mL/min) and group 2 (patients with GFR > 60 mL/min) (Table 1). The mean FGF23, NGAL, and endostatin levels were significantly higher in group 1 than in group 2 (Table 2).

In correlation analysis, FGF23 was negatively correlated with eGFR (r = -0.267, P = .023). When we investigated the correlations among FGF23, NGAL, and endostatin, we observed that FGF23 was positively correlated with levels of NGAL (r = 0.258, P = .036) and endostatin (r = 0.321, P = .006). In addition, serum endostatin levels were positively correlated with PWv (r = 0.276, P = .019).

In linear regression analysis, eGFR was detected as the unique predictor of NGAL (P = .001). In addition, each 1 mL/min decrease of eGFR resulted in an increase in FGF23 of 0.281 pg/mL (P = .023) and...
an increase of 0.04 ng/mL for NGAL (P = .007); each 1 cm/s increase in PWV resulted in an increase in endostatin of 3648.7 U/L (P = .019).

### Table 1. Demographic and Laboratory Parameters of Patients According to Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 25)</th>
<th>Group 2 (n = 48)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>18</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>7</td>
<td>15</td>
<td>.497</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.92 ± 9.93</td>
<td>39.13 ± 10.77</td>
<td>.147</td>
</tr>
<tr>
<td>Transplant duration, y</td>
<td>8.39 ± 7.45</td>
<td>5.74 ± 4.11</td>
<td>.123</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.38 ± 7.33</td>
<td>25.84 ± 4.03</td>
<td>.117</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>129.92 ± 18.62</td>
<td>122.45 ± 17.59</td>
<td>.095</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>94.68 ± 17.84</td>
<td>89.10 ± 14.33</td>
<td>.552</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>2.06 ± 0.99</td>
<td>1.07 ± 0.21</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>42.00 ± 13.45</td>
<td>81.75 ± 14.28</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>136.68 ± 4.68</td>
<td>137.72 ± 3.02</td>
<td>.317</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.24 ± 0.43</td>
<td>4.08 ± 0.34</td>
<td>.084</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>466.37 ± 649.53</td>
<td>1225.1 ± 89.87</td>
<td>.070</td>
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<tr>
<td>CRP, mg/L</td>
<td>4.49 ± 4.61</td>
<td>7.38 ± 15.17</td>
<td>.357</td>
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<td>LDL, mmol/L</td>
<td>131.13 ± 48.25</td>
<td>136.70 ± 36.32</td>
<td>.585</td>
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<tr>
<td>TG, mmol/L</td>
<td>187.28 ± 104.09</td>
<td>174.04 ± 92.54</td>
<td>.582</td>
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<tr>
<td>HDL, mmol/L</td>
<td>50.27 ± 12.68</td>
<td>58.6 ± 44.10</td>
<td>.555</td>
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<tr>
<td>GFR, mL/min</td>
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<tr>
<td>HDL, mmol/L</td>
<td>50.27 ± 12.68</td>
<td>58.6 ± 44.10</td>
<td>.555</td>
</tr>
</tbody>
</table>

### Abbreviations: CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone; SBP, systolic blood pressure; TG, triglyceride

### Table 2. Fibroblast Growth Factor 23, Neutrophil Gelatinase-Associated Lipocalin, and Endostatin Levels According to Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF23, pg/mL</td>
<td>45.6 ± 5.3</td>
<td>42.9 ± 3.4</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>NGAL, pg/mL</td>
<td>643.0 ± 42.3</td>
<td>515.0 ± 28.3</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Endostatin, U/L</td>
<td>6149.1 ± 1178.9</td>
<td>5538.7 ± 291.0</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

### Abbreviations: FGF23, fibroblast growth factor 23; NGAL, neutrophil gelatinase-associated lipocalin

### Discussion

This study showed that serum FGF23, NGAL, and endostatin levels were higher in renal transplant recipients with impaired glomerular filtration than in renal transplant recipients with normal glomerular function.

An increased level of FGF23 is a result of kidney failure; with progression of kidney disease, it can reach up to 1000-fold above the normal range. In a study performed by Gutierrez and associates, serum FGF23 levels were compared in 200 patients who died and 200 who survived during the first year of hemodialysis treatment; they used multivariable adjusted analyses and found that increasing FGF23 levels were associated with an increasing risk of death (odds ratio per unit increase in log-transformed C-terminal FGF23 values of 1.8; 95% confidence interval, 1.4-2.4). In another study performed by Larsson and colleagues, serum concentrations of FGF23 were measured in 20 patients at different stages of renal failure (creatinine range of 155-724 μmol/L), in 33 patients with end-stage renal disease on dialysis treatment, in 30 patients with functioning renal grafts, and in 6 healthy male patients given oral phosphate binders in combination with low dietary phosphate intake for 2 days followed by 3 days of repletion with inorganic phosphate. The group found that circulating FGF23 was significantly elevated in patients with CKD and its concentration correlated with renal creatinine clearance. Pande and associates studied FGF23 levels in patients with all stages of CKD and in renal transplant recipients before and after renal transplant. In patients who showed a rapidly decreased posttransplant level of FGF23, the group suggested that FGF23 was cleared by the functional graft. In our study, we observed a negative correlation between GFR and FGF23 levels in renal transplant recipients similar to these studies, which confirm a continuing relation between renal function and FGF23 level in the posttransplant period.

Plasma NGAL levels were first confirmed to be a novel marker for acute kidney injury; however, recently, authors aimed to evaluate whether it is only a novel specific biomarker of acute kidney injury or whether it could predict the progression of CKD. Bolignano and associates performed a study in 96 CKD patients and demonstrated that NGAL represents a novel, independent renal predictor of CKD progression that also provides a good reflection of the severity of renal disease. In another study performed by Hall and colleagues, urinary NGAL was shown to be an early, noninvasive, accurate predictor of both the need for dialysis within the first week of kidney transplant and 3-month recovery of graft function. In our study, there was a significant difference in NGAL levels between the 2 groups composed according to GFR levels.

The effect of angiogenesis and related factors on the development and progression of CKD has been recently examined. Endostatin, which is an angiogenesis inhibitor molecule, is one of these biomarkers. In a study performed with 200 CKD patients and 200 controls, Chen and associates showed that the plasma endostatin levels were higher in patients with CKD than in controls and that the difference was significant. However, as far as we know, there is no previous study about endostatin in renal transplant recipients. Our study is the first...
study to compare endostatin levels and GFR in a population of renal transplant recipients, and we found a significant negative correlation between GFR and endostatin levels. A second important finding was the significant association between serum endostatin levels and PWv, which is an established marker of arterial stiffness.

The findings in this study confirm that levels of FGF23, NGAL, endostatin are still affected by the degree of renal impairment in renal transplant recipients. Although we found a significant correlation between endostatin and PWv, this does not imply causation because this is a cross-sectional study. Further studies with larger sample sizes are required to better define the role of these markers in the development of arterial stiffness.

In conclusion, elevated FGF23, NGAL, and endostatin levels were associated with loss of graft function in kidney transplant recipients. Moreover, endostatin can be used as an independent predictor for cardiovascular morbidity in this population.

References

Morphologic and Immunologic Characteristics of Hepatocellular Carcinoma for Prognosis of Surgical Intervention

Gulziya Ismailova, Eugene Yenin, Shokan Kaniev, Dinara Bayguisova, Talgat Tajibaev

Abstract

Objectives: Hepatocellular carcinoma is the predominant malignancy in patients with cirrhosis and chronic liver disease. Our aim was to assess the morphologic, radiologic, and immunologic characteristics of hepatocellular carcinoma and liver cirrhosis concerning surgical treatment tactics.

Materials and Methods: We performed a cross-sectional analysis of a prospective study performed at the JSC National Scientific Center of Surgery (named after A. Syzganov). The study included 58 patients: 31 with hepatocellular carcinoma (53.4%) and 27 with chronic liver disease (46.6%). The average age of patients was 55.6 ± 1.7 years.

Results: Patients were tested for hepatitis B virus and hepatitis C virus infection. Patients with elevated levels of alfa-fetoprotein, alanine aminotransferase, and total bilirubin were detected. Morphologic signs of hepatocellular carcinoma with a predominance of a trabecular type rather than a solid type of tumor were found. Patients with hepatocellular carcinoma underwent surgical liver resection and transarterial chemoembolization before living-donor liver transplant. One-year survival rate of patients with hepatocellular carcinoma was 93.5%.

Conclusions: The diagnosis and surgical options for hepatocellular carcinoma should be studied, taking into account the expanded laboratory characteristics of cancer.

Key words: Cirrhosis, Liver disease, Liver transplant

Introduction

In Asia and Africa, which have the greatest prevalence of hepatitis infection, the incidence of hepatocellular carcinoma (HCC) is 120 per 100,000.1 Those with a combination of risk factors, chronic hepatitis B virus (HBV), and cirrhosis have a 100-fold increased risk of HCC. Approximately 5% to 30% of patients with hepatitis C virus (HCV) will have chronic liver disease, and 30% will have cirrhosis and HCC.2,3 In Kazakhstan, diagnostic and treatment issues have remained focused on liver tumors,4 due to the complexity of early diagnosis, chemotherapy’s lack of effectiveness, the primary diseases underlying cirrhosis, and the complexity of choosing treatment options with invasive methods.5

In this study, our objective was to assess the morphologic, radiologic, and immunologic characteristics of HCC and liver cirrhosis with regard to surgical treatment options.

Materials and Methods

We conducted a cross-sectional analysis of a prospective study that included patients with HCC and chronic liver disease who had been treated in the Department of Hepatopancreatic Surgery from 2015 to 2017. Of 58 patients treated, 31 had HCC (53.4%) and 27 had other chronic liver diseases (46.6%). Our total patient group included 30 women (51.7%) and 28 men (48.3%) with an average age of 55.6 ± 1.7 years. The 31 patients with HCC ranged in age from 34 to 70 years (60.2 ± 1.5; 61.3% men and 38.7% women) (Table 1).

All patients had laboratory tests for alfa-fetoprotein (AFP), total bilirubin, nondirect bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Patients also had immunologic assays for HBV and HCV, histologic analyses of liver tissue, and computed tomographic (CT) scans.
Treatment strategies for HCC with or without liver cirrhosis were determined according to the Barcelona clinic liver cancer (BCLC) staging of HCC and with application of the Milan criteria. Data were collected prospectively in our institutional HCC registry. The study protocol was approved by our Institutional Local Research Ethics Committee (June 26, 2016), and the study protocol conformed with the ethical standards of the Declaration of Helsinki. All participants in the study submitted informed consent.

All analyses were conducted with SPSS software (SPSS: An IBM Company, version 18.0, IBM Corporation, Armonk, NY, USA) and MedCalc. We used *t* tests and chi-square tests, with a relative *P* < .05 used to determine significance. Continuous data are presented as mean and standard deviation or median, and categorical data are presented as frequency. Comparisons of patient characteristics and outcomes were conducted in the 2 patient groups (those with HCC and those with chronic liver disease).

**Results**

The study group included 14 patients with HCC and liver cirrhosis (45.2%) (Figure 1) and 17 patients with HCC without liver cirrhosis (54.8%) (Figure 2). The

### Table 1. Main Features of Participants

<table>
<thead>
<tr>
<th>Feature</th>
<th>HCC</th>
<th>CLD</th>
<th>95% CI</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>31 53.4</td>
<td>27 46.6</td>
<td>20.6-33.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Age, years</td>
<td>60.2 ± 1.5</td>
<td>44.5 ± 3.4</td>
<td>14.3-17.1</td>
<td>23.3*</td>
</tr>
<tr>
<td>No. of women</td>
<td>7 15.6</td>
<td>18 66.7</td>
<td>0.5-76.1</td>
<td>5.1</td>
</tr>
<tr>
<td>No. of men</td>
<td>19 61.3</td>
<td>9 33.3</td>
<td>16.2-61.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; CLD, chronic liver disease; HCC, hepatocellular carcinoma

*Statistical significance level is *P* ≤ .05.

(A) Structure of the parenchyma is not homogeneous, due to presence of volumetric formation in segments VI, VII, VIII, with clearly uneven outlined and hypodense areas in structure (15.8×12.9×16.4 cm) and uneven accumulations of contrast agent. (B) Formation feeds to right hepatic artery (with the arterial network inside), in the process involving the right portal vein, which is intimately adjoined to the right branch of the portal vein.

(A) Formation of 16.7 × 15.8 × 13.6 cm and density of +34/+54 Hounsfield unit occupies the entire right lobe; a contrast agent is accumulating predominantly around the peripheral. (B) There are small branches of right hepatic artery proper in formation structure. The formation intimately adjoins the right adrenal, slightly pressing on the right branch of portal vein and pushing aside the intrahepatic part of the inferior vena cava.
control group (patients with chronic liver disease) included 12 patients with liver fibrosis (44.5%), 7 patients with primary biliary cirrhosis (25.9%), 3 patients with autoimmune hepatitis (11.1%), and 5 patients with cirrhosis due to other causes (18.5%).

In patients with HCC, enzyme-linked immunosorbent assay detected antibodies with titer positive to HBV in 14 patients (45.2%) and titer positive to HCV in 10 patients (32.3%), of whom 1 patient (3.2%) had positive results for both HBV and HCV; in addition, 7 patients (22.6%) were HBV/HCV negative. In patients with chronic liver disease, 4 patients (14.8%) showed antibodies with titer positive for HBV (14.8%) and 4 patients (14.8%) tested positive for HCV (Table 2).

Morphologic data were characterized for signs of HCC. Trabecular-type HCC was predominant, shown in 26 patients (83.9%), versus solid tumor type, shown in 5 patients (16.1%). Degree of malignancy according to the Edmondson-Steiner system showed 8 patients (25.8%) having grade I, 10 patients (32.3%) having grade II, 9 patients (29.0%) having grade III, and 4 patients (12.9%) having grade IV (Figures 3-6 show resection of archived materials).

**Surgical treatment**

In the 14 patients (45.2%) with clinical signs of HCC and liver cirrhosis (AFP of 35.5 ± 11.3 U/mL, ALT of 80.6 ± 11.9 U/mL, and total bilirubin of 26.2 ± 5.2 μmol/L), transarterial chemoembolization

---

**Table 2. Clinical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCC</th>
<th>%</th>
<th>CLD</th>
<th>%</th>
<th>95% CI</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV positive</td>
<td>14</td>
<td>45.2</td>
<td>4</td>
<td>14.8</td>
<td>33.7-61.8</td>
<td>1.1</td>
</tr>
<tr>
<td>HCV positive</td>
<td>10</td>
<td>32.3</td>
<td>4</td>
<td>14.8</td>
<td>46.0-55.6</td>
<td>0.4</td>
</tr>
<tr>
<td>HBV/HCV positive</td>
<td>1</td>
<td>3.2</td>
<td>70.4</td>
<td>50.0-70.9</td>
<td>4.6*</td>
<td></td>
</tr>
<tr>
<td>HBV/HCV negative</td>
<td>7</td>
<td>22.6</td>
<td>19</td>
<td>0.0-3.9</td>
<td>7.1*</td>
<td></td>
</tr>
<tr>
<td>AFP, U/mL</td>
<td>48.7 ± 14.0</td>
<td>3.9 ± 1.3</td>
<td>33.0-55.6</td>
<td>7.1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, μmol/L</td>
<td>41.7 ± 9.7</td>
<td>59.8 ± 21.4</td>
<td>10.5-25.7</td>
<td>4.8*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT, U/mL</td>
<td>72.7 ± 9.1</td>
<td>77.4 ± 15.2</td>
<td>1.2-10.6</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, U/mL</td>
<td>83.4 ± 10.4</td>
<td>98.1 ± 16.2</td>
<td>8.2-21.2</td>
<td>4.5*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistical significance level is P ≤ .05.

**Abbreviations:** AFP, alfa-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
(TACE) was performed. Living-donor liver transplant was performed in 9 patients (29.0%) with HCC according to the BCLC stage (0-1) and cirrhosis score (Child-Pugh A or A/B) after TACE procedures.

In the 17 patients (54.8%) with HCC without cirrhosis (AFP of 5.21 ± 1.7 U/mL, ALT of 46.5 ± 26.7 U/mL, and total bilirubin of 17.8 ± 4.5 μmol/L), liver resection and TACE were performed. Eight patients (25.8%) had partial liver resection by laparotomy or a mini laparotomy approach, with 3 of these patients (9.7%) having liver resection as a second-stage treatment after TACE.

In total, 26 patients (83.9%) with HCC had TACE repeatedly at intervals of 4 to 6 months, at 5 times for 1 patient (3.2%), 4 times for 1 patient (3.2%), 3 times for 2 patients (6.5%), 2 times for 4 patients (12.9%), and 1 time for 18 patients (58.1%).

Among the control group patients with chronic liver disease, 4 patients (14.8%) underwent liver transplant, of whom 2 (7.4%) received livers from living donors and 2 (7.4%) received livers from deceased donors. In addition, 8 patients (29.6%) underwent selective chemoembolization and 15 patients (55.6%) are continuing to receive conservative therapy.

One-year survival rate was 93.5%. In patients with HCC, 2 patients (6.5%) died less than 1 year after repeated TACE.

**Discussion**

Surgical options for patients with HCC with and without liver cirrhosis depend on the pathologic and morphologic characteristics. Options (liver transplant, resection, ablation, and TACE) should depend on the stage of liver cirrhosis and the size of tumor according to the Milan criteria.6,7

According to the literature, liver resection to obtain R0 (tumor-free marginal resection) provides a 3-year survival of 54% in patients with HCC and noncirrhotic liver. Liver transplant can offer better long-term survival for patients with HCC and cirrhosis because it offers the possibility to treat the tumor and the main disease, although use of liver transplant to treat HCC is controversial.7,9 Patients with a single node smaller than 5 cm or 3 nodes smaller than 3 cm who are not suitable for resection are encouraged to have liver transplant. When these Milan criteria guidelines are followed, patients have a 5-year survival rate and a disease-free overall survival rate of more than 65%.7,10 In cases when recipients have waited for a donor for a long time (more than 6 months), they are encouraged to undergo resection, local ablation, or TACE to avoid tumor progression risk and to offer a bridge to transplant.11

Transarterial chemoembolization for HCC with cirrhosis, or palliative care, are generally accepted standard treatments as “bridge” options when waiting for transplant.12,13 Transarterial chemoembolization is recommended for patients for HCC and BCLC B stage without vascular invasion and extrahepatic metastases and multinodal asymptomatic HCC.13,14

**Conclusions**

The diagnosis and determination of the strategy for surgical treatment of HCC should be further studied, taking into account the expanded laboratory characteristics of cancer.

**References**


Abstract

Objectives: Despite surgical advances and effective prophylactic strategies in liver transplant, infection is still a major cause of morbidity and mortality. Up to 80% of liver recipients will develop at least 1 infection during the first year after liver transplant. The spectrum and manifestations of these infections are broad and variable. Their diagnosis and treatment are often delayed because immunosuppressive therapy diminishes inflammatory responses. However, if an infection is not identified early enough and treated properly, it can have devastating consequences. In addition, prophylactic approaches remain controversial. Our aim was to review our early postoperative infection management after liver transplant.

Materials and Methods: We retrospectively evaluated infections that occurred during the first hospital stay of transplant patients. Infections were grouped as surgical site and nonsurgical site infections. Consequences and treatment protocols of infections were stratified according to the Clavien scale.

Results: Between December 1988 and January 2017, we performed 561 liver transplants at our center (patient age range, 6 months to 64 years), which included 401 living-donor (72%) and 160 deceased-donor (28%) liver transplants. Early postoperative infections were detected in 131 patients (23.3%), comprising 67 surgical site (51%), 56 nonsurgical site (43%), and 8 combined surgical and nonsurgical site infections (6%). Although no mortalities occurred in patients with single nonsurgical or surgical site infections, there were 4 mortalities in patients with combined surgical and nonsurgical site infections. In the 4 other patients with combined infections, 3 patients required endoscopic or radiologic intervention and 1 recovered from single-organ dysfunction.

Conclusions: Initiation of appropriate prophylactic and therapeutic protocols at the right time decreases morbidity and mortality due to infection in liver transplant recipients. Increased understanding and effective approaches to prevent infection are essential to improving both graft and recipient survival.

Key words: Cytomegalovirus, End-stage liver disease; Pneumocystis jiroveci, Surgical site infection

Introduction

Liver transplantation is the standard therapeutic procedure for patients with end-stage liver disease. Liver transplant survival rates are reported as 85% in the first year. Despite surgical advances and effective prophylactic strategies, infection is still a major cause of morbidity and mortality after liver transplant. The incidence of infectious complications in liver transplant recipients remains higher than in any other solid-organ transplant procedure, with up to 80% of liver recipients developing at least 1 infection during the first year after transplant.1 The incidence of infection-related mortality has decreased from more than 50% before 1980, to 25% to 35% in the 1980s, and to less than 10% in the 1990s.2

The spectrum and manifestations of these infections are broad and variable. Liver transplant patients are in impaired states of health before transplant, liver transplant is a technically complex operation, and liver transplant patients require lifelong immunosuppressive therapy, contributing to risk of infection. In addition, immunosuppressive therapy may be intensified due to possible rejection. Infections not diagnosed early enough or treated appropriately can have devastating consequences. Diagnosis and treatment are often delayed because
immunosuppressive therapy diminishes inflammatory responses, and clinical signs of infection may be blunted or absent, symptoms of infection may mimic rejection, and it may be difficult to distinguish between true rejection and colonization. Although most infections are successfully treated, some will cause death.

Most infections are seen in the first 2 months after transplant. The prophylactic approaches for these early postoperative infections require proper patient monitoring, including knowledge of the time course of infections and possible risk factors. In this study, we aimed to review our early postoperative infection management after liver transplant.

Materials and Methods

All patients who underwent liver transplant at our center from December 1988 to January 2017 were investigated for occurrence of infections during their first hospital stay. The demographic findings and preoperative and intraoperative features were retrospectively recorded. All patients initially received a standard triple immunosuppressive regimen, consisting of prednisone, tacrolimus/cyclosporine, and mycophenolate mofetil.

Our standard surgical procedure starts with standard asepsis and preparation; a primary bilateral subcostal incision is then made and extended in the midline. The liver is then mobilized with dissection and cautery. The graft is placed in the abdominal cavity to determine the most appropriate site of hepatic venous anastomosis. Thereafter, portal vein anastomosis is constructed, which is followed by arterial anastomosis. Biliary anastomosis is performed last, via duct-to-duct or hepatica-jejunostomy anastomosis. Intraoperative hepatic blood flow and graft status are assessed routinely by Doppler ultrasonography. After suction drainage catheters are placed, the incision is closed and the patient is brought to the intensive care unit for postoperative follow-up. We follow a fast-track surgery pathway for patient care. Liver function is monitored by Doppler ultrasonography and liver function tests (twice per day during the first week); on day 7 after transplant, computed tomography scans are obtained.

For our patients, infections were defined as established previously. Organisms were identified using conventional methods and automated systems. Antimicrobial susceptibility was tested according to the criteria of the Clinical and Laboratory Standards Institute. Prophylaxis consisted of cefotaxime and ampicillin for 3 days before transplant. Recipients also received trimethoprim-sulfamethoxazole for Pneumocystis jiroveci prophylaxis and valganciclovir for Cytomegalovirus prophylaxis. Fluconazole prophylaxis was provided for 2 weeks.

For this study, we classified infections as surgical site infections (SSI) and nonsurgical site infections (NSSI). Infections with microbiologic evidence in the superficial and deep fascia and in the organ site were classified as SSI. Infections with microbiologic evidence in other systems (respiratory tract, blood, urinary tract) were classified as NSSI. Consequences and treatment protocols of infections were stratified according to the Clavien scale shown in Table 1.

Results

Between 1988 and 2017, we performed 561 liver transplant procedures at our centers (age range of patients, 6 months to 64 years), which included 401 living-donor (72%) and 160 deceased-donor (28%) liver transplants. Early postoperative infections were detected in 131 liver transplant procedures (23.3%). The consequences and treatment protocols of infectious complications were stratified according to the Clavien classification scale (Table 2). Of 131 cases, we detected 67 with SSI (51%), 56 was NSSI (43%), and 8 with combined SSI and NSSI (6%).

There were no mortalities due to NSSI. Of 56 cases of NSSI, 34 patients (62%) were treated without any additional intervention, just with therapeutic regimens like antiemetic, antipyretic, analgesic, diuretic, and electrolyte agents and physiotherapy. Nine other patients with NSSI (16%) received

<table>
<thead>
<tr>
<th>Table 1. Clavien Scale</th>
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<tbody>
<tr>
<td>Clavien Scale</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Grade 3a</td>
</tr>
<tr>
<td>Grade 3b</td>
</tr>
<tr>
<td>Grade 4a</td>
</tr>
<tr>
<td>Grade 4b</td>
</tr>
<tr>
<td>Grade 5</td>
</tr>
</tbody>
</table>
pharmacologic treatment (including antibiotics, blood transfusion, and parenteral nutrition), 7 (12%) required endoscopic or radiologic intervention with or without general anesthesia, and 6 (10%) survived and recovered from single or multiorgan dysfunction.

We also observed no mortalities due to SSI. Of 67 cases of SSI, 37 patients (55%) were treated without any additional intervention, just with wound care and antibiotics. In the remaining SSI cases, 29 patients (44%) required endoscopic or radiologic intervention with or without general anesthesia and 1 (1%) survived and recovered from single or multiorgan dysfunction.

In the combined NSSI plus SSI group, we observed 4 mortalities (due to sepsis and multiorgan dysfunction). Three of the 8 patients with combined NSSI plus SSI required endoscopic or radiologic intervention with or without general anesthesia and 1 patient survived and recovered from single organ dysfunction. All patients with combined NSSI plus SSI were classified with Child class C disease (mean Model for End-Stage Liver Disease [MELD] score of 20) and impaired health status. Two patients had hepatic artery complications and repeated percutaneous interventions and surgical procedures (1 patient had 3 laparotomies, the other had 2 laparotomies for hepatic artery reconstruction), which were done in the first week posttransplant. Although patients are treated with fast-track surgery pathway protocol, all patients with combined NSSI plus SSI stayed more than 48 hours in the intensive care unit. Length of hospital stay in this patient group was also longer than in other patients (mean of 17 days).

**Discussion**

Despite remarkable advances in liver transplant, infection can still be a frequent cause of morbidity and mortality posttransplant. Liver transplant recipients are more vulnerable to infection than other solid-organ transplant recipients due to the technical complexities of surgery, contamination in the abdominal cavity, and the preoperative impaired health status of recipients. Most infections occur in the early period posttransplant (in the first month) due to the technical difficulties of the surgery.5 Infections are associated with either pretransplant conditions or postoperative complications.6 Because symptoms of infection may mimic rejection and may be difficult to distinguish between true infection and mere colonization, a close follow-up of both recipient status and graft function is mandatory in the early postoperative period. At our center, to detect infections and implement therapy earlier, we monitor the transplanted liver with Doppler ultrasonography and liver function tests and obtain computed tomography scans on day 7 posttransplant.

The type, severity, and incidence of observed infections often depend on prophylactic practices. Because immunosuppressive regimens have been standardized, a timetable for determining when postoperative infections are most likely to occur has been developed. Knowledge of this timetable may allow clinicians to form differential diagnoses, initiate monitoring procedures for infection, and implement effective management strategies. Specific risk factors for infection in liver transplant recipients include underlying medical conditions, environmental exposures in the community or hospital, technical complications of the surgery, and the state of immunosuppression. Knowledge of these risk factors may allow identification of liver transplant recipients at greatest risk for infection and early management. Previous medical conditions, chronic underlying diseases, renal failure, mechanical ventilation, malnutrition, and high MELD score may predispose recipients to infection.7,8 Indeed, all patients with NSSI and SSI were classified with Child class C disease (mean MELD score of 20) and impaired health status.

Exposure to nosocomial pathogens is also concerning. Risk factors for these pathogens include central venous or urinary tract catheters, extended use of systemic antibiotics or corticosteroids, colonization by a fungal pathogen, and total parenteral nutrition. To decrease infections caused by these factors, we follow a fast-track surgery pathway.9 Factors related to surgical procedures are also important. Disruption

<table>
<thead>
<tr>
<th>Table 2. Infections According to Clavien Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>NSSI</td>
</tr>
<tr>
<td>SSI</td>
</tr>
<tr>
<td>NSSI+SSI</td>
</tr>
</tbody>
</table>

Abbreviations: NSSI, nonsurgical site infection; SSI, surgical site infection
of the integrity of gastrointestinal tract and anastomotic leaks may cause infections by endogenous flora. Any technical complication that leads to devitalized tissue, vascular thrombosis, or fluid accumulation can enhance infection. Vascular devices and drainage catheters are also risk factors for infection since they disturb the physical barrier and provide entry portals for both endogenous and nosocomial organisms. The transplanted liver can also be a focus of infection as a result of ischemia and rejection. Infections are shown to be higher in liver transplant recipients who require prolonged operative time, retransplant, or repeat laparotomy. Retransplant, prolonged ventilator support, renal failure, extended renal replacement therapy, prolonged use of antimicrobial agents, colonization with resistant hospital flora, and immunosuppression play critical roles in postoperative development of infections. Our findings were similar, as 4 patients in our study group with combined NSSI plus SSI died from sepsis and multiorgan dysfunction. Two patients had hepatic artery complications, and repeated percutaneous interventions and surgical procedures were done in the first week posttransplant. In addition, all patients with NSSI plus SSI were in the intensive care unit for more than 48 hours and had longer hospital stays.

Multiple recipient and external factors increase infection risk for liver transplant patients. It is important to identify patients at greatest risk for serious infection. In our study, higher MELD scores and complicated and repeated surgical procedures increased incidence of infections. Initiation of appropriate prophylactic and therapeutic protocols at the right time can decrease morbidity and mortality due to infection in liver transplant recipients. A better understanding of infection risk and effective approach to prevent infection are also essential to improving graft and recipient survival.

References

Liver Peliosis: A Life-Threatening Condition With No Clear Indication for Liver Transplant

Kakhraman Yesmembetov,1,2 Natalya Satlikova,1,3 Zhanat Spatayev,4 Kulpash Kaliaskarova1,2

Abstract

We present a 21-year-old patient, remarkable for huge hepatomegaly with the liver, occupying almost the entire abdominal cavity, and mild portal hypertension due to splenic vein compression. After ultrasonography-guided liver biopsy, performed to establish the diagnosis, the patient had bleeding from the liver. Fortunately, emergency laparotomy was started immediately, and the patient was saved. Macroscopically, the liver appeared to be of purple-red color, flabby to the touch, and able to be easily wrinkled with fingers. When all available clinical data were considered, a diagnosis of liver peliosis was made. The patient was recommended close follow-up at the specialized liver surgery clinic with access to emergency surgical procedures, including liver transplant.

Key words: Emergency laparotomy, Hemangiomatosis, Hepatomegaly, Liver biopsy, Liver rupture

Introduction

A 21-year-old Russian male patient presented at an outpatient clinic with feeling of heaviness in the right upper abdominal quadrant in June 2016. The disease first manifested itself as nausea and feeling of heaviness in the right upper abdominal quadrant in October 2015. Evaluation at a regional hospital found no markers of viral hepatitis and no signs of autoimmune-related, alcohol-induced, and metabolic liver disease. Hepatomegaly and splenomegaly, along with multiple hypoechoic structures in the liver according to abdominal ultrasonography, resulted in a diagnosis of polycystic liver disease.

The patient was referred to our clinic and underwent evaluation for the cause of liver disease. He appeared to be well-developed with body mass index of 24 kg/m². The patient had no previous medical history and did not report taking any medications, including over-the-counter and herbal supplements. Physical examination was remarkable for huge hepatomegaly with right liver lower margin reaching the right iliac bone. Visual stigmata of chronic liver disease were absent. Evaluation revealed mild elevation of liver function tests and leukopenia (Table 1). Abdominal ultrasonography demonstrated mild splenomegaly, due to compression of the splenic vein, with no signs of thrombosis in liver and portal vein system. There were no signs of portal hypertension according to esophagogastroscopy. Computed tomography also showed no signs of liver and portal vein system thrombosis and no contrast-enhanced lesions in the liver, apart from multiple hypoechoic zones in the liver parenchyma (Figure 1). Hepatobiliary zone oncomarkers, positron emission tomography of the whole body, endoscopic evaluation, and other visualizing methods did not identify any neoplasms in the liver and abdominal cavity.

When we considered all of the clinical information available, a differential diagnosis was made among liver polycystic disease, peliosis, and hemangiomatosis. To establish the diagnosis, a percutaneous blind ultrasonography-guided liver biopsy was performed on an outpatient basis. The patient tolerated the procedure well, but follow-up abdominal ultrasonography 1 hour after the biopsy revealed up to 500 mL of free fluid in the abdominal cavity, suggestive of bleeding from the liver.
patient was admitted immediately, and an emergency laparotomy was started after the patient’s approval was obtained.

<table>
<thead>
<tr>
<th>Test</th>
<th>Admittance Day</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>107</td>
<td>130-160 g/L</td>
</tr>
<tr>
<td>White blood cells</td>
<td>2.9</td>
<td>4-9 x 10^9/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>300</td>
<td>150-320</td>
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<tr>
<td>Total protein</td>
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<td>Creatinine</td>
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<td>AST</td>
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<td>0-32 IU/L</td>
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<tr>
<td>ALT</td>
<td>60.3</td>
<td>0-33 IU/L</td>
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<tr>
<td>Total bilirubin</td>
<td>16.4</td>
<td>1.7-21.0 µmol/L</td>
</tr>
<tr>
<td>INR</td>
<td>1.09</td>
<td>0.85-1.15</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio

When the open abdominal cavity was visualized, macroscopically, the liver was remarkable for its huge size, purple-red color, flabbiness to the touch, and ability to be easily wrinkled with fingers (Figure 2). The puncture hole in the liver was detected and sutured, ensuring adequate hemostasis, with total blood loss of up to 1 L. Because of potential risk of bleeding from the liver, no further biopsy was performed during surgery. Histologic examination of the liver biopsy specimen showed only traces of blood. The patient was discharged without any postoperative complications.

To clarify further management options and prognosis, the patient was discussed among consultant transplant specialists from Kazakhstan, Russia, and South Korea. The above-mentioned evaluation resulted in a differential diagnosis of liver peliosis or hemangiomatosis and excluded polycystic liver disease because of lack of family history among close relatives. The danger of rupture of the liver from the slightest trauma, the lack of liver decompensation, and the potential high risk of bleeding during the operation made it difficult to recommend liver transplant to the patient. With consideration of the scarcity of information regarding treatment of patients with liver peliosis, the multidisciplinary group recommended close follow-up and emergency surgery, including liver transplant, if life-threatening situations arise.

**Discussion**

Liver peliosis is an uncommon condition associated with cavities of different sizes, filled with blood, in the liver parenchyma. This disease was first named in 1916 by Schoenlank and believed to be described in 1861 by Wagner. Causes of this condition remain unknown, although different theories have been proposed, including drug usage, infections (both bacterial and viral), immunodeficiency, and others. More data are available on the pathogenesis of the disease, with damage of the liver sinusoidal-lining cells being described as the starting point of the chain of changes. The latter leads to sinusoidal obstruction, necrosis of the liver cells, and subsequently damage of the sinusoidal barriers.

Discovery of liver peliosis is usually incidental. In some cases, it manifests with life-threatening complications, such as liver rupture or hemorrhage after blind transcutaneous biopsy, and can lead to death if timely treatment is not applied. This, in part, occurred in our case, with our patient fortunately saved by emergency laparotomy and quick discovery of the puncture hole thanks to expertise of surgeons.
Our case of liver peliosis, with the process involving both lobes, is seen in a minority of cases (14%), with rates of incidence limited to left lobe of only 11% and limited to the right lobe of 75%. The treatment algorithm for this condition is lacking due to the scarcity of information regarding its natural history; however, close follow-up at a specialized liver surgery clinic and the ability to have access to emergency surgical procedures, including liver transplant when needed, seem to be reasonable options. All available diagnostic modalities should be used before performing liver biopsy due to the high risk of liver rupture and/or bleeding, and open procedures should be considered for this reason so that possible complications can be treated immediately.

References

Prognosis of Patients Following Liver Transplant From Deceased and Living Donors

Kakharm Yesmembetov,1,2 Tokan Sultanaliyev,3 Adilbek Mukazhanov,4 Assan Zhexembayev,4 Gani Kuttymuratov,5 Zhanat Spatayev,4 Yevgeniy Mussin,6 Yerlan Umbedzhanov,7 Damesh Orazbayeva8

Abstract

Objectives: Liver transplant is the only treatment option for patients with end-stage liver disease. Materials and Methods: Liver transplant procedures performed from June 2013 to March 2017 were evaluated. We evaluated the postoperative period in recipients of livers from deceased and living donors. Results: Of 31 liver transplant procedures in 30 recipients, 12 were from deceased and 19 from living donors. The final analysis included 24 liver transplants (11 males, 13 females), with 10 from deceased and 14 from living donors. No deaths or life-threatening and debilitating complications were shown in liver donors. All living-donor liver transplants were performed utilizing the right lobe, the volume of which was calculated using contrast-enhanced computed tomography. Most living-donor liver recipients had viral hepatitis, whereas most deceased-donor liver recipients had autoimmune liver disease. Median age of recipients of deceased donations was 39.3 years (median admission duration of 28.1 days), and median age of recipients of donations from living donors was 45.4 years (median admission duration of 36.4 days). All patients were started on an immunosuppression protocol, which included basiliximab on days 0 and 4, tacrolimus, mycophenolate, and prednisolone. Of 24 recipients, 5 were taking prednisolone 10 mg/day or less at discharge. Conclusions: Most of our liver transplant procedures were living-donor liver transplants (61.3%). Most patients who received living donations had viral hepatitis, with all cases related to autoimmune liver disease receiving deceased donations. This may be related to the possibility of antiviral therapy controlling all stages of liver disease versus no chance of controlling autoimmune liver disease. Living-donor liver transplant recipients required more time to recover to reach initial liver volume; 20.8% of recipients were discharged with prednisolone of 10 mg/day or less. Our results suggest a need for further development of nonsteroidal immunosuppression strategies to minimize infections and steroid-related adverse effects.

Key words: Deceased-donor liver transplantation, End-stage liver disease, Etiology of liver disease, Immunosuppression, Living-donor liver transplantation

Introduction

Liver transplant is the only curative treatment option for patients with end-stage liver disease. In December 2011, a liver transplant program was started in Kazakhstan, and 183 operations in total have been performed up to January 1, 2017.1 Of these, 151 (82.5%) were from living donors (living-donor liver transplantation; LDLT) and 32 (17.5%) were from deceased donors (deceased-donor liver transplant; DDLT). In 2016, 496 adult and 9 pediatric patients with end-stage liver disease were on wait lists for liver transplant in Kazakhstan, but only 13.3% received transplants the same year.

Materials and Methods

Liver transplant procedures performed at the National Scientific Center for Oncology and Transplantation in Kazakhstan from establishment of a transplant program in June 2013 to March 2017 were evaluated. We aimed to assess the postoperative period in recipients of livers from deceased and living donors to study differences in causes of liver disease,
causes of prolonged hospital stay, and immunosuppression in these patients.

Results

From June 2013 to March 2017 in our clinic, 31 liver transplants in 30 recipients were performed, with 12 (38.7%) from deceased and 19 (61.3%) from living donors. We analyzed the data from all transplants, excluding 1 pediatric transplant in a 6-year-old boy and 5 transplants in recipients with survival of less than 1 month. Thus, the final analysis included 24 liver transplant recipients (11 males, 13 females), with 10 from deceased and 14 from living donors. No deaths or life-threatening and/or debilitating complications were shown in the liver donors. All LDLTs were performed utilizing the right lobe, with volume calculated using contrast-enhanced computed tomography. Causes of initial liver disease were as follows for LDLT/DDLT recipients: 0/1 with autoimmune hepatitis, 0/3 with primary biliary cirrhosis, 2/0 with hepatitis B infection, 6/1 with hepatitis B and D infections, 2/0 with hepatitis C infections, 1/0 with hepatitis B, C, and D infections, 2/0 with nonalcoholic steatohepatitis, and 1/2 with alcoholic liver disease. Median age of DDLT recipients was 39.3 years (range, 15-57 years), and median age of LDLT was 45.4 years (range, 30-62 years). The median admission durations were 28.1 days (range, 23-54 days) for DDLT recipients and 36.4 days (range, 28-50 days) for LDLT recipients.

Induction immunosuppression included administration of basiliximab (20 mg) on days 0 and 4 and prednisolone (500-1000 mg), followed by gradual tapering down to 20 mg/day by mouth. From day 2 posttransplant, tacrolimus (starting dose of 1.0 mg/day with dose titration to reach blood levels of 7-8 ng/mL) and mycophenolate (1000 mg/day) were added. All recipients were on prednisolone at discharge, with eventual withdrawal of the drug at 6 months posttransplant. Of 24 transplant recipients at the point of hospital discharge, only 5 patients were on prednisolone dose of 10 mg/day or less, whereas the remaining 19 patients were still taking 10 to 20 mg/day.

Discussion

In late 2011, a liver transplant program was launched in Kazakhstan. Since then, 183 operations have been performed up to January 1, 2017, with the leading source of organs being living donors (82.5%). The low number of deceased donations in Kazakhstan, despite the state legislation following examples of developed nations, may be related to lack of organ donation advocates and need for its promotion, like in South Korea. Because of the shortage of donor organs, only 67 patients (13.3%) with end-stage liver disease were transplanted of 505 in total (496 adults, 9 children) listed for liver transplant in 2016. This clearly warrants more efforts to increase the number of liver transplants to meet the demand for this life-saving procedure.

When we compared rates with other nations that performed mostly LDLTs, we found that Turkey had 1150 liver transplants in 2013 for the 2065 patients on wait lists for the procedure. Most liver transplant procedures in our center were performed with living donors (61.3%), which is in line with data from other centers in Kazakhstan.

We found that most liver transplants due to viral hepatitis were performed using living donors and that all liver transplants related to autoimmune liver disease were performed using deceased donors. The reason that patients with viral end-stage liver disease receive donations from living donors may be related to the possibility of use of antiviral therapy at nearly any stage of liver disease as opposed to there being no chance to control autoimmune liver disease; therefore, these patients require urgent operations from deceased donors.

Recipients of livers from living donors need more time to recover from the operation because of the need to reach initial liver volume. Only 20.8% of recipients were discharged from the transplant unit with a prednisolone dose of 10 mg/day or less. This warrants the need for further development of nonsteroidal immunosuppression strategies to minimize infections and steroid-related adverse effects.

References

Liver Transplant and Reexpansion Pulmonary Edema: A Case Report

Sibel Kara,1 Nazan Sen,2 Sule Akcay,3 Gokhan Moray,4 Murat Kus,5 Mehmet Haberal4

Abstract

Hydrothorax occurs frequently in patients with end-stage liver disease and usually requires drainage of pulmonary effusion during the heptectomy phase of liver transplant. Reexpansion pulmonary edema is a rare but potentially fatal complication seen after rapid reexpansion of the collapsed lung following thoracentesis of pleural fluid or tube drainage of pneumothorax. This condition, which manifests with various degrees of clinical severity, is rarely reported following liver transplantation. Herein, we present a 62-year-old male patient who developed reexpansion pulmonary edema after drainage of massive pleural effusion, which caused a total collapse in the right hemithorax during liver transplant. Six hours after pleural fluid drainage, the patient developed a nonproductive cough, mild tachypnea, shortness of breath, and low oxygen saturation (88%). His chest radiograph showed diffuse heterogeneous opacities in the right hemithorax. Computed tomography of the thorax revealed consolidations containing air bronchograms and ground glass opacities in the parenchyma of the right lung; these findings did not extend to the periphery and were observed less frequently in the inferoposterior left lung. These symptoms and radiologic findings were diagnosed as reexpansion pulmonary edema. Complete clinical and radiologic improvements were achieved within 72 hours of mechanical ventilatory support.

Key words: Collapsed lung, Mechanical ventilatory support, Pleural effusion, Thoracentesis

Introduction

Reexpansion pulmonary edema (RPE) is an uncommon but potentially fatal condition that occurs due to immediate reexpansion of a collapsed lung following thoracentesis or tube drainage performed to remove fluid (pleural effusion) or air (pneumothorax) from the pleural space.1 Its incidence ranges from 1% to 14%.2,3 Hepatic hydrothorax is a complication of cirrhosis, and the fluid is usually drained before liver transplant or during the procedure.4 When RPE occurs after rapid and excessive fluid drainage from the pleural space, clinical manifestation varies from radiologic alterations alone to rapidly progressive respiratory failure requiring mechanical ventilation.5 The pathophysiology of RPE remains unclear. The mechanisms suggested include mechanical stress-induced free radical increases secondary to capillary injury during pulmonary reexpansion or to reperfusion-induced increases in pulmonary capillary permeability that result in pulmonary edema.6

Case Report

Herein, we present a 62-year-old male patient with RPE. Reexpansion pulmonary edema occurred after the removal of massive pleural effusion from the right hemithorax via a drainage catheter during liver transplant performed for Child class B cirrhosis and hepatocellular carcinoma. His medical history revealed glottic laryngeal carcinoma in remission, diabetes mellitus, and no smoking or alcohol consumption.

On his physical examination before surgery, he was mildly icteric and his oxygen saturation was 95% to 96%. Auscultation of the respiratory system was unremarkable, except for the absence of breath sounds in the right hemithorax. Laboratory analysis revealed total serum bilirubin of 2.6 mg/dL, an albumin level of 2.6 g/dL, and a blood glucose level...
of 161 mg/dL; other biochemical, electrolyte, and coagulation parameters were within the normal limits. Posteroanterior lung radiography demonstrated homogenously increased parenchymal density secondary to massive pleural effusion in the right lung (Figure 1).

Nearly 2.5 L of pleural fluid was drained during liver transplant via an F8 drainage catheter inserted into the right hemithorax. The patient’s hemodynamic parameters were within the normal limits throughout the surgical procedure, and his general status was stable. The patient, who was monitored in the intensive care unit after transplant and had no respiratory complaints, developed a nonproductive cough, mild tachypnea, and shortness of breath with low oxygen saturation 6 hours after surgery. The patient’s vital signs were as follows: body temperature, 36.4°C; blood pressure, 130/80 mm Hg; respiratory rate, 26 breaths/min; and pulse rate, 100 beats/min. His blood gases were pH 7.40, partial pressure of oxygen of 54 mm Hg, partial pressure of carbon dioxide of 38.8 mm Hg, and oxygen saturation of 88%. Chest examination revealed rales in the bilateral inferior zones and in the entire right lung.

Posteroanterior lung radiography showed diffuse heterogeneous opacities in the right hemithorax (Figure 2). Computed tomography of the thorax revealed extensive consolidation and ground glass densities in the lung parenchyma; the periphery was partially preserved, and less extensive consolidation was observed in the inferoposterior zone of the left lung (Figure 3). Echocardiography was unremarkable, and there were no signs of fluid overload. These clinical and radiologic findings were consistent with RPE. His shortness of breath worsened, and mechanical ventilation and hemodynamic support were started. Monitoring of blood gases revealed

**Figure 1.** Posteroanterior Lung Radiograph Showing Homogenously Increased Parenchymal Density Secondary to Massive Pleural Effusion in the Right Lung

![Figure 1](image1.png)

**Figure 2.** Anteroposterior Lung Radiograph Showing Diffuse Heterogeneous Opacities in the Right Hemithorax

![Figure 2](image2.png)

**Figure 3.** Computed Tomography of the Thorax Showing Extensive Consolidation and Ground Glass Opacities in the Right Lung Parenchyma

![Figure 3](image3.png)

The periphery is partially preserved, and less extensive consolidation is seen in the posteroinferior zone of the left lung.
improvements, showing pH 7.40, partial pressure of oxygen of 80 mm Hg, partial pressure of carbon dioxide of 36.4 mm Hg, and oxygen saturation of 95%. The patient was extubated after 3 days, and complete clinical and radiologic remission was achieved.

Discussion

Noncardiogenic acute pulmonary edema (PE) occurs frequently following liver transplant and makes perioperative progress difficult.7,8 Whereas 25% of patients undergoing lung transplant develop sudden and relatively benign PE that improves within the first 24 hours, 18% develop persistent permeability-type PE that lasts longer than 16 hours. This diffuse edema may be associated with numerous causes, including acute fluid overload, transfusion-associated acute lung injury (TRALI), acute respiratory distress syndrome, and fulminant hepatic failure. The underlying pathology is associated with impaired balance of transcapillary hydrostatic pressure (hydrostatic-type PE) or an impaired permeability barrier (permeability-type PE).8

Reexpansion pulmonary edema is the non-diffuse permeability-type PE of noncardiogenic edema that occurs after acute drainage of air or fluid from the pleural space, which allows rapid expansion of a collapsed lung. During liver transplant, acute drainage is required for large amounts of pleural effusion, and subsequent RPE may be a factor that contributes to early postoperative respiratory distress. The collapsed lung is typically affected; the contralateral lung may also be affected. Reexpansion pulmonary edema may overlap with other perioperative pulmonary complications, such as pleural effusion, atelectasis, TRALI, and hydrostatic PE due to nonspecific radiologic findings because of the clinical course, which is normally benign and temporary. The process usually lasts less than 72 hours, but a mortality rate as high as 20% has been reported.9 Reexpansion pulmonary edema occurs within the first hour or subsequent 24 hours in 64% of patients.1,10 In the present case, RPE occurred 6 hours postoperatively and improved within 72 hours. The right lung, of which a substantial portion was collapsed, was affected as was the contralateral lung, albeit less extensively.

Although the pathophysiology of RPE is unclear, risk factors include young age, female sex, large or long-lasting lung collapse, reexpansion of the lung in < 10 minutes, use of negative pressure while draining air or fluid from the pleural space, and a drained fluid volume > 2000 mL.1 In the present case, the large amount of pleural fluid resulted in recurrent total collapse in the right hemithorax 3 months previous, and the drainage of 2500 mL of fluid in a short time might have played a role in the development of RPE.

In our case, the findings were considered to be consistent with RPE because of the history of pleural fluid drainage, relatively benign initial symptoms, normal hemodynamic parameters, radiologic patchy consolidations more remarkable in 1 hemithorax, and absence of typical signs of cardiogenic PE, TRALI, or acute respiratory distress syndrome, which cause PE.

Treatment of RPE includes ventilatory and hemodynamic support. The primary treatment is positive-pressure mechanical ventilation. End-expiratory positive pressure helps reexpansion of the collapsed alveoli, resulting in increased functional residual capacity and decreased shunting. Moreover, diuresis and vasopressor support may be included in the treatment, but the role of medications remains unclear.11 In addition, some measures are recommended to lower the risk of developing RPE, such as limiting the amount of drainage (< 1.5 L) and avoiding extremely negative pleural pressure.12 In our patient, clinical and radiologic improvements were achieved after 72 hours with mechanical ventilatory support.

A case of early perioperative death secondary to RPE during liver transplant13 and a single case of RPE with benign progress despite severe hypoxia14 were reported. Herein, we presented a case of RPE with benign progress.

In conclusion, RPE is a rare but serious complication seen after thoracentesis. This complication may occur after fluid drainage from the pleural space, which is a common procedure during liver transplant, and is among the causes of PE likely to occur in the early period. Early diagnosis and treatment are important to prevent death due to this life-threatening complication.

References


Budd-Chiari Syndrome Diagnosed in a Patient Listed for Liver Transplant and Considered to be Contraindicated for the Operation

Kakharman Yesmembetov,1,2 Zhansaya Muratova,1,3 Sergey Borovskiy,4,5 Irina Ten,4 Kulpash Kaliaskarova1,2

Abstract

We report the clinical case of 23-year-old patient with liver cirrhosis of unknown genesis, significant resistant ascites, and 2 episodes of bleeding from esophageal varices. Evaluation did not find any cause of liver disease, and the patient was placed on the transplant wait list due to subcompensated liver function (Model for End-Stage Liver Disease score of 16, Child-Pugh class B) and poorly controlled severe portal hypertension. After treatment with diuretics, large-volume paracentesis, antibiotics, and vasoconstrictors, hepatorenal syndrome and spontaneous bacterial peritonitis resolved and liver function improved significantly. Because the patient showed consistently good liver function and resistant portal hypertension, liver transplant was delayed with decision to perform transjugular intrahepatic portosystemic shunting instead. During the attempt of shunting, occlusive thrombosis of the iliac veins, inferior vena cavae, and hepatic veins were diagnosed and the procedure was stopped. Therefore, considering preserved liver function and severe portal hypertension, diagnosis of Budd-Chiari syndrome with subsequent development of liver cirrhosis was made. The patient was recommended to undergo evaluation to exclude thrombophilia as a cause of thrombosis.

Key words: Hepatic vein thrombosis, Inferior vena cavae thrombosis, Liver cirrhosis, Portal hypertension, Transjugular intrahepatic portosystemic shunt

Introduction

In November 2015, a 23-year-old Kazakh male patient was admitted with enlargement of the abdomen with hernia, weakness, and feeling of heaviness in the right upper abdominal quadrant. The disease had first manifested itself with asthenia and swelling of the feet in 2012, with later development of ascites and profound weight loss of up to 30 kg in 3 months (initial weight of 91 kg). The ascites was successfully treated with diuretics. Evaluation at a regional hospital found no markers of viral hepatitis and no signs of autoimmune- and alcohol-related, drug-induced, or metabolic liver disease. Portal hypertension with esophageal varices and splenomegaly were unlikely to be related to liver cirrhosis due to normal liver function and no signs of decompensation.

In January 2013, the patient experienced the first bleeding from esophageal varices, followed by a second episode in October 2013, both controlled by Sengstaken-Blakemore tube insertion. In March 2014, paracentesis was performed for therapeutic purposes with removal of up to 12 L of ascitic fluid.

At admittance to our inpatient clinic in November 2015, the patient appeared to be well developed, but undernourished, with body mass index of 19 kg/m². Physical examination was remarkable for significant ascites with reducible umbilical hernia of up to 10 cm in diameter and multiple caput medusae on the abdominal wall (Figure 1). Chronic liver disease stigmata, including telangiectases on chest and palmar erythema, were also present. Contrast-enhanced computed tomography (CT) revealed no signs of vascular thrombosis in portal vein/inferior vena cava and up to 6 L ascitic fluid; we also observed 2 lesions in liver of up to 15 mm in segmented V and VI, with wash-out phenomenon in venous phase (Figure 2). We could not obtain a biopsy because of significant ascites and the small
size of lesions. A diagnosis of hepatocellular carcinoma (HCC) was made due to characteristic features by CT.

The patient was started on diuretics and paracentesis with removal of up to 5 L of ascitic fluid. The latter was unremarkable for other causes other than portal hypertension at assessment. Hepatorenal syndrome, diagnosed at admittance, and spontaneous bacterial peritonitis were successfully treated with octreotide and ceftriaxone, with subsequent normalization of kidney function (Table 1). Ligation of esophageal varices was performed due to endoscopic stigmata of the risk of bleeding. Because the umbilical hernia was reducible and did not require immediate operation, it was recommended to be addressed later.

The patient was on a transplant wait list and discharged in early December 2015.

Despite recommendations at discharge regarding need for evaluation and consultation of a hepatologist and transplant specialist every 3 months, the patient was not seen at our facility until September 2016. He had undergone another abdominal tapping with removal of 11 L of ascitic fluid in May 2016. The patient was admitted to our inpatient clinic in September 2016 with his 30-year old brother as a potential living liver donor. The appearance of the patient had not changed compared with that of November 2015, with significant resistant ascites, caput medusa, and inguinal hernia still present. Due to no signs of thrombosis and lesions in the liver by abdominal ultrasonography, preserved liver function (Table 2), and resistant

### Table 1. Laboratory Tests at Day of First Admittance and at Days 5 and 10 of Inpatient Treatment

<table>
<thead>
<tr>
<th>Test</th>
<th>Admittance</th>
<th>Day 5</th>
<th>Day 10</th>
<th>Normal Value</th>
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<td>Hemoglobin</td>
<td>122</td>
<td>130</td>
<td>160 g/L</td>
<td>35-52 g/L</td>
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<td>White blood cells</td>
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<td>150-320</td>
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<td>Platelet count</td>
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<td></td>
<td>150-320</td>
<td></td>
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<tr>
<td>GGT</td>
<td>59.30</td>
<td></td>
<td>0-60 IU/L</td>
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<td>ALP</td>
<td>178.00</td>
<td></td>
<td>35-98 IU/L</td>
<td></td>
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<tr>
<td>Albumin</td>
<td>36.9</td>
<td>37.9</td>
<td>38.3</td>
<td>35-52 g/L</td>
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<td>Total protein</td>
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<td>79.3</td>
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<td>Creatinine</td>
<td>167.0</td>
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<td>64.9</td>
<td>62-106 µmol/L</td>
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<tr>
<td>Serum urea nitrogen</td>
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<td>5.50</td>
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<tr>
<td>AST</td>
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<td>0-32 IU/L</td>
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<tr>
<td>ALT</td>
<td>21.8</td>
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<td>0-33 IU/L</td>
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<tr>
<td>Total bilirubin</td>
<td>17.4</td>
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<td>1.7-21.0 µmol/L</td>
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<tr>
<td>Direct bilirubin</td>
<td>10.4</td>
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<td>0.3-5.0 µmol/L</td>
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<tr>
<td>Potassium</td>
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<td>4.3</td>
<td>3.5-5.1 mmol/L</td>
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<tr>
<td>Sodium</td>
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<td>130</td>
<td>129</td>
<td>136-146 mmol/L</td>
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<tr>
<td>Alfa-fetoprotein</td>
<td>1.57</td>
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<td>0-10 ng/mL</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.13</td>
<td></td>
<td>0.85-1.15</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio
ascites, liver transplant was delayed, with the decision to insert a transjugular intrahepatic portosystemic shunt (TIPS) instead.

During the attempt to insert the TIPS, the shunt failed to pass further to the level of confluence of hepatic veins in the inferior vena cava (IVC) (Figure 3). Further attempts to visualize the IVC system via iliac veins revealed signs of thrombosis extending to the IVC and hepatic veins (Figures 4-6). Occlusive thrombosis of the iliac veins, IVC, and hepatic veins were contraindications for TIPS, and the procedure was stopped.

The patient was started on low-molecular-weight heparin (0.6 mL/day) and then switched to rivaroxaban (10 mg/day) for long-term use. Further evaluation did not find any other sites of thrombosis, including legs, chest area, and neck. When we considered the severe portal hypertension without signs of decompensated liver disease and occlusive thrombosis of the hepatic veins, extending to IVC and iliac veins, a diagnosis of Budd-Chiari syndrome with subsequent development of liver cirrhosis was made. The patient has been recommended to undergo evaluation by a hematologist to exclude thrombophilia as a cause of thrombosis.

### Table 2. Laboratory Tests at Second Admittance

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>132</td>
<td>130-160 g/L</td>
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<tr>
<td>White blood cells</td>
<td>7.3</td>
<td>4.9 × 10^9</td>
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<tr>
<td>Platelet count</td>
<td>222</td>
<td>150-320 × 10^9</td>
</tr>
<tr>
<td>Serum urea nitrogen</td>
<td>4.2</td>
<td>2.8-8.1 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
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<tr>
<td>Total protein</td>
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<td>g/L</td>
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<tr>
<td>Albumin</td>
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<td>g/L</td>
</tr>
<tr>
<td>Total bilirubin</td>
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<td>1.7-21.0 μmol/L</td>
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<tr>
<td>Sodium</td>
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<td>136-146 mmol/L</td>
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<tr>
<td>Potassium</td>
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<tr>
<td>INR</td>
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<td>0.85-1.15</td>
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<tr>
<td>Antithrombin III</td>
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<td>79.4-112%</td>
</tr>
<tr>
<td>Homocysteine</td>
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<td>5.4-11.7 μmol/L</td>
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<tr>
<td>D-dimers</td>
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<td>0.443 ng/mL</td>
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<tr>
<td>Fibrinogen</td>
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<td>1.8-3.5 g/L</td>
</tr>
<tr>
<td>aPTT</td>
<td>30.3</td>
<td>24-31.3 s</td>
</tr>
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</table>

**Abbreviations:** aPTT, activated partial thromboplastin time; INR, international normalized ratio

**Figure 3.** Attempt to Pass (Arrow) Through Cava Atrial Junction Failed Due to Occlusive Thrombosis of Inferior Vena Cava

**Figure 4.** Arrow Shows Collateral Venous Blood Flow Through Dilated Subcutaneous Veins During Left-Sided Cavagraphy Due to Occlusion of Inferior Vena Cava

**Figure 5.** Arrow Shows Collateral Venous Blood Flow Through Dilated Paravertebral Veins Due to Thrombosis of Inferior Vena Cava
Discussion

Budd-Chiari syndrome is a rare condition associated with obstruction of the hepatic venous outflow, which could occur anywhere from the hepatic venules up to the junction of the IVC and right atrium. The disease usually progresses, leading to a worsening patient state if no intervention is applied. Because most treatment decisions of patients with Budd-Chiari syndrome are based on an expert opinion and are not evidence-based, a clear management algorithm for this life-threatening condition has not yet been established. Although 4325 publications on Budd-Chiari syndrome have been published up to 2014, only 421 (9.7%) have been cohort studies, 45 (1%) have been case-control studies, and none have been randomized controlled trials.1 This demonstrates the need for adequately powered cohort studies or controlled trials to determine the natural history of this disease and the optimal intervention strategy.

To stratify patients into subgroups with the subsequent optimal treatment options, several prognostic scores have been applied to patients with Budd-Chiari syndrome, such as Budd-Chiari syndrome-TIPS, Child-Pugh, the Clichy prognostic index, Model for End-Stage Liver Disease, the new Clichy prognostic index, and the Rotterdam index.2 None have been able to reach an area under the curve value of more than 0.7, thus being difficult to recommend for treatment of an individual patient.3 Thus, in clinical practice, the optimal strategy would be a step-wise move to a more invasive therapeutic option if there have been no adequate responses to less invasive treatments.4

A reasonable step-wise strategy for most cases would be starting anticoagulation, then angioplasty or stenting, followed by vascular decompression (surgical shunting or TIPS), and finally liver transplant in case of hepatic failure. Resistant ascites, persistent encephalopathy, and decompensation of the liver function have been proposed as criteria for stepping up.5 Different types of liver lesions have been described in patients with Budd-Chiari syndrome, including large regenerative nodules, mimicking HCC.6 Our patient also had liver lesions when first admitted resembling HCC, but follow-up evaluation did not confirm it. Considering the liver cirrhosis in the patient, they were most likely regenerative nodules.

Our patient received anticoagulation therapy, with obvious contraindications for TIPS. Liver transplant was not needed at the patient’s current stage due to normal liver function, absence of HCC, and occlusive thrombosis of the IVC and hepatic veins. According to the above-mentioned step-wise strategy, angioplasty/stenting or surgical decompression/shunting might be optimal treatment options for our patient; however, since discharge in October 2016, we have lost contact with this patient.

References

Abstract

Objectives: Smoking is an important risk factor for development of complications in heart transplant patients and plays an important role in the mortality of these patients. The aim of this study was to compare the survival of heart transplant patients after transplant versus their smoking status before transplant.

Materials and Methods: Patients who had heart transplant procedures at the Baskent University Hospital Cardiovascular Surgery Department between 2005 and 2016 were analyzed retrospectively with regard to their smoking status and survival after transplant. We divided the 51 included adult patients into 2 groups: nonsmokers and ex-smokers. Data were analyzed with SPSS software (Statistical Package for Social Sciences for Windows, version 23.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics are shown as means ± standard deviation, and differences between means were determined with t tests. Survival statistics were evaluated with Kaplan-Meier analyses using log-rank test.

Results: Of 51 heart transplant patients, 40 were male (78.4%) and 11 were female (21.6%) patients. Mean age was 42.5 ± 14.2 years in male patients and 30.4 ± 13.2 years in female patients (95% confidence interval, 2.4-21.8). Although 36 patients (70.6%) were still living at follow-up, 15 patients had died (29.4%). According to smoking status, 30 patients (58.8%) were nonsmokers and 21 patients (41.2%) were ex-smokers, who showed smoking rate of 23.7 ± 26.0 packs/year. We found that patients who were nonsmokers survived longer; however, at time of analysis (September 30, 2017), survival was not mature yet for the nonsmoking group. Median survival time for patients who were ex-smokers was 93.0 months (log-rank test = .099).

Conclusions: Our study showed that patients in the nonsmoking group survived longer after heart transplant. Early smoking cessation can prolong survival of heart transplant patients.

Key words: Hypertension, Survival, Vascular disease, Vasculopathy

Introduction

Patient outcomes after heart transplant have improved with advances in treatment strategies. Graft failure, infection, and multiorgan dysfunction are the most common causes of mortality during the first year after heart transplant. In the long term, malignancy, graft failure, cardiac vasculopathy, and infections are the most common causes of mortality. Smoking is an important risk factor for the development of vasculopathy, and it also induces development of hypertension, diabetes mellitus, and malignancies in heart transplant patients. Therefore, smoking plays an important role in mortality of these patients.

The aim of this study was to determine the smoking status of heart transplant patients before transplant and compare survival of heart transplant patients after transplant versus their smoking status before transplant.

Materials and Methods

Patients who had heart transplants at the Baskent University Hospital Cardiovascular Surgery Department between 2005 and 2016 were analyzed retrospectively with regard to their smoking status and survival after transplant. In total, 51 adult patients had heart transplants during this period. These patients were divided into 2 groups: nonsmokers and ex-smokers. We performed data analyses using SPSS software (Statistical Package for Social Sciences for Windows, version 23.0, SPSS Inc., Chicago, IL, USA).
Results

Of 51 heart transplant patients, 40 were male (78.4%) and 11 were female (21.6%) patients. Mean age was 42.5 ± 14.2 years in male patients and 30.4 ± 13.2 years in female patients (95% confidence interval, 2.4-21.8). At follow-up, 36 heart transplant patients (70.6%) were still alive and 15 patients (29.4%) had died. According to their smoking status, 30 patients were nonsmokers (58.8%) and 21 patients were ex-smokers (41.2%). Of 11 female patients, 1 was an ex-smoker who had quit smoking 2 years before the transplant procedure. All female patients who were non-smokers were alive at follow-up except for 1 patient who died because of acute rejection. Among the 40 male patients, 20 were nonsmokers, with 12 still alive at follow-up. In male patients who smoked, 5 patients had quit smoking more than 5 years before transplant, with all patients still alive at follow-up. Of 12 patients who had quit smoking 1 to 3 years before transplant, 8 had died. Two patients who were still living at follow-up had quit smoking after transplant. Finally, 1 patient who continued smoking posttransplant also died. For ex-smokers, the mean packs/year was 23.7 ± 26.0 (median of 15 packs/year).

When we compared survival of patients after transplant, patients who were nonsmokers survived longer (Figure 1). However, at time of analysis (September 30, 2017) survival was not mature yet for the nonsmoking group. Median survival time for the ex-smoking group was 93.0 months (log-rank test = .099).

Discussion

Our study showed that patients who are nonsmokers demonstrated longer survival after heart transplant. Nägele and associates also found smoking to be much more important than other risk factors regarding contribution to mortality.² Dellgren and associates reviewed 595 heart transplant patients and found history of smoking to be one of the predictors of long-term mortality.³ Patients who smoked until shortly before heart transplant also showed poorer prognosis and decreased survival.⁴ Although only 1 patient in our group continued smoking even after transplant, it is known that many patients continue smoking after transplant and many ex-smokers start smoking again after heart transplant.¹,₅

Because this was a retrospective study, we were not able to assess the exposure to second-hand smoke, which is an important health hazard. Gali and associates compared the mortality of nonsmokers versus ex-smokers who were on wait lists and found that smoking at time of listing may increase risk of mortality during the waiting period.⁶

In conclusion, it is important to encourage smoking cessation as early as possible, even at the time of initial transplant evaluation. Because time on heart transplant wait lists are known to be long, starting smoking cessation therapies in these patients as early as possible can increase the success of this difficult and precious procedure. Family members, relatives, and friends of these patients should be informed about the hazards of second-hand smoking for these patients, and they should also be also encouraged to enter smoking cessation programs. Because of the high risk of return to smoking, patients who are ex-smokers should be followed closely.

References


Treatment of Left Ventricular Assist Device Thrombosis: Single-Center Experience

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Abstract

Heart failure is one of the biggest health problems in the world. Because of limited donors for heart transplant procedures, the ventricular assist device has become a solution for heart failure therapy. With the increase in number of ventricular assist devices, the incidence of complications has also increased. One of the most important life-threatening complications is ventricular assist device thrombosis. Medical therapy and changes in the ventricular assist device are the main therapy methods for ventricular assist device thrombosis. In this study, we showed our clinical experience with treatment of ventricular assist device thrombosis.

Key words: Heart failure, Heart transplantation, Stroke

Introduction

Heart failure is a progressive disease; with the increased duration of life in the population, it is increasingly seen. The criterion standard treatment for late-stage heart failure is heart transplant. However, because of limited donors for transplant, use of ventricular assist devices (VAD) has increased. The latest technology in VAD is continuous flow VAD. Continuous flow VADs are divided into 2 groups: axial flow devices (Heart mate II, Thoratec Corp., Pleasanton, CA, USA) and centrifugal flow devices (HeartWare, HeartWare Inc, Framingham, MA, USA; and HeartMate III, Thoratec Corp.). In our clinic, we use continuous flow centrifugal VAD. Ventricular assist devices are used for 3 indications:

- Destination therapy, bridge to transplant, and bridge to recovery. After VAD implantation, anticoagulants are used to prevent thrombosis and thromboembolism in patients.
- In many cases, thrombosis occurs because of the inflow cannula taking tissue inside. It can also occur because of the wrong position of an inflow cannula and insufficiency of anticoagulants.
- After blood interacts with the prosthetic surface, inflammatory and immunologic reactions may start. After VAD is implanted, intracellular adhesion molecules, E-selectin, tissue factors, and D-dimer are upregulated.

Most patients present to hospitals with increased pump power and flow. Upon first examination, if there is doubt about the pump validity, thrombosis blood tests are performed (haptoglobin, bilirubin, lactate dehydrogenase [LDH], and free plasma hemoglobin).

If thrombosis is present, treatment methods include medical treatment, pump exchange, and emergency heart transplant. Medical treatment options include heparin, glycoprotein 2b/3a inhibitors, and thrombolytic treatment.

Materials and Methods

Between April 2012 and January 2017, our clinic implanted 55 VADs (53 HeartWare, 2 HeartMate). All patients were administered warfarin sodium and 100 mg acetylsalicylic acid. All operations were done by the same surgeon and with the same method. All in-flow cannula positions were corrected with transesophageal echocardiography. All out-flow graft anastomosis were to the ascending aorta.

All patients were followed for international normalized ratio (INR), with goal of maintaining INR between 2.5 and 3.5. All patient data were inspected weekly. Of 55 patients with VAD, 9 patients (16.4%) were hospitalized in an intensive care unit for...
suspected thrombosis. All patients were monitored daily, and highest pump power (watt) and flow (L/min) were recorded. High pump power was determined as an increase of more than 1 W from baseline. In all patients with high power or flow of pump, hematuria, blood tests (levels of LDH, haptoglobin and total direct bilirubin, complete blood counts, activated partial thromboplastin time [aPTT], urea, creatine, sodium, potassium, calcium, alanine aminotransferase, aspartate aminotransferase), chest radiography, and pump auscultations and vibrations were evaluated. Inflow and outflow cannulas were checked versus thoracic-abdominal computed tomography angiography and echocardiography results. Before treatment started, the central venous catheter was fitted.

All patients took heparin infusion, and we aimed to maintain aPTT at between 60 and 80 seconds. Our thrombolytic procedure included a 5-mg bolus of intravenous alteplase. Follow-up occurred at 1 hour after thrombolytic treatment. If pump power and flow were still high, an additional 5 mg alteplase in 50 cm² of isotonic solution (0.9% NaCl) was given to the patient in 1 hour. After infusion ended, the patient was again evaluated. If pump power and flow returned to normal levels, thrombolytic treatment was stopped. Otherwise, procedures continued until a maximum dose of 50 mg alteplase. If any adverse effects occurred, thrombolytic treatment ended. During patient follow-up, if heart failure symptoms were shown, we started inotropic and diuretic treatment. Only when the VAD parameters and blood tests returned to normal levels was therapy ended. Once therapy was ended, we started warfarin sodium and heparin infusion until INR became greater than 2.5.

If alteplase and heparin infusion were not successful, we began the process of emergency cardiac transplantation.

Results

In 55 patients, 9 (16.4%) had pump thrombosis. All patients had high pump power and high flow at presentation to the hospital. Only 3 patients had INR levels lower then 2.5. Eight patients received thrombolytic and heparin treatment. The other patient could not take that treatment because of a contraindication (cerebral bleeding 1 month previously). For this patient, we requested emergency heart transplant, with heart transplant performed in that patient. In patients who underwent thrombolytic treatment, 1 patient (12.5%) died from cerebral bleeding. In 2 other patients, treatment was not successful; therefore, we requested emergency heart transplant. One patient underwent heart transplant, and the other patient received a pump exchange. Both patients were alive at last follow-up. Five patients (62.5%) had successful treatment.

In treated patients, LDH, haptoglobin, and bilirubin levels returned to baselines levels. There were no other adverse effects except the 1 patient with cerebral bleeding. Four patients had hematuria at presentation, which normalized after treatment. Five patients needed inotropic and diuretic treatments, which were discontinued and normalized after thrombolytic treatment.

As part of thrombolytic treatment, we use alteplase. Alteplase dose ranges from 10 to 50 mg, but the mean value for alteplase is 37.5 mg. All patients also took heparin infusion; we followed its effectiveness with aPTT, which we aimed to maintain at between 60 and 80 seconds. None of the patients had a recurrent thrombosis over a 12-month follow-up.

Discussion

The incidence of continuous flow VAD thrombosis is between 3% and 18%. In our center, the incidence was 16.3%. The protocol used by Schrage and associates is without bolus, only giving 5 mg/hour alteplase infusion. If parameters return to baseline levels 1 hour later, they stop the infusion. They also stop infusion if any adverse effects occur. In other studies, the incidence of stroke ranged from 10% to 15%; our study showed an incidence of 11.1%. An important part of our study is the fact that we give smaller doses of thrombolytic treatment with heparin infusion, with success of 62.5%. In the literature, the success of other protocols has been reported to be between 37.5% and 70%. Our results are similar to the literature, although close to the upper rate. In our study, we give alteplase to the systemic circulation. Schlendorf and associates gave alteplase with a catheter directly to the ventricle. They also used unfractionated heparin with activated clotting time of > 200. Their rate of success was 38%. Nair and associates described their protocol as 5-mg bolus of intravenous alteplase at 3 mg/h over
a 10-hour infusion. If laboratory parameters do not return to normal levels, the group reported continuing infusion of alteplase at 1 mg/h for 48 hours. Their upper limit for alteplase was 100 mg. They reported a stroke incidence of 10% and success rate of 70%. Age, sex, body mass index, ethnicity, ejection fraction, VAD implantation time, VAD power, flow, and revolutions per minute were not reported as risk factors for thrombosis. Pump thrombosis rate has been reported as 8.1% with median time to thrombosis of 245 days, whereas we observed time to thrombosis of 572.5 days. Najjar and associates reported that risk factors for VAD thrombosis include INR of > 2, mean arterial pressure > 90 mm Hg, > 81 mg acetylsalicylic acid usage, and Interagency Registry for Mechanically Assisted Circulatory Support score of > 3.3 Another article by Weber and associates added hypovolemia and infection as predisposing factors for thrombosis formation.

There is no consensus about VAD thrombosis treatment. In this article, we showed that our protocol is an effective way to treat VAD thrombosis. In addition, it should be noted that our protocol should be altered according to patient need.
Objectives: Our objective was to determine transforming growth factor β1 levels in patients with type 2 diabetes mellitus after fetal pancreatic stem cell transplant.

Materials and Methods: We examined 10 patients (age range, 41-65 y) with type 2 diabetes mellitus, which we subsequently divided into 2 groups. Group 1 comprised 5 patients who received fetal pancreatic stem cell transplant (cells were 16-18 wk gestation) performed by intravenous infusion. Group 2 comprised 5 patients (control group) who were on hypoglycemic tablet therapy or insulin therapy. The quantity of fetal stem cells infused was 5 to 6 × 10⁶. We analyzed transforming growth factor β1, C-peptide, and glycated hemoglobin levels in patients before and 3 months after fetal pancreatic stem cell transplant.

Results: In patients with type 2 diabetes mellitus, fetal pancreatic stem cell transplant led to a significant increase in transforming growth factor β1 levels, from 16 364.8 to 35 730.4 ng/mL (P = .008), with trend in decreased glycated hemoglobin levels, from 7.96% to 6.98% (P = .088) after 3 months.

Conclusions: Transforming growth factor β1 levels increased significantly within 3 months after fetal pancreatic stem cell transplant in patients with type 2 diabetes mellitus.

Key words: Adipokines, C-peptide, Pancreatic islet cell regeneration

Introduction

Over recent decades, diabetes mellitus (DM) has become a main public healthcare problem worldwide, showing a tendency of steady growth. According to the International Diabetes Federation in 2015, there were 415 million patients with DM in the world; by 2040, it is expected that this number will reach 642 million people. According to data from the International Diabetes Federation, the prevalence of DM among the adult population (20-79 years old) is 6.2% in Kazakhstan. However, the actual prevalence of type 2 DM among adults (20-79 years old) in Kazakhstan was higher than expected, amounting to 8.2% according to the Kazakh epidemiologic study NOMAD. Diabetes mellitus is a major risk factor for ischemic heart disease and stroke, collectively accounting for high rates of morbidity and mortality among adult patients.

Strategies to improve both peripheral insulin resistance and beta-cell regeneration may be an ideal therapy for type 2 DM. Transplantation of insulin-producing cells has been considered to be the most promising treatment approach for type 2 DM. A fetal pancreatic stem cell transplant (FPSCT) has attracted attention for being a potentially effective therapeutic approach to regenerating islet cells and for treatment of type 2 DM.

Transforming growth factor β1 (TGF-β1) is a well-known cytokine regulator of cellular responses, including proliferation, differentiation, migration, and regeneration. Recent cell therapy studies have shown that stem cells secrete TGF-β1, which is critical for suppression of inflammatory cytokines and for inhibiting an inflammatory response. Therefore, investigating the dynamics of TGF-β1 levels in patients with type 2 DM after FPSCT is considered to be a scientifically interesting subject.

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Materials and Methods

This prospective cohort study included 10 patients (41-65 years old) with type 2 DM who were divided into 2 groups and subsequently examined. Group 1 comprised 5 patients who received FPSCT (cells were at 16- to 18-wk gestation) performed by intravenous infusion. Group 2 comprised 5 patients (control group) who were on tablet hypoglycemic therapy or insulin therapy. The quantity of fetal stem cells infused was 5 to 6 × 10^6. We analyzed TGF-β1, C-peptide, and glycated hemoglobin (HbA1c) levels in patients before and 3 months after FPSCT. Fetal pancreatic stem cells were extracted from the pancreatic tissue of an aborted fetus at 16- to 18-wk gestation. The stem cell procedure was performed using intravenous infusion at a rate of 50 mL/hour. This clinical study and its methods were approved by the Local Ethics Committee following Helsinki Declaration guidelines at our institution. All patients signed written informed consent forms before recruitment.

Statistical analyses were performed using standard methods and Statistitica software (StatSoft Inc., version 6.0, Tulsa, OK, USA). Clinical assessments of patients were calculated using averages, margins of error, and standard deviations. To compare independent groups, we used the nonparametric Mann-Whitney U test.

Results

Before the FPCST procedure, all patients with type 2 DM had poor glycemic control. Among all the patients, the HbA1c level was more than 7%. We did not observe any complications after the FPSCT procedure.

In our examination of baseline TGF-β1 levels in both groups of patients, we found that the mean baseline level of TGF-β1 in the control group was 13 401.4 ± 2602.1 ng/mL, which is in the normal range. The mean baseline level of TGF-β1 for patients with type 2 DM in the FPSCT group was 16 364.8 ± 1616.7 ng/mL, which is higher than the established normal level (Table 1). These mean baseline TGF-β1 levels were not significantly different between the 2 groups of patients (P = .222).

On the day of FPSCT, patients with type 2 DM were given hypoglycemic agents in the form of tablets or subcutaneous insulin. Patient dose was adjusted according to blood glucose level performance, which was examined once every 3 hours during the first day of FPSCT. During the subsequent 3 days, fasting glucose and postprandial glucose levels were well controlled.

The baseline laboratory data and their changes after FPSCT are presented in Table 1. In patients with type 2 DM in the FPSCT group, 3 months after the procedure, the mean TGF-β1 level increased significantly from 16 364.8 ± 1616.7 ng/mL to 35 730.4 ± 4081.0 ng/mL (P = .008); mean C-peptide and HbA1c levels also changed but not significantly, from 4.42 ± 0.97 to 3.28 ± 0.61 ng/mL (P = .095) and from 7.96 ± 0.75% to 6.98 ± 0.71%, respectively (P = .088; Table 1).

The corresponding mean TGF-β1, C-peptide, and HbA1c levels did not significantly change in the control group of patients with type 2 DM, with baseline versus 3-month TGF-β1 levels of 13 401.4 ± 2602.1 ng/mL versus 15 250.8 ± 2944.9 ng/mL (P = .547) and baseline versus 3-month C-peptide and HbA1c levels of 3.75 ± 0.93 ng/mL versus 3.93 ± 0.97 ng/mL and 7.85 ± 0.68% versus 7.23 ± 0.76%, respectively (P > .05; Table 1).

Discussion

Three months after the FPSCT procedure, patients with type 2 DM showed significantly increased TGF-β1 levels. According to some studies, TGF-β1 levels are also elevated in patients after organ transplant. An increased level has a positive

| Table 1. Changes in Transforming Growth Factor β1, C-Peptide, and HbA1c Levels After Fetal Pancreatic Stem Cell Transplant in Patients With Type 2 Diabetes Mellitus |
| Baseline Level | Level After 3 Months | P Value |
| TGF-β1, ng/mL | C-peptide, ng/mL | HbA1c, % |
| Type 2 DM with FPSCT (n = 5) | 16364.8 ± 1616.7 | 3.28 ± 0.61 | 6.98 ± 0.71 | .008 | .095 | .088 |
| Type 2 DM control group (n = 5) | 13401.4 ± 2602.1 | 3.93 ± 0.97 | 7.23 ± 0.76 | > .05 | > .05 | > .05 |

Abbreviations: DM, diabetes mellitus; FPSCT, fetal pancreatic stem cell transplant; HbA1c, glycated hemoglobin; TGF-β1, transforming growth factor-β1
correlation with neovascularization after organ transplant.\textsuperscript{12} In addition, TGF-\(\beta\)1 plays a role in modulation of immune responses, including inhibiting T-cell proliferation and suppressing immune response in clinical conditions during cell or organ transplant.\textsuperscript{13}

The observed significant increase in TGF-\(\beta\)1 levels and the tendency of decreased HbA1c levels in patients who received the FPSCT procedure versus the finding of no significant increase in these parameters in the control group may indicate the efficacy of FPSCT.

References

Clinical Characteristics of *Acinetobacter baumannii* Infection in Solid-Organ Transplant Recipients

Irem Serifoglu,1 Balam Er Dedekarginoglu,1 Serife Savas Bozbas,1 Sule Akcay,1 Mehmet Haberal2

**Abstract**

**Objectives:** *Acinetobacter baumannii*, depending on the immune status of the host, may result in one of the most serious hospital infections. Infections involving *A. baumannii* infection have been recently rising. However, little is known about the clinical features of *A. baumannii* infection in solid-organ transplant recipients. We aimed to share our clinical experiences with *A. baumannii* infection in our transplant recipients.

**Materials and Methods:** Between 2011 and 2017, 41 solid-organ transplant patients developed *A. baumannii* infection at Baskent University Hospital. Medical records were reviewed, and patient demographics, microbiology results, and overall outcome data were noted.

**Results:** Of 41 solid-organ transplant patients with *A. baumannii* infection, 29 were male and 12 were female patients with mean age of 47.15 ± 13.24 years. Our infection rate with *A. baumannii* infection was 6.1%. The most common sites of infection were deep tracheal aspirate (48.8%) and bloodstream (36.6%). Onset of infection 1 year posttransplant was identified in 58.5% of recipients. Risk factors included presence of invasive procedures (56.1%) and administration of high-dose corticosteroids for rejection 1 year before infection (68.3%). Thirty-day mortality rate was 41.5% (17/41 patients) and was not associated with the infection site, microbiological cure, clinical cure, and drug resistance in our study group.

**Conclusions:** *Acinetobacter baumannii* is an important cause of hospital-acquired infection and mortality worldwide. A major problem with *A. baumannii* infection is delayed initiation of appropriate antibiotic treatment and the rising numbers of extensively drug-resistant organisms. Predicting the potential risk factors, especially in the already at-risk solid-organ transplant population, has an important role in patient outcomes.

**Key words:** Hospital-acquired infection, Immunosuppression, Mortality

**Introduction**

*Acinetobacter* species are aerobic, gram-negative coccobacillus, which are mostly isolated in hospitalized patients and hospital environments; however, they are also normally found in nature. *Acinetobacter* species prefer to be in a moist environment, which is why they are usually cultured from respiratory secretions, urine, and wounds of hospitalized patients. *Acinetobacter* species are capable of being causative pathogens of serious infections, especially in critically ill patients; however, colonization rather than infection can also exist.1 The most common isolated species, *Acinetobacter baumannii*, is known to produce nosocomial outbreaks, resulting in ventilator-associated pneumonias, bacteremia, and urinary tract and wound infections.2 Over the past decades, the prevalence of *Acinetobacter infection* has risen.2,3 One of the major problems with *A. baumannii* infection is its resistance to many antibiotics and its rapid development of resistance to available antibiotics.2,4-6

A number of factors, including prolonged hospitalization, especially in intensive care units, prolonged broad spectrum antibiotic use, invasive procedures, and the severity of the underlying diseases, are already known to contribute to development of *Acinetobacter infection* worldwide.4,7 Solid-organ transplant (SOT) patients are also a susceptible group for *A. baumannii* infection because of possessing these risk factors. Herein, we shared our clinical experiences regarding *A. baumannii* infection in SOT patients.
Materials and Methods

Solid-organ transplant patients who developed *A. baumannii* infection between 2011 and 2017 at Baskent University Hospital were included in the study. The Centers for Disease Control criteria were used to define the presence of infection, including surgical site infection, bloodstream infection, pneumonia, and urinary tract infection. Infections described as colonizations by at least one infectious disease specialist were excluded. Multidrug resistance (MDR) was defined as resistance to 3 or more major classes of antibiotics effective against *Acinetobacter* species (fluoroquinolones, carbapenems, aminoglycosides, penicillins, and cephalosporins). Extensively drug-resistant (XDR) *Acinetobacter* was defined as resistance to all antimicrobials with the exception of colistin. Between 2011 and 2015 at our hospital, we followed the Clinical and Laboratory Standards Institute recommendations for bacterial identification and antimicrobial susceptibility. Since 2015, *Acinetobacter* species identification and antimicrobial susceptibility testing were performed according to the European Committee on Antimicrobial Susceptibility Testing Clinical Breakpoint Tables version 7.0. Results of colistin and tigecycline susceptibility testing were interpreted by minimum inhibitory concentrations according to the European Committee on Antimicrobial Susceptibility Testing.

Medical records were reviewed for patient demographics, laboratory and microbiology results, treatment, and outcomes. Presence of previously known risk factors, timing to onset of *A. baumannii* infection, initiation of appropriate antibiotics within 3 days, and pulse steroid treatment for rejection were also noted. Clinical cure was described as the resolution of symptoms related to the organ infected by *A. baumannii*. Microbiological cure was defined as negative follow-up cultures for *A. baumannii* within 1 month after the first documented infection. The study was approved by the Ethical Review Committee of the Institute. All of the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Statistical analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 21.0, IBM Corporation, Armonk, NY, USA). Descriptive statistics are presented as means ± standard deviation, median (minimum to maximum), frequency distribution, and percent. Fisher exact test was used for categorical variables when any cell had an expected count < 5; otherwise, binary logistic regression was also used for continuous variables. We compared continuous variables with t test and qualitative variables with chi-square test. All P values were 2-sided; P values less than .05 were considered significant.

Results

Our study included 41 patients (29 male, 12 female) who were infected with *A. baumannii* (mean age of 47.15 ± 13.24 years). Characteristics and clinical features of SOT patients with *A. baumannii* infection are shown in Table 1. Of the 41 patients, 19 (46.6%) were kidney transplant recipients, 15 (36.3%) were liver transplant recipients, and 7 (17.1%) were heart transplant recipients. The 3 most common underlying diseases were chronic renal failure, hepatitis B virus infection, and diabetes mellitus. Immunosuppression was maintained with a regimen that included prednisone, cyclosporine, mycophenolate mofetil, and sirolimus. According to previously known risk factors, all SOT patients received antibiotics within 2 weeks before the initial *A. baumannii* infection, which may have enhanced the MDR-causing, hospital-acquired *A. baumannii* infection. Patients who received high-dose corticosteroids for rejection treatment represented 68.3% of those with infection; 36.6% of patients with infection were reoperated during their hospitalization. Nephrostomy tube, biliary stent, tracheostomy, and surgical drain were the invasive procedures conducted in 23 patients (56.1%).

The features of the *A. baumannii* infection are presented in Table 2. Mean time to onset of *A. baumannii* infection after transplant was 746 days (range, 1-5666 d). Almost all *A. baumannii* infections

| Table 1. Characteristics of Solid-Organ Transplant Recipients (N = 41) |
|---------------------------------|-----------------|
| Demographic                     | No.(%)          |
| Mean age, y                     | 47.15 ± 13.24   |
| Male/female                     | 29/12           |
| Organ transplanted              |                 |
| Kidney                          | 19 (46.6%)      |
| Liver                           | 15 (36.3%)      |
| Heart                           | 7 (17.1%)       |
| Risk factor                     |                 |
| Receipt of antibiotics within 2 weeks | 41 (100%)     |
| Receipt of corticosteroids within 1 year | 28 (68.3%) |
| Reoperation during hospitalization | 15 (36.6%)   |
| Invasive procedure              | 23 (56.1%)      |
were hospital acquired (97.6%). Multiple site infections were documented in 28 patients (68.3%), with the most common site of infection being deep tracheal aspirate (48.4%), bloodstream (36.6%), bronchoalveolar lavage (31.7%), and intraabdominal region (31.7%) (Table 2).

Polymicrobial infection was detected in 16 patients (38.1%) and was more common in the bloodstream and abdominal region, followed by deep tracheal aspirate. Regarding isolates, 58.5% were MDR isolates and 41.5% were XDR isolates. Laboratory findings within 24 hours of proven infection were as follows: white blood cell count of 10.1 ± 8.8 × 10^3/mm^3, platelet count of 113.7 ± 71.4 × 10^3/mm^3, and C-reactive protein level of 128.2 ± 107.8 mg/L (Table 2). Initiation of appropriate antibiotics within 3 days before the documented A. baumannii infection was proven occurred in 10 patients (24.4%), which was not associated with 30-day mortality (P > .05).

Clinical outcomes are shown in Table 3. Septic shock developed in 25 patients (61%). Of 34 patients with follow-up culture data, microbiological cure was sustained in 4.9% and clinical cure was achieved in 34.1%. Duration of treatment for A. baumannii was 21.4 ± 11.8 days, and mean hospitalization duration after initial A. baumannii infection was 35.5 ± 41.2 days (range, 1-201 d). Hemodialysis during hospitalization, either before or after proven A. baumannii infection, was conducted in 26 SOT patients (61.9%). Thirty-day mortality was 41.5% (17/41 patients) and was not associated with the infection site, microbiological or clinical cure, or drug resistance in our study group (P > .05).

**Discussion**

Acinetobacter baumannii is a clinically important species and opportunistic pathogen, especially in immunocompromised patients.12 In our 6-year study, we found 41 SOT patients with documented A. baumannii infection. Our study showed an infection rate of 6.1% (4.6% in kidney, 8.1% in liver, and 9.5% in heart recipients) and 30-day mortality rate from infection of 41.5%. The overall infection rate of A. baumannii has been reported to be 1.4% to 6.1% in the literature.13-15 However, in SOT patients, mortality rates have ranged from 39% to 80%.13-17 In our patient group, 24 patients (58.5%) had MDR isolates and 17 patients (41.5%) had XDR isolates. The existence of XDR Acinetobacter species has been shown to be related to increased mortality in several studies.13,14,18,19 However, we did not find an association between drug resistance and 30-day mortality in our study. Another study also showed no significant association between XDR organisms and mortality.15 The authors argued that this conflicting result may be due to inadequate statistical power, and it is also possible that the baseline clinical severity of the study populations was not matched. We believe that there were many confounding factors influencing mortality besides clinical condition, including initiation of appropriate antibiotics, reoperation, health worker-associated contamination of new pathogens, and the microbiological flora of patients hospitalized.

The analysis of 30-day mortality is defined as a primary outcome in many studies.15,18 We also assessed 90-day mortality because of the prolonged course of A. baumannii infection; however, 90-day mortality was also not associated with drug resistance. Unless we minimize the confounding factors influencing mortality, it is important to continue studying the impact of these factors on patient outcomes.

**Table 2. Characteristics of Acinetobacter baumannii Infection in Solid-Organ Transplant Recipients (N = 41)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to infection after transplant, d</td>
<td>746 (range, 1-5666)</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td>40 (97.6%)</td>
</tr>
<tr>
<td>MDR</td>
<td>24 (58.5%)</td>
</tr>
<tr>
<td>XDR</td>
<td>17 (41.5%)</td>
</tr>
<tr>
<td>Multiple site infection</td>
<td>28 (68.3%)</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
</tr>
<tr>
<td>Deep tracheal aspirate</td>
<td>20 (48.4%)</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>15 (36.6%)</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>13 (31.7%)</td>
</tr>
<tr>
<td>Intraabdominal region</td>
<td>13 (31.7%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>9 (22%)</td>
</tr>
<tr>
<td>Urine</td>
<td>7 (17.1%)</td>
</tr>
<tr>
<td>Catheter</td>
<td>5 (12.2%)</td>
</tr>
<tr>
<td>Wound</td>
<td>3 (7.3%)</td>
</tr>
<tr>
<td>Tissue</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Laboratory parameters from blood</td>
<td></td>
</tr>
<tr>
<td>WBC, count × 10^3/mm^3</td>
<td>10.1 ± 8.8</td>
</tr>
<tr>
<td>Platelets, count × 10^3/mm^3</td>
<td>113.7 ± 71.4</td>
</tr>
<tr>
<td>Creatinine, mg/L</td>
<td>1.8 ± 1.19</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>2.79 ± 0.59</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>128.2 ± 107.8</td>
</tr>
<tr>
<td>3-day onset of appropriate antibiotics</td>
<td>10 (24.4%)</td>
</tr>
</tbody>
</table>

**Table 3. Outcomes of Solid-Organ Transplant Recipients**

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>25 (61%)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>14 (34.1%)</td>
</tr>
<tr>
<td>Microbiological cure*</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>Hospitalization after the initial infection, mean days</td>
<td>35.5 ± 41.2</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>17 (41.5%)</td>
</tr>
</tbody>
</table>

*34 patients had follow-up cultures within 1 month after initial A. baumannii infection.
factors and include a larger study population, there will be a wide range of infection-related mortalities.

Rapidly developing drug resistance by *A. baumannii* infection is a major problem for successfully getting rid of the infection. It has been reported that chromosomally located transposons carry multiple antibiotic resistant genes in clinical isolates of *Acinetobacter* species. Some reports have suggested that *A. baumannii* has geographic specificity, and the genetic relatedness of isolates differs in different region. When resistance mechanisms differ from one geographic region to another, it may explain the range of occurrences of MDR and XDR isolates, as well as the infection-related mortality.

In our hospital, a carbapenem-colistin combination regimen was the treatment choice for patients with XDR isolates of *A. baumannii* infection. Three-day early initiation of appropriate antibiotics has been shown to be associated with lower mortality. Of 41 patients in our study, 10 (24.4%) received the carbapenem-colistin combination 3 days before the proven *A. baumannii* infection; treatment was not associated with 30-day mortality in the study. We were more likely to delay early initiation of appropriate antibiotics before the proven *A. baumannii* infection. This may be due to fear of increasing the prevalence of resistant bacteria and/or difficulty in reaching a definite decision for initiation of antibiotic therapy because of involvement of several disciplines like infectious diseases, pulmonologists, and intensivists.

The most common infected sites were deep tracheal aspirate (48.4%), followed by bloodstream (36.6%), bronchoalveolar lavage (31.7%), and intraabdominal region (31.7%). The respiratory tract was the most common infected site, similar to that shown in the literature. This is because *A. baumannii* uses fimbria-like protrusion, which has a high capacity to adhere to bronchial epithelial cells. The 30-day mortality and 90-day mortality rates were not associated with site of infection in our study. We suggest that the use of a larger sample size, allowing us to categorize the infection site as respiratory system and nonrespiratory system infections, may have shown infection site to be significantly associated with higher mortality, similar to that in the literature. Polymicrobial infection was proven in 28 patients (68.3%) and more common in blood stream and intraabdominal region cultures.

Mean time of infection onset after transplant was 746 days (range, 1-5666 d) with time of 541.7 days (range, 1-3612 d) for kidney recipients, 850 days (range, 4-5566 d) for liver recipients, and 1075 days (range, 30-3546 d) for heart recipients. Onset of infection can occur on day 152 (range 2-6387 d). Early infection has been described as 2 months and as 1 year or less after transplant in prior studies. We had a wide range of mean times to onset of infection after transplant, similar to prior studies. The SOT population remains at risk of developing *A. baumannii* infection due to possessing risk factors that include high-dose steroid treatment against rejection and prolonged hospitalization for invasive procedures.

Mean days of treatment for *A. baumannii* was 21.4 ± 11.8 days; when clinical or microbiological cure was not obtained, treatment was prolonged based on the clinical severity of the patient. Most *A. baumannii* infections (97.5%) were hospital-acquired in our study, similar to a study that showed nosocomial *A. baumannii* infection rate of 79%. Our study showed more nosocomial infections, which may be because our hospital has an active SOT program that treats patients from many regions, resulting in prolonged hospitalization for minimal invasive procedures or routine check-up.

Our study showed microbiological cure in only 4.9% of our patients, but clinical cure was achieved in 34.1% of the patients. The patients who did not recover from *A. baumannii* microbiologically but cured clinically (n = 10) were alive for 90 days except for 1 patient. This suggests that resolving clinical symptoms of the infected site with appropriate antibiotic therapy may not lead to microbiological cure but can show a clinical cure; therefore, such cases should not be considered colonization.

We did not find any association between *A. baumannii* infection-related mortality and drug resistance, early initiation of antibiotics, infection site, and microbiological and clinical cure. These findings may be due to the low power of our study and the relatively small number of patients included.

**Conclusions**

We described the wide range of mortality related to antibiotic resistance, timing of initiation of appropriate antibiotics, and clinical condition at time of diagnosis of *A. baumannii* infection in SOT patients. Because data regarding factors influencing outcomes
of A. baumannii infection remain conflicting, more multicenter studies with larger populations are necessary.

References

Radiologically Occult Invasive Pulmonary Aspergillosis in a Patient With Liver Transplant

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Abstract
Invasive pulmonary aspergillosis is an infection seen in patients receiving intensive immunosuppressive regimens, such as transplant recipients. Some risk factors that increase the incidence of infection have been determined, and patients defined as having high risk are recommended to take antifungal prophylaxis and be monitored closely. Here, we present a liver transplant patient with mild respiratory symptoms and a normal chest radiography on day 26 post-transplant. However, he had acute renal failure and underwent hemodialysis, which are both defined to increase significantly the risk of aspergillosis. Although the radiographic scan was initially normal, thorax tomography and later bronchoscopy showed findings compatible with pulmonary aspergillosis, and the patient was started on antifungal treatment. The nonspecific mild symptoms and an initial normal radiology can make diagnosis of invasive fungal infections difficult; thus caution and close follow-up of high-risk patients should be performed.

Key words: Antifungal, Aspergillus fumigatus, Pulmonary infection, Renal failure

Introduction
Invasive fungal infection, especially aspergillosis, is a matter of concern in immunocompromised patients, particularly solid-organ transplant recipients. The presence of nonspecific and mild symptoms during follow-up in these patients can lead to delay in diagnosis of local and even disseminated infections, which unfortunately increases the overall mortality rates.

Case Report
A 46-year-old patient who was diagnosed with cirrhosis underwent a deceased-donor liver transplant. After the procedure, he underwent hemodialysis because of acute renal failure. The patient received high-dose corticosteroids because of acute rejection shown in liver biopsy 10 days later. The patient was consulted for cough and purulent sputum at day 26 post-transplant. His physical examination was unremarkable, and chest radiography showed no obvious infiltration (Figure 1). Treatment with ceftriaxone and clarithromycin was started after screening for possible pathogens, and a thorax tomography was requested. The tomography showed multiple nodular infiltrates in the right upper lobe (Figure 2). Bronchoscopy was planned as inflammation markers did not decrease, and blood galactomannan was found to be positive (0.83).

Surprisingly, disseminated white plaques were present in the mucosa of all segments and both main bronchi (Figure 3). Mucosal biopsy and bronchoalveolar lavage were obtained for further investigation. Galactomannan antigen level in the bronchoalveolar specimen was high (6.6). Pathologic examination and culture results together confirmed the fungal infection to be compatible with Aspergillus fumigatus. The patient was started on voriconazole treatment.

Bronchoscopy performed 1 week later showed a remarkable regression of the mucosal findings. However, a change in the patient’s mental status was detected. Brain magnetic resonance imaging showed nodular lesions compatible with abscess, and liposomal amphotericin B was added to the treatment, with intrathecal amphotericin B also

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administered. One month later, scans showed regression of both lung and brain findings, and the overall health status of the patient was improved.

**Discussion**

Invasive aspergillosis has been considered as a common complication in solid-organ transplant recipients and estimated to have a frequency that varies from 1% to 15%. In liver transplant recipients, invasive aspergillosis has been found to occur in 1% to 9.2% of patients. Important risk factors that increase the frequency of invasive aspergillosis in liver transplant patients include renal failure, retransplant, reoperation, and transplants performed for fulminant hepatitis. Renal replacement therapies, including hemodialysis, increase risk by about 15- to 25-fold. In our case, the patient had acute renal failure within the first week posttransplant and underwent hemodialysis, which increased the risk for invasive aspergillosis, in accordance with risk factors shown in the literature.

Most invasive fungal infections usually appear during the first month posttransplant, with median time of 16 or 17 days. Recent cohort studies have shown that there is a tendency for invasive aspergillosis to develop at late onset, with median time found to be 60 days posttransplant. The shift of infection incidence in later stages might be due to improved surgical techniques, better follow-up, and decreased incidence of risk factors, such as cytomegalovirus infection during the early post-transplant period. Our patient had pulmonary symptoms at day 26 posttransplant, and a positive galactomannan at day 32 when the antifungal treatment was started. The delay in diagnosis is a problem because cultures of respiratory tract secretions have a low sensitivity, and usually *Aspergillus* species is detected at late stages of disease when dissemination is present. Galactomannan positivity in blood has a sensitivity of 55.6% and a specificity of 93.9% to 98.5% for invasive aspergillosis diagnosis in liver transplant patients, whereas galactomannan in bronchoalveolar lavage has a sensitivity of 81.8% and a specificity of 95.8%. It should be noted that use of antibiotics, especially piperacillin/tazobactam, can lead to false-positive results.

Another tool that can aid in diagnosis is the computed tomography scan, where findings like the “halo” sign and presence of multiple nodules/masses with a low-density center are typical for invasive fungal infection. As shown in Figure 2, the patient had multiple nodular lesions, especially in the right upper lobe.

Concerning the antifungal choice for treatment of invasive aspergillosis, lipid formulation of amphotericin B was the preferred treatment during the early 1990s because of a lower nephrotoxicity rate. However, recent randomized trials have shown that voriconazole is much better as a primary therapy and is thus recommended by guidelines of the Infectious Diseases Society of America. Data are still scarce regarding combination therapies of antifungals, but some studies have shown decreased mortality rate when a combination was used, especially in patients with renal failure and in those infected with *Aspergillus fumigatus*. Surgery could also be a choice of treatment for patients who are refractory to...
treatment and have persistent hemoptysis and progressive cavitary lesions.\textsuperscript{9}

In liver transplant patients diagnosed with invasive fungal infections, overall mortality rates are high, ranging from 83\% to 88\%. Therefore, early diagnosis and intervention remain critical steps.\textsuperscript{11,12} The nonspecific mild symptoms can make it difficult to suspect disseminated invasive fungal infections; therefore, caution and close follow-up of high-risk patients should be performed.

There is still no consensus concerning prophylaxis with antifungals in liver transplant patients. Identification of the high-risk population from the start seems to be the key factor for early diagnosis and intervention. Lipid formulation of amphotericin B at 3 to 5 mg/kg/day or an echinocandin can be given as a prophylaxis in high-risk patients, which may help to decrease the overall morbidity and mortality.\textsuperscript{13-15}

References

Intracranial Fungal Infection After Solid-Organ Transplant

Fikret Şahintürk,1 Hamiyet Demirkaya,2 Ümit Akin Dere,1 Erkin Sönmez,1 Nur Altınörs,1 Gökhan Moray,3 Mehmet Haberal3

Abstract

Neurologic complications after solid-organ transplant reveal a great spectrum of pathologies. Intracranial hemorrhages, cerebral ischemic lesions, infarctions, lymphoproliferative disorders, and infections, including aspergillosis, have been observed after liver transplant. Fungi constitute nearly 5% of all central nervous system infections, mainly occurring in immunocompromised patients. The most common causative agent is Aspergillus species. It presents either as maxillary sinusitis or pulmonary infection. Brain involvement of Aspergillus carries a high rate of mortality. Aspergillosis presents in the forms of meningitis, mycotic aneurysms, infarctions, and mass lesions. Aspergillosis does not have a specific radiologic appearance. Parenchymal aspergillosis has heterogenous signal intensity (hypointense on T1-weighted and hyperintense on T2-weighted images). Here, we present 3 patients who underwent solid-organ transplant and developed central nervous system aspergillosis. Different modalities of neurosurgical intervention were performed in combination with chemotherapy as part of their fungal therapy.

Key words: Liver transplantation, Neurosurgical intervention, Renal transplantation

Introduction

The term “aspergillosis” refers to a clinical condition related to Aspergillus species infection, most commonly A. fumigatus, A. niger, A. flavus, or A. terreus.1 Liver transplant recipients are particularly vulnerable to aspergillosis infection.2,3 If aspergillosis is further complicated by central nervous system (CNS) involvement, neurosurgical procedures may be required.

Neurosurgical interventions aim to relieve neurologic symptoms by removing mass lesions, to aid with diagnosis in suspicious cases, and to treat increased intracranial pressure by cerebrospinal fluid diversion techniques and placement of reservoirs. Patients who undergo neurosurgical procedures during treatment of fungal CNS infections have significantly improved survival. Preoperative antifungal treatment, particularly with itraconazole, has been reported to have a positive effect on outcome.4 The Infectious Diseases Society of America has stated that the response to antifungal therapy is closely associated with host factors, including resolution of neutropenia, control of immunosuppression, and return of graft function after organ transplant.4

Here, we present 3 patients, one who demonstrated histopathologic verification after intracranial fungal infection was considered, based on radiologic scan, and who showed a positive response to medical treatment.

Case Report

Patient 1

In January 2017, a 46-year-old male patient underwent a deceased-donor liver transplant at the Ankara Hospital of Başkent University. He was discharged on postoperative day 16 with medical therapy prescription. Three months later, he was again hospitalized because of high fever. The patient showed disturbance of consciousness; therefore, cranial magnetic resonance imaging (MRI) was performed, revealing thickening of the maxillary sinus, contrast enhancement around the fourth ventricle, and abscesses, including in the corpus callosum and vicinity of the left lateral ventricle (Figure 1, A and B). He received 6 cycles of intrathecal antifungal therapy.
A cranial computerized tomography showed hydrocephalus (Figure 1C). An external ventricular drainage was inserted, with subsequent insertion of a ventricular-peritoneal shunt. The patient was discharged 1 month later in good neurologic condition, with recommendation to continue oral antifungal therapy.

**Patient 2**
In January 2017, a 61-year-old male patient underwent deceased-donor liver transplant at the Ankara Hospital of Başkent University. The patient presented with right hemiplegia and fluctuation of consciousness. A cranial MRI showed a hemorrhagic lesion in the left thalamic region. Ring-enhancing lesions suggestive of abscess were observed in the right occipital and right temporal lobes (Figure 2). Serum galactomannan was positive. The right occipital lesion was totally removed via craniotomy. Culture from the surgical specimen and histopathologic evaluation both confirmed aspergillosis. The patient received antifungal therapy and rehabilitation. The patient is in stable condition with minimal neurologic deficit.

**Patient 3**
In 2006, a 38-year-old female patient received a living-donor renal transplant at the Ankara Hospital of Başkent University. She was treated for chronic renal disease after kidney rejection in 2011. She was readmitted to the nephrology clinic in March 2017 with high fever and severe headache. Cranial MRI showed bilateral thalamic enhancing abscesses (Figure 3). Urgent brain scan was performed because of sudden unconsciousness. The scan revealed acute hydrocephalus. Urgent external ventricular drainage was inserted. The following day, she experienced intraparenchymal hemorrhage, which was followed by death the next day. Table 1 summarizes the 3 cases.
Discussion

A wide variety of complications may be seen during the postoperative period after transplant. Intracranial hemorrhages, cerebral ischemic lesions, infarctions, lymphoproliferative disorders, infections, including aspergillosis, lymphoma, and progressive multifocal leukoencephalopathy have been reported after liver transplant.\(^5,6\) In a retrospective study of 200 liver transplant patients, 3% were diagnosed with aspergillosis.\(^7\)

Fungal CNS infections are rare and are secondary in nearly all cases to a primary pathology in a different location of the body. Individuals with acquired immunodeficiency syndrome, posttransplant patients, and patients with diabetes of long duration are prone to CNS fungal involvement. In a study of 595 patients with proven or probable invasive aspergillosis, major risk factors included bone marrow transplant (32%) and hematologic malignancy (29%). Solid-organ transplants accounted for 9%, acquired immunodeficiency syndrome for 8%, and pulmonary disease for 8%.\(^8\)

Walsh and associates\(^9\) studied the clinical, laboratory, and pathologic features of aspergillosis of the CNS in a series of 17 patients at autopsy. In 8 patients, diseases and events associated with CNS aspergillosis included leukemia, aplastic anemia, and renal transplant. The remaining 9 patients had illnesses not generally known to be associated with aspergillosis. On the basis of the study, the authors suggested considering CNS aspergillosis as a cause of new-onset focal neurologic deficits in patients who have illnesses not usually associated with aspergillosis.

Donor-derived fungal infections in organ transplant recipients are also possible.\(^4\) The infection reaches the CNS either by direct extension from nasal sinuses or by hematogenous spread from lungs and gastrointestinal tract.\(^10\)

The clinical symptoms and signs are generally nonspecific, and fever may be absent. For this reason, diagnosis in most cases is difficult. Other infectious pathologies or neoplastic diseases may present with similar clinical and radiologic features. Neurologic symptoms due to aspergillosis are mental status changes, epileptic fits, and focal neurologic deficits. Diagnosis of aspergillosis relies on radiology, presence of fungi elsewhere in the body, and microbiologic investigations. There may be clinical symptoms similar to meningitis and subarachnoid hemorrhage. The pathology of CNS aspergillosis has been classified in 3 forms: infarction, granulomas, and meningitis.

Aspergillosis does not have a specific radiologic appearance. Computed tomography and MRI are the primary tools for radiologic diagnosis. Computed tomography scans demonstrate isodense to hyperdense attenuation of primary sinus disease with bony destruction. Dural-based lesions show isodense to hyperdense attenuation. Magnetic resonance imaging scans show iso- to hypointense signal intensity on T1-weighted and T2-weighted images in cases of sinonasal origin and dural-based lesions. Primary parenchymal lesions are reported to show heterogenous signal intensity with mainly hypointense signal on T1-weighted and hyperintense on T2-weighted images.\(^11\)

The radiologic features of aspergillosis have been reported as edematous lesions, hemorrhagic lesions, and solid lesions (called aspergilloma or tumoral form).\(^10\) Multiple areas of hypointensity on computed tomography or hyperintensity on T2-weighted MRI involving the cortex and/or subcortical white matter consistent with multiple areas of infarction have been reported as a common radiologic finding in \textit{Aspergillus} infection.\(^10\)

Intracranial aspergillosis has been noted in 4% of children and 10% of adults after liver transplant.\(^6\) In a Mayo Clinic report, of 405 liver transplant patients, 13% had aspergillosis as an invasive form of fungal infection.\(^12\)

Brain involvement of \textit{Aspergillus} has a mortality rate of up to 90.9% (20/22) in patients after organ
transplant. A study from our center reported 75% (6/8) mortality in patients with invasive fungal infection after solid-organ transplant.

In a report from Wasay and associates of 25 cases of confirmed cerebral aspergillosis, overall mortality was 40%. The author suggested preoperative administration of antifungal therapy based on their results.

Therapy includes total removal of the aspergilloma combined with chemotherapy. Srinivasan reported the long-term outcomes of 3 patients treated with radical surgery followed by oral itraconazole. A dose of oral itraconazole 200 mg twice daily for at least 6 months was recommended; this chemotherapy combined with surgery resulted in nearly complete cure in 5 years.

In a study from Schwartz and associates, 17 of 81 patients, 48 patients had definite diagnosis of aspergillosis and 33 had probable diagnosis. In 31 patients, various neurosurgical treatments were conducted (abscess removal in 14, abscess drainage in 12, ventricular shunt in 4, and Ommaya reservoir placement in 1). Overall evaluation revealed that neurosurgical interventions were associated with improved survival. The authors concluded that voriconazole treatment combined with neurosurgical intervention, whenever possible, is the best approach to treat patients with CNS aspergillosis.

Experimental data and case reports agree that underlying immunosuppression is one of the most important factors regarding outcomes of invasive aspergillosis. Among the various factors affecting the outcomes of patients with aspergillosis, hematopoietic stem cell transplant has a high mortality rate. Complete and partial responses have been reported only in 15% of patients with bone marrow transplant and invasive aspergillosis at any site. Surgery has been advocated for patients with invasive aspergillosis of the lung, sinuses, and bone. Surgical experience for CNS involvement of aspergillosis is limited; however, neurosurgical interventions are needed for better neurologic outcomes and decreased mortality.

References

Utility of Mean Platelet Volume to Diagnose Pneumonia in Patients With Solid-Organ Transplant

Gaye Ulubay,1 Ebru Ayvazoglu Soy,2 Irem Serifoglu,1 Fisun Sozen,3 Gokhan Moray,2 Mehmet Haberal2

Abstract

Objectives: Despite improved success with solid-organ transplant procedures, recipients remain at risk for infections, including pneumonia, due to their immunosuppressive regimens. In solid-organ transplant patients, clinical findings of pneumonia can be nonspecific, and diagnosis of pneumonia may be difficult as several conditions (drug lung, hypervolemia, infections, hemorrhage) can lead to pulmonary infiltrates, mimicking pneumonia in these patients. The role of mean platelet volume, a predictor of inflammatory disease, with elevated values inversely correlated with inflammatory problems, in the diagnosis of pneumonia has not yet been investigated in solid-organ transplant patients. Here, we retrospectively investigated mean platelet volume in diagnosis of pneumonia in transplant patients.

Materials and Methods: Medical records of solid-organ transplant patients from 2011 to 2016 were reviewed for demographic, clinical, radiographic, laboratory, and microbiology data. Transplant type, immunosuppressive drugs, and clinical outcomes were noted. Pneumonia diagnosis was based on clinical respiratory symptoms and signs, imaging findings, positive microbiological tests, pathologic findings, laboratory findings, or effective clinical treatment trials.

Results: Our study included 70 patients (47 male/23 female; mean age of 46 ± 14 years), comprising 26 liver and 44 renal transplant recipients. Pneumonia was diagnosed radiologically in 30 patients (42.9%), with procalcitonin positive in 11 patients (36.7%), C-reactive protein elevated in 29 patients (96.7%), and leukocytes increased in 6 patients (20%). When laboratory measurements were compared with mean platelet volume, mean platelet volume values were significantly lower in patients with pneumonia who had elevated procalcitonin levels ($P = .038$).

Conclusions: We found that mean platelet volume for diagnosis of pneumonia in solid-organ transplant patients was not a promising tool. Considering the difficulties in caring for transplant patients with pulmonary infiltrates, clinical decisions should be based on clinical, laboratory, microbiological, and radiologic findings.

Key words: Diagnosis, Infection, Procalcitonin, Pulmonary infiltrates

Introduction

Immunosuppressive therapies for patients after solid-organ transplant (SOT) have evolved with a goal of minimizing toxicity and adverse effects while optimizing organ function. However, infection remains a major complication in renal transplant recipients, including pneumonia, one of the most frequent life-threatening complications of long-term immunosuppression.1 Pneumonia has an incidence of 19.4 episodes per 1000 on follow-up/year and can lead to death in SOT patients.2,4 Physical examination and laboratory and radiologic findings of pneumonia can be nonspecific, leading to difficulties in diagnosis in SOT patients because of infectious and noninfectious causes (drug lung, hypervolemia, infections, hemorrhage) that result in pulmonary infiltrates in these patients.5,6 To date, many diagnostic methods, including noninvasive (serologic, radiologic and microbiological testing) and invasive procedures (fiberoptic bronchoscopy and percutaneous trans-thoracic procedures), are used to establish pneumonia in SOT patients.5,9

In this study, we conducted a retrospective analysis to investigate the role of mean platelet volume (MPV) in the diagnosis of pneumonia in SOT patients.
Materials and Methods

Seventy SOT patients with pneumonia who had procalcitonin and MPV levels at Baskent University between 2011 and 2016 were included in the study. Medical records of these patients were reviewed retrospectively for demographic, clinical, radiographic (chest radiography), and/or laboratory and microbiology data. Exclusion criteria included the following: (1) < 18 years old, (2) lack of regular follow-up data, and (3) having uncertain diagnosis of pneumonia. Type of SOT, immunosuppressive drugs, and clinical outcome data were all noted.

Diagnosis of pneumonia

Pneumonia was defined as the onset of pulmonary infiltrate on chest radiographs and/or computed tomography scans of the thorax plus at least 2 of the following criteria: fever > 38°C, cough, purulent sputum, dyspnea or > 20 breaths/min, pleuritic chest pain, and leukocyte count of > 10000/mm³ or < 4000/mm³.¹⁰

Clinical, laboratory, pathologic, and radiologic (chest radiography and/or computed tomography) findings; positive microbiology tests from respiratory specimens; and effective clinical treatment approaches were obtained from data at the time of diagnosis of pneumonia. Chest radiographs were independently reviewed by 2 pulmonologists who were unaware of each other and the patient’s clinical course.

Laboratory measurements

Complete blood cell counts were measured by an automatic blood counter (A Cell-Dyn 3700, Abbott, Chicago, IL, USA). Blood samples were collected in potassium ethylenediaminetetraacetic acid tubes and measured within 1 hour after venipuncture. Normal range of MPV values are between 7.0 and 12.0 fL in our laboratory. C-reactive protein (CRP) levels were determined by the immunoturbidimetric method. Procalcitonin levels were measured using an automatic analyzer (Elecsys BRAHMS procalcitonin assay, Mannheim, Germany). The lower limit of detection of the assay is 0.05 ng/mL with this method. A sample of spontaneous sputum or induction sputum was obtained before treatment for Gram stain and Ziehl-Neelsen stain. After the sample was assessed for adequacy (epithelial cells < 10 per lower power fields, polymorphonuclear neutrophils > 25 per lower power fields), it was sent for bacterial, Mycobacterium tuberculosis, and fungal cultures. If the patient was receiving mechanical ventilation, had toxic signs, diffuse lung infiltrates, hypoxemia, or had no sputum production, fiberoptic bronchoscopy was performed only once with bronchoscopic-protected specimen brush biopsy or bronchoalveolar lavage because of great concern for the safety of this population. Bronchoalveolar lavage was performed with 120 mL of sterile saline solution in six 20-mL aliquots. In patients with localized pulmonary infiltrates, lavage was performed in the affected lobe; in patients with diffuse pulmonary infiltrates, lavage was done in the middle lobe or lingular segment. Bronchoalveolar lavage fluid was centrifuged, and the cell pellet was stained with Gram stain, the direct immunofluorescent staining method for Legionella pneumophila, Wright Giemsa stain, Gomori silver stain for Pneumocystis carinii, and Papanicolaou stain. Protected specimen brush biopsy and bronchoalveolar lavage samples were cultured for bacterial pathogens, fungi, virus, and Mycobacteria.

The study protocol complied with the Helsinki Declaration of 1975, and our Institutional Review Board approved the research protocol.

Statistical analyses

Data analyses were performed with SPSS software (SPSS: An IBM Company, version 20.0, IBM Corporation, Armonk, NY, USA). Variables are expressed as mean ± standard deviation. Frequencies are expressed as numbers and percentages. Because the log-transformed MPV levels were normally distributed, the t test was used to compare this variable between the procalcitonin-negative and procalcitonin-positive groups. The level of significance was set at P < .05.

Results

This study included 70 SOT patients (47 male/23 female, with mean age of 46 ± 14 years), comprising 26 liver transplant and 44 renal transplant recipients who had procalcitonin levels determined at our hospital (Table 1). Forty-four patients (63%) had a definite diagnosis of pneumonia, with diagnostic bronchoscopy performed in 24 of these patients (54%). The dominant causative agents were bacteria in 41 patients and fungi in 3 patients, with multiple pathogens in 11 episodes. Cytomegalovirus (CMV) pneumonia was diagnosed via bronchoalveolar
lavage polymerase chain reaction in 1 patient. No other virus groups were detected. The identified microorganisms in sputum and/or tracheal aspirate culture according to the time of onset of pneumonia are shown in Table 2.

Table 1. Patient Demographics (N = 70 Patients)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, y</td>
<td>46.16 ± 14.04</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>23/47</td>
</tr>
<tr>
<td>Smoking history, No. (%)</td>
<td>34 (48.5)</td>
</tr>
<tr>
<td>Renal transplant recipients, No. (%)</td>
<td>44 (63)</td>
</tr>
<tr>
<td>Smoker/non-smoker</td>
<td>24/20</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>13/31</td>
</tr>
<tr>
<td>Cause of renal disease, No. of patients</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
</tr>
<tr>
<td>Ureteral factors</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
</tr>
<tr>
<td>Other factors</td>
<td>4</td>
</tr>
<tr>
<td>Liver transplant recipients, No. (%)</td>
<td>26 (37)</td>
</tr>
<tr>
<td>Smoker/non-smoker</td>
<td>10/16</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>10/16</td>
</tr>
<tr>
<td>Cause of liver disease, No. of patients</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>8</td>
</tr>
<tr>
<td>HCV</td>
<td>4</td>
</tr>
<tr>
<td>ETOH</td>
<td>2</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>2</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>1</td>
</tr>
<tr>
<td>PSC</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 2. Identified Microorganisms in Sputum and/or Tracheal Aspirate Culture

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple pathogens</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Proteus</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
</tr>
</tbody>
</table>

Abbreviations: ETOH, alcoholic liver disease; F, female; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; M, male; PSC, primary sclerosing cholangitis

Of 30 patients diagnosed with pneumonia radiologically, procalcitonin was positive in 11 patients (36.7%), MPV was low in 6 patients (20%), CRP was elevated in 29 patients (96.7%), and leukocyte count was increased in 6 patients (20%) (Table 3).

Serum procalcitonin, CRP levels, complete blood count, and MPV results were compared in SOT patients with pneumonia. We found that MPV values were significantly lower in patients with pneumonia and elevated serum procalcitonin levels (P = 0.038). However, in patients with radiologic pneumonic infiltration, we found no significant difference in terms of MPV values and high and normal procalcitonin groups (P = 0.048). Patients with elevated and normal CRP value were also compared with MPV values, and no statistical significant difference was found (P = 0.042).

Table 3. Patient Laboratory Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liver Transplant Recipients</th>
<th>Renal Transplant Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>64 ± 55</td>
<td>99 ± 97</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10 ± 3</td>
<td>10.2 ± 2.4</td>
</tr>
<tr>
<td>Leukocyte, 10^9/L</td>
<td>7.5 ± 4.5</td>
<td>8.5 ± 6.6</td>
</tr>
<tr>
<td>Neutrophil, 10^3/µL</td>
<td>6.02 ± 4.4</td>
<td>7.4 ± 6.2</td>
</tr>
<tr>
<td>Procalcitonin, ng/dL</td>
<td>0.46 ± 0.58</td>
<td>0.65 ± 0.77</td>
</tr>
<tr>
<td>Mean platelet volume, fl</td>
<td>1.52 ± 0.80</td>
<td>1.59 ± 1</td>
</tr>
</tbody>
</table>

Results are presented as mean ± standard deviation.

Both renal and liver transplant recipients in our study population received a similar immunosuppressive regimen. The most common agent was prednisolone; however, mycophenolate mofetil, sirolimus, tacrolimus, and cyclosporine were also administered in all renal transplant patients. All liver transplant patients were treated with tacrolimus or cyclosporine, mycophenolate mofetil, and steroids after transplant. Patients also received prophylactic sulfamethoxazole and trimethoprim against Pneumocystis carinii, and ganciclovir as antiviral treatment was also administered in all patients after transplant.

Discussion

In SOT patients, the use of clinical signs either alone or in combination in the diagnosis of pneumonia is limited because known specific symptoms of pneumonia (including fever, cough, and sputum) may not appear in these patients.5 Radiographic evidence of pneumonia may not occur due to poor immune response in lungs and other organs in SOT patients.6,11 When pulmonary infiltration occurs, its presence may interfere radiologically with fluid or solid material within the airways caused by excessive liquid loading, drug toxicity, and acute respiratory distress syndrome in SOT patients, resulting in relative attenuation of the lung via transudate, pus, blood, cells, and protein.8,12-14

Serologic testing, such as CRP and procalcitonin, is generally not useful in the acute care of immunocompromised patients because SOT patients often fail to generate an adequate antibody response against infection.15,16 Results for microbiology tests, including antigen detection and/or nucleic acid
detection-based assays, cultures, and sputum sampling and bronchoscopy may take days to receive, delaying treatment initiation.

Microbicidal therapy must be started even empirically after exclusion of other possible serious pulmonary problems, including liquid loading, immunosuppressive drug toxicity, and acute respiratory distress syndrome, to reduce mortality. Therefore, clinicians need to have stronger laboratory methods to differentiate pneumonia to avoid overtreatment for other conditions.

Mean platelet volume is a parameter measured by routine blood count that clinicians do not usually consider. Normally, there is an inverse relationship between platelet volume and blood counts. Platelet volume is known to be a marker determined from megakaryocytes during platelet production, which is associated with platelet function and activation. Recently, MPV has been shown to reflect inflammatory burden in different inflammatory diseases. We know little about the role of MPV in the diagnosis of pneumonia in SOT patients.

Overproduction of proinflammatory cytokines and acute-phase reactants can suppress the size of platelets by interfering with megakaryopoiesis, with subsequent release of small-size platelets from the bone marrow. We did not find a significant correlation among MPV, procalcitonin, and CRP, although MPV was significantly lower in patients with pneumonia and elevated serum procalcitonin levels in our study. We suggest that altered procalcitonin, CRP, and MPV by immunosuppressives could be responsible for this result.

Recent studies have shown that MPV was significantly lower in patients with community-acquired pneumonia and predicted mortality of disease among immune-competent patients with community-acquired pneumonia. In our study, MPV was lower than normal in patients with pneumonia and elevated serum procalcitonin levels in our study. We suggest that altered procalcitonin, CRP, and MPV by immunosuppressives could be responsible for this result.

Cytomegalovirus is the most common virus of concern in immunocompromised patients, especially SOT patients. The radiographic manifestations of CMV pneumonia can take many forms, but a bilateral, symmetrical, peribronchovascular, and alveolar process predominantly affecting the lower lobes is the most frequent. Less common is a focal consolidation, which is more suggestive of a bacterial or fungal infection, or a solitary pulmonary nodule. Mixed patterns on chest radiography should suggest dual infection; CMV, pneumocystis pneumonia, and Aspergillus are common infections that may coexist in these patients. In our study, CMV pneumonia plus a concomitant Aspergillus infection was detected by
bronchoalveolar lavage in 1 patient, although CMV polymerase chain reaction tests were performed in 6 patients. The dominant radiologic features were not specific for CMV, showing bilateral nonsymmetrical consolidation accompanied with lung micronodules. We suggest that CMV should be considered and investigated routinely, even when radiologic features are not suggestive for CMV in SOT patients with pneumonia.

In our study, all patients were receiving immunosuppressive agents at different doses and combinations because our study involved patients during different times of the posttransplant period. A common adverse effect of immunosuppressive drugs is immunodeficiency because most immunosuppressives act nonsellectively. Glucocorticoids influence all types of inflammatory events, and steroids lead to decreased activation status of platelets, with steroid treatment leading to changes in platelets. In our study, MPV levels were variable in 6 patients (20%), showing low levels in patients with pneumonia. We suggest that inconsistent MPV levels could be a result of different combined immunosuppressive regimens used in our patients.

Conclusions

Pneumonia has high mortality rates in transplant recipients due to the use of immunosuppressive agents, including corticosteroids. Difficulties in the diagnosis of pneumonia in SOT patients have directed clinicians to search for new parameters to indicate lung infection. This study demonstrated that measurement of serum MPV may not be a promising parameter for this purpose. A combined evaluation with clinical, laboratory, and radiologic findings still remains the most reliable method to avoid a delay in optimal treatment of pneumonia in SOT patients.

References

Natural Thermal Spa Water Versus Hyperthermic Tap Water for Treatment of Recalcitrant Hand Warts in Organ Transplant Recipients: A Patient-Blinded, Comparative Preliminary Study

A. Tülin Güleç

Abstract

Objectives: Cutaneous warts represent a major problem in organ transplant recipients because of their extensive involvement and persistent course. Current therapeutic modalities often fail to achieve a successful response in patients with warts. We experienced a case involving an organ transplant recipient with recalcitrant mosaic warts who presented with complete clearance of lesions in 3 days after thermal spa bathing. Here, we evaluated the efficacy of natural thermal water versus hyperthermic tap water for treatment of recalcitrant hand warts in organ transplant recipients.

Materials and Methods: In this preliminary study, the right hands of 5 organ transplant recipients with hand warts were immersed in thermal water, while the left hands were soaked in tap water at 44°C to 47°C. Treatment involved three 45-minute sessions per week for 1 month. The total number and size of the warts and the hyperkeratosis severity grade were noted.

Results: After 12 sessions, none of the patients exhibited any marked improvement in the size or number of warts, although 3 patients had a slight decrease in their hyperkeratosis severity grade.

Conclusions: Our preliminary data indicate that neither thermal spa water nor hyperthermic tap water is effective for treatment of recalcitrant hand warts in organ transplant recipients. However, new trials using thermal water supplied from different geographical locations should be performed before this observation can be generalized.

Key words: Cutaneous warts, Hyperthermic water treatment, Thermal water, Transplantation

Introduction

Organ transplant recipients (OTRs) undergoing long-term immunosuppressive treatment are highly susceptible to the development of common warts, which remain a significant therapeutic problem in their dermatologic surveillance.1 Human papillomavirus-induced warts are frequently large, widespread, and numerous in this patient population. Moreover, they are considered potential precursors to the development of nonmelanoma skin cancer in OTRs.1,2

Unlike immunocompetent individuals, spontaneous regression of warts is rather rare in OTRs, and current treatment options such as cryotherapy, topical salicylic acid, and 5-fluorouracil often fail to clear the lesions.1 Consequently, new effective therapeutic alternatives are needed.

The current study originated from a 37-year-old female renal transplant recipient with a 2-year history of mosaic warts (Figure 1, left). Numerous treatment modalities including salicylic acid and cryotherapy were applied for 2 years without success. Then, she had gone to a natural thermal spa for vacation, and had a 30-minute thermal bath for 2 days that induced complete clearance of the warts in 3 days. (Figure 1, right). Two possible explanations for the therapeutic effects of thermal bathing were considered: the chemical effect of the thermal water and/or local hyperthermia.

Several studies have investigated the therapeutic efficacy of local hyperthermia for warts.3-6 However, there are no reports on the response of warts to thermal water bathing. Therefore, we evaluated the efficacy and safety of natural thermal spa water...
versus hyperthermic tap water for the treatment of recalcitrant hand warts in OTRs.

Materials and Methods

Study population
This study included 5 OTRs (2 female, 3 male patients) with recalcitrant hand warts who were seen at the Dermatology Department of Baskent University in Ankara, Turkey from January 2012 to April 2012. The mean patient age was 30 ± 9 years (range, 19-43 years), and the mean time since transplant was 71 ± 41 months (range, 42-143 months). The patients’ immunosuppressive drugs are shown in Table 1.

The inclusion criteria were the presence of numerous warts on both hands; failure of response to previous cryotherapy, topical salicylic acid, imiquimod, and 5-fluorouracil; and lack of any treatment within the last month. All participants gave informed consent before study participation.

Study procedure
This preliminary study was designed as a prospective, patient-blinded, side-by-side comparative clinical trial. Two hydrocollator heating units (Hydrocollator E-2 Stationary Heating Unit; Chattanooga Group, Hixson, TN, USA) were used as the hyperthermia device, which provided a water bath with a temperature that fluctuated from 44°C to 47°C. Thermal water was supplied from a thermal resort (Patalya Thermal Resort, Kızılcahamam/Ankara, Turkey). This was not the same spring from which our index patient obtained the spa water and experienced her cure. The chemical composition of the 2 thermal spa waters could not be analyzed.

The patients soaked their right hands in the heating unit filled with thermal water, while their left hands were immersed in the other unit filled with tap water. Each treatment session lasted 45 minutes and was performed 3 days per week (every other day) for 4 weeks. Digital pictures of the hands were obtained at every visit. Hyperkeratosis of the lesions (1: mild, 2: moderate, 3: severe) and any change in their number or size were evaluated by visual and photographic assessment. Each patient served as his or her own control during the pre- and posttreatment comparisons.

Adverse effects such as pain, burning, erythema, and bullae formation were self-assessed by each

Table 1. Demographic Details and Results of the Organ Transplant Recipients With Hand Warts

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age, y</th>
<th>Graft Type</th>
<th>Duration Since IS, mo</th>
<th>IS Drugs</th>
<th>Duration, mo</th>
<th>Number</th>
<th>Size, mm</th>
<th>Hyperkeratosis Grade Pre-TX</th>
<th>Post-TX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/43</td>
<td>Kidney</td>
<td>143</td>
<td>P, CSA, MMF</td>
<td>96</td>
<td>63</td>
<td>2-20</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>M/28</td>
<td>Kidney</td>
<td>42</td>
<td>P, RAPA, MMF</td>
<td>12</td>
<td>15</td>
<td>2-20</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>F/25</td>
<td>Kidney</td>
<td>47</td>
<td>P, TAC, MMF</td>
<td>12</td>
<td>33</td>
<td>2-5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>M/19</td>
<td>Liver</td>
<td>61</td>
<td>P, RAPA, MMF</td>
<td>96</td>
<td>12</td>
<td>2-10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>F/36</td>
<td>Kidney</td>
<td>65</td>
<td>P, RAPA, MMF</td>
<td>36</td>
<td>16</td>
<td>2-20</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, cyclosporine; F, female; IS, immunosuppression; M, male; MMF, mycophenolate mofetil; P, prednisolone; RAPA, rapamycin; TAC, tacrolimus; TX, treatment
participant using a semiquantitative scale of discomfort (1: mild, 2: moderate, 3: severe).

This study was approved by the Baskent University Institutional Review Board and Ethics Committee (project no. KA11/199) and supported by the Baskent University Research Fund. It was conducted in conformity with the 1975 Helsinki Declaration.

Results

The demographic and clinical details of the OTRs are presented in Table 1. Four participants had warts on the dorsum of the hands, and 1 had warts on the palmar surface. The duration of the warts ranged from 12 to 96 months with a mean of 50 ± 43 months, whereas the mean number of lesions was 28 ± 21 (range, 12-63). The lesion size varied from 2 to 20 mm, and 3 patients had mostly large-sized warts.

After 12 sessions, none of the warts displayed any marked improvement in size or clearance (Figures 2 and 3). Three of the patients had a slight reduction in their hyperkeratosis grade (Figure 2, right), whereas 2 showed no change (Figure 3, right, Table 1).

Both therapies were well tolerated by all patients. There were no complaints of pain or burning sensation due to hot water, and no serious adverse effects occurred except mild erythema and edema lasting for 30 to 90 minutes after each session.

Discussion

Up to 92% of all OTRs develop viral warts almost 5 years after transplant, and they frequently present with extensive involvement and persistent disease.
course, creating a therapeutic challenge.\textsuperscript{1,2,7} After observation of complete clearance of recalcitrant mosaic warts of an OTR in 3 days following 2 thermal baths, the efficacy of thermal spa water and/or hyperthermic tap water was evaluated in this context.

Organ transplant recipients with recalcitrant hand warts were included in this study because it would have been impossible to immerse the feet into the heating units used. The researcher selected patients with both large and/or small lesions with either an extensive or limited distribution to evaluate possible improvement differences. However, excluding slight reduction in the hyperkeratosis of some lesions, none of the warts benefited from either hyperthermic tap or thermal spa water therapy over the 4-week study period. Thus, treatment sessions were discontinued after the 12th session. No delayed improvement was observed upon follow-up.

Thermal water is hot water that emerges from natural thermal springs and is composed of salts, minerals such as sulfur and selenium, and gases such as carbon dioxide.\textsuperscript{8} Thermal baths have had a curative effect in cases of psoriasis and atopic dermatitis.\textsuperscript{9,10} Some of the minerals in thermal water have been proposed to have keratolytic, anti-inflammatory, and antiproliferative properties that may play a role in wart regression.\textsuperscript{8} However, no reports in the literature support this hypothesis. Hyperthermia is defined as exogenous elevation of tissue temperature to 39°C to 48°C. Although the exact mechanism remains uncertain, several reports have described the therapeutic efficacy of hyperthermia for warts.\textsuperscript{3-6} However, these studies used different devices such as infrared emitting sources, lasers, and thermal patches as sources of heat ranging from 40°C to 50°C.

Only two reports have addressed the efficacy of hot water treatment for warts. The first was a study performed in 1962 involving 15 immunocompetent patients with recalcitrant warts on the feet, hands, or face.\textsuperscript{11} The patients were treated with water baths at 45°C to 48°C for 30 to 90 minutes once or twice per week for 3 to 8 weeks. Nine participants exhibited either regression or resolution of the warts within 3 months without serious adverse effects.

The second article was a case report published in 1994.\textsuperscript{12} A 42-year-old man with human immunodeficiency virus infection and psoriasis was undergoing etretinate therapy. The authors applied hot water therapy at 45°C using a whirlpool apparatus to treat the warts on his toes. After notable improvement was achieved on his right foot, the therapy was extended to the left foot, resulting in resolution on both sides. The authors declared that unilateral improvement noted only on the hyperthermia-treated side after the first session proved the independent therapeutic activity of hot water. However, the added effect of etretinate therapy cannot be completely excluded in this case.

The complete clearance of the mosaic warts in our index patient might also be explained by suggestive hypnotic therapy, the particular chemical composition of the thermal water bath, or spontaneous regression of the warts. In terms of hypnosis, she strongly denied that she had any belief that thermal water could treat her warts. The hydrogeology origins, temperatures, and chemical contents differ considerably among thermal waters.\textsuperscript{8} The water in which she bathed may have possessed different properties that exerted therapeutic activity in her warts. Additionally, these waters have volatile elements such as sulfurous gases that might dissipate with storage, time, or reheating of the water in a clinical setting.\textsuperscript{8} Moreover, she underwent total body immersion while bathing, which may have a different therapeutic benefit. Finally, spontaneous regression is always a probability in warts, although it is rare in immunosuppressed individuals.\textsuperscript{1,2,7} However, no treatment-related or spontaneous regression had been observed throughout the 2-year period.

A limitation of the present study is the small sample size and short treatment duration. If encouraging improvements had been obtained, the investigator planned to enroll more patients and extend the treatment course. Other limitations included the use of thermal spa water different from the one that the index patient used, not performing whole-body immersion, and not using the thermal spring water at its source.

In conclusion, our preliminary data do not confirm the previous observations that hot water treatment as a form of local hyperthermia is curative for warts. Furthermore, we revealed that thermal water was not therapeutic in recalcitrant hand warts in OTRs. Nevertheless, new trials using thermal waters originating from different geographic locations should be performed before this observation can be generalized.
References

Aesthetic Surgery in Transplant Patients: A Single Center Experience

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Abstract

Objectives: Transplant patients, like the nontransplant population, can have surgical interventions for body shape disorders. Studies on aesthetic surgeries in transplant patients are scarce. Our aim was to share our experiences with various aesthetic procedures in solid-organ transplant recipients.

Materials and Methods: Six (5 female, 1 male) transplant patients who received surgical corrections of the aging face, ptosis and lipodystrophy of the breast, and abdomen at the Baskent University Plastic Reconstructive and Aesthetic Surgery Department between 2010 and 2017 were included. Five patients had renal transplants, and 1 patient had liver transplant. Minimal aesthetic procedures, including botulinum toxin, dermal filler injections, and scar revisions, were excluded. All patients were consulted to transplant team preoperatively and hospitalized in the transplant inpatient clinic.

Results: Mean age was 46 years. Aesthetic surgeries included breast reduction (2 patients), high superficial musculoaponeurotic system face lift (1 patient), blepharoplasty (2 patients), and dermofat grafting (1 patient). Mean hospitalization duration was 2.5 days. Four patients had no minor or major complications. One patient had skin flap necrosis, which healed with secondary intention. Another patient had ectropion after lower lid blepharoplasty, which was corrected with another procedure.

Conclusions: Transplant patients are a special group of patients who receive long-term immunosuppressive treatment and medications like high-dose steroids. These treatments can lead to dermal atrophy and cause pseudo-skin laxity. Removal of excess skin and fat tissue should be considered. Efforts should be made to avoid complications such as skin necrosis and unpredictable wound healing problems when resecting the excess tissue. Preoperative consultation with transplant surgeons and keeping operative times short are other important factors. Body dysmorphologies that interfere with normal life activities and demand for younger appearance are the main reasons of aesthetic procedures. Transplant patients can be operated safely with preoperative planning, consultation with transplant surgeons, and close follow-up.

Key words: Cosmetic procedures, Liver, Renal

Introduction

The demand for aesthetic surgery is increasing in direct proportion to health and wealth status worldwide. Aesthetic plastic surgery is safe and reliable in experienced professionals and has become more popular with increased awareness.1

With advances in immunosuppressive drugs and treatment protocols, transplant success rates and survival of younger adults have been increasing. Transplant procedures result in patients feeling healthy, able to be independent, and able to regain damaged self-esteem.2 Similarly to that shown in the nontransplant population, solid-organ transplant (SOT) patients can consult a plastic surgery department with concerns regarding body shape disorders or to have a younger appearance. Every surgery has its own complications, depending on the anatomic site, the local tissue characteristics, and patient comorbidities. However, the use of immunosuppressive drugs in transplant patients should not be underestimated. Adverse effects of these drugs on wound healing and viability of skin flaps have been demonstrated in several studies.3-7 Immunosuppressive-related complications regarding aesthetic surgery procedures in SOT patients and
studies reporting their long-lasting results are limited in the literature.\(^8,9\) Our goal was to share our experience with aesthetic surgery outcomes in SOT patients.

**Materials and Methods**

Between 2010 and 2017, 1833 patients underwent SOT at the Başkent University Faculty of Medicine Organ Transplantation Center. Patient medical records were reviewed retrospectively. Exclusion criteria included patients who required reconstructive surgery and minimal aesthetic procedures, such as botulinum toxin and dermal filler injections and scar revisions. Immunosuppressive drug use and complications were noted. Results were not evaluated statistically due to a limited number of cases. All patients were consulted preoperatively by the transplant team and hospitalized in the transplant department inpatient clinic.

This study was approved by our Institutional Review Board and Ethics Committee and conducted in conformity with the 1975 Helsinki Declaration.

**Results**

We identified 6 SOT patients (5 female, 1 male) who underwent aesthetic surgery at the Başkent University Plastic Reconstructive and Aesthetic Surgery Department. The average age of the 6 patients was 46 years (range, 38-60 years). Five patients had received a kidney transplant and 1 patient had received a liver transplant. Mean elapsed time after transplant was 7.6 years (range, 2-13 years). Two patients underwent blepharoplasties, 2 patients had breast reduction surgery, 1 had superficial muscularaponeurotic system facelift, and 1 had dermofat grafting. Mean hospitalization time was 2.5 days.

Of the 6 patients, 4 had no minor or major complications. Early onset of ectropion was seen in a lower blepharoplasty patient who healed without surgical intervention (Figure 1). One partial flap necrosis was seen as a major complication, but this healed secondarily with wound dressings in the facelift patient. Mean follow-up was 4 years (range, 2-6 years). During follow-up, patients were checked and queried regarding concerns on asymmetries and scar formations.

**Discussion**

Due to advances in transplant surgeries and immunosuppressive treatments, life expectancy and survival of SOT patients have been dramatically increased. This has led to an increased number of SOT patients seeking plastic surgery departments for reconstructive and cosmetic disorders. We usually perform reconstructive surgeries for immunosuppressive-related skin malignancies and lower extremity wounds in SOT patients at our institution.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Transplant Type</th>
<th>Aesthetic Surgery</th>
<th>Elapsed Time After Transplant, years</th>
<th>Complication</th>
<th>IS Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>F</td>
<td>Liver</td>
<td>Breast reduction</td>
<td>2</td>
<td></td>
<td>CS/Tac/MMF</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>Kidney</td>
<td>Dermo grafting</td>
<td></td>
<td></td>
<td>CS/MMF</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>F</td>
<td>Kidney</td>
<td>Breast reduction</td>
<td></td>
<td></td>
<td>CS/Tac/MMF</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>F</td>
<td>Kidney</td>
<td>Face lift</td>
<td></td>
<td></td>
<td>CS/Tac/MMF</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>F</td>
<td>Kidney</td>
<td>Blepharoplasty (lower lid)</td>
<td>8</td>
<td>Ectropion</td>
<td>CS/Tac/MMF</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>F</td>
<td>Kidney</td>
<td>Blepharoplasty (upper lid)</td>
<td></td>
<td>Flap necrosis</td>
<td>CS/Tac/MMF</td>
</tr>
</tbody>
</table>

*Abbreviations:* CS, corticosteroid; F, female; IS, immunosuppressive; M, male; MMF, mycophenolate mofetil; Tac, tacrolimus
Care of reconstructive cases provides us clinical experience about the healing processes of immunocompromised patients, changes in their skin quality, and management of their complications. Similar to our experience, carefully selected SOT patients can safely receive plastic reconstructive procedures.10,11

Zellner and associates advocated that emergency or urgent cases have higher complication rates than elective operations.9 Thus, the plastic surgeon has an advantage to manage cases of aesthetic surgery through careful patient selection, investigation of medications, preoperative anesthesiology consultations, and informing patients for possible complications. In our series, we consulted our patients preoperatively with anesthesiology and transplant teams for approval before the surgical procedures. It is advised that mean elapsed time after transplant should be more than 6 months for elective cases to prevent graft rejection.12 In our study, the shortest time for aesthetic surgery after transplant was 2 years for the liver transplant patient. Another issue is the importance of keeping the operative time shorter for a lower surgical stress level.13 Therefore, we recommend avoiding combined surgical procedures and guiding patients in the direction of separating the sessions or correcting the most desired disorder.

In our study, we encountered 2 complications. The first complication was ectropion after lower blepharoplasty in a kidney transplant patient. The patient was taking maintenance dose glucocorticoids, sirolimus, and mycophenolate mofetil. She had increased skin laxity due to dermal atrophy, which is a result of chronic steroid usage.14 The other complication was in the patient who received a facelift; the patient had slough of skin and skin flap necrosis in the first week after the operation. The patient healed in 3 months with topical wound care provided secondarily. She was taking maintenance-dose corticosteroids and sirolimus, and she was 60 years old, the oldest of our patients. Dermal atrophy and pseudo-skin laxity misguided our group, resulting in excessive skin removal. Although some studies support positive effects of glucocorticoids on skin flap viability,15,16 sirolimus and steroids have been shown to have negative synergetic effects on wound tensile strength.3,4,17 Another dermal atrophy was seen in a patient who had a dermofat graft. We had to retrieve more dermofat than estimated due to dermal atrophy for fixing atrophic scar of mandibula (Figure 2).

Meticulous removal of the excess skin and closing the wound without tension is crucial in SOT patients. We did not have any complications in the cases of breast reduction, in which we carefully adapted tensionless flaps. We believe our complications were due to immunosuppressive drugs and patient age. We suggest that elderly SOT patients be informed about possibilities of complications. The main limitation of our study was the small number of patients. To understand the long-term outcomes of aesthetic surgeries in SOT patients and complications related to immunosuppressive drugs, more patients should be evaluated in the future.

Conclusions

Demand for aesthetic surgery can be an indirect success marker of transplant surgery. As a result of increased rates of transplant surgeries, more SOT patients will seek plastic surgeons for cosmetic disorders. We believe that SOT patients are safe candidates for cosmetic surgeries when there is good evaluation of the patients and a preoperative multidisciplinary approach is used. Avoiding tension in wound closure and being aware of immunosuppressive drug-related complications are the technical factors for satisfactory results.

References


A Multicenter Survey: How Do Transplant Dermatologists Monitor Organ Transplant Recipients With Nevi?

Deren Özcan,1 Deniz Seçkin,1 Mehmet Haberal2

Abstract

Objectives: The incidence and mortality of melanoma are increased in organ transplant recipients. Multiple acquired common and dysplastic nevi are risk factors for melanoma. A new or changing nevus may suggest melanoma. Strategies used by transplant dermatologists to monitor nevi are unknown. Herein, we aimed to assess the methods used by transplant dermatologists for monitoring multiple acquired common nevi, dysplastic nevi, and new or changing nevi.

Materials and Methods: A questionnaire was e-mailed to 63 members of the Skin Care in Organ Transplant Patients, Europe.

Results: Thirty-eight (92.7%) of 41 responders reported that they instruct their patients to perform regular self-skin examinations. Of 41 responders, 41.5% prescribed screening every 6 months, 36.6% prescribed it every 12 months, 12.2% prescribed it every 3 months, and 9.7% performed screening without regular intervals. Regarding type of examination, 80.5% performed full-body skin examinations with the naked eye, 70.7% performed dermoscopy of clinically suspicious nevi, 53.6% offered dermoscopic photography of dermoscopically suspicious nevi, 36.6% provided close-up photography of clinically suspicious nevi, 34.1% performed baseline total body photography, and 24.4% conducted dermoscopy of all nevi. We also found that 7.3%, 4.9%, and 4.9% performed only full-body skin examination with the naked eye, only dermoscopy of clinically suspicious nevi, and only dermoscopy of all nevi, respectively.

Conclusions: Dedicated transplant dermatologists perform a wide variety of nevi screening procedures in organ transplant recipients. Transplant dermatologists should include sequential digital dermoscopic imaging in their armamentarium to follow organ transplant recipients with melanocytic lesions. A combination of techniques is advisable for detecting early posttransplant melanomas.

Key words: Dermoscopy, Melanocytic lesions, Melanoma, Self-skin examination

Introduction

Organ transplant recipients (OTRs) are at increased risk of developing melanoma, and OTRs with thicker melanomas have poorer outcomes than patients with thicker melanomas who did not receive transplant procedures.1-5 The presence of more than 50 acquired common melanocytic nevi or 5 dysplastic nevi increases an individual’s risk for developing melanoma.6 Any change in a preexisting nevus or the appearance of a new nevus, especially in patients over 50 years of age, is highly suspicious of melanoma development.7,8 According to the findings of a multicenter melanoma study in OTRs, more than half (54.5%) of patients with melanoma had more than 50 nevi, 37% had atypical nevi, and 38% developed melanoma in a preexisting nevus.1 Given the lack of effective treatment options for advanced melanoma and the worse outcomes in OTRs than in the general population, regular skin surveillance and identifying melanoma in its early stage is even more important in this group of patients.5,9 The strategies currently used by dedicated transplant dermatologists for monitoring nevi to detect early melanoma in OTRs are unknown.

In this study, we sought to assess the daily clinical practice of dedicated European transplant dermatologists in screening OTRs with acquired multiple common melanocytic nevi, dysplastic nevi, or new or changing nevi.
Materials and Methods

A questionnaire (Table 1) was e-mailed to 63 members of the Skin Care in Organ Transplant Patients, Europe (SCOPE), a society formed by a group of European dermatologists who are interested in transplant-associated skin infections and skin cancers. The questionnaire was designed to obtain information from members regarding their screening practices for OTRs who attend for routine check-up examinations with acquired multiple common melanocytic nevi, dysplastic nevi, or new or changing nevi. The data obtained from the SCOPE members were compared with evidence-based suggestions for screening the general population at risk for melanoma.

Table 1. Questionnaire Responses From 41 Transplant Dermatologists Regarding Monitoring Nevi in Organ Transplant Recipients

<table>
<thead>
<tr>
<th>Question</th>
<th>Responses, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you instruct your OTRs to perform regular self-skin examinations for &quot;new&quot; and &quot;Changing&quot; nevi?</td>
<td>Yes: 38 (92.7) No: 3 (7.3)</td>
</tr>
<tr>
<td>How often do you screen your OTRs with multiple common melanocytic nevi and/or dysplastic nevi?</td>
<td>Every 3 months: 5 (12.2) Every 6 months: 17 (41.5) Every 12 months: 15 (36.6) Screening without regular intervals: 4 (9.7)</td>
</tr>
<tr>
<td>How do you screen your OTRs with multiple melanocytic common nevi and/or dysplastic nevi? (Please mark each method if you use multiple methods)</td>
<td>Full-body nevi examination with naked eye: 33 (80.5) Dermoscopic photography of clinically suspicious nevi: 29 (70.7) Dermoscopic photography of dermoscopically suspicious nevi: 22 (53.6) Close-up photography of clinically suspicious nevi: 15 (36.6) Baseline total body photography: 14 (34.1) Dermoscopy of all nevi: 10 (24.4)</td>
</tr>
</tbody>
</table>

Abbreviations: OTRs, organ transplant recipients

*Nine responders were from the United Kingdom, 5 were from France, and 3 were from Germany. The other countries were Spain, Hungary, Sweden, Norway, Italy, Greece, Denmark, and Switzerland (each with 2 dermatologists) and Turkey, Poland, Czech Republic, Austria, Portugal, Finland, Belgium, and Netherlands (each had 1 dermatologist responding).

Results

A total of 41 dedicated transplant dermatologists, working at universities or state hospitals, from 19 European countries participated in the survey and answered the questionnaire. The participants’ responses and countries are listed in Table 1. Three responders (7.3%) screened their patients by performing only full-body skin examination with the naked eye, 2 (4.9%) by performing only dermoscopy of clinically suspicious nevi, and 2 (4.9%) by performing only dermoscopy of all nevi. The remaining 34 participants (82.9%) performed more than one screening modality (Table 2). Two transplant dermatologists (from Turkey and Greece) screened their patients using all 6 screening methods. Five dermatologists from the United Kingdom screened their OTRs by performing 5 screening methods (full-body nevi examination with naked eye, dermoscopy of clinically suspicious nevi, dermoscopic photography of dermoscopically suspicious nevi, close-up photography of clinically suspicious nevi, and baseline total body photography). Otherwise, the screening methods used by transplant dermatologists were quite heterogenous, even among the participants from the same country.

Table 2. Combinations of Different Screening Modalities Performed by 34 Transplant Dermatologists to Monitor Nevi in Organ Transplant Recipients

<table>
<thead>
<tr>
<th>Combination</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>2. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi; dermoscopic photography of dermoscopically suspicious nevi; close-up photography of clinically suspicious nevi; baseline total body photography</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>3. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi; dermoscopic photography of dermoscopically suspicious nevi; close-up photography of clinically suspicious nevi</td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>4. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi; dermoscopic photography of dermoscopically suspicious nevi</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>5. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi; dermoscopic photography of dermoscopically suspicious nevi; baseline total body photography; dermoscopy of all nevi</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>6. Dermoscopy of all nevi; dermoscopic photography of dermoscopically suspicious nevi</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>7. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi; dermoscopic photography of dermoscopically suspicious nevi; baseline total body photography</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>8. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi; close-up photography of clinically suspicious nevi</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>9. Full-body nevi examination with naked eye; dermoscopy of clinically suspicious nevi; baseline total body photography</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>10. Full-body nevi examination with naked eye; close-up photography of clinically suspicious nevi</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>11. Full-body nevi examination with naked eye; close-up photography of clinically suspicious nevi; baseline total body photography</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>12. Full-body nevi examination with naked eye; dermoscopy of all nevi; dermoscopic photography of dermoscopically suspicious nevi; baseline total body photography</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>13. Full-body nevi examination with naked eye; dermoscopy of all nevi; dermoscopic photography of dermoscopically suspicious nevi</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>14. Dermoscopy of clinically suspicious nevi; dermoscopic photography of dermoscopically suspicious nevi</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>15. Baseline total body photography; dermoscopy of all nevi</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>16. Full-body nevi examination with naked eye; dermoscopy of all nevi</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>
In the comments section of the questionnaire, 4 dermatologists stated that “nevi and melanoma are not really an issue in OTRs,” with 3 of these dermatologists reporting that they did not perform a specific screening with regular intervals for their OTRs with multiple common melanocytic nevi and/or dysplastic nevi. Two of those responders did not instruct their patients to perform regular self-skin examinations for “new” and “changing nevi,” and 2 used only full-body skin examination with the naked eye for melanoma screening. One dermatologist noted that the morphologic features of melanocytic nevi in OTRs frequently differ from those of melanocytic nevi in immunocompetent patients, and one stated that OTRs with difficult nevi should be followed in a dedicated clinic treating pigmented lesions.

**Discussion**

Although the 5-year survival rate is reported to be as high as 85% in immunocompetent individuals with early melanoma (stage I/II), increased time to diagnosis is associated with a higher disease stage (stage III/IV), with 5-year survival rates ranging from 6% to 69.5%.\(^1,10\) Melanoma-specific mortality is higher among OTRs than in nontransplant recipients.\(^1,2,11,12\) A multicenter SCOPE study showed that prognosis is significantly worse for post transplant patients with T3 melanoma or greater than prognosis for the general population with T3 or greater disease.\(^1\) Another study reported that OTRs with thicker melanomas have significantly lower cause-specific survival rates than nonimmunosuppressed individuals with thicker melanomas. The same study also showed that overall survival rates were lower in patients with a prior history of organ transplant regardless of Breslow thickness or Clark level.\(^2\)

Similar to that for the general population, melanoma screening in OTRs should aim to diagnose and treat this cancer in its early stages to reduce its mortality rate.\(^5-7\) A recent systematic review showed that, although the long-term monitoring of individuals at high risk of primary cutaneous melanoma is strongly recommended, there is disagreement in screening and follow-up strategies, screening intervals, and duration of follow-up.\(^13\) The present survey showed that the current practices of transplant dermatologists with respect to screening OTRs with acquired multiple common melanocytic nevi, dysplastic nevi, or new or changing nevi were quite heterogeneous. Eighty-two percent of the responders performed a combined approach using more than one screening modality. In contrast, the remaining participants performed only one method, either naked eye examination, dermoscopy of clinically suspicious nevi, or dermoscopy of all nevi. Because this was not questioned, we do not know the exact reasons behind this heterogeneity.

Our survey showed that 92.7% of the participants gave instruction for self-skin examinations. Various studies in the literature have indicated that a deliberate self-skin examination is associated with greater detection of thinner and prognostically favorable melanomas.\(^14,15\) However, a recent systematic review underlined that the strength of evidence to recommend self-skin examinations was low.\(^13\)

Although the level of evidence has been shown to be low for defining strict screening intervals,\(^13\) a first follow-up examination is recommended 3 months after the baseline visit and then every 3 to 6 months thereafter.\(^7,16\) A prolonged annual monitoring is suggested so that indolent, slow-growing melanomas are not missed.\(^16\) Most responders in our survey screened their OTRs every 6 or 12 months. However, 4 (9.7%) did not perform a specific melanoma screening with regular intervals, with 3 stating that nevi and melanoma are not really an issue in OTRs.

In our survey, 80.5% of the responding dermatologists performed full-body skin examinations with the naked eye, with 7.3% using only this method for melanoma screening. However, many studies have shown that the diagnostic accuracy of melanoma screening by skin examination with only the naked eye is around 60%.\(^8,17\) The clinical ABCD criteria have been proven to be useful and are commonly used to guide melanoma detection.\(^9\) However, small-diameter (< 5 mm), nodular, desmoplastic, or amelanotic melanomas do not usually meet these criteria.\(^18\) Conversely, many dysplastic nevi and seborrheic keratoses fulfill most of the clinical ABCD criteria.\(^9,18\) Therefore, full-body skin examinations with the naked eye should not be performed solely for melanoma screening.\(^9,19\) Additional screening methods such as dermoscopy and photography (total body, dermoscopic, or clinical close-up photography of suspicious nevi) are suggested so that suspicious lesions can be recognized and unnecessary biopsies can be reduced.\(^7,9,19\)
In patients with melanoma, dermoscopy by an experienced dermatologist can increase the diagnostic sensitivity of skin examinations with the naked eye from 60% to 90%. In the present survey, 70.7% of the respondents used dermoscopy solely for clinically suspicious nevi, whereas 24.4% performed dermoscopy for all nevi. Because early dermoscopic signs are visible before classical clinical findings, especially in small (< 6 mm) or clinically banal-looking melanomas, the use of dermoscopy should not be limited to skin lesions that are clinically suspicious of melanoma. A high level of evidence supports using dermoscopy, which is particularly useful for following dysplastic nevi, improving diagnostic accuracy, and reducing unnecessary excisions of benign melanocytic lesions.

Because melanoma is a dynamic process, a new or changed nevus, especially in patients older than 50 years, should raise the suspicion of melanoma development and require serial observations. By using different photography methods concurrently, small changes in a nevus over time can be observed, featureless melanomas are not overlooked, and the excision of benign lesions is minimized. A recent systematic review reported that the level of evidence is low for total body photography, but there is a high level of evidence for monitoring melanocytic lesions with sequential digital dermoscopic imaging. In our survey, 34.1% of the dermatologists performed total body photography, 36.6% took close-up photographs of clinically suspicious nevi, and 53.6% took dermoscopic photographs of dermoscopically suspicious nevi, whereas only 19.5% performed all three photography methods together.

There are several melanoma screening modalities; the advantages and limitations of each technique may necessitate the combination of those techniques to improve the diagnostic yield and reduce the unnecessary biopsy rates. The diagnostic sensitivity of different combinations of screening techniques in OTRs with multiple common melanocytic nevi and/or dysplastic nevi is, however, presently unknown. As shown in our survey, most transplant dermatologists performed more than 1 melanoma screening method in their OTRs; however, the combinations were quite heterogenous.

Our study has some limitations. Not all of the SCOPE members answered the questionnaire; therefore, this study may not represent the approaches of all SCOPE members for monitoring nevi. In addition, screening strategies used for early diagnosis of melanoma in OTRs may vary among different countries. Because some European countries have few SCOPE members, it was not possible for us to determine the different approaches within the same country and between different countries.

In conclusion, our survey showed that dedicated transplant dermatologists perform a wide variety of nevi screening procedures in their OTRs. According to a recent systematic review, dermatologists should include sequential digital dermoscopic imaging in their armamentarium to follow melanocytic lesions in their patients. The combination of as many techniques as possible may be useful to detect early post-transplant melanomas. Further studies, however, are needed to investigate the possible beneficial effects of using combined screening methods.

References

Abstract

Objectives: Solid-organ transplant recipients are at an increased risk of developing skin cancer; this risk is due to long-term graft-preserving immunosuppressive therapy, and excessive sun exposure is a major contributing factor to this process. The aim of this study was to evaluate the skin cancer awareness and sun-protective behavior of solid-organ transplant recipients.

Materials and Methods: In all, 70 consecutive solid-organ transplant recipients were evaluated regarding knowledge of their increased skin cancer risk and regarding the influence of this knowledge on their sun-protective practices, by applying a questionnaire during their routine check-up visits.

Results: Of 70 solid-organ transplant recipients, 38 (54.3%) stated knowledge of hazardous consequences of sun exposure; however, only 28 (40%) had the knowledge of causal relationship between sun and skin cancer development. There were 31 patients (44.3%) who were unable to recall anybody giving any information to them about sun protection, and 40 patients (57.1%) had never visited a dermatology clinic. The 10 solid-organ transplant recipients (14.3%) who used sunscreen creams daily had been undergoing regular dermatologic examination. Regarding sun-protective clothing, only 8 patients (11.4%) had been wearing a suitable hat, long sleeves, and sunglasses when outdoors. There was a statistically significant difference between the groups who had visited a dermatology clinic versus those who had not regarding knowledge of sun protection, the causal relationship between sun exposure and skin cancer, the use of sunscreens, and use of sun-protective clothing ($P < .05$).

Conclusions: Our data showed that dermatologic examination and education of patients about skin cancer development and sunscreen measures improved the sun-protective habits of solid-organ transplant recipients. Therefore, orderly visits once or twice a year should be strongly advised for this patient population by their medical care providers.

Key words: Photoprotection, Sunscreen, Transplantation, Ultraviolet radiation

Introduction

A higher-than-normal frequency of cutaneous malignancies is expected among solid-organ transplant recipients (SOTRs), who have a 100-fold increased risk of squamous cell carcinoma (SCC). Furthermore, more aggressive SCCs can develop in this patient population compared with immunocompetent individuals.1-4 This increased risk and aggressive behavior of SCC are mainly due to the long-term graft-preserving immunosuppressive therapies.5 However, ultraviolet (UV) radiation is another well-established risk factor that significantly contributes to skin cancer development, and the amount of sun exposure both before and after transplant plays a role.6 Therefore, the only option for SOTRs to lower the risk of skin cancer occurrence is reducing sun exposure by using sunscreen creams, protective clothing, and above all by keeping away from sun as much as possible. There are only 2 studies in Turkey concerning the knowledge of SOTRs on the increased risk of skin cancer and a preventive approach to this situation.7,8 This study was undertaken to evaluate skin cancer awareness of SOTRs and inquire about their sun-protective behavior.

Materials and Methods

Study population

The study included 70 consecutively registered SOTRs (15 female and 55 male) who attended the
Transplantation Unit at Baskent University Hospital, Ankara, Turkey, for routine check-up examinations between January 2017 and March 2017. The mean age in the group was 36.0 ± 13.3 years (range, 18-63 years), and the mean time since transplant was 6.4 ± 5.5 years (range, 1-23 years). Individuals under 18 years of age, as well as patients with a history of skin cancer, were not included in the study.

Study procedure
The interview was performed in a face-to-face manner by the same dermatologist, and the short questionnaire was prepared by the researchers based on literature. After obtaining data about the demographic characteristics of the patients (Table 1), we used a series of 8 questions to survey the knowledge of SOTRs concerning increased skin cancer risk and their sun-related behavior (Table 2).

Statistical analyses
We used SPSS software (version 23; IBM Corp. Inc., Armonk, NY) to assess the statistical significance of the data. The chi-square test was used to find correlations between the awareness of SOTRs of skin cancer and sun protection behavior. In all statistical tests, \( P < .05 \) was considered significant.

Results
Demographic and baseline characteristics of the patients are given in Table 1. The knowledge and practices of SOTRs regarding skin cancer and sun protection are shown in Table 2.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (n = 55)</th>
<th>Female (n = 15)</th>
<th>Overall (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>36.3 ± 13.5</td>
<td>34.9 ± 13.2</td>
<td>36.0 ± 13.3</td>
</tr>
<tr>
<td>Skin type, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick type II</td>
<td>15 (27.3%)</td>
<td>7 (46.7%)</td>
<td>22 (31.4%)</td>
</tr>
<tr>
<td>Fitzpatrick type III</td>
<td>31 (56.4%)</td>
<td>7 (46.7%)</td>
<td>38 (54.3%)</td>
</tr>
<tr>
<td>Fitzpatrick type IV</td>
<td>9 (16.4%)</td>
<td>1 (6.7%)</td>
<td>10 (14.3%)</td>
</tr>
<tr>
<td>Elapsed time posttransplant, years</td>
<td>6.9 ± 5.9 (1-23)</td>
<td>4.7 ± 3.3 (1-11)</td>
<td>6.4 ± 5.5 (1-23)</td>
</tr>
<tr>
<td>Transplanted organ, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>45 (81.8%)</td>
<td>10 (66.7%)</td>
<td>55 (78.6%)</td>
</tr>
<tr>
<td>Liver</td>
<td>10 (18.2%)</td>
<td>5 (33.3%)</td>
<td>15 (21.4%)</td>
</tr>
</tbody>
</table>

Values for age of solid organ transplant recipients (SOTRs) and years of time posttransplant are means and SD, with ranges of values shown in parentheses.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes Answers, No. of responses (%)</th>
<th>No Answers, No. of responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you know that you have to be protected from the sun?</td>
<td>48 (68.6%)</td>
<td>22 (31.4%)</td>
</tr>
<tr>
<td>Do you know hazardous consequences of sun exposure?</td>
<td>38 (54.3%)</td>
<td>32 (45.7%)</td>
</tr>
<tr>
<td>- Relation with cancer, 28 (40.0%)</td>
<td>- Other, 10 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Have you ever been informed of why you should be protected from sunlight?</td>
<td>39 (55.7%)</td>
<td>31 (44.3%)</td>
</tr>
<tr>
<td>- By a dermatologist, 26 (37.1%)</td>
<td>- By a nurse, 13 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>Have you ever applied to the dermatology clinic before?</td>
<td>30 (42.9%)</td>
<td>40 (57.1%)</td>
</tr>
<tr>
<td>Do you visit dermatology clinic regularly?</td>
<td>10 (14.3%)</td>
<td>60 (85.7%)</td>
</tr>
<tr>
<td>Were you using sunscreen creams before transplant?</td>
<td>3 (4.3%)</td>
<td>67 (95.7%)</td>
</tr>
<tr>
<td>Do you use sunscreen creams now?</td>
<td>28 (40.0%)</td>
<td>42 (60.0%)</td>
</tr>
<tr>
<td>- Regular, 10 (14.3%)</td>
<td>- Irregular, 18 (25.7%)</td>
<td></td>
</tr>
<tr>
<td>Do you wear sun-protective clothes? (hat/long-sleeved outfit/sunglasses)</td>
<td>19 (27.1%)</td>
<td>51 (72.9%)</td>
</tr>
<tr>
<td>- Long-sleeved outfit, 4 (5.7%)</td>
<td>- Hat, 5 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>- Hat and sunglasses, 2 (2.9%)</td>
<td>- All of them, 8 (11.4%)</td>
<td></td>
</tr>
</tbody>
</table>

There were 48 SOTRs (68.6%) who were informed that protection from sun exposure is an important health safety consideration, whereas 38 patients (54.3%) were informed that exposure to UV radiation may have hazardous consequences. However, only 28 patients (40%) were aware of the causal relationship between sun exposure and skin cancer development. There were statistically significant differences between the group of patients who had knowledge of sun protection and the group who did not regarding causal relationship between sun and skin cancer, having information on sun-protective behavior, being informed by a dermatologist, the use of sunscreens, and the use of sun-protective clothing (\( P < .05 \)).

There were 31 patients (44.3%) who were unable to recall ever receiving any information from clinic staff about sun protection, whereas 39 patients (55.7%) had been informed by a dermatologist (\( n = 26 \)) and/or
a nurse (n = 13). There were 40 patients (57.1%) who had never visited a dermatology clinic, whereas 30 SOTR patients (42.9%) had been examined by a dermatologist at least once since transplant, with 10 patients (14.3%) having had regular visits (once or twice a year) to the dermatology department. There was a statistically significant difference between the groups who had been examined at our dermatology clinic versus those who had not been examined regarding knowledge of sun protection, the causal relationship between sun and skin cancer, the use of sunscreens, and the use of protective clothing (P < .05).

Before transplant, 3 patients were using sunscreen creams infrequently, that is, only on sunny holidays. After transplant, 25 patients had started to use these creams, with a total of 28 patients (40%) stating that they were using sunscreen. Ten patients (14.3%) stated a daily usage, and all patients stated that they were having regular dermatologic examinations. However, 18 patients (25.8%) stated using sunscreen creams only on sunny days or at vacation time. Remarkably, 3 of those patients from the group of 18 pointed out that they had formerly visited the dermatology clinic regularly, and during that period they were using sunscreens daily. Statistically significant differences were shown between the group with knowledge and the group without such knowledge concerning the causal relationship between sun exposure and skin cancer and the application of sunscreens (P < .05).

In terms of sun-protective clothing (hat, sunglasses, long sleeves), 19 patients (27.1%) were using one or more of these items, and the most common item was a hat (21.4%). Only 8 patients (11.4%) were wearing all types of sun-protective clothing when outdoors, and these patients were also attending regular dermatologic examinations. Statistically significant differences were shown between the group of patients who did have knowledge and those who did not with regard to the causal relationship between sun exposure and skin cancer and the habit of using sun-protective clothing (P < .05).

Discussion

The main risk factors for the development of skin cancer in SOTRs include long-term immune suppression, oncogenic viruses, and sun exposure.5,6,9 Among them, UV radiation remains the major avoidable cause by fundamentally keeping away from sun, applying sunscreen creams, and wearing sun-sheltering clothes such as wide-brimmed hats and long-sleeved shirts.9

There are several studies about sun protection knowledge and attitude among SOTRs in the literature, yet only 2 of these studies were performed in Turkish individuals.6,8,10,12 In the first Turkish study, Haney and associates studied 104 liver transplant recipients with regard to their knowledge of the link between skin cancer and sun exposure and their sun-protection behaviors; results were compared with knowledge and behaviors in the general population. Haney and associates found that the number of patients informed about this causal link (skin cancer and sun exposure) was significantly lower (60.6% of the patients were informed) versus the general population (81%), and yet sun-protection behavior scores were similar between the 2 groups.7 The second study focused on complications encountered by Turkish kidney transplant recipients and their knowledge and practices regarding healthy living; therefore, skin cancer awareness and sun-protective habits constituted just a small part of the study. Among 125 patients, 24.6% had knowledge regarding why sunlight should be avoided and 55.2% were working to prevent/reduce their exposure to the sun.8 Likewise, variable data about sun-related knowledge of SOTRs have been found in literature. In a study by Robinson and associates, 22% of SOTRs were aware of their increased risk of developing skin cancer, whereas 59% of patients in another study were aware of this risk.6,9 In the present study, this proportion of informed patients was even higher; that is, 68.6% of SOTRs had the knowledge, although only 40% were aware of the causal relationship between sun and skin cancer. The marked differences among the studies may partly be due to the varied education levels of the participants, as well as the diverse training programs that the centers provide to them. In a study by Imko-Walczuk and associates, 51.6% of renal transplant recipients considered themselves as a group of patients with higher risk of skin cancer; however, only 18.7% of these patients had been using sunscreen creams daily or frequently.5 Therefore, Imko-Walczuk and associates concluded that skin cancer awareness does not correlate with sun-protective attitude. In our study, 68.6% of patients knew the importance of protection from sun exposure, and 40% were using
sunscreen. Hence, in disagreement with the previous study, we demonstrated a positive correlation between the knowledge of skin cancer risk and sun-protective behavior among SOTRs. In accordance with our study, Haney and associates noted that the only variable affecting sun protection was the knowledge of skin cancer occurrence caused by UV radiation. Therefore, education about sun protection seems to be a very important step to lower the risk of skin cancer development.

In the literature, the rate of obtaining information about sun protection among SOTRs varies between 34% and 96%. Haney and associates showed that 65.4% of the patients had not been informed about the consequences of sun exposure, and, among those who had been informed (34.6%), 26.9% received the information directly from a doctor. In our study, 55.7% of the patients were informed about sun protection, and 66.6% were educated by a dermatologist. In a study by Cowen and associates, 73% of the patients had not been examined by a dermatologist since transplant. Likewise, in our present study, most SOTRs (57.1%) had not visited a dermatology clinic, as they were not guided by their transplant surgeons to do so regularly unless a dermatologic problem arose. However, we observed that information provided by a dermatologist significantly increased the consciousness of sun protection, namely, that one should avoid UV exposure during sunny hours, use sunscreen creams in a proper manner, and wear protective clothing. Therefore, this study emphasizes the importance of the active participation of dermatologists to engage with SOTRs regarding sun-protection awareness during their health care visits, thereby contributing to the broad medical efforts to prevent skin cancer. Regular dermatologic follow-up and repetitive education about sun protection may be life-saving.

Most studies have reported that the frequency of sunscreen cream application varies greatly (5% to 77%) among SOTRs. In our study, most patients (60%) were not applying sunscreen. This condition is attributable to the inadequate or deficient knowledge of SOTRs regarding the interaction between sun and skin cancer. Our study demonstrated that dermatologic examination, even if a patient has attended only once, resulted in increased use of sunscreens in these patients. We believe that this is because of the detailed information given by our dermatology team in a repetitive manner. Although only 4.3% of our patients had been using sunscreen creams before transplant, it is noteworthy that 35.7% of the patients started using sunscreen creams after transplant. However, this ratio remains in need of improvement.

We also found that 72.9% of our patients were not using any type of sun-protective clothing while outdoors. Haney and associates demonstrated that 46.2% of liver transplant recipients were wearing clothing that covers the skin. In a study by Donovan and associates, 19.2% of patients had never used sun-protective clothing. Similarly, Imko-Walczuk and associates showed that 17.6% of their renal transplant recipients had never worn sun-sheltering clothing. Our study demonstrated that there was a positive correlation between gaining information about sun-induced skin cancer from a dermatologist and establishing the habit of using sun-protective clothing. Therefore, we can say that education leads to heightened awareness and improved attitude regarding protection against sun exposure.

The potential limitations of the present study include the lack of a control group and the undetermined education level of the patients.

In conclusion, our data showed that dermatologic examination and education of SOTRs regarding cutaneous malignancies and sunscreen measures improved their sun-protective attitudes prominently, even when the information exchange occurred only once. Therefore, orderly visits once or twice a year should be strongly advised to this patient population by all their medical care providers.

References