Abstract

Objectives: There has been no improvement in long-term graft survival rates in renal transplant-recipients during the past decade. We evaluated patients who underwent renal transplant and experienced late (≥ 3 years) antibody-mediated rejection, after an immunologically uneventful course early after transplant.

Materials and Methods: Between 2003 and 2010, twenty-one of 312 patients who had kidney transplants at our center were diagnosed with antibody-mediated rejection according to the Banff 97 criteria. The patients’ information from their files was retrospectively evaluated.

Results: Of the 7 male and 3 female patients (mean age, 33 ± 11, range, 18-52 y), 5 received deceased-donor kidneys, and 5 had living-related donor kidneys. The average basal and third-year serum creatinine levels were 1.24 ± 0.31 mg/dL and 1.36 ± 0.43 mg/dL (P < .001). The mean follow-up until rejection was 64 ± 23 months (range, 37-101 mo). Medical history revealed recurrent bacterial infections in 4, cytomegalovirus infection and post-transplant diabetes each in one patient and drug withdrawal in 2 patients. For this reason, maintenance immunosuppressive therapy was reduced and/or replaced. In kidney biopsies, 6 patients had acute findings of antibody-mediated rejection, and chronic features were predominant in 4 cases. Renal function improved in 8 patients after treatment, but rejection remained progressive in 2 patients. Three patients lost their grafts during follow-up. Noncompliance was the cause of graft loss in 2 cases. In the remaining 7 patients, the mean follow-up after rejection treatment was 18 ± 14 months (range, 6-48 mo), and the average serum creatinine level was 3.0 ± 0.93 mg/dL (range, 2.3-4.7).

Conclusions: Late antibody-mediated rejection can emerge soon after the modification of immunosuppressive drug dosages and may be responsible for graft dysfunction or loss.

Key words: C4d-mediated rejection, Chronic rejection, Graft survival, Late antibody-mediated rejection, Renal transplant

Introduction

Deceased-donor grafts survive as well as living-related kidney transplants during the first year. The survival rate is almost 90%. However, this rate is only about 50% at 10 years after transplant. Developments in transplant immunology and immunosuppressive therapy have led to a significant decrease in the incidence of acute rejection and rejection-induced early graft loss. However, there has been no significant improvement in long-term graft survival during the past decade. Recent publications have emphasized the importance of antibody-mediated rejection (AMR) as a major cause in late graft loss.

The purpose of this study is to evaluate the kidney transplants performed in our center between January 2003 and December 2010, of whom had an uneventful course during the first 3 years after surgery, but presented with late graft dysfunction caused by biopsy-proven C4d-mediated rejection.
Materials and Methods

Among 312 patients who underwent renal transplantation at our center between January 2003 and December 2010, twenty-one patients with a diagnosis of C4d-mediated rejection were evaluated. Of those; 10 patients with good and stable graft function in the first 3 years, but had had deteriorating graft function due to late C4d-mediated rejection were analyzed.

Results

Of the 10 patients, 5 received deceased-donor and 5 living-donor kidneys. 7 patients were men and 3 were women with a mean age of 40 ± 10 years (range, 23-56 y). The mean age of the donors was 48 ± 18 years (range, 10-66 y). One patient received an expanded-criteria donor kidney. The primary kidney diseases of the patients were unknown in 4, chronic glomerulonephritis in 4, chronic tubulointerstitial nephritis in 1, and amyloidosis in 1. All recipients were serologically negative with regard to hepatitis B and C. Those with living-related donor kidneys received 1 haplotype-matched graft. The primary kidney diseases of the patients were unknown in 4, chronic glomerulonephritis in 4, chronic tubulointerstitial nephritis in 1, and amyloidosis in 1. All recipients were serologically negative with regard to hepatitis B and C. Those with living-related donor kidneys received 1 haplotype-matched graft. The average mismatch was 3.8 ± 0.4 in patients who received deceased-donor kidneys. Pretransplant panel reactive antibody levels were present in 7 cases, and both class I and class II antibody titers were negative. Implantation biopsies were present in 7 cases, and 3 had donor-derived mild histologic injury. Delayed graft function (mean 11.2 ± 6.7, range 3-20 d) was observed in 5 patients. Induction immunosuppressives were antithymocyte globulin in 9 cases and basiliximab in 1 case. Maintenance immunosuppression consisted of prednisolone + azathioprine + cyclosporine, prednisolone + mycophenolate mofetil + cyclosporine and prednisolone + mycophenolate mofetil + tacrolimus in 2 patients each and prednisolone + mycophenolate mofetil + mammalian target of rapamycin inhibitors in the remaining 4 patients.

Average serum creatinine (SCr) levels at discharge and at 1 and 3 years posttransplant were 1.24 ± 0.31 mg/dL, 1.35 ± 0.41 mg/dL, and 1.36 ± 0.43 mg/dL. The difference between SCr level at discharge and the third year was statistically significant (P < .001). The average pretransplant, first- and third-year body mass indexes were 22.3 ± 4.5 kg/m², 26.1 ± 4.8 kg/m², and 26.4 ± 3.1 kg/m². The difference between pretransplant and third-year body mass index levels was significant (P < .001).

Maintenance immunosuppression and SCr levels throughout the follow-up are shown in the Table. The clinical histories of the patients revealed recurrent bacterial infections with high fever in 4 patients and cytomegalovirus infection in 1 patient. Additionally, 2 patients were noncompliant and stopped taking immunosuppressive drugs, and 1 patient had posttransplant diabetes. Immediately before rejection, it was found that maintenance doses of immunosuppressive therapy had been significantly reduced and only 1 patient had been treated with prednisolone + mycophenolate mofetil + tacrolimus (Table). The follow-up duration until rejection was 64 ± 23 months (range, 37-101 mo). The average SCr values about 6 months earlier and at the time of rejection were 1.4 ± 0.3 mg/dL (range, 0.7-1.9 mg/dL) and 2.7 ± 1.0 mg/dL (range 2-5.6) (P < .001). The mean SCr value after treatment was 2.5 ± 0.9 mg/dL (range 1.6-4.4).

In 8 patients, a decrease of SCr was detected early after treatment, and 2 patients had a progressive course. One patient had early graft loss. Rejection therapy was composed of 2 g/kg intravenous immunoglobulin (IVIG) for every patient. Six patients received 3- or 5-session double-filtration plasmapheresis. In addition to IVIG, 8 patients had pulse steroid treatment, 5 patients received antithymocyte globulin, and 3 patients had rituximab therapy. Apart from the 1 patient with early graft loss, the mean follow-up after rejection treatment was 21 ± 15 months (range, 5.2-48 mo). Among the graft losses, 1 was early, 1 other occurred at 45 months after treatment, and one was due to the patient’s noncompliant cessation of immunosuppressive medication 15 months after rejection treatment. Panel reactive antibody titers were positive in all patients with graft loss, but positive in only 50% of the remaining 7 patients with functioning grafts (Table). The mean follow-up of 7 patients after treatment was 18 ± 14 months (range, 6-48 mo). The average SCr level was 3.0 ± 0.93 mL/dL (range, 2.3-4.7), and the mean quantitative proteinuria level was 1.7 ± 1.4 g/d.

Discussion

Late graft dysfunction is a major problem in the daily practice of organ transplant. Death with a functioning graft and chronic allograft nephropathy
(also termed interstitial fibrosis and tubular atrophy) are decreasing in frequency as the most common causes of graft loss.5,6 Today, immune factors have come to the forefront in the pathogenesis of chronic allograft nephropathy.3,6,7 In patients with biopsy-proven chronic allograft nephropathy, acute rejection within the first year, infection, and/or the use of low-dose immunosuppression have been reported to be significant causative factors leading to long-term graft loss.3,8 Immune-mediated injury in the pathogenesis of chronic allograft nephropathy may be due to low-dose immunosuppression.3,8 Similarly, 1 of every 3 patients develop de novo donor-specific antibodies after renal transplant, and these lead to immunologically mediated late graft loss.7 The early uneventful course observed in our cases are attributable to negative pretransplant panel reactive antibody levels in 7 patients, each of whom was at low risk immunologically; first transplant and at least 1 haplotype histocompatibility in all patients. The development of late humoral rejection, even in these low-risk patients, may have been associated with drug withdrawal (2 patients), mTOR-based triple immunosuppression (3 patients), double immunosuppression (1 patient), or azathioprine containing regimen (1 patient), and, more consistently, may have been caused by immunosuppressive drug dosage modifications for treating and preventing recurrent infections.

There are various modalities for treating humoral rejection, such as pulse steroids, antilymphocyte therapy, plasmapheresis and immunoadsorption, IVIG, rituximab, bortezomib, and eculizumab.8-10 Data on the most effective treatment are insufficient. Treatment efficacy is especially low in patients with late AMR with biopsy-proven chronic histologic changes. There are many studies in the literature on the effectiveness of plasmapheresis, IVIg, and rituximab treatment in different combinations as rituximab-IVIg or plasmapheresis-IVIg.9-10 However, there are no definitive data, particularly on the optimal dose of IVIg therapy, and total doses varying from 400 mg/kg to 2 g/kg have been proposed.

When considering the dual effect, such as replacement of gamma globulin loss and neutralization of antibodies against rebound phenomenon after plasmapheresis, IVIg emerges as an important treatment option, especially in combination therapy with plasmapheresis. In addition IVIg decreases infection risk during AMR treatment. Most of our patients had recurrent infections before AMR, but 2 g/kg IVIG treatment yielded good and safe responses, and no severe infectious complications were observed during follow-up. High-dose IVIg therapy (2 g/kg) combined with plasmapheresis in patients with late occurring AMR seems to be a good treatment option. Novel small-scale studies on the efficacy of bortezomib in patients with late AMR refractory to conventional treatment have been reported in the literature.8-10 The results of the BORTEJECT study, a randomized, controlled trial designed to evaluate the treatment effectiveness of bortezomib in patients with late AMR, are eagerly awaited.11

C4d-mediated rejection may be responsible for late graft dysfunction, even in renal transplant patients with low immunological risk. Low-dose

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age / Gender</th>
<th>TX Date / Type</th>
<th>3-Year Serum Creatinine</th>
<th>3-Year Posttransplant Immunosuppressive Complication</th>
<th>Posttransplant Complication</th>
<th>Rejection Date / PRA</th>
<th>Rejection Serum Creatinine (mg/dL)</th>
<th>Outcome</th>
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<td>2003 / DD</td>
<td>1.25</td>
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Abbreviations: AZA, azathioprin; CMV, cytomegalovirus; CSA, cyclosporin A; DD, deceased-donor; EVO, everolimus; F, female; LR, living-related; M, male; MMF, mycophenolate mofetil; NODAT, new onset diabetes after renal transplant; P, prednisolone; PRA, panel reactive antibody; SIR, sirolimus; TAC, tacrolimus
immunosuppression and drug withdrawal are important predisposing factors of C4d-mediated rejection.

References


