Long-Term Risk of Pulmonary Embolism in Solid-Organ Transplant Recipients

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Abstract

Objectives: Solid-organ transplant recipients can develop chronic hypercoagulation that increases the incidence of pulmonary embolism. Here, we evaluate the frequency of pulmonary embolism in solid-organ transplant recipients during the first 10 years after transplantation and evaluate the risk factors for its development.

Materials and Methods: The medical records of solid-organ transplant recipients who were treated between 2003 and 2013 were retrospectively reviewed. The reviewed data included demographics, type of transplant, comorbidities, procoagulation factors, thromboembolism prophylaxis, and the timing and extent of pulmonary embolism.

Results: In total, 999 solid-organ transplant recipients are included in this study (661 renal and 338 liver transplant recipients) (male: female ratio = 665:334). Twelve renal (1.2%) and 1 liver transplant recipient (0.3%) were diagnosed with pulmonary embolism. Pulmonary embolism developed 1 year after transplantation in 10 patients: 1 patient developed pulmonary embolism < 3 months after transplantation, and the other 9 patients developed pulmonary embolism within 3 to 6 months. No patients had a prior history of deep venous thrombosis or pulmonary embolism. Five patients received tacrolimus, 7 patients received sirolimus, and 1 patient received cyclosporine. Ten patients received prednisolone, and 8 patients received mycophenolate mofetil.

All patients were homozygous normal for factor V Leiden and prothrombin genes. One patient was homozygous abnormal, and 1 patient had a heterozygous mutation in the methylenetetrahydrofolate reductase gene. Two patients were treated with low-molecular-weight heparin, while the remaining patients received warfarin. Eight patients were treated for 6 months, and the remainder received longer treatments.

Conclusions: Here, the incidence of pulmonary embolism in solid-organ transplant recipients is 1.2%. Renal transplant recipients are at higher risk of developing pulmonary embolism than liver transplant recipients. The factors that increase the risk of pulmonary embolism in solid-organ transplant recipients appear to be multifactorial and include genetic predisposition.

Key words: Hypercoagulation

Introduction

Solid-organ transplant recipients can develop chronic hypercoagulation, which increases the incidence of thromboembolic complications. Prothrombotic changes may present without other comorbidities, especially in renal transplant recipients, thereby suggesting its development as the primary cause of hypercoagulability. Hypercoagulation appears to be a lifelong condition; however, the risk is greatest during the first 6 months after transplant. Here, our aim is to evaluate the frequency of pulmonary embolism in solid-organ transplant recipients during the first 10 years after transplantation and evaluate the effect of venous thromboembolism prophylaxis and immunosuppressive therapies on its development.
Materials and Methods

Study population
The medical records of patients who underwent solid-organ transplantation at our institution between 2003 and 2013 were retrospectively reviewed. Data included patient demographics, type of transplant, comorbidities, immunosuppressive therapies, degree and onset time of pulmonary embolism, deep venous thrombosis, factor V Leiden mutations, prothrombin (PT G20210A) and methylenetetrahydrofolate reductase (MTHFR C677T) gene mutations, other procoagulation factors (eg, protein C or S deficiency, hyperhomocysteinemia), and venous thromboembolism prophylaxis.

In the present study, pulmonary embolism was suspected based on the patient’s clinical presentation, laboratory data (eg, D-dimer, chest radiograph, arterial blood gas analysis) and objectively confirmed using computed tomography pulmonary angiography. The extent of pulmonary embolism was established using echocardiography and categorized as massive, submassive, or nonmassive. Deep venous thrombosis was diagnosed using bilateral deep venous compression and Doppler ultrasonography.

Data were analyzed using commercially available software (SPSS version 15.0; SPSS Inc., Armonk, NY, USA). Data are presented as the mean ± standard deviation (SD). All of the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all subjects.

Results

In total, 999 patients underwent solid-organ transplant during the study period; 661 renal and 338 liver transplants were performed, and 665 patients were male.

A total of 12 patients (1.2%) (9 males; mean age, 49.5 ± 7 y) were diagnosed with pulmonary embolism. Eleven patients underwent renal transplantation, while the remaining patients underwent liver transplantation. Nine, 2, and 1 patients were diagnosed with nonmassive, massive and submassive pulmonary embolism.

The clinical characteristics of the renal transplant recipients with pulmonary embolism are included in Table 1. Pulmonary embolism developed 1 year after transplantation in 10 patients; however, 1 patient developed pulmonary embolism < 3 months after transplantation, and the remainder developed pulmonary embolism within 3 to 6 months after transplantation. No patients had prior diagnoses of deep venous thrombosis or pulmonary embolism.

Preoperative venous thromboembolism prophylaxis was not administered to any patients, although 2 patients received postoperative venous thromboembolism prophylaxis. Five patients had ≥ 1 comorbidity such as diabetes (n = 2), chronic obstructive pulmonary disease (n = 1), atherosclerotic heart disease (n = 2), or hypertension (n = 1).

All patients received ≥ 1 immunosuppressive drug such as tacrolimus (n = 5), sirolimus (n = 7), cyclosporine (n = 1), prednisolone (n = 10), or mycophenolate mofetil (n = 8) (Table 1). Genetic tests were performed on 5 patients (42%) to evaluate the cause of pulmonary embolism and determine the optimal duration to administer anticoagulation treatments. All patients were homozygous normal for the factor V Leiden and prothrombin genes (eg, PT G20210A), and other procoagulation factors were normal. One patient had a homozygous mutation and 1 patient had a heterozygous mutation for the methylenetetrahydrofolate reductase gene (MTHFR C677T).

Two patients received low-molecular-weight heparin and the rest received warfarin to manage

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<th>MMF</th>
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Abbreviations: CMV, cytomegalovirus; HD, hemodialysis; HT, hypertension; MMF, mycophenolate mofetil; Tx, transplant
pulmonary embolism following the initially administered intravenous heparin therapy. Eight patients were treated for 6 months, and 4 patients were treated > 6 months because of genetic mutations or persistent residual thrombosis. No pulmonary embolism-associated deaths occurred during the 10-year follow-up.

Discussion

Hypercoagulation in solid-organ transplant recipients is a multifactorial pathologic condition that develops in association with various risk factors. Renal transplant recipients are at higher risk of developing hypercoagulation than other solid-organ transplant recipients, especially during the immediate and early postoperative period.\(^1\)

Previously reported series on renal transplant recipients report an incidence rate of 2% to 14% for pulmonary embolism and a mortality rate of 13.4%.\(^3\) A retrospective study that enrolled 480 renal transplant recipients over a 10-year period reported that 8.3% of the patients developed venous thrombosis.\(^4\) In the present study, the incidence of pulmonary embolism was 1.6% among 661 renal transplant recipients, but no instances of mortality occurred. In a study by Allen and associates, the combined incidence of deep venous thrombosis and pulmonary embolism was highest within the first 4 months after surgery. Here, only 1 patient developed pulmonary embolism within the first 4 months, and the other patients developed pulmonary embolism within 1 year after transplantation.

The increased risk of thromboembolic events in renal transplant recipients appears to be multifactorial. While these patients can present with the known risk factors for thromboembolic complications at similar rates as the general population, they can also present with other conditions such as primary nephropathy that can also lead to transplant, dialysis, immunosuppression and infection.

Cyclosporine, a calcineurin inhibitor, is believed to increase the risk of thromboembolic complications in renal transplant recipients; however, data remain controversial.\(^5\)\(^-\)\(^7\) The role of tacrolimus, a relatively new calcineurin inhibitor, in the development of thromboembolic is not fully understood. It has been reported that the antithrombotic effects of tacrolimus result from inhibiting platelet activity.\(^8\) In renal transplant recipients, long-term steroid treatment results in hypercoagulation and hypofibrinolysis (similar to patients with Cushing disease) and leads to thrombotic complications.\(^9\) The role of sirolimus in the development of thromboembolic events has not been evaluated in renal transplant recipients. It has been reported that the addition of sirolimus to cyclosporine-steroid regimens does not increase the incidence of thromboembolic events in renal transplant recipients.\(^10\) The relation between mycophenolate mofetil and thromboembolic events has not been established either. A monograph on mycophenolate mofetil reported that thrombosis is an adverse effect in renal transplant recipients, but further investigations are needed to confirm this relation.\(^11\)\(^,\)\(^12\) Here, tacrolimus, sirolimus, prednisolone, and mycophenolate mofetil were the most common drugs administered to renal transplant recipients. We suggest that combining these drugs might have played a role in the development of pulmonary embolism in our patient population.

Original nephropathy, which might lead to end-stage renal disease, is also associated with a high risk of thromboembolism and could contribute a similar risk even after transplantation. Lupus nephropathy, Fabry disease, and nephritic syndrome also reportedly contribute to thrombotic events.\(^13\)\(^-\)\(^15\) Here, 1 patient had Fabry disease, which may have led to the development of pulmonary embolism (Table 1). We suggest screening for Fabry disease before renal transplantation and especially resistance to protein C activation, and patients should receive venous thromboembolism prophylaxis if coexistence is diagnosed.

Hypercoagulation also reportedly develops in patients receiving continuous ambulatory peritoneal dialysis because of transperitoneal protein loss.\(^16\) Peritoneal dialysis patients also demonstrate significantly higher levels of blood coagulation factors in comparison with healthy controls. Therefore, peritoneal dialysis patients may demonstrate clinical thromboembolic patterns during the early posttransplant period. Incidentally, in the present study, no patients were receiving peritoneal dialysis before transplantation.

The incidence of erythrocytosis (> 52% hematocrit in men; > 49% in women) in renal transplant recipients reportedly varies between 8% and 22%.\(^17\) Long-term hemodialysis, polycystic kidney disease,


References