ABSTRACT

Pericardial effusion in a renal transplant recipient represents a diagnostic conundrum with a variety of differential diagnoses. Immunosuppressive medications such as sirolimus have been linked to pericardial effusions in the reported literature. Tacrolimus has been reported to be associated with pleural effusions and ascites. We present a case of a patient with tacrolimus as the likely cause of a recurrent pericardial effusion.

Key words: Pericardial effusion, tacrolimus, renal transplant

INTRODUCTION

Tacrolimus is one of the most widely used calcineurin inhibitors (CNIs) for immunosuppression in kidney transplant recipients. The major drawbacks of tacrolimus are its narrow therapeutic window, unpredictable bioavailability, and nephrotoxicity. Fluid retention and pleural effusions are rarely reported side effects. We present a unique case of a patient with a large pericardial effusion associated with tacrolimus use that resolved on switching from tacrolimus to cyclosporine.

CASE PRESENTATION

A 51-year-old Caucasian female with chronic kidney disease stage 5, secondary to autosomal dominant polycystic kidney disease, received a preemptive deceased donor kidney transplant at our institution. Her donor was a 51-year-old male who had succumbed to cardiovascular death. She had a history of hypertension, hyperlipidemia, and left inguinal hernia repair. Her pretransplant workup including a chest X-ray, echocardiogram, and age-appropriate cancer screening was unremarkable. Calculated panel reactive antibodies were 0%, and she received induction therapy with rabbit anti-thymocyte globulin. Intraoperative course was uneventful with cold ischemia time of 17 h and 34 min and warm ischemia time of 42 min. Immediate posttransplant course was complicated by delayed graft function, and she required hemodialysis for 2 weeks after her transplant, following which her allograft function improved and she maintained a baseline creatinine of 1.2–1.4 mg/dl.

Maintenance immunosuppression regimen consisted of tacrolimus, which was adjusted to maintain trough levels of 10–12 ng/ml for the first 3 months posttransplant and 5–10 ng/ml afterward. She also received mycophenolate mofetil 1000 mg twice a day orally, which was later changed to mycophenolic acid because of induced heartburn and chronic diarrhea. Furthermore, the patient received prednisone at an initial dose of 30 mg daily which was gradually tapered during a 6-month period to 5 mg daily. Her posttransplant course over the next year was complicated by one episode of urinary tract infection, issues with hypomagnesemia, and detection of de novo donor-specific antibodies, without clinical evidence of rejection.

During a routine follow-up visit 1 year after her transplant, the patient complained of mid and upper
back pain, more with exertion and relieved when lying down, that started about 2 months ago before her visit. As a workup for the back pain, a computed tomogram of the thoracic spine without contrast was performed, which incidentally revealed a moderate-sized pericardial effusion, approximately 2 cm in greatest thickness near the lower right cardiac border. To further characterize the effusion, a two-dimensional echocardiogram was performed which revealed ejection fraction of 65% and a moderate pericardial effusion circumferentially located around the entire heart without any evidence of cardiac tamponade physiology [Figure 1]. Over the next 1 week, the patient also complained of worsening pain under left breast, but there was no history of fever, cough, or shortness of breath. There was no evidence of adventitious heart sounds or lower extremity edema on physical examination. There were no electrocardiography changes suggestive of pericarditis.

Given the overall immunosuppressed state of the patient and the wide range of differential diagnosis for pericardial effusion in this scenario, a decision to pursue diagnostic and therapeutic pericardiocentesis was made. An ultrasound-guided pericardiocentesis was done and 410 ml of straw-colored fluid was drained. The fluid chemistries revealed a transudative effusion with no evidence of infection or hemorrhage. The fluid white cell count was 78 cells/mm³, out of which 30% were neutrophils, 11% were lymphocytes, and there were no eosinophils. She did not have peripheral blood eosinophilia, and her serum antinuclear antibody test was negative as well. An echocardiogram performed soon after the procedure confirmed decrease in size of the pericardial effusion.

The patient continued to have intermittent left-sided chest pain, and another echocardiogram was performed 1 month later to assess for recurrence of the effusion. It revealed a large pericardial effusion circumferentially located around the entire heart, with diastolic right ventricular wall collapse and systolic right atrial wall collapse indicating signs of early tamponade physiology [Figure 2]. The patient was however hemodynamically stable. A presumptive diagnosis of viral pericarditis causing pericardial effusion was made, and the patient was offered a trial of prednisone 30 mg daily for 2 weeks which was gradually tapered by 5 mg weekly until off, in addition to colchicine 0.6 mg twice a day for 3 months. Unfortunately, within 1 week, the patient developed severe abdominal cramping with nausea, mandating hospital admission; hence, colchicine had to be discontinued. The patient continued treatment with steroids; however, another echocardiogram done 1 month later demonstrated increase in size of the effusion with persistent tamponade physiology.

At this time, the option of surgical management with a pericardial window was discussed; however, due to
the patient’s stable hemodynamics and relatively mild symptomatology, surgical management was deferred. After lengthy discussions between the transplant nephrologist and cardiologist, a decision to switch tacrolimus to cyclosporine was made since the diagnostic workup had excluded all the possible infectious and autoimmune etiologies and the patient was unresponsive to the conventional treatment. Within 2 months of stopping tacrolimus, her symptoms resolved and a follow-up echocardiogram revealed a marked decrease in the size of the pericardial effusion. The patient currently remains stable off tacrolimus with a serum creatinine of 1.4 mg/dl and no evidence of recurrence of pericardial effusion on echocardiogram at 1 year.

**DISCUSSION**

Tacrolimus is the most widely used CNI after renal transplantation for immunosuppression.\(^1\) Nephrotoxicity manifesting as oliguria, increased serum creatinine, and hyperkalemia has been reported as the major side effect of tacrolimus;\(^2\) however, fluid and salt retention (with massive pleural effusions and ascites) induced by tacrolimus in the immediate posttransplant period have also been described.\(^3\)

Although we did not find any published reports on development of pericardial effusion after the use of tacrolimus for immunosuppression in renal transplant recipients, pericardial effusion has been reported in one of the postmarketing surveillance side effects by the Food and Drug Administration.\(^4\)

In a study on patients postliver transplantation, 20%–30% of patients receiving tacrolimus were found to have fluid retention manifesting as peripheral edema, ascites, and pleural effusion.\(^5\) In another study in liver transplant recipients, the incidence of peripheral edema and ascites was <15% and pleural effusion was 35% in patients receiving tacrolimus.\(^6\) These studies seem to indicate that in addition to nephrotoxicity, tacrolimus may have properties causing serosal inflammation leading to fluid accumulation in body cavities, including pericardial space. In our patient, we tried conventional medical therapy and treating the patient for presumed pericarditis; however, the pericardial effusion ultimately responded only to stopping tacrolimus, indicating a likely underlying mechanism related to the drug.

The range of differential diagnosis for pericardial effusion in transplanted immunosuppressed individuals is wide; hence, extensive investigation needs to be performed to exclude the majority of the potential causes, including viral pericarditis, bacterial infection, malignancy, and drug-induced and rheumatologic causes. Pericarditis leading to pericardial effusion is a very rare but known complication following renal transplantation, with a reported incidence of 2.4% in the first 2 months.\(^6\)
Among the etiologies, tuberculosis is the most common in developing countries. Uremic pericarditis is not uncommon in renal transplant patients with insufficient allograft function; however, the condition should regress along with the recovery of allograft function. In certain cases, undiagnosed viral infections may be the cause, and due to the limitation of the availability and prognostic implications of etiological tests, viral causes are unable to be excluded in most of the cases. In our case, we treated the patient with conventional therapy for viral or idiopathic pericarditis without any improvement. Tacrolimus-induced pericardial effusion was a diagnosis of exclusion after ruling out other infectious and autoimmune processes. Resolution of the pericardial effusion after stopping tacrolimus and no recurrence confirmed this presumptive diagnosis.

While sirolimus has been reported to cause pericardial effusion and even tamponade in renal transplant patients, no such reports for tacrolimus are known. Therefore, in renal transplant recipients known to have a pericardial effusion, it is imperative to keep a close eye and look out for signs and symptoms of cardiac tamponade. In addition to drainage of the effusion, stopping the offending drug and switching to an alternative immunosuppressive regimen should be strongly considered if no other etiologies for the effusion are found.

**CONCLUSION**

The interest of this case resides in the question of the approach toward pericardial effusion in an immunocompromised host. Recurrent effusions with negative workup for infectious and autoimmune etiologies should always raise the possibility of drug-induced pericarditis. Prompt diagnosis and stopping the offending drug are the mainstays of successful management of this rare but potentially lethal entity.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/ have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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