CASE REPORT

Tacrolimus-induced leukopenia in a kidney transplant recipient: A case study

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ABSTRACT

Introduction: Leukopenia occurs in 10%-55% of patients after kidney transplant and neutropenia occurs in approximately 28% of patients after kidney transplant. Resolution of leukopenia and neutropenia is done through treatment of the pathogen, such as cytomegalovirus, or removing the offending medication. Medications that are first thought to contribute to leukopenia include Valganciclovir, Sulfamethoxazole-Trimethoprim, and Mycophenolic Acid. Tacrolimus rarely contributes to leukopenia and neutropenia post kidney transplantation.
Case presentation: This case study presents a patient who developed leukopenia and neutropenia 13 weeks after solitary kidney transplantation.
Management: Mycophenolate Mofetil, Valganciclovir, Ergocalciferol, Aspirin, Famotidine, and Sulfamethoxazole-Trimethoprim were all discontinued. Filgrastim was used intermittently to increase white blood cell count. Ultimately, Tacrolimus was switched to Cyclosporine.
Outcome: Leukopenia was resolved by switching Tacrolimus to Cyclosporine-based immunosuppression.
Discussion: A systematic approach should be taken to resolve leukopenia post-kidney transplant. When a kidney transplant recipient is on Tacrolimus-based immunosuppression, Tacrolimus should be the last medication changed when attempting to resolve leukopenia.

Key Words: Tacrolimus, Leukopenia, Neutropenia, Kidney transplant

1. INTRODUCTION

Leukopenia occurs in 10%-55% of patients post kidney transplantation.[1] Leukopenia can be caused by corticosteroids, Mycophenolic Acid, or, in rare cases, Tacrolimus.[2] The prevalence of neutropenia is around 28% post kidney transplantation.[3] Oftentimes, neutropenia can be attributed to cytomegalovirus or medications such as Valganciclovir or Mycophenolic Acid.[3] Treatment of leukopenia and neutropenia in patients post kidney transplantation involves determining whether a patient has an underlying illness causing neutropenia and treating that illness or either reducing or discontinuing the offending medication.[3,4]

In a perfect world, a patient who receives a kidney transplant from a living donor has immediate graft function. They begin to produce urine early post-transplant and the creatinine decreases to normal range. Electrolyte abnormalities would be corrected in the outpatient clinic and white blood cell count would remain normal. The kidney recipient would be cleared to discharge from the kidney transplant clinic four to six weeks post-kidney transplant. We present a case of a

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46 year old Caucasian female with a history of hypertension, hyperlipidemia, and CKD stage 3b due to IgA nephropathy post-kidney transplant presenting with Tacrolimus-induced leukopenia and neutropenia, an uncommon phenomenon.

2. Case report

The patient was a 46-year-old Caucasian female with past medical history significant for chronic kidney disease stage 3b due to IgA nephropathy who received a living unrelated kidney transplant in March 2020. She was pre-emptive to dialysis, meaning that she had not yet started dialysis prior to transplant. The patient received induction with Alemtuzumab and a rapid taper of Prednisone to 5mg daily as per institution protocol. She had immediate graft function as evidenced by robust urine output and rapid decline in creatinine post-transplant. This indicates that the kidney allograft is functioning. Per institution protocol, the patient was started on Tacrolimus with a goal trough of 8-10 for the first month post-transplant and reduction in goal trough to 6-8 after the first month. Patient was started on Mycophenolate Mofetil one gram twice a day. The patient was on reduced Mycophenolate Mofetil and Azathioprine prior to transplant to manage IgA nephropathy. Per institution protocol, valganciclovir was started for cytomegalovirus prophylaxis, Fluconazole was started for antifungal prophylaxis, and Sulfamethoxazole-Trimethoprim single strength was started for pneumocystis and nocardia prophylaxis. The patient's early post-transplant course was relatively unremarkable and the patient was discharged to her primary nephrologist six weeks post kidney transplant.

The patient began to develop leukopenia post-transplant starting 13 weeks post-transplant. A complete blood count (CBC) showed white blood cell (WBC) count of 0.8 and absolute neutrophil count (ANC) of 0.4. The patient's primary nephrologist transferred the patient's post-transplant care back to the transplant center until the leukopenia was resolved. Mycophenolate Mofetil, Valganciclovir, Ergocalciferol, Aspirin, Famotidine, and Sulfamethoxazole-Trimethoprim were all discontinued, and 300 mcg Filgrastim was administered to the patient. WBC improved to 2.8 and ANC improved to 1.6 the following week. Given the improvements in WBC and ANC, Mycophenolate Mofetil was restarted at 250 mg twice a day, and the patient's care was transferred back to the patient's primary nephrologist. The patient's care was transferred back to the transplant center at 33 weeks post-transplant when the patient began to develop neutropenia with an ANC of 0.71. At 35 weeks post-transplant, Mycophenolate Mofetil was discontinued due to ANC levels that continued to decline. At 41 weeks post-transplant, the Mycophenolate Mofetil was restarted at 250mg twice a day since the WBC and ANC counts normalized. Approximately two weeks later, the Mycophenolate Mofetil was discontinued due to a sharp decline in ANC count. The patient's ANC count continued to stay low for the next 22 weeks despite holding Mycophenolate Mofetil. At 44 weeks post-transplant, hematology was consulted for assistance in managing leukopenia. Hematology requested an extensive workup was completed 46 weeks post-transplant. Hepatitis C was negative. Folic acid was 9.7, vitamin B12 was 901, and copper level was 2.44. ESR was greater than 140, CRP had decreased from 36.4 to 3.0, ANA was less than 0.02. A peripheral blood smear showed no reportable WBC, platelet, or RBC morphology, no schistocytes, no circulating blasts. Complement studies showed C3 of 142 and C4 of 24. Parathyroid hormone was normal at 46.2 and the patient was negative for pregnancy. The patient visited hematology again once bloodwork was completed, and hematology recommended that if the patient's leukopenia does not improve within the next couple months, a bone marrow biopsy should be performed. The patient did not end up following up with hematology and a bone marrow biopsy was not completed. It was decided 64 weeks post-transplant that Tacrolimus should be discontinued and switched to Cyclosporine to see if there would be any improvement in ANC count. The Cyclosporine goal trough was 100-200. Cyclosporine was titrated 65 to 68 weeks post-transplant to achieve a therapeutic Cyclosporine trough. Four weeks after discontinuing Tacrolimus and starting Cyclosporine, the ANC count normalized and stayed within a normal range (see Table 1).

Table 1. Normal lab values

Lab	Normal Range
WBC	4.5 to 11.0 × 10^9/L
ANC	1.5-6.5 × 10^9/L
Folic Acid	3.1-17.5 ng/mL
Vitamin B12	> 300 pg/mL
Copper Level	62-140 mcg/dL
ESR	< 20 mm/hr
CRP	< 0.3 mg/dL
ANA	1:40
C3	75-175 mg/dL
C4	15-45 mg/dL
Parathyroid Hormone (PTH)	10-55 pg/mL
Tacrolimus	6-8 ng/mL after 1 month post-transplant
Cyclosporine	100-200 ng/mL after 1 month post-transplant

3. Discussion

There are four hypotheses as to how Tacrolimus may lead to leukopenia or neutropenia. First, it is possible Tacrolimus could induce a maturation stop in myeloid precursor cells; this first hypothesis was rejected through in vivo experiments.[4,5] The patient did not have a bone marrow biopsy completed. A bone marrow biopsy would have assisted to de-

termine if the patient had an occurrence of myeloid suppression. The second hypothesis is that Tacrolimus may affect the balance between production of cytokines by lymphocytes or monocytes inhibiting hematopoiesis and inducing apoptosis.[4, 5] Tacrolimus may indirectly alter the balance between neutrophil death and survival; however, some experiments have made this second hypothesis less likely.[5] The patient's peripheral smear was negative for schistocytes or blast cells which refutes the second hypothesis. The third hypothesis is that Tacrolimus increases Mycophenolic Acid bioavailability through inhibition of mycophenolic acid glucuronidation[4, 5] In this case study, Mycophenolic Acid was discontinued indefinitely while Tacrolimus continued to be used for immunosuppression. The leukocyte and neutrophil counts remained low while the patient was off Mycophenolic Acid and continued with Tacrolimus. This scenario would refute the third hypothesis. The fourth hypothesis is that the patient develops autoantibodies after the introduction of Tacrolimus exposure.[4, 5] Tacrolimus is a potent drug in the treatment of autoimmune disorders, so the fourth hypothesis is less supported.[5] By discontinuing Tacrolimus and switching to cyclosporine, the patient's leukopenia was resolved. There are not any tests available at present to determine the specific medication that may cause a patient's neutropenia.[5]

This case presents an opportunity to analyze management of leukopenia post kidney transplant. Management of leukopenia post-transplant is generally guided by a transplant center's protocol or guidelines. Typically, this is achieved through reduction of Mycophenolic Acid followed by Valganciclovir if leukopenia does not resolve.[6–8] If leukopenia is still not resolved, the patient's proton pump inhibitor and Sulfamethoxazole-Trimethoprim should be discontinued. A thorough review of the patient's medications and any supplements should be completed to determine if the patient is taking any myelosuppressive medications that can be discontinued. Finally, one may consider switching Tacrolimus to an alternative agent, such as Cyclosporine.[9] The only way to determine Tacrolimus is the cause of the patient's leukopenia is through the process of elimination.[5]

This case presents a rarely reported cause for leukopenia post-kidney transplant. Tacrolimus should be considered as a cause of last resort for leukopenia. A systematic approach should be taken to resolve leukopenia post-kidney transplant to improve patient outcomes and prevent infection post-transplant.

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AUTHORS CONTRIBUTIONS

Dr. Rios was responsible for study design, drafted the manuscript, and revised it. Dr. Mead drafted the manuscript and revised it. Both authors read and approved the final manuscript.

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DATA SHARING STATEMENT

No additional data are available.

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