Tacrolimus-Induced Leukopenia in Kidney Transplant: A Case Report

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ABSTRACT
Tacrolimus has become an important cornerstone in the prevention of rejection after kidney transplantation. However, its use has been complicated by several side effects, including chronic allograft nephropathy, diabetes mellitus, arterial hypertension, and neurotoxicity. Tacrolimus-induced neutropenia is a less recognized, but potentially life-threatening complication. We describe one patient with leukopenia developing within 49 days after renal transplant. After excluding other potential causes, tacrolimus was considered the most probable culprit. Definitive proof of this hypothesis was obtained by discontinuation of tacrolimus and switching to cyclosporine, which led to recovery of white blood cell count. With this case report, we aim to make others aware of the potential neutropenia induction by tacrolimus.

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Introduction
Leukopenia refers to a low total white blood cell count and may be due either to lymphopenia and/ or neutropenia. Different definitions of leukopenia have been used in the literature; but most publications use leukopenia and neutropenia interchangeably, which may be a source of confusion. Leukopenia is considered in the presence of a total white blood count (WBC) inferior to 4.000/μL and neutropenia is defined as, at least, a neutrophil value (ANC) < 2000/μL [1].

Leukopenia is frequently encountered following renal transplantation. The incidence of leukopenia and neutropenia in kidney transplant recipients ranges from 10% to 55.5% and from 4.9% to 37.5% respectively [2]. In the first year post-transplant; the incidence is significantly associated with mycophenolate mofetil (MMF)-tacrolimus (TAC) combination therapy [1]. The etiology may be diverse and multifactorial. It includes infections, post-transplant lymphoproliferative disease, and medications. Several drugs are pointed out: Antithymocyte globulin, MMF, azathioprine, and antiviral drugs (acyclovir, ganciclovir, and valganciclovir) [3].

Tacrolimus has become an important cornerstone of current immunosuppressive protocols after renal transplantation. Other than its known side effects, little information is available about the association between TAC and myelosuppression; and very few cases are described in the literature. [1]

Abbreviation
ANC: Absolute neutrophil count
CSF: Granulocyte colony-stimulating factor
G-CSF: Granulocyte colony-stimulating factor
LC: Lymphocyte count
MMF: Mycophenolate mofetil
TAC: Tacrolimus
WBC: Total white blood count

We report a case of post-transplant leukopenia in a renal transplant recipient under tacrolimus therapy, where tacrolimus is the responsible agent.

Case report
A 46-year-old women with end-stage renal failure of unknown etiology underwent living donor renal transplantation. At the time of transplantation, peripheral blood count was normal. Initial immunosuppressive therapy combined rabbit antithymocyte globulin (rATG), prednisolone, and MMF. Co-trimoxazole was also introduced for prevention of Pneumocystis and toxoplasmosis infection; valganciclovir was used for targeted prophylaxis of CMV infection with doses adjusted to renal function. There were no surgical or infectious complications, delayed graft function, neither acute rejection episodes. Peripheral blood count was normal and renal function remained stable at levels of plasmatic creatinine (Cr) of 70.4 μmol/L, for the first post-transplantation months. Maintenance therapy consisted in prednisolone, MMF, TAC with recommended target range for blood TAC concentration, trimethoprim-sulphamethoxazole, valganciclovir and omeprazole.

Fourty-nine days later, leukopenia (2880/μL) and neutropenia (2000/μL) were documented. Hemoglobin and platelet counts were normal and renal function remained stable (Cr = 73 μmol/L).

Bacterial, fungal and viral infections [including cytomegalovirus (CMV), Epstein-Barr virus (EBV), BK virus; hepatitis virus and human immunodeficiency virus] were excluded. Bone marrow examination revealed no abnormalities, in particular no dysplastic changes, maturation stop, or arguments for malignant invasion were found.

Drug-induced neutropenia was suspected; MMF and valganciclovir were suspended without improvement of leukocyte count. Two days after (day 51), trimethoprim-sulphamethoxazole and omeprazole were discontinued, but the leukopenia was not resolved. Although treatment...
with granulocyte colony-stimulating factor (G-CSF) was initiated (for 3 days) on day 53, to enhance myeloid differentiation and to shorten the neutropenic period, leukopenia (950/µl) and neutropenia (520/µl) worsened. TAC was considered to be the causative factor, and was replaced by cyclosporine (CsA). In four days, WBC normalized, and MMF, trimethoprim-sulphamethoxazole, valganciclovir and omeprazole were reintroduced two days later, with persistence of normal WBC count until the last follow-up 45 months after calcineurin-inhibitor conversion. Figure 1 describes the main neutropenia-related characteristics of the patient.

**Figure 1. Management of tacrolimus-induced neutropenia after kidney transplant.**

Abbreviations: ANC: Absolute neutrophil count, CSF: Granulocyte colony-stimulating factor, G-CSF: Granulocyte colony-stimulating factor, LC: Lymphocyte count, MMF: Mycophenolate mofetil, TAC: Tacrolimus, WBC: Total white blood count

**Discussion**

The pharmacologic management of kidney recipients involves the administration of numerous drugs with the potential to cause leukopenia, but the contribution of individual agents is difficult to establish in the era of combination therapies. The reported incidence of leukopenia for commonly used medications in transplantation including rATG, alemtuzumab, MMF, and valganciclovir ranges from 7% to 88%. Leukopenia was recognized as a frequent adverse event related to MMF, but appears to be even more common when given in combination with lymphocyte depleting agents or valganciclovir [4]. In our case, Co-administered agents with myelosuppressive effects: TAC, MMF, rATG, especially valganciclovir, increasing the risk of leukopenia.

Although transplant clinicians commonly encounter leukopenia or neutropenia in kidney transplant recipients; there are no published guidelines on management of leukopenia in the current era of immunosuppressive therapies. As yet; the management of leukopenia post-transplant is controversial and complicated by variable practice patterns. The degree of dose reduction of transplant-related medications and the threshold at which to treat neutropenia with G-CSF remains uncertain. Usually, when leukopenia occurs in the early post-transplant period, the initial approach often includes a reduction in the MMF dose, which may place patients at a heightened risk of acute rejection, especially in the era of prednisone-free regimens.

In our case, MMF was reduced in dose without improvement of blood neutrophil count and stopped completely (day 50) but neutropenia persisted.

The diagnosis of neutropenia induced by medication is made by exclusion, because there are no tests proving a direct effect of medication at the bone marrow level [5]. It’s a very concerning situation because dose reduction or discontinuation of critical anti-rejection and/or antinfecctive drugs in the early post-transplant period may place organ transplant recipients at risk for either rejection or infection, respectively [4]. The potential risk of infection is also resulting from neutropenia in vulnerable host, and increases with its severity and duration [6]. In our case: after having excluded viral infections and bone marrow pathology by blood and marrow investigation, potentially leucopenia-inducing medications were discontinued or tapered (Figure 1).

The association between TAC and myelosuppression has been suspected for a long time, but very few cases are described in the literature [7]. The exact mechanism remains unclear and hypotheses include:

1) Direct inhibition of myelopoiesis,
2) Effect on mononuclear accessory cells,
3) Interaction between tacrolimus and MMF,
4) And formation of autoantibodies against myeloid cells or mature neutrophils. [5]

Indepenently of the pathophysiologic mechanism, in our case; MMF; valganciclovir, trimethoprim-sulphamethoxazole and omeprazole interruption did not lead to resolution of leukopenia and TAC-induced leukopenia was suspected. The last drug to be discontinued, tacrolimus, proved in our opinion, unequivocally, to be the responsible agent. There was a clear correlation between the suspension of TAC and the reemergence of a normal neutrophil count. The conversion of TAC to CsA allowed the resolution of leukopenia and the reintroduction of MMF, with the use of G-CSF.

G-CSF induces neutrophilia by increasing the production rate of neutrophils from precursor cells, and by shortening the time required for neutrophil precursors to mature and appear in the circulation. It reduces the duration of neutropenia, raised the nadir level and it’s well tolerated in solid organ transplant recipients [8].G-CSF is an effective treatment in reversing neutropenia in renal transplant recipients and does not precipitate or aggravate allograft rejection [9]. As yet, there are no current guidelines on the use of G-CSF for the treatment of leukopenia after kidney transplantation, it’s associated with a reduction in time of agranulocytosis, antibiotic use and length of hospital stay, without side-effects, such as acute rejection [7, 10]. Some authors suggest using G-CSF to allow maintenance of MMF in low dose, reducing the risk of acute rejection. However, its use is not associated with reduction of mortality and definitive treatment of leukopenia requires a reduction or suspension of the culprit drug [1]

**Conclusion**

TAC induced leucopenia is made after excluding medication, viral and malignancy causes. It’s often sever and occurred in the first year after transplantation. Although the exact mechanisms leading to neutropenia in our patient on tacrolimus have not been elucidated, this example demonstrates that the association exists and can only be resolved by replacing immunosuppressive treatment.

**References**