



Neutropenia due to Tacrolimus in a Cadaveric Renal Transplant Patient

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Abstract

Myelosuppression is known to occur in kidney transplant recipients because of widely used immunosuppressant chemotherapeutic agents. Myelosuppression usually results with leukopenia and less often with neutropenia representing with percentages of 10 to 55% and 4.9 to 37.5% respectively [1,2]. Bone marrow toxicity caused by medications, systemic infections or post-transplant lymphoproliferative disease are the possible etiology of neutropenia. Also neutropenia can both be the result of decreased neutrophil production from inefficient granulopoiesis because of afore-mentioned reasons or increased peripheral destruction. Tacrolimus, which is one of the most important part of kidney transplantation immunosuppressive protocols, has a very rare effect of myelosuppression other than metabolic side effects which are more common. In this case report we aimed to describe a patient with severe neutropenia developed six months after a cadaveric renal transplantation.

Case Presentation

A 42-years-old woman with end stage renal failure due to unknown etiology, who is on continuous ambulatory peritoneal dialysis treatment, underwent cadaveric kidney transplantation on November 2015. Laboratory values including haemoglobin, leucocyte and platelet counts were completely normal at the time of transplantation.

Right after transplantation Anti-Thymocyte Globulin (ATG) induction was initiated with triple immunosuppressive regimen including tacrolimus, mycophenolate mofetil (MMF) and prednisolone. Patient was discharged with full recovery sent home with adding fluconazole, trimethoprim-sulfamethoxazole (TMP) and valganciclovir for infection prophylaxis.

On the 50th day of transplantation, leukopenia detected with leucocyte count of 2800 / mm³ (normal range 4.000-10.000/mm³). Viral infections including cytomegalovirus, parvovirus B19 were excluded with appropriate testing. MMF dose was reduced from 1000 mg/day to 500 mg/day. Following achieving normal leucocyte count on a week follow up, MMF dose were increased back to 1000 mg/day. Fluconazole and valganciclovir therapies were stopped on day 90 according to our department's transplantation follow up protocol. On 104th day of transplantation, BK virus PCR was found to be positive in both blood and urine samples as 1027 copies/ml and 868.120 copies/ml respectively, so then she was put on levofloxacin therapy.

On 220th day of transplantation while patient was still on prednisolone 5 mg/day, a constant level of tacrolimus achieved as 4-6 ng/ml, MMF 1.000 mg/day, TMP and levofloxacin, she was subjected to an ovarian cyst operation to rule out a possible malignancy. On the 3rd day of ovarian operation leucocyte count and neutrophil count as 2.200/mm³ and 1.100/mm³ (normal range 1.500-9.000/mm³) respectively, resulted with immediate cessation of MMF and TMP therapies. Parvovirus B19 testing came back negative and cytomegalovirus PCR testing resulted as low titered positive (2.300 copies/ml). Two days after immediate initiation of valganciclovir, neutrophil count decreased to 20/mm³ leading to cessation of levofloxacin which thought as a possible reason for neutropenia. Bone marrow aspiration and biopsy examination revealed neither malignancy nor a finding suggesting cytomegalovirus infection. Following having a second result on cytomegalovirus PCR which was negative, and finding out that bone marrow was hypo-cellular, valganciclovir was stopped after 7 days.

Patient responded to changing tacrolimus therapy with cyclosporine therapy in two days.

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Leucocyte count increased from 1.600/mm³ to 2.600/mm³ and neutrophil count increased from 20/mm³ to 530/mm³ in four days. MMF was restarted after a month of clinical alleviation. Following two months did not make any change on leucocyte count which were 4.300/mm³ and neutrophil count which were 3.300/mm³. Patient's renal functions had not been deteriorated throughout the neutropenic period.

Discussion

Immunosuppressant's such as MMF, ATG, tacrolimus and azathioprine are indicated for post kidney transplantation phase. They have lots of common and from time to time life threatening side effects such as myelosuppression [1,2]. Other supportive drugs like omeprazole, angiotensin converting enzyme inhibitor, valgancyclovir and TMP reported as causes for neutropenia. A retrospective study in kidney recipients reported MMF-tacrolimus combination therapy was associated with a 28% chance of neutropenia in the first year period of transplantation [3]. It is really hard to establish a link between possible causes and myelosuppression with conventional testing methods so clinicians usually rule out other factors like infections and malignancies first and then medications are stopped to increase neutrophil count [4].

Cyclosporine and tacrolimus are both effective with inhibition of calcineurin-mediated T-cell receptor signal transduction and inhibition of interleukin-2 (IL-2) transcription [5]. When compared in efficacy, tacrolimus is found to reduce risk of acute rejection and steroid resistant rejection [6].

The causative link between tacrolimus and myelosuppression is not clear [7]. There is a hypothesis expressing the fact that it could stop maturation in myeloid precursor cells. However *in vitro* experiments, has shown this hypothesis is not true [8,9]. Likewise other published case reports and our case report had bone marrow biopsy done, with results revealing no clue for maturation arrest [4].

Cytokines produced by lymphocytes or monocytes inhibiting granulopoiesis and increasing apoptosis is another hypothesis for tacrolimus induced neutropenia [4]. Hirao et al. [8], experimented adding antibodies against these cytokines resulted with no differences in myeloid progenitor cell colony forming units. In a third hypothesis, tacrolimus was thought to increase mycophenolic acid (MPA) bioavailability as with another study it was demonstrated that MPA when used as combination therapy with cyclosporine found out to have lower serum concentration [10]. Even though we think that this might be the correct pathway to understand tacrolimus induced neutropenia, all cases found in literature and also our case showed persistence of neutropenia even though MMF was discontinued. Another hypothesis is formation of antibodies against myeloid precursors or mature neutrophils. However, not a single study was able to confirm the presence of antibodies [11]. In our case following exclusion of all well-known reasons of neutropenia in a kidney transplant recipient, changing tacrolimus to cyclosporine seemed to do the trick.

Conclusion

Even though MMF is the drug accused of neutropenia in kidney transplant recipients, myelosuppression can be because of an extremely rare side effect of tacrolimus. There are only a few cases reported in literature about this phenomenon so clinicians should keep tacrolimus in mind as a possible reason for neutropenia.

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