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Case Report

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Tacrolimus-Induced Pure Red Cell Aplasia Following Renal Transplantation: A Case Report and Literature Review

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Abstract

Anemia is common in end-stage renal disease, but it resolves rapidly after transplantation due to normalization of kidney function. Acquired pure red cell aplasia (PRCA) is an infrequent complication in kidney recipients. PRCA is a rare cause of profound anemia characterized by reticulocytopenia and marked reduction or absence of erythroid precursor. In this condition, all other cell lines are found in standard numbers and appear morphologically normal in the bone marrow. We herein report a case of a living-related kidney recipient who presented with severe anemia and developed PRCA associated with tacrolimus. The patient was successfully treated by switching tacrolimus to cyclosporine.

Keywords: Cyclosporine, pure red cell aplasia, renal transplantation, tacrolimus

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INTRODUCTION

Renal transplantation is the best option for renal replacement therapy. Post-transplantation anemia may occur commonly due to drugs and infections (1). Pure red cell aplasia (PRCA) is a rare condition characterized with severe normochromic, normocytic anemia, reticulocytopenia, and erythroblast absence. Tacrolimus is widely used in solid organ transplantation and is an immunosuppressive agent without significant myelosuppression. PRCA, which is associated with tacrolimus, has been reported in a few studies (2) Here, we present a case of tacrolimus-induced PRCA in a post-renal transplant patient who recovered completely with cessation of tacrolimus.

CASE PRESENTATION

A 42-year-old male with chronic kidney disease due to hypertensive nephropathy underwent a living-related renal transplant. The donor was his sister. Induction therapy included 2 mg/kg/day of Antithymocyte globulin (ATG) for three days. The patient was treated with triple-drug immunosuppression comprising 5 mg/day of prednisolone, 0.1 mg/kg/day of tacrolimus, and 2 g/day of mycophenolate mofetil. Serum creatinine level remained between 1.3 and 1.5 mg/dL after transplantation. Although the patient was not receiving any immune or bone marrow suppressive agent pre-transplantation simultaneously, we noticed that his hemoglobin level started declining in the 2nd month of the post-transplant period, and he had complaints of extreme pallor and decreased exercise tolerance. Physical examination revealed the paleness of the skin and conjunctivae. Laboratory data were as follows: hemoglobin: 5.1 g/dL, white blood cell: 2.5×103/mL, platelet count: 264×103/mL, reticulocyte: 0.16%, mean corpuscular volume: 72/fL, and lactate dehydrogenase: 246 U/L (range, 150-250 U/L). The Coombs' tests, hepatitis B, C, CMV, EBV, and Parvo B19 were all negative. The levels of Vitamin B12: 495 pg/mL, folic acid: 5.3 pg/mL, transferrin saturation: 94%, and ferritin: 446 ng/mL and serum haptoglobin level were normal. Schistocytes were not seen in the peripheral blood smear. Test for blood in the stool was

positive. Gastric ulcerations were observed in the gastroscopy, and anal fissure and hemorrhoids were observed in the colonoscopy. The results of the bone marrow examination showed a normocellularity and slight left shift in the erythroid series. Severe anemia requiring multiple blood transfusions continued. Therefore, we switched from mycophenolate to everolimus, whose myelosuppressive effect is well known. After three weeks of switching drugs, and in the 4th month after transplantation, we again hospitalized the patient with severe anemia. Laboratory findings showed a hemoglobin level of 4.5 g/dL, leukocyte count of 4.5×103/mL, platelet count of 223×103/mL, and there was no evidence of blood loss or hemolysis. The serum iron studies, vitamin B12, and folic acid levels were normal. Parvovirus B19 was negative in the blood and bone marrow examination. Peripheral blood smear was similar to previous. Bone marrow examination showed a marked reduction in the erythroid series (Figure 1). Immunohistochemical evaluation of bone marrow was negative for Parvo B19. The presumptive diagnosis of tacrolimusinduced PRCA was kept, and the patient was switched from tacrolimus to cyclosporine (5 mg/kg). Two months after beginning the cyclosporine therapy, his hemoglobin level increased to 9.1 g/dL followed by a further increase 2 months later; it was 13.4 g/dL in 4 months from the start. Following the cessation of tacrolimus, PRCA did not relapse.

Informed consent was obtained from the patient.

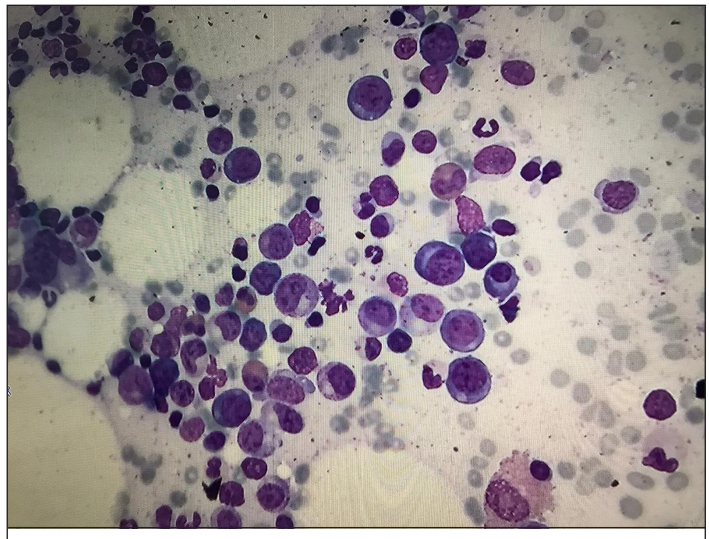

Figure 1. Bone marrow biopsy findings showing reduction in erythroid precursors

DISCUSSION

Multiple etiologies can cause post-transplant anemia. Acquired PRCA is an extreme form of anemia characterized by a complete or almost complete cessation of red blood cell production in the bone marrow, with no effect on other hematopoietic cells (2). Acquired PRCA in adults can be classified into primary and secondary PRCA. Common secondary causes are thymoma, leukemia, immune disorders, infections, particularly parvovirus B19 and medications that are the most commonly implicated drugs, including antimicrobials, anticonvulsants, and myelosuppressive agents. The exact pathophysiology of PRCA is currently unknown. In PRCA, the attack target is an antigen expressed on an early erythroid precursor or progenitor cell rather than a multipoint hematopoietic stem cell. The suppression of erythropoiesis in PRCA is immunologic, antibody-mediated, or mediated by other immune effectors such as T lymphocytes that are associated with lymphoproliferative disorders. Recovery from anemia after drug discontinuation varies depending on the pharmacokinetics of drug metabolism, duration of treatment, and mechanisms by which erythropoiesis is suppressed.

Our patient developed severe anemia in the 2nd month after transplantation. The bone marrow biopsy findings suggested diagnosis of PRCA and the patient was diagnosed with PRCA due to severe anemia requiring multiple blood transfusions, reticulocytopenia, no evidence of bleeding or hemolysis. Tacrolimus was replaced with cyclosporine due to a possible diagnosis of pure red cell aplasia associated with tacrolimus. Using cyclosporine-based therapy, the patient recovered from anemia within two months. Hemoglobin levels were normal after four months of cyclosporine-based therapy.

Tacrolimus is widely used in post-renal transplant patients, and rare cases of PRCA associated with tacrolimus have been reported before (Table 1). Cyclosporine A appears to be an effective alternative immunosuppressive agent for kidney recipients who have PRCA (3).

We did a literature search and found six cases of tacrolimus-associated PRCA confirmed by bone marrow examination. The diagnosis age varied between 20 and 54 years; the mean age was 31.1 years. Of the patients, two were male and four were female. All of the patients were treated with triple-drug immu-

Main Points

- Acquired pure red cell aplasia (PRCA) is an extreme form of anaemia characterized by a complete or almost complete cessation of red blood cell production in the bone marrow, with no effect on other hematopoietic cells.
- Acquired PRCA in adults can be classified into primary and secondary PRCA. Common secondary causes are thymoma, leukemia, immune disorders, infections, particularly parvovirus B19 and medications that are the most commonly implicated drugs, including antimicrobials, anticonvulsants, and myelosuppressive agents.
- Tacrolimus is widely used in solid organ transplantation and is an immunosuppressive agent without significant myelosuppression. PRCA, which is associated with tacrolimus, has been reported in a few studies.
- Early diagnosis and management of anemia in the post-renal transplant period is critical.
- Nephrologists should be alert for PRCA in patients receiving tacrolimus who have refractory anemia and who fail to recover with routine management of anemia.

Table 1. Clinical features of patients with tacrolimus-induced pure red cell aplasia after kidney transplantation

Case	Age	Sex	Primary kidney disease	Maintenance therapy: Tac, MMF,PRD	Time period between Tx and presentation	Mean Hb at presentation	Switch of tacrolimus to cyclosporine	Time taken for recovery	Bone marrow biopsy
Case 1 (4)	20	F	LN	+	2 months	6.12 g/dL	+	2 months	+
Case 2 (5)	40	F	Adult PKD	+	9 months	4 g/dL	+	4 months	+
Case 3 (5)	30	M	Unknown	+	2 months	5.5 g/dL	+	2 months	+
Case 4 (5)	35	F	Unknown	+	4 months	6.3 g/dL	+	3 months	+
Case 5 (6)	20	F	Unrecorded	+	1 month	4.6 g/dL	+	3 months	+
Case 6 (7)	54	M	Unrecorded	+	5 weeks	5.3 g/dL	+	2,5 months	+
Index case	42	M	HN	+	2 months	5.1 g/dL	+	2 months	+

Hb: hemoglobine; HN: hypertensive nephropathy; LN: lupus nephropathy; MMF: mycophenolate mophetil; PKD: polycystic kidney disease; PRD: prednisolone; Tac: tacrolimus; Tx: transplantation

nosuppression comprising prednisolone, tacrolimus, and mycophenolate mofetil. All six cases presented with profound anemia requiring multiple transfusions. All cases were verified by bone marrow biopsy. The period between transplantation and presentation was between 1 and 9 months. Mean hemoglobin levels ranged from 4 to 6.3 g/dL. Tacrolimus was replaced with cyclosporine A in all cases. Recovery from anemia after drug discontinuation varied between 2 and 4 months (4-7).

In contrast, in another case report, a 78-year-old woman who suffered from PRCA with generalized myasthenia gravis and thymoma, despite the administration of cyclosporine A and corticosteroid therapy, needed a blood transfusion. After the administration of tacrolimus, her anemia improved. Similarly, in another case study, a 73-year-old man who was diagnosed with an anti-EPO PRCA was given cyclosporine and experienced side effects of the treatment. As a result, he was switched from cyclosporine to tacrolimus, following which his anemia resolved in 6 months. Therefore, tacrolimus is an alternative treatment option for PRCA in patients who do not respond to cyclosporine (8, 9).

CONCLUSION

In conclusion, early diagnosis and management of anemia in the post-renal transplant period is critical. In our case, we conclude that tacrolimus is associated with PRCA. Nephrologists should be alert for PRCA in patients receiving tacrolimus who have refractory anemia and who fail to recover with routine management of anemia.

Informed Consent: Informed consent was obtained from the patient.

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