Refractory Anemia in a Kidney Transplant Recipient

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ABSTRACT

Anemia is a common finding after kidney transplantation (KT). Herein, we present a 34-year-old man who received a deceased-donor KT in 2017. Induction immunosuppression therapy consisted of thymoglobulin, tacrolimus (TAC) and methylprednisolone; the maintenance therapy included mycophenolate (MMF) 500 + 500 mg, TAC 4 + 4 mg and prednisolone (PD) 5 mg. One year after KT, he progressively developed dyspnea and fatigue. Laboratory exams revealed hypochromic microcytic anemia unresponsive to increasing doses of darbepoetin. Upper endoscopy and colonoscopy were normal. Bone marrow examination revealed erythroid hyperplasia with numerous proerythroblasts. Serology and viral load for human parvovirus B19 were both positive. Immunosuppression was reduced; he was treated with immunoglobulin. After one week, anemia improved. After 2 months the patient remained asymptomatic with stable hemoglobin. Although rare, PVB19 infection is a clinically significant infection that often presents as aplastic anemia in the post-transplantation period.

KEYWORDS: Refractory anemia; Kidney transplant; Parvovirus B19 infection

INTRODUCTION

Anemia is a common finding after kidney transplantation (KT). It can have several causes and sometimes a clinical challenge. It is commonly associated with the use of immunosuppressive drugs and some infections. Parvovirus B19 (PVB19) is a small, single-stranded DNA virus that infects and replicates in erythroid progenitor cells of the bone marrow and blood. Its incidence remains unknown although 1%–12% of KT recipients have symptomatic B19 infection within the first year of transplantation [1].

The most commonly reported consequence of PVB19 infection in organ transplant recipients is inhibition of erythropoiesis causing acute anemia and chronic pure red cell aplasia. Neutropenia, thrombocytopenia, fever, and arthralgia have also been reported.

Since immunocompromised patients are unable to develop an appropriate humoral and cellular responses, a negative PVB19 IgM serological test result does not exclude the diagnosis of the infection; polymerase chain reaction (PCR) should be used whenever a diagnosis of acute PVB19 infection is suspected. If PCR testing is negative but PVB19 is highly suspected, the diagnosis may be confirmed by bone marrow examination [2].

Reducing immunosuppression is frequently needed in combination with intravenous immunoglobulin (IVIG). The role of recombinant human erythropoietin (rHuEPO) in treating anemia in this setting is still questionable.

CASE PRESENTATION

A 34-year-old Pakistani male with hypertension and chronic kidney disease due to an IgA nephropathy was referred to our center. He received a living-donor renal transplant in 2011 with chronic dysfunction. Due to progressive decline in his renal function, he was on hemodialysis for 24 months and had a deceased-donor renal transplant in 2017. Induction immunosuppression therapy included thymoglobulin, tacrolimus (TAC) and methylpred-

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nisolone; the maintenance therapy consisted of mycophenolate (MMF) 500 + 500 mg, TAC 4 + 4 mg and prednisolone (PD) 5 mg. The baseline creatinine was 2.3 mg/dL. One year after the transplantation, he developed hypochromic microcytic anemia (Hb 5.8 g/dL, Hct 18.6%, MCV 75.4 fL, MCH 23.6 pg) with dyspnea and fatigue. He did not have fever, loss of appetite, gastrointestinal bleeding or other organ symptoms. At presentation, he was pale but no other alteration was found.

Laboratory examinations revealed normal LDH and haptoglobin, low reticulocyte count, serum iron of 125 µg/mL, ferritin 321 ng/mL, and a normal platelet and white blood cell counts; hepatic tests were normal. Upper endoscopy and colonoscopy were unremarkable. Treatment with subcutaneous rHuEPO was initiated. Despite increasing doses of rHuEPO, the hemoglobin concentration and the reticulocyte count remained low, and the patient required transfusion of two packed cell units. Cytomegalovirus and Epstein Barr viral load were negative. Bone biopsy revealed erythroid hyperplasia with numerous proerythroblasts. Serological test for IgM was positive for PVB19 with a DNA PCR of 777,500 UL/mL.

Darbepoetin doses and immunosuppression were reduced; immunoglobulin 0.5 g/kg/day for seven days was administered. After one week, his blood work revealed a Hb of 8 g/dL. After two months, the patient remained asymptomatic with a Hb of 10 g/dL.

DISCUSSION

Erythropoiesis is a complex process that involves an erythropoietin (Epo)-independent early phase, in which hematopoietic progenitor cells give rise to committed erythroid progenitor cells, and an Epo-dependent late phase, during which these precursors mature into terminally differentiated erythrocytes [3-5].

PVB19 is a single-stranded DNA capsid virus, devoid of DNA polymerase, which can only replicate in cells in which DNA polymerase is activated [4]. PVB19 has tropism for erythroid progenitors, which was initially believed to be due to cell type-specific expression of the blood group P antigen (globoside). Indeed, erythrocyte P antigen is necessary for B19V binding and entry into the cell, along with two co-receptors—integrin α5β1 and KU80 [6]. EpoR signaling is also required for B19V replication after the initial entry of the virus; the replication response seems to be dose-dependent as demonstrated by Chen, *et al* [5].

The clinical manifestations of B19V infection, seen in both aplastic crisis and pure red-cell aplasia, result from the direct cytotoxicity of the virus inducing apoptosis. This typically results in normocytic normochromic anemia with low reticulocyte count due to the PVB19-associated erythroid progenitor differentiation arrest in the proerythroblast phase. Although rare, parvovirus infection is an important differential cause of anemia in renal transplant recipients.

The authors present a patient with hypochromic microcytic anemia with low reticulocyte count. Hemolysis and iron deficiency were excluded as well as cytomegalovirus and Epstein Barr infection. Nevertheless, the bone biopsy result was atypical with unexpected erythroid hyperplasia and numerous proerythroblasts. This could be explained by the use of high doses of Epo with a stimulating effect on erythroid proliferation.

Indeed, the fact that anemia improved only after darbepoetin dose reduction was another aspect reinforcing this concept, which was in line with the case reported by Arzouk, *et al*, who also reported a case of anemia due to PVB19 infection that resolved only after discontinuation of rHuEPO [7]. This supported the conviction that rHuEPO might promote PVB19 replication in the Epo-dependent phase of erythropoiesis.

To the best of our knowledge, this is the first reported case of anemia due to PVB19 infection presenting with erythroid hyperplasia in a KT recipient and highlights the importance of considering PVB19 in the diagnosis of ane-

mia and the ineffectiveness of rHuEPO therapy. Further studies are required to ascertain the accurate relationship between PVB19 infection and rHuEPO. Until then, caution is advised in treating anemia with rHuEPO when PVB19 infection is suspected.

ACKNOWLEDGMENTS

We would like to thank all staff who supported our work in the Department of Nephrology and Kidney Transplant in Centro Hospitalar Universitário Lisboa Norte.

CONFLICTS OF INTEREST: None declared.

FINANCIAL SUPPORT: This work was supported by the corresponding author.

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