Pure red cell aplasia in a simultaneous pancreas-kidney transplantation patient: inside the erythroblast

Francesca Labbadia, Eduardo Salido-Fierréz, Juliana Majado-Martinez, Valentin Cabañas-Perianes, José M. Moraleda Jiménez

Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

Abstract

A case of pure red cell aplasia in a simultaneous kidney-pancreas transplant recipient on immunosuppressive therapy is reported here. The patient presented with anemia unresponsive to erythropoietin treatment. Bone marrow cytomorphology was highly suggestive of parvovirus pure red cell aplasia, which was confirmed with serology and polymerase chain reaction positive for parvovirus B19 DNA in peripheral blood. After the administration of intravenous immunoglobulin the anemia improved with a rising number of the reticulocytes.

Introduction

Parvovirus B19 (PVB19) is a non-enveloped, icosahedral small virus containing a single strand of DNA. It is highly tropic to human bone marrow and replicates only in erythroid progenitor cells, due to the unique tissue distribution of the PVB19 cellular receptor, the blood group P antigen. Clinical manifestations of PVB19 infection vary according to the immunological status of the host.

In immunocompromised patients, persistent viremia causes a chronic pure red cell aplasia (PRCA). PRCA due to parvovirus B19 infection after solid organ transplantation has been rarely reported and most of the cases were renal transplant recipients.

We describe a case of pure red cell aplasia secondary to B19 infection in a simultaneous kidney-pancreas recipient.

Case Report

A 42-year old female patient with an end-stage renal disease due to diabetic nephropathy received a simultaneous renal and pancreatic transplant in April, 2002. Since then immunosuppressive therapy consisting of Prednisone (5 mg/48 h) plus Mycofenolate-Mofetil (180 mg c/12h) plus Tacrolimus (2-3mg c/12h) was required. In addition she was receiving erythropoietin (EPO) 2000 UI twice a week since June of 2008.

In June 2010 the patient was admitted to the Nephrology Department because of fatigue, malaise and fever of two weeks duration. The physical examination was unremarkable except for pallor. The temperature was 37.5ºC, the blood pressure 120/70, the pulse 72 bpm, the oxygen saturation 100, the capillary glycemia 125 mg/dL.

The hemoglobin concentration was 80 g/L, hematocrit 24%, MCV 85.9 fL, reticulocytes 0.1% (56.4×10^3/L), platelets 297×10^9/L, and leukocytes 1.5×10^9/L (neutrophils 0.490×10^9/L, lymphocytes 0.6×10^9/L, monocytes 0.4×10^9/L).

Renal and liver function test, electrolytes and coagulation test were normal.

Anti-human globulin test and autoimmune markers were negative. Studies of serum vitamin B12, folic acid and iron metabolism were normal. Stool and urine examination were negative for occult blood.

Blood and urine cultures were negative. Serology of hepatitis B and C virus, HIV, Epstein-Barr virus, Citomegalovirus, HSV 1-2, Toxoplasma, Treponema Pallidum, Listeria and Leishmania were negative.

The serum level of Tacrolimus and Mycofenolate-Mofetil were in the therapeutic range. The EPO level was 21.1 mU/mL (2.59 -18.50).

The Hematology Department was consulted for the assessment of anemia unresponsive to erythropoietin (2000 UI twice a week) and neutropenia. Further investigations were performed. The peripheral blood cytology showed neutropenia without atypical cells and a normocytic-normochromic anemia with anisopoikilocytosis. The diagnosis of PRCA secondary to anti-EPO antibodies was ruled out because of the absence of anti-EPO antibodies. The serology of PVB19 (IgM) and the detection of human parvovirus B19 DNA by real-time qualitative PCR (Nanogen®) in serum were both positive. The bone marrow aspirate revealed a decreased erythropoiesis and giant proerythroblasts with nuclear inclusions characteristic of parvovirus infection (Figure 1). The granulocytic and megakaryocytic series were normal.

With the diagnosis of PRCA due to PVB19, the patient was treated with intravenous immunoglobulin (IVIG) 500 mg/Kg/day, five days. After three days, the Hemoglobin recovered to a level of 10.4 g/dL and the reticulocytes count to 80.100/μL (Figure 2). The neutropenia improved after the withdrawal of Mycofenolate-Mofetil. In January 2011 the hemoglobin was 14.1 g/dL, hematocrit 43%, the leukocyte and platelet counts were normal and the polymerase chain reaction of the virus was negative.

Correspondence: Francesca Labbadia, Hematology Departement, Hospital Universitario Virgen de la Arrixaca, Carretera Cartagena, KM 7, 30120 Murcia, Spain.
Tel. +34.968.369500.
E-mail: francesca.labbadia@gmail.com

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Discussion

PVB19 virus was discovered in 1975 (Cossart *et al.*) and it shows tropism to the haematopoietic system. The cellular receptor for PVB19 is a globoside, a neutral glycosphingolipid known as the blood group P antigen which is found predominantly on erythroid cells and their progenitors.

The presence of the P antigen is essential for the infection, so that people who lack P antigen cannot be infected *in vitro* by Parvovirus.[1] Beside the importance of the viral receptor as determinant of hosting cell specificity, there is also evidence of the existence of a co-receptor and an intracellular blockade in non permissive cells. The PVB19 replication depends on mitotically active cells and susceptibility to infection increases in the erythroid precursors with differentiation. The virus has a direct toxicity on human erythroid cells causing a lysis which is characteristically manifested as pure red cell aplasia on bone marrow examination. Viral replication in the S phase of the giant normoblasts is an early marker for human papillomavirus infection.[2] Leukopenia and thrombocytopenia are unusual but have been reported in some cases. The pathophysiology probably implies an autoimmune mechanism or hemophagocytosis related with viral nonstructural proteins.[3]

Seroepidemiologic studies demonstrate that 60-90% of adults have antibodies against PVB19. It is responsible for a wide range of diseases (acute and chronic) depending on the host immune response.[4]

The first reported human disease associated to PVB19 infection was a transient aplastic anemia in a patient with sickle cell disease.[5] In immunocompromised patients, persistent infection results from the inability to produce neutralizing antibodies. It can occur in congenital, iatrogenic and infective immunodeficiency. The dominant clinical manifestation is anemia secondary to pure red cell aplasia.[6]

The first report of PVB19 infection after transplantation was published in 1986.[7] PVB19 induced PRCA associated with solid organ transplantation is a significant but rare infectious complication.

Although large, prospective surveillance studies are lacking, some studies reported an incidence of PVB19 disease of ~2% after transplantation.[8] More recently, it has been suggested that up to 20% of organ transplant recipients develop PVB19 viremia after transplantation.[9] In the largest series of transplanted patients reported in the literature,[10] the patient population consisted of kidney transplant (54%), liver transplant (9%), heart or lung transplant (12%), and autologous (4%) or allogenic (24%) hematopoietic stem cell transplants. To our knowledge, no case of PVB19 infection has been described in simultaneous kidney-pancreas transplantation.

The median time to onset of PVB19 disease is 7 weeks after transplantation and most cases reported 1 year after transplantation are due to persistent infection.[11]

Our patient had an acute non regenerative normocytic anemia unresponsive to EPO with a moderate neutropenia and a normal platelet count. The clinical onset of acute PVB19 infection was eight years after double transplantation, since we did not have evidence of a positive serology and PCR for PVB19 until now. As she had neutropenia and anemia, a marrow aspiration was performed to exclude drug toxicity. The bone marrow cytology disclosed the typical cytological findings of PVB19 infection and oriented the final diagnosis.

There are not established guidelines for the screening or for the treatment of PVB19 infection in organ transplant recipients. Nevertheless, there are sufficient data to give some recommendations in patients with erythropoietin-resistant anemia once all other causes of anemia have been excluded.[12]

In this regard, the diagnostic test with the highest specificity in the appropriate clinical setting is the PVB19 PCR in peripheral blood, a noninvasive test particularly useful in immunocompromised patients in whom the PVB19 serology can be negative at the onset of the disease.[13] In patients with a suspected PVB19-induced red cell aplasia, a bone marrow examination provides fast and helpful diagnostic information.

The distinctive morphologic abnormalities include the presence of very large pronormoblasts with occasional intranuclear inclusions along with a relative paucity of more mature polychromic erythroid precursors. Examination of formalin-fixed bone marrow aspirate smears seems to facilitate the identification of the typical intranuclear inclusions.[14]

Regarding the treatment, most patients benefit from IVIG therapy and/or reduction of immunosuppressive therapy. The standard doses of 0.4-1.0 g of IVIG/ kg daily for 5 days appear to be clinically effective in most cases with no subsequent adverse effects. The goal of the treatment should be the eradication of viremia as evidenced by a negative PCR study, not only the clinical remission as judged by resolution of the anemia.[15]

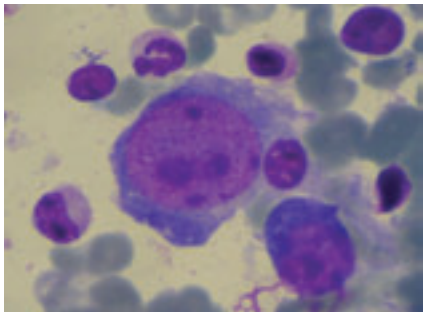

Figure 1. Giant proerythroblasts with nuclear inclusions.

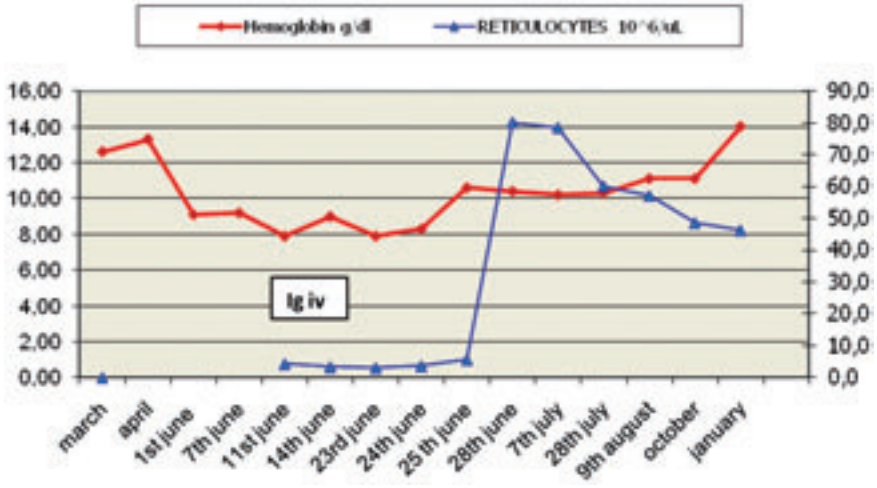

Figure 2. Blood count evolution after treatment with intravenous immunoglobulin.

Conclusions

We report the first case of PRCA due to PVB19 infection in a combined kidney-pancreas transplant recipient. Our case confirms that PVB19 infection is a rare but possible cause of anemia unresponsive to EPO in immunosuppressed transplanted patients. We underline the importance of a diagnostic screening using the PCR-PVB19 test and bone marrow cytology, and the rapid response to IVIG therapy.

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