



Severe Anemia From Parvovirus B19 Infection in Pediatric Renal Transplant Recipients: Two Case Reports

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ABSTRACT

Human parvovirus B19 (PVB19) is the etiologic agent of erythema infectiosum (fifth disease), a common childhood exanthema. Immunocompromised patients risk developing chronic infections leading to pure red blood cell aplasia. Herein we have reported our experience with two pediatric renal transplant recipients who had severe pure red cell aplasia in the early period after surgery, accompanying PVB19 infection.

First Case. A 6-year-old boy underwent pro emptive living-related renal transplantation in September 2006. On day 4, he developed abdominal discomfort and diarrhea. After transplantation, he began an asymptomatic drop in hematocrit without reticulocytosis, which was unresponsive to recombinant erythropoietin. Diarrhea also persisted. Polymerase chain reaction (PCR) was positive for cytomegalovirus (CMV) in the gastrointestinal tract. PVB19 was confirmed by PCR on a bone marrow sample. He was transfused with packed red cells and treated with ganciclovir and intravenous immunoglobulin (IVIG). His hematocrit increased and diarrhea ended. Six months later anemia recurred requiring a second infusion of IVIG. Subsequently he has done well.

Second Case. A 15-year-old boy received a living-related renal transplant in October 2006, after 2 years on automated peritoneal dialysis. One month later he developed a progressive, nonregenerative anemia. A bone marrow aspirate confirmed a PVB19 infection by PCR. He received a blood transfusion and IVIG with a favorable response.

Conclusions. The presence of persistent anemia in immunocompromised hosts with a low reticulocyte count suggests PVB19 infection. IVIG therapy is effective to treat chronic PVB19 infections.

PARVOVIRUS B19 (PVB19) was discovered in 1975 when it was identified in a healthy blood donor.^{1,2} It is the only parvovirus linked to human disease, and is associated with a wide range of disease manifestations. The severity of disease depends on the immunologic and hematologic status of the patient. Among children, it is classically manifested as erythema infectiosum (fifth disease), an acute infection, which is typically manifested with rash, fever, and arthralgias. In adolescents and adults it shows arthralgia, or hydrops fetalis during pregnancy. Among individuals with decreased erythrocytes caused by conditions such as iron-deficiency anemia, sickle cell disease, spherocytosis, or thalassemia, transient aplastic crises occur.^{1,3} PVB19 infection is increasingly implicated in the pathogenesis of pure red cell aplasia after solid organ and bone marrow transplantation. Also it is believed to have a role in the patho-

genesis of glomerulopathies, both in native and transplanted kidneys.^{1,2,4} Among immunocompetent hosts, clearance of the virus is assumed to result from the production of an efficient neutralizing antibody response, whereas in immunocompromised hosts the inability to produce neutralizing antibodies can lead to persistent or chronic viral infections.^{1,4,5} PVB19 infection is global and seroprevalence increases with age.^{6,7}

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In England and Wales, epidemiologic studies suggest that the seroprevalence is 5% to 15% for children 1 to 5 years old; 50% to 60% in adolescents and young adults as well as more than 85% of the population over 70 years. Immunoglobulin (Ig)G antibody in serum samples, are similar in the United States, Europe, and Asia. In the healthy Chilean population, Abarca et al⁶ in an epidemiologic study showed a 21% of IgG antibody in serum samples of children younger than 5 years. Gaggero et al⁷ reported an overall prevalence of IgG G antibodies of 54.8% among adult blood donors. Herein we have reported two pediatric renal transplant recipients who developed severe hyporegenerative anemia caused by PVB19 infection, in the early post-transplant period, which was associated with cytomegalovirus (CMV) infection in one of them. Furthermore, we have presented brief review of the literature.

CASE REPORTS

Patient 1 was a 6-year-old boy with end-stage renal disease (ESRD) secondary to renal dysplasia who underwent a preemptive living-related renal transplant from his father in September 2006. Immunosuppression consisted of induction with basiliximab and methylprednisolone followed by maintenance with prednisone, tacrolimus (FK), and mycophenolate mofetil. He had good initial allograft function. On day 4, he developed abdominal discomfort and diarrhea, so mycophenolate mofetil was changed to the enteric-coated mycophenolate sodium formulation. Diarrhea persisted and the mycophenolate was discontinued and replaced by azathioprine on day 10. The tacrolimus (Prograf, Astellas) level was maintained at 10 to 15 ng/mL for the first month. The postoperative course was remarkable for an asymptomatic drop in hematocrit from 35% immediately pretransplant to 23% on day 30, with a reticulocyte count of 1.5%. Iron deposits were normal, so erythropoietin (EPO) was added. Intermittent diarrhea persisted. His renal function, routine urinalysis, and urine culture were unremarkable. CMV antigenemia and serial stool cultures were negative.

Seven weeks later, he was hospitalized because of a low-grade fever, sore throat, and arthralgia of his knees. Laboratory investigations showed a serum creatinine level of 0.6 mg/dL, hematocrit of 24%, reticulocyte count, 3.5%, and total leukocyte count, 9,000/mm³ with a normal differential. After 24 hours, he was asymptomatic. At 8 to 9 weeks posttransplant, we observed again a progressive drop in hematocrit, with a reticulocyte count of 0.2%, transient leukopenia of 2900 leukocytes/mm³, and normal platelet count. EPO was stopped. Upper gastrointestinal endoscopy and colonoscopy were done; polymerase chain reaction (PCR) for CMV was positive in a colon biopsy. A bone marrow examination showed the characteristic findings of pure red cell anemia. PVB19 infection was confirmed by PCR. The patient was treated with ganciclovir for 21 days, intravenous immunoglobulin (IVIg) at 1 g/kg per day for 2 days and transfused with packed red cell. His hematocrit level increased from 16% to 29% with a reticulocyte count of 1%. The diarrhea resolved. Three months later (6 months posttransplant) the anemia recurred, with a hematocrit of 22%, and a reticulocyte count of 0.2%. PVB19-specific DNA was detected on bone marrow biopsy. He required a second IVIg treatment (1 g/kg per day) for a 2-day period. Subsequently, he has done well, with normal renal function. The course is summarized in Figure 1.

Serology for PVB19 at 6 months postinfection was negative for IgG and IgM. During this first period after transplantation, the patient shared with other patients a similar condition in the same foster care house; they lived in a rural area, far from the hospital.

Patient 2, A 15-year-old boy with ESRD secondary to renal dysplasia and obstructed megaureter received a living-related renal transplant in October 2006 (1 month after case 1), after 15 months on automated peritoneal dialysis (APD). Induction therapy with basiliximab and methylprednisolone was followed by maintenance immunosuppression with prednisone, FK, and mycophenolate mofetil. With good allograft function, he was discharged after 10 days with a creatinine level of 1.05 mg/dL and a hematocrit of 34%. The same condition of rural residence forced him to stay the first month posttransplantation in the same foster care house as patient 1.

Four weeks after transplantation, he began to progressively drop his hematocrit, and at 8 weeks he was readmitted for evaluation of

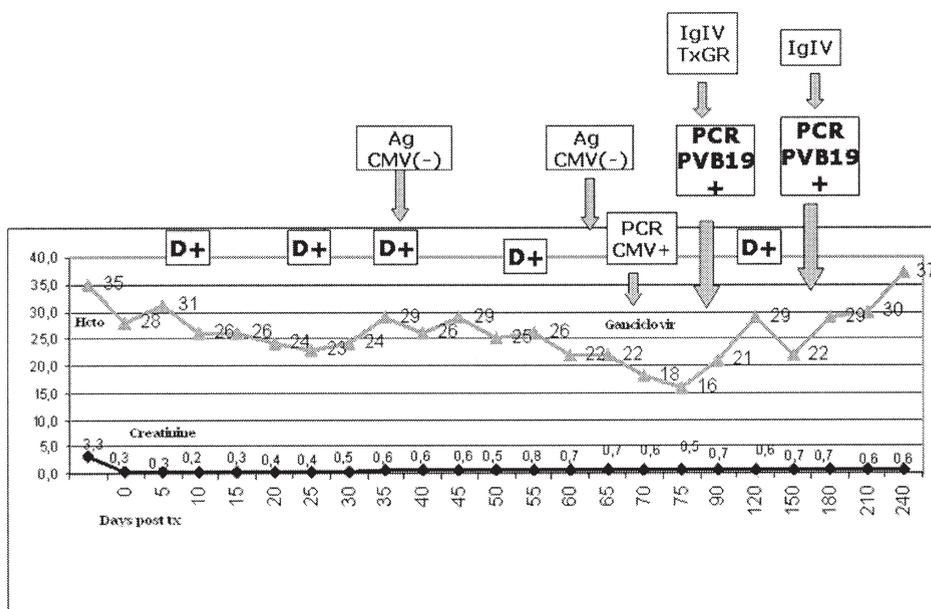


Fig 1. Serum creatinine and hematocrit results in patient 1. *Abbreviations:* D+, diarrhea; Ag CMV (-), cytomegalovirus antigenemia; PCR CMV+, polymerase chain reaction for CMV; Ig IV, intravenous immunoglobulin; Tx GR, red blood transfusion; PCR PVB19 +, polymerase chain reaction for PV.

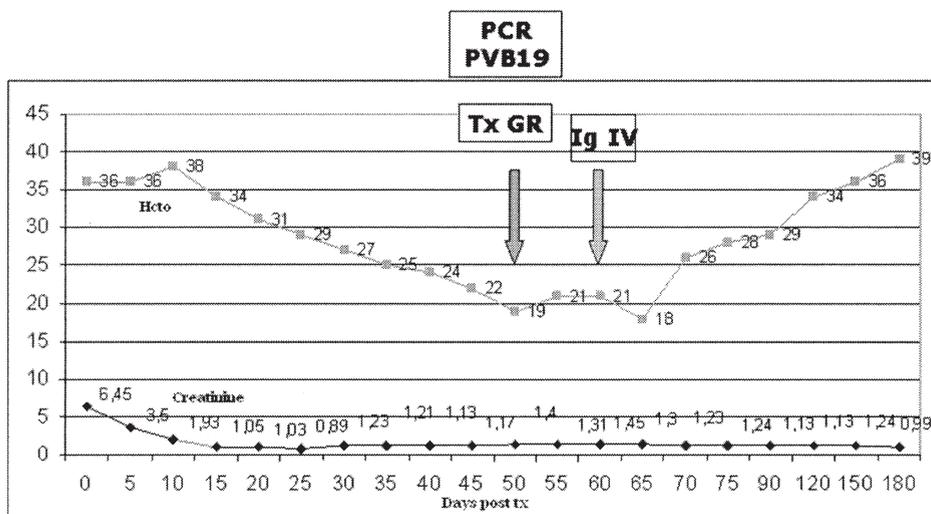


Fig 2. The serum creatinine and hematocrit values in patient 2. *Abbreviations:* Ig IV, intravenous immunoglobulin; Tx GR, red blood transfusion; PCR PVB19+, polymerase chain reaction for PVB19.

anemia. Laboratory investigations showed a serum creatinine level of 1.31 mg/dL, a hematocrit of 19%, and a reticulocyte count of 0.5%, with normal leukocyte and platelet counts. A bone marrow aspirate showed erythroid hypoplasia and PVB19 DNA was isolated by PCR. At this moment, the hematocrit dropped to 17% and the reticulocyte count to 0.1%. He received a blood transfusion and IVIG (1g/kg per day for 2 days) with a favorable response. After 6 months specific IgG antibodies against PVB19 were detected in blood; the IgM was negative. The hematocrit rose to 39% and his creatinine level was 1.4 mg/dL. His course is summarized in Figure 2.

DISCUSSION

PVB19, a small single-stranded DNA virus, is a member of the genus *Erythrovirus* of the family *Parvoviridae*. It was first linked to human disease in 1981; the first report of PVB19 infection after transplantation was published in 1986.^{1,3-5}

This DNA virus characteristically replicates in erythroid progenitor cells of bone marrow. Its viral receptor, blood-group P antigen, is a glycolipid named globoside (Gb4), that is present in erythroblasts, megakaryoblasts, liver, lung, heart, kidney, synovium, vascular smooth muscle, endothelial cells, and fetal myocardial cells.^{2,3} Most symptoms occur secondary to immune complex formation, so that when the rash appears patients are no longer contagious. Immunocompromised patients may not develop the typical parvovirus rash because it occurs secondary to antibody-antigen complex deposition in the skin.²

Anemia is the predominant clinical manifestation after transplantation. In normal hosts, at approximately 8 days after infection, PVB19 induces lyses of infected erythroid progenitor cells, which results in reticulocytopenia and mild anemia that is prolonged for about 10 days.²⁻⁵ In the immunocompromised host, PVB19 infection may not be fully eradicated, resulting in a state of chronic anemia. Cavallo et al⁸ showed that 23% of renal transplant recipients with anemia showed PVB19 DNA in their serum. Eid et al⁵ highlighted the importance of PVB19 as a cause of refractory and severe anemia in transplant patients. The

pathognomonic morphology of PVB19 infection in the bone marrow is giant proerythroblasts with intranuclear inclusions and the absence of intermediate and late normoblasts.^{1,4,5}

The role of PVB19 infection to cause glomerular lesions is not clearly established, but it is known that it can affect both native and transplanted kidneys. It may present as de novo or recurrent disease. Moudgil et al⁴ reported that PVB19 may be responsible for causing various forms of focal sclerosis, among renal transplant patients with chronic infections. Barsoum, et al² described the association of various types of glomerulopathies, most commonly focal segmental glomerulosclerosis, collapsing glomerulopathy, and endocapillary proliferative glomerulonephritis from a pathologic standpoint. The existence of Gb4 receptors in human kidney and endothelium, suggests the potential of the virus to infect the kidney.^{2,4,9,10}

PVB19 chronic infection has also been associated with hepatitis, pneumonitis, myocarditis, encephalitis, and central nervous system vasculitis.^{1,2,11} Nonetheless, the full spectrum of clinical manifestations of PVB19 infection among allograft recipients has not been well characterized.

The route of PVB19 transmission is well established. The principal route occurs via respiratory secretions, primarily during the week before the development of the rash.^{1,3,4,5} It also can be transmitted vertically from mother to fetus. The estimated risk of transplacental infection is 30%. In transplant patients, the infection may be acquired by the respiratory route, donor organ, or blood products. Immunosuppression may reactivate latent virus or result in persistent infection, caused by an inability to mount a full immune response. Independent of specific immunosuppressive regimens, prolonged PVB19 infection may occur in patients after transplantation. It is not known whether chronic infection in the bone marrow is associated with persistent infectivity in the respiratory secretions.^{1,2,4,5}

Nosocomial transmission has also been documented. In our patients, case 2 followed case 1, in clinical presentation,

and both shared the same foster care house. Probably case 1 acquired the infection from the community, and transmitted PVB19 to case 2. The lack of a lipid envelope makes PVB19 resistant to physical inactivation with heat or detergents; the DNA may persist for many days on surfaces.^{12,13}

Serum IgM testing is recommended to diagnose acute viral infection in immunocompetent hosts, with 89% sensitivity and 99% specificity.³ IgG testing only indicates a previous infection and immunity. Among immunosuppressed hosts viral DNA testing (PCR) is crucial for the diagnosis of infection. Among patients who are highly suspected to have PVB19 disease but whose peripheral blood PCR assay result is negative, the diagnosis may be confirmed by bone marrow examination.^{3,5}

Multiple recent reports have suggested therapeutic benefits to treat PVB19 infection with high-dose IVIG in immunosuppressed patients.^{4,5,14} It provides passive immunity with high titers of PVB19-specific neutralizing IgG antibodies. Nevertheless, Barsoum, et al² reported unfavorable responses to multiple aggressive courses of IVIG in a patient with a third cadaver transplant who developed refractory anemia and nephrotic range proteinuria associated with PVB19 chronic infection. Successful eradication was only possible when immunosuppression was discontinued. It seems that the response to IVIG therapy is related to the degree of immunosuppression. Reactivation or increased replication should be an anticipated consequence of intense immunosuppression after transplantation. So, if feasible, reduction in immunosuppression should be part of the treatment of PVB19 disease.^{2,4,5} The association of IVIG with acute renal failure was also been described in adults and children. The mechanism of injury is associated with IVIG formulations that contain sucrose as a stabilizer. One possible mechanism is that intravenous sucrose is filtered by the glomerulus causing an osmotic injury.¹⁵

In conclusion the presence of anemia along with a low reticulocyte count after transplantation, should suggest PVB19 infection in the differential diagnosis. Serology may be useful among the pretransplant studies. The anemia may be chronic or recurrent. Generally, high-dose IVIG successfully resolves parvovirus disease, but reduction of immuno-

suppression may be necessary. Nosocomial transmission of PVB19 can occur from immunocompromised patients.

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