Effects of Parvovirus B19 Infection in Renal Transplant Recipients: A Retrospective Review of Three Cases

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Abstract

Parvovirus B19 (PVB19) is a DNA virus which causes clinically relevant infection in renal transplant recipients (RTR) leading to significant morbidity. Manifestations include erythropoietin resistant anemia, proteinuria, and glomerulosclerosis in the allograft. Severe infection may require administration of intravenous immunoglobulin, reduction in immunosuppression and transfusions. The major challenge in managing and preventing the infection in RTR involves the act of balancing the decreased level of immunosuppression and the risk of rejection. The objective of this article is to understand the importance of PVB19 infection and its outcome in RTR. We reviewed the medical records of three RTR with confirmed PVB19 infection and recorded patient information including demographics, clinical and laboratory data, management, and outcome. The average time of occurrence of PVB19 infection as transplant was 8.6 weeks and they presented with symptomatic anemia. Elevated creatinine values were noted in two of them. Following treatment, anemia improved and creatinine values returned to baseline. One of them developed an early relapse and had to be treated once again similarly. We emphasize the importance of maintaining a high index of suspicion for PVB19 infection in patients with anemia in the posttransplant phase, especially in patients on higher doses of immunosuppressants. Early and proper treatment can prevent worsening clinical condition and possible effects on the allograft.

Keywords
- allograft
- anemia
- immunosuppression
- intravenous immunoglobulin
- parvovirus B19
- renal transplant

Parvovirus B19 (PVB19) is a nonenveloped DNA virus which is a ubiquitous human pathogen, primarily spread via respiratory droplets. The infection can be symptomatic or asymptomatic according to the host's age and immunologic status. The natural course of the infection in immunosuppressed individuals such as renal transplant recipients (RTR) are varied.[1] Although anemia is the most common manifestation,[2] PVB19 can also cause pancytopenia, hepatitis, myocarditis, neurological disease,[1,3,4] and allograft dysfunction.[5] Transmission can occur to the recipient from the allograft itself, as the virus may persist for years in seropositive individuals.[6] Therefore, it may be relevant to screen selected

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Table 1 General information of the recipients and donors

	Patient 1	Patient 2	Patient 3
Age (y)	58	44	30
Gender	M	F	M
Comorbidities	DM, HTN	HTN	HTN
Cause of ESRD	DM, HTN	Obstructive uropathy	Chronic glomerulonephritis
Year of transplant	2013	2010	2008
Age of donor (y)	23	41	22
Type of donor	Live	Live	Live
HLA mismatches	5/6	6/6	5/6
Induction protocol	Basiliximab, steroid	Basiliximab, steroid	Basiliximab, steroid
Immunosuppression protocol	Tacrolimus, MMF, prednisone	Tacrolimus, MMF, prednisone	Tacrolimus, MMF, prednisone
Acute rejection	Acute cellular rejection at 2 weeks posttransplant, confirmed with biopsy, treated with pulse IV Solumedrol	No	No
Baseline creatinine (mg/dL)	1.3	1.12	1.2

Abbreviations: DM, diabetes mellitus; ESRD, end-stage renal disease; F, female; HLA, human leukocyte antigen; HTN, hypertension; M, male; MMF, mycophenolate mofetil.

donors for PVB19 and monitor for possible manifestations such as resistant anemia in RTR. The major challenge in managing and preventing PVB19 infection in RTR involves the act of balancing the decreased level of immunosuppression and the risk of rejection.

Patients and Methods

We retrospectively reviewed the medical records of 144 RTR who were followed up at a tertiary care hospital affiliated transplant program from January 2007 to June 2013 and selected three patients with confirmed PVB19 infection. The maintenance immunosuppression protocol that was followed consisted of tacrolimus, mycophenolate mofetil, and prednisone. These patients presented with anemia in the posttransplant period, and were subsequently diagnosed with PVB19 infection. We collected patient information including demographics, clinical, and laboratory data. The detection of infection was done by polymerase chain reaction (PCR) or immunoglobulin M (IgM) serology of blood samples or bone marrow study indicative of PVB19. The management and outcome was also recorded. The study has been approved by the Institutional Review Board at the hospital.

Results

Of 144 RTR, there were 3 cases (2%) of PVB19 infection. All recipients had normal baseline creatinine posttransplant. The average time for detection of PVB19 infection since transplant was 8.6 weeks and they presented with symptomatic anemia. The lowest hemoglobin (Hb) value noted was 6 mg/dL. Epstein-Barr virus and cytomegalovirus were the associated coinfections. Elevated creatinine values were noted in two of them. Following treatment, anemia improved and creatinine values returned to baseline. Sustained improvement in Hb was seen after 4 weeks in two of them and after 12 weeks in the third patient. One of them developed an episode of recurrence.

Refer to ►**Tables 1** to **3** for details regarding patient characteristics, presentation and investigations, treatment and outcome, respectively.

Refer to ►**Fig. 1** for graph showing variations in Hb of the three patients and ►**Fig. 2** showing variations in creatinine values of the three patients.

Discussion

RTR are highly susceptible to infections such as PVB19[7] because of the increased use of induction therapy to prevent early acute rejection and because of the effect of sustained long-term immunosuppression to prevent chronic rejection.

A study in 2006 identified that the median time for occurrence of PVB19 infection after transplantation was around 1.75 months, with majority of the cases occurring within 3 months posttransplant.[5]

Chronic anemia is well-recognized complication in approximately 39% of RTR, with erythropoietin-resistant anemia occurring in almost 9% of them.[8] PVB19 is capable of targeting erythroid progenitor cells in the bone marrow leading to a cessation in erythropoiesis. This usually reverts back to normal by the production of antibodies against the virus in immunocompetent individuals. However in RTR, such infections often lead to persistent pure red cell aplasia with normal white cell and platelet counts.[8] Studies suggest that nearly 23% of RTR with persistent anemia had positive PCR values for PVB19.[8]

Table 2 Parvovirus B19 infection presentation and investigations

	Patient 1	Patient 2	Patient 3
Time of parvovirus infection posttransplant	8 wk	7 wk	11 wk
Presentation	Dizziness, dyspnea on exertion, dark stools	Dizziness, dark stools	Dizziness, dyspnea on exertion, palpitation
Physical exam	HR, 89; BP, 134/74; RR, 18; Temp, 98, SpO_2, 96%	HR, 100; BP, 130/54; RR, 18, Temp, 98.6; SpO_2, 98%	HR, 86; BP,110/68; RR,18; Temp, 98.4; SpO_2, 98%
Investigations: blood	Hb, 6.6; Hct, 19.6; RBC count, 2.34; TC, 4,600; Plt, 295, RBC indices, normal	Hb, 7.1; Hct, 21.2; RBC count, 2.31; TC, 6,300; Plt, 419; RBC indices, normal	Hb, 6.3; Hct, 18.4; RBC count, 2.22; TC, 4,600; Plt, 320; RBC indices, normal
	Reticulocyte count, 0.3%	Reticulocyte count, 0.2%	Reticulocyte count, 0.2%
	RBS, 230; Na, 140; K, 4.1; Cl, 106; HCO_3, 21	RBS, 86; Na, 137; K,4.5; Cl, 105; HCO_3, 20	RBS, 113; Na, 130; K,4.7; Cl, 100; HCO_3, 21
	BUN/Cr, 31/1.51	BUN/Cr, 20/1.27	BUN/Cr, 13/1.1
	LDH, 134	LDH, 188	LDH, 144
	Iron studies-increased iron and ferritin, decreased TIBC	Iron studies-normal iron, increased ferritin, decreased TIBC	Iron studies-increased iron and ferritin, decreased TIBC
	Haptoglobin, normal; B_{12} and folate, normal	Haptoglobin, normal; B_{12} and folate, normal	Haptoglobin, normal; B_{12} and folate, normal
	Urinalysis, no proteinuria	Urinalysis, no proteinuria	Urinalysis, no proteinuria
Others	FOB, negative	FOB, positive	Not indicated
	CT abdomen-no evidence of bleeding	CT abdomen-no evidence of bleeding	CT abdomen-no evidence of bleeding
	OGD-erosive gastropathy	OGD-normal	Not indicated
	Colonoscopy- normal	Colonoscopy-pan colitis	Not indicated
Initial management	Aspirin stopped and patient monitored for bleeding. In spite of no active bleeding, Hb continued to drop rapidly and Parvovirus infection was suspected	Treated conservatively for colitis, no further bleeding but Hb continued to drop, BMA done and showed erythroid aplasia. Renal biopsy was done due to rise in creatinine and it showed hydropic changes in tubular epithelial cells	Hb continued to drop, BMA done which showed erythroid aplasia.
Detection of parvovirus	Positive PCR	Bone marrow study, positive PCR	Positive PCR, positive IgM serology, bone marrow study
Co infections	CMV PCR positive, EBV antigen positive	EBV antigen positive	CMV PCR positive
Lowest Hb level after diagnosis	6	6.2	6
Highest Cr level after diagnosis	1.74	2.25	1.3

Abbreviations: BP, blood pressure (mm Hg); BMA, bone marrow aspiration; BUN, blood urea nitrogen (mg/dL); Cl, chloride (mEq/L); CMV, cytomegalovirus; Cr, creatinine (mg/dL); EBV, Epstein-Barr virus; FOB, fecal occult blood; Hb, hemoglobin (g/dL); HCO_3, bicarbonate (mEq/L); Hct, hematocrit (%); HR, heart rate (no of beats/min); K, potassium (mEq/L); LDH, lactate dehydrogenase (IU/L); Na, sodium (mEq/L); OGD, esophagoduodenoscopy; PCR, polymerase chain reaction; Plt, platelet; RBS, random blood sugar (mg/dL); RBC, red blood cells; RR, respiratory rate (per min); TC, total count; Temp, temperature (°F); TIBC, total iron binding capacity.

Immunosuppression is the major risk factor for the infection in RTR, indicated by improvement in anemia when immunosuppression is decreased.[9] Induction with antithymocyte globulin is found to have a higher risk for the infection compared with basiliximab.[10] Substitution of tacrolimus with cyclosporine was also followed by viral clearance and resolution of anemia.[9,11] Vigilance should be observed during high-risk periods such as early after transplantation and after treatment for rejection, when the dose of immunosuppressants are high.[4]

Table 3 Treatment and outcome of the patients

	Patient 1	Patient 2	Patient 3
Treatment	IVIG infusion, decreased immunosuppression, 3 units PRBC transfusion	IVIG infusion, decreased immunosuppression, 4 units PRBC transfusion	IVIG infusion, decreased immunosuppression, 2 units PRBC transfusion
Hb posttreatment (g/dL)	12.1	13.1	11.5
Cr posttreatment (mg/dL)	1.19	1.15	1.3
Sustained Hb improvement	After 4 wk	After 4 wk	After 12 wk
Recurrences	No	No	Yes, one recurrence. treated similarly
Allograft dysfunction	Transient	Transient	No
Outcome	Anemia resolved, no allograft dysfunction, viral titers decreased on follow-up, patient is still on routine immunosuppression protocol because of his history of acute rejection	Anemia resolved, no allograft dysfunction, viral serology became negative on follow-up. Patient is on a reduced dose of immunosuppression as the infection	Anemia resolved, no allograft dysfunction, viral IgM serology became negative. Patient is on a reduced dose of immunosuppression since the infection

Abbreviations: Cr, creatinine; Hb, hemoglobin; IgM, immunoglobulin M; IVIG, intravenous immunoglobulin; PRBC, packed red blood cells.

Coinfection of PBV19 and other viruses such as cytomegalovirus and with human herpes virus 6 have also been reported.[12]

Detection of PVB19 can be done via molecular techniques or by measurement of viral antibodies. IgM assays will detect a recent infection,[13] but it is less reliable due to delayed or inadequate humoral response.[14] Viral DNA can be detected in blood, bone marrow, and infected organs using PCR[15] and is also detected in asymptomatic individuals.[16] However, the detection of viral DNA with clinical findings is likely to represent active infection. If serology and PCR are negative but the clinical suspicion is high, examination of bone marrow specimen using immunohistochemical staining or in situ hybridization is helpful in establishing the diagnosis.[5]

The main histopathological pictures of PVB19 infection of allograft kidney are thrombotic microangiopathy and collapsing glomerulopathy.[17–19] Reports have shown an elevation of plasma creatinine and proteinuria.[20]

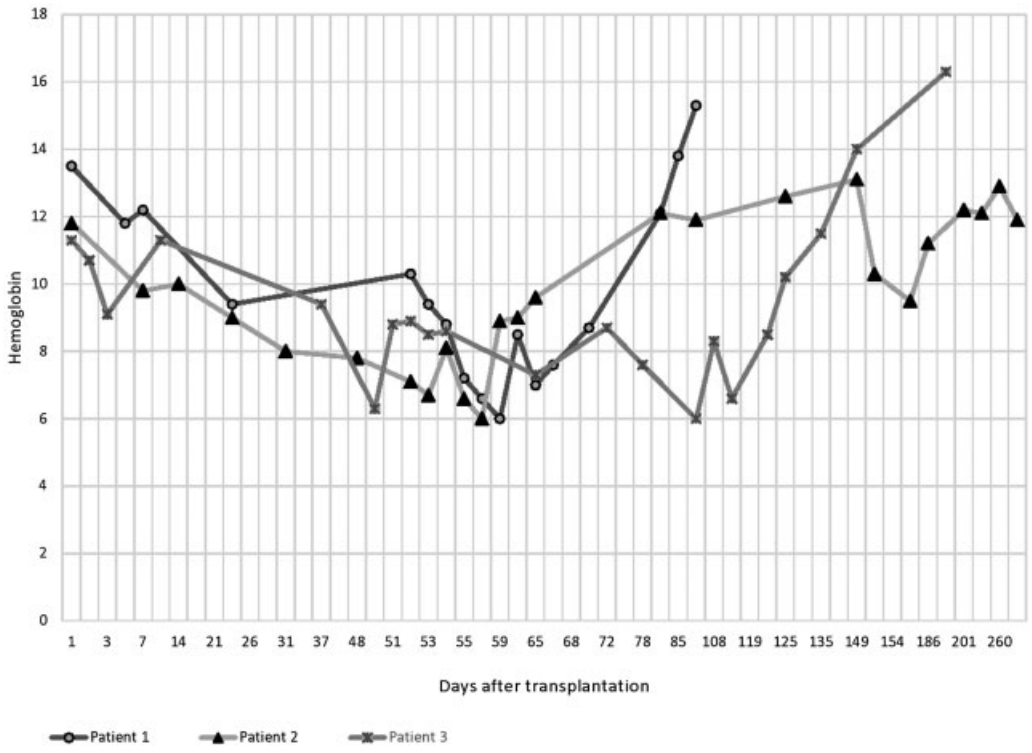

Fig. 1 Graph showing variations in hemoglobin of the three patients.

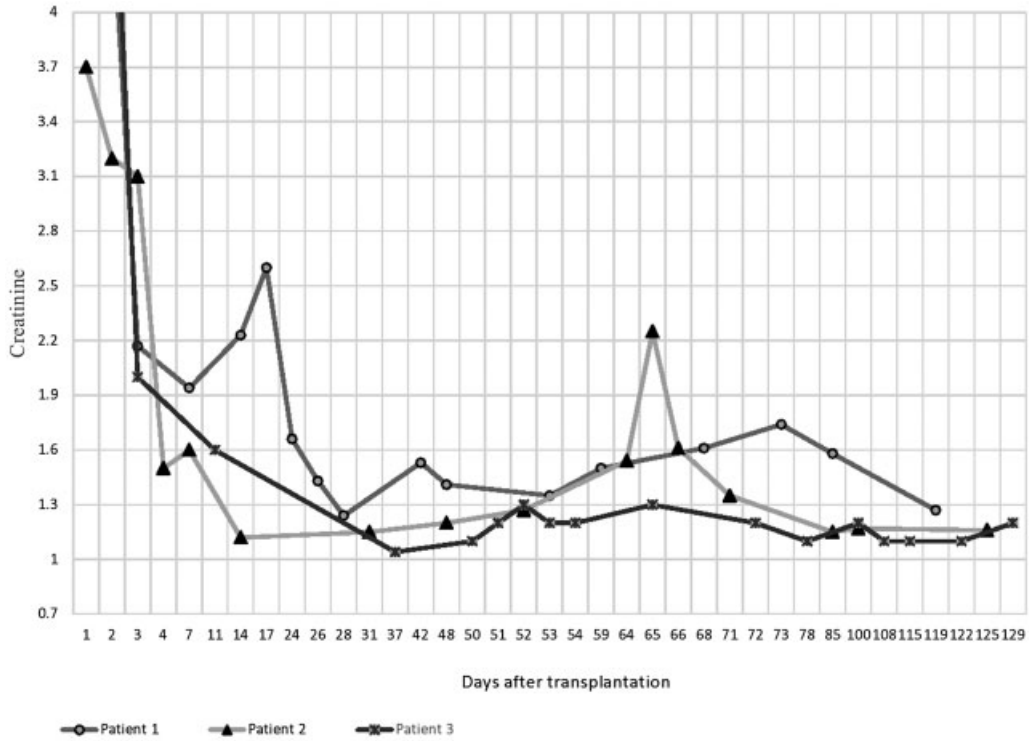

Fig. 2 Graph showing variations in creatinine values of the three patients.

The treatment of PBV19 is reduction of immunosuppression and intravenous immunoglobulin (IVIG) administration.[21] It is also important to avoid the use of erythropoietin to combat the anemia while treating PVB19, as this can lead to a resistance of the virus to proven treatment.[22]

Conclusion

PVB19 is an important treatable cause of anemia in RTR. A high index of suspicion should be maintained in patients with anemia in the posttransplant phase, especially those who have received higher doses of immunosuppressants. It may be relevant to screen-selected donors for asymptomatic PVB19 infection and to keep an eye out for anemia in RTR if the donor has the infection. Further studies on a larger sample are required to determine whether recommendations for routine donor screening need to be made. Early diagnosis and appropriate intervention can minimize the negative impacts of the infection.

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