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Case report

Parvovirus B19 infection and anemia after kidney transplantation: a report of two cases

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Abstract: Post-transplantation anemia is common among renal transplant recipients (RTR). The most frequent causes are erythropoietin deficiency, acute allograft rejection, iron deficiency, hemolytic anemia, adverse effects of immunosuppressive therapy, and virus infection. Human parvovirus B19 (HPV B19) can cause persistent viremia and erythropoietin-resistant erythroid aplasia in immunosuppressed patients. This case report describes two male renal transplant recipients who infected HPV B19 after kidney transplantation with severe anemia. Rapid and severe anemia that did not respond to blood transfusion. Adjustment of immunosuppressive drugs and intravenous immunoglobulin treatment resolved severe anemia after two months. In conclusion, when anemia develops rapidly and severely in renal transplant recipients in the absence of rejection and hemolysis, parvovirus B19 infection should be considered.

Keywords: Parvovirus B19; anemia; kidney transplantation; intravenous immunoglobulin.

1. INTRODUCTION

Anemia is a major problem for renal transplant recipients (RTR). The prevalence of anemia is 90% in patients after the first-month post-transplant and decreases to 35-45% in patients after one-year post-transplant [1]. Some common causes are erythropoietin deficiency, acute rejection, iron deficiency, gastrointestinal blood loss, myelosuppression due to immunosuppressive drugs, and viral infections such as CMV, EBV, parvovirus B19 [2].

In our case report, HPV B19 infection caused a transient aplastic crisis in patients after kidney transplantation with immunosuppressive therapy. Diagnosis of HPV B19 infection based on rapid and severe anemia, erythroid aplasia on bone marrow aspiration, active HPV B19 DNA level in blood detected by real-time polymerase chain reaction (PCR).

Currently, HPV B19 infection is primarily symptomatic and varies with the clinical manifestation, and there is no specific antiviral drug available for the treatment of HPV B19 infection [3-7]. In our patients, intravenous immunoglobulin (IVIG) therapy combined with adjusting of immunosuppressive drugs and blood transfusion was a feasible regimen in treating HPV B19 infection. Therefore, our report aims to supplement a strategy helping the effective management of HPV B19 infection in post-transplant patients with anemia.

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2. CASE REPORTS

Chief complaints

Both patients presented with persistent fatigue after kidney transplantation.

History of present illness

Patient 1: a 40-year-old white-collar worker, male with hypertension, end-stage renal failure, was diagnosed in November 2012. A blood test before the transplantation yielded creatinine level: 6.37 mg/dL and measurement of GFR using radioactive tracers: 10.2 mL/min/1.73 m2, Hgb level: 119 G/L. He then received kidney transplantation in October 2015. The organs were recovered from his father. CMV immunoglobulin (Ig) G antibodies in the peripheral venous blood, from both the donor and recipient, were positive, and both IgM yielded negative results, and CMV DNA was: 3.35 x 10^3 cp/mL. No blood transfusion was performed during the operation. Maintenance immunosuppression consisted of tacrolimus: 7 mg BID, mycophenolate: 360 mg BID, and prednisone with a total dose of 30 mg, along with mekoferrat B9. The patient was also treated for CMV with valcyte 450 mg OD for 2 months.

After 3 months, the patient reported weakness without other discomforts. The hemoglobin level declined from 76 to 63.9 G/L with Hct: 18.6%, a bone marrow aspirate and biopsy were taken, which showed normochromic anemia, with a mild decrease in WBC, normal platelet level, and decreased erythropoiesis. The patient was diagnosed with severe anemia and tardyferon B9, ethryropoietin 6000 IU per week, and blood transfusion of 20 units in 5 months was given.

On 3rd June 2016, HPV B19 DNA with sequence reading revealed the presence of HPV with a total number of 1.91 x 10^9 cp/mL, and the diagnosis of HPV B19-related PRCA (Pure Red Cell Aplasia) was made also the new-onset of diabetes mellitus type 2 and hyperuricemia. Treatment with insulin and intravenous immunoglobulin (IVIG) was started and continued for 5 days, however symptoms of anemia persisted, and HPV B19 DNA with sequence reading revealed HPV with a total number of 8,91 x 10^9 cp/mL in July 2016, the second course of treatment with IVIG was started, tacrolimus was also reduced in the dose and came into cessation eventually due to lack of response to IVIG therapy and cyclosporine was introduced to therapy. After that, the patient's overall status was getting better. Quantitative CMV and HPV PCR tests yielded a negative result.

Patient 2: A 46-year-old male was diagnosed with hypertension, end-stage renal failure in October 2015. He received kidney transplantation in December 2015 from an altruistic donor. CMV immunoglobulin (Ig) G antibodies, IgM, and CMV DNA quantitative test in the peripheral venous blood, from both the donor and recipient, were negative. No blood transfusion was performed during the operation. Maintenance immunosuppression consisted of tacrolimus and prednisone 10 mg OD.

After 4 months, the patient reported dizziness and fatigue. The HCT level decreased to 29.5%, a bone marrow aspirate and biopsy were taken, which showed normochromic anemia, with decreased erythropoiesis, HPV B19 DNA with sequence reading revealed the presence of HPV with total number of: 5.2 x 10^{10} cp/mL and the diagnosis of HPV B19-related PRCA was made. The patient was treated with tardyferon B9 and a blood transfusion of 60 units. Infusion of immunoglobulin (IVIG) was started and continued for 5 days. However, symptoms of anemia persisted, and HPV B19 DNA with sequence reading revealed HPV with total number of 1.95 x 10^9 in April 2017, the second course of treatment with IVIG was started, tacrolimus was also reduced in the dose and came into cessation eventually due to lack of response to IVIG therapy and started with cyclosporine 200 mg per day since May 2017. Dose adjustment was made based on the results of drug concentration in the patient's blood every week. After that, patient's overall status was getting better, quantitative HPV PCR test yielded negative result. In October 2017, Everolimus was introduced to the regimen with the dose of 1 mg per day since then.

History of past illness

Patient 1: He was treated with Coversyl 5 mg OD and Betaloc zok 25 mg OD to control his blood pressure. There were no records of blood transfusion and the use of ethryropoietin. The patient receiving hemodialysis, and his urine output was approximately: 3100 mL per day before the kidney transplantation.

Patient 2: There were no records of blood transfusion and the use of ethryropoietin. The patient was on hemodialysis before the kidney transplantation through arteriovenous fistula.

Clinical examination

Both patients were awake, but they appeared pale. Vital signs were typical, and clinical examination did not detect any abnormalities.

Outcome and follow up

After 2 courses of treatment, two patients were discharged and followed up regularly with stable kidney function and normoglycemia until writing this report. No recurrence of anemia or any adverse effect from therapy has been observed. However, the first patient has been diagnosed and treated for tuberculous pneumonia since March 2021.

3. DISCUSSION

Two reported patients suffered from severe anemia with severely reduced to undetected erythroid lineage due to bone marrow aspiration (**Table 1**) and a decreased count of red blood cells in peripheral blood after 3 -4 months after kidney transplantation and did not respond to blood transfusion. The common causes of severe anemia post-transplantation such as acute allograft rejection, iron deficiency, hemolytic anemia, adverse effects of immunosuppressive therapy were screened but not detected based on clinical examination and laboratory tests (**Table 2**). Active HPV B19 DNA level in blood detected by real-time polymerase chain reaction (PCR) helped confirm the diagnosis (**Table 3**). The host cell for human parvovirus B19 is human erythroid progenitor cells [8]. The erythrocyte P antigen is the cell receptor for B19 virus, so the virus binds to the P-antigens on the surface of the progenitor cells of the red blood cell, causing lysis of these susceptible cells and transient loss of all erythrocyte precursors from the bone marrow, which then leads to severe anemia [9]. Infection with HPV B19 virus in kidney transplant recipients is transmitted most via the respiratory route and transplanted kidney [1], although blood-borne transmission following whole blood or factor VIII transfusion has been reported [10].

Moreover, patients with dormant viral infection are susceptible to viral reactivation after transplantation. One study found that 73% of patients with a history of dialysis had antibodies to HPV B19 [11]. Two of our patients were not tested for HPV B19 before transplantation, so it was not known whether these patients were infected with the virus before or after the transplantation. This is an issue of concern for RTR who should be screened for HPV B19 infection before kidney transplantation. Tests for antibodies and DNA of HPV B19 were conducted. IgM antibodies usually appear during acute infection while IgG antibodies indicate a past infection. However, IgM antibodies may not be detected in patients on immunosuppressants, so real-time PCR is important to detect HPV B19 DNA [11],[12],[13]. The results of real–time PCR in two patients indicated active HPV B19 infection (**Table 3**) and helped confirm the diagnosis.

Table 1. Bone marrow exam

Bone marrow exam	Patient 1	Patient 2
Bone marrow aspirate smear	Normochromic anemia Mildly reduced WBC count Normal platelet count	Normochromic anemia Normal WBC count Normal platelet count
Bone marrow aspiration	Average of nucleated cell count Severely reduced erythroid lineage Mildly reduced myeloid, and monocytic linage Normal megakaryocytic lineage Conclusion: Pure red cell aplasia	Average of nucleated cell count Undetected erythroid lineage Normal myeloid, monocytic, and megakaryocytic lineage Conclusion: Pure red cell aplasia

Table 2. Laboratory tests

Tests	Normal range	Patient 1	Patient 2
RBC (x 10^{12} cells/L)	3.8 – 5.5	1.8	1.7
Hb (G/L)	120 - 170	48	44
HCT (%)	38 - 45	16.4	13.9
WBL (x 10^9 cells/L)	4 - 11	4.3	5.3
Platelet (x 10^9/L)	150 - 450	369	297
Coomb's test	Negative	Negative	Negative
EPO (mU/mL)	4-24	376	Not done
Creatinine (mg/dL)	0.8-1.2	1.76	1.22
eGFR (ml)	> 60	46.8	69.5
Ferritin (ng/mL)	20-280	829	632
Transferrin (mg/dL)	204 – 360	133	140
Transferrin saturation (%)	20 – 50	107	84.9

EPO, Erythropoietin; eGFR, estimated glomerular filtration rate; RBC; Red blood cell; Hct, Hematocrit.

Table 3. Microbiology tests

Test	Patient 1	Patient 2
CMV IgM	(-)	(-)
CMV IgG	(-)	(-)
CMV-DNA	20th October 2015: 3.35 x 10^3 6th December 2018: Negative	(-)
EBV IgM	(-)	(-)
EBV IgG	(-)	(-)
BK/JC virus	(-)	(-)

CMV: Cytomegalovirus, EBV: Epstein-Barr virus

Currently, there is no specific antiviral drug available for the treatment of HPV B19 infection. Management of HPV B19 infection is primarily symptomatic and varies with the clinical manifestation. The usual course of parvovirus associated anemia is spontaneous resolution within a few days to weeks [14]. Using IVIG helps shorten the recovery time. In the setting of HPV B19 infection with severe anemia in immunosuppressed patients after kidney transplant blood transfusion, IVIG with reduction of immunosuppression, if possible, may resolve problems [15]. Intravenous immunoglobulin (IVIG) is frequently used to the treat solid organ transplant recipients with symptomatic parvovirus B19 infection [16]. In our patients, after 3 weeks of IVIG therapy combined with adjusting of immunosuppression drugs, their red blood cell count recovered, and blood transfusion was no longer required. However, the virus was not eradicated. A few months later, the virus load increased (**Table 4**), and symptoms of anemia began to reappear. Patients were given a second cycle of IVIG and replacement of tacrolimus with cyclosporine-A [17], the virus load disappeared in the first patient. It decreased below the active level in the second patient, and symptoms of anemia disappeared with hemoglobin level in the normal range.

However, our reported has some limitations; this is the first case report of HPV B19-related PRCA after kidney transplantation in Cho Ray hospital. The delay in progress of

making diagnosis and initiation of the treatment cause severe damage to patient quality of life and a substantial financial burden. Therefore, well-designed research needs to be conducted to develop practicable approaches in diagnosing and managing HPV B19-related PRCA after kidney transplantation.

Table 4. Diagnosis and treatment

		Patient 1	Patient 2
Donor		Living biological father	Living altruistic donor
Post-transplantation anemia		After 3 months	After 4 months
Diagnosis		Parvovirus B19 infection CMV infection	Parvovirus B19 infection
Blood transfusion		20 units	60 units
PCR result	**1st**	3rd June 2016: 1.91 x 10^9 (+ IVIG)	30th June 2016: 5.2 x 10^{10} (+ IVIG)
	2nd	28th June 2016: 9.98 x 10^6	1st August 2016: 4.67 x 10^2
	3rd	18th July 2016: 8.91 x 10^9 (+ IVIG)	22nd December 2016: 2.21 x 10^8
	4th	15th August 2016: 1.9 x 10^3	17th April 2017: 1.95 x 10^9 (+ IVIG)
	5th	3rd May 2017: negative	25th May 2017: 1.07 x 10^4
Intravenous immunoglobulin		IVIG 0.4 g/kg/day x 5 days x 2 cycles	IVIG 0.4g/kg/day x 5 days x 2 cycles
Immunosuppressant adjustment		- Mycophenolate mofetil cessation - Tacrolimus dose reduction and cessation - Cyclosporine and Prednisone commencement	- Tacrolimus cessation - Cyclosporine and Prednisone commencement
Recovery time		9 months	10 months

Conclusion

This case reports highlight the importance of screening for human parvovirus B19 infection prior to kidney transplantation in donors and recipients and in renal transplant recipients with anemia. PCR for HPV B19 should be considered to rule out coinfection. Appropriate adjustment of immunosuppressive drugs along with timely administration of blood transfusion and intravenous immunoglobulin are necessary to improve patient condition.

ETHICS STATEMENT

This study has been approved by the Institutional Review Board at the hospital.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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