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CASE REPORT

Pure red cell aplasia due to parvovirus B19 infection after liver transplantation: A case report and review of the literature

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Abstract

Pure red cell aplasia (PRCA) due to parvovirus B19 (PVB19) infection after solid organ transplantation has been rarely reported and most of the cases were renal transplant recipients. Few have been described after liver transplantation. Moreover, little information on the management of this easily recurring disease is available at present. We describe the first case of a Chinese liver transplant recipient with PVB19-induced PRCA during immunosuppressive therapy. The patient suffered from progressive anemia with the lowest hemoglobin level of 21 g/L. Bone marrow biopsy showed selectively inhibited erythropoiesis with giant pronormoblasts. Detection of PVB19-DNA in serum with quantitative polymerase chain reaction (PCR) revealed a high level of viral load. After 2 courses of intravenous immunoglobulin (IVIG) therapy, bone marrow erythropoiesis recovered with his hemoglobin level increased to 123 g/L. He had a low-level PVB19 load for a 5-mo follow-up period without recurrence of PRCA, and finally the virus was cleared. Our case indicates that clearance of PVB19 by IVIG in transplant recipients might be delayed after recovery of anemia.

Key words: Pure red cell aplasia; Parvovirus B19; Intravenous immunoglobulin; Recurrence; Liver transplantation

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INTRODUCTION

Pure red cell aplasia (PRCA) is a relatively rare disease characterized by the inhibition of bone marrow erythropoiesis with multiple factors involved in its development[1]. Solid organ transplantation-associated PRCA may be attributed to immunosuppressants and parvovirus B19 (PVB19) infection. An increasing number of reports on PRCA caused by PVB19 after renal transplantation are available[2], but there are very few cases describing liver transplant recipients. Furthermore, this severe complication usually responds to high-dose intravenous immunoglobulin (IVIG) therapy with recovery of erythropoiesis, but relapses are common and experience in dealing with this rare and easily recurring disease is insufficient. We describe the first case of a Chinese liver transplant recipient with severe PRCA due to PVB19 infection and show our experience in managing this disease. Accidentally, the patient's blood group was preoperatively identified as Rho (D)-negative that is extremely rare in China and he received a Rho (D)-incompatible liver transplantation, which made the severe anemia embarrassing. We also made a review of the literature and discussed several key points of PVB19-induced PRCA.

CASE REPORT

A 38-year old Chinese man was diagnosed as hepatocellular carcinoma with hepatitis B in a cirrhosis background. The tumor was within 3 cm in diameter without extrahepatic metastasis. Peripheral blood cell counts were all normal. Blood group was A and Rho (D)-negative. In August 2005, he received orthotopic liver transplantation (OLT) from a donor. The donor's blood group was A and Rho (D)-positive. Packed red blood cells transfused intraoperatively were all Rho (D)-negative. The patient recovered uneventfully after the operation, and a triple-immunosuppressant protocol consisting of tacrolimus (FK506), mycophenolate mofetil (MMF) and prednisolone was adopted.

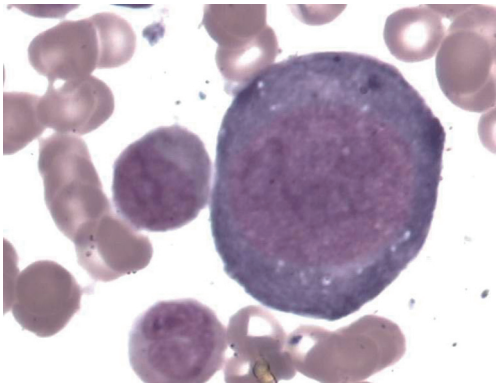

Figure 1 Initial bone marrow aspirate smear showing decreased erythroid precursors and a giant pronormoblast (Wright-Giemsa stain, × 1000).

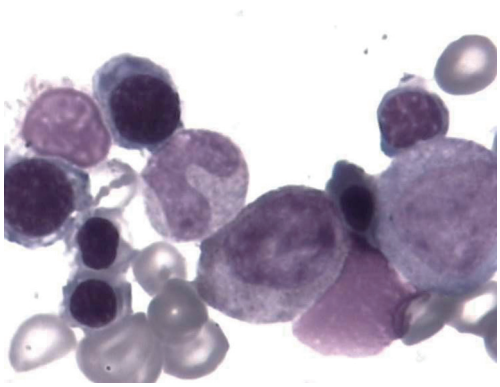

Figure 2 Second bone marrow aspirate smear showing recovery of the bone marrow (Wright-Giemsa stain, × 1000).

Three weeks after transplantation the patient began to suffer from a progressive anemia with a drop of hemoglobin level from 127 g/L and 4.2×10^{12}/L to 49 g/L and 1.69×10^{12}/L in a month, respectively. The hematocrit decreased but the red blood cells kept normocytic and normochromic. The leukocyte and platelet counts were normal. Except for pallor, his physical examination was non-contributory. Laboratory tests revealed a marked reticulocytopenia (11.9×10^9/L, 0.4% of total red blood cells). Stool and urine examination for occult blood and antihuman globulin test were negative. Anti-Rho (D) antibodies and autoimmune markers were undetectable. Studies of serum vitamin B-12, folic acid and iron revealed no abnormality. Titers of hepatitis B virus, Epstein-Barr virus and cytomegalovirus were negative. No evidence of tumor recurrence was found. Administration of recombinant human erythropoietin (rHuEPO) (9000 IU hypodermatic injection every other day) was introduced but the hemoglobin level remained low. For the scarceness and considerable expense of the rare Rho (D)-negative blood, only 10 units of packed red blood cells was transfused. The hemoglobin level just reached around 60 g/L. Bone marrow biopsy in October 2005 revealed selectively decreased erythroid precursors with giant pronormoblasts, establishing the diagnosis of PRCA (Figure 1). There was no evidence of thymoma on radiographic studies. We discontinued MMF and changed tacrolimus to cyclosporine A (CsA) (4 mg/kg per day) with a concentration level between 200 to 265 ng/mL. Two weeks later, he remained severely anemic with the hemoglobin level progressively dropped to 31 g/L. Serum EPO level was elevated (200 mIU/mL, reference 4 to 21 mIU/mL). Detection of PVB19-DNA with quantitative polymerase chain reaction (PCR) revealed a high load of virus (9.73×10^9 genome copies/mL). Then a diagnosis of PRCA caused by PVB19 infection after liver transplantation was made.

Then rHuEPO was discontinued and a course of IVIG therapy (0.4 g/kg per day for 5 d) was performed. Two weeks later, reticulocytosis (161.88×10^9/L, 11.4% of red blood cells) was noted and hemoglobin levels were elevated to 70 g/L with a sharp decline of PVB19-DNA in blood (2.12×10^5 genome copies/mL). The patient's condition gradually improved and became transfusion-independent. However, one month later a remarkable decline of hemoglobin levels (21 g/L) and a large amount of PVB19-DNA in blood emerged again. Another course of IVIG (0.4 g/kg per day for 5 d) was adopted. One month after the second therapy his hemoglobin level rose to 123 g/L and bone marrow biopsy showed a recovery of erythropoiesis (Figure 2). However, PVB19-DNA was still detectable in blood with a lower level (3.47×10^4 genome copies/mL). We kept on monitoring his progress in the outpatient department. He maintained normal hemogram results and still held a low-level viral load (4.26×10^3 genome copies/mL). Finally, PVB19-DNA was undetectable during the fifth-month follow-up. Hemoglobin levels maintained normal until he died of tumor recurrence 17 mo after OLT.

MEDLINE search for English language articles published between 1974 and January 2007 revealed only 7 reports of PVB19 producing PRCA after liver transplantation. Herein, we describe the eighth liver transplant patient. To our knowledge, this is the first reported case associated with liver transplantation in China. The main characteristics of the 8 cases are listed in Table 1.

Four of the 8 patients were children, and 5 of them were male. Their median age at the time of presentation with anemia was 13.7 years (range 1.4 to 43 years). Six patients had tacrolimus-based immunosuppression and 2 had CsA-based immunosuppression. Severe anemia with reticulocytopenia was seen in all cases. The lowest median hemoglobin level was 69.5 g/L (range 21 to 75 g/L). In addition, 2 patients had fever, one with leucopenia, one child with a typical rash of erythema infectiosum and one adult suffering from arthralgia. Bone marrow biopsies were performed on 4 patients and all revealed erythroid hypoplasia with presence of giant pronormoblasts. Four patients were positive for both PVB19-IgM and IgG at the time of evaluation, 2 were IgM positive and IgG negative and one was IgM negative and IgG positive. The patient we report in this paper was not tested for antibodies at the time of diagnosis. Viral DNA detection was made in 4 patients and all showed positive results. All reports could not demonstrate the source and route of virus infection. Except for one report that did not offer the treatment information, the other 7 cases required treatment with

Table 1 Main characteristics of 8 liver transplant recipients with PRCA due to PVB19 infection

Case	1	2	3	4	5	6	7	8
Age when anemia (yr)	1.8	4.7	1.4	1.4	26	43	41	38
Sex	F	F	M	M	F	M	M	M
Immunosuppression	FK	CsA	FK	FK	AZA + FK + Co	AZA + FK	CsA + AZA + Co	FK + MMF + Co
Anemia onset (month after LTx)	2	34	6	8	30	1	11 d	3 wk
Lowest Hb (g/L)	46	73	69	70	33	54	75	21
Reticulocyte count	0	0.40%	0	0.80%	0	0	ND	0.40%
Other manifestation	Erythema infectiosum	None	Fever, stridor, leucopenia	None	Arthralgia	None	Fever	None
Bone marrow biopsy	ND	ND	GP	ND	GP	GP	ND	GP
PVB19 IgM	P	P	P	P	P	P	N	ND
PVB19 IgG	P	P	N	P	P	N	P	ND
PVB19 DNA	ND	ND	ND	ND	P	P	P	P
Treatment	IVIG: 1 g/d × 3 d	IVIG: 0.4 g/kg per day × 10 d, 12 courses	IVIG: 0.4 g/kg per day × 5 d	IVIG: 0.4 g/kg per day × 5 d	IVIG: 0.4 g/kg per day × 10 d, plasmapheresis	IVIG	ND	IVIG: 0.4 g/kg per day × 5 d × 2 courses
Outcome	Hb normalized 4 wk after IVIG	Hb normalized 2 wk after IVIG	Hb normalized 4 wk after IVIG	Hb normalized 2 wk after IVIG	Hb normalized and virus DNA negative 16 wk after plasmapheresis	Hb normalized and virus DNA negative 3 wk after IVIG	ND	Hb normalized 12 wk after IVIG with long-term low-level viral load and virus DNA negative 5 mo after Hb normalization
Reference	[16]	[16]	[16]	[16]	[17]	[18]	[19]	This case

PRCA: pure red cell aplasia; PVB19: parvovirus B19; F: female; M: male; FK: FK506; CsA: cyclosporine A; AZA: azathioprine; MMF: mycophenolate mofetil; Co: corticoteroids; LTx: liver transplantation; Hb: hemoglobin; ND: not determined; GP: giant pronomorblasts; P: positive; N: negative; IVIG: intravenous immunoglobulin.

commercial IVIG. Five patients had good response to the treatment and obtained long-term recovery from anemia, while recurrence of the disease appeared in 2 patients, one recovered after a second course of IVIG therapy, the other needed repeated IVIG infusion combined with plasmapheresis. Of the 4 patients detected for viral DNA, PVB19 viremia was successfully resolved in 2 patents after the treatment. Unlike the previous cases, our case had a persistent low viral load without recurrence of PRCA for a 5-mo follow-up period.

DISCUSSION

PRCA can be inherited as a primary hematologic disorder or occurs secondary to autoimmune diseases, thymoma, hematologic malignancies, chronic hemolytic anemia, exposure to a variety of drugs and toxins, various infections, ABO-incompatible bone marrow or stem cell transplantation and anti-EPO antibodies[1]. The pathogenesis of PRCA remains unclear and the pathophysiology is heterogeneous due to various causes. Acquired PRCA associated with solid organ transplantation rarely occurs and may be caused by immunosuppressants and PVB19 infection. Such immunosuppressants include azathioprine[3], MMF[4] and tacrolimus[5], except for CsA. Such a diagnosis was not considered because this patient did not respond to discontinuation of MMF and replacement of tacrolimus by CsA.

PVB19 is a small, non-enveloped and single-stranded DNA virus[6]. The virus is widespread, and manifestations of its infection vary with the immunologic status of the host[7]. In immunocompetent hosts, PVB19 can cause erythema infectiosum (fifth disease) in children and acute symmetric polyarthropathy in adults. Infection in such patients results in a relatively short period of viremia followed by the production of specific antibodies, IgM class first and IgG class several days later, and clearance of virus. In contrast, immunocompromised hosts are unable to produce an effective antibody response to the virus and persistent PVB19 infection is manifested as PRCA. The pathogenesis may be due to its tropism and direct cytotoxicity to erythroid progenitor cells[8]. Diagnosis is made upon bone marrow biopsy, antibodies screening and viral DNA detection using PCR tests[9].

IVIG therapy can terminate post-transplant PRCA due to PVB19 infection[10]. Commercial IVIG is a good source of neutralizing antibodies against the virus and high-dose IVIG has been proven to be of great value in curing the disease[10]. It is based on the fact that the virus is a global and common infectious pathogen in humans and the prevalence of IgG antibodies against it ranges from 30% to 60% in adults and more than 85% in the elderly population[8]. The amount and duration of IVIG therapy are dependent on the response of patients. The most adopted dose is 0.4 g/kg per day for 5 d or 1 g/kg per day for 2 to 3 d[8]. This regimen has been very often curative with clearance of virus accompanied with marked reticulocytosis and rise in hemoglobin. However, immunosuppressed transplant patients are unable to produce persistent and efficient antibodies to the virus

and the inadequate clearance of virus after cessation of IVIG may easily induce recurrence. Geetha[11] identified a 10% recurrence rate in 22 cases of PRCA due to PVB19 infection in transplant recipients treated with IVIG through reviewing the literature. Recurrence of viraemia and anemia may require repeated courses of IVIG infusion.

The patient we described here was faced with the same situation and the relapse of PRCA was successfully cured after a repeated course of IVIG without any maintenance therapy. However, unlike the previous cases he maintained a long-term low-level viremia without recurrence of PRCA during the 5-mo follow-up period. For all the literature offered sparse information on alteration of viral DNA during the period of recovery, little is known about the viral clearance after treatment. Our results indicate that the clearance of PVB19 by IVIG therapy in immunosuppressed transplant recipients might be delayed for a relatively long period after the reversion of anemia. We therefore recommend that it would seem more reasonable to simply follow the serial monitoring of viral DNA and hemoglobin levels instead of preventative maintenance therapy with high-dose IVIG in such patients. Re-administration of IVIG would be considered if increase of viral load or drop of hemoglobin levels was observed.

In addition, it is notable that some side effects of high-dose IVIG infusion, such as fever, headache, myalgia, hypertension and acute renal failure, have been reported in some patients receiving IVIG therapy[12]. Furthermore, IVIG has been reported to be contaminated by PVB19 and might be a source of infection[13]. All these reports may raise important questions concerning the safety of IVIG therapy. Though such effects were absent in the 8 liver transplant recipients, attention is needed when we perform the therapy.

No proven specific strategy for preventing PVB19 infection is available. Transmission of the virus infection may occur through the respiratory tract, blood-derived products[8] and donated organs containing the virus[10]. Accordingly, avoiding PVB19 exposure to patients, virus screening of blood products before transfusion and testing organ donors prior to transplantation may be considered as preventive strategies. Since transmission via blood products is rare, universal blood screening is not recommended, though the risk of PVB19 infection is of great concern for blood and blood product suppliers[14]. Strategies for reducing the viral load in the manufacture plasma pool by discarding PVB19-DNA-positive donations and developing new strong virus inactivation methods are recommended to these suppliers. Finally, PVB19 vaccines are being explored[15]. Results achieved appear promising, and following researches are on the way.

In conclusion, liver transplant recipients are also at risk of developing PRCA due to PVB19 infection after transplantation. PRCA can be reversed by IVIG therapy but easily recurs. Little is known about the host-pathogen interaction after therapy which is related to recurrence. Our case signifies that clearance of PVB19 by IVIG infusion in transplant recipients might be delayed for a relatively long time after recovery of anemia. Further researches are needed to find out most effective modalities of therapy and preventative strategies.

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