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American Journal of Transplantation 2008; 8: 1340–1344
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2008.02244.x

Case Report

Postrenal Transplant Hemophagocytic Lymphohistiocytosis and Thrombotic Microangiopathy Associated with Parvovirus B19 Infection

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Persistent anemia is a known consequence of Parvovirus B19 (B19) infection following renal transplantation. However, to date, no description of B19-related hemophagocytic lymphohistiocytosis (HLH) exists in renal transplant recipients. We report a 24-year-old male kidney recipient, who presented with fever, severe anemia and allograft dysfunction two years following transplantation. Hyperferritinemia, hypertriglyceridemia, elevated serum lactate dehydrogenase, pancytopenia and fragmented red blood cells on the peripheral blood were also noted. Bone marrow examination revealed giant pronormoblasts and frequent histiocytes with intracellular hematopoietic elements, consistent with HLH. Renal allograft biopsy revealed closure of the lumen of glomerular capillaries and thickening of the capillary walls compatible with thrombotic microangiopathy. The presence of anti-B19 IgM antibody and viral DNA in the patient's serum (detected by real-time PCR) confirmed an acute B19 infection. Following high-dose intravenous immunoglobulin therapy, the anemia gradually resolved and renal function improved. As far as we know, this is the first report of B19-associated HLH and thrombotic microangiopathy in a renal transplant recipient.

Key words: Hemophagocytic lymphohistiocytosis, intravenous immunoglobulin, Parvovirus B19, renal transplantation, thrombotic microangiopathy

Received 04 January 2008, revised 25 February 2008 and accepted for publication 12 March 2008

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a heterogeneous clinicopathological entity associated with uncontrolled and ineffective immune activation leading to cellular damage and multiorgan dysfunction as well as excessive activation of the benign macrophages in the bone marrow, spleen and lymph nodes (1,2). The activated macrophages then transform into histiocytes phagocytizing erythrocytes, leukocytes, platelets and their precursor cells leading to various degrees of cytopenia, hepatosplenomegaly and lymphadenopathy. Excessive production of different cytokines including tumor necrosis factor (TNF)-alpha, interleukin-6, interleukin-8 and interferon-gamma are implicated in the pathogenesis of HLH (2). HLH can develop in patients with hereditary immune dysfunction, infections, neoplastic or autoimmune diseases (1). A familial form of HLH does also exist. The presence of hemophagocytosis in the bone marrow, spleen or lymph nodes, elevated serum lactic dehydrogenase (LDH >1000 IU/L), hyperferritinemia (>500 ng/mL), hypertriglyceridemia (>3 mmol/L), hypofibrinogenemia (<1.5 g/L), low or absent natural killer cell cytotoxicity, elevated soluble IL-2 receptor (>2400 U/mL), cytopenia affecting at least two cell lineages (platelets <100 000/μL or neutrophils <1000/μL) are suggestive of this entity (1–4).

Parvovirus B19 (B19) is the only member of the family *Parvoviridae*. Infection with B19 is a known cause of erythema infectiosum, polyarthropathy syndromes, erythroid hypoplasia and aplastic anemia in healthy individuals (5). In renal transplant recipients, B19 infection may enter the body via the respiratory tree or transplanted organ, or may be reactivated from a latent infection (6). This infection is associated with refractory and recurrent anemia, glumerulopathy, proteinuria, microscopic vasculitis, thrombotic microangiopathy (TMA), hepatitis and severe encephalitis in renal transplant recipients (7–13). Herein, we report a renal transplant recipient with severe anemia, allograft dysfunction, TMA and HLH two years following transplantation. Acute B19 infection was ascertained by positive anti-B19 IgM titer and the presence of high-serum viral load. To the best of our knowledge, this is the first report of B19-associated HLH in a renal transplant recipient.

Case Report

In April 2007, a 24-year-old male was admitted for a three-week onset of fever and severe anemia. The patient had received a living, unrelated renal transplantation two years previously and was on triple immunosuppressive therapy including cyclosporine (200 mg/day), mycophenolate mofetile (2 gm/day) and prednisolone (5 mg/day). The baseline blood cyclosporine level was 280 ng/mL, and the serum creatinine level was 1.2 mg/dL. His past medical history revealed the onset of postrenal transplant diabetes mellitus three months earlier after which the patient had received insulin. At that time, his hemoglobin level was 17.5 g/dL. The family history was unrevealing.

On physical examination, blood pressure was 100/60 mmHg and body temperature was 38°C. The patient was alert and oriented. No rash or icter was noted. Hepatosplenomegaly or lymphadenopathy was not found. The physical examination was otherwise unremarkable. On admission laboratory findings are summarized in Table 1. There was a normochromic-normocytic anemia. The patient received packed red blood cell infusion. Serum ferritin, LDH and fasting triglyceride levels were elevated. Serum creatinine level was 3 mg/dL. A urine dipstick test revealed moderate proteinuria. A 24-hour urine volume was 2200 mL with a urine protein-to-creatinine ratio of 0.51. Prothrombin and partial thromboplastin times were within normal limits. Peripheral blood examination revealed frequent helmet cells. Renal allograft Doppler ultrasonography disclosed a normal size renal allograft with normal corticomedullary differentiation and echogenicity. Intra-renal arterial resistive index was within normal limit. Upper gastrointestinal endoscopy was unrevealing. The platelet and white blood cell count nadirs were 39 000/μL and 2400/μL (53% polymorphonuclear cells) at days 5–7 of admission.

Table 1: On admission laboratory findings in the present patient

	Level	Normal range (for male)
Hemoglobin (g/dL)	5.5	13–18
White blood cell count (μL^{-})	5200	3600–11 200
Platelet count (μL^{-})	120 000	140 000–440 000
Mean corpuscular volume (fL)	94	74–96
Mean corpuscular hemoglobin (pg)	30	28–32
Mean corpuscular hemoglobin concentration (g/dL)	31.8	30–36
Serum ferritin (ng/mL)	> 800	12–300
Fasting triglyceride (mg/dL)	372 (or 4.2 mmol/L)	<265 (or <3 mmol/L)
Lactate dehydrogenase (U/L)	3124	90–250
Alanine aminotransferase (U/L)	113	10–55
Aspartate aminotransferase (U/L)	132	10–40
Total cholesterol (mg/dL)	185	<200
Fasting blood sugar (mg/dL)	82	<100
Serum cyclosporine (ng/L)	195	-

Serological studies for Epstein-Bar virus (EBV), hepatitis B, C and E and human immunodeficiency virus (HIV) were negative. Hepatitis B surface antigen was negative. Anti-hepatitis A IgM antibody was negative and IgG antibody was positive, consistent with previous infection. A negative anticytomegalovirus IgM and positive IgG titer were also detected (anti-CMV IgG also was positive before transplantation). Serological tests for parovirus B-19 infection were performed (using enzyme-linked immunosorbent assay; DRG instruments, GmbH, Germany), which was positive for anti-B19 IgM antibody. Subsequently, B19 viral DNA was detected in the serum by nested polymerase chain reaction (PCR) using the major capsid protein (VP2)-encoding sequence of B19 as described by Cassinotti et al. (14). The real-time PCR (with Artus RealArt™ Parvo B19 LC PCR kit) revealed a viral load higher than 10^4 IU/L.

Bone marrow aspiration and biopsy disclosed erythroid immaturity with a left shift and occasional giant pronormoblasts with dark-blue cytoplasm (Figure 1). Myeloid and megakaryocytic linages were normal in appearance. Numerous large histiocytes with engulfed lymphocyte, polymorphonuclear and red blood cells were prominent, which

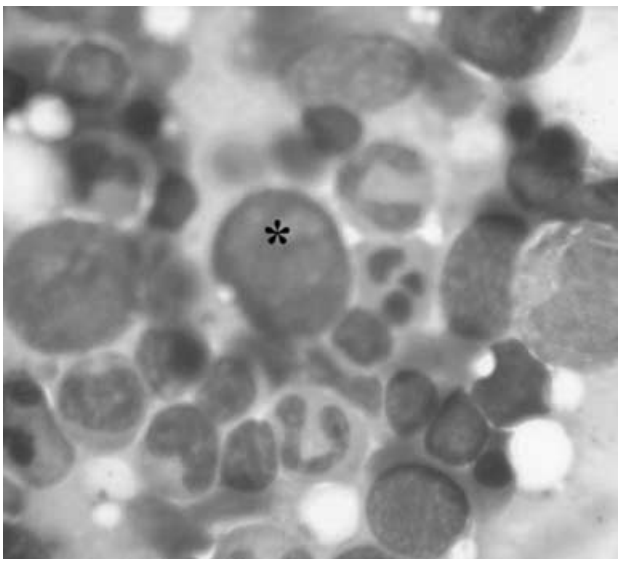

Figure 1: Bone marrow containing giant pronormoblasts (star) with dark-blue cytoplasm (Giemsa, 1000×).

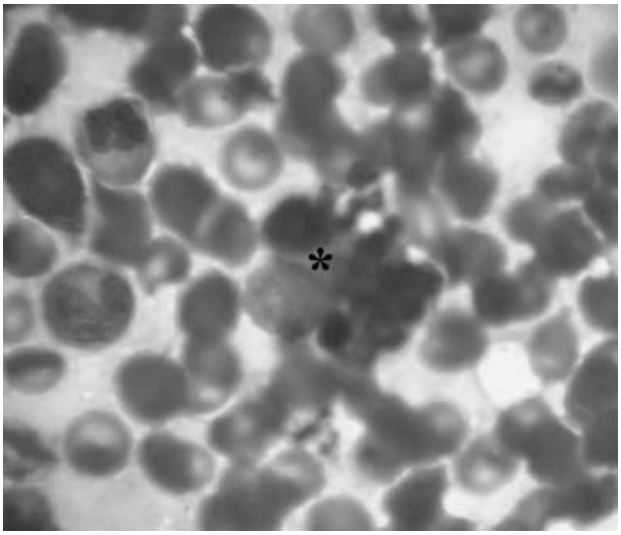

Figure 2: Bone marrow histiocyte (star) with intracellular hematopoietic elements (Giemsa, 1000×).

were suggestive of hemophagocytosis (Figure 2). A percutaneous renal allograft needle biopsy was performed at day 3 of admission. Light microscopic examination of renal biopsy specimens (Figure 3) revealed the luminal narrowing of glomerular capillaries, thickening of glomerular capillary walls and duplication of the glomerular basement membrane, endothelial swelling and some areas of capillary loop closure, all of which were compatible with subacute glomerular involvement due to thrombotic microangiopathy.

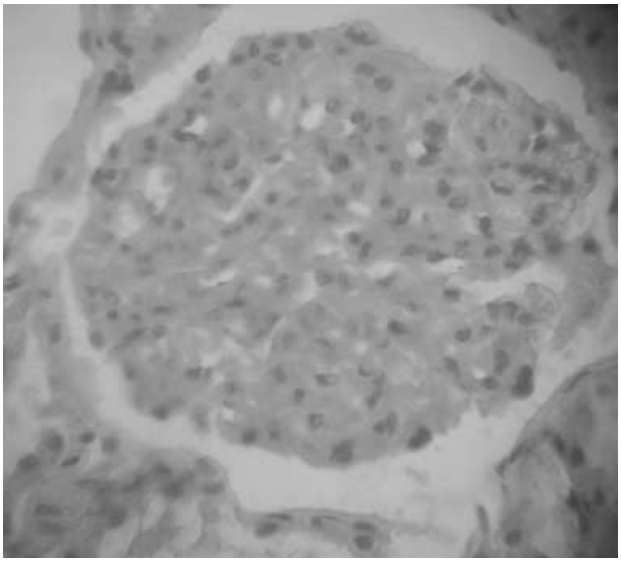

Figure 3: Glumerulus showing closed capillary lumens, thickening of capillary walls and duplication of the glomerular basement membrane.

Subsequently, high-dose intravenous immunoglobulin (IVIG, 400 mg/kg/day for five days) was administered at day 8 of admission. The prescribed dose of mycophenolate mofetil was reduced to 1 gm/day. The patient's general condition gradually improved and his fever subsided. On day 20 of admission, the patient's serum creatinine declined to 2 mg/dL and hemoglobin level increased to 9.5 mg/dL. On a follow-up visit, three months following discharge, hemoglobin was 14 g/dL, WBC count 9000/μL and platelet count 234 000/μL. Serum creatinine level was 1.2 mg/dL. Serological studies revealed a positive anti-B19 IgG and negative IgM titers. A 2 g/day dose of MMF dosage was restarted and the patient was scheduled to have regular follow-up visits.

Discussion

In the present case, the diagnosis of HLH was made by the suggestive bone marrow and laboratory findings (2,15,16). Elevated serum ferritin, hypertriglyceridemia, severe anemia and decreased platelet count were also compatible with HLH (1,3). The diagnosis of B19 infection was primarily obtained by the presence of anti-B19 IgM antibodies and viral DNA in the patient's serum. Additionally, the presence of fragmented red blood cells in the peripheral blood, hemolysis and renal histopathology were consistent with TMA. The temporal association of HLH, TMA and positive B19 serology and PCR led us to attribute the present scenario to an acute B19 infection.

The natural history and outcome of infection-associated HLH may depend on the inciting pathogen. EBV is the most common triggering agent (2). In a series of 219 children with infection-associated HLH, EBV infection was associated with a higher mortality (17). Usually treatment of the triggering infections is ineffective and severe cases may require chemotherapy and bone marrow transplant (2). Cytomegalovirus has been described as a cause of HLH in transplant recipients and is associated with a poor outcome (2,18). However, recovery has been reported following specific anticytomegalovirus therapy (19). HLH due to B19 infection carries a better prognosis compared with other virus-associated HLH and most patients with this complication may survive without specific therapy (2). The most common underlying disease in B19 related HLH is hereditary spherocytosis (2).

Since the first report of B19 associated HLH (20), few similar cases have been described (21–24). To date about 30 such cases have been reported in children and adults. None of these has occurred following kidney transplantation. In a series of 17 renal transplant recipients with HLH, nine patients had viral infection with cytomegalovirus, Epstein-Barr virus and human herpesvirus 6 and 8, while no case of B19 infection was reported (25). Infections with BK virus, Mycobacterium tuberculosis, Toxoplasma, Escherichia coli, Bartonella henselae and Pneumocystis

carinii have also been reported as the cause of HLH following renal transplantation (25–28). Hence, performing an extensive workup for the infectious causes of HLH is necessary as some infections can trigger HLH and the management is different depending on the case.

In the present patient, renal allograft histopathology was compatible with TMA. This type of B19-related glomerulopathy has been reported by Murer et al. (7). Collapsing glomerulopathy, minimal change disease and TMA with nephrotic syndrome have been described in a small series of HLH patients (29). It has been proposed that in HLH, high levels of inflammatory cytokines particularly TNF-alpha can injure podocytes leading to glomerular collapse and tubular necrosis with subsequent proteinuria and renal dysfunction (29–31). In the present patient, anemia, proteinuria and renal allograft function improved with high-dose IVIG therapy. The efficacy of high-dose IVIG in the eradication of postrenal transplant B19 infection has been demonstrated previously (9,32). Positive seroconversion and long-term remission of recurrent anemia with IVIG therapy has been reported in a renal transplant recipient despite persistence of viral genome (33). Nonetheless, in a series of 13 renal transplant recipients with HLH, complete recovery was obtained in those received high-dose IVIG therapy (26).

Finally, diagnosis of B19 infection requires a high index of suspicion. Clinicians should consider this infection as a potential cause of HLH and TMA in renal transplant recipients.

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