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BRIEF COMMUNICATION

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Parvovirus B19-induced severe anemia in heart transplant recipients: Case report and review of the literature

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Abstract

We report a case of a 64-year-old woman who developed transfusion-dependent anemia after cardiac transplantation, the etiology of which was unknown after initial comprehensive evaluation. At the suggestion of the Transplant Infectious Diseases consultant, microbial agents with red blood cell tropism pertinent to this patient such as Parvovirus B 19 (B19V) were investigated. The B19V viral load by PCR in peripheral blood was >100 000 000 copies/ml and after treatment with intravenous immunoglobulin (IVIG), her anemia resolved. Here, we summarize the clinical and virologic characteristics, treatment, and outcome of fifteen cases of B19V-induced anemia in heart transplant recipients. Spontaneous recovery from anemia secondary to B19V has also been reported in some heart transplant recipients, possibly due to an absence of their B19V P-antigen receptor and/or reduction in their immunosuppression. Therefore, in heart transplant patients, B19V should be suspected early as a cause of severe anemia of unknown etiology. The extent that B19V-induced anemia is underdiagnosed in heart transplant recipients is unknown.

KEYWORDS
anemia, heart transplantation, intravenous immunoglobulin, Parvovirus B19

1 | INTRODUCTION

Parvoviridae (*Parvum*: Latin for small) are among the smallest known DNA-containing viruses that infect humans. Parvovirus B19 (B19V) is classified as a member of the *Erythroparvovirus* genus given its unique ability to infect red blood cells. B19V was observed initially as a small particle in serum in 1974 but was officially recognized as a member of the parvoviridae family in 1985.[1] The association of B19V with significant clinical disease was first made in 1981 as a cause of transient aplastic crisis in patients with sickle cell anemia. B19V was subsequently recognized as the etiologic agent of a wide variety of disease manifestations depending on the immunologic and

hematologic status of the host. In the immunocompetent host, B19V causes erythema infectiosum (EI), migratory polyarthropathy, papular-purpuric "gloves and socks" syndrome (PPGSS) and congenital infection resulting in fetal loss, hydrops fetalis, and neonatal anemia. In immunocompromised patients or those with underlying hemolytic anemias, transient pure red cell aplastic crises have been described.[1] In addition, persistent B19V viremia associated with severe transfusion-dependent anemia in immunocompromised patients was recognized in the late 1980s.[2] B19V-induced anemia has been related to the virus particular tropism for erythrocytes partially mediated by the P antigen present in human erythroid progenitor cells.[3] However, the definitive entry of B19V into red blood cells requires the presence of two co-receptors in addition to the P antigen.[4,5] In solid organ transplant (SOT) patients including heart recipients, only few cases of B19V induced anemia have been reported.[6] Although the etiology of anemia in heart transplant patients is multifactorial, B19V should be considered in any patient with persistently low hemoglobin, particularly below 8 g/dL and without an obvious etiology.

We report a case of a 64-year-old woman with a history of heart transplantation 5 years prior who presented to clinic complaining of severe fatigue. She was found to be severely anemic, work up was notable for B19V viremia and treatment with intravenous immunoglobulin (IVIG) led to her full recovery. We also reviewed the literature on published cases of B19V-induced anemia in heart transplant recipients and their outcome after treatment.

2 | CASE REPORT

A 64-year-old woman underwent heart transplantation in 2012 for giant cell myocarditis. Her post-transplantation course was complicated by recurrent antibody-mediated rejection (AMR) and new donor-specific antibodies (DSA) in 2014 that was treated with plasmapheresis and rituximab followed by monthly intravenous immunoglobulin (IVIG) until May 2015. Later, she also developed mild cardiac allograft vasculopathy (CAV), prompting the conversion of her immunosuppression from tacrolimus and mycophenolate mofetil to tacrolimus and everolimus. Follow-up surveillance did not show evidence of rejection, until a biopsy in November 2015 revealed asymptomatic AMR (pAMR2). However, because absence of donor-specific antibodies (DSA) and normal graft function, the decision was made not to treat. In her follow-up visit of June 2017, she was seen in the cardiac transplant clinic and reported 1 month of severe fatigue associated with intermittent palpitations, several episodes of loose stools per day, nausea, and emesis. She did not report melena, hematochezia, vaginal bleeding, sick contacts, or weight loss. Her occult blood test was negative. She was seen again in clinic with symptoms of fatigue in July 2017, for which she was admitted and evaluated for unexplained anemia of 9.3 g/dL without evidence of overt blood loss. She previously had a normal colonoscopy and an upper endoscopy that revealed Barrett's esophagus without dysplasia. Laboratory testing revealed a white blood cell count (WBC) of 3.3×10^9 cells per liter and a platelet count of 146×10^9 per liter. Iron storage studies did not support the possibility of iron-deficiency anemia, iron total = 221 μg/dL (normal range: 20-160 μg/dL); total iron binding capacity (TIBC) = 343 (normal range: 200-450 μg/dL); ferritin = 363.9 (normal range: 5-114 ng/mL); transferrin saturation = 64% (normal range: 20%-60%). Renal function testing revealed serum creatinine at baseline (0.9 mg/dL) and tacrolimus serum levels were in therapeutic range. PCR testing was negative in peripheral blood for CMV and EBV and negative in stool for a multiplex gastrointestinal panel (FilmArray™ Gastrointestinal panel) and *Clostridium difficile*. She also had a normal thyroid function test and a negative DSA. Blood cultures were reported no growth at 5-days of incubation. Incidentally, her endomyocardial biopsy showed evidence of AMR (pAMR2) without hemodynamic compromise. Finally, following recommendations from the Transplant Infectious Diseases consultant, a peripheral blood quantitative PCR detected Parvovirus B19 DNA at >100 000 000 (>one-hundred million) copies/mL. Treatment was started with IVIG given at 1 g/kg for 3 days, in addition to plasmapheresis for AMR. After therapy, she experienced significant improvement of her fatigue and by (November 2017) her hemoglobin normalized to 12.8 g/dL. At her last follow-up in May 2018, she reported a considerable improvement in her daily activities, such as tolerating short periods of exercise (walking) without chest pain or episodes of palpitation. Follow-up testing has revealed normal red blood cell counts (RBC = 4.24×10^6/μL, normal range $3.80\text{-}5.20 \times 10^6$/μL; MCV = 92.2), hemoglobin concentration (12.3 g/dL), and undetectable B19V by PCR (<100 copies/mL).

3 | REVIEW OF THE LITERATURE

A search for case-reports in English language medical literature via PubMed and ScienceDirect with the following <Mesh> terms: "heart transplant," "heart transplantation," "anemia," "refractory anemia," and "parvovirus B19" was performed. The first case of anemia secondary to B19V in a heart transplant patient was reported in 1993.[6] Since then only 15 additional heart transplant patients (including this case report) have been reported to have developed anemia, including transfusion-dependent anemia secondary to B19V.[6-19] References from all of the articles were examined for additional cases (Table 1). Clinical characteristics, immunosuppressive regimens, laboratory findings, diagnostic testing, B19V therapy and outcomes, including our case, are presented in Table 1. The mean age (±SD) was 37.2 ± 21.8 years. Fifty percent of the cases were female. The mean hemoglobin level (±SD) before diagnosis was 5.91 ± 1.08 g/dL. In cases, in which information was available, the reticulocyte count was low; anemia was most often transfusion dependent; diagnosis was frequently made by PCR in peripheral blood and/or bone marrow specimens and by immunohistochemistry in bone marrow biopsy; IVIG was given to 11 cases with good outcome in all of them. In three cases, treatment with IVIG was not required. Serologies for B19V IgG

TABLE 1 Reported cases of Parvovirus B19 infection in heart transplant recipients (1993-2018)

ID	Reference	Age (y)/Sex	Immuno-suppressive therapy	Type of anemia	Reticulocyte count	Hgb before diagnosis	Transfusion-dependent anemia	Parvo B19 PCR	Parvo B19 IgG and IgM	Therapy	Outcome
1	Nour et al[6]	1.8/F	TAC	N/A	0%	5.4 g/dL	N/A	N/A	N/A	No treatment	Good
2	Bergen et al[7]	53/F	CSA, PRED, AZA, MTX	N/A	0%	6.5 g/dl	Yes	Positive IHC and PCR in peripheral blood	N/A IgG and Positive IgM	IVIG 400 mg/kg for 5 d	Good
3	Thio et al[8]	10/F	CSA, MTX, PRED	N/A	N/A	5.5 g/dL	N/A	Positive PCR in peripheral blood	Negative IgG and Negative IgM	IVIG 400 mg/kg for 5 d	Good
4	Wicki et al[9]	29/M	CSA, AZA, PRED	N/A	N/A	4.8 g/dL	N/A	Positive PCR in peripheral blood	Positive IgG and Positive IgM	IVIG 400 mg/kg for 5 d	Good
5	Amiot et al[10]	61/M	CSA, MTX, PRED	N/A	Non-detect-able	5 g/dL	Yes	Positive PCR in peripheral blood and Bone marrow	Negative IgG and Negative IgM	No treatment	Good
6	Bisognano et al[11]	55/M	CSA, MMF, PRED	N/A	1.40%	7.2 g/dL	No	Not done	Negative IgG and Positive IgM	No treatment	Good
7	Lower et al[12]	57/F	TAC, MMF, PRED	N/A	"Low"	5.9 g/dL	Yes	Positive IHC in bone marrow	Positive IgG and Equivocal IgM	IVIG 30 000 mg/d for 5 d	Good
8	Eid et al[13]	34/M	N/A	N/A	N/A	6 g/dL	N/A	Positive IHC and PCR in peripheral blood	Negative IgG and Negative IgM	IVIG 1000 mg/kg for 2 d	Good
9	Fong et al[14]	29/F	"High-dose immunosupp-ression"	Normochromic Normocytic	0.04%	7.7 g/dL	N/A	Positive IHC and PCR in Bone marrow	Negative IgG and Negative IgM	IVIG 1000 mg/kg followed by IVIG 400 mg/kg every 4 wk	Good
10	Bansal et al[15]	12/F	TAC, SIR, PRED	N/A	<0.5%	3.2 g/dL	Yes	Positive PCR in peripheral blood > 10 billion DNA copies/mL	Negative IgG and positive IgM	IVIG 1000 mg/kg followed by IVIG every 2-3 wk	Good
11	Kelleher et al[16]	11/M	TAC, MF, PRED	Normochromic Normocytic	Low	5.6 g/dL	Yes	Positive PCR in peripheral blood	N/A	IVIG 1000 mg/kg every 2 wk for 2 mo	Good
12	Invernizzi et al[17]	46/M	N/A	Normochromic Normocytic	Low	6.7 g/dL	N/A	Positive IHC and PCR in Bone marrow	N/A IgG and Positive IgM	High-dose IVIG	Good
13	Sadigh and Frank[18]	66/M	TAC, MMF, PRED	N/A	0.20%	6.6 g/dL	Yes	Positive PCR in peripheral blood	Negative IgG and positive IgM	IVIG	Good
14	Shao et al[19]	30/M	N/A	N/A	N/A	6.3 g/dL	Yes	Positive pericardial fluid PCR and PCR peripheral blood	Negative IgG and positive IgM	IVIG for 2 d, every 4 wk for 8 mo	Good
15	Pinto et al (This article)	64/F	TAC, EVE, PRED	Microcytic	1.16%	6.3 g/dL	Yes	Positive PCR in peripheral blood > 100 million DNA copies/mL	N/A	IVIG 1000 mg/kg/d every day for 3 d	Good

AZA, azathioprine; CSA, cyclosporine; EVE, everolimus; HgB, hemoglobin; IHC, immunohistochemistry; MMF, mycophenolate mofetil; MTX, methotrexate; PCR, polymerase chain reaction; PRED, prednisone; SIR, sirolimus; TAC, tacrolimus.

and IgM were performed in 11 cases, B19V IgM was positive in six cases, suggesting acute infection.

4 | DISCUSSION

Heart transplantation is the gold standard treatment for end-stage heart disease refractory to medical therapy, with a median survival of more than 12 years.[20,21] Advancements in the fields of organ transplantation surgical techniques, immunosuppression, molecular diagnostics, and antimicrobial prophylaxis have transformed heart transplantation from what was once considered an experimental intervention to routine treatment. Following heart transplantation, anemia is frequent, with a reported prevalence anywhere between 0% and 91.6%, likely due to widely variable definitions of anemia.[22]

The etiology of post-heart transplant anemia is multifactorial and includes medications (eg, those used as immunosuppressive and antimicrobial prophylaxis), perioperative bleeding, decrease in intestinal absorption of vitamins (eg, folic acid, vitamin B12), renal failure with low levels of erythropoietin (EPO), and elevated levels of hepcidin associated with inflammation and decreased iron availability.[23] Furthermore, organisms with red blood cell tropism (eg, Parvovirus B19, *Babesia microti*, *Plasmodium* spp) can also significantly contribute to anemia. Patients with babesiosis or malaria should be suspected based on their travel history. However, anemia associated with B19V may be easily overlooked since the epidemiologic risk factor may not be obvious in SOT recipients similar to our patient's case. In this case, a 64-year-old heart transplant patient with no evidence of blood loss, hemolysis, or vitamin deficiency (folic acid, B12), developed refractory and transfusion-dependent anemia. A search for the etiology of her severe anemia revealed a positive PCR with more than 100 000 000 viral copies of B19V. Treatment with IVIG infusions over several days was successful to return her hemoglobin levels to baseline.

B19V depends on the surface P-antigen receptor for cellular entry. However, it appears that for complete cellular invasion, two additional co-receptors (α5 β1 integrin and Ku80) are required.[4,24,25] The P-antigen receptor is primarily found in erythroid progenitor cells often leading to hematological complications in healthy individuals and immunocompromised patients including transient aplastic crisis, red cell aplasia, or transfusion-dependent anemia.

There is no specific method for viral isolation from clinical specimens. Thus, the diagnosis of the disease primarily relies on the detection of IgM and IgG antibodies and of viral DNA PCR. During primary infection, B19V DNA is detectable at high titers (>10^9 IU/mL) for two to 4 days, then drops to between 10^2 and 10^4 IU/mL, and usually disappears by day 14, when an appropriate humoral immune response fully develops. In immunocompetent individuals, the diagnosis relies on the serological detection of Parvovirus B19 IgG and IgM. However, in immunocompromised patients, an antibody response is often lacking. Thus, diagnosis of the B19 infection in immunocompromised patients requires the detection of B19V DNA by quantitative PCR in peripheral blood, blood marrow sample, or biopsy-tissue specimens.

The majority of individuals with transfusion-dependent anemia secondary to B19V post-heart transplantation initially report fatigue and malaise.[13] Hemoglobin levels below 8 g/dL were reported in all cases (Table 1). Half of the patients presented with anemia refractory to multiple blood transfusions that, upon diagnosis of BV19 infection and treatment with IVIG, led to resolution of the anemia. Notably, in three cases, spontaneous recovery of B19V-induced anemia occurred after epoetin alfa, iron supplementation, and blood transfusions. It is possible that in these three patients, lack of the P-antigen receptor ("phenotype p" blood type) played a role in their ability to recover spontaneously. Individuals with "phenotype p" have been studied since its discovery in 1951. In the absence of the P receptor, B19V ceases its ability to hemagglutinate erythrocytes. Therefore, it has been hypothesized that people with this variation could be naturally immune to B19V.[26]

In heart transplant recipients who present with severe anemia of unknown etiology, the presence of B19V infection should be sought by PCR testing in serum or bone marrow biopsy immunohistochemistry (IHC). B19V serologies are less helpful, but positive B19V IgM can aid to the diagnosis. In patients with B19V-induced anemia, treatment with IVIG is associated with favorable outcomes. If possible, reduction in the patient's overall immunosuppressive state should be considered to allow for the patient's own immune response to control B19V replication. After treatment, periodic B19V monitoring may also be warranted as relapses can occur several months after completion of treatment if complete eradication of B19V viremia was not initially achieved.

Anemia associated with B19V in heart transplant recipients can lead to significant morbidity and it is likely to be significantly overlooked and underdiagnosed. B19V should be diligently sought as the cause of unexplained anemia in heart transplant patients.

CONFLICT OF INTEREST

The authors have no conflicts of interest or funding to disclose.

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