Parvovirus B19 Infection after Transplantation: A Review of 98 Cases

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Background. Infections with parvovirus B19 (PVB19) can cause significant morbidity in transplant recipients.

Methods. To characterize the epidemiology and clinical spectrum of posttransplant PVB19 infection, we reviewed all cases at our institution during a 16-year period, summarized the data from 91 cases published in the medical literature, and performed longitudinal molecular surveillance for PVB19 DNAemia among 47 solid organ and hematopoietic stem cell transplant recipients.

Results. The median time to onset of PVB19 disease was 7 weeks after transplantation. Anemia, leukopenia, and thrombocytopenia were present in 98.8%, 37.5%, and 21.0% of patients, respectively. Hepatitis, myocarditis, and pneumonitis were also reported in association with PVB19 disease. Allograft tissue loss or dysfunction was observed at the time of PVB19 disease in 10% of cases. At the onset of disease, PVB19 IgM serological test results were negative in 29% of cases. Almost all patients (96%) with anti-PVB19 IgM had a positive PVB19 polymerase chain reaction assay result. Intravenous immunoglobulin was the most commonly used treatment modality. Three of 98 patients died of myocarditis and cardiogenic shock associated with PVB19 disease. Molecular surveillance throughout the first year after transplantation did not reveal PVB19 DNAemia in 47 anemic solid organ and hematopoietic stem cell transplant patients.

Conclusions. PVB19 is a rare but clinically significant infection that manifests as refractory anemia during the posttransplantation period. The use of polymerase chain reaction for diagnosis is particularly helpful in immunosuppressed transplant patients who may fail to mount antibodies against PVB19 during active infection.

Parvovirus B19 (PVB19) is a single-stranded DNA virus that infects the majority of humans [1]. Seroepidemiologic studies demonstrate that 60%–90% of adults have antibodies against PVB19 [2]. Classically, primary PVB19 infection, which occurs most commonly in children, manifests as erythema infectiosum [3]. In adults, primary PVB19 infection may manifest as arthropathy [4], and infection during pregnancy can lead to hydrops fetalis [5]. PVB19 has a propensity to infect erythroid progenitor cells and leads to severe anemia in individuals with hemolytic disorders [6].

The first report of PVB19 infection after transplantation was published in 1986 [7]. Since then, numerous cases of PVB19 infections after solid-organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) have been reported. Anemia is the predominant clinical manifestation. However, PVB19 has also been associated with hepatitis, pneumonitis, myocarditis, and allograft dysfunction. Nonetheless, the full spectrum of clinical manifestations of PVB19 infection among transplant recipients is not well characterized.

Only a few studies have assessed the incidence of PVB19 infection among transplant patients. The preponderance of case reports and the relative lack of large case series imply that PVB19 infection is rarely encountered after transplantation. However, recent studies using molecular surveillance have challenged this view by demonstrating PVB19 DNA in the blood of 23%–31% of kidney transplant recipients, particularly those with anemia [8, 9]. Because anemia is a common complication after transplantation, and because PVB19 surveillance is not performed in clinical practice, it is possible that the magnitude of PVB19 infection is underestimated.

To characterize the clinical features of posttransplantation PVB19 infection, we performed 3 lines of clinical investigation. First, we reviewed all cases of
PVB19 infections at Mayo Clinic (Rochester, MN) during a 16-year period, 1990–2005. Second, we reviewed all cases of PVB19 infection after SOT and H SCT in the medical literature. And third, we performed PVB19 infection surveillance using PCR on serially collected blood samples from transplant patients. Collectively, our study suggests that PVB19 is a significant but rare infectious complication of transplantation.

PATIENTS, MATERIALS, AND METHODS

Case definition. PVB19 infection was defined as the detection of PVB19 in clinical samples or as a positive PVB19 IgM serological test result. PVB19 disease was defined as PVB19 infection in the presence of anemia, with clinical symptoms or bone marrow biopsy findings consistent with the diagnosis. Patients were considered to have organ-invasive PVB19 disease if, concomitant with PVB19 infection, organ-specific findings (as indicated by biochemical markers, pathological findings, or radiographic imaging) were present. Organ-invasive PVB19 disease was considered definite, probable, or possible on the basis of the following criteria: (1) detection of PVB19 by PCR or other methodology in tissue specimens, (2) response to PVB19-directed therapy, and (3) absence of other infectious or noninfectious processes that could explain the organ-specific findings. A definite case of organ-invasive PVB19 disease had to satisfy all 3 criteria. A probable case had to satisfy 1 of the first 2 criteria in addition to the third criterion. All other cases reported as organ-invasive disease that did not satisfy the criteria for a definite or probable case were considered possible cases.

Case series. Using the Mayo Clinic Medical Diagnostic Index and Clinical Microbiology Laboratory database, we searched all cases of PVB19 infection among transplant patients from 1990 through 2005. This search yielded 8 cases. One subject was subsequently excluded, because PVB19 infection occurred before transplantation. Thus, 7 cases are presented in this report.

Review of the literature. A search of the English-language medical literature was performed using the PubMed and Medline databases. Secondary references were reviewed. Sixty-one publications describing 91 unique cases of PVB19 infection were retrieved [7, 10–70]. Using a standardized case report form, data regarding patient demographic characteristics, type of transplant, onset of disease, immunosuppressive therapy, serological findings, PCR and bone marrow biopsy results, clinical manifestations, treatment, and outcomes were collected.

Detection of PVB19 DNAemia. Stored blood samples from 47 patients who underwent transplantation (32 SOTs and 15 H SCTs) were retrieved for PVB19 DNA detection. These patients were selected based on the availability of samples for serial testing for a 1-year period. PVB19 detection was performed using a clinically validated LightCycler PCR (Mayo Clinic) that detects the nonstructural protein NS and capsid protein VP genes. Each transplant patient had 12 blood samples that were collected serially every 2–8 weeks during the first year after transplantation. Seventy-five percent of samples were collected during the first 6 months. The 1-year period of surveillance was anticipated to capture the majority of PVB19 infections. This study was approved by the Institutional Review Board of the Mayo Foundation.

Statistical analysis. Descriptive statistics were used in data analysis. These included mean, median, range, proportions, SDs, and 95% CIs.

RESULTS

Case Study

Illustrative case. A 43-year-old female patient underwent simultaneous kidney and pancreas transplantation in March 2000 because of end-stage renal disease resulting from diabetes mellitus. Before this transplantation, she lost 2 renal allografts because of chronic rejection. She received induction immunosuppression with thymoglobulin and maintenance with tacrolimus, mycophenolate mofetil, and prednisone. During the first year after transplantation, she had hemoglobin levels that ranged from 8.2 mg/dL to 10.4 mg/dL, and she received periodic blood transfusions. Thirteen months after transplantation, she developed severe weakness and dyspnea. The findings of the laboratory examination were remarkable; they showed a hemoglobin level of 4.9 mg/dL, a WBC count of 2.0 x 10^8 cells/L, and red cell aplasia that was revealed in a bone marrow examination.

Because PVB19 IgG and IgM serological test results were negative, she was considered to have drug-induced myelosuppression; thus, mycophenolate mofetil was discontinued, and blood was transfused. Two months later, she was admitted to the hospital with anemia (hemoglobin level, 5.3 mg/dL) and leukopenia (WBC count, 2.8 x 10^7 cells/L). Subsequent serological evaluation results at the Mayo Clinic were positive for anti-PVB19 IgM, and bone marrow examination showed giant pronormoblasts and viral inclusions consistent with PVB19. The patient received 2 doses of intravenous Ig (1g/kg/day). Three months after treatment, recurrence of anemia (hemoglobin level, 5.6 mg/dL) was observed, and she was re-treated with 6 doses of intravenous Ig (1g/kg/day). Her clinical follow-up during the subsequent 3 years did not suggest further recurrence.

Summary of 7 cases. In addition to the illustrative case, 6 other cases of PVB19 infection were seen at the Mayo Clinic from 1990 through 2005 (table 1). Six cases affected recipients of kidney transplants (with or without pancreas), and 1 case affected a heart transplant recipient. No patients had HIV infection or other immunodeficiency illnesses prior to trans-
Table 1. Demographic and clinical characteristics of 7 patients with parvovirus B19 (PVB19) infection after transplantation, Mayo Clinic (Rochester, MN), 1990–2005.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>M</td>
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<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Type of transplant</td>
<td></td>
<td>KP</td>
<td>LRDK</td>
<td>LRDK</td>
<td>LRDK</td>
<td>LRDK</td>
<td>HT</td>
<td>DDK</td>
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<td>Time to onset of PVB19 infection after transplantation, months</td>
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<td>1.5</td>
<td>1</td>
<td>1.25</td>
<td>1.5</td>
<td>24</td>
<td>20</td>
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<td></td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>ND</td>
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<td>+</td>
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<td>ND</td>
<td>ND</td>
<td>PRCA</td>
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<td>ND</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>5.5</td>
<td>5.3</td>
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<td>2</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>Symptoms</td>
<td></td>
<td>Weakness and dyspnea on exertion</td>
<td>Fever, headache, myalgia, nausea</td>
<td>Fever</td>
<td>Fatigue, dyspnea, weakness</td>
<td>Fever</td>
<td>…</td>
<td>Fatigue, lightheadedness, dyspnea</td>
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<td>IVIG</td>
<td>IVIG and IS reduction</td>
<td>IVIG and IS reduction</td>
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<td>IVIG</td>
<td>IVIG</td>
<td>MD</td>
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<td>1 g/kg/day for 2 days</td>
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<td>500 mg/kg/day for 2 days</td>
<td>400 mg/kg/day for 5 days</td>
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<td>1 g/kg/day for 2 days</td>
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<td>Recurrence of PVB19 infection</td>
<td></td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

NOTE. DDK, deceased donor kidney transplant; Hgb, hemoglobin; HT, orthotopic heart transplant; IS, immunosuppression; IVIG, intravenous immunoglobulin; KP, kidney-pancreas transplant; LRDK, living donor related kidney transplant; MD, missing data; ND, not done; PRCA, pure red cell aplasia.
plantation. Coinfection with other viruses was not observed. The median time to onset of symptoms was 1.5 months (range, 1–24 months) after transplantation. Anemia was observed in all patients (range of lowest hemoglobin level, 4.9–6.8 mg/dL). Leukopenia was observed in 5 patients (range of lowest WBC count, 2.0–2.5 × 10^9 cells/L). Fever was documented in 3 cases. Allograft dysfunction was observed at the time of PVB19 infection in 1 patient. Four patients had negative serological test results for anti-PVB19 IgG and IgM at the onset of disease. All 5 patients who had PCR performed had positive results. All 4 patients who underwent bone marrow examination had pure red cell aplasia. Six patients received intravenous Ig (doses ranged from 0.5 to 1 g/kg/day for 2 doses in 5 patients to 0.4 g/kg/day for 5 doses in 1 patient). One patient did not receive intravenous Ig, because the anemia was resolving at the time of diagnosis. Four of 6 patients treated with intravenous Ig had relapse of anemia, and all responded to retreatment with intravenous Ig. At the end of our study (31 December 2005), all patients were alive with functioning allografts.

**Molecular Surveillance of PVB19 DNAemia after Transplantation**

The identification of only 7 cases during the 16-year period suggests that PVB19 infection occurs rarely after transplantation. To gain more insight into the incidence of PVB19 infection and to determine whether subclinical PVB19 infection occurs, we performed longitudinal PCR testing in 47 transplant patients (3 with heart transplants, 20 with liver transplants, 9 with kidney transplants, and 15 with allogeneic bone marrow transplants). A review of the medical records of these patients revealed varying degrees of anemia after transplantation (or after engraftment for HSCT patients). The mean (± SD) lowest hemoglobin for male patients was 8.47 ± 0.9 g/dL, and for female patients it was 7.95 ± 0.97 g/dL. The mean (± SD) duration of anemia was 23.6 ± 25.3 weeks. None of the transplant patients had PVB19 DNAemia during the first year after transplantation (95% CI, 0%–7.6%). None had received intravenous Ig for any reason after transplantation.

**Review of the Literature**

To comprehensively capture all clinical features of PVB19 infection after transplantation, we performed a review of the medical literature. Ninety-one cases of PVB19 infection were reported. Including the 7 cases we described here, the data from a total of 98 patients are summarized in table 2. The population consisted of kidney transplant (54%), liver transplant (9%), heart or lung transplant (12%), and autologous or allogeneic HSCT (24%) recipients. The mean age (± SD) of the patients was 35.2 ± 17.1 years. The majority (58%) were male. None of the patients had HIV infection.

**Clinical features of PVB19 infection.** The median time to onset of PVB19 disease was 1.75 months (range, 1 week–96 months) after transplantation. In 65% of patients, the onset was within 3 months after transplantation (figure 1). The most common manifestation was anemia (98.8% of all patients), that manifested clinically as weakness, dyspnea, and orthostasis. Leukopenia was observed in 37.5% of patients, and thrombocytopenia was observed in 21.0% of patients. Fever and flu-like manifestations occurred in 25.9% of patients [7, 10, 11, 16, 18, 24, 26, 30–32, 36, 39, 44, 45, 47, 48, 58, 68], skin rash occurred in 13.3% [12, 24, 28, 31, 36, 39], and arthralgia occurred in 6.0% of patients [18, 22, 35, 38, 68]. PVB19-associated anemia was accompanied by organ-invasive manifestations in 11% of patients, including myocarditis (probable cases in 2% of patients; possible cases in 2% of patients) [17, 22, 28, 43, 57], pneumonitis (definite cases in 1%; probable cases in 1%; possible cases in 1%) [22, 31, 68], hepatitis (probable cases in 2%; possible cases in 2%) [28, 58, 63, 66], and collapsing glomerulopathy (probable cases in 1%) [26]. Thrombotic microangiopathy was reported in 4% of patients [54]. Allograft loss, rejection, or dysfunction (or failure of engraftment in HSCT patients) occurred in 10.4% of patients [18, 26, 27, 44, 54, 57, 66]. Coinfections with cytomegalovirus (1% of patients) [66] and human herpesvirus–6 (1% of patients) [36] were also reported. Death that was directly attributed to PVB19 disease occurred in 3% of patients [17, 28, 43]. All deaths were due to cardiogenic shock related to myocarditis in patients with PBV19 disease [17, 28, 43]. The clinical features of PVB19 disease are summarized according to transplant type in table 2.

**Diagnosis of PVB19 infection.** At the onset of disease, PVB19 IgM was not detected in 29% of patients. In contrast, PVB19 IgM or IgG was detected in 79% of patients, including 45% of patients whose serological test results were IgM positive and IgG negative or IgG unknown, 26% whose results were IgM positive and IgG positive, and 7% whose results were IgM negative and IgG positive. Among the patients whose serological test results were IgM negative and IgG positive, the diagnosis of PVB19 infection was confirmed by PCR with blood or bone marrow specimens (5 patients) and/or a bone marrow biopsy finding of pure red cell aplasia (4 patients). Overall, PVB19 PCR with the blood or bone marrow samples was positive in 85% of patients. However, all except 1 of the 23 patients (96%) who did not have PVB19 IgM detected had a positive PCR result. Among 57 patients with simultaneous bone marrow examination and PCR, 5 (8.8%) had negative PCR results but had bone marrow findings suggestive of PVB19 disease, and 6 (10.5%) had positive PCR results but inconclusive bone marrow examination findings.

**Treatment of PVB19 infection.** Intravenous Ig was used as treatment for PVB19 infection, with or without reduction in immunosuppression, for 85.3% of patients. The dose and duration of intravenous Ig regimens varied. In 5% of patients,
Table 2. Clinical characteristics of 98 patients with parvovirus B19 (PVB19) infection after solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT).

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>All patients (n = 98)</th>
<th>SOT patients (n = 74)</th>
<th>HSCT patients (n = 24)</th>
<th>Kidney transplant patients (n = 53)</th>
<th>Liver transplant patients (n = 9)</th>
<th>Heart/lung transplant patients (n = 12)</th>
<th>Allogeneic HSCT patients (n = 20)</th>
<th>Autologous HSCT patients (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD</td>
<td>36.3 ± 17.1</td>
<td>34.4 ± 18.2</td>
<td>38 ± 12.9</td>
<td>36.7 ± 15.5</td>
<td>21.7 ± 23.4</td>
<td>33.7 ± 23.3</td>
<td>34.5 ± 11</td>
<td>55.5 ± 3.6</td>
</tr>
<tr>
<td>No. of male/female subjects</td>
<td>57/41</td>
<td>44/30</td>
<td>13/11</td>
<td>34/19</td>
<td>5/4</td>
<td>5/7</td>
<td>12/8</td>
<td>1/3</td>
</tr>
<tr>
<td>Median time to onset, months</td>
<td>1.75</td>
<td>1.75</td>
<td>3</td>
<td>1.25</td>
<td>8</td>
<td>16</td>
<td>16</td>
<td>3</td>
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<td>Detection of PVB19 IgG at onset of disease</td>
<td>38</td>
<td>38.9</td>
<td>33.3</td>
<td>15</td>
<td>62.5</td>
<td>30</td>
<td>44.4</td>
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<td>Detection of PVB19 IgM at onset of disease</td>
<td>71.2</td>
<td>75</td>
<td>50</td>
<td>79.5</td>
<td>87.5</td>
<td>45.4</td>
<td>44.4</td>
<td>66.6</td>
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<td>Positive PVB19 PCR result at onset of disease</td>
<td>90.4</td>
<td>87</td>
<td>100</td>
<td>87.5</td>
<td>100</td>
<td>80</td>
<td>100</td>
<td>100</td>
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<td>Bone marrow findings positive for PVB19 infection</td>
<td>84.3</td>
<td>84.2</td>
<td>84.5</td>
<td>89.1</td>
<td>40</td>
<td>88.8</td>
<td>90</td>
<td>66.6</td>
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<td>98.6</td>
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<td>98.1</td>
<td>100</td>
<td>100</td>
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<td>Lowest Hgb level, mean mg/dL ± SD</td>
<td>6.4 ± 15</td>
<td>6.4 ± 15</td>
<td>6.35 ± 15</td>
<td>6.2 ± 12</td>
<td>7.3 ± 25</td>
<td>6.1 ± 18</td>
<td>6.4 ± 19</td>
<td>6.2 ± 0.8</td>
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<td>61.5</td>
<td>34</td>
<td>33.3</td>
<td>27.2</td>
<td>70</td>
<td>33.3</td>
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<td>Lowest WBC count, mean ¥10^9 cells/L ± SD</td>
<td>2.1 ± 1</td>
<td>2.2 ± 0.9</td>
<td>1.2 ± 1.2</td>
<td>2.1 ± 0.7</td>
<td>2.1 ± 2.2</td>
<td>2.8 ± 1.2</td>
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<td>38.4</td>
<td>19.1</td>
<td>22.2</td>
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<td>28.5</td>
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<td>22.2</td>
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<td>66.6</td>
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<td>33.3</td>
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<td>83.8</td>
<td>90</td>
<td>86</td>
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<td>93.7</td>
<td>75</td>
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<td>IVIG dose, mean g/kg/day ± SD</td>
<td>0.53 ± 0.3</td>
<td>0.58 ± 0.33</td>
<td>0.38 ± 0.17</td>
<td>0.55 ± 0.26</td>
<td>0.7 ± 0.3</td>
<td>0.62 ± 0.6</td>
<td>0.33 ± 0.04</td>
<td>0.6 ± 0.3</td>
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<td>1.57 ± 1</td>
<td>3 ± 1.6</td>
<td>3.2 ± 1.6</td>
<td>2.2 ± 0.7</td>
<td>1.5 ± 1.1</td>
<td>1.8 ± 0.8</td>
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</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>40.2</td>
<td>45.1</td>
<td>10</td>
<td>58.5</td>
<td>0</td>
<td>33.3</td>
<td>14.2</td>
<td>0</td>
</tr>
<tr>
<td>Recurrence of PVB19 infection</td>
<td>23.2</td>
<td>27.6</td>
<td>9.5</td>
<td>34</td>
<td>11.1</td>
<td>16.6</td>
<td>11.7</td>
<td>0</td>
</tr>
<tr>
<td>Graft loss/dysfunction</td>
<td>10.4</td>
<td>12.5</td>
<td>4.1</td>
<td>15.6</td>
<td>0</td>
<td>8.3</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Death from PVB19 infection</td>
<td>3</td>
<td>1.3</td>
<td>8.3</td>
<td>0</td>
<td>11.1</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

**NOTE.** Data are % of patients, unless otherwise indicated. Hgb, hemoglobin; IVIG, intravenous immunoglobulin; NR, not reported.
leads to persistent PVB19 infection that manifests as chronic anemia. Not surprisingly, almost all patients in our series had chronic anemia, many patients did not possess PVB19-specific Ig at the onset of clinical disease, and almost all transplant patients without PVB19 IgM had parvoviremia.

Our review demonstrates that the spectrum of clinical illness related to PVB19 is broad. This reflects the ability of PVB19 to infect other cells [76]. The cardiotropism of PVB19 is suggested by its association with myocarditis [77–79] and left ventricular dysfunction [80] and by the demonstration of PVB19 DNA in fetal myocardial cells [81]. These data support the suggestion that myocarditis may occur in transplant patients with PVB19 disease, and this may be misdiagnosed as acute rejection and could result in death from cardiogenic shock [17, 28, 43]. The most likely cardiac target of PVB19 is the endothelium [81–83], because endothelial cells in small cardiac vessels also carry P antigen [54]. Likewise, endothelial infection could serve as the mechanism for PVB19-associated thrombotic microangiopathy [54].

Studies of paroviruses that infect animals demonstrate the virions in various organs [84]. Parvovirus related to Aleutian mink disease was detected in alveolar cells in mink with acute interstitial pneumonitis [85]. Intact Aleutian mink disease paroviral DNA has also been detected in glomeruli [85]. These animal data support the suggestion that PVB19 is a potential cause of pneumonitis [22, 31, 68], hepatitis [28, 58, 63, 66, 86], and collapsing glomerulopathy [26] in humans. Indeed, PVB19 has been demonstrated in the renal tissue and blood of patients with collapsing glomerulopathy and in hepatocytes of a patient with fibrosing cholestatic hepatitis [58]. Nevertheless, the reported associations between PVB19 and organ-specific syndromes do not definitely indicate causality.

Reassuringly, PVB19 appears to be uncommon after transplantation. Our search over a 16-year period yielded only 7 cases, and our review of the literature yielded only 91 cases. Furthermore, our 1-year surveillance did not demonstrate clinical or subclinical PVB19 DNAemia in 47 patients. Although the lack of PVB19 in our cohort may reflect our small number of subjects, the incidence would still have remained low had we increased the number of patients tested. Hypothetically, had 1 of 47 patients developed PVB19 DNAemia, the incidence would be ∼2%—a rate that is consistent with estimates of other investigators [16, 87, 88]. This low incidence is somewhat surprising, considering the numerous circumstances that permit infection after transplantation. PVB19 persists in the tissues of PVB19-seropositive individuals [76], and in some instances, it may persist for years [73, 89]. Therefore, the transplanted allograft and the blood that is transfused to transplant patients could potentially transmit the virus [90–93]. Reactivation or increased replication should be an anticipated consequence of intense immunosuppression after transplantation [26].

Our review of the methods used to diagnose PVB19 infection
References


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