

## Parvovirus B19 Infection in a Patient with Sickle Cell Crisis

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**A**plastic crisis in patients with hemolytic disease has been shown to be of infectious etiology based on reports of outbreaks and clusters of attack.<sup>1</sup> However, the fact that parvovirus B19 infection, the only known parvovirus pathogenic to humans,<sup>2</sup> is the most common infectious cause of aplastic crisis is not widely known. This article describes a patient with sickle cell disease who develops aplasia and pain crisis after parvovirus B19 infection and is successfully treated with intravenous immunoglobulin. Etiology, pathogenesis, diagnosis, and treatment are also discussed.

### CASE PRESENTATION

A 19-year-old black man with sickle cell disease presents to the emergency department with a 3-day history of fever and moderately severe pain in the chest and extremities.

### Patient History

Three days prior to presentation, the patient developed a temperature of 104°F that was not relieved by antipyretics and was associated with nasal congestion, headache, and dry cough. The following day, the patient experienced pain in his left chest, back, and legs. The patient has no history of alcohol or drug use. His history is significant for sickle cell crises, laparoscopic cholecystectomy, pneumonia, and otitis media.

The patient's older sister also has sickle cell disease and was discharged from the hospital after treatment for pain crisis and anemia 2 weeks prior to the patient's presentation. The patient's sister's parvovirus B19 IgM and IgG indices obtained on outpatient follow-up were 2.81 and 7.42, respectively (values greater than 1.2 are considered seropositive).

### Physical Examination

On admission, physical examination reveals a well-developed, alert, and oriented man in pain. His blood pressure is 110/60 mm Hg, pulse is 90 bpm, respiration is 20 breaths/min, and temperature is 101.2°F.

The patient has pale conjunctivae without icterus, no cervical lymphadenopathy is present, and jugular venous pressure is normal. Chest examination is normal; a grade II/VI systolic murmur at the left parasternal border is evident. Abdominal examination shows a healed surgical scar at the right upper quadrant without hepatosplenomegaly. The genitalia and extremities are normal. Neurologic examination is also normal.

### Laboratory and Imaging Studies

Laboratory evaluation is performed on admission to the hospital. The patient's hemoglobin is 3.7 g/dL, the hematocrit is 10.5%, and the leukocyte count, platelet count, and erythrocyte indices are normal. Absolute reticulocyte count is 2150/mm<sup>3</sup> (normal range, 25,000 to 75,000/mm<sup>3</sup>) with 0.1% reticulocytes (normal range, 0.5% to 1.5%). Peripheral blood smear shows moderate sickling, poikilocytes, and occasional target cells. Results of blood chemistry, urinalysis, and chest radiography are normal.

### Treatment

The patient is initially treated with parenteral analgesics and fluids. Intravenous antibiotic therapy is started after blood cultures are obtained. Throughout the next 3 days, the patient is transfused with 4 units of erythrocytes. His hemoglobin increases to 8.1 g/dL and then declines to 6.5 g/dL; the reticulocyte count improves minimally. Acute parvovirus B19 infection is suspected and confirmed by B19-specific serology that reveals an IgM value of 2.94 and IgG of 4.02. Intravenous immunoglobulin (400 mg/kg) is given with a gradual increase in hemoglobin; no further transfusions are needed. The patient's pain and fever resolve by hospital day three and antibiotic therapy is discontinued after negative blood culture results.

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## DISCUSSION

### Etiology

Parvovirus B19 is the only known parvovirus pathogenic to humans.<sup>2</sup> The virus was designated as B19 by taxonomists. The mode of transmission is most likely via the respiratory route, although oral-fecal and oral-oral routes cannot be discounted.

### Clinical Manifestations

**Table 1** summarizes the clinical manifestations of parvovirus B19 infection. This infection causes erythema infectiosum (fifth disease) in children, aplastic crisis in patients with hemolytic disorders,<sup>3</sup> hydrops fetalis in infants who acquire the infection prenatally,<sup>4,5</sup> arthropathy in adults, and persistent bone marrow infection in immunocompromised hosts.<sup>6</sup> More than 50% of affected patients initially present with flu-like symptoms including fever, headache, myalgia, and malaise.<sup>7</sup> In adults, parvovirus B19 infection presents as influenza-like symptoms, rash, arthropathy, or a combination of these symptoms. Joint symptoms (ie, pain and swelling) are more common in women than in men and may be associated with the absence of human leukocyte antigen-DR1 major histocompatibility complex.<sup>7</sup>

### Pathophysiology

Parvovirus B19 infection causes a biphasic illness in which viremia occurs 1 week after infection and viral titers are high as in patients who develop aplastic crisis.<sup>8</sup> During the influenza-like symptoms experienced in the first phase of illness, the virus is found in nasal secretions. At approximately the tenth day of the incubation period, reticulocytopenia occurs accompanied by an absence of erythroid cells in the bone marrow. The second phase of the disease occurs 2 weeks after infection with parvovirus B19 and is marked with the appearance of an erythematous rash. The rash lasts for 2 to 3 days and is associated with arthralgia or arthritis. The second phase of B19 infection is believed to be immune-mediated.<sup>8</sup>

Parvovirus B19 causes aplastic crisis by inhibiting erythroid series formation through the pathogen's direct cytotoxic effect on erythroid burst and colony-forming units.<sup>9</sup> Parvovirus B19 is dependent on the S phase activity of the host cells for viral replication; B19 commonly infects rapidly-dividing cells such as bone marrow or developing fetal tissues.<sup>1</sup> Myeloid series and platelets are seldom affected during the infection. Bone marrow suppression is usually transient and clinically insignificant except in cases of decreased erythrocyte life span, as in patients with hemoglobinopathy.<sup>10</sup> In one study, more than 90% of patients with underlying

**Table 1.** Clinical Manifestations of Parvovirus B19 Infection

Host	Syndrome
Young children	Erythema infectiosum/ fifth disease
Adults	Arthropathy
Fetus	Hydrops fetalis
Patients with hemolytic disorders	Transient aplastic crisis
Immunocompromised patients	Persistent anemia

hereditary hemolytic anemias who developed aplastic crisis had positive serology for acute B19 infection.<sup>1</sup>

### Infection in Specific Patient Populations

**Patients with sickle cell disease.** A prospective controlled study by Serjeant et al<sup>11</sup> followed 308 children with sickle cell disease. Within the study group, 91 episodes of aplastic crisis secondary to B19 infection were documented by serology and were directly correlated to four separate B19 epidemics between 1973 and 1991. Interestingly, 20% of the study group showed positive B19 serology, but hematologic abnormalities were either mild or absent.<sup>11</sup> A prospective study by Rao et al<sup>12</sup> evaluated 53 pediatric patients with sickle cell disease who developed transient aplastic crisis. In the study group, 68% had positive B19 IgM and 20% had B19 DNA.<sup>12</sup> Extensive bone marrow necrosis has been reported in sickle cell patients who present with aplastic and pain crisis after acute B19 infection. The cell death is presumed to be secondary to hypoxemia during the systemic viral infection.<sup>13,14</sup> In contrast to patients with such immunodeficiencies as AIDS,<sup>15</sup> the reticulocytopenia and aplasia in sickle cell patients tends to be self-limiting and relapse has not been reported once B19 IgG is detected in serum.<sup>11</sup>

**Immunocompromised patients.** Immunocompromised individuals, such as patients with congenital or acquired immunodeficiency syndromes, patients undergoing chemotherapy for malignancies, or patients receiving organ transplant, may develop chronic B19 infection characterized by persistent viremia and bone marrow suppression.<sup>9,15-19</sup> Frickhofen et al<sup>15</sup> described a series of seven patients with AIDS who presented with pure red cell aplasia and reticulocytopenia. B19 DNA was detected by dot blot hybridization in all patients' sera and three of the bone marrow samples. The viral loads were higher when compared with other cases of

**Table 2.** Diagnosis and Treatment of Parvovirus B19 Infection

**Laboratory tests**

B19 IgG and IgM  
Nucleic acid hybridization assay  
Polymerase chain reaction  
Bone marrow biopsy

**Treatment**

Erythrocyte transfusions if indicated  
Intravenous immunoglobulin at 400 mg/kg (up to 5 days)  
Supportive therapy

persistent B19 infection but lower than the viral loads of patients with transient aplastic crisis. Bone marrow examination showed giant pronormoblasts; Southern blot analysis demonstrated evidence of active viral replication in the bone marrow of three of the patients.<sup>15</sup>

The postulated mechanism for persistence of B19 infection in HIV patients is the absence of antiparvovirus antibody production. This mechanism is probably secondary to a basic defect in antigen presentation by the macrophages or by impaired T-cell function. B19 IgG and IgM measurements may not be useful in immunocompromised patients as exemplified by the absence of IgG in all seven patients and the detection of very low levels of IgM in only one patient in the Frickhofen study group. Viremia persisted in the study group despite the absence of symptoms. In general, parvovirus infection relapse usually correlates with increasing B19 DNA levels and may indicate the need for retreatment with commercial intravenous immunoglobulin.<sup>15</sup>

**Diagnosis and Treatment**

**Table 2** summarizes the diagnostic and treatment modalities employed against B19 infection. The detection of parvoviral antibodies (IgG, IgM) in serum is the most common diagnostic test. However, serology may be negative in immunocompromised patients; nucleic acid amplification techniques (eg, polymerase chain reaction) are more sensitive.<sup>20</sup> Viremia is of brief duration and tests for viral culture are not commercially available. The presence of giant pronormoblasts with few erythrocyte precursors in the bone marrow is characteristic but not specific for B19 infection.<sup>8</sup>

Management of B19 infection includes supportive therapy with erythrocyte transfusions; intravenous im-

munoglobulin should be administered in patients with severe anemia or underlying immunodeficiencies because these patients are at risk for chronic infection.<sup>9,17</sup> The manner in which commercially available intravenous immunoglobulin dramatically improves reticulocytosis and decreases viremia in B19 infected patients is unclear. The mechanism of action is hypothesized to include the blockade of Fc receptors and the neutralization of host antibodies with transfused anti-idiotypic IgG.<sup>17</sup>

**SUMMARY**

Pure red cell aplasia in patients with hemoglobinopathies and in immunocompromised hosts (eg, patients with AIDS, transplant recipients) should alert the clinician to the possibility of parvovirus B19 infection. Tests are available to confirm the diagnosis. Management includes erythrocyte transfusions and, in cases of immunocompromised patients, administration of intravenous immunoglobulin. **HP**

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