Persistent and Prolonged Parvovirus B19 Viremia in a Pediatric Patient With Acute Lymphoblastic Leukemia

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Parvovirus B19 is a small single-stranded DNA virus of the Parvoviridae family. Depending on host factors, it may produce a wide array of clinical disease states. Disease severity can range from self-limited to severe, requiring significant supportive care. Immunocompromised patients are generally affected more severely but rarely develop prolonged and persistent infections. Here, we describe a patient who was diagnosed with parvovirus during maintenance therapy for acute lymphoblastic leukemia and required therapy with intravenous immunoglobulin; the patient remained parvovirus positive according to a polymerase chain reaction testing but had no clinical symptoms for 27 months off chemotherapy.

Key words. anemia; immunocompromised; leukemia; parvovirus; pediatric.

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CASE REPORT

An 11-year-old boy with standard-risk pre-B acute lymphoblastic leukemia (diagnosed at 8 years of age) was treated according to Children’s Oncology Group protocol AALL0331. Maintenance therapy was well tolerated, with 100% dosing of oral methotrexate, oral 6-mercaptopurine, and oral dexamethasone and intravenous vincristine pulses. Twenty-eight months into maintenance therapy, he developed fever and pancytopenia (hemoglobin concentration, 4.3 g/dL; absolute neutrophil count, 36 cells/µL; platelet count, 41 × 10^9/µL; and absolute reticulocyte count, 1.5 × 10^9). The results of qualitative parvovirus PCR testing were positive. Parvovirus immunoglobulin (Ig)G and IgM titers were negative (0.06 and 0.05 IU/mL, respectively. A bone marrow evaluation was not performed. Packed red blood cells (PRBCs) were transfused, 0.5 g/kg IVIg was administered, and oral chemotherapy was held (Figure 1). After count recovery 2 weeks later (hemoglobin concentration, 10.3 g/dL; absolute reticulocyte count, 58.3 × 10^9/µL; platelet count, 85 × 10^9/µL; and absolute neutrophil count, 912/µL), chemotherapy was restarted at half doses of methotrexate and 6-mercaptopurine. He tolerated the resumption of chemotherapy until 2 months later, when he again became anemic (hemoglobin concentration, 6.1 g/dL) and required a PRBC transfusion. At that time, quantitative parvovirus PCR testing revealed 555 000 IU/mL parvovirus B19 viral copies. He subsequently underwent treatment with 0.5 to 1 g/kg/dose IVIg every 2 to 4 weeks for the following 2 months (5 total doses of IVIg, with a cumulative dose of 3 g/kg) and required no additional transfusions (Figure 1). After completion of the planned chemotherapy 4 months later, the patient’s parvovirus PCR copy number had declined to 7000 IU/mL, and the IVIg therapy was
discontinued (Figure 1). One month later, his parvovirus PCR titer increased to 2 900 000 IU/mL without him having clinical symptoms, and his hemoglobin concentration was 13.3 g/dL. He has received no further therapy directed against parvovirus and has not had any further clinical evidence of disease, despite persistently positive parvovirus PCR results. Nine months off chemotherapy for leukemia, the results of repeat parvovirus IgG testing were positive at 4.11 IU/mL; results of IgM testing were negative. Thirty-one months after his parvovirus diagnosis and 27 months off therapy for leukemia, the patient continues to have measurable parvovirus PCR titers of 1000 IU/mL and normal hemoglobin levels. He continues to be on droplet precautions to avoid exposing immunocompromised individuals.

DISCUSSION
Parvovirus B19 is a small single-stranded DNA virus of the Parvoviridae family. Up to 60% of children aged 6 to 19 years and more than 85% of the geriatric population have IgG antibodies against parvovirus. Depending on host factors, parvovirus can produce a wide array of clinical disease states. In healthy children, it commonly causes erythema infectiosum (fifth disease), with classic symptoms including fevers and slapped-cheek exanthem [1]. Adults more commonly develop polyarthralgias, and in pregnant women, it may cause fetal anemia, hydrops fetalis, and even fetal death. In patients who depend on increased erythropoiesis, such as those with congenital hemolytic anemias, parvovirus often leads to transient aplastic crises, which are most often self-limited and require no or minimal supportive therapy.

In immunocompetent hosts, transient viremia results in the formation of protective antibodies, which leads to the neutralization and elimination of disease [2]. It is not surprising that immunocompromised patients produce weak antibody responses, which limits their ability to neutralize or eliminate parvovirus [2]. Rarely, immunocompromised patients develop chronic persistent parvovirus infection that requires therapy with IVIg. Subsequent doses of IVIg are often required after the initial resolution of anemia; however, IVIg therapy may fail to eradicate the virus, as we observed in our patient. Crabol et al [3] reported an overall relapse rate of 34% at a mean of 4.3 months after infection. Treatment failure rates were higher with lower doses of IVIg (0.25–1 g/kg), and improved outcomes were observed with cumulative doses of 2.3 ± 1.3 g/kg. This group recommended a treatment dose of 2 g/kg IVIg for each course in an effort to eradicate infection and prevent its recurrence [3]. Our patient experienced a 2-log reduction in parvovirus PCR titers after IVIg treatment (total 3 g/kg), but the titer increased dramatically within

Figure 1. Hemoglobin, reticulocyte (Retic), and parvovirus titer trends. Treatment was initiated with IVIg (arrows) and PRBC transfusions (dashed arrows) at the time of presentation with anemia. Five doses of IVIg were given, with a cumulative dose of 3 g/kg. In the upper panel, the solid line represents hemoglobin concentrations (g/dL), and gray squares represent reticulocyte percentages. In the lower panel, dark bars denote the parvovirus PCR copy numbers (in IU/mL; 1 IU = 0.73 copies) in logarithmic scale. Viral loads were not evaluated in months for which no dark bar is shown in the lower panel. The end of maintenance therapy for ALL is indicated by the solid vertical line.
4 months (to 2 900 000 IU/mL), which suggests that the IVIg effect had worn off. Despite this elevated titer, we chose not to re-treat the patient with IVIg, because he was asymptomatic.

Parvovirus infection is usually diagnosed in patients with leukemia and acute anemia during maintenance therapy. It is not uncommon, however, for patients to present with thrombocytopenia [4]. Providers should consider parvovirus as a cause of persistent anemia or thrombocytopenia of unclear etiology [4]. Diagnosing parvovirus in immunocompromised patients can be challenging, because these patients often do not have an appropriate antibody response; thus, standard parvovirus antibody titers are not reliable [5]. Many patients with ALL are unable to generate IgM during acute infection; therefore, evaluation by DNA PCR is critical for diagnosis in immunocompromised hosts [1]. Zaki and Ashray [6] reported the cases of several patients undergoing therapy for acute leukemia who had positive parvovirus IgM titers but negative PCR test results, which emphasizes the importance of obtaining antibody titers and performing PCR testing.

Cytopenias caused by parvovirus infection lead to delays in chemotherapy and raises concern for potential relapse. Chemotherapy is held 59 days on average, for patients with parvovirus who are receiving maintenance ALL therapy [7]. After diagnosis and therapy with IVIg, our patient’s chemotherapy was stopped for only 14 days. Significant delays, and reduced doses of chemotherapy, may place patients at increased risk for relapse. Katragadda et al [4] reported a reduction of viral load with IVIg therapy and the resumption of safe and timely antineoplastic therapy even in the presence of persistent parvovirus disease. Currently, no specific antiviral agents exist for the treatment or prevention of parvovirus. A phase II parvovirus vaccine trial had been under way but was terminated (ClinicalTrials.gov identifier, NCT00379938). After immune system recovery (6–12 months after chemotherapy), patients are generally able to clear persistent parvovirus infection. It is rare to have persistent parvovirus infection months after cessation of and recovery from immunosuppressive therapy, as occurred in our patient. To our knowledge, only 2 other similar patients have been reported in the literature: a 2-year-old with combined immunodeficiency and a 24-year-old with pure red cell aplasia who was believed to have a congenital immune deficiency [5].

The case of the patient described in our report emphasizes that parvovirus infection in immunocompromised hosts may lead to chronic infection with or without recurrent anemia. The cause of persistent infection is unclear; it is thought to be partially because of the host’s inability to produce adequate neutralizing antibodies to eliminate the virus. This may explain why higher genome copy numbers ($10^{10}$–$10^{14}$ copies/mL) are found in patients with acute illness than in those with chronic infection ($10^{2}$–$10^{4}$ copies/mL) [5]. Chronic infection may also result from parvovirus infection of nonerythroid cells. Parvovirus has been found in leukocytes, macrophages, and myocardial cells [5]. These cells permit restricted gene expression without efficient viral replication [5]. Chronic infection with lower copy numbers may lead to asymptomatic infection.

In conclusion, parvovirus B19 is an important cause of anemia and thrombocytopenia in patients with ALL. Diagnostic testing with standard parvovirus immunoglobulin titers and serum PCR for viral DNA is critical. IVIg therapy in infected patients is instrumental in reducing chemotherapy delays. Rapid improvement in cytopenia may avert the need for bone marrow aspiration/biopsy and its attendant morbidity related to sedation, along with alleviating anxiety related to concern for relapse. Finally, our case report demonstrates that asymptomatic parvovirus infection may persist for months after recovery of postchemotherapy immune function.

Potential conflicts of interest. All authors: No reported conflicts.

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References