

Chronic Anemia Due to Parvovirus B19 Infection in a Patient With Multiple Myeloma

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Human parvovirus B19 (PVB19) is a small, non-enveloped, single-stranded DNA virus that has been associated with an acute form of bone marrow failure in susceptible hosts.¹ It is now well established that PVB19 is cytotoxic for human erythroid precursors and causes a lytic process in infected cells.² Many conditions are associated with PVB19-induced chronic anemia, including acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, Burkitt lymphoma, myelodysplastic syndrome, HIV infection, bone marrow transplantation, organ transplantation, and systemic lupus erythematosus.³ However, to the best of our knowledge, there is no known association of PVB19-induced chronic anemia in a patient with multiple myeloma.

Case Report

An 84-year-old woman with immunoglobulin (Ig) A-κ multiple myeloma was admitted for evaluation of chronic anemia that had been present for 6 months. The patient complained of dyspnea and fatigue. She denied any hematemesis, hematochezia, melena, or bleeding diathesis. Her medications were melphalan and prednisone.

The patient's hematocrit was 22.7%, hemoglobin 7.6 g/dL, platelet count 6,100 cells/mL, white blood cell count 4,900 cells/mL, prothrombin time 14.1 seconds, international normalized ratio 1.3, partial thromboplastin time 37.1 seconds, and reticulocyte count 1%. The direct antiglobulin test (Coomb's test) was negative and the peripheral blood smear was consistent with a normocytic, normochromic anemia. Upper and lower endoscopies were normal.

Anti-PVB19 IgM (>6) and IgG (5.6) antibodies assessed by enzyme-linked immunosorbent assay were

elevated. Parvovirus infection was confirmed by positive polymerase chain reaction (PCR).

Immunoglobulin therapy was administered at 400 mg/kg daily for 6 days. Two weeks after the completion of treatment the patient's hematocrit was 30% and hemoglobin 9.8 g/dL, and her clinical condition improved.

Discussion

A growing number of cases of PVB19 infection associated with chronic anemia have been reported. PVB19 has a marked tropism for erythroid progenitor cells, which may lead to chronic anemia in predisposed individuals. Most of these patients with PVB19 infection and chronic anemia are immunodeficient. Immunocompromised patients with acute PVB19 infection can develop potentially life-threatening anemia due to their inability to mount an immune response to control the virus. Chronic infection, on the other hand, leads to chronic hypoplasia or aplasia of the erythroid series in the bone marrow, resulting in a reticulocytopenic anemia.⁴ The accompanying anemia is usually of moderate degree, reflecting the low-grade infection in these patients; the serum concentration of PVB19 among chronically anemic patients is usually much lower than that detected during an acute aplastic crisis.⁵ The chronic anemia has shown good response to immunoglobulin therapy treatment with a reticulocytosis within 1 week.⁶

The clinical hallmarks of this condition are fatigue and pallor due to the anemia, though immunologically mediated symptoms such as rash and arthralgia are generally not present.⁷

In conclusion, we believe that evidence of PVB19 infection should be sought in any immunocompromised patient with chronic anemia, particularly when associated with reticulocytopenia. Treatment with intravenous immunoglobulins should be promptly initiated and is generally associated with a gratifying response.

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Review

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In the case presented by Muslimani and Daw,¹ they report an elderly patient on melphalan and prednisone for an IgA- κ multiple myeloma who presented with a 6-month history of a persistent anemia, reticulocytopenia, and thrombocytopenia. The evaluation undertaken to rule out alternative or concurrent causes for these findings, rather than making the assumption that these results were due solely to the underlying myeloma itself and/or chemotherapy, is important. In addition, having considered PVB19 in the differential diagnosis as a possible underlying etiology is noteworthy, as it rarely has been reported in myeloma, although clinicians do not often look for it.

PVB19 is a single-stranded DNA virus with primary infection occurring commonly in children as erythema infectiosum (fifth disease). In the adult population, overall seroprevalence is estimated at 60–90%,² with primary infection often presenting with fatigue, rash, arthralgias, and fever. In nonimmune pregnant women, primary infection can lead to hydrops fetalis. PVB19 infections

present frequently with an anemia and reticulocytopenia, as a result of PVB19 tropism for the P antigen on erythroid progenitor cells, leading to cell lysis and pure red cell aplasia, as manifested in the bone marrow by loss of erythroid precursors and the presence of giant pronormoblasts. Varying degrees of neutropenia and thrombocytopenia may also be present.³⁻⁵ Control of the infection in immunocompetent patients is believed to result from a largely humoral immune response, given that reduction in peripheral viremia parallels the development of PVB19-specific antibodies.⁶

Immunocompromised patients may be unable to mount an appropriate antibody response to PVB19 infection, potentially leading to persistent chronic infection. In these patients, the use of PVB19 DNA-specific PCR on bone marrow and serum samples has been invaluable in diagnosing infection in those otherwise unable to generate an antibody response detectable by standard serologies. However, studies evaluating the incidence, prevalence, and clinical relevance of PVB19 infection in this subpopulation are relatively few, with reports consisting primarily of case studies and a small number of larger case series. Data evaluating these parameters have been collected and reported in the solid organ and hematopoietic allogeneic and autologous transplantation literature, but are conflicting, even in this profoundly immunosuppressed patient group. This may in part be due to the wide spectrum of PVB19 presentations and definitions, including infection (by serology and/or PCR) without associated symptoms or signs, PVB19 disease, defined as PVB19 infection with anemia and clinical symptoms/signs or bone marrow biopsy findings consistent with the diagnosis, or organ-invasive disease, with the presence of infection and organ-specific pathologic or radiographic findings consistent with PVB19 and not attributable to another disease process.⁷

Cavallo and colleagues⁸ evaluated 48 anemic renal transplant patients for the presence of PVB19 infection by serum PCR and compared them to 21 nonanemic controls. Twenty-three percent of those with anemia versus 5% in those without showed PVB19 viremia. Ki and associates⁹ evaluated 167 renal transplant patients for the incidence and clinical significance of PVB19 infection. Thirty-one percent displayed at least one positive serum PCR, and 12% showed PCR positivity more than two consecutive times, with significantly lower hemoglobins than those patients who had only negative or a single positive PCR.⁹ Two patients developed pure red cell aplasia documented by bone marrow biopsy. Renal allograft function, however, was not affected in these patients.⁹

In contrast, Eid and coauthors⁷ reviewed solid organ and hematopoietic allogeneic and autologous transplant patient data (n=98) covering a 16-year period at the Mayo Clinic Rochester (7 cases), summarized the medical litera-

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ture data on 91 cases, and performed a 1-year longitudinal molecular surveillance for PVB19 DNA in samples from 47 patients, which were all negative. Importantly, at the onset of disease, PVB19 IgM was not detectable in 29% of patients.⁷ In the 23 patients who did not have detectable IgM, all but one had a positive PCR result. The conclusions drawn from this review were that PVB19 is relatively uncommon after transplantation but clinically significant. PVB19-associated anemia was accompanied by evidence for organ-invasive disease in 11% of patients, including myocarditis, hepatitis, pneumonitis, and collapsing glomerulopathy.⁷ Thrombotic microangiopathy was found in 4% and allograft loss, rejection, dysfunction, or failure to engraft in hematopoietic transplants occurred in 10.4%.⁷ Three percent of deaths were directly attributed to cardiogenic shock as a result of PVB19-associated myocarditis.⁷

A group of 100 prospectively enrolled patients with a variety of hematologic malignancies and at various points in their treatments were evaluated for the prevalence of PVB19 by serum and marrow PCR, as well as by serology.¹⁰ Of these 100 patients, only 4 had positive PCRs of the marrow but without accompanying positive serum PCRs.¹⁰ Serologies were consistent with past infection. Persistence of a positive PCR of the marrow was not clearly correlated with symptomatic PVB19 infection. The seroprevalence for PVB19 IgG was 59%. Notably, only 1 of the 9 patients with myeloma had PVB19 IgG.

Treatment for symptomatic PVB19 infection has consisted of reducing a patient's immunosuppression, if feasible, in order to maximize the possibility of a humoral response. Additionally, patients have been treated with intravenous Ig with varying success. Relapses are not unusual and the optimal dosing, frequency, and duration of therapy are not known. In this particular case, with the relatively small amount of data presented, it is unclear as to whether the melphalan and prednisone were continued throughout the PVB19 diagnostic workup and treatment with intravenous Ig, or whether these medications were held. If held, the improvement in the anemia and the reported reticulocytosis may in fact be at least partially due to the relative decrease in immunosuppression rather

than to the effects of intravenous Ig per se. This patient may have gone on to clear the infection on her own as she did have both IgG and IgM responses.

Possible sources for PVB19 infection in patients with hematologic malignancies, besides reactivation of disease under immunosuppressive conditions, include iatrogenic transmission via blood and blood products such as, ironically, intravenous Ig, clotting factor concentrates, and allogeneic peripheral blood or marrow collections.¹¹

In conclusion, PVB19 infection should be considered in patients with myeloma or other malignancies in the setting of an anemia or other cytopenias, particularly in those patients with symptoms suggestive of infection, such as fever, arthralgias, and rash, or signs of organ dysfunction not attributable to other causes. The absence of an IgG or IgM response does not rule out the possibility of infection and serum and/or bone marrow PCR should be considered under these circumstances.

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