Common Variable Immunodeficiency Presenting With Persistent Parvovirus B19 Infection

abstract

Parvovirus B19 infection in healthy hosts is self-limited, but persistent infection has been described in patients with cellular immune defects. A 6-year-old boy presented with a 6-month history of weight loss and malaise and a 1-month history of fever and polyarticular arthritis. Parvovirus DNA was detected in plasma at 10,300 copies/mL. Levels of immunoglobulin (Ig)G, IgA, IgM, IgG-1, and IgG-2 were low, and antibody responses to vaccine antigens were impaired. HIV antibody and DNA polymerase chain reaction were negative, and the patient had normal immunophenotype, mitogen stimulation response, CD40 ligand and inducible costimulator expression, transmembrane activator and CAML interactor sequencing, genomic analysis, and fluorescent in situ hybridization for deletions at 22q11.2. Common variable immunodeficiency was diagnosed and replacement therapy with immune globulin intravenous was initiated. The parvovirus DNA level declined by half over 3 months and was undetectable at 15 months. Constitutional symptoms improved but arthritis persisted and eosinophilic fasciitis eventually developed. This case demonstrates that persistent parvovirus infection may be a presenting feature of humoral immune deficiency and can mimic juvenile rheumatoid arthritis. The infection may respond to immune globulin intravenous therapy. Pediatrics 2012;130:e1711–e1715

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KEY WORDS

human parvovirus B19, common variable immunodeficiency, juvenile idiopathic arthritis

ABBREVIATIONS

CVID—common variable immunodeficiency
Ig—immunoglobulin
IGIV—immune globulin intravenous
JIA—juvenile idiopathic arthritis
RA—rheumatoid arthritis

Drs Adams, Schmidt, and Marshall provided medical care to the patient; Dr Adams abstracted the clinical data and contributed to its analysis and interpretation; Drs Schmidt, Cost, and Marshall contributed to analysis and interpretation of the clinical data; Dr Marshall conceived and designed the project; and all authors participated in review and substantive revision of the manuscript and approved the final version of the manuscript as submitted.

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Parvovirus B19 infection is self-limited in healthy hosts, commonly manifesting as erythema infectiosum. Persisting infection, described in patients with HIV infection, therapeutic immunosuppression, and primary cellular immunodeficiency, is not classically associated with humoral immune defects. This report describes a 6-year-old boy who presented with persistent parvovirus infection and arthritis and was found to have common variable immunodeficiency (CVID).

**PATIENT PRESENTATION**

A 6-year-old white boy presented with a 6-month history of decreased energy and 5-pound (2.3-kg) weight loss. Other symptoms included cough, dyspnea, malaise, decreased appetite, and abdominal pain. For the preceding month he was pale, had night sweats associated with temperatures to 101°F (38.3°C), and had swelling and stiffness in large and small joints that impaired his usual activities. Nine months before presentation, he began experiencing watery, nonbloody diarrhea, which lasted until 3 months before presentation.

On physical examination he appeared chronically ill (Fig 1), with weight, height, and BMI below the 10th percentile. He had pale conjunctivae, a 2/6 systolic murmur, multiple small, mobile, nontender anterior cervical lymph nodes, and a 1-cm-diameter mobile inguinal lymph node. He had a shuffling gait and swelling; warmth; pain on motion; and decreased range of motion of his shoulders, elbows, wrists, and metacarpophalangeal, proximal interphalangeal, knee, ankle, and metatarsophalangeal joints. There were no skin lesions or rash.

Laboratory investigation showed microcytic anemia (hemoglobin 6.8 gm/dL, mean corpuscular volume 55.8 fl, reticulocyte count 1.3%), eosinophilia (22%, 1562 cells/μL), and thrombocytosis (691 000 cells/μL). Iron level was <10 μg/dL and iron saturation was 3%, but total iron-binding capacity, transferrin, and ferritin were normal. Erythrocyte sedimentation rate was 70 mm/h and C-reactive protein level was 139 mg/L. Renal, hepatic, and muscle laboratory evaluation were normal; total protein was 5.4 mg/dL and albumin was 2.7 mg/dL. Endoscopic gastric biopsy showed moderate chronic active gastritis, but biopsies of the esophagus, duodenum, terminal ileum, cecum, colon, and rectum were normal. Computed tomography demonstrated axillary and inguinal lymphadenopathy with a soft tissue mass abutting the head of the pancreas. Laparotomy revealed mesenteric lymphadenopathy, with enlarged lymph nodes behind the head of the pancreas. Biopsies from these showed sinus histiocytosis with mild eosinophilia. Flow cytometry on lymph node samples demonstrated a predominance of lymphocytes (57% to 68% T cells, 29% to 38% B cells) without evidence of monoclonality or aberrant antigen expression. Radiographic studies revealed osteoporosis, periarticular soft tissue swelling, and advanced bone maturation. Results of the following tests were normal or negative: rheumatoid factor; antinuclear antibody screen; C3 and C4 levels; antibodies to proteinase-3, myeloperoxidase, cyclic citrullinated peptide, dsDNA, RNP, Smith, SS-A (Ro), SS-B (La), Scl-70, thyroid peroxidase, mitochondria M2, myocardial cells, parietal cells, actin, striated muscle, and ribosomal P. The patient was seronegative for Epstein-Barr virus and cytomegalovirus but was not tested for mycoplasma. Stool culture was not done. Parvovirus B19 DNA was detected in whole blood by polymerase chain reaction at a copy number of 10 300 copies/mL (Fig 2). Both IgG and IgM antibodies to parvovirus B19 were detected (IgG 2.61 index value, IgM 2.20 index value).

Immunologic evaluation revealed hypogammaglobulinemia with normal immunophenotype and lymphocyte function (Table 1) and abnormal antibody responses to vaccination (Table 2). HIV antibody and HIV DNA polymerase chain reaction on blood were negative. CD40 ligand and inducible costimulator expression were normal. Fluorescent in situ hybridization showed no deletions at 22q11.2. Sequencing of the gene for transmembrane activator and CAML interactor, also known as TNFRSF13B, or tumor necrosis factor receptor superfamily, member 13B, showed homozygosity for a synonymous mutation, c.81G>A, which is not associated with CVID. Microarray genome analysis failed to reveal major deletions in the genes for CD19, CD20, and CD81; deletions in B cell-activating factor receptor, also known as TNFRSF13C, or...
tumor necrosis factor receptor superfamily, member 13C, were not assessed by this method, and sequencing of CD19, CD20, CD81, and B cell-activating factor receptor was not done. No mutations were found in the X-linked lymphoproliferative syndrome gene baculoviral IAP repeat-containing protein 4, also known as XIAP, or X-linked inhibitor of apoptosis. The diagnosis of CVID was made based on the demonstrated quantitative and qualitative humoral immune deficiency in the absence of a defined cellular defect or syndrome. Interestingly, before the presenting illness he had had recurrent episodes of acute otitis media.

Two months after presenting, the patient was started on immune globulin intravenous (IGIV) replacement therapy at a dose of 400 mg/kg per month. Parvovirus DNA levels in the blood declined during the first 3 months of therapy and were consistently undetectable beginning at 15 months (Fig 2). The arthritis responded initially to corticosteroids and naproxen, and within a few months, the anemia, eosinophilia, and thrombocytosis resolved; however, arthritis persisted, and methotrexate was started at 1 mg/kg weekly. At 5 months, etanercept was added at a dosage of 0.4 mg/kg twice weekly. At 8 months, methotrexate was discontinued because of transaminase elevation.

Fifteen months after starting IGIV, he was gaining weight (Fig 1) but still had active arthritis. Adalimumab 20 mg every 2 weeks was substituted for etanercept. Eighteen months into his disease course, he developed sclerodermatous changes over both lateral ankles, with no peau d’orange, as well as recurrence of eosinophilia (1425 cells/μL). Interleukin-5 was slightly elevated at 6 pg/mL. Repeat endoscopy showed mild gastritis and duodenitis with increased tissue eosinophils. Full-thickness skin biopsy revealed marked collagen deposition within the dermis and subcutis and sparse perivascular and interstitial chronic inflammation with lymphocytes and eosinophils, consistent with eosinophilic fasciitis. Echocardiogram, pulmonary function tests, and computed tomography of the chest were normal. Weekly and then monthly intravenous pulses of corticosteroids were started; adalimumab was discontinued and abatacept was started.

Two years out from diagnosis and initiation of immune globulin replacement and disease-modifying antirheumatologic drugs, he had not experienced neuropathies, myositis, weakness, Raynaud phenomenon, or ophthalmic involvement. Serial pulmonary function tests were normal and he had no unusual, recurrent, or opportunistic infections.

**DISCUSSION**

Human parvovirus B19 replicates in erythroid progenitor cells. In immunocompetent patients, acute viremia resolves within 1 week, coincident with the appearance of specific IgM antibody. Persistent parvovirus infection has been associated with deficient antibody responses to the capsid protein. It is not surprising, therefore, that a patient with humoral immune deficiency, as the patient presented here, might develop persistent parvovirus...
infection; however, to our knowledge, only 1 other case of persistent infection in the setting of CVID has been reported. There, parvovirus infection manifested as erythema infectiosum with reticulocytopenia and was not the presenting feature of the immune deficiency. IGIV was started 2 weeks into the illness, resulting in prompt recovery of the reticulocyte count. Two months later, parvovirus DNA was not detectable.

We are unaware of other reports of persistent parvovirus infection leading to a diagnosis of CVID. In our case and the case cited in the preceding paragraph, the clinical and virologic response to IGIV, which contains antibodies to parvovirus, supports a role for humoral immune deficiency in predisposing to persistent parvovirus infection (in the present case, the endogenous antibody response was quantitatively or quantitatively inadequate to clear the virus). There are 2 reports of persistent parvovirus infection in apparently healthy host who were treated with IGIV; in one, arthritis and viremia resolved, whereas in the other arthritis resolved but viremia persisted.

Autoimmune diseases occur in about 20% of patients with CVID. In those with arthritis, synovial biopsy may demonstrate hyperplasia, as is typical of rheumatoid arthritis (RA), but with few B cells and no plasma cells. It is possible that some cases of RA in patients with CVID are caused by unrecognized parvovirus infection. One report described 2 young children who presented with arthritis and anemia and were later diagnosed with CVID. They were treated with IGIV and both recovered; in light of the present case, one might wonder whether these patients might have had persistent parvovirus infection. It is worth noting here that a dermatomyositislike syndrome has been described in patients with X-linked agammaglobulinemia in association with chronic enterovirus or adenovirus infection.

Parvovirus causes chronic arthritis in adults. In children, parvovirus infection can mimic juvenile idiopathic arthritis (JIA). In a series of 22 children with recent parvovirus infection and arthritis and/or arthralgia, 6 developed chronic arthritis that fulfilled the diagnostic criteria of JIA. Another study of 50 children with JIA found that 48% had laboratory evidence of parvovirus viremia, as compared with 0% of a control group. Similarly, in a study of 74 children with active RA, 30% had detectable amounts of parvovirus DNA in serum, as compared with 7% of 124 controls; 22% had parvovirus DNA in synovial fluid. It is not clear whether the arthritis of persistent parvovirus viremia, which is presumably attributable to the formation of circulating antigen-antibody complexes, simply mimics that of JIA and RA, or whether parvovirus infection has a more direct role in the pathogenesis of rheumatic disease. It is possible that some of the improvement seen in our patient resulted from the antinflammatory effects of IGIV.

Our patient presented with polyarthritis and subsequently developed eosinophilic fasciitis, of which there are fewer than 35 reported pediatric cases. Eosinophilic fasciitis is a subtype of deep morphea with unclear etiology, and arthritis occurs in 40% of patients. Interestingly, patients can present with polyarthritis and subsequently develop eosinophilic fasciitis, as did our patient. The few reported cases of eosinophilic fasciitis in patients with CVID have been in adults, although a 13-year-old child presented with polyarthritis and IgA deficiency and developed eosinophilic fasciitis 4 months later.

Persistent parvovirus infection can be a presenting feature of CVID, and IgM globulin replacement can result in clearance of viremia. Chronic polyarticular arthritis or anemia in a patient with CVID should prompt an evaluation for parvovirus infection.

Table 2: IgG Vaccine Responses at the Time of Presentation

<table>
<thead>
<tr>
<th>Vaccine Antigen</th>
<th>Time since Vaccination</th>
<th>Result</th>
<th>Expected Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal polysaccharide*</td>
<td>6 y after last dose of PCV7</td>
<td>0 of 14 serotypes $&gt;1.0 \mu/mL$</td>
<td>Note*</td>
</tr>
<tr>
<td>Measles virus</td>
<td>6 y after last dose of MMR</td>
<td>1 of 14 serotypes $&gt;1.0 \mu/mL$</td>
<td></td>
</tr>
<tr>
<td>Diphtheria toxoid</td>
<td>4 y after fifth dose of DTaP</td>
<td>0.05 IU/mL</td>
<td>$&gt;0.10$</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>4 y after fifth dose of DTaP</td>
<td>0.21 IU/mL</td>
<td>$&gt;0.10$</td>
</tr>
<tr>
<td>Measles virus</td>
<td>1 y after second dose of MMR</td>
<td>0.08 relative fluorescence value</td>
<td>$\geq 0.50$</td>
</tr>
</tbody>
</table>

* Measured serotypes: 1, 3, 4*, 5, 6B*, 7F, 8, 9N, 9V*, 12F, 14*, 18C*, 19F*, 23F* (*included in PCV7; all measured serotypes included in PPSV23).


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