Occult Hereditary Spherocytosis And Human Parvovirus Infection

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The human parvovirus (HPV) is believed to be the causative agent of erythema infectiosum, or fifth disease.[1] Transient aplastic crisis linked to HPV infection has been described in several types of hemolytic anemias, congenital or acquired, such as sickle cell disease, thalassemia, autoimmune hemolytic anemias, and hereditary spherocytosis.[2-8] In some instances, the underlying hemolytic anemia was not recognized until the patient developed transient aplastic crisis secondary to HPV infection. The B19 HPV has a propensity for the erythrocyte progenitor cells, to which it is cytotoxic.[7] It is generally believed that a decrease in erythroblasts occurs in all patients on first contact with HPV B19, but a crisis reveals itself only in patients whose erythrocytes have an inherent shortened life span (as in some hemolytic anemias).

Hereditary spherocytosis is the most common hemolytic anemia in persons of Northern European extraction, occurring in 1 person in 5000.[9] Although classically believed to be autosomal dominant in inheritance, 20 to 25 percent of patients with hereditary spherocytosis have normal parents, raising the question of mutation, incomplete penetrance, or recessive forms of the disease.[9] The red cells of patients with hereditary spherocytosis have a membrane defect causing decreased cell surface area, leading to a spheroidal shape and osmotically fragile cells. Selectively trapped by the spleen, these cells have a shortened life span. The most common complication is gallbladder disease, with 55 to 85 percent of untreated patients eventually developing pigment gallstones.[10]

Patients with hereditary spherocytosis may develop one of three types of crises, including (1) *mild hemolytic crisis*, with mild anemia, transient mild jaundice, and splenomegaly (usually associated with viral syndromes); (2) *aplastic crisis*, with nausea, vomiting, abdominal pain, and headache (also associated with viral syndromes), typically lasting 10 to 14 days, with the hemoglobin falling to approximately one-half of the usual value[11]; or (3) *megaloblastic crisis* secondary to insufficient dietary intake of folic acid for increased needs (such as seen during pregnancy).[12]

We report a patient with previously undiagnosed hereditary spherocytosis who presented with an aplastic crisis resulting from an HPV infection. Considerations for diagnosing this infection and treating patients with unexpected aplastic crisis are discussed.

Case Report

A 23-year-old white woman who had been in good health had a 3-day history of aching low-back pain, arthralgias, fever, nausea, vomiting, and diffuse abdominal pain. She was seen 1 day before admission to the hospital and was thought to have gastroenteritis. On the following day she complained of the same symptoms, as well as some dyspnea on exertion. Her temperature was 37°C (98.6°F), pulse rate 96 beats per minute, and blood pressure 120/80 mmHg. Head, neck, chest, skin, and neurological examinations were normal. Her heart rate and rhythm were regular, and she had a grade II/VI systolic ejection murmur without radiation. Her abdomen was soft with active bowel sounds and mild tenderness in both the right upper and right lower quadrants, without rebound. A spleen tip was palpable. Pelvic examination showed cervical motion tenderness, bilateral adnexal tenderness, and a yellowish vaginal discharge. Laboratory studies showed her to be leukopenic (white cell count, 4.2×10^9/L [4200/mm^3]) and anemic (hemoglobin, 81 g/L [8.1 g/dL]), with a white cell differential of 0.02 band cells, 0.79 neutrophils, 0.01 eosinophils, 0.16 lymphocytes, and 0.02 monocytes. No comment was made on red cell morphology on the initial peripheral smear. Electrolytes were nor-

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mal, and blood urea nitrogen was 10 mmol/L (27 mg/dL; normal 10 to 20 mg/dL). Total bilirubin was 52 μmol/L (3.0 mg/dL), and conjugated bilirubin was 20 μmol/L (1.2 mg/dL). Serum amylase was normal, and erythrocyte sedimentation rate was elevated to 41 mm/h. Urinalysis showed trace amounts of protein and ketones and bilirubinemia (1+).

She was admitted to the hospital with a diagnosis of anemia, probably secondary to hemolysis, and acute pelvic inflammatory disease. Results of repeat laboratory studies after admission were hemoglobin 61 g/L, platelet count 127×10^9/L (127×10^3/mm^3), and a corrected reticulocyte count 0.001 (0.1 percent). Serum haptoglobin was less than 0.05 g/L (5 mg/dL; normal 27–139 mg/dL), and Coombs tests (direct and indirect) were negative. Liver enzymes were normal with the exception of an elevated lactate dehydrogenase (5.46 μKat/L [328 U/L]). Initially, intravenous doxycycline therapy was started; however, because a persistent fever and a decreasing white cell count (2.5×10^9/L) raised a question of sepsis, ampicillin and gentamicin were added. She developed a generalized, nonpruritic macular rash after the first dose of ampicillin, and her antibiotic was then changed to cefoxitin.

Bilateral iliac bone marrow aspirates and biopsies showed pure red cell aplasia with normal megakaryocyte and myeloid cells, consistent with an infectious process. The Ham test was negative, as were tests for disseminated intravascular coagulopathy. The peripheral smear contained spherocytes, and osmotic fragility testing was increased, diagnostic of hereditary spherocytosis. While hospitalized, the patient required transfusion of five units of packed red cells. Ultrasonography of her right upper quadrant revealed numerous gall stones and "sludge." Findings on her pelvic examination returned to normal. Blood cultures were negative, as were cervical cultures for *Neisseria gonorrhoeae* and *Chlamydia*. Her blood count improved; at time of discharge, her hemoglobin was 123 g/L; white cell count was 8.6×10^9/L, reticulocyte count was 0.014; and she was afebrile and feeling well.

Serum samples obtained from the patient 6 weeks after onset of illness were sent to the Centers for Disease Control (CDC). They showed both IgG and IgM antibodies to human parvovirus B19 by enzyme-linked immunoassay technique "consistent with recent infection." She continued to do well and 3 months after discharge underwent cholecystectomy and splenectomy after receiving pneumococcal vaccine. Subsequent studies of her family showed hereditary spherocytosis in her father, sister, niece, and nephew.

Discussion

The human parvovirus, the smallest DNA-containing animal virus, is a single-stranded DNA, nonenveloped virus. It requires actively dividing cells for autonomic replication; therefore, the bone marrow is a "favorable milieu." HPV was originally discovered in the blood of 9 healthy donors during evaluation of second-generation tests for hepatitis B surface antigen.[13] A viruslike particle 23 nm in diameter was revealed by electron microscopy and was originally labeled B19 or parvoviruslike agent or serum parvovirus-like virus.[14]

HPV infection is common worldwide, and it usually occurs in children of primary school age.[15] The antibody is detectable most often in children between the ages of 4 and 10 years, and studies report a seroprevalence from 2 to 15 percent in children aged 1 to 5 years and from 30 to 60 percent in adults.[16] The respiratory tract is the most likely portal of entry, although blood products can also transmit the virus. HPV spreads easily among children within families, with an estimated 50 percent attack rate in susceptible household contacts.[15] Annual and seasonal (winter, spring) variations are noted.

HPV is believed to be the causal agent of the exanthem erythema infectiosum (fifth disease), a febrile illness with mild flulike symptoms, a typical rash on the face (described as "slapped-cheek" in appearance), and a lacey, reticulated rash on the trunk and extremities. Up to 20 percent of infections are asymptomatic. The incubation period of erythema infectiosum is 4 to 14 days based upon studies of secondary household infections. Studies in volunteers have reported onset of the rash 17 to 18 days after inoculation.[16]

Although benign infection with HPV is the usual case, adults can occasionally develop a self-limited, moderately severe symmetrical peripheral polyarthropathy, primarily involving the hands, wrists, and knees.[17] No recent literature

supports an association between pelvic inflammatory disease symptoms and HPV infection. Severe complications of the infection are also known. The virus appears to have the potential to be embryocidal, although not teratogenic.[18,19] Fetal infection can cause severe anemia, congestive heart failure, fetal hydrops, and death.[15,19-21] A study from the United Kingdom found the risk of fetal death to be up to 10 percent during the 10th to 20th weeks of pregnancy.[22] Congenital anomalies after B19 infection in the mother do not seem to occur.[23,24]

HPV is cytotoxic to erythrocyte progenitors, and although this cell line is the main target, other cell lineages also can be involved, causing thrombocytopenia and, less often, leukopenia. In immunocompromised patients, chronic infection with HPV can cause a persistent and severe anemia.[25]

It is well known that patients with chronic hemolytic anemia can develop episodes of medullary aplasia of brief duration and spontaneous resolution (transient aplastic crises) in association with infections, particularly of viral origin. Several studies have reported this occurrence in patients with known occult diseases, such as sickle cell disease, hereditary spherocytosis, various thalassemias, and pyruvate kinase deficiency. Aplastic crises associated with HPV infection are commonly accompanied by fever, headache, abdominal pain, generalized fatigue and weakness, nausea, vomiting, and rigors.

It has been postulated that aplasia can occur in normal persons, but because of normal red cell survival and short duration of the illness, such episodes go unnoticed. The crisis is more readily detected in the immunocompromised person.[7] Mortimer[26] conducted a retrospective study of 16 reports published between 1935 and 1984 and concluded that HPV was the primary cause of aplastic crises occurring in patients with hereditary spherocytosis. To support his hypothesis, he pointed out that these patients had no history of aplastic crisis attacks, and the interval between index and other cases was relatively constant at approximately 9 days. Also, the duration of the aplastic crisis was regular and invariable at 10 to 12 days after onset. Kelleher, et al.[3] also have shown that HPV is serologically linked to aplastic crisis in a population of pediatric patients with hereditary spherocytosis. Lefrere and colleagues[8] have concluded that in a previously healthy patient who experiences an aplastic crisis that is due to HPV, the diagnosis of hereditary spherocytosis should be investigated.

The diagnosis of HPV infection is made by demonstrating the virus by electron microscopy or by demonstrating seroconversion of IgM class-specific antibodies to HPV in a recovering patient by enzyme-linked immunoassay or radioimmunoassay techniques. IgM antibodies are present in approximately 90 percent of cases by the 3rd day after onset of symptoms of erythema infectiosum or transient aplastic crisis and decline 30 to 60 days after onset. IgG antibodies appear by the 7th day of illness and persist for years. Transmission electron microscopy can demonstrate inclusions containing parvoviruslike particles, where light microscopy of the erythroid precursor cells shows eosinophilic nuclear inclusions and chromatin peripherally.

The CDC has submitted guidelines in *Morbidity and Mortality Weekly Report* for preventing HPV infection and caring for persons exposed to or infected with the virus. It was believed that those patients with clinical erythema infectiosum are no longer infectious, and isolation procedures are not needed for them. Patients with transient aplastic crisis or immunodeficient patients with chronic anemia should be considered to be infectious. Masks are suggested, as well as gloves and gowns, if a caretaker is likely to have contact with respiratory tract secretions.[15] A study of two separate outbreaks of illness resembling erythema infectiosum occurred recently in a hospital setting. Two immunocompromised patients, both with sickle cell disease and transient aplastic crisis, had suspected and later proved HPV infection. Attack rates of susceptible contacts were 36 to 38 percent, with development of clinical symptoms in an average of 12.6 days.[27] The authors' recommendation was that all patients with hereditary hemolytic anemias who are admitted for febrile illness be evaluated for aplasia and promptly placed in respiratory and contact isolation if an aplastic crisis is suspected. In the nonhospital environment, there are fewer options for decreasing transmission of the virus. The efficacy of hand washing and decontamination of toys and environmental surfaces has not been studied.

Conclusion

This report presents a case of occult hereditary spherocytosis diagnosed after the patient developed an aplastic crisis resulting from an acute human parvovirus infection. We believe that it is important for physicians to be aware of the relation between HPV infection and aplastic crises in patients with various chronic hemolytic anemias.

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