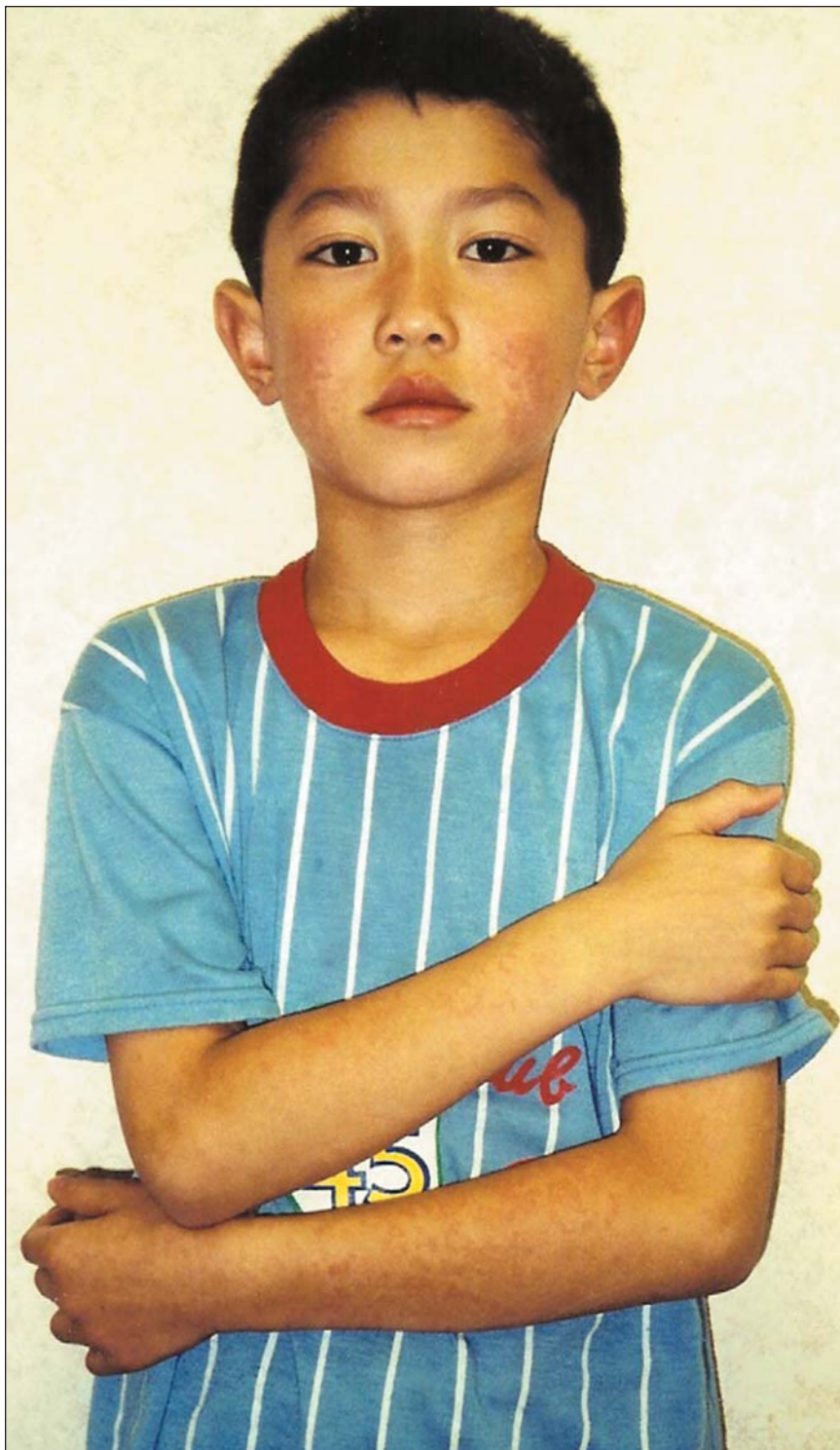# Consultant
WHAT'S YOUR DIAGNOSIS?®

Sharpen Your Diagnostic Skills

By ALEXANDER K. C. LEUNG, MD—Series Editor, and WM. LANE M. ROBSON, MD

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HISTORY

Seven-year-old boy with red, nonpruritic rash that appeared first on the cheeks and then spread to the trunk, extremities, and buttocks. No history of respiratory, GI, or other symptoms in the several weeks before the onset of the rash. Patient is otherwise healthy.

PHYSICAL EXAMINATION

The child is afebrile. A lacy erythematous rash is noted on the trunk, extremities, and buttocks.

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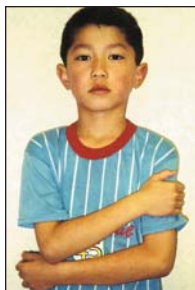
ANSWER:
ERYTHEMA INFECTIOSUM (FIFTH DISEASE)

Erythema infectiosum—also known as fifth disease—is a benign self-limited exanthematous illness of childhood. The condition was the fifth common childhood exanthem to be named (after measles, scarlet fever, rubella, and Filatov-Dukes disease [an atypical scarlet fever]).

ETIOLOGY

Erythema infectiosum is caused by parvovirus B19—a member of the genus *Erythrovirus* in the family Parvoviridae. Parvovirus B19 is the only member of the Parvoviridae family known to cause disease in humans.[1] The virus was first discovered in 1975.[2] The name is derived from the Latin word *parvum,* which means small. The designation B19 refers to the laboratory number that was used to identify the first positive isolate, which was located in the 19th cell in row B of a panel of sera.

Parvovirus B19 is a nonenveloped, icosahedral, single-stranded DNA virus that is composed of approximately 5600 nucleotides, and is 20 to 25 nm in diameter.[3,4] The capsid structure and the absence of an envelope are responsible for the resistance of the virus to heat, cold, and detergents.[5] The viral genome encodes 1 nonstructural protein, NS1, and 2 capsid proteins, VPI and VP2. NS1 is involved in the regulation of viral promoter and replication functions and is toxic to the host cells. Four percent of the capsid protein is VP1 and 96% is VP2.[5] VP1 and VP2 self-assemble to form viral particles in vitro.[3]

PATHOGENESIS

After infection, there is a brisk viremia. Parvovirus B19 has an affinity for late erythroid progenitor cells in the bone marrow[6] and leads to transient erythroid aplasia. Erythrocyte P blood group antigen—a surface glycolipid present in erythroid cells—is a cellular receptor for parvovirus B19. These receptors are also found on endothelial cells and on cells in the placenta, fetal heart, and liver.

The rash appears after the viremia has cleared and coincides with the development of IgG antibody to parvovirus B19.[7] Persons who lack the blood group P antigen are immune to parvovirus B19 infection.[8]

EPIDEMIOLOGY

Infection with parvovirus B19 is reported worldwide and is common. Children between the ages of 6 and 14 years are most often affected.[9] The prevalence of IgG antibodies against parvovirus B19 ranges from 2% to 15% in children under 5 years, 15% to 60% in those aged 6 to 19 years, and 30% to 60% in adults; these antibodies are present in more than 85% of the pediatric population.[10]

Most community outbreaks occur in the winter and spring.[5] Parvovirus B19 is spread mainly by respiratory droplets.[4] Secondary spread among susceptible school contacts and family members occurs in 20% and 50% of cases, respectively.[11] Transmission usually occurs during the week before the onset of symptoms. Transmission via percutaneous exposure to parvovirus B19–infected blood or blood products and vertical transmission from a mother to a fetus can also occur.[11] The incubation period is 4 to 21 days.[12]

CLINICAL MANIFESTATIONS

Prodromal symptoms occur in 20% to 60% of cases.[13] These are usually mild and consist of low-grade fever, headache, malaise, myalgia,

and coryza.[14] A symptom-free period of 1 to 7 days usually follows the prodrome and precedes the exanthem.[13] Because symptoms are so mild and temporally separated from the onset of the rash, the prodrome is often not recollected.

The rash typically evolves in 3 stages. The initial stage is an erythematous rash on the cheeks, with a characteristic "slapped cheek" appearance. A circumoral pallor is usually present. In the second stage, the rash spreads concurrently or quickly to the trunk, extremities, and buttocks as a diffuse macular erythema.[1] The rash tends to be more intense on extensor surfaces. The palms and soles are spared.[14] Central clearing of the rash results in the characteristic lacy or reticulated appearance. Pruritus is noted in up to 15% of patients. The rash usually resolves spontaneously within 3 weeks.[1]

The third stage is characterized by evanescence and recrudescence.[15] Triggers for recrudescence include exercise, emotional stress, hot baths, and sunlight.[13] The third stage usually lasts for a few weeks, but recurrences may be noted for months.[13]

COMPLICATIONS

Arthritis and arthralgia can occur as a complication of erythema infectiosum or as the sole clinical manifestation of parvovirus B19 infection. Although common in adults and older adolescents, arthropathy occurs in only 8% to 10% of children with erythema infectiosum.[16] Arthropathy is more common in females than males.[1,3] The most commonly affected joints are the metacarpophalanges, followed by the knees, wrists, and ankles.[10] Symptoms are usually bilateral.[1,16] The arthropathy might be immunologically mediated because its onset coincides with the appearance of circulating antibodies.[10]

The arthropathy is self-limited and does not cause destruction of the affected joints. The condition usually resolves in a few weeks.[4,5]

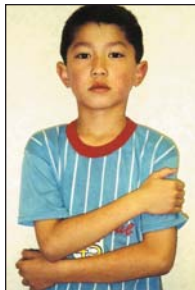Transient aplastic crisis, another potential complication, results from an arrest of erythropoiesis and the reticulocytopenia induced by parvovirus B19. It usually lasts for 7 to 10 days.[17] The transient reticulocytopenia usually has little impact on an otherwise healthy child. However, children with decreased red cell production are especially prone to a transient symptomatic aplastic crisis.[3,13,18] (This includes children with iron deficiency anemia; ongoing blood loss; or a chronic hemolytic anemia, such as hereditary spherocytosis, sickle cell disease, thalassemia, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, or an autoimmune hemolytic anemia.) Persistent parvovirus B19 infection may develop in immunodeficient patients with resultant severe anemia from pure red cell aplasia.[3,13]

Other less commonly reported hematologic complications following parvovirus B19 infection include transient neutropenia, thrombocytopenic purpura, Henoch-Schönlein purpura, hemophagocytic syndrome, and Diamond-Blackfan syndrome.[10,19-22]

Other rare complications that have been reported in association with erythema infectiosum or parvovirus B19 infection include aseptic meningitis, encephalitis, brachial plexus neuropathy, carpal tunnel syndrome, Guillain-Barré syndrome, acute cerebellar ataxia, myocarditis, hepatitis, hypocomplementemic post-infectious glomerulonephritis, chronic fatigue syndrome, Gianotti-Crosti syndrome, Kawasaki disease, and papular-purpuric gloves-and-socks syndrome.[4-6,23-29]

Maternal infection with parvovirus B19 during pregnancy is associated with nonimmune hydrops fetal-

is, fetal anemia, high output cardiac failure, and spontaneous abortion.[30,31] The highest risk is during the first 20 weeks of gestation.[32] The risk of fetal loss in the first 20 weeks of gestation is 15%, compared with 5% in controls.[33] A congenital infection syndrome in newborn infants has been described and includes anemia, a blueberry-muffin rash, and hepatosplenomegaly.[34]

DIAGNOSIS/THERAPY

The diagnosis is based on the typical clinical presentation of a "slapped cheek" appearance, with absent or mild prodromal symptoms, followed by a symmetrical, reticulated rash that waxes and wanes. Laboratory diagnosis is rarely necessary.

When laboratory confirmation is required, determination of anti-parvovirus B19 IgM antibody is the preferred diagnostic test in an immunocompetent host. IgM antibody is detectable within 1 to 3 weeks of exposure and is generally present for 2 to 3 months.[11] The presence of serum IgG antibody indicates previous infection and immunity, although seroconversion from an IgG-negative to an IgG-positive state suggests recent infection.[1]

In an immunocompromised patient, serologic diagnosis is unreliable. In this setting, demonstration of the virus by nucleic acid hybridization or polymerase chain reaction assay is the optimal diagnostic method.

Differential diagnostic considerations include scarlet fever, rubella, measles, enteroviral infection, drug reaction, and collagen vascular disease.

In immunocompetent patients, there is no specific antiviral therapy and treatment is symptomatic. The rash develops after the viremia has cleared. Because the virus can no longer be transmitted, there is no need to isolate affected children or to restrict attendance at school or child care facilities. ∎

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