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LEARNING OBJECTIVES

- Describe the etiology and epidemiology associated with fifth disease
- Review the various clinical manifestations of this illness and how it is diagnosed
- Explain options for symptomatic treatment of fifth disease
- Discuss the extensive differential diagnosis for infection with the B19 virus

Erythema infectiosum: Recognizing the many faces of fifth disease

Four patient histories are presented. Although each case is different, all of these patients have the same illness. Would you be able to recognize the common etiology?

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Fifth disease is a common childhood viral illness that poses a threat of few sequelae in the healthy child. However, the infection can masquerade as other disorders in patients of all ages, leading to misdiagnosis, failure to diagnose, and, at times, overtreatment. Clinician awareness of the many “costumes” worn by this viral infection is key to improved diagnosis and treatment for patients with the disease.

What do these presentations have in common? A 52-year-old, generally healthy white male schoolteacher presents with new-onset symmetric joint pain localized to the hands and wrists for the past 3 to 4 weeks. He has also experienced profound fatigue for 6 to 7 weeks.

A 31-year-old female presents with facial rash, fever, arthropathy, and myalgia. Initial laboratory test results indicate cytopenia, hypocomplementemia, anti-DNA, and antinuclear antibodies (ANAs).

A 36-year-old, gravid pediatric nurse in her third trimester notes an absence of fetal movement 1 week after having a mild flulike illness.

A 50-year-old male presents with the classic signs and symptoms of acute MI with normal cardiac angiography. He later develops left ventricular dysfunction (LVD).

HISTORICAL PERSPECTIVE

Fifth disease, another name for erythema infectiosum (EI), follows measles, scarlet fever, rubella, and Filatov-Dukes disease in the classification of common childhood exanthems (70% of patients are age 5 to 15 years) and is caused by the parvovirus B19 (B19).^{1,2} In 1975, Yvonne Cossart, an Australian virologist, noted an anomalous reaction of normal blood donors' sera corresponding to position 19 in an

assay for hepatitis B, thus identifying the first parvovirus of human blood.³ Eight years later, investigators found a connection between the human parvovirus and EI;⁴ 10 years after that, they determined that viral replication occurs only in erythroid progenitor cells, specifically to the blood-group P antigen.⁵ Distinct B19 syndromes are widespread, and known manifestations are seen in pediatrics, obstetrics, dermatology, rheumatology, and hematology.⁶

ETIOLOGY AND EPIDEMIOLOGY

B19, a single-strand, nonenveloped DNA virus that contains two capsid proteins (VP1 and VP2) and one nonstructural



A “slapped cheek” appearance is the classic sign of fifth disease.

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protein (NS1), is an erythrovirus that infects only mammals.⁷ B19 infection is common throughout the world. Outbreaks are observed in late winter or early spring. Viral transmission occurs via inhalation of infected droplets or transfusion of infected blood products and vertically from mother to fetus. Incubation ranges from 4 to 14 days and up to 21 days. The transmission rate is about 50% for household exposures and approximately 20% to 30% for susceptible teachers and day-care workers.^{1,7,10} B19 infection among health care workers supports transmission within and across patient wards via common staff areas and handling contaminated materials.¹¹ However, one hospital outbreak demonstrated the ease of community-acquired infection when the rate of infection among medical students who had been exposed while in hospital attendance was lower (33.6%) than that of students who had not been in hospital attendance (42.6%).¹²

CLINICAL MANIFESTATIONS

Classic childhood B19 infection manifests as rash with the distinctive appearance of a slapped cheek or facial flush following a low-grade fever, coryza, headache, and nausea. The infection completes its course with a diffuse macular, lacy, reticulated-appearing rash on the trunk and extremities. The rash can be exacerbated by sunlight, heat, exercise, and stress for up to 3 weeks. The infection ultimately resolves spontaneously, leaving the child with lifelong immunity. Children often recover without sequelae; 85% of the elderly show seropositivity. Older children may experience mild pruritus; lymphadenopathy; and atypical papular, purpuric, or vesicular rashes.^{1,7,8} However, less common childhood and adult manifestations, such as those presented by the four patients previously described, can occur.

DIAGNOSIS AND TREATMENT

In immunocompetent persons, diagnosis is based on presence of B19 IgM antibodies within 10 to 12 days after infection. Antibodies remain detectable for approximately 3 to 4 months. B19 IgG is detectable within 2 weeks of illness and persists for life. The virus tapers off within 2 weeks, with DNA detectable by polymerase chain reaction (PCR) assay for months or years.^{2,9} A transient drop in the reticulocyte count and he-

moglobin concentration starts 1 to 2 weeks after infection, and normalization occurs by 1 month after infection.⁹

Symptomatic treatment with NSAIDs prevails, with most patients experiencing a self-limited B19 infection. Other treatments include blood transfusions for patients with reduced erythropoiesis or intrauterine infections and immunoglobulin for immunosuppressed patients.^{7,8} Immunoglobulin dosages are 0.4 g/kg/d for 5 days or 1 g/kg/d for 2 to 3 days.⁹

Autoimmune diseases B19 infection should be included in the differential diagnosis for patients with new-onset systemic lupus erythematosus (SLE), as both diseases may manifest with malar rash, fever, arthropathy, and myalgia. Laboratory test results may include the presence of cytopenia (often transient), anti-DNA and ANAs, and hypocomplementemia. B19 infection masquerading as SLE has an improved prognosis for being a self-limited illness; improvement is noted within several weeks.¹³ However, B19 infection may also exacerbate symptoms in patients with known SLE. B19 DNA was detected in the sera of 17 of 72 (24%) patients with known SLE but not in patients with other autoimmune diseases.¹⁴ Levels of B19 IgM or IgG were lower than expected, leading to concerns that disease-mediated immunosuppression or use of immunosuppressive agents may result in persistent infection. Concomitant B19 infection and SLE may be a specific subset of cases requiring further study.¹⁴

Arthritic disorders The relationship between arthropathy and a viral etiology has been considered for decades, but the role of B19 could not be confirmed until serum B19 antigen detection became available in the early 1980s. Joint symptoms occur in approximately 8% of infected children and 60% of infected adults. Prevalence of joint symptoms is higher in women (59%) than in men (30%). The typical presenting pattern is an acute onset of symmetric polyarticular arthritis, particularly affecting the proximal interphalangeal and metacarpophalangeal joints.¹⁵ A study published in 1985 associates B19 infection with acute arthropathy in 19 of 24 patients; all 19 patients were female.¹⁶ In 1992, a prospective study reported serologic evidence of recent B19 infection in 3 of 21 patients with early synovitis.¹⁷

Serum samples that test negative for B19 IgM or IgG when synovial membrane test results are positive for B19

KEY POINTS

- Fifth disease, another name for erythema infectiosum, follows measles, scarlet fever, rubella, and Filatov-Dukes disease in the classification of common childhood exanthems and is caused by the parvovirus B19 (B19). Distinct B19 syndromes are widespread, and known manifestations are seen in pediatrics, obstetrics, dermatology, rheumatology, and hematology.
- Classic childhood B19 infection manifests as rash with the distinctive appearance of a slapped cheek or facial flush following a low-grade fever, coryza, headache, and nausea. The infection completes its course with a diffuse macular, lacy, reticulated-appearing rash on the trunk and extremities. The infection ultimately resolves spontaneously, leaving the child with lifelong immunity. Older children may experience mild pruritus; lymphadenopathy; and atypical papular, purpuric, or vesicular rashes.
- Symptomatic treatment with NSAIDs prevails with most patients experiencing a self-limited B19 infection. Other treatments include blood transfusions for patients with reduced erythropoiesis or intrauterine infections and immunoglobulin for immunosuppressed patients.
- B19 infection is a vital addition to the differential diagnosis, whether the patient has a suspected virus-related illness or a condition not classically considered viral in etiology. The many faces of B19, as well as other emerging members of the Parvoviridae family, can challenge the best diagnostician. Therefore, maintaining an index of suspicion for this tiny virus is good medicine.

DNA are of particular concern as this leads to the presumption that B19 is not implicated in these patients. One study reported the rate of B19-positive synovium results as 40%, but 100% of sera results were negative.¹⁸ In a case of painful asymmetrical polyarthritis followed by erosive polyarthritis with documented B19 infection, radiographic evidence of cortical erosion was not seen until 8 months after infection.¹⁹ B19 was detected in the synovial tissues of 30 of 39 patients with rheumatoid arthritis (RA) but infrequently in patients with osteoarthritis and traumatic joints; demonstrating a connection between B19 infection and both initiation and perpetuation of RA synovitis.²⁰ Although rare, B19 infection has also been linked to remitting seronegative symmetrical synovitis with pitting edema.²¹

Fibromyalgia, a condition with uncertain etiology, has also been associated with B19 infection. Three women with classic signs and symptoms of fibromyalgia, including generalized aches, fatigue, and difficulty sleeping for more than 3 months, tested positive for B19 IgM and IgG. Two of the three patients were pediatric nurses, and the infection was transmitted to the third patient from her infected daughter. Clinicians are encouraged to consider B19 infection in the etiology of fibromyalgia, particularly if the initial symptoms follow a flulike illness.²²

“Confounding issues are uncertain maternal immunity and concerns about screening individual patients or all pregnant patients.”

Including B19 infection in the arthritis differential diagnosis may alter treatment and enable reassurance of a less chronic disease course.^{18,23-28} If chronicity occurs, consider possible immunocompromise as the cause of viral persistence.²⁹

Hematologic disorders An association between aplastic crisis in patients with B19 infection and known RBC cell disorders, such as sickle cell anemia and congenital hereditary spherocytosis has been established.^{30,31} B19 infection is also implicated in aplastic crisis in patients who do not have blood disorders as well as in patients with idiopathic thrombocytopenic purpura (ITP). Increased morbidity prompts a need for a vaccine.³² In a controlled study of 27 patients, positive B19 PCR viral DNA and IgM were detected in approximately 41% of patients in aplastic crisis.³³ Thrombocytes are also targeted. In a study involving 19 children with ITP, 47% had positive B19 PCR virus; the children also tested positive for IgM (57%) and IgG (73%), leading to questions of the putative cause of thrombocytic attack by B19.³⁴

Maternal and fetal disorders B19 affects 1% to 5% of pregnant women, mainly with normal pregnancy outcome, and infection is associated with higher prevalence during epi-

demics (3%-20%) and sera conversion rates of 3% to 34%. Adverse outcomes are more prevalent when infection occurs during the first two trimesters, and risk of fetal loss is higher when infection occurs during the second half of pregnancy. B19 infection may cause fetal anemia with shortened half-life of fetal erythroid progenitor cells, causing high-output cardiac failure.³⁵

The relationship between B19 and fetal death was first recognized in 1984 in an index case of a 35-year-old para 1 + 0. The pregnancy was uneventful until week 39, when the mother reported a flulike illness. Spontaneous labor with ultrasound-confirmed intrauterine death of a normal infant (normal amniotic α -fetoprotein, chromosomal assessment, and detailed ultrasound at 16 weeks) occurred 1 week later. At necropsy, the 3,840-g delivered infant was macerated and had severe meconium ileus and peritonitis-related ascites. TORCH (toxoplasma, rubella, cytomegalovirus, herpes virus) screening was negative; however, both maternal and fetal sera contained B19 IgM indicating recent maternal and congenital fetal infection.³⁶

Other studies found B19 to be the causative agent in the intrauterine deaths of 10 anatomically normal infants with nonimmune hydrops fetalis; the researchers noted that 3 out of 10 (27%) of the mothers exhibited subclinical B19 infections during pregnancy, implicating myocardial-associated fetal demise.³⁷ A review of 14,147 deliveries that took place in three Stockholm hospitals found that 7 of 47 cases (15%) of intrauterine fetal death were positive for B19 infection.³⁸ The infection was also implicated in 2 of 37 (5%) spontaneous miscarriages. Researchers contend that B19 infection could be more common than previously reported, citing an affinity for such fetal tissues as the liver, myocardium, and endothelium.³⁸

Questions from pregnant women regarding risk of exposure at home, school, and work settings pose special challenges. Confounding issues are the uncertainty of maternal immunity, followed by concerns about screening individual patients or all pregnant patients as B19 is generally endemic and not treatable. A vaccine is not currently available.⁸ Information from a large Danish study focused on the first trimester of pregnancies (N = 30,946 serum samples) provides some insight and highlights screening issues.³⁹ A total of 65% of the women had evidence of past infection; odds of seropositivity were increased in those women who had a higher number of siblings, a sibling of the same age, more children of their own, and occupational exposure to children. Compared with other pregnant women, nursery-school teachers had a threefold increased risk of acute infection. Researchers note that susceptible women are at substantial risk during epidemics, along with nursery-school teachers and those in contact with children aged 5 to 7 years.³⁹ If needed, treatment with intrauterine RBC blood transfusions can improve survival in the severely anemic fetus. High-dose IV gamma globulin has been used in placental exchange during pregnancy in infected women.³⁵

Cardiac disorders Intrauterine B19 has a particular affinity for the P antigen expressed on fetal cardiac myocytes, which

leads to high-output cardiac failure and nonimmune hydrops fetalis.³⁵ This affinity continues into adulthood, and B19 infection and other viruses should be included in the differential of acute myocarditis and dilated cardiomyopathy. In one study of 24 consecutive patients who had normal results on emergent coronary angiography, endomyocardial biopsy specimens revealed virus-positive results in 17 patients (71%). Twelve patients were infected with B19; three patients were infected with enterovirus; and two patients were infected with adenovirus.⁴⁰ Another study found B19 in 49 of 87 (56%) endomyocardium biopsies, human herpesvirus 6 (HHV6) in 16

“An absent IgM response despite persistent infection may be the result of a failure to produce neutralizing IgM antibodies.”

(18%), and combined B19 and HHV6 in 15 (17%).⁴¹ Compared with the HHV6-infected patients, the clinical course for those with B19 infection was primarily benign. Most patients experienced significant or complete recovery. Furthermore, B19 did not directly infect the myocytes; rather myocardial damage was secondary to inflammatory cell migration.⁴¹ Clinicians should be aware of potential viral etiology in patients presenting with acute MI. Recovery may depend upon the type of virus. Study outcomes differed, ranging from full recovery to progressive LVD clinically diagnosed as dilated cardiomyopathy.^{40,41}

Dermatologic disorders A known adage is that when confronted with an atypical rash, clinicians reflect that it “must be viral.” Time may prove this diagnosis correct more often than not as B19 seems to have an affinity for the skin and atopy may predispose to it. Researchers documented the persistence of the B19 genome in the cutaneous lesions of seven patients with connective tissue diseases, including dermatomyositis, SLE, RA, necrotizing vasculitis, and microscopic polyarteritis nodosa. An absent IgM response despite persistent infection may be the result of a failure to produce neutralizing IgM antibodies caused by a specific immune defect.⁴² B19 PCR DNA was also significantly elevated in 36 of 48 patients (75%) with systemic sclerosis compared with 53 of 97 (55%) normal controls. The occurrence rate of B19 infection in study patients with SLE, dermatomyositis, morphea, or graft-versus-host disease showed no difference from controls.⁴³

Globalization necessitates knowledge of rashes that are rare in the United States but more common in other parts of the world. Although considered more common in Europe and the Middle East, papular-purpuric gloves and socks syndrome (PPGSS)—characterized by fever, acral pruritus, edema, petechiae, and oral erosions—has been seen in the United States. A case report from Yale-New Haven Hospital reported a positive IgM finding in serum drawn on day 9 of an illness in a

20-year-old female patient; 9 months later, the patient tested positive for B19 IgG.⁴⁴ An interesting case of mother-to-daughter transmission of PPGSS found presence of B19 IgM in the mother on day 3 and in the daughter on day 4.⁴⁵ Three weeks later, both patients were IgM- and IgG-positive. This is the first documented case of mother and daughter presenting together with PPGSS.⁴⁵ Researchers note that sufficient evidence exists to suggest that PPGSS is a rare but distinctive manifestation of primary B19 infection in young adults.

Hepatic disorders The B19 etiology of unexplained fulminant hepatitis was shown when the B19 genome was isolated in 4 of 11 children admitted to a Belgian hospital. The distinguishing points in these children were that there was no jaundice, a low bilirubin level, high ALT or AST activity, and a rapid return to normal function.⁴⁶ A Japanese study revealed that 4 out of 15 patients (aged 7 months to 5 years) who tested positive for B19 IgM, IgG by PCR had acute hepatitis of unknown origin. In all of the cases, serum concentrations of AST and ALT normalized within 3 weeks. Clinicians should recognize that fulminant hepatitis caused by B19 may have a significantly better prognosis.⁴⁷

CONCLUSION

B19 infection is a vital addition to the differential diagnosis, whether the patient has a suspected virus-related illness or a condition not classically considered viral in etiology, such as the four cases presented in this article. In addition, questions about more widespread screening of blood products, pregnant women, and even vaccine development exist for clinicians to consider.⁴⁸ The many faces of B19, as well as other emerging members of the Parvoviridae family, can challenge the best diagnostician.⁴⁹ Therefore, maintaining an index of suspicion for this tiny virus is good medicine. **JAAPA**

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