



Parvovirus B19: a review

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Background

Parvovirus B19 is a human pathogen that may result in a spectrum of clinical findings. Clinical features range from subclinical infection to dermatologic, rheumatologic, and hematologic findings, to potentially fatal effects. New evidence even suggests a role in the pathogenesis of collagen-vascular diseases. Parvovirus B19 is the only parvovirus clearly linked with human disease. The virus belongs to the family Parvoviridae and the genus Erythrovirus and is a nonenveloped, single-stranded DNA virus [1]. It is resistant to heat and detergent because of its small genome and lack of a membrane [2]. The virus itself was originally discovered in 1974, and the name B19 refers to the blood bank code by which the original positive serum sample was labeled [3].

The virus is highly tropic for erythroid progenitor cells and thus is classified as an erythrovirus. In fact, complete replication of the virus has been found only in these cells [2]. The cellular receptor for B19 is a globoside, also known as blood group P antigen. Clinically, this classification means that those persons lacking this antigen on their erythroid cells are not susceptible to infection with B19 [2]. The virus is composed of three proteins in association with a DNA molecule. These proteins include one nonstructural protein, NS1, and two structural proteins, VP1 and VP2. Although not fully defined, studies have made some progress in identifying antigenic regions on these proteins [4,5].

Epidemiology

Infection with parvovirus is ubiquitous and occurs worldwide. The prevalence of immunity to parvovirus, indicative of prior infection, has been shown to rise with age. In Australia, this prevalence was

demonstrated to rise from approximately 40% in children and adolescents, to 60% in adults, to 75% in adults older than 40 [6]. The prevalence varies among countries, and interestingly, it seems to be more common in temperate versus tropical countries. Although the prevalence in England and Wales is similar to that of Australia, countries such as Singapore and South Africa demonstrate a lower prevalence of immunity in adults [6].

Transmission

Transmission of the virus occurs through the respiratory route in most cases. The virus is shed in nasal and oral secretions during periods of viremia, so patients may transmit the virus before development of rash [7]. Much less likely is transmission by way of blood products or bone marrow. Evidence supports transmission through transfusion with blood products, primarily pooled blood products [8,9]. Because parvovirus B19 lacks a lipid envelope, it is not inactivated during treatment with solvents and detergents [9]. Although neutralizing antibodies present in pooled plasma may prevent transmission, the infectivity of donor blood is not fully understood [2,8]. A workshop convened by the National Heart, Lung, and Blood Institute recommended additional research in this area but concluded that there was insufficient evidence to recommend universal testing [2]. Transmission by way of bone marrow (during bone marrow transplant) also has been demonstrated [10].

Clinical features

The main clinical features of infection with B19 include dermatologic manifestations, rheumatologic findings, and hematologic effects. It should be noted

specifically that asymptomatic infection with parvovirus B19 is considered common. In one outbreak, 26% of adults were reported to be asymptomatic [11]. Less commonly, infection may result in neurologic and hepatic disease [3].

Much of what is known concerning the clinical features of B19 infection comes from epidemiologic studies and case reports; however, Anderson et al [12] studied patients with experimental infection. After intranasal administration of virus to healthy adults, some patients were asymptomatic, whereas others experienced fever, chills, headache, and myalgias on day 6. These symptoms correlated with a peak in viremia. On approximately day 10, IgM anti-B19 antibody appeared, followed by IgG anti-B19 a few days later. The appearance of IgG correlated with appearance of the classic dermatologic findings of “slapped-cheek” appearance of the face and reticular erythema on the extremities. Although these healthy volunteers did not develop anemia, they did exhibit reticulocytopenia. In outbreaks of natural infection, the incubation period has been reported to vary between 6 to 18 days, although incubation as long as 28 days has been reported [7]. The IgG antibody has been demonstrated to persist for many years, probably lifelong, and confers long-lasting immunity.

Dermatologic manifestations

The first description of parvovirus infection was made by a dermatologist two centuries ago with a report of clinical features recognized today as erythema infectiosum [3]. It has since been shown that B19 infection may result in a spectrum of dermatologic diseases. Infection may result in two specific B19-related dermatologic diseases, erythema infectiosum and papular purpuric “gloves-and-socks” syndrome. Infection also may result in nonspecific findings, such as reticular erythema, maculopapular eruptions, and purpuric eruptions. Other dermatologic entities, such as erythema multiforme and Gianotti-Crosti syndrome, which may occur because of a number of causes, also have been linked to B19 infection.

The most well-known dermatologic manifestation of parvovirus B19 is erythema infectiosum. This well-recognized exanthem also is called fifth disease, and it often is described with the term “slapped cheek.” Less widely recognized and described only a decade ago, papular purpuric “gloves-and-socks” syndrome also is associated with parvovirus B19.

Nonspecific dermatologic findings are linked less frequently to parvovirus, which is understandable, because such nonspecific findings typically are not

investigated; however, Seishima et al [13] undertook a study of the clinical features of adults with IgM antibodies positive to B19. In their study of 22 adults, they found that the cutaneous manifestations fell into three groups. In the first, reticular erythema occurred, similar to that seen in erythema infectiosum. The second group exhibited maculopapular eruptions similar to rubella. The third group exhibited petechiae and purpura, although none of the cases were limited to the hands and feet. Most of these patients were febrile and complained of multiple arthralgias and general fatigue. In approximately one fourth to one third of cases, lymph node swelling, lower extremity edema, and swelling of the fingers were seen. In their series of 16 patients, Cathebras et al [14] also noted dermatologic findings of vascular purpura and edema.

Magro et al [15] described patients with cutaneous findings associated either with serologic evidence of B19 infection or documentation of B19 genome in lesional skin. In their series of 14 patients, 3 patients presented with typical erythema infectiosum. Other presentations included eruptions resembling cutaneous lupus, dermatomyositis, and Sweet’s syndrome, in addition to two cases of palpable purpura.

Scattered case reports also describe nonspecific findings. One case described generalized livedo reticularis [16]. Others have described desquamation [17] and vesiculopustular skin eruptions [18]. Pruritus in the absence of rash has been described [19]. Numerous case reports have described other types of specific dermatologic disorders in association with parvovirus infection. Erythema multiforme has occurred in association with acute infection [20], as has erythema nodosum [21]. Angioedema has been described with B19 infection, both in adults [22] and in a neonate after intrauterine infection [23]. Gianotti-Crosti syndrome, also known as papular acrodermatitis of childhood, has been noted after B19 infection [24].

The purpuric manifestations of B19 infection merit special mention. Several types of purpuric manifestations have been described [25], including nonspecific vascular petechiae and purpura [26]. Thrombotic thrombocytopenic purpura [27] and idiopathic thrombocytopenic purpura [28] have been described in case reports. Other specific syndromes manifesting purpura have been described, including the aforementioned papular purpuric “gloves-and-socks” syndrome, leukocytoclastic vasculitis, and Henoch-Schonlein purpura.

Erythema infectiosum

The distinct clinical features of erythema infectiosum were recognized well before the discovery of the

virus. Confirmation of viral infection is not necessary, because the diagnosis usually is made easily on the basis of the characteristic and unique clinical features. Infected persons experience a nonspecific prodrome followed by an exanthem that typically proceeds through three stages. The distinctive dermatologic signs of infection include a “slapped-cheek” appearance and reticulated erythema of the trunk and extremities. The other primary clinical findings are rheumatologic.

The clinical features of erythema infectiosum vary depending on the age of the patient. In children, the classic rash typically is present, whereas in adults, the rash is more subtle. Adults experience a higher incidence of associated arthralgia and arthritis and typically experience more severe constitutional symptoms, however.

The distinctive “slapped-cheek” appearance of an infected child represents the first stage of the exanthem (Fig. 1). In this stage, erythema of the cheeks is associated with relative circumoral pallor [1]. In the second stage, an erythematous maculopapular rash is noted 1 to 4 days later on the trunk and extremities. During this stage, another distinctive clinical feature of the rash may be seen. Central clearing of the rash results in the characteristic reticular pattern (Fig. 2) [29]. In the last stage, which may last from 1 to 3 weeks, the exanthem persists and may vary related to factors such as sunlight and heat.

Healthy individuals, by the time they present with a rash, are no longer infectious. The prognosis in

these individuals is excellent; although the rash may recur or persist for months, no long-term sequelae are expected. It is important, however, to determine any possible exposures to members of at-risk populations, as discussed in a following section.

Papular purpuric “gloves-and-socks” syndrome

Papular purpuric “gloves-and-socks” syndrome is a distinctive rash that was described only in the past decade [30]. The typical features include acral purpuric erythema, occasionally associated with fever and oral lesions. The rash typically occurs in young adults, but it has been reported in children. A seasonal incidence is noted, with most cases occurring in the spring and summer [31].

Clinically, the rash consists of symmetric erythema and edema of the hands and feet, with gradual progression to petechiae and purpura. One of the clinical hallmarks of the rash is the sharp demarcation on the wrists and ankles, leading to the name “gloves-and-socks” syndrome. The rash typically is painful. It has been reported that other areas of the body have been involved, albeit less frequently, including the cheeks, thighs, elbows, knees, and buttocks [31]. Mucosal involvement is a common finding. Oral erosions, petechiae, and edema may involve the lips, buccal mucosa, and palate.

In immunocompetent patients, some cases may be associated with systemic symptoms, typically fever and arthralgias; however, the patients usually appear



Fig. 1. Erythema of the cheeks in a child, resulting in the “slapped-cheek” appearance of erythema infectiosum.



Fig. 2. Reticulated erythema of the trunk and extremities typical of erythema infectiosum, in a child seated in a bathtub. (Courtesy of Denise Metry, MD.)

nontoxic. On laboratory examination, lymphopenia often is seen, whereas findings such as elevated liver enzymes and transient anemia are much less frequent. The overall prognosis for this exanthem is excellent. Resolution occurs within 1 to 2 weeks, and no permanent sequelae are expected. In immunosuppressed patients, however, papular purpuric “gloves-and-socks” syndrome may lead to more serious complications. The eruption may cause prolonged cutaneous lesions and pruritus and has been shown to cause persistent anemia [32].

The link to parvovirus B19 is widely accepted. Other viruses have been implicated based on serologic evidence, including cytomegalovirus, Coxsackievirus, measles virus, and human herpesviruses 6 and 7 [33]. At present, the evidence linking the syndrome to parvovirus B19 is more convincing, however. Serologic studies of patients with papular purpuric “gloves-and-socks” syndrome have demonstrated the widespread prevalence of IgM antibodies to parvovirus B19 [34]. In addition, tissue studies have supported the role of parvovirus B19, with demonstration of viral antigens in dermal vessel walls and keratinocytes by immunohistochemistry, and demonstration of specific viral DNA in skin biopsy samples by polymerase chain reaction [35]. Unlike patients with erythema infectiosum, patients are considered infectious when the rash is present [31]. Counseling of these patients against ongoing exposures to at-risk populations, as discussed later, is mandatory.

Histopathology

Skin biopsy is not typically needed or performed in most patients suspected of parvovirus infection; however, in cases in which a biopsy is performed, certain histopathologic features may be more suggestive of the diagnosis. Magro et al [15] examined a series of patients presenting with skin eruptions accompanied by clinical signs or serology suggestive of B19 infection. In 11 of 14 patients, B19 genome was present in the skin biopsy specimen. Most cases revealed interstitial histiocytic and lymphocytic infiltrates along with collagen fragmentation. Some cases also revealed findings of interface dermatitis, lymphocytic vasculitis, or leukocytoclastic vasculitis. The additional findings correlated in some cases with unusual clinical features, resembling connective tissue disease or cutaneous vasculitis. Takahashi et al [36] obtained a biopsy sample from a truncal rash in a patient with features typical of erythema infectiosum. Light microscopy showed dilated and irregular-shaped dermal vessels, with swelling of endothelial cells. Mild to moderate perivascular infiltrates of mononuclear cells were noted.

Diagnosis

In most cases, the diagnosis rests on the characteristic clinical features; however, serology may be useful in atypical cases. Enzyme immunoassay may

be used to test for parvovirus IgG and IgM. The test has been shown to have a high sensitivity (97%–100%) and a relatively high specificity (79%–99%) [37]. Detection of IgG antibody is not likely to be helpful diagnostically, because seroprevalence in most countries, particularly in adults, is relatively high. Detection of IgM may be more useful clinically, because it may be present for as long as 2 to 3 months after acute infection [7].

In the patient who presents with an atypical skin eruption, punch biopsy is used mainly to exclude other processes. Although suggestive features may be found, features diagnostic of parvovirus infection have not been identified. Culture of the virus is not performed in most settings, because the virus is not culturable using routine diagnostic methods. Erythroid progenitor cell culture is needed for successful culture [1]. Multiple investigators have used the technique of polymerase chain reaction to amplify and identify B19 DNA in tissue samples, such as synovium or skin [15,35,38]. Electron microscopy may demonstrate viral particles in involved tissues [36]. Both of these techniques are primarily of use in research settings.

Pathogenesis

In the case of erythema infectiosum, many authors hypothesize that the clinical findings result from the humoral response exhibited by patients. Although patients often experience bone marrow suppression during the initial viremic phase, the typical dermatologic and rheumatologic symptoms appear only with the development of specific B19 antibodies, suggesting that deposition of immune complexes in skin, joints, and other organs results in the typical pattern of clinical findings [2]. In support of this hypothesis, patients with arthritis caused by B19 infection demonstrate low serum complement levels and circulating immune complexes [39].

Others have hypothesized that the typical cutaneous findings result from an inflammatory reaction to parvovirus antigens in the skin. Takahashi et al [36] examined involved skin by immunohistochemistry and electron microscopy. Positive reactions with parvovirus monoclonal antibody were seen in endothelial cells, whereas examination by electron microscopy revealed virus particles in the cytoplasm of endothelial cells. In the perivascular region, deposits of C3 were seen, along with a mild to moderate infiltrate of mononuclear cells. The authors hypothesized that the clinical finding of skin rash was attributable to the inflammatory reaction directed against these parvovi-

rus antigens. In the case of collagen-vascular diseases such as systemic lupus erythematosus, it has been suggested that B19 infection serves as one of many possible triggers resulting in a disordered immune response and the resulting clinical complex [1].

At-risk populations

In certain populations, infection with parvovirus B19 may lead to devastating complications. These populations include patients with hematologic disease, immunosuppressed patients, and pregnant women. Because B19 exhibits tropism for erythroid progenitor cells, any individual who has a shortened red blood cell survival time is at risk for an aplastic crisis. Because patients are no longer able to compensate for shortened red blood cell survival with increased red blood cell production, their anemia worsens. In fact, in patients with chronic hemolytic anemia, parvovirus B19 is the most common cause of transient aplastic crisis. Patients with sickle cell anemia, thalassemia, autoimmune hemolytic anemia, and other conditions involving red blood cell destruction are susceptible. These diseases may even be initially diagnosed because of the aplastic crisis. These patients rarely exhibit a rash; they present with fever, constitutional symptoms, and worsening anemia [3]. The crisis is indeed transient; most patients recover in a week, although fatalities do occur.

Patients who are immunocompromised represent another population prone to complications from B19 infection. In this population, chronic anemia may be seen. In patients who are immunocompromised because of HIV infections [40], transplantation, [41], or congenital immunodeficiencies [42], chronic B19 infection may occur. This infection results in persistent lysis of red blood cell precursors, which results in prolonged anemia. Prolonged cutaneous signs and symptoms also have been reported [32]. The other main population at risk of serious complications caused by B19 infection is pregnant women. In this case, devastating effects on the fetus may result. This population is reviewed in greater detail.

Pregnancy

The diagnosis of parvovirus B19 in any individual, child or adult, necessitates inquiries as to all possible exposures to pregnant women. Although the risk of fetal infection and subsequent adverse outcomes is not high, when infection occurs it can be devastating. In the patient who presents with parvovirus infection, this aspect of counseling is crucial.

Unfortunately, by the time a patient presents with the rash of erythema infectiosum, the damage has been done already. Because the virus is transmitted before the rash appears, any exposures in the household, at the workplace, or at school or daycare centers must be reviewed carefully.

Although an infected patient may have been exposed to a pregnant woman, many factors affect the likelihood of transmission to that woman. These factors range from duration and type of exposure to immune status of the woman. In one study conducted in Denmark, several factors were related to increased risk of acute B19 infection during pregnancy, including having children at home, a history of serious medical disease, and having a stressful job [43].

Overall, even if a pregnant woman is infected by the virus, most fetuses are not infected, and even if infected, they usually do not experience adverse outcomes. In infected pregnant women, parvovirus B19 is believed to affect the fetus approximately 30% of the time; however, only 9% of infected fetuses experience poor outcomes [44]. Possible adverse fetal outcomes range from hydrops fetalis to congenital anemia to death.

Hydrops fetalis, also known as nonimmune fetal hydrops, is the most common complication. The fetus is quite dependent on increased erythropoiesis because of decreased erythrocyte survival and an increased red cell mass. When erythropoiesis is decreased during fetal B19 infection, an aplastic crisis results, which leads to the clinical findings of nonimmune fetal hydrops with high-output cardiac failure and edema. This complication may result in diverse outcomes: complete recovery with no permanent sequelae, congenital anemia, cardiac or hepatic dysfunction, or fetal death [7]. Prolonged congenital anemia also may result [45].

Fetal death also may result from fetal infection, with miscarriage more likely in the first half of pregnancy. In one study, women infected during weeks 9 to 20 of pregnancy had a 10% incidence of fetal loss. If infection occurred later than week 20, fetal loss was rare [46]. Another study estimated the overall risk of fetal death as 6.5% in infected mothers [47].

If a pregnant woman has been exposed to an infected individual, serologic testing for IgG and IgM should be performed. Infected women are monitored closely by their obstetricians with examinations and serial ultrasounds. Even in fetuses displaying evidence of infection, spontaneous resolution is common. The monitoring and treatment of hydrops fetalis has improved with advances in fetal medicine, including the use of ultrasound and intrauterine transfusions [48].

Systemic diseases

A number of systemic illnesses have been noted to occur in association with B19 virus infections. It is unclear if the virus occurs coincidentally, acts as an exciting agent, or is causal [3]. The list is impressive and includes systemic vasculitic disorders and rheumatologic disorders. A brief review follows.

Vascular effects

A number of case reports and case series have described vascular effects in association with B19 infection. The clinical manifestations have ranged from vasospasm to leukocytoclastic vasculitis to specific vasculitic syndromes. These vascular effects are not unexpected. In an infected patient, viral particles were found to concentrate in endothelial cells [36], and in the human fetus infected by B19, placental villi demonstrate histologic features of vasculitis [49].

Clinically, multiple case reports have described leukocytoclastic vasculitis [50,51] during B19 infection. Multiple cases of Henoch-Schonlein purpura have occurred in conjunction with acute infection in children and adults [25,52–54]. A link also has been suggested in children with Kawasaki disease [52]. Apart from inflammation of vessel walls, B19 infection may lead to other vascular effects. In one case, bilateral digital arterial occlusive disease was reported, in the absence of vasculitis [55]. Raynaud's phenomenon induced by B19 also has been reported [56].

B19 infection also has been linked to specific vasculitic disorders, including giant cell arteritis, polyarteritis nodosa, and Wegener's granulomatosis. An association between parvovirus infection and giant cell arteritis initially was suggested on the basis of epidemiologic studies. In Denmark, surveillance serologic data compared with histopathologic data revealed that peaks of positive temporal artery biopsies occurred after major parvovirus epidemics [57]. Investigators in the United States also have noted this association, and in addition found significantly higher levels of B19 DNA in temporal artery biopsy tissues of affected patients [58]. The evidence supporting a link between B19 infection and polyarteritis nodosa or Wegener's granulomatosis is weaker. Although case reports have described an association, no significant prevalence of B19 infection was found when screening larger series of patients with polyarteritis nodosa and Wegener's granulomatosis [7].

Rheumatologic findings

Parvovirus may lead to either acute or chronic rheumatologic symptoms. The clinical pattern of these symptoms has been noted by many clinicians to bear several striking similarities to specific rheumatologic diseases. Investigators have taken these observations further and have attempted to determine whether parvovirus is involved in the pathogenesis of certain rheumatologic diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Conflicting evidence has made it difficult to draw any definite conclusions on the subject, however.

Joint symptoms are a major clinical feature of parvovirus infection, and nonspecific arthritis and arthralgias often are seen. Joint symptoms occur only in approximately 8% of infected children, whereas that number rises to approximately 60% of infected adults [59]. The joint symptoms may either coincide with or follow the skin eruption. Many infected adults experience arthritis alone. The joints typically involved in children are the large joints, particularly the knees. In adults, the pattern is that of acute-onset symmetric polyarthritis, typically of the small joints of the hands or the knees, with women affected more frequently than men [59]. The incidence of chronic joint symptoms has been difficult to determine. In one study of patients followed up for a mean of almost 5 years, 80% of patients had arthritis acutely, whereas 17% noted chronic joint pain [60]. Another study, however, found that although 61% of patients had arthritis acutely, none had chronic arthritis after 5 years [61]. Even in the absence of obvious acute infection, parvovirus has been suggested as a cause of chronic undifferentiated arthritis, owing to the findings of viral DNA in synovial tissue [38]. Such findings are difficult to interpret, however. In another study of patients with rheumatoid arthritis, B19 DNA was found in the synovial tissue of 28% of patients; however, it also was seen in half of adults without rheumatoid arthritis [62].

Parvovirus infection has been linked to several chronic rheumatologic disorders. Several investigators have studied a possible link to systemic lupus erythematosus. A number of investigators also have examined the role that parvovirus may play in the pathogenesis of rheumatoid arthritis and juvenile idiopathic arthritis (Still's disease). A smaller body of evidence has proposed a role for B19 in the pathogenesis of scleroderma and dermatomyositis.

Several investigators have focused on a link between B19 infection and systemic lupus erythematosus. The clinical features of these diseases exhibit several similarities, with the presence of fever, rash,

joint symptoms, and hematologic abnormalities. Acute B19 infection may not only mimic systemic lupus erythematosus but also exacerbate it [63]. One study of seroprevalence, however, found no difference between patients with systemic lupus erythematosus and control patients [64]. It has been suggested that parvovirus may serve as only one of many possible triggers in induction of systemic lupus erythematosus [1].

Parvovirus has been hypothesized to play a role in the pathogenesis of rheumatoid arthritis for multiple reasons, including the fact that chronic arthritis after B19 infection may be clinically indistinguishable from rheumatoid arthritis. Supportive studies also have investigated rheumatoid factor production, IgM B19 antibodies, and the presence of B19 DNA in involved tissues [1]; however, these studies have provided conflicting evidence. Similar issues have been raised in the pathogenesis of Still's disease; although the clinical presentation of acute B19 infection is similar to Still's disease, studies have provided conflicting data. In both cases, it is again believed that parvovirus B19 may serve as only one of many possible triggers [1].

A link with systemic sclerosis also has been suggested. A comparison of affected patients with control patients showed a marked increase in the presence of B19 DNA in bone marrow biopsy specimens as detected by polymerase chain reaction. Serum antibodies to parvovirus B19 were detected more frequently in affected patients [65]. Such findings do not confirm causality, however, and further evidence is needed to draw any such conclusions.

The same difficulty arises when examining the evidence linking parvovirus to dermatomyositis. Skin biopsy samples of two patients with dermatomyositis were examined because of atypical clinical features and atypical histology. Investigation of the skin biopsy specimens by polymerase chain reaction revealed the B19 genome, suggesting that persistent B19 infection may be of importance in pathogenesis [66]. In another patient with dermatomyositis, molecular evidence revealed parvovirus B19 DNA in two muscle biopsy samples. The authors suggested that an aberrant host immune response triggered by the parvovirus led to muscle destruction [67].

Treatment

Treatment of patients with either dermatologic or rheumatologic symptoms is primarily symptomatic. In the immunocompetent, healthy individual, patients do well, and the acute symptoms typically resolve

without complications. Some persons may develop chronic arthritis, however, and should be referred for appropriate care. Treatment of certain groups of patients raises more challenges. In pregnant women, immunosuppressed persons, or those with any type of chronic hemolytic anemia, care must be coordinated with a specialist (ie, infectious disease, obstetrics, hematology). In these patients, devastating systemic effects may occur, and early monitoring for complications is crucial.

One advance in treatment is the use of high-dose intravenous immunoglobulin in immunocompromised patients at high risk of complications [68]. Intravenous immunoglobulin has been used to treat B19-induced anemia in patients with immunodeficiency [42], transplant recipients [41], and in patients with AIDS [40]. Intravenous immunoglobulin from a variety of sources has been demonstrated by immunoblot to have high titers of antibody against VP1 and VP2. These antibodies lead to clearance of the virus from blood and bone marrow and thus permit recovery of erythropoiesis [2].

One aspect of treatment should never be overlooked. Even in the healthy patient, an important aspect of care is identifying any prior or ongoing exposure to susceptible populations. These populations, as mentioned previously, include pregnant women, immunosuppressed persons, or those with any type of chronic hemolytic anemia. If a member of these groups has been exposed, notification of the patient and subsequent observation by his or her treating physician are necessary.

A frequent question that arises is the issue of contagion. In infected adults or children, recommendations vary depending on the type of dermatologic manifestations seen. In the case of erythema infectiosum, patients with the rash are no longer considered contagious, and if feeling well, may attend school. Patients with papular and purpuric “gloves-and-socks” syndrome are considered contagious, however, and should take appropriate steps to avoid infecting others.

Summary

Infection with parvovirus B19 may result in a wide range of dermatologic manifestations. The specific skin findings include erythema infectiosum and papular purpuric “gloves-and-socks” syndrome. The nonspecific findings include reticular erythema, maculopapular eruptions, and petechiae and purpura, as well as other less frequently described findings. Associations with other dermatologic diseases, such as

erythema multiforme and erythema nodosum, also have been described. A role in the pathogenesis of various collagen vascular disorders has been suggested and is under investigation. The diagnosis of infection rests on the typical clinical findings. Whenever parvovirus B19 infection is diagnosed, the physician must ensure that neither the patient nor his or her contacts is a member of certain vulnerable populations. In these populations, infection with parvovirus B19 may result in devastating complications. The vulnerable populations include those with hematologic disease, immunosuppressed patients, and pregnant women. Treatment of infection in the healthy immunocompetent individual is asymptomatic, and the acute infections typically resolve without complications.

References

- [1] Kerr JR. Pathogenesis of human parvovirus B19 in rheumatic disease. *Ann Rheum Dis* 2000;59:672–83.
- [2] Brown KE, Young NS, Barbosa LH. Parvovirus B19: implications for transfusion medicine. Summary of a workshop. *Transfusion* 2001;41:130–5.
- [3] Cherry JD. Parvovirus infections in children and adults. *Adv Pediatr* 1999;46:245–69.
- [4] Tolfvenstam T, Lundqvist A, Levi M, Wahren B, Broliden K. Mapping of B-cell epitopes on human parvovirus B19 non-structural and structural proteins. *Vaccine* 2000;19:758–63.
- [5] Tolfvenstam T, Oxenius A, Price DA, et al. Direct ex vivo measurement of CD8+ T-lymphocyte responses to human parvovirus B19. *J Virol* 2001;75:540–3.
- [6] Kelly HA, Siebert D, Hammond R, et al. The age-specific prevalence of human parvovirus immunity in Victoria, Australia compared with other parts of the world. *Epidemiol Infect* 2000;124:449–57.
- [7] Naides SJ. Infection with parvovirus B19. *Curr Inf Dis Reports* 1999;1:273–8.
- [8] Koenigbauer UF, Eastlund T, Day JW. Clinical illness due to parvovirus B19 infection after infusion of solvent/detergent-treated pooled plasma. *Transfusion* 2000;40:1203–6.
- [9] Teitel JM. Viral safety of haemophilia treatment products. *Ann Med* 2000;32:485–92.
- [10] Heegaard ED, Petersen Laub B. Parvovirus B19 transmitted by bone marrow. *Br J Haematol* 2000;111:659–61.
- [11] Woolf AD, et al. Clinical manifestations of human parvovirus B19 in adults. *Arch Intern Med* 1989;149:1153–6.
- [12] Anderson MJ, Higgins PG, Davis LR, et al. Experimental parvoviral infection in humans. *J Infect Dis* 1985;152:257–65.
- [13] Seishima M, Kanoh H, Izumi T. The spectrum of cutaneous eruptions in 22 patients with isolated serological evidence of infection by parvovirus B19. *Arch Dermatol* 1999;135:1556–7.

- [14] Cathebras P, Robert F, Guglielminotti C, et al. Primary parvovirus B19 infection in immunocompetent adults: clinical and biological manifestations. Retrospective study of 16 patients. *Rev Med Interne* 2000;21:324–9.
- [15] Magro CM, Dawood MR, Crowson AN. The cutaneous manifestations of human parvovirus B19 infection. *Hum Pathol* 2000;31:488–97.
- [16] Dereure O, Montes B, Guilhou JJ. Acute generalised livedo reticularis with myasthenia-like syndrome revealing parvovirus B19 primary infection. *Arch Dermatol* 1995;131:744–5.
- [17] Yetgin S, Cetin M, Yenicesu I, et al. Acute parvovirus B19 infection mimicking juvenile myelomonocytic leukemia. *Eur J Haematol* 2000;65:276–8.
- [18] Naides SJ, Piette W, Veach LA, Argenyi Z. Human parvovirus B19-induced vesiculopustular skin eruption. *Am J Med* 1988;84:968–72.
- [19] Lyon CC. Severe acral pruritus associated with parvovirus B19 infection. *Br J Dermatol* 1998;139:152–4.
- [20] Lobkowitz F, Ring J, Schwarz TF, et al. Erythema multiforme in a patient with acute human parvovirus B19 infection. *J Am Acad Dermatol* 1989;20:849–50.
- [21] Imbert B, Brion JP, Janbon B, et al. Erythema nouveau associe a une infection par le parvovirus B19. *Presse Med* 1989;18:1753–4.
- [22] Fawaz-Estrup F. Human parvovirus infection: rheumatic manifestations, angioedema, C1 esterase inhibitor deficiency, ANA positivity, and possible onset of systemic lupus erythematosus. *J Rheumatol* 1996;23:1180–5.
- [23] Miyagawa S, Takahashi Y, Nagai A, et al. Angio-oedema in a neonate with IgG antibodies to parvovirus B19 following intrauterine parvovirus B19 infection. *Br J Dermatol* 2000;143:428–30.
- [24] Carrascosa JM, Just M, Ribera M, et al. Papular acrodermatitis of childhood related to poxvirus and parvovirus B19 infection. *Cutis* 1998;61:265–7.
- [25] Veraldi S, Rizzitelli G. Henoch-Schonlein purpura and human parvovirus B19. *Dermatology* 1994;189:213–4.
- [26] Mortimer PP, Cohen BJ, Rossiter MA. Human parvovirus and purpura. *Lancet* 1985;2(8457):730–1.
- [27] Kok RH, Wolfhagen MJ, Klosters G. A syndrome resembling thrombotic thrombocytopenic purpura associated with human parvovirus B19 infection. *Clin Infect Dis* 2001;32:311–2.
- [28] Lefrere JJ, Courouce AM, Kaplan C. Parvovirus and idiopathic thrombocytopenic purpura. *Lancet* 1989;1(8632):279.
- [29] Feder HM, Anderson I. Fifth disease: a brief review of infections in childhood, in adulthood, and in pregnancy. *Arch Intern Med* 1989;149:2176–8.
- [30] Harms M, Feldmann R, Saurat JH. Papular-purpuric ‘gloves and socks’ syndrome. *J Am Acad Dermatol* 1990;23:850–4.
- [31] Nelson JS, Stone MS. Update on selected viral exanthems. *Curr Opin Pediatr* 2000;12:359–64.
- [32] Ghigliotti G, Mazzarello G, Nigro A, et al. Papular-purpuric gloves and socks syndrome in HIV-positive patients. *J Am Acad Dermatol* 2000;43(5 Pt 2):916–17.
- [33] Ongradi J, Becker K, Horvath A, et al. Simultaneous infection by human herpesvirus 7 and human parvovirus B19 in papular-purpuric gloves-and-socks syndrome. *Arch Dermatol* 2000;136:672.
- [34] Trattner A, David M. Purpuric ‘gloves and socks’ syndrome: histologic, immunofluorescence and polymerase chain reaction study. *J Am Acad Dermatol* 1994;30:267–8.
- [35] Aractingi S, Bakhos D, Flageul B, et al. Immunohistochemical and virological study of skin in the papular-purpuric gloves and socks syndrome. *Br J Dermatol* 1996;135:599–602.
- [36] Takahashi M, Ito M, Sakamoto F, et al. Human parvovirus B19 infection: immunohistochemical and electron microscopic studies of skin lesions. *J Cutan Pathol* 1995;22:168–72.
- [37] Sloots T, Devine PL. Evaluation of four commercial enzyme immunoassays for detection of immunoglobulin M antibodies to human parvovirus B19. *Eur J Clin Microbiol Infect Dis* 1996;15:758–61.
- [38] Stahl HD, Seidl B, Hubner B, et al. High incidence of parvovirus B19 DNA in synovial tissue of patients with undifferentiated mono- and oligoarthritis. *Clin Rheumatol* 2000;19:281–6.
- [39] White DG, Woolf AD, Mortimer PP, et al. Human parvovirus arthropathy. *Lancet* 1985;1:419–21.
- [40] Frickhofen N, Abkowitz JL, Safford M, et al. Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type I (HIV-1): a treatable cause of anemia in AIDS. *Ann Intern Med* 1990;113:926–33.
- [41] Geetha D, Zachary JB, Baldado HM, Kronz JD, Kraus ES. Pure red cell aplasia caused by parvovirus B19 infection in solid organ transplant recipients: a case report and review of literature. *Clin Transplant* 2000;14:586–91.
- [42] Kurtzman GJ, Ozawa K, Cohen B, et al. Chronic bone marrow failure due to persistent B19 parvovirus infection. *N Engl J Med* 1987;317:287–94.
- [43] Jensen IP, Thorsen P, Jeune B, Moller BR, Vestergaard BF. An epidemic of parvovirus B19 in a population of 3,596 pregnant women: a study of sociodemographic and medical risk factors. *BJOG* 2000;107:637–43.
- [44] Public Health Laboratory Service Working Party on Fifth Disease. Prospective study of human parvovirus (B19) infection in pregnancy. *BMJ* 1990;200:1166–70.
- [45] Heegaard ED, Hasle H, Skibsted L, et al. Congenital anemia caused by parvovirus B19 infection. *Pediatr Infect Dis J* 2000;19:1216–8.
- [46] Miller E, Fairley CK, Cohen BJ, et al. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. *Br J Obstet Gynaecol* 1998;105:174–8.
- [47] Levy R. Infection by parvovirus B19 during pregnancy: a review. *Obstet Gynecol Surv* 1997;52:254–9.
- [48] Sahakian V, Weiner CP, Naides SJ, et al. Intrauterine transfusion treatment of nonimmune hydrops fetalis secondary to human parvovirus B19 infection. *Am J Obstet Gynecol* 1991;164:1090–1.

- [49] Morey AL, Keeling JW, Porter JH, et al. Clinical and histopathological features of parvovirus B19 infection in the human fetus. *Br J Obstet Gynaecol* 1992;99: 566–74.
- [50] Chakravarty K, Merry P. Systemic vasculitis and atypical infections: report of two cases. *Postgrad Med J* 1999;75:544–6.
- [51] Martinelli C, Azzi A, Buffini G, et al. Cutaneous vasculitis due to human parvovirus B19 in an HIV-infected patient: report of a case. *AIDS* 1997;11: 1891–3.
- [52] Diaz F, Collazos J. Glomerulonephritis and Henoch-Schoenlein purpura associated with acute parvovirus B19 infection. *Clin Nephrol* 2000;53:237–8.
- [53] Hakim A. Concurrent Henoch-Schonlein purpura and papular-purpuric gloves-and-socks syndrome. *Scand J Rheumatol* 2000;29:131–2.
- [54] Lefrere JJ, Courouce AM, Soulier JP, et al. Henoch-Schonlein purpura and human parvovirus infection. *Pediatrics* 1986;78:183–4.
- [55] Dingli D, Pfizenmaier DH, Arromdee E, et al. Severe digital arterial occlusive disease and acute parvovirus B19 infection. *Lancet* 2000;356:312–14.
- [56] Harel L, Straussberg R, Rudich H, et al. Raynaud's phenomenon as a manifestation of parvovirus B19 infection: case reports and review of parvovirus B19 rheumatic and vasculitic syndromes. *Clin Infect Dis* 2000;30:500–3.
- [57] Elling H, Olsson AT, Elling P. Human parvovirus and giant cell arteritis: a selective arteritic impact? *Clin Exp Rheumatol* 2000;18(4 Suppl 20):S12–4.
- [58] Gabriel SE, Espy M, Erdman DD, et al. The role of parvovirus B19 in the pathogenesis of giant cell arteritis: a preliminary evaluation. *Arthritis Rheum* 1999; 42:1255–8.
- [59] Moore TL. Parvovirus-associated arthritis. *Curr Opin Rheumatol* 2000;12:289–94.
- [60] Kerr JR, Coyle PV, Deleys RJ, et al. Follow-up study of clinical and immunological findings in patients presenting with acute parvovirus B19 infection. *J Med Virol* 1996;48:68–75.
- [61] Speyer I, Breedveld FC, Dijkmans BAC. Human parvovirus B19 infection is not followed by inflammatory joint disease during long-term follow-up. *Clin Exp Rheumatol* 1998;16:576–8.
- [62] Soderlund M, von Essen R, Haapasaari J, et al. Persistence of parvovirus B19 DNA in synovial membranes of young patients with and without chronic arthropathy. *Lancet* 1997;349:1063–5.
- [63] Trapani S, Ermini M, Falcini F. Human parvovirus B19 infection: its relationship with systemic lupus erythematosus. *Semin Arthritis Rheum* 1999;28:319–25.
- [64] Bengtsson A, Widell A, Elmstahl S, Sturfelt G. No serological indications that systemic lupus erythematosus is linked with exposure to human parvovirus B19. *Ann Rheum Dis* 2000;59:64–6.
- [65] Ferri C, Zakrzewska K, Longombardo G, et al. Parvovirus B19 infection of bone marrow in systemic sclerosis patients. *Clin Exp Rheumatol* 1999;17:718–20.
- [66] Crowson AN, Magro CM, Dawood MR. A causal role for parvovirus B19 infection in adult dermatomyositis and other autoimmune syndromes. *J Cutan Pathol* 2000;27:505–15.
- [67] Chevrel G, Calvet A, Belin V, et al. Dermatomyositis associated with the presence of parvovirus B19 DNA in muscle. *Rheumatology (Oxford)* 2000;39: 1037–9.
- [68] Keller MA, Stiehm ER. Passive immunity in prevention and treatment of infectious diseases. *Clin Microbiol Rev* 2000;13:602–14.