Raynaud’s Phenomenon as a Manifestation of Parvovirus B19 Infection: Case Reports and Review of Parvovirus B19 Rheumatic and Vasculitic Syndromes

Liora Harel, Rachel Straussberg, Hagit Rudich, Avner H. Cohen, and Jacob Amir

Infection with human parvovirus B19 is manifested as erythema infectiosum, transient aplastic crisis, or hydrops fetalis. Rheumatic manifestations include arthropathy and various vasculitic syndromes. Isolated Raynaud’s phenomenon due to parvovirus B19 has never been described. We report on 2 previously healthy sisters with new-onset Raynaud’s phenomenon accompanied by severe generalized polyarthralgia. A full workup was negative, except serology for parvovirus B19, which was positive. All symptoms gradually subsided within 3–5 months, and no recurrence has been noted during the 3 years since onset. We review all the studies in the English-language literature on parvovirus B19–induced rheumatic and vasculitic syndromes. We hypothesize that the pathogenesis of Raynaud’s phenomenon in our patients involved immune-mediated endothelial damage leading to platelet activation and vasoconstriction. We recommend that in cases of unexplained Raynaud’s phenomenon, serology for parvovirus B19 be included in the evaluation.

Human parvovirus B19 was discovered in 1974 [1]. Several well-defined clinical syndromes have since been attributed to parvovirus B19 infection, such as transient aplastic crisis, erythema infectiosum, hydrops fetalis, acute and chronic arthropathy, polyarteritis nodosa, and Wegener’s granulomatosis. To the best of our knowledge, isolated Raynaud’s phenomenon due to parvovirus B19 has never been described in the literature.

The present report describes 2 previously healthy young sisters with new-onset Raynaud’s phenomenon in whom parvovirus B19 was implicated as the causative agent. The literature on all the rheumatic and vasculitic syndromes known to be induced by parvovirus B19 is reviewed.

Case Reports

A 14-year-old girl was referred to the Pediatric Rheumatology Clinic at the Schneider Children’s Medical Center in Israel in December 1995 for severe generalized arthralgia. Her medical history was unremarkable except for mononucleosis at age 9 years. She had undergone all routine immunizations at the appropriate ages, including vaccination for rubella at age 12 years. Ten days before admission she began to experience pain and stiffness in her shoulders, elbows, wrists, fingers, hips, knees, ankles, toes, and cervical spine. There was no swelling or redness of the joints. She also noted the onset of episodic blanching and cyanosis of the fingers and toes. She reported at presentation that she had not had fever, weight loss, rashes, mouth sores, or sore throat recently. She was not taking drugs and had made no recent visits to wooded areas.

On physical examination, the patient was afebrile. The blood pressure was 114/67 mm Hg and heart rate was 96/min. Her fingers and toes were cold and blue but not tender, with no sclerodactyly or ulcers. Nail-fold capillaroscopic findings were normal. Joint examination revealed severe, exquisite, generalized symmetric arthralgia without localized changes. The rest of the physical and neurological examination revealed no abnormalities.

Laboratory tests showed the following values: erythrocyte sedimentation rate, 20 mm/h; C-reactive protein, <0.1 mg/dL; hemoglobin, 12.4 g/dL; WBCs, 6,000/mm³, with a normal differential; and platelets, 176,000/mm³. Liver and kidney function test results, muscle enzyme levels, and urinalysis findings were within normal limits. Other test findings were as follows: thyroid function and immunoglobulin levels, normal; antinuclear antibodies and rheumatoid factor, negative; prothrombin time and partial thromboplastin time, normal; VDRL, lupus anticoagulant, and anticardiolipin IgG, IgM, and IgA, negative; and complement, normal. Serology for Epstein-Barr virus, cytomegalovirus, rubella, Mycoplasma species, and hepatitis B virus excluded recent infections; the antistreptolysin O level was 200 IU/mL. Cold agglutinins and cryoglobulins were absent. A chest film and electrocardiogram revealed no abnormalities. Abdominal ultrasonographic findings were unremarkable, except for an enlarged spleen. Serology for parvovirus B19 yielded the following findings: IgM, moderately positive, and IgG, weakly positive. Analysis of a second specimen 2 months later showed no significant change in the titer (Parvo Scan B19 IgM and IgG; Eurodiagnostica, Malmo, Sweden [2, 3]). These serological findings confirmed recent parvovirus infection.

A course of treatment with nonsteroidal anti-inflammatory drugs (naproxen and aspirin) was started but resulted in no improvement.

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The patient continued to complain of weakness and severe disabling arthralgia, which prevented her from normal daily functioning and woke her up at night at the slightest movement. Raynaud’s phenomenon was persistent. A 2-week trial of prednisone (40 mg/d) had little effect.

Only after 4–5 months did the symptoms gradually subside. Thereafter, neither arthralgia nor Raynaud’s phenomenon was noted on follow-up. A third titer determination, 6 months after the diagnostic one, showed that IgM had disappeared and the level of IgG was moderately positive. The patient remains asymptomatic at present, 3 years after onset.

Three months after the index patient was first seen in our clinic, her 13-year-old sister presented because of the onset of episodic blanching and cyanosis of the fingers. On examination, her fingers and toes were cold and blue-purple but not tender or itchy. The rest of the physical examination findings were unremarkable.

A laboratory workup showed the following values: erythrocyte sedimentation rate, 30 mm/h; hemoglobin, 13.5 g/dL; WBCs, 7300/mm³; platelets, 275,000/mm³; and antinuclear antibodies, negative. Serology for parvovirus yielded the following results: IgM, highly positive, and IgG, negative. Six months later, serology for IgM was negative, and for IgG, positive. Within 2–3 months after the laboratory workup, the vasomotor changes gradually subsided and did not recur during the 3 years of follow-up.

Discussion

Human parvovirus B19 is a single-stranded DNA virus. Its major clinical manifestations are erythema infectiosum, transient aplastic crisis in chronic hemolytic anemia, arthropathy, and hydrops fetalis with fetal death [1].

Arthralgia and arthritis may be a component of erythema infectiosum, and are seen more commonly in adults than in children. The rash in adults tends to be more subtle than in children. Symptomatic adults have a severe flulike illness in which polyarthralgia and joint swelling are prominent [4]. Parvovirus B19 arthropathy occurs predominantly in women and is characterized by acute onset of symmetric polyarthropathy, most often affecting the joints of the hands, followed by the knees, wrists, and ankles [1].

Parvovirus B19–associated arthritis is believed to be immune-mediated. This etiology is supported by the observation that the arthritis occurs at the same time as the development of B19-specific antibodies. Joint fluid analysis shows a modest WBC count elevation, to 3000–6000 cells/mm³, with mononuclear cell dominance [5]. Joint changes are usually self-limited and show improvement within 2 weeks [1]. However, in 5%–10% of women, joint symptoms persist for >2 months and can recur after apparent resolution [6]. Rarely, symptoms persist for several years [7]. Parvovirus B19 infection usually does not have long-term joint sequelae, though there are reports of B19-induced chronic rheumatoid-like arthropathy [6, 8–11]. The development of erosions and joint destruction have not been described.

The question of whether parvovirus B19 infection can cause rheumatoid arthritis remains open. The distribution, the symmetry of joint involvement, and the morning stiffness associated with B19 arthropathy are all rheumatoid. Approximately half of all patients whose symptoms become chronic meet the diagnostic criteria of the American Rheumatism Association for rheumatoid arthritis. Reports have described transient expression of low-to-moderate titers of autoantibodies (including the rheumatoid factor, anti-DNA antibodies, and antinuclear antibodies) during acute B19 infection [5, 12, 13]. However, rheumatoid factor is absent; this, together with the absence of rheumatoid nodules and joint destruction, helps to differentiate parvovirus B19 disease from classic rheumatoid arthritis.

Furthermore, attempts to associate chronic B19 arthropathy with major histocompatibility antigen HLA-DR₄, as in classic erosive rheumatoid arthritis, have failed [7, 14], and serological surveys of the rheumatoid arthritis population for evidence of parvovirus B19 or an increased prevalence of IgG antibody to the virus have yielded negative results [15–19]. According to Naides [4], chronic B19 arthropathy is notable for the absence of synovial inflammation; therefore, in patients with B19 infection and chronic synovial inflammation, the presence of a second, concurrent process should be considered. Nevertheless, parvovirus B19 infection should be included in the differential diagnosis of every case of suspected early classic rheumatoid arthritis, even with a positive rheumatoid factor.

Chronic arthritis rarely occurs in children infected with parvovirus B19. It has been suggested that B19 infection has a role in the pathogenesis of juvenile rheumatoid arthritis [20], with a monoarticular or oligoarticular presentation [21].

A few patients with parvovirus B19 infection have met the clinical criteria for fibromyalgia [22] and systemic lupus erythematosus (SLE) [23]. However, B19 infection and SLE may occur simultaneously in some patients, and a causal relationship between the virus and classic idiopathic SLE has not been demonstrated.

There have been several reports connecting parvovirus B19 with vasculitis. The histopathologic features of B19-infected human fetuses include evidence of vasculitis within placental villi [24]. The virus has also been associated with leukocytoclastic vasculitis (Henoch-Schönlein purpura), in both adults and children [25–27], and with Wegener granulomatosis [28, 29] and polyarteritis nodosa [30, 31], mainly in children but also in adults [32, 33].

An association of the rare papular-purpuric “gloves and socks” syndrome with acute parvovirus infection has been reported [34]. This syndrome is characterized by edema, erythema, and pruritic petechial rash involving the distal upper and lower extremities and various oral lesions. Perivascular lymphocytic infiltrate of the papillary dermis and the presence of parvovirus B19 in endothelial cells of the dermal vessel walls also have been reported. Another report has linked B19 infection to sporadic cases of Kawasaki disease [35].

The pathogenesis of parvovirus B19–induced vasculitis is ob-
out. Structural causes such as thoracic outlet syndrome and nomenon or ingestion of drugs, and because the condition to-
to the patients had no history of primary Raynaud’s phe-
vovirus infection. The vasospastic mechanism was ruled out was of acute onset and was undoubtedly induced by the par-
activation.
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as platelet activation and release of vasoconstrictive substances, in primary
vascular injury by circulatory immune complexes or cytotoxic se-
initial lesion of vas-
smooth-muscle tone. Cold apparently augments platelet-
activation, which is associated with the local release of sub-
stances (thromboxane A2, serotonin) that locally affect vascular
superimposed on a local digital vascular disease.
Pathophysiologically, the cold-induced episodic digital ischemia
in general.
Raynaud’s phenomenon is classified into 3 types: vasospastic,
structural, and hemorrhagic (disorders of blood flow) [46]. Pathophysiologically, the cold-induced episodic digital ischemia
may be secondary to exaggerated sympathetic vasoconstriction, or the digital vascular responsiveness to cold or to normal sympathetic stimuli may be enhanced. Alternatively, like in systemic sclerosis, normal sympathetic vasoconstriction may be superimposed on a local digital vascular disease.
Other factors participate in systemic sclerosis, such as platelet
activation, which is associated with the local release of sub-
stances (thromboxane A2, serotonin) that locally affect vascular smooth-muscle tone. Cold apparently augments platelet-
induced vasoconstrictive responses. The initial lesion of vas-
cular injury by circulatory immune complexes or cytotoxic se-
rum factor perpetuates a variety of local tissue responses, such as platelet activation and release of vasoconstrictive substances, which worsen the narrowing of the digital arteries. In primary Raynaud’s phenomenon, there is no evidence of platelet activation.
In the 2 patients we describe here, Raynaud’s phenomenon was of acute onset and was undoubtedly induced by the parvovirus infection. The vasospastic mechanism was ruled out because the patients had no history of primary Raynaud’s phenomenon or ingestion of drugs, and because the condition totally disappeared. A hemorrhagic mechanism was also ruled out. Structural causes such as thoracic outlet syndrome and Takayasu’s disease were excluded, and there was no evidence of underlying connective tissue disease, such as systemic sclerosis or SLE.

Given the connection between parvovirus B19 and vasculitis, we hypothesize that following a B19 infection, transient, immune-mediated vascular endothelial damage may occur, inducing platelet activation with subsequent vasoconstrictive responses. In our patients, the simultaneous occurrence of Raynaud’s phenomenon and the arthralgia, which paralleled the B19 antibody rise, supports the hypothesis that the vascular damage had an immunologic basis and explains why it disappeared after a few months, when the IgM titer gradually decreased.

**Conclusion**

We describe the first cases of isolated Raynaud’s phenomenon induced by parvovirus B19 infection. The pathogenesis is unknown and may involve immune-mediated endothelial damage leading to activation of platelets, with a consequent vaso-
constrictive response. The occurrence of this rare manifestation in 2 sisters raises the question of genetic susceptibility to parvovirus-induced vasculopathy. In cases of unexplained Raynaud’s phenomenon, we recommend that evaluation include serology for parvovirus.

**References**

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**Table 1. Review of the rheumatic and vasculitic syndromes of parvovirus B19 infection.**

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Reference(s)</th>
<th>Cases reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parvovirus B19-associated arthropathy</td>
<td>[5, 6, 8, 20, 36–39]</td>
<td>Frequently</td>
</tr>
<tr>
<td>Chronic rheumatoid-like disease</td>
<td>[6, 8–11, 37, 40]</td>
<td>Frequently</td>
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<tr>
<td>Still’s disease</td>
<td>[41]</td>
<td>Rarely</td>
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<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>[20, 21, 37, 42]</td>
<td>Rarely</td>
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<tr>
<td>Fibromyalgia</td>
<td>[22]</td>
<td>Rarely</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>[23, 36, 43]</td>
<td>Rarely</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>[35]</td>
<td>Rarely</td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis (Henoch-Shönlein purpura)</td>
<td>[25–27]</td>
<td>Rarely</td>
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<tr>
<td>Polyarteritis nodosa</td>
<td>[30–33]</td>
<td>Rarely</td>
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<tr>
<td>Wegener’s granulomatosis</td>
<td>[28–30]</td>
<td>Rarely</td>
</tr>
<tr>
<td>Petechial “gloves and socks” syndrome</td>
<td>[34, 44, 45]</td>
<td>Rarely</td>
</tr>
</tbody>
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