Papular-Purpuric Gloves and Socks Syndrome Associated with Acute Parvovirus B19 Infection: Case Report and Review

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The papular-purpuric gloves and socks syndrome (PPGSS) was first described in 1990. This syndrome is characterized by fever, acral pruritus, edema, petechiae, and oral erosions. Subsequently, parvovirus B19 has been implicated, in most cases, as the causative agent of this syndrome. To date, with two exceptions, all published cases of PPGSS have been from Europe and the Middle East and have been mainly reported in the dermatology literature. Herein, we report what we believe to be only the second case of documented parvovirus B19–associated PPGSS occurring in the United States. The patient presented with the typical clinical syndrome, and the diagnosis of acute parvovirus B19 infection was documented by serial serologies that demonstrated development of IgM antibody to virus during the acute phase of infection and seroconversion to IgG antibody in the convalescent period. We then review the existing literature on this unusual syndrome and its association with parvovirus B19.

In 1990, Harms et al. [1] reported five cases of an acute self-limited dermatosis that initially presented as pruritic and painful edema and erythema localized to the distal upper and lower extremities in a gloves and socks distribution. This syndrome was further characterized by the subsequent appearance of acral petechiae and oral ulcerations followed by rapid clearing of all mucocutaneous changes. No obvious infectious or noninfectious etiologic agent was identified. The dermatosis, which has since been well described in the dermatology literature, is termed the papular-purpuric gloves and socks syndrome (PPGSS).

In 1991, Bagot and Revuz [2], in a letter to the editor, described a patient who presented with an identical syndrome in association with acute infection with parvovirus B19, the latter documented by acute seroconversion by means of serial serologies for IgM antibody. Subsequently, Harms et al. [3] agreed that an association between PPGSS and parvovirus B19 was apparent in the patient described by Bagot and Revuz; however, they could not adequately prove that association in their patients. They were only able to identify IgG antibody to parvovirus B19 in a single, preserved, convalescent-phase serum specimen from one of their previously described patients.

More recently, Halasz et al. [4] reported the first case of parvovirus B19–associated PPGSS occurring in the United States. Herein, we report only the second case of documented parvovirus B19–associated PPGSS occurring in the United States. Similar to prior reports, through serological analysis, we were able to implicate parvovirus B19 as the causative agent. We then review the existing data on this unusual syndrome, with particular attention paid to the data supporting parvovirus B19 as the primary causative agent.

Case Report

A 20-year-old woman presented in April 1997 to Yale–New Haven Hospital (New Haven, CT) for evaluation of acute-onset pain and swelling of her hands, feet, and oropharynx. Four days before admission, a cutaneous eruption appeared on the dorsum of both hands and feet, which subsequently progressed to involve the palmar surfaces. During this time, she also noted increasing pruritus of her hands and feet, which was not relieved by dipheniramine, prescribed 2 days before by her primary care physician whom she had seen because of these symptoms. One day before admission, she noted swelling of her lower lip followed by the onset of oropharyngeal pain and odynophagia, which ultimately precluded oral intake and prompted presentation to the emergency department and hospitalization.

At the time of evaluation in the emergency department, with the exception of arthralgias of the knees and ankles, the patient denied any associated systemic or localizing symptoms, including fever, chills, headache, neck stiffness, nausea, vomiting, diarrhea, abdominal pain, dysuria, or vaginal discharge. She denied taking any new prescribed or over-the-counter medications before the onset of this illness.

She was currently in a monogamous heterosexual relationship and denied other risk factors for HIV infection. A test for HIV infection was negative within the last year while she was pregnant with her son. She had received all her routine child-
On the day of admission, the patient was seen by both the infectious disease and dermatology consult services. A broad differential diagnosis was initially generated. However, on the basis of her clinical presentation, the most likely diagnosis entertained was PPGSS. A variety of blood analyses were recommended, samples for many of which were sent to our laboratory as noted. A skin biopsy of the petechial lesions was entertained but not thought likely to contribute to making a specific diagnosis.

Forty-eight hours into the hospitalization, the patient continued to be ill, and increasing mucocutaneous swelling and pain were noted. She became febrile (temperature to 38.6°C), and even though her hemoglobin level, hematocrit, and platelet count remained normal, her WBC count had declined from 5,600/mm³ at the time of admission to 2,200/mm³ with 16% eosinophils, and her absolute neutrophil count was 800/mm³. Although the diagnosis remained unclear, a decision was made to administer intravenous steroids (methylprednisolone, 40 mg every 8 hours) in an attempt to alleviate primarily the oropharyngeal pain and swelling that the patient was experiencing and, as a result, improve her oral intake. Within 24 hours, the patient’s lip swelling, mouth pain, and acral pruritus markedly decreased, and her hematologic abnormalities resolved. On day 9 of her illness the patient was discharged to home, at which time samples for repeated serologies for parvovirus B19 were obtained.

Following discharge, results of parvovirus B19 serologies became available. IgM but not IgG antibody to parvovirus B19 was detected in the serum sample drawn on day 9 of the patient’s illness. The blood specimen obtained on day 2 of her illness was negative for both IgM and IgG antibodies to parvovirus B19. All other diagnostic tests, including that for antibody to HIV, were negative. Testing of convalescent-phase serum samples, obtained 9 months after the illness when the patient returned for follow-up, revealed IgG but not IgM antibody to

Figure 1. A photograph revealing the oral manifestations of papular-purpuric gloves and socks syndrome in a 20-year-old woman that included moist mucous membranes, palatal ulcerations, and erythema. A whitish plaque also coated her tongue.

Figure 2. A photograph revealing the petechial rash on the dorsum of the feet of a 20-year-old woman with papular-purpuric gloves and socks syndrome.
parvovirus B19. Repeated testing for HIV infection was negative. At this time, the patient’s only complaints were persistent fatigue and arthralgias.

Discussion

Parvovirus B19 is the etiologic agent of the common childhood exanthem erythema infectiosum (EI), also known as fifth disease. Less frequently, acute parvovirus B19 infection may manifest as an atypical dermatosis. Unusual cutaneous manifestations described to date include a vesiculopustular skin eruption [5], generalized erythematous lesions, an erythematocutaneous rash [6], erythema multiforme amputalum [7], and PPGSS [2, 4, 6, 8–16].

To date, 25 cases of PPGSS have been reported, primarily in the European literature and largely by dermatologists [1, 2, 4, 8–16]. PPGSS is a rare dermatosis that appears to preferentially afflict young adults, usually occurring in the spring and summer months. Systemic manifestations may proceed or present concomitantly with the skin lesions and are usually quite mild and transient. They include a low-grade fever (52% of reported cases), fatigue (20%), myalgias (16%), anorexia (16%), lymphadenopathy (16%), and arthralgias (12%).

The distinctive manifestations of this syndrome are a rapidly progressive painful and highly pruritic, symmetric swelling and erythema of the distal hands and feet. Confluent papular-purpuric lesions then develop that involve the dorsal and palm surfaces of the distal extremities, with sharp margins at the wrists and ankles. Subsequently, most patients develop a polymorphous exanthem involving the hard and soft palates, buccal mucosa, and lips. Several oropharyngeal changes have been described, the most common being diffuse erythema and swelling of the lips, accompanied by vesicles, shallow ulcerations, and/or petechiae localized to one or both palates. These oral lesions are quite painful, are often pruritic, and have been described in over one-half of the cases reported to date.

The entire syndrome generally clears spontaneously within 1 to 2 weeks. Unlike our case, patients are usually able to maintain adequate oral intake and require only symptomatic treatment for pain and pruritus. Three patients have been noted to have desquamation of the hands and feet as the syndrome resolved [8].

Laboratory findings for patients with PPGSS are variable. The most common hematologic manifestations described have been mild leukopenia, transient neutropenia, and one episode of eosinophilia [1, 4, 8]. The RBC indices and platelet counts appear to remain normal. Other laboratory abnormalities have included mild elevations of transaminase levels and erythrocyte sedimentation rates. No abnormalities in renal function have been reported to date.

On the basis of our experience and more recently published data, parvovirus B19 appears to be associated with most cases of PPGSS, as outlined in table 1. Parvovirus B19 has previously been implicated as the etiologic agent of PPGSS in 14 cases on the basis of serological evidence of IgM antibody in acute-phase serum samples. In each of these 14 cases, serum samples assayed for IgM antibody to parvovirus B19 were positive within the first 23 days following the onset of skin manifestations. In 11 of these cases, seroconversion from IgM to IgG antibody was documented. IgG antibody was subsequently detected no earlier than day 9 and persisted for >6 months after the illness [8]. In three cases, diagnosis was further confirmed by plasma viremia in acute-phase serum samples by means of PCR analysis for DNA [8].

Other etiologic agents implicated as possible causes of PPGSS include cytomegalovirus, coxsackie B6 virus, and measles virus. Carrascosa [9] suggested that cytomegalovirus could be the causative agent in one case (table 1). IgM antibody to cytomegalovirus was present in a single serum sample. No serological evidence of parvovirus was detected, but the analysis was carried out at only one unspecified time early in the course of illness.

Feldmann et al. [10] suggested a diagnosis of acute coxsackie B6 virus infection in another case of PPGSS based on the detection of decreasing antibody titers (1:40 to 1:20) by means of CF assay (table 1). However, these antibody titers were only a twofold dilution apart. A fourfold difference is usually considered significant. Serology for parvovirus B19 was negative in both acute- and convalescent-phase serum samples from this patient, as was PCR analysis of acute-phase serum.

Finally, measles virus was implicated as the causative agent of PPGSS in an additional case when positive titers of IgM and IgG antibodies were noted (table 1) [11]. However, oral mucosal involvement did not manifest in this patient. Therefore, this case may not, in fact, truly be PPGSS. In addition, in this last case, the investigators stated that serology for parvovirus was not available in their laboratory at the time of the case.

In our case, infections with each of the above-mentioned viruses, as well as HIV, were considered at the time of the initial evaluation. A diagnosis of acute parvovirus B19 infection was ultimately made on the basis of the presence of IgM antibody in serum samples assayed at two different times during the patient’s illness and was confirmed by sequential assays for IgG antibody to virus that employed acute- and convalescent-phase serum samples. Although PCR analysis for DNA can provide further confirmation of parvovirus B19 infection, it is not clinically indicated for a healthy host.

A third-generation EIA (Biotrin, Dublin, and Tri-Delta Diagnostics, Cedar Knolls, NJ) was used by our laboratory to detect IgM antibodies (class-capture sandwich EIA) and IgG antibodies (sandwich EIA) to parvovirus B19. False positivity for IgM antibodies is always a concern. We are confident, however, that the results for this patient are accurate. First, results of IgM and IgG serologies evolved in a pattern coincident with her clinical illness, which is characteristic of acute infection. Second, her illness occurred in the midst of a large epidemic of parvovirus B19 infection in the community. Finally, parvovirus
In contrast Borradori et al. [14] reported a case in which skin analyses for patients with either pruritus. In addition, PCR analysis of serum from a limited immune response to one or more viral antigens. However, at this point, on the basis of results of limited detailed blood and skin analyses that have been carried out for patients with EI vs. those with parvovirus B19±associated PPGSS persistence of the papillary dermis that was associated with extravasation of RBCs in the dermis. No evidence or changes diagnostic of papular-purpuric gloves and socks syndrome.

<table>
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<tr>
<th>[Reference(s)]</th>
<th>No. of cases</th>
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<tr>
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<td>1</td>
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<td>Serologies for IgM (A) and IgG (C)</td>
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NOTE. A = acute-phase serum sample; C = convalescent-phase serum sample; PPGSS = papular-purpuric gloves and socks syndrome.

activity is common in April in Connecticut; in contrast, enterovirus infections in April are extremely rare.

Previously, it has been noted that parvovirus B19 infection manifests as a biphasic illness, characterized by a viremic phase that subsequently is followed by the host’s development of an immunologic response to virus. As described by Anderson et al. [17], when healthy volunteers were inoculated intranasally with parvovirus B19, viral DNA was detected in the blood 6 days following infection. The previously seronegative healthy donors developed a mild illness manifested as pyrexia, malaise, myalgia, and generalized pruritus. Clearance of viremia was correlated with the development of IgM antibodies by days 10 to 13 and of IgG antibodies that appeared following day 13. IgM antibody levels began to fall after the second month of illness, whereas IgG antibody levels persisted indefinitely.

It is interesting that there appear to be differences in the timing of antibody responses in relation to the clinical syndromes of EI and PPGSS. In patients with EI, typical symptoms usually develop following the clearance of viremia, in the setting of rising titers of IgM and IgG antibodies to virus. By the time the facial rash characteristic of EI develops, virus is usually no longer detectable in the blood, and IgM and IgG antibodies are present [8, 12].

By contrast, in patients with PPGSS, on the basis of limited data that exist, it would appear that the mucocutaneous lesions develop during the period of viremia, following which antibodies appear. Several patients, including ours, did not have IgM antibodies at the time of their initial presentation with rash and pruritus. In addition, PCR analysis of serum from a limited number of these patients revealed circulating viral DNA [8, 12]. In contrast Borradori et al. [14] reported a case in which they failed to detect viral DNA in serum by PCR analysis.

There was, however, IgG antibody to parvovirus already present in their specimens, which likely implies that the viremia had resolved (table 1). Limited pathological data exist to help further delineate the pathogenesis of PPGSS. Only a handful of patients have undergone skin biopsies, and, unfortunately, results of detailed virologic and immunologic studies on plasma specimens obtained from these same patients are lacking. Skin biopsies were performed on three patients with PPGSS described by Aractingi et al. [12]. By means of histological analysis, they found predominantly a CD3+/CD30+ lymphocytic, perivascular infiltrate of the papillary dermis that was associated with extravasation of RBCs in the dermis. No evidence or changes diagnostic of a vasculitis were noted. However, by means of immunofluorescence with use of antibodies to parvovirus B19, intense labeling revealed the presence of virus in the endothelial cells of the dermal vessel walls. Virus was also noted in the epithelial cells of the sweat glands and ducts and in the epidermis. PCR analysis of skin biopsy specimens from all three patients further confirmed the presence of parvovirus B19 DNA in these lesions. In another study [13], direct immunofluorescence of skin biopsy specimens obtained from patients with PPGSS revealed deposition of IgM antibody and C3 in the walls of papillary dermal vessels in a granular pattern, thus suggesting a vascular reaction to an antigenic stimulus.

The different dermatologic manifestations noted in patients with EI vs. those with parvovirus B19–associated PPGSS perhaps reflect differences in the host’s cellular and/or humoral immune response to one or more viral antigens. However, at this point, on the basis of results of limited detailed blood and skin analyses that have been carried out for patients with either syndrome, it is difficult to speculate further regarding the pre-
cise nature of the host-virus interactions that occur in these two illnesses. It is possible, although supporting data are currently lacking, that differences in host HLA type, preexisting immunologic milieu, and/or level of viral inoculum may contribute to the variant clinical presentations seen with these two dermatoses.

**Conclusion**

PPGSS is an unusual dermatosis typically characterized by edema, erythema, and a highly pruritic, petechial rash involving the distal upper and lower extremities and various oral lesions that are associated with mild systemic manifestations, including low-grade fever and myalgias. The syndrome is generally self-limited, but, as in our case, patients may occasionally require hospitalization for supportive therapy.

At the time of initial presentation, additional diagnoses to be considered include an allergic reaction to medication or other inciting antigens, particularly if eosinophilia is present, and various infectious diseases such as Rocky Mountain spotted fever or other rickettsial diseases, atypical measles, hand-foot-and-mouth disease, or other enterovirus infections [14]. In addition, an atypical presentation of a collagen vascular disorder (such as Behçet’s disease) or an idiopathic syndrome (such as adult-onset Kawasaki disease) should be entertained.

There now appears to be sufficient evidence to suggest that PPGSS is a rare but distinctive manifestation of primary infection with parvovirus B19 in young adults. On the basis of the clinical presentation alone, our patient was thought to have this syndrome, and on the basis of exposure history and serological data, the causative agent was believed to be parvovirus B19.

Serum samples from different intervals following the initial presentation should be obtained in an attempt to document seroconversion to parvovirus B19. PCR analysis of serum for DNA, if available, may be employed for diagnosis, particularly for immunocompromised hosts; its utility is likely greatest for patients presenting early in the disease course, before the induction of an antibody response to virus.

At this point, the pathogenesis of PPGSS remains incompletely defined. Further investigation into the pathogenesis of this unusual syndrome is encouraged, in particular as it relates to characterizing both the kinetics of viremia and the host’s immunologic response to the virus. Correlating these results with findings of histological analysis of skin biopsy specimens could further enhance our understanding of the pathological basis of this disease.

**References**