Parvovirus B19 infection in an adult presenting with connective tissue disease-like symptoms: a report of the clinical and histological findings

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Abstract

Parvovirus B19 infections in adults are usually associated with nonspecific and mild symptoms. However, cases presenting with a lupus-like syndrome have been described, leading to the hypothesis that parvovirus infection can induce connective tissue disease. Various histopathologic features of cutaneous manifestations of parvovirus have been reported, including features which overlap with those of connective tissue disease. Herein, we discuss an unusual case of Parvovirus B19 infection in a middle-aged woman. The biopsy results showed granulomatous vasculitis and were consistent with the previously described superantigen id reaction. This case demonstrates that infectious causes should be considered in the differential diagnosis for granulomatous vasculitis and clinicopathologic correlation is required for accurate diagnosis. We also provide a review of the literature highlighting the possible role of parvovirus in induction of a connective tissue disease-like presentation.

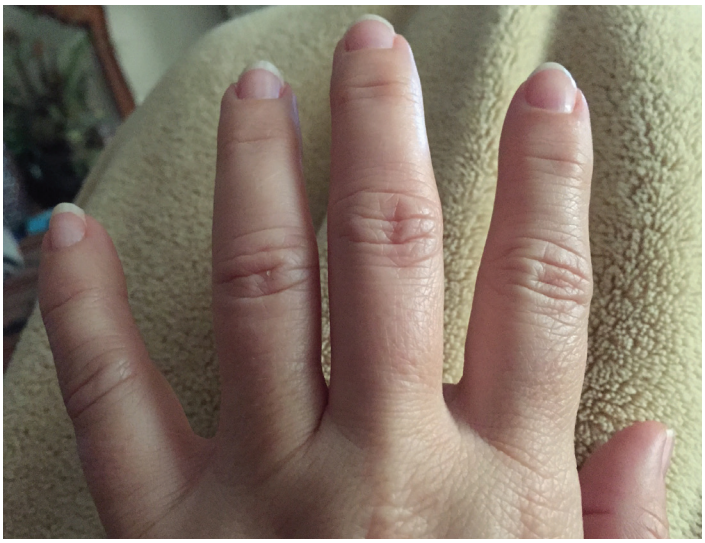
Keywords: Parvovirus B19, granulomatous vasculitis, connective tissue disease

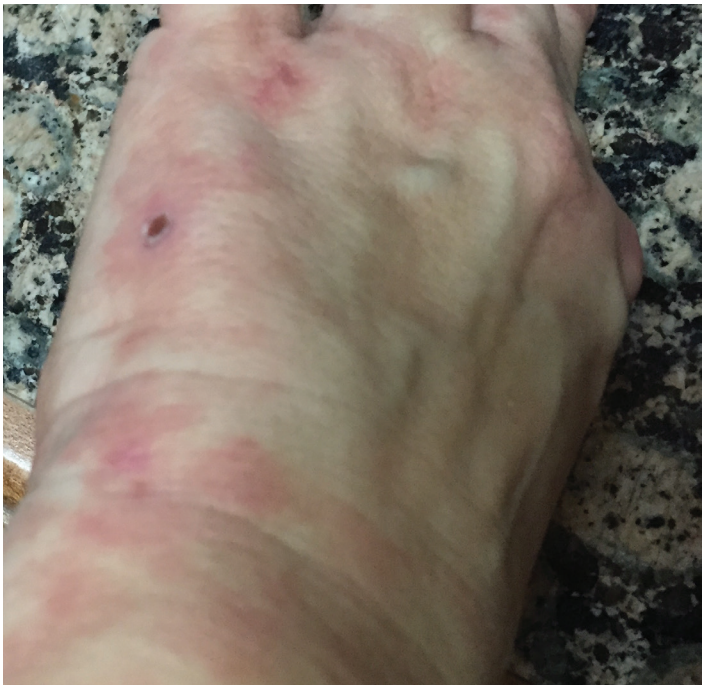
Introduction

Parvovirus B19 is a single stranded DNA virus that infects human erythroblast progenitors. It is known for its role as the causative agent of erythema infectiosum, or fifth disease, which is a common childhood exanthem characterized by a prodromal phase of fever, coryza, headache, and nausea, followed by erythema of the bilateral cheeks giving a "slapped cheek" appearance. The eruption then may generalize to the rest of the body and take on a lacy and reticular appearance, lasting from one to six weeks. It is usually mild and self-limiting [1].

In adults, the clinical presentation is more diverse. Between 60 and 80 percent of adults are seropositive, which indicates the widespread nature of this infection [2]. Most infections occur in childhood, but it is possible for an adult to manifest symptoms of infection if they have not been previously exposed. Infection in adults is commonly asymptomatic. However, when symptoms do occur, they are frequently nonspecific and include fever, arthralgias, and upper respiratory symptoms [1, 3]. Adults may or may not have an associated maculo-papular rash that is most often located on the trunk, neck, and extremities [3]. A subset of adults have a cutaneous eruption limited to the hands and feet up to the level of the wrists and ankles. This may be accompanied by mucosal involvement, such as palatal petechia as well as erosions of the lip, oral mucosa, and genital mucosa. This specific distribution of Parvovirus B19 is known as papular-purpuric gloves and socks syndrome (PPGSS) and is a relatively common presentation of the infection in young adults [4].

The non-specific signs and symptoms of Parvovirus B19 infection can mimic symptoms of autoimmune and connective tissue diseases such as systemic lupus erythematosus, dermatomyositis, and rheumatoid arthritis [5].The association of Parvovirus B19 infection with connective tissue disease (CTD) stigmata has been well-documented. It has been hypothesized that Parvovirus B19 may in fact play a causative role in the development of these diseases





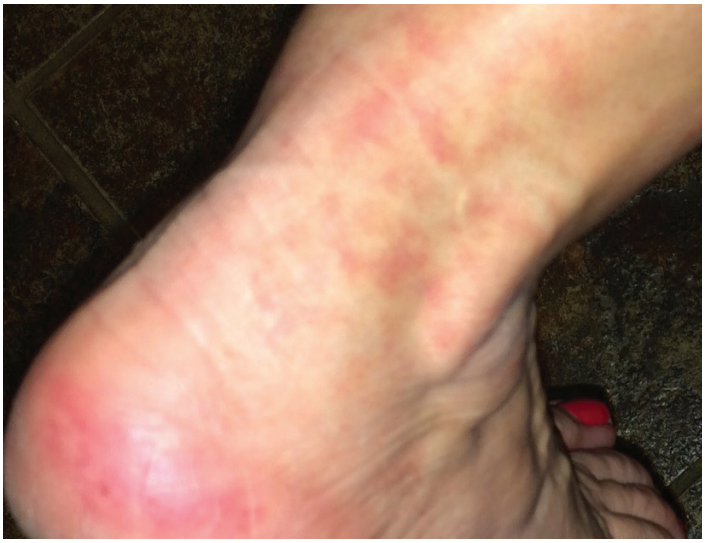


Figure 1. *Clinical pictures of the patient during the acute phase of her illness. (Top) Swelling of fingers. (Middle, Bottom) Erythematous patches on dorsum of hand, wrists and ankles.*

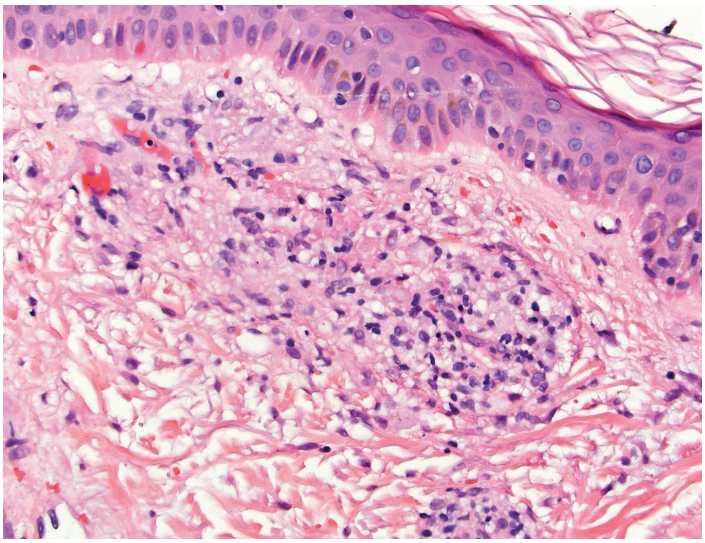
or may trigger an exacerbation in a patient already affected by a CTD [5-7]. In certain atypical cases, the systemic effects of parvovirus can be so profound as to cause patients to meet criteria for CTD [8].

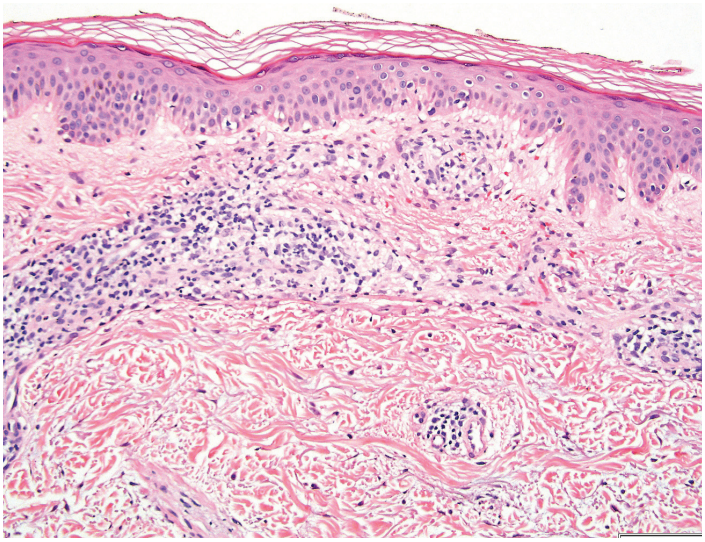
Classic parvovirus-induced skin lesions are not commonly biopsied, thus the histologic features are not well described. Limited reports suggest that the histopathologic changes are non-specific. Reported findings include epidermal spongiosis and parakeratosis, a mild superficial perivascular inflammatory infiltrate of lymphocytes with some neutrophils and eosinophils, and rarely, leukocytoclastic vascultis [2, 4]. Magro et al. studied 14 cases of confirmed parvovirus-induced skin lesions and reported consistent findings, including an interstitial histiocytic infiltrate with degeneration of collagen fibers, interface dermatitis, increased interstitial mucin, and a granulomatous or lymphocytic vasculitis [8]. Of interest, a previous study by Magro et al. described an identical reaction pattern in the setting of antecedent or concurrent infection with not only Parvovirus B19, but also with other reactive arthropathy-associated microbial pathogens such as Cytomegalovirus, Streptococcus, Mycoplasma, Klebsiella, and Borrelia burgdorferi. These pathogens all have superantigen properties, the ability to generate a robust cell-mediated immune response. The authors thus coined the term "superantigen id reaction" to describe these immunologically-mediated cutaneous changes. The authors hypothesize that this robust immune response to such pathogens leads to the histologic as well as the clinical manifestations that recapitulate CTD [9].

Herein, we discuss the clinical presentation and biopsy of a middle aged woman who was ultimately diagnosed with Parvovirus B19 infection.

Case Synopsis

A 46-year-old woman was evaluated by the departments of rheumatology and dermatology for chief complaints of joint pain and rash. A week after one of her children experienced red cheeks and fever, she developed a fever of 102F, posterior cervical lymphadenopathy, and aches in her joints accompanied by swelling of the fingers (**Figure 1A**). Over the next six weeks these symptoms continued,





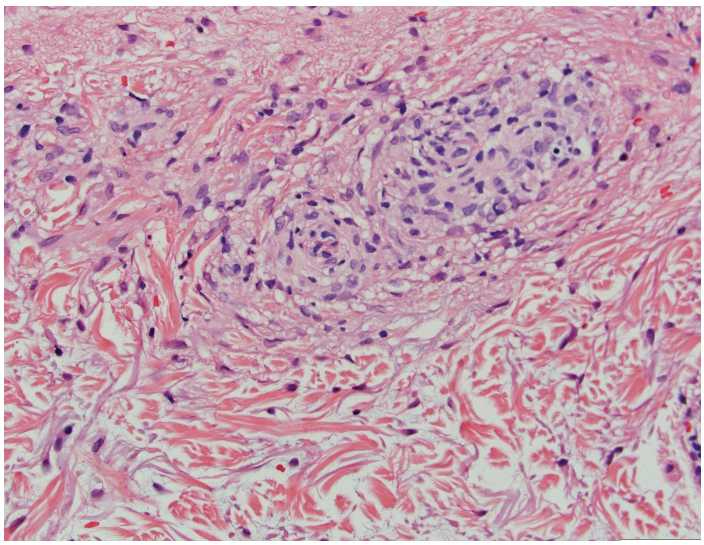


Figure 2. *Punch biopsy of the skin demonstrating perivascular lymphohistiocytic infiltrate with extravasion of erythrocytes and focal fibrin deposition. Top) H&E, 200x. Middle, Bottom) H&E, 400x.*

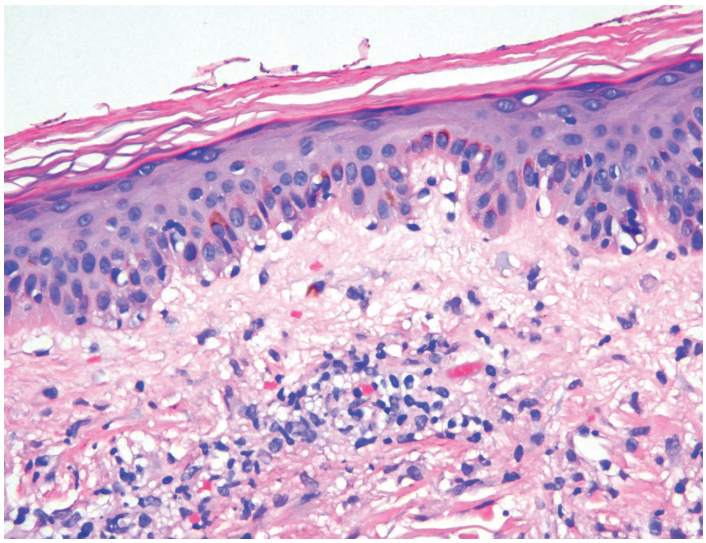


Figure 3. *Subtle vacuolar alteration of the basilar layer and thickened basement membrane zone. H&E, 200x.*

accompanied by severe fatigue and development of a rash. On physical exam, she was noted to have multiple erythematous patches concentrated on the wrists and ankles but tracking up the extremities bilaterally to the level of the elbows and knees (**Figure 1B and C**). Some patches were discrete whereas others had coalesced. Owing to her history of exposure to a likely parvovirus infection, she was tested for Parvovirus B19. Her IgM titer was highly reactive during the acute phase of her infection.

Given her unusual presentation and long duration of symptoms, a punch biopsy of a skin lesion was performed. The provided clinical impression at the time of biopsy included lupus erythematosus versus vasculitis. Histopathology showed a mildly thickened basement membrane zone with focal basal vacuolization of basilar keratinocytes. Rare apoptotic keratinocytes were noted in the epidermis. There was a perivascular lymphohistiocytic infiltrate with associated extravasated erythrocytes and endothelial swelling, consistent with granulomatous vasculitis (**Figures 2A, 2B and 2C** and **Figure 3**). Discussion with the treating clinician revealed the concurrent Parvovirus B19 infection confirmed by IgM serology. A subsequent immunohistochemical stain for parvovirus was non-reactive, though this result was not surprising given the absence of viral cytopathic changes in the biopsy sample. Additional testing via RT-PCR, a more sensitive method, was not pursued as Parvovirus B19 infection was confirmed by serology. The clinical presentation, in conjunction

with confirmed Parvovirus B19 infection by serology and these distinctive histomorphologic features, was characteristic of the so-called superantigen id reaction [9].

After three months, the patient's Parvovirus B19 IgM titer was negative and the IgG titer had increased from the initial reading. All other labs were negative, including anti-neutrophil cytoplasmic antibody, Rocky Mountain spotted fever antibody/antigen, complements, tuberculosis spot test, and blastomyces and histoplasma antigens. Of note, an antinuclear antibody titer was 1:160, but all confirmatory tests were negative. The patient's symptoms slowly resolved over the following three months and she returned to her baseline of functioning.

Case Discussion

Clinical manifestations of Parvovirus B19 in adults can be quite protean and may mimic those of connective tissue disease. Indeed, similarities between B19 infection and SLE may be so striking that patients may initially be diagnosed with lupus erythematosus [5]. A study and literature review conducted by Seve et al. in 2004 [5] documented 21cases of Parvovirus B19 infection presenting with features strongly overlapping those of SLE, including fever, rash, arthritis, malar rash, photosensitivity, hepatosplenomegaly, renal involvement, and CNS impairment. All of the patients were found to have acute Parvovirus B19 infections and the lupus-like symptoms ultimately resolved, usually within 3 months [5, 10-19]. Interestingly, this was the same time frame that it took our patient's symptoms to resolve. The course of the disease in conjunction with parvovirus serologies is crucial for diagnosis; lupus is characterized by its chronicity whereas parvovirus is self-limiting. Seve et al.'s review also reported 6 patients in whom the clinical and biologic features persisted for several months to years after recovery from the viral infection, suggesting possible induction of SLE [5, 20-24]. A recent review article by Kerr et al. hypothesized that Parvovirus B19 may play a role in inducing autoimmunity through molecular mimicry and/or Parvovirus B19-induced apoptosis with subsequent presentation of self-antigens to T lymphocytes [6]. This is supported by the aforementioned histological reaction pattern, which is typical for a cell-mediated immune reaction [8].

Magro et al. proposed a pathogenic mechanism specific for Parvovirus B19's role in inducing CTD [25, 26]. Using RT-PCR techniques, these authors demonstrated that in patients who met the American College of Rheumatology (ACR) criteria for CTD, Parvovirus B19 RNA was found in higher concentrations than controls and that the Parvovirus B19 RNA was concentrated in endothelial cells. Globoside, referred to as the blood group P antigen, is the receptor for B19 and is found in endothelial cells as well as erythrocytes. They suggest that Parvovirus B19 binds endothelial cells through this receptor and enters, bringing a non structural (NS)-1 protein, which has been shown to induce DNA fragmentation characteristic of apoptosis. Furthermore, NS-1 protein and parvovirus B19 infection itself also sensitize cells to tumor necrosis factor mediated apoptosis. As such, Parvovirus B19 infection increases apoptosis of the endothelial cells, leading to the displacement of various intranuclear and cytoplasmic proteins, including Ro, La, and RNP, which then serve as neoantigens. Thus, the humoral immune system is activated and formation of antibodies against endothelial cells infected by parvovirus ensues [25, 26]. Additionally, because of parvovirus's superantigen properties, parvovirus infection is capable of activating the cell-mediated immune response as well as the humoral one. Pathogens classified as superantigens have oligopeptides that bind to the variable region of the T cell beta chains, thus activating a larger proportion of T cells compared to pathogens without superantigen properties. Thus, parvovirus infection activates both the humoral and cell-mediated immune systems, triggering the inflammation that characterizes autoimmune and CTD states [7, 9].

Conclusion

In conclusion, we present a case of Parvovirus B19 infection in a middle aged woman who presented with CTD-like symptoms and had a skin biopsy showing granulomatous vasculitis and interface dermatitis. The clinical and histopathologic findings in our patient further supports the literature regarding the relationship between atypical parvovirus infections and autoimmune CTD and serves as an example of the superantigen id reaction related to parvovirus infection. The ability of Parvovirus B19 to mimic CTD both clinically and histopathologically should be

kept in mind when evaluating patients with CTD-like symptoms. Although an association has been established and there is some evidence for a causal role, more studies are needed to truly delineate the relationship between infection with Parvovirus B19 and development of CTD.

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