

Immunohistochemical Demonstration of Parvovirus B19 Viral Protein 2 in Periflexural Exanthema in an Adult, Supporting Antibody-Dependent Enhancement as Means of Endothelial Uptake of the Virus

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Abstract: Human parvovirus B19 (B19V) causes a number of skin exanthemas and has been related to both cutaneous and systemic diseases. Tropism of the virus for the rapidly proliferating erythroid progenitor cells in the bone marrow and fetal liver explains the pathogenesis of anemia and fetal hydrops. The cutaneous lesions of erythema infectiosum and other B19V-related exanthemas have been attributed to the deposition of immune complexes in the skin. We report on the immunohistochemical detection of B19V protein in the cytoplasm of dermal endothelial cells in a case of periflexural exanthema in a 28-year-old woman. An antibody-dependent enhancement mechanism of entry has been suggested for B19V in myocardial endothelial cells and could also be involved in B19V-related exanthemas.

Key Words: parvovirus B19, immunohistochemistry, antibody-dependent enhancement, skin, pathogenesis

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INTRODUCTION

Primary infection by human parvovirus B19 (B19V), the etiologic agent of erythema infectiosum in infancy and childhood, can result in cutaneous lesions in adults, with patterns designated as exanthema, “gloves and socks,” periflexural and palpable purpura¹ that can either appear isolated or overlap. Moreover, around 5% of atypical exanthemas (ie, those whose morphology and etiology depart from the 6 classic ones)² have been found to be related to B19V infection, both in children and in adults. These skin manifestations are believed to be due to specific immunological reaction to the virus. In the rarely biopsied cases of primary B19V infection, a dermal mononuclear perivascular lymphocytic infiltrate with erythrocyte extravasation, as well as leukocytoclastic vasculitis, have been reported. Immunohistochemistry has surprisingly been used only anecdotally, but it can reveal viral

proteins in epidermal keratinocytes or within endothelial cells of the superficial dermis, a finding of uncertain significance.^{3,4} We report for the first time on the immunohistochemical detection of B19V viral protein 2 (VP2) within dermal endothelial cells in periflexural and purpuric involvement in primary B19V infection in an adult patient, review previous reports in the literature, and discuss the possible relationship of this finding with the recently described antibody-mediated enhancement (ADE) as the uptake mechanism of B19V.⁵

MATERIALS AND METHODS

The skin biopsy was fixed in formalin and embedded in paraffin. Five-micrometer sections were stained with hematoxylin and eosin. Immunohistochemical study of B19V VP2 structural protein (Polyclonal Rabbit Anti-PVB19; DakoCytomation, Glostrup, Denmark) was performed following the manufacturer's instructions and was visualized using the DAKO EnVision system. Liver tissue from a B19V-associated fetal hydrops was used as positive control. Polymerase chain reaction (PCR) techniques for molecular detection of B19V were performed according to Aractingi et al.³ The serological detection of antibodies against B19V was performed using enzyme-linked immunosorbent assay.

RESULTS

Clinical History

A 28-year-old white woman was seen at the Emergency Department of Fundación Jiménez Díaz with a 24-hour history of fever, pruritus, and a rash. She described the latter as macules and papules that had first appeared on her vulva, inguinal folds, and thighs, spreading later on to her axillae, arms, and legs. Her medical history included type II diabetes, obesity, and a nonsecreting pituitary microadenoma diagnosed several years earlier in Cuba (her home country), for which she received linagliptin and metformin. On admission, her temperature was 37.6°C. She had mild tachycardia and normal blood pressure. On examination, an extensive exanthema of erythematous papules with petechial lesions was observed involving particularly axillae, anogenital region, inner thighs, buttocks, and antecubital fossae

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(Fig. 1). She had no lesions in oral mucosa, palms, or soles. Laboratory data showed leukocytosis (15,820 cells per microliter), with neutrophilia, mild hyperglycemia (serum glucose 127 mg/dL), and a mixed hyperbilirubinemia. Serum tryptase levels were normal. Urinalysis disclosed pyuria, hematuria, and bacteriuria. Abdominal ultrasonography and computed tomography revealed cholelithiasis with no signs of cholecystitis and left renal lithiasis without dilatation of the excretory system. With the clinical suspicion of urinary versus biliary tract infection, the patient was admitted, receiving antibiotic coverage and antihistamines. Dermatological evaluation the following day suggested baboon/like syndrome caused by primary B19V infection. Clinical evolution was favorable, with disappearance of fever and gradual fading of her cutaneous lesions over the course of 7 days. During her hospital stay, she developed pancytopenia, with nadir values of white cell count, hematocrit and platelets of 1360 cells/ μ L, 29.6%, and 102,000 cells/ μ L, respectively. All these parameters spontaneously had returned to normal 4 weeks later. Serologic results for hepatitis A, B, and C, syphilis, HIV, Epstein–Barr virus, cytomegalovirus, rheumatoid factor, and antinuclear and anti-neutrophil cytoplasmic antibodies were negative. A serologic test for B19V-specific IgM antibodies to viral capsid antigen was positive.

Pathologic Features

A skin biopsy performed on the third day of admission showed unremarkable epidermis and a moderate, mostly, perivascular mononuclear inflammatory infiltrate with some eosinophils and rare extravasated erythrocytes (Fig. 2). No evidence of vasculitis was seen. An immunohistochemical

study for B19V VP2 revealed positive granular material within the cytoplasm of superficial dermal blood vessels (Fig. 3).

DISCUSSION

Primary infection by B19V (family Parvoviridae, genus *Erythroparvovirus*, species *Primate erythroparvovirus 1*) is involved in 2 dermatological conditions with distinct cutaneous eruptions, namely erythema infectiosum in childhood and papular and purpuric “gloves and socks syndrome” (PPGSS) in adults. It can also cause other exanthemas in adults and children, designated palpable purpura, periflexural and atypical exanthemas.^{1,2} Serological conversion (ie, IgM followed by IgG-positive serology) and detection of viral DNA in serum by PCR have linked these dermatologic manifestations to PVB19. The presence of B19V DNA in biopsy specimens needs to be matched to serum samples, to confirm an acute infection, because the virus can persist for a long time in a number of tissues, including the skin.^{6,7} Thus, the wide array of cutaneous ailments that along the years have been assumed to be related to PVB19 needs to be critically reviewed, accepting only those instances in which seroconversion and/or serum B19V can be proven (Table 1).^{3,8–37}

The specific tropism of PVB19 for bone marrow erythroid progenitor cells (due to their expression not only of the globoside receptor/P antigen but also of coreceptors $\alpha 5 \beta 1$ integrin and Ku80) and the consequent cessation of erythropoiesis explain some of the pathological conditions with which PVB19 is associated: anemia in immunocompromised patients, transient aplastic crises, and hydrops fetalis.³⁸ Other ailments, such as arthropathy and the above-mentioned



FIGURE 1. Papular and purpuric exanthema involving inguinal regions (A), antecubital fossae (B), and axillae (C and D) in a 28-year-old woman with fever and positive IgM for B19V.

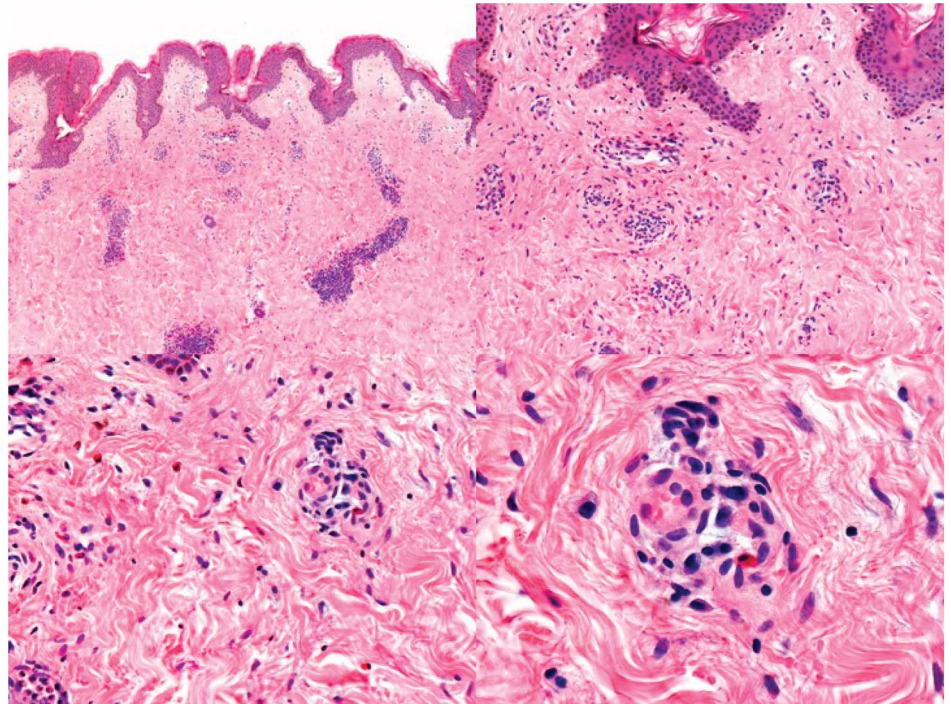


FIGURE 2. Histopathologic appearance of a skin biopsy, showing mild perivascular, mostly lymphohistiocytic inflammation. No evidence of vasculitis was found.

cutaneous eruptions, have been attributed to viral activation of synoviocytes or to the deposition of immune complexes, respectively.^{39,40}

Few reports have addressed the cutaneous histopathologic findings of exanthemas caused by PVB19. The described lesions consist for the most part of extravasation of erythrocytes and a perivascular lymphohistiocytic

infiltrate,^{3,4,41,42} but other patterns have been reported. Among them are vesicular, bullous, or pustular lesions,^{32,43,44} necrosis of keratinocytes,²⁵ interface dermatitis,²⁷ interstitial eosinophilic infiltrates,³⁰ and cutaneous vasculitis^{18,21,29,45} (Table 1).

Other than by means of PCR detection of B19V DNA, a specific search of B19V virion components in skin specimens has been performed occasionally. As early as 1994,

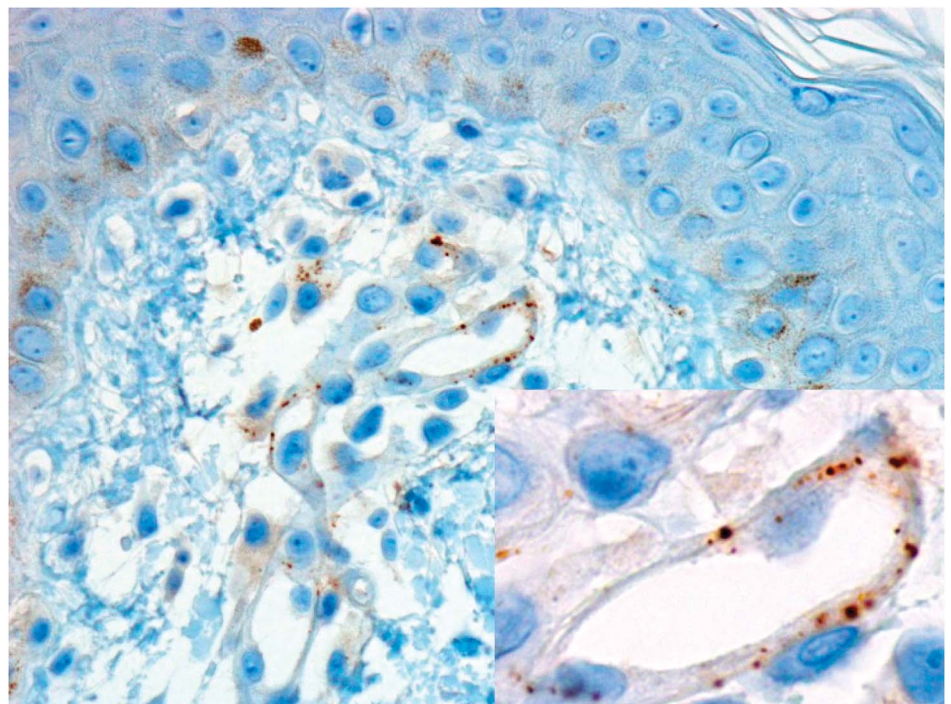


FIGURE 3. Immunohistochemistry for B19V VP2. Note granular material within the cytoplasm of the endothelial cells of the upper dermis.

TABLE 1. Dermatologic Clinical Entities Associated With B19V in the Literature, Pathologic Findings in Biopsies and Means of B19V Detection

Disease/Clinical Pattern	Pathologic Findings in Skin	B19V Serum Antibodies	Serum B19V	Tissue B19V PCR	IHC Detection of B19V
Erythema infectiosum ^{9,10,46}	No biopsy ⁹ ; no details given ⁴⁶ ; interstitial/perivascular dermatitis ¹⁰	IgM	ND	ND	ND
Henoch–Schönlein ¹¹	No biopsy	IgM	ND	ND	ND
Papular petechial vesiculopustular eruption ⁴³	vesiculopustular lesions, eosinophils	IgM, IgG	ND	ND	ND
Pruritic macular erythematous rash ¹²	No biopsy	IgM, IgG	ND	ND	ND
Pruritus, measles-like rash ¹²	No biopsy	IgM, IgG	ND	ND	ND
Pruritic rash ¹²	No biopsy	IgM, IgG	ND	ND	ND
Erythema nodosum ¹³	No biopsy	IgM	ND	ND	ND
Erythema multiforme ¹⁴	Erythema multiforme	IgM, IgG	–	ND	ND
Keratolysis exfoliativa ¹⁵	No biopsy	IgM, IgG	ND	ND	ND
PPGSS ^{3,4}	Slight acanthosis, PVD, purpura	ND, IgM, IgG	ND, +	ND, +	ND, +
Morbilliform rash ¹⁶	No biopsy	IgM	ND	ND	ND
Gianotti–Crosti ¹⁶	No biopsy	IgM	ND	ND	ND
Purpura, Koplik spots ¹⁷	No biopsy	IgM, IgG	ND	ND	ND
Palpable purpura, Wegener granulomatosis ¹⁸	Leukocytoclastic vasculitis	IgM, IgG	+	+	–
Livedo reticularis and myasthenia ¹⁹	Vascular telangiectasias	IgM	–	ND	ND
Polyarteritis nodosa ¹⁸	Leukocytoclastic vasculitis	IgM, IgG	+	+	ND
Unilateral laterothoracic exanthem ²⁰	PVD + hemorrhage	IgM, IgG	–	ND	ND
Papular dermatitis, Sweet-like granuloma annulare–like, dermatomyositis-like, lupus-like, palpable purpura ¹⁰	Incipient GA: interstitial infiltration, interface dermatitis, vasculitis, lymphocytic or granulomatous, dermal mucinosis, leukocytoclastic vasculitis	IgM, IgG	ND	+	ND
Connective tissue disease (DM, LE, vasculitis, PAN) ²¹	Vacuolar interface dermatitis, incipient GA, mucinosis, PVD, leukocytoclastic vasculitis	IgM, IgG	–	+	ND
Digital ischemia ²²	No biopsy	IgM, IgG	ND	ND	ND
Chronic urticaria, normal skin ²³	Not described	IgG	–	+	ND
Pseudo-cellulitis plaques ²⁴	No biopsy	IgM	ND	ND	ND
Pityriasis lichenoides ²⁵	Wedge-shaped infiltrate, extravasated erythrocytes, variable necrosis of keratinocytes	ND	ND	+	ND
Baboon syndrome-like ²⁶	PVD hemorrhage interface dermatitis	IgM	+	ND	ND
Asymmetric periflexural exanthem ²⁷	Interface dermatitis, syringotropic lymphocytic infiltrate	IgM, IgG	ND	ND	ND
Psoriasis ²⁸	NA	IgG, IgM	+	ND	ND
Behçet's disease ²⁹	Leukocytoclastic vasculitis	IgG	ND	+	ND
Wells' syndrome ³⁰	Eosinophilic interstitial infiltrate with flame figures	IgM, IgG	+ (ND)	+ (ND)	ND
Melkersson–Rosenthal syndrome ³¹	Multiple granulomas in lip and paranasal sinus	IgG	+	ND	ND
Hydroa vacciniforme ³²	Intraepidermal bullae, lymphocytic dermal infiltrate	ND	ND	+	ND
Sweet's syndrome ³³	Dermal neutrophils, also lymphocytes and plasma cells	IgM, IgGH	ND	ND	ND

TABLE 1. (Continued) Dermatologic Clinical Entities Associated With B19V in the Literature, Pathologic Findings in Biopsies and Means of B19V Detection

Disease/Clinical Pattern	Pathologic Findings in Skin	B19V Serum Antibodies	Serum B19V	Tissue B19V PCR	IHC Detection of B19V
Febrile ulceronecrotic Mucha–Habermann disease ³⁴	Psoriasiform dermatitis, exocytosis of lymphoid cells, dermal edema, and erythrocyte extravasation	IgM, IgG	+	–	ND
Acute exanthematous pustulosis ³⁵	Subcorneal pustules, dermal perivascular and interstitial inflammation	IgM, IgG	ND	ND	ND
Flagellate erythema ³⁶	No biopsy	IgM	ND	ND	ND
PPGSS and bathing-trunk eruption ³⁷	Lymphocytic exocytosis, edema in dermis, extravasated red blood cells, perivascular lymphohistiocytic infiltrate	IgM, IgG	ND	ND	–
Present case, periflexural exanthema	Perivascular mononuclear inflammatory infiltrate, eosinophils, extravasated erythrocytes	IgM	ND	ND	+

+, positive; –, negative; DM, diabetes mellitus; GA, granuloma annulare; IHC, immunohistochemical; LE, lupus erythematosus; ND, not done; PAN, polyarteritis nodosa; PVD, perivascular dermatitis.

Schwarz et al⁴⁶ described the presence of B19V viral particles using electron microscopy and indirect immunofluorescence within cells of the epidermis in a skin biopsy of the exanthema of erythema infectiosum in a child. One year later, Takahashi et al reported the involvement of vascular endothelial cells in an adult patient with primary B19V infection, demonstrating within their cytoplasm viral particles using electron microscopy and viral proteins (VP) by immunohistochemistry. No immune complexes were identified by immunofluorescence, although C3 was deposited in the perivascular regions of the dermis.⁴⁷ A few years later, viral proteins were detected by immunohistochemistry in 3 cases of PPGSS. The staining was seen not only in dermal endothelial cells but also in keratinocytes and sweat gland epithelial cells.³ In situ reverse transcriptase PCR was used by Magro et al⁴⁸ to demonstrate viral RNA in endothelial cells (and adjacent mononuclear cells) in skin biopsy specimens of several patients with positive IgG/IgM B19V serology and clinical manifestations of connective tissue disease (including petechial and purpuric eruptions and confluent rashes). The same method was used to demonstrate the virus in cases of endothelialitis allegedly secondary to B19V infection.^{49,50} Finally, positive immunohistochemical staining of the endothelium was reported in 2011 in 3 instances of PPGSS.⁴ This study was negative in an additional case of mixed PPGSS and “bathing-trunk” eruption.³⁷ In all cases in which the endothelium has been shown to contain B19V VP2 by immunohistochemistry, this was restricted to granular material within the cytoplasm of endothelial cells, although nuclear localization of this protein should be expected and has been elegantly demonstrated in infected placental tissue with the same technique.⁵¹

In the natural history of PB19V infection, an initial viremic phase (clinically undetected) allows the virus to gain access to permissive bone marrow erythroid progenitor cells, where it actively replicates and causes apoptosis, with release

of progeny virus in the blood.⁵² The normally nonpermissive endothelium has been recently shown to allow the entrance of PVB19 by means of ADE (in which B19V-antibody complexes use complement factor C1a and CD93 surface protein to facilitate endocytosis).⁵ Thus, the immune response to the virus in the form of IgM antibodies contributes to its spread to other tissues, including the skin, synovial joints, or endothelial cells of the myocardium. This infection, however, seems to be non-productive, so that only under specific conditions (hypoxia and cytokine stimulation) would endothelial cells support the synthesis of viral proteins.⁵ The detected VP2 in our case could represent unpackaged B19V particles, acquired by the ADE mechanism. It remains to be seen whether damage to the endothelium could follow, as has been speculated in the pathogenesis of B19V-related vasculitis and autoimmune diseases.^{48,50,53}

In summary, we present the first case of B19V-related flexural-type exanthema with immunohistochemical demonstration of viral proteins within the cytoplasm of superficial dermal vessels endothelium and propose that ADE-mediated uptake is responsible for this finding, as has been hypothesized for the endothelium of myocardial vessels.

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