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Epstein-Barr virus-related cutaneous necrotizing vasculitis in a girl heterozygous for factor V Leiden

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Abstract

Background: Necrotizing vasculitides are basically characterized by vessel wall neutrophil infiltration and necrosis and they can occur as a primary process or secondary to an underlying disease. Although Henoch-Schönlein purpura (HSp) is the more frequent primary vasculitis in childhood, sometimes it has to be distinguished from other secondary vasculitides induced by infections, drugs, vaccines, or immune-mediated disorders.

Main observations: We report a case of a 14-year-old girl with cutaneous necrotizing vasculitis, appearing in the course of acute Epstein-Barr virus infection. Physical examination revealed highly aching erythematous-purple lesions with reticular edges localized on the back of feet. Pain was non-responsive to ibuprofen and required administration of tapentadol and pregabalin. The patient was also heterozygous for factor V Leiden that might have contributed to the development of cutaneous painful lesions.

Conclusions: To our knowledge this is the first documented pediatric case of necrotizing vasculitis associated with acute EBV infection in a girl heterozygous for factor V Leiden. In this patient the severity of skin manifestations might have been influenced by the concomitant factor V Leiden, which gave rise to hypercoagulability and occlusive vasculopathy with markedly severe pain, a symptom rather infrequent in other childhood vasculitides. (*J Dermatol Case Rep*. 2017; 11(2): 25-28)

Introduction

Necrotizing vasculitides are basically characterized by vessel wall neutrophil infiltration and necrosis, following a local overload of chemotactic factors and deposition of immune complexes: the most frequently involved antigens are the streptococcal M protein, hepatitis B surface antigen, and *Mycobacterium tuberculosis*.[1] The inflammation in a blood vessel may occur as a primary process or secondary to an underlying disease. Henoch-Schönlein purpura (HSp) is the more frequent primary vasculitis in childhood, though sometimes it requires to be distinguished from other inflammatory reactions due to several infections, drugs, vaccines, or immune-mediated disorders. In particular, HSp is caused by immunoglobulin A deposits in the small vessels of skin, gastrointestinal tube, joints, kidneys, and its exact pathogenic mechanism, probably related to an initial bacterial, viral, or parasitic agent, is still unraveled.[2] Epstein-Barr virus (EBV) infection has been implicated in the pathogenesis of different vasculitic syndromes, such as polyarteritis nodosa and anti-neutrophil cytoplasmic antibody-associated vasculitis.[3,4] Herein, we report a case of EBV-related necrotizing vasculitis in a girl heterozygous for factor V Leiden.

Case report

A 14-year-old girl was admitted in our Emergency Room with an erythematous purpura-like rash localized over the feet, associated with local severe pain and fever. Her parents

declared that fever started one week before, followed by eruption of skin purple lesions on the hands and on the back. After that, further similar but more severe manifestations appeared on both feet. The girl was treated with ibuprofen and paracetamol to control pain without any effect. Consequently, she was referred to our hospital. Physical examination revealed confluent erythematous-purple lesions with reticular edges localized on the back of feet, in correspondence with the metatarso-phalangeal joints, which seemed unaffected. Some tense blisters filled with a clear fluid were present at the edge of lesions (Fig. 1, 2). Feet were cold and swollen, intensely aching at the palpation. Pain was so severe that the patient could not stand upright or walk. Skin lesions on hands and the back disappeared rapidly. Despite high fever (38.5 C°) and pain, her general condition was good and vital parameters were all within normal limits. All the vascular pulses were preserved and regular. Physical examination showed also diffuse lymphonode enlargement and splenomegaly. On dermoscopy examination of the cutaneous lesions on the feet we observed no specific clues for the diagnosis: only a purpuric homogeneous area with glomerular vessels was present (Fig. 3). Patient's medical history revealed also positivity of factor V Leiden in heterozygosis. Blood tests showed mildly increased transaminases and lymphocytosis (total white blood cell count 8670/mm^3, with 65.8% of lymphocytes), while platelet count was normal. Inflammatory markers were elevated (C-reactive protein 27.4 mg/L, normal value <5). Clotting tests were normal, with elevated D dimer (10.552 ng/ml) and positive lupus-like anticoagulant (dRVV time: 39.8", n.v. 20-36). Activated protein C resistance was 0.68 (n.v. 0.76-5), factor V Leiden (R506Q) was present in a heterozygous state, and mutated prothrombin (G20210A) was absent. Serum levels of immunoglobulins showed increased IgA and IgM. Pharyngeal swab was negative for bacteria, and serology tests for infectious mononucleosis revealed positive anti-VCA IgM and IgG; all other tests revealing infections as well as blood cultures were negative. Anti-nuclear antibodies were weakly positive (1/160), while other tests for autoimmunity (anti-DNA, anti-extractable nuclear antigens, anti-neutrophil cytoplasmic and anti-cardiolipin antibodies, rheumatoid factor, cryoglobulins, C_3 and C_4) were all negative. Abdominal ultrasound confirmed the presence of splenomegaly (diameter: 13.5 cm). Urinalysis showed only transient minimal hemoglobinuria and albuminuria. Electrocardiogram and Doppler ultrasound of the lower limb veins showed no abnormalities. Skin biopsy was taken from the edge of a purpuric lesion on the back of the left foot: the histopathological examination found a necrotizing vasculitis with necrosis in both epidermis and dermis and occlusive vasculopathy of little vessel walls (Fig. 4). Direct immunofluoresce studies on the perilesional skin were negative. Enoxaparin was administered during the first week of hospitalization in combination with ibuprofen; in addition, the girl received tapentadol and

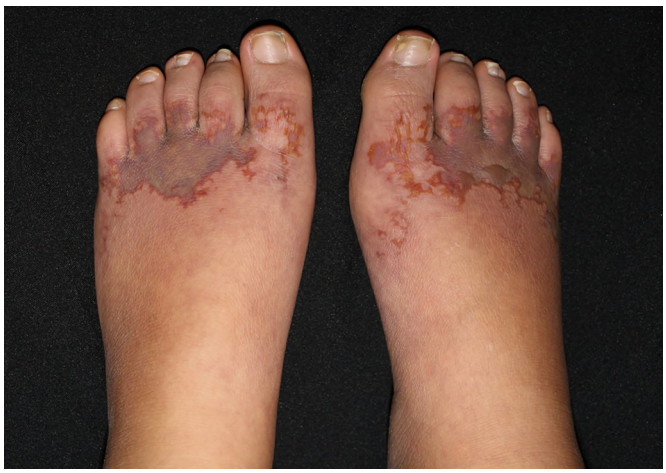

Figure 1

Bilateral confluent erythematous-purple lesions with reticular edges localized on the back of feet in a 14-year-old girl.

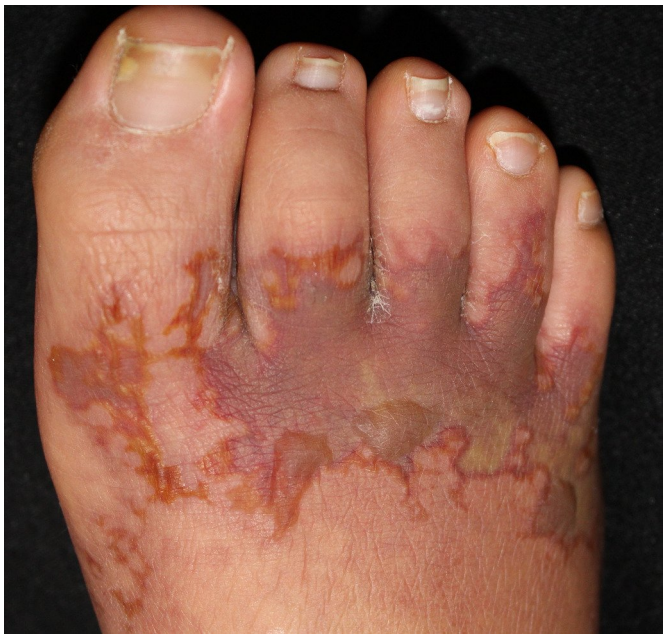

Figure 2

Magnification of a clinical image that shows tense blisters at the edge of the purple lesions.

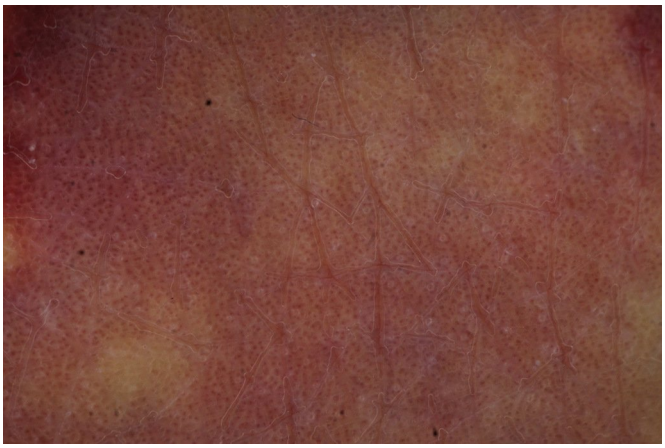

Figure 3

Dermoscopic imagine of vasculitic lesion localized on the back of feet.

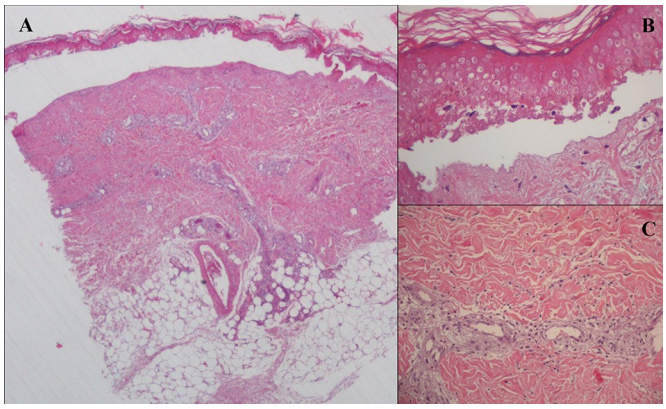

Figure 4

(A) Histologic exam: necrotizing vasculitis with occlusive vasculopathy of little vessel walls (B): High power view of necrotic keratinocites (C). Inflammatory perivascular infiltrate with neutrophils and eosinophils.

pregabalin for one week, then tapered and discontinued in the following week, to control severity of pain in her feet. Fever disappeared on the fifth day of hospitalization. Necrotic lesions went ahead ulceration, and wounded areas were treated with topic hyaluronic acid and covered with emollient sterile gauzes. The girl was then discharged after 2 weeks and prescribed to continue ibuprofen at full dose for 1 month. Thereafter, all lesions were healed, without any post-inflammatory signs. At the 2 month-follow up visit, she was healthy and experienced the complete resolution of every skin lesion.

Discussion

To the best of our knowledge this is the first pediatric case of a necrotizing vasculitis associated with acute EBV infection. Vasculitides are frequently induced by infections, mainly viral, such as HBV and also Cytomegalovirus or Parvovirus: pathogens could act as trigger factors ad activate the inflammatory cascade leading to vascular inflammation.[5] In particular, in both adulthood and childhood EBV has been linked in different reports with various types of vasculitis, including leucocytoclastic or granulomatous vasculitides, Kawasaki disease, polyarteritis nodosa, Duncan disease, systemic lupus erythematosus, and rheumatoid arthritis.[6-10] Sometimes, like in our case, the cutaneous manifestation, characterized by purpura and petechiae in the lower limbs, can be misdiagnosed as HSp. A chronic active EBV infection may be also associated with a vasculitis mimicking HSp in children.[11] In our case skin signs resembling HSp were present, but no other typical criteria required for establishing HSp diagnosis, i.e. abdominal pain, arthritis, proliferative glomerulonephritis with IgA deposits, were noted.[12] Our differential diagnosis included also acute hemorrhagic edema of infancy, which is a benign self-limiting leukocytoclastic vasculitis affecting very young children, manifesting as edema of the extremities with rosette-shaped purpuric rash.[13] The pathogenesis of virus-associated vasculitides is yet unclear. During the course of infections, viruses have been thought to cause vasculitis either directly by replication in the vascular endothelium or indirectly by induction of an autoimmune response based on molecular mimicry mechanisms.[14] Other reported modalities of vascular injuries are increased procoagulant activity and blockage of apoptosis in the endothelium.[15] An inflammatory cascade triggered by immune-complexes produced against EBV antigens and deposited in the vascular endothelium has been suggested to explain our patient's picture. However, necrotizing vasculitis was histologically confirmed and limited to skin, as she did not display any sign of systemic involvement. Thrombotic events are rare complications in children with HSp, following activation of the coagulation system, elevation of both factor VIII and homocysteine, or presence of anti-phospholipid antibodies, which are claimed as potential prothrombotic triggers in HSp.[16] Thrombophlebitis can also occur, being masked by typical joint involvement in children with HSp.[17] In particular, our patient was also heterozygous for factor V Leiden, a condition widely considered to be predisposing to thrombotic events. Some cases of livedoid vasculitis associated with factor V Leiden have been described, and all were characterized by painful bilateral ulcerations, probably due to dermal blood vessel occlusion.[18-20] Factor V has a critical position in both the coagulant and anticoagulant pathways, resulting in a hypercoagulable state, either increasing coagulation or decreasing anticoagulation: the factor V Leiden R506Q mutation heterozygotes, often found in Caucasians, have a 7-fold risk of developing venous thrombosis compared to non-carriers, as the mutation causes factor V to be resistant to being cleaved and inactivated by activated protein C. As a result, more factor V is available within the prothrombinase complex, increasing coagulation.[21] The severity of skin manifestations in our patient has been probably induced by the concomitant factor V Leiden, which gave rise to hypercoagulability and occlusive vasculopathy with markedly severe pain, a symptom rather infrequent in other childhood vasculitides. As regards therapeutic management of vasculitides in children, we have clear recommendations for Kawasaki disease,[22] but not for other disorders. It is important to distinguish between cutaneous and systemic forms, as the first can be treated with supportive measures, antihistamines, nonsteroidal anti-inflammatory drugs, or corticosteroids, given the fact that they generally tend to be self-limited in the mid-long term.[23] Otherwise when a patient presents with cutaneous signs of vasculitis, irrespective of the size of affected vessels, the possibility of systemic involvement should be always evaluated, combined with an overall work-up to rule out eventual infections or other underlying systemic diseases.

Conclusions

In conclusion, our case highlights that during EBV infection a necrotizing vasculitis may develop also in children, probably with the promotion of concomitant thrombofilic factors. Further studies would be needed to better understand the pathogenesis of necrotizing vasculitis developed in the course of infection.

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