

Non-blanching rash in a child with EBV infection: A pediatric diagnostic puzzle

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ABSTRACT:

Background: Epstein Barr Virus (EBV) infection is highly prevalent worldwide and commonly presents as infectious mononucleosis in children. Although cutaneous manifestations are well described, vasculitic presentations are rare and often under-recognized. **Case Presentation:** We report a 10-year-old previously healthy boy presenting with 16 days of persistent fever and sore throat, unresponsive to antibiotics. On admission, he developed a non-itchy, palpable, non-blanching erythematous maculopapular rash over the face, neck, chest, and abdomen, along with exudative tonsillitis, lymphadenopathy, and splenomegaly. Laboratory findings revealed lymphocytosis with atypical lymphocytes, elevated liver enzymes, LDH, and ferritin. EBV serology confirmed acute infection. Hemophagocytic lymphohistiocytosis was ruled out. The patient was managed conservatively with supportive care, leading to complete resolution within two weeks. **Discussion:** Investigations concluded acute EBV infection with associated rash. The non-blanching, non-itchy, palpable, maculopapular rashes were suggestive of vasculitis with no evidence of systemic involvement in this patient. We could not have a histopathological diagnosis as his parents declined consent for a skin biopsy. **Conclusion:** This case highlights the rare occurrence of cutaneous vasculitis in pediatric EBV infection. It underscores the importance of clinical vigilance when biopsy is not feasible and adds to the current literature on the clinical presentation, diagnosis and management of EBV associated vasculitis in the pediatric population.

Keywords: Epstein-Barr Virus, vasculitis, maculopapular rash, pediatric

INTRODUCTION:

Epstein-Barr Virus (EBV) is a ubiquitous virus infecting over 90% of the population and could persist in a latent state for the host's lifetime. Acute EBV infections present in children with a spectrum of clinical manifestations. The triad of fever, tonsillar pharyngitis and lymphadenopathy is referred to as infectious mononucleosis (IM). It has also been linked to lymphoma and certain carcinomas.

CASE PRESENTATION:

We report a 10-year-old previously healthy boy who presented with 16 days of persistent fever, sore throat which had not responded to Co-amoxiclav and cotrimoxazole. On the day of admission he developed a non-itchy, palpable, non-blanching erythematous maculopapular rash over the face, neck, chest, and

abdomen, accompanied by exudative tonsillitis, submandibular lymphadenopathy, and splenomegaly. He was investigated as a case of prolonged fever. Laboratory workup revealed lymphocytosis with atypical lymphocytes, mild anemia, elevated liver enzymes, LDH and ferritin. Other infectious and autoimmune tests were unremarkable. EBV Viral Capsid Antigen IgM (VCA) was positive, EBV VCA IgG positive, EBV Early Antigen IgG (EA) was positive, EBV Nuclear Antigen IgG (NA) was negative indicating an acute infection. Hemophagocytic Lymphohistiocytosis (HLH) a complication of EBV was ruled out in the context of the prolonged fever. The patient received supportive care with IV fluids, antipyretics, and topical steroids, leading to resolution of fever and rash in 2 weeks.

Figure 1: Non-blanching erythematous maculopapular rash over both lower limbs (legs), suggestive of cutaneous vasculitis.



Figure 2: Diffuse erythematous maculopapular rash over the upper limb (arm), non-itchy and non-blanching in nature.



DISCUSSION:

EBV associated rashes can arise due to multiple reasons. Around 5-10% of EBV patients can develop a mild maculopapular rash without antibiotics. This is usually a faint, transient, non-itchy, morbilliform or maculopapular rash which is typically seen on the trunk, upper arms and face. If the patient is given ampicillin or related amino penicillins the frequency of rashes can increase upto 90% which is usually a generalized non-urticarial, erythematous maculopapular rash. It generally appears 2-10 days after starting antibiotics. Some cephalosporins

can also cause rashes in EBV patients, though less commonly. There are reports of mild rashes that have occurred even with macrolides or non-beta lactam antibiotics. This is a non-allergic, non- IgE mediated rash. This is thought to result from virus induced immune dysregulation. The rash is self limiting and resolves after stopping the drug. Therefore aminopenicillins are to be avoided to treat sore throat in a suspected or confirmed case of IM. If a bacterial super infection is suspected, alternative antibiotics such as clindamycin or azithromycin are preferred. As this is not a true allergy

patients can be treated with penicillins for subsequent infections.

Sometimes the patient can also develop hives as in a urticarial rash mimicking allergic reactions. Petechial rashes on the palate are classic for IM and can often aid diagnosis. Occasionally EBV can trigger self-limiting target lesions as in erythema multiforme.

EBV can also cause rashes due to vasculitis which is much rarer than classic exanthems. EBV can cause vasculitis during the acute phase or as a part of Chronic active EBV infection (CAEBV).

PATHOGENESIS OF EBV-ASSOCIATED VASCULITIS:

Although the exact mechanism is not fully understood, EBV induced vasculitis is thought to be a combination of immune dysregulation and direct viral effects. The possible pathogenic mechanisms are:

- Immune complex deposition: EBV infection can trigger the formation of autoantibodies and immune complexes which deposit in the vessel walls and cause inflammation as in Henoch Schönlein purpura and cryoglobulinemic vasculitis.
- Molecular mimicry: Similarities between viral antigen and human antigen can cause the immune system to mistakenly attack blood vessel walls as seen in ANCA-associated vasculitis.
- Lymphocytic infiltration: In CAEBV infection, EBV infected T or NK cells can proliferate and directly infiltrate the blood vessel walls, triggering inflammation leading to structural damage and even aneurysm formations.

Types of EBV vasculitis:

EBV infection associated vasculitis can affect vessels of various sizes:

Small vessel vasculitis:

- Henoch schonlein purpura: This is the most common form of vasculitis in children, presenting with palpable purpura, joint pain, abdominal pain and kidney involvement.
- Cutaneous leukocytoclastic vasculitis: inflammation of the small blood vessels in the skin presents as palpable purpura.
- ANCA - associated vasculitis: EBV can induce the formation of ANCA autoantibodies. Therefore EBV can trigger or exacerbate ANCA-associated vasculitis such as microscopic polyangiitis.

Medium size vasculitis:

- Chronic Active EBV vasculopathy: the infiltration of the EBV infected lymphocytes into the vessel walls and subsequent inflammation, leads to vessel wall damage and aneurysm formation, which can affect coronary, cerebral and abdominal arteries. This is the most severe form of vasculopathy.
- Kawasaki's disease (KD): some studies have found an association between EBV co-infection and development of KD.

CLINICAL MANIFESTATIONS:

The clinical manifestations depend on the organs involved:

Cutaneous manifestation of EBV induced vasculitis could present as palpable, non-blanching, purpuric rash as in small vessels, leukocytoclastic vasculitis. It can present as petechiae or ecchymosis mimicking thrombocytopenic purpura. In rare cases such as in immuno-compromised patients it may even present as necrotic skin lesions.

Although cutaneous vasculitic lesions are more frequent, EBV vasculitis can affect systemic organs. Involvement of the CNS vasculature can cause stroke-like events or cerebral encephalopathy due to cerebral vasculitis. Involvement of the gut vasculature can cause gut ischemia with abdominal pain and bleeding. Involvement of renal vasculature can present as glomerulonephritis.

Diagnosis:

EBV serology and viral load: EBV specific antibodies and viral DNA levels helps to confirm the diagnosis of acute or reactivated EBV infection.

Figure 1: Maculopapular rash over chest

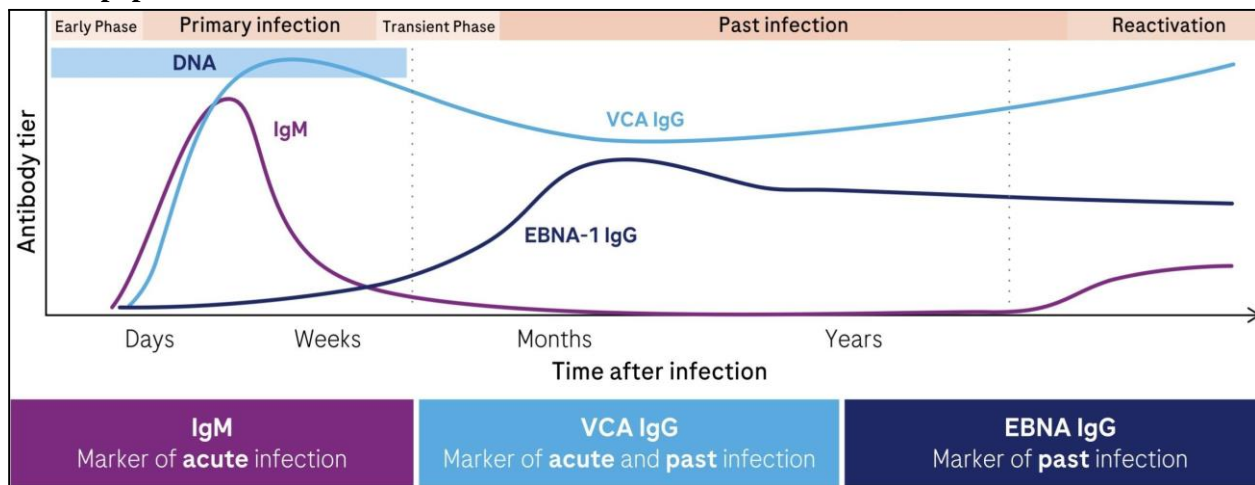


Figure 2: Non-blanching lesions over abdomen

<u>Diagnostic Markers</u>		References		Products
	Not immune	Acute infection	Transient phase**	Past infection
VCA IgM	-	+	+	-
VCA IgG	-	+	+	+
EBNA-1 IgG	-	-	+	+

* Can be negative in very early phase of acute infection

** Indeterminate infection stage. Requires additional testing. Same result constellation can be observed during reactivation of infection.

Demonstrating elevated EBV DNA in the peripheral blood is a key diagnostic feature of CAEBV.

Biopsy: biopsy of the affected tissue (e.g, skin) is necessary to confirm the diagnosis of vasculitis. Histo-pathology shows neutrophilic infiltration around vessels, nuclear debris, and immune complex deposition. EBV DNA may be demonstrable in the affected tissue by PCR or in-situ hybridization.

TREATMENT:

Mild cutaneous vasculitis requires only symptomatic treatment. Severe systemic vasculitis would require corticosteroids and sometimes immunosuppressants such

as cyclophosphamide or rituximab. Antivirals such as Acyclovir or Gancyclovir have limited benefit and may be considered in severe EBV disease to suppress the viral load. The only curative treatment for CAEBV related vasculitis is allogeneic hemopoietic stem cell transplantation

CONCLUSION:

In our patient, who presented with prolonged fever and rash, investigations concluded EBV infection with associated rash. The non-blanching, non-itchy, palpable, maculopapular rashes, were suggestive of vasculitis with no evidence of systemic involvement in this patient. We could not have a histopathological diagnosis as his parents

declined consent for skin biopsy.

This case highlights the rare occurrence of vasculitic manifestations in pediatric EBV infection. It underscores the importance of clinical vigilance when biopsy is not feasible and adds to the current literature on the clinical presentation, diagnosis, and management of EBV - associated vasculitic rashes in the pediatric population.

Ethical Approval and Consent to Participate:

Ethical approval was not required for this case report as per institutional guidelines.

Consent for Publication:

Written informed consent was obtained from the patient's parents/legal guardians for publication of this case report and accompanying images.

Conflict of Interest:

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Author Contributions:

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