

CASE REPORT

Paraviral bullous eruption in a 7-year-old child during acute Epstein–Barr virus infection: A case report

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Key Clinical Message

We present the case of a child developing widespread vesicle-bullous lesions during an acute and symptomatic Epstein–Barr Virus infection. Antibody serology, biopsy, and direct immunofluorescence allowed the diagnosis of a paraviral bullous eruption. To our knowledge, this is the first report of bullous eruption following Epstein–Barr virus infection in childhood.

KEYWORDS

immunology, infectious diseases, pediatrics and adolescent medicine, virology

1 | INTRODUCTION

Bullous eruptions in children can be a diagnostic challenge even for the most experienced clinician. In fact, they encompass a wide range of entities, including acquired and congenital disorders.

It is well recognized that viral infections can act as trigger factors for bullous diseases in adults, while few data are available in children.^{1–3} In this regard, it is postulated that autoimmune bullous disorders develop following an interaction between genetic and environmental factors. Various members of the human herpes virus (HHV) family may act as potential triggers or exacerbators of pemphigus vulgaris. Among these viruses are included varicella zoster virus (VZV), herpes simplex virus (HSV), cytomegalovirus (CMV), human herpes virus 8 (HHV 8), and Epstein–Barr virus (EBV).^{4–6}

In this article, we present the case of a 7-year-old girl developing widespread vesicle-bullous lesions after an acute and symptomatic EBV infection, in the presence of both virus-specific IgG and IgM.

2 | CASE HISTORY

A 7-year-old female child was referred to our Pediatric Dermatology Unit following several dermatological consultations with the suspect of monkey-pox infection. General conditions were good and objective examination was negative apart from retroauricular lymphadenopathy. The mother reported only few acute episodes of mild cough in the previous 10 days.

Skin inspection revealed a diffuse vesicle-bullous eruption, with involvement of neck and face and sparing of

Elisa Milan and Jacopo Tartaglia contributed to this paper.

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FIGURE 1 Panoramic picture of vesiculobullous lesions, some with de-epithelialized center, on the trunk and limbs.

palmo-plantar surfaces. At a closer observation, lesions were diffuse but tended towards coalescence into a rosette-like appearance (Figure 1, Figure 2A,B).

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

A combined systemic therapy with amoxicillin-clavulanate and betamethasone was recommended in an attempt to reduce new lesions and pruritus and to prevent superinfections, with a progressive improvement of skin lesions.

Meanwhile, a biopsy with perilesional direct immunofluorescence was performed to exclude autoimmune bullous disease, lichenoid dermatitis, drug induced reaction, a Langerhans cell histiocytosis or a vasculitis.

At the same time, antibody serology tests for CMV, EBV, Parvovirus, and *Mycoplasma pneumoniae* were prescribed.

Positive results of anti-VCA-EBV IgM, anti-VCA-EBV IgG, anti-EBNA-IgG, and EBV-DNA tests were obtained, denoting an acute EBV infection.

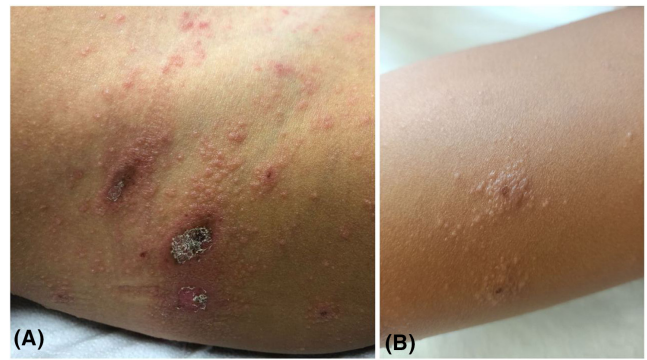


FIGURE 2 (A, B) Close-up picture showing relatively monomorphic lesions coalescing into a rosette-like appearance.

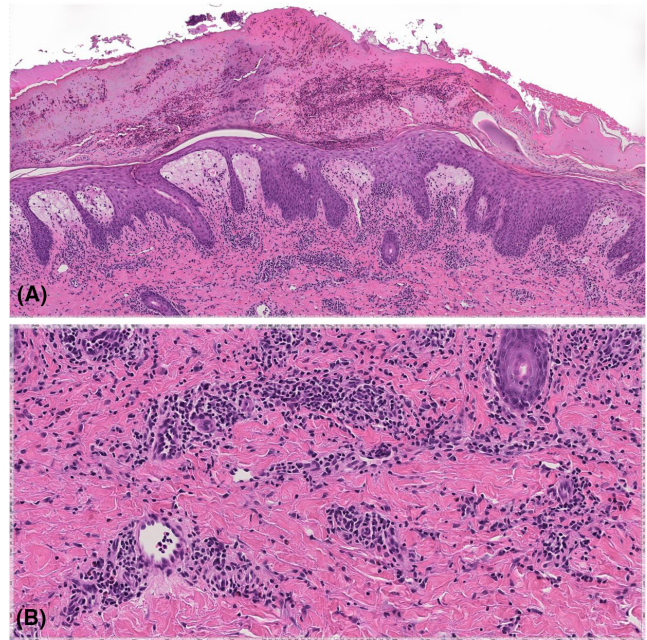


FIGURE 3 (A, B) Biopsy specimen showing a marked papillary dermis edema with a lymphocytic and neutrophilic infiltrate. A perivascular lymphocytic infiltrate was present deeper in the dermis. Finally, hyperkeratosis, acanthosis, and spongiosis of the epidermis were present.

Histologic examination showed hyperkeratosis, acanthosis, and spongiosis of the epidermis, while, in a markedly edematous papillary dermis, a lymphocytic and neutrophilic granulocytic infiltrate was observed. A monomorphic perivascular lymphocytic infiltrate was present deeper in the dermis. Histopathologic findings supported the hypothesis of a paraviral rash (Figure 3).

The presence of small deposits of C3 in the absence of IgG, IgA, or IgM at the dermoepidermal junction allowed us to exclude autoimmune bullous disease. The patient underwent close dermatological follow-up during the course of EBV infection, observing

a progressive resolution of skin lesions and no clinical relapses.

4 | DISCUSSION

The role of EBV as a potential inducer or exacerbator of autoimmune blistering disorders in children is debated, while there seems to be sufficient evidence to support its role as an infectious trigger factor in adults. In fact, DNA sequences of EBV have been found in 5% of skin biopsies of adult patients affected by bullous pemphigoid (BP).⁶ F. Drago et al. detected DNA sequences of HHV, including EBV, in 27% of skin samples, further supporting the potential role of herpesviruses as elicitors of an autoimmune response in genetically predisposed patients. Regarding PV, the evidence supporting the role of EBV as a trigger is scarce.⁴ In their study, Sagi et al. found no significant difference in EBV antibodies between patients with autoimmune blistering diseases (comprehending both BP and PV patients) and healthy controls. The authors concluded that their findings suggest a minor contribution of EBV in autoimmune blistering disorders.³ Finally, to date, there are no reports of other autoimmune bullous diseases (such as linear IgA bullous dermatosis or epidermolysis bullosa acquisita) associated with EBV in adult patients.

On the other hand, EBV is more commonly associated with paraviral skin eruptions. In adolescents and young adults, primary EBV infection frequently results in infectious mononucleosis. In approximately 5% of patients affected by mononucleosis, the viral infection is associated with skin eruption characterized by heterogeneous lesions (such as macular, petechial, urticarial, scarlatiniform or erythema multiforme-like lesions).⁷ A transient erythematous, maculopapular eruption involving trunk and upper extremities is also common in patients affected by mononucleosis who received antibiotic therapy in the previous 10 days.⁸ In children, EBV is one of the most common infectious agents associated with Gianotti–Crosti syndrome (GCS). GCS (also referred to as papular acrodermatitis of childhood) is an acute, autolimited eruption involving acral skin sites. Clinically, GCS is characterized by symmetrical, monomorphic papular lesions tending to be asymptomatic. The most frequently involved sites are cheeks, buttocks, extensor aspects of arms, hands and thighs. Viral antigens have not been demonstrated in skin on ultrastructural or immunohistochemical studies.⁹ GCS can rarely manifest with vesicubullous lesions: a bullous form of GCS also falls within the differential diagnosis of paraviral bullous eruptions.

To date, there is only one case report of an EBV-induced autoimmune bullous disease in a child. Baldari

et al. reported the case of a 3-year-old girl developing chronic bullous disease of childhood (a variant of linear IgA bullous dermatitis) following recent EBV seroconversion. The authors hypothesized that EBV was able to stimulate the patient's immune system (through immortalization of B lymphocytes and activation of T lymphocytes) ultimately leading to the development of an autoimmune disease.¹⁰ Case reports of autoimmune bullous diseases in children induced by other Human-Herpes viruses (such as HSV and VZV) were also reported.^{2,11}

5 | CONCLUSION

In our case, the final diagnosis was a paraviral bullous skin eruption following a primary EBV infection.

In fact, the temporal association with an acute viremic EBV infection and the progressive improvement of skin lesions with the resolution of the viremia supported the hypothesis of a paraviral skin eruption.

On the other hand, the negativity of the direct immunofluorescence assay, the self-limiting course and the excellent response to small doses of systemic steroid did not support the hypothesis of an autoimmune bullous disease.

Further studies are needed in order to elucidate the association between EBV infection and bullous eruption.

In clinical practice, in case of an acute skin bullous eruption the possible etiology of EBV infection should be considered, also in pediatric age.

AUTHOR CONTRIBUTIONS

Elisa Milan: Conceptualization; data curation; methodology; software; writing – original draft. **Jacopo Tartaglia:** Conceptualization; data curation; formal analysis; methodology; writing – original draft. **Maria Ludovica Deotto:** Conceptualization; investigation; methodology; visualization. **Roberto Salmaso:** Data curation; supervision; visualization. **Francesca Caroppo:** Conceptualization; project administration; supervision; writing – review and editing. **Anna elloni Fortina:** Methodology; project administration; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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