Acute generalized exanthematous pustulosis associated with primary Epstein-Barr virus infection

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Key words: acute generalized exanthematous pustulosis; children; Epstein-Barr virus.

Acute generalized exanthematous pustulosis (AGEP) is a rare severe cutaneous reaction characterized by the acute onset of generalized nonfollicular sterile pustules arising on an edematous erythema. The eruption is usually associated with fever and neutrophilic leukocytosis.[1] Although AGEP is precipitated by drugs in most cases, there have been isolated reports of AGEP associated with infections (parvovirus B19, cytomegalovirus, coxsackie B4, *Mycoplasma pneumoniae*), mercury exposure, and spider bites.[2-5] Herein, we report the occurrence of AGEP possibly triggered by an acute primary Epstein-Barr virus (EBV) infection in a 16-year-old girl.

Abbreviations used:

AGEP: Acute generalized exanthematous pustulosis
EBV: Epstein-Barr virus

CASE REPORT

The girl presented to the emergency department with a 3-day history of a generalized pruritic eruption of abrupt onset. She complained of fever (39.4°C) and chills in addition to a sore throat and fatigue. She denied taking any medications before the skin eruption occurred, and she had no personal or family history of skin disease. Physical examination found erythematous and edematous patches, with numerous nonfollicular pustules on the face, trunk, and extremities (Fig 1). The patient had minimal pharyngeal erythema and enlarged cervical lymph nodes. The remainder of the examination findings were normal.

Laboratory studies found marked leukocytosis of 19100/μL, with neutrophilia (9220/μL; normal, 1800-7500/μL), eosinophilia (2670/μL; normal, <800/μL), lymphocytosis (5520/μL; normal, 1000-4000/μL), monocytosis (1580/μL; normal, <1000/μL), and an elevated C-reactive protein level (38.5 mg/L; normal, <10 mg/L). Liver function test results and urea and creatinine levels were within the normal limits. Blood, urine, and pustule cultures for bacteria were negative. Serologic tests for parvovirus B19,

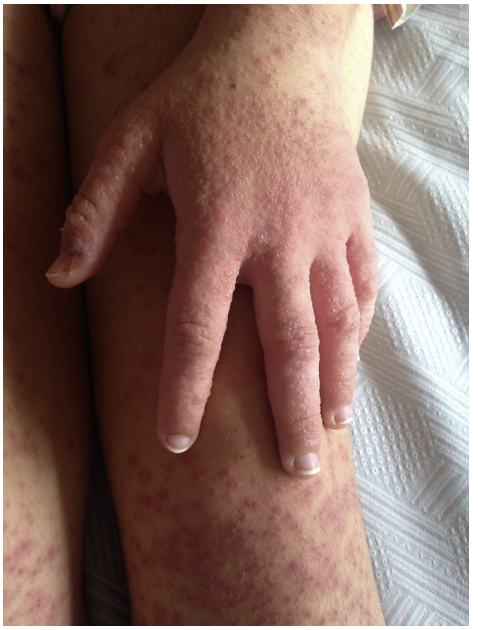

Fig 1. Acute generalized exanthematous pustulosis. Erythematous and edematous eruption, with numerous pinpoint pustules on the dorsum of the hand.

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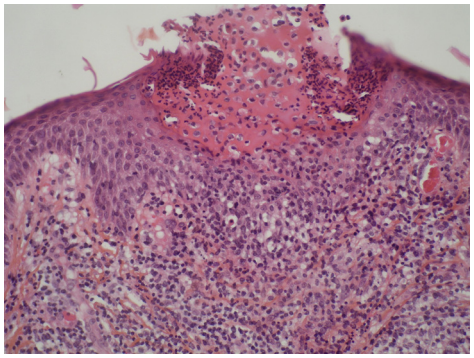

Fig 2. Acute generalized exanthematous pustulosis. A skin biopsy shows a subcorneal pustule filled with neutrophils. Note the presence of necrotic keratinocytes in the epidermis. Papillary dermal edema and superficial mixed infiltrate composed of lymphocytes and neutrophils can also be seen. (Hematoxylin-eosin stain; original magnification: ×200.)

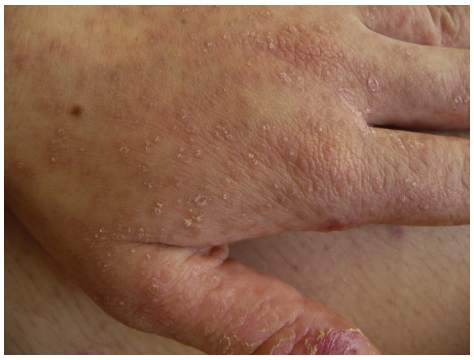

Fig 3. Acute generalized exanthematous pustulosis. Typical superficial postpustular desquamation after 2 weeks.

enterovirus, cytomegalovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and toxoplasmosis were all negative. EBV serologic test result was positive for immunoglobulin M against viral capsid antigen, consistent with an acute EBV infection. A skin biopsy found spongiform subcorneal and intraepidermal neutrophilic pustules along with papillary dermal edema, superficial lymphocytic infiltrate with neutrophils, and focal necrosis of keratinocytes (Fig 2). According to the EuroSCAR study group criteria,[1] our patient had a score of 11, indicating a definite diagnosis of AGEP. The patient was then treated symptomatically with topical corticosteroids and emollients, resulting in rapid resolution of the rash within 2 weeks followed by a postpustular desquamation (Fig 3).

Table I. AGEP validation score of the EuroSCAR study group

Morphology	
Pustules	
Typical*	+2
Compatible†	+1
Insufficient‡	0
Erythema	
Typical	+2
Compatible	+1
Insufficient	0
Distribution/pattern	
Typical	+2
Compatible	+1
Insufficient	0
Postpustular desquamation	
Yes	+1
No/insufficient	0
Course	
Mucosal involvement	
Yes	−2
No	0
Acute onset (<10 d)	
Yes	0
No	−2
Resolution (<15 d)	
Yes	0
No	−4
Fever (>38°C)	
Yes	+1
No	0
PNN (>7000/μL)	
Yes	+1
No	0
Histology	
Other disease	−10
Not representative/no histology	0
Exocytosis of PNN	+1
Subcorneal and/or intraepidermal non spongiform or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustules without papillary edema	+2
Spongiform subcorneal and/or intraepidermal pustules with papillary edema	+3

Interpretation: ≤0: no AGEP; 1-4: possible; 5-7: probable; 8-12: definite.

NOS, not otherwise specified; *PNN*, polymorphonuclear neutrophils.

*Typical: typical morphology.

†Compatible: not typical, but not strongly suggestive of other disease.

‡Insufficient: lesions cannot be judged.

DISCUSSION

AGEP is a rare acute pustular reaction that is most often caused by drugs. It is a self-limiting disease, usually arising rapidly, within 48 hours after drug exposure, and resolving quickly, within 2 weeks after withdrawal of the causative agent. In typical cases, the pustules are followed by characteristic

postpustular pinpoint desquamation.[1] According to the EuroSCAR study, antibiotics (such as aminopenicillins, pristinamycin, and quinolones), terbinafine, antimalarials, and calcium channel blockers (diltiazem) are the most frequently reported triggers of AGEP.[6] The diagnostic criteria include an acute pustular eruption, fever (>38°C), blood neutrophilia (>7000/μL), spongiform subcorneal or intraepidermal pustules on skin biopsy, and acute evolution and spontaneous resolution of the pustules in less than 15 days.[1] Our patient fulfilled the diagnostic criteria for AGEP (Table I). AGEP is, however, an uncommon condition in children, and certain investigators have suggested that viral infections might be the most frequent triggers in the pediatric population.[7] The main differential diagnosis of AGEP is generalized pustular psoriasis. In our patient, the absence of a personal or family history of psoriasis, the acute course and rapid resolution of the rash, and the presence of necrotic keratinocytes on histologic examination supported a diagnosis of AGEP. Although the pathogenesis of AGEP is not well understood, it is postulated to include T cell−mediated neutrophilic inflammation involving drug-specific CD4+ T cells, cytotoxic CD8+ T cells, and inflammatory cytokines and chemokines.[8] In immunocompetent patients, infectious mononucleosis represents a benign, self-limiting lymphoproliferative disorder characterized by primary EBV infection of B lymphocytes and massive proliferation of highly activated cytotoxic CD8+ T cells, believed to be responsible for the control of viral replication and the establishment of latency.[9] In our patient, it might be hypothesized that this vigorous immune response to EBV by cytotoxic CD8+ lymphocytes triggered the appearance of AGEP. To the best of our knowledge, in addition to our case, there has been only one other reported case of AGEP associated with acute EBV infection.[10] However, in that case, AGEP developed 4 days after starting treatment with amoxicillin/clavulanic acid, which represents the most likely inciting agent.

The current case suggests that acute EBV infection should be considered as an additional trigger of AGEP, particularly in the pediatric population.

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