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SHORT COMMUNICATION

Severe Acute Generalized Exanthematous Pustulosis Successfully Treated by Spesolimab

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Acute generalized exanthematous pustulosis (AGEP) is a severe acute reaction characterized by the abrupt onset of small, sterile, non-follicular pustules arising on extensive erythematous plaques (1). More than 90% of AGEP cases are drug-induced, though other causes such as viral infections and vaccinations have occasionally been implicated. Typically, a short time (<4 days) between drug administration and onset of the eruption is observed. Treatment primarily involves immediate withdrawal of the causative drug; topical or even systemic corticosteroids may be required (2).

The pathophysiology remains unclear but AGEP is considered a T-cell mediated disease. CD8+ lymphocytes produce large quantities of interleukin-8 (IL-8), a strong neutrophil chemoattractant, which seems to promote neutrophils' survival and recruitment to the skin into the intraepithelial pustules (3). Recently, the IL-36 pathway has also been described in the pathogenesis of AGEP: the culprit drugs could directly induce enhanced IL-36 expression in the lesional skin of AGEP patients (4).

We present here a case of a severe AGEP, successfully treated with spesolimab, an IL-36 receptor antagonist that has been recently approved by the FDA and EMA for the treatment of generalized pustular psoriasis (GPP) flares.

CASE REPORT

A 70-year-old female patient was hospitalized for an extensive febrile pustular skin rash that appeared 5 days after receiving a flu vaccine. She had been on oral terbinafine for a month for onychomycosis; the latter was discontinued upon her arrival at the hospital. The laboratory workup showed neutrophilia at 9 g/L. A differential diagnosis of AGEP induced by flu vaccine, or GPP, was suspected, the imputability of terbinafine being less likely, given the long delay between the beginning of therapy and the appearance of symptoms. Skin biopsy disclosed a picture consistent with AGEP (**Fig. 1**). The absence of psoriasiform hyperplasia, and the presence of keratinocytes necrosis and eosinophils were not consistent with a diagnosis of GPP. A formal calculation of AGEP score proposed by the EuroSCAR group was 8, which was consistent with a "definite" diagnosis of AGEP (2).

Treatment with daily oral prednisone 1 mg/kg and topical clobetasol propionate was initiated. After 3 weeks of treatment, skin involvement worsened with persistent high fever (**Fig. 2**a, b). Due to clinical deterioration, a second skin biopsy was performed, revealing exactly the same picture, consistent with AGEP and not suggestive of GPP. Spesolimab was then administered; the patient received a single 900-mg intravenous dose. High fever resolved and all pustular lesions regressed within 48 h; oral prednisone was progressively withdrawn. A significant improvement of the erythema and the desquamation was observed at 1-week follow-up (Fig. 2c, d). The patient presented with complete healing of skin lesions at 3 weeks and no disease flare-up at 1-year follow-up.

DISCUSSION

AGEP usually has a good prognosis with resolution occurring in less than 2 weeks. However, it may be life-threatening in elderly patients or those with chronic diseases with few available therapeutic options. The use of biologics has been reported for the treatment of AGEP: 1 case successfully treated by secukinumab, and 3 cases with infliximab (2).

Clinically, AGEP and GPP share similarities, making their distinction challenging. The pathophysiology of GPP involves a dysregulation of the IL-36 signalling pathway, induced by either dysfunctional IL-36 receptor antagonist

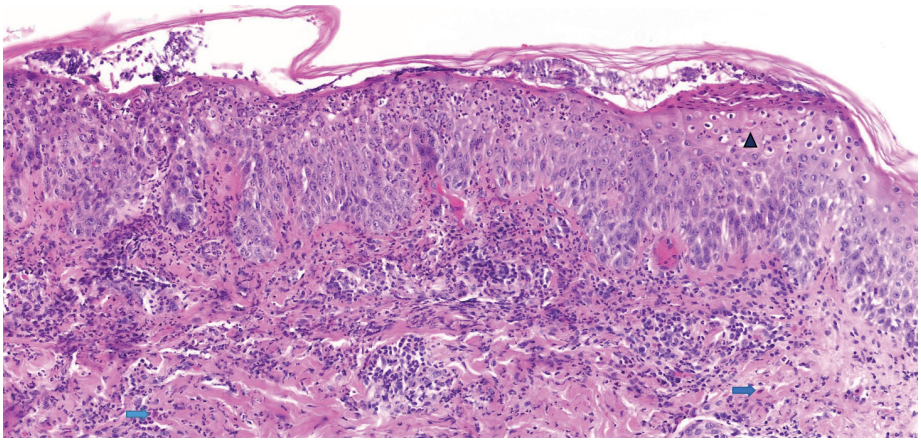

Fig. 1. Histology. Haematoxylin and eosin stain x 10. Subcorneal pustule with intraepidermal neutrophil exocytosis, a few keratinocyte necroses (black arrowhead). Presence in the superficial dermis of an infiltrate composed of neutrophils, lymphocytes, and a few eosinophils (blue arrows).

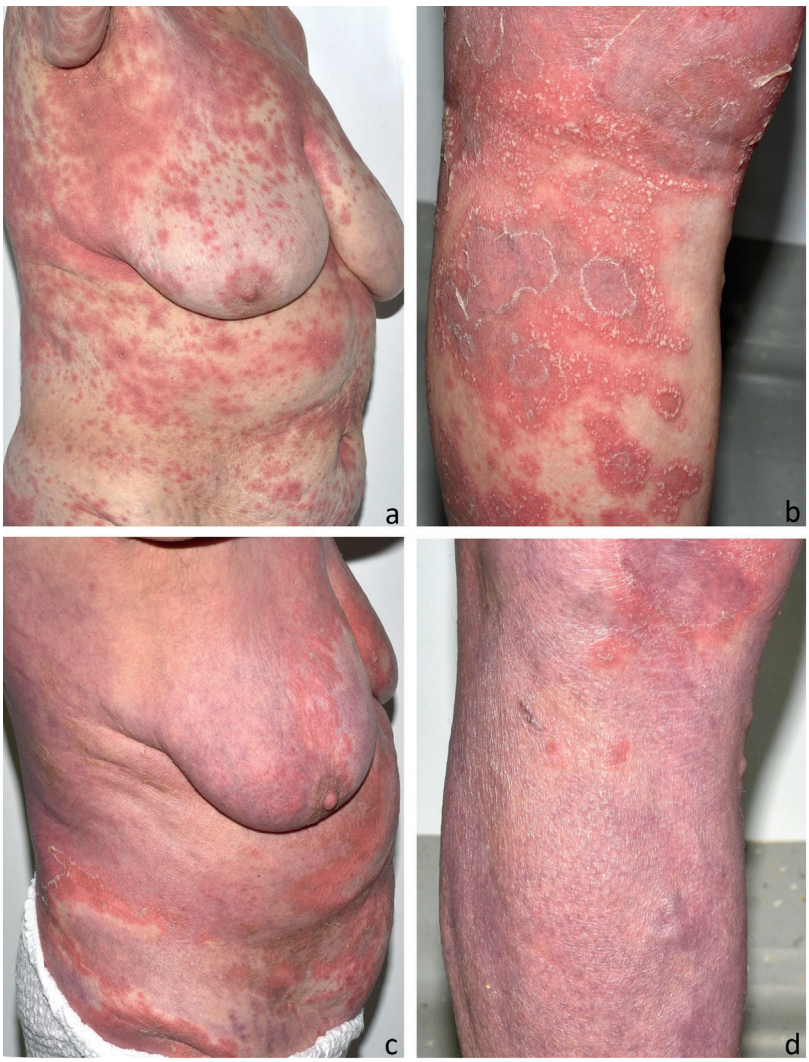

Fig. 2. (A, B) Extensive erythematous plaques with numerous pustules. (C–D) Complete healing of all pustular lesions with significant improvement of the erythema at 1-week follow-up. Permission from the patient is given to publish these photos.

(IL36RN) or the overexpression of IL-36 agonists. Mutations in IL36RN have also been reported in AGEP as well as IL-36 overexpression in lesional skin of AGEP patients, suggesting that IL-36 signalling dysregulation is involved in the physiopathology of both pustular diseases (5).

Spesolimab is an anti-interleukin-36 receptor monoclonal antibody approved to treat GPP flares (6). To our knowledge, this is the first case of AGEP successfully treated with spesolimab. It demonstrates the potential use of spesolimab in severe potential life-threatening forms of AGEP, and indirectly suggesting the critical role of IL-36 pathway in the pathophysiology of this disease.

Conflict of interest disclosures: EL has served as an investigator and adviser for Boehringer Ingelheim. The other authors have no conflicts of interest to declare.

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