SHORT COMMUNICATION

Dupilumab-induced Acute Generalized Exanthematous Pustulosis in a 17-year-old Female Chinese Patient with Atopic Dermatitis

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Acute generalized exanthematous pustulosis (AGEP) is caused primarily by drugs and is characterized by the rapid onset of numerous pinhead-sized non-follicular, sterile pustules on an erythematous base, fever, and neutrophilia. We describe here a case report of AGEP in a teenage female patient treated with dupilumab for refractory atopic dermatitis.

CASE REPORT

A 17-year-old Chinese female patient presented at our dermatology clinic (Hangzhou First People's Hospital, Hangzhou, Zhejiang, China) with a 3-day history of acute onset of a diffuse, rapidly progressing cutaneous rash. She had had severe atopic dermatitis (AD) for over 10 years, mainly involving the face and neck. The patient's general health was good and she was not pregnant. Except for AD, she had a history of rhinitis and asthma and no prior personal or family history of psoriasis. Before the onset of the new rash, the patient had commenced subcutaneous injection of dupilumab 600 mg as the first loading dose for her severe refractory AD. There was no history of any other systemic treatment in the last 3–4 weeks, except for dupilumab. The rash began in the face on the second day after initiation of dupilumab, and expanded rapidly to her neck, flexure joints of the bilateral upper limbs, and the dorsum of the hands. Clinical examination revealed numerous non-follicular, pinhead size pustules on diffuse oedematous and erythematous plaques, and patches (**Fig. 1**). The patient had fever (38.4°C). No mucous membrane involvement, lymphadenopathy, or organomegaly were seen. AGEP and generalized pustular psoriasis were considered as differential diagnoses (1, 2).

Laboratory investigation revealed a white blood cell (WBC) count of 138,000 cells/mm^3, and elevated neutrophils (9,100 cells/mm^3), eosinophils (9.5%, normal range 0.4–8.0%), and C-reactive protein (13.4 mg/l). Liver and kidney function tests were both normal. Bacterial growth was negative in pustules, peripheral blood, and urine cultures. The clinical history, lesions, and laboratory evaluations were consistent with AGEP. No biopsy was performed, because histopathological confirmation is not required for typical drug-related AGEP (1); in addition, the patient refused biopsy.

The European Study of Severe Cutaneous Adverse Reactions (EuroSCAR) study group scoring system and Naranjo's algorithm scale were used to check the possibility of an adverse drug reaction (ADR). According to the EuroSCAR, the AGEP validation scores were 9 (Table SI), and the diagnosis was considered definite (3). Naranjo's algorithm resulted in a score of +6, indicating a possible ADR to dupilumab (Table SII) (4). The additional details are described in Tables SI and SII. The morphology of the lesions, disease pattern, physical examination, blood and urine investigations,

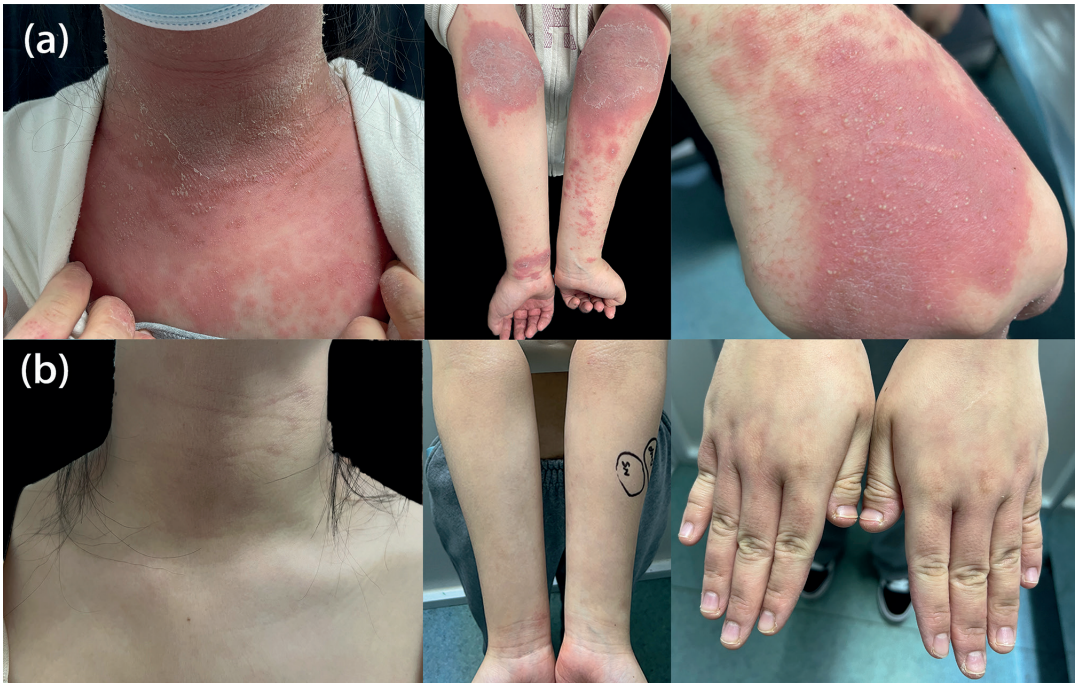

Fig. 1. (a) Diffuse oedematous and erythematous plaques and patches with numerous, non-follicular, pinhead size pustules on the neck and flexural arms, and dorsum of the hands, which developed after the first injection of dupilumab. (b) Clearance of lesions after discontinuation of dupilumab.

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were consistent with a diagnosis of AGEP. Dupilumab therapy was discontinued, and a combination of topical and systemic drugs was initiated.

Azithromycin (0.5 g, once a day for 3 days), compound glycyrrhizin (75 mg, 3 times a day), potassium chloride (25 mg, 3 times a day), and antihistamines (ebastine) (20 mg, once a day), were given, together with tacrolimus 0.1% ointment. The patient experienced substantial improvement on this treatment regimen, and the progression of the skin eruptions stopped within a few days. After 2 weeks of symptoms, the pustules were resolved, leaving mild erythematous plaques on the dorsum of the hands. One month later, the lesions were almost cleared (Fig. 1b). At 3-month follow-up the AD on the patient's face and neck had recurred, showing scattered itching eczematous plaques without other skin problems.

DISCUSSION

AGEP is a severe cutaneous reaction associated with an abrupt onset of rash with pinhead non-follicular erythematous pustules, accompanied by fever (temperature > 38°C) and leukocytosis (5). The most prevalent drugs associated with AGEP are pristinamycin, aminopenicillins, quinolones, diltiazem, hydroxychloroquine, sulphonamides, terbinafine, ketoconazole, and fluconazole. Corticosteroids, macrolides, and oxicam non-steroidal anti-inflammatory drugs (NSAIDs) have a less strong association with AGEP (6, 7) and the association of AGEP with biological drugs is uncommon. There are few published case reports on biological drugs inducing AGEP. Izquierdo et al. (8) presented a case report of AGEP in a patient with rheumatoid arthritis due to tocilizumab therapy. Bomfim (9), and Kavala et al. (10), reported AGEP triggered by etanercept. Masood et al. (11) reported a squamous cell carcinoma patient with AGEP caused by cetuximab administration. Daneshpazhooh et al. (12), discussed a case of AGEP followed by rituximab infusion in a patient with pemphigus vulgaris (PV).

To the best of our knowledge, reports on association of AGEP with biological drugs are rare, and no reports regarding drug-related rash and exanthematous eruptions with dupilumab were found. Dupilumab safety concerns are similar to those with other biological drugs. AGEP is mostly self-limiting. The preferred treatment is to discontinue the triggering drugs. However, in mild cases, topical antiseptics and steroids are applied. Systemic steroids are given in severe cases for a short period. The teenage female patient reported here had severe AD, and safe and effective therapies were urgently needed. She was treated with azithromycin, and compound glycyrrhizin. As Azithromycin is reported as an effective inhibitor of neutrophil inflammatory mediator of mRNA expression, it has a favourable influence on healing and resolution of inflammation (13). The anti-inflammatory effects of glycyrrhizin are comparable to those of glucocorticoids; it has few side-effects compared with steroids (14) and it has been used for immunological skin conditions (15). Moreover, potassium chloride was used to avoid hypokalaemia, and antihistamines (ebastine) together with tacrolimus 0.1% ointment was used to treat AD.

In conclusion, we report here a case of a young Chinese female patient with AGEP probably caused by a single injection of dupilumab. Nevertheless, dupilumab is a safe and effective therapeutic alternative for individuals with AD. Drug reaction to dupilumab is rare, but possible, and practitioners should be familiar with this uncommon adverse effect.

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