Severe cutaneous reaction with initiation of dupilumab for atopic dermatitis and prurigo nodularis: An unusual adverse effect

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INTRODUCTION

Dupilumab is a human immunoglobulin (Ig)-G4 monoclonal antibody that has demonstrated significant efficacy in treating various inflammatory skin conditions, including atopic dermatitis (AD) and prurigo nodularis.[1,2] The most common treatment-emergent adverse events include nasopharyngitis (28.1%), conjunctivitis (19.5%), AD exacerbation (16.4%), upper respiratory infections (13.1%), and injection site reactions (9.7%).[1]

Severe cutaneous reactions have rarely been reported with dupilumab but have been noted with the use of many biologics, including anti-tumor necrosis factor therapeutics, interleukin 6, and interleukin 12/23 inhibitors. These reactions include, but are not limited to, new-onset psoriasis, erythema multiforme (EM), lupus-like reactions, and hypersensitivity reactions.[3]

Herein we report a patient with AD who developed a severe cutaneous drug eruption on sun exposed skin following initiation of dupilumab.

Abbreviations used:

AD: atopic dermatitis
DIF: direct immunofluorescence
EM: erythema multiforme
IG: immunoglobulin
SJS: Stevens-Johnson syndrome

Case report

A 74-year-old woman with a past medical history of hypertension, hypothyroidism, and osteoporosis, presented to the clinic with AD. Other significant medical history included bronchiectasis with significant secondhand smoke exposure and sputum positive for Mycobacterium avium-intracellulare and acid-fast bacillus, along with Sjogren's syndrome and rheumatoid arthritis. She also had an allergic history of acetaminophen-induced angioedema and a penicillin rash. The patient had been taking adalimumab (40 mg/0.4 mL injector) for rheumatoid arthritis for 2 years, in addition to synthroid (112 mcg), alendronate (70 mg), albuterol sulfate aerosol (90mcg/actuation), benzonatate (100 mg), losartan (50 mg), omeprazole (40 mg), and tralokinumab-ldrm injections (150 mg/mL syringe). She began the tralokinumab-ldrm injections for AD 2 months before presentation. The patient presented to the clinic with persistent itching and a burning rash accompanied by chronic joint pain, that showed minimal response to the tralokinumab-ldrm injections.

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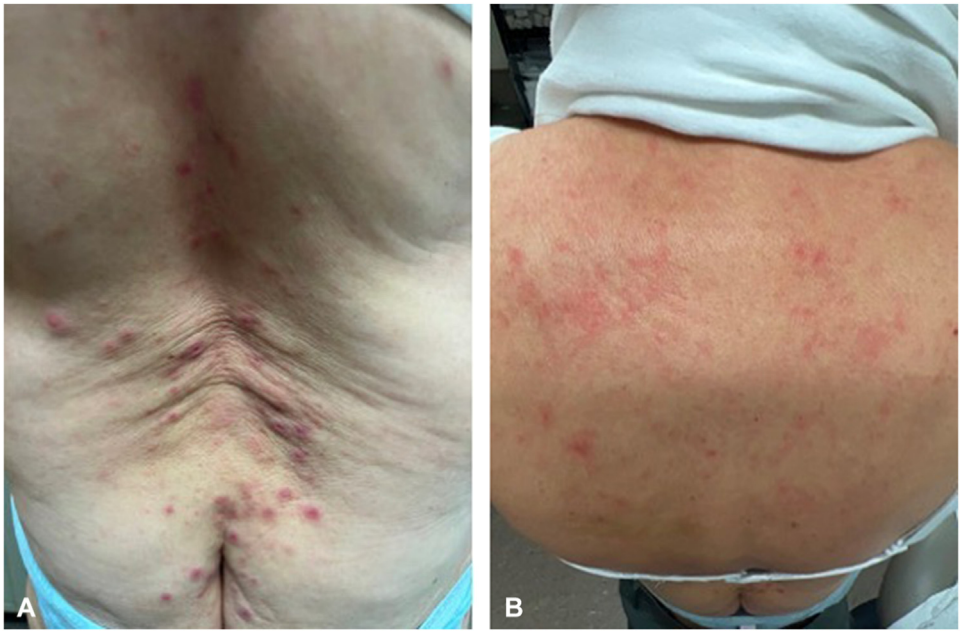

Fig 1. Initial visit. **A,** Excoriated, lichenified papules and nodules on sacrum and lower back, greater than 14 lesions. **B,** Erythematous, scaly papules and plaques throughout over 25% of body surface area.

On physical exam, the patient had erythematous, scaly papules and plaques throughout her body, with a body surface area greater than 25%, as well as excoriated, lichenified papules and nodules on her sacrum and lower back (Fig 1). The patient was diagnosed with AD and prurigo nodularis and told to discontinue tralokinumab-ldrm. A 600 mg loading dose of dupilumab was subcutaneously injected.

After 6 days, the patient described a burning scalp, face, chest, and upper back rash that developed 3 days after receiving the loading dose. On physical exam, 10 days after receiving the loading dose, the patient presented with polymorphic annular patches and plaques on sun exposed areas on her face, scalp, upper back, and upper chest, with some erosions with hemorrhagic crusting and impetiginization (Fig 2). She denied fever, worsening joint pains, or headaches. Biopsy for hematoxylin and eosin stain and direct immunofluorescence (DIF) was performed on a perilesional, sun protected area of the upper back. A prednisone taper (20 mg for 5 days) was given and dupilumab was discontinued. Systemic lupus erythematosus serologies were not performed.

Histopathology showed superficial perivascular pattern infiltration of mononuclear inflammatory cells predominated by lymphocytes, with scattered exocytosis. Overlying epidermis was marked by clefting and dyskeratotic keratinocytes. Areas of full thickness epidermal necrosis were also noted. These microscopic features were consistent with disease in the EM spectrum; DIF did not show staining for IgG, IgA, IgM, C3, or fibrinogen, it did show colloid bodies (Fig 3, *A* and *B*).

Two months after the initial dupilumab loading dose, the patient's face, scalp, and neck rash was fully resolved, and only mild AD and prurigo nodularis of the back remained. Dupilumab was not restarted.

DISCUSSION

Dupilumab is a first-line treatment for patients with moderate-severe AD. Treatment-emergent adverse events include nasopharyngitis, upper respiratory infection, conjunctivitis, oral herpes, and injection site reactions.[1] Except for 1 prior international case report of dupilumab-induced EM,[4] data on severe cutaneous adverse reactions to dupilumab are sparse.

The temporal relationship of severe cutaneous lesions appearing less than 1 week after the dupilumab loading dose, disappearance of the lesions after medication discontinuation and oral corticosteroids, as well as the histomorphologic features on the EM spectrum, is concerning for a dupilumab-induced severe cutaneous reaction. A Naranjo Adverse Drug Reaction Probability Scale,[5] which standardizes assessment of causality for all adverse drug reactions, was calculated as a 5, or "Probable ADR." Differential diagnosis for this patient's severe reaction includes

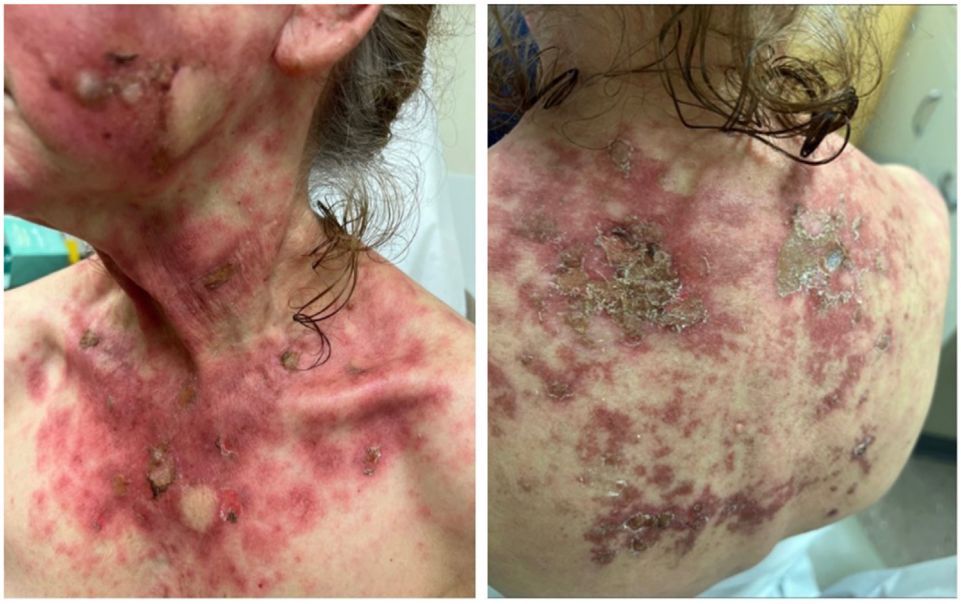

Fig 2. Probable dupilumab reaction, 10 days after loading dose received.

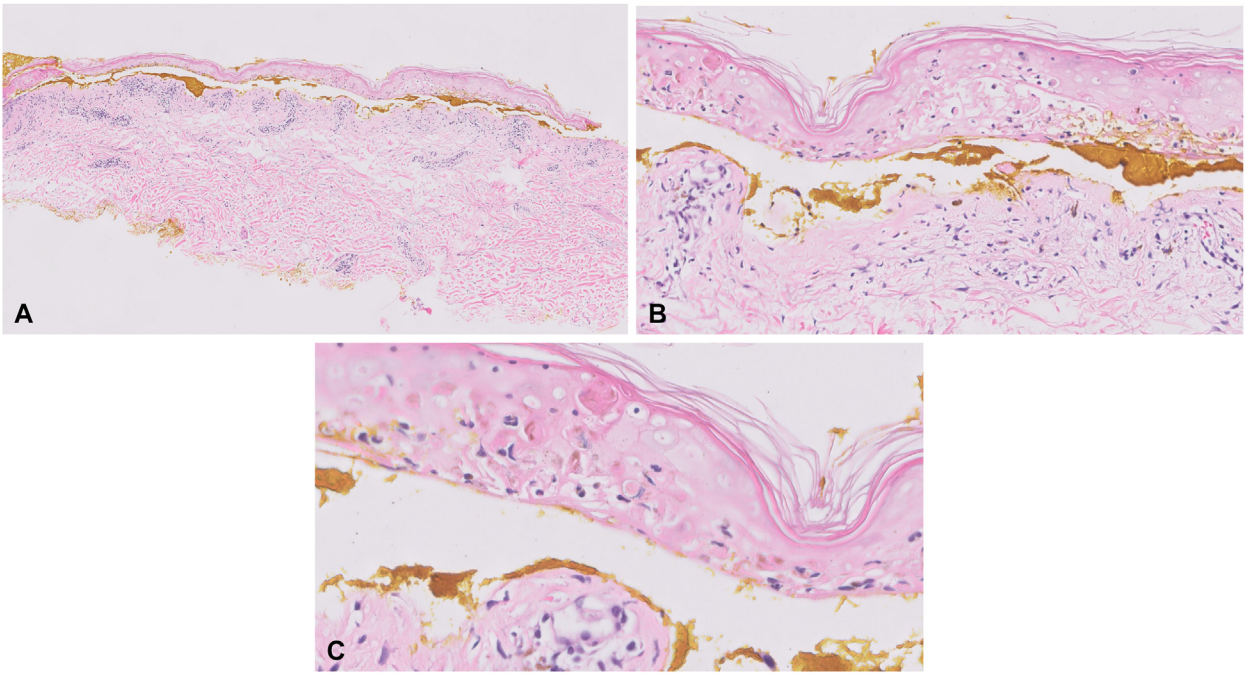

Fig 3. A, Hematoxylin and Eosin (H&E) slide in low, 5× magnification showing a portion of skin marked by full thickness necrosis of epithelium and subepidermal bullous formation. The papillary dermis is marked by superficial perivascular inflammation and fibrinoid necrosis. **B** and **C,** H&E slides, in high magnification (20× and 40×, respectively), showing epidermal clefting. The separated epidermal layer exhibits a full thickness necrosis, marked by dyskeratotic keratinocytes and cellular debris. Underlying dermis features mononuclear inflammatory infiltrates.

atypical EM, acute phototoxic dermatitis, systemic cutaneous lupus erythematosus, or early Stevens-Johnson syndrome (SJS). Although there have been paradoxical Th1 reactions triggered by biologics,[6] including EM,[4] given the patient was on adalimumab for 2 years, this is an unlikely trigger.

EM is marked by interface dermatitis with necrotic keratinocytes and mononuclear inflammatory infiltrates, predominantly lymphocytes.[7] Histopathol ogical differentiation between SJS/toxic epidermal necrolysis and EM is very challenging, as they share the same microscopic presentation and spectrum of appearances. While some advocate that epidermal necrosis is known to be more prevalent in SJS and toxic epidermal necrolysis than EM, this feature can be also present in EM.[7] Thus, the case was signed out as EM spectrum.

Systemic cutaneous lupus erythematosus and lupus erythematosus spectrum diagnoses were deemed unlikely due to a negative DIF. The non-prominent interface changes and lack of deep infiltration, mucin in dermis, and basement wall thickening on hematoxylin and eosin also argued against connective tissue disease. In phototoxic reactions of photodermatoses, one would expect epidermal spongiosis and perivascular inflammatory infiltrate with papillary dermal edema. Dermal papillae are preserved while full thickness epidermal necrosis and epidermolysis are also not typical of phototoxic reactions of photodermatoses.[8]

Literature review revealed 1 prior report of an EM side effect after dupilumab, outside of the United States.[4] This case was similar to ours regarding onset time: the patient developed skin manifestations days after receiving the dupilumab loading dose. However, that patient was febrile and lesions presented on the lower extremities only, rather than on sun exposed skin as in our case. Both cases had atypical lesions rather than the targetoid lesions classically seen with EM. Histopathology of the lesions was similar in both cases showing necrotic/dyskeratotic keratinocytes with a mixed superficial infiltrate and subepidermal blister. Both cases showed resolution of rash with the discontinuation of dupilumab and initiation of systemic steroids.

Other dupilumab-associated skin manifestations, such as general erythematous rashes and scaling, have been noted, but those reactions have been limited to the head and neck.[9] One other case report discussed development of SJS/toxic epidermal necrolysis and dupilumab was listed as a chronic medication.[10] However, the patient had multiple comorbidities and new medications, including cephalosporins and antiepileptics.

Herein, we describe a case of dupilumab-induced severe cutaneous reaction, constituting a rarely reported adverse reaction to this common medication. This case contributes to the characterization of rare adverse effects of dupilumab, a relatively new medication.

Conflicts of interest

None disclosed.

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