Lichenoid-granulomatous drug reactions to dupilumab: A report of 2 cases

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INTRODUCTION

Dupilumab is a fully humanized monoclonal antibody to the interleukin 4 (IL-4) receptor alpha subunit, inhibiting IL-4 and IL-13 signaling pathways which leads to downregulation of T helper (Th) 2 mediated inflammation.[1] There are several reports of drug hypersensitivity reactions (DHR) to dupilumab, including conjunctivitis, psoriasiform, eczematous, and lichenoid eruptions.[2-4] It has been theorized that dupilumab-mediated inhibition of Th2 pathways may upregulate Th1/Th17 dominated response in patients with atopic dermatitis (AD); a Th1 hyper-response can lead to development of psoriasiform dermatitis.[4] Herein, we report 2 patients, who developed lichenoid granulomatous eruptions several months after dupilumab initiation, with complete resolution upon discontinuation, supportive of DHR.

Abbreviations used:

AD:	atopic dermatitis
CBC:	complete blood count
CTCL:	cutaneous T-cell lymphoma
DHR:	drug hypersensitivity reactions
LGD:	low-grade dysplasia
NACDG:	North American Contact Dermatitis Group
TCR:	T-cell gene rearrangement
Th:	T helper

CASE 1

A 72-year-old female with history of AD presented to the clinic with recent onset of episodic severe eczematous eruptions affecting her face, hands, and upper extremities. Subsequent patch testing with the NACDG (North American Contact Dermatitis Group) standard screening series, and chemotechnique cosmetic and steroid series were done for evaluation of suspected allergic contact dermatitis. This revealed thiuram (2+), bacitracin 20% pet (3+), budesonide 0.1% pet (3+), and propylene glycol 100% aq (2+). Despite allergen avoidance and topical therapies, AD/allergic contact dermatitis with episodic flares continued, with development of prurigo nodularis. Further patch testing revealed additional allergens, including iodoproponyl butylcarbamate 0.5% pet, fragrance mix 8% pet, oxybenzone 10.5% pet, and linalool 1% pet. In addition to counseling on allergen avoidance and topical therapies, she was started on dupilumab 600 mg subcutaneous injection (SC), then 300 mg SC every other week, with sustained improvement for over 1 year (EASI75, IgA = 1). Fifteen months after initiating dupilumab, the patient developed erosive lichenoid mucositis. Biopsy of the oral mucosa showed lichenoid inflammation. She was started on prednisone and then alitretinoin, both of which she was intolerant. 9 months later, she developed new widespread violaceous, papulo-squamous indurated plaques with follicular prominence and the biopsies showed a granulomatous and lichenoid pattern in 4 specimens, with histocytes, eosinophils,

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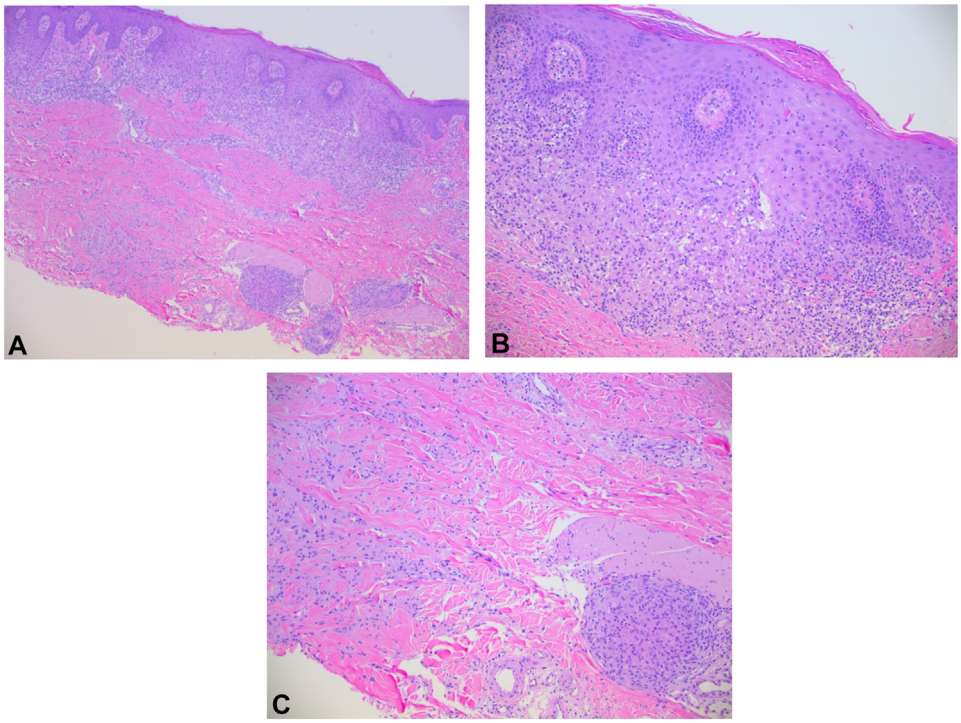

Fig 1. Shave biopsy from the left thigh of case 1 (Fig 2), demonstrating a lichenoid reaction with lymphocytes and histiocytes, epidermal acanthosis, and some parakeratosis. The dermis contains granulomas that are both sarcoidal and interstitial in type (**A**). In addition to the previous features, apoptotic keratinocytes are more readily appreciated (**B**). Granulomas, both interstitial (*left*) and sarcoidal (*right*) types (**C**). (**A-C,** hematoxylin and eosin stain; original magnifications: **A**, 40×; **B**, 100×; and **C**, 100×).

and lymphocytes (Fig 1, *A-C*). She was systemically well without fevers or joint pain. At this point, the patient was started on another course of prednisone along with betamethasone valerate 0.1% and tacrolimus 0.1% ointments. Despite this, her symptoms continued to worsen over the next 4 months. Two years after initiating dupilumab, she progressed to erythroderma of the trunk and extremities, clinically concerning for possible cutaneous T-cell lymphoma (CTCL) (Fig 2, *A* and *B*). Biopsies at 4 different sites showed a lichenoid granulomatous pattern consistent with previous biopsy findings. Systemic workup including complete blood count (CBC), chemistries, and flow cytometry were normal. A molecular clonality screen for gamma T-cell gene rearrangement (TCR) was normal as well. She was started on acitretin with no improvement after 2 months, and then switched to methotrexate 10 mg orally weekly. Several months after starting methotrexate, dupilumab was discontinued, and within 6 months, there was a gradual complete clearance of lesions (Fig 2, *C*). Methotrexate was discontinued at this point. Follow-up is ongoing and there has been no recurrence of low-grade dysplasia (LGD) for over 1 year since discontinuing methotrexate.

CASE 2

A 51-year-old female with history of AD presented to the clinic with recent onset of pruritic vesicular eruptions on her fingers consistent with hand dyshidrotic hand dermatitis, as well as eczematous lesions affecting her lower extremities. After failing multiple topical medications, including fluocinonide 0.05% ointment, eucrisa 2% ointment, and protopic 0.1% ointment, she was started on dupilumab 600 mg SC, then 300 mg SC every other week in December 2019 for the treatment of AD with dyshidrosis (EASI12.6). At 6 months follow-up she had complete response (EASI0). In November 2020, she developed flaring of dermatitis on hands and feet. Patch testing with the North American 80 Comprehensive series was negative. In January 2021, methotrexate 10 mg by mouth weekly was added. In March 2021, she presented with new-onset widespread erythematous and indurated plaques with lichenification and fissuring, predominantly affecting her hands, concerning for possible mycosis fungoides (MF) or dermatomyositis (Fig 3). She was systemically well without fevers or joint pain. Shave and punch biopsies performed on the fingers and elbows showed a lichenoid psoriasiform-spongiotic-granulomatous dermatitis

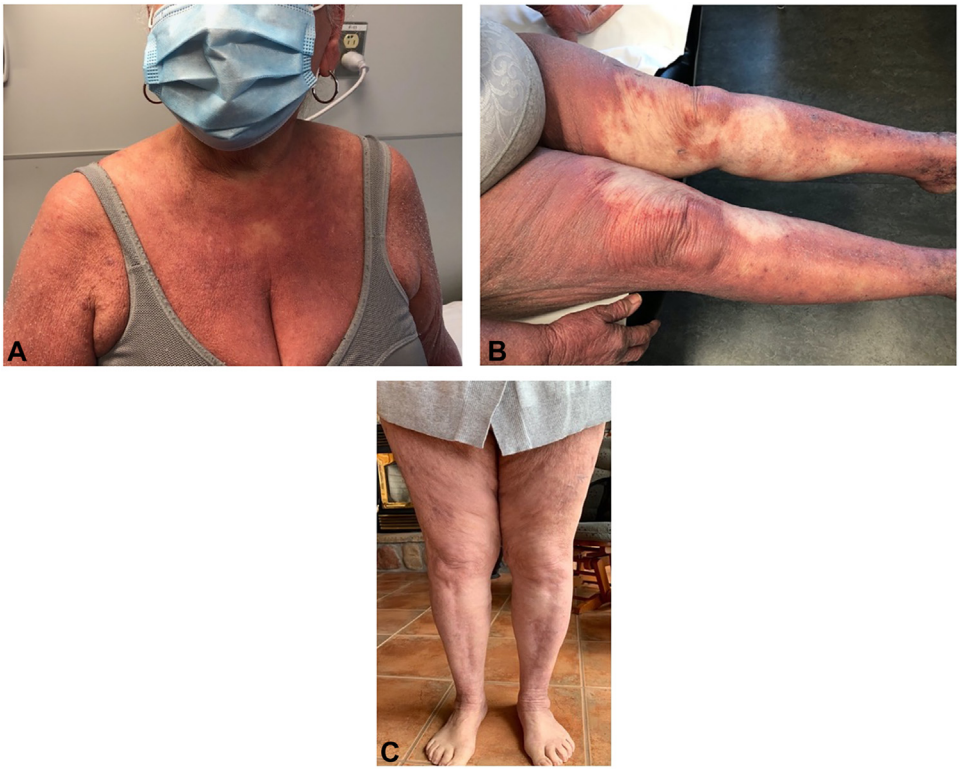

Fig 2. Suspected drug hypersensitivity reaction to dupilumab. A 72-year-old female with atopic and allergic contact dermatitis presented with widespread erythematous-violaceous indurated plaques on the trunk (**A**) and extremities (**B**) 2 years after initiating dupilumab. Biopsies at 4 different sites showed a lichenoid granulomatous pattern. She was initially treated with acitretin and then methotrexate. Eventually dupilumab was discontinued and she had complete clearance approximately 6 months later without relapse (**C**).

with limited epidermotropism. Molecular clonality screen for gamma TCR showed a reproducible peak below the diagnostic threshold for monoclonality. Systemic workup, including CBC and chemistries were normal. Dupilumab was discontinued and methotrexate was increased to 25 mg by mouth weekly. Upon discontinuation of dupilumab, she had gradual improvement over a period of months and eventually complete clearance. She stopped methotrexate for several months but restarted, due to worsening hand dermatitis with good response. Follow-up is ongoing and there has been no recurrence of LGD for over 1 year at the time of manuscript submission.

DISCUSSION

Lichenoid granulomatous reaction is an uncommon histopathologic pattern associated with drug eruptions, CTCL, rheumatoid arthritis, infectious etiologies, and autoimmune phenomenon.[5] In a recent retrospective case series of 56 patients reported by Braswell et al, the most common diagnoses with lichenoid granulomatous pathologies were drug eruptions and lichenoid keratoses.[6] The most associated drug classes are calcium-channel blockers, angiotensin-converting-enzyme inhibitors, tumor necrosis factor-α inhibitors, selective-serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, and hypoglycemic agents.[6] The latency period for drug-induced LGD has not been established.[7]

It is thought that Th2 inhibition by dupilumab may enhance Th1/Th17 dominated responses in patients with AD, thus explaining previous reports of paradoxical psoriasiform reactions.[8] Lichenoid and granulomatous reactions are primarily initiated by Th1 cells[6]; therefore, upregulation of Th1 pathways may explain dupilumab-induced lichenoid and/or granulomatous eruptions.

In a recent case report, Kim and Shin described a patient with severe AD who was started on dupilumab with initial improvement, but subsequent deterioration after several months of therapy, with new onset of lichenoid papules and plaques on the dorsal hands.[4] Histopathology revealed degeneration of the basal cell layer and a band-like lymphocytic infiltrate

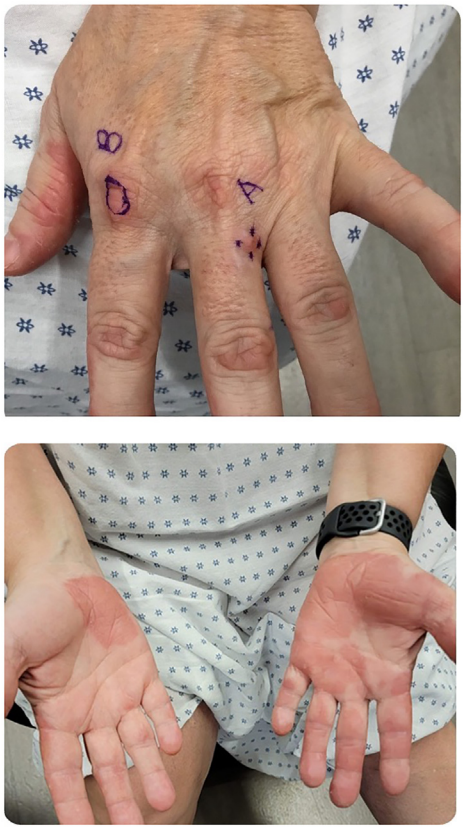

Fig 3. Suspected drug hypersensitivity reaction to dupilumab. **A** and **B,** A 51 year old female with atopic dermatitis affecting her hands and feet, who initially had complete response to dupilumab, presented 11 months after initiation of dupilumab with erythematous indurated papules and plaques predominantly involving her hands. Shave and punch biopsies performed on the fingers and elbows showed a lichenoid psoriasiform-spongiotic-granulomatous dermatitis. Upon discontinuation of dupilumab, she had gradual complete clearance over a period of months.

of the upper dermis, consistent with lichenoid drug eruption. After terminating dupilumab, the lichenoid lesions resolved.

In both of our reported cases, there was clinical suspicion for possible new-onset MF, and pathology findings raised concerns for possible granulomatous MF. However, pathologic criteria for CTCL were not met, and systemic workups were negative. There have been several reports of new or worsening MF with dupilumab treatment.[9,10] Caution should be taken when using dupilumab in patients with atypical presentations, especially with older adults who present with "late-onset AD". In these cases, preliminary biopsies should be considered to rule out CTCL. If a patient receiving dupilumab develops a new-onset cutaneous eruption suggestive of possible CTCL, treatment should be discontinued immediately and workup for CTCL should be performed, including a complete history and physical examination (in particular lymph nodes), skin biopsies for hematoxylin and eosin stain, immunohistochemistry, TCR, CBC, chemistries, flow cytometry, and imaging.

Our study describes 2 cases of lichenoid granulomatous eruptions consistent with DHR to dupilumab. To our knowledge, there is limited reporting that documents lichenoid-granulomatous eruptions to using dupilumab. At the time of manuscript preparation, both patients demonstrated complete clearance after discontinuation of dupilumab.

Conflicts of interest

None disclosed.

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