Can't handle the itch? Refractory immunotherapy-related transient acantholytic dermatosis: prompt resolution with dupilumab

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INTRODUCTION

Transient acantholytic dermatosis (TAD; Grover disease) is an inflammatory immune condition characterized by small, erythematous papules most commonly affecting the trunk and extremities of middle-aged men with a history of sun exposure. Skin pathology characteristically demonstrates acantholytic dyskeratosis within the epidermis with varying degrees of associated dermal inflammation, often with eosinophils. Lesions typically last for weeks to months, though there is a propensity for recurrence. In some cases, the course can be prolonged and can last for years (such cases are often labeled "persistent acantholytic dermatosis"). Common treatments include pramoxine, topical vitamin D analogues, topical corticosteroids, tetracycline antibiotics and antihistamines for mild cases, while oral corticosteroids, oral retinoids, narrow-band ultraviolet B, and psoralen plus ultraviolet A are usually reserved for more severe, refractory disease.

The pathophysiology of TAD has yet to be elucidated, though some recent evidence suggests that overexpression of interleukin 4 (IL-4) may play a role.[1,2] Here we report a patient with refractory TAD triggered by antecedent immunotherapy, who was successfully treated with dupilumab (IL-4 receptor antagonist). We moreover explore the pathophysiologic mechanisms for how this modality of therapy may represent a promising therapeutic avenue for TAD.

Abbreviations used:

IL-4: interleukin 4
TAD: transient acantholytic dermatosis; Grover disease

CASE REPORT

A 71-year-old man with metastatic renal cell carcinoma presented with a highly pruritic rash over his chest, arms, and back resulting in sleep disturbance 2 months following 4 doses of ipilimumab and nivolumab. He was initially treated with topical steroids and antihistamines, with worsening of symptoms, at which point he was placed on an oral 60-mg prednisone taper for eight days. When this failed, he was referred for dermatologic evaluation.

Physical examination at initial evaluation was notable for scattered eroded, erythematous macules and papules on the trunk and arms (Fig 1).

The clinical differential diagnosis included folliculitis, miliaria, lichenoid dermatitis, TAD, incipient bullous pemphigoid, and pemphigus. Histologic analysis of a punch biopsy of the left arm showed suprabasal acantholysis with occasional dyskeratotic cells and perivascular lymphocytic inflammation with eosinophils (Fig 2). Direct immunofluorescence studies were negative. A diagnosis of immunotherapy-induced TAD was made.

He was subsequently trialed on a variety of therapies, including 0.1% triamcinolone ointment

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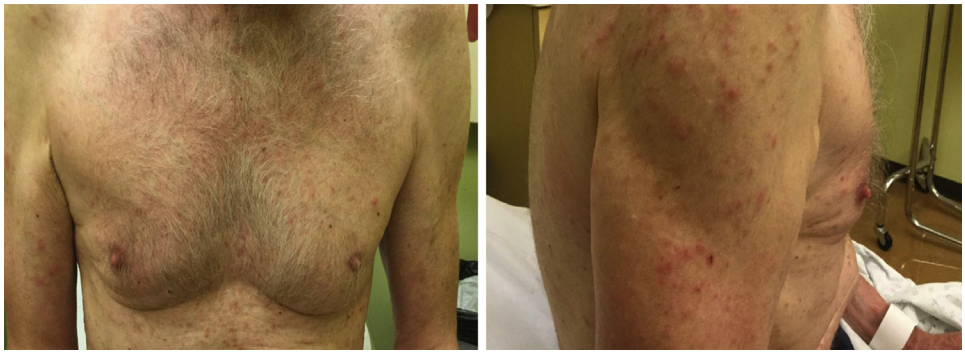

Fig 1. Highly pruritic scattered, erythematous papules with overlying erosions on the torso and arms.

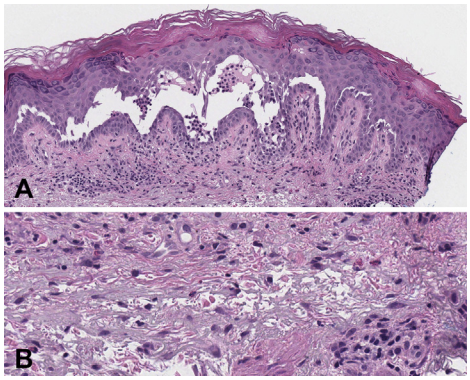

Fig 2. A, Medium-power view of the epidermis showing intraepidermal acantholysis with dyskeratosis. **B,** High-power view of the dermis showing numerous perivascular and interstitial eosinophils.

under occlusion with a sauna suit, gabapentin, longer courses of prednisone, aprepitant, hydroxyzine, diphenhydramine, cetirizine, and eventually 16 sessions of narrow-band ultraviolet B phototherapy, none of which provided any relief. Nivolumab monotherapy was discontinued 4 months after symptom onset due to the severity of his cutaneous reaction. Ten months following rash onset, he was transitioned to dupilumab at standard dosing (loading with 600 mg subcutaneously followed by 300 mg every 2 weeks thereafter), and within a week of his first injection, he noticed a significant reduction in the itch and near-total resolution of his rash, with complete resolution of itch and rash noted at his 3-month follow up. To date (12 months following initiation of dupilumab), he remains in remission of his TAD despite having restarted immunotherapy with ipilimumab and nivolumab for progression of his metastatic disease. Given the severity of symptoms in the past and likely need for continued treatment, there are no plans to discontinue dupilumab.

DISCUSSION

TAD has been reported in a variety of different settings, involving various conventional chemotherapies as well as checkpoint (cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1) inhibitor therapies.[3-6] Patients receiving checkpoint inhibitor therapies have been found to have higher serum levels of IL-4,[7,8] and it is plausible that IL-4 upregulation plays a part in the pathogenesis of TAD in this setting.

IL-4 has also been found to play an important role in many other inflammatory skin disorders, such as atopic dermatitis and bullous pemphigoid.[9,10] The inflammatory cascade has been elucidated in murine models of atopic dermatitis and is thought to begin with T-helper 2 cell and mast cell activation, leading to the release of IL-4, which activates eosinophils, macrophages, B cells, and ultimately results in increased immunoglobulin E levels.[11-13] In humans, lesional skin from bullous pemphigoid patients also shows an overexpression of these same inflammatory markers.[14] These findings inform the potentially important role of IL-4 in the development of many skin-related immune related adverse events. Thus, as an IL-4 inhibitor, dupilumab serves as a promising treatment for these disorders.[15-19]

Dupilumab is an attractive choice in the treatment of many immune-related adverse events in the setting of immunotherapy for cancer due to its infrequency of dosing, quick onset of action, lack of need for laboratory monitoring, low side effect profile, and minimal immune suppression. On the other hand, it is expensive and often requires multiple appeals with insurance for approval of off-label use.

Our patient represents the first reported, to the best of our knowledge, case of immunotherapy-related TAD successfully treated with dupilumab, as

we were unable to find any previously reported cases in the existing literature. We surmise the severity and refractory nature of this patient's disease to be related to the long-lasting effects of immunotherapy, often appreciated long after drug discontinuation. The implications of this remarkable case are 2-fold: 1) TAD may be driven in part by IL-4 overexpression, and 2) dupilumab serves as a promising treatment for refractory cases of TAD. The upregulation of IL-4 in the setting of various immunotherapies, the existing evidence linking IL-4 to the pathophysiology of TAD, and the success of our treatment all lend credence to dupilumab as a promising treatment for both idiopathic TAD,[19] TAD in the setting of immunotherapy, and possibly other skin immune-related adverse events related to checkpoint inhibitor therapy.

Conflicts of interest

None disclosed.

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