CASE REPORT

Acceleration of cutaneous T-cell lymphoma following dupilumab administration

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INTRODUCTION

Recent advances in the treatment of moderate-to-severe atopic dermatitis have led to increased use of dupilumab, which is a human monoclonal antibody that binds to the interleukin (IL) 4-receptor-alpha subunit. Reports have recently been published describing worsening of disease in patients with cutaneous T-cell lymphoma (CTCL) treated with dupilumab either inadvertently or as off-label use. We present an additional case of worsening CTCL following treatment with dupilumab for presumed atopic dermatitis.

CASE PRESENTATION

A 43-year-old otherwise healthy African American male presented to dermatology for the evaluation and management of chronic severe atopic dermatitis diagnosed in childhood. His eczema had previously been mild but persistent, with flares in the winter typically managed with intramuscular triamcinolone. He had been experiencing significant worsening of disease over the prior 12 months and became concerned when his response to corticosteroid injections lasted only weeks instead of months. Instead of his typical discrete plaques of eczema, he began noticing more diffuse involvement with worsening dryness and flakiness. He also noted painful fissures on his hands and feet uncharacteristic of his typical disease (Figs 1 and 2). He had been hospitalized twice prior to presentation, once for cellulitis and subsequently for bacteremia attributed to fissuring of his skin.

Available outside dermatology records included pathology reports from 2 recent punch biopsies noting spongiotic dermatitis with eosinophils without evidence of CTCL. Allergy/immunology had recently evaluated the patient and initiated workup for an acquired ichthyosis vulgaris. HIV testing was negative, and primary care referral for malignancy screening was unrevealing. Blood testing showed immunoglobulin E levels of 356 IU/mL (0-100 IU/mL) and peripheral eosinophilia. The allergist had attempted to order dupilumab; however, due to insurance denial, intramuscular and topical corticosteroids were continued.

Physical examination on initial evaluation revealed diffuse ill-defined, lichenified, and hyperpigmented plaques with sparing of the flexural and intertriginous surfaces as well as the genitalia (Fig 3). There was prominent ichthyosiform scaling and diffuse thinning of the hair on the scalp and eyebrows. Palpable lymphadenopathy measuring approximately 1-2 cm in diameter in the inguinal and axillary regions was appreciated.

Given the available information, dupilumab was re-ordered and was accepted by insurance. He initiated injections shortly after, beginning with a 600 mg subcutaneous loading dose followed by 300 mg every 2 weeks thereafter. He subsequently reported significant improvement in pruritus, but only mild improvement of his dermatitis. Two months later, the patient returned with significant...
worsening of his dermatitis, weight loss of 10-15 pounds, and marked lymphadenopathy—up to 8 cm in size in the inguinal region. This prompted repeat punch biopsies, revealing an atypical lymphoid infiltrate (Figs 4 and 5) and thus he was immediately referred to oncology. He subsequently underwent flow cytometry, bone marrow and lymph node biopsies, confirming T2bN3M0B1b (stage IVA2) mycosis fungoides with 40% expression of CD30. There was no evidence of large cell transformation. He was initiated on brentuximab monotherapy, and given a suboptimal response, pralatrexate was added as an adjunct therapy. His disease is currently stable, and he follows closely with dermatology and oncology for management and care.

**DISCUSSION**

Dupilumab has proven to be a revolutionary treatment option for patients suffering from moderate-to-severe atopic dermatitis. With more widespread use, however, there have been increasing reports of CTCL exacerbation in the setting of either off-label or inadvertent treatment for presumed atopic dermatitis. A recent report by Espinosa et al. examined the charts of 7 such patients and found that 6 treated with dupilumab experienced initial improvement of symptoms followed by worsening of rash, lymphadenopathy, pruritus, and systemic symptoms. Three patients developed worsening of disease, as evidenced by flow cytometry, and were ultimately diagnosed with Sézary syndrome. We observed an almost identical phenomenon of worsening dermatitis, lymphadenopathy, and systemic symptoms following a 2-month period of initial improvement.

Dupilumab is a monoclonal antibody directed against the IL-4-receptor-alpha subunit, which

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**Fig 1.** Clinical image of the chest depicting diffuse xerosis, lichenification, and ichthyosiform scaling.

**Fig 2.** Clinical image of the dorsal aspect of the hands depicting deep, painful fissures and erosions.

**Fig 3.** Clinical image of the palmar aspect of the hands, displaying the severity of the fissures, as well as xerosis and scaling.

**Fig 4.** Hematoxylin-eosin staining of the skin biopsy, displaying a superficial dermal infiltrate of atypical lymphocytes and histiocytes.
modulates both the IL-4 and IL-13 pathways. CTCLs are a group of heterogeneous cutaneous malignancies, the pathogenesis of which is incompletely understood. It has been shown that IL-13 and its receptors are highly expressed in affected skin. IL-13 and IL-4 together inhibit cellular proliferation in CTCL. It has been thought that due to overexpression of IL-13 in CTCL, dupilumab might be of benefit to affected patients. These case reports suggest, however, that the dupilumab-specific modulation of this cytokine profile may instead cause an acceleration of disease process in CTCL.

We believe that with more widespread use of dupilumab for atopic dermatitis, dermatologists are increasingly likely to have similar experiences with undiagnosed CTCL patients. CTCL may mimic atopic dermatitis, and especially in its early stages, histopathologic examination may not readily reveal the diagnosis. It is currently unknown if dupilumab simply unmasks underlying CTCL by way of the acceleration of the disease process, or, albeit unlikely, triggers conversion to CTCL through an immunomodulatory shift, and therefore it is of critical importance to exclude the diagnosis thoroughly prior to initiation.

Of additional interest, there is a higher incidence and worse prognosis in patients with skin of color affected by CTCL in the United States. Even after adjusting for socioeconomic factors, disease characteristics, and treatment types, patients with skin of color affected by mycosis fungoides have a significantly shorter overall survival, suggesting a biological difference in disease and the need to consider earlier and more aggressive treatment. We speculate that this may have contributed at least in part to the severity of disease observed in this case.

There is much to be learned about the complex interplay between CTCL, the immunomodulatory effects of dupilumab, and population-specific variations in disease pathogenesis and drug response. Increased awareness and reporting are essential for improving understanding and providing comprehensive and individualized care to patients. We advocate for the diligent monitoring of disease course after dupilumab initiation. At the first sign of inadequate treatment response, there must be prompt evaluation for CTCL and alternative diagnoses, particularly in patients with skin of color.

Conflicts of interest
None disclosed.

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