BRIEF ARTICLES

Dupilumab-Induced Psoriasiform Dermatitis

Karlee D Novice MD,[1] Jesse Veenstra MD, PhD,[1] Holly Kerr MD,[1] Dana Siegel BS[2]

[1]Department of Dermatology, Henry Ford Hospital, Detroit, MI
[2] Wayne State Medical School, Detroit, MI

ABSTRACT

Atopic dermatitis (AD) is a common inflammatory skin condition. The newly FDA approved biologic dupilumab has demonstrated significant improvement in the signs and symptoms of AD, including pruritus as well as those of anxiety and depression.[1] The most frequently reported adverse effects of dupilumab include injection site reactions, nasopharyngitis, upper respiratory infections, and conjunctivitis.[1-5] We report a case of dupilumab-induced psoriasiform dermatitis. To our knowledge, there have been no reports to date of a dupilumab-induced psoriasiform dermatitis. There has been one report of an erythrodermic presentation of psoriasis in a patient treated with dupilumab.[8] As novel immunotherapy treatments are developed and employed in the treatment of common conditions such as AD, it is important to better understand and be aware of the potential side effects and immune-based sequelae that may arise in addition to available treatment options for these adverse reactions.

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin condition that affects up to 20-30% of children and 2-10% of adults. In the past, therapeutic options were limited to emollients, topical glucocorticoids and calcineurin inhibitors, phototherapy, and systemic corticosteroids and anti-inflammatory therapies (e.g., methotrexate, mycophenolate mofetil, azathioprine, cyclosporine).

The newly FDA approved biologic dupilumab has demonstrated significant improvement in the signs and symptoms of AD, including pruritus as well as those of anxiety and depression.[1] Dupilumab is a fully human monoclonal IgG4 antibody against interleukin-4 receptor alpha thereby inhibiting signaling of both interleukin-4 and interleukin 13, which are among the principle drivers of a type 2 immune response important in the diathesis of atopic disease.[1] The most frequently reported adverse effects of dupilumab include injection site reactions, nasopharyngitis, upper respiratory infections, and conjunctivitis.[1-5] We report a case of dupilumab-induced psoriasiform dermatitis.

CASE REPORT

A 40-year-old Indian male with a long-standing history of severe AD, asthma, and allergic rhinitis was started on dupilumab after failing multiple treatment modalities including topical steroids and calcineurin inhibitors, NB-UVB, in-office triamcinolone ointment wet wraps, methotrexate, and

mycophenolate mofetil. Two weeks post dupilumab 600 mg subcutaneous injection loading dose, a striking decrease in the degree and severity of eczematous lesions and pruritus was noted. Following the fourth injection over approximately two months of treatment, an asymptomatic pink scaly eruption developed on his forehead that was clearly distinct in nature compared to his typical eczematous eruption. Over the subsequent three months, asymptomatic pink scaly plaques spread to involve more facial areas in addition to the scalp, chest and upper arms in a seborrheic distribution (Figure 1, 2). A punch biopsy was performed on his right shoulder that demonstrated psoriasiform epidermal acanthosis with perifollicular parakeratosis favoring psoriasiform dermatitis with a differential including seborrheic dermatitis, partially treated psoriasis or chronic AD (Figure 3). A PAS stain was negative. Ketoconazole cream twice daily as a 3-month trial resulted in moderate improvement of the erythema and scale. The patient declined additional treatment.

Figure 1. pink to erythematous patches to thin plaques on the forehead extending into the scalp with fine white flaky scale

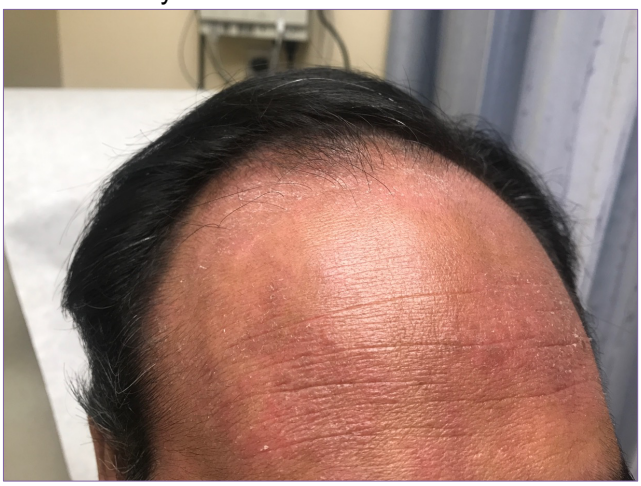
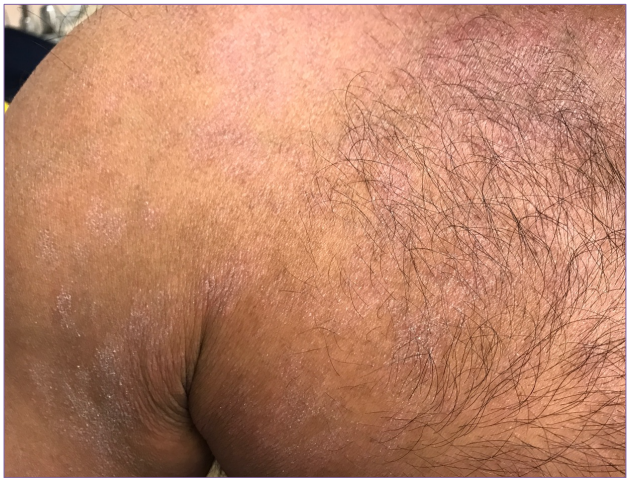


Figure 2. scattered pink thin plaques with fine white scale throughout the upper chest and arms



DISCUSSION

AD is a complex immunologic disorder characterized by the overexpression of Th2 cytokines, with IL-4 and IL-13 considered the primary inflammatory mediators. Traditionally, treatment of moderate to severe AD is challenging, however, greater elucidation of AD disease pathogenesis has led to the development of targeted therapies such as dupilumab. In three clinical trials of dupilumab (SOLO 1, SOLO 2, CHRONOS), the overall incidence of adverse events was comparable in the dupilumab and placebo groups.[6-7] The most common adverse events in all trials were nasopharyngitis, upper respiratory tract infection, injection site reactions, skin infections, and conjunctivitis of unspecified cause. To our knowledge, there have been no reports to date of a dupilumab-induced psoriasiform dermatitis. There has been one report of an erythrodermic presentation of psoriasis in a patient treated with dupilumab.[8]

Although the pathogenesis of dupilumab-induced psoriasiform dermatitis is not clear, several hypotheses are advanced. The pathogenesis of AD is multifactorial as in other immunologically-based disorders and

includes an effect on numerous direct and reciprocal signaling pathways. While dupilumab has been highly successful in significantly decreasing the signs and symptoms of AD in most treated patients via decreasing Th2 signaling, it is not clear if this form of immune modulation allows for the development or dysregulation of other pathways (i.e. Th1, Th17, Th22) in a subset of patients. To this point, a small subset of patients placed on dupilumab have demonstrated exacerbations of their disease for unknown reasons. Additionally, the mechanism of dupilumab-induced conjunctivitis has yet to be fully elucidated but is known to be different from the etiology of ordinary allergic conjunctivitis. Thus, dupilumab-induced psoriasiform dermatitis may similarly arise from a unique immune dysregulation.

Alternatively, the psoriasiform dermatitis could be related to an altered immune homeostasis to normal cutaneous flora such as *Malassezia.* Our patient's rash occurred primarily in a seborrheic distribution, consistent with areas containing a higher density of *Malassezia,* and showed a partial response to a topical antifungal. While histological exam did not show any evidence of *Malassezia* overgrowth, dupilumab may have altered the natural host response to the organism. Under physiological homeostasis, there is little to no immunological response to *Malassezia*, but with significantly decreased Th2 signaling this balance could potentially be disrupted manifesting as a cutaneous eruption similar to the one seen in our patient.

Psoriasis was considered in the differential diagnosis and could be considered analogous to the paradoxical reaction seen with anti-TNF alpha inhibitors, although this seems less likely given the seborrheic distribution and lack of a micaceous scale, nail pitting or joint involvement. The most frequently reported areas of involvement of paradoxical psoriasis include scalp, flexures and palmoplantar areas, with more than 50% of cases presenting as pustular psoriasis affecting the palm and soles.[9] There has been one report of an erythrodermic presentation of psoriasis in a patient treated with dupilumab in which authors hypothesized that blockage of Th2-mediated inflammation with a resultant shift toward Th1 activity was a pathogenic factor in the development of erythrodermic psoriasis[8].

As novel immunotherapy treatments are developed and employed in the treatment of common conditions such as AD, it is important to better understand and be aware of the potential side effects and immune-based sequelae that may arise in addition to available treatment options for these adverse reactions.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
Karlee Novice, MD
Department of Dermatology
Henry Ford Hospital
7456 Paddlewheel Ct
Bloomfield Hills, MI
48301
Phone: 248-535-8288
Fax: 313-916-5334
Email: karleenovice@gmail.com

References:

1. Beck LA, Thaci D, Hamilton JD, et al. *Dupilumab treatment in adults with moderate-to-severe atopic dermatitis.* N Engl J Med, 2014. 371(2): p. 130-9.
2. Fleming P, Drucker AM. *Risk of infection in patients with atopic dermatitis treated with dupilumab: A meta-analysis of randomized controlled trials.* J Am Acad Dermatol, 2018. 78(1): p. 62-69 e1.

3. Hamilton JD, Ungar B, Guttman-Yassky E. *Drug evaluation review: dupilumab in atopic dermatitis.* Immunotherapy, 2015. 7(10): p. 1043-58.
4. Sidbury R, TOm WL, Bergman JN, et al. *Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches.* J Am Acad Dermatol, 2014. 71(6): p. 1218-33.
5. Vangipuram R, Tyring SK. *Dupilumab for Moderate-to-Severe Atopic Dermatitis.* Skin Therapy Lett, 2017. 22(6): p. 1-4.
6. Simpson EL, Bieber R, Guttman-Yassky Emma. et al. *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. 375(24): p. 2335-2348.
7. Blauvelt A, de Bruin-Weller, Gooderham M, et al. *Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.* Lancet, 2017. 389(10086): p. 2287-2303.
8. Tracey EH, Elston C, Peasel P, et al. *Erythrodermic presentation of psoriasis in a patient treated with dupilumab.* JAAD Case Rep, 2018. 4(7): p. 708-710.
9. Toussirot E, Aubin F. *Paradoxical reactions under TNF-alpha blocking agents and other biological agents given for chronic immune-mediated diseases: an analytical and comprehensive overview.* RMD Open, 2016. 2(2): p. e000239.