SKIN

BRIEF ARTICLE

Pustular Psoriasis After Dupilumab: A Case Report and Systematic Review

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ABSTRACT

Dupilumab is a human monoclonal antibody targeting the interleukin-4 receptor alpha subunit, inhibiting type-2 inflammatory responses through its dual blockade of interleukin-4 (IL-4) and IL-13 signaling. Dupilumab is approved for the treatment of moderate to severe atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyposis. However, recent reports have documented the emergence of pustular psoriasis (PP) during treatment of AD with dupilumab. Whether dupilumab causes pustular psoriasis or merely renders its presentation in patients misdiagnosed with AD remains unclear. By presenting this case and conducting a systematic review, we aim to contribute to the understanding of the potential association between dupilumab therapy and the development of pustular psoriasis. This knowledge will help clinicians in accurately diagnosing and managing patients who develop pustular psoriasis while on dupilumab.

CASE REPORT

A 72-year-old male presented with multiple pustules and eroded plaques with overlying crust on his back, chest, scalp, and neck. These areas were exquisitely sensitive and accompanied by a burning sensation. The patient had a history of chronic atopic dermatitis diagnosed clinically by a previous dermatologist, and had been started on dupilumab therapy 5 months ago for the treatment of AD. He initially received a subcutaneous injection of 600 mg loading dose followed by 300 mg every other week, and his symptoms began to improve within one month. However, 4 months after initiating dupilumab therapy, he experienced burning-like pain on his scalp that migrated inferiorly, manifesting as erythematous pustules. He consequently came to our office, where we obtained punch biopsies of the affected regions, which featured diffuse, eroded plaques with crusting and dispersed excoriations. The patient was afebrile and was not exposed to new chemical irritant or drugs within the preceding month. He did not have a personal or family history of psoriasis. Our initial differential diagnosis included pemphigus foliaceous, IgA pemphigus, infected generalized atopic dermatitis, and pustular psoriasis. His complete blood count was solely notable for mild lymphocytosis of 4,208 cells/μL, and culture from a pustular region of the right lower back isolated *Pseudomonas aeruginosa*, *Enterobacter gergoviae*, *Proteus hauseri*, and *Klebsiella aerogenes*. Skin biopsy of this area revealed

parakeratosis, mild spongiosis, and intraepidermal and intracorneal neutrophilic abscesses. Based on these findings, the diagnosis of pustular psoriasis was made and attributed to recent dupilumab use, which was promptly halted. The patient was treated with a ten-day course of oral ciprofloxacin per microbial susceptibility testing, along with cyclosporine and the tumor necrosis factor (TNF) blocker adalimumab with noticeable improvement in symptoms within 6 weeks.

METHODS

We evaluated the Cochrane reviews, Embase, and PubMed/Medline based on the search strategy, which was built around the key terms 'dupilumab' or 'dupixent' and 'pustular psoriasis.' For this study, through PRISMA, reports of patients with pathology-confirmed pustular psoriasis during treatment of dupilumab for presumed AD were identified from 2017 through 2023 (**Figure 1**).

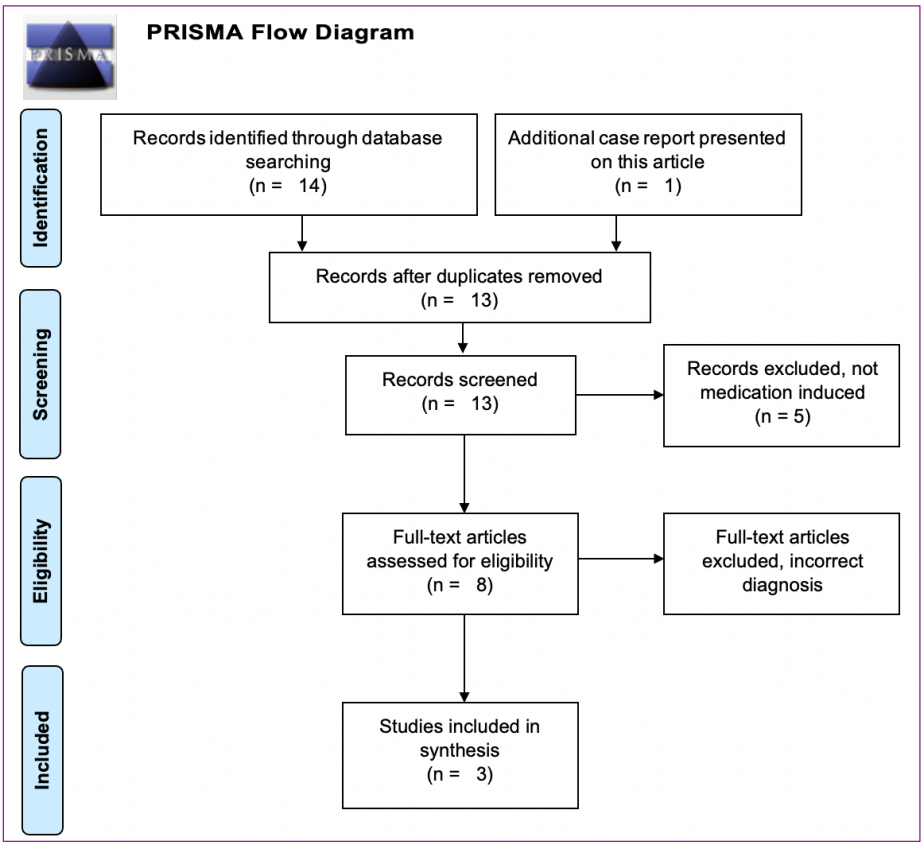

Figure 1: Prisma flow diagram search criteria

The diagnosis of PP was made based on a combination of clinical features (pustular prominence on physical exam), laboratory findings (leukocytosis, hypocalcemia, increased liver enzymes), systemic symptoms (fever, chills, headaches, etc.) and histopathological findings (neutrophilic prominence on the papillary dermis, superficial micro-abscess in combination with classic features of psoriasis). Three studies met inclusion criteria, with a median latency to onset of 4 weeks (range 10 days to 12 weeks). The mean age at onset of pustular psoriasis was 32 years (range, 22-51 years). Two of the three cases occurred in men under the age of 25, while one case describes a 51-year-old woman (**Table 1**). Of note, the two younger men remained

Table 1. Pustular psoriasis cases per review of literature

Case	Age Sex	AD Duration	Pre-Dupilumab Biopsy	Physical Exam Findings (Post-Dupilumab)	Post Dupilumab Diagnosis	Post-Dupilumab Biopsy	Dupilumab Initiation to Psoriasis Diagnosis (Months)	Overall Outcome	Naranjo Score*
1st	23 M	Childhood	ND	Superficial erythematous tiny pustules with scale on bilateral lower extremities	Pustular Psoriasis	Spongiform abscesses. Parakeratosis, epidermal hyperplasia, and lymphocyte infiltrate in the upper dermis.	<1 (10 days)	Pustular psoriasis resolved 2 weeks post dupilumab discontinuation and addition of cyclosporine	5
2nd	22 M	NR	ND	Confluent yellow pustules within the plaques on bilateral dorsal hands	Pustular Psoriasis	Psoriasiform acanthosis and parakeratosis of the epidermis with elongated rete ridges. Sub corneal spongiotic pustule of neutrophils	3	NR	5
3rd	51 F	NR	ND	Disseminated erythema papules with multiple small sterile pustules and crust	Pustular Psoriasis	Parakeratosis, psoriatic hyperplasia, and dilated tortuous vessels in the papillary dermis. The superficial dermis was infiltrated by large quantities of lymphocytes peri vascularly and neutrophils	1	Pustular psoriasis resolved after a 3-week course of steroids	5

*Naranjo score: total: -4 to +13; the reaction is defined: ≥9, probable: 5-8, possible:1-4, and doubtful: ≤0[1–8] , ND= no data, NR= no report

afebrile throughout the course of dupilumab treatment and subsequent pustular psoriasis, which occurred gradually and solely affected one body region (dorsal hands or lower extremities). The female patient, by contrast, developed generalized pustular psoriasis accompanied by fever, eosinophilia, hypocalcemia, and hypoproteinemia. All patients demonstrated significant improvement following systemic corticosteroid treatment. The Naranjo Adverse Drug Reaction Probability Scale was used to determine the likelihood that dupilumab caused pustular psoriasis in each case. This involved a structured questionnaire evaluating factors such as temporal association, dechallenge and rechallenge results, alternative causes, and objective evidence. Each case scored 5 on the Naranjo scale, indicating a probable reaction.

DISCUSSION

While dupilumab is generally well-tolerated with few known adverse effects including injection-site reactions, conjunctivitis, and blepharitis, reports of plaque psoriasis during dupilumab treatment have recently garnered attention.[1] Dupilumab may also be associated with new-onset pustular psoriasis, a subtype warranting immediate treatment.[1,2,3,4] The median time to PP after dupilumab treatment was 4 weeks. Psoriasis results from aberrant activation of IFN-gamma secreting T-helper 1 (Th1) cells and Th17 cells, which produce IL-17 and IL-22. More recently, IL-36 has been shown to predominantly orchestrate PP.[3,4] AD, however, is primarily driven by Th2 immune responses, triggering profound IL-4 and IL-13 release. Dupilumab, which blocks IL-4 and

IL-13 through its antagonism of IL4Ra, may preferentially favor Th1 cascading through its Th2 inhibition, contributing to PP development. Recent genetic profiling of skin samples from patients who developed PP following dupilumab demonstrated increased expression of IL-23, which promotes differentiation of naïve T-cells into Th1 and Th17 subsets.[2]

The use of dupilumab may occasionally cause a rare but potentially serious adverse event called pustular psoriasis, which needs to be promptly identified and treated. We hope to draw attention to this entity and increase awareness of this potential side effect. Limitations to this study reflect the small number of patient reports that met our search criteria. In addition, skin biopsy results from patients prior to treatment with dupilumab were unavailable to confirm the presence of atopic dermatitis, potentially undermining the accuracy of this diagnosis. It also may be possible that some patients did not develop dupilumab-induced pustular psoriasis, but rather a secondary dermatosis unrelated to dupilumab use. Differentiating between co-occurrence versus causative reaction to dupilumab therapy may require additional investigation with mammalian models of keratinocyte lineage-traced atopic dermatitis. The incidence, risk factors, and ideal management of this adverse event require further research.

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