Severe, ulcerative, lichenoid mucositis associated with secukinumab

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INTRODUCTION

Secukinumab is a new human monoclonal antibody targeting interleukin (IL)-17A, a cytokine involved in the pathogenesis of psoriasis. The US Food and Drug Administration approved secukinumab for psoriasis in 2015. Because the medication has been on the market for a short time, adverse events involving the oral mucosa are rarely reported. We report a case of severe, ulcerative, lichenoid mucositis associated with secukinumab use.

CASE REPORT

A 62-year-old white man underwent follow-up for long-standing, intractable, erythrodermic psoriasis. He did not respond to tumor necrosis factor (TNF) inhibitors such as adalimumab and etanercept and could not tolerate cyclosporine. Because methotrexate was only mildly efficacious, secukinumab was added. Less than 1 week into secukinumab treatment, very painful erosions and ulcers developed on the lower lip (Fig 1). The patient was taking no other medications and had no history of recurrent orolabial herpes simplex virus infection or other oral disease such as aphthosis. Viral culture was negative for herpes simplex virus. A potassium hydroxide preparation and fungal culture were negative, and lesions did not respond to oral fluconazole.

Because secukinumab was showing efficacy for his psoriasis, and in the absence of a clear etiology of the labial lesions, the patient elected to continue taking the drug. The lesions persisted and remained painful for 3 months, finally prompting discontinuation of secukinumab. Shave biopsy found ulceration with a dense lichenoid inflammatory infiltrate with scattered eosinophils, neutrophils, and plasma cells (Figs 2 and 3). The presence of eosinophils and deeper inflammatory infiltrate (Fig 2) suggested a lichenoid drug eruption. Direct immunofluorescence of perilesional mucosa found nonspecific basal epithelium staining for C3, IgG, and IgM. The patient started using 0.1% triamcinolone in Orabase paste. It was not until approximately 6 weeks from secukinumab discontinuation and 1 week of steroid paste use that the labial lesions showed substantial improvement.

Abbreviations used:

EM:	erythema multiforme
IL:	interleukin
LP:	lichen planus
MMP:	mucous membrane pemphigoid
PV:	pemphigus vulgaris
TNF-α:	tumor necrosis factor-α

DISCUSSION

There are sparse reports of oral adverse events associated with new anti–IL-17 drugs (Table I).[1-3] However, oral adverse effects of other biologic agents such as TNF inhibitors, which have longer track records, are well described (Table I).[4-8] Mouth ulceration was reported in 2 patients in a phase 2 secukinumab trial, but specifics were not provided.[1] The differential diagnosis of our patient's labial lesions includes candidiasis, oral lichen planus (LP), drug-induced LP, lichenoid contact dermatitis, erythema multiforme (EM), major aphthae, complex aphthosis, pemphigus vulgaris (PV), and mucous membrane pemphigoid (MMP). Oral candidiasis, reported in 1.8% of patients at 52 weeks in a

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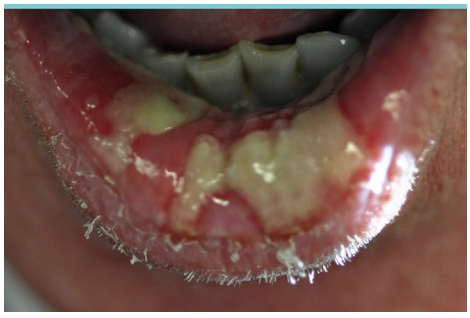

Fig 1. Multiple coalescing large ulcerations on an erythematous base are shown on the vermillion and labial mucosa.

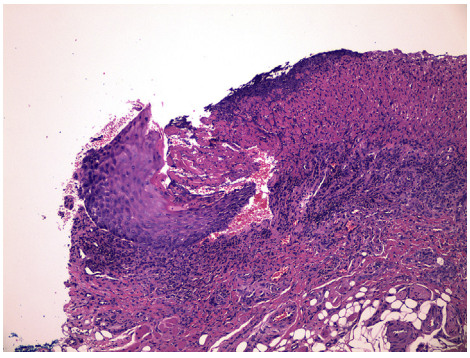

Fig 2. Mucosal ulceration shows dense lichenoid infiltrate with focal intact epithelium. (Hematoxylin-eosin stain; original magnification: ×100.)

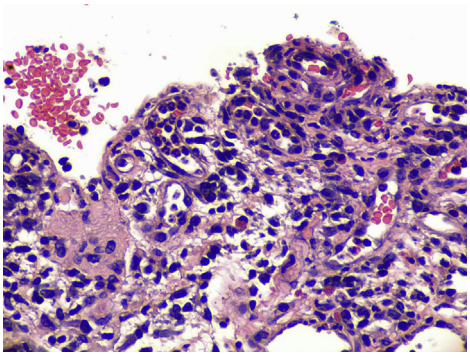

Fig 3. Eosinophils were noted throughout the inflammatory infiltrate, including in the deep inflammatory infiltrate. (Hematoxylin-eosin stain; original magnification, ×400.)

secukinumab trial,[2] was ruled out by negative potassium hydroxide preparation and fungal culture, and no response to oral fluconazole.

Unlike erosive oral LP that typically manifests with lesions on buccal mucosa, gingivae, and tongue that tend to run a chronic course, the lesions in our patient were located on the lip and noted during a short course of secukinumab. As highlighted in Table I, LP-like reactions have developed secondary

Table I. Oral adverse effects associated with anti-IL-17 drugs and TNF-α inhibitors

Drug class	Adverse effect
Anti—IL-17 drugs	Ulcerative, lichenoid mucositis (current case)
	Mouth ulceration[1]
	Oral candidiasis[2]
	Sialadenitis[3]
TNF-α inhibitors	Lichen planus—like reactions[4,5]
	Erythema multiforme[6]
	Oral candidiasis[7]
	Pemphigus vulgaris[8]

to use of TNF inhibitors.[4,5] These reactions arose most commonly within 2 months (range, 3 weeks to 16 months) of TNF inhibitor therapy. Oral LP in patients on TNF inhibitor therapy manifested with Wickham's striae, with only 3 reports of erosive disease.[4,5] Wickham's striae were not noted in our patient. Unlike this case, most TNF inhibitor—associated cases presented also with cutaneous LP, and lesions were not exquisitely painful. TNF-α levels are elevated in saliva and serum of patients with LP; therefore, the appearance of oral LP in the context of TNF-α blockade is paradoxical. TNF-α inhibition leads to upregulation of interferon-α, a pro-inflammatory cytokine implicated in LP.[4] It is possible that anti—IL-17 drugs, which counteract the synergistic effects of IL-17 and TNF-α,[9] can provoke a similar reaction.

Our patient was not on any other drugs known to cause oral LP-like reactions.[10] Methotrexate can cause mucositis, which typically affects several sites and is associated with cutaneous involvement, hematologic abnormalities, and keratinocyte dystrophy.[11] These features were absent in our case. Our patient was on methotrexate long before the lesions developed, and lesions resolved after discontinuation of secukinumab despite continued methotrexate treatment. Our patient was not using any topical medications that could have caused lichenoid contact dermatitis at the time that the labial lesions developed.

Additional diagnoses considered include EM, aphthae, PV, and MMP. Features of EM such as white pseudomembranes and targetoid and necrotic lesions were missing in our case, and the 3-month duration without periods of healing was not consistent with EM. Furthermore, EM diagnosis was not supported by the histopathologic findings. Typical features of major aphthae, such as a large, discrete, deep ulcers with yellow cratered base and healing with scarring were not noted in this case.[12]

Histopathologic features of major aphthae such as necrosis, presence of neutrophils below the ulcer, and involvement of salivary glands were absent. Furthermore, our case did not show features of complex aphthosis, such as almost constant presence of ≥ 3 oral aphthae. Our patient had no vesiculobullous lesions affecting the skin or other mucosal surfaces, and direct immunofluorescence ruled out immunobullous disease such as PV and MMP.

An association between secukinumab and labial lesions in this case is supported by the onset of lesions shortly after secukinumab administration and resolution after discontinuation of the drug. The underlying mechanism of our patient's labial lesions may be similar to that proposed for TNF inhibitor—associated oral LP (upregulation of interferon-α),[4] because IL-17 inhibitors downregulate the synergy of IL-17 with TNF-α.[9] Furthermore, decreased IL-17—positive cells are seen in oral LP when compared with nonspecifically inflamed mucosa,[13] and it is possible that drugs such as secukinumab may enhance a similar disturbance in local immune regulation, causing oral lichenoid reactions. As additional anti—IL-17 drugs are approved, it is important to further characterize such adverse events. Clinicians must be aware of this possible class effect, as early diagnosis helps decrease morbidity, given the extended time to recovery in our patient and the potential for significant quality-of-life disruption with these painful labial lesions.

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