

## Mucocutaneous findings associated with interleukin (IL)-17 inhibition

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### INTRODUCTION

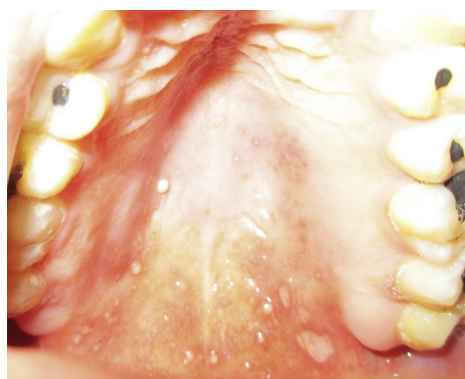
Sialadenitis, inflammation of a salivary gland, typically presents with pain, swelling, and erythema of the oral mucosa. In particular, lymphocytic sialadenitis is most commonly associated with Sjögren's syndrome and hepatitis C viral infection but has never been described in the setting of interleukin (IL)-17 inhibition. We report a case of lymphocytic sialadenitis in the setting of ixekizumab treatment for psoriasis.

### CASE REPORT

A 25-year-old man with a medical history of psoriasis presented to the University hospital complaining of severe pain associated with oral ulcers and difficulty swallowing. The ulcers developed 1 week before presentation. His primary care physician prescribed valacyclovir, prednisone, and viscous lidocaine without improvement. The patient reported being enrolled in a clinical trial for psoriasis. Chronic plaque psoriasis was diagnosed 8 years prior, which was treated with ustekinumab with significant but incomplete improvement. He started the trial several months before presentation. The patient reported no other recent medication changes and felt well until the development of the ulcers. On examination, the oral mucosa showed multiple erosions and vesicles with underlying background erythema. The hard and soft palate, gingivae, and lips were primarily involved (Fig 1). Over the next 24 hours, the patient became febrile, and erythematous tender nodules developed on the extensor surfaces of the legs and distal upper

*Abbreviation used:*

SAE: serious adverse event



**Fig 1.** Oral mucosa shows multiple erosions and vesicles with underlying background erythema. The hard and soft palate, gingivae, and lips were primarily involved.

extremities. These nodules appeared clinically consistent with those of erythema nodosum. Contact with the unblinded clinical trial administrator found that the patient was receiving the active agent, ixekizumab, an IL-17 inhibitor, and not placebo. A biopsy of the mucosal upper lip found a dense lymphoplasmacytic infiltrate surrounding the minor salivary glands and the salivary duct with mucositis and surface ulceration (Fig 2). Direct immunofluorescence findings were negative. A biopsy of the lower extremity found an early septal panniculitis consistent with the clinical impression of erythema nodosum. Laboratory workup findings

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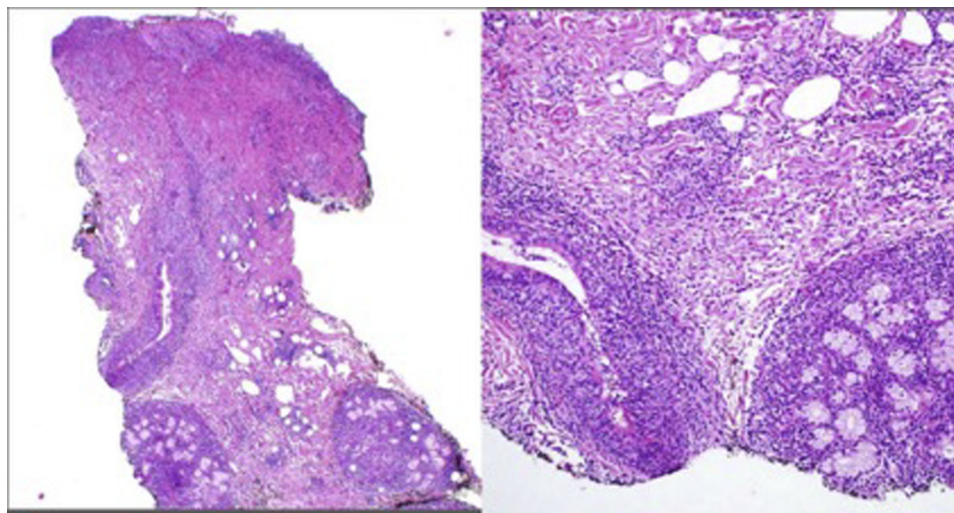
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**Fig 2.** Punch biopsy results show a dense lymphoplasmacytic infiltrate surrounding the minor salivary glands and the salivary duct with mucositis and surface ulceration of the upper lip.

**Table I.** Adverse events associated with ixekizumab treatment in phase II clinical trials<sup>3</sup>

Nasopharyngitis
Injection site reaction
Elevation of creatine kinase
Grade II neutropenia
Peripheral edema*
Urticaria*
Upper respiratory infection
Headache
Elevation of liver transaminases
Minor infections
Hypersensitivity*

\*Patient discontinued trial because of adverse event.

were notable for a mild elevation of aspartate transaminase (87), alanine transaminase (105), erythrocyte sedimentation rate (30), and C-reactive protein (29). Findings were negative for rapid plasma reagin, cytomegalovirus serology, viral cultures, human immunodeficiency virus, antistreptolysin O antigen, and hepatitis panel. The patient was started on methylprednisolone and converted to an oral steroid taper and showed marked improvement. He was discharged after a 3-day admission.

## DISCUSSION

Recent evidence suggests that psoriasis is dependent on T helper 17 (Th17) cells. In peripheral tissues, Th17 cells develop after exposure to transforming growth factor beta 1 and IL-6 and are sustained by IL-23, produced by both keratinocytes and dendritic cells. Th17 cells produce and secrete a variety of proinflammatory cytokines, most notably

IL-17 and IL-22. IL-17 is mainly involved in the recruitment and activation of neutrophils and is able to directly inhibit apoptosis of neutrophils in inflamed tissues. IL-22 is responsible for keratinocyte hyperproliferation.<sup>1</sup> The efficacy of ustekinumab, a monoclonal antibody directed against IL-12 and IL-23, further supports the role of Th17 cells.<sup>2</sup>

In a phase II trial of ixekizumab, no serious adverse events (SAEs) were reported, but there were several mild adverse events including injection site reactions, nasopharyngitis, upper respiratory infection, and headache (Table I).<sup>3</sup> In another phase II trial of ixekizumab, there were 15 SAEs reported in 10 (8%) patients (Table II), none that were major cardiac events.<sup>4</sup> Among both of these studies, neither sialadenitis nor erythema nodosum was reported.

Lymphocytic sialadenitis can be present in both Sjögren's syndrome and hepatitis C viral infection but has not been reported in association with IL-17 inhibition. In patients with annular erythema associated with Sjögren's syndrome, IL-17 producing Th17 cells and regulatory T cells are found to play a role in maintaining mucocystitis. The pattern of infiltration observed among patients with annular erythema associated with Sjögren's syndrome compared with other Th17 cell-mediated diseases, such as systemic lupus erythematosus, atopic dermatitis, and psoriasis, was found to be unique, as dense dermal infiltrates are seen as opposed to superficial infiltration.<sup>5</sup> Compared with this case, however, the clinical and histologic presentations do not fit that of Sjögren's syndrome or hepatitis C virus infection.<sup>6-8</sup> This case shows an unusual and not previously reported side effect of IL-17 inhibition.

**Table II.** Serious adverse events associated with ixekizumab treatment in phase II clinical trials<sup>4</sup>


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Rectal cancer
Depression
Atherosclerosis
Urinary tract infection
Pyelonephritis
Nephrolithiasis
Laceration of the left arm
Exacerbation of hidradenitis suppurativa
Suicide attempt
Congestive heart failure
Cellulitis
Acute coronary syndrome
Wrist fracture

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None of these SAEs were major cardiac events.

Evidence of other causes for this reaction pattern were not found, and the degree of symptomatology was striking compared with other causes of sialadenitis. The response to systemic glucocorticoids was rapid.

## CONCLUSION

As the use IL-17 inhibitors becomes more widespread in the treatment of plaque psoriasis, clinicians need to be aware of unusual side effects not previously described in clinical trials. Although headache, injection site reaction, nasopharyngitis, and upper respiratory infection seem to most commonly result,

other adverse reactions can include neutropenia, elevation of liver transaminase levels, sialadenitis, and erythema nodosum. Vigilant monitoring of patients receiving this novel drug is warranted to assess for unusual reactions, as this highly efficacious biologic is adapted into clinical use.

## REFERENCES

1. Fitch E, Harper E, Skorcheva I, Kurtz SE, Blauvelt A. Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. *Curr Rheumatol Rep.* 2007;9(6):461-467.
2. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet.* 2008;371(9625):1665-1674.
3. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med.* 2012;366(13):1190-1199.
4. Gordon KB, Leonardi CL, Lebwohl M, et al. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. *J Am Acad Dermatol.* 2014;71(6):1176-1182.
5. Itoi S, Tanemura A, Tani M, et al. Immunohistochemical Analysis of Interleukin-17 Producing T Helper Cells and Regulatory T Cells Infiltration in Annular Erythema Associated with Sjögren's Syndrome. *Ann Dermatol.* 2014;26(2):203-208.
6. Carrozzo M, Scally K. Oral manifestations of hepatitis C virus infection. *World J Gastroenterol.* 2014;20(24):7534-7543.
7. Haddad J, Deny P, Munz-Gotheil C, et al. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. *Lancet.* 1992;339(8789):321-323.
8. Pawlotsky JM, Ben Yahia M, Andre C, et al. Immunological disorders in C virus chronic active hepatitis: a prospective case-control study. *Hepatology.* 1994;19:841-848.