

Candida Esophagitis Associated With Adalimumab for Hidradenitis Suppurativa

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PRACTICE POINTS

- Adalimumab is an effective treatment for patients with hidradenitis suppurativa.
- There is risk for opportunistic infections with adalimumab, and patients should be monitored closely.

To the Editor:

Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterized by the development of painful abscesses, fistulous tracts, and scars. It most commonly affects the apocrine gland-bearing areas of the body such as the axillary, inguinal, and anogenital regions. With a prevalence of approximately 1%, HS can lead to notable morbidity.¹ The pathogenesis is thought to be due to occlusion of terminal hair follicles that subsequently stimulates release of proinflammatory cytokines from nearby keratinocytes. The mechanism of initial occlusion is not well understood but may be due to friction or trauma. An inflammatory mechanism of disease also has been hypothesized; however, the exact cytokine profile is not known. Treatment of HS consists of several different modalities, including oral retinoids, antibiotics, antiandrogenic therapy, and surgery.^{1,2} Adalimumab is a well-known biologic that has been approved by the US Food and Drug Administration for the treatment of HS.

Adalimumab is a human monoclonal antibody against tumor necrosis factor (TNF) α and is thought to improve HS by several mechanisms. Inhibition of TNF- α and other proinflammatory cytokines found in inflammatory lesions and apocrine glands directly decreases the severity of lesion size and the frequency of

recurrence.³ Adalimumab also is thought to downregulate expression of keratin 6 and prevent the hyperkeratinization seen in HS.⁴ Additionally, TNF- α inhibition decreases production of IL-1, which has been shown to cause hypercornification of follicles and perpetuate HS pathogenesis.⁵

Adalimumab is considered a safe medication with a low toxicity profile and rarely is associated with serious adverse effects. The most common adverse effects are injection-site reaction, headache, and rash. However, as with any immunosuppressant, there is an elevated incidence of opportunistic infections. Anti-TNF medications have been associated with an increased incidence of viral, bacterial, and fungal infections. We present a patient who developed *Candida* esophagitis 6 weeks after starting treatment with adalimumab for the treatment of HS. This case highlights the development of esophageal candidiasis as a notable adverse event.

A 41-year-old woman with a history of endometriosis, adenomyosis, polycystic ovary syndrome, interstitial cystitis, asthma, fibromyalgia, depression, and Hashimoto thyroiditis presented to our dermatology clinic with active draining lesions and sinus tracts in the perivaginal area that were consistent with HS, which initially was treated with doxycycline 100 mg twice daily. She experienced minimal improvement of the HS lesions at 2-month follow-up.

Due to disease severity, adalimumab was started. The patient received a loading dose of 4 injections totaling 160 mg and 80 mg on day 15, followed by a maintenance dose of 40 mg/0.4 mL weekly. The patient reported substantial improvement of pain, and complete resolution of active lesions was noted on physical examination after 4 weeks of treatment with adalimumab.

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The authors report no conflict of interest.

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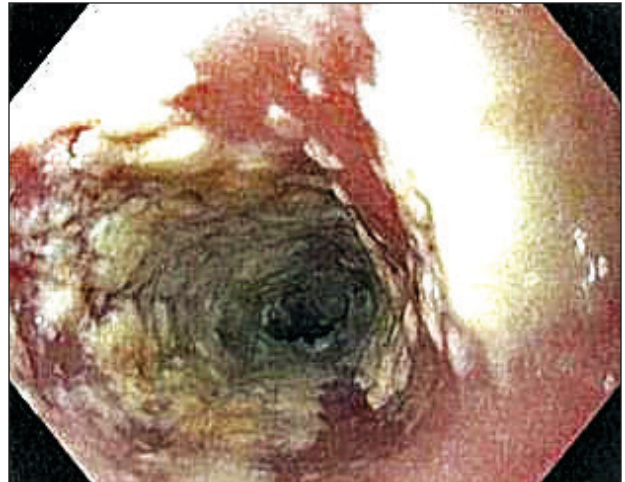
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Six weeks after adalimumab was started, the patient developed severe dysphagia. She was evaluated by a gastroenterologist and underwent endoscopy (Figure), which led to a diagnosis of esophageal candidiasis. Adalimumab was discontinued immediately thereafter. The patient started treatment with nystatin oral rinse 4 times daily and oral fluconazole 200 mg daily. The candidiasis resolved within 2 weeks; however, she experienced recurrence of HS with draining lesions in the perivaginal area approximately 8 weeks after discontinuation of adalimumab. The patient requested to restart adalimumab treatment despite the recent history of esophagitis. Adalimumab 40 mg/0.4 mL weekly was restarted along with oral fluconazole 200 mg twice weekly and nystatin oral rinse 4 times daily. This regimen resulted in complete resolution of HS symptoms within 6 weeks with no recurrence of esophageal candidiasis during 6 months of follow-up.

Although the side effect of *Candida* esophagitis associated with adalimumab treatment in our patient may be logical given the medication's mechanism of action and side-effect profile, this case warrants additional attention. An increase in fungal infections occurs from treatment with adalimumab because TNF- α is involved in many immune regulatory steps that counteract infection. *Candida* typically activates the innate immune system through macrophages via pathogen-associated molecular pattern stimulation, subsequently stimulating the release of inflammatory cytokines such as TNF- α . The cellular immune system also is activated. Helper T cells (T_{H1}) release TNF- α along with other proinflammatory cytokines to increase phagocytosis in polymorphonuclear cells and macrophages.⁶ Thus, inhibition of TNF- α compromises innate and cellular immunity, thereby increasing susceptibility to fungal organisms.

A PubMed search of articles indexed for MEDLINE using the terms *Candida*, *candidiasis*, *esophageal*, *adalimumab*, *anti-TNF*, and *TNF* revealed no reports of esophageal candidiasis in patients receiving adalimumab or any of the TNF inhibitors. *Candida* laryngitis was reported in a patient receiving adalimumab for treatment of rheumatoid arthritis.⁷ Other studies have demonstrated an incidence of mucocutaneous candidiasis, most notably oropharyngeal and vaginal candidiasis.⁸⁻¹⁰ One study found that anti-TNF medications were associated with an increased risk for candidiasis by a hazard ratio of 2.7 in patients with Crohn disease.⁸ Other studies have shown that the highest incidence of fungal infection is seen with the use of infliximab, while adalimumab is associated with lower rates of fungal infection.^{9,10}

Although it is known that anti-TNF therapy predisposes patients to fungal infection, the dose of medication known to preclude the highest risk has not been studied. Furthermore, most studies assess rates of *Candida* infection in individuals receiving anti-TNF therapy in addition to several other immunosuppressant agents (ie, corticosteroids), which confounds the interpretation



Candida esophagitis. Image of the mid esophagus obtained during a therapeutic upper endoscopy.

of results. Additional studies assessing rates of *Candida* and other opportunistic infections associated with use of adalimumab alone are needed to better guide clinical practices in dermatology.

Patients receiving adalimumab for dermatologic or other conditions should be closely monitored for opportunistic infections. Although immunomodulatory medications offer promising therapeutic benefits in patients with HS, larger studies regarding treatment with anti-TNF agents in HS are warranted to prevent complications from treatment and promote long-term efficacy and safety.

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