Laryngeal Histoplasmosis in patients with Crohn’s Disease undergoing treatment with HUMIRA (adalimumab): A Case Series

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Abstract
The FDA has advocated for increasing awareness of histoplasmosis for patients undergoing TNF blockers as delay in diagnosis can lead to a poor outcome.\(^1\) Laryngeal histoplasmosis is a rare entity that should be part of the differential diagnosis in patients receiving immune suppression for Crohn’s disease. Patients with laryngeal histoplasmosis often report hoarseness, mucosal ulcerations, dysphagia, and odynophagia. We present a series of two cases of laryngeal histoplasmosis in patients with Crohn’s. These cases illustrate the high index of suspicion required to make the diagnosis of laryngeal histoplasmosis, especially in the Midwestern United States. Diagnosis is made quickly and cost-effectively with proper staining. Delayed diagnosis may lead to dissemination, increased morbidity, and mortality.

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Laryngeal Histoplasmosis in Patients With Crohn’s Disease Undergoing Treatment With HUMIRA (adalimumab): A Case Series

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Introduction

Involvement of the larynx in Crohn’s disease is rarely described, but may be associated with symptoms such as dysphonia, dysphagia and globus sensation, correlating to examination findings including ulceration, granuloma formation, laryngeal edema, and vocal fold hypomobility.1,2 With biologics like Humira (adalimumab) leading to improved management of Crohn’s disease, side effects of immune suppression should be considered in the differential diagnosis for patients with symptoms in the upper aerodigestive tract. The FDA has advocated for increasing awareness of histoplasmosis for patients undergoing treatment with TNF blockers as delay in diagnosis can lead to a poor outcomes.3

Histoplasmosis, a granulomatous disease caused by the intracellular organism Histoplasma capsulatum, is the most commonly diagnosed endemic mycosis in the United States, and is most prevalent in the Ohio and Mississippi River Valleys.3,4 Laryngeal histoplasmosis rarely presents as an isolated primary lesion and is more often associated with disseminated histoplasmosis. Due to its low prevalence, laryngeal histoplasmosis is often not included in the differential diagnosis of many clinicians. In the absence of other symptoms, such as laryngeal lesions associated with histoplasmosis, it may easily be confused with laryngeal Crohn’s, carcinoma or tuberculosis.4,5 We report two cases of laryngeal histoplasmosis in patients with Crohn’s disease receiving adalimumab therapy and discuss the clinical presentation, diagnosis, and management of this disease. Consent was obtained for usage of patient photographs.

Case

Two individual patients presented to our clinic for evaluation of new onset voice changes with associated odynophagia and dysphagia. Upon evaluation, it was noted that both patients were on immunosuppression medication including Humira (adalimumab) for Crohn’s disease and both were non-smokers.

The endoscopic evaluation revealed laryngeal lesions suspicious for malignancy with diffuse laryngeal disease with ulceration and thickening of the supraglottic larynx (Figure 1A). Biopsy of both patients was performed to rule out laryngeal malignancy. One patient was diagnosed after Gomori Methenamine Silver Stain showed the presence of intracellular organisms consistent with histoplasmosis (Figure 2). The second patient’s diagnosis was delayed until bowel resection pathology showed disseminated histoplasmosis. The laryngeal slides were reviewed in light of the bowel resection and were indeed positive for fungal elements that were not diagnosed on the original pathology slides. Both patients were seen by Infectious Disease specialists and received antifungal therapy in addition to discontinuation of Humira, ultimately leading to resolution of their symptoms. Follow up endoscopic examination after two months of therapy showed marked improvement of laryngeal lesions (Figure 1B), and complete resolution by six months for the first patient and three months for the second.

Discussion

Laryngeal histoplasmosis is a relatively rare presentation of this mycosis and can widely vary in its presentation. Typically, histoplasmosis is inhaled from spores within the soil, first causing pulmonary infection, and can subsequently spread hematologically to other organ systems. Although the involvement of the larynx is usually associated with disseminated disease, there have been cases reported in the literature of primary laryngeal histoplasmosis.6

The majority of infected patients are immunocompetent and asymptomatic or may present with a mild, flu-like illness which resolves without treatment. Immunocompromised patients, however, have an increased risk of disseminated disease, which can progress to fatality if left untreated.7 Of note, both patients in this series were receiving adalimumab for immunosuppressive therapy at the time of diagnosis.

In patients taking TNF blockers, histoplasmosis is the most common invasive fungal infection, and is a more common cause of serious infections than tuberculosis.3 TNF-α has been identified as an integral cytokine for developing protective immunity against Histoplasma capsulatum, and inhibiting this cytokine can lead to macrophage dysfunction.8 Infections in patients with TNF blockade tend
to present with pneumonia or other pulmonary symptoms and/or signs of progressive disseminated histoplasmosis, but may also present with symptoms including skin necrosis, or bowel perforation and laryngeal lesions as seen in our patients.

Sonkhya et al. reported that the most common primary laryngeal lesions were located on the false cords and aryepiglottic folds, with an endophytic pattern of growth. However, an exophytic pattern of growth has also been reported, as have locations involving the laryngeal surface of the epiglottis, the vocal cords, cricoid region, and supraglottic region.

The diagnosis of laryngeal histoplasmosis is challenging secondary to the varied physical presentation of the lesions, and their similarity to malignancy. While suspicion must be high in an immunocompromised patient, the key to diagnosis is histopathologic identification. It is imperative to biopsy the lesions and communicate your suspicions to the examining pathology, as Grocott and Gomori silver staining can distinguish the yeast forms.

Therapy for histoplasmosis varies according to the immune status of the patient, as well as the extent and severity of the disease. Intravenous Amphotericin B for 7-10 days followed by oral Itraconazole for 9-12 months is the treatment of choice for disseminated disease with pulmonary involvement. It is not currently recommended to routinely screen for histoplasma antigen or to treat patients taking TNF blockers prophylactically with anti-fungal therapy.

**Conclusion**

Laryngeal histoplasmosis is an unusual presentation of this dimorphic fungus, one that can easily be mistaken for malignancy or inflammatory etiologies. It is important to have a high index of suspicion of this disease, especially in immunocompromised patients and in endemic areas, so that appropriate testing is performed. Indeed, upper aerodigestive tract findings may be present in patients with Crohn’s disease undergoing surveillance endoscopy who are on treatment with Humira (adalimumab). Delay may lead to further dissemination of the disease, resulting in increased morbidity and mortality. It is especially important to consider this diagnosis if the patient is immunocompromised and pathologic examination has ruled out malignancy.

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**References**