**Histoplasmosis of the Larynx**

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**Abstract**

Histoplasmosis is a granulomatous disease caused by Histoplasma capsulatum that has a variety of presentations, including acute and chronic pulmonary disease or disseminated disease. Laryngeal histoplasmosis, an uncommon presentation of disseminated disease, should be considered in the differential diagnosis for certain patients presenting with hoarseness, particularly those who are immunocompromised. We describe a case of laryngeal histoplasmosis in an elderly woman with rheumatoid arthritis taking immunosuppressive medications.

**Case Presentation**

A 72-year-old Caucasian female with seropositive rheumatoid arthritis (RA) presented with progressive hoarseness, difficulty breathing, and mild dysphagia over the previous 6 months. She initially presented to an outside clinic where she was diagnosed with laryngopharyngeal reflux and a paralysed right vocal cord, and was treated for a throat ulcer of uncertain etiology. When her symptoms and exam did not respond to anti-reflux therapy, a biopsy was performed that was consistent with inflammation with mild atypia and no evidence of carcinoma.

The patient’s medical history was significant for nine years of seropositive rheumatoid arthritis (RA) controlled with infliximab and hydroxychloroquine. She was a lifelong non-smoker with no significant history of alcohol consumption. She had spent the entirety of her life living in the Mississippi River Valley region in southeast Louisiana.

Upon initial physical exam, the patient was notably hoarse with mild bibasal stridor. Flexible fiberoptic laryngoscopy revealed multiple exophytic nodular lesions across the laryngeal epiglottis and vocal folds (Figure 1a). The patient had a fixed right vocal cord and paretic left cord, with a tenuous airway.

The patient was taken to the operating room for direct microlaryngoscopy with biopsy and tracheostomy. Her larynx was noted to be friable, with a diffuse ulceronodular appearance (Figure 1b). Biopsy revealed fragments of benign squamous mucosa with minor salivary gland tissue exhibiting extensive ulceration, acute and chronic inflammation without dysplasia (Figure 2). Due to a medical history significant for advanced RA, she was presumptively diagnosed with RA involving the circoarytenoid joints and rheumatoid nodules of the larynx. A modified barium swallow showed aspiration, and she required gastrostomy tube placement. She was continued on infliximab and hydroxychloroquine with the addition of prednisone, but did not respond. She was switched to a course of trimethoprim 150 mg, twice per day. Near complete resolution of the lesions and relative return of normal vocal cord function was seen in two months (Figure 1c,d). She was able to undergo decannulation and removal of her gastrostomy tube.

Histoplasmosis is a granulomatous disease that is caused by *Histoplasma capsulatum*, a dimorphic intracellular fungus. In the United States, Histoplasmosis is endemic to the Mississippi and Ohio River valleys and particularly thrives in soil rich with bird and bat droppings. Primary infection occurs from passive exposure where infectious microconidia are inhaled and then transform into their yeast phase within host macrophages. *H. capsulatum* then travels to mediastinal and hilar lymph nodes, from where it disseminates throughout the reticuloendothelial system of the host.

The main predisposing factors for histoplasmosis, particularly the disseminated form, include increasing age and decreasing cell-mediated immunity due to immunosuppressive agents.2 Endemic fungal infections have been increasing in frequency in recent years, which may be related to increasing age of aggressive chemotherapeutic agents, organ transplantation, and use of immunosuppressive drugs for autoimmune or rheumatologic diseases. Additionally, because cell-mediated immunity tends to wane with age, increasing longevity in today’s population indicates that more people are at risk.

The disease can manifest in several ways after primary inhalation of the spores, determined by inoculum size and immunity status of the host. Various presentations can be classified as acute pulmonary, chronic pulmonary and disseminated disease.3 For the majority of immunocompetent patients, the disease is asymptomatic or presents with mild influenza-like symptoms which resolve without treatment in less than 4 weeks.4 In those exposed to a high inoculum or in immunocompromised patients, acute severe pulmonary infection may occur which can progress to acute respiratory distress syndrome and death. Chronic pulmonary histoplasmosis is most often seen in older patients, particularly those with underlying pulmonary disease.4 In acutely disseminated cases, predominantly seen in the severely immunocompromised, patients present with fever and respiratory distress, as well as meningitis, pericarditis, and adrenalitis.5 In the chronic disseminated form of the disease, seen in immunocompetent adults, pulmonary symptoms are often less prominent and lesions of the skin and mucous membranes are more common, particularly oropharyngeal ulcerations.6

Laryngeal involvement occurs in the chronic disseminated form of histoplasmosis. Distinguishing laryngeal histoplasmosis from laryngeal carcinoma can be challenging, as in this case. Clinical suspicion and timely diagnosis of this disease is important in order to ensure patients receive appropriate treatment. Typical initial manifestations include hoarseness, dysphagia, and odynophagia, as well as fatigue and weight loss.7 Painful raised mucosal ulcerations may involve the oral cavity, tongue, pharynx, and larynx. Nodules appear as submucosal masses.

When histoplasmosis is suspected, laboratory technicians should be warned of this possibility, as special stains and cultures must be used for identification of the organism. Diagnosis can be achieved using clinical examination, cultures, histopathologic examination, antigen detection, or antibody assays, including complement fixation and immunodiffusion.

**Discussion**

Growth of *H. capsulatum* from tissue or body fluids is the definitive diagnostic test. Samples can be obtained from various sites in patients with disseminated infection, including blood, skin, or mucosal lesions.1 Organisms can be successfully isolated on Sabouraud’s agar, although this process can take up to 6 weeks.8 Histopathologic examination can be performed on biopsies of oral and laryngeal masses. Special stains such as Gomori silver methenamine or periodic acid– Schiff stain may be used and will reveal multiple small, oval, budding yeast, typically found within macrophages.1 Also typical of histoplasmosis is granuloma formation with caseous necrosis. Biopsy will reveal granulomatous tissue infiltrated with giant cells, lymphocytes, and numerous macrophages.8

Circulating *H. capsulatum* antigen can be detected in the urine or serum of patients with disseminated disease. Antibody levels can also be followed to detect response to treatment or recurrence of disease. However, for patients with less severe and chronic forms of pulmonary histoplasmosis, antigen detection only occurs in 10-20% of cases.1

Assays for antibodies to *H. capsulatum* include the complement fixation (CF) test and the immunodiffusion (ID) assay. A CF titer of 1:32 or a four-fold rise in titer is indicative of active infection. The ID assay is more specific than the CF assay and tests for M and H precipitin bands.1 However, serologic assays are rarely helpful in immunosuppressed patients who are unable to mount a significant antibody response.

Laryngeal histoplasmosis, as a form of disseminated infection, should initially be treated with amphotericin B for 1-2 weeks followed by itraconazole for severe cases, or only oral itraconazole for mild cases.1 Mucosal lesions typically respond within 6-8 weeks.2

**Conclusions**

Histoplasmosis of the head and neck may be more commonly encountered due to rising numbers of immunocompromised patients and increasing frequency of endemic fungal infections. Laryngeal histoplasmosis should be suspected in patients with chronic hoarseness or a laryngeal mass, particularly if immunosuppressed or living in endemic regions. If suspected, specific diagnostic modalities can be utilized in order to ensure that appropriate treatment is offered.

**References**


