Epiglottic Histoplasmosis Presenting in a Nonendemic Region

A Clinical Mimic of Laryngeal Carcinoma

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Histoplasma capsulatum is a dimorphic fungus endemic to North America. Histoplasmosis is primarily an inhalation-acquired mycosis that is encountered rarely outside of endemic regions. In nonendemic regions, histoplasmosis may present a diagnostic challenge and both clinical and laboratory vigilance are required to accurately identify infection. Unusual clinical presentations with limited physical findings may compound the difficulty in diagnosis. We describe a 78-year-old retired soil science professor who presented with an eroded epiglottic mass secondary to disseminated histoplasmosis in a nonendemic region (Alberta). Clinically, this mass was thought to represent a primary laryngeal carcinoma, as no other buccal or oropharyngeal ulcers were identified. Histoplasmosis was confirmed by tissue biopsy and a positive immunodiffusion test for immunoglobulin G. Disseminated histoplasmosis is often associated with laryngeal and oropharyngeal disease; however, isolated epiglottic histoplasmosis is rare. Histoplasmosis should be included in the differential diagnosis of neoplasms and chronic ulcers of the upper aerodigestive tract.

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Histoplasma capsulatum is a dimorphic fungus, closely related to Blastomyces dermatitidis, that is endemic to river basins of the United States and Canada, including the Mississippi, Missouri, Ohio, and St. Lawrence River valleys.1-4 Rare cases of histoplasmosis have been described in nonendemic regions and are difficult to recognize.3,5 Histoplasmosis is primarily an inhalation-acquired mycosis with rare cases of cutaneous inoculation histoplasmosis being described.1 In most immunocompetent hosts, H capsulatum infection is self-limited. Disseminated histoplasmosis may occur in immunocompromised hosts and in those exposed to large inoculums of fungal organisms.1,4 Oropharyngeal and laryngeal ulcers are common clinical manifestations of disseminated histoplasmosis.6 We describe a 78-year-old man with disseminated histoplasmosis who presented in a nonendemic region (Alberta) with an eroded epiglottic mass that was initially thought to represent a primary laryngeal carcinoma. This case illustrates that disseminated histoplasmosis should be included in the differential diagnosis of laryngeal neoplasms and chronic ulcers of the upper aerodigestive tract, even in patients who live in nonendemic regions.

REPORT OF A CASE

A 78-year-old man presented to his physician complaining of a 2-month history of progressive odynophagia associated with a 7-kg weight loss during this period of time. Further questioning revealed an 18-kg weight loss during the past 5 years. He also gave a history of night sweats on several occasions, sometimes severe enough to necessitate changing of bed clothes. There was no history of cough or hemoptysis. He had a negative smoking history and only occasionally consumed alcohol. He denied any changes in his voice. A barium swallow study suggested a slightly irregular and globular contour to the epiglottis. On physical examination, the buccal cavity and the oropharynx appeared normal and no neck lymphadenopathy was identified. Results of a cardiopulmonary examination were unremarkable. On laryngoscopy, the superior right free edge of the epiglottis showed an irregular mass with focal ulceration suggestive of an epiglottic carcinoma (Figure 1). The patient was taken to the operating room for a suspension laryngoscopy and biopsy. As the presumptive diagnosis was that of a neoplasm, no fresh tissue was submitted for microbiologic examination.

After pathologic examination of the epiglottic mass, the patient was further questioned with regard to his travel history. He revealed that he was a retired soil science professor who had an extensive travel history, including frequent travel to Africa and Asia. Three months prior to his clinical presentation, he had traveled to India for a 2-week period. Additional investigations were performed. A chest radiograph showed normal lung fields. Laboratory studies revealed a hemoglobin level of 11.8 g/dL, platelet count of 224 × 10^3/μL, and leukocyte count of 4.8 × 10^3/μL. The leukocyte differential, serum electrolytes, and renal function tests were within laboratory reference intervals. Blood cultures were drawn and held for a 3-week incubation period and were negative for bacterial and fungal pathogens. A H capsulatum immunodiffusion test was positive for immunoglobulin G.

The patient was treated with itraconazole 200 mg once daily.
Figure 1. Epiglottic mass identified at laryngoscopy.

Figure 2. Histology of epiglottic mass demonstrating sheets of eosinophilic histiocytes (hematoxylin-eosin, original magnification ×100).

Figure 3. Histiocytic intracellular inclusions with peripheral haloes (hematoxylin-eosin, original magnification ×400).

Figure 4. Uninucleated yeast forms morphologically resembling Histoplasma species (hematoxylin-eosin, oil immersion, original magnification ×1000).

Figure 5. Histoplasma organisms accentuated by periodic acid–Schiff stain (oil immersion, original magnification ×1000).

Figure 6. Histoplasma organisms accentuated by Gomori methenamine-silver stain (oil immersion, original magnification ×1000).
Within 2 weeks, his odynophagia had largely resolved. Within 6 weeks of therapy, his pain had resolved completely and his weight had begun to increase. He completed a 9-month course of oral antifungal therapy, at which point he had no further symptoms or evidence of active histoplasmosis.

**PATHOLOGIC FINDINGS**

Biopsies of the epiglottic mass showed fragments of a superficially ulcerated lesion overlying a dense histiocytic infiltrate (Figure 2). The histiocytes contained multiple intracellular inclusions with peripheral haloes (Figures 3 and 4). These intracellular inclusions stained with periodic acid–Schiff and Gomori methenamine-silver stains and were morphologically consistent with _Histoplasma_ species yeast forms (Figures 5 and 6). The organisms were small (3 μm), uninucleated, and lacked intracellular densities and broad-based budding. No hyphal fragments were identified. No foreign body giant cell reaction was present. There was no evidence of a primary or secondary neo-plastic process.

**COMMENT**

Like _B. dermatitidis_ and _Coccidioides immitis_, _H. capsulatum_ is a dimorphic fungus endemic to certain regions of North America.2 At body temperatures and temperatures greater than 35°C, _H. capsulatum_ grows primarily as a yeast, although hyphal fungal forms may be observed in intravascular infections1 and cases of endocarditis.8 Soil is the natural environment of _H. capsulatum_, and the fungus is often found in moist, acidic soils with high organic content.1 Large quantities of fungal organisms may be found in soils enriched by avian and bat excreta and these soils may remain infectious for years.1,13 Histoplasmosis is rarely encountered in nonendemic regions and may present a diagnostic challenge.5 These isolated cases of histoplasmosis are likely due to geographic microfoci of disease, in addition to reactivation of latent infections in hosts with a previous travel history to endemic areas.7,8 Inhalation of either fungal conidia or mycelial fragments is the primary mode of infection for histoplasmosis.1 Once inhaled, these fungal elements transform into yeast forms and may disseminate systemically. Primary pulmonary histoplasmosis in the vast majority (approximately 90%) of cases presents as asymptomatic or subclinical disease.1,14 Symptomatic hosts with primary pulmonary histoplasmosis often present with nonspecific symptoms that are self-limited. Immunocompetent hosts are able to control and limit infections with _H. capsulatum_; however, hosts with defective cell-mediated immunity, including patients with hematolymphoid malignancies, solid-organ transplants, and those exposed to chemotherapeutic and immunosuppressive agents, are at risk of developing progressive disseminated histoplasmosis (PDH).1,6 Acute PDH is also recognized as an acquired immunodeficiency syndrome (AIDS)–defining illness.1,3

Laryngeal and oropharyngeal involvement is commonly observed in disseminated histoplasmosis.6,9 Goodwin et al6 determined that 66% of patients with chronic PDH and 31% with subacute PDH developed laryngeal or oropharyngeal disease. Involvement of the larynx and oropharynx was seen in only 19% of patients with acute disseminated histoplasmosis. Epiglottic histoplasmosis has been described rarely.6,9,10–12 In a series of 29 patients presenting with acute, subacute, and chronic PDH, Goodwin et al6 described 58 otolaryngologic lesions with only a single one involving the epiglottis. In that same series, the tongue and the buccal mucosa were the most frequent sites of oropharyngeal histoplasmosis. The majority of their patients presented with painful ulcers; however, verrucous excrescences were also clinical presentations of oropharyngeal and laryngeal histoplasmosis. The diagnosis of histoplasmosis in the upper aerodigestive tract requires a high index of suspicion, as disease localized to the larynx and oropharynx may mimic both primary malignancies and tuberculosis.5,8,9,13,14 The diagnosis of disseminated histoplasmosis may be especially difficult as oropharyngeal and laryngeal disease may be the only evidence of systemic histoplasmosis.13,14 Laryngeal tuberculosis is rarely associated with concurrent oropharyngeal ulcers, whereas laryngeal histoplasmosis is often associated with multifocal oropharyngeal disease.8 Laryngeal tuberculosis has a tendency to involve the posterior larynx with sparing of the epiglottis, whereas histoplasmosis is more likely to involve the anterior larynx and epiglottis. The diagnosis of both laryngeal-oropharyngeal histoplasmosis and tuberculosis requires culture confirmation or tissue biopsy with microorganism identification.5,9,14

Depending on the host immune response, the histopathologic presentation of histoplasmosis is variable and may range from a dense histiocytic response to well-formed granulomata with or without necrosis.5,6 In profoundly immunocompromised hosts, there may be a subtle inflammatory response to _H. capsulatum_ and tissue necrosis may predominate.6 The histopathologic evaluation of laryngeal and oropharyngeal ulcers from patients with profound immune deficits should include special histochemical stains for fungi (eg, Gomori methenamine-silver). The yeast forms of _H. capsulatum_ are small (2–4 μm), uninucleated, and have single, narrow-based buds.1,13 _Histoplasma capsulatum_ may be confused with other microorganisms and must be distinguished from microforms of _B. dermatitidis_, which are multinucleated, have broad-based buds, and are often intermixed with larger, more typical _Blastomyces_ species yeast forms, and other fungi, including _Candida_ species and _Pneumocystis carinii_.15 Laryngeal and oropharyngeal involvement may also be seen with blastomycosis.9 In addition to tissue diagnosis and culture confirmation of _H. capsulatum_, serologic studies may be of some value in confirming infections, as demonstrated in our patient.1 Skin testing is rarely useful for the diagnosis of active histoplasmosis, as large proportions of populations in endemic regions are skin-test positive, indicating previous exposure.1,12

Our patient had an unusual presentation of chronic disseminated histoplasmosis as an ulcerated epiglottic mass. Clinically, this mass mimicked a laryngeal carcinoma and there were specifically no other oropharyngeal ulcers or masses to suggest an inflammatory or infectious process. The correct diagnosis of epiglottic histoplasmosis was established only after _Gomori_ methenamine-silver– and periodic acid-Schiff–stained tissue biopsies were obtained. The most significant aspect of this patient’s presentation was that his disseminated histoplasmosis developed in a nonendemic region (Alberta). His previous occupation as a soil science professor and his extensive travel history established a previous exposure history. His epiglottic presentation of chronic PDH is best explained by reactivation of latent disease, likely due to waning immunocompetence.

This case demonstrates that, with the mobility of pop-
ulations, infectious diseases may present in nonendemic regions and that both clinical and laboratory vigilance are required to accurately identify them. The otolaryngologic appearance of histoplasmosis is nonspecific and disseminated histoplasmosis should be included in the differential diagnosis of chronic ulcers and verrucous masses of the larynx and oropharynx.

References


