Case report

Oropharyngeal histoplasmosis: The diagnosis lies in the biopsy

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ABSTRACT

\textit{Histoplasma capsulatum}, a dimorphic fungus found world-wide, is endemic to regions of the Mississippi and Ohio River valleys and portions of Central and South America. Initial infection can present with acute pulmonary symptoms or remain clinically asymptomatic, with disease course generally guided by degree of inoculum and underlying immunosuppression. A chronic, progressive course of weight loss, oral ulceration, and fatigue has been associated with elderly males. We present a 79-year-old man with a chronic, progressive course of oral lesions, odynophagia, and weight loss who was found to have histoplasmosis on oral biopsy performed for suspicions of oropharyngeal squamous cell carcinoma. Histoplasma urine antigen, serum complement fixation antibody titers, and fungal tissues were all negative despite validated sensitivities in the > 90% range. Our case report highlights the critical role of tissue biopsy in establishing a diagnosis of oropharyngeal histoplasmosis.

Case report

A 79-year-old Haitian man with a three-year history of painful oral ulcerations, progressive dysphagia, and weight loss who presented to our medical center directly after arrival from Haiti. On evaluation, the patient complained of acute worsening of oral pain, odynophagia, dysphagia and a two-week history of hoarseness. He also described weight loss, generalized weakness, and an intermittent non-pruritic, keloid-like rash present on his torso and bilateral upper extremities. Nonspecific gastritis and a hiatal hernia were found on endoscopy; no further evaluation was performed and the patient was lost to follow-up. The patient traveled frequently between Haiti and New Jersey and had been a plantation farmer in Haiti since childhood. He worked primarily with vegetable crops, but had exposure to chickens, cows, and pigs. His sexual history was significant for multiple female sexual partners with only occasional condom use. He denied prior history of sexually transmitted diseases. He denied tobacco, alcohol, or illicit drug use.

On initial examination the patient was cachectic and appeared chronically ill. Vital signs included a temperature of 37.3 °C, heart rate of 84 beats per minute, respiratory rate of 16, and blood pressure of 221/105 mmHg. Oxygen saturation was 100% on room air. His weight was 42.9 kg with a body mass index of 14.8. He had pronounced bilateral wasting, bilateral erythema of the forehead and cheeks and diffuse left-sided facial swelling. Multiple 3-5 mm ulcerations were present throughout the oral cavity, including on the hard and soft palate, tongue, and buccal mucosa. There was diffuse oropharyngeal edema and mucosal pallor and dryness. He was breathing comfortably with no stridor or wheezing. Additional findings included bilateral anterior cervical chain lymphadenopathy and hypopigmented and hyperpigmented areas of skin on the thorax, abdomen and extremities, including the soles of both feet.

Significant laboratory findings included hyperkalemia (potassium 5.2 mg/dL), anemia (hemoglobin 11.6 g/dL) and hypoalbuninemia (albumin 3.3 mg/dL). Chest radiographs demonstrated pronounced airway narrowing and neck radiographs severe oropharyngeal and hypopharyngeal airway narrowing with subepiglottic stenosis. Computed tomography of the neck was performed and revealed diffuse thickening of the mucosal oropharynx, supraglottic larynx, aryepiglottic folds, piriform sinuses, and true/false vocal cords (Figs. 1 and 2). Subsequent evaluation by otolaryngology with laryngoscopy revealed a granular edematous epiglottis, right aryepiglottic fold, and nasal vestibules without evidence of any distinct masses.

Malignancy, autoimmune, and infectious etiologies were considered and further diagnostic studies were obtained. HIV antigen/antibody testing, HTLV, HSV, CMV, and RPR antibody tests were negative. His CD4 count was 345 cells/μL (normal 300–1400 cells/μL) with a decreased CD4 percentage of 21.3% (normal 28–57%) and an inverted CD4/CD8 ratio of 0.35 (normal 1.0–3.6). Histoplasma urine antigen and serum complement fixation antibody were negative. Interferon-gamma...
release assay (QuantiFERON®-TB Gold) was negative. Epstein-Barr virus IgM and IgG were both positive. ANA was positive at a low titer (1:160) with a non-specific pattern. C3 and C4 values were within normal limits. Anti-Smith, anti-RNP, anti-SSA/SSB, and Cl esterase inhibitor antibodies were negative. Serum protein electrophoresis was notable for an elevated IgG level of 1964 mg/dL, of which 30.7% was composed of gamma globulin. His sedimentation rate was 59 mm/h and C-reactive protein was 10 mg/L. Blood cultures, including fungal blood cultures, were negative. Throat cultures grew *Klebsiella pneumoniae* and *Serratia marcescens*.

Oral pharyngeal squamous cell carcinoma was considered the leading diagnosis and a biopsy of a labial mucosal ulcer was performed. Histologic examination of the biopsy revealed granulomatous mucositis with multinucleated giant cells containing multiple budding yeast forms (Fig. 3) that stained with Grocott’s methenamine silver (Fig. 4) and were consistent with histoplasma species. Staining for acid-fast organisms was negative. Histoplasma was not recovered from tissue fungal cultures.

On histologic identification of yeast consistent with *Histoplasma*, therapy with daily intravenous liposomal amphotericin B (5 mg/kg daily) was initiated [2]. Despite aggressive intravenous saline

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**Fig. 1.** Thickened mucosa throughout oropharynx, supraglottic larynx including the epiglottis, aryepiglottic folds, piriform sinuses, and false vocal cords. Narrowing of the airway including effacement of the piriform sinuses and vallecula. Mild thickening of the true vocal cords. Prominent soft tissue with erosive change in the maxilla in the midline.

**Fig. 2.** Thickened mucosa throughout oropharynx, supraglottic larynx including the epiglottis, aryepiglottic folds, piriform sinuses, and false vocal cords. Narrowing of the airway including effacement of the piriform sinuses and vallecula. Mild thickening of the true vocal cords. Prominent soft tissue with erosive change in the maxilla in the midline.

**Fig. 3.** Hematoxylin and eosin stained section demonstrating multiple multinucleate giant cells containing numerous organisms consistent with *Histoplasma* spp. (40×).

**Fig. 4.** Grocott’s methenamine silver stain demonstrating numerous organisms within the multinucleate giant cells (40×).
hydration, acute kidney injury developed after only three doses of amphotericin, necessitating a change in antifungal therapy to itraconazole suspension. Due to the patient’s extensive oropharyngeal inflammation and failed fiberoptic endoscopic gastroscopic evaluations, a percutaneous endoscopic gastrostomy was placed for nutrition and administration of itraconazole. Computed tomography of the chest, abdomen and pelvis obtained to evaluate for disseminated histoplasmosis were unremarkable. The patient had rapid clinical improvement in his symptoms with initiation of antifungal therapy. His serum itraconazole levels were measured and were therapeutic. He was discharged home with a planned 12-month course of itraconazole.

Discussion

Histoplasma capsulatum, the causative agent for most cases of histoplasmosis, is a dimorphic fungus found worldwide, with the exception of Antarctica. It is endemic in regions of the Mississippi and Ohio River valleys, as well as in Central and South America [2,4]. Infection typically occurs after inhalation of the organism’s microconidia and classically after exposure to bird and bat guano, but may occur anytime that there is significant disruption of organism-containing soil [1,2,5]. Following inoculation, some individuals may develop acute pulmonary histoplasmosis, which is characterized primarily by fever, non-productive cough, occasional hypoxia, and chest radiograph findings. A large proportion of those infected remain clinically asymptomatic, a finding that is related to both the degree of inoculating dose and state of immunocompetency. [1,2,4,6]. Cellular immunity is essential in clearing initial infection, but organisms may not be eradicated completely and reactivation of disease is possible [3,5].

In immunocompromised patients, initial dissemination by the reticuloendothelial system can result in invasion of bone-marrow structures and occasionally even the adrenal gland, manifesting symptomatically as fever, weight loss, oral ulcerations, lymphadenopathy, and splenomegaly [3,4,5,7]. This form of disseminated histoplasmosis has been well-studied in HIV-infected and immunosuppressed transplant populations and may be the first manifestation of AIDS in affected individuals [1,5]. In contrast, chronic progressive disseminated histoplasmosis, the condition that best characterizes our patient, occurs primarily in middle-aged or elderly men without obvious sources of immunosuppression. It typically presents as a long-term syndrome of weight loss, fatigue, wasting, and painful oral ulcerations, with the degree of weight loss suggestive of the duration of infection [1,3]. Our patient’s symptoms were chronic in nature, indolent in onset, and were not associated with any recognizable immunosuppression. Additionally, his labial biopsy demonstrated diffuse macrophage proliferation in addition to well-formed granulomas and abundant yeast, both characteristics of chronic progressive disease. We do not know if our patient’s decreased CD4 cell percentage and inverted CD4/CD8 ratio were due to his chronic infection and/or malnutrition, or whether he had underlying cellular immune dysfunction or dysregulation that predisposed him to infection. This is crucial, as studies suggest that resistance to histoplasma infection requires synchronicity between innate and adaptive immune systems, with augmented anti-microbial responses dependent on initial macrophage cytokine secretion [8,9].

Our patient highlights the critical role of tissue biopsy in establishing a diagnosis of oropharyngeal histoplasmosis, particularly in conditions mimicking malignancy [3]. It is likely the diagnosis would have been established earlier if an oral biopsy would have been performed when he first presented with oral ulcers and dysphagia. Although histoplasmosis was considered in our patient’s differential diagnosis, his histoplasma urine antigen (with sensitivity reported to be > 90% [2]), serum complement fixation antibody titers (with sensitivity reported > 90% [4], and fungal tissue cultures were all negative. The diagnosis for our patient, and his appropriate therapy, lie in the histopathology alone.

Conflict of interest

All authors report no conflict of interest relevant to this article. The patient provided consent for images to be used for educational purposes.

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