Histoplasmosis Presenting as a Hypopharyngeal Mass in an Immune Compromised Host

by Arnab Ray, Mona K. Gahunia

Histoplasmosis is a common infection in endemic areas among patients with a compromised immune system. Disseminated infection frequently involves the gastrointestinal system, but esophageal involvement with symptoms is rare. We present a case of an immune compromised patient presenting with dysphagia and odynophagia secondary to esophageal histoplasmosis. We discuss the clinical presentation, differential diagnosis, diagnostic approaches, and available treatments.

A 31-year-old African-American female presented to a local emergency department with a three week history of dysphagia, odynophagia and twenty pound weight loss in the last month. The patient also reported subjective fevers at home. Review of symptoms was significant for a rash which reportedly began on her face and spread to her arms.

The patient’s medical history was remarkable for HIV/AIDS diagnosed eleven years earlier with a most recent CD4 count of 5 mm$^3$ (6.5%). She had been on antiretroviral therapy during two prior pregnancies, but had no consistent follow-up for the last four years. Of note, she was diagnosed with esophageal candidiasis approximately three and a half months prior to this presentation. The patient had no known drug allergies and her only medication was trimethoprim/sulfamethazone double strength once daily.

On initial presentation, the patient had a temperature of 99.3 F and all other vital signs were normal. The patient was cachectic and ill-appearing. She had poor dentition with a foul oropharyngeal odor. On closer examination, she also had a visibly atrophic uvula, multiple erythematous patches in her oropharynx and shotty anterior cervical lymphadenopathy. In addition, a maculopapular rash with lesions of varied sizes was noted on her face and upper extremities with minimal extension to the lower extremities and sparing of the palms and soles. The remainder of the patient’s physical exam was unremarkable.

The patient’s initial blood work revealed a white blood cell count of 4.0 $\times$ 10$^3$ $\mu$L with 85% segmented neutrophils, 4% band forms, 5% lymphocytes, 4% monocytes and 2% eosinophils. She had a microcytic anemia with a hemoglobin of 9.1 gm/dL and mean corpuscular volume of 78 fl. The patient’s three AFB sputum smears were negative. In addition, she had a negative cryptococcal antigen & rapid plasma regain (RPR). All other initial laboratory evaluation was unremarkable.

Endoscopy was performed and revealed a large, firm, friable mass which distorted most of the hypopharynx in a hemi-circumferential manner. There

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was no evidence of candida or cytomegalovirus esophagitis and there was a high level of suspicion for malignancy.

The pathology report from the hypopharyngeal biopsy revealed disseminated histoplasmosis characterized by the presence of polypoid granulation tissue with marked acute and chronic inflammation and some organisms within macrophages. Gomori’s methenamine silver (GMS) (Figure 1) and periodic acid-Schiff (PAS) (Figure 2) stains showed numerous, small budding yeast and gastroesophageal junction biopsy showed reflux esophagitis.

Subsequently, the urine histoplasma antigen was resulted as positive (10.59 ng/mL). In addition, a skin biopsy was consistent with disseminated histoplasmosis. It should also be noted that four additional sets of blood cultures during the hospital course were all negative.

After the pathology report was obtained, the patient was started on amphotericin B one mg/kg daily for four weeks which was to be followed by a regimen of itraconazole five to ten mg/kg daily in two divided doses for a minimum of three months. The patient had a good response to therapy with resolution of fever and rash and marked reduction in pain. In addition, the patient had adequate oral intake of liquids and solids prior to discharge home.

**ESOPHAGEAL HISTOPLASMOSIS CASE DISCUSSION**

**Background**

Histoplasmosis infections caused by *Histoplasma capsulatum*, an ascomycete, were first described in humans in 1906 by Samuel Darling; therefore, it is also known as Darling’s disease. Since that time, it has been described in a variety of patients, both immune competent and immune compromised. The majority of infections are limited to those residing in endemic regions in the Americas, Africa and Asia or those with a history of travel or prior residence in these areas. There are two varieties of *H. capsulatum* that cause disease in humans, *var capsulatum* and *var dubiosii* which differ in geographic distribution (the latter being generally confined to Africa).

Infection is believed to occur after inhalation of microconidia of the mold phase of the organism from a contaminated site, usually soil with an accumulation of bird and bat excrement. After inhalation and localization to the respiratory system, the mold transforms into yeast form and then spread hematogenously to other organ systems, including the gastrointestinal sys-
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tem. Exposure to *H. capsulatum* in endemic areas is widespread, by some estimates as high as 80% of young adults have been exposed; however, clinical disease is only seen in a limited number of cases secondary to an appropriate cell-mediated immune response (1). Case reports classically involve farmers, chicken coop cleaners, and pipe line workers. Clinical disease is usually related to a high degree of inoculum or an immunosuppressed state such as in the case of HIV/AIDS, transplant recipients and those taking tumor necrosis factor antagonists.

The spectrum of clinical disease ranges from self-limited acute pulmonary infection to chronic cavitary pulmonary disease to granulomatous or fibrosing mediastinitis to focal organ-specific diseases to progressive disseminated disease. In states of immunosuppression, severity of clinical disease is usually exaggerated. In patients with AIDS living in endemic areas the incidence of progressive disseminated histoplasmosis (PDH) is as high as five percent (2).

In this report we discuss an unusual manifestation of disseminated disease presenting as a hypopharyngeal mass. Gastrointestinal manifestations of histoplasmosis can be a result of focal disease or PDH. Although 70–90% of autopsy cases of patients with Histoplasma reveal gastrointestinal involvement, it is relatively uncommon to present with symptoms referable to the gastrointestinal tract. Diarrhea appears in about 20% of patients. On physical examination, hepatomegaly and splenomegaly are commonly seen due to dissemination to the reticuloendothelial system. Lesions can occur anywhere along the length of the gastrointestinal tract, although, more commonly, Histoplasma will manifest in the right side of the colon, possibly due to the abundance of lymphoid tissue found in the Peyer’s patches. This is followed in frequency by small bowel involvement. As a result of such localization, Crohn’s disease, adenocarcinoma, and a nonspecific colitis are usually in the differential diagnosis.

Clinical Presentation

Histoplasmosis involving the esophagus is especially rare, but when it does occur it can manifest with varied presentations. Schneider et al. describe a case of an ulcerated submucosal mass in the mid esophagus occluding two-thirds of the lumen in an otherwise healthy 15 year old male. At surgery, the mass was found to be a necrotic lymph node with methenamine-silver stain positive for *H. capsulatum*. Schneider notes that esophageal involvement typically occurs only when posterior mediastinal lymph nodes are involved (3). Incidentally, this patient had cleaned out a chicken coop two years prior to presentation.

Esophageal histoplasmosis can also present with melena, as in a case described by Forsmark et al. A 49 year old gentleman with AIDS taking Coumadin for a DVT presented with melena and a fever, but without dysphagia or odynophagia. EGD revealed multiple, small, round, umbilicated submucosal nodules ranging from 3-8 mm. in the distal half of the esophagus. The remaining esophageal mucosa was erythematous and friable with shallow erosions, but no plaque formation. Esophageal biopsies were positive for numerous organisms in the squamous mucosa consistent with Histoplasmosis (4).

Histoplasmosis can also involve the esophagus indirectly. Steiner et al. report three, otherwise healthy, children from the ages of 8–14 who presented with dysphagia and odynophagia. They were found to have mid-esophageal diverticula resulting from traction induced fibrotic changes from para-esophageal lymph node granulomatous inflammation. Other diseases which act in this manner are tuberculosis, anthracosis, sarcoidosis, and radiation induced mediastinitis. The symptoms resolved with medical therapy in all of these patients.

A chart review of thirteen benign broncho-esophageal fistulas done at Massachusetts General Hospital revealed that three of the cases were due to histoplasmosis. All three of these patients lived in endemic areas. It is interesting to note, that although the left main bronchus has a more intimate anatomic relationship to the esophagus, all of the broncho-esophageal fistulas in these patients communicated between the right main bronchus and the distal esophagus between 27 and 30 cm from the incisors. This is likely due to mediastinal involvement of the lymph nodes which lie between the right bronchus and the esophagus (5).

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Diagnosis

Biopsy of a focal site or bone marrow that yields characteristic histopathologic findings is the mainstay of diagnosis. Hematoxylin and eosin (H&E) stains usually show a halo around the yeast due to retraction of the basophilic cytoplasm from the cell wall, if there are an abundant number of organisms. Cells typically stain positive for Gomori’s methenamine-silver and periodic acid-Schiff staining. Surrounding macrophages form granulomas and contain the small rounded yeast forms in clusters. Granulomas are typically accompanied by lymphocytes, plasma cells, neutrophils, and eosinophils (6).

Culture is less clinically useful because multiple specimens are usually required to yield a positive result and growth can take four to six weeks.

Another diagnostic tool is antigen detection, specifically in the urine. Published reports reveal that, in cases of disseminated histoplasmosis in patients with AIDS, sensitivity of urine antigen detection was 95% versus 86% for serum antigen (7). The sensitivity is not known when the disease is just confined to the gastrointestinal tract. Urine antigen levels can also be followed to assess response to treatment.

The role of serology has limited utility to specific cases or presentations (chronic or acute pulmonary histoplasmosis). In a series of twenty-five AIDS patients with gastrointestinal histoplasmosis, serologic IgG testing was only positive in four out of nine patients and urine antigen testing was positive in three out of four patients (8).

Treatment

Systemic antifungal therapy is the basis of treating gastrointestinal histoplasmosis. Induction therapy with amphotericin B is superior to itraconazole, with an 80% response rate. Itraconazole may be used in mild to moderate cases and for prevention of relapse after initial induction with amphotericin B (8). Relapse rates may be as high as 80% in AIDS patients with disseminated histoplasmosis (6); therefore, a chronic suppressive regimen is recommended until immune reconstitution with antiretrovirals can be achieved (2).

With mediastinal histoplasmosis involving the esophagus, no studies have compared esophageal stenting for palliation against surgical or medical therapies. Neither approach is likely to help when mediastinitis reaches the fibrosing stage.

In conclusion, our patient responded very well to standard therapy. Continued success of treatment as an outpatient will depend on monitoring of clinical symptoms, itraconazole levels and histoplasma urine antigen levels as well as immune reconstitution. In endemic areas, it is important to remember the varied and often unforeseen presentations of H. capsulatum, especially in an immune compromised host, including manifestations specific to the gastrointestinal system.

References