Review

Colonic Histoplasmosis: A Difficult Diagnostic Problem

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Histoplasmosis is caused by inhaling the microconidia (spores) formed by the environmental mold *Histoplasma capsulatum*, an organism endemic to the Ohio and Mississippi River Valleys in the United States. Histoplasmosis is the most common endemic fungal disease in both normal and immunocompromised hosts; several hundred thousand people are infected with *H. capsulatum* yearly. Healthy hosts, unless they inhale a large number of conidia, remain asymptomatic or have only mild pulmonary symptoms when exposed to *H. capsulatum*.

H. capsulatum is one of several thermally dimorphic fungi; at 35–37° C in the lungs, it transforms from a mold state into a yeast state. The yeasts are phagocytized by the alveolar macrophages and are then able to multiply in that intracellular milieu until T cell–mediated immunity against *H. capsulatum* develops and arms the macrophages to kill the invaders.[1] Before immunity develops, in almost all cases, the organism is disseminated by the macrophages moving to local mediastinal and hilar lymph nodes and, more widely, to the liver, spleen, lymph nodes, and other organs. This dissemination is asymptomatic in most individuals but can lead to progressive disseminated infection in people who are immunosuppressed. *H. capsulatum* has the ability to remain within the host for years after the initial infection. This presence allows reactivation to occur when cellular immunity is diminished, sometimes long after the individual has left the endemic region. Risk factors for dissemination associated with either primary or reactivated infection include age extremes, AIDS, hematologic cancers, bone marrow or solid organ transplantation, the use of corticosteroids, tumor necrosis factor antagonists and other immunosuppressive agents, and rare congenital diseases such as interferon-gamma receptor deficiency and hyperimmunoglobulin M syndrome.[2] In some cases, older patients with no identifiable risk factors develop progressive disseminated infection; it has been postulated that an unknown defect in cellular immunity leads to an inability to contain the infection in these hosts.[3]

All gastrointestinal (GI) forms of histoplasmosis are likely manifestations of disseminated disease.[4] Acquisition by the GI route through water or food ingestion has been suggested, but this has never been proven and remains a very unlikely possibility. The colonic histoplasmosis described in the case presented by Ghassemi and associates is most likely a manifestation of disseminated histoplasmosis in an immunosuppressed transplant patient.[5] Unfortunately, this cannot be verified without further data regarding other specific clinical manifestations in this case.

There is a striking discrepancy between the incidence of clinically diagnosed GI disease due to *H. capsulatum,* which is found in only an estimated 3–12% of patients with disseminated histoplasmosis,[6] and the high frequency of GI involvement in autopsy series, in which *H. capsulatum* could be identified in the GI tract of as many as 70% of cases of disseminated histoplasmosis.[3]

H. capsulatum can be found throughout the GI tract, from the mouth to the anus.[7-10] It is likely that lymph nodes throughout the GI tract, especially the numerous lymph nodes in the ileocecal region, are seeded during the course of hematogenous dissemination. The pathologic findings of GI tract histoplasmosis include mucosal ulceration, diffuse lymphohistiocytic infiltration of the bowel wall, submucosal nodules, polypoid lesions, and obstructing masses. The terminal ileum and the colon are the most frequently involved organs,[8] and bowel perforation and hemorrhage are noted as the most serious complications.

The most common presenting symptoms of GI histoplasmosis are abdominal pain and diarrhea.[9,10] The diarrhea is often intermittent and typical of that seen in many other diseases. Unremitting diarrhea with malabsorption has been noted,[11] as has bloody diarrhea mimicking inflammatory bowel disease.[12] Patients with AIDS are often thought to have infections with other organisms that cause diarrhea such as *Giardia*, *Entamoeba*, or cytomegalovirus,[9] and the diagnosis of histoplasmosis is considered only after a biopsy shows the characteristic organisms. Many patients have only mild symptoms of abdominal pain and occasional diarrhea but

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have prominent systemic manifestations of disseminated histoplasmosis, including fevers, night sweats, weight loss, and fatigue.

Radiologic findings include bowel wall thickening, as in the case reported by Ghassemi and coworkers, mass-like lesions, signs suggesting small-bowel obstruction, and, occasionally, free intraperitoneal air, if there is bowel perforation. Because GI involvement is part of disseminated infection, the findings of hepatosplenomegaly, diffuse nodular or interstitial pulmonary infiltrates, and generalized lymphadenopathy (when noted on imaging studies) can help direct the physician to the possibility of histoplasmosis. Mucosal ulcerations, as described by Ghassemi and associates, are the most common endoscopic finding and may be multiple or unifocal; polypoid lesions, strictures, and obstructing masses have also been noted on endoscopy.[8,9]

The case presented by Ghassemi and colleagues highlights the increased risk of disseminated histoplasmosis in transplant recipients. The incidence in a recently reported prospective surveillance study was 1.6 per 1,000 transplants performed. The greatest incidence was noted among liver transplant recipients, but, not surprisingly, the largest number of cases was seen in kidney transplant recipients.[13] During a massive outbreak of histoplasmosis in Indianapolis in the 1970s, the rate of infection among renal transplant recipients increased from 0.5% prior to the outbreak to 2.1%.[14] Although it is emphasized in the case report that the patient lived in a nonendemic area (ie, San Francisco), she must have either traveled to or previously lived in an area endemic for *H. capsulatum*; presumably, this patient developed reactivated histoplasmosis after she left the endemic area.

Histoplasmosis has been reported to develop from several weeks to as long as 20 years after transplantation.[15] Transmission of infection from the donor organ has been documented in fewer than 10 patients and never as long as 3 years after the transplant, which is the time frame in this case.[15,16] Thus, it seems highly unlikely that the histoplasmosis in this patient was related to the donor kidney.

GI histoplasmosis has not been well characterized in the transplant population, but given the fact that disseminated infection is the rule in transplant recipients, it is likely that GI involvement is common. However, only a few cases, including this one, have had prominent GI symptoms. Persistent profuse watery diarrhea has been noted in two other transplant recipients, one of whom developed ileal perforation and died.[17,18] Other recipients have had mild GI symptoms that resolved with antifungal therapy.[16]

In this case, the diagnosis of histoplasmosis was established by histopathologic examination of biopsy material from mucosal ulcerations. It would have been preferable to have culture evidence of *H. capsulatum*, as well. However, the appearance of the 1–4 μm tiny oval budding yeasts is mimicked by only three organisms: *Leishmania* species and *Penicillium marneffei*, neither of which occur in the United States, and *Candida glabrata*, which has different clinical manifestations. Thus, it is highly likely that this patient did indeed have histoplasmosis.

Growth of *H. capsulatum* from tissues can take as long as 4–6 weeks and often confirms a presumptive diagnosis of histoplasmosis that was made weeks earlier. In addition to histopathologic examination using special stains to visualize the organisms, another rapid test for disseminated histoplasmosis is the detection of *H. capsulatum* antigen in urine or serum by enzyme immunoassay (EIA).[19] The sensitivity of the EIA assay for disseminated histoplasmosis in AIDS patients is reported to be approximately 90%. The test is more sensitive in urine than in serum and is useful for monitoring the efficacy of therapy and relapse during or after therapy. False-positives can result with other disseminated fungal infections, including blastomycosis and coccidioidomycosis. There are few reports on the usefulness of the antigen assay in GI histoplasmosis.[9] It would be of interest to perform this assay in patients who have primarily GI symptoms and only a few constitutional symptoms to assess its usefulness in that setting.

Guidelines for the treatment of histoplasmosis have been recently updated by the Infectious Diseases Society of America.[20] Initial therapy for patients who have moderately severe to severe histoplasmosis should consist of a lipid formulation of amphotericin B at a dosage of 3–5 mg/kg. After patients show clinical improvement and are able to absorb oral medications, therapy can be changed to itraconazole. Patients who have mild to moderate disease can be treated with oral itraconazole as initial therapy. Itraconazole is best administered as an oral solution at a dosage of 200 mg three times daily for 3 days as a loading dose and then twice daily for 12 months. Itraconazole levels should be monitored after the second week of therapy to be certain that serum levels are at least 2 μg/mL. The oral solution is given on an empty stomach. If the patient cannot tolerate the solution, capsules can be substituted. Itraconazole capsules must be given with food and require acid for absorption, so acid-inhibiting drugs cannot be prescribed for these patients. Fluconazole has been shown to be less effective than itraconazole for the treatment of histoplasmosis. The role of the newer azoles, voriconazole and posaconazole, has not been established for histoplasmosis, and echinocandin antifungal agents are not effective and should not be used.[20]

Most patients with disseminated histoplasmosis respond well to antifungal therapy. Early diagnosis of GI involvement with *H. capsulatum* is important in the

prevention of bowel perforation and hemorrhage, the two most serious complications of this disease. The realization that histoplasmosis can occur years after exposure in an immunosuppressed patient who no longer resides in an area endemic for the organism is key to early diagnosis. Histopathologic examination of the involved tissues for fungi and the use of the EIA assay for *Histoplasma* antigen in urine or serum are rapid diagnostic methods that contribute to an early presumptive diagnosis of disseminated histoplasmosis and initiation of appropriate treatment.

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