Intestinal histoplasmosis in an immunocompromised patient. A case report

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Background: Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*, with gastrointestinal involvement being an uncommon manifestation, particularly in immunocompromised individuals. Diagnosis is often delayed due to nonspecific symptoms and clinical resemblance to inflammatory bowel disease (IBD). We report the case of a 34-year-old female with a history of renal transplantation on immunosuppressive therapy, later transitioned to hemodialysis due to graft rejection. She presented with a three-month history of chronic diarrhea with intermittent blood and mucus, fever, asthenia, weight loss, and a nonspecific rash. Initial studies revealed leukopenia, renal dysfunction, and inflammatory diarrhea without parasitic etiology. Infectious serologies, including HIV and viral panels, were negative. Empirical treatment for suspected IBD with mesalamine was ineffective. Colonoscopy showed ulcerative colonic lesions. Histopathologic evaluation of biopsies revealed numerous intracellular yeasts consistent with Histoplasma capsulatum, confirming intestinal histoplasmosis. Antifungal therapy with liposomal amphotericin B was initiated, with clinical improvement in gastrointestinal symptoms. Unfortunately, the patient succumbed to severe hospital-acquired pneumonia during hospitalization. This case underscores the diagnostic challenge of intestinal histoplasmosis, particularly in immunosuppressed patients, due to its overlap with IBD. Prompt recognition and appropriate antifungal therapy are critical. Clinicians must maintain a high index of suspicion for fungal infections in endemic areas or among high-risk patients presenting with chronic gastrointestinal symptoms.

Key words: Histoplasmosis, chronic diarrhea.

Histoplasmosis is a systemic fungal infection caused by the dimorphic fungus *Histoplasma capsulatum*, endemic in various regions of Latin America. While pulmonary involvement is most common, dissemination to extrapulmonary sites—including the gastrointestinal tract—can occur, particularly in immunocompromised individuals such as those with HIV/AIDS, organ transplantation, or receiving corticosteroid therapy. Gastrointestinal histoplasmosis (GIH) represents a rare but significant diagnostic challenge, as it can mimic inflammatory bowel disease (IBD) both clinically and histologically. This report describes a case of intestinal histoplasmosis in a post-transplant patient with chronic diarrhea, initially misdiagnosed as IBD, highlighting the importance of considering opportunistic infections in differential diagnoses, especially in endemic areas.

Case report

The case of a 34-year-old immunocompromised female patient with a clinical history of chronic diarrhea is presented. She has a medical record of kidney transplantation 5 years ago with immunosuppression based on tacrolimus, mycophenolate and prednisone, with subsequent graft rejection and new start of renal replacement therapy with hemodialysis.

The patient's clinical history shows the presence of diarrhea with mucus and blood occasionally for 3 months, accompanied by fever, asthenia, weakness, weight loss, and a generalized, nonspecific rash. Her initial laboratory studies showed leukopenia and signs of impending renal failure. The coprological examination showed signs of

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Comparison of Different Diagnostic Test on Disseminated Cases				
Test	AIDS	OIC	NIC	All
Culture	70.8	76	77.8	74.2
Histopathology	72	74.4	98	76.3
Antigen	94.6	93.1	73.3	91.8
Antibody	78.9	71.2	88.9	75

Table 1. Comparison of different diagnostic test sensitivity for detection of disseminated histoplasmosis. AIDS acquired immunodeficiency syndrome, OIC other causes of immunocompromise, NIC non-immunocompromised. Modified from Hage et al 2011.

inflammatory diarrhea, and no parasites were isolated in the examination. Tests for HIV, hepatitis B, hepatitis C, cytomegalovirus, and Epstein-Barr virus were negative. She was evaluated by a physician who suspected inflammatory bowel disease, who started a therapeutic trial with mesalamine without obtaining improvement.

Subsequently, a colonoscopy was performed as part of the diagnostic approach where macroscopically ulcerative lesions were observed in the colon mucosa. The pathology results show biopsies of the ascending and descending colon, sigmoid colon and rectum, showing acute ulcerative colitis associated with abundant yeasts compatible with *Histoplasma capsulatum*. The ileal biopsy is reported with normal findings.

Based on these results, we initiated treatment for intestinal histoplasmosis with liposomal amphotericin B at a dose of 5 mg/kg/day intravenously with the goal of completing 2 weeks of initial treatment and then continuing itraconazole as manteinement treatment. After completing the first week of treatment, the diarrhea stopped. However, during hospitalization the patient developed severe hospitalization-associated pneumonia, and despite life support and ventilatory management, she unfortunately died.

Discussion

1. Epidemiology

In Latin America, histoplasmosis is highly endemic, with a prevalence of 32%. Intestinal manifestations occur in 2–3% of cases, characterized by abdominal pain, diarrhea, and fever. Histoplasmosis can affect the entire gastrointestinal tract, from the oral cavity to the anus, being the ileum and colon the most commonly involved segments. Colonic histoplasmosis may appear in endoscopy as either an ulcerative or pseudotumoral form. Most common complications are gastrointestinal hemorrhage, bowel obstruction, or intestinal perforation.

2. Microbiology and Pathogenesis

Histoplasmosis in humans is primarily caused by *Histoplasma capsulatum* var. *capsulatum* and var. *duboissi*, dimorphic fungi with expanding geographic distributions due to climate change and the growing population of immunocompromised individuals. *H. capsulatum* exhibits thermal dimorphism: it exists in the mycelial phase in the environment at ambient temperatures and transitions to a yeast phase at 37°C or within the human host. In its environmental form, the fungus produces hyphae (1.25–2.0 µm in diameter) that generate two types of conidia—macroconidia (8–15 µm) and microconidia (2–5 µm), the latter being the presumed infectious form due to their aerosolization potential. Once inhaled into the lungs, the microconidia convert into yeast cells, which are oval, thin-walled, and measure 2–5 µm in diameter.

The host immune response, particularly cellular immunity, has a critical role in controlling

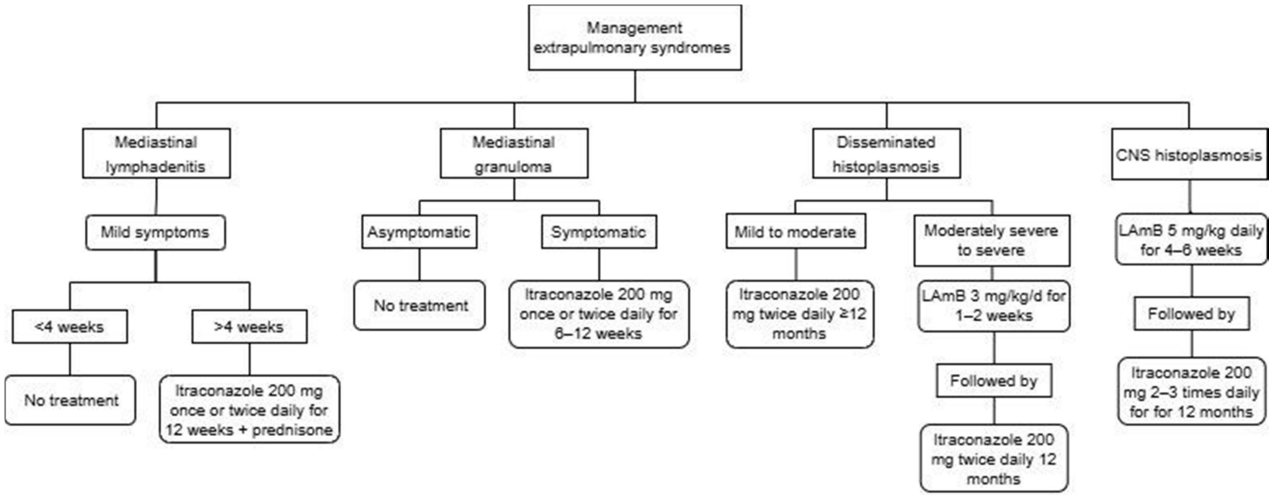

Figure 1. Management of the extrapulmonary histoplasmosis syndromes, including intestinal histoplasmosis (similar to disseminated histoplasmosis). LAmb liposomal amphotericin B, CNS central nervous system. Modified from Munoz et al 2025.

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Histoplasma infection. Neutrophils are among the first responders in the lung, limiting early fungal proliferation. T-cell–mediated immunity is central to disease resolution; CD8+ T cells contribute to the initial clearance of yeast cells, while CD4+ T cells are essential for long-term survival. Activated macrophages, stimulated by cytokines such as IL-12 and IFN-γ, play a key role by exerting fungicidal activity against intracellular yeasts. In patients with disseminated histoplasmosis—typically those with impaired cellular immunity—macrophages are often engorged with yeast forms, reflecting the organism's ability to survive and proliferate intracellularly. Failure to activate macrophage fungicidal mechanisms is thought to be a major immunologic defect in such individuals. Other cytokines, including TNF-α, IL-17, and GM-CSF, also contribute to protective immunity.

3. Diagnostic approach

The diagnosis of disseminated histoplasmosis requires microscopic demonstration or isolation of *Histoplasma* from extrapulmonary sites. Other tests such as *Histoplasma*-specific antibodies, antigen detection, and PCR can be used to help make the diagnosis, with a varying diagnostic performance (table 1).

Although cultures should be performed in all suspected cases, they have a slow growth rate (4-6 weeks) which makes them of little use for timely initiation of treatment. Antibody tests both by immunodiffusion and complement fixation are useful in the chronic forms of disseminated histoplasmosis, but they may be negative in acute illness and are often negative in patients who are immunocompromised.

Rapid diagnosis is better achieved either by urine and serum antigen detection or cytologic/histopathologic examination obtained from tissue samples, respiratory secretions or blood smear. Antigen detection, particularly via urinary ELISA, shows high sensitivity in disseminated disease (up to 95%) and is valuable for both diagnosis and monitoring treatment response. The histopathologic examination of intracellular yeast in macrophages is better visualized using Wright staining, Gomori Methenamine Silver or Periodic Acid-Schiff (PAS) staining.

4. Differential diagnosis

Gastrointestinal histoplasmosis (GIH) can mimic the clinical, endoscopic, and histopathological features of inflammatory bowel disease (IBD), particularly Crohn's disease. Therefore, a comprehensive approach is required, considering epidemiological, clinical, endoscopic, histopathological, and laboratory factors.

In the clinical and epidemiological evaluation, key factors include residence in or recent travel to areas endemic for Histoplasma capsulatum, which serves as a critical differentiating factor from IBD, as the latter lacks specific geographic associations. Risk factors for GIH include immunosuppression (e.g., HIV, organ transplantation, chronic alcoholism, corticosteroid therapy). Symptoms shared by both conditions such as diarrhea, abdominal pain, weight loss, fatigue, fever, oral or pharyngeal ulcers may cause diagnostic confusion. Less common symptoms like night sweats and respiratory signs are more suggestive of GIH.

Endoscopically, both conditions may present with aphthous ulcers, erosions, or chronic inflammation in the terminal ileum and colon. However, GIH lesions tend to be more diffuse or patchy, with deeper, irregularly bordered ulcers in advanced cases.

Histopathologically, GIH shows chronic inflammation and non-caseating granulomas resembling Crohn's disease. Special fungal stains, such as Grocott-Gomori's methenamine silver (GMS) and periodic acid-Schiff with diastase (PAS-D), are essential to detect intracellular yeast forms of *H. capsulatum*. Thus, requesting fungal staining for biopsies in patients suspected of having IBD particularly in endemic regions or high risk individuals is crucial.

The use of fungal biomarkers, such as *Histoplasma* antigen in urine or serum, tissue PCR, serological tests, fungal cultures, and IBD markers (e.g., ASCA, ANCA), is key to ruling out differential diagnoses. These steps are vital in endemic areas or high-risk populations to avoid unnecessarily immunosuppressed patients.

5. Treatment

The therapeutic management of histoplasmosis depends on the clinical presentation, disease stage, severity, and the patient's immune status. In general, itraconazole and liposomal amphotericin B constitute the cornerstone pharmacological agents. Figure 1 summarizes the antifungal regimens in presentations of extrapulmonary histoplasmosis, including intestinal histoplasmosis.

Conclusion

This case highlights the importance of considering opportunistic infections such as intestinal histoplasmosis in immunocompromised patients presenting with chronic diarrhea. Endoscopic and histopathological evaluation are key to establishing the differential diagnosis. Despite adequate antifungal

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treatment, immunocompromised patients are vulnerable to other infectious and noninfectious complications that can worsen the prognosis. This demonstrates the vulnerability of immunocompromised post-transplant patients, who require vigilance and multidisciplinary care.

Conflicts of interests

None declared by the authors.

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