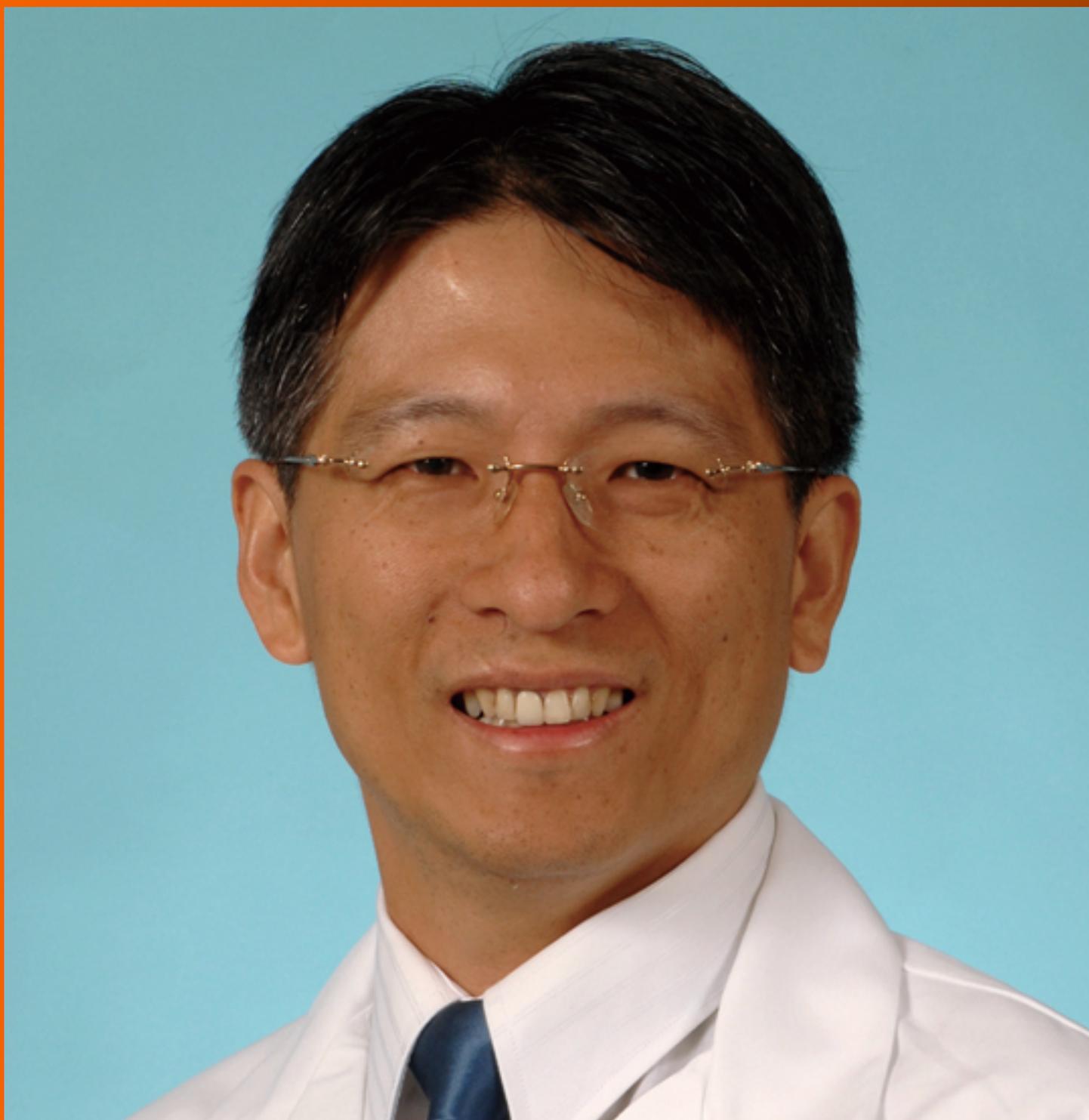


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## Histoplasmosis and inflammatory bowel disease: A case report

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### Abstract

#### BACKGROUND

Infection with *Histoplasma capsulatum* can lead to a disseminated disease involving the gastrointestinal tract presenting as diffuse abdominal pain and inflammatory diarrhea which may mimic inflammatory bowel disease (IBD).

#### CASE SUMMARY

In the current report, we discuss the case of a 41-year old male who presented to the emergency department with complaints of high-grade intermittent fevers and severe abdominal pain with associated diarrhea and hematochezia. Laboratory results demonstrated transaminitis and elevated erythrocyte sedimentation rate, C-reactive protein and ferritin levels. The patient's presentation was thought to be an exacerbation of his underlying IBD, but further investigations revealed a positive *Histoplasma* antigen in the urine. The patient was offered a colonoscopy and biopsy to confirm the diagnosis; however, he refused. He was treated with itraconazole and showed significant improvement of his symptoms, thereby confirming the diagnosis of gastrointestinal histoplasmosis.

#### CONCLUSION

Here within, we provide a review of IBD, evaluation of chronic diarrhea, and gastrointestinal histoplasmosis.

**Key Words:** Histoplasmosis; Inflammatory bowel disease; Intestine; Endoscopy; Gastroenterology; Case report

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**Core Tip:** Histoplasmosis can lead to a disseminating disease state affecting a large number of organ systems, leading to a wide range of pathology. This includes the gastrointestinal tract. We present herein, a case of gastrointestinal histoplasmosis in a patient with long standing ulcerative colitis that presented in a manner very similar to acute exacerbation of inflammatory bowel disease. This case highlights the importance of keeping gastrointestinal histoplasmosis amongst the differential diagnoses in cases that present similarly to acute exacerbation of inflammatory bowel disease in order to prevent inappropriate delays in diagnosis, unnecessary procedures, and increased morbidity and mortality.

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## INTRODUCTION

*Histoplasma capsulatum* (*H. capsulatum*) var. *capsulatum* is a dimorphic fungus that is known to have prevalence throughout the world. In the United States, *Histoplasma capsulatum* is mainly endemic in the Ohio and Mississippi valley regions<sup>[1]</sup>. In the environment, it exists in its hyphal form, producing spores which are inhaled by humans initiating the infection<sup>[2]</sup>. In the body, the spores transform into the yeast phase, evading intercellular killing and being transported by macrophages to any organ in the body. This leads to disseminated histoplasmosis (DH). Dissemination to the gastrointestinal (GI) tract, known as gastrointestinal histoplasmosis (GIH), most commonly involves the colon and terminal ileum<sup>[3]</sup>. The most common presenting symptoms in patients with GIH are abdominal pain and inflammatory diarrhea<sup>[4]</sup>. Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the intestinal mucosa through a complex immune mediated mechanism. The 2 main subtypes of IBD, Crohn's disease and ulcerative colitis (UC), are based on the histological involvement of the bowel. Common symptoms of IBD include diarrhea or constipation, hematochezia, severe diffuse abdominal pain, unintentional weight loss, significantly reduced appetite, fatigue and fever. Inflammatory diarrhea is a common feature seen both in GIH and IBD. The similarities in presentation, the pattern of the involvement of the gastrointestinal (GI) tract and the associated inflammation is the reason GIH is considered an IBD mimic. However, it is not commonly considered as one of the differential diagnoses in these patients. In patients with diagnosed IBD, GIH may be mistaken for an acute exacerbation of the underlying pathology. Our case report and review of the literature provides a step by step approach regarding IBD, GIH, and evaluating patients with chronic diarrhea. We strongly advocate and urge physicians to test patients with inflammatory diarrhea for *H. capsulatum*, particularly in endemic regions and those diagnosed with IBD presenting with a clinical picture suggesting exacerbation. Early diagnosis of GIH prevents inappropriate or delayed therapy, unnecessary surgical interventions and adverse outcomes.

## CASE PRESENTATION

### Chief complaints

A 41-year old male presented to the emergency department (ED) with chief complaints of high-grade intermittent fevers and severe abdominal pain.

### History of present illness

The patient described the fever as episodic, high grade (maximum temperature of 103F), without chills or rigors, and associated with a non-productive cough for one week. He also complained of severe, intermittent, diffuse abdominal pain associated with diarrhea and hematochezia for 2 d prior to this ED visit. He did not have a sore throat, rhinorrhea, abdominal pain, joint pain or rash.

### **History of past illness**

The patient had a past medical history significant for UC. The patient had lived in the Great Lakes region for his entire life, worked in construction for many years and had no history of recent travel. He lived with 3 young children who all had recently suffered from a viral respiratory tract infection lasting approximately 1 wk. He had pets at home including a gecko, a rabbit and 2 dogs. 10 mo prior, he had presented to the ED with similar complaints of diffuse abdominal pain and diarrhea associated with haematochezia for 6 wk. Investigation for common conditions such as gastrointestinal infections, endocrine disorders, food allergies and medication changes were ruled out, and a decision was made to perform a colonoscopy with tissue biopsy. Biopsy from the colon revealed non-specific histological findings *i.e.* crypt abscess, mild architectural distortion of the lamina propria and chronic inflammation. Markers of acute inflammation such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) were also found to be elevated, suggesting a diagnosis of UC. The patient was started on prednisolone 40 mg daily which led to resolution of his symptoms. A decision was made to have the patient continue on prednisolone 40 mg daily after failed attempts to switch the regimen to mesalamine led to mesalamine-induced pancreatitis, and treatment with Vedolizumab led to an allergic reaction after the second dose.

### **Personal and family history**

Family history was significant for IBD in his mother. The patient had no other significant past medical history.

### **Physical examination**

On examination, he was febrile with a temperature of 103F, heart rate 112 beats/min, and blood pressure 124/74 mmHg. On abdominal examination, no tenderness was noted but mild splenomegaly was appreciated. The working diagnosis of the patient's presentation at this time was believed to be an acute exacerbation of his underlying UC.

### **Laboratory examinations**

Laboratory investigations were ordered, and infectious disease was consulted, with recommendations to start broad spectrum antibiotics until a definite cause could be established. Laboratory investigations revealed a Hemoglobin of 11.8 g/dL, white blood cell (WBC) count of  $4.1 \times 10^9$  cells/L with 70% granulocytes, 22% lymphocytes and 0.1% eosinophils. Procalcitonin was elevated at 0.39 and elevations in the liver enzymes were also noted with alanine aminotransferase 232 U/L, Alkaline phosphatase 266 U/L and aspartate transaminase 79 U/L. Blood cultures showed no growth, and stool analysis was negative for *Clostridium difficile* (*C. diff*) and parasites. Interestingly, *H. capsulatum* antigen was detected in the urine. Hence, the working diagnosis was changed from an acute exacerbation of UC to GIH.

### **Imaging examinations**

To confirm the diagnosis of GIH, the patient was offered a colonoscopy with biopsy, however he refused this stating that he preferred treatment for *H. capsulatum* based on the high specificity of the urine antigen testing.

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## **FINAL DIAGNOSIS**

Based on the positive urine antigen for *H. capsulatum*, and the patient's refusal to have repeat colonoscopy with biopsy, the presumed diagnosis was GIH.

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## **TREATMENT**

The patient was started on oral itraconazole 200 mg twice daily for presumed GIH infection.

## OUTCOME AND FOLLOW-UP

Over the next several days, the patient experienced significant improvement of his symptoms confirming our diagnosis of GIH. He was subsequently discharged home on oral itraconazole for 6 mo, oral corticosteroids for his UC and an appointment to follow-up with his gastroenterologist within 6 wk.

## DISCUSSION

This case report and brief review of the literature places great emphasis on keeping *H. capsulatum* as one of the differential diagnoses in patients with IBD presenting to the hospital with a clinical picture of an acute exacerbation of their underlying disease. In patients presenting to the ED with complaints of diffuse abdominal pain and chronic diarrhea with hematochezia, it is standard clinical practice to obtain a stool analysis and rule out *C. diff* and parasitic infection. However, specific tests for *H. capsulatum* are not usually performed. In this article, we discuss the presentation and management of patients with IBD. We also review the classification of specific subtypes of chronic diarrhea and further investigations that might be necessary to investigate the underlying pathology. Furthermore, we discuss the presentation and management of GIH, a subtype of DH, and advocate for the importance of considering *H. capsulatum* infection as a differential diagnosis in patients with IBD.

### Diarrhea in IBD

IBD is a disease characterized by chronic inflammation of the intestinal mucosa through a complex immune mediated mechanism. The exact cause of IBD is currently unknown, but it is believed to be due to an abnormal intestinal mucosal immune response to environmental triggers leading to inflammation of the epithelial lining of the GI mucosa<sup>[5]</sup>. The immune system of the GI tract plays a vital role in providing an appropriate immune response to harmful pathogens, while inducing an immune tolerance to harmless food materials and commensal flora<sup>[6]</sup>. Literature reports a rise in incidence and prevalence of IBD in the adult and pediatric populations<sup>[7]</sup>. Although the exact reason for this increase is not clear, it is believed that an alteration in lifestyle and nutritional habits may play a significant role<sup>[8]</sup>. The Rochester epidemiology project noted an increase in the incidence and prevalence of IBD between 2001 and 2011, but this was attributed to an increase in overall life expectancy<sup>[9]</sup>. In light of increasing westernization and industrialization, Asian countries such as India, China and Iran are reporting significantly increased numbers of cases of IBD<sup>[10]</sup>.

IBD can be classified into 2 major subtypes based on the clinical picture and distinct pathological characteristics<sup>[11]</sup>:

**Ulcerative colitis:** A chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited only to the mucosal layer of the colon. The mucosa is involved in a continuous fashion with almost all cases reporting involvement of the rectum.

**Crohn's disease:** A chronic inflammatory condition characterized by a full thickness (transmural) involvement of the bowel and the presence of skip lesions (areas of disease between normal appearing bowel). It most commonly involves the ileum and the proximal part of the colon; however, any part of the GI tract may be involved.

The spectrum of symptoms in patients with IBD depend on the severity of the inflammation and can range from very mild to severe. The common symptoms of IBD include diarrhea or constipation, hematochezia, severe diffuse abdominal pain, unintentional weight loss, significantly reduced appetite, fatigue, and fever.

The initial step in the evaluation of a patient with IBD includes a detailed history and physical examination. The history may be critical in differentiating patients with IBD from other organic and functional causes. A thorough physical examination in patients with IBD may reveal mild to moderate abdominal tenderness without distention. Initial laboratory investigations may reveal an elevation of the markers of inflammation *i.e.* ESR and CRP. In patients with acute diarrhea as the presenting symptom, stool studies to rule out infectious etiologies such as *C. diff* and parasites should also be performed. Fecal calprotectin, a stool marker for inflammation, can also be used to determine the presence of intestinal inflammation in patients with clinical suspicion of IBD<sup>[12]</sup>. If the fecal calprotectin value is above the reference range (50 mcg/g), ileocolonoscopy with biopsy and/or small bowel imaging can be used to diagnose IBD and assess the degree of mucosal inflammation<sup>[13]</sup>. Although

ileocolonoscopy with biopsy is the preferred method to establish a definitive diagnosis and assess the degree of inflammation, radiological imaging modalities such as computed tomography (CT) enterography, magnetic resonance enterography (preferred over CT enterography), capsule endoscopy, or GI Ultrasound can also be used in certain situations<sup>[14]</sup>. The management of IBD is primarily focused on providing symptomatic relief, rapid induction of steroid-free remission, and prevention of complications of the disease and its treatment<sup>[15]</sup>. The choice of therapy is based on the extent and degree of the severity of the disease, its responsiveness to previous therapy, and the individual patient characteristics<sup>[15]</sup>. Some agents used in the treatment of IBD include Sulfasalazine, Mesalamine, Olsalazine, Balsalazide, Corticosteroids, Azathioprine, 6-Mercaptopurine, Methotrexate, Infliximab, Adalimumab and Tacrolimus.

Due to the chronic inflammation in IBD, patients can present with multiple complications. These complications are usually associated with a specific subtype of IBD due to the pattern of the inflammation, but some may be shared between the two. The complications include<sup>[16]</sup>:

**Common complications:** Colon cancer, Arthritis, Uveitis, Primary Sclerosing Cholangitis and hypercoagulable states.

**Ulcerative colitis:** Toxic Megacolon, perforation of the colon and severe dehydration.

**Crohn's disease:** Bowel obstruction, ulcers, fistulas and anal fissures.

### **Evaluation of patients with chronic diarrhea**

Diarrhea is objectively defined as passing a stool weight or volume greater than 200 g or 200 mL per 24 h<sup>[17]</sup>. According to the Centers for Disease Control and Prevention, chronic diarrhea is defined as diarrhea that lasts for longer than 2-4 wk<sup>[18]</sup>. The initial investigation into the evaluation of chronic diarrhea starts with an extensive history and examination to formulate a preliminary differential diagnosis. The appearance of the stool can be categorized into one of the three major subtypes for further diagnostic investigations<sup>[19]</sup>:

**Fatty (Malabsorptive) diarrhea:** The initial investigations in patients with malabsorptive diarrhea are aimed at ruling out anatomic defects. Radiological investigations of the abdomen, and sigmoidoscopy or colonoscopy with or without biopsy may help to diagnose the specific underlying etiology. A positive stool chymotrypsin level confirmed with a positive secretin test is diagnostic for pancreatic insufficiency.

**Inflammatory diarrhea:** In patients with a suspected inflammatory cause of their diarrhea, stool analysis is always the initial investigation of choice. Stool analysis positive for blood, WBC, and fecal calprotectin points toward a diagnosis of IBD. This can be confirmed with a colonoscopy and biopsy of the involved bowel. In patients with absence of WBC in the stool and a negative stool analysis, additional investigations are needed to identify the underlying cause. Testing for *C. diff* has become standard practice in patients with inflammatory diarrhea. We strongly advocate and urge physicians to test for *H. capsulatum*, particularly for patients in endemic regions and in those with IBD, as literature reports a high prevalence of GIH in autopsy specimens.

**Watery diarrhea:** The initial investigation of choice is the measurement of the fecal osmotic gap. A high fecal osmotic gap (> 125 mOsm per kg) along with a history of increased diarrhea on consumption of dairy products and a positive hydrogen breath test confirms the diagnosis of lactose intolerance. A normal fecal osmotic gap with improvement in the symptoms on dietary modification is usually seen in patients with irritable bowel syndrome. However, patients with a normal fecal osmotic gap and no improvement with dietary modifications may require further workup for Celiac disease, which includes a celiac panel. Patients with low osmolar gap (< 50 mOsm per kg) may need additional imaging, blood, and urine testing to investigate other possible etiologies.

It is important to recognize that diarrhea is not a disease but rather a symptom of the underlying pathology. Patients with ulcerative colitis will have inflammatory diarrhea with the presence of pus and blood on stool analysis. Furthermore, mimics of IBD such as GIH may also present with inflammatory diarrhea such as that in our case report. Therefore, it becomes extremely important to differentiate an acute exacerbation of UC from other causes in order to initiate appropriate therapy early and

prevent adverse outcomes.

### ***H. capsulatum* and the gastrointestinal tract**

Histoplasmosis is an endemic mycosis caused by a dimorphic fungus called *H. capsulatum*. The two distinct varieties of *Histoplasma* that are pathogenic to humans include *H. capsulatum* var. *capsulatum* which is prevalent worldwide in endemic areas, and *H. capsulatum* var. *duboisii* which is restricted to the Sub-Saharan Africa region<sup>[1]</sup>. In the United States, endemic regions with a high prevalence of histoplasmosis include areas centered in the Ohio and Mississippi river valleys. An analysis of the data from hospital records in 2002 revealed 3370 inpatient stays and 254 deaths associated with histoplasmosis with almost 90% of these hospitalizations in the midwestern and southern regions of the United States<sup>[20]</sup>. *H. capsulatum* var. *capsulatum* is dimorphic meaning that it exists in two distinct forms. It grows in its hyphal form in soil, and bird and bat guano, but upon inhalation of the spores, it transforms into the pathogenic yeast form, replicating inside the macrophages<sup>[2]</sup>. These macrophages can transport the yeast to virtually any organ in the body leading to DH<sup>[2]</sup>. Although *H. capsulatum* is non-contagious and humans are the dead-end or accidental hosts for fungal replication, it appears to be specifically well adapted to the mammalian host cells. The pathogenic yeast phase is equipped to evade intercellular killing by macrophages with mechanisms to degrade reactive oxygen species, regulate lysosomal pH and capture essential nutrients that might otherwise be deprived<sup>[2]</sup>. Human infections by *H. capsulatum* usually present as acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis, cutaneous histoplasmosis, rheumatologic histoplasmosis, ocular histoplasmosis, mediastinal histoplasmosis, broncholithiasis, and progressive disseminated histoplasmosis extending to the brain<sup>[21]</sup>. DH is commonly seen in immunocompromised states with low CD4 cell counts (< 200 cells/mm<sup>3</sup>), such as in acquired immune deficiency syndrome patients and also rarely in patients with human T-lymphotropic virus 1 infection.

DH to the GI tract, also known as GIH, is a rare entity. Involvement of the GI tract in DH is very non-specific, may involve any area of the GI tract and is usually seen in immunocompromised patients. However, the most common sites of involvement are the terminal ileum and the colon due to abundance of lymphoid tissue<sup>[3]</sup>. The involvement becomes less common more proximally in the intestine<sup>[3]</sup>. Literature reports high rates of GIH in autopsy specimens, indicating a higher prevalence of asymptomatic disease<sup>[22]</sup>. The most common presenting symptoms in patients with GIH are abdominal pain and diarrhea<sup>[4]</sup>. This diarrhea could be intermittent and typical of that seen in other diseases, or could be unremitting and associated with malabsorption<sup>[23]</sup>. Bloody diarrhea may also be present in a subset of patients with GIH and often mimics IBD, thereby making it difficult to differentiate between IBD and GIH, such as that in our case<sup>[24]</sup>. Other symptoms associated with GIH may include irregular fevers with or without chills and night sweats, anorexia, weight loss of varying degrees, and abdominal distention<sup>[25]</sup>. On physical examination, patients may have hepatosplenomegaly, peripheral lymphadenectasis, abdominal tenderness and rebound tenderness concerning for peritonitis<sup>[25]</sup>. The similarities in presentation, the pattern of the involvement of the GI tract and the associated inflammation is the reason as to why GIH is considered a mimic of IBD.

Laboratory investigations in patients with GIH may reveal an elevation in the alkaline phosphatase levels, lactate dehydrogenase, and increased levels of markers of inflammation such as ESR, CRP and serum ferritin levels<sup>[26]</sup>. In our case, elevations in all of the liver enzymes were noted along with elevations in the ESR and CRP. Pancytopenia may indicate an underlying immunocompromised state. Although none of these investigations are diagnostic for *H. capsulatum*, they direct the physician to consider an infectious etiology as a differential diagnosis for the presenting symptoms. For patients with suspected DH, Histoplasma antigen enzyme immunoassay of the serum and urine should be performed. Urine antigen-enzyme immunoassay has a high sensitivity (89.47%) and specificity (100%) in the detection of *H. capsulatum*<sup>[27]</sup>. Radiological investigations such as CT scan and magnetic resonance imaging may also help point physicians towards a diagnosis of GIH, while ruling out other etiologies of bloody diarrhea. The radiological findings with GIH may include<sup>[28]</sup>: Bowel wall thickening; Mass-like lesions in the bowel; Signs suggesting small bowel obstruction; Bowel perforations, although rare, may show free intraperitoneal air; Hepatosplenomegaly; Generalized lymphadenopathy.

The most common endoscopic findings in patients with GIH are unifocal or multifocal mucosal ulcerations<sup>[28]</sup>. Polypoid lesions, strictures, and obstructing masses may also be noted<sup>[29]</sup>. The definitive diagnosis of GIH is always established with colonoscopy and biopsy of the lesions which may reveal the typical 2 to 4-micron yeast

structure of *H. capsulatum*. Although the histopathology specimens of the fungus can be stained with hematoxylin and eosin, it is better visualized using the methenamine silver or periodic acid-schiff stain. It is also always preferable to have culture evidence of *H. capsulatum* for diagnosis. However, in our case, a colonoscopy with biopsy was offered to the patient, who refused the procedure as he had a colonoscopy with biopsy 10 mo prior to establish a diagnosis of UC and did not wish to undergo the procedure again. After learning about the positive results of the urine antigen testing for *H. capsulatum* and that GIH can be a mimic for an acute exacerbation of UC, the patient wanted to proceed with the treatment for GIH and deferred the procedure to a later date if there was no improvement in his symptoms.

The treatment of DH and the selection of the appropriate agent for therapy depends primarily on the severity of the disease. The treatment strategy (summarized in Table 1) can be classified as<sup>[30]</sup>:

**Severe disease:** Liposomal Amphotericin B 3 mg/kg daily, or Amphotericin lipid complex 5 mg/kg daily, or Amphotericin deoxycholate 0.7 to 1 mg/kg daily for one to two weeks followed by itraconazole 200 mg twice daily for a minimum of 2 mo.

**Mild to moderate disease:** Itraconazole 200 mg twice daily for a minimum of 2 mo.

**CNS histoplasmosis:** Liposomal Amphotericin 5 mg/kg daily for four to six weeks followed by itraconazole 200 mg two to three times daily for a minimum of 2 mo.

Most patients with disseminated Histoplasmosis respond well to antifungal therapy. Early diagnosis and treatment of the GIH is essential to prevent serious adverse outcomes. Perforation of the bowel and hemorrhage are two of the most serious complications reported in patients with GIH.

The clinical manifestations of GIH may mimic other GI diseases such as IBD, including UC and Crohn's disease, tuberculosis, carcinomas and lymphomas. However, it is commonly not considered as one of the differential diagnoses in patients presenting with abdominal pain and chronic diarrhea with hematochezia<sup>[4]</sup>. This usually leads to inappropriate or delayed therapy, unnecessary surgical interventions and adverse outcomes. Our article places great emphasis on the importance of testing in order to rule out GIH in patients who present with clinical characteristics of a sudden onset acute exacerbations of IBD without an underlying cause.

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## CONCLUSION

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*H. capsulatum* is a dimorphic fungus endemic in the Ohio and Mississippi valley regions. *H. capsulatum* var. *capsulatum* is prevalent worldwide and is seen in the United States. *H. capsulatum* exists in its hyphal form in the environment and inhalation of the spores produced by this form are infectious to humans. After infection of the host, it transforms into the pathogenic yeast form which replicates inside the macrophages and evades intracellular killing. Macrophages can disseminate the fungus to any organ in the body leading to DH. In the gastrointestinal tract, most common sites of involvement are the terminal ileum and the colon due to abundance of lymphoid tissue. The most common presenting symptoms in patients with GIH are abdominal pain and diarrhea. GIH often mimics IBD due to similarities in presentation, the pattern of the involvement of the GI tract and the associated inflammation. Hence, for patients with inflammatory diarrhea, or those with diagnosed IBD with clinical characteristics of a possible acute exacerbation without an underlying cause, GIH should be among the differential diagnoses. The diagnosis of GIH is confirmed with colonoscopy and biopsy of the involved region of the GI tract. The treatment of DH depends on the severity of the disease.

**Table 1 Treatment strategies based on the severity of disseminated histoplasmosis**

Disseminated histoplasmosis	Mild disease	Moderate disease	Severe disease	CNS histoplasmosis
Treatment	Itraconazole 200 mg twice daily (minimum of 2 mo)	Itraconazole 200 mg twice daily (minimum of 2 mo)	Liposomal Amphotericin B 3 mg/kg daily for 1-2 wk or Amphotericin lipid complex 5 mg/kg daily for 1-2 wk or Amphotericin deoxycholate 0.7 to 1 mg/kg daily for 1-2 wk followed by Itraconazole 200 mg twice daily (minimum of 2 mo)	Liposomal Amphotericin 5 mg/kg daily for 4-6 wk followed by Itraconazole 200 mg 2-3 times daily (minimum of 2 mo)

CNS: Central nervous system.

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