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Brief Report

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Isolated gastrointestinal histoplasmosis with a negative urine antigen test mimicking ulcerative colitis flare: a case report

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Introduction

Histoplasmosis is a mycotic infection caused by *Histoplasma capsulatum*. The usual clinical presentation is pulmonary disease. Disseminated disease can occur and involve multiple organs [1]. Gastrointestinal (GI) involvement can be seen in 70% of autopsy cases, but only 3%–12% are symptomatic [1]. Moreover, isolated GI histoplasmosis without accompanying pulmonary symptoms is exceedingly rare. Recognizing this rare entity can be difficult, especially in patients with pre-existing GI disorders such as inflammatory bowel disease (IBD).

Here, we present a case of isolated GI histoplasmosis with negative urine antigen in a patient with ulcerative colitis (UC) treated with infliximab. Our case illustrates the importance of considering histoplasmosis as a differential diagnosis and using endoscopic tissue sampling rather than relying on lab tests alone for prompt diagnosis. Our case also highlights the need for further studies to determine the optimal IBD pharmacotherapy following the treatment of histoplasmosis.

Case report

A 21-year-old woman with a history of UC was admitted for progressively worsening abdominal pain, nausea, vomiting, low-grade fever and weight loss. Her symptoms began 8 weeks prior to presentation. She did not report any pulmonary symptoms or new skin lesions. Her symptoms were similar to those during her prior index flare of UC, but lacked the diarrhea and hematochezia she previously experienced. Her original diagnosis of UC was made 1 year prior during a hospitalization for acute severe UC, when she required rescue therapy with infliximab. She subsequently achieved endoscopic and histologic remission 4 months later after discharge.

Before this admission, her new symptoms did not improve despite increasing infliximab from 10 mg/Kg every 8 weeks to every 4 weeks and a 4-week trial of budesonide. She worked as a medical technologist in a microbiology lab in North Texas. She attended college in Oklahoma (USA) and traveled to Missouri (USA) 2 months prior to presentation.

On admission, she had a temperature of 38.1°C and mild tenderness to palpation in the mid-epigastric abdomen. Her labs were notable for C-reactive protein of 660 nmol/L and fecal calprotectin of 604 μg/g. Computed tomography revealed mild wall thickening with surrounding fat stranding in the duodenum, jejunum and proximal colon. Antegrade enteroscopy and ileocolonoscopy showed numerous superficial ulcers in the duodenum, jejunum, cecum and transverse colon (Figure 1A and 1B), without inflammation in the ileum, left colon and rectum. Of note, jejunal biopsy revealed granulomatous inflammation with fungal organisms on Grocott's methenamine silver stain, consistent with *Histoplasma* infection (Figure 1C and 1D). Her urine antigen test for *Histoplasma* by enzyme immunoassay was negative.

Due to *Histoplasma* infection, infliximab was discontinued, and she was treated with amphotericin B followed by itraconazole. Her symptoms improved significantly over a few days. Then, she started mesalamine for maintenance therapy for UC. Three months later, repeat endoscopic evaluation showed resolution of duodenal, jejunal and colonic ulcers without histologic evidence of *Histoplasma* infection, and her UC condition remained in remission. However, a new jejunal stricture was noted, for which she underwent serial dilations. A year later, she completed antifungal treatment and opted to continue mesalamine as maintenance therapy.

In retrospect, the clinical improvement and persistent histologic remission following anti-fungal therapy and de-escalation of IBD pharmacotherapy suggested GI histoplasmosis over UC flare as the cause of her presentation. For the same reason, the jejunal stricture was more likely a sequela of GI histoplasmosis [2] rather than a manifestation of possibly unrecognized Crohn's disease.

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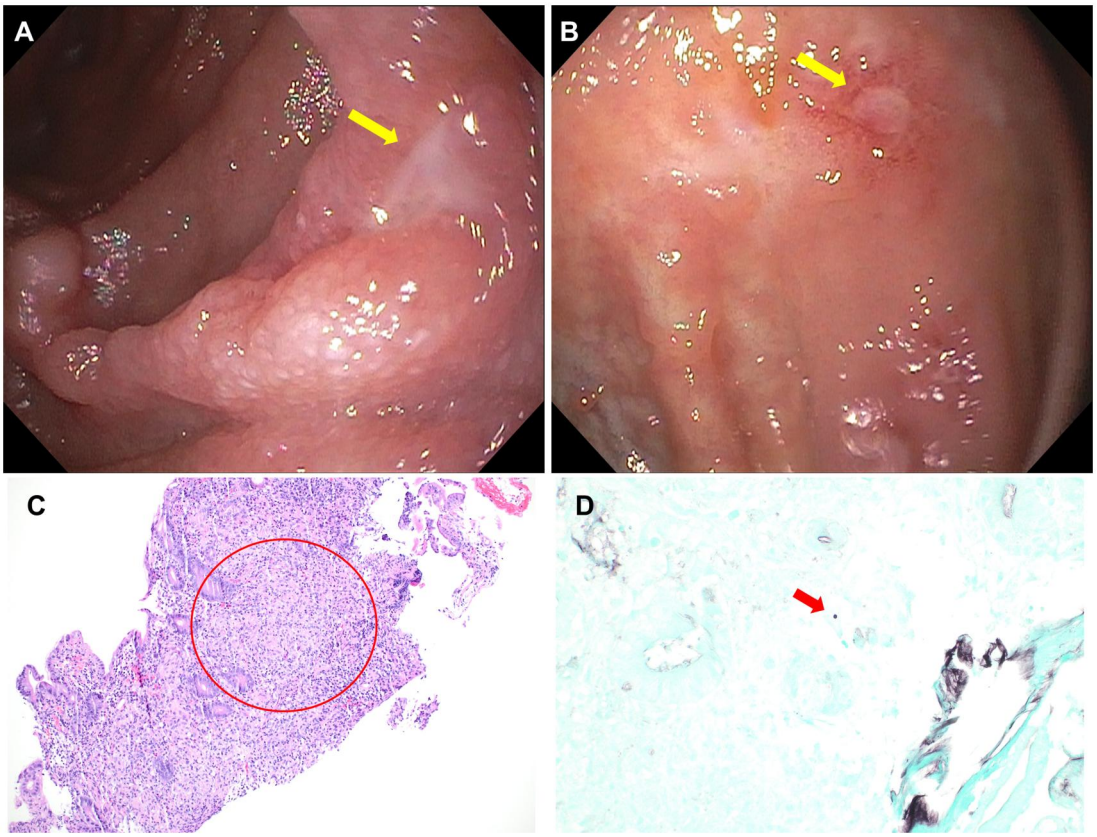

Figure 1. Endoscopic findings of ulcerations (arrows) in the jejunum (**A**) and colon (**B**), and histological findings of jejunal biopsy, notable for granulomatous inflammation on hematoxylin and eosin stain (**C**, 100 × magnification, circle), with fungal organisms on Grocott's methenamine silver stain (**D**, 400 × magnification, arrow).

Discussion

Here, we describe a patient treated with infliximab for UC who developed isolated GI histoplasmosis. This case is unusual in several aspects. First, this patient presented with isolated GI histoplasmosis without any pulmonary symptoms. Secondly, the partial overlap in clinical manifestations between GI histoplasmosis and UC flare made differential diagnosis difficult. Thirdly, her urine antigen test for *Histoplasma* was falsely negative, and the final diagnosis was established based on endoscopic tissue sampling.

Early diagnosis of histoplasmosis is crucial, as untreated cases can be fatal. Recognizing isolated GI histoplasmosis without pulmonary involvement in patients with pre-existing IBD can be difficult, due to their overlapping clinical manifestations. Urine antigen test is widely used in the USA for diagnosing histoplasmosis, with a sensitivity reportedly greater than 90% in patients with disseminated disease [3]. However, the test is highly dependent on the fungal burden and may be falsely negative, as in our case and a few others in the literature [4, 5]. In addition, the test is not readily available in many parts of the world outside the USA. Our case suggests the importance of not relying solely on the urine antigen test for distinguishing GI histoplasmosis from IBD flare. Rather, early endoscopic evaluation with tissue sampling can be useful in promptly establishing the diagnosis.

Anti-tumor necrosis factor (anti-TNF) therapy is known as a risk factor for *Histoplasma* infection. Discontinuation of anti-TNF therapy is considered standard of care upon diagnosis of histoplasmosis. However, limited evidence is available to guide the re-initiation of IBD pharmacotherapy. In a single-center retrospective study, 19 of 49 patients continued or resumed anti-TNF therapy for IBD after *Histoplasma* infection [5]. No recurrence of histoplasmosis was observed except in a patient who self-discontinued itraconazole. In another single-center study, immunosuppressive therapy was re-introduced in 10 out of 17 patients with IBD, including two patients who resumed anti-TNF therapy, and no recurrence of histoplasmosis was reported [6]. Despite these data, non-anti-TNF therapies are often favored as an alternative regimen in patients with history of severe infections on anti-TNF therapy, as they are considered safer with respect to the risk of opportunistic infection. However, case reports of patients who developed histoplasmosis on ustekinumab [7, 8], vedolizumab [9, 10] or tofacitinib [6] have been described, and it remains unclear which non-anti-TNF therapy has the best safety profile in such cases. T cell-mediated adaptive immunity is a major immune mechanism to clear *Histoplasma* infection. Mechanistically, vedolizumab may greatly affect the T cell-mediated response in the GI tract, whereas ustekinumab theoretically may have a less profound effect. Therefore, we speculated that ustekinumab might be more favorable than vedolizumab in this case of isolated GI histoplasmosis if escalation of IBD pharmacotherapy was needed, but this needs to be evaluated by further studies.

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Informed consent was obtained for this case report.

Conflicts of Interest

D.I.F. has served on advisory boards for Janssen, Fresenius Kabi and Pfizer. Other authors declare that there are no conflicts of interest in this study.

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