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Perianal Histoplasmosis Presenting as a Mass Suspicious for Malignancy: A Case Report with Review of Gastrointestinal Manifestations of Histoplasmosis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 66
Final Diagnosis: Perianal histoplasmosis
Symptoms: Perianal pain
Medication: —
Clinical Procedure: Surgical biopsy of the lesion
Specialty: Pathology

Objective: Unusual clinical course

Background: Disseminated histoplasmosis, a disease that can present years after exposure to the causative organism, may manifest in many diverse ways. Although the gastrointestinal tract is involved in most cases, the initial presentation occurring along the gastrointestinal tract, including the colon and rectum, is infrequent.

Case Report: This case report describes a 66-year-old male patient who presented with an indurated painful perianal lesion that appeared highly suspicious for malignancy on imaging. The patient had no known history of well-established immunocompromised state except for a short course of prednisolone for chronic obstructive pulmonary disease management. A biopsy of the mass was performed, showing chronic inflammation with clusters of epithelioid histiocytes containing characteristic, PAS-fungus stain-positive, intracellular yeast forms consistent with histoplasmosis. There was no evidence of malignancy. A subsequent work-up revealed perihilar nodularity on chest X-ray suggestive of calcified granuloma, a positive Histoplasma Capsulatum Antigen test result, and mildly decreased CD4: CD8 ratio of unknown significance. HIV testing was negative. Treatment with itraconazole and terbinafine was initiated, and at 5-months follow-up, the patient reported significant improvement in signs and symptoms, with undetectable Histoplasma antigen on repeat testing.

Conclusions: This case represents an extremely rare presentation of histoplasmosis infection, and highlights the fact that presenting symptoms of histoplasmosis can be vague and may mimic other disease processes, including neoplasia. Biopsy of the lesion with PAS staining and serologic testing is critical in establishing the correct diagnosis.

MeSH Keywords: Histiocytes • Histoplasmosis • Lower Gastrointestinal Tract

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/918220

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Background

Histoplasma capsulatum is an opportunistic fungal pathogen endemic to the Ohio, Mississippi, and Missouri River valleys in the United States [1]. It enters the host through the lungs, where warm body temperatures cause the fungus to transform into a yeast form. Macrophages phagocytose the yeast, disseminating it through the lymphatic system to lymph nodes and peripheral organs [2,3]. The fungus may cause primary pulmonary disease, or may remain dormant in the host for years. Individuals who become symptomatic are most often immunocompromised; they often have a history of HIV, solid- or liquid-organ transplant, and long-term systemic steroids or immunosuppressive medications [4].

Disseminated histoplasmosis frequently involves the gastrointestinal tract. There are several case reports in the literature of patients who presented with gastrointestinal symptoms, but who lacked systemic, pulmonary, or cutaneous symptoms [5]. Histoplasmosis can cause malabsorption [6], lower gastrointestinal tract bleed [7], colonic pseudotumor [8,9], or nonspecific gastrointestinal symptoms such as diarrhea, bloating, constipation, abdominal pain, and weight loss [10]. The differential diagnosis for these patients is broad and includes inflammatory diseases such as tuberculosis, inflammatory bowel disease, and opportunistic infections, as well as malignancy. Furthermore, clinical presentation, endoscopic findings, and imaging features of histoplasmosis can overlap substantially with malignancy and non-fungal infections or inflammatory conditions, which can pose a diagnostic dilemma if one is not familiar with the unusual clinicopathologic manifestations of histoplasmosis.

Gastrointestinal histoplasmosis may be distinguished from other conditions by use of several diagnostic tools [11]. Histology is frequently an initial step, relying on biopsies taken during colonoscopy or anoscopy. Microscopy usually demonstrates a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, plasma cells, and multinucleated epithelioid giant cells, although not all cell types may be present, and inflammatory cells may not be seen in an immunocompromised host [12]. Necrotizing or non-necrotizing granulomas may be present. The yeast can be recognized as spherical structures surrounded by a clear pseudocapsule, and budding may be seen. Periodic acid-Schiff (PAS) and silver-based stains such as Gomori methenamine silver (GMS) can confirm the presence of fungi. The diagnosis of histoplasmosis should be confirmed by either a serum or urine antigen test followed by fungal culture [11].

In this case report we describe an extremely rare clinical presentation of histoplasmosis involving the anal region, and discuss the sequence of investigations that ultimately led to the correct diagnosis. A review of the literature with emphasis on gastrointestinal manifestations of histoplasmosis is presented.

Case Report

A 66-year-old man who lives in Minnesota, USA with a past medical history significant for coronary artery disease, long-term tobacco use, chronic obstructive pulmonary disease, dyslipidemia, aortic aneurysm, colon adenomas, and aorto-bifemoral bypass surgery presented to the colorectal surgeon with a several-week history of progressive anal pain and intermittent anal seepage. He denied hematochezia, increased fecal urgency, or fecal incontinence, and denied systemic symptoms such as fever or chills. He denied history of diabetes mellitus or HIV, and was not on any long-term immunosuppressive medications. However, he did receive a short-term course of prednisone several months ago for his chronic obstructive pulmonary disease exacerbation and also mentioned having been told about "low T-cells" in the past. On physical exam, he was found to have a 2.0×2.0-cm area of induration at the right lateral anus (Figure 1). His white blood cell count was normal. Magnetic resonance imaging demonstrated a right-sided 4.2-cm intramural mass posterolateral to the anus that extended from the internal anal sphincter to the external anal sphincter (Figure 2). Due to significant suspicion for malignancy, an evaluation under anesthesia with biopsies was performed. This revealed circumferential superficial fissuring and induration of the perianal skin, but no palpable masses, and no evidence of perianal inflammation, abscess, or fistula. Colonoscopy demonstrated mild diverticulosis, but no bleeding or inflammation throughout the colon and rectum. Intraoperative consultation was obtained and frozen sections of the biopsy tissue showed inflammation but no clear evidence of malignancy or organisms. Additional core biopsies were also concurrently taken and submitted in formalin; however, no tissue was submitted for culture during this procedure.

Low-power microscopic examination of hematoxylin and eosin (H&E)-stained sections revealed hyperplastic squamous epithelium without evidence of dysplasia, and a diffuse subepithelial inflammatory infiltrate extending to the edges of the biopsy specimen (Figure 3A). On higher magnification, the inflammatory infiltrate was noted to be predominantly mononuclear with a mix of histiocytes, plasma cells, and lymphocytes, but no neutrophils. Clusters of epithelioid histiocytes were present, but well-formed granulomas were not seen (Figure 3B). There were no areas of necrosis. Scattered throughout the infiltrate, predominantly located within the cytoplasm of histiocytes, were several eosinophilic spheres 2–5 µm in diameter with clear halos, suggestive of fungal yeast forms (Figure 3C). These organisms stained positive with PAS-fungus stain (Figure 3D), which stains the fungal cell wall. The PAS stain also demonstrated

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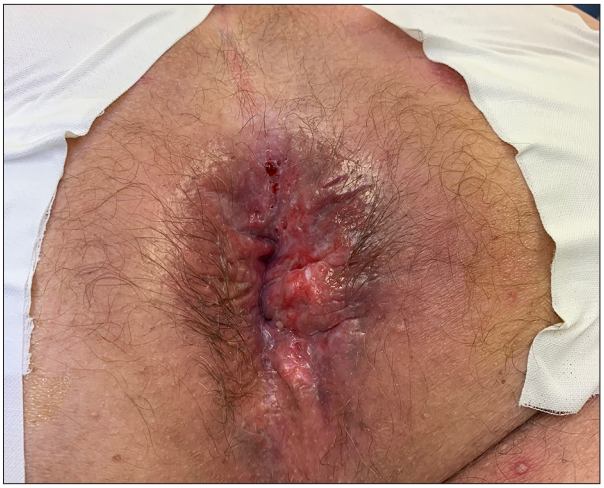

Figure 1. Examination of the anal region showing a 2.0×2.0-cm area of induration at the right lateral anus.

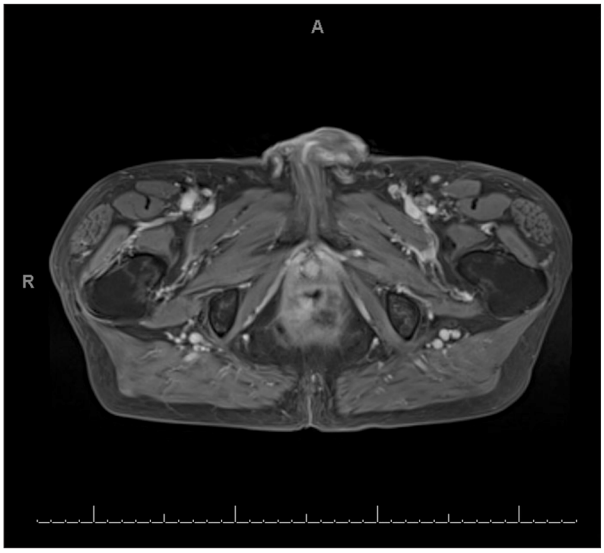

Figure 2. Pelvic T1-weighted MRI demonstrating a 4.2-cm hypoattenuated lesion posterolateral to the anal canal and completely intramural.

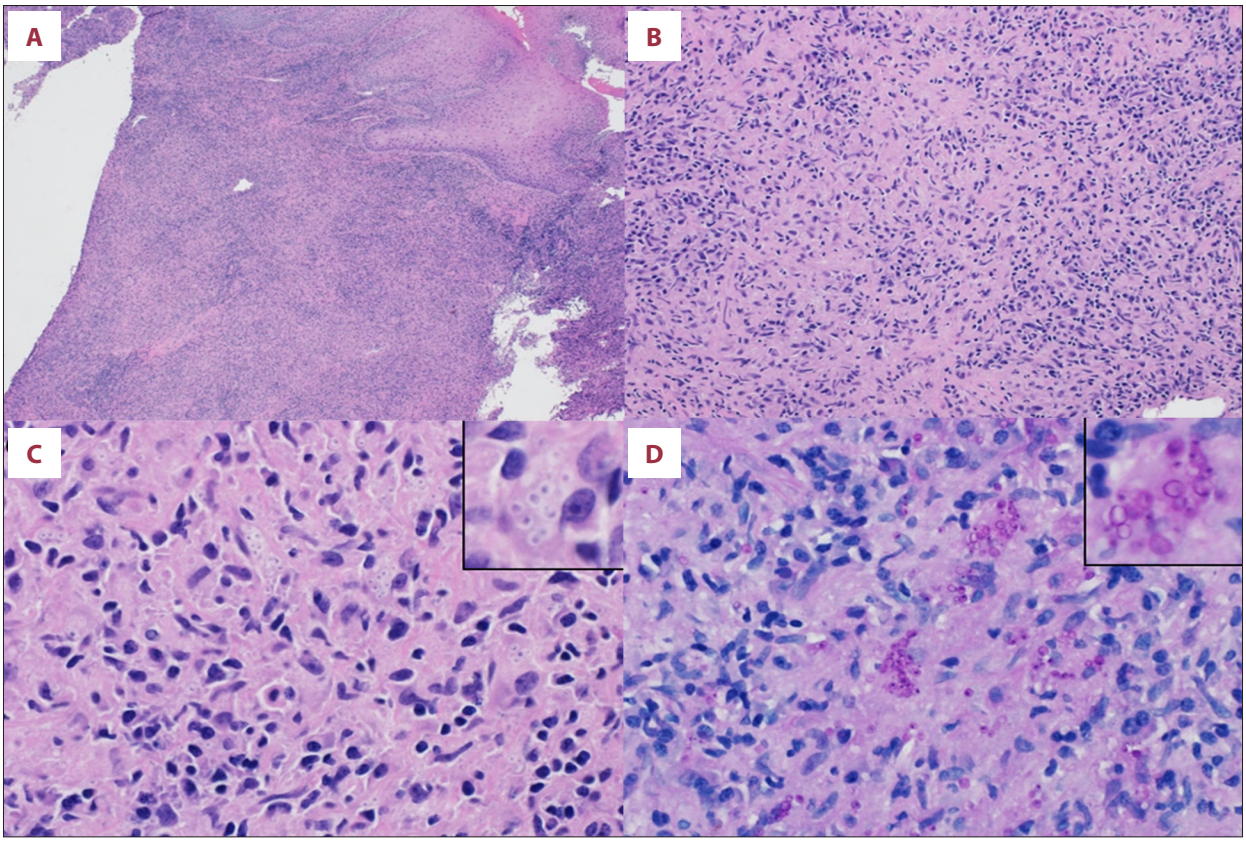

Figure 3. Histologic features of perianal biopsy: (**A**) Low-power view (40×) of H&E-stained section demonstrates hyperplastic squamous epithelium with underlying dense inflammatory infiltrate extending to the edges of the biopsy specimen; (**B**) Medium-power view (200×) of H&E-stained section demonstrates a mononuclear inflammatory infiltrate composed of histiocytes, lymphocytes, and plasma cells; (**C**) High-power view (600×) of H&E-stained section shows histiocytes with intracytoplasmic fungal yeast forms (2–5 µm) with characteristic halo (inset image); (**D**) PAS-fungus stain (600×) highlights spherical intracellular fungal organisms with occasional narrow-based budding (inset image), consistent with histoplasmosis.

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Table 1. Clinicopathologic manifestations of gastrointestinal histoplasmosis based on 2 large case series [16,17].

Site	Frequency of involvement	Clinicopathologic manifestation	Frequency
Small intestine	56–79% (ileum most common)	Ulceration (ileum most common)	30–49%
Large intestine	55–65%	Mucosal nodules	21%
Stomach	14–17%	Stricture or mass	18%
Esophagus	8–18%	Lymphoid hyperplasia	15%
Rectum	13%	Hemorrhage or petechiae	13%
Pancreas	6%	Mass	6%
Gallbladder	6%	Perforation	5.2%
Anus	2%	Ulceration	
Appendix	2–2.5%	–	–

occasional narrow-based budding, a characteristic feature of histoplasmosis.

Subsequent work-up of the patient showed hyperattenuating perihilar nodularity on chest X-ray, suggestive of calcified granuloma. A repeat chest X-ray showed no evidence of pneumonia. Serologic testing for fungal organisms revealed positive *Histoplasma capsulatum* antigen test. Additional work-up for immunodeficiency showed a mildly decreased CD4: CD8 ratio of 1.11 (ref range 1.40–2.60) with otherwise normal absolute CD3 and CD8 counts and normal immunoglobulin levels. HIV testing was negative. Treatment with itraconazole and terbinafine was initiated as per the Clinical Practice Guidelines of the Infectious Diseases Society of America. At 5-months follow-up, the patient reported significant improvement in signs and symptoms, with undetectable *Histoplasma* antigen on repeat testing.

Discussion

This case represents an unusual presentation of disseminated histoplasmosis that is unique in several ways. First, perianal histoplasmosis is rare and generally presents in the context of wider gastrointestinal or systemic symptoms such as diarrhea, abdominal pain, constipation, gastrointestinal bleeding, or weight loss due to malabsorption. Second, in contrast to other reports of anal histoplasmosis [13,14], the initial presentation in this case was a mass on physical exam, as opposed to ulceration, and further work-up by pelvic imaging revealed a mass that was highly suspicious for neoplasia. Finally, while the vast majority of patients with disseminated histoplasmosis have a known history of immunosuppression such as active HIV infection or chronic immunosuppressive therapy, our patient had no such history. The only minor immune abnormality found was a mildly decreased CD4: CD8 ratio of unknown etiology.

Disseminated histoplasmosis, which involves the gastrointestinal tract in up to 70–90% of cases, rarely presents with perianal pathology, and almost never presents as being isolated to the anus. A review of the literature suggests that gastrointestinal histoplasmosis most frequently involves the small or large intestine, infrequently involves other organs such as the stomach or rectum, and very rarely (2% cases) involves the anus (Table 1) [15–17].

Case reports of anal histoplasmosis are rare and illustrate the more typical presentation, which in most cases is ulceration [13,14]. Weiss et al. published a case report in 1952 describing, for the first time, anorectal manifestations of disseminated histoplasmosis [18]. The report described a 62-year-old man with systemic symptoms, dysphagia, and weight loss, who was found to have lesions in many organs, including his tongue, vocal cords, nasal septum, and spleen. Proctoscopy revealed polyps in the anal canal and rectum that were biopsied and were positive for histoplasmosis. Another case, reported by Mullick et al., involved a 69-year-old man with an apparently non-compromised immune system who presented with lower gastrointestinal tract bleeding [8]. Colonoscopy revealed a fungating anal mass that was biopsied because of suspicion for squamous cell carcinoma. Microscopy revealed histoplasmosis highlighted by PAS and GMS stains. This patient was later found to have noncaseating granulomas of the bone marrow, with negative PAS and GMS stains, and no growth of fungal organisms on bone marrow cultures. In both of these cases, anorectal involvement of histoplasmosis presented as ulceration of polyps or fungating masses, showing how unique our patient's presentation is in comparison.

Perianal Crohn's disease has significant overlap with perianal histoplasmosis both clinically and morphologically. However, treatment for these conditions is quite different. Fungal infections, including histoplasmosis, have been reported after the initiation of treatment for Crohn's disease, due to

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immune-modifying effect of the drugs used. Serologic tests and skin tests are sometimes negative for histoplasmosis. Therefore, inclusion of this entity in the differential diagnosis is necessary for accurate diagnosis and treatment [19].

Patients who initially present with gastrointestinal manifestations of histoplasmosis are likely to exhibit involvement of other sites later in the clinical course. For example, Hong et al. published a report of a 71-year-old man with no known history of immunosuppression who presented with a minimally symptomatic perianal ulcer [14]. Biopsy and microscopy revealed mixed inflammatory infiltrate and histiocytes with intracellular organisms that stained positive with GMS and PAS stains, consistent with histoplasmosis. This patient was later found to have lung nodules on CT scan. Follow-up chest X-rays performed on our patient did reveal perihilar nodularity, suggestive of calcified granuloma, but no evidence of pneumonia or lung nodules. The patient currently is scheduled for a follow-up pelvic MRI, which is pending.

Conclusions

This case contributes to the small but significant body of literature on atypical presentations of disseminated histoplasmosis infection, and highlights the fact that the diagnosis of disseminated histoplasmosis is neither simple nor easy. The presenting symptoms of histoplasmosis are frequently vague and may mimic other disease processes, including neoplasia. It is important for the managing physician to be familiar with the unusual clinical presentations of histoplasmosis and to have a low threshold for ordering biopsy and serological testing. Appropriate imaging alongside testing for immunosuppression should typically be considered.

Department and Institution where work was done

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Conflicts of interest

None.

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