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BRIEF REPORT

Acute Peritoneal Histoplasmosis Mimicking Ovarian Cancer and Review of the Literature on *Histoplasma* Peritonitis

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Peritoneal histoplasmosis is a rare entity with few cases reported in the literature. We present a case of isolated acute peritoneal histoplasmosis that mimicked an advanced ovarian malignancy in a patient undergoing antitumor necrosis factor therapy for rheumatoid arthritis. We also reviewed the literature on *Histoplasma* peritonitis.

Keywords. cancer; fungal; histoplasma; mimicking; peritonitis.

Acute peritoneal histoplasmosis is an uncommon manifestation of disseminated *Histoplasma capsulatum* infection. Most cases of acute peritoneal histoplasmosis have been described in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Here, we present a case of acute *Histoplasma* peritonitis in a patient with history of rheumatoid arthritis undergoing treatment with the tumor necrosis factor (TNF) blocker infliximab, and we also review the existing published literature on peritoneal histoplasmosis. As the geographic range, clinical manifestations, co-infection rates, and possibly the underlying hosts of *Histoplasma capsulatum var duboisii* are different, we restricted our search and analysis to *Histoplasma capsulatum var capsulatum* [1].

CASE PRESENTATION

A 68-year-old woman presented with a 3-week-long history of persistent mid-abdominal pain, bloating, and frequent episodes of fever (38.3°C–38.8°C). She had a history of rheumatoid arthritis that was diagnosed 3 years before and was under treatment with infliximab and hydroxychloroquine with good control of her disease. She was seen at a local hospital where, as part of an investigation for fever of unknown origin, she underwent a computed tomography (CT) scan of the abdomen and pelvis that showed ascites and diffuse omental caking concerning for ovarian cancer. She was referred to The University of Texas MD Anderson Cancer Center for further workup and treatment. A second CT scan of the chest, abdomen, and pelvis with intravenous contrast (Figure 1 *A* and *B*) revealed no pulmonary or mediastinal lesions. However, findings were concerning for diffuse carcinomatosis throughout the abdomen and pelvis, manifested as soft tissue stranding throughout the omentum with no distinct peritoneal mass identified. No lesions in the ovaries and uterus were present. Lymphadenopathy was seen in a right anterosuperior diaphragmatic location and was thought to be metastatic disease related to the presumed peritoneal malignancy. No hepatosplenic calcifications were present. Serum CA-125 levels were elevated (618.4 U/mL, reference range: ≤ 38 U/mL).

Due to persistent daily fevers, the patient was also referred to the infectious diseases department. No obvious source of infection was present at the time of evaluation. The patient's current use of an anti-TNF drug raised concern for granulomatous infectious etiologies including tuberculosis, histoplasmosis, and cryptococcosis. The interferon gamma release assay T-spot was negative, and the patient denied history of tuberculosis or recent exposure to a known case. The cell blood count showed moderate lymphocytopenia (420 cells/mL). A fourth-generation human immunodeficiency virus test was negative. Blood cultures had no microbial growth. A percutaneous transabdominal omental biopsy and paracentesis were performed. The ascitic fluid had 1939 white blood cells, comprised of 71% lymphocytes, 18% histiocytes, 4% neutrophils, and 7% others. No malignant cells or microorganisms were present. The omental biopsy had granulomatous inflammation and fungal forms on Gömöri methenamine silver stain, suggestive of *Histoplasma*. No acid-fast bacilli were seen (Figure 2).

The patient was admitted to the hospital. Intravenous liposomal amphotericin B at 3 mg/kg was started and infliximab was stopped. The following day, the urine *Histoplasma* antigen (IMMY Histoplasma capsulatum galactomannan EIA, Mayo Clinic Laboratories, Rochester, MN) value was 0.65 ng/mL (negative: 0.00–0.10 ng/mL, indeterminate: 0.11–1.10 ng/mL, positive, ≥1.11 ng/mL). *Histoplasma* immunodiffusion and mycelial antibody tests were negative, but a complement fixation test for yeast antibodies was positive with a titer of 1:64. The fever resolved by day 4 of antifungal treatment. After

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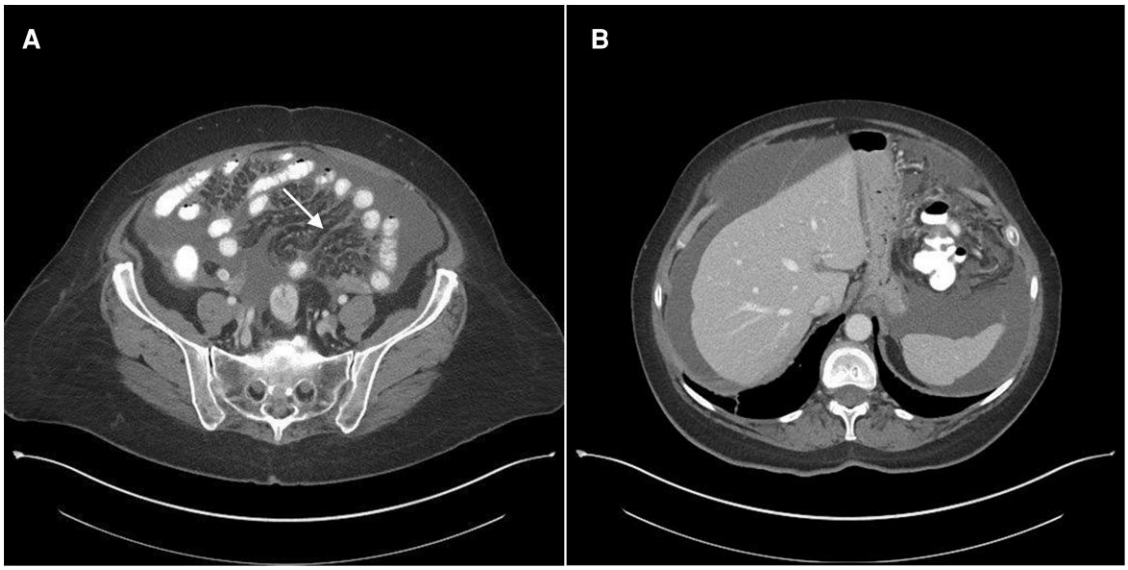

Figure 1. CT scan of the abdomen and pelvis with contrast. (*A*) Soft tissue stranding throughout the omentum (arrowhead), mild dilation of proximal small bowel, and no distinct mass. (*B*) Moderate to large ascites.

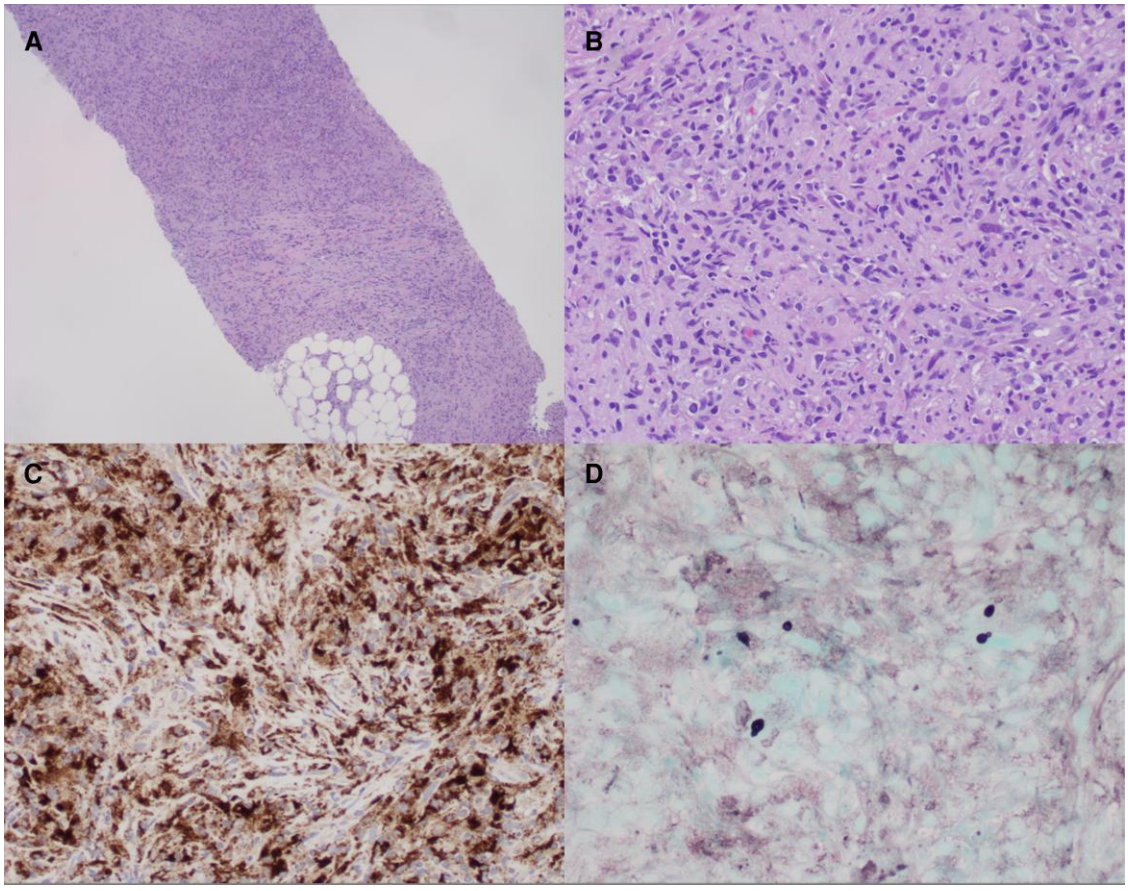

Figure 2. (*A*) Hematoxylin and eosin (H&E) stain, 4× image of the diagnostic core biopsy showing a diffuse cellular process infiltrating adipose tissue; (*B*) H&E stain, 20× image showing the cell population composed of epithelioid histiocytes; (*C*) CD68 immunostain, 10× image highlighting the cellular infiltrate that confirms the histologic impression of histiocytes; (*D*) Gömöri methenamine silver stain, 40× image showing the presence of budding yeast forms suggestive of Histoplasma.

14 days of amphotericin B treatment, the patient was discharged from the hospital on oral capsules of itraconazole, administered at 200 mg 3 times a day for 3 days as a loading dose, followed by 200 mg twice a day thereafter, achieving a therapeutic serum level of >1.1 mg/mL (reference values: > 0.5 mg/mL for a localized infection and >1.0 mg/mL for a systemic infection) and serum hydroxyitraconazole level of 1.9 mg/mL (no therapeutic range was established). A few weeks later, the omental biopsy lesion culture grew *Histoplasma capsulatum*. After further questioning, the patient stated that her next-door neighbor's empty pool was a bat reservoir and that the wind occasionally blew dust likely containing desiccated bat droppings into her yard.

The urinary *Histoplasma* antigen became negative by week 4 of antifungal therapy. Serum CA-125 levels rapidly normalized in a few weeks. After 1 year of antifungal treatment, the patient continues to do well with no symptoms. A follow-up CT scan of the abdomen and pelvis was obtained after 12 months of antifungal treatment and showed almost complete interval resolution of peritoneal histoplasmosis with persistent mild diffuse omental stranding. No ascites or residual lymphadenopathy were present in the imaging study.

LITERATURE REVIEW AND DISCUSSION

H. capsulatum is acquired by inhalation of microconidia, most commonly from a soil source. The transformation of *H. capsulatum* from conidia to yeast occurs in the alveoli and is followed by phagocytosis by pulmonary macrophages. Innate and cell-mediated immune responses are initiated to limit the replication of the fungus. The organisms may disseminate from the lungs to other organs, but symptomatic disseminated infection is uncommon in immunocompetent patients. *H. capsulatum* may persist in granulomas for life in healthy hosts. If an infected individual subsequently develops depressed cell-mediated immune responses, reactivation leading to disseminated disease may occur [2].

Gastrointestinal manifestations of histoplasmosis are pleiotropic and occur most commonly as a result of a disseminated infection. Indeed, *H. capsulatum* has been identified in the gastrointestinal tract of 70%–90% of autopsy cases as part of disseminated disease. However, only 3%–12% of those patients were symptomatic at presentation [3, 4]. Gastrointestinal histoplasmosis lesions appear to be most common in the ileocecal valve region because of the abundance of lymphoid tissue. Symptoms are non-specific and may include fever, abdominal pain, diarrhea, or oropharyngeal ulceration. The disease can also present with gastrointestinal bleed, obstruction, and perforation leading to peritonitis. Large obstructing intraluminal inflammatory colonic masses mimicking malignancy appear to be more common in patients with acquired immune deficiency syndrome . Small bowel histoplasmosis can result in strictures, inflammation, and mucosal ulcers at any site between the duodenum and terminal ileum, and can be misdiagnosed as inflammatory bowel disease, malignancy, tuberculosis, actinomycosis, or appendicitis. Other accompanying manifestations of gastrointestinal histoplasmosis include extensive retroperitoneal or mesenteric lymphadenopathy, hepatomegaly, splenomegaly, and omental thickening and nodularity [5]. We consider that the omental and peritoneal seeding in our patient was the result of hematogenous dissemination. Our patient did not present nausea, vomiting, or signs of bowel obstruction in the initial CT scan. However, as we did not perform gastrointestinal endoscopic studies, we could not rule out presence of asymptomatic intraluminal lesions.

Histoplasmosis presenting solely as peritonitis is an unusual event. Peritoneal infection has been described in patients who undergo CAPD and more rarely in cases of gastrointestinal histoplasmosis complicated by bowel perforation. Isolated CAPD-associated *Histoplasma* peritonitis, without concomitant evidence of disseminated infection, is extremely uncommon with only 8 cases reported between 1991 and 2020 [Table 1]. Although not proven, the role of the peritoneal dialysis catheter in the pathogenesis of histoplasmosis is suspected [6–13].

To our knowledge, our report describes the second case of isolated peritoneal infection unrelated to CAPD or bowel perforation. Bosshardt et al. reported a case of *Histoplasma* peritonitis in a 53-year-old man with Crohn's disease on adalimumab who presented with new-onset ascites, abdominal pain, and thickening of the ileum and cecum [14]. This patient's urine *Histoplasma* antigen was positive but below the limit of quantification, and the serum antigen was weakly positive at 2.4 U/mL. The diagnosis was made by exploratory laparoscopy with findings of characteristic fungal forms in the peritoneal biopsy. No evidence of dissemination outside the peritoneal cavity was present. The infection resolved after 2 weeks of treatment with liposomal amphotericin B followed by a 1-year-long course of itraconazole. Adalimumab was stopped once the diagnosis of histoplasmosis was made.

Patients receiving TNF inhibitors (eg, infliximab and adalimumab) are at increased risk of life-threatening *Histoplasma* infection with an associated mortality rate of 20%. These monoclonal antibodies impair the activation of macrophages and disrupt established granulomas [15]. Histoplasmosis is the most frequent invasive fungal infection among patients receiving TNF inhibitors and is 3-fold more common than tuberculosis. Reactivation of latent infection is suspected if calcified lesions in the lung or spleen are present, but a new infection appears to be the most frequent occurrence of *Histoplasma* infection [16]. The most common presentation of histoplasmosis in patients on TNF inhibitors is pulmonary infection, frequently accompanied by dissemination. Prompt initiation of antifungal therapy and discontinuation of the TNF inhibitor is usually

Table 1. Localized Peritoneal Histoplasmosis in Peritoneal Dialysis Patients: Case Reports, 1991–2020

Author Year	Age/ Sex	Histoplasma Growth in Peritoneal Fluid Culture	Histoplasma Serology/ Histoplasma Antigen	Antifungal Treatment and Duration	Catheter Removal	Outcome
Lim 1991 [6]	46/M	Positive	+/+	Fluc; IP 5-FC and AmB, UD	No	Resolved
Lopes 1993 [7]	50/F	Positive	ND/ND	AmB, UD	Yes	Asymptomatic at 6 mos.
Lopes 1994 [8]	64/F	Positive	ND/ND	AmB, UD	Yes	Asymptomatic at 6 mos.
Marcic 2006 [9]	27/F	Positive	ND/ND	AmB and Itra, 12 mos.	Yes	Resolved
Ijaz 2010 [10]	62/M	Positive	+/ND	Itra, 6 mos.	Yes	Resolved
Jain 2012 [11]	75/M	Positive	ND/-	Itra, 12 mos.	Yes	Resolved
Sardar 2018 [12]	75/M	Positive	ND/ND	Fluc, UD	No	Unknown
Ounsinman 2020 [13]	85/F	Positive	ND/ND	AmB and Itra, 6 mos.	Yes	Resolved

Abbreviations: AmB, amphotericin B; Fluc, fluconazole; 5-FC, 5-flucytosine; IP, intraperitoneal; Itra, itraconazole; mos., months; ND, not done; UD, unknown duration.

highly effective in controlling the infection, but a delayed diagnosis may have fatal consequences [17]. Secondary antifungal prophylaxis after resolution of the infection should be considered if the patient undergoes further treatment with TNF blockers or immunosuppressants that affect T cell immunity.

In our case, elevated CA-125 levels and CT findings with the appearance of omental caking and associated ascites were highly suspicious of an ovarian malignancy. This case that mimicked an advanced cancer is an example of the protean clinical presentations of histoplasmosis. However, tumor-like lesions of the peritoneal cavity with granulomatous inflammation (granulomatous peritonitis) encompass other etiologies, some of them infectious, with *Mycobacterium tuberculosis* being the most common. CA-125, a glycoprotein expressed in normal tissue, is a non-specific marker that can be elevated as a result of extensive peritoneal inflammation, most commonly associated to a malignancy such as ovarian cancer, as well as benign entities including endometriosis, pelvic inflammatory disease, peritoneal coccidioidomycosis, acute appendicitis and peritoneal tuberculosis. Level monitoring has been proposed to assess disease activity and response to treatment of peritoneal tuberculosis [18–22].

CONCLUSIONS

Isolated *Histoplasma* peritonitis is a very rare entity. Our case exemplifies histoplasmosis' elusive manifestations, including simulation of an advanced pelvic malignancy. A high level of suspicion and invasive procedures were required for diagnosis. TNF inhibitors are a predisposing factor for histoplasmosis, which is the most common invasive fungal infection in patients undergoing this therapy. Clinical clues of latent infection, such as pulmonary, splenic, or mediastinal lymph node granulomas, may be absent. Elevated CA-125 levels do not preclude the diagnosis of histoplasmosis, as this non-specific marker is elevated not only in malignancies but also in a variety of inflammatory conditions.

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Patient consent statement. Appropriate written authorization for the use and disclosure of protected health information was obtained from the patient with *Histoplasma* peritonitis. No Institutional Review Board approval was required.

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