Disseminated histoplasmosis presenting as pelvic inflammatory disease

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Introduction
Histoplasmosis is a common mycosis that is caused by Histoplasma capsulatum and is asymptomatic in most cases. Of those patients with acute infection, approximately 1 in 2000 will develop progressive disseminated infection, which occurs most frequently in patients with immunosuppressive conditions or extreme ages [1]. Chronic progressive disseminated infection rarely occurs in older adults who do not have immunosuppressive conditions [2]. The typical presentation is fever, fatigue, and weight loss. Disseminated histoplasmosis usually presents as diffuse or focal granuloma, which is described as macrophage infiltration into infected tissues. Although they are less common, tuberculoid granulomas do occur but tend to be seen in patients with lower fungal burden. Differential diagnosis for infectious granulomas includes histoplasmosis, tuberculosis, leprosy, cryptococcosis, coccidiomycosis, and cat scratch disease. The differential diagnosis for noninfectious granulomas includes sarcoidosis, Crohn’s disease, berylliosis, and Wegener’s granulomatosis. Histoplasmosis, particularly pulmonary histoplasmosis, is a great mimic of tuberculosis due to its similar symptoms of fever, weight loss, and night sweats. Once its yeast form is inhaled, it is carried throughout the body inside macrophages via the reticuloendothelial system, similar to tuberculosis. The lesions found in patients with chronic infection are usually oropharyngeal or gastrointestinal [3]. We report a 39-year-old immunocompetent female patient with no known significant medical history who presented initially with unilateral fallopian tube abscess and had a final diagnosis of disseminated multisystem histoplasmosis.

Case Report
A 39-year-old, white, female healthcare worker, with a past medical history significant for diverticulosis, was presented to the emergency department with acute abdominal pain. She also complained of increased stress, severe night sweats, and progressive weight loss beginning more than 10 weeks prior to admission. On physical examination, she was febrile and cachectic with no appreciable clinical lymphadenopathy. Erect chest radiograph was done to rule out cardiopulmonary causes, and the results were normal. Due to a history of diverticulosis, CT of the pelvis and abdomen was done to rule out diverticulitis.
The result showed abnormally dilated loops of the small bowel throughout the abdomen and pelvis, with the gas/fluid levels as shown in Figure 1. Multiple loops of distal small bowel demonstrated abnormal circumferential wall thickening with extensive mesenteric fat edema and inflammation. There was a large amount of free fluid in the pelvis and a 5.0 × 3.6 cm low-density lesion in the right adnexa with a thick ring of soft tissue. Laboratory tests revealed WBC 16,500 with a differential of 40 polymorphonuclear leukocytes with 58 bands, one metamyelocyte, and one mononuclear cell; hemoglobin 12.3, CA-125 39 U/mL, Na 132, K 3.4, Cl 93, CO2 26, and creatinine 0.93. Due to the patient’s reproductive age combined with the CT and laboratory results, pelvic inflammatory disease leading to tubo-ovarian abscess was suspected, and the gynecology service was consulted.

Diagnostic laparoscopy followed by laparotomy was performed. The laparoscopy on the right adnexa revealed an enlarged ovary with multiple small cystic lesions. The cyst was characterized as a mucinous-like yellow cyst measuring approximately 5 × 5 mm and was sent for culture. The left ovary was normal. Further dissection revealed extensive peritonitis with granuloma located at the left upper abdominal wall near the splenic flexure (Fig. 2), which was biopsied. Pathology reported signs of chronic inflammation but no malignancy. The culture obtained from draining the pyosalpinx was negative for aerobes and anaerobes; however, the cytology was not ordered. Special bacteriological stain used to identify acid-fast organisms, such as Ziehl–Neelson stain, was also not sent despite the clinical suspicion of tuberculosis. The postoperative diagnoses were right pyosalpinx and clinical tuberculous peritonitis. The patient was then discharged because the pathology report did not support the clinical diagnosis of tuberculosis.

Ten days later, she presented back to the hospital Emergency Room complaining of pleuritic chest pain. CT scan of the chest showed calcified granuloma in the right lower lobe with no hilar adenopathy and nonspecific pleural thickening, which corresponded to the location of the pain. Electrocardiogram and cardiac enzymes were negative. Quantiferon gold was obtained and was equivocal. The pain was believed to be secondary to pleurisy. After re-evaluating the patient’s symptoms and CT results, disseminated tuberculosis was suspected. A biopsy was planned to rule out histopathology diagnosis with diagnostic laparoscopy. Thoracoscopy was declined by chest surgeons due to insufficient evidence of pulmonary TB to justify a lung biopsy.

A second laparoscopy was performed to obtain biopsies of the clinically suspected tuberculous lesions, which showed similar – but more extensive – findings as the first laparoscopy. Disseminated lesions were observed throughout the abdomen and pelvic/parietal/visceral peritoneum (Fig. 3). Biopsies and documentary digital photographs were obtained. Cultures were sent for tuberculosic, actinomyces, and fungus, and they all came back negative. Due to continued symptoms of severe night sweats and fever, other possible etiologies were considered, including histoplasmosis. This was tested for using a histoplasmosis urine antigen test that returned positive at 6.47 (negative results are 0.00–3.50, positive results are >4.50). The patient was placed on itraconazole for disseminated histoplasmosis. After several weeks of treatment, the patient was symptom free.

**Discussion**

*Histoplasmosa capsulatum*, which is a soil fungus, is a common endemic mycosis that is found worldwide but is concentrated mainly in North and Central America. Within the United States, the infection is most common in the Midwestern states located in the Ohio and Mississippi River Valleys. Human infection with histoplasmosis is largely asymptomatic in patients who are immunocompetent. Symptoms that are closely associated with long-term inhalation exposure occur only when the inoculum is particularly heavy and cause acute pulmonary histoplasmosis [4]. Most patients who develop disseminated histoplasmosis are immunosuppressed (e.g., AIDS, solid organ transplantation, treatment with TNF alpha inhibitors). In addition, chronic progressive disseminated histoplasmosis occurs rarely in adults with no known immunosuppressive conditions [3]. Although most histoplasmosis infections are asymptomatic, pulmonary infection is the primary manifestation, and it varies from mild pneumonitis to severe acute respiratory distress syndrome [5]. Nonpulmonary histoplasmosis, particularly in the female genital
tract, is extremely rare. Although ovarian histoplasmosis has been reported in patients with systemic lupus erythematosus, this is a rare presentation for histoplasmosis [6]. Our case report involves a 39-year-old, immunocompetent, female patient who presented with the usual presentation of histoplasmosis mimicking tuberculosis, with symptoms of productive cough, night sweats, weight loss, fever, and shortness of breath, which are typical symptoms of tuberculosis infection. The unusual feature in this case of disseminated histoplasmosis was the presence of unilateral fallopian tube abscess in the female genital tract as the initial presentation. This is the first case to our knowledge, based on review of the English literature, of histoplasmosis presenting as tubal abscess to be reported.

Figure 2. The picture in the left upper quadrant shows extensive adhesion of the peritoneum. The picture in the left lower quadrant shows a granuloma at left upper abdominal wall near the splenic flexure. A–D: abdominal wall and abdominal cavity.

Figure 3. The pictures in all four quadrants show extensive spread of the granulomas throughout the abdominal cavity. A and B: abdominal wall; C and D: abdominal cavity.
The operative findings of the first laparoscopy and exploratory laparotomy were right pyosalpinx, right ovarian cyst, and extensive granulomatous peritonitis. It was clear that the patient had a right pyosalpinx due to the dark brown tissue, and approximately 50 mL of pus was drained from the site even though the cytology of the pus was not done. However, the extensive granulomas in the abdomen and pelvis (Fig. 1) made the pathology diagnosis of primary tubal abscess of pelvic inflammatory disease questionable. This patient’s clinical presentation combined with the appearance of the lesion during the surgery gave a high degree of suspicion for disease characterized by granulomas, such as tuberculosis. Being a young immunocompetent individual with no preexisting conditions, this patient should not have been at risk for infection with histoplasmosis, but having been a healthcare worker is indeed a risk factor for tuberculosis. The patient further denies any risk factors for exposure to histoplasmosis, such as living in a highly endemic area or in an area with poultry farms or other associated risk factors. Thus, disseminated tuberculosis was the primary differential diagnosis. Although fungal elements are occasionally visible, histoplasmosis is often difficult to identify on histological sections [7]. However, due to the nonspecific surgical pathology report of the sample lesion as chronic inflammation and the equivocal QuantiFERON test, the patient was discharged home with the diagnoses of right pyosalpinx with chronic pelvic inflammation.

The patient presented 10 days after discharge with persistent symptoms of night sweats, chills, intermittent fever, and an additional symptom of acute severe pleuritic chest pain. CT of the chest revealed thickening of the pleura with calcified granuloma in the right lower lobe plus multiple opacities. The fact that the patient’s original symptoms did not improve and new symptoms developed made the diagnosis of chronic pelvic inflammatory disease very unlikely. Disseminated tuberculosis was still favored due to clinical presentation, the initial lesion findings, and the calcified granuloma with multiple opacities on the CT of the chest. A second operation was performed to obtain biopsies from the granuloma and to rule out disseminated tuberculosis. Cultures were negative for tuberculosis, actinomycosis, and fungus. Due to high degree of suspicion of the false negative results, the patient was referred to an infectious disease specialist, who evaluated her for histoplasmosis with a histoplasmosis urine antigen assay. This assay returned a strongly positive result of 6.47 (negative results are 0.00–3.50, positive results are >4.50). Although the suspicion was high for tuberculosis, histoplasmosis should have also been one of the differentials because it is a great ‘masquerader’ of tuberculosis. Awareness of this infection is very important because the treatment can significantly lower the mortality rate. According to Kauffman et al. [8], mortality in patients who had disseminated disease and were not treated was 83% compared with 23% in patients who received treatment. Histopathology provides rapid diagnosis, but its sensitivity is <50% compared with urinary antigen detection, whose sensitivity can reach 95%. Routine histopathology plays an essential role in immunosuppressed or acutely ill patients to look for disseminated disease. If tissue is obtainable, it should be stained with methenamine silver or periodic acid–schiff stains as these are best to visualize \( H. capsulatum \). Therefore, a negative fungal culture should still raise suspicion of histoplasmosis [8].

**Conclusion**

Awareness of histoplasmosis infection is important because its progression to disseminated histoplasmosis can be fatal. When a patient presents with the usual symptoms of tuberculosis, such as weight loss, fever, night sweats, and shortness of breath, histoplasmosis should also be considered in the differential. Histoplasmosis is often misdiagnosed as tuberculosis. Physicians should maintain a high index of suspicion when a diagnosis of tuberculosis is not supported by the work up for the disease, as occurred in this case.

**Conflict of Interest**

The authors declare no conflict of interests.

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