

Peritoneal Coccidioidomycosis: a Rare Case Report and Review of the Literature

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ABSTRACT

Coccidioidomycosis is a fungal infection endemic to the southwestern United States that typically causes a self-limited pulmonary illness. Extrapulmonary dissemination is extremely rare and typically localized to the skin, bone, and meninges. The gastrointestinal system has generally been thought to be spared from this disease. This report describes a patient who was initially diagnosed with pulmonary coccidioidomycosis with mediastinal lymphadenopathy and skin dissemination. Ten months after completion of treatment, he presented with nonspecific abdominal pain and diffuse musculoskeletal and constitutional symptoms. Radiographic imaging revealed near resolution of previously noted thoracic findings but new peritoneal thickening and enhancement suggestive of peritoneal carcinomatosis. Laparoscopic biopsies confirmed *Coccidioides immitis* by culture and histology without evidence of other abnormalities.

This case is unique for several reasons. It is one of a relatively small number of cases that describes a diagnosis of peritoneal coccidioidomycosis and the first case identified in which a healthy patient developed extensive peritoneal disease in spite of near-complete resolution of pulmonary and skin manifestations after appropriate treatment. This case underscores the complexity of this disease and motivates more investigation into pathophysiology and treatment considerations of coccidioidomycosis in the gastrointestinal system. We will review the risk factors associated with dissemination, the interpretation of serologies, the characteristics of patients with peritoneal involvement, and finally, the current treatment guidelines.

Key words: coccidioidomycosis – disseminated – peritoneal – gastrointestinal

Abbreviations: AIDS: Acquired Immunodeficiency Syndrome; CF: complement fixation; HIV: Human Immunodeficiency Virus; ID: immunodiffusion; IDCF: quantitative immunodiffusion.

CASE REPORT

A 52-year-old Caucasian male presented with an acute respiratory illness followed by chest pain, dyspnea, nonproductive cough, weight loss, and sweats. The patient's medical history was only notable for localized melanoma status post definitive resection with negative margins and sentinel lymph nodes. He was not taking any medications. The patient reported traveling to construction sites in Arizona and San Diego three weeks preceding symptom onset. An emergency CT angiography was negative for a pulmonary embolus, but revealed one calcified tiny granuloma and

one noncalcified nodule in the periphery of the right lower lobe. Five months later, he developed fever, arthralgias, and the appearance of tender, subcentimeter nodular skin lesions on his chin and sternum. Repeat CT angiography was remarkable for new mildly enlarged lymph nodes in the mediastinum and numerous small nodules scattered through the bilateral lung fields. He underwent mediastinoscopy with video-assisted thoracoscopic surgery. Biopsies of his skin lesion and mediastinal lymph node confirmed *Coccidioides immitis* by histology and culture. An MRI brain, cerebrospinal fluid analysis, and coccidioidomycosis immunodiffusion (ID) were negative. He was treated with itraconazole tablets, and subsequently solution for six months with therapeutic levels. His symptoms improved but never resolved.

Ten months following completion of treatment, he was referred to our center for further evaluation of worsening fatigue, diffuse arthralgias, chest pain, weight loss, new and progressive abdominal bloating, vision changes, and occipital headaches. His evaluation to date had included negative HIV antibody, hepatitis B and C panels and normal complete blood count, comprehensive metabolic panel and total IgG level. Physical exam was notable for nystagmus at far right gaze, clear lungs, mild abdominal

distention with diffuse tenderness, and normal joints without synovitis. He had a white blood cell (WBC) count of 8,000 with relative lymphopenia of 16%. Flow cytometric analysis revealed normal lymphocyte subset profile with exception of an absolute CD19+ count of 50/ μ L (normal range 73-605). He was evaluated by our hematology colleagues, who concluded that the patient was low-risk for lymphoma or leukemia and that his lymphopenia was likely the result of acute inflammation. Recommended evaluation included a CT chest, abdomen and pelvis. CT chest was notable for resolution of previously seen multiple small pulmonary nodules along with decreased mediastinal lymphadenopathy. CT abdomen and pelvis, however, demonstrated new omental thickening with areas of loculated ascites and abnormal peritoneal thickening and enhancement, concerning for peritoneal carcinomatosis (Fig. 1). Diagnostic laparoscopy was performed, which was notable for moderate ascites and multiple whitish plaques along the omentum and peritoneum. Fluid aspiration as well as peritoneal and omental biopsies were obtained. Cytology was negative for malignancy, but histopathology and culture confirmed *C. Immitis* (Fig. 2). Serologic testing (Dr. Demosthenes Pappagianis at UC Davis performed all subsequent serological testing) was positive for both IgG and IgM; complement fixation (CF) was negative, but quantitative ID was positive at a 1:16 titer. Ophthalmologic evaluation, MRI, cerebrospinal fluid analysis, and nuclear bone scan were negative. The patient was admitted to the hospital and antifungal therapy with liposomal amphotericin B 5mg/kg daily was initiated. The patient developed acute renal injury, and his antifungal therapy was switched to voriconazole 4mg/kg intravenously twice daily after standard loading dosing. After three weeks of uninterrupted therapy, his abdominal discomfort had improved, his weight had stabilized, and his lymphocyte count had normalized. The coccidioidomycosis quantitative antibody remained stable at 1:16 titer, but the CT abdomen and pelvis revealed near resolution of ascites and peritoneal inflammation. Susceptibility testing was performed and the patient's antifungal therapy was changed to itraconazole

solution 200 mg by mouth twice daily. The patient's antibody titer decreased to 1:8.

DISCUSSION

Coccidioidomycosis is a fungal infection endemic to the southwestern United States and Mexico [1]. Infection occurs through inhalation of airborne spores. In 2011, the incidence of coccidioidomycosis was approximately 150,000 cases in the United States [1, 2]. From 1990 to 2008, an estimated 3,000 deaths in the United States were attributable to coccidioidomycosis [3]. Most infected patients develop a self-limited pulmonary illness with a rare number progressing to extrapulmonary disease [4]. The gastrointestinal tract is generally thought to be spared [5]. Risk factors for dissemination include: immunocompromised state, third trimester pregnancy, and malignancy [6]. For unknown reasons, African-Americans and Filipinos have a 10-175-fold higher risk for dissemination when compared to other ethnic groups [7]. There is also an association with individuals with blood group B and dissemination [8]. Our patient did not have any known risk factors, nor was an immunodeficiency identified after extensive evaluation. Although we initially queried the significance of his isolated lymphopenia, the fact that the lymphocyte profile normalized with treatment led to the conclusion that this was a manifestation as opposed to a risk for infection.

Serologies, such as CF and ID, are useful for both diagnosis and management of coccidioidomycosis. IgM is primarily detected with the ID method, whereas IgG can be detected using ID, quantitative ID (IDCF) and CF. The ID assay is a qualitative test, whereas the CF and IDCF allow for quantitative results. For the quantitative tests, it is recommended that the same laboratory performs the serial testing as titers can vary between laboratories [9]. Blair et al. conducted a retrospective review on serological tests of both immunocompetent and immunosuppressed patients diagnosed with coccidioidomycosis by histopathological



Fig. 1. (A) Mild peritoneal thickening and enhancement is seen, adjacent to the right hepatic lobe. Subtle nodularity is also present. (B) Peritoneal thickening and nodularity is noted (arrows). (C) There is mild peritoneal thickening and enhancement (arrow) in addition to areas of peritoneal nodularity (arrowheads) within the right hemipelvis.

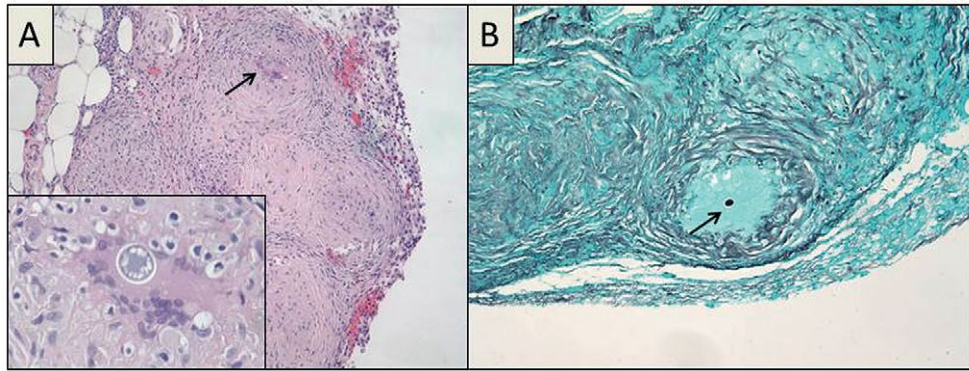


Fig. 2. A biopsy specimen obtained from the omentum demonstrates fibroadipose tissue involved by granulomatous inflammation surrounding spherules containing endospores of *Coccidioides immitis* (arrow; inset shows higher magnification of spherule with round fungal endospores) (Panel A, H&E). Low power view of spherule with thick cyst wall highlighted with Gomori methenamine silver stain (arrow) (Panel B, GMS stain).

confirmation [10]. Immunosuppressed individuals were less likely to be seropositive than immunocompetent individuals. In the immunocompetent group, 75% tested positive with CF and 73% tested positive with ID; whereas in the immunosuppressed group, only 67% and 53% tested positive using CF and ID, respectively. It is recommended that multiple serological methods be used in immunocompromised patients to maximize the diagnostic yield. The limitations of serologic testing were apparent in our patient; despite serious disseminated disease, his titer by quantitative ID was only 1:16. Studies demonstrate that individuals with disseminated disease have titers exceeding 1:16 [11]. In one study specifically looking at peritoneal coccidioidomycosis, the median antibody titer was 1:128 [12]. On the other hand, a review of thirty cases of peritoneal coccidioidomycosis demonstrated that those with negative CF titers had isolated peritoneal involvement, as seen in our patient [5]. This suggests that patients with isolated peritoneal coccidioidomycosis do not achieve high titers on serological testing, underscoring the need for further diagnostic investigation in this specific subgroup.

Extrapulmonary dissemination is seen in less than 1% of those diagnosed with coccidioidomycosis, most commonly involving the skin, bones, joints, and meninges [13]. A search of MEDLINE, PubMed, Embase, the Cochrane Library, and

the Index-Catalogue of the Library of the Surgeon-General's Office United States Army revealed 34 published cases of peritoneal coccidioidomycosis [5]. Both hematogenous spread from primary lung infection and ingestion of pulmonary secretions have been proposed as the underlying pathogenesis [14, 15]. Crum-Cianflone et al. reviewed published cases of peritoneal coccidioidomycosis from 1939 to 2006 (n=30) [5]. Since 2006, there have been four additional cases published (Table I). Among all 34 cases, the mean age at diagnosis was 38.2 years, and 76% were male. Most patients were Caucasian (n=15) followed by African-Americans (n=6) and Asian/Pacific Islanders (n=5). Although medical history was often not reported, 7 were previously healthy while 7 had histories notable for: renal failure (n=3), AIDS (n=2), status-post liver transplant (n=1), and lymphoma (n=1). The most common presenting complaint was abdominal distention (50%), followed by abdominal pain, hernia, and fever. Complement fixation titers ranged from negative (n=4) to 1:1024 (n=1) with a median of 1:128. Nine of the 34 patients were untreated and the majority (n=7) survived, possibly explained by the fact that this subset of patients had isolated peritoneal disease or peritoneal disease with only pulmonary involvement. Survival percentages for patients who received amphotericin B monotherapy (n=10) and fluconazole monotherapy (n=3)

Table I. Review of cases of peritoneal coccidioidomycosis published since 2006

| Author [ref] | Year | Age | Sex | Race | Medical history | Symptoms | Organ involvement | CF titer | Treatment | Outcome |
|--------------|------|-----|-----|------------------|--------------------------------------|---|--------------------------------|-----------------|-----------------------------|------------------------|
| Zhou [11] | 2014 | 21 | M | African American | Alcohol use disorder, Asthma | Abdominal pain and distention, nausea, dyspnea, weight loss | Lungs, duodenum, peritoneum | 1:256 | Amphotericin B, fluconazole | Died, 1.5 months later |
| Smith [16] | 2011 | 86 | M | NR | NR | Fatigue, nausea, weight loss | Small bowel, peritoneum | 1:8 | Fluconazole | Survived |
| Kokseng [17] | 2011 | 64 | M | White | ESLD with HCC s/p deceased-donor OLT | Cough | Lungs, peritoneum | Peaked at 1:512 | Fluconazole | Survived |
| Chung [18] | 2011 | 47 | F | NR | None | Abdominal bloating | Lungs, small bowel, peritoneum | 1:16 | NR | NR |

Abbreviations: CF: complement fixation; ESLD: end-stage liver disease; OLT = Orthotopic Liver Transplant; NR = Not Reported

were 80% and 100%, respectively. Four patients were treated with amphotericin then fluconazole, 3 of whom survived. Less commonly used treatment regimens included ketoconazole then amphotericin (n=2, both survived), amphotericin then ketoconazole (n=2, both died), and amphotericin then ketoconazole then itraconazole (n=1, survived).

For treatment of nonmeningeal disseminated coccidioidomycosis, the general consensus is to initiate azole therapy, the details of which are discussed elsewhere [2, 19-23]. With respect to peritoneal coccidioidomycosis, effective treatments have yet to be established. Limited published data exists regarding efficacy of amphotericin in the peritoneal fluid when compared to fluconazole. A study analyzing the concentrations of each drug in the peritoneal fluid of a patient with *Candida albicans* peritonitis showed that fluconazole achieved better penetration than amphotericin B [24]. Another case report supported fluconazole superiority, demonstrating a peritoneal penetration of greater than 60% [25]. The current treatment guidelines rely mostly on case studies and opinions of respected authorities.

CONCLUSION

This case underscores the complexity of treating this common disease and a need to further understand the biology of this pathogen even with our current armamentarium of antifungal agents. The unique aspect of our patient's case raises further questions, namely, the progression of clinically significant and extensive peritoneal disease despite the resolution of the pulmonary disease and near-resolution of his lymphadenopathy.

Conflicts of interest: No conflict to declare.

Authors' contributions: T.R.S. treated the patient, performed literature review, prepared manuscript. J.S. reviewed omental biopsy, prepared figure 2. J.B. supervised treatment of the patient specified in report, reviewed and edited manuscript. All authors approved manuscript to be published.

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