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REVIEW ARTICLE

Coccidioidal Peritonitis: A Review of 17 Cases

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Coccidioidomycosis is the second most common endemic fungal infection in the United States. Prior descriptions of coccidioidal peritonitis include only single cases. We describe 17 new cases previously unreported from healthcare institutions in California. The majority of cases presented with nonspecific abdominal complaints. PubMed and Google Scholar were searched for additional case series and only single case reports and reviews of single cases were found.

The diagnosis was confirmed by culture or histopathology and/or serology in each patient. All patients were treated with antifungal therapy. This case series demonstrates that coccidioidal peritonitis may be asymptomatic or present with only subtle abdominal symptoms. In a minority of our patients, the diagnosis was established incidentally during surgery. Based on this series, the overall outcome of coccidioidal peritonitis is favorable with long-term triazole treatment. The term cure is not usually used in disseminated coccidioidal disease because of the risk of late relapse.

Keywords. coccidioidal peritonitis; peritoneal coccidioidomycosis and omental caking; peritonitis.

Coccidioides immitis and *posadasii* are dimorphic fungi that cause coccidioidomycosis ([CM] Valley Fever). It is endemic to the Western Hemisphere and particularly the desert regions of the southwestern United States [1, 2]. Disseminated coccidioidomycosis was first reported in 1892 in Argentina. It is currently the second most common fungal infection in the United States [3]. Sixty percent of infections are asymptomatic, whereas others have a mild respiratory illness with only 10% ultimately diagnosed with any manifestation of the disease. One percent develop extrapulmonary disease [2]. *Coccidioides* may disseminate to any area of the body but is most commonly found in the soft tissues, bone, joint, and central nervous system ([CNS] eg, meningitis) [2]. Infection may occur at any site within the human body as demonstrated on prior autopsy studies [4].

Coccidioidal peritonitis is an uncommon site of disseminated infection and relevant understanding is limited. An assessment of typical presenting signs and symptoms and patient outcomes in a cohort of patients with this uncommon manifestation have not been previously described. This report details 17 new cases previously unreported.

METHODS

This study was approved by the Kern Medical Institutional Review Board (IRB). *International Classification of Diseases, Ninth Revision* (ICD-9) and ICD-10 codes were used to query the Kern Medical System electronic health record for a period of 10 years (2009–2019). Literature search was conducted on Marshal J. Fiese's monograph, PubMed, and Google Scholar using the following search terms: peritonitis, coccidioidal peritonitis, peritoneal CM, and omental caking. The search criteria included dates from 1939—present. A query of colleagues from other institutions resulted in an additional 9 cases for inclusion. A search of the Valley Fever Institute database was also used for case finding.

Patient charts were manually reviewed and clinical variables were collected including the following: demographic data, comorbid conditions, patient symptoms, type of infection, radiographic and serologic data, treatment, and outcomes. A waiver of consent was granted given the retrospective nature of the project. Inclusion required histopathologic and/or culture confirmation [5]. Cases that had inadequate data for diagnosis or analysis were excluded. Cases of secondary

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coccidioidal peritonitis related to a ventriculoperitoneal shunt in coccidioidal meningitis were not included.

Ethics Approval

Ethical approval to report this study was obtained from the Kern Medical IRB. Informed consent for patient information to be published in this article was not obtained.

Patient Consent Statement

The design of this work has been approved by Kern Medical IRB. Institutional Review Board exemption was obtained for waiving the patients' consent because this was not applicable to this study.

RESULTS

Analysis of the 17 cases revealed a mean age of 44 years (range, 21 to 66). Twelve patients were male, 5 patients were Latino, 7 patients were black, 4 patients were non-Hispanic white, and 1 patient was of Asian descent (Table 1).

The most common way these patients present (11 patients) is with abdominal pain. Two patients were found incidentally during the course of surgical procedures for another indication. The other 4 patients had nonspecific presentation (see Table 1).

In 9 cases, the diagnosis was suspected based on antecedent data and clinical presentation. In 4 cases, the diagnosis was not suspected and was ascertained via laparoscopy and histopathology. The remaining 4 cases were found with direct visualization of omental studding or pelvic mass during laparoscopic procedure.

Seven patients had a prior history of coccidioidal pneumonia presented with peritonitis less than 1 year from their diagnosis of pulmonary infection. Two patients had documented disseminated disease for at least 6 months before their diagnosis of peritonitis. The remaining patients presented with peritonitis as their initial presentation of CM. No patient presented with active lung and peritoneal disease simultaneously.

Imaging studies were performed on all patients. Three patients had ultrasonographic imaging, which revealed ascites and a "solid ovarian mass" in one. Thirteen patients had computerized tomography. Computerized tomography images found omental or mesenteric "caking" in 5 cases and ascites in 9 cases (Table 2).

Paracentesis was performed in 6 of the 17 cases. Serum ascites albumin gradient (SAAG) scores were calculated on only 4 cases and were all below 1.1 g/dL. Two were culture positive for *C immitis*. The other 4 cases were diagnosed serologically.

Table 1. Patients' Demographics, Medical History, Presenting Signs and Symptoms, SAAG Scores, and Mode of Diagnosis

Patient Numbers	Gender	Age	Ethnicity	Medical History	Presenting Symptoms	Presenting Signs	SAAG Score	Incidental Diagnosis
1	F	47	Black	Primary CM	Headache, loss of appetite, 100 lb weight loss	None	0.2	No
2	M	24	Latinx	Disseminated CM	Abdominal pain	Abdominal distention	N/A	No
3	M	66	Latinx	HTN, ESRD w/ Hemodialysis, DM1	Headache, abdominal pain	None	N/A	No
4	F	57	White	Primary CM	RUQ pain, nausea, vomiting, 15 lb weight loss	None	N/A	Yes
5	M	52	Black	Primary CM	Abdominal pain, 15 lb weight loss	Abdominal distention	0.2	No
6	M	33	Latinx	Primary CM	Abdominal pain	Increased abdominal girth	N/A	No
7	M	21	Latinx	None	Abdominal pain, nausea and vomiting	Abdominal distention	N/A	Yes
8	F	32	Black	Primary CM	Pelvic/flank pain	None	N/A	No
9	M	23	Latinx	None	Nausea, vomiting	None	N/A	No
10	M	47	Black	HTN, Cervical spinal stenosis	Abdominal pain, ascites, cutaneous lesions	None	0.8	No
11	F	37	White	COPD	Abdominal pain, cutaneous lesions	Abdominal distention	N/A	No
12	M	65	White	Eczema, Bronchitis	Fatigue, dry cough, weight loss, arthralgias, petechial rash on extremities, fever, night sweats	Abdominal distention	N/A	No
13	M	44	Asian	Irritable bowel syndrome	Myalgia, nausea, fatigue, weight gain, poor appetite, shoulder pain	None	N/A	No
14	F	44	White	None	Abdominal bloating, fever and malaise	None	0.4	No
15	M	53	Black	None	Abdominal pain, nausea, and vomiting	Abdominal distention	N/A	No
16	M	47	Black	None	Abdominal pain	Abdominal distention	N/A	No
17	M	55	Black	Disseminated CM	Nausea	None	N/A	No

Abbreviations: CM, coccidioidomycosis; COPD, chronic obstructive pulmonary disease; DM1, type 1 diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; N/A, not applicable; RUQ, right upper quadrant; SAAG, serum-ascites albumin gradient.

Table 2. Patients Radiographic, Procedural, and Serological Findings: Treatment Used and Clinical Outcomes

Patient Numbers	Diagnostic Imaging and Findings	Procedures and Findings	ID IgM	ID IgG	CF	Antifungal Therapy	Outcome
1	CT Chest: upper abdominal ascites with omental caking	Paracentesis	Reactive	Reactive	1: ≥512	IV AMB-L simultaneously with isavuconazonium	Continued therapy, no clinical evidence of peritonitis
2	CT Abdomen: ascites with omental caking and pelvic abscess	Paracentesis abdominal fluid grew *Coccidioides immitis*	Reactive	Reactive	1: ≥512	Initial AMB-L[b] transitioned to isavuconazonium	Continued therapy, no clinical evidence of peritonitis
3	CT Abdomen: peritoneal thickening of colon wall, bladder, and retroperitoneum	None	Nonreactive	Reactive	1:128	Fluconazole	Lost to follow-up
4	None	Laparoscopic cholecystectomy: visualized peritoneal studding Soft tissue biopsy positive for CM	Reactive	Reactive	1:2	Initial AMB-L[b] transitioned to posaconazole	Continued therapy, no clinical evidence of peritonitis
5	US and CT Abdomen: ascites with omental caking	Paracentesis	Reactive	Reactive	1:128	Fluconazole	Deceased secondary to CVA
6	CT Abdomen: ascites	None	Reactive	Reactive	1: ≥512	Fluconazole	Lost to follow-up
7	CT Abdomen with contrast: multiple fluid levels	Soft tissue biopsy: histopathology consistent with CM	Reactive	Reactive	1:64	Initial AMB-L[b] transitioned to voriconazole	Off therapy, no clinical evidence of peritonitis
8	Pelvic US: solid ovarian mass	Diagnostic laparoscopy: granuloma Soft tissue biopsy: fungus resembling *Coccidioides* spp	Reactive	Reactive	1:256	Fluconazole	Transferred to a different geographic location
9	US and MRI Abdomen: ascites	Paracentesis	Reactive	Reactive	>1:8	Fluconazole	Lost to follow-up
10	CT Abdomen and Pelvis: ascites and omental caking	CT guided needle biopsy of omentum: nonmalignant and GMS stain positive	Reactive	Reactive	1:128	Fluconazole	Lost to follow-up
11	CT Abdomen with contrast: ascites with omental caking	Paracentesis	Reactive	Reactive	1:256	Fluconazole	Lost to follow-up
12	CT Abdomen: miliary studding	Abdominal laparoscopy: ascites and studding visualized Biopsy: fungal culture grew *C immitis*	Reactive	Reactive	1:128	Initial AMB-L[b] transitioned to fluconazole	Off therapy, no clinical evidence of disease, followed[a]
13	None	Exploratory laparoscopy: miliary studding Fungal culture: *Coccidioides* Peritoneal biopsy: *Coccidioides*	Reactive	Reactive	1: ≥512	Isavuconazonium	Off therapy, no clinical evidence of disease, followed[a]
14	CT chest: multiple nodules CT abdomen/pelvis: ascites	Paracentesis grew *Coccidioides* spp	Positive	Positive	1:2	Fluconazole transitioned to posaconazole	Continued therapy, no clinical evidence of peritonitis[a]
15	CT Abdomen and Pelvis: studding of peritoneum	Diagnostic laparoscopy with cultures positive for *Coccidioides* spp	Positive	Positive	1:16	Fluconazole	Continued therapy, no clinical evidence of peritonitis[a]
16	CT abdomen/pelvis: military studding, omentum nodule and ascites	Diagnostic laparoscopy—positive histopathology	Positive	Positive	1:32	Fluconazole	Continued therapy, no clinical evidence of peritonitis[a]
17	CT chest: large mass CT abdomen/pelvis: ascites	None	Positive	Positive	1:8	Fluconazole transitioned to itraconazole	Continued therapy, no clinical evidence of peritonitis[a]

Abbreviations: AMB-L, amphotericin B liposomal; CF, complement fixation; CT, computed tomography; CVA, cerebrovascular accident; GMS, Grocott-Gomori's (or Gömöri) methenamine silver stain; ID, immunodiffusion; Ig, immunoglobulin; IV, intravenous; MRI, magnetic resonance imaging; US, ultrasound.

NOTE: Histopathology positivity defined in accordance with current European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions.

[a]Followed = still under care.

Six cases were diagnosed by laparoscopic visualization and biopsy. In case 4, peritoneal and omental "studding" were noted during cholecystectomy [6]. In case 7, omental seeding was noted during a laparoscopic procedure for small bowel obstruction and was therefore biopsied. Coccidioidal peritonitis presenting as a small bowel obstruction seems to be a unique presentation. In case 8, a laparoscopic evaluation was performed for an ovarian mass. Pathology and culture demonstrated *C immitis* [7]. This latter case demonstrated granulomatous inflammation and grew *Coccidioides* species. Case 3 showed "nodular lesions" on the small intestine, colon, uterus, liver, and gallbladder that were biopsied, and pathology noted granulomas and endosporulating spherules. In cases 4, 12, 15, and 16, studding was visualized during laparoscopy.

All 17 cases were serologically positive by immunodiffusion and complement fixation (CF). The CF titers varied from 1:2 to ≥1:512 (Table 1).

All patients with coccidioidal peritonitis received antifungal therapy [8]. Twelve patients were treated with fluconazole, 4 of whom were subsequently transitioned to broad-spectrum triazoles: 2 to posaconazole, 1 to itraconazole, and 1 to isavuconazonium. There are no clear data regarding perceived intolerance or perceived failure being the cause of change in drug treatment. Five were initially treated with amphotericin B liposomal then transitioned to triazole therapy: 1 each to fluconazole, voriconazole, and posaconazole and 2 to isavuconazonium. Ten patients are in continuing care, 1 patient transferred to an outside facility, 5 patients were lost to follow-up, and 1 patient died secondary to unrelated cerebrovascular accident.

DISCUSSION

Disseminated CM is associated with significant patient morbidity and mortality. In the absence of treatment, infection of the CNS is uniformly fatal [9]. Other forms of dissemination exhibit similarly high mortality rates with recent evidence finding a mortality rate of ~30% in those with non-CNS disseminated infection [10]. However, clinical experience has found different forms of non-CNS infection have widely disparate outcomes. Those with multisite dissemination or spinal disease exhibit a higher associated morbidity than those with isolated skin disease.

Peritonitis represents an uncommon form of disseminated coccidioidomycosis [11]. Our report of 17 patients found successful therapy with a complete clinical response to antifungals and no attributable mortality. The immunologic underpinning of disseminated coccidioidomycosis has not been fully elucidated, and it is possible the deficits predisposing towards peritoneal disease are less severe than those causing CNS or bone/soft tissue infection. The favorable outcomes we observed may also be secondary to the ability to achieve adequate antifungal drug concentrations within the peritoneum as opposed to other sequestered sites [12].

Peritonitis is a subtle manifestation of disseminated CM, and the diagnosis is almost always incidentally discovered after evaluation for malignancy or other concerns. Common presentations are vague abdominal pain, nausea, vomiting, and subclinical ascites [13, 14]. Complaints of subjective fever were also common. One case demonstrated small bowel obstruction. Imaging may demonstrate ascites, mesenteric, or peritoneal caking thus prompting concerns of underlying malignancy, although the differential diagnosis of intra-abdominal caking should include the following: CM or other fungal diseases, tuberculosis (Tb), and carcinomatosis [15].

In those patients with ascites, the diagnosis can be attempted based on standard peritoneal fluid analysis. Although rare, a positive culture is diagnostic. Ascites demonstrates an SAAG of <1.1 g/dL as expected for ascites from causes other than portal hypertension. Coccidioidal titers may be performed on peritoneal fluid, although only serum and cerebrospinal spinal fluid have been validated. Peritoneal fluid positivity may reflect serum serology. More commonly, the peritoneal fluid and serologic confirmation including SAAG and cell count are used to make the diagnosis. In patients without ascites, the differential diagnosis is more extensive and may require a more complicated diagnostic evaluation (laparoscopy and or other surgeries) [16].

It is of interest that no patient in our series was found to have concurrent active pulmonary and peritoneal disease. This lends further credibility to the working hypothesis that dissemination generally occurs at the time of initial infection [10].

Treatment includes long-term antifungal therapy [17–19]. Triazole antifungals, such as fluconazole, are frequently prescribed for a course of 2–3 years [19]. Consideration of a trial off antifungal therapy is then offered after extensive discussions with the patient [20]. Amphotericin B liposomal is rarely required. A minimum of 2-year follow-up posttreatment with appropriate coccidioidal serologic monitoring is proposed because coccidioidal disease is notorious for relapsing [8].

CONCLUSIONS

This patient series demonstrates the subtle presentation of abdominal symptoms in coccidioidal peritonitis. This diagnosis should be suspected in those within or traveling to coccidioidomycosis-endemic regions, although other granulomatous diseases (eg, Tb) and peritoneal carcinomatosis should also be considered [21, 22].

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