Coccidioidal pericarditis: a case presentation and review of the literature

Edward L. Arsura\textsuperscript{a,b,c,*}, Ravi K. Bobba\textsuperscript{b}, Chakradhar M. Reddy\textsuperscript{b}

\textsuperscript{a}University of Virginia, Charlottesville, Virginia, USA
\textsuperscript{b}Salem Veterans Medical Center, 1970 Roanoke Salem Boulevard, Salem, VA 24153, USA
\textsuperscript{c}Kern Medical Center, 1830 Flower Street, Bakersfield, CA 92305, USA

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Summary

Background: Pericardial involvement with \textit{Coccidioides immitis} is an infrequent occurrence with a relatively unfavorable prognosis.

Methods: A case of coccidioidal pericarditis is presented along with a review of the medical literature on coccidioidal pericarditis to give the clinician a better understanding of the various presentations, complications and outcomes of this disease. Medline (National Library of Medicine, Bethesda) was electronically searched covering the years 1966–2003 using search words coccidioidomycosis and pericarditis.

Results: Sixteen patients were identified from the literature review and one new patient was added. All the patients were males with a mean age of 37.5 years. Chest pain, dyspnea and cough were the most common presenting symptoms. Five patients had evidence of pericardial tamponade, pulsus paradoxus was noted in three patients and three patients presented with pericardial constriction. One patient had Kussmaul’s sign, one patient had pericardial frictional rub and another had pericardial knock. Cardiomegaly on chest x-ray was present in ten patients; EKG was noted to have low voltage in five and ST segment elevation in four patients. Delayed hypersensitivity to coccidioidal antigen was reported in nine patients and positive in eight patients. Complement fixation titters were positive in all 11 patients in whom it was assayed. Fifty-three percent of the patients with coccidioidal pericarditis died.

Conclusion: Coccidioidal pericarditis is a rare disease entity that has a relatively unfavorable prognosis, yet many patients present with diagnostic clues to this disorder. An enhanced understanding of the clinical features of coccidioidal pericarditis may lead to improved outcomes.

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Introduction

Infection with the pathogenic fungus *Coccidioides immitis* can lead to several clinical outcomes. Sixty percent of those exposed to the organism remain asymptomatic or demonstrate symptoms so mild that medical intervention is not sought. Approximately 40% develop symptoms which are usually pulmonary and self-limited in nature. In symptomatic patients, disseminated disease may develop in up to 5%. Extrapulmonary spread of the fungus is associated with significant morbidity and occasional mortality, especially in those with factors such as an ethnic predisposition or an immunocompromized state. The most frequent sites of dissemination include lymph nodes, skin and subcutaneous tissue, meninges and bones.¹

Pericardial involvement with *Coccidioides immitis* is an infrequent occurrence with fewer than 20 cases reported in the medical literature. Involvement of the pericardium can lead to diagnostic confusion with other disease entities that cause pericarditis and given its infrequent occurrence the diagnosis can be overlooked. In this article, a case of pericardial involvement due to *Coccidioides immitis* is presented along with a review of the medical literature on coccidioidal pericarditis. The clinical syndromes that may occur are highlighted, which may give the clinician a better understanding of the various presentations and complications of this disease.

In the literature review, 16 cases with pertinent clinical information were discovered.²⁻⁹,¹²,¹³ One additional case of coccidioidal pericarditis seen by the authors is added to bring the total to 17 patients. Two autopsy series¹⁰,¹¹ with 25 cases of coccidioidal pericarditis that did not include any relevant details were also reviewed, however these studies were not incorporated in this review.

Methods

Medline (National Library of Medicine, Bethesda) was electronically searched covering the years 1966–2003 using search words coccidioidomycosis and pericarditis. Case series focusing on coccidioidomycosis identified through Medline from 1966–2003 and culled cases with coccidioidal pericarditis from these series were also reviewed. To identify additional original studies, reference lists of reviewed articles dating back to 1929, the published meeting proceedings from the International Symposium on Coccidioidomycosis which meets every five years, and leading infectious diseases texts were also reviewed.

The identified patients’ demographic data reviewed clinical symptoms and associated findings were tabulated. Laboratory findings, EKG, chest x-ray, fluid analysis, therapy provided and clinical outcome were the noted parameters.

Case report

A 34-year-old Hispanic male presented in July 1996 after two months of fever, night sweats and a 20-pound weight loss. There was a non-productive cough. Chest x-ray revealed an anterior mediastinal mass, which on fine needle aspiration was positive for acid-fast bacilli. Skin tests for tuberculosis and coccidioidomycosis were both negative. The patient was started on isoniazid, rifampin and pyrazinamide and cultures were subsequently positive for *Mycobacterium tuberculosis*. He was found to have human immunodeficiency virus (HIV) infection and was started on antiretroviral therapy and trimethoprim/sulfamethoxazole. The CD4 count was 30/ mm³. Symptoms improved with weight gain and cessation of cough. In December 1996, the cough reappeared and a sputum analysis was positive for *Coccidioides immitis*. A complement fixation titer for *Coccidioides immitis* was positive at a dilution of 1:32. An evaluation for fungal dissemination including a lumbar puncture and bone scan were negative. Chest x-ray showed improvement in the mediastinal mass. Fluconazole at a dose of 400 mg daily was started.

Three months later a 3 × 5 cm left supraclavicular mass was noted, which on fine needle aspirate yielded both *Mycobacterium tuberculosis* and *Coccidioides immitis*. His medications were continued and there was a 50% reduction in the size of the supraclavicular mass although constitutional symptoms recurred along with a five-pound weight loss. Within two months a right 4 cm, right axillary lymph node was noted. A fine needle aspirate revealed spherules with endosporulation and culture of the lymph node was positive for *Coccidioides immitis*. The dose of fluconazole was increased to 800 mg/day.

Despite this therapeutic change additional lymph node enlargement occurred. The complement fixation titer for coccidioidomycosis was 1:256. He completed 12 months of antituberculosis therapy and was continued on fluconazole 400 mg daily.

Seventeen months after his initial presentation, he was admitted for worsening fever, weight loss, fatigue and anterior chest pain. Chest x-ray on admission revealed an increase in the cardiac silhouette consistent with pericardial effusion. An echocardiogram revealed a large pericardial...
effusion without evidence of pericardial tamponade. Analysis of pericardial fluid revealed a total white count of 3200 cells/mm$^3$ with 91% lymphocytes and 9% neutrophils. Pericardial fluid culture was positive for *Coccidioides immitis*. Acid fast stain and culture for *Mycobacterium tuberculosis* were negative. Treatment with amphotericin B was discussed, however the patient declined this option. The dose of fluconazole was increased to 1000 mg daily. The patient’s fever, chills, fatigue, and anorexia improved transiently, however within several weeks of discharge they recurred with consequent, progressive decline. At this point, the patient elected to have only comfort measures instituted and he died within several weeks.

Results

Age, sex and race

The present review describes 17 patients with coccidioidal pericarditis. All patients were male with a mean age 37.5 years (range 20–78 years). Ethnicity was described in 13 patients: four Caucasian, three African-American, three Hispanic, two Filipino and one Pacific Islander.

Clinical presentation

Chest pain was the most common symptom occurring in 12 patients. Dyspnea was noted in 11 patients, cough in six patients and orthopnea in four patients (Table 1).

Five patients showed evidence of pericardial tamponade with pulsus paradoxus in three patients. Equalization of pressures was noted in two patients (one patient had pericardial tamponade and the other had pericardial constriction). Four patients had pericardial constriction. Two of these patients had progression of pericarditis with tamponade to pericardial constriction. At times it was difficult to discern whether tamponade or constriction was the most prominent component and in one case there was clear evidence of effusive-constrictive physiology. One patient had Kussmaul’s sign. One patient had a pericardial friction rub and another had a pericardial knock. Two patients had physical findings of right-sided volume overload.

Seven patients had disseminated disease, with cutaneous spread or extrathoracic lymph node involvement being the most common sites of dissemination. Three patients had widespread dissemination. The underlying myocardium was involved in four patients (autopsy report).

Radiology, laboratory and microbiology

Chest x-ray findings were notable for cardiomegaly in ten patients and mediastinal adenopathy in four patients.

Electrocardiograms were performed in 12 patients. Five patients had low voltage, four patients had ST elevation, four patients had T wave inversions and two patients had non-specific ST-T wave changes.

In four patients, the diagnosis of coccidioidal pericarditis was made based on clinical findings with laboratory, x-ray and EKG support. The diagnosis was confirmed by culture of pericardial fluid in three patients and pericardial biopsy in four patients. In six patients, the diagnosis was established at autopsy.

Delayed hypersensitivity to coccidioidal antigen was reported in nine patients. It was positive in eight patients and negative in one (this patient was HIV positive and profoundly immunocompromized). In one patient, who developed disseminated disease, the skin test went from positive to negative. The complement fixation titer was positive in all 11 patients in whom it was assayed.

Pericardial fluid was obtained in nine patients and analysed in three patients, with lymphocytic predominance in two (WBC 50 x 10$^9$/L, 99% lymphocytes and 3.2 x 10$^9$/L, 91% lymphocytes) and 45% lymphocytes (WBC 4.7 x 10$^9$/L) in the third patient.

Treatment and outcome

Of the nine patients treated with antifungal agents, seven received amphotericin B, and two received fluconazole.

Nine patients died; six of these patients had disseminated disease. One patient died of tamponade, one patient died from pericardial constriction and one patient died in the first post-pericardectomy day. Eight patients recovered and three of these patients required pericardiectomy.

Discussion

Coccidioidal pericarditis is an infrequent complication of infection with *Coccidioides immitis*, a fungus endemic in desert regions of the southwestern United States, Central and South America. The pericardium is the primary cardiac structure that is involved by *C. immitis* with neither the myocardium nor endocardium being recognized clinically, although there have been reported autopsy
Table 1: Clinical, laboratory characteristics, treatments and outcomes of patients with coccidioidal pericarditis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
<th>Clinical features</th>
<th>Lab</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chest pain, dyspnea, orthopnea</td>
<td>NA</td>
<td>+CST</td>
<td>None</td>
<td>2 recurrences, died</td>
<td>Autopsy</td>
</tr>
<tr>
<td>2</td>
<td>Chest pain, dyspnea, orthopnea</td>
<td>Subcutaneous abscess</td>
<td>+CST</td>
<td>None</td>
<td>Died</td>
<td>Autopsy</td>
</tr>
<tr>
<td>3</td>
<td>Cough, dyspnea, orthopnea</td>
<td>Papular skin lesions</td>
<td>NA</td>
<td>None</td>
<td>Died</td>
<td>Autopsy</td>
</tr>
<tr>
<td>4</td>
<td>Cough</td>
<td>Right heart failure, constriction</td>
<td>+CST</td>
<td>None</td>
<td>Died</td>
<td>Autopsy</td>
</tr>
<tr>
<td>5</td>
<td>Chest pain</td>
<td>NA</td>
<td>+CST, +CFT</td>
<td>None</td>
<td>4 recurrences, recovered</td>
<td>Clinical</td>
</tr>
<tr>
<td>6</td>
<td>Chest pain, cough, dyspnea</td>
<td>Pericardial friction rub</td>
<td>+CST, +CFT</td>
<td>None</td>
<td>Recovered</td>
<td>Clinical</td>
</tr>
<tr>
<td>7</td>
<td>Chest pain, dyspnea, orthopnea</td>
<td>Tamponade</td>
<td>+CFT 1:128</td>
<td>Amphotericin B</td>
<td>Recurrent tamponade, died</td>
<td>Pericardial fluid analysis</td>
</tr>
<tr>
<td>8</td>
<td>Chest pain, dyspnea</td>
<td>Tamponade, pulsum paradoxus</td>
<td>+CFT, +CFT 1:32</td>
<td>Amphotericin B</td>
<td>Recovered</td>
<td>Culture of pericardial fluid</td>
</tr>
<tr>
<td>9</td>
<td>Chest pain</td>
<td>Pulsus paradoxus, right heart failure, pericardial knock, tamponade, constriction, adenopathy</td>
<td>+CFT, +CFT 1:128</td>
<td>Amphotericin B</td>
<td>Pericardiectomy recovered,</td>
<td>Pathologic study of pericardium</td>
</tr>
<tr>
<td>10</td>
<td>Cough</td>
<td>Skin lesions, adenopathy</td>
<td>+CST, +CFT 1:512</td>
<td>Amphotericin B</td>
<td>Recovered</td>
<td>Clinical</td>
</tr>
<tr>
<td>11</td>
<td>Chest pain, dyspnea</td>
<td>NA</td>
<td>NA, +CFT 1:128</td>
<td>Fluconazole</td>
<td>1 recurrence, recovered</td>
<td>Clinical</td>
</tr>
<tr>
<td>12</td>
<td>Cough, dyspnea</td>
<td>Pulsus paradoxus, equalization of pressures, constriction</td>
<td>NA</td>
<td>None</td>
<td>Pericardiectomy, died</td>
<td>Clinical</td>
</tr>
<tr>
<td>13</td>
<td>Chest pain</td>
<td>Adenopathy</td>
<td>−CST+CFT 1:256</td>
<td>Fluconazole</td>
<td>1 recurrence, died</td>
<td>Culture of pericardial fluid</td>
</tr>
<tr>
<td>14</td>
<td>Chest pain, dyspnea</td>
<td>Kussmaul sign, tamponade, equalization of pressures, constriction</td>
<td>+CFT 1:8</td>
<td>Amphotericin B</td>
<td>Recovered, pericardiectomy</td>
<td>Pathologic study of pericardium</td>
</tr>
<tr>
<td>15</td>
<td>Chest pain, cough, dyspnea, facial plethora</td>
<td>NA</td>
<td>NA</td>
<td>Amphotericin B</td>
<td>Pericardiectomy, died</td>
<td>Pathologic study of pericardium</td>
</tr>
<tr>
<td>16</td>
<td>Dyspnea, weight loss</td>
<td>NA</td>
<td>+CFT 1:2</td>
<td>Amphotericin B &amp; Fluconazole</td>
<td>Complete Pericardiectomy</td>
<td>Autopsy</td>
</tr>
<tr>
<td>17</td>
<td>Dyspnea and chest pain</td>
<td>NA</td>
<td>+CFT 1:16</td>
<td>None</td>
<td>Complete pericardiectomy</td>
<td>Autopsy</td>
</tr>
</tbody>
</table>

CST: coccidioidal skin test; CFT: complement fixation titer; NA: not applicable; Patient numbers and references: (1,2,3)4 (4,5,6)7 (7,8,9)10 (11)11 (12)12 (14)15 (15)16 (16,17)17.
Clinical pericardial involvement is detailed in only 17 patients.\textsuperscript{2–9,12,13} The presentation can be acute, progress rapidly to effusive-constrictive physiology or the presentation can be that of a chronic constrictive process.\textsuperscript{5,6}

Relapsing pericarditis is seen in some patients. The initial symptom complex for patients with coccidioidal pericarditis is usually nondescript, and does not differ significantly from pulmonary coccidioidomycosis, with chest pain and pulmonary symptoms predominating. However, certain features of coccidioidal pericarditis such as orthopnea, pulsus paradoxus, Kussmaul’s sign, pericardial friction rub, and a pericardial knock can help the clinician arrive at the correct diagnosis. Four patients had a history of coccidioidomycosis treated with antifungals and then developed symptomatic pericardial disease.

The organism may arrive at the pericardium by one of several routes. In many of the patients, the exact mechanism is unclear. For example, eight patients had pulmonary infiltrates and three patients had pleural effusions, which could be the source of contiguous spread. Mediastinal lymphadenopathy in four patients could be the source of lymphatic spread. Hematogenous spreading to the pericardium is a possibility in those with disseminated disease.

The most sensitive finding in coccidioidal pericarditis was the presence of cardiomegaly on chest x-ray that was found in nine patients. EKG abnormalities were present in all patients who had the study performed. Four patients had EKG changes that were highly suggestive of pericardial fluid (low voltage) and four patients had EKG abnormalities indicative of pericarditis (diffuse ST segment elevation).

Eight of nine patients had positive delayed hypersensitivity to coccidioidal antigen and serum complement fixation titer was positive in all patients in whom it was measured. These findings in the appropriate clinical context of patients living in or visiting an endemic area would assist with the diagnosis. Pericardial fluid, when analysed, revealed a lymphocytic predominance in two patients and 45% lymphocytes in the third.

Only two patients, including the additional case, were immunocompromized (HIV infection and non-Hodgkin’s lymphoma).

Seventy-five percent of the reported cases occurred in individuals with an ethnic/racial predisposition.

The morbidity and mortality of coccidioidal pericarditis is significant. Fifty-three percent of the patients with coccidioidal pericarditis died. The majority of those who died had disseminated disease, which has an intrinsically worse prognosis.

Four patients who died were diagnosed before the advent of effective antifungal therapy. Autopsy series of disseminated coccidioidomycosis identified pericardial infection in 5–14%.\textsuperscript{9}

Pericardiectomy for coccidioidal pericarditis has been successful in young patients.\textsuperscript{6} The goal is complete resection, freeing the heart from the constrictive process. Pericardiectomy was necessary in seven patients and was planned in one patient who died. Nine patients had pericardial constriction. Pericardiocentesis was carried out in four patients and one patient required pericardiectomy.

An interesting and striking finding in coccidioidal pericarditis is that all reported cases were males. A male predominance is noted in other forms of coccidioidomycosis but not in such a marked fashion as seen in coccidioidal pericarditis. There is no obvious explanation for this gender preference, however occupational exposure or a hormonal influence on the growth of \textit{C. immitis} has been postulated.

Coccidioidal pericarditis is a rare disease entity that has a relatively unfavorable prognosis. Many patients present with clues to the presence of this disorder and it is hoped that an enhanced understanding of coccidioidal pericarditis will lead to improved outcomes.

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