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Case Report

Fulminant Acute Intrathoracic Coccidioidomycosis in South Texas: Case Report and Mini-Review of the Literature

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Abstract

Coccidioidomycosis, also known as San Joaquin Valley Fever or Valley Fever, is a fungal infection caused by Coccidioides spp (*Coccidioides immitis* or *Coccidioides posadasii*). The disease is endemic to the semi-arid regions of The Americas. It is especially prevalent at the border between the United States and Mexico. We present a rare case of fulminant disseminated coccidioidomycosis with the involvement of pericardium, skin, and lungs with cavitary disease-causing recurrent bilateral pneumothoraces. Pericarditis due to Coccidioidomycosis is extremely rare and has been reported in the literature in at least 23 cases. Despite the high mortality of such cases (55%), this young patient survived. For an aggressive short-term treatment at the hospital, Amphotericin B at 5 mg/kg/day was superior to Amphotericin B at 3 mg/kg/day and 400 mg fluconazole. However, the patient was later switched to 200 mg fluconazole twice a day for long-term treatment due to a reaction after prolonged exposure to Amphotericin B.

Keywords: *Pulmonary Coccidioidomycosis; Disseminated Coccidioidomycosis; Pericardial Effusion; Pneumothoraces; Amphotericin B; Fluconazole*

Abbreviations

ANA: Antinuclear Antibodies; ANCA: Anti-Nuclear Cytoplasmic Antibodies; ARDS: Acute Respiratory Distress Syndrome; CF: Complement Fixation; EIA: Enzyme Immunoassay; HIV: Human Immunodeficiency Virus; IDCF: Immunodiffusion Assay for Complement Fixation; IDTP: Immunodiffusion Assay for Tube Precipitin Antibody; IL-17: Interleukin-17; PCR: Polymerase Chain Reaction; SpO_2%: Oxygen Saturation of Hemoglobin %; TLR2: Toll-Like Receptor 2; TLR4: Toll-Like Receptor 4; TP: Tube Precipitin

Introduction

Coccidioidomycosis, also known as cocci, Valley fever, California fever, desert rheumatism, and San Joaquin Valley fever, is a disease caused by the fungi *Coccidioides immitis* or *Coccidioides posadasii*. Coccidioidomycosis is endemic to several semi-arid regions of The Americas. Most pulmonary infections due to cocci resolve spontaneously in the immunocompetent host. However, a minority of the patients with pulmonary coccidioidomycosis develop life-threatening dissemination, particularly the immunosuppressed population. There are cases of immunocompetent patients who develop a fulminant course.

Case Presentation

A 23-year-old white Hispanic male with diabetes mellitus type 2 living in the South Texas area of United States was admitted with productive cough of thick white sputum, progressive dyspnea, night sweats, poor appetite, and loose stools diarrhea for one week before admission. He had a weight loss of 15.4 kg (34 lbs.) in one month.

At admission, the patient temperature was 36.9ºC, pulse was elevated at 130 beats-per-minute, respiratory rate rapid of 22 breaths-per-minute, normal blood pressure of 114/67 mmHg, pulse oximetry (SpO_2%) at 96%. Upon a pertinent physical exam, he looked acutely ill, tachypneic and sweating. The patient had dry mucous membranes at the mouth with an oral thrush. The lungs had bilateral inspiratory fine crackles with expiratory rhonchi. The heart had regular rate and rhythm with tachycardia without murmurs, gallops or rubs. The abdominal exam was benign, non-tender without masses, organomegaly with normal bowel sounds. There was no clubbing or cyanosis at the extremities. He had a faint pink discoloration at both lower extremities anteriorly, not painful to touch. There was no lymphadenopathy at axillary, neck or inguinal lymph nodes.

The chest x-rays showed bilateral lung infiltrates consistent with pneumonia. He denied hemoptysis, pleuritic chest pain, polyuria, polydipsia, headaches, nausea, vomiting, gluten intolerance, HIV, congenital diseases, cigarette smoking, recreational drug use, alcohol use or sexually transmitted diseases.

He was started on broad-spectrum antibiotics including vancomycin, levofloxacin and a piperacillin/tazobactam combination according to the antibiotic stewardship program in our region. After therapy failure, he was intubated and connected to a mechanical ventilator. The chest x-rays demonstrated an enlarged cardiac silhouette with an echocardiogram showing a large pericardial effusion without tamponade. Night sweats, spiking fever and diarrhea persisted for more than a week.

The laboratories showed leukocytosis with white blood cells (WBC) count of 17 530 cells/µL, Hemoglobin A1c was 8.7 mg/dL and Fasting Blood Glucose 197 mg/dL. The sputum culture, blood, and urine culture were negative for bacteria and viruses. The following blood laboratories were negative: human immunodeficiency virus (HIV), antinuclear antibodies (ANA), anti-cytoplasmic nuclear antibodies (ANCAS), and antiphospholipid panel. The stool samples were negative for viruses, bacteria, ova and parasites, and fat despite the presence of fecal leukocytes.

A diagnostic bronchoscopy was done, revealing spherules in the transbronchial biopsy tissue specimen, diagnostic of acute pulmonary coccidioidomycosis (Figure 1). The AFB and the PCR for Mycobacterium tuberculosis were both negative in the bronchoalveolar lavage. The patient was added high doses of fluconazole 400 mg daily, but without response for 5 days. It was then switched to liposomal Amphotericin B 3 mg/kg/day due to renal insufficiency with acute tubular necrosis. However, the patient continued in a critical state with fever and chills. The Amphotericin B dose was increased to 5 mg/Kg/day and after 3 days, he was afebrile and without night sweats. However, he had persistent hypotension and hyponatremia requiring norepinephrine as a vasopressor. The cortisol levels were low at 5 µg/dL considering the significant stress with multiorgan failure suggestive of acute adrenal insufficiency.

Hydrocortisone improved hypotension allowing to wean off the vasopressor norepinephrine. After 2 weeks, he was extubated, and the pericardial effusion decreased to small in size, but he developed bilateral pneumothoraces with multiple cavities seen in the CT scan of the chest, requiring bilateral chest tubes. The skin lesions were attributed to erythema nodosum; it persisted despite treatment. After 6 weeks of treatment with Amphotericin B, the patient had a fever and a pruritic skin rash that improved after diphenhydramine and discontinuation of Amphotericin B. He was started then in fluconazole 400 mg orally every 12 hours with a good response. After fluconazole, the pleural effusion decreased significantly without air leak and the chest tubes were removed.

The patient had a wasting syndrome at the end of 8 weeks of hospitalization complicated with critical illness myopathy. The pericardial effusion resolved, as well as the erythema nodosum. He was discharged home with minimal walking capacity and an excellent appetite. Hydrocortisone was discontinued without complications. On a follow-up at the clinic, he was able to walk and increased 30 pounds of weight in 3 months with oral treatment of fluconazole 200 mg orally twice a day. The treatment is expected to conclude after a year.

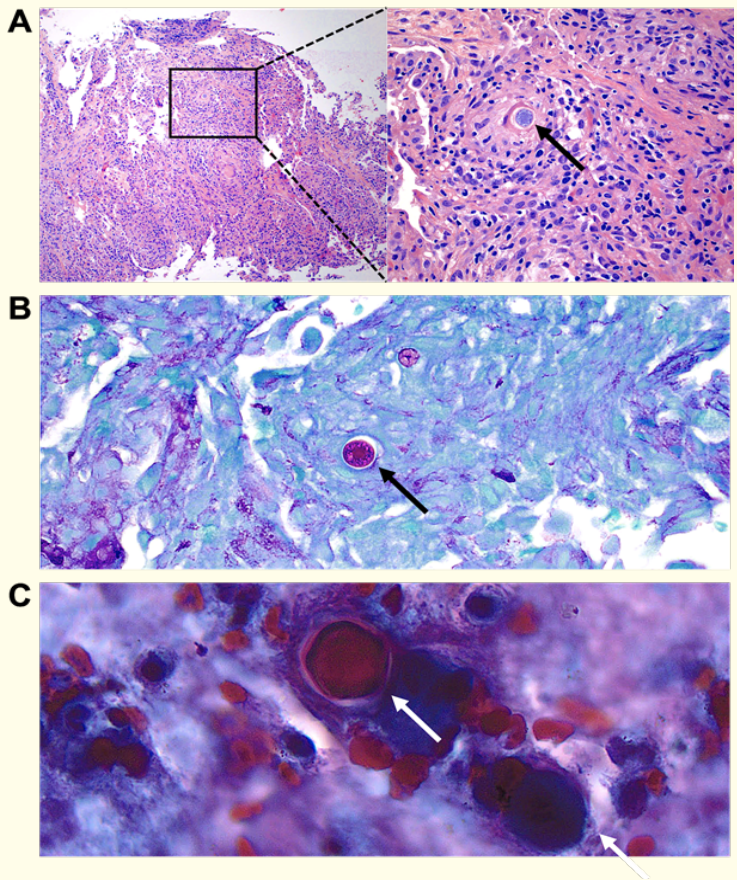

Figure 1: *Bronchial tissue with spherules. (A) Hematoxylin and Eosin (H&E) stain. (B) Periodic Acid Schiff (PAS) stain. (C) Field stain.*

Discussion

Pulmonary coccidioidomycosis is a primary pulmonary infection caused by soil fungi *Coccidioides immitis* and *Coccidioides posadasii* [1]. Coccidioidomycosis is restricted to the Americas, and is endemic to semi-arid areas, having been found in patients at the Mexican-American border, the Venezuelan states of Zulia, Lara and Falcón, the Northeast Region of Brazil, and the Gran Chaco comprised of Argentina, Bolivia, and Paraguay [2]. While *Coccidioides immitis* is seen in North America, *Coccidioides posadasii* is found in Brazil [3].

Occupations with a greater risk of exposure are those involving disturbed soil, including construction, military trainees, farming and archaeology [4]. If the soil is disturbed, the spores become airborne. Strong winds can transport the spores to great distances [5]. It can also be seen after earthquakes and other events where large portions of soil are disturbed [6]. In 2016, the state of California saw 13.7 cases per 100 000, the most seen in Kern County of the Central Valley, where 250 cases per 100 000 were reported [7].

African-Americans have 10 times more risk to develop disseminated disease [8-10] and hospitalizations [11]. Filipino also had 10 times increased the risk of disseminated disease [12]. These data suggest an underlying immune defect among African-Americans and Filipinos that place them at risk for dissemination. However, for American Indians, they have 3 times the risk of disseminated disease [13] and mortality compared to whites [14] suspected due to higher environmental exposure than genetics [15].

Immunocompetent patients with diabetes mellitus are more likely to develop a cavitary disease and relapsed infection [16]. If the serum glucose is more than 12.2 mmol/L (220 mg/dl) the diabetic patients are more likely to develop a disseminated infection and to require treatment, but their infection was less likely to resolve [17].

In nature, the fungi are arthroconidia, and in a host are spherules, so the biology is dysmorphic [18]. The hallmark of human systemic dimorphic fungi (*Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis, Penicillium marneffei, Sporothrix schenckii*) is a phase transition that's temperature-induced. At ambient temperature, these fungi grow as mold; in humans, they convert to yeast after inhalation [3].

On 2006, twenty-three cases of coccidioidal pericarditis were found in the literature [19-22]. Of these twenty-three cases, only 55% survived. Acute respiratory distress syndrome (ARDS) with pulmonary coccidioidomycosis has a high mortality [23,24]. Other places of dissemination involve bone/joints [25,26], spine [27-29] and meningitis. Meningitis carries a poor prognosis, present in 33 to 55% of severe cases, requiring lifetime treatment with fluconazole in survivors because the relapses can be as high as 78% and azoles can be tolerated for years [30-33]. Coccidioidal meningitis treated with adjunctive corticosteroid therapy produces a significant reduction in secondary cerebrovascular events [34].

Pleural coccidioidomycosis produces an exudative effusion [35-37]. Pulmonary manifestations include cystic lung lesions with rupture into pleural space, miliary dissemination [38-42]. Erythema nodosum occurs in 50% of cases [43]. Other skin manifestations of coccidioidomycosis include non-pruritic papular lesions, erythema multiforme, molluscum contagiosum like lesions, acute generalized exanthema, reactive interstitial granulomatous dermatitis and Sweet's syndrome [38,43-45]. More rare organs involved in cocci include the placenta [46], small bowel [47], mediastinum [35], cardiac valves [48], genitourinary [49] and the liver [50].

The incubation period is 7 - 21 days [7,51]. The clinical spectrum of the disease varies in severity: 60% are asymptomatic that usually resolves without intervention [32,52]. Less than 1% of patients have mild signs and symptoms, 38% have pneumonia with a flu-like illness that usually resolves and also results in long-lived immunity [53]. Fewer than 1% have life-threatening pneumonia with disseminated life-threatening infection [54,55]. This last group lacks a proper immune response and is associated with a poor outcome [55]. At-risk populations include organ transplant recipients, chemotherapy for cancer, patients using biological therapy agents such as anti-tumor necrosis factor for rheumatoid arthritis cytokine therapy (especially lack of IL-2 or Interferon gamma) [56-58].

The standard diagnostic tool is through the identification of spherules with either the superior silver stain or hematoxylin and eosin (H&E) [59]. A commercially available skin test for the spherule derived skin test antigen (Spherusol, Nielsen Biosciences: San Diego, California, USA) was approved in 2011 in the USA [60-62]. There have been cases of cross-reactions to histoplasmin and paracoccioidin [63].

Serologic tests are the most widely used tests. These include complement fixation (CF), which uses an IgG-reacting antigen that binds to fungal chitinase, and tube precipitin (TP), an antigen that reacts with IgM and binds to the fungal cell wall polysaccharide [64]. TP antibodies may be detected earlier in infection than CF antibodies. Later, Immunodiffusion (ID) test were developed known as immunodiffusion assay for complement fixation (IDCF) and immunodiffusion assay for tube precipitin antibody (IDTP), respectively. The newest, most sensitive serologic tests are commercial enzyme immunoassay (EIA) kits which may detect infection earlier than any other aforementioned diagnostic [65]. These use proprietary coccidioidal antigens [66].

While there are several molecular diagnostics available, no routine test is specific to coccidioidomycosis. Diagnosis is therefore challenging. Enzyme Immunoassay IgM identifies 90% of cases, but the diagnosis is delayed due to results wait time with false positive results in asymptomatic patients [67-69].

Complement fixation test can also be used for diagnosis and is useful to assess the severity of the disease and the response to the infection [70]. Polymerase chain reaction (PCR), especially real-time PCR tests are not commercially available due to cross-reactivity concerns but showed high sensitivity and specificity [71,72].

Coccidioidal galactomannan antigen test in urine (MiraVista Diagnostics: Indianapolis, Indiana, USA) has a sensitivity of 71%, but a cross-reactivity of 11% of other endemic mycoses, particularly histoplasmosis [73]. However, in disseminated coccidioidomycosis, 100% cases do not have cross-reactions. This last test is particularly useful in the immunocompromised population [64,67-69,74,75].

Coccidioides cultures are particularly dangerous due to reports of inhalation of arthroconidia in laboratory employees [52]. Even at biosafety level 3, employee safety may be compromised. Therefore, routine *Coccidioides* tests are not proactively performed. Nevertheless, routine fungi culture can see *Coccidioides* flourish.

Amphotericin B is the drug of choice for disseminated coccidioidomycosis [33]. The polyenes interact with ergosterol-containing fungal membranes and disrupt them by puncturing these membranes, but they can also interact with cholesterol-containing membranes and thus injure host cells [75]. Besides the pore creation in the membranes, Amphotericin B induced oxidative damage to the cells and produce immunomodulation through Toll-like receptors: TLR2 and TLR4 in conjunction with the CD14 receptor. The signal is converted via adaptor protein MyD88. Then, NF-kB is activated and migrates to the nucleus. Depending on the Amphotericin B and receptors involved, pro or anti-inflammatory cytokines are expressed. Amphotericin B also induces the Accumulation of free radicals (reactive oxygen intermediates, and nitric oxide) through induction of nitric oxide synthase and NADPH oxidase.

Lipid formulations of Amphotericin B allow to use higher doses and decrease renal toxicity [33,76]. The pleural concentration of Amphotericin B is 50% of plasma concentration. However, liposomal preparation has 5 - 25% of plasma levels. Voriconazole is the best antifungal agent penetrating the pleura and lung with similar concentration to plasma levels. Fluconazole has an excellent concentration in lung tissue, but studies in pleural fluid concentrations are unknown [77,78]. In this report, the patient had no more air leaks with decreased pleural fluid output after the change from Amphotericin B to fluconazole at the last week of hospitalization.

Azoles have multiple mechanisms for the development of both primary and acquired resistance, including mutations in the gene encoding lanosterol 14α-demethylase (ERG11), so that azoles can no longer block its catalytic activity, and amplification of ERG11, so that Erg11 molecules overwhelm the inhibitory capacity of the azole [79-81]. Also, some fungal species have amplified or induced efflux pumps to remove azoles from the fungal cell and therefore from the target. This rise in azole resistance has been observed consistently in hospitals for years and has even been linked, in some cases, to the environmental use of fungicides in agriculture.

Adrenal insufficiency was not attributed, directly, to the infection because CT abdomen did not show enlarged adrenal glands as found in many cases of adrenal gland infection by fungi [82].

Chronic mucocutaneous candidiasis genetic defects may cause coccidioidomycosis susceptibility by decreasing T cell number with impairment of IL-17 function. This patient had oropharyngeal candidiasis on admission treated with fluconazole. Patients with active coccidioidomycosis have persistent present IL-17A, making their cytokine profile distinct. Also, those with a non-meningeal disseminated disease have an increased inflammatory cytokine response and diminished Th1 responses that modulate over time [83,84].

Conclusion

Fluconazole was inferior to Amphotericin B in severe disseminated coccidioidomycosis. Amphotericin B dosage increased from 3 mg/kg/day to 5 mg/kg/day made a positive difference in the patient's response. Immunocompetent patients with uncontrolled diabetes mellitus have been associated with cavitary lung disease and disseminated disease. Pneumothorax can develop in cavitary coccidioidomycosis and can be recurrently requiring chest tubes. Pericardial effusion due to coccidioidomycosis is rare but improved after antifungal therapy without surgery. Temporary adrenal insufficiency occurs in patients with coccidioidomycosis. On the other side, replacement therapy with corticosteroids improved hypoglycemia and hypotension by adrenal insufficiency.

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