CLINICAL VIGNETTE

Pulmonary Coccidioidomycosis Requiring High Flow Nasal Cannula

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Case Presentation

A 64-year-old male presented with one week of a cough productive of yellow sputum that was associated with subjective fevers and night sweats. He denied shortness of breath and sore throat and had no recent history of travel, sick contacts, outdoor gardening, cave exploration, or pets. He had lived for many years in the Antelope Valley, north of Los Angeles, was retired without any known exposure to dusts, chemicals, or molds. He drank about 5 alcoholic drinks per week, did not smoke or use illicit drugs. His past medical history included recently diagnosed type 2 diabetes mellitus and hypertension controlled on daily amlodipine and losartan. Surgical history included an open reduction and internal fixation of his left lateral ankle 10 years ago.

On examination, the patient was afebrile with a heart rate of 118 beats/minute, respiratory rate of 20, blood pressure of 181/95 mmHg, BMI 35.1, and an oxygen saturation of 90% on room air. Physical examination was notable for numerous dental caries, a chronic ulcer over the old surgical site on his left lateral ankle, and decreased breath sounds in the right lower and left upper lung fields without significant respiratory distress. Initial laboratory studies were significant for sodium 134 mEq/L, glucose 194 mg/dL, WBC 21.6K cells/cm^3 (91% neutrophils, 1.2% eosinophils), and HgA1c 7.1%. Apart from a slightly elevated alkaline phosphatase level at 179 IU/L, his liver function tests were otherwise within normal limits. Procalcitonin was 1.28 ng/mL and d-dimer 5.01 mg/L. A respiratory viral panel was negative for SARS-CoV2, respiratory syncytial virus, and influenza A/B. Urine legionella antigen was negative, HIV nonreactive, and an evaluation for tuberculosis was initiated and eventually resulted negative. Coccidioides serologies were obtained.

The patient's initial chest x-ray demonstrated bilateral infiltrates (Figure 1A), and subsequent CT thorax with contrast showed near total consolidation of the left upper lobe with air bronchograms as well as ground-glass opacities of the bilateral lobes (Figures 2A and 2B). Pulmonology and Infectious Disease specialists consulted after admission. The patient was initially empirically treated for community acquired pneumonia with ampicillin/sulbactam, ceftriaxone, and azithromycin and placed on supplemental nasal oxygen. On hospital day four, the coccidioidal serologies returned positive for IgM and IgG with absolute values of 0.384 IV and 2.068 IV, with antibody complement fixation dilution of 1:8.

Intravenous amphotericin B at 5 mg/kg/day was initiated for severe pulmonary coccidioidomycosis given the patient's respiratory compromise. On hospital day 5, the Podiatry was consulted to examine the chronic left ankle ulcer, with radiographs to evaluate for possible disseminated coccidioidomycosis. Repeat examination and imaging were unremarkable. By hospital day 6, the patient's oxygenation status continued to decline, and he was started on high flow nasal cannula (HFNC) oxygen with FiO_2 of 80%. A repeat CXR demonstrated severe diffuse and bilateral patchy pulmonary consolidations, especially in the left lower lung zone and right lung base, that were significantly worse compared to admission (Figure 1B). Given his declining respiratory status, a broad pneumonia testing was repeated and ultimately resulted negative. On hospital day 7, a lumbar puncture showed CSF: WBC 3k cells/cm^3, RBC 3k cells/cm^3, glucose 102 mg/dL, protein 29 mg/dL, and CSF positive for coccidioidal IgG but negative for IgM. The positive CSF coccidioidal IgG raised concern for coccidioidal meningitis and daily oral fluconazole, 800 mg was given for 4 days before discontinued given the absence of clinical evidence of fungal meningitis.

The patient's oxygenation status gradually improved with amphotericin B treatment. Three days before discharge, he was weaned off HFNC, and intravenous amphotericin B was discontinued, replaced with oral fluconazole 600 mg daily. After a 22-day hospital stay, the patient was discharged home with home oxygen and plans to continue an extended course of oral fluconazole. Outpatient follow-up was scheduled with Pulmonology and Infectious Diseases.

Discussion

Coccidioidomycosis is an infection caused by fungi of the genus *Coccidioides*. This infection is caused by the inhalation of *Coccidioides* spores, called arthroconidia, and occurs in the southwestern United States, primarily in Arizona and in the San Joaquin Valley of California.[1] There are two species of *Coccidioides* that are known to cause disease in humans: *Coccidioides immitis* in California and *Coccidioides podsadasii*

in Arizona. Infections due to *Coccidioides* have greatly increased over the last two decades, rising almost 800% in California from 2000 to 2018.[2] The reasons for this increase are likely multifactorial, including increased testing, climate factors that favor *Coccidioides* proliferation and dispersal, and increasing land development in endemic areas. Risk factors for acquiring coccidioidomycosis include living in an endemic area, exposure to a recent dust-spreading event, and older age.[1] The risk of severe coccidioidomycosis is increased in patients with diabetes, recent history of cigarette smoking, lower income, patients of African and Filipino descent, and older age.[3,4]

Primary pulmonary infections are by far the most common manifestations of coccidiodomycosis infections, although rarely, there can be dissemination to skin, bones, other soft tissues, and the meninges.[3] Most cases of pulmonary coccidiodomycosis are asymptomatic or minimally symptomatic and therefore do not come to medical attention.[5] However, when symptomatic, patients frequently present with pleuritic chest pain, cough, and fever 1 to 3 weeks after exposure. Additionally, patients can present with other systemic complaints including drenching night sweats, prolonged fatigue, arthralgia, erythema nodosum, and weight loss.[6] Laboratory studies typically show only mild leukocytosis, and in a minority of patients, eosinophilia may be found.[3] Imaging may mimic community acquired pneumonia and often show a dense, unilateral infiltrate with ipsilateral hilar adenopathy often in the upper lung lobes. Rarely, pleural effusions, empyema, or pulmonary nodules develop. Some patients may have imaging findings suggestive of a diffuse reticulonodular pneumonia which is associated with more severe disease and is best visualized on CT imaging.[6]

Pulmonary coccidioidomycosis should be considered in any patient presenting with symptoms suggestive of community acquired pneumonia in an endemic area. Additional reasons to suspect Coccidioides infection include recent travel to endemic areas, prolonged respiratory illness, imaging findings consistent with coccidioidomycosis, continued pneumonia after appropriate antibiotic treatment, presence of erythema nodosum or erythema multiforme, and presence of systemic symptoms including night sweats, weight loss, and marked fatigue.[6] Serological testing is usually performed for the diagnosis of coccidioidomycosis using enzyme-linked immunoassays (EIA) for IgM and IgG, with follow-up immunodiffusion testing if the initial EIA is positive.[6] Oftentimes, in early infection, antibody testing may be negative. Therefore, it is important that a fungal culture and KOH preparation of sputum or bronchioalveolar lavage with direct examination be obtained in a patient with high suspicion for coccidioidomycosis.[6,7] Patients with coccidioidomycosis and a new persistent headache should undergo a diagnostic lumbar puncture with CSF antibodies and fungal culture. There should be a high index of suspicion for coccidioidal meningitis as it presents often nonspecifically and without nuchal rigidity or positive Brudzinski or Kernig signs.[8]

Treatment of pulmonary coccidioidomycosis depends on disease severity and patient risk factors. In patients without significant risk factors and with mild disease, supportive care is sufficient. Current guidelines recommend oral fluconazole 400 to 800 mg daily or itraconazole 200 mg twice daily for 6-12 weeks for patients who have infiltrates involving more than half of one lung or bilateral lungs, symptoms longer than 3 weeks, loss of >10% of body weight, severe immunocompromised states, 2nd or 3rd trimester pregnancy, or anticoccidioidal complement-fixing antibody concentrations $\geq$ 1:32.[4,9] Azole therapy may also be indicated in frail, elderly patients, patients of African or Filipino descent, or patients with diabetes. Instead of azoles, the intravenous lipid formulation of amphotericin B dosed at 3-5 mg/kg/day is indicated in patients with severe disease who require respiratory support. These patients should be transitioned to azole therapy once their respiratory status significantly improves.

Patients with pulmonary coccidioidomycosis require long-term monitoring. Patients with mild disease not requiring antifungal treatment should be monitored for clinical, radiographic, and serologic improvement every 3 months for 1 full year. Patients who received antifungal therapy have a higher risk of relapse, so monitoring should be continued for 2 years.[3] Long-term sequelae of pulmonary coccidioidomycosis can include prolonged fatigue and lethargy that does not respond to antifungals. In some cases, permanent damage to lung tissue can occur, resulting in chronic supplemental oxygen dependence.

Conclusion

Coccidioidomycosis is a common infection in Southern California and Arizona and should always be considered in patients from endemic areas presenting with symptoms suggestive of community acquired pneumonia, especially in those with insidious onset of symptoms or symptoms that persist after initial treatment. While most patients with coccidioidomycosis require only supportive care or a 1-2-week treatment course with azoles, some patients develop severe coccidioidomycosis. Risk factors for severe coccidioidomycosis includes older age, diabetes, smoking, low-income status, and African or Filipino descent. Severe coccidioidomycosis requires respiratory support and prolonged antifungal therapy, beginning with amphotericin B and then transitioning to azole therapy once respiratory status improves. Recovery may be prolonged, and patients should be closely monitored for 1-2 years after their initial treatment course for signs and symptoms of disease relapse.

Figures

A) **B)**

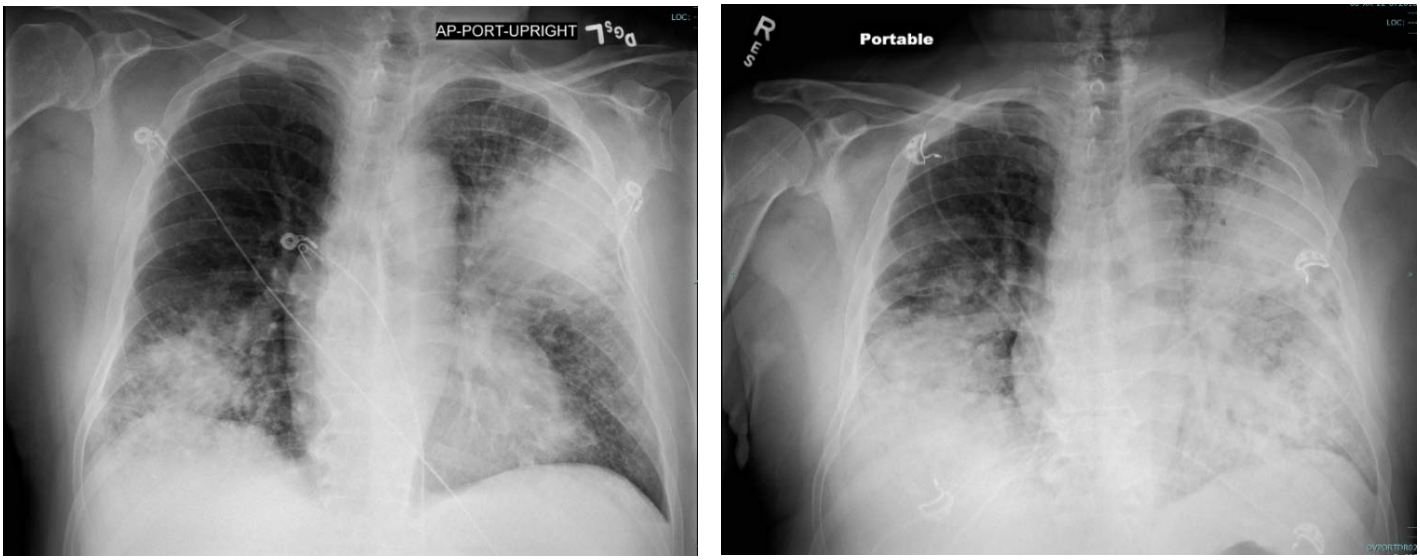

Figure 1: A) Chest x-ray on day of admission showing larger areas of confluent airspace disease in left upper lung zone and right lower long zone, consistent with pneumonia. B) Chest x-ray from hospital day 5. Worsened diffuse and bilateral pulmonary consolidations are visible, especially in the left lower lung zone (severe) and right lung base (severe).

A) **B)**

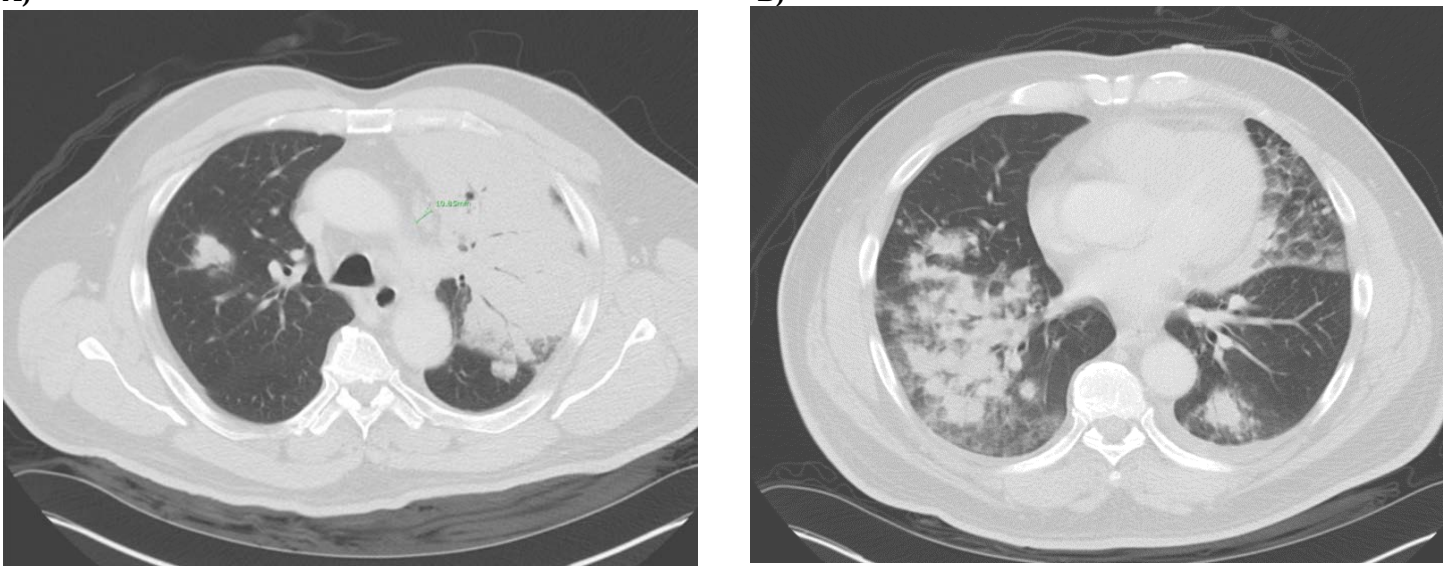

Figure 2: CT thorax with contrast from day of admission with findings consistent with multifocal pneumonia. A) CT imaging showing near total consolidation of left upper lobe with air bronchograms and borderline enlarged mediastinal lymph nodes, with one marked by a green line. B) CT imaging showing patchy consolidations and ground glass opacifications in the bilateral lower lobes.

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