CLINICAL VIGNETTE

Coccidioides Infection with Nonspecific Radiological Findings and Atypical Pathological Findings

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Case Report

A 72-year-old man, who is a lifelong nonsmoker with a past medical history of essential thrombocytosis, hypertension, gastroesophageal reflux disease and coronary artery disease, presented with a five-day history of dry cough, left sided pleuritic chest pain, and shortness of breath. He is retired and does home remodeling as a hobby. He recently was pressure treating a wood door and was not wearing a mask. He was seen at his primary care doctor's office, and a chest radiograph was performed and was interpreted as left lung pneumonia. He started a course of levofloxacin and later switched to amoxicillin/clavulanate as his symptoms progressed, including a fever of 101.6^{O}F. He presented to the emergency room one week after starting antibiotics. Repeat chest radiograph demonstrated increased left lung opacification and a left pleural effusion that was small in size (Figure 1). Patient was admitted and treated for community acquired pneumonia with intravenous antibiotics including ampicillin/sulbactam and azithromycin. Chest computed tomography (CT) scan demonstrated left upper and lower lobe interlobular septal thickening, ground-glass opacities, and consolidative opacities (Figure 2). Laboratory tests showed a white blood count of 18,070/uL, 78% polymorphonuclear cells, 7% bands, 2.6% lymphocytes, 6.1% monocytes, and 2.6% eosinophils, sedimentation rate was 32 mm/hour (0-20), and a serum C-reactive protein level was 18.30 (<0.744).

Bronchoscopy showed marked acute inflammation and bronchoalveolar lavage revealed coccidioides spherules on Grocott methenamine silver stain. Transbronchial biopsies of the left upper lobe revealed focal alveolar septal fibrosis, mild and chronic inflammation, and focal necrosis (Figure 3a-c). The biopsies were negative for carcinoma, and no granulomas were identified. *Coccidioides* serologies later resulted positive for IgM, IgG, and tube precipitin assay with prior negative studies in 2006. Twenty days after the bronchoscopy, cultures of the bronchoalveolar lavage grew *Coccidioides immitis*.

The patient was initially started on high dose oral fluconazole of 800 mg daily, which was decreased to 400 mg daily for six months total. His symptoms of dry cough, dyspnea, and pleuritic chest pain resolved within a month of treatment; however, symptoms recurred approximately 6 months later. A repeat CT scan demonstrated substantial decrease in the amount of ground-glass and consolidative opacities in the left upper and lower lobes but persistent ground-glass and consolidative opacities in the lingula. Fluconazole was restarted for an additional three months with complete symptom resolution.

Discussion

Coccidioidomycosis is a common cause of fungal pneumonias caused by direct inhalation of spores that live in the soil of endemic areas.[1,2,3] *Coccidioides* spp. are divided into *Coccidioides immitis*, located primarily in California, and *Coccidioides posadasii*, generally located outside of California.[2,4] Most infections are caused by the inhalation of spores after soil disruption.[1,2] Pulmonary coccidioidomycosis has been seen with increasing frequency in those working with soil, particularly in circumstances that result in aerosolization of dust such as construction sites, farms, excavation sites, and military training sites.[1,3,5] Incidence of pulmonary coccidioidomycosis and hospitalizations have been rising over the past several years,[6,7] making accurate and rapid diagnosis increasingly important. Diagnosis relies on clinical presentation, laboratory findings, and radiographic features.[1]

Most people with *Coccidioides* spp. infection are asymptomatic or have a mild self-limiting disease.[1,2] Symptomatic primary pulmonary infection manifests similar to other community acquired pneumonias with fatigue, fevers, chills, and cough found in almost all patients presenting with mild to moderate disease.[8] The classic triad of "desert rheumatism" may appear in some acute cases and include symptoms of fever, arthralgia, and erythema nodosum.[1] In endemic regions, pulmonary

coccidioidomycosis can account for up to 29% of community acquired pneumonias.[2,3] Severe coccidioidomycosis, defined as requiring hospitalization, occurs in about 20% of cases.[9] Risk factors for severe disease compared to mild disease include older age (average age 42 years in one study), active smoking history, and diabetes.[9] Disseminated coccidioidomycosis, including skin, soft tissue, bone, and neurologic involvement occurs in only about 1% of all patients and is more common in the immunocompromised host.[1] Resolution of symptoms once on treatment takes up to 19 weeks on average;[10] therefore, expedient diagnosis of pulmonary coccidioidomycosis is important.

Diagnosis of coccidioidomycosis is often made by the combination of clinical, radiographic, and laboratory findings. Serologic testing for *Coccidioides* including IgM and IgG enzyme immunoassay (EIA) can be unreliable and produce high rates of false negative in the early phase of infection, and the positive predictive value of this test relies largely on the pretest probability of pulmonary coccidioidomycosis.[1,11] IgM antibodies by immunodiffusion are positive in about 50% of patients within 1 week and positive in up to 90% of patients within 3 weeks of infection, while the IgG antibodies are detected within 1-3 months of infection.[3] One study found that 87% of immunocompetent and only 67% of immunosuppressed patients with coccidioidomycosis had positive antibody EIA.[10] The incidence of false positive *Coccidioides* IgM antibody EIA approaches 20%, and the cause of false positives is not known.[12] Similarly, serum complement fixation, which allows for antibody quantification and serologic confirmation after positive antibody EIA, peaks about 4 weeks after exposure, and may not be reliable during early acute infection.[1,8] However, when all serologic modalities are combined, one study found at least one test was positive in 95% of immunocompetent and 84% of immunosuppressed patients with microbiologically or histopathologically confirmed coccidioidomycosis.[10]

Radiographic features of acute pulmonary coccidioidomycosis are varied and non-specific.[1,3] Similar to bacterial pneumonias, chest radiographs commonly show lobar or segmental pulmonary opacities.[1,2,3,13,14] Consolidative opacity is seen in up to three quarters of patients with acute disease and is most commonly unilateral with a perihilar or basilar predominance.[4,14] Small and/or large nodular opacities may also be seen.[4,10] A small case series reviewing chest CTs during acute pulmonary coccidioidomycosis show the most common finding is multiple nodular opacities, present in 87% of patients. Just under half of these patients had accompanying interlobular septal thickening.[15] Mediastinal lymphadenopathy is present in 20-40% of cases on chest CT and is more often seen in severe disease.[2,3,5,14] Typically only 2-8% will have cavitary opacities on chest radiographs during acute primary infection,[1,5] but many will have cavitary nodular opacities visualized on chest CTs.[15]

Microbiologic analysis by culture and histopathologic staining of body fluid or tissue biopsy remains the gold standard for diagnosis of coccidioidomycosis. *Coccidioides* spp. are identified on microscopic examination by presence of the spherule filled with endospores.[1] Bronchoscopy with bronchoalveolar lavage can result in rapid diagnosis in the majority of cases.[1,16] Respiratory culture can take three days to upwards of three weeks to grow *Coccidioides* spp.[2,16] Cytological analysis, available more quickly than final culture results, is positive in up to one-third of patients with eventual culture positive pulmonary coccidioidomycosis.[16] Transbronchial biopsy can increase the diagnostic yield of bronchoalveolar lavage.[1,16] Lung tissue biopsy has been shown to reveal *Coccidioides* spp. after fungal staining in all patients with culture positive pulmonary coccidioidomycosis.[16] However, if there are hyphal elements present, *Coccidioides* spp. can be difficult to distinguish from other mold, such as *Histoplasma* spp. and *Blastomyces* spp.[11] Biopsies also classically show granulomatous inflammation, both necrotizing and non-necrotizing.[17] Cavitary lesions are distinguished pathologically by palisading fibroblasts and fibrosis with chronic inflammation in the cavity wall, neutrophils with necrosis inside the cavity, and lymphoid hyperplasia with chronic bronchiolitis in adjacent lung tissue.[18]

Conclusions

Our patient presented with a subacute, nonspecific respiratory illness. Imaging findings were not specific for classic pulmonary coccidioidomycosis. Diagnosis was definitively made with microscopy and culture. Histologic tissue examination was markedly different than reported finding in the literature, with notable absence of granulomatous inflammation and instead dominated by alveolar septal fibrosis, which is a nonspecific finding that can be seen in chronic interstitial lung diseases such as nonspecific interstitial pneumonia or smoking related respiratory bronchiolitis-associated interstitial lung disease. This case demonstrates nonspecific and atypical radiographic and pathologic findings in acute pulmonary coccidioidomycosis and should alert clinicians to consider pulmonary coccidioidomycosis in patients from endemic areas even with atypical presentations.

Figures

Figure 1: Frontal chest radiograph demonstrates left lung opacification and left pleural effusion.

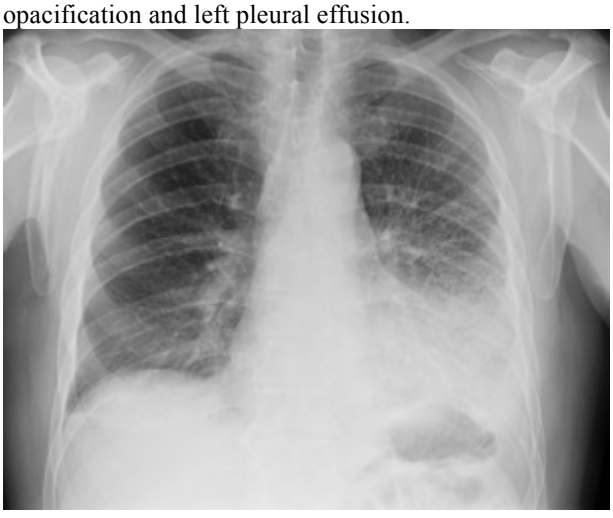


Figure 2: Axial chest CT scan image demonstrates left upper and lower lobe interlobular septal thickening, ground-glass opacities, and consolidative opacities.

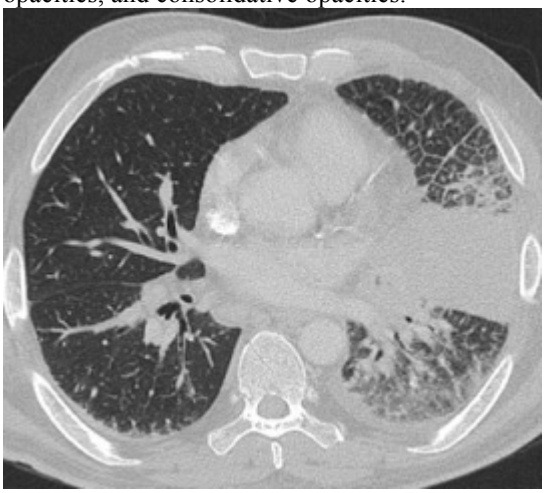
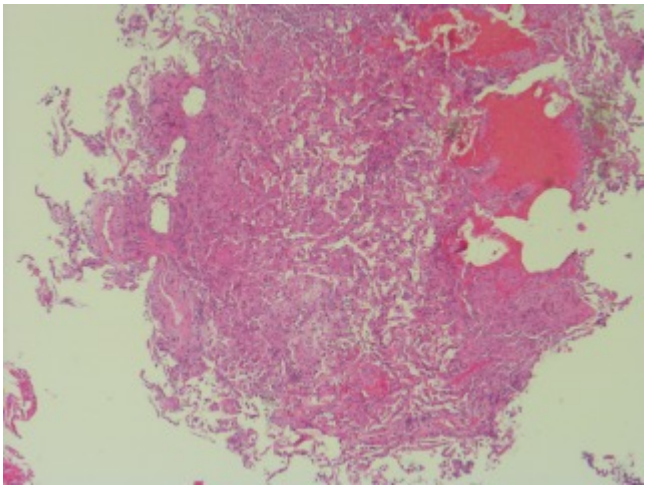
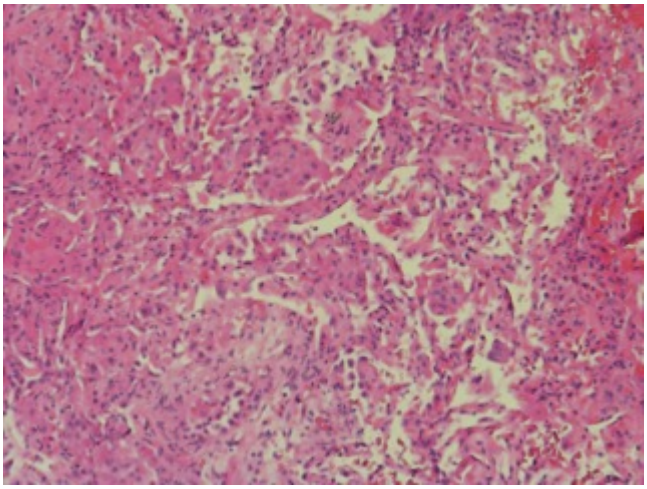


Figure 3a, b, c: H&E 20x, 60x, and GMS 60x of transbronchial biopsies of the left upper lobe revealed fragments of lung with focal alveolar septal fibrosis, mild and chronic inflammation, and focal necrosis.

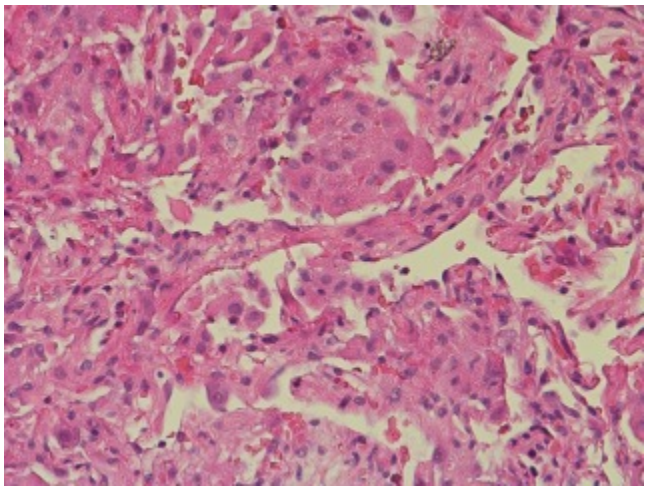
a



b



c



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