

CLINICAL VIGNETTE

“Thank Goodness it’s Cocci, not Metastatic Lung Cancer”

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Introduction

Coccidioides is a fungus endemic to the Southwest United States. Coccidioidomycosis typically presents with symptoms and signs of a community acquired pneumonia. We present a patient where the imaging and presentation were concerning for metastatic lung cancer, with direct referral from the emergency department to medical oncology.

Case

A 64-year-old male was referred to oncology for evaluation of multiple lung masses seen on CT scan of the chest. His history includes hypertension, mitral valve prolapse, Mobitz 2 AV block, and prostate cancer under surveillance. About 1 month prior to presentation the patient developed flu-like symptoms including fever, chills, dyspnea, fatigue, and myalgias. His symptoms persisted despite a course of antibiotics. His primary care provider (PCP) sent a d-dimer test due to dyspnea and concern for pulmonary embolism. The d-dimer test was positive and patient was referred to the emergency department (ED). In the ED a chest CT angiogram demonstrated an irregular mass in right lower lobe measuring 4.2 x 4.0 cm [Figure 1], with numerous nodules scattered throughout the bilateral lungs measuring up to 1.2 cm. Enlarged paratracheal, subcarinal, and right perihilar lymph nodes were seen measuring up to 2.1 cm. The findings were concerning for metastatic disease and the patient was discharged from the hospital and referred to medical oncology. The patient was given a second course of antibiotics and his symptoms improved in the two weeks following discharge from the hospital.

Review of systems was positive for 5-6 lb. weight loss. He was non-smoker with possible remote asbestos exposure as a plumber. The prostate cancer had Gleason score of 6, on watchful waiting, and he had resected basal cell skin cancer. Family history included prostate cancer in his brother, without other cancer in the family.

Laboratory evaluation demonstrated mild anemia with hemoglobin 12.8, mild eosinophilia at 640/microliter, normal CEA, and unchanged PSA of 7. Coccidioidomycosis (cocci) serologies were sent by his oncologist. PET/CT performed prior to return of cocci serologies, demonstrated an intensely FDG-avid mass in the superior segment of the right lower lobe, highly suspicious for primary lung carcinoma [Figure 2], enlarged and FDG-avid multi-station intrathoracic and right

supraclavicular lymph nodes suggestive of nodal metastases, numerous diffuse predominately sub- and peri-centimeter bilateral pulmonary nodules concerning for pulmonary metastases, and mild prostatomegaly with FDG uptake reflecting known prostate cancer. Cocci serologies resulted with positive IgG by EIA 2.353 (normal < 0.150), positive IgM EIA 0.965 (normal < 0.150), positive immunodiffusion, and elevated complement fixation titer 1:32. However given the findings on PET/CT and the high concern for metastatic lung cancer as foremost diagnosis, the patient underwent CT-guided biopsy of his lung mass. Biopsy showed necrotizing granulomatous inflammation with prominent eosinophils and plasma cells. GMS stain showed fungal spore forms consistent with Coccidioides. The patient was started on fluconazole 400 mg orally daily for pulmonary coccidioidomycosis. There was no evidence of disseminated disease.



Figure 1. Chest CT scan with large right lower lobe lung mass.

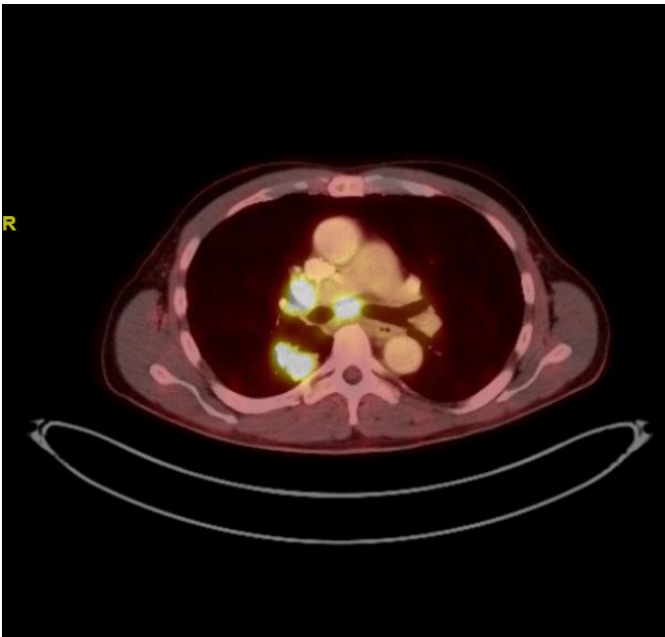


Figure 2. PET CT scan with FDG-avid right lower lobe lung mass and mediastinal and hilar adenopathy.

Discussion

Coccidioides (cocci) is a dimorphic fungus that causes coccidioidomycosis, otherwise known as San Joaquin Valley fever. This fungus is endemic to the dry regions in the Southwest United States, including California, Arizona, Utah, Nevada and New Mexico. Cocci has a wide spectrum of clinical manifestations ranging from asymptomatic to fatal disease. When symptoms do occur, the presentation is often similar to bacterial pneumonia. Illness manifests approximately three weeks after inhalational exposure to spores. Common symptoms include fever, cough, shortness of breath and chest pain. Rash often predates these symptoms but can be mild and is often missed. Erythema nodosum or multiforme are also seen, most commonly associated with arthralgias. The triad of fever, arthralgias and erythema nodosum is referred to as “Desert rheumatism”. Laboratory findings can include elevated erythrocyte sedimentation rate and eosinophilia. Chest x-ray usually shows unilateral infiltrate. Hilar and paratracheal adenopathy can also be seen. Lung cavitation is seen less commonly. Disseminated disease can occur, particularly in the immunocompromised.¹

A diagnosis of coccidioidomycosis is established with histopathologic identification of spherules, positive culture from an affected site, and immunologic serologies. Immunodiffusion (ID) testing detects cocci IgG and IgM, and positive results may signal early infection. Complement fixation (CF) testing identifies cocci IgG specific antibody and serves as a quantitative assay in monitoring response to treatment. Enzyme-linked immunoassays (EIA) can be used for screening in endemic areas, although false positive IgM antibodies have been reported. Serum (1-3)-beta-D-glucan testing has poor specificity and is generally not clinically useful.²

The treatment of coccidioidomycosis follows recommendations from the Infectious Disease Society of America criteria. Up to 60% of cases are asymptomatic or have only mild respiratory illnesses, and do not require treatment. Pulmonary infections, if severe, should be treated with antifungal medications. Risk factors for severe infection include diabetes, tobacco use disorder, age over 65 years, or massive exposure e.g. in construction work. Symptoms that indicate severe infection and warrant antifungal treatment include weight loss, night sweats persisting longer than two weeks, pulmonary infiltrates involving more than half of one lung or bilateral lung involvement, prominent hilar lymphadenopathy, CF antibody titers equal or greater than 1:16, or inability to work due to symptoms. Pleural effusions occur in 5 to 15% of cases of primary pulmonary cocci. Pleural fluid is exudative and cell count may demonstrate eosinophilic predominance. The optimal treatment for pulmonary cocci has not been evaluated in prospective randomized controlled clinical trials. 95% of cases resolve without treatment, and antifungal treatment has not been demonstrated to prevent dissemination. Overall mortality is 1-2%. When opting to treat more severe cases of pulmonary cocci, the regimen typically includes three to six months of an oral azole such as fluconazole. Cocci can also cause diffuse pneumonia complicated by acute respiratory distress syndrome (ARDS), which requires antifungal treatment, typically with amphotericin B.²

Primary pulmonary coccidioidomycosis leaves a residual pulmonary nodule in 5% of cases. In an endemic area such as California, one-third of all lung nodules are attributable to cocci. However, serologies may be unreliable for diagnosis, and in some cases tissue sampling is needed to exclude malignancy. Cocci can also leave residual lung cavities which can lead to superinfection with bacteria or aspergillus, or rupture with pyopneumothorax. Rarely primary pulmonary cocci leads to chronic fibrocavitary disease which may require prolonged antifungal treatment.²

Cocci can disseminate to the meninges, bones, joints, and skin. Surgery may be required for source control of disseminated disease. All disseminated disease requires treatment with antifungal therapy, frequently for long duration. Coccidioidal meningitis presents with altered mental status, headache, and meningismus, and is diagnosed based on serologic testing or CSF culture. Coccidioidal meningitis is fatal without treatment, and requires lifelong antifungal therapy.²

This case of coccidioidomycosis is notable for abnormal imaging highly concerning for metastatic lung cancer. The large pulmonary mass, multiple pulmonary nodules along with significant hilar and mediastinal lymphadenopathy is more characteristic of metastatic lung cancer than infection. However, it is well described that many lung infections can mimic malignancy. Petrini, et al., described a case of cocci presenting as a lung mass suspicious for lung cancer,³ and Bunkar, et al., reported a case of actinomycosis masquerading as lung cancer.⁴ In a retrospective case series⁵ of infections presenting as “pseudotumors”, the etiologies identified were tuberculoma,

aspergilloma, actinomycotic pseudotumor, and coccidioidoma. The authors note that clinical suspicion for infection may be raised by careful history taking including a history of time spent in an endemic area, and assessment for risk factors for infection such as chronic lung disease, poor dental status, alcoholism, and immunodeficiency. The authors also note that lung cancer can coexist with infection, and tissue sampling may be necessary to rule out lung cancer.⁵ Our case demonstrates how infection can appear highly concerning for malignancy on PET/CT imaging, and the importance of biopsy to definitively exclude malignancy and confirm the serologic diagnosis of coccidioidomycosis. In a study of CT-guided lung biopsies in an area endemic for cocci, 19% of 203 biopsies revealed coccidioidomycosis. In this series CT-guided lung biopsy for diagnosis of cocci demonstrated a sensitivity of 83% and specificity of 100%.⁶

Although our patient presented with a dominant lung mass with multiple other pulmonary nodules and extensive lymphadenopathy highly suggesting lung cancer, in the consultation with the oncologist noted fever and congestive symptoms atypical for lung cancer presentation, and therefore resulted in cocci testing in addition to PET/CT imaging. The enhancing metabolic activity of the lung mass and lymphadenopathy on PET/CT was concerning for malignancy and therefore, despite the positive cocci titer, CT-guided biopsy fortunately confirmed diagnosis of coccidioidomycosis. The patient clinically improved with antifungal therapy and follow-up imaging showed a stable residual small lung nodule.

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