

A textbook case of coccidioidomycosis

Fungal disease should be part of the differential diagnosis when a patient presents with influenza-like symptoms after traveling to regions where *Coccidioides* species are endemic, such as the American southwest and parts of Central and South America.

ABSTRACT: As many British Columbians venture to regions where coccidioidomycosis is endemic, such as Arizona, California, Texas, and parts of Central and South America, physicians should consider this fungal disease when returned travelers present with influenza-like symptoms. Commonly mistaken for bacterial pneumonia, pulmonary coccidioidomycosis may go undetected if it is not part of the differential diagnosis. A recent case of coccidioidomycosis diagnosed in a 58-year-old male provides examples of typical presentation, the results of laboratory and radiographic investigations, and treatment options. This case highlights the need for considering immunocompromised states like diabetes in patients diagnosed with fungal infections, and demonstrates the impact of these states on the severity and management of coccidioidomycosis in particular.

Coccidioidomycosis, also known as Valley Fever, is a fungal infection caused by the spores of *Coccidioides immitis* and *Coccidioides posadasii*. Areas where *Coccidioides* species are endemic include the American southwest, northern Mexico, and parts of Central and South America. About 50% of coccidioidomycosis cases in the United States occur in Arizona. An increasing number of outbreaks have been seen in California recently, particularly among prison inmates and construction workers employed on projects at arid locations.¹ Cases in patients without a history of travel to endemic regions have also been reported in Washington state, suggesting that the range of *C. immitis* may be expanding or may be broader than originally thought.²

Many residents in endemic areas have been exposed, as demonstrated by positive reactions to antigen skin tests. No cases of human-to-human transmission have been reported.³

Typically, weather events, including droughts, downpours, and windstorms, disrupt the soil and release the soil-dwelling spores of *Coccidioides* species into the air. About 60% of individuals who inhale the spores of

C. immitis or *C. posadasii* develop no symptoms. Extrapulmonary infection occurs infrequently; most symptomatic cases are pneumonias.

Common symptoms include fever, myalgia, arthralgia, headache, cough, and rash. Key risk factors are travel to an endemic area, exposure to dust, and immunocompromise.³

Acute pulmonary coccidioidomycosis is often confused with community-acquired pneumonia. A failed response to antibiotics, fatigue, night sweats, eosinophilia, a rash in the form of erythema nodosum or erythema multiforme, and hilar lymphadenopathy found on X-ray may point to coccidioidomycosis. Many cases resolve spontaneously, but because coccidioidomycosis is frequently misdiagnosed as community-acquired pneumonia, it may resolve incidentally with antibiotic treatment for pneumonia.⁴

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This article has been peer reviewed.

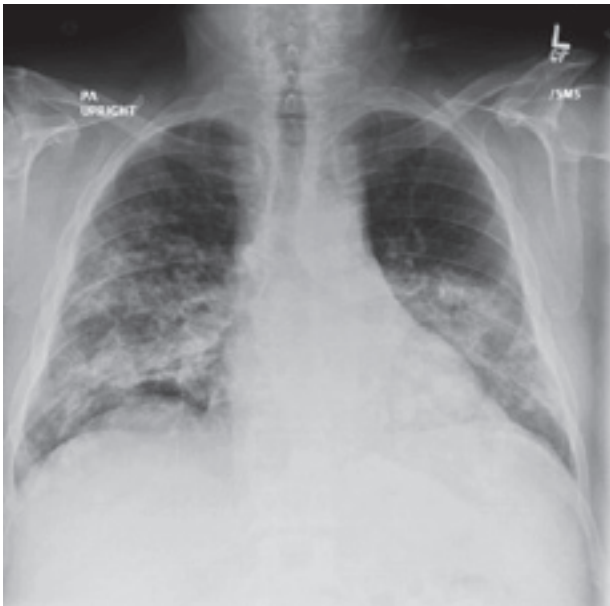


Figure 1. Chest X-ray, posteroanterior view.

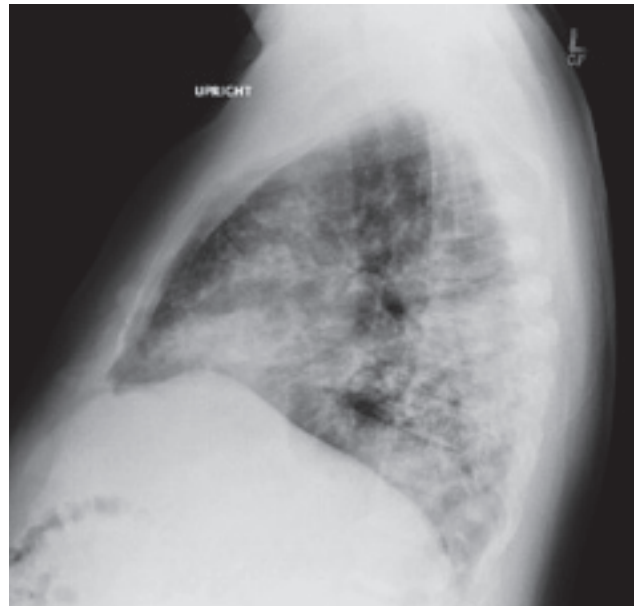


Figure 2. Chest X-ray, lateral view.

Case data

A 58-year-old Caucasian male presented to the emergency department of a regional hospital. He reported being sick intermittently with a cough, fever, night sweats, myalgia, and shortness of breath for 4 weeks while traveling in Arizona. The patient's family physician had initiated treatment with clarithromycin, but the cough and shortness of breath had persisted.

The patient described having an itchy, red-spotted rash on his trunk that appeared and vanished 3 to 4 weeks before he presented to the emergency department. He denied experiencing chest pain, hemoptysis, joint pain, and headache.

The patient had not smoked for decades. He and his wife had no known exposure to tuberculosis, did not own any birds or other pets, and had not traveled overseas lately. During their time in Arizona, they had traveled in a recreational vehicle and stayed at campsites in Tucson. While in the area,

they encountered dust storms that alternated with heavy rain. An outbreak of influenza occurred in that region.

History taking revealed the patient had an allergy to cats, and in the past had experienced nephrolithiasis, gout, benign prostatic hyperplasia, and a meniscal tear. He had no history of immunosuppression or autoimmune disorder. The patient was on no medications except the recently initiated clarithromycin.

Upon examination, the patient's vital signs were found to be within normal limits except for oxygen saturation, which was 88% on room air. Head and neck, cardiovascular, abdominal, dermatological, neurological, and musculoskeletal examinations revealed no concerns. A respiratory exam revealed some accessory muscle use, decreased breath sounds to bases bilaterally, and no adventitial sounds. There was no clubbing or cyanosis.

A complete blood count with differential revealed a white cell count of

15.1 (reference range $4.0-10.5 \times 10^9/L$), with elevated neutrophils at 10.2 (reference range $2.0-6.0 \times 10^9/L$), elevated monocytes at 0.91 (reference range $0.1-0.8 \times 10^9/L$), and markedly elevated eosinophils at 2.54 (reference range $0.00-0.45 \times 10^9/L$). Electrolytes were within the expected range, with the exception of a sodium level of 131 (reference range 135-145 mmol/L). Renal function and liver enzymes were unremarkable. The patient's random blood glucose was elevated at 17.5 (reference range 3.9-11.0 mmol/L) and his HbA1c level was 10.3% (reference range 4.0%-6.0%).

An ECG showed sinus-tachycardia and no ST changes, and a chest X-ray (Figure 1 and Figure 2) revealed extensive bilateral infiltrates. The radiologist's interpretation of the image was "airspace disease involving both lungs and consistent with bilateral pneumonia. Follow-up is indicated."

Sputum samples were taken for culturing, a nasopharyngeal swab for viruses was performed, and blood

was drawn for *Cryptococcus*, *Coccidioides*, and HIV antibody testing. While culture and serology tests were being completed, the patient was admitted and started on cefuroxime and azithromycin for treatment of probable bacterial pneumonia, in accordance with hospital guidelines.

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Subsequently, the nasopharyngeal swab for respiratory viruses was found to be negative for all tested viruses, including influenza A and B, and RSV. When the preliminary sputum culture for fungi showed +1 *C. immitis* and a KOH prep showed +2 spherules and endospores resembling *C. immitis*, the patient was started on oral fluconazole. A week later, serology results for HIV and the *Cryptococcus* antigen were found to be negative, while IgG and IgM enzyme immunoassay results confirmed exposure to *Coccidioides*.

The final diagnosis was pulmonary coccidioidomycosis, secondary to *C. immitis*, and newly identified diabetes mellitus. Treatment consisted of a 3-month course of oral fluconazole, as well as metformin, long-acting insulin, and diet control.

Discussion

The presence of coccidioidomycosis on a differential diagnosis should

trigger broader consideration of other pulmonary conditions, such as viral pneumonia, hypersensitivity pneumonitis, pneumoconiosis (e.g., silicosis), nocardiosis, sarcoidosis, strongyloidiasis, and tuberculosis. Respiratory symptoms can be due to infection with fungi other than *Coc-*

cidoidal antibodies in blood and cerebrospinal fluid. Enzyme immunoassay for coccidioidomycosis is the most readily available test. A result that is positive for IgG and either positive or negative for IgM is confirmatory. A result that is positive for IgM and negative for IgG is usually a false-positive and cannot be relied upon for diagnosis. In this case, other tests are needed for verification.

Immunodiffusion serology is less sensitive but more specific than enzyme immunoassay. Complement fixation serology for coccidioidomycosis is sometimes used, particularly for analyzing cerebrospinal fluid in cases with neurological symptoms and for monitoring resolution of the disease during treatment.

No matter which serologic test is used, immunocompromised patients have lower rates of positive reactivity. Combining tests will increase detection sensitivity.⁵

Where uncertainty persists, chest CT or bronchoscopy with biopsy and culture can be used.

Diagnosis of coccidioidomycosis can prevent unnecessary administration of antibiotics, thereby reducing associated complications and decreasing the need for further diagnostic tests. Early detection and treatment may also reduce morbidity from sequelae.⁶

Treatment

According to the American Thoracic Society Fungal Working Group, treatment depends on the patient's clinical and immune status. No treatment is required if symptoms are mild and the patient is immunocompetent. For the patient with severe disease or who is immunocompromised, 400 mg of oral fluconazole daily for 3 to 6 months is the usual therapy. Other antifungals, including amphotericin B, liposomal amphotericin B, and itraconazole, are

cidoides (pulmonary histoplasmosis, blastomycosis, cryptococcosis, sporotrichosis, aspergillosis), lung cancer, or lymphoma, which can be associated with lymphocytic interstitial pneumonia.

Testing

If coccidioidomycosis is suspected, several tests can be helpful. A complete blood count and differential may show eosinophilia or inflammatory markers such as ESR or CRP, and a chest X-ray may show any range of lobar consolidation, nodular infiltrate, cavitation, and hilar or mediastinal lymphadenopathy. Given that none of the aforementioned results are specific, culture and antibody testing are usually necessary.

A positive culture for *Coccidioides* or direct visualization of the spores in any clinical specimen, such as a sputum sample, is definitive.³ However, sputum collection may be difficult.

Most labs can assess for anticoc-

reserved for pregnant patients and cases involving diffuse pulmonary, disseminated, or meningeal disease variants.⁴

There have been no randomized, prospective clinical trials of antifungals to assess whether treatment lowers complication rates or improves symptoms.⁶ Recently, short courses of corticosteroids in immunocompetent patients have been found to improve hypersensitivity-type symptoms, such as rash and wheeze with no significant adverse effects, but further research is necessary.⁷

Role of immunocompromise

Testing for immunocompromised states is recommended to determine the necessity of treatment and risk of complications.

A retrospective review of records showed an association between the glycemic status of patients with coccidioidomycosis and extent of disease. Of 329 immunocompetent patients with coccidioidomycosis, 44 had diabetes.⁸ Those with diabetes were more likely to develop cavitating lung lesions than those without diabetes. Of the diabetic patients, those with higher blood glucose levels were more likely to have disseminated infection and to require antifungal treatment. The authors recommend monitoring blood glucose levels in patients with coccidioidomycosis to identify those with greater risk of complicated infection.⁸

Monitoring

Regardless of whether patients are treated, they should be monitored for clinical resolution, usually for 1 to 2 years. Initially, ESR and serum antibody levels should be measured every few weeks, since these values should decrease as the infection abates. If ESR and antibody levels do not normalize, complications such as dis-

semination and cavitary disease must be considered. Chest X-ray should be performed every few weeks or months to ensure resolution,⁶ and patients taking antifungals should have regular follow-up to monitor for toxicity.

Summary

When assessing a returned traveler with influenza-like symptoms, it is important to keep regional illnesses in the differential diagnosis. Consider coccidioidomycosis in travelers returning from areas where *C. immitis* is endemic, including the American southwest, northern Mexico, and parts of Central and South America. A failed response to antibiotics, fatigue, night sweats, eosinophilia, a rash, and hilar lymphadenopathy found on X-ray can help differentiate coccidioidomycosis from community acquired pneumonia.

Compromised immune status should guide management, since immunocompromised patients, including diabetic and pregnant patients, are at greater risk of acquiring serious infection and are more likely to need treatment.

Acknowledgments

Thanks to Dr Dave Forrest for his expertise and ongoing management of the patient.

Competing interests

None declared.

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