The Cautionary Tale of Coccidioidomycosis

Ramzi M. Helewa, MD; and John M. Embil, MD, FRCPC

Often quoted as the "great imitator," coccidioidomycosis is a fungal infection caused by *Coccidioides immitis*. This endemic mycosis leads to a variety of clinical presentations, thus challenging physicians in its diagnosis. Since the incidence of infection is increasing, *C. immitis* is this month's **Bug of the Month**.

What are Coccidioides spp*?*

The first description of coccidioidomycosis was in 1892 in Argentina. It was not until 1900 that *C. immitis* was recognized as a fungus. Prior to this, it was believed to be a coccidian protozoan. By the 1930s, it was determined that *C. immitis* was the infectious agent that caused the so-called "valley fever." *Coccidioides spp* are dimorphic fungi that are endemic in the alkaline soil found in the arid and hot areas of the southwestern US and Latin America. This includes the geographic region known as the Lower Sonoran Life Zone. The San Joaquin Valley in California and south-central Arizona have the highest concentration of *Coccidioides spp*. A majority of cases of coccidioidomycosis are reported from this area. This fungus can be found as a mould in the soil that has easily aerosolized arthrospores. Aerosolization can occur with soil disruption that often accompanies storms, earthquakes, or certain occupational activities. The inhalation of arthrospores can lead to pulmonary deposition in humans. They then differentiate into spherules that house numerous endospores. These mature spherules may rupture, releasing the endospores that can disseminate to form new spherules and the cycle can repeat. Infection incites a cell-mediated immune reaction.

What is the spectrum of disease?

It is estimated that there are over 100,000 individuals infected with coccidioidomycosis per year. Up to 60% of individuals remain asymptomatic, form antibodies and develop a reactive skin test. Symptomology of primary pulmonary infection can range from mild respiratory illness to severe pneumonia.

Clinical manifestations usually occur two weeks post-exposure. In primary coccidioidomycosis, self-limiting symptoms such as fever, malaise, chest discomfort and cough can last several days to several weeks. In approximately 10% of cases, several hypersensitivity reactions such as erythema nodosum, erythema multiforme, or arthralgias may appear. The cutaneous finding of erythema nodosum is an indicator of an effective underlying cell-mediated response to the fungal antigens. Half of patients develop pleural effusions, infiltrations, or adenopathy. Although a complete resolution is common, residual radiographic evidence of a coccidioidoma, a coin-like lesion on chest radiograph, may be seen. The syndrome known as "Desert Rheumatism" or the "Valley Fever" in the San Joaquin Valley in California or Arizona respectively, is associated with the cutaneous findings of erythema nodosum, fever and arthralgias.

Evidence of ongoing fever, night sweats, lymphadenopathy, elevated erythrocyte sediment rate should be concerning for disseminated coccidioidomycosis. This uncommon complication, occurring in approximately 1% of infections, is a result of a defect in cell-mediated immunity. African American individuals, individuals of Filipino descent, as well as pregnant women (especially in the third trimester) have higher incidences of dissemination. This is also true for patients who are immunocompromised as a result of HIV/AIDS or immunosuppressive therapy.

Dissemination can affect any organ. The most feared complication of disseminated disease, meningitis, may develop in 30% to 50% of cases. Soft-tissue and pulmonary abscesses, pustular infections, empyemas and productive cough can occur. Erythematous maculopapular rash may present. Diffuse pulmonary infiltration on radiographs heralds a very poor prognosis. Untreated disseminated coccidioidomycosis has a high rate of mortality.

How is infection diagnosed?

There are a number of different tests available to help establish the diagnosis of infection caused by *C. immitis*. Tissue biopsy revealing a mature spherule is diagnostic. Collection of urine, pus, or sputum can be examined by culture and wet smear. As with many fungal infections, serologic testing (IgM and IgG) may be employed. Complement fixation antibody titers can be monitored and increase with dissemination. Blood cultures are often sterile but a complete blood count may reveal eosinophilia. Skin test with spherulin can be positive (> 5 mm induration after two days) approximately two weeks post infection, but it is unable to differentiate a previous infection from a current infection. It may also be non-reactive in cases of widespread dissemination.

Radiographic evidence of a segmental pneumonia is often noted in symptomatic coccidioidomycosis. While this finding is helpful, it does not establish the diagnosis. Imaging can also be used to detect:

- pleural effusions,
- abscess formation,
- nodular formation,
- lung cavitation,
- hilar and
- mediastinal adenopathy.

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How is coccidioidomycosis treated?

Only symptomatic management is necessary for the majority of cases of coccidioidomycosis. No intervention is required for asymptomatic individuals. Primary pulmonary coccidioidomycosis is often self-limiting and there is a controversy surrounding the use of antifungal therapy in immunocompetent patients. Still, antifungal therapies, such as amphotericin B, are often employed for symptomatic lung involvement or disseminated coccidioidomycosis. Pregnancy necessitates the use of antifungal therapy given the high risk of dissemination. The presence of meningitis necessitates the use of lifelong fluconazole therapy. Effective treatment can be monitored by both clinical improvement and the complement fixation antibody titer. Unresolved pulmonary cavitations may need to be surgically removed if they continue to persist beyond one year.

Prevention is the best medicine

There is new fear that *Coccidioides spp* may be used for terrorist activities given its highly infectious and easily aerosolized nature. Recognizing coccidioidomycosis poses a clinical challenge for many physicians and a high level of clinical suspicion is a must. Like many systemic mycoses infections, presentation may be insidious and extremely diverse. A thorough exposure and travel history is a vital aspect of history taking. This is especially true if the patient presents to the physician in a non-endemic area after visiting an endemic area. Avoidance of exposure is important, especially for those patients who have some degree of an immunocompromised state. Counselling and appropriate education can help prevent infection with this potentially devastating microorganism.

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Dr. Helewa is a Resident, General Surgery, University of Manitoba, Winnipeg, Manitoba.

Dr. Embil is a Consultant, Infectious Diseases and Associate Professor, University of Manitoba. He is also Medical Director, Infection Prevention and Control Program, Health Sciences Centre and Winnipeg Regional Health Authority, Winnipeg, Manitoba.