

CLINICAL CASE OF THE MONTH

A 48-Year-Old Man with a Non-Healing Wound

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CASE PRESENTATION

A 48-year-old African American man presented to the emergency department with a chief complaint of a groin wound that would not heal. He had seen a physician in another state approximately two weeks prior at which time incision and drainage (I&D) of a wound in his left groin was performed. Despite completing a course of antibiotics, the wound continued to drain purulent fluid and did not appear to be healing. The patient also complained of a large swelling on his right hip which was causing some pain and discomfort. The patient denied any significant past medical history and had no prior hospitalizations or surgical procedures. Importantly, the patient was present in New Orleans during Hurricane Katrina and evacuated approximately six days later by wading through waist deep water. He and his mother relocated to Arizona where they spent approximately six months before relocating to Texas for four months. Prior to leaving Arizona the patient noted the swellings in his groin and hip though the discomfort was tolerable. The patient reported a 20 to 30 pound weight loss over the prior two months which he attributed to a decreased appetite.

Physical exam performed in the emergency department included the following vital signs: temperature of 98.2°F, heart rate of 84 beats per minute, respiratory rate of 14 breaths per minute, and blood pressure of 110/62 mmHg. The patient was thin and in no apparent distress. His physical exam was remarkable for three small incisions in the left groin, each less than 1 cm in length and each associated with foul-smelling purulent drainage. The area surrounding the incision had very minimal erythema and there was no surrounding induration or fluctuance noted. A large firm mass overlying the iliac crest on the right hip was also appreciated. This mass, which measured 9 cm x 7 cm, was firm and mildly tender to palpation. There was no induration or erythema of the surrounding tissue. Also noted on exam was a 1.5 cm x 1.5 cm cervical lymph node that was mildly tender, firm, and somewhat mobile. The remainder of the physical examination was unremarkable.

In the emergency department, cultures were obtained from the left groin wound as well as a needle aspirate from the right hip abscess. Peripheral blood cultures and additional laboratory data were also obtained. The comprehensive metabolic profile did not reveal any abnormalities in electrolytes or liver function studies. The

TARGET AUDIENCE

The July/August Clinical Case of the Month is intended for general practitioners, medicine subspecialists including infectious diseases, orthopedic surgeons, emergency medicine physicians, radiologists, dermatologists, and pathologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be better able to identify and understand the pathophysiology, microbiology, epidemiology, clinical presentation, diagnosis and treatment of coccidioidomycosis. Estimated time to complete this activity is one (1) hour.

CME INFORMATION

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

Drs. Peacock, Heinrich, Schieffelin, Chaudhry, Maffei, Daberkow, and Olivier have nothing to disclose. Dr. Lopez discloses that he is a member of the *Journal* Board of Trustees and the *Journal* Editorial Board.

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initial complete blood count revealed a white blood cell count of $8.2 \times 10^3/\text{uL}$ [$4\text{-}10 \times 10^3/\text{uL}$], hemoglobin 10 g/dl [$13\text{-}17.5 \text{ g/dl}$], hematocrit 33% [$39\text{-}52\%$], platelets of $566 \times 10^3/\text{ul}$ [$140\text{-}410 \times 10^3/\text{uL}$], mean corpuscular volume of 75 FL [$81\text{-}99 \text{ FL}$], and red cell distribution width of 16.9% [$11.5\text{-}15\%$]. The white blood cell differential demonstrated 74% neutrophils [$32\text{-}64\%$], 13% lymphocytes [$25\text{-}48\%$], 6% monocytes [$4\text{-}6\%$], and 7% eosinophils [$2\text{-}3\%$]. Urinalysis revealed no abnormalities. HIV test and tuberculin skin test were reported as negative. A chest radiograph manifested no abnormalities.

The patient was started on empiric broad spectrum intravenous antibiotic coverage including vancomycin and piperacillin/tazobactam. Computed tomography of the chest, abdomen, and pelvis demonstrated several mediastinal lymph nodes that were approximately 1.2 cm in diameter and also revealed a 6 cm x 5 cm fluid collection, suspicious for an abscess, adjacent to the right iliac crest (Figure 1). Also noted was erosion of the iliac crest and inflammatory changes in the pubic bodies suspicious for osteomyelitis. Cultures obtained from the left groin were positive for *Bacteroides* species and *Escherichia coli* and the right hip culture was positive for "fungal elements." Infectious disease was consulted, and the patient was placed on pathogen-directed antibiotics and voriconazole. Excisional biopsy of the right cervical lymph node, incision and drainage of the right hip abscess, and bone biopsy of the right iliac crest were subsequently performed. Pathology of the lymph node, bone biopsy, and hip abscess all showed fungal elements with spherules and endospores consistent with diagnosis of coccidioidomycosis (Figure 2). Magnetic resonance imaging of the pelvis showed that the osteomyelitis involved the upper right sacroiliac joint, lateral right iliac crest, bilateral pubic bodies, and lateral right femoral epicondyle. Further evaluation determined that the bone involvement was too extensive at that time for debridement without risking significant disability. The



Figure 1. CT scan of the pelvis showing a large 5 cm x 6 cm loculated fluid collection adjacent to the right iliac crest.

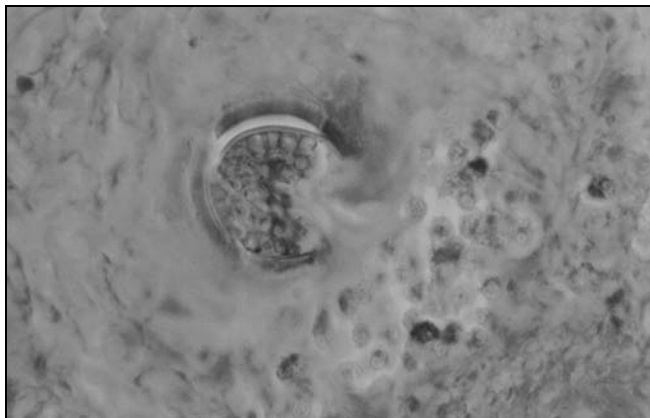


Figure 2. Gomori methenamine silver (GMS) stain of right cervical lymph node demonstrates a spherule with endospores being released into the surrounding tissue.

antifungal agent was changed to oral itraconazole with plans for close follow up as an outpatient with both the medical and surgical services.

DISCUSSION

Coccidioidomycosis is a disease endemic to the southwestern United States and northern Mexico desert regions (San Joaquin Valley) that is primarily caused by the inhalation of the spores of the dimorphic fungi, *Coccidioides immitis* and *C. posadasii*.¹ The term dimorphic refers to the ability of *Coccidioides* to exist in two different forms, as a mold in the soil and laboratory-based culture and as yeast in the host. Infection may be caused by inhalation of as little as a single spore which will ultimately produce compartments with individual endospores. When the compartments (i.e., spherules) rupture, the endospores are released into the surrounding tissues, and each can produce additional spherules with endospores.² The endospores may remain localized to the pulmonary system and may often times go unrecognized or manifest as an acute respiratory infection. Other individuals may present with a more severe respiratory infection known as Valley Fever, which includes symptoms of fever, cough, and chest pain; the symptoms resemble community acquired pneumonia or influenza, and individuals are often misdiagnosed. This entity does not usually present a problem as most affected individuals will spontaneously clear the infection. A small subset of patients may present with rheumatologic complaints including arthralgias, erythema nodosum, or erythema marginatum. Rarely, patients develop more serious pulmonary or systemic complications including persistent pneumonia, chronic pulmonary coccidioidomycosis, or disseminated disease.³ The severity of the infection may be due to the number of spores inhaled by the individual. This effect has been seen in those with intense prolonged exposure such as military personnel and workers at archaeological digs.^{4,5}

Disseminated disease is a very rare condition with an incidence of less than one percent of all individuals exposed to the inhaled spores of *Coccidioides*. Those who are immunocompromised due to AIDS, organ transplantation, or pregnancy are at much higher risk of developing severe illness or extra-pulmonary infections. Certain ethnic groups, including African-Americans and Filipinos, are also at increased risk of developing disseminated disease. The exact mechanism of this increased susceptibility is not known, though it is presumed to be genetic in origin.³ There are essentially no organ systems that are free of the risk of disseminated disease, though involvement in the form of skin lesions or abscesses, bone or joint infections, or meningitis are most frequently observed. Occasionally there is also local dissemination to the pleura or pericardium.⁶ Even with medical/surgical and antifungal therapies, many of these diseases become chronic and result in severe disability or death.

Diagnosis is often delayed due to the non-specific patterns of illness. When suspected, however, fungal cultures, histopathologic studies, and immunologic serologies are the primary diagnostic tools. *Coccidioides* grows very easily on a wide variety of culture media to reveal mycelia of barrel-shaped spores interspersed with other non-spore forming cells known as ghost cells. Although one will always see this morphology with *Coccidioides*, it is not unique to this species and thus not sufficient for definitive identification.

In order to make the definitive identification, the cultured mold may be grown in a specialized media at 39°C in order to revert back to the yeast form and demonstrate production of spherules, or the specimen may be identified by antigen detection or DNA probe. *Coccidioides* must be handled by the laboratory with special precautions including a laminar flow hood as the mycelia are very fragile and may break loose in the environment and be inhaled by laboratory personnel. Histopathologic testing may be done on tissues obtained from infected organs using several staining processes, including PAS (periodic acid-Schiff), hematoxylin-eosin, or silver staining. Tissues will show spherules with endospores, which is the feature that differentiates *Coccidioides* from the handful of other organisms that may appear as spherules on staining. If diagnosis is uncertain, serologic specimens may be forwarded to the Centers for Disease Control for antibody staining. Immunologic methods include ELISA (100% sensitivity and 99% specificity), complement fixation, and immunodiffusion. Titers from these methods may be useful in diagnosis as well as in following the progression of chronic or disseminated disease.⁶

Treatment has traditionally been reserved for those with disseminated or complicated infections, though physicians are increasingly treating primary infections in most patients in order to prevent more serious infections and to decrease the duration of the illness.¹ Antifungal azole agents such as itraconazole, ketoconazole, and fluconazole have the advantage of being administered orally and producing very few adverse side effects; thus, these are the agents of choice in most cases of coccidioidomycosis. Current recommendations by the Infectious Disease Society of America provide some guidelines as to which individuals may warrant consideration of antifungal therapy.² These groups include individuals who are immunosuppressed by AIDS or due to organ transplantation, women who are pregnant or in the post-partum period, and/or those with chronic medical conditions such as diabetes mellitus or cardio-pulmonary disease. Most of these individuals can be treated with azoles, though these should not be used in pregnancy due to the risk of teratogenicity. In patients who are pregnant or in those with severe progressive disease, treatment should be initiated with amphotericin B or one of its lipid formulations.² In most cases the oral azoles are felt to be equally effective, though there are some circumstances in which one may warrant consideration over the others. Current recommendations suggest that fluconazole is the preferred treatment for *Coccidioides*-associated meningitis despite studies that indicate itraconazole may be equally effective.⁷ Another study comparing itraconazole to fluconazole suggests that there is no significant difference in efficacy of the two drugs except in patients with skeletal lesions in which itraconazole was nearly twice as effective.⁸ Amphotericin B is the alternative therapy for rapidly worsening bone lesions, particularly in locations such as the vertebral column.² Length of treatment is not definitively stated in guidelines, but may be as short as three to six months in uncomplicated primary disease or as long as

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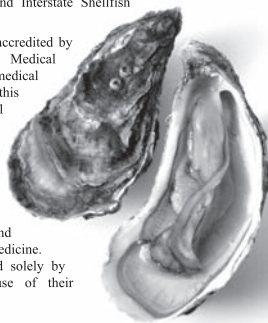
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years in disseminated disease. Patients with meningeal involvement are typically treated with life-long antifungal therapy.²

CONCLUSION

Though many infections with *Coccidioides* go unrecognized, the impact of this disease in areas where it is endemic is quite substantial. Even among patients in whom the disease goes unrecognized or those who clear the infection without therapy, there are significant disruptions to life and considerable financial impact as patients may experience symptoms for weeks and even months. One report followed a group of students in Tucson and found that they visited a clinic an average of six times before the resolution of the disease.³ Patients who develop disseminated disease may have even greater morbidity requiring multiple surgical procedures and long-term antifungal therapy. In regions where *Coccidioides* is endemic, this disease has a profound impact on health-care expenditures.

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CME QUESTIONS

Read the preceding CME article and complete the registration, evaluation, and answer form on page 230 to earn CME credit. Mail or fax the registration, evaluation, and answer form to the LSMS Educational and Research Foundation. Answers must be postmarked or faxed prior to July 31, 2008. Participants must attain a minimum score of 75% to receive credit. LSMS members may also go online at http://www.lsms.org/Pubs/Journal/journal_cme.asp and complete the interactive answer sheet for each CME article.

1. All of the following are true concerning coccidioidomycosis except:
 - a. Coccidioidomycosis is endemic in the Mississippi River valley and eastern United States.
 - b. Severity of infection with *Coccidioides* may be due to the number of spores inhaled by the individual.
 - c. Disseminated *Coccidioides* infection is rare.
 - d. Certain ethnic groups, including Filipinos and African-Americans, are at increased risk of developing disseminated disease.
2. True/False:
Individuals who are immunocompromised due to AIDS, organ transplantation, or pregnancy are at higher risk for developing severe illness or extra-pulmonary infection with *Coccidioides*.
3. All of the following are true concerning coccidioidomycosis except:
 - a. Diagnosis is often delayed due to the non-specific patterns of illness.
 - b. *Coccidioides* must be handled with special precautions by the laboratory as the mycelia are fragile and may break loose in the environment and be inhaled.
 - c. Histopathologic examination of infected tissue will reveal spherules with endospores.
 - d. Serologic studies are not available for assisting in the diagnosis of *Coccidioides*-associated infections.
4. True/False:
Fluconazole, itraconazole, and amphotericin B have been used in the management of patients with coccidioidomycosis.