CLINICAL RESEARCH STUDY

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The Spectrum and Presentation of Disseminated Coccidioidomycosis

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ABSTRACT

PURPOSE: Extrapulmonary dissemination of *Coccidioides* species is associated with significant morbidity and mortality. The clinical manifestations vary widely according to the host, the severity of illness, and location of dissemination. The morbidity and mortality can be reduced by early recognition and treatment, which in turn depends on understanding the spectrum and presentation of disease.

METHODS: We performed a retrospective analysis of 150 cases with extrapulmonary nonmeningeal disease seen from 1996 to 2007 at a referral medical center in an endemic region.

RESULTS: Hematogenous dissemination was associated with high mortality and occurred primarily in immunocompromised patients, but only 30% of patients with more limited forms of dissemination were immunocompromised. In keeping with prior studies, there was a preponderance of males (nearly 2:1) and people of African or Asian (especially Pacific Islanders) descent. In contrast, Hispanics and diabetics were not at increased risk. Serology was frequently negative in immunocompromised patients, but the diagnosis could be established by isolation of the organism in culture, or in histologic or cytologic specimens.

CONCLUSIONS: Although coccidioidomycosis is a great imitator, the diagnosis can usually be made readily if a high level of suspicion is maintained and appropriate diagnostic testing is performed. In most patients, that will include serologic testing in addition to cultures and histology or cytology of appropriate samples.
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KEYWORDS: Cardiac; Cytology; Diagnosis; Ethnicity; Immunocompromised; Peritonitis; Prognosis; Skeletal; Vertebral

Coccidioidomycosis is an invasive fungal disease caused by a species of *Coccidioides* and is common in the Sonoran desert region of southern Arizona and northern Mexico and the San Joaquin valley region of California. It also is found in other desert or semidesert regions of the western hemisphere. Infection rates are estimated at 3% per year in southern Arizona.[1,2] Approximately one third of infections are symptomatic,[3] usually presenting with a systemic or respiratory illness that resolves spontaneously over a period of weeks to months. About 30% of cases of community-acquired pneumonia in Tucson are caused by *Coccidioides spp*.[4] Whether or not the primary infection is treated, a minority of cases are complicated by persistent symptomatic pulmonary disease or by extrathoracic (disseminated) disease. In contrast to primary infection, disseminated infections seldom resolve spontaneously and are frequently fatal in the absence of effective systemic antifungal therapy.

Coccidioidomycosis is a reportable disease in Arizona and, in addition to an increase in number of cases coincident with increased reporting requirements in 1997, there has continued to be an increase in numbers of reported cases. The growing elderly population of Arizona that is fueled by people moving to southern Arizona for retirement may be part of the reason, adding people who may have waning immunity due to age or medical problems. In addition, advances in medical therapy that result in impaired cell-mediated immunity, such as tumor necrosis factor-alpha blockade[5] or organ transplantation,[6,7] may increase the number of people who are at risk. *Coccidioides* infections may involve most systems of the body, so awareness of

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disseminated coccidioidomycosis requires knowledge of potential presenting signs and symptoms and maintenance of a high degree of suspicion in patients with a compatible illness. We have performed a review of the cases of extrapulmonary coccidioidomycosis seen at our institution from 1996 through 2007, focusing on the cases that included involvement of organ systems other than the central nervous system.

CLINICAL SIGNIFICANCE

- Hematogenous disease occurs primarily in immunocompromised patients and has a high mortality. Serologies are frequently negative, but the diagnosis can often be made by bronchoscopy with bronchoalveolar lavage.
- Males and people of African and possibly Pacific Isles descent are at markedly increased risk, but Hispanics are not, nor are diabetics.
- Coccidioidomycosis involving a joint is typically associated with adjacent osseous disease.

METHODS

We retrospectively reviewed cases of disseminated coccidioidomycosis seen at the University Medical Center (UMC), the primary teaching hospital for the University of Arizona College of Medicine in Tucson, Arizona, and certain affiliated outpatient clinics. UMC has approximately 300 beds and is a referral center for all of Arizona, especially including trauma, cancer, and solid-organ transplantation. Metropolitan Tucson comprises most of the population of Pima County and is located in southern Arizona within an area of endemic transmission of *Coccidioides* species. Eighty-five percent of the patients with known county of origin were from Pima County. Patients were considered for inclusion if they received at least a portion of their care for coccidioidomycosis at the hospital or one of its affiliated clinics and sufficient information was available for analysis.

Patients were considered to have disseminated coccidioidomycosis if they had evidence of extrathoracic infection. In addition, patients were included if they had diffuse nodular pulmonary disease even if there was no other evidence of extrapulmonary infection, because this manifestation usually results from hematogenous dissemination.[8,9] Patients with central nervous system disease were included in this report only if there also was evidence of dissemination to other parts of the body.

Records of infectious disease consultations, culture, cytology, and histologic results, and discharge diagnoses were reviewed to identify patients with extrapulmonary coccidioidomycosis. Each potential case was reviewed individually to determine whether it fit the criteria for disseminated coccidioidomycosis.

Fungi grown from clinical specimens that were suspected to be *Coccidioides immitis/posadaseii* were submitted to ARUP Laboratories in Salt Lake City, Utah, for confirmation as *Coccidioides* species by DNA testing. The presence of spherules with endospores in histologic or cytologic preparations from clinical specimens is diagnostic of coccidioidomycosis. Screening serologic tests consisted of qualitative immunodiffusion tests mimicking tube-precipitin (immunoglobulin M) or complement-fixing (immunoglobulin G) antibody tests;[10] a positive result, even in an undiluted sample, is highly specific. Positive immunodiffusion tests were sent to a reference laboratory for complement fixation titer (1996 to 2000) or for immunodiffusion (ID) titer (2000 to 2007, performed at the Southern Arizona VA Health Care system). The ID and complement fixation results correlate well with each other, allowing direct comparison of the titers.[11]

RESULTS

Types of Coccidioidomycosis

We identified 207 patients with disseminated coccidioidomycosis, including 136 cases with only extra-central nervous system (central nervous system), 57 with only central nervous system dissemination, and 14 with both. The 150 cases with extra-central nervous system dissemination were classified as shown in Table 1. *Coccidioides* species commonly cross tissue boundaries, so clinical cases often overlap categories. Therefore, we established a hierarchical system based on decreasing severity as shown by the descending rows in the table (hematogenous > multisystem > axial > peripheral skeletal > soft tissue > skin). Cases of visceral coccidioidomycosis did not overlap with the other groups.

Table 1 Types of Coccidioidomycosis

Classification	Numbers	Male	Systemic Risk Factor*	Death†
Hematogenous	41	22	36	14
Multisystem	15	10	5	1
Axial skeleton	28	21	6/26	
Peripheral skeleton	26	18	11	
Soft tissue (muscle or lymph node)	15	13	4/14	
Skin	16	9	2/15	
Visceral organ	9	4	3	
Totals	150	97	67/147	15 (8 male; 14 had risk factors)

*Risk factors included corticosteroid therapy (19), tumor necrosis factor-alpha blockade (2), organ transplantation (11: 5 kidney, including 1 with pancreas, 2 lung, 2 liver, 2 heart), HemLymph malignancy (7), chronic renal disease (4), chronic liver disease (4), autoimmune; no steroids (3), pregnancy (2), Ifn-gamma receptor def (1), unknown (3), none (80).

†Death occurring during the initial hospitalization for disseminated disease.