Diagnosis and Management of Coccidioidomycosis

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KEYWORDS

• Coccidioidomycosis • Fungal infections • Diagnosis • Treatment

KEY POINTS

- Coccidioidomycosis is a primary cause of community-acquired pneumonia in endemic regions.
- The disease burden is rapidly growing within endemic areas secondary to population and environmental changes. Coccidioidomycosis is also seen far outside traditional boundaries in an increasingly mobile society.
- Recent arrival to an endemic area, certain ethnicities, advanced age, pregnancy, and defects in cellular immunity all influence disease severity.
- Coccidioidomycosis is definitively diagnosed when *Coccidioides* is demonstrated on pathology or in culture but is most commonly diagnosed via serology. The use of serology requires an understanding of the testing involved, and results must be interpreted in the context of time and capacity to develop a host immune response.
- Azoles, especially fluconazole, are the mainstay of therapy. The need to treat mild pulmonary disease is controversial but treatment is obligatory in severe or prolonged disease, dissemination, or severe immunosuppression. Treatment duration is months to a year and may be lifelong, depending on the clinical scenario.

INTRODUCTION

Coccidioides spp are a leading cause of community-acquired pneumonia in endemic regions. Although formerly well confined to these endemic areas, broad social and environmental changes have extended the reach of *Coccidioides* beyond traditional geographic boundaries and should be of interest to clinicians worldwide. Its manifestations are protean and many methods of diagnostic testing are available, each with limitations. Treatment, likewise, is commonly tailored to the patient, taking into account the severity and chronicity of the disease as well as the immune status and perceived vulnerability of the host.

HISTORY, ECOLOGY, AND EPIDEMIOLOGY

Coccidioidomycosis was first described in 1892 when an Argentinian medical student discovered spherical organisms resembling the protozoan Coccidia[1,2] in the biopsy specimens of a patient with progressive skin lesions. Similar lesions and biopsy findings were observed from a patient in the San Joaquin Valley of California several years later, and the organism was named *Coccidioides* (resembling Coccidia) *immitis* (not mild). As with *Histoplasma*[3] and *Blastomyces*,[4] *Coccidioides* was initially miscategorized as a protozoan,[1] a mistake perpetuated by its dimorphic nature (**Fig. 1**). Its true identity as a dimorphic fungus

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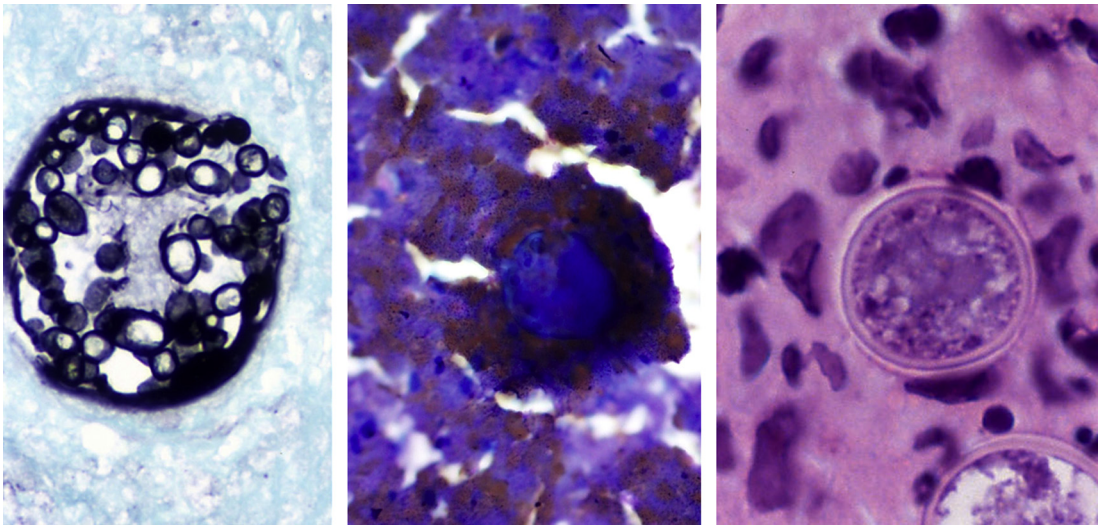

Fig. 1. Light microscopy demonstrating *Coccidioides* in spherular phase, characterized by a circular capsule-bound structure containing numerous small circular endospores. Microscopy findings are demonstrated using Grocott methenamine silver (*left*, original magnification × 400), Papanicolaou (*middle*, original magnification × 100), and hematoxylin-eosin stains (*right*, original magnification × 100).

was later recognized when mycelia were demonstrated to cause disease when injected into animals.[1,5] Subsequent case reports in patients and laboratory workers noted dissemination during the course of infection and emphasized the lungs as the portal of entry with development of lobar pneumonia, pleuritic chest pain, and often erythema nodosum.[1,6] This syndrome, now known in California as San Joaquin fever or valley fever, led to the identification of *Coccidioides* as the cause. A second species, *C posadasii*, was eventually identified.[7] *C immitis* mostly inhabits the San Joaquin Valley of California whereas *C posadasii* inhabits all other endemic regions. Overlap of these endemic regions is now known to exist and the clinical manifestations are indistinguishable between species.

Coccidioides spp are endemic to arid regions of the American Southwest, Northern Mexico, and several desert regions of Central and South America (**Fig. 2**). The organism tends to grow in sandy soil 10 cm to 30 cm below the surface,[8,9] where in wet conditions it grows as a mold with septate hyphae. In dry conditions, the hyphae desiccate to form small arthroconidia, or spores, 3 μm to 5 μm in diameter, later to be dispersed by aerosolization when the soil is disturbed by weather or commercialization. Spores are then inhaled, the route via which virtually all human disease occurs, although direct inoculation through broken skin is occasionally reported.[10] Once deposited in the periphery of the lungs the organism progresses to form much larger spherules, 20 μm to 100 μm in diameter, which eventually contain hundreds of 2 μm to 4 μm endospores; the spherule ruptures and releases these endospores, each of which is capable of creating a new spherule.

Rising Incidence in Endemic Areas

Arizona and California are the 2 states where the burden of coccidioidomycosis permits an estimation of incidence. Data for other areas are largely limited to coccidioidin skin testing surveys: positive skin reactivity in Mexican endemic regions ranges from 10% of the population (Baja California) to 93% (Coahuila).[10–12] Based on skin testing, 3% of endemic inhabitants seem to be newly infected each year.[13,14] Reports increasingly occur after dust storms,[15] military exercises,[16] earthquakes and landslides,[17] and outdoor recreation and during the dry season.[18,19] Consequently, up to 30% of cases of community-acquired pneumonia in Arizona may be due to coccidioidomycosis.[20]

Within Arizona and California, available data suggest a dramatic increase in disease burden. Although recent changes in laboratory-based case reporting in Arizona may partially be responsible for the increased incidence, from 2001 to 2010, the incidence of coccidioidal infection in Arizona increased from 12 cases to 58.2 cases per 100,000.[21,22] *Coccidioides*-specific diagnostic testing is only performed in a minority of patients presenting for care with compatible symptoms, suggesting that even these data are underestimates of true incidence.[23]