Coccidioidomycosis
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Abstract
Coccidioidomycosis is a common, environmentally acquired, pulmonary fungal infection in arid and semi-arid regions of the West, especially Arizona and California. The infection is frequently associated with striking cutaneous manifestations. Reactive, immunologically mediated eruptions include erythema nodosum, a generalized exanthem, Sweet syndrome, and reactive granulomatous dermatitis. Less commonly, the skin can harbor the actual organisms as a result of dissemination from the lungs. Dermatologists may play a key role in the recognition of coccidioidomycosis.

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Since the initial description of coccidioidomycosis in the late 19th century, the skin has frequently provided key clues to the diagnosis of this unusual fungal infection. The first published description of coccidioidomycosis was in an Argentine soldier who developed disseminated cutaneous nodules clinically resembling mycosis fungoides. Skin biopsy revealed distinctive spherical organisms now known to represent Coccidioides species.

Initially thought to be a rare and often fatal infection, coccidioidomycosis was later discovered to be common in endemic areas and to follow a mild clinical course in most cases. In the San Joaquin Valley of California during the 1930s, Coccidioides immitis was identified as the cause of Valley Fever, a self-limited syndrome characterized by respiratory symptoms, fever, and erythema nodosum. Subsequently, coccidioidomycosis became increasingly common during the latter half of the 20th century, as cities of the southwestern deserts transformed into heavily populated urban centers and popular tourist destinations.

Recent decades have brought epidemics of the infection in parts of Arizona and California. In Arizona the incidence of coccidioidomycosis increased more than 8-fold from 30.5 cases per 100,000 in 1998 to 247.7 cases per 100,000 in 2011. Climatic factors are believed to be at least partly responsible. Exposure to the airborne organisms is increased by environmental events and by human activities that disrupt the soil. Widespread epidemics of coccidioidomycosis have been precipitated by dust storms, earthquakes, and droughts. Clusters of cases have been reported among construction workers, archeologists, and military personnel.

In the Central Valley of California, a recent epidemic of coccidioidomycosis among the inmates of 2 prisons resulted in over 36 deaths, and led in 2013 to the court-ordered relocation of nearly 2,000 prisoners at high risk for the infection.

Coccidioidomycosis has had increasingly important implications for public health in endemic areas. Even outside endemic areas, knowledge of coccidioidomycosis is important for health care providers, since tourists exposed to the organism may develop signs of the illness after returning home.

Coccidioides species
Coccidioides sp. are soil-dwelling fungi found in arid and semi-arid regions of the New World, from the western United States to Argentina. Two species are generally recognized, C. immitis mostly within California and C. posadasii mostly outside California. The 2 closely related species produce infections with clinically similar features. The organisms grow best in regions with hot summers, mild winters, low annual rainfall, and alkaline soil. The most highly endemic areas include the Phoenix and Tucson areas of Arizona and the Central Valley of California.

In the upper few inches of the soil, the organisms exist as filamentous mycelia, which give rise to boxcar-shaped arthrospores. Arthrospores are carried by the wind and may implant in favorable soil to produce additional mycelia. If inhaled by a suitable host, such as a human, dog, or horse, the arthrospores embed in the lungs and transform into spherules. Through a process of internal septation, mature spherules produce numerous round endospores. As the spherules grow and eventually burst, the enclosed endospores are released into the adjacent tissues and enlarge to form additional spherules. The infection is thus propagated throughout the adjacent tissues, and in severe cases, may spread hematogenously to distant anatomic sites. The infectious form of the organism is the arthrospore, which is found in the environment or in culture; person-to-person transmission of the infection generally does not occur.

Pulmonary and systemic manifestations
The lungs are nearly always the primary focus of infection. The severity of the respiratory infection is partly related to the number of inhaled arthrospores and partly related to immunologic factors of the host. Most infected patients are asymptomatic or may develop mild respiratory symptoms mimicking the common “cold”. More severe respiratory symptoms do sometimes occur, and may be associated with a severe influenza-like illness, with signs of cough, fever, and prolonged fatigue. Respiratory failure from severe pneumonia is rare and may be fatal.

Disseminated coccidioidomycosis may secondarily involve the
skin, bones, meninges, or other organs. Skeletal involvement may be disabling, and coccidioidal meningitis may be associated with prolonged morbidity or death.

**Host factors**
Host factors have a significant influence upon the clinical course of coccidioidomycosis. Otherwise healthy persons from specific ethnic groups are at much greater risk of fulminant respiratory disease and dissemination of the infection to other organs. When compared to the general population, Filipinos and African Americans have a markedly increased risk of dissemination. Inherited immunologic factors appear to be responsible but are not yet completely understood. Even among patients with no ethnic predisposition, otherwise healthy persons of all ages may occasionally develop severe infection. Pregnant women from all ethnic groups have an increased risk of severe respiratory infection or dissemination, particularly during the third trimester and post-partum period. Predisposition to severe coccidioidomycosis also occurs in immunosuppressed individuals including HIV-infected patients, organ transplant recipients, and patients receiving tumor necrosis factor-alpha inhibitors.

**Cutaneous manifestations**
Cutaneous findings in coccidioidomycosis include a variety of reactive, immunologically mediated manifestations, which are often clinically striking. These include erythema nodosum, a generalized exanthem, Sweet syndrome, and reactive granulomatous dermatitis. Several of the reactive cutaneous manifestations erupt early in the course of the infection, and the dermatologist may be the initial health care provider to evaluate the patient. In addition to the common reactive manifestations, the skin may also be the site of disseminated infection via hematogenous spread from the lungs. Primary cutaneous infection is extremely rare and occurs by traumatic implantation of organisms directly into the skin from an environmental source.

**Erythema nodosum**
Erythema nodosum is a classic cutaneous sign of pulmonary coccidioidomycosis. One to three weeks after the onset of respiratory symptoms, painful red nodules erupt on the lower extremities (Figure 1). The anterior tibial areas and ankles are typically involved. Erythema nodosum is a particularly common manifestation of coccidioidomycosis during pregnancy. As a reflection of a strong cell-mediated immune response, erythema nodosum is generally associated with a favorable prognosis. The eruption is typically self-limited and may be treated symptomatically.

**Exanthem**
The exanthem or toxic erythema of coccidioidomycosis (Figure 2) is a florid, generalized, symmetrical, morbilliform eruption, abruptly arising within the first few days of illness. Pruritus is frequently present and may be severe. Target-like lesions and palmar involvement are common and may simulate erythema multiforme or an allergic drug reaction (Figure 3). Despite the striking clinical presentation, the histopathologic features are mild and nonspecific, typically showing slight spongiosis or subtle interface vacuolization. In contrast to true erythema multiforme, necrotic keratinocytes are absent or very rare within skin biopsy specimens. The exanthem resolves spontaneously over days to weeks. The significance of the exanthem lies in its role as an early cutaneous clue to the diagnosis of coccidioidomycosis. Because it occurs early in the course of infection, the eruption may precede the development of detectable antibodies in the serum.

**Sweet syndrome**
Sweet syndrome is recognized as a distinctive reactive eruption, often occurring in association with underlying systemic diseases, such as a viral respiratory infection or myeloid malignancy. Features of the syndrome include painful edematous red nodules and plaques, associated with fever, peripheral blood neutrophilia, and dermal neutrophilic infiltrates. Pustular features are clinically evident in some cases. In endemic areas, Sweet syndrome (Figure 4) has recently been recognized as a common reactive manifestation of coccidioidomycosis. Distinguishing Sweet syndrome from disseminated infection is important. In skin biopsy specimens of coccidioidomycosis.

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**FIGURE 1.** Erythema nodosum associated with pulmonary coccidioidomycosis. Red subcutaneous nodules on the leg.

**FIGURE 2.** The exanthem of pulmonary coccidioidomycosis. Florid generalized eruption arising abruptly during the first few days of illness.
Sweet syndrome, the dermis contains a dense band-like neutrophilic infiltrate with leukocytoclasis and marked subepidermal edema. No organisms are detectable within the skin lesions by microscopic examination or by culture. Like the exanthem of coccidioidomycosis, Sweet syndrome may occur early in the course of the illness. Systemic immunosuppressant medications are commonly used to treat idiopathic Sweet syndrome, but should be avoided or approached cautiously in the setting of coccidioidomycosis. The cutaneous plaques of Sweet syndrome resolve over a period of weeks or months as the patient recovers from the pulmonary infection.

**Reactive granulomatous dermatitis**

A reactive granulomatous dermatitis (Figure 5) has recently been described as a manifestation of coccidioidomycosis, and is a relatively common sign of the infection. Early in the course of the illness, edematous or firm red papules or plaques arise on scattered or widespread areas of the trunk and extremities. The plaques sometimes have annular features. Skin biopsy reveals interstitial granulomatous dermal infiltrates, often accompanied by scattered neutrophils and subepidermal edema. Some cases appear to be on a histologic continuum with histiocyte-rich Sweet syndrome, while others more closely resemble granuloma annulare microscopically. By definition, no organisms are detectable within the skin by microscopic examination or by culture. The eruption resolves spontaneously over a period of weeks or months as the patient recovers from the pulmonary infection. Recognition of this reactive eruption is important in order to distinguish it from the granulomatous infiltrates of disseminated coccidioidomycosis.
Erythema multiforme
Since the early 20th century, erythema multiforme has been cited as a common reactive manifestation of coccidioidomycosis. However, the histopathologic definition of erythema multiforme has evolved over the decades, and by its current definition, erythema multiforme rarely if ever occurs in association with coccidioidomycosis. Annular erythematous cutaneous eruptions are common reactive manifestations of pulmonary coccidioidomycosis, but these cases may currently be classified more accurately as the exanthem of coccidioidomycosis, Sweet syndrome, or reactive granulomatous dermatitis, all of which frequently have annular features clinically. The necrotic keratinocytes, which histologically define erythema multiforme, are not seen in these annular eruptions.

Disseminated coccidioidomycosis
In contrast to all of the above reactive cutaneous signs, disseminated coccidioidomycosis is characterized by the presence of identifiable organisms within the skin. The lungs are almost always the primary site of infection. Cutaneous involvement occurs through hematogenous dissemination from the lungs, and is more likely to occur in immunosuppressed or genetically predisposed individuals. The skin is the most common site of dissemination and may serve as a clue for possible involvement of other organs such as the skeleton or meninges.

Dissemination to the skin typically occurs several months after the onset of pulmonary infection, but in some cases, is the initial diagnostic sign. The severity of preceding pulmonary infection varies widely among patients with dissemination. Some have fulminant concurrent respiratory illness, while others have moderate, minimal, or no respiratory symptoms. Occasionally, nondescript cutaneous papules, which are biopsied to rule out a skin cancer, reveal the surprising diagnosis of disseminated coccidioidomycosis in an otherwise healthy-appearing individual.

Disseminated cutaneous lesions of coccidioidomycosis (Figure 6) may be solitary or multiple and have highly variable clinical morphology. Nodules, papules, plaques, pustules, abscesses, or sinus tracts may occur. Ulceration is frequently present. The lesions may involve any cutaneous site but are commonly located on the face. Unusual clinical presentations may mimic lupus vulgaris, mycosis fungoides, or lepromatous leprosy.

In skin biopsy specimens, the coccidioidal organisms are visible in the dermis and subcutis as distinctive spherical structures, 10 to 80 microns in diameter, with thick cell walls (Figure 7). The spherules are readily visualized with routine hematoxylin-eosin stains, and are highlighted by special fungal stains, such as periodic acid-Schiff or methenamine silver stains. The organisms range in number from very sparse to extremely numerous. Internal septa or endospores may occasionally be identified within mature, large spherules (Figure 8). Epithelial hyperplasia or ulceration may be present, and transepidermal elimination of organisms sometimes is seen. In the dermis, the spherules are often present intracellularly within multinucleate giant cells. The associated inflammatory infiltrate is highly variable and may consist of suppurrative granulomas, lymphoplasmacytic infiltrates, sarcoid-like granulomas, or rarely, eosinophil-predominant infiltrates.
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*Coccidioides sp.* may also be detected in skin biopsy specimens by culture. The organism grows rapidly on standard fungal culture media and sometimes grows on bacterial culture media. The cultured form of the organism is highly infectious. Specialized laboratory procedures must be employed to protect laboratory personnel from the infectious aerosolized arthrospores.

Chronic cutaneous infection occasionally occurs and may resist standard oral antifungal therapy. The skin may serve as a persistent nidus of infection, even after apparent resolution of the respiratory findings.23

**Primary cutaneous coccidioidomycosis**

Primary cutaneous coccidioidomycosis results from direct traumatic inoculation of arthrospores into the skin, typically by a laboratory instrument, splinter, or cactus spine. This presentation of coccidioidomycosis is very rare; approximately 22 cases have been reported in the literature.28-30 The usual location is an extremity. The infection leads to cutaneous nodules, ulcers, abscesses, or sinus tracts. Organisms are identifiable within the skin by biopsy or by culture. The infection may remain localized or may spread along the pathways of lymphatics in a sporotrichoid pattern. Regional lymph nodes may be involved.

Distinction from disseminated infection is important. Cutaneous nodules of coccidioidomycosis are more commonly due to primary pulmonary coccidioidomycosis that has spread secondarily to the skin. Serologic studies may be helpful in the distinction. High IgG titers to *Coccidioides* sp. suggest dissemination, rather than primary cutaneous infection. In contrast to disseminated cases, the lesions of primary cutaneous coccidioidomycosis usually resolve without treatment.28

**Serologic and radiographic findings**

Commonly used serologic tests for *Coccidioides* species include enzyme immunoassay, complement fixation, and immunodiffusion.31 Enzyme immunoassay (EIA) is a rapid, sensitive, and readily available serologic test for the qualitative detection of IgM and IgG antibodies to *Coccidioides* species. EIA offers the advantage of detecting antibodies earlier than other methods. A positive IgM by enzyme immunoassay is usually indicative of coccidioidomycosis, even in the absence of detectable IgG antibodies, although false positive results sometimes occur with IgM.32 Positive results by enzyme immunoassay are typically confirmed by other methods, such as complement fixation and immunodiffusion, both of which are performed at reference laboratories. In contrast to EIA, serologic testing by complement fixation provides quantitative results. Even low titers, such as 1:2, are consistent with a true infection. Higher titers (1:16, 1:32, or higher) are more commonly seen in patients with severe pulmonary infection or dissemination. Immunocompromised patients with coccidioidomycosis are more likely than immunocompetent patients to have falsely negative serologies; however, serologic testing by multiple methods increases the sensitivity.31

In both immunocompromised and immunocompetent patients, serologic tests for coccidioidomycosis may also be falsely negative early in the course of the disease. The exanthem of coccidioidomycosis erupts very early in the course of the illness and may precede the development of detectable antibodies.19 Repetition of serologic tests in 2 or 3 weeks may help to confirm the diagnosis. During the course of the illness, serologic testing by complement fixation may assist in monitoring the resolution of the infection. The serologic titers diminish over a period of months.

Chest x-ray and CT scans are helpful in evaluating patients for suspected coccidioidomycosis. Typical findings include pulmonary consolidations, patchy infiltrates, or lung nodules.33 Hilar lymphadenopathy, pleural effusion, or pulmonary cavities also sometimes occur. In some very mild cases, the chest radiograph may demonstrate minimal findings,35 despite the development of positive serologies and reactive cutaneous manifestations.19

**Treatment**

In uncomplicated cases of coccidioidomycosis, treatment is controversial. Without treatment most patients recover uneventfully from the infection over a period of several weeks. At the present time, antifungal medication is generally believed to be unnecessary in most cases.34

Antifungal therapy is indicated for immunosuppressed patients with coccidioidomycosis. Treatment may also be considered in uncomplicated coccidioidal infections in otherwise healthy patients of Filipino or African ancestry. Regardless of ethnicity, patients with severe coccidioidal pneumonia or disseminated infection do require treatment with systemic antifungal medications.24

Typical treatment regimens include fluconazole 400 mg/d or itraconazole 400-600 mg/d.34 Higher doses are sometimes needed if standard doses are ineffective. Voriconazole and posaconazole are newer azoles that may be helpful when standard therapy fails to resolve the infection.35 Treatment failures sometimes occur with any of the currently available medications. Amphotericin B is another therapeutic option, particularly in severe infections. Because the azoles are teratogenic, amphotericin B is considered for pregnant patients requiring treatment.35 Progress is being made towards the development of a vaccine for prevention of coccidioidomycosis.36

**Conclusion**

Coccidioidomycosis is an environmentally acquired pulmonary fungal infection with striking cutaneous findings, including both reactive, immunologically mediated eruptions and, less commonly, the actual presence of coccidioidal organisms in the skin. The cutaneous clues are often among the earliest signs of the infection and may aid in the diagnosis. Although most infections are asymptomatic or have a mild clinical course, the disease may occasionally be debilitating or fatal. Systemic antifungal medications are recommended for patients with severe infections and for patients who have risk factors for dissemination. Dermatologists may play a key role in the recognition of this unusual infection.

**References**
