

Locally recurrent primary cutaneous coccidioidomycosis



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INTRODUCTION

Coccidioidomycosis is a highly infectious mycosis endemic to the southwestern and western United States and northern areas of Mexico. It is caused by 2 dimorphic species, *Coccidioides immitis* and *Coccidioides posadasii*.¹⁻³ Coccidioidomycosis is primarily contracted via the respiratory route from inhaling fungal spores. Clinical manifestations vary but predominantly involve the lung (eg, mild upper respiratory infection or community-acquired pneumonia), with occasional lymphatic or hematogenous spread to the bone, brain, and/or skin. Cutaneous manifestations include, in the following order of prevalence, reactive skin lesions, such as erythema nodosum or erythema multiforme; secondary cutaneous lesions from disseminated infection; or primary cutaneous lesions.¹ Primary cutaneous coccidioidomycosis (PCC) is extremely rare, since direct inoculation or trauma to the skin is required rather than inhalation of spores. PCC, unlike the disseminated form, has an excellent prognosis, usually requiring only supportive treatment.⁴ In this report, we discuss an unusual case of locally recurrent PCC.

CASE REPORT

A 50-year-old woman from southern California with a history of lupus (on hydroxychloroquine and low-dose prednisone) grazed her thigh while running in California. The area became red over 3 to 4 weeks, and she was subsequently diagnosed with coccidioidomycosis based on biopsy and culture. She had no pulmonary symptoms and a normal chest x-ray. After 6 months of fluconazole 200 mg twice daily, the lesion

Abbreviation used:

PCC: primary cutaneous coccidioidomycosis

resolved with some residual skin discoloration. She subsequently moved to Rochester, New York.

One year later, she presented with a 3-week history of an asymptomatic enlarging lesion in the area that had remained discolored. On examination, a 2 × 4-cm nontender violaceous plaque with a firm 1-cm central nodule was noted (Fig 1). She had an oxygen saturation of 98% with ambulation and a normal chest x-ray. Because coccidioidomycosis can be a relapsing disease and the enlarging lesion was in the same location, she was empirically started on fluconazole 200 mg twice daily for 6 months, the same regimen she tolerated well previously, which led to resolution of the lesion again. The risk of increased QT prolongation with the coadministration of hydroxychloroquine and azoles was monitored. Although she did have a prolonged QT (QTc = 524), her echocardiogram was unremarkable, and she did not exhibit any cardiac arrhythmias throughout her treatment course. Alternative agents, such as itraconazole, voriconazole, and posaconazole, were considered but not pursued because of strong drug interactions with prednisone and other potential side effects.

Four months after she finished fluconazole with no side effects, a tender nodule reappeared in the same location. A punch biopsy showed an epidermoid inclusion cyst. Fungal and acid-fast bacterial

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Fig 1. Clinical examination revealed a 2 × 4-cm non-tender rectangular violaceous plaque with a firm 1-cm central nodule on the lateral aspect of the middle portion of the left thigh.

cultures and stains were negative. Because recurrent coccidioidomycosis is very rare, particularly after being appropriately treated, it was assumed that this was an inflamed epidermoid inclusion cyst, for which intermittent flares would be more common.

The patient desired to have the lesion excised because of its painful and recurrent nature. During surgery, a single discernable cyst wall was not identified; in fact, multiple small cysts were seen, and the decision was made to excise the whole lesion because of concern for a multiloculated cyst. Histologic examination revealed a necrotizing and granulomatous inflammatory cell infiltrate with spherules of approximately 30 μm embedded in the necrotic debris (Fig 2, A and B), highlighted by Grocott-Gomori methenamine–silver nitrate stain (Fig 2, C). The surgical margins were clear of coccidioides organisms. A coccidioides antibody titer by complement fixation was minimally positive at 1:2. Urine was negative for *Histoplasma capsulatum* antigen. The patient had an uncomplicated recovery from excision. Given the localized nature of the infection and the likelihood that the lesion had been fully excised, the patient declined further treatment, and she remains symptom-free after 5 months.

DISCUSSION

The most common form of coccidioidomycosis is primary pulmonary coccidioidomycosis, which is

asymptomatic in approximately 60% of patients or presents as a self-limited pneumonia.⁵ Cutaneous manifestations of coccidioidomycosis, such as reactive skin lesions from pulmonary infections or disseminated lesions, are common; however, PCC is rare.^{1,6} An extensive literature search by Reyna-Rodriguez et al¹ revealed only 82 cases of PCC published from January 1929 to December 2019.

Wilson et al⁷ outline the diagnostic criteria for PCC as follows: no pulmonary involvement preceding the cutaneous lesion; a history suggestive of traumatic inoculation; a short incubation period of 1 to 3 weeks before appearance of the lesion; chancreiform primary lesion (a relatively painless, firmly indurated nodule or nodular plaque); an early positive precipitin reaction; an early positive coccidioidin skin test; a negative or low complement fixation reaction; development of regional lymphadenitis and lymphadenopathy; and spontaneous healing of the primary cutaneous lesion occurring within a few weeks, unless the patient is immunologically compromised.

Diagnosis of PCC is usually made by a combination of the abovementioned criteria, histologic findings of coccidioides spherules, and a negative chest x-ray. Our patient presented with a painless nodular plaque on her thigh that occurred 3 times in the same location, which first manifested from a traumatic event. She had no pulmonary symptoms at the time of her initial diagnosis and clear chest imaging studies. Biopsy showed granulomatous inflammation and spherules of the fungus with serology titers low at 1:2. Any positive titer suggests past or current infection; however, titers need to be lower than 1:32 for the infection to be considered a self-limited disease as opposed to a systemic one.^{4,5} Therefore, her presentation strongly suggests the recurrence of PCC.

PCC can affect both immunocompetent and immunosuppressed individuals, although the latter are at increased risk of infection. In general, unlike the disseminated form, the prognosis of PCC is excellent, with the majority of patients noting spontaneous healing without treatment.⁴ Resolution of the disease occurs spontaneously, with antifungal treatment, or with surgical resection together with antifungal treatment.¹ Our patient had a relapse of her PCC twice in the span of 2 years despite receiving adequate treatment (fluconazole 400 mg daily for 6 months), which is an unusual presentation. The latest Infectious Diseases Society of America Clinical Practice Guideline for the Treatment of Coccidioidomycosis recommends fluconazole 400 to 800 mg daily or itraconazole 200 mg twice daily for at least 6 to 12 months.⁸

We suspect the relapse of her disease was due to her immunosuppressed state. The immune

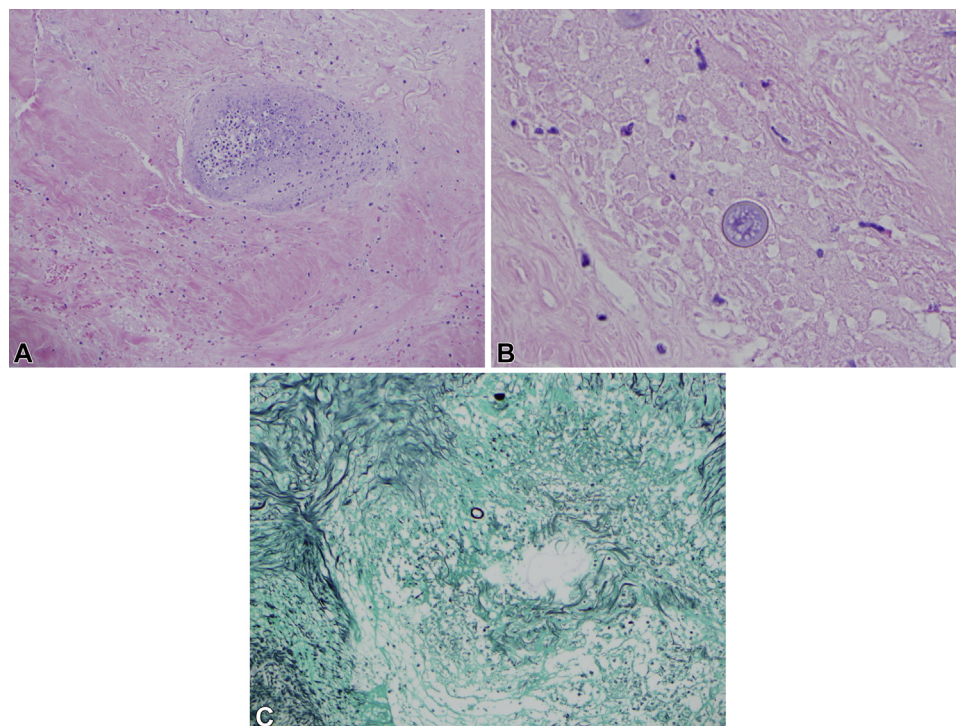


Fig 2. Histologic analysis of the excisional specimen demonstrates necrotic tissue and spherules approximately 30 μm in size consistent with coccidioidomycosis. Multiple endospores were observed within the tissue (not shown). Immature spherules, with indistinct endospores, consistent with coccidioidomycosis, were also observed. (**A** and **B**, Hematoxylin-eosin stain; **C**, Grocott-Gomori methenamine–silver nitrate stain; original magnifications: **A**, $\times 100$; **B**, $\times 400$; **C**, $\times 100$.)

response to coccidioidomycosis infection involves the development of delayed-type hypersensitivity and cellular immunity,⁹ which appears to be long-lived and protective, since the majority of those infected are asymptomatic or have benign outcomes. Reactivation of clinical infection after resolution of the initial disease appears to occur mainly in patients with profound immunosuppression, such as those receiving corticosteroids, anticancer therapy, or tumor necrosis factor α inhibitors, or those with HIV infection, hematologic malignancies, and autoimmune diseases.^{5,9} The nature of azoles probably contributed to our patient's disease relapse as well. Azoles are fungistatic, preventing the growth and reproduction of fungi but are not fungicidal.¹

We present an unusual case of localized recurrent PCC. We hope that this case highlights the importance of keeping a high level of suspicion of relapsing coccidioidomycosis in someone with a history of PCC who is immunosuppressed.

Conflicts of interest

None disclosed.

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