



Erythema Multiforme–Like Hypersensitivity Reaction with Pustules: A Clinical Clue to Coccidioidomycosis

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Introduction

Coccidioides is a highly infectious fungus endemic to the soil in the southwestern United States. When inhaled as arthroconidia, it can cause coccidioidomycosis, commonly called Valley Fever.¹ In 2019, the U.S. Center for Disease Control and Prevention (CDC) reported 20,003 cases of coccidioidomycosis, mostly in Arizona and California, with incidence likely underestimated due to misdiagnosis and low testing rates.² Older adults, especially those over 60, are disproportionately affected.²

Most cases of coccidioidomycosis are discovered incidentally as infected individuals are typically asymptomatic. Infected individuals who develop symptoms often present with pneumonia, fever, chest pain, and headache. In rare cases, infection results in disseminated disease—causing meningeal, osteoarticular, or integumentary disease.¹ Individuals with underlying HIV, solid organ or hematopoietic stem cell transplant, or those on biologic response modifiers are at increased risk of developing severe or disseminated infection with increased mortality.³

Cutaneous manifestations of coccidioidomycosis vary. Primary cutaneous lesions are rare and result from direct inoculation into the skin. Secondary cutaneous lesions result from disseminated infection, with pulmonary coccidioidomycosis as the most common source. Reactive lesions are the most common cutaneous manifestations of coccidioidomycosis and can present as erythema multiforme, erythema nodosum, Sweet's syndrome, and others.⁴ Erythema nodosum is the most recognized reactive eruption associated with coccidioidomycosis, but generalized exanthem and erythema multiforme are also common presentations.⁵

Histopathology of reactive cutaneous coccidioidomycosis commonly shows mild perivascular lymphocytic infiltrates, neutrophils, eosinophils, spongiosis, and keratinocyte vacuolization.⁵ The histopathology of primary or disseminated cutaneous coccidioidomycosis may contain double-walled refractile spherules (10 to 80 μ m) with endospores.⁶

While therapy is not always required for mild illness, triazole antifungals have replaced amphotericin B as the gold standard of treatment due to better tolerability and improved safety profile. Amphotericin B is reserved for more serious disease or those resistant to azoles.⁷ Recent studies, however, have raised concerns about fluconazole susceptibility, with reports indicating that up

to 37% of *Coccidioides* isolates exhibit reduced in vitro sensitivity to the drug.⁸ This underscores the need for antifungal stewardship and further research into novel antifungal agents, particularly for central nervous system or refractory infections.

Most literature on *Coccidioides* hypersensitivity focuses on more common, reactive cutaneous manifestations such as erythema nodosum and erythema multiforme, without mention of pustule formation. A thorough literature review revealed no cases of reactive hypersensitivities with pustules in the skin secondary to pulmonary coccidioidomycosis. We present two cases of a unique dermatologic manifestation of primary pulmonary coccidioidomycosis - an erythema multiforme-like exanthem, separate from a true erythema multiforme, without necrotic keratinocytes histologically, and clinically with pinpoint follicular pustules uncharacteristic of erythema multiforme.

Cases

Case 1

A 23-year-old woman with no significant past medical or dermatological history presented to the emergency room after two days of fevers and chills with subsequent eruption of a rapidly spreading, diffuse, non-painful but pruritic rash. She was admitted to the hospital for concern of a drug eruption due to isotretinoin which she began one month earlier, and dermatology was consulted. Physical exam revealed a widespread rash of pink-red papules and plaques with central dusky erythema and pinpoint follicular pustules (Figures 1A and 1B). Skin biopsy revealed prominent epidermal spongiosis with formation of spongiotic vesicles and dermal perivascular infiltrate composed of lymphocytes, histiocytes, and scattered eosinophils (Figures 2A and 2B). The infectious workup was negative for acute infection of mycoplasma pneumonia and EBV. Chest x-ray revealed an ill-defined opacity in the right lower lung, representing possible airspace disease. Coccidioidomycosis serologies yielded indeterminate results, but complement fixation titers were positive confirming active pulmonary infection with coccidioidomycosis (Table 1). Of note, isotretinoin as the cause was considered, but biopsy did not support drug eruption, and later the patient was reinstated on isotretinoin after she completed treatment for her coccidioidomycosis without recurrence of rash.

Case 2

A 21-year-old woman with no significant past medical history presented with three days of myalgias, lightheadedness, fatigue, and a nearly identical exanthem diagnosed as atypical erythema multiforme-like hypersensitivity reaction with uncharacteristic pinpoint follicular pustules (Figures 1C and 1D). There were no new medications prior to onset. This increased clinical suspicion for coccidioidomycosis infection.

The infectious workup was negative for acute infection of chlamydia, gonorrhea, trichomonas, HIV 1/2, EBV, Hepatitis B, and Hepatitis C. Chest x-ray identified an extensive airspace opacity in the lingula and left lower lobe with a small left parapneumonic effusion reflecting multifocal pneumonia. Subsequent coccidioidomycosis serology was positive for acute infection (Table 1).

Table 1: Patient Serologies

Serology	Patient 1	Patient 2
Mycoplasma pneumonia Ab, IgM	309 U/mL	167 U/mL
Mycoplasma pneumonia Ab, IgG	1.80 (H)	< 0.90
Coccidioides EIA Ab, IgM	Indeterminate	Positive
Coccidioides EIA Ab, IgG	Negative	Negative
Coccidioides Comp Fix	1:4	< 1:2
EBV VCA IgG	6.4 AI	4.6 AI
VC IgG	Positive A	Positive A
EBV VCA IgM Index	0.2 AI	< 0.2 AI
VC IgM	Negative	Negative
EBV, Nuclear Ag Index	> 8.0 AI (H)	> 8.0 AI (H)
EBV, Nuclear Ag (EBNA)	Positive A	Positive A

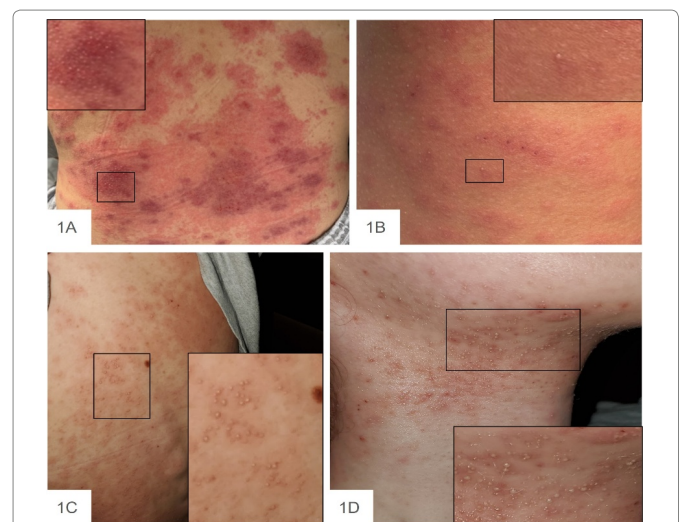


Figure 1: “Case presentations. 1A and 1B: Case 1 presentation with pink-red papules and plaques with central dusky erythema and pinpoint follicular pustules. 1C and 1D: Case 2 presentation with atypical erythema multiforme with uncharacteristic pinpoint follicular pustules.”

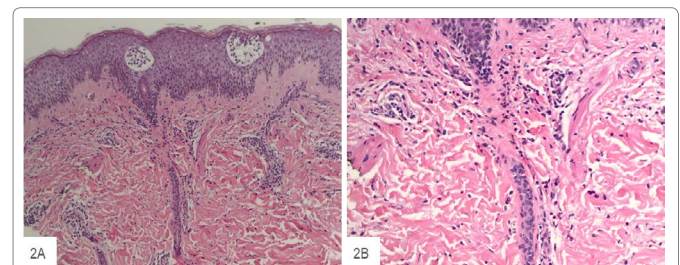


Figure 2A-B: “Case 1 skin biopsy: prominent epidermal spongiosis with formation of spongiotic vesicles and dermal perivascular infiltrate composed of lymphocytes, histiocytes, and scattered eosinophils”

Discussion

While most cases of coccidioidomycosis are asymptomatic or mild, and therefore undiagnosed, disseminated disease and infection in immunocompromised individuals can have considerable implications regarding disease morbidity and mortality. Both patients were from Arizona, an endemic area where coccidioidomycosis is a leading cause of community-acquired pneumonia, with clinical and radiographic findings that may present similarly to other causes of pneumonia.⁹ Work-up of pneumonias may include serologies, sputum culture, bronchoalveolar lavage fluid analysis, and/or lung biopsies to confirm diagnosis.⁹ H&E staining of skin biopsy specimens revealed features consistent with a hypersensitivity reaction rather than that of a primary cutaneous infection or dissemination, which conversely presents as papules, ulcers, or verrucous plaques.¹⁰ In our cases, special fungal stains like GMS were not performed on skin biopsy specimens as there was not a clinical or histologic suspicion of a primary cutaneous or disseminated coccidioidomycosis.

These cases demonstrate a unique reactive cutaneous manifestation of primary pulmonary coccidioidomycosis. In our cases, circulating fungal antigens from the pulmonary focus may have incited a more intense immune response, manifesting as pustular lesions in addition to the erythematous or target-shaped plaques of typical erythema multiforme.

Classically, erythema multiforme has been described as a type-IV hypersensitivity reaction in the setting of coccidioidomycosis, without a pustular component. The presence of pustules in our patients suggests a more intense immune response, consistent with reports of severe hypersensitivity reactions to fungal infections where inflammation can classically result in pustular formation, such as those to dermatophytid or candida infections, where antigenic fragments or metabolites from the primary fungal site trigger cutaneous inflammation.^{3,11} Such exaggerated immune activity may result from antigenic stimulation in genetically predisposed hosts, potentially by HLA associations or cytokine polymorphisms, leading to robust dermal infiltration, edema and pustule formation, though these mechanisms remain speculative and warrant further investigation.

Awareness of the broad spectrum of presentations of coccidioidomycosis, including dermatologic hypersensitivity, is important for accurate diagnosis, particularly in endemic areas where *Coccidioides* is a common cause of community-acquired pneumonia.⁹ Recognition of these reactive phenomena in our patients facilitated rapid identification of the diagnosis through serologic testing and chest imaging. Positive IgM and IgG serologies supported acute pulmonary infection, and other infectious causes of pustular dermatoses (e.g., herpesvirus, staphylococcal folliculitis) were ruled out.

Increased awareness and early diagnosis can decrease unwarranted diagnostic testing, avoid incorrect treatments, reduce patient anxiety about their condition, and allow more accurate prognostic information.¹²

These cases expand the differential diagnosis of pustular eruptions and highlight an underrecognized manifestation of coccidioidomycosis. Larger case series and mechanistic studies are needed to further delineate the immunopathogenesis and guide diagnostic criteria for reactive fungal dermatoses. With these case reports, we hope to build the literature for how reactive skin manifestations of coccidioidomycosis may present, in an effort to improve recognition and appropriate treatment for persons with significant disease.

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None.

Conflict of Interest

None declared. Funding sources: None.

No Patient Consent on File: No identifiable material is used by the authors.

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