The Exanthem of Acute Pulmonary Coccidioidomycosis

Clinical and Histopathologic Features of 3 Cases and Review of the Literature

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Background: Coccidioidomycosis may be associated with a reactive generalized cutaneous eruption early in the course of the illness. Detailed descriptions in the literature are scarce.

Observations: We describe 3 patients with a florid eruption associated with pulmonary coccidioidomycosis. The exanthem mimicked erythema multiforme clinically but not histologically. In 2 of the patients, the eruption began before the presence of detectable antibodies in the serum.

Conclusion: The presence of the exanthem, in combination with fever and/or pneumonia, was a helpful clue to the diagnosis of coccidioidomycosis.

Arch Dermatol. 2006;142:744-746

Coccidioidomycosis is endemic in arid and semi-arid regions of North and South America. In the United States, the highest incidence is in the Southwest, particularly in the desert regions of Arizona and California. The causative agents are fungi of the genus Coccidioides, which includes the California species Coccidioides immitis and the recently renamed non-California species Coccidioides posadasii. The organisms live in the soil and release arthroconidia into the air. Inhalation by a host may produce respiratory infection in both healthy and immunocompromised persons. The yearly incidence is estimated to be 100,000 in the United States. Although most infections are mild or asymptomatic, severe illness or death may occur in rare cases.

Coccidioidomycosis is associated with a remarkable variety of cutaneous manifestations. The skin may be involved by immunologically induced reactive eruptions or, more rarely, by dissemination of the organisms from the lungs. Erythema nodosum is the most well-recognized reactive eruption associated with coccidioidomycosis. A generalized exanthem and erythema multiforme have also been reported to be common reactive manifestations of the infection. The literature contains few clinical descriptions of the exanthem and, to our knowledge, the histopathologic features have not previously been reported. We present 3 patients with the acute exanthem of coccidioidomycosis.

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METHODS

The Mayo Clinic institutional review board approved the retrospective review of medical records and skin biopsy slides of the 3 patients.

CASE 1

A 75-year-old woman abruptly developed a severely pruritic eruption on her back, chest, and upper extremities over a 24-hour period. Two days later, she developed cough and pleuritic chest pain. She presented to her primary-care physician. A chest radiograph revealed an infiltrate in the right lower lobe. For presumed bacterial pneumonia, she was treated with ceftriaxone sodium, 1000 mg injected intramuscularly. Levofloxacin, 500 mg daily by mouth, was prescribed for a 10-day course. Both antibiotic treatments were initiated 3 days after the onset of the rash.

She was referred to the dermatology department. Smooth red-violaceous plaques and coalescent papules were present on the back, shoulders, inframammary areas, and upper extremities. Scattered lesions on the axillae, chest, and buttocks had a targetlike appearance. Poorly margined, pink annular patches were present on the palms. The dermatologist's clinical impression was erythema multiforme. In the absence of any temporally related medications, the constellation of rash and pneumonia made pulmonary coccidioidomycosis the most likely suspected cause.

A skin biopsy specimen was obtained from the back. Histopathologic features are described at the end of the “Methods” section. Treatment with triamcinolone acetonide cream and oral doxepin hydrochloride alleviated the pruritus.
Although results from initial Coccidioides serologic tests were negative, seroconversion was demonstrated 11 days later. By the time of seroconversion, the patient’s respiratory symptoms had begun to improve. No antifungal medications were given. The eruption cleared after a total duration of approximately 3 weeks. Respiratory symptoms resolved within 6 weeks. Coccidioides serologic status reverted to negative 6 weeks after the onset of the eruption.

CASE 2

A 58-year-old man was admitted to the hospital for cough, myalgia, and intermittent fever of 2 weeks’ duration. A generalized, pruritic eruption had begun suddenly 24 hours prior to admission.

At admission, the oral temperature was 38.8°C. A chest radiograph revealed a left lower lobe infiltrate. Bacterial pneumonia was initially suspected, and the patient was treated with ceftriaxone sodium, 2 g daily by intravenous administration.

During hospitalization, dermatologic consultation was obtained. Physical examination revealed erythematosus urticarial coalescent papules involving the trunk, upper extremities, and genitalia. Targetlike purpuric plaques were present on the lower extremities. The face, scalp, and oral cavity were spared. The dermatologist’s clinical impression was erythema multiforme. The combination of fever, pneumonia, and rash led to clinical suspicion for pulmonary coccidioidomycosis.

A skin biopsy specimen was obtained from the left thigh. Histopathologic features are discussed at the end of the “Methods” section. Treatment with triamcinolone cream and oral diphenhydramine hydrochloride alleviated the pruritus.

The patient was dismissed from the hospital 36 hours after admission. The cutaneous eruption resolved after a total duration of less than 2 weeks. He developed superficial desquamation of the palms as the eruption faded. Despite resolution of his cutaneous symptoms, his fevers and myalgias continued.

He returned to his primary care physician for outpatient evaluation. Sputum cultures, which had been obtained during his previous hospitalization, yielded growth of Coccidioides. Results from serologic tests also confirmed coccidioidomycosis. Because of his persistent systemic symptoms, he was treated with fluconazole, 200 mg by mouth every 12 hours for 6 weeks. During the course of treatment, his fevers and myalgias gradually improved, and the cutaneous eruption did not recur.

CASE 3

A 63-year-old woman suddenly developed a severely pruritic, generalized eruption over a 24-hour period. Mild nausea, fatigue, and fever occurred at the onset of the rash. The systemic symptoms resolved after 1 day, but the eruption persisted. She presented to the emergency department on the second day of the rash. Urticaria was suspected. Treatment with a tapering dose of prednisone was initiated at 60 mg daily. Over-the-counter antihistamines were recommended for treatment of pruritus. She obtained no relief of her symptoms. Individual cutaneous lesions persisted in fixed locations on her trunk and extremities.

The patient was referred for dermatologic consultation. A further history review revealed exposure to blowing dust at a construction site in Arizona 2 weeks before the onset of her symptoms. A physical examination revealed a bright red morbilliform eruption with edematous confluent papules involving the back, chest, axillae, buttocks, and anterior aspect of the thighs. A chest radiograph was normal.

Skin biopsy specimens were obtained from the abdomen for histologic examination, direct immunofluorescence, and fungal and mycobacterial cultures. The histopathologic and direct immunofluorescence findings are discussed in the following subsection. The cultures yielded no growth. The presence of a generalized eruption and the history of exposure to blowing dust led to clinical suspicion for pulmonary coccidioidomycosis. Though results from initial serologic testing showed equivocal or negative results by multiple techniques, acute coccidioidomycosis was confirmed 3 weeks later by documenting seroconversion. The cutaneous eruption and systemic symptoms resolved over the following 3 weeks. Prednisone therapy was tapered and discontinued. She recovered completely and received no antifungal medications.

HISTOPATHOLOGIC AND IMMUNOPATHOLOGIC FINDINGS

Histopathologic findings are shown in Figure 2 and Figure 3. Skin biopsy specimens from all 3 patients showed a mild perilobar lymphocytic infiltrate with variable numbers of neutrophils and eosinophils. Karyorrhectic debris was present, but specific evidence of vasculitis was not seen. Epidermal changes varied from mild spongiosis in case 2 to marked basilar keratinocyte vacuolization in case 3. Necrotic keratinocytes were rare or absent.

Direct immunofluorescence was performed in case 3. Fibrinogen was diffusely present throughout the dermis. No deposits of immunoglobulin or C3 were seen.
A generalized exanthem or “toxic erythema” occurs in approximately 12% of patients with symptomatic pulmonary coccidioidomycosis. During localized outbreaks in California, the exanthem has affected up to 50% to 60% of patients. Typically beginning during the first few days of the illness, the eruption is widespread and confluent. Clinical descriptions in the literature include diffuse erythematous, morbilliform, maculopapular, or urticarial eruptions. Pruritus may be severe. An oral exanthem is associated in some cases.

In our 3 patients, the eruption preceded, accompanied, or followed the onset of systemic symptoms. In 2 of the 3 cases, the eruption was the sole or predominant symptom on the first day of the illness. These 3 cases exemplify the variability of systemic symptoms among patients with the exanthem. In case 2, the patient experienced continual fevers and myalgias, and in cases 1 and 2, the patients had significant pulmonary symptoms. The symptoms in case 3, however, were almost entirely to the skin. No respiratory complaints were noted during the course of her illness. In these 3 patients, resolution of the exanthem did not necessarily coincide with the resolution of systemic symptoms.

This report demonstrates that the exanthem may, in some cases, erupt before the presence of detectable antibodies in the serum. In 2 of the cases, results from initial serologic tests were negative or equivocal, but seroconversion was subsequently demonstrated. The eruption persisted up to 3 weeks. Following recovery from the illness, serum antibodies became undetectable in 1 patient, who was subsequently retested.

Although the exanthem is not uncommon, detailed histopathologic descriptions have not previously been recorded. In the analysis of these 3 cases, the histopathologic features appeared to be nonspecific and variable. Shaped features included a mild perivascular lymphocytic infiltrate with karyorrhectic debris and variable numbers of neutrophils and eosinophils. The differential diagnosis would include an allergic drug eruption or viral exanthem. However, the clinical histories did not suggest a drug eruption, and no other infectious causes were found.

In cases 1 and 2, erythema multiforme was suspected clinically but was not supported by the histopathologic or immunopathologic findings. Erythema multiforme–like features included palmar involvement in case 1 and target-shaped lesions in both cases 1 and 2. However, necrotic keratinocytes, which are the earliest and most characteristic histologic feature of erythema multiforme, were rare or absent.

Recognizing the acute exanthem may be helpful in the early diagnosis of coccidioidomycosis. In a patient who lives in or who has traveled to an endemic area, the presence of a florid, generalized eruption, in combination with fever or respiratory symptoms, should lead to clinical suspicion for the infection. The eruption may begin even before the presence of detectable antibodies in the serum. The exanthem may clinically mimic erythema multiforme, but the 2 entities appear to differ histologically. Additional observations are needed to delineate further the relationship between the acute exanthem, erythema multiforme, and coccidioidomycosis.

Accepted for Publication: October 8, 2005.
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Author Contributions: Study concept and design: DiCaudo. Acquisition of data: DiCaudo, Yiannias, Laman, and Warschaw. Drafting of the manuscript: DiCaudo. Critical revision of the manuscript for important intellectual content: DiCaudo, Yiannias, Laman, and Warschaw. Statistical analysis: Laman. Administrative, technical, and material support: DiCaudo and Yiannias. Study supervision: Yiannias.

Financial Disclosure: None.

REFERENCES


Figure 3. Case 3. Prominent vacuolization of keratinocytes along the epidermal basilar layer (hematoxylin-eosin, original magnification x20).