CASE REPORT

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Coccidioidomycosis and erythema nodosum in pregnancy

Yousef Usta, Wesley Shealey

ABSTRACT

Introduction: Erythema nodosum may be the first sign of a systemic disease such as tuberculosis, viral, bacterial or fungal infections such as coccidioidomycosis. Other causes include sarcoidosis, inflammatory bowel disease, cancers, pregnancy/hormone related, idiopathic, and medication side effects. Diagnosing the primary cause of this skin manifestation may help a clinician find the underlying disease. **Case Report:** A 24-year-old, gravida 1, para 1, 8 weeks pregnant Mexican-American female living in Phoenix Arizona presented with symptoms of shortness of breath of 2 weeks duration. She complained of shortness of breath, pleuritic chest pain, and persistent productive cough. She also developed new painful lesions on her lower extremities that were found to be erythema nodosum. Coccidioidomycosis IgM and IgG serologies were positive. She was started on amphotericin B 5 mg/kg IV three days/week for four weeks and her skin lesions and respiratory symptoms subsided within a few days. At the start of her second trimester of pregnancy she was switched to fluconazole 400 mg PO for four more weeks. **Conclusion:** Coccidioidomycosis during

pregnancy shows a more favorable outcome when erythema nodosum is present. Therapy for this fungal infection remains to be based on expert opinion. Amphotericin B is considered relatively safe in pregnancy, and there is insufficient evidence for the safety of fluconazole. Keeping high clinical suspicion of coccidioidomycosis for patients who present with erythema nodosum in the south-west United States, especially in pregnant patients with respiratory symptoms, will help clinicians not miss this commonly seen fungal disease.

Keywords: Erythema Nodosum, Coccidioidomycosis, Pregnancy

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Yousef Usta¹, Wesley Shealey²

Affiliations: ¹MD, Department of Internal Medicine St Joseph Hospital and Medical Center, Phoenix, Arizona 85014, USA; ²MD, Department of Infectious Diseases St Joseph Hospital and Medical Center, Phoenix, Arizona 85014, USA.

Corresponding Author: Yousef Usta, MD, 350 West Thomas Road, Phoenix, Arizona, 85013; Phone: 6024063106; Email: yosusta@hotmail.com

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INTRODUCTION

Erythema nodosum may be the first sign of a systemic disease such as tuberculosis, viral, bacterial or fungal infections. Other causes include sarcoidosis, inflammatory bowel disease, cancers, pregnancy/hormone related, idiopathic, and medication side effects. The hallmark of erythema nodosum is tender, erythematous, subcutaneous nodules that are typically located symmetrically on the anterior surface of the lower extremities [1]. Diagnosing the primary cause of this skin manifestation may help a clinician find the underlying disease.

CASE REPORT

A 24-year-old, gravida 1, para 1, 8 weeks pregnant Mexican-American female presented with symptoms of shortness of breath of two weeks duration and new painful lesions on her lower extremities. As an outpatient, she was found to have a left lower lobe consolidation on chest X-ray and was treated with azithromycin 500 mg PO daily for five days for a presumed community acquired pneumonia. One week later, she presented to the hospital after no improvement of her respiratory systems and was assumed to have failed outpatient medical PO antibiotic therapy. She continued to complain of shortness of breath, pleuritic chest pain, and a persistent productive cough. She reported a new onset of subjective fevers and chills of two days duration. She also developed new tender lesions on her thighs, shins and ankles of two days duration. She complained of a 9 lb weight loss over a two-week period. Patient had lived in Phoenix Arizona for the last 17 years. She denied any sick contacts, recent travel contacts, or history of any tuberculosis and malignancy in her family. She also denied alcohol, tobacco and drug abuse. Sexual history included her husband only. Past medical history included latent tuberculosis with complete therapy for nine months with isoniazide 5 mg/kg PO one year ago. Physical examination showed relatively normal heart and lungs sounds. She had multiple red tender macular lesions with poorly defined borders all over her feet, shins, and thighs sparing her soles. Lesions were hard, and very tender that varied from 0.5–2 cm. These lesions had no bruising or ulceration. On admission, her vital signs were as follows: heart rate 80 bpm, temperature 36.6°C, respiratory rate 16 bpm, blood pressure of 109/78 mmHg, and SpO_2 100% on room air. White blood cell count $7.1 \times 10^6/\mu\text{L}$ ($4\text{--}10 \times 10^6/\mu\text{L}$), hemoglobin 10.9 g/dL (12–16), hematocrit 31.7% (36–47%), platelet count $216 \times 10^9/\text{dL}$ ($150\text{--}350 \times 10^9/\text{L}$). A complete metabolic panel, urine analysis, urine strep antigen, nasal viral swab, and blood cultures were all negative. Sputum culture was negative and grew mixed oral flora. Her chest X-ray revealed a $3 \times 5 \times 9$ cm ill defined consolidation in the medial left lower lobe with associated air bronchogram. There was no evidence of pneumothorax or pleural effusions. The patient was started on rocephin 1 g IV daily and azithromycin 500 mg IV BID to treat community acquired pneumonia. Throughout her stay, patient was afebrile with no leukocytosis. Deep skin punch biopsy showed septal panniculitis with inflammation in the fat and around blood vessels consistent with erythema nodosum. The positive skin findings prompted testing for coccidioidomycosis IgM and IgG serologies which were also positive. Previous antibiotics were discontinued and she was started on amphotericin B 5 mg/kg IV daily, and her symptoms of shortness of breath, chest pain, and lower extremity lesions all subsided over three days and she was discharged home on amphotericin B IV 5 mg/kg for 3 days per week for 4 weeks until the completion of her first trimester of pregnancy. At that

point, she was symptom free and was started on fluconazole 400 mg PO daily to avoid relapse of the disease. She will be monitored monthly for symptom recurrence and the unlikely possibility of fetal malformations.

DISCUSSION

Coccidioides immitis is endemic in certain parts of the desert south-west-region and is commonly referred to as Valley Fever. It is a fungus that resides in the soil that breaks off into airborne spores. Infection is caused by inhalation of the particles and is not transmitted from person to person. Serious complications include severe pneumonia, lung nodules, and disseminated disease. The disseminated form of coccidioidomycosis can devastate almost any organ in the body, causing skin ulcers, abscesses, bone lesions, meningitis, and often death [2, 3].

Coccidioidomycosis during pregnancy is a serious illness for which high rates of mortality have been reported [4–6]. It has been associated with a greater likelihood of extrapulmonary dissemination and more serious outcomes. A small study looked at the outcome of erythema nodosum on coccidioidomycosis infections. Sixty-one pregnant patients with coccidioidomycosis were studied. Thirty (49%) were found to have erythema nodosum. Ninety-seven percent of these patients had full recovery and none were found to have disseminated fungal disease, showing a more favorable outcome when erythema nodosum was present [4].

There is minimal literature and evidence on therapy for pregnant patients infected with coccidioidomycosis. Therapeutic options remain to be based on expert opinion only. Case reports have suggested a link between the maternal use of fluconazole and craniofacial abnormalities in the newborn [7]. Based on expert opinion, prompt initiation of antifungal medication should be started for patients who are expected to become more severely ill with pulmonary coccidioid infection. These patients include diabetics, patients with pre-existing cardiopulmonary disease, and pregnant patients, especially in the third trimester or immediately postpartum [2]. During pregnancy, amphotericin B is the treatment of choice because of fluconazole's possible teratogenicity [2, 8]. More recent studies have failed to show an association between maternal use of fluconazole during the first trimester and congenital malformations in the offspring [8–10]. Recent studies also showed that fluconazole use at anytime during pregnancy had no associated link to pre-term birth, lower birth weights, or still births. Although their sample size remained insufficient for examining the risks of specific birth defects [8].

Although we predominantly thought that coccidioidomycosis was the most likely precipitating cause for erythema nodosum, our differential diagnosis included viral and bacterial infections, idiopathic causes, pregnancy, hormonal changes, and medication induced side effects. In our case, the patient does not improve

with antibiotics, the negative blood, urine, and sputum cultures helped ruling out a bacterial infection. Since the viral swabs were negative and the patient's symptoms got worse over a two-week period makes viral upper respiratory infection was considered unlikely. We believe that this pregnant patient's relative immune-compromise made her more susceptible to developing coccidioidomycosis. Because she had both positive IgM serologies for coccidioidomycosis, and her severe respiratory symptoms and lower extremity erythema nodosum subsided immediately after beginning amphotericin B, we are confident that her symptoms were related to this fungal infection rather than having an idiopathic cause. Erythema nodosum in subsequent pregnancies will help reveal if the erythema nodosum was strictly secondary to her fungal infection or whether her pregnancy played a role in its development.

CONCLUSION

Coccidioidomycosis during pregnancy shows a more favorable outcome when erythema nodosum is present. There is minimal evidence on therapy for pregnant patients infected with coccidioidomycosis and therapy remains to be based on expert opinion. Diagnosing the precipitating source for erythema nodosum may be quite challenging. Having a broad differential diagnosis for erythema nodosum will avoid missing rare and life threatening infections. Keeping high clinical suspicion of coccidioidomycosis for patients who present with erythema nodosum in the south-west United States, especially in pregnant patients with respiratory symptoms, will help clinicians not miss this commonly seen fungal disease.

Author Contributions

Yousef Usta – Substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be published

Wesley Shealey – Substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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