

Edematous Erythema, Subcutaneous Plaques, and Severe Pain in the Lower Extremities in an Immunocompromised Patient



Figure 1. Image of case patient's lower extremity lesions.

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A 57-YEAR-OLD WOMAN WHO RECEIVED A RENAL TRANSPLANT 10 YEARS AGO is admitted for evaluation of edematous erythema, subcutaneous plaques, and severe lower extremity pain for 1 month. She has had a fever (39.2°C) for 10 days but denies headaches, nausea, and vomiting. Her lesions and fever have not responded to 3 separate courses of intravenous antibiotics (penicillin, ceftriaxone, imipenem). She denies any preceding injury or insect bite. Skin examination reveals diffuse tender edematous erythema and multiple ill-defined, indurated subcutaneous plaques on most of the lower extremities, without abscess or ulceration (FIGURE 1). Neurologic examination results are normal. Her medications include mycophenolate mofetil (1.75 g/d), cyclosporine (120 mg/d), and prednisone (15 mg/d). White blood cell count is normal, with 90% neutrophils; C-reactive protein level is elevated at 31.3 mg/L (298.1 nmol/L). IgG level is 677 mg/dL. Two repeat blood cultures are negative. Ultrasound and magnetic resonance imaging of lower extremities show no sign of abscess.

What Would You Do Next?

- Obtain a biopsy of the lesion for pathology and fungal culture
- Perform dermatoscopic examination of the skin lesions
- Prescribe another course of antibiotics
- Prescribe high-dose prednisone

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Diagnosis

Cutaneous cryptococcosis

What to Do Next?

A. Obtain a biopsy of the lesion for pathology and fungal culture

The key clinical feature is a history of progressive skin lesions in a febrile renal transplant recipient previously unresponsive to intravenous antibiotics. Immunosuppressed patients can present with unusual infections or infections that mimic other diseases.^{1,2} A tissue sample is needed to make the diagnosis.

Discussion

Cryptococcosis is an opportunistic fungal infection that causes substantial morbidity and mortality in immunocompromised patients. The most common species is *Cryptococcus neoformans*, which is found throughout the world, predominantly in pigeon droppings, as well as in soil and on plants.^{2,3}

Immunocompromised patients with low CD4⁺ lymphocyte counts are particularly susceptible to infection with cryptococcus. Except for patients with AIDS, organ transplant recipients are at highest risk of acquiring this infection.^{1,3} Other predisposing conditions include hematologic malignancies, immunosuppressive medications, diabetes mellitus, and hepatic cirrhosis.^{3,5}

Cryptococcal infections are usually asymptomatic with painless lesions and can present as pustules, abscesses, vegetating plaques, infiltrated nodules, cellulitis ulcers, or solid tumors.¹⁻⁹ Primary cutaneous cryptococcosis occurs through direct inoculation of the skin in both immunocompetent and immunocompromised patients and is considered a distinct clinical entity.^{1,9} Most cutaneous cryptococcosis, however, occurs as a secondary manifestation of disseminated disease, which results from hematogenous spread of the fungus.^{2,3}

Disseminated cryptococcus is characterized by multiple umbilicated papules simulating molluscum contagiosum, with multicentric skin involvement.^{3,6} The differential diagnosis of painful cutaneous cryptococcosis mani-

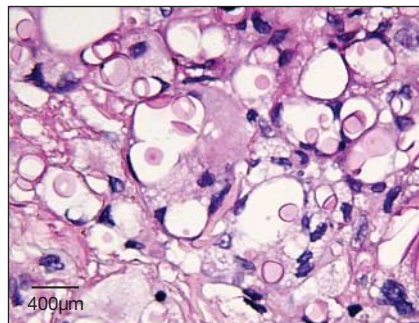


Figure 2. Skin biopsy from right thigh reveals red spherules with characteristic peripheral capsular halo, consistent with *Cryptococcus neoformans* (periodic acid–Schiff, original magnification $\times 400$).

festing with nonulcerative subcutaneous swellings is different from painless cryptococcus and includes folliculitis, bacterial erysipelas or cellulitis, necrotizing fasciitis, vasculitis or panniculitis, and cutaneous tumors. A biopsy is important in distinguishing among these conditions. Cryptococcus infection mimicking nonulcerative erysipelas or panniculitis is rare and deceptive.⁴

Treatment depends on the immune status of the patient and the severity of the disease. The current guidelines of the Infectious Diseases Society of America recommend amphotericin B–based combination therapy with flucytosine as primary induction therapy for all severe forms of disseminated cryptococcosis, followed by fluconazole consolidation therapy.¹⁰

Patient Outcome

Skin biopsy revealed a diffuse granulomatous inflammatory infiltrate with numerous encapsulated yeast forms in the dermis and subcutaneous fat. Periodic acid–Schiff staining (FIGURE 2) revealed structures consistent with *C neoformans* subsequently confirmed by culture of skin tissue. Moreover, *C neoformans* var *grubii* was identified by polymerase chain reaction. The result of a serum cryptococcus latex agglutination test was positive. Cerebrospinal fluid examination was notable for leukocytosis but negative for cryptococcus antigen. Although magnetic

resonance imaging of the brain showed no obvious signaling suggestive of meningitis, a pulmonary computed tomography scan revealed a peripheral solid lesion as well as a thick-walled cavity on the superior lobe of the left lung. Sputum cultures verified cryptococcal infection.

Because of her lack of central nervous system involvement and reduced renal function, the patient began receiving intravenous itraconazole (500 mg/d) in view of the fungal sensitivity report. Her fever disappeared in 3 days, and the skin lesions improved.

After 2 weeks of therapy she was transitioned to fluconazole (400 mg/d) because of deteriorating renal function. She died of meningoencephalitis 4 months later. Her family declined autopsy.

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