

Cryptococcal cellulitis in a heart transplant recipient



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Key words: cryptococcal cellulitis; cryptococcosis; cryptococcus neoformans; immunocompromised; mucocutaneous; opportunistic infection; transplant; yeast.

INTRODUCTION

Cryptococcosis is an invasive fungal infection most often caused by the encapsulated yeasts *Cryptococcus neoformans* and *Cryptococcus gattii*. *C neoformans* is the major pathogenic member of the genus, thought to account for approximately 80% of isolates worldwide, and is found in pigeon droppings, soil, and rotting vegetation.¹ The incidence in the United States is approximately 5 cases per 100,000.² However, the global burden is much more significant, with more than 1 million new cases and more than 600,000 deaths a year.³

Most patients with cryptococcosis are immunocompromised because of HIV infection, immunosuppressive therapy, or malignancy. Although cryptococcal infections begin in the lungs via inhalation of the basidiospore, the classical clinical manifestation is meningoencephalitis. Nonmeningeal, nonpulmonary symptoms are less common and generally reflect disseminated disease. Cutaneous manifestations are seen in approximately 15% of patients with systemic cryptococcosis and can have a variety of presentations, including papules, plaques, and ulcers.⁴ Here we present an uncommon case of cutaneous cryptococcosis presenting as cellulitis in a heart transplant recipient.

CASE REPORT

A 45-year-old African-American man, 10 years post–heart transplant for end-stage nonischemic cardiomyopathy, presented to our hospital with a

Abbreviation used:

CNS: central nervous system

2-week history of erythema, tenderness, and swelling of his right thigh. His immunosuppressive regimen included tacrolimus, 1 mg twice daily, prednisone, 10 mg daily, and mycophenolate mofetil, 500 mg twice daily. Upon arrival at our hospital, the patient was afebrile, and vital signs were within normal limits. On physical examination he had a large erythematous patch on his right medial thigh that extended down his medial leg to his ankle. His preliminary laboratory results showed a white blood cell count of $14.6 \times 10^3/\mu\text{L}$, with a neutrophilic predominance of 93%. Blood cultures were sent before starting the patient on cefepime and vancomycin for presumed bacterial cellulitis.

Over the next few days, the patient's symptoms improved but did not resolve. The redness regressed, leaving behind 2 distinct, indurated, red-brown patches on his medial thigh and medial distal calf (Fig 1, A and B). The dermatology department was consulted and performed biopsies of both sites. Histopathologic evaluation found granulomatous inflammation throughout the mid-to-reticular dermis extending in some areas to the superficial subcutaneous fat, with scattered budding yeast (Fig 2, A through C). Subsequent workup included a lumbar puncture, which found an elevated opening

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Funding sources: None.

Conflicts of interest: None declared.

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JAAD Case Reports 2016;2:403-5.

2352-5126

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<http://dx.doi.org/10.1016/j.jidcr.2016.08.005>

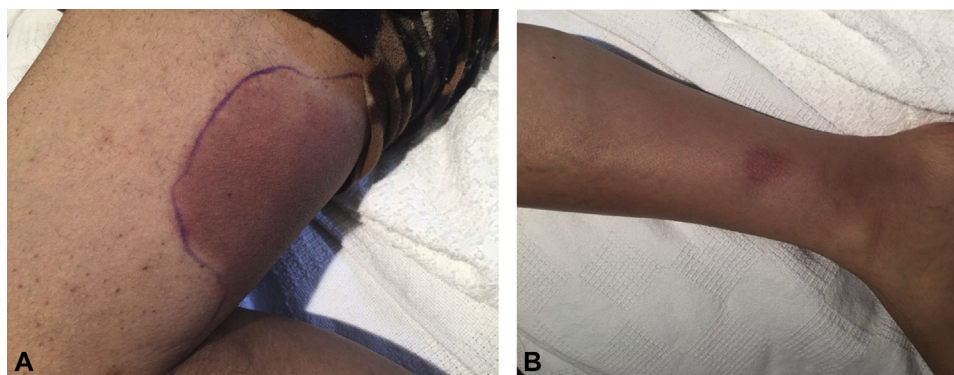


Fig 1. Cryptococcal cellulitis. **A**, A 45-year-old man with a dull, red-brown patch with dermal induration on the right medial thigh. **B**, A second similar but smaller patch on the medial right leg.

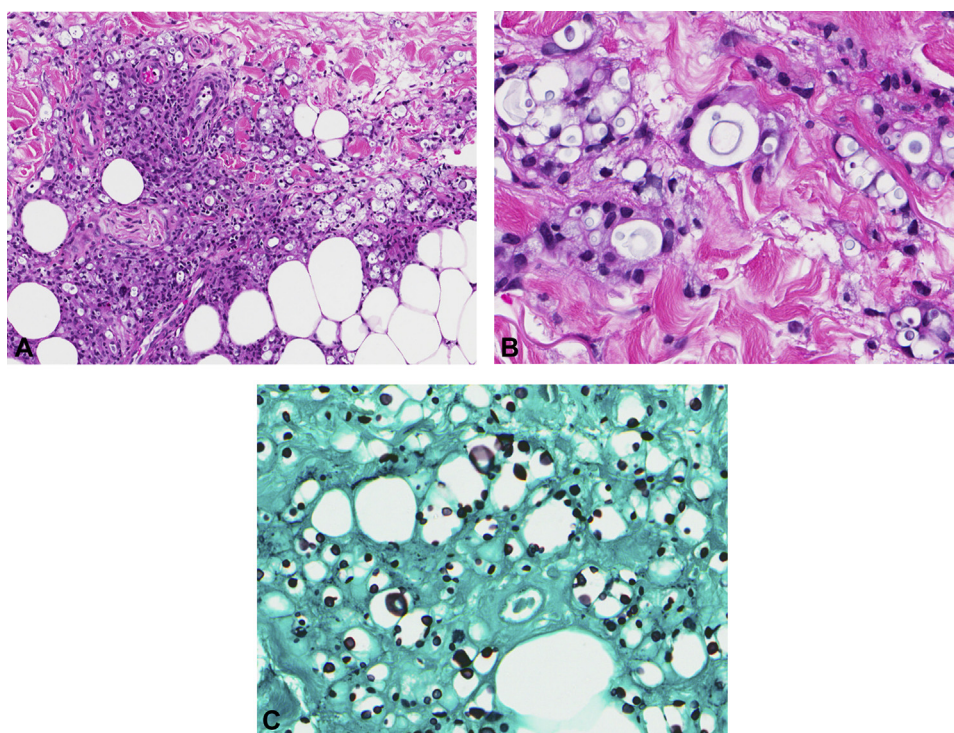


Fig 2. **A**, Skin biopsy from the right medial thigh shows extensive granulomatous inflammation and scattered encapsulated and budding yeast. **B**, Higher-power image shows numerous round fungi with thick, gelatinous capsules. **C**, Methenamine silver stain shows abundant budding yeast. (**A**, and **B**, Hematoxylin-eosin stain; **C**, methenamine silver stain; original magnifications: **A**, $\times 10$; **B**, and **C**, $\times 40$.)

pressure of 37 cm H₂O and a positive cryptococcal antigen. Cerebrospinal fluid and blood cultures were normal. The patient was started on a 2-week course of liposomal amphotericin B and 5-flucytosine with improvement in his cellulitis and was discharged on fluconazole for maintenance therapy.

DISCUSSION

Cryptococcal infection in immunocompetent adults is most commonly asymptomatic but rarely can lead to a focal pneumonitis.⁵ Immunocompromised patients,

in contrast, have a much higher risk of having disseminated disease that can affect any organ system in the body. Historically, HIV-infected patients had the greatest risk for disseminated cryptococcosis. However, with improving highly active antiretroviral therapy, organ transplant patients are emerging as a prominent group affected by this opportunistic infection. The mean incidence of *C neoformans* infection in organ transplant recipients is 3 per 100 patients, with a mortality rate of approximately 40%.⁶

Cutaneous manifestations in cryptococcosis are rare overall but may be more common in organ transplant recipients.⁷ One prominent theory for this occurrence is that tacrolimus is toxic to *C neoformans*, especially in the central nervous system (CNS) where it effectively inhibits calcineurin at 37°C.⁸ This inhibition likely breaks down at cooler sites of the body, such as the skin, which may allow the organism to thrive. This theory is supported by studies that found that cutaneous manifestations of disseminated cryptococcosis are more common than CNS manifestations in organ transplant recipients on tacrolimus therapy—67% present with cutaneous manifestations versus 17% with CNS manifestations.⁶

The classical cutaneous manifestation of cryptococcosis is umbilicated papules, most commonly seen in AIDS patients, but it can also present as acneiform papules, plaques, and ulcers.⁴ In our patient, the persistence of erythema despite appropriate antibiotic treatment for bacterial cellulitis, the red-brown color, and the indurated feel of the skin were all clues to an atypical infectious process. Interestingly, a brown hue may be an important clue to cryptococcosis. *C neoformans* possesses a virulence factor, phenol oxidase, which catalyzes one step in the conversion of phenolic compounds (namely, catecholamines such as dopamine) into melanin. Melanin accumulates in the tissue and cell wall of *C neoformans*, where it acts as an antioxidant and protects against attack by immune modulator cells.⁹ This finding likely explains the brown coloration of the skin and perhaps also the predilection of *Cryptococcus* for the CNS, where there are high concentrations of dopamine.

Cutaneous cryptococcosis in immunocompromised patients should be viewed as a sign of disseminated disease and should prompt further evaluation. Early diagnosis and treatment are critical, as mortality rates are alarmingly high. Treatment of disseminated

cryptococcosis in transplant patients is divided into 3 phases. Generally, the treatment of choice is liposomal amphotericin B (3–4 mg/kg/d) with or without flucytosine (50–150 mg/kg/d) for 2 weeks of induction therapy, followed by fluconazole, 400 mg/d for 8 weeks of consolidation therapy, and fluconazole, 200 mg/d for 6 months of maintenance therapy.¹⁰

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