Persistent Cellulitis in a Patient Receiving Renal Dialysis

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Cryptococcus neoformans, *an opportunistic fungus, may cause cutaneous disease by dissemination from primary lung infection or, more rarely, by direct cutaneous inoculation. Cellulitis in an immunocompromised host who does not respond to conventional antibacterial therapy should alert the physician to consider other diagnoses, including cryptococcal skin infection.*

Cutis. 2003;72:320-322.

Cryptococcus neoformans is an encapsulated budding yeast that ranges in size from 2 to 20 μm. It is most commonly found in bird feces, as well as in contaminated fruits, milk, and soil.[1] This opportunistic fungus primarily invades and infects the lungs and often disseminates through the blood to the skin and other organs, with special affinity for the central nervous system. In most cases of skin or central nervous system cryptococcosis, lung involvement is no longer detected.[2] On rare occasion, primary cutaneous cryptococcosis may occur because of entry of the yeast through minor injury to the skin.

Clinically, skin lesions are present in 10% to 15% of disseminated disease cases and can manifest as papules, pustules, nodules, herpeslike vesicles, abscesses, granulomas, infiltrated plaques,[3] and molluscum contagiosum–like lesions.[4] The lesions even have been reported to mimic basal cell carcinoma[5] and chickenpox.[6] Rarely, cryptococcal skin disease may present as cellulitis.[1,7,8]

Case Report

A 26-year-old woman with a history of renal transplant and subsequent acute graft rejection requiring maintenance hemodialysis was admitted to the hospital for suspected lower extremity bacterial cellulitis of one-week duration. The patient first noted erythema and pain in both legs after wading in a river. After unsuccessful therapy with oral amoxicillin and amoxicillin/clavulanate, the patient was admitted to the hospital and received intravenous antibiotics. She was then discharged and placed on oral cephalexin but was readmitted 3 weeks later with progression of tender erythematous plaques on her skin accompanied by fever, chills, nausea, and vomiting. The patient's previous medications were noted to include prednisone, which was first prescribed after her transplant 2 years earlier and had since been tapered to 5 mg daily.

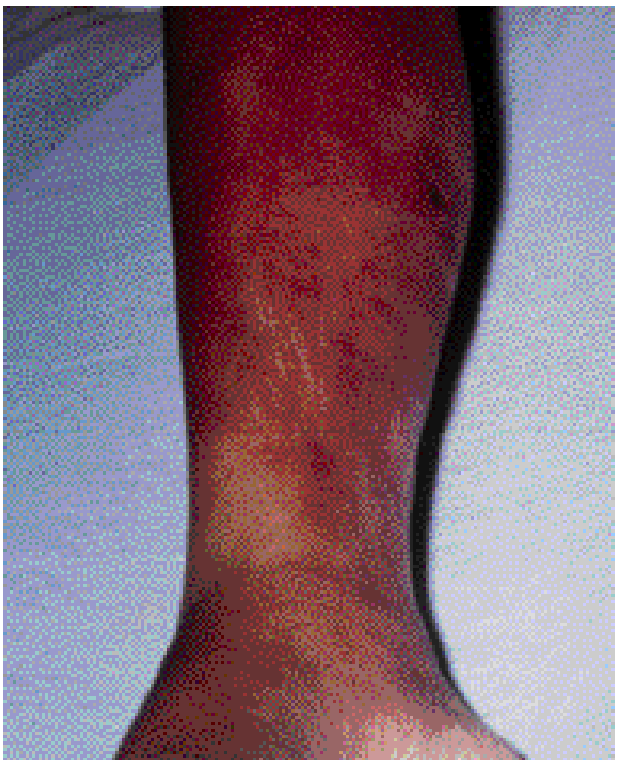

Figure 1. Confluent erythematous plaques on the leg.

Physical examination showed confluent erythematous and violaceous patches, plaques, and nodules

Accepted for publication October 7, 2002.

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The authors report no conflict of interest.

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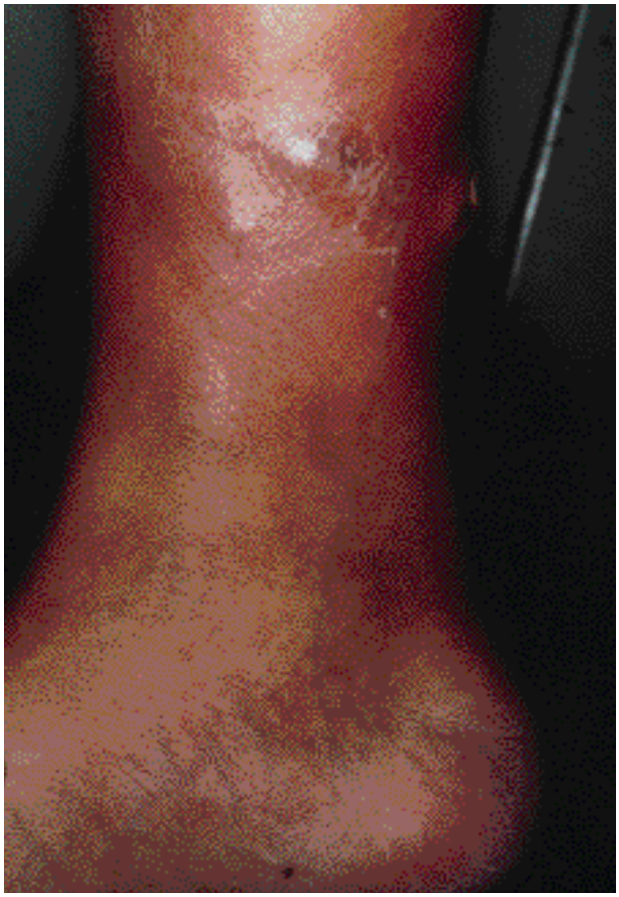

Figure 2. Nodule and ulceration on the left calf.

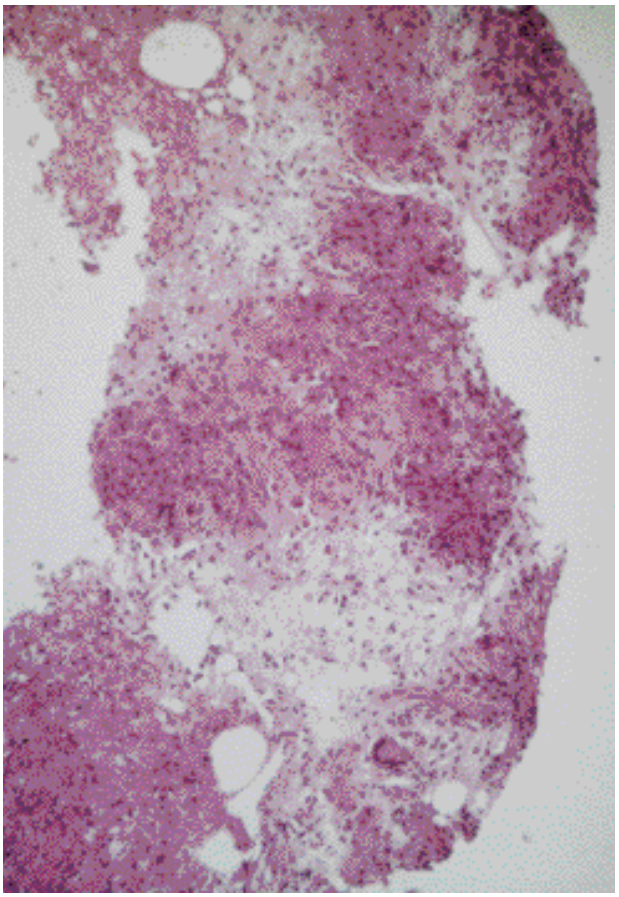

Figure 3. Suppurative and granulomatous inflammatory infiltrate in the dermis with numerous budding yeasts (H&E, original magnification ×100).

on both lower extremities (Figure 1), with a single punched-out ulceration on the left calf (Figure 2); this ulceration likely represented a sinus tract as it occurred subsequent to the initial clinical onset of cellulitis.

Laboratory test results on readmission noted a serum urea nitrogen level of 46 mg/dL, creatinine level of 8.40 mg/dL, white blood cell count of 11.2×10^9/L, and hemoglobin level of 8.0 g/dL. Results of a chest x-ray revealed a left-sided pleural mass; computed tomography scan–guided biopsy results were consistent with a benign pleural tumor.

Results of a skin biopsy demonstrated a suppurative and granulomatous inflammatory infiltrate in the dermis with numerous budding yeasts (Figure 3). Individual yeasts were surrounded by a mucicarmine-positive capsule (Figure 4), diagnostic of cryptococcosis.

The patient was treated intravenously with 40-mg amphotericin B daily with 2500-mg oral flucytosine every 6 hours. Lumbar puncture was performed under fluoroscopy after 2 prior failed attempts; thus, the patient had already received antifungal therapy for 3 days. The abnormal results of the puncture showed an elevated protein level and a positive cerebrospinal fluid cryptococcal antigen titer of 1:16. Three weeks after discharge, the patient was readmitted with a *Xanthomonas* bacteremia and persistent cryptococcal skin infection. A repeat lumbar puncture was performed, this time showing a cerebrospinal fluid cryptococcal antigen titer of 1:4; the patient's protein level remained elevated. Intravenous amphotericin B with flucytosine were continued for 8 weeks followed by 200-mg oral fluconazole daily for 6 months. Following the full course of treatment, the patient's cerebrospinal fluid cryptococcal antigen titer was negative, and there was no clinical recurrence of cutaneous disease.

Comment

Disseminated infection with *Cryptococcus neoformans* presumably occurs only in individuals with depressed immune systems; however, there have been reported cases presenting in immunocompetent hosts.[1,2] More typically, infection has been reported in patients who have undergone renal[7] or liver[9] transplants and in those with chronic autoimmune

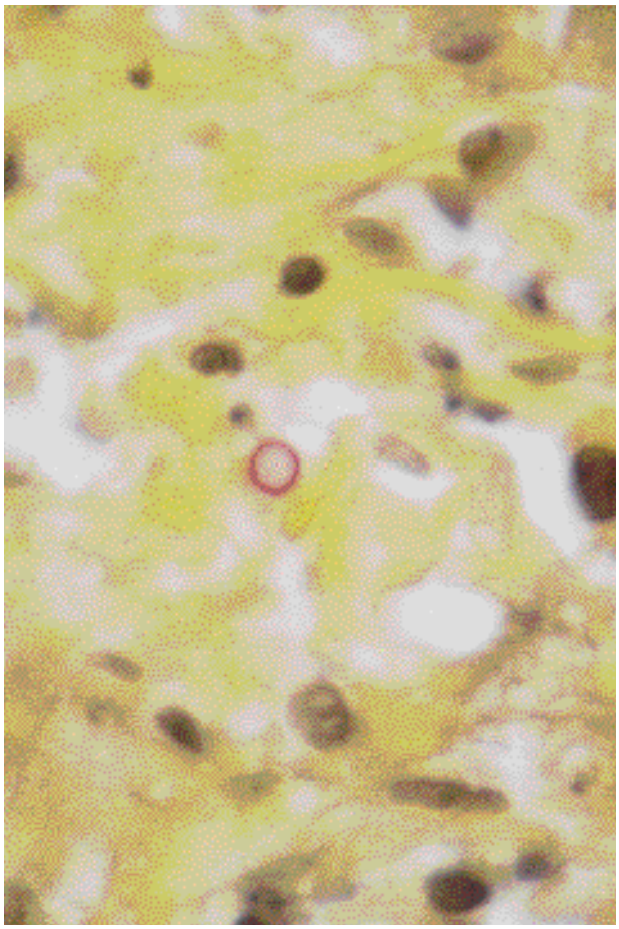

Figure 4. Mucicarmine stain demonstrating mucin-positive capsule (H&E, original magnification ×600).

hepatitis,[10] systemic lupus erythematosus,[11] multiple myeloma,[11] leukemia,[11] cervical medullary tumor,[12] and congenital lymphedema.[1]

Early recognition of cutaneous lesions is important because the lesions can be the first sign of disseminated disease. On rare occasions, primary skin inoculation may occur. Our patient had no history of known trauma to her legs; wading in a river may have allowed direct inoculation from an occult injury. However, the involvement of the central nervous system strongly favors hematogenous dissemination; the possibility of an undetected primary lung infection, which perhaps spontaneously cleared, thus remains most likely.

Regardless of the mode of infection, treatment is based on dissemination and central nervous system involvement. Initial treatment is with intravenous amphotericin B (with or without flucytosine) for a minimum of 6 weeks (or a total of 1.5 g)[1] followed by 200-mg oral fluconazole daily for 6 months.[13] With this treatment, the 2-year survival rate for patients with cryptococcal meningitis reaches 90%. Following completion of therapy, appropriate patient follow-up includes determination of cerebrospinal fluid cryptococcal antigen titers through lumbar punctures performed at 2-month intervals for 2 years.[1]

Untreated disseminated cryptococcal infection results in a fatal outcome in most cases; thus, timely diagnosis and appropriate treatment are of utmost importance. Cellulitis may be the first presenting sign of disseminated disease. A thorough evaluation, including skin biopsies, is warranted in any immunosuppressed patient presenting with cellulitis refractory to standard antibiotic therapy.

REFERENCES

1. Krywonis N, Kaye V, Lynch P. Cryptococcal cellulitis in congenital lymphedema. *Int J Dermatol*. 1990;29:41-44.
2. Hamann ID, Gillespie RJ, Ferguson JK. Primary cryptococcal cellulitis caused by *Cryptococcus neoformans* var gattii in an immunocompetent host. *Australas J Dermatol*. 1997;38:29-32.
3. Vandersmissen G, Meuleman L, Tits G, et al. Cutaneous cryptococcosis in corticosteroid-treated patients without AIDS. *Acta Clin Belg*. 1996;51:111-117.
4. Blanco P, Viallard JF, Beylot-Barry M, et al. Cutaneous cryptococcosis resembling molluscum contagiosum in a patient with non-Hodgkin's lymphoma. *Clin Infect Dis*. 1999;29:683-684.
5. Ingleton R, Koestenblatt E, Don P, et al. Cutaneous cryptococcosis mimicking basal cell carcinoma in a patient with AIDS. *J Cutan Med Surg*. 1998;3:43-45.
6. Martinelli C, Comin CE, Ambu S, et al. Solitary cutaneous cryptococcosis resembling chickenpox: a case report [letter]. *AIDS*. 1997;11:260-261.
7. Horrevorts A, Huysmans F, Koopman R, et al. Cellulitis as first clinical presentation of disseminated cryptococcosis in renal transplant recipient. *Scand J Infect Dis*. 1994;26:623-626.
8. Anderson DJ, Schmidt C, Goodman J, et al. Cryptococcal disease presenting as cellulitis. *Clin Infect Dis*. 1992;14:666-672.
9. Singh N, Rihs JD, Gayowski T, et al. Cutaneous cryptococcosis mimicking bacterial cellulitis in a liver transplant recipient: a case report and review in solid organ transplant recipients. *Clin Transplan*. 1994;8:365-368.
10. Pineski R, Mathurin SA, Ruffinengo O, et al. Cutaneous cryptococcosis in a patient receiving chronic immunosuppressive therapy. *Cutis*. 1996;57:229-231.
11. Schupbach CW, Wheeler CE, Briggaman RA, et al. Cutaneous manifestations of disseminated cryptococcosis. *Arch Dermatol*. 1976;112:1734-1740.
12. Bernhardt MJ, Ward WQ, Sams MW Jr. Cryptococcal cellulitis. *Cutis*. 1984;34:359-361.
13. Coulter C, Benson SM, Whitby M. Fluconazole for cryptococcal cellulitis. *Clin Infect Dis*. 1993;16:826-827.