Disseminated Cryptococcosis Presenting as Cellulitis with Necrotizing Vasculitis

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Patients with disseminated cryptococcosis infrequently present with cutaneous involvement. Skin lesions, when present, are usually multiple and polymorphous in appearance. Cellulitis caused by Cryptococcus neoformans is rare, and necrotizing vasculitis associated with cryptococcal vascular invasion has not to our knowledge been reported. We report here a case of disseminated cryptococcosis in a renal transplant recipient who had cellulitis and necrotizing vasculitis and in whom a diagnostic skin biopsy allowed for early therapy with cure and salvage of the renal allograft.

Immunosuppressed hosts with disseminated cryptococcosis usually present with either central nervous system or, less frequently, pulmonary involvement (2-4, 6-9). Cutaneous involvement occurs in approximately 10 to 15% of cases (2-4, 6-9). When present, skin lesions are usually multiple and often polymorphous in appearance. Cellulitis caused by Cryptococcus neoformans is rare, having been reported in only 16 patients (4, 7-9), and necrotizing vasculitis associated with cryptococcal vascular invasion has not to our knowledge been reported. We report here a case of disseminated cryptococcosis with a newly recognized presentation, cellulitis with necrotizing vasculitis, in which the skin biopsy was diagnostic.

Case report. A 57-year-old man with a 10-month-old adequately functioning cadaveric renal allograft for end-stage polycystic kidney disease was hospitalized with a 3-day history of swelling, erythema, induration, and tenderness in the right medial thigh region, low-grade fever, and chills. He was receiving maintenance immunosuppressive therapy with prednisone (25 mg/day) and azathioprine (125 mg/day). On admission, the patient denied any trauma to the area, cough, sputum production, dyspnea, chest pain, or headache. Ten weeks before admission he had developed herpes zoster involving the L3 to L4 dermatomes of the right leg. This infection was complicated by a severe staphylococcal superinfection for which he required prolonged nafcillin therapy and subsequent skin grafting.

Initial physical examination disclosed a well-developed man in no distress. His vital signs were normal except for an oral temperature of 37.5°C. Examination of the heart and lungs was unremarkable. His right thigh was involved by an area (4 by 2 cm) of erythema, warmth, induration, and tenderness. The overlying skin was intact. No streaking or palpable cords were noted, and there was no lymphadenopathy.

Admitting laboratory studies included a total leukocyte count of 5,900/mm³, with slight lymphopenia. Urinalysis was unremarkable, and blood urea nitrogen and serum creatinine were stable at 31 and 2.3 mg/dl, respectively. A chest roentgenogram before admission revealed no infiltrates or effusions.

The clinical impression was bacterial cellulitis of the thigh. After two sets of blood cultures were obtained, the patient was treated parenterally with nafcillin, 2 g every 6 h. He remained febrile during the next 2 days, with temperature elevations to 38.5°C, and the area of cellulitis progressed. Blood cultures were reported as negative. The azathioprine was stopped, and a needle aspirate of the inflamed area revealed only a few neutrophils and no organisms by Gram stain. The next day, the patient developed marked tachypnea and a nonproductive cough. Physical examination disclosed dullness to percussion and decreased breath sounds in the left base. A chest roentgenogram revealed a large left pleural effusion. Diagnostic thoracentesis revealed serosanguineous fluid with a pH of 7.39; protein, 4.8 g%; glucose, 98 mg% (serum glucose, 120 mg%); and 450 erythrocytes per mm³ and 1,200 leukocytes per mm³ (65% polymorphonuclear cells). Gram-stained smears revealed no organisms. Several more blood samples were drawn, and treatment with nafcillin was continued.

The next day, cultures from the needle aspirate were positive for a germ-tube-negative yeast. Nafcillin treatment was discontinued, and the area of cellulitis was biopsied (Fig. 1). Once the biopsy report was known, a lumbar puncture was performed. All studies of the cerebrospinal

FIG. 1. Clinical appearance of cellulitis after biopsy. Note distribution of healed herpes zoster infection.
the completion of therapy, his serum cryptococcal antigen titer was 1:2,048. He remains asymptomatic 18 months after discharge and is back at full-time employment.

**Comments.** Our patient almost certainly had clinically inapparent pulmonary cryptococcosis with limited cutaneous dissemination. This conclusion is supported by the observations that the cutaneous involvement predominated in the deep dermis and subcutaneous tissue while sparing the epidermis, that vascular invasion with cryptococci was present, and that extracutaneous involvement was recognized early in his hospital course. Additionally, the very high titer of cryptococcal antigen found in his serum is consistent with disseminated infection.

Although cutaneous involvement occurs in up to 15% of patients with disseminated cryptococcosis, cellulitis has been reported infrequently (4, 7-9). Most patients with cutaneous involvement have lesions consisting of subcutaneous masses, abscesses, draining sinuses, ulcers, granulomas, papulonodules, pustules, and plaques, especially involving the head and neck region (1-3, 5, 7-9). Greene et al. (5) described a patient with disseminated cryptococcosis who presented with palpable purpura. Although cryptococci were observed within the blood vessels, necrotizing vasculitis did not occur, as it did in our patient.

Skin lesions such as cellulitis may occur before other manifestations of systemic cryptococcosis (9). These patients are frequently treated empirically for a presumed bacterial cellulitis without response, as in the present case. Needle aspiration or biopsy of new cutaneous lesions must be performed early in immunocompromised hosts. These minimally invasive procedures frequently result in a definitive diagnosis, allowing for the early institution of specific antimicrobial therapy, as in the present case. Early diagnosis and therapy is essential if the case-fatality rates associated with disseminated infection are to be improved. Our patient not only has returned to work and is free of disease 18 months later, but his cadaveric renal graft continues to function at baseline.

The fluid were negative, including the cryptococcal antigen titer. Treatment with amphotericin B (up to 0.3 mg/kg per day) and flucytosine (75 mg/kg per day) was begun.

Histologic examination of the skin biopsy specimen disclosed acute necrotizing panniculitis of the subcutaneous tissue with extension into the overlying dermis. The epidermis was uninvolved. Small arteries and veins near the junction of dermis and subcutaneous tissue were involved by acute necrotizing vasculitis (Fig. 2). Lakes of refractile, yeastlike cells spread throughout the areas of inflammation, and individual yeastlike cells were present within the necrotic vascular walls. The fungal cells were round or oval, 2 to 12 μm in diameter, and surrounded by nonstaining haloes (Fig. 3A). Oval blastoconidia were attached to parent cells by narrow necks. Mucicarmine and alcian blue stains demonstrated abundant mucopolysaccharide capsular material around individual fungal cells (Fig. 3B), consistent with the diagnosis of cryptococcosis. Cryptococcosis caused by C. neoformans was confirmed upon isolating an encapsulated yeast at 37°C from the cultures of the needle aspirate and skin biopsy specimens which displayed characteristic assimilation patterns and had production of brown colonies on birdseed agar. The serum cryptococcal antigen titer by latex agglutination was 1:4,096, and the pleural fluid titer was 1:2,048. The patient received 6 weeks of combination chemotherapy, during which he became afebrile, the area of cellulitis resolved, and the pleural effusion was resorbed. At the completion of therapy, his serum cryptococcal antigen titer was 1:2,048. He remains asymptomatic 18 months after discharge and is back at full-time employment.

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LITERATURE CITED