Cutaneous Cryptococcosis Clinically Mimicking Necrotizing Fasciitis

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Secondary cutaneous cryptococcosis may occur earlier than other manifestations of disseminated cryptococcosis. A 68-year-old woman presented with multiple ulcerative lesions on the right calf of 2 weeks duration. She had been treated with antibiotics, but the lesions spread rapidly. The initial clinical impression was necrotizing fasciitis, but routine KOH mounting from the ulcerative lesions showed numerous budding yeast cells with peripheral clear zones and further investigations including a skin biopsy, tissue cultures and India ink preparations allowed a rapid and definitive diagnosis of cutaneous cryptococcosis. Studies for other evidence of infection elsewhere revealed an asymptomatic pulmonary lesion. We report a case of secondary cutaneous cryptococcosis clinically mimicking necrotizing fasciitis that occured before other manifestations of disseminated cryptococcosis.

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Key Words : Cutaneous cryptococcosis, Disseminated cryptococcosis

Cryptococcosis is caused by *Cryptococcus neoformans*, an encapsulated yeast-like fungus. Human infection is mainly through the lungs, from which hematogeneous dissemination to other organs such as the central nervous system(CNS), kidney, and skin may ensue. Pulmonary cryptococcosis varies in humans from asymptomatic to active pulmonary disease with or without dissemination. Host susceptibility appears to be an important part of the clinical disease, and the illness is often seen in immunosuppressed patients[1].

Cutaneous involvement occurs in up to 10 to 15% of patients with disseminated cryptococcosis[2-4]. It is an important feature of disseminated cryptococcosis, which carries a very poor prognosis if unrecognized. Cutaneous manifestations have various morphological features, including subcutaneous swelling, abscesses, tumor-like masses, papules, plaques or large ulcers[2,5].

We report a case of disseminated cryptococcosis that presented itself as secondary cutaneous cryptococcosis clinically mimicking necrotizing fasciitis.

CASE REPORT

A 68-year-old woman presented with a chief complaint of dark red, painful erythema with multiple satellite ulcerative lesions on the right calf(Fig. 1). Two weeks before presentation, the patient had developed edema, erythema, and local tenderness on the right calf without any history of preceding trauma. Within a few days they produced ulcertive lesions that tended to coalesce. She was treated with antibiotics, but the lesions enlarged rapidly. She was a farmer and had a long history of congestive heart failure and steroid administration due to arthralgia.

On physical examination, she was afebrile with no lymphadenopathy. Initial laboratory findings in-

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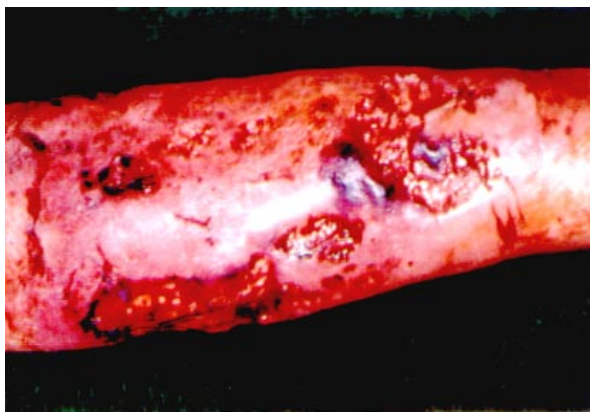

Fig. 1. Large painful ulcerations clinically mimicking necrotizing fasciitis on the right calf.

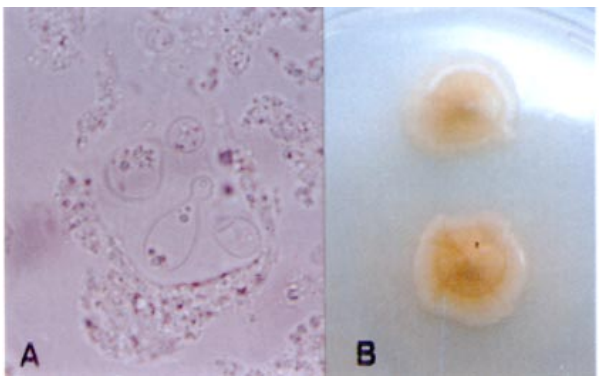

Fig. 2. A. Budding yeast cells with peripheral clear zones on the direct KOH mounting from the initial ulcerative lesion(× 400).
B. Culture of tissue scraping showed smooth, creamy colonies.

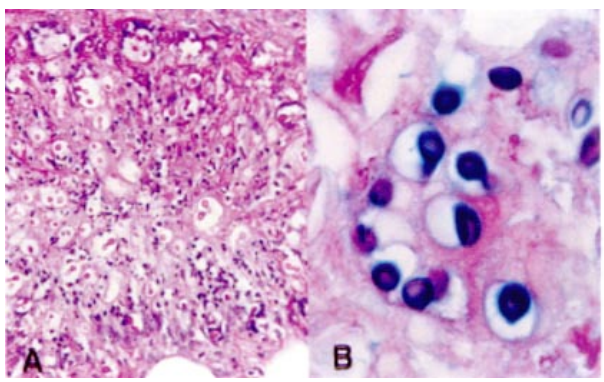

Fig. 3. A. Many round or oval PAS-positive yeast cells are seen in vacuolated spaces(PAS, × 200).
B. When the alcian blue stain and the PAS reaction are combined, the yeast cells stain red and the surrounding capsule blue(Alcian blue & PAS, × 1,000).

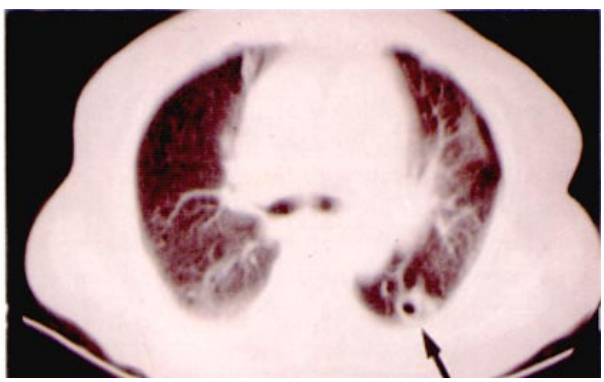

Fig. 4. A chest dynamic CT scanning shows a cavitary lesion (arrow) in the left lower lung field.

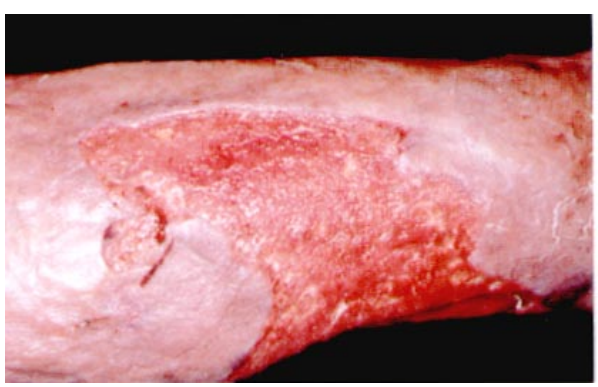

Fig. 5. After antifungal therapy with tissue debridement and wet dressing, there was good clinical response on the 21st hospital day.

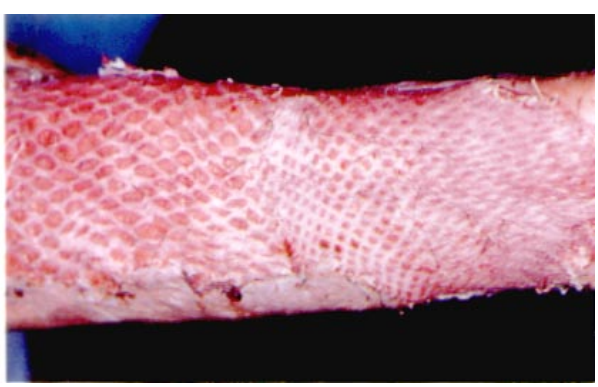

Fig. 6. A skin graft had taken successfully on the 5th postoperative day.

cluded the following: white cell count, 10,200/μl with 11.5% lymphocytes; hematocrit level, 27.3%; platelet count, 265,000/μl; ESR, 92mm/hr; BUN, 20.9mg/dl; creatinine, 0.9mg/dl; pan T cells(CD3), 81.1%; pan B cells(CD19), 6.2%; T-helper cells(CD4), 59.6%; T-suppressor cells(CD8), 34.5%; CD4/CD8 ratio, 1.73; anti-HIV antibody, negative.

A direct KOH mounting from the ulcerative lesion showed numerous yeast cells(Fig. 2A) and a skin biopsy also showed numerous yeast cells stained with the PAS reaction in the dermis and subcutaneous fat tissue(Fig. 3A). The yeast cells were surrounded with thick capsules stained blue with alcian blue(Fig. 3B). Tissue and sputum cultures on a Sabouraud agar medium at 37℃ showed smooth, creamy colonies(Fig. 2B) and microscopically revealed encapsulated organisms typical of *Cryptococcus neoformans* in India ink preparation. The organisms were identified as *Cryptococcus neoformans var. neoformans* by using VITEK (bio-Merieux, USA) which is a commercially available yeast identification system[6]. A chest X-ray showed marked cardiomegaly with little evidence of cavitary lesions, but on CT scanning a large cavitary lesion was found(Fig. 4). A lumbar puncture yielded normal cerebrospinal fluid(CSF). Cultures for *Cryptococcus neoformans* from blood, urine, and CSF were negative.

She was treated with a combination of antibiotics and antifungal agents, itraconazole orally (300mg/day) and fluconazole intravenously (200mg/day). Necrotic tissue debridement and wet dressing were also started. On the fifteenth day of treatment, there was a good clinical response with healing of the ulcers and then fluconazole was discontinued. About 3 weeks later, no organism was grown from repeated skin and blood cultures(Fig. 5). However, the skin defect was so severe that a skin graft was done and it had taken successfully(Fig. 6). Unforfunately, her complicated congestive heart failure and liver cirrhosis resulted in death on the 45th hospital day. A autopsy was not performed.

DISCUSSION

Cryptococcosis is an infection caused by the encapsulated fungus *Cryptococcus neoformans*. The first description was made in 1894 by Busse who observed the round-to-oval corpuscles in a sarcoma-like lesion of the tibia of a 31-year-old woman. Recently an unprecedented rate of increase has been seen from the early 1980s, as AIDS has become the leading predisposing factor in Cryptococcosis[1]. Between 1.9% and 9.0% of patients with AIDS may present with disseminated cryptococcosis[7].

This fungus is found in the respiratory tract or skin in healthy people as well as in patients with various bronchopulmonary diseases other than cryptococcosis, as transient flora or as an incidental colonizer[1]. In some studies, *Cryptococcus neoformans* was isolated from the sputum of as many as 80 patients, but only 28 of them were proven to have definite or probable pulmonary disease due to *Cryptococcus neoformans*[8]. Infection is initiated by inhalation into the lungs, but the subsequent hematogeneous dissemination to all organs results in clinical illness. Generally, asymptomatic normal hosts in whom dissemination has been excluded do not need antifungal theapy, but immunocompromised hosts with pulmonary cryptococcosis should receive antifungal therapy because of the high propensity for dissemination[9]. The most frequent site of secondary spread is the CNS, which is the most common cause of death from this disease[1,2,5]. However, skin lesions may occur before other manifestations of the disseminated cryptococcosis[2,3,10-12] or as the initial manifestation of AIDS[13]. Cutaneous cryptococcosis has therefore been described as a 'sentinel of disseminated disease'[13], although rare primary cutaneous cryptococcosis has been reported[14-20].

Cutaneous involvement of patients with cryptococcosis occurs in 10% to 15% of cases[2-4]. The cutaneous manifestations are usually polymorphic and non-specific. Lesions may appear as subcutaneous swelling, abscesses, tumor-like masses, papules, plaques or large ulcers[2,5]. They mimic a broad spectrum of lesions, including bacterial cellulitis[2,5,10,12,13,15,17,21], Kaposi's sarcoma[11], molluscum contagiosum[7], basal cell carcinoma, squamous cell carcinoma or sarcoidosis[1]. The lesions most often seem to be confused with bacterial cellulitis and are erroneously treated with antibiotics. Cellulitis with necrotizing vasculitis[10] or septic arthritis[21] have also been reported. Cutaneous involvement occurs most frequently on the head and neck[2,13]. However, in solid organ transplant recipients taking prednisone with or without immunosuppressants at the time of infection, the lower extremities

were the most common involved sites and most of the clinical manifestations were cellulitis[21]. Interestingly, our patient had a long history of corticosteroid administration and the lesions were on the lower extremity. This may help explain the increased incidence of cyptococcosis in immumosuppressed patients, especially those receiving corticosteroids. Cutaneous infections in immunocompetent hosts have also been rarely reported[12,15,16].

Diagnosis of cutaneous cryptococcosis is quite difficult and often delayed. As previously described, the gross morphology of the lesions is quite different from case to case to preclude a firm clinical diagnosis. The similarity to other lesions, especially bacterial cellulitis, obviously leads to a delay in diagnosis and treatment in most cases. Therfore, atypical or non-healing skin lesions should be evaluated with a smear for Gram's staining, India ink preparations, scraping for bacterial and fungal cultures, and biopsies. A Tzanck smear should be obtained to exclude herpetic infection if the lesion is vesicular. Diagnosis is confirmed by cultures, using biopsy specimens or swabs of ulcers, exudates, blister fluids, or aspirated fluids. Moreover, clinical suspicion is very important in diagnosis, and a KOH mounting with exudate cultures is of great use in ulcerative lesions. In our case, the initial clinical impression was necrotizing fasciitis, but routine KOH mounting revealed numerous budding yeast cells with peripheral clear zones, so we could easily suspect cryptococcal infection.

Once cutaneous cryptococcosis is diagnosed, all patients should be investigated for evidence of infection elsewhere. Sputum, urine, prostatic secretions and blood should be cultured. A chest X-ray and lumbar puncture to rule out CNS involvement should be performed[2,16]. Disseminated cryptococcosis is almost always fatal if untreated. Although there is no evidence of disseminated disease, namely in primary cryptococcosis, antigungal therapy is neccessary in most cases. However, Sussman et al[14]. in 1984 described a 64-year-old woman with self-healing cutaneous cryptococcosis who was only monitored, but not treated for 5 years.

Amphotericin B is a long-established effective treatment for cryptococcosis. However, this drug can cause a large number of toxic effects and has a substantial relapse rate. The addition of flucytosine produced fewer failures or relapses, more rapid sterilization of the CSF and less nephrotoxicity than did amphotericin B alone[22]. So, this regimen has been the cornerstone of therapy for a long time.

More recently, other antifungal agents, such as azoles, have become available and show considerable promise as an effective alternative to amphotericin B. Fluconazole is administrated intravenously or orally, and is effective in both cutaneous cryptococcosis[5,15,16,20] and cryptococcal meningitis[23]. However, there is no established standard for dosage or duration of therapy. Itraconazole, a highly lipid soluble triazole, has also been used successfully in the treatment of both cutaneous cryptococcosis[17] and cryptococcal meningitis with and without AIDS[24].

In our case, we started therapy with itraconazole, but the lesions spread so rapidly that fluconazole was also given soon after. In two weeks, there was a good clinical improvement of the lesions and the fluconazole was stopped. Unfortunately, her complicated congestive heart failure and liver cirrhosis resulted in death on the 45th hospital day. This treatment regimen does not appear to have been previously reported, but the clinical result in our patient suggests that it may be useful.

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