Cutaneous *Cryptococcus* in an Elderly Woman With Chronic Essential Dermatitis

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Cryptococcus neoformans *is a common cause of life-threatening infection. Cutaneous manifestations of* Cryptococcus *can be primary or secondary, most commonly from immunosuppression. With the global emergence of acquired immunodeficiency syndrome (AIDS), incidence of cryptococcosis is increasing and now represents a major life-threatening fungal infection in these patients. Nonspecific lesions may cause misdiagnosis. Disseminated* Cryptocoocus *requires early clinical diagnosis and effective management to decrease mortality. We review a case of cutaneous* Cryptococcus *as a complication of chronic essential dermatitis treated with long-term immunosuppressive agents and discuss updated guidelines on the treatment of* Cryptococcus.

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An encapsulated yeastlike fungus, *Cryptococcus neoformans* is present in dried pigeon droppings and bat guano and can remain viable for more than 2 years. C *neoformans* has 2 varieties—*neoformans* and *gattii*.[1] C *neoformans* var *neoformans* is the most common variety in the United States and other temperate climates throughout the world. It usually infects the host by inhalation of spores, causing a mild and asymptomatic pulmonary infection while the fungus disseminates in susceptible individuals.[1] The host responses range from a harmless colonization of the airways that are asymptomatic, to meningitis or disseminated disease.[2,3] Host immune status is an essential factor in the clinical presentation; the virulence of the organism determined by the strain of *Cryptococcus* is less important. Dissemination of cryptococcal infection is almost exclusively seen in individuals who are immunocompromised because they have defective cell-mediated immunity. C *neoformans* var *neoformans* serotype A mostly infects individuals who are immunosuppressed, while C *neoformans* var *gattii* infects individuals who are immunocompetent. Cutaneous manifestations after hematogenous spread are seen in approximately 10% to 20% of human immunodeficiency virus–negative patients.[2,3] Other common sites of dissemination include the central nervous system (CNS), skin, prostate, and bones. The existence of primary cutaneous *Cryptococcus* is controversial; however, a few cases of primary skin infection resulting from direct inoculation at sites of injury are reported.[4,5]

We present a patient with a history of chronic essential dermatitis managed using long-term immunosuppressant therapy and complicated by cutaneous *Cryptococcus* that improved with prompt treatment consisting of intravenous antifungal agents.

Case Report

A 62-year-old white woman presented with 2 painful ulcers on her right arm and an enlarging subcutaneous nodule on her abdomen. The patient had been followed in the dermatology clinic for 6 years for chronic essential dermatitis treated most recently with azathioprine and systemic corticosteroids without resolve. She lived on a farm, raising more than 144,000 chickens. The patient denied having any systemic symptoms.

The results of a physical examination revealed a tender, well-circumscribed, 6×2-cm ulcerated nodule on the right forearm; a tender 2×3-cm ulcerated nodule on the right upper arm (Figure 1); and a 1.5×3-cm subcutaneous nodule on the left lower abdomen. She had generalized background coalescing red patches. There was no lymphadenopathy or mucosal involvement. Biopsy specimens were obtained from the nodule on the right upper arm (Figure 2) and left lower abdomen.

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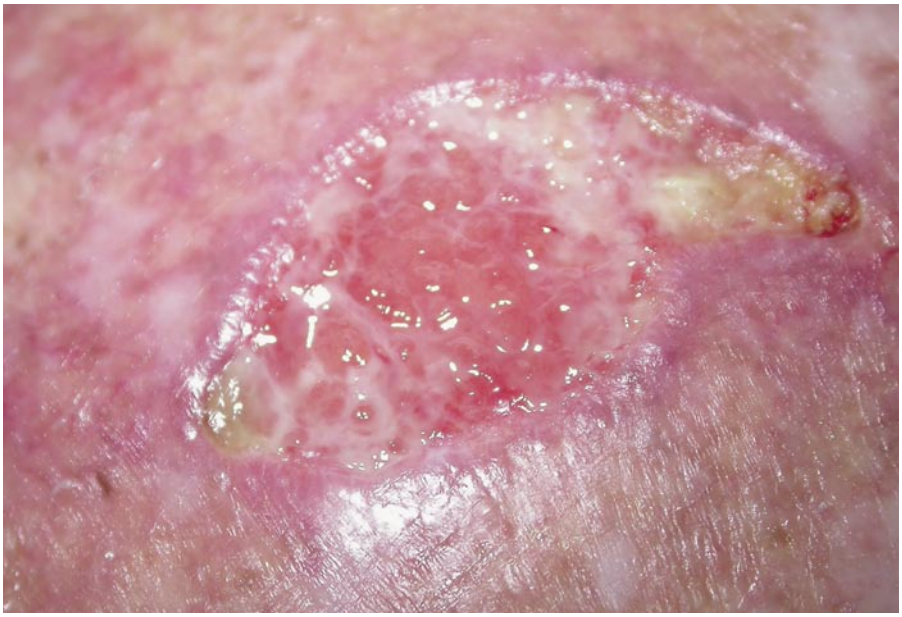

Figure 1. Ulcerated nodule on the right upper arm.

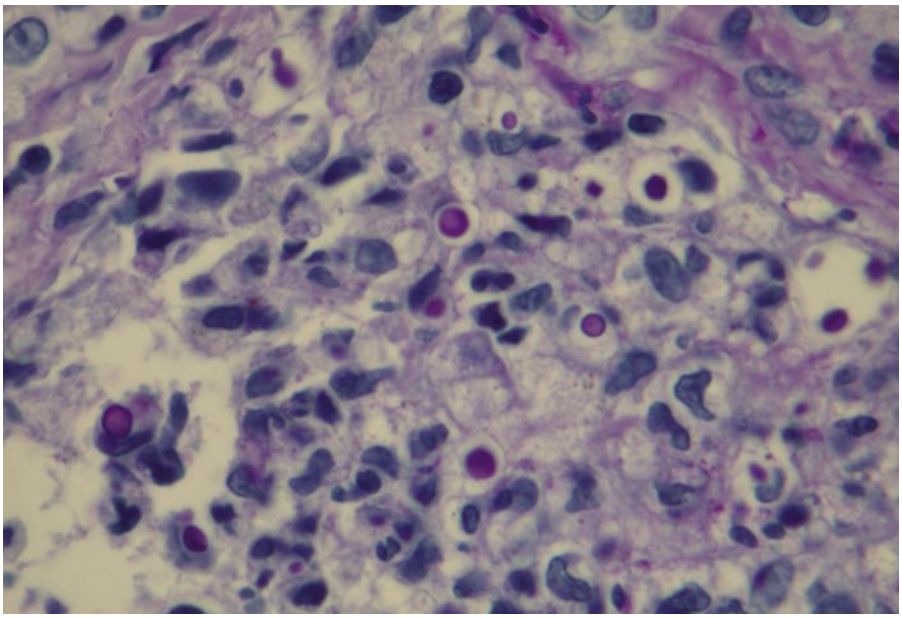

Figure 2. Biopsy of a nodule on the right upper arm shows encapsulated yeast (periodic acid-Schiff, original magnification ×400).

A microscopic examination of both biopsy specimens revealed a lymphohistiocytic infiltrate, and periodic acid-Schiff staining demonstrated cryptococcal organisms. A tissue culture from the right upper arm grew C *neoformans*. The results of 2 sets of blood cultures were negative; however, cryptococcal antigen was detected in the blood (titer 1:128). Results of a chest x-ray showed no evidence of acute pulmonary abnormalities.

The patient was admitted to the hospital with presumed primary cutaneous *Cryptococcus* and treated with amphotericin B and 5-flucytosine. A lumbar puncture to determine CNS involvement was not performed because of the patient's weight and intervening chronic essential dermatitis. Amphotericin B and 5-flucytosine were discontinued 10 days later secondary to acute renal failure and the patient was switched to oral fluconazole 400 mg once daily. The patient's skin lesions improved dramatically within one week of treatment and resolved one month later. Her dermatitis dramatically improved but remained active.

Comment

Since the development and use of immunosuppressant therapy and improvement in patient survival, the

reported incidence of cryptococcal disease is increasing. Since its discovery 100 years ago, *Cryptococcus* has been a leading cause of morbidity and mortality in patients with acquired immunodeficiency disease (AIDS) and has been implicated in immunocompromised patients on chronic immunosuppressants and post–organ transplantation.[6]

Clinical diagnosis of cutaneous *Cryptococcus* can be difficult because of its various gross morphologic presentations.[4] Early infection usually is characterized by little or no necrosis or organ dysfunction, partly because of the lack of identifiable endotoxins or exotoxins. Manifestations of cutaneous *Cryptococcus* include papules, pustules, nodules, ulcers, subcutaneous abscesses, draining sinuses, and cellulitis.[1,7] Skin lesions may resemble acne vulgaris, molluscum contagiosum, sarcoidosis, and bacterial cellulitis.[8] The characteristic lesion consists of a cystic cluster of yeast with no well-defined inflammatory response, as our patient had demonstrated. However, the most commonly reported morphologic finding is molluscum contagiosumlike lesions. Interestingly, *Cryptococcus* has been diagnosed 2 to 3 times more frequently in men than women, and it has been suggested that estrogens have protective effects.[8] Asymptomatic cryptococcal prostatitis has been found in a large number of men with AIDS,[8] another possible cause of male predominance.

Diagnosis is best established by biopsy and culture results. *C neoformans* reproduces by budding and forms round yeastlike cells with a large polysaccharide capsule surrounding each cell in the host and culture media at 20°C to 37°C. Most strains can use creatinine as a nitrogen source, which partially may explain the growth of the organism in creatine-rich avian species. On biopsy, the cell wall of *C neoformans* will stain with periodic acid-Schiff or methenamine silver, and the capsule will stain with mucicarmine or Alcian blue. Fontana-Masson silver stains melanin precursors in the cell well and can be helpful in differentiating from other yeast.[9] Without cutaneous involvement, diagnosis of systemic cryptococcosis depends on demonstration of *C neoformans* in cerebrospinal fluid by India ink stains or culturing the blood and urine. Anticryptococcal antibodies may not have diagnostic significance because low concentrations can develop in a substantial percentage of healthy individuals. Computed tomography or magnetic resonance imaging of the brain should be performed in patients with focal neurologic deficits or a history of slowly progressive meningitis. A spinal tap should be performed on all patients with known or suspected cryptococcal disease.[10]

As is true for other systemic mycoses, treatment of disease caused by *C neoformans* has dramatically improved over the past 2 decades. Before 1950, disseminated cryptococcal disease was uniformly fatal. With the advent of polyene antifungal agents, particularly amphotericin B, successful outcomes have been achieved in as many as 60% to 70% of patients with cryptococcal meningitis.[10] The goal of treatment is to cure the infection and prevent dissemination of disease to the CNS.

The practice guidelines for the management of cryptococcal disease state that treatment depends on both the anatomic sites of involvement and the host's immune status.[10] For individuals with non–CNS-isolated cryptococcemia (a positive serum cryptococcal antigen titer >1:8) or urinary tract or cutaneous disease, recommended treatment is oral fluconazole for 3 to 6 months. For CNS involvement in human immunodeficiency virus–negative hosts, a regimen of amphotericin B (0.7–1 mg/kg/d) plus 5-flucytosine (100 mg/kg/d) for 2 weeks followed by fluconazole (400 mg/d) for a minimum of 10 weeks is recommended.[10] Amphotericin B has a rapid onset of action and often leads to clinical improvement more rapidly than either intravenous or oral fluconazole. Renal function should be monitored because amphotericin B is nephrotoxic. Flucytosine is unreliable if used alone and resistance develops rapidly. Serum concentrations of flucytosine should be monitored because of the potential for gastrointestinal toxicity and bone marrow suppression. Because our patient did not have a lumbar puncture performed secondary to overlying dermatitis, she was assumed to have CNS involvement and treated with amphotericin B with 5-flucytosine, followed by oral fluconazole. According to the practice guidelines for the management of cryptococcal disease, it is imperative that all patients with pulmonary and extrapulmonary cryptococcal disease have a lumbar puncture performed to rule out concomitant CNS infection.[10]

It is debatable if primary cutaneous disease exists. Therefore, cutaneous manifestation may confirm systemic involvement and appropriate antifungal therapy should begin immediately. For these reasons, cutaneous *Cryptococcus* has been recognized as a sentinel of disseminated disease.[5]

Conclusion

Cryptococcus should always be part of the differential diagnosis in immunocompromised patients with unusual cutaneous findings. Cell-mediated immunity is critical in host defense and susceptibility to dissemination. Therefore, risk factors associated with the development of *Cryptococcus* include long-term

corticosteroid use, organ transplantation, sarcoidosis, AIDS, and immunosupression.[3] A skin biopsy with special stains for fungal organisms, chest x-ray, and lumbar puncture for *Cryptococcus* should be performed as part of any diagnostic workup. Skin involvement in immunosuppressed patients is a marker of disseminated disease. Without treatment, disseminated *Cryptococcus* has a mortality rate of 80% in 2 years. Appropriate antifungal treatment with amphotericin B and 5-flucytosine reduces mortality rates by 10% to 20%.[5]

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