Cutaneous cryptococcosis

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SUMMARY

Cutaneous cryptococcosis, caused by the encapsulated yeast, *Cryptococcus neoformans*, is generally associated with concomitant systemic infection. The authors report a case of a man with isolated cutaneous cryptococcosis of his right foot without obvious systemic manifestations. A review of the clinical aspects, pathogenesis and management of cutaneous cryptococcosis is also presented.

KEY WORDS

cryptococcosis, cutaneous, foot, male patient, positive histopathology

Introduction

Cryptococcosis is a systemic infection caused by the encapsulated yeast, *Cryptococcus neorformans*. Cryptococcus is ubiquitously found in the soil, in pigeon droppings and in their nesting places. In the non-human environment it is not encapsulated and measures less than 2 µm. Its usual route of entry into humans is via inhalation of this non- or poorly encapsulated form of the organism. In the lungs, the organism develops its polysaccharide capsule, which is responsible for most of its virulence. Even though the lungs are the site of inoculation, pulmonary infection, even in the immunocompromised, tends to be asymptomatic. Immunocompetent hosts tend to remain asymptomatic, but reactivation or spread to the lymph nodes, blood, central nervous system and any other tissue may occur in immunosuppressed individuals or those with low CD4 counts. (1,2,3)

The most common manifestation of disseminated cryptococcosis is infection of the central nervous system, which produces meningitis or encephalitis. However, systemic spread can cause almost any organ to become infected. The skin is the most common extraneural site of infection, affecting 10-20% of those with systemic involvement. (2) Cutaneous lesions are an ominous sign as they are often the first presenting symptom of systemic disease. However, rare cases of primary inoculated cutaneous lesions, without evidence of disseminated disease, have been reported.

Case report

A 48-year-old male presented with a 1 month history of an enlarging nodule on his right foot near the

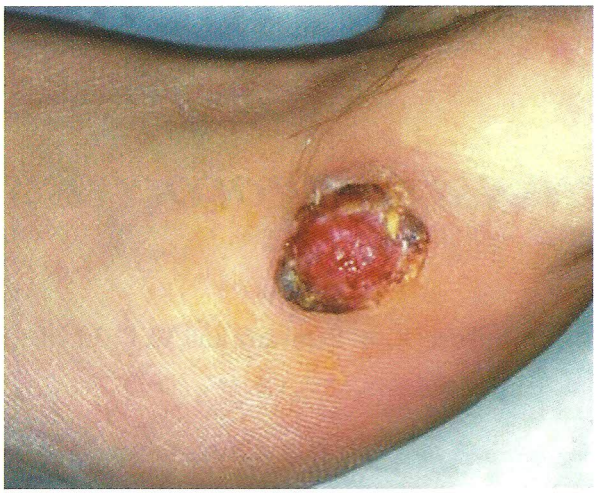


Figure 1. Solitary erythematous nodule on the medial aspect of the foot.

base of his big toe. The patient denied any history of trauma to the site and did not report any bleeding associated with this lesion. The patient was seen by a podiatrist who diagnosed the lesion as cellulitis and initiated treatment with ciprofloxacin without improvement. The patient had a medical history significant for diabetes mellitus as well as a liver transplant secondary to cirrhosis 3 years prior to presentation for which he was being maintained on both tacrolimus and prednisone. Cutaneous examination revealed a 1.5 cm circular glistening erythematous nodule on the medial aspect of the foot near the base of the hallux (Figure 1).

Histopathologic exam (shown in Figure 2) revealed ulceration and pseudoepitheliomatous hyperplasia of the epidermis. In the dermis, there was granulomatous inflammation composed of multinucleated giant cells, lymphocytes, histiocytes, eosinophils, neutrophils, and plasma cells. Numerous yeast-like organisms in small clear spaces were present both freely and in the histiocytes and giant cells. The organisms mostly ranged from 5 to15 μm in diameter and had refractile walls. Periodic acid-Schiff (PAS) and Gomori's methenamine-silver ni-

Figure 2. Hematoxylin and eosin staining from shave biopsy of the lesion showing ulceration and pseudoepitheliomatous hyperplasia of the epidermis and granulomatous inflammation in the dermis.

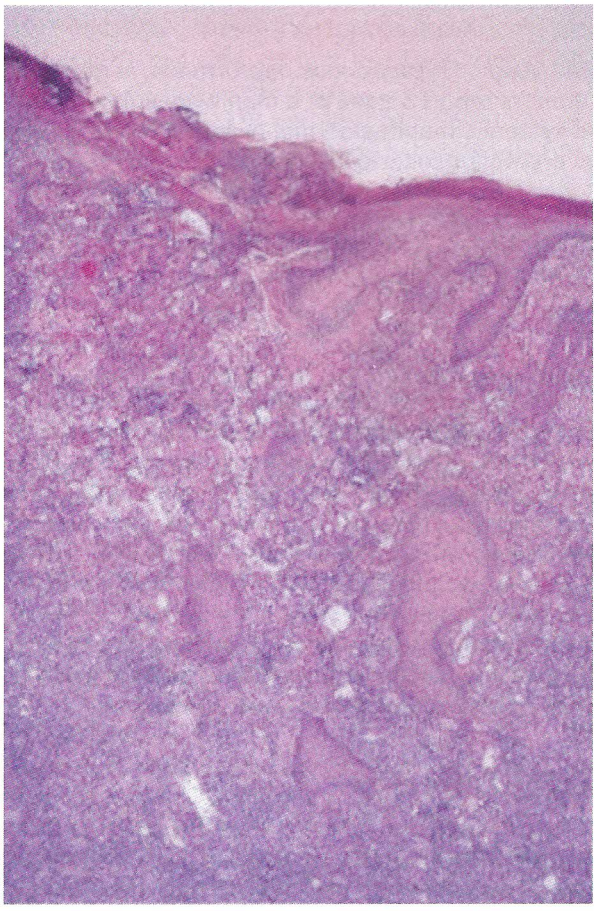
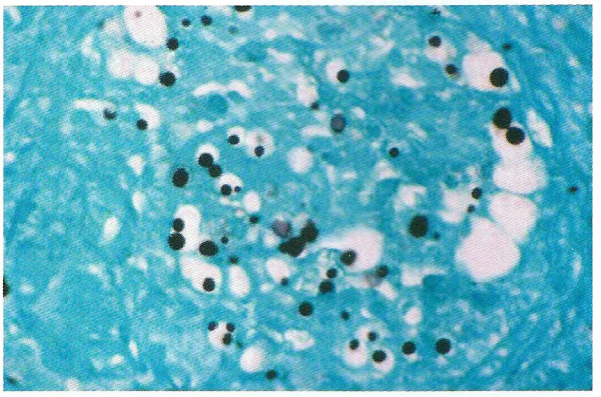


Figure 3. Gomori's methenamine-silver stain revealing numerous yeast-like organisms.



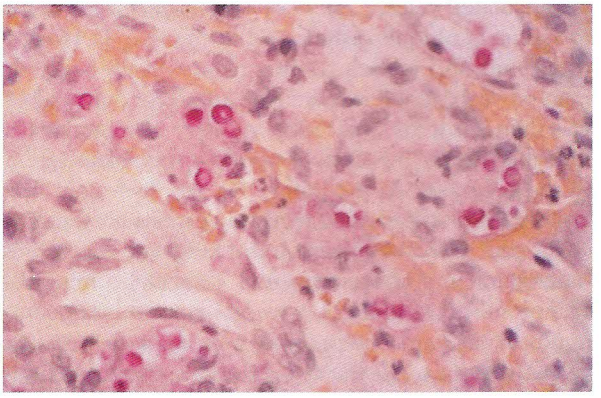


Figure 4. Cryptococcal capsules stained positively with mucicarmine.

trate (GMS) stains were both positive for the organisms (GMS stain shown in Figure 3). Mucicarmine stained positively for the capsules of the organisms (Figure 4). These findings are characteristic for cryptococcosis.

After positive identification of the organism, a search for signs of systemic infection was initiated. Chest roentegram demonstrated a 1.6 cm nodule in the right upper lung field, however, a biopsy of this lesion was deferred. Blood and cerebral spinal fluid (CSF) cultures were negative for cryptococcus. The patient was started on IV amphotericin B for 6 days, however, it was discontinued due to elevated blood urea nitrogen and creatinine levels and was replaced with fluconazole. The patient was discharged and is being followed up as an outpatient.

Discussion

Primary cutaneous cryptococcosis is a rare occurrence, as skin lesions are generally accompanied by systemic infection. However, there is evidence that some cases of primary cutaneous cryptococcus occur by direct inoculation of the organism into sites of injury or trauma but in most instances there is metastatic spread from other parts of the body—usually the lung. Our patient had an isolated skin lesion without CSF or hematologic evidence of disseminated disease; however, the lung nodule found by chest roentegram indicates that his lesion probably resulted from pulmonary seeding.

A high index of suspicion is mandatory because cryptococcal skin involvement is non-specific and produces a wide variety of lesions. A wide variety of morphologies may be seen, including: papules, nodules, plaques, vesicles, bullae, pustules, abscesses, cellulitis, ulcers and purpura, as well as acneiform, herpetiform, Kaposi sarcoma or basal cell carcinoma-like nodules. (3,4) The lesions are most often confused with bacterial cellulitis and are erroneously treated with antibacterial agents. Thus, any new skin lesion in a high risk individual should be evaluated.

Biopsy specimens reveal one of 2 types of pathologic reactions that are described as either gelatinous or granulomatous. Gelatinous lesions show numerous cryptococci and little if any inflammatory reaction whereas granulomatous lesions show fewer cryptococci and marked inflammation consisting of lymphocytes, mononuclear cells, and occasionally giant cells. The gelatinous type of response is seen with cryptococci that have large capsules while cryptococci with thinner or no capsules are found with the granulomatous response. Although the organisms can generally be seen with hematoxylin and eosin stained tissue, special stains such as GMS, PAS and mucicarmine make them easier to see. GMS stains the organism black while PAS and mucicarmine stains the polysaccharide capsule red. Mucicarmine has the added advantage in that it does not stain pathogenic fungi other than cryptococcus.(1)

Once a diagnosis of cutaneous cryptococcal infection has been made it is imperative to initiate a search for systemic involvement including obtaining a chest X-ray, blood, urine, and CSF cultures, India ink stain of CSF from lumbar puncture, and testing for the presence of the cryptococcal antigen in the serum and CSF. Chest X-ray may reveal signs of pulmonary infection including lobar consolidation or nodular lesions. Patients with cryptococcal meningitis generally have an elevated opening pressure during lumbar puncture and CSF analysis demonstrates a preponderance of lymphocyes, with a total leukocyte count of 40-400.(2,5) India Ink preparations are positive in only 50% of patients with CNS disease, latex agglutination is positive in about 93% of patients but CSF cultures are eventually positive in 95% of all patients with cryptococcal meningitis.(1)

The mainstay of treatment for cryptococcosis is amphotericin B with/without flucytosine. Unfortunately, it is highly toxic, has poor CSF penetration and has a substantial relapse rate. More recently, the azoles have emerged as alternate therapies in patients that cannot tolerate amphotericin B. Fluconzaole has been found to be particularly effective due to its high bioavailability, excellent CSF penetration and long half life. It is because of these properties that it is now the drug of choice for prophylactic therapy. In addition, it has been associated with fewer relapses and less drug toxicity. The mortality of disseminated cryptococcosis is 70-80% in untreated patients compared with 17% treated with systemic anti-fungal agents.(4,6) Again, it is critical to commence a thorough investigation into any cutaneous lesion in high risk individuals in order to initiate rapid therapy.

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