Disseminated Cryptococcosis with Cutaneous and Central Nervous System Involvement in a Diabetic Patient

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Abstract

Disseminated cryptococcosis has been a common cause of infective morbidity and mortality in patients with immunocompromising diseases. The most frequent sites following hematogenous dissemination from the lungs are the central nervous system and skin. The majority of patients with skin lesions have disseminated infection. Disseminated cryptococcosis without treatment is nearly fatal. We reported a case of disseminated cryptococcosis with initial presentation on the face in a patient who had diabetes mellitus. The diagnosis was delayed because of we did not recognize the cutaneous lesion earlier and the patient developed symptoms of central nervous system involvement subsequently. Early recognition of the disseminated cryptococcosis can help us prescribe appropriate systemic antifungal therapy and improve the outcome. (J Intern Med Taiwan 2009; 20: 187-191)

Key Words：Cryptococcosis, Skin, Diabetes mellitus

Introduction

Cryptococcosis is a life-threatening opportunistic fungal infection worldwide. The predisposing factors of cryptococcosis include acquired immunodeficiency syndrome (AIDS), cancer, sarcoidosis, Hodgkin's lymphoma, diabetes mellitus and organ transplantation. The central nervous system (CNS) and skin are common sites following hematogenous dissemination from the lungs[1]. It is important to make early diagnosis and start appropriate treatment for disseminated cryptococcosis, because disseminated cryptococcosis without treatment is nearly fatal. Appropriate systemic antifungal therapy can significantly improve the outcome[2,3]. Herein, we reported a case of skin and CNS involvement of disseminated cryptococcosis in a patient who had diabetes mellitus and was successfully treated by antifungal therapy.

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Case report

A 58-year-old man visited our hospital due to fever and headache for 3 days. He had a history of diabetes mellitus for half a year. This patient had been diagnosed as having pulmonary cryptococcosis 2 months prior to this admission but the patient did not receive any treatment after the pulmonary cryptococcosis was diagnosed and he was lost for follow up. In addition, multiple facial nodules were noted one week prior to this admission. The patient had visited our general surgery department but the cutaneous lesion was not surveyed. At admission, the patient was conscious, alert and oriented. His body temperature was 38 ℃, pulse rate was 80 beats/minute, respiratory rate was 20 breaths/minute and blood pressure was 110/70 mmHg. Physical examination was unremarkable except neck stiffness and multiple nodules on his face (figure 1). The nodules had a reddish base and the largest one was on the brow area and was about 2 cm in diameter. Laboratory data showed white blood cell (WBC) count of 12,900/mm^3, WBC differential counts revealed neutrophil of 80.6%, hemoglobin of 13.7 gm/dl, platelet count of 446,000/mm^3, blood urea nitrogen (BUN) of 22 mg/dl, and creatinine of 1.2 mg/dl. Chest X-ray showed infiltration at the left lower lung field. Computed tomography of the brain was negative. Lumbar puncture was performed for the suspected meningitis. The white blood cell count of the cerebrospinal fluid (CSF) sample was 9/mm^3, the WBC differential counts of CSF showed lymphocytic pleocytosis with lymphocytes to neutrophils of 90/10 and the India ink smear showed encapsulated budding yeast cells in CSF. The serum cryptococcal antigen titer was 1:4096. In addition, we performed an incisional biopsy of the skin nodule. On microscopy (Mucicarmine stain 400X), the section showed protruding, seemingly edematous, and subepidermal nodular areas of dermis containing budding yeast forms with clear mucoid capsule and admixed with aggregates of foamy histiocytes (figure 2).

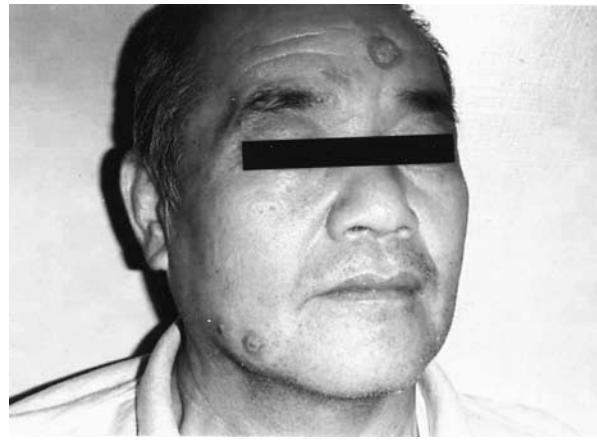

Fig.1. Multiple facial nodules with round reddish base over the patient's face.

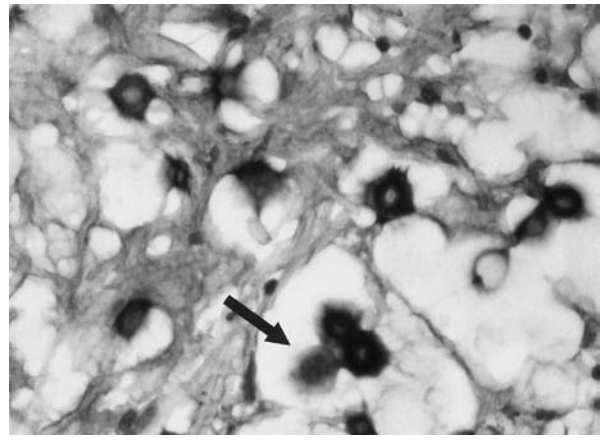

Fig.2. Biopsy of the skin nodules revealed budding yeast with clear mucoid capsule and admixed with aggregates of foamy histocytes (arrow) (Mucicarmine stain 400X)

Disseminated cryptococcosis was diagnosed according to the pulmonary, central nervous system and skin involvement. We checked anti-human immunodeficiency virus (HIV) antibody for this patient and the result was negative. The patient did not have cirrhosis and did not receive immunosuppressive or steroid therapy. The only risk factor for this patient was diabetes mellitus. Intravenous amphotericin B 30 mg daily was prescribed for 6 weeks which was switched to oral

fluconazole 400 mg daily. The symptoms of fever and headache improved gradually and the skin nodules were also decreasing in size. After 6 weeks of treatment, the serum cryptococcal antigen titer decreased to 1:256 from 1: 4096 initially and the India ink smear of a CSF sample was negative. After the symptoms subsided and the results of CSF study normalized, the patient was discharged and followed up at our outpatient department with oral fluconazole. There was no recurrence of cryptococcosis after 5 years of follow up.

Discussion

Cryptococcosis is a fungal infection caused by *Cryptococcus neoformans* which is an encapsulated, basidiomycetous yeast that is present in the environment worldwide. It comprises the infections caused by two variants of the fungus, *C. neoformans var. neoformans* and *C. neoformans var. gattii. C. neoformans var. neofromans* is commonly associated with infections in immunocompromised patients, while *C. neoformans var. gattii* affects predominantly immunocompetent hosts[1]. Cryptococcosis usually occurs in males between the age of thirty and fifty[4]. The most important predisposing condition is AIDS, but the disease can also occur in individuals receiving immunosuppressive therapy, such as patients with cancer, sarcoidosis, Hodgkin's lymphoma and those who have undergone organ transplantation[1]. Early in the epidemic of human immunodeficiency virus infection, cryptococcosis emerged as the most important fungal opportunistic infection, but declined since the mid-1990s due to the development of highly active antiretroviral therapy and prophylactic treatment to prevent fungal infections[4]. Cryptococcosis is probably initiated by the inhalation of the fungus and development of a primary focus at the lungs, and following hematogenous dissemination from the lungs, CNS and skin are the two most common sites of infection[1]. Skin involvement has been described in disseminated forms and in primary cutaneous infections caused by *C. neoformans*[5-8].

Disseminated cryptococcosis without treatment has a high mortality rate, and appropriate systemic antifungal therapy can significantly improve the outcome[2,3]. Primary cutaneous cryptococcosis is a distinct epidemiological and clinical entity with a favorable prognosis even for immunocompromised hosts[9]. Cutaneous cryptococcosis may be one of the first manifestations of disseminated cryptococcosis or a primary disease both in immunocompetent and immunocompromised hosts[9-11]. Cutaneous lesions commonly affect the face and neck with different presentations including papules, pustules, plaques, ulcers, subcutaneous masses, cellulitis or acneiform lesions[1]. Primary cutaneous cryptococcosis had a lower percentage with underlying immunosuppression[9]. Neuville et al. proposed criteria for diagnosing the primary cutaneous cryptococcosis in 2003. According to these criteria, cutaneous lesions in primary cryptococcosis are solitary or confined to a limited area and located on unclothed areas, usually the limbs, whereas secondary cutaneous cryptococcosis are usually multiple and scattered, located both in clothed and exposed areas[9]. Diagnosis of cutaneous cryptococcosis depends on skin histopathology and cultures. In our case, this patient presented a picture of secondary cutaneous cryptococcosis because the location was on the face, the lesion was multiple and the patient had other systemic signs.

The neurologic deficit was noted initially in 37.8% of HIV-negative patients and 39.6% of HIV-positive patients with cryptococcosis in one study[12]. Neurologic sequelae in cryptococcal meningitis may include abnormal mental status (33%), motor or cranial nerves palsies (15%) and seizures (10%)[12]. The neurologic deficit subsided after appropriate treatments. Satishchandra et al. had reported that 24% of the patients had neurologic symptoms at 30

days, 10% at 60 days and 7% at more than 120 days after treatment[13].

The Infectious Diseases Society of America proposed the 2000 Practice Guidelines for the Management of Cryptococcal Disease, which are summarized in table 1 for HIV-negative patients. This guideline also emphasized that when other disseminated sites of infection are noted or the patient is at risk for disseminated infection, it is important to rule out CNS disease[14]. Asymptomatic individuals in whom cryptococci have been isolated from respiratory secretions have been observed without treatment and no clinical relapse has occurred1. The overall mortality rate was 27% in HIV-negative patients who had cryptococcosis and the mortality rate rose to 64% in disseminated cryptococcosis[2,3]. Kiertiburanakul at al. reported five patients had cryptococcosis who were initially misdiagnosed and three patients died among them because they were not treated with any antifungal drugs[3]. Factors predictive of deaths within three months after the diagnosis were underlying hematological malignancy, presence at baseline of abnormal neurology, or abnormal brain imaging[12]. For these reasons, regardless of the treatment chosen, it is important that all patients with pulmonary and extrapulmonary cryptococcal disease perform a lumbar puncture to rule out concomitant CNS infection[14]. Some patients had asymptomatic meningitis and asymptomatic meningitis has been mentioned as being of possible use in early diagnosis of the disease[3]. In our case, the cutaneous lesion developed one week prior to the admission. The patient had visited our hospital but we did not survey the cutaneous lesion. If death or neurologic sequela developed after antifungal therapy, this delay in diagnosis might be relate to the adverse outcome. However, the symptoms and signs of meningitis subsided after treatment and the patient did not develop any neurologic sequela. The skin lesions regressed gradually after 8 months of oral fluconazole. In conclusion, where newly onset of skin lesion by skin biopsy in a patient who had pulmonary cryptococcosis was observed, facilitation of early diagnosis of disseminated cryptococcosis should be considered. The early diagnosis and appropriate systemic antifungal therapy will improve the outcome.

Table 1: Preferred treatment options for cryptococcal disease in HIV-negative patients

Cryptococcal disease, treatment regimen
Pulmonary
Mild-to-moderate symptoms or culture-positive specimen from this site
Fluconazole, 200-400 mg/d for 6-12 months
Itraconazole, 200-400 mg/d for 6-12 months
Amphotericin B, 0.5-1 mg/kg/d (total, 1000-2000 mg)
Severe symptoms and immunocompromised hosts
Treat like CNS disease
CNS
Induction/consolidationd: amphotericin B, 0.7-1 mg/kg/d plus flucytosine,
100 mg/kg/d for 2 weeks, then fluconazole, 400 mg/d for minimum 10 weeks
Amphotericin B, 0.7-1 mg/kg/d plus flucytosine, 100 mg/kg/d for 6-10 weeks
Amphotericin B, 0.7-1 mg/kg/d for 6-10 weeks
Lipid formulation of amphotericin B, 3-6 mg/kg/d for 6-10 weeks

*CNS denotes central nervous system

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瀰漫性隱球菌病於一糖尿病患者的皮膚與中樞神經表現

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摘　要

瀰漫性隱球菌病於有免疫抑制疾病的病人是常見的感染性罹病及致命原因。中樞神經系統及皮膚是較常從肺中經血行傳播出來的地方。而大部分皮膚有病灶的病人都有瀰漫性的感染。瀰漫性的隱球菌感染若沒有治療近乎致命。在此我們報告一糖尿病患者得到以皮膚症狀爲初始表現的瀰漫性隱球菌感染，因爲我們沒有及早辨認此一皮膚表現所以診斷延遲並造成後續中樞神經系統症狀的出現。早期辨認可能的瀰漫性隱球菌感染可幫助我們及早使用適當的抗黴菌治療且改善預後。