

Case Blog

Title: Fatal Primary Cutaneous Cryptococcosis

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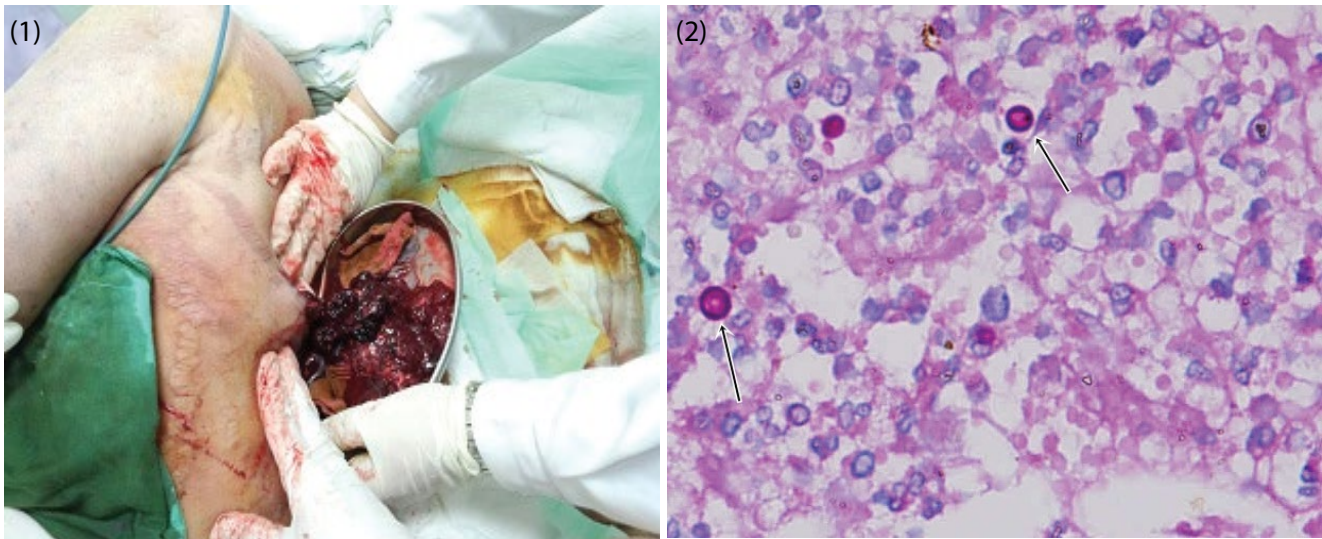


Figure 1: Periodic acid-Schiff (PAS) staining of the dermis and soft tissue.

Figure 2: Surgical debridement was performed every day.

Introduction

Cryptococcus is a type of opportunistic encapsulated yeast with a worldwide distribution [1]. Cryptococcosis continues to cause significant morbidity and mortality, especially in immunocompromised patients such as those with AIDS, organ transplants, haematological malignancies, and corticosteroid treatment [2]. Primary cutaneous cryptococcosis (PCC), lesions associated with a skin portal of entry without systemic infection, is rare but life threatening [3]. Here, we report one case of rare fatal PCC in an immunosuppressed patient. The clinical diagnosis corroborated histological findings and causative agent was confirmed as *Cryptococcus neoformans* in culture isolate.

Case Blog

A 23-year-old man was admitted to our hospital with fever and swelling, painful lesions in both the anterior and the posterior of his trunk, with no history of cough, headache or vomiting. He received a massage half a month prior to admission.

In his 20-month history of nephrotic syndrome, the patient was diagnosed with IgA nephropathy by renal biopsy and treated with prednisone (30-60 mg/d) for more than 1 year. Leflunomide and cyclophosphamide were each added once for a brief period. He had no known history of human immunodeficiency virus (HIV) infection and reported no contact with doves, poultry or other types of animals. On physical examinations, the patient had erythema, tenderness, edema and soft swelling skin lesions around the trunk. Cutaneous ulcers developed with time, with necrotic subcutaneous soft tissue and perilesional edema. The laboratory examination showed that peripheral white blood cell, CD4+ T cell count, CD8+ T cell count, CD20+ B cell count and the CD4+/CD8+ T cell ratio were $23.9(3.5-9.5) \times 10^9/L$, $143(651.3 \pm 273.6)/\mu l$, $236(452.62 \pm 210.83)/\mu l$, $159(125.22 \pm 51.55)/\mu l$ and 0.6, respectively, and that total blood immunoglobulin and immunoglobulin G were 17.9 (20-30) g/l and 4.8(7-16) g/l, respectively. The serum creatinine level was elevated at 1.86 mg/dl, and the cystatin C level increased to 2.50 mg/dl. Antibodies to HIV and to hepatitis B and C were all negative, and blood cultures were negative. The serum cryptococcal antigen latex agglutination test (Immuno-Mycologics, Inc., Norman, OK, USA) was positive at a titer of 1: 32. Chest computed tomography (CT) scan on Hospital Day 1 revealed signs of mild pulmonary infection without nodules. A cultural examination of necrotizing

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tissue on Sabourad glucose agar at 37°C for 3 days yielded cream-like colonies. The isolate was identified as *C. neoformans* by API 20C AUX (Biomerieux, Marcy, France). The antifungal susceptibility test showed that the fungus was sensitive to itraconazole but resistant to fluconazole. Skin biopsy revealed chronic inflammation with necrosis and numerous variably sized, round-to-oval budding organisms. Periodic acid-Schiff (PAS) staining of the dermis and soft tissue revealed blue, positive capsulated organisms (Figure 1) that were consistent with *Cryptococcus*. Cerebrospinal fluid examination, brain magnetic resonance imaging and abdominal ultrasound examination did not show any abnormality.

Fungal culture of the soft tissue revealed the growth of *Cryptococcus* and confirmed our clinical diagnosis of PCC. The patient was started on fluconazole (600 mg/d for 4 days) intravenously and then changed to itraconazole (500 mg/d for 5 days) intravenously according to the result of antifungal sensitivity test. Surgical debridement was performed every day (Figure 2). There was no evidence of disseminated intravascular coagulation. However, on the twenty-second day since admission, the patient died following continuous capillary haemorrhage.

Discussion

Cryptococcus neoformans is an opportunistic yeast discovered from soil, decaying wood, fruits and vegetables in the environment worldwide. The most characteristic feature of the yeast is its polysaccharide capsule, which is the most important virulence factor and can be visualized with India Ink, methylene blue and mucicarmine staining. Four serotypes of *Cryptococcus neoformans* have been identified: serotype A, D and serotype B and C. Serotype A (*C. neoformans* var. *grubii*) distribute ubiquitously, serotype D (*C. neoformans* var. *neoformans*) is found mainly in Europe, and serotypes B and C (*C. neoformans* var. *gattii*) are limited to tropical and subtropical areas [1]. The clinical isolate of *C. neoformans* var. *neoformans* predominate in non-HIV patients in China [4].

PCC often affects patients from rural areas with trauma or pre-existing cutaneous lesions and is defined as *Cryptococcosis* in the skin lesion biopsy specimen or by culture and either clinical criteria or histological criteria, together with the absence of dissemination [1]. Its common dermatological features include cellulitis, ulceration, whitlow, abscesses, lupus-erythematosus, eczema and nodules in the face, hand, arm, leg or any limited portion of the unclothed body [3]. Routine laboratory test results were usual normal for immunocompetent patients, and most case were treated by azoles such as itraconazole and fluconazole and showed good outcome. The reported case was immunosuppressed due to treatment for nephropathy, and clinically documented diagnose was made based on histological findings and culture isolate.

The immune response to *Cryptococcus neoformans* is probably efficient, for the low frequency of PCC in the whole population [5]. Both the innate and adaptive immune systems attack established cryptococcal infections, but the organism employs several specific strategies to neutralise the host's immune system [6]. In the AIDS population, *Cryptococcosis* has been well analysed and considered as AIDS-defining illness. Steroids and immunosuppressive therapy are widely used to treat nephrotic syndrome, which caused CD4+ T cell count falling down in many patients [7]. Possible causes of infection in this described patient were down-regulation of T-cell response and a possible micro-trauma on his thinning skin, which served as the portal of entry during massage in a moist and contaminated environment. Even low-dosage (e.g., 10 mg daily) Corticosteroid monotherapy can increase the possibility of a *Cryptococcal* infection. A similar case of PCC on a 55-year-old renal transplant recipient with multiple cutaneous lesions on left thigh and nasal bleeding has been described [8]. Many other cases have been attributed to consumption of steroids or other immunosuppressant agents following solid organ transplantation [7,9-12]. The majority of these patients showed an excellent outcome upon treatment with azoles, and multiple successful regimens have also been described [8,1,13-16].

This is, to our best knowledge, the most severe case of fatal PCC due to *Cryptococcus neoformans* in an immunocompromised patient. There is a possibility that *cryptococcosis* affected coagulation then caused death of the described patient, confirmation of which awaits further study [17-19]. PCC should be considered as a possible cause of skin lesion resistant to empirical antibiotic therapy in immunosuppressed patients and appropriate investigations and antifungal treatment should be initiated at an early stage [20-26].

Consent

Written informed consent was obtained from next of kin for publication of this case report and accompanying images. A copy of the parental written consent is available for reviewing by the editors of this journal.

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