

Case Report

Cutaneous cryptococcosis in a diabetic renal transplant recipient

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PO Box 24923, Safat, Kuwait 13110Received 25 June 2003
Accepted 5 January 2004

A diabetic renal transplant recipient with cellulitis caused by *Cryptococcus neoformans*, serotype A, is described. The diagnosis was based on the demonstration of capsulated, budding yeast cells in the aspirated material and tissue from the cellulitic lesion and isolation of the aetiological agent in culture. The isolate formed well-developed capsules in the brain tissue of experimentally infected mice and produced cherry-brown colonies on niger seed medium. The patient's serum was positive for cryptococcal antigen (titre 1 : 4) with no other evidence of systemic infection. He was successfully treated with AmBisome, followed by fluconazole, resulting in the complete resolution of cellulitis and disappearance of the cryptococcal antigen. This report underscores the fact that patients with cutaneous cryptococcosis should be thoroughly evaluated, as it may be the first manifestation of a systemic disease. Prompt diagnosis and treatment are important to improve survival.

Introduction

Cryptococcus neoformans is an encapsulated, basidiomycetous yeast that is present in the environment worldwide. It has been isolated from a large variety of natural substrates, especially soil contaminated with pigeon droppings (Khan *et al.*, 1978; Li *et al.*, 1993; Lopez-Martinez & Castanon-Olivares, 1995), decaying wood in tree trunk hollows (Lazera *et al.*, 2000; Randhawa *et al.*, 2003) and fruit and vegetables (Pal & Mehrotra, 1985; Lopez-Martinez & Castanon-Olivares, 1995). The main portal of entry is the respiratory tract, and lungs are the primary site of infection. In most instances, the infection is subclinical and self-limiting. However, the infection may be reactivated during immunosuppression of the host, particularly under the conditions of depressed T-cell-mediated immunity. The most important predisposing condition is AIDS (Pema *et al.*, 1994; Mitchell & Perfect, 1995), but the disease can also occur in individuals receiving immunosuppressive therapy, such as patients with cancer, sarcoidosis, Hodgkin's lymphoma or those who have undergone organ transplantation (Mitchell & Perfect, 1995). Following haematogenous dissemination from the lungs, the central nervous system (CNS) and skin are the preferred sites of infection in about 6–15% of patients (Powderly, 1993; Christianson *et al.*, 2003). Primary cutaneous crypto-

coccosis (PCC) has also been reported in immunocompetent as well as immunocompromised individuals (Reventa *et al.*, 2002; Neuville *et al.*, 2003; Christianson *et al.*, 2003).

Cryptococcosis from the Middle East has been sporadically reported (Abdel-Fattah *et al.*, 1975; Al-Rasheed & Al-Fawaz, 1990; Sa'adah *et al.*, 1995; Nampoory *et al.*, 1996; Khan *et al.*, 2003; Abdel-Salem, 2003). Of the three cases of cryptococcosis in renal transplant recipients from Kuwait reported previously, one had cutaneous lesions with CNS involvement, but chest X-rays were normal (Nampoory *et al.*, 1996). In this communication, we describe a case of cutaneous cryptococcosis in a renal transplant recipient manifesting as cellulitis, which was the only sign of the disease when diagnosis was made.

Case report

A 60-year-old Kuwaiti male underwent live-unrelated renal transplant in April 1988. Earlier, he had adult dominant polycystic kidney disease (ADPKD), which required pre-transplant bilateral nephrectomy. His post-transplant course was uncomplicated. He was maintained on triple immunosuppression comprising prednisolone, azathioprine and cyclosporine A with normal graft function. His serum creatinine levels were maintained between 110 and 120 $\mu\text{mol l}^{-1}$. In 1992, he developed mild hypertension and diabetes mellitus that was adequately controlled by a calcium channel blocker and sulphonylurea derivatives. In May 2000, he developed a chest infection with bilateral pulmonary infiltrates caused by *Haemophilus influenzae* that was re-

Abbreviations: BAL, bronchoalveolar lavage; PCC, primary cutaneous cryptococcosis.

solved completely by macrolides. Two years later, in February 2002, he presented with fever and features of cellulitis involving the calf region of the left leg (Fig. 1a). The examination revealed a tender, indurated, erythematous lesion, about 20 cm in diameter, with bullae formation. Clinically, he did not look toxic, and there was no evidence of lymphadenopathy or abdominal organomegaly. His lungs were clear and he showed no neurological deficit including meningeal signs. His total white blood cell count ranged between 6 and $8 \times 10^9 \text{ l}^{-1}$, platelet count was $160 \times 10^9 \text{ l}^{-1}$ and haemoglobin was 10.6 g dl^{-1} . Blood coagulation profile, liver and renal function tests were within normal limits.

The summary of laboratory investigations is presented in Table 1. Since urine and blood cultures did not reveal any pathogen, he was empirically treated with parenteral third-generation cephalosporin, cloxacillin and clindamycin on the assumption that his cellulitis was probably of bacterial origin. However, no clinical improvement was observed with this therapeutic regimen. Subsequently, the infected area was debrided and the swab, tissue and aspirate were sent for microbiological examination. Direct microscopic examination of the aspirated material, swab smears and tissue showed poorly capsulated budding yeast cells and yielded *C. neoformans* in culture. The identity of the isolate was confirmed with the Vitek 2 yeast identification system, by the ability to produce brown colonies on niger seed agar at 28°C , and by a mouse pathogenicity test which showed the formation of large capsulated yeast cells when examined 5 days post-intracerebral inoculation. His serum was positive for cryp-

tococcal antigen (titre 1:4) by latex agglutination kit (Pastorex Crypto Plus; Bio-Rad). He was immediately given liposomal amphotericin B (AmBisome) at a dose of $3 \text{ mg kg}^{-1} \text{ day}^{-1}$. The isolate was susceptible to amphotericin B ($0.016 \mu\text{g ml}^{-1}$) and fluconazole ($2.0 \mu\text{g ml}^{-1}$) but resistant to flucytosine ($> 16 \mu\text{g ml}^{-1}$) by E-test on RPMI agar (NCCLS, 1997). A week later, he developed bilateral chest infiltrates with drowsiness. A CT scan of his brain and cerebrospinal fluid (CSF) were normal. India ink examination of CSF was negative for *C. neoformans* and the pathogen did not grow in culture. The latex agglutination test for cryptococcal polysaccharides in CSF was also negative. However, his bronchoalveolar lavage (BAL) grew *Pseudomonas aeruginosa*. He was treated with meropenem, which resulted in complete resolution of the chest infiltrates. Since the patient responded to AmBisome, he continued to receive the drug for 21 days (total dose 4.8 g), followed by oral fluconazole (Diflucan) 200 mg daily for 4 months and then 100 mg daily for another 4 months. The patient's cellulitic lesion gradually resolved completely (Fig. 1b). When examined for the last time on 18 June 2003, he was afebrile and his renal and liver function parameters were within the normal range. He is being maintained on minimal triple immunosuppression regimen.

Discussion

Cutaneous cryptococcosis in most immunocompromised patients is a sign of disseminated disease (Thomas & Schwartz, 2001). However, critical analysis of the literature



Fig. 1. (a). Cryptococcal cellulitis on the left leg of the patient before initiation of antifungal therapy. (b) Complete resolution of the lesion after 10 weeks of therapy.

Table 1. Laboratory findings of cutaneous cryptococcosis case

Specimen	Examination dates	Results
Swab, tissue and aspirated fluid from skin lesion	11–13 March 2002	Capsulated, budding yeast cells in direct microscopy, culture yielded <i>C. neoformans</i> var. <i>grubii</i> (serotype A)*
Serum	12 March 2002, 23 March 2002	Cryptococcal polysaccharide detected (1 : 4)
Serum	14 January 2003, 18 June 2003	Cryptococcal antigen negative
CSF	21, 31 March 2002	Direct microscopy by India ink, culture and antigen negative for <i>Cryptococcus</i>
BAL	12 March 2002, 27 March 2002	<i>P. aeruginosa</i> , coagulase-negative staphylococci and <i>Candida albicans</i>
Blood	7, 8, 21 March 2002	No growth
Urine (collected after prostatic massage)	17, 25 March 2002	No growth

*Determined by Crypto Check, Iatron Laboratories Inc., Japan.

in two recent reviews (Neuville *et al.*, 2003; Christianson *et al.*, 2003) suggests that cutaneous cryptococcosis can also occur as a primary disease both in immunocompetent and immunocompromised individuals, where skin serves as the primary portal of entry. This observation is noteworthy since the existence of PCC as a distinct clinical entity has been controversial, despite some well-documented case reports (Goonetilleke *et al.*, 1995; Hamann *et al.*, 1997; Handa *et al.*, 1998). *C. neoformans* has been shown to cause almost every type of cutaneous lesion. The lesions may occur as ulcers (Birkett & McMurray, 1976), pustules (Crouse & Lerner, 1958), granulomata (Crouse & Lerner, 1958; Rook & Woods, 1962), abscesses (Rook & Woods, 1962) and herpetiform or molluscum contagiosum-like lesions (Borton & Wintroub, 1984; Concus *et al.*, 1988; Pema *et al.*, 1994). Although a rarity, several cases of cellulitis have also been reported (Anderson *et al.*, 1992; Gloster *et al.*, 1994; Horrevorts *et al.*, 1994), which appear to be mainly restricted to lower parts of the body, especially the legs (Horrevorts *et al.*, 1994), as was seen in the present case. Based on the analysis of 28 cases of PCC, Neuville *et al.* (2003) proposed criteria for diagnosing this entity. According to these criteria, cutaneous lesions in secondary/disseminated disease are usually multiple and scattered, located both in clothed and exposed areas, whereas skin lesions characterizing PCC are solitary or confined to a limited area and located on unclothed areas. On the other hand, Christianson *et al.* (2003) reviewed 73 cases of PCC and drew a distinction in location of lesions between non-immunocompromised and immunocompromised individuals. Involvement of finger and facial sites was more commonly seen in non-immunocompromised hosts, whereas multiple sites of infection or infection localized to extremities of the lower body or to the trunk were seen more frequently in the immunocompromised patients.

Despite the asymptomatic nature of pulmonary cryptococcosis in most cases, symptoms are non-specific when

manifested, and hence are not helpful in clinical diagnosis. Fever, dyspnoea, cough, chest pain or haemoptysis may be observed in about 18–54% of patients (Campbell, 1996; Diamond, 1990). Since the organism has a preference to invade the CNS, meningitis or meningoencephalitis is often the first clinical evidence of infection. In severely immunocompromised patients, such as those with AIDS, meningeal signs may be subdued and inflammatory response in the CSF reduced, which may result in diagnostic delays. However, our patient had no pulmonary or meningeal signs or symptoms at the time of diagnosis of cutaneous cryptococcosis and culture of BAL and CSF were negative on repeated occasions (Table 1). Other preferred sites of *C. neoformans* infection include the urinary tract (prostate), bone and the skin. Some 20–30% of transplant recipients may develop skin lesions weeks to months prior to development of CNS manifestations (Rubin, 1988). Our patient appears to fall into this category, since he had no CNS manifestations or positive CSF findings at the time of diagnosis, although he had a low cryptococcal antigen titre (1 : 4) in serum, which may be attributed either to an early stage of the disease or to the weakly capsulated nature of the strain, or both.

The dermatotropic characteristic of *C. neoformans* may vary depending upon the strain or serotype involved (Mitchell & Perfect, 1995; Dromer *et al.*, 1996). Although our patient was infected with serotype A, it has been reported that serotype D has a greater propensity to cause skin lesions (Naka *et al.*, 1995; Dromer *et al.*, 1996). Besides dermatotropism, differences in temperature tolerance and geographical distribution between serotypes could be other factors (Chen *et al.*, 2000; Martinez *et al.*, 2001). In renal transplant recipients, infection due to *C. neoformans* occurs almost exclusively in the late post-transplant phase, from 4 months after transplantation and onwards. The incidence of the infection appears to vary between 0.8 and 5.8% depending upon the type and intensity of immunosuppression used (Gallis *et al.*, 1975; Nampoory *et al.*, 1996; Husain *et al.*, 2001). Our patient was

on triple immunosuppression including prednisolone, and also had diabetes mellitus. Usage of corticosteroids has been found to be the most common risk factor in an analysis of 37 patients with PCC (Christianson *et al.*, 2003). Recently, increased risk of dermatological presentation and decreased risk of CNS infection has been noted with the use of tacrolimus in solid organ transplant recipients (Husain *et al.*, 2001). Cyclosporine A and tacrolimus have been shown to suppress the growth of *C. neoformans* *in vitro* by inhibiting the calcineurin pathway at 37 °C but not at 24 °C (Cruz *et al.*, 2000). However, cyclosporine A fails to cross the blood–brain barrier effectively, while tacrolimus achieves a good CNS concentration. Thus, temperature-dependent inhibition of cryptococci by tacrolimus may prevent CNS infection, but allow the growth of the fungus at cooler body sites, such as the skin.

Regardless of the primary or secondary nature of cutaneous cryptococcosis, the most sensitive and specific approach for its diagnosis is microscopic examination and culture of a skin biopsy specimen or material aspirated from the skin lesion. Direct microscopic examination of the material in potassium hydroxide or India ink can reveal encapsulated yeast cells. Additional diagnostic evidence should be obtained to rule out systemic dissemination. This may include culture of sputum, BAL, CSF and urine (preferably after prostatic massage), as well as serological evidence for cryptococcal polysaccharide in serum and/or CSF specimens. Culture for *C. neoformans* should be positive in 3–7 days, colonies appearing as white to cream coloured with a mucoid consistency, but growth is inhibited by the presence of cycloheximide in the medium (Diamond, 1990). Being a basidiomycetous yeast, it is urease-positive. In addition, this yeast produces phenoloxidase, an enzyme that is associated with melanin synthesis, which turns the colour of the colonies brown on a medium containing a specific Dopa-like substrate, such as the one provided by niger seed medium. Capsular polysaccharide, urease and phenoloxidase are known virulence factors of *C. neoformans* and thus play an important role in the pathogenesis of the disease (Casadevall & Perfect, 1998).

Considering the asymptomatic nature of pulmonary cryptococcosis in the majority of cases, and the demonstration of a low antigen titre (1 : 4) in our patient, it may be inferred that he was probably in the early phase of a disseminated disease where the cutaneous lesion appeared as the first clinical manifestation. This observation is consistent with the prevailing view that all cases of cutaneous cryptococcosis in immunocompromised patients should be assumed to be due to disseminated infection until proved otherwise (Casadevall & Perfect, 1998). Such patients need aggressive antifungal chemotherapy. Our patient was given AmBisome for 3 weeks, followed by fluconazole. He responded to this therapy adequately, resulting in resolution of cellulitis and clearance of the cryptococcal antigen from the serum. Since the isolate was resistant to flucytosine and the patient had no meningeal involvement, this drug was not included in the treatment

regimen. Primary resistance to flucytosine in clinical isolates of *C. neoformans* has been reported previously (Cuenca-Estrella *et al.*, 2001; Kantarcioglu & Yucel, 2002).

Acknowledgements

The authors thank Rachel Chandy for excellent technical assistance.

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