Primary cutaneous cryptococcosis in a renal transplant recipient: case report

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Summary

We report a kidney transplant recipient with severe skin- and soft-tissue infection mimicking necrotising fasciitis. Patient failed to respond to empirical antibiotic therapy for presumed bacterial cellulitis. Culture of aspirate from the wound and tissue samples revealed *Cryptococcus neoformans*. No signs of systemic cryptococcal infection were found. After antifungal treatment and surgical intervention, complete healing was achieved. Clinical and microbiological characteristics of this patient are discussed. Our case indicates that primary cutaneous cryptococcosis must be included in the differential diagnosis of severe cellulitis in solid organ transplant recipients not responding to broad-spectrum antibiotic regimens. In our case, prompt diagnosis and treatment could dramatically modify the outcome.

Introduction

Cryptococcus neoformans is encapsulated yeast that has become a common opportunistic human pathogen especially in immunocompromised hosts. It is present worldwide as a saprobe in nature and was recovered from fruits, hay, rotting wood and soil contaminated with bird droppings (Ellis DH *et al*., *Lancet* 1990; **336**: 923–5; Levitz SM, *Rev Infect Dis* 1991; **13**: 1163–9; Ruiz A *et al*., *Infect Immunol* 1981; **31**: 560–3; Kumlin U *et al*., *Lancet* 1998; **351**: 1181). The vast majority of patients with cryptococcosis have an underlying immunocompromised condition, the most common being AIDS, prolonged treatment with corticosteroids or organ transplantation. Most infections are acquired primarily by inhalation and may disseminate via haematogenous route to almost any tissue in the body. A 10–15% of patients with disseminated cryptococcosis present with secondary skin lesions that show themselves in variety of shapes: as papules, nodules, pustules, ecchymoses, granulomas, abscesses (Anderson JA *et al*., *Clin Infect Dis* 1992; **14**: 666–72; Lopez FA, *Infect Dis North Am* 2001; **15**: 671–702; Yu RY, *Mycoses* 1996; **39**: 207–10). Most often cryptococcal skin disease is a marker of disseminated disease, but more recently it was proposed that primary cutaneous cryptococcosis (PCC) is a distinct clinical entity. The infection to the skin appears to be with direct inoculum of *Cryptococcus* to the skin, which is the only organ or tissue affected (Neuville S *et al*., *Clin Infect Dis* 2003; **36**: 337–47). *C.neoformans* rarely causes cellulitis (Jennings HS 3rd *et al*., *South Med J* 1981; **74(9)**: 1150–3; Pasqualotto AC *et al*., *Nephrol Dial Transplant* 2005; **20**: 2007–8; Singh N *et al*., *Clin Transplant* 1994; 8: 365–8). We report a kidney transplant recipient with PCC of an upper limb.

Case report

A 60-year-old male had undergone cadaveric kidney transplant for idiopathic chronic glomerulonephritis 3 years before. His immunosuppressive regimen consisted of prednisone (6 mg daily) and cyclosporine A (125 mg daily). Eight days before presentation to our clinic, he suffered a minor scratch-wound to the palm of his right hand by a domestic cat. Three days later, he presented to his general practitioner with local signs of inflammation at the site of the scratch-wound. Antibiotic regimen with amoxicillin and clavulanic acid was started but the inflammation rapidly proceeded proximally. Over the ensuing 4 days, inflammation worsened, two surgical procedures were performed:

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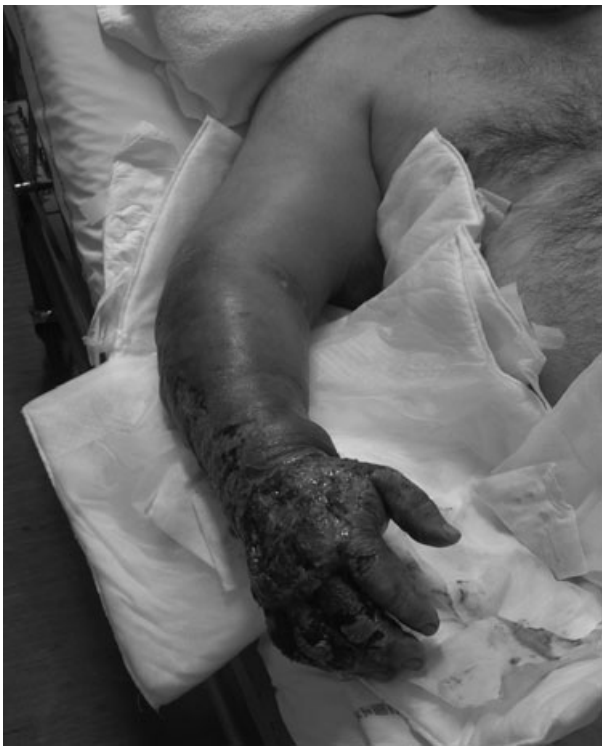

Figure 1 Right upper limb of the patient demonstrating tissue necrosis of the hand and cellulitis with haemorrhagic blisters on the forearm.

first, only a small incision on the palm, later a surgical debridement. Wound swabs taken at operation revealed growth of encapsulated yeasts, but no bacteria. Patient was switched to clindamycin, ciprofloxacin and fluconazole in the dosage of 200 mg daily p.o. Despite antimicrobial treatment, the patient's condition deteriorated, he showed signs of systemic infection, and was transferred to our hospital. At the time of transfer he was febrile, fully oriented. Clinical examination revealed severe swelling of the right upper limb, with blisters containing haemorrhagic fluid, palm and fingers revealed severe soft tissue necrosis (Fig. 1). Regional lymphadenopathy at the right axilla was present, but there was no involvement of other skin sites. Laboratory findings were significant: elevated C-reactive protein levels (288 mg l^{-1}), procalcitonin, white blood cell count revealed shift to the left (leucocyte 7800 ml^{-1}, with 17% rods). Ultrasound of the soft tissue of the right arm showed signs of cellulitis with diffuse oedema and fluid collections, but no obvious signs of necrotising fasciitis. Patient was immediately started with a broad-spectrum antibiotic regimen with imipenem, and antifungal therapy with liposomal amphotericin B

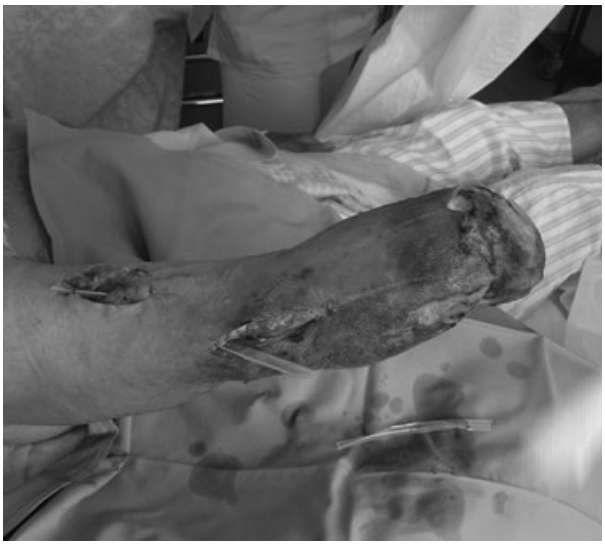

Figure 2 Presentation after surgical intervention and after 2 days of antifungal therapy.

(3.5 mg kg^{-1} daily). He was presented to a surgeon. At operation, tissue revealed signs of soft-tissue and muscle necrosis, so amputation of the arm above the wrist had to be performed. After surgical intervention and antimicrobial treatment, the patient showed fast recovery (Fig. 2). Blood cultures remained negative, serum cryptococcal antigen was positive. Histopathological examination of the tissue sample taken at the operation revealed numerous encapsulated yeast-like organisms, later identified as *C. neoformans*. All wound swabs taken pre- and intraoperatively revealed *C. neoformans* but showed no signs of bacterial growth. Patient did not develop signs of any other organ involvement during our treatment. Chest X-rays were normal. Lumbar puncture was not performed, because the patient showed no signs of central nervous system (CNS) involvement. He was treated with liposomal amphotericin B for 3 weeks intravenously, and was then switched to fluconazole orally for another 15 weeks. Immunosuppressive regimen was continued and function of the renal graft remained almost normal throughout the treatment. Cryptococcal antigen in blood was negative 17 days after the initiation of antifungal therapy. After 9 months, he remains without any signs or symptoms of skin or systemic infection and the wound has almost been completely healed.

Discussion

Most infections with *C. neoformans* are acquired primarily by inhalation and disseminate via haematogenous

route to the skin. In the past few years, it became obvious that primary infection of the skin is possible with direct inoculation of the pathogen through a (minor) skin wound. PCC proved to be a distinct clinical entity (Neuville S *et al.*, *Clin Infect Dis* 2003; **36**: 337–47; Hafner C *et al.*, *Infection* 2005; **33**: 86–9). In severely immunocompromised patients, skin infection can evolve and progress rapidly with the extent of infection that mimics bacterial cellulitis (Anderson JA *et al.*, *Clin Infect Dis* 1992; **14**: 666–72; Singh N *et al.*, *Clin Transplant* 1994; **8**: 365–8; Mayers DL *et al.*, *South Med J* 1981; **74**: 1032; Horrevorts AM *et al.*, *Scand J Infect Dis* 1994; **26**: 623–6). In our case, the patient suffered a cat-scratch on the palm of his hand few days before the inflammation started. It was an outdoor cat and it is the most possible source of infection. Environmental studies to isolate *C. neoformans* from the cat were not performed. Patient did not perform any other activity that would have enabled him to come into contact with possible source of infection (i.e. gardening in contaminated soil).

No other sites of skin or other tissue involvement were found during the hospitalisation and during the 9-month follow-up. Contrary to the proposed criteria for PCC from *Neuville* et al., our patient presented with systemic signs of infection and positive antigen to *C. neoformans* in serum was detected. Systemic signs of infection and antigenaemia were probably caused by large area affected and the extent of the inflammation and not because of systemic fungal infection. Hafner *et al.* (Hafner C *et al.*, *Infection* 2005; **33**: 86–9) already proposed that antigenaemia should not be an excluding criteria for PCC. Seventeen days after the institution of antifungal therapy, serum antigen for *C. neoformans* was negative and remained so through the follow-up period.

Cryptococcosis occurs in 2.8% patients undergoing solid organ transplant, the highest rate is among kidney and liver transplant recipients (Husain A *et al.*, *Emerg Infect Dis* 2001; **7**: 375–381; Singh N *et al*, *Clin Infect Dis* 1997; **24(2)**: 179–84). Cellulitis is quite rare among skin presentations of cryptococcosis, but appears to be more common in patients with organ transplantation. In one study discussing patients with solid organ transplant, 72% of cryptococcal skin lesions were cellulitis (Husain A *et al.*, *Emerg Infect Dis* 2001; **7**: 375–381). A strong cellular immune response is essential for limiting cryptococcal infection. Our patient was seriously immunosuppressed because of the immunosuppressive regimen with corticosteroids and cyclosporine. This is obviously the reason for rapid progression of inflammation into deeper structures.

The choice of treatment for cryptococcal disease depends on anatomic site of infection and the host's immune status. According to the Practice guidelines for the management of Cryptococcal disease (Saag MS *et al.*, *Clin Infect Dis* 2000; **30**: 710–18) cutaneous disease in immunocompetent hosts should be treated with oral azole therapy, with more severe disease initial treatment with amphotericin B is advised. Immunocompromised patients should be treated in the same fashion as patients with CNS disease (Dromer F *et al.*, *Clin Infect Dis* 1996; **22**: S154–60; Yamaguchi H *et al.*, *Eur J Clin Microbiol Infect Dis* 1996; **15**: 787–92). Among patients with solid organ transplants, aggressive early treatment of cryptococcal disease may prevent loss of the transplanted organ. Most patients with PCC responded favourably to short-term monotherapy, the role of surgery remains questionable (Neuville S *et al.*, *Clin Infect Dis* 2003; **36**: 337–47). Different authors describe successful results with amphotericin B alone or in combination with 5-fluorocytosine, fluconazole, itraconazole (Anderson JA *et al.*, *Clin Infect Dis* 1992; **14**: 666–72; Jennings HS 3rd *et al.*, *South Med J* 1981; **74(9)**: 1150–3; Singh N *et al.*, *Clin Transplant* 1994: **8**: 365–8; Hafner C *et al.*, *Infection* 2005; **33**: 86–9; Horrevorts AM *et al.*, *Scand J Infect Dis* 1994; **26**: 623–6; Sato T *et al.*, *Mycoses* 1990; **33**: 455–63; Armstrong D, *Clin Infect Dis* 1993; **16**: 1–7). There are no clear guidelines on maintenance of immunosuppressive regimen, although it is advised to eliminate it or at least decrease it (prednisone to maximum 10 mg daily) (Kumlin U *et al.*, *Lancet* 1998; **351**: 1181). Patients should be evaluated at frequent intervals for at least 1 year, relapse after 1 year is rare (Anderson JA *et al.*, *Clin Infect Dis* 1992; **14**: 666–72).

Our case illustrates that it is important to consider primary cryptococcal cellulitis in immunocompromised hosts presenting with skin- and soft-tissue infection that does not respond to broad-spectrum antibiotic regimens.