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CASE BASED REVIEW

Fatal primary cutaneous cryptococcosis: case report and review of published literature

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Abstract
Objective Cryptococcus is an opportunistic yeast with a worldwide distribution that primarily causes significant infections in immunocompromised individuals, generally by affecting the respiratory tract. But primary cutaneous cryptococcosis (PCC) without systemic infection is rare. We report a case of PCC in a patient with nephrotic syndrome.
Methods The 23-year-old man developed severe necrotising cellulitis on both the anterior and posterior of his trunk following a massage. He had been treated with systemic corticosteroids over 20 months for nephrotic syndrome. A skin biopsy of the wound area revealed cutaneous vasculitis and chronic inflammation with yeast-like organisms. Periodic acid-Schiff (PAS) staining indicated that the structures were consistent with Cryptococcus. A *Cryptococcus neoformans* infection was confirmed by culture. Azole therapy was begun, and the skin ulcers gradually stopped disseminating. However, the patient died following continuous capillary haemorrhage on the 22 day since admission.
Conclusion Cryptococcus is crucial to be considered in the differential diagnosis of subcutaneous necrosis in any patient on immunosuppressive therapy.

Keywords Cryptococcus · Primary cutaneous cryptococcosis

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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 report

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/day) 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)/μl, 236 (452.62 $\pm$ 210.83)/μl, 159 (125.22 $\pm$ 51.55)/μl 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 tissue on Sabouraud 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 resistent 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 (Fig. 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/day for 4 days) intravenously and then changed to itraconazole (500 mg/day for 5 days) intravenously according to the result of antifungal sensitivity test. Surgical debridement was performed every day (Fig. 2). There was no evidence of disseminated intravascular coagulation. However, on the 22 day since admission, the patient died following continuous capillary haemorrhage.

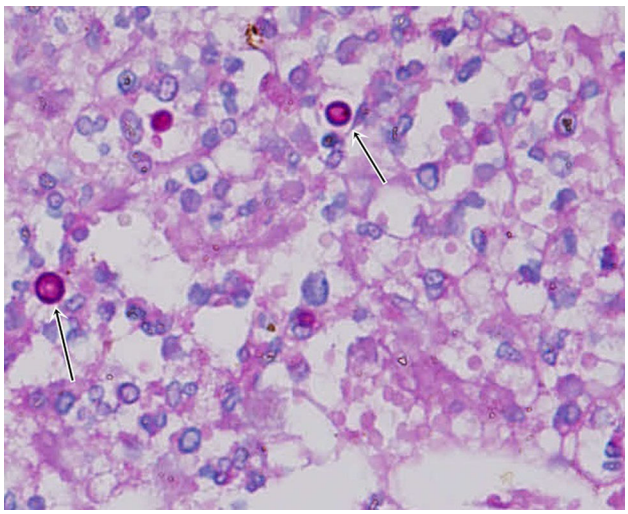

Fig. 1 Light microscopy findings of a skin biopsy specimen from the abdomen. The biopsy specimen revealed an inflammatory infiltration that contained PAS-positive microorganisms (*arrows*). Magnification ×400, PAS stain

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 visualised with India Ink, methylene blue and mucicarmine staining. Four serotypes of *C. neoformans* have been identified: serotype A, D and serotype B and C. Serotype A (*C. neoformans* var.*grubii*) distributes 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* predominates in non-HIV patients in China [4].

Primary cutaneous cryptococcosis 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

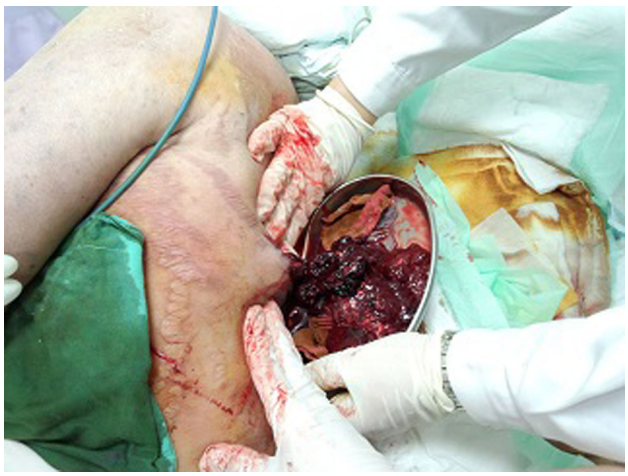

Fig. 2 Swelling skin with a very large ulceration, necrotising fasciitis, blood clots and liquefied fat, Hospital Day 10

Table 1 Review of cases with PCC

References	No.	Age/sex	Immunosuppression	Site	Symptoms	Treatment	Duration	Outcome
[5]	1	8/F	No	Forearm	Solitary lesion	Fluc 3 mg/kg	2 weeks	Cure
[6]	2	72/M	No	Forearm	NA	Itra 200 mg/day	4 months	Cure
	3	79/M	No	Arm+forearm	NA	Fluc 300 mg/day	2 months	Cure
	4	70/M	No	Forearm	NA	Itra 100 mg/day	3 months	Cure
	5	75/M	No	Forearm	NA	Fluc 400 mg/day + Anf.B	3 months	Cure
	6	68/M	Corticosteroid 20 mg/day-months	Forearm	NA	Fluc 300 mg/day	6 months	Cure
	7	58/M	Corticosteroid 20 mg/day-years	Forearm	NA	Fluc 300 mg/day	30 days	Cure
	8	89/M	Corticosteroid 20 mg/day-years	Hand+forearm	NA	Itra 100 mg/day	3 months	Cure
	9	84/M	Corticosteriod 10 mg/day-months	Forearm	NA	Fluc 150 mg/day	1 month	Cure
	10	80/M	Corticosteroid 10 mg/day-years	Hand+forearm+arm	NA	Itra 200 mg/day	6 months	Cure
	11	39/M	Corticosteroid 40 mg/day-months	Forearm	NA	Fluc 400 mg/day	2 months	Cure
	12	39/M	Corticosteroid 40 mg/day-months	Forearm	NA	Fluc 400 mg/day	2 months	Cure
[7]	13	55/M	Steroids + rapamycin + mycophenolate mofetil	Thigh	Necrotic umbilicated lesions with raised edges	Anf. B + Fluc	NA	Die
[8]	14	89/M	No	Forearm	Ulcerated lesion	Itra 400 mg/day	3 months	Cure
[9]	15	58/M	No	Hand	Granulomatous lesion with regional ulceration	Fluc 200 mg/day	2 weeks	Cure
	16	67/F	No	Finger	Painful lesion	Fluc 200 mg/day	2 weeks	Cure
						Fluc 100 mg/day	2 weeks	Cure
[10]	17	67/M	No	Forearm	Nodular, erythematous, ulcers with exudation	Fluc 450 mg/day	40 days	Cure
[11]	18	37/M	No	Scalp	Nodule	Excision	NA	Cure
[12]	19	31/M	A liver transplant recipient	Elbow	Solitary ulcer	Fluc 6 mg/kg/day+ surgical debridement	4 months	Cure
[13]	20	89/M	No	Forearm	Ulceration with irregular erythematous purple borders	Itra 400 mg/day	3 months	Cure
[14]	21	75/M	No	Forearm	Nodules and ulcerations	High Fluc doses	5 months	Cure
[15]	22	60/M	A kidney transplant recipient	Palm	Cellulitis with diffuse edema and fluid collection	Anf. B 3.5 mg/kg/day and amputation	18 weeks	Cure
[16]	23	58/M	No	Hand	Red-purple nodule	Itra 200 mg/day	4 months	Cure
[17]	24	43/M	AIDS	Upper and lower extremities	Multiple irregular, painful and hemorrhagic ulcers	Itra 400 mg/day	1 month	Cure
[18]	25	66/F	Corticosteroid 5 mg/day	Wrist	Tumour increasing in size	Itra 400 mg/day + Itra 200 mg/day	2 weeks	Tumour
							10 weeks	Decreased
[19]	26	74/M	Corticosteroid 15 mg/day	Leg	Ulcers with peripheral erythema	Anf.B 300 mg/day + Fluc 400 mg/day	NA	Improved

Table 1 continued

References	No.	Age/sex	Immunosuppression	Site	Symptoms	Treatment	Duration	Outcome
[20]	27	71/M	No	Thumb	Erythematous and oedematous skin lesion	Fluc 400 mg/day + Fluc 200 mg/day	1 month 2 months	Cure
[21]	28	76/M	Corticosteroid 12 mg/day	Lower leg	Swelling, erythema, induration, tenderness and ulceration	Fluc+Anf.B	9 weeks	Cure
[22]	29	26/M	Corticosteroid 60 mg/day + Azathioprine 50 mg/day	Lower leg	Cutaneous nodules	Intravenous fluc	3 months	Cure
[23]	30	71/M	Corticosteroid	Forearm	Cellulitis	Fluc 400 mg/day + surgical debridement	5 months	Cure
[24]	31	35/M	No	Thigh	Painless, dull nodule	Fluc 400 mg/day Fluc 200 mg/day	4 days 2 months	Cure
[25]	32	81/M	No	Forearm	Plaque	Fluc 400 mg/day	8 weeks	Cure

M male, *F* female, *N/A* not accessible, *Anf.B* amphotericin B, *Fluc* fluconazole, *Itra* itraconazole

laboratory test results were usually normal for immunocompetent patients and most case were treated by azoles such as itraconazole and fluconazole and showed good outcome (Table 1). 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 *C. neoformans* is probably efficient, for the low frequency of PCC in the whole population [9]. 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 [26]. 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 [22]. 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 (Table 1). 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 [7]. Many other cases have been attributed to consumption of steroids or other immunosuppressant agents following solid organ transplantation [12, 15, 21–23]. The majority of these patients showed an excellent outcome upon treatment with azoles, and multiple successful regimens have also been described [6, 7, 21].

This is, to our best knowledge, the most severe case of fatal PCC due to *C. 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. 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.

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.

Compliance with ethical standards

Conflict of interest None.

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