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CASE REPORTS

Fungaemia due to *Cryptococcus laurentii* and a review of non-*neoformans* cryptococcaemia

Fungämie durch *Cryptococcus laurentii* und eine Übersicht über Nicht-*neoformans*-Cryptococcämien

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Schlüsselwörter. *Cryptococcus laurentii*, *Cryptococcus* non-*neoformans*, Fungämie.

Summary. *Cryptococcus laurentii* is one of several non-*neoformans* cryptococci that have rarely been associated with human infection. The spectrum of clinical infection due to non-*neoformans* species ranges from skin lesions to fungaemia. Most cases of non-*neoformans* fungaemia have been nosocomially acquired and have been associated with indwelling intravascular catheters and neutropenia. Limited data on *in vitro* susceptibilities of non-*neoformans* cryptococci show these species to be more resistant to fluconazole and flucytosine than most *Cr. neoformans*. Two such cases are presented here.

Zusammenfassung. *Cryptococcus laurentii* ist eine von mehreren nicht-*neoformans*-*Cryptococcus*-Arten, die selten mit Krankheiten am Menschen in Zusammenhang gebracht werden. Das Spektrum durch Nicht-*neoformans*-Arten bedingter klinischer Infektionen reicht von Hautläsionen bis zur Fungämie. Die Mehrzahl der Fälle von nicht-*neoformans*-Fungämie waren nosokomial bedingt und mit intravasalen Dauerkathetern und Neutropenie assoziiert. Die wenigen Daten über In-vitro-Suszeptibilität von Non-*neoformans*-Arten für Fluconazol und Flucytosin sprechen dafür, daß diese Arten resistenter als die meisten *Cr. neoformans*-Stämme sind. Zwei solcher Fälle werden vorgestellt.

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Introduction

Cryptococcus laurentii rarely causes infection in humans [1–6]. Previous reports have noted the usually avirulent nature of this organism, and fungaemia has been documented in only one previous case [6]. We describe the course of two patients who had fungaemia due to *Cr. laurentii* and report on the *in vitro* susceptibility of these two isolates to standard antifungal agents.

Case reports

Case 1

A 27-day-old boy was born 3 weeks premature with hypoplastic lungs and bilateral hydronephrosis secondary to posterior urethral valves. He required mechanical ventilation and a urinary catheter. Two weeks after birth, urine cultures revealed candiduria, and a renal ultrasound revealed fungus balls in both calyces. The patient was treated with intravenous amphotericin B at a dosage of 0.5 mg kg^{-1} day^{-1}. A Broviac central venous catheter was placed, and the posterior urethral valves were ablated. As the urine continued to grow *C. albicans*, 5-flucytosine (5-FC) was added at a dosage of 150 mg kg^{-1} day^{-1}.

The patient developed hypotension and tachycardia. Vancomycin and tobramycin were given,

and the amphotericin B dosage was increased to 1 mg kg^{-1} day^{-1}. Three days later, a yeast identified as *Cr. laurentii* grew from a blood sample taken from the Broviac catheter. The patient's Broviac catheter was pulled, and culture of the tip yielded no growth. The patient improved after several days and received amphotericin B and flucytosine for a total of 2 weeks after the positive culture had been obtained. The patient was slowly weaned off ventilatory support, his renal function improved, and he was discharged home.

Case 2

A 27-year-old woman was admitted with a 3-day history of fevers, chills and painful cutaneous nodules. Her past medical history was significant for intravenous drug use, pelvic inflammatory disease, bacterial endocarditis and bipolar disorder. Her admission medications included methadone, methylphenidate and valproic acid. Physical examination revealed three large erythematous, warm, non-ulcerated skin nodules located on the right and left ankles and the left side of the abdomen.

Laboratory studies revealed a white blood cell count of 8400 mm^{-3}, haemoglobin 11.6 g dl^{-1} and platelets 139000 mm^{-3}. Cultures of blood yielded no organisms, and the patient was treated with vancomycin. The abdominal lesion was subsequently incised and drained, but cultures were not obtained.

The patient continued to be febrile, the white blood cell count rose to 24000 mm^{-3} and new lesions appeared on her lower extremities. A transoesophageal echocardiogram showed tricuspid valve thickening. On hospital day 7, blood was again taken for culture and on day 10 grew *Cr. laurentii*. A peripheral intravenous central catheter, placed on hospital day 4, was removed because it was suspected that the patient was injecting drugs through the device. The patient was treated with 400 mg of oral fluconazole daily, and vancomycin was discontinued. Defervescence occurred and the skin lesions resolved over the next 1–2 weeks. She was treated with a total of 4 weeks of fluconazole. On follow-up examination, after the discontinuation of fluconazole therapy, she had no recurrence of fever and felt well.

Methods

Macrodilution susceptibility testing with amphotericin B, fluconazole and itraconazole was performed using the National Committee for Clinical Laboratory Standards (NCCLS) protocol M27-T [7]. Flucytosine susceptibilities were performed following NCCLS guidelines with the exception that yeast nitrogen base (YNB) broth without MOPS buffering was used for the assay. Drug concentrations tested were: amphotericin B 0.009–5 μg ml^{-1}; flucytosine 0.009–5 μg ml^{-1}; fluconazole 0.125–64 μg ml^{-1}; and itraconazole 0.007–4 μg ml^{-1}.

After 72 h of incubation at 35 °C, visually determined end points were read by resuspending the fungal growth in each tube and comparing the turbidity with that of a 1:5 dilution of the growth control (80% growth suppression). The minimum inhibitory concentration (MIC) was defined as the lowest concentration with ≥80% inhibition of growth.

Results

The results of the susceptibility testing on our two isolates are noted in Table 1. Both isolates had low MICs for itraconazole and amphotericin B, but the MICs for fluconazole were relatively high. Interestingly, both isolates appeared to be resistant to 5-FC.

Discussion

There are 19 species of the genus *Cryptococcus*. Only one of these species, *Cr. neoformans*, is generally viewed as a pathogen. *Cr. neoformans* is a ubiquitous encapsulated yeast that causes meningitis, pneumonia and disseminated infection, mostly in immunosuppressed hosts [8–10].

Infections with non-*neoformans* cryptococci have been less commonly reported [11–17]. The first description of infection due to a non-*neoformans*

Table 1. Results of *Cryptococcus laurentii* antifungal susceptibility testing

	Amphotericin B	Itraconazole	Fluconazole	Flucytosine
Case 1	0.037	0.25	8	500
Case 2	0.075	0.5	16	>500

All minimum inhibitory concentration values expressed as μg ml^{-1}.

Cryptococcus species was pulmonary infection due to *C. luteolus* [11]. Several cases of meningitis [12, 13] and one case of pulmonary infection [14] with *Cr. albidus* have been reported previously. Localized infections with *Cr. laurentii* involving the lung, skin and peritoneal fluid have also been described (Table 2).

Four cases of fungaemia with non-*neoformans* cryptococci have been reported previously [6, 15–17] (Table 3). All four patients were immunosuppressed from various causes, including chemotherapy, corticosteroids and HIV infection. Regarding the two cases presented in this report, the premature neonate had both central venous and urinary catheters in place and was quite ill. The young woman had a long history of intravenous drug use, prior endocarditis and was felt to be injecting drugs through her central intravenous catheter. The presumption was that this non-sterile use of the catheter led to infection with *Cr. laurentii*. The underlying risk factors for non-*neoformans* fungaemia are similar to those noted by others for *Cr. neoformans* [9, 10], although corticosteroid use and HIV infection appear to be more common in patients with *Cr. neoformans* fungaemia [9, 10].

The natural habitat of *Cr. laurentii* and *Cr. albidus* is unknown. Potential sources for bloodstream infection include dissemination from a pulmonary source or transmission along intravenous catheters. Both species have been described as a cause of pulmonary infection [2, 14], and thus acquisition of the organism by inhalation is possible. In all three cases of *Cr. laurentii* cryptococcaemia, the patients had a central venous catheter present at the time of fungaemia. Four of the six cases were acquired during the course of a long hospitalization (6, 15, 16, case 1). Another patient developed cryptococcaemia 2 months after the placement of a semipermanent indwelling intravascular catheter [17]. In case 2, it is unclear whether the patient's initial illness represented cryptococcemia or whether she acquired nosocomial *Cr. laurentii* infection.

Four of five patients experienced fevers, and one patient (case 1) had hypotension. The presence of cutaneous lesions in case 2 may have represented cutaneous dissemination of *Cr. laurentii*. Alternatively, these lesions could have represented localized primary infection secondary to direct inoculation of *Cr. laurentii*. Cutaneous involvement is frequent among patients with *Cr. neoformans* fungaemia [18].

The diagnosis in all six cases was made by culture of blood. Three also had measurement of cryptococcal antigen in the serum; two showed negative results and one was positive at a titre of 1:40 [17]. Cerebrospinal fluid analysis in two patients revealed a negative cryptococcal antigen, negative India ink preparation and no fungal growth.

The therapeutic approaches to patients with non-*neoformans* fungaemia have varied. Three patients received fluconazole, two amphotericin B and 5-FC and one patient ketoconazole. Among the four patients who were successfully treated, the length of therapy ranged from 2 to 4 weeks. Two of the six patients died, including one who remained neutropenic [15] and another who had HIV infection [17]. The other patient who had neutropenia survived after the absolute neutrophil count increased to $>1000\,mm^{-3}$ [6]. Three patients in whom the central venous catheter was removed survived, whereas the patient with an

Table 2. Reported *Cryptococcus laurentii* non-bloodstream infections

Reference	Age, sex	Source	Predisposing condition	Therapy	Outcome
1	40 M	Cutaneous nodules	Mycobacterial skin infection	Amphotericin B, potassium iodide	Survived
2	55 F	Lung abscess	Corticosteroids	Amphotericin B	Survived
3	13 F	Peritoneal fluid	Chronic ambulatory peritoneal dialysis	Amphotericin B	Survived
4	54 F	Pneumonia	None known	Amphotericin B, flucytosine	Survived
5	37 M	Lung (mycetoma)	None known	Surgery	Survived

Table 3. Reported fungaemias due to non-*neoformans* cryptococci

Reference	Age, sex	Isolate	Predisposing condition	Therapy	Outcome
15	65 F	*Cr. albidus*	Neutropenia	Amphotericin B, flucytosine	Died
16	45 M	*Cr. albidus*	Corticosteroids	Ketoconazole	Survived
17	38 M	*Cr. albidus*	AIDS	Fluconazole	Died
6	17 M	*Cr. laurentii*	Neutropenia	Fluconazole	Survived
PR	27 day M	*Cr. laurentii*	Prematurity	Amphotericin B, flucytosine	Survived
PR	27 F	*Cr. laurentii*	Intravenous drug use	Fluconazole	Survived

indwelling intravascular catheter that could not be removed died [17]. Thus, it appears that the removal of indwelling intravascular catheters and correction of neutropenia may improve outcome.

Susceptibility testing was reported for only three isolates, including our two isolates. One *Cr. albidus* isolate was found to be sensitive *in vitro* to amphotericin B, fluconazole, itraconazole, miconazole and 5-FC [17]. Our isolates appeared less sensitive to fluconazole than most *Cr. neoformans* and were resistant to 5-FC. Clinical correlations between susceptibility testing results and treatment outcome are lacking, but these limited data suggest that non-*neoformans* cryptococci are susceptible *in vitro* to amphotericin B and several azoles, and either class of antifungal agents could be used for non-*neoformans* cryptococcaemia.

References

1 Kamalam, A., Yesudian, P. & Thambiah, A. S. (1977) Cutaneous infection by *Cryptococcus laurentii*. *Br. J. Dermatol.* **97**, 221–223.

2 Lynch, J. P., Schaberg, D. R., Kissner, D. G. & Kauffman, C. A. (1981) *Cryptococcus laurentii* lung abscess. *Am. Rev. Respir. Dis.* **123**, 135–138.

3 Sinnot, J. T., Rodnite, J., Emmanue, P. J. & Campos, A. (1989) *Cryptococcus laurentii* infection complicating peritoneal dialysis. *Pediatr. Infect. Dis. J.* **8**, 803–805.

4 Krajden, S., Summerbell, R. C., Kane, J., *et al.* (1991) Normally saprobic cryptococci isolated from *Cryptococcus neoformans* infections. *J. Clin. Microbiol.* **29**, 1883–1887.

5 Winn, R. E., Rinaldi, M. G., Galbraith, M. & Bower, J. H. (1985) Refractory pneumonia due to *Cryptococcus laurentii variety laurentii* in a non-immunocompromised host (abstract F37). Abstract at Annual Meeting American Society of Microbiology. American Society of Microbiology: Washington, DC, p. 370,

6 Kreméry, V. Jr, Kunova, A. & Mardiak, J. (1997) Nosocomial *Cryptococcus laurentii* fungemia in a bone marrow transplant patient after prophylaxis with ketoconazole successfully treated with oral fluconazole. *Infection* **25**, 130.

7 National Committee for Clinical Laboratory Standards (NCCLS) (1995) Reference method for broth dilution antifungal susceptibility testing for yeasts: document M27-T. Villanova, PA: NCCLS.

8 Diamond, R. D. & Bennet, J. E. (1974) Prognostic factors in cryptococcal meningitis. *Ann. Intern. Med.* **80**, 176–181.

9 Perfect, J. R., Durack, D. T. & Gallis, H. A. (1983) Cryptococcemia. *Medicine* **62**, 98–109.

10 Rozenbaum, R. & Goncalves, J. R. (1994) Clinical epidemiological study of 171 cases of cryptococcosis. *Clin. Infect. Dis.* **18**, 369–380.

11 Binder, L., Csillag, A. & Toth, G. (1956) Diffuse infiltration of the lungs due to *Cryptococcus luteolus*. *Lancet* **2**, 1043–1045.

12 Melo, J. C., Srinivasan, S., Scott, M. L., *et al.* (1980) *Cryptococcus albidus* meningitis. *J. Infect.* **2**, 79–82.

13 DaCunha, T. & Lusins, J. (1973) *Cryptococcus albidus* meningitis. *South. Med. J.* **66**, 1230–1231.

14 Krumholz, R. A. (1972) Pulmonary cryptococcosis: a case due to *Cryptococcus albidus*. *Am. Rev. Respir. Dis.* **105**, 421–424.

15 Gluck, M. D., Myers, J. P. & Pass, L. M. (1987) Cryptococcemia due to *Cryptococcus albidus*. *South. Med. J.* **80**, 511–513.

16 Lin, S. R., Peng, C. F., Yung, S. A., *et al.* (1989) Isolation of *Cryptococcus albidus* var. *albidus* in a patient with pemphigus foliaceus. *Kao-Hsiung I Hsueh Ko Hsueh Tsa Chih.* **5**, 126–128.

17 Loison, J., Bouchara, J. P., Guého, E., *et al.* (1996) First report of *Cryptococcus albidus* septicaemia in an HIV patient. *J. Infect.* **33**, 139–140.

18 Schupbach, C. W., Wheeler, C. E., Briggaman, R. A., *et al.* (1976) Cutaneous manifestations of disseminated cryptococcosis. *Arch. Dermatol.* **112**, 1734–1740.