Cryptococcus laurentii Fungemia in a Premature Neonate

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Received 14 August 2000/Returned for modification 26 November 2000/Accepted 26 January 2001

***Cryptococcus* spp. other than *Cryptococcus neoformans* are generally considered nonpathogenic to humans. There are only 15 case reports of disease in humans caused by *Cryptococcus laurentii* infection. Underlying diseases and predisposing risk factors seem to play an important role in these cases. Our patient is the first case of an extremely low birth weight infant with *C. laurentii* fungemia reported in the English literature. In our case, the MIC of amphotericin B for *C. laurentii* was 0.25 to 1 µg/ml and the patient had a good outcome following the administration of amphotericin B at 10 mg/kg combined with central venous catheter removal. There will undoubtedly be an increasing occurrence of unusual fungal infections accompanying further advances in medicine. A high degree of suspicion and improvements in the techniques for culture and identification will contribute to the earlier diagnosis and treatment of unusual fungal infections.**

Cryptococcus spp. other than *Cryptococcus neoformans* were previously considered saprophytes and thought to be nonpathogenic to humans. However, infections caused by species other than *C. neoformans* have been increasingly recognized. We report a case of fungemia caused by *Cryptococcus laurentii* in a premature infant in which complete clinical resolution occurred after amphotericin B administration and central venous catheter removal. The organism was isolated twice from blood cultures drawn 2 days apart.

Case report. A female newborn with a gestation age of 27 weeks was admitted to our neonatal intensive care unit due to prematurity. The neonate was delivered via spontaneous vaginal delivery following premature rupture of the amniotic membrane. The birth weight was 940 g, and the Apgar score was 5 after 1 min. Physical examination was significant for rapidly progressive respiratory distress, and the patient was intubated soon after delivery and mechanically ventilated. Chest radiography confirmed grade III respiratory distress syndrome. Synthetic surfactant (colfosceril palmitate [Exosurf Neonatal]; Glaxo Wellcome, Inc.) was administered with a good response, and the patient was started on empiric antibiotic therapy with ampicillin and gentamicin. The hemogram on admission was normal, as was screening for toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex virus. Initial cultures of blood and cerebrospinal fluid (CSF) revealed no growth of bacteria or fungi.

Because of a transient worsening of the infant's ventilator settings at day 4 of life, coupled with yellowish endotracheal secretions and leukocytosis (absolute neutrophil count, 22,350/mm³), broad-spectrum antibiotic therapy was continued with gentamicin replaced with ceftizoxime. The patient improved clinically, was extubated for the first time on day 9, and was placed on nasal continuous positive airway pressure. However, on day 11, increasing respiratory distress was noted, necessi-

tating reintubation and mechanical ventilation. Chest radiography demonstrated a new right upper lung opacification. A hemogram was normal. Due to growth of oxacillin-resistant *Staphylococcus aureus* in the culture of the tip of the removed endotracheal tube, antibiotic therapy was changed to ceftizoxime and teicoplanin. The patient's condition improved gradually over the next few days. On day 20, a repeat chest X-ray was normal. The infant was extubated, and antibiotic therapy was discontinued.

On the 25th day of life, the infant appeared less active and had occasional episodes of apnea and bradycardia. Over the following 24 h, a sepsis syndrome evolved with respiratory and circulatory insufficiency, hypothermia, abdominal distension, leukocytosis (white blood cell count, 19,080/mm³; 21% band forms), and thrombocytopenia (platelet count, 54,000/mm³). The infant was started on an empirical antibiotic regimen of ceftazidime and teicoplanin with no appreciable clinical response. Two sets of blood cultures (BACTEC 860 system; Becton Dickinson, Inc., Sparks, Md.) were drawn on days 27 and 29. Both sets of blood cultures were positive 72 h later and yielded the same encapsulated, round-to-oval, yeast-like fungus that grew at 37°C, produced urease, had a slight capsule, and was nonfermentative. Colonies were cream colored and darkened with age. The ID 32C system (bioMérieux Vitek, Inc., St. Louis, Mo.) was used to identify *C. laurentii* by noting the utilization of lactose and melibiose. A negative caffeic acid test and absence of KNO₃ utilization reliably differentiated this species from *C. neoformans* and *C. albidus*. The MICs of amphotericin B and fluconazole were determined by the broth microdilution method according to the National Committee for Clinical Laboratory Standards guidelines (12). The MIC of amphotericin B was 0.25 to 1 µg/ml, and that of fluconazole was 4 µg/ml. A central venous line, placed in the right cubital fossa shortly after birth, was removed, parenteral nutrition was temporarily discontinued, and amphotericin B administration was started. Examination of CSF obtained prior to the start of amphotericin B administration was negative by routine bacteriology culture, India ink stains, and cryptococcal antigen test. The tip of the withdrawn central venous line was negative by

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TABLE 1. Summary of data from cases of *C. laurentii* infection in humans^a

Yr (ref.)	Age (yr)	Sex	Underlying condition(s)	Prior antibiotic exposure	Prior steroid exposure	Prior catheter use	Prior neutropenia	Clinical diagnosis	Clinical presentation	Treatment	Outcome
1977 (5)	40	M	Remote dog bite	Yes	NR	NR	NR	Cutaneous infection	Cutaneous granuloma, regional lymph node enlargement	D-Amb	Resolved
1980 (9)	55	F	Adenocarcinoma, dermatomyositis	NR	Yes	NR	NR	Lung abscess	Asymptomatic right upper lobe cavity lesion	D-Amb	Resolved
1985 ^b	37	M	None known	NR	NR	NR	NR	Pneumonia	NR	Surgery	Resolved
1989 (17)	13	F	ESRD, peritoneal dialysis	Yes	NR	NR	NR	Peritonitis	Fever, abdominal pain, cloudy dialysate fluid	Catheter removal D-Amb	Resolve
1989 (10)	14	F	ESRD, peritoneal dialysis	Yes	NR	NR	NR	Peritonitis	Fever, abdominal pain, cloudy dialysate fluid	Catheter removal peritoneal lavage with saline	Resolved
1995 (2)	61	F	Chronic uveitis	NR	Yes	NR	NR	Endophthalmitis	Deteriorating vision	Fluconazole	Resolved
1997 ^c	17	M	Leukemia BMT	Yes	NR	Yes	Yes	Fungemia	Fever	Fluconazole	Resolved
1997 (14)	51	NR	Diabetes contact lens wearing	NR	NR	NR	NR	Keratitis	Central corneal ulceration	Enucleation, D-Amb miconazole	Resolved
1997 (4)	0.074	M	Premature birth	Yes	NR	Yes	NR	Fungemia	Hypotension, tachycardia	Catheter removal D-Amb	Resolved
1997 (4)	27	F	Bacterial endocarditis	Yes	NR	Yes	NR	Fungemia	Fever, chills, painful cutaneous nodules	Catheter removal Fluconazole	Resolved
1998 (6)	34	M	AIDS	NR	NR	NR	NR	Meningitis	Hypotension, fever, dyspnea, headache, dizziness, diplopia	D-Amb Flucytosine	Resolved
1998 (7)	26	M	Solid tumor	Yes	NR	Yes	Yes	Fungemia	NR	Catheter removal fluconazole	Resolved
1998 (7)	50	M	NHL	Yes	Yes	Yes	Yes	Fungemia	NR	Catheter removal D-Amb	Death due to NHL
1999 (7)	57	M	AML	Yes	Yes	Yes	Yes	Fungemia	NR	Catheter removal D-Amb	Resolved
2000 (PR)	0.074	F	Premature birth	Yes	NR	Yes	No	Fungemia	Apnea, bradycardia, hypotension, hypothermia, abdominal distension	Catheter removal D-Amb	Resolved

^a Abbreviations: AML, acute myelogenous leukemia; BMT, bone marrow transplantation; ESRD, end stage renal disease; F, female; M, male; NHL, non-Hodgkin's lymphoma; NR, not reported; PR, present report; ref., reference; TPN, total parenteral nutrition; D-Amb, amphotericin B.
^b Winn et al., Abstr. Ammu. Meet. Am. Soc. Microbiol.
^c Kremer et al., letter.

routine bacteriology culture. Therapy with amphotericin B (initial dosage; 0.1 mg/kg/day; maximum dosage, 1 mg/kg/day; total cumulative dose, 10 mg/kg) was rapidly successful and tolerated without nephrotoxicity. A repeat culture of blood drawn on the 37th day was negative, and the infant was weaned from pressure agents and extubated within 3 days after the start of antifungal therapy. The remaining course in the nursery was uneventful, and the infant was discharged at an age of 70 days. Regular postdischarge follow-up for 1 year showed age-appropriate development with no evidence of late complications of fungemia.

Discussion. Major risk factors for fungemia include intravascular catheters, parenteral hyperalimentation, and broad-spectrum antibiotics. Premature infants are at particularly increased risk due to their extremely low body weight, poor nutrition, enteral malabsorption, insufficient microbial defenses, and underdeveloped anatomic barriers (13, 16). All of these risk factors were present in our case.

Cryptococcosis is an infectious disease of worldwide occurrence caused by an encapsulated, basidiomycetous, yeast-like fungus. Cryptococci are generally found in soil contaminated by pigeon feces, as well as on the surfaces of certain vegetables and in milk from infected dairy cow herds (1). Cryptococci are transmitted to humans primarily through inhaled fomites, although direct entry through the digestive tract or skin can also occur. Species other than *C. neoformans* have generally been thought to be nonpathogenic to humans (2, 9, 14).

Including the present report, there are a total of 15 case reports of disease in humans caused by *C. laurentii* infection, 7 of which were of fungemia cases. These cases are summarized in Table 1. Underlying diseases and predisposing risk factors seem to have played an important role in these cases. Signs and symptoms varied considerably according to sites of infection. In fungemia patients, abnormal temperature and hypotension were the most common presentations. Measurement of cryptococcal antigen in serum or CSF was not reported in the majority of these cases; however, if reported, the results were consistently negative. One patient died due to the underlying disease, but the others recovered after treatment in these cases (2, 4–7, 9, 10, 14, 17; V. Kremery, Jr., A. Kunova, and J. Mardiak, Letter, Infection 25:130, 1997; R. E. Winn, M. G. Rinaldi, M. Galbraith, and J. H. Bower, Abstr. Annu. Meet. Am. Soc. Microbiol. 1985, abstr. F37, p. 370, 1985). Our patient is the first case of an extremely low birth weight infant with *C. laurentii* fungemia reported in the English literature.

In the clinical microbiology laboratory, the finding of a mucoid colony is usually the first clue to the presence of cryptococci and this suspicion is further heightened when encapsulated, budding yeasts are observed on an India ink preparation of the colony. There are 37 members of the genus *Cryptococcus*, and virtually all members of the genus assimilate inositol, produce urease, and are nonfermentative. The identification of *C. laurentii* specifically can be confirmed by using various biochemical tests, and most clinical laboratories use a battery of biochemical tests contained in commercially available kits. A negative caffeic acid test, absence of KNO_3 utilization, and the utilization of lactose and melibiose may differentiate *C. laurentii* from other species (8).

Because of the limited number of reported cases, there is no validated standard treatment for *C. laurentii* infection. Prompt

removal of a central venous catheter is well documented as an important measure for clearing fungemia and preventing complications (3, 15). Correlations between in vitro antifungal susceptibility test results and treatment outcome do not exist for *C. laurentii*. The organism was susceptible to amphotericin B in this case and those previously reported, with MICs ranging from 0.037 to 1 $\mu\text{g/ml}$, but its susceptibility to fluconazole seemed to be equivocal, with MICs ranging from 4 to greater than 64 $\mu\text{g/ml}$ (4, 6, 11, 12). We observed a favorable outcome following the administration of accumulative dose of 10 mg of amphotericin B per kg, combined with central venous catheter removal. Although we encountered no toxicity due to amphotericin B, detailed analysis of toxicity in premature neonates is limited and merits more attention.

Undoubtedly, there will be an increasing number of unusual fungal infections concomitant with further advances in medicine, especially in areas involving immunosuppressive therapy, use of corticosteroids and antibiotics, and widespread use of central venous catheters. Improvements in the identification of unusual pathogens will, in turn, contribute to the increased recognition of cases. However, a high degree of suspicion, particularly in predisposed patients, teamed with newly developed techniques for culture and identification, will likely allow earlier diagnosis and, it is hoped better treatment of such unusual fungal infections.

We thank Andreas H. Groll, National Cancer Institute, and L. Clifford McDonald, University of Louisville Hospital, for expert discussion and review of the manuscript. We are also indebted to Hsiu-Jung Lo and Tsai-Ling Lauderdale, National Health Research Institutes, Taipei, Taiwan, for editorial assistance.

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