Cryptococcus laurentii Fungemia in a Premature Neonate

MING-FANG CHENG,1,3 CHRISTINE C. CHIOU,1,3* YUNG-CHING LIU,3,4
HAO-ZAN WANG,1 AND KAI-SHENG HSIEH1

Department of Pediatrics1 and Microbiology Laboratory,1 Veterans General Hospital-Kaohsiung, Kaohsiung, and Division of Clinical Research, National Health Research Institutes,2 and National Yang-Ming University,3 Taipei, Taiwan

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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 C. 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 rapid 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/µm3), 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, necessitating 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/µm3; 21% band forms), and thrombocytopenia (platelet count, 54,000/µm3). 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 (bioMerieux Vitek, Inc., St. Louis, Mo.) was used to identify C. laurentii by noting the utilization of lactose and melibiose. A negative caffeine acid test and absence of KNO3 utilization reliably differentiated this species from C. neoformans and C. albidas. 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

*Corresponding author. Present address: Infectious Disease Section, VA Medical Center, University Dr. C. Pittsburgh, PA 15240. Phone: (412) 688-6179. Fax: (412) 688-6950. E-mail: chenchia@yahoo.com.

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<table>
<thead>
<tr>
<th>Yr (ref.)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Underlying condition(s)</th>
<th>Prior antibiotic exposure</th>
<th>Prior steroid exposure</th>
<th>Prior catheter use</th>
<th>Prior neutropenia</th>
<th>Clinical diagnosis</th>
<th>Clinical presentation</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td>1977 (5)</td>
<td>40</td>
<td>M</td>
<td>Remote dog bite</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Cutaneous infection</td>
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<td>D-AmB</td>
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<td>F</td>
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<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td></td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Peritonitis</td>
<td>Fever, abdominal pain, cloudy dialysate fluid</td>
<td>Catheter removal, peritoneal lavage with saline</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td></td>
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<td>Yes</td>
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<td>Fever</td>
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<td>Fever</td>
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<td>NR</td>
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<td>Yes</td>
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<td>No</td>
<td>NR</td>
<td>Fungemia</td>
<td>Hypotension, bradycardia, hypothermia, abdominal distension</td>
<td>Catheter removal, D-AmB</td>
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</table>

**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.

**Notes:**
- Kremery et al., letter.
of the colony. There are 37 members of the genus C. laurentii produced urease, and are nonfermentative. The identification of C. laurentii may be confirmed by using various biochemical tests contained in commercially available kits. A negative caffeic acid test, absence of KNO₃ utilization, and 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. 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 in an India ink preparation of the colony. There are 37 members of the genus Cryptococcus, and virtually all members of the genus assimilate inositol, negative caffeic acid test, absence of KNO₃ 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 μg/ml, but its susceptibility to fluconazole seemed to be equivocal, with MICs ranging from 4 to greater than 64 μg/ml (4, 6, 11, 12). We observed a favorable outcome following the administration of cumulative 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.

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REFERENCES