Candida lusitaniae: A Cause of Breakthrough Fungemia in Cancer Patients

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Candida lusitaniae is an infrequent cause of fungemia. We identified 12 cases of C. lusitaniae fungemia that occurred at the University of Texas M. D. Anderson Cancer Center from 1988 to 1999. The mean age of patients was 48 years (range 20–70 years). Eight patients had hematologic malignancy or had received a bone marrow transplant, and 4 had a solid tumor. Most patients (75%) were neutropenic (<10^3/mm^3). Treatment with amphotericin B alone failed for 3 of 6 patients, irrespective of neutropenic status. Fluconazole was effective as a single agent in 3 patients with solid tumors. The combination of amphotericin B plus fluconazole was effective treatment for two-thirds of patients with hematologic malignancy, despite persistence of neutropenia. The mortality rate associated with C. lusitaniae infection was 25%. C. lusitaniae presents as breakthrough fungemia in immunocompromised patients and is associated with failure of amphotericin B therapy. Fluconazole may be a useful agent in the treatment of this infection.

Despite the steady increase in the frequency of fungemia caused by non-albicans species of Candida, Candida lusitaniae is rarely reported and accounts for only 1% of all candidemias cited in 2 large prospective studies [1, 2] and at our center. C. lusitaniae fungemia has been associated with a high mortality rate because of its resistance to amphotericin B [3]. C. lusitaniae has also been reported to be resistant to other antifungal agents, such as 5-fluorocytosine and fluconazole [4–7].

C. lusitaniae was first isolated in 1959 from the gastrointestinal tract of warm-blooded animals [8]. In 1979, it was first reported as an opportunistic human pathogen in a patient with acute myelogenous leukemia [9]. Thirty cases of C. lusitaniae fungemia were reported in the English literature from 1979 to 1998 [2–5, 9–25]. A total of 67% of those patients were immunocompromised (12 had cancer, 2 were receiving steroids, 5 had immature immune systems, and 1 had AIDS). Because most institutions have had limited experience with C. lusitaniae fungemia and because the largest series of candidemia related to this organism consisted of only 5 cases [7], we conducted a retrospective review of all cases of C. lusitaniae fungemia that occurred at our institution during an 11-year period.

PATIENTS AND METHODS

The records of the microbiology laboratory at the University of Texas M. D. Anderson Cancer Center were reviewed for the period 1 January 1988 through 31 December 1998 to identify all cases of hematogenous candidiasis. Of the 961 cases of candidemia, 12 were caused by C. lusitaniae, and the medical records of all 12 patients were available for review. The following information for all 12 patients reflects their status during the 30 days before the collection of the first blood samples that yielded positive results on culture and reflects the subsequent course of infection: age, sex, underlying malignancy, acute physiology and chronic health evaluation (APACHE) II score (at the onset of fungemia), duration of hospitalization, duration of stay in the intensive care unit, mechanical ventilation, and duration of neutropenia. For the same time period, we
Table 1. Clinical characteristics of 12 patients with Candida lusitaniae fungemia.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Underlying disease or condition</th>
<th>APACHE II score</th>
<th>Duration of neutropenia, d</th>
<th>Treatment</th>
<th>Chemotherapy</th>
<th>Steroids</th>
<th>Duration of IVH, d</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>65/M</td>
<td>Leukemia</td>
<td>16</td>
<td>9</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>65/M</td>
<td>Mesothelioma</td>
<td>19</td>
<td>0</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>41/M</td>
<td>Leukemia</td>
<td>14</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>39/M</td>
<td>Leukemia</td>
<td>16</td>
<td>8</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>59/F</td>
<td>Lymphoma</td>
<td>19</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>70/M</td>
<td>SCC pharynx</td>
<td>19</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>28/F</td>
<td>Leukemia</td>
<td>12</td>
<td>70</td>
<td>Yes</td>
<td>No</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>46/M</td>
<td>Bile duct carcinoma</td>
<td>13</td>
<td>0</td>
<td>No</td>
<td>No</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>20/F</td>
<td>Leukemia, BMT</td>
<td>12</td>
<td>&gt;100</td>
<td>Yes</td>
<td>Yes</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>49/M</td>
<td>Leukemia</td>
<td>16</td>
<td>&gt;8</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
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<tr>
<td>11</td>
<td>47/F</td>
<td>Breast cancer, BMT</td>
<td>18</td>
<td>13</td>
<td>Yes</td>
<td>No</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
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<td>57/M</td>
<td>Melanoma</td>
<td>17</td>
<td>16</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE. APACHE, acute physiology and chronic health evaluation; BMT, bone marrow transplant; F, female; IVH, intravenous hyperalimentation; M, male.

also recorded the administration of corticosteroids, antibiotics, cancer therapeutic agents, parenteral alimentation, and antifungal prophylactics.

Identifications and definitions. C. lusitaniae were identified as follows: germ tube-negative Candida organisms were evaluated using commercial yeast identification systems—the Vitek YBC (bioMérieux), the cornmeal agar morphology, and the API 20 c (bioMérieux).

C. lusitaniae fungemia was defined as isolation of the organism from ≥1 culture of a blood sample associated with fever or other signs of infection (e.g., chills, hypothermia, hypotension). Breakthrough fungemia was defined as the development of C. lusitaniae candidemia while the patient was receiving prophylactic or empiric systemic antifungal agents ≥2 days before the onset of the fungemia [1]. Microbiological persistence of candidemia was defined as isolation of the organism from any normally sterile site after ≥4 days of systemic fungal therapy. Dissemination was defined as the clinical or histopathologic evidence of Candida infection in ≥1 internal organ or isolation of the same species from a tissue specimen and the bloodstream. Catheter-related fungemia was defined as the isolation of C. lusitaniae from the catheter tip (>15 cfu/4 cm) by the roll-plate semiquantitative method as well as from the bloodstream. Neutropenia was defined as a neutrophil count <1000 cells/mm³.

Response was defined as resolution of all signs and symptoms of infection with concurrent negative results of blood cultures for Candida species ≥1 week after therapy. Failure to respond was defined as the persistence of clinical signs and symptoms of infections or persistent candidemia or candiduria caused by C. lusitaniae 96 h after the onset of therapy. Associated mortality was defined as death contributed to C. lusitaniae candidemia with or without therapy.

In vitro susceptibility. Nine isolates were available from 5 patients for susceptibility testing. MIC analyses were performed for amphotericin B, fluconazole, and itraconazole. The microbroth dilution assay was used as proposed by the National Committee for Clinical Laboratory Science (NCCLS) using RPMI 1640 synthetic medium (Gibco BRL; with glutamine, without bicarbonate, and with a pH indicator). The inoculum was prepared by picking colonies from 24-h-old cultures of Candida species isolated from our patients. The isolates were suspended in normal saline, and the cell density was adjusted by spectrophotometry in order to obtain a final yeast stock suspension of 1 × 10⁶ cells/mL. We then used a 1:10 dilution series, with final antifungal concentration in the range of 16–0.0313 μg/mL as desired. MICs were read after 24 and 48 h of incubation. Interpretation of the results was guided with the following susceptibility breakpoints [26]: fluconazole, ≤8 μg/mL; itraconazole, ≤0.125 μg/mL; and amphotericin B, ≤2 μg/mL.

RESULTS

Characteristics of patients. All 12 patients who were determined to have C. lusitaniae fungemia had a central venous catheter (CVC) and were exposed to broad-spectrum antibiotics for 12–46 days. Ten patients (83%) had received cytotoxic drugs within 3 weeks of the first positive results of blood cultures. Nine patients (75%) were neutropenic (table 1). Only 1 patient recovered from the neutropenia before the onset of fungemia. Seven patients were on total parenteral nutrition. Two patients had solid tumors without any risk factors, such as neutropenia or recent exposure to cytotoxic or corticosteroid drugs; both had major surgery at the tumor site.

Seven patients (58%) had breakthrough fungemia. Three ep-
isodes occurred during treatment with amphotericin B. Three other episodes occurred during treatment with fluconazole. The remaining patient had received a long course of empiric amphotericin B and itraconazole.

Portal of entry. All of the *C. lusitaniae* fungemias occurred in hospitalized patients 1–6 weeks after admission. The CVC was the possible portal of entry for 2 patients with solid tumor. Results of the catheter tip culture were positive (>1000 cfu) by roll-plate semiquantitative culture method for both patients. Gastrointestinal tract erosion and colonization or urinary tract infections were suspected portal of entry in the other cases. All patients had oral mucositis or gastrointestinal bleeding, and 2 patients also had urinary-tract infections with *Candida* species within 1 week prior to the candidemia.

Clinical manifestation. Fever was the most common clinical presentation, occurring in 11 patients (92%). One patient had hypothermia, and 4 had hypotension (systolic blood pressure, <90 mm Hg). The mean APACHE II score was 16 (range, 12–19) on the first day when there were positive results of blood cultures (table 1). All patients had experienced a serious medical condition before the onset of candidemia. Eight patients developed bacterial pneumonia, and 2 developed viral pneumonia (respiratory syncitial virus or cytomegalovirus); 6 had bacteremia; and 4 had multiorgan failure.

Therapy and outcome. Six patients were initially treated with amphotericin B or one of its lipid formulations. Microbiological persistence occurred in 3 (50%) of the patients, despite 4–15 days of therapy (table 2). Among the patients for whom amphotericin B therapy failed, 1 responded to the addition of high-dose (1200 mg/day) iv fluconazole (table 3). The site of persistence included blood (2 patients) and urine (1 patient). Neutropenic status did not influence the outcome; however, all 3 patients who experienced treatment failure had breakthrough fungemia while on amphotericin B.

Three patients with solid tumor were initially treated with fluconazole, and all were cured (table 2). Combination therapy, mainly with amphotericin B plus azoles, was initiated in 3 patients with hematologic malignancy. Two of the 3 patients who received combined therapy were cured despite persistent neutropenia and absence of remission. Although the mortality rate was high among the 12 patients (67%), the mortality rate associated with the *C. lusitaniae* was 3 patients (25%).

Blood isolates were saved for 3 of the 6 patients treated with an amphotericin B regimen. All exhibited susceptibility to amphotericin B (MIC ≤ 1.0 µg/mL), despite evidence of microbiological failure. In 1 patient (patient 9), however, there was a decrease in the susceptibility to amphotericin B (the MIC increased from 0.25 µg/mL to 1.0 µg/mL) on treatment associated with emergence of resistance to fluconazole and itraconazole (table 3). There were 2 additional isolates from 2 other patients. These 2 isolates were susceptible to amphotericin and the azoles (table 3). One patient was successfully treated with fluconazole, and the other died before receiving any therapy.

**DISCUSSION**

Although this is the largest study of *C. lusitaniae* fungemia thus far reported in the literature, this infection remains an infrequent cause of candidemia in patients with cancer. In our study, *C. lusitaniae* fungemia accounted for only 1.3% of all cases of candidemia diagnosed at our center during the 11-year study period.

The fact that *C. lusitaniae* fungemia was not reported in large-scale studies of candidemia before 1990 [27–33] and only appeared as an infrequent cause of candidemia in large prospective studies in the 1990s [1, 2] suggests that it has emerged as a problem during the past decade. A thorough review of the literature suggests that this fungemia is emerging as a breakthrough fungemia in patients with cancer [7, 16, 25], especially in an era when antifungal prophylaxis is heavily used for patients with cancer. Hence, breakthrough fungemia is becoming the predominant mode of presentation for this infection because of known resistance of *C. lusitaniae* to various antifungal drugs and the wide empirical use of antifungal agents in patients with cancer in the 1990s. During a retrospective study of nosocomial breakthrough fungemias in cancer patients, Krcmery

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**Table 2. Outcome of *Candida lusitaniae* fungemia according to treatment regimen.**  

<table>
<thead>
<tr>
<th>Antifungal therapy</th>
<th>MDACC cases</th>
<th>Literature cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Persistent neutropenia</td>
</tr>
<tr>
<td>Amphotericin B alone</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Combinationa</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**NOTE.** “Literature cases” refers to *C. lusitaniae* fungemia in cancer patients reported in references 7, 9, 10, 12, 16, 18, and 25. MDACC, M. D. Anderson Cancer Center.

a For 1 patient, amphotericin B therapy initially failed, but the patient responded to the addition of high-dose fluconazole 1200 mg/day; therefore the patient was counted twice.
et al. [25] identified 3 cases of *C. lusitaniae* fungemia. In that study, the authors reported that one of the risk factors for breakthrough candidemias was the prophylactic use of quinolones (*P* < 0.0001). In our series, breakthrough fungemia was not associated with quinolone use during the 30 days prior to the onset of the fungemia.

The epidemiology of *C. lusitaniae* fungemia among cancer patients suggests that this infection occurs predominantly in adult patients with hematologic malignancy or following bone marrow transplantation (BMT) [7, 9, 10, 12, 16, 18, 25]. In our series, two-thirds of the patients had underlying hematologic malignancy or had undergone BMT.

Resistance to amphotericin B has been an important clinical finding in *C. lusitaniae* isolates. A wide variety of nonstandardized methods had been used for susceptibility testing before the introduction of the standardized NCCLS methods. In most patients with *C. lusitaniae* fungemia who were treated with amphotericin B and for whom susceptibility testing of their isolates was performed, according to the nonstandardized methods, clinical outcome correlated with susceptibility. In our series, however, the susceptibility pattern did not influence clinical response to amphotericin B. All 3 patients who were unsuccessfully treated with amphotericin B or its lipid derivatives remained susceptible to amphotericin B, despite a 4-fold increase in susceptibility in 1 patient, according to the NCCLS method. Similarly, 2 cases of *C. lusitaniae* fungemia unsuccessfully treated with amphotericin B reported by Nguyen and Fawler [7, 24] had isolates that were susceptible to amphotericin B, according to the NCCLS method. The suitability of the NCCLS proposed standard method for detecting amphotericin B resistance has been questioned by Rex et al. [34]. Similarly, Pfaffer found [35] that when using the NCCLS method, if the incubation period was extended to 72 h, susceptibility to amphotericin B would increase to ≥2 μg/mL in 50%–70% of *C. lusitaniae* isolates. Therefore, the NCCLS method might not be the most suitable method for determining the appropriate susceptibility of *C. lusitaniae* to amphotericin B, and this might explain the lack of correlation between susceptibility, outcome, and response to amphotericin B in our study.

*C. lusitaniae* fungemia is a serious bloodstream infection with poor response to amphotericin B, especially in immunocompromised patients. In our study (patient 5, table 3) and the reported cases from the literature, a total of 3 patients died before the initiation of therapy [11, 18]. In addition, 15 of the 38 patients treated experienced microbiological failure after initiation of antifungal therapy. Amphotericin B as a monotherapy was associated with poor response in patients with hematologic malignancy or BMT, or in premature infants.

The observation from the literature and our study is that the response to amphotericin B improved when it was used in combination with fluconazole or other antifungal agents, such as 5-fluorocytosine, as administered to patient 7 [19, 21]. Treatment with fluconazole as a single agent was highly effective in patients with solid tumor and in immunocompetent patients [2, 7, 25]. The effectiveness of treatment with the combination of amphotericin B with azole for *Candida* infection has not been determined and is still controversial. Fluconazole and amphotericin B have been shown to be antagonistic against *C. albicans* under carefully selected in vitro conditions [36]. An in vivo study by Sugar et al. [37], however, did not demonstrate this antagonism against *C. albicans*. On the basis of our data, it is advisable that amphotericin B not be administered as a single agent to neutropenic patients with *C. lusitaniae* but rather substituted by or used in combination with fluconazole. In non-neutropenic patients or patients with solid tumor, it would be reasonable to use fluconazole as a single agent.

**CONCLUSION**

*C. lusitaniae* fungemia presents as a breakthrough fungemia in immunocompromised patients. In the cancer setting, it oc-
curs as a nosocomial infection predominantly in patients with hematologic malignancy or who have undergone BMT. Amphotericin B is not sufficiently active against this organism in immunocompromised patients and may be substituted or combined with fluconazole. In immunocompetent patients, fluconazole appears to be useful as a single agent.

References