Failure of Systemic Empirical Treatment with Amphotericin B to Prevent Candidemia in Neutropenic Patients with Cancer

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We undertook a retrospective review of all patients with hematologic malignancies in whom candidemia developed during chemotherapy-induced neutropenia in 1989 and 1990. Candidemia developed in 11 patients; five were receiving therapeutic doses of amphotericin B at the time of infection. Disseminated infection occurred in 2 of 5 patients with breakthrough infection and 3 of 6 patients with candidemia before receipt of amphotericin B. Among patients with breakthrough candidemia there was a trend toward more-prolonged neutropenia prior to infection ($P = .069$), but otherwise they were indistinguishable from other candidemic patients with regard to risk factors for candidemia. Amphotericin B–susceptible Candida albicans was isolated from two patients and Candida krusei from three patients with breakthrough infection. All patients were treated with amphotericin B; all breakthrough infections responded to treatment. Neutropenic patients with breakthrough candidemia were clinically similar to those whose candidemia preceded amphotericin B therapy, and there was no increase in morbidity and mortality among individuals with breakthrough infection.

Candidal infections are a major cause of morbidity and mortality among neutropenic patients undergoing chemotherapy or bone marrow transplantation for the treatment of leukemia or lymphoma [1–4]. Multiple trials have investigated the use of prophylactic antifungal agents, including nonabsorbable nystatin, fluconazole, and low-dose intravenous amphotericin B, to prevent fungal infections in this patient population [5–8]. None of these interventions has been uniformly effective, and there have been reports of suspected or documented breakthrough fungal infections, in some cases with more resistant fungal pathogens [9, 10]. As a consequence, patients frequently require moderate to high doses of amphotericin B as empirical or specific therapy for fungal infection.

Empirical therapy with amphotericin B has been a generally successful intervention for febrile neutropenic patients receiving broad-spectrum antibiotics following chemotherapy for hematologic malignancies, an intervention that is associated with decreased morbidity and mortality [3]. Long-term antifungal therapy with amphotericin B is rarely associated with the development of resistance among candidal isolates, and the occurrence of candidemia in this population of patients receiving empirical therapy with amphotericin B is unusual [11]. Nevertheless, when candidal superinfections do occur, amphotericin B–resistant Candida species have been reported to be involved [12, 13]. A detailed review of the literature has revealed only seven patients in whom fungemia with amphotericin B–susceptible Candida krusei or Candida glabrata developed while they were receiving empirical therapy with amphotericin B for febrile neutropenia, following chemotherapy for hematologic malignancies [12, 14]. We report a series of cases and describe five persons who had breakthrough candidemia with susceptible organisms despite empirical therapy with amphotericin B; in two cases amphotericin B–susceptible Candida albicans was isolated.

Methods

We retrospectively reviewed all cases of candidemia occurring in patients who had neutropenia following cytolytic chemotherapy for hematologic malignancies during 1989 and 1990. This review included but was not restricted to patients undergoing bone marrow transplantation. These years were chosen because we had identified five patients during that time who had candidemia while receiving empirical therapy with amphotericin B for prolonged febrile neutropenia. Patients with and without breakthrough candidemia were compared with regard to demographic characteristics, duration and depth of neutropenia, development of mucositis, occurrence of diarrhea, concurrent infections, type of intravascular access, results of surveillance cultures for Candida species, nature of candidemia (transient vs. disseminated), treatment regimens, and outcome.

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In the two cases of breakthrough *C. albicans* fungemia, assays for MICs of amphotericin B were performed by the Microbiology Reference Laboratory (Cypress, CA), using broth macrodilution techniques according to the procedures of the National Committee for Clinical Laboratory Standards [15]. The minimal fungicidal concentrations were determined by the same reference laboratory by the subculturing of 50 μL from those dilutions that did not yield growth on Sabouraud dextrose agar. Cidal activity was defined as the absence of any growth at 48 hours.

Breakthrough candidemia was defined by the finding of at least one blood culture positive for *Candida* species at a time when the patient was receiving therapeutic doses (≥0.6 mg/[kg·d]) of amphotericin B (for a minimum of 3 days, with a minimum dose of 100 mg received prior to the time at which the positive blood culture specimen was drawn). Transient candidemia was defined by a single blood culture positive for *Candida* species, without any evidence of additional sites of infection (excluding mucocutaneous candidiasis). Disseminated infection was defined by (1) multiple positive blood cultures or (2) a single positive blood culture associated with histopathologic evidence of deep organ involvement or radiographic evidence consistent with hepatosplenic candidiasis, or the presence of pathognomonic skin lesions or ocular findings. Neutropenia was defined by an absolute neutrophil count of <1,000/μL.

We compared the groups with and without breakthrough candidemia using both Fisher's exact test and an unpaired Student's t-test. We considered results to be statistically significant if the two-tailed P value was ≤.05.

**Illustrative Case**

A 38-year-old woman with acute lymphocytic leukemia was admitted for reinduction chemotherapy for relapsed leukemia. Her medical history was remarkable for splenectomy, *Haemophilus influenzae* aortic valve endocarditis, and multiple Hickman catheter infections, all of which had occurred during earlier admissions for treatment of leukemia. On admission a Hickman catheter was placed, and the patient subsequently received high-dose therapy with cytosine arabinoside and amsacrine. She also received prophylactic nystatin. Because of prolonged neutropenia and persistent fever, therapy with broad-spectrum antimicrobial agents was initiated, and ultimately her regimen was escalated to include ceftazidime, gentamicin, metronidazole, vancomycin, and amphotericin B (0.6 mg/[kg·d]).

After receiving amphotericin B for 23 days (770 mg), she became candidemic, and all blood culture specimens drawn via her Hickman catheter on hospital days 29 and 30 were positive for *C. albicans*. The isolate was susceptible to amphotericin B, with minimal inhibitory and fungicidal concentrations of 0.08 μg/mL and 0.16 μg/mL, respectively. At the time candidemia occurred, the patient's absolute neutrophil count was 0/μL, and she had persistent diarrhea. When the initial positive blood culture results became available on day 32 of hospitalization, the Hickman catheter was removed. A set of blood culture specimens drawn on hospital day 34 were still positive for *C. albicans*, but all blood cultures performed after that were negative.

She was afebrile by day 36. A transthoracic echocardiogram and three sequential abdominal ultrasonograms revealed no evidence of fungal dissemination. Funduscopic examination revealed a retinal hemorrhage. The patient's candidemia resolved with high-dose therapy with amphotericin B (1.3 mg/[kg·d]), and by day 42 her granulocyte count exceeded 1,000/μL. She experienced two isolated episodes of bacteremia, one with coagulase-negative staphylococci (on day 39) and the second with enterococci (on day 48). She ultimately died on day 52, 4 days following the onset of an acute cerebral infarction. By the time of her death, she had received a total of 2,280 mg of amphotericin B.

**Results**

During a 2-year period, candidemia developed in 11 patients who became neutropenic following cytolytic chemotherapy for hematologic malignancy. Five of these individuals were receiving empirical therapy with amphotericin B at doses ≥ 0.6 mg/[kg·d] when the candidemia developed. The characteristics of these patients are summarized in table 1. All were being treated for acute leukemia; one was a bone marrow transplant recipient. Three patients had transient fungemia (2 with *C. krusei* and 1 with *C. albicans*), and two had evidence of disseminated infection (1 with *C. krusei* and the other with *C. albicans*). Four of the five had experienced prolonged neutropenia (≥23 days) and had received a minimum of 550 mg of amphotericin B prior to the development of candidemia. The fifth patient had been neutropenic for 5 days and had received 200 mg of amphotericin B. Two patients, both of whom had transient candidemia, had received in excess of 2,500 mg of amphotericin B prior to the onset of fungemia.

The isolates from both patients who had *C. albicans* fungemia were considered to be susceptible to amphotericin B. Although there are no established interpretive breakpoints for susceptibility testing of *Candida* species isolates, the low minimal inhibitory and fungicidal concentrations suggested that our patients' isolates were amphotericin B-susceptible. All patients' candidemia resolved after removal of the indwelling intravascular catheters and following additional amphotericin B therapy. Only one patient died, after a cerebral infarction of unknown etiology occurred 22 days after the initial positive blood culture. No autopsy was performed; consequently, we were unable to determine whether this patient's demise was related to her candidemia.

A comparison of those patients in whom breakthrough candidemia developed and those who were not receiving amphotericin B at the time of their candidemia reveals few differences in the two populations, other than the administration of ampho-
tericin B prior to occurrence of candidemia (table 2). The underlying malignancies were similar, and all patients were receiving broad-spectrum antibiotics prior to onset of candidemia. All patients who had non-breakthrough infections had been receiving nystatin orally. All patients in both groups had a form of central venous access; all but one had a Hickman catheter and/or a Port-a-Cath device (Pharmacia; Piscataway, NJ). There was no difference in the age of the catheters; virtually all had been placed during the hospitalization in which candidemia developed. One patient with breakthrough candidemia had a temporary central venous catheter at the time of his infection.

All patients were profoundly neutropenic at the time of candidemia; there was a trend toward more prolonged neutropenia prior to candidemia in the group with breakthrough infection, but this did not reach statistical significance. In some cases, patients with breakthrough infection had a greater number of febrile episodes or days of fever that resulted in their receipt of empirical therapy with amphotericin B prior to onset of candidemia. Evidence of chemotherapy-induced mucosal damage was common in both groups, and the majority of patients had diarrhea and/or oral mucositis.

There were no standard protocols for surveillance cultures. Blood cultures were routinely performed during febrile episodes, and weekly rectal or throat swab specimens were obtained from many patients; these latter surveillance cultures were usually negative in both groups. A history of neutropenia or prior fungal infection and dissemination. There was a higher death rate in the non-breakthrough-infection group; this was not statistically significant.

### Discussion

Fungal infection is a common sequela of treatment for hematologic malignancy; *Candida* species are the most common isolates identified [1–4]. When candidemia develops while patients are receiving systemic antifungal therapy, the organisms may be resistant to the prophylactic agent. Most commonly this occurs in individuals receiving fluconazole [9]. Low-dose prophylaxis with intravenous amphotericin B has not been associated with breakthrough candidemia, although there have been sporadic reports of amphotericin-resistant *Candida* species causing infection in patients receiving empirical therapy with amphotericin B at therapeutic doses [12, 13]. This is not clearly related to prior therapy with amphotericin B [10, 12].

Only two previous reports have mentioned the occurrence of candidal sepsis with presumably susceptible organisms in patients receiving amphotericin B [12, 14]. It is notable that the isolates were *C. krusei* and *C. glabrata* and that the majority of the patients had received limited amounts of amphotericin B prior to the development of their infections. Ours is the first report of candidemia in individuals infected with presumably susceptible *C. albicans*, and all but one of our patients had received substantial amounts of amphotericin B prior to onset of fungemia. Although we do not have susceptibility data for those individuals who became candidemic with *C. krusei*, it is likely that these isolates were susceptible to amphotericin B, as all of the patients did respond to continued amphotericin B therapy at higher doses.

We believe that the isolation of *Candida* species in the blood cultures of our patients was consistent with infection in all cases. In two patients there was definitive evidence of deep-seated infection, including persistence of candidemia following removal of their Hickman catheters. The three patients who had transient fungemia were all febrile and appeared to be acutely ill; in each case there was a definite response to catheter removal and escalation of the amphotericin B dose. This response could not be explained by the prompt return to normal of granulocyte counts; neutropenia persisted beyond clinical
improvement in two of the three patients with transient candidemia. There were no other clearly demonstrable factors to account for the clinical response in these patients. At least one patient with transient candidemia had catheter-related infection, a diagnosis based on the presence of consistent local signs. The other patients did not have local signs of catheter infection or positive catheter-tip cultures; however, the response to catheter removal suggests that the catheter may have been the source.

Our study raises a number of questions that our small sample size prevents us from answering. The risk factors for breakthrough candidemia are unknown, and our patient population is not known. In the absence of another defined source of infection, catheter removal appears to be a prudent intervention.

### Table 2. Clinical features of patients with and without breakthrough candidemia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breakthrough candidemia (n = 5)</th>
<th>Non-breakthrough candidemia (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female ratio</td>
<td>4:1</td>
<td>3:3</td>
</tr>
<tr>
<td>Median years of age (range)</td>
<td>49 (27–75)</td>
<td>34.5 (19–47)</td>
</tr>
<tr>
<td><em>Candida</em> species isolated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>albicans</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>tropicalis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>glabrata</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>krusei</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Median absolute neutrophil count (range)</td>
<td>0/µL (0–80)</td>
<td>0/µL (0–280)</td>
</tr>
<tr>
<td>Median duration (d) of neutropenia pre-candidemia (range)</td>
<td>59 (5–62)</td>
<td>14 (3–24) (P = .069)</td>
</tr>
<tr>
<td>No. of patients with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mucositis</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Positive surveillance culture(s)</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>History of disseminated fungal infection¹</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other infection(s) prior to candidemia</td>
<td>5²</td>
<td>4³</td>
</tr>
<tr>
<td>Disseminated fungal infection³</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No. of patients who died⁴</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**NOTE.** No statistically significant differences were noted in any category.

* This patient had *C. krusei* fungemia, and a throat specimen culture was positive for an unidentified (non-*albicans*) *Candida* species.

¹ One patient with breakthrough *C. krusei* fungemia had had presumptive hepatosplenic candidiasis (without positive cultures) 3 years earlier. One patient with non-breakthrough *C. tropicalis* fungemia had had disseminated *C. tropicalis* infection 6 months earlier.

² Mucocutaneous herpes simplex infection (3), presumed pulmonary aspergillosis (1), coagulase-negative staphylococcal bacteremia (3), and Hickman catheter tunnel infection (1); 3 patients each had ≥2 infections.

³ *Escherichia coli* bacteremia (1), *Clostridium difficile* colitis (1), coagulase-negative staphylococcal bacteremia (2), and cytomegalovirus pneumonia (1); 1 patient had 2 infections.

⁴ Multiple positive blood cultures only (1 breakthrough, 1 non-breakthrough); candidemia and pathognomonic skin rash (1 breakthrough, 1 non-breakthrough); candidemia and endophthalmitis (1 non-breakthrough).

⁵ Two patients died as a consequence of non-breakthrough candidal infection; the other 2 deaths were not clearly related to the candidal infections.
It is notable that the outcome for our patients who became candidemic with amphotericin B–susceptible organisms while receiving amphotericin was not necessarily worse. They were no more likely than other patients either to have disseminated infection or to die. This characteristic differentiates this population from those in whom amphotericin B–resistant candidal infections develop. Amphotericin B–resistant infection has been associated with increased morbidity and mortality [12]. We await additional reports to see if our observations will be supported.

Previous reports have suggested that antifungal prophylaxis and therapy do not necessarily eradicate colonization with susceptible fungal isolates [16, 19]. Consequently, the development of breakthrough infection should not be unexpected. Fungal colonization was not readily apparent, as evidenced by surveillance cultures. In general, the utility of surveillance cultures as predictors of fungal infection is highly debatable [20]. These cultures were not useful in our population, presumably because oral and rectal specimen cultures may not have accurately predicted sites of colonization in the small bowel and colon. What factors were critical in the progression from undetected colonization to overt infection remain unclear. Whether the breakthrough isolates may have been characterized by specific tissue-invasive virulence factors is unknown.

We conclude that significant candidal infection can occur in neutropenic patients with indwelling intravascular catheters receiving therapeutic doses of amphotericin B. These infections are not uniformly due to amphotericin B–resistant isolates. In our experience, these patients were clinically indistinguishable from those in whom candidemia developed before amphotericin B therapy. There was no impact on morbidity and mortality. Prolonged neutropenia may be a risk factor for breakthrough candidemia. It may be noteworthy that we have not seen additional cases coincident with the introduction of colony-stimulating factors. Additional reports of this phenomenon may help to further elucidate risk factors, optimal management, and prognosis for patients with breakthrough candidemia.

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References