Candida guilliermondii Fungemia in Patients with Hematologic Malignancies

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The microbiological, clinical, and epidemiological features of most non-Candida albicans Candida species are well known, but much less is known about species such as Candida guilliermondii, an uncommon pathogen causing a variety of deep-seated infections in immunocompromised hosts. To characterize C. guilliermondii fungemia in patients with hematological malignancies and its susceptibility to antifungal drugs, all cases of C. guilliermondii fungemia diagnosed in our department between 1983 and 2005 were retrospectively analyzed and the literature was reviewed. C. guilliermondii caused 29/243 (11.7%) candidemia episodes diagnosed during the study period. Central venous catheters were the documented sources of candidemia in 19/29 episodes (65.5%), and invasive tissue infections were documented in 2 (6.9%). In the remaining eight, the catheter was not removed and the source of the fungemia remained obscure. Seven episodes ended in death, but only one could be attributed to invasive C. guilliermondii infection. Molecular typing data reveal no evidence of common infection sources. Isolates displayed high rates of in vitro susceptibility to amphotericin B (100%), voriconazole (95%), and fluconazole (90%) and lower rates of in vitro susceptibility to flucytosine (86%), itraconazole (76%), and caspofungin (33%). Our literature review confirms that C. guilliermondii is a significantly more frequent cause of candidemia among cancer patients compared with the general hospital population. It accounted for <1% of the total number of Candida bloodstream isolates reported in the articles we reviewed, with higher rates in Europe (1.4%) and Asia (1.8%) compared with North America (0.3%).

MATERIALS AND METHODS

Definitions of fungemia. The cases analyzed in this study were collected from the medical records of the Institute of Hematology, Dipartimento di Biotecnologie Cellulari ed Ematologia, of the University La Sapienza of Rome Medical Center. These records were retrospectively reviewed to identify all patients (inpatients and outpatients) with hematological diseases who were diagnosed with candidemia between September 1983 and August 2005. Cases were included only when the diagnosis was confirmed by isolation of Candida spp. from one or more blood cultures which had been performed with Trypticase soy broth (BCG System, Roche, and Sygnal System, Oxoid, Hants, United Kingdom) and examined daily for at least 2 weeks. Yeast isolates had been identified at the species level with the VITEK and API yeast biochemical systems (BioMérieux Italia, Rome, Italy). Surveillance culture of sputum, urine, and stool specimens were performed weekly for all patients with fungemia.

All episodes of fungemia caused by C. guilliermondii were selected for detailed analysis. Patient charts (including autopsy data when present) were analyzed to characterize the fungemic episode, including its duration, presentation, and treatment; the presence of deep-seated C. guilliermondii tissue infections; outcome, etc. Particular attention was focused on its possible association with a central venous catheter (CVC). Cases were thus analyzed to determine whether the patient had a CVC when the fungemia was diagnosed and whether or not it was removed. In those cases where the CVC was removed, the results of semi-quantitative cultures of the catheter tip (26) and the patient’s response in terms of fever curves and candidemia clearance after CVC removal were noted. Isolates of C. guilliermondii that had been recovered from these patients and stored (as water suspensions) in the Clinical Microbiology Laboratory of the University La Sapienza of Rome Medical Center were subjected to independent blind testing in a second laboratory to confirm the original species level identification. Most of these strains underwent additional testing as described in the following sections.

Non-Candida albicans Candida species have been recognized as emerging pathogens in cancer patients, particularly those with hematological malignancies. Not only are serious infections caused by these yeast species increasing in frequency, but in a number of cases the strains responsible for the infection display tolerance or resistance to antymycotics (13, 41, 67). The microbiological, clinical, and epidemiological features of Candida paraapsilosis, Candida tropicalis, Candida krusei, and Candida glabrata are well known, but much less is known about other non-C. albicans Candida species. The few reports in the literature on Candida guilliermondii infections suggest that they are associated with poor clinical outcomes. This species has caused a variety of deep-seated infections in immunocompromised hosts and, less frequently, intravenous drug users. Like Candida lusitaniae, it is one of the fungal pathogens most likely to display in vitro resistance to amphotericin B and fluconazole (8, 19, 20, 28, 33, 49, 60, 63, 68). The present study was an attempt to learn more about the clinical characteristics of infections caused by C. guilliermondii and its antifungal susceptibility pattern. All cases of candidemia diagnosed in our department over the past 22 years were retrospectively analyzed to identify the prevalence and clinical features of C. guilliermondii fungemia in patients with hematological malignancies, risk factors for these infections, and their probable susceptibility to treatment with commonly used antymycotic agents. We also reviewed the literature to evaluate the epidemiological impact of this fungal pathogen.

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Antifungal susceptibility tests. Twenty-one isolates of \textit{C. guilliermondii} were available for in vitro antifungal susceptibility testing. Prior to testing, each isolate was passaged at least twice on Sabouraud dextrose agar.

Quality control strains \textit{C. albicans} ATCC 90028 and \textit{C. parapsilosis} ATCC 22019 were included in every test run.

Susceptibility to voriconazole (Pfizer, Inc., New York, NY), fluconazole (Pfizer), itraconazole (Janssen, Beerse, Belgium), amphoterocin B, and fluconazole (both from Sigma, St. Louis, MO) was tested by the broth microdilution method in accordance with the M27-A2 protocol published by the Clinical and Laboratory Standards Institute (CLSI [formerly NCCLS]) (31). Results were read after 48 h of incubation at 35°C. The lowest drug concentration producing complete growth inhibition (for amphoterocin B) or inhibition of 50% or more compared with control growth (for fluconazole, itraconazole, voriconazole, and fluconazole) was recorded as the MIC.

As the broth microdilution method became available, a standard powder preparation of the drug could not be obtained from the manufacturer. Susceptibility to this drug was thus assessed by the E-test method (AB Biodisk, Solna, Sweden) and RPMI 1640–2% glucose agar (Difco Laboratories) in accordance with the manufacturer’s instructions. This approach has displayed 100% concordance with the CLSI microdilution method for evaluation of caspofungin susceptibility in \textit{C. guilliermondii} isolates (39).

Interpretive breakpoints established by the CLSI were used to define susceptibility to fluconazole (MIC, ≤8 \text{μg/mL}), itraconazole (MIC, ≤0.125 \text{μg/mL}), fluconazole (MIC, ≤4 \text{μg/mL}) (31), and voriconazole (MIC, ≤1 \text{μg/mL}; minutes of the CLSI Antifungal Subcommittee meeting, 2005) (46). Since CLSI-validated breakpoints have not been established for amphoterocin B or caspofungin, we adopted the criteria proposed by Pfaffer et al. (40, 44), who considered MICs of ≤1 \text{μg/mL} indicative of susceptibility to these drugs.

Genotypic characterization. Genotyping was performed on 19 isolates of \textit{C. guilliermondii}. Isolates from 48- to 72-h cultures were suspended in 20 ml yeast peptone glucose (1% peptone yeast extract, 2% glucose, 2% Bacto Peptone). After 24 h of incubation with agitation at 35°C, yeasts were harvested by centrifugation and genomic DNAs were extracted as described by Scherer and Stevens (58). DNA typing was performed by random amplification of polymorphic DNA (RAPD) with primers R5412 (5′CCGAGCGCC3′) (57) and OPE03 (5′CCAGATGCA3′) (50) (M-Medical/Genenco, Florence, Italy). Thermocycling was performed with a Gene Amp PCR System 9700 (Applied Biosystems, Monza, Italy). PCR was performed with a 50-μl volume of PCR master mix containing approximately 200 ng of yeast DNA as the template, 5 μl of 10× PCR buffer (200 mM Tris-HCl [pH 8.4], 500 mM KCl), 200 μM deoxynucleoside triphosphates, 25 mM MgCl2, 1 μM primer, and 1.5 U of Taq polymerase (Life Technologies). The PCR conditions used have been described elsewhere (58).

The PCR products were electrophoresed in an agarose gel (1.2%) for approximately 2 h at room temperature in Tris-borate-EDTA buffer (89 mM Tris, 89 mM boric acid, 25 mM EDTA [pH 8.0]), stained with ethidium bromide, and visualized with UV light.

Review of the literature. We conducted a MEDLINE-based search of the English language literature published since 1966 to identify articles containing the term “candidemia,” “fungemia,” and/or “Candida/fungal bloodstream” in the title and abstract. All articles describing studies including at least 150 cases of candidemia were reviewed to estimate the relative weight of \textit{C. guilliermondii} fungemia.

RESULTS

Prevalence of \textit{C. guilliermondii} fungemia. During the 22-year period considered in this study, 247 \textit{Candida} bloodstream isolates were recovered from patients treated by our staff for hematological malignancies (Fig. 1). They were responsible for a total of 243 episodes of candidemia, 29 (11.7%) of which were caused by \textit{C. guilliermondii}. No case was observed in patients with nononcologic hematological diseases. Since 1988, when the first case occurred, the incidence of \textit{C. guilliermondii} fungemia has been 2 per 1,000 admissions. Corresponding values for \textit{C. parapsilosis}, \textit{C. albicans}, and \textit{C. tropicalis} fungemia are 4.5, 3.9, and 2.4 per 1,000 admissions, respectively.

Patients and predisposing factors. Tables 1 and 2 summarize the patient characteristics, clinical features, and outcomes of the 29 episodes of \textit{C. guilliermondii} fungemia. As shown in Table 1, more than half the cases occurred in patients with acute nonlymphoid leukemia and almost all were diagnosed during periods of hospitalization (1 to 60 days after admission; mean, 23 days). However, four (cases 4, 8, 12, and 25 in Table 2) occurred while the patient was at home (12, 25, 40, and 65 days after the most recent hospital discharge, respectively) and were treated on an outpatient basis. When the fungemia was diagnosed, well over half of the patients had neutropenia, which had been present for 5 to 60 days (mean, 20.8 days).

Most patients were receiving antibiotic therapy, and antifungal prophylaxis was being administered in 13 cases; in 7/29 (24.1%) cases, the patient was receiving fluconazole (mean dosage, 400 mg/day) and 6 (20.7%) were taking oral nonabsorbable amphotericin B (mean dosage, 2,000 mg/day). Colonization with \textit{C. guilliermondii} was documented in only one episode (3.5%) (stool culture positivity in case 2).

Clinical characteristics and outcome of \textit{C. guilliermondii} fungemia. The mean duration of candidemia (from the first positive blood culture to negative blood culture or death) was 11 days (range, 1 to 82 days), and a mean of seven positive blood cultures were collected per episode (range, 1 to 25). As shown in Table 2, all 29 episodes were associated with fever.
TABLE 1. Patient characteristics in 29 episodes of fungemia caused by *C. guilliermondii*

| Patient characteristic                              | No./total (%) |
|---------------------------------------------------|---------------|
| Total no. of episodes*                            | 29 (100)      |
| Males                                             | 21/29 (72)    |
| Inpatients                                        | 25/29 (86)    |
| Hematological malignancies                        |               |
| Acute nonlymphoid leukemia                        | 16/29 (55)    |
| Acute lymphoid leukemia                            | 7/29 (24)     |
| Non-Hodgkin’s lymphoma                            | 4/29 (14)     |
| Multiple myeloma                                  | 3/29 (10)     |
| Non-Hodgkin’s lymphoma                            | 4/29 (14)     |
| Total parenteral nutrition                         | 9/29 (31)     |
| Fluconazole prophylaxis                            | 7/29 (24)     |
| Previous antibiotic therapy                        | 23/29 (79)    |
| Colonization by same organism                      | 1/29 (3)      |

* Two patients experienced a second episode of fungemia during the study period. For this analysis, their characteristics are listed twice (once for each episode).

b Defined as <.500 polymorphonuclear cells/mm³.

Two (6.9%) were considered secondary to invasive tissue infections, i.e., case 17, which was associated with skin lesions (culture positive for *C. guilliermondii*) and cellulitis at the CVC insertion site, and case 2, in which there was multiorgan failure due to disseminated *C. guilliermondii* candidiasis. In the other 27 (93.1%), there was no clinical or microbiological evidence of invasive *C. guilliermondii* tissue infection. In 19 of these episodes, the CVC was removed, and within 24 h both the fever and candidemia had cleared. Semiquantitative cultures of the catheter tips were all positive for *C. guilliermondii*. The percentage of cases caused by *C. guilliermondii* appeared to be significantly higher in Europe and Asia compared with North America. Rates among cancer patients were also higher than those among the general hospital populations, and even lower rates emerged from the three population-based surveillance studies (7, 12, 15).

**DISCUSSION**

*C. guilliermondii* is part of the normal flora of human skin and mucosal surfaces, but it is occasionally implicated as a cause of chronic onychomycosis, acute osteomyelitis, septic arthritis, endocarditis, fungemia, and disseminated invasive infections (56). It is one of the opportunistic fungi recovered most frequently from severely immunocompromised patients. Our literature review confirmed that *C. guilliermondii* is a more common cause of candidemia in cancer patients than it is in general hospital populations, but it is rarely implicated in bloodstream infections occurring in other high-risk categories, such as intensive care unit patients (62). Even among cancer patients, the actual incidence appears to be quite low. A review of 37 reports published between 1952 and 1992 revealed that *C. guilliermondii* was responsible for only 0.8% of all systemic *Candida* infections in this risk group (67). The largest reported series includes nine cases (two-thirds occurring in leukemia patients) observed over 11 years (1988 to 1998) at the M. D. Anderson Cancer Center (28).

In comparison, the rates observed in our institute appear fairly high. The first case was observed in 1988, and since then, 28 other episodes have been diagnosed. *C. guilliermondii* accounted for 11.7% of the *Candida* bloodstream isolates recovered from our patients during the 22-year study period. Its frequency was inferior only to those of *C. parapsilosis*, *C. albicans*, and *C. tropicalis*. It is important to note, however, that the incidence of *C. guilliermondii* fungemia in our institute is by no means uniform. Approximately 80% of the cases were observed between 1992 and 2001, and only one has occurred since then.

It is difficult to pinpoint specific reasons for the relatively high frequency of *C. guilliermondii* candidemia in our institution. Cases of *C. guilliermondii* fungemia were documented in patients with different hematological malignancies who underwent various chemotherapy treatments and only in a minority of cases received systemic antifungal prophylaxis. Molecular analyses of 19 isolates recovered from our patients from 1992 to 2001 do not support the possibility of a common source of
TABLE 2. Clinical features and outcomes of 29 episodes of *Candida guilliermondii* fungemia in patients with hematological malignancies

| Case no. | Onset date | Clinical presentation | Genotype | Fungemia outcome |
|----------|------------|-----------------------|----------|------------------|
| 1        | Sept. 1988 | Fever                 | NT       | Cleared (11)     |
| 2        | March 1989 | Fever, multiple organ failure | NT NR | Present at death (7) |
| 3        | Dec. 1989 | Fever                 | NT       | Cleared (82)     |
| 4        | May 1990  | Fever                 | NT       | Cleared (2)      |
| 5        | May 1990  | Fever                 | NT       | Cleared (7)      |
| 6        | Sept. 1992 | Fever, pulmonary aspergillosis | INR AmB | Present at death (3) |
| 7        | Dec. 1992 | Fever                 | II       | Cleared (2)      |
| 8        | April 1993 | Fever                 | III      | Cleared (8)      |
| 9        | Oct. 1993 | Fever                 | I        | Cleared (7)      |
| 10       | Nov. 1993 | Fever                 | INR AmB | Cleared (7)      |
| 11       | Jan. 1994 | Fever                 | IV       | Cleared (30)     |
| 12       | Sept. 1994 | Fever                 | IV       | Cleared (6)      |
| 13       | March 1995 | Fever                 | NT       | Cleared (17)     |
| 14       | March 1995 | Fever                 | III      | Cleared (12)     |
| 15       | April 1995 | Fever                 | IINR     | Cleared (5)      |
| 16       | June 1995 | Fever                 | III      | Cleared (3)      |
| 17       | Aug. 1995 | Fever, CVC exit site infection, multiple skin lesions | I       | Cleared (19)     |
| 18       | July 1996 | Fever, septic shock   | I        | Present at death (4) |
| 19       | June 1997 | Fever                 | III      | Cleared (6)      |
| 20       | Dec. 1997 | Fever                 | NT NR    | Fluconazole Cleared (1) |
| 20a      | Feb. 1998 | Fever                 | NT       | Fluconazole Cleared (6) |
| 21       | Jan. 1998 | Fever                 | II       | Fluconazole Cleared (24) |
| 22       | March 1998 | Fever                 | II       | Fluconazole Cleared (8) |
| 23       | Aug. 1999 | Fever                 | III      | Fluconazole Cleared (6) |
| 24       | Jan. 2000 | Fever, pulmonary aspergillosis | NT       | Fluconazole-AmB Cleared (10) |
| 25       | Oct. 2000 | Fever                 | III      | Itraconazole Cleared (16) |
| 26       | Jan. 2001 | Fever                 | I        | Fluconazole-AmB Cleared (8) |
| 26a      | April 2001 | Fever                 | IV NR    | No Present at death (5) |
| 27       | Sept. 2003 | Fever                 | NT       | Present at death (3) |

*Note:* CVCs were present at diagnosis in all episodes. Culture of the removed CVCs always grew *C. guilliermondii*.

*Abbreviations:* AmB, amphotericin B; CVC, central venous catheter; NT, not tested; NR, CVC was not removed.

Candidemia cleared 5 days after CVC removal in all other cases where CVCs were removed; candidemia cleared 24 h later in all other cases where CVCs were not removed.

Candidemia was documented while the patient was not hospitalized; the remaining 25 cases occurred during hospitalization.

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Itraconazole during the first 10 years of the study, and this increase could institute. The number of CVC insertions rose progressively insertions. In addition, both types of fungemia increased in fre-

tions. Our cases occurred in patients with indwelling CVCs, at least 19 episodes (65.5%) could be classified as catheter  

guilliermondii seems to resemble that caused by C. parapsilosis. Regionally variations have been documented, and European rates episodes were usually due to genetically different strains. Re-

temperally related candidemia was removed. In case 3, the CVC was removed after 82 days of  

candidemia. Indeed, most of the other patients had been patient with disseminated infection (case 17) whose fungemia Candida with no evidence of secondary deep-seated foci. In  

candidemia clearance within 24 h. The only exception was a  

mained fairly stable and the same type of central line was used. The decreasing frequencies of C. guilliermondii and C. parapsilosis infection during this period might thus reflect improved management of these catheters. Furthermore, it should be noted that the same blood culture method in the same laboratory was used over the years of study.  

Catheter removal had a major impact on the outcome of treatment. It was almost always followed by defervescence and candidemia clearance within 24 h. The only exception was a patient with disseminated infection (case 17) whose fungemia persisted for 5 days after CVC removal. It should be noted that when the CVC was removed, this patient had been receiving antifungal therapy for 2 weeks with no sign of resolution of the candidemia. Indeed, most of the other patients had been treated unsuccessfully for more than a week before the CVC was removed. In case 3, the CVC was removed after 82 days of candidemia with no evidence of secondary deep-seated foci. In four of the nine episodes in which the CVC could not be removed, the duration of candidemia was still brief, but in the other five, the fungemia persisted and was still present when death occurred. Two patients experienced a second episode of  

infection. In fact, there were no case clusters during any of the periods considered, and even temporally related candidemia episodes were usually due to genetically different strains. Regional variations have been documented, and European rates episodes were usually due to genetically different strains. Regionally variations have been documented, and European rates periods considered, and even temporally related candidemia episodes were usually due to genetically different strains. Regional variations have been documented, and European rates episodes were usually due to genetically different strains. Regionally variations have been documented, and European rates periods considered, and even temporally related candidemia episodes were usually due to genetically different strains. Regional variations have been documented, and European rates
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