

## Emergence of a New Opportunistic Pathogen, *Candida lusitanae*

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***Candida lusitanae* has been an infrequently reported opportunistic pathogen. Most previously reported cases of serious infection caused by this organism have proven fatal and were associated with amphotericin resistance of the organism. We report two patients with hematologic malignancies undergoing cytotoxic chemotherapy who developed fungemia with this organism while they were granulocytopenic. The organisms isolated from each patient were fully susceptible and were treated successfully with amphotericin B. When isolated from an immunocompromised host, *C. lusitanae* should be considered an opportunistic pathogen and undergo antifungal susceptibility testing. Amphotericin B should be considered the drug of choice, but a poor clinical response may be indicative of a resistant isolate.**

The yeast *Candida lusitanae* was first described by van Uden and do Carmo-Sousa as a common organism in the gastrointestinal tracts of warm-blooded animals (21). Although an infrequent isolate overall (0.64% of 9,105 yeast isolates in the experience of Merz [13]), it recently has been recovered from a variety of clinical specimens (3-5, 8, 9, 11-15, 17; M. I. Pensler, P. Krawczyk, and W. D. LeBar, Clin. Microbiol. Newsl. 7:86-87, 1985). Pappagianis et al. (15) and Holzschu et al. (11) published the first documented case of opportunistic infection caused by *C. lusitanae* in a patient with acute leukemia and also demonstrated the capacity of this strain to develop resistance to amphotericin B. Two months before the initial case description, Merz and Sandford (14) reported a polyene-resistant variant of *Candida tropicalis* that was later reidentified as *C. lusitanae* (13). In 1985, Pensler et al. (Clin. Microbiol. Newsl. 7:86-87, 1985) reported the first successful therapy of *C. lusitanae* fungemia. Before that, with the exception of a case of urinary tract infection (3) and a case of transient fungemia not requiring therapy (4), all reported infections with *C. lusitanae* had proven fatal, generally because of amphotericin B resistance (8, 11-15). We report two cases of *C. lusitanae* fungemia occurring in patients with hematologic malignancies on the same oncology ward that were successfully treated with amphotericin B. We also review the English literature on cases of fungemia caused by this recently recognized opportunistic pathogen.

### CASE REPORTS

**Case 1.** A 60-year-old female was diagnosed as having chronic lymphocytic leukemia 8 months before the current admission after presenting with diffuse lymphadenopathy, hepatosplenomegaly, anemia, and a mature lymphocytosis of 175,000/mm<sup>3</sup>. Systemic chemotherapy was of only transient benefit, and 2 months before admission, a course of total body irradiation was given. Two weeks before admission, biopsy of an enlarging right axillary node revealed malignant lymphoma of the diffuse large cell type. Several erythematous plaques noted on the upper and lower extremities were also biopsied and revealed lymphoma cutis.

The patient was admitted with symptoms of fever and cough, a leukocytosis, and a new right lower lobe infiltrate

on chest roentgenogram. Cultures of blood, urine, and sputum were obtained and were negative. Mezlocillin and tobramycin were empirically administered, and the temperature of the patient returned to normal with resolution of her infiltrate. Antibiotics were discontinued on hospital day 5. Diarrhea developed; and culture, examination of stool for ova and parasites, and assay of stool for *Clostridium difficile* toxin were negative. On hospital day 6, a chemotherapy regimen of prednisone, cyclophosphamide, doxorubicin, etoposide (VP-16), and methotrexate was begun. On day 10, oral candidiasis was documented and treated with clotrimazole oral troches. On hospital day 16, granulocytopenia and a temperature of 39.6°C were noted. Mezlocillin, nafcillin, tobramycin, and trimethoprim-sulfamethoxazole were administered. Two of three blood cultures were documented to contain both *Staphylococcus aureus* and *Klebsiella pneumoniae*. The temperature of the patient returned to normal within 72 h. On day 21, her temperature again was noted to be 39.5°C, and amphotericin B was begun empirically. On day 24, one of two blood cultures grew *C. lusitanae*. Severe nausea and vomiting and persistent diarrhea developed, and a subsequent stool culture also grew *C. lusitanae*. Nodular purpuric skin eruptions with surrounding petechiae were noted on the forearms and lower extremities on day 26 (Fig. 1). Her granulocyte count improved, and her temperature returned to normal. Antibacterial therapy was discontinued on day 35. A biopsy of one of the nodular skin lesions on hospital day 38 revealed dermal necrosis with acute inflammation suggestive of, but not conclusive for, disseminated candidiasis.

The patient was discharged home with no improvement in her measurable hematologic disease and completed a 6-week course of amphotericin B (700 mg) as an outpatient with complete resolution of her skin lesions and diarrhea. Two months after the admission, she was readmitted with *Salmonella* septicemia and died. Postmortem examination revealed no evidence of tissue invasion (liver, kidney, etc.) consistent with persistent fungal disease.

**Case 2.** A 43-year-old male with relapsed acute nonlymphocytic leukemia was admitted to the same oncology ward 7 days after patient 1. He was admitted to a different room but was managed by the same medical staff. A Broviac catheter was inserted into the saphenous vein, and he was given cytosine arabinoside (3 g/m<sup>2</sup> every 12 h for 12 doses) and daunorubicin. On day 8, ketoconazole was empirically

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FIG. 1. Nodular purpuric skin eruption on forearm of patient 1 consistent with disseminated candidiasis.

begun for oropharyngeal antifungal prophylaxis. On day 10, granulocytopenia and a temperature of 38.5°C were noted. Mezlocillin, vancomycin, and tobramycin were administered without defervescence. Blood, sputum, and urine cultures were obtained and were negative. On day 13, nausea, vomiting, and diarrhea developed, and ketoconazole was discontinued. On day 14, amphotericin B was begun because of persistent fever in the setting of continued granulocytopenia. On day 17, one of two blood cultures was documented to contain *C. lusitaniae*. This occurred 48 h after patient 1 was documented to have a positive blood culture for the same organism. Subsequent stool and oral cultures also contained *C. lusitaniae*. By day 30, the patient's granulocyte count had recovered without evidence of leukemic cells, and antibacterial therapy was discontinued. By day 38, he had received 680 mg of amphotericin, and blood and stool cultures were negative for *C. lusitaniae*. Blood cultures obtained through the Broviac catheter remained sterile as well. Amphotericin B was discontinued because of persistent nausea and vomiting, and the patient was discharged home. By the 12-month follow-up, he had remained in hematologic remission without evidence of systemic candidiasis.

#### MATERIALS AND METHODS

Fungal cultures were incubated at 25°C on Sabouraud dextrose agar and on gentamicin-cycloheximide-containing medium and at 37°C on Sabouraud dextrose agar and brain heart infusion agar. One or two colonies of each fungal isolate were incubated in bovine serum for 3 to 4 h at 37°C and subsequently inspected microscopically for germ tube production. If no germ tube was produced, the fungal isolate was incubated on urea agar at 37°C. If no urease reaction was observed (presumptively excluding *Cryptococcus neo-*

*formans*), the isolate was identified with the API 20C system (Analytab Products, Plainview, N.Y.). In vitro susceptibilities of each fungal isolate to amphotericin B, flucytosine, miconazole, and ketoconazole were determined by methods described by Shadomy et al. (19).

#### RESULTS

*C. lusitaniae* colonies on Sabouraud dextrose agar were cream colored, smooth, and glistening with slightly spreading edges. The organism grew at both 25 and 37°C. Growth was inhibited on cycloheximide-containing medium. There was no germ tube production in bovine serum, and there was no urease reaction on urea agar. Identification was based on the API 20C system supplemented with a positive rhamnose assimilation test.

The susceptibilities of the *C. lusitaniae* blood isolates are shown in Table 1. Both isolates were susceptible to amphotericin B and flucytosine, with minimal fungicidal concentration cutoff values of 2.0 µg/ml and 8 to 16 µg/ml, respectively. Both isolates were resistant to the imidazole derivatives ketoconazole and miconazole.

#### DISCUSSION

Of over 600 species of yeasts in the current literature, only approximately 25 species are pathogens in humans. The most common isolates associated with human infections are *Candida albicans* and *C. tropicalis* (1). *C. lusitaniae* has been a rare opportunistic pathogen, but when isolated it has caused serious and usually fatal disease. This report describes two patients with serious infections caused by *C. lusitaniae* that were successfully treated. As the case of transient fungemia caused by *C. lusitaniae* reported by Bradsher illustrates, fungemia alone, especially if associated with an intravascular catheter, does not imply tissue invasion and may resolve after removal of the catheter without parenteral therapy (4). Our patients were febrile, granulocytopenic patients with clinical manifestations consistent with serious fungal infection. In each patient, *C. lusitaniae* was isolated from blood and at least one additional extravascular source. Characteristic nodular skin lesions were noted in patient 1. Both patients demonstrated a clinical response to therapy. Although patient 2 had an indwelling Broviac catheter, the catheter was not believed to be the source of his fungemia, and he was successfully treated without its removal.

The possibility of nosocomial transmission was considered since both patients developed intestinal colonization and fungemia within 48 h of each other while hospitalized on the same oncology ward. Stool cultures obtained from other patients with diarrheal illnesses on the same ward yielded no further isolates of *C. lusitaniae*. Furthermore, no additional isolations of *C. lusitaniae* were reported from the oncology unit in the 12-month period after these two cases. Although the antifungal susceptibility patterns for both isolates were

TABLE 1. Antimicrobial susceptibilities of *C. lusitaniae* blood isolates<sup>a</sup>

Patient	AMB		5-FC		KTZ		MCZ	
	MIC (µg/ml)	MFC (µg/ml)	MIC (µg/ml)	MFC (µg/ml)	MIC (µg/ml)	MFC (µg/ml)	MIC (µg/ml)	MFC (µg/ml)
1	0.39	0.78	0.20	0.78	12.5	100	3.12	25
2	0.39	1.56	0.20	0.39	12.5	50	3.12	50

<sup>a</sup> Abbreviations: AMB, amphotericin B; 5-FC, flucytosine; KTZ, ketoconazole; MCZ, miconazole; MFC, minimal fungicidal concentration.

TABLE 2. Characteristics of patients with *C. lusitaniae* fungemia<sup>a</sup>

Case	Author(s) (reference)	Age, sex	Underlying disease or condition	Cytotoxic or steroid therapy	Granulocytopenia	Intra-vascular catheter	Prior anti-biotics	Positive extra-vascular cultures	Ampho-tericin B therapy	Outcome
<b>Adult</b>										
1	Pappagianis et al. (15)	47 yr, M	MM, ANNL	Yes	Yes	No	Yes	Oral, NP, RT, stool	981 mg	Death
2	Merz and Sandford (14)	—	Bone marrow transplant	Unk	Unk	Unk	Unk	Oral, NP, PF, stool, urine	Yes	Death
3	Guinet et al. (8)	—	Peritonitis	No	No	Yes	Yes	Catheter tip	Unk	Death
4	Libertin et al. (12)	27 yr, F	Vasculitis	Yes	No	Yes	Yes	RT, catheter tip	300 mg	Death
5	Bradsher (4)	43 yr, F	Small bowel obstruction	No	No	Yes	Unk	None	No	Recovery
6	Pensler et al. <sup>b</sup>	84 yr, M	Pneumonia	No	No	Unk	Yes	RT	Yes	Recovery
7	Hadfield et al. (9)	66 yr, M	ANLL	Yes	No	Unk	Yes	Urine	No	Death
8	Thomas et al. <sup>c</sup>	22 yr, F	Trauma	No	No	Yes	Yes	Catheter tip	498 mg (+ 5-FC)	Death
9	Present case 1	60 yr, F	CLL, lymphoma	Yes	Yes	No	Yes	Stool	710 mg	Recovery
10	Present case 2	43 yr, M	ANLL	Yes	Yes	Yes	Yes	Oropharynx, stool	680 mg	Recovery
<b>Pediatric</b>										
11	Merz (13)	13 yr, F	Acute leukemia	Yes	Yes	Yes	Unk	Catheter tip, urine, RT	Yes	Death
12	Christenson et al. (5)	2 mo, M	Congenital heart disease	No	No	Yes	Yes	RT	21.7 mg/kg	Recovery
13	Sanchez and Cooper (17)	26 wk, M	Prematurity	No	No	Yes	Yes	Urine, CSF	30 mg/kg	Recovery

<sup>a</sup> Abbreviations: M, male; F, female; MM, multiple myeloma; ANLL, acute nonlymphocytic leukemia; CLL, chronic lymphocytic leukemia; Unk, unknown; NP, nasopharynx; RT, respiratory tract; PF, pleural fluid; CSF, cerebrospinal fluid; 5-FC, flucytosine. —, Not specified in original publication.

<sup>b</sup> Clin. Microbiol. Newsl. 7:86–87, 1985.

<sup>c</sup> Clin. Microbiol. Newsl. 7:142–143, 1985.

nearly identical, conclusive identification of the isolates as the same strain was not possible. The role of nosocomial transmission in this instance remains speculative.

The clinical characteristics of our patients were quite similar to those of previously reported patients with *C. lusitaniae* fungemia (Table 2). Eleven cases have been reported in the English literature. Of these, eight patients were adults, two patients were neonates, and one patient was a teenager. As can be seen in Table 2, most patients with *C. lusitaniae* fungemia were immunocompromised, usually owing to an underlying malignancy. Not surprisingly, the use of broad-spectrum antibiotics (10 of 13 patients), the presence of an intravascular catheter (8 of 13), the use of cytotoxic or corticosteroid therapy (6 of 13), and the occurrence of granulocytopenia (4 of 13) were noted frequently. Total parenteral nutrition, a known risk factor for the development of fungemia caused by other *Candida* species (6), could not be assessed as a predisposing factor because of a lack of documentation in previous reports. Both of our patients received some form of parenteral nutrition at various times during their hospitalizations.

To date, over 100 clinical isolations of *C. lusitaniae* have been reported (Table 3). Three-fourths of the isolates have been recovered from the blood, urine, or respiratory tract. The relative paucity of isolates involving the oral and vaginal mucosae and nasopharynx may reflect either a failure to conclusively identify non-*C. albicans* *Candida* species recovered from these sites or a lesser likelihood of obtaining fungal cultures in these areas. Positive extravascular cultures in patients with *C. lusitaniae* fungemia reported in the literature (Table 2) were obtained most commonly from the respiratory tract and pharynx, stool, urine, or intravascular

catheters; and many patients had positive cultures from more than one extravascular site. In view of these data, the most likely portals of entry for *C. lusitaniae* appear to be the genitourinary and respiratory tracts or colonized indwelling intravascular catheters.

Identification of *C. lusitaniae* has proven to be problematic, with many earlier reported cases (cases 1, 2, 3, and 13 [Table 2]) being misidentified initially as *Candida parapsilosis* or *C. tropicalis* (8, 11, 14, 15, 17) or even *Saccharomyces* species (case 7; 9). The morphologic characteristics, fermentation and assimilation reactions, and growth on selected media have been well documented for this species (21). The main differential characteristics of *C. lusitaniae* relate to the assimilation of cellobiose and fermentation of trehalose (both negative for *C. parapsilosis*) (8, 11). The lack of growth on cycloheximide-containing medium, pink-appearing colonies on triphenyltetrazolium chloride agar, the assimilation of rhamnose, and the absence of maltose and sucrose fermentation serve to distinguish *C. lusitaniae* from *C. tropicalis* (8, 18). Shinoda et al. found that serological screening classified *C. lusitaniae* with *C. albicans* serotype A, whereas the API 20C system classified *C. lusitaniae* with *C. tropicalis* (20). The latter observation contrasts with more recent experience with the API 20C system, which has often provided reliable separation of *C. lusitaniae* from *C. tropicalis* (3–5, 9, 12–14, 17; Pensler et al., Clin. Microbiol. Newsl. 7:86–87, 1985).

Resistance to amphotericin B has been an important clinical finding in *C. lusitaniae* isolates, since all fatal cases of *C. lusitaniae* fungemia have involved a resistant isolate (8, 11, 13–15); the exception being the report by Libertin et al. (12) in which susceptibility testing was not performed. The

TABLE 3. Clinical isolations of *C. lusitaniae*

Author(s) (reference)	No. of isolations <sup>a</sup>									
	Oral, nasopharynx	Resp. tract, sputum, lung	Pleural fluid	Stool	Urine	Blood	Vasc. cath.	Soft tissue, skin	Vagina	CSF
Pappagianis et al. (15)	2	4		1		3				
Merz and Sandford (14)	3		3	2	9	3				
Guinet et al. (8)						3	2			
Baker et al. (3)					1					
Merz (13)		24		8	15	8	1	1	1	
Libertin et al. (12)		2				10	1			
Bradsher (4)						1				
Christenson et al. (5)		1			1	4		1		
Sanchez and Cooper (17)					4	13				1
Pensler et al. <sup>b</sup>		3				3				
Hadfield et al. (9)					1	4				
Thomas et al. <sup>c</sup>						1	1			
Present report	1			2		2				
Total (%)	6 (4)	34 (23)	3 (2)	13 (9)	31 (21)	55 (36)	5 (3)	2	1	1

<sup>a</sup> Abbreviations: Resp. tract, respiratory tract; Vasc. cath., vascular catheter; CSF, cerebrospinal fluid.

<sup>b</sup> Clin. Microbiol. Newsl. 7:86-87, 1985.

<sup>c</sup> Clin. Microbiol. Newsl. 7:142-143, 1985.

development of resistance to amphotericin B by *C. lusitaniae* during therapy was first noted by Pappagianis et al. (15) and later described by Merz and Sandford (14). Guinet et al. (8) described the first case of a *C. lusitaniae* isolate resistant to amphotericin B before therapy. Of 58 isolates of *C. lusitaniae* from 13 patients reviewed by Merz (13), only 2 isolates were found to be resistant to amphotericin B, these being recovered from a child undergoing cytotoxic therapy for leukemia. Ahearn and McGlohn (2) reviewed the susceptibilities of seven isolates of *C. lusitaniae* and found that, although the MICs of amphotericin B fell within attainable levels in serum, the minimal fungicidal concentrations were more than two dilutions greater. Relative resistance to ketoconazole and miconazole was noted among their isolates, yet all were susceptible to flucytosine. They concluded that flucytosine may be the drug of choice for *C. lusitaniae* infections. Thomas et al. reported a patient with *C. lusitaniae* fungemia involving an amphotericin B-susceptible isolate whose fungemia persisted despite 12 days of amphotericin B therapy (M. G. Thomas, D. H. Parr, M. diMenna, and S. D. R. Lang, Clin. Microbiol. Newsl. 7:142-143, 1985). The addition of flucytosine to the therapeutic regimen resulted in sterilization of the blood. This probably represented the development of amphotericin B resistance during therapy, but repeat susceptibility testing was not performed. Susceptibility to flucytosine has not been a universal finding, however. Baker et al. (3) described a failure of flucytosine in a patient with a *C. lusitaniae* urinary tract infection that was eradicated with amphotericin B bladder irrigation. Both of our patients had isolates of *C. lusitaniae* resistant to ketoconazole and miconazole but susceptible to amphotericin B and flucytosine. Our patients' patterns of susceptibility to amphotericin B were in agreement with the report of Ahearn and McGlohn (2).

The frequent demonstration of resistance to amphotericin B in *C. lusitaniae* isolates was unexpected. Despite the widespread use of the polyene antibiotics amphotericin B and nystatin for over 20 years, the isolation of resistant yeast strains from clinical specimens has been rare (10). In a review of 864 clinical yeast isolates, Safe et al. found only 3 (0.4%) that could be classified as resistant (16). Dick et al. examined 1,372 yeast isolates from 308 patients, including

those from an oncology subpopulation, and found 55 resistant isolates from 6 patients, for an overall incidence of 4% (7). Their primary observation was that the emergence of polyene-resistant yeasts occurred only in patients undergoing treatment for acute leukemia or in aplastic patients after bone marrow transplantation. All these patients experienced extended periods of hospitalization, granulocytopenia, therapy with cytotoxic agents, and extended antibiotic therapy. Dick et al. concluded, as had Pappagianis et al. (15), that the use of cytotoxic drugs should be considered a contributing factor in the development of resistance. The clinical characteristics of the patients reviewed in this paper bear a striking resemblance to those of the subgroup of patients believed to be at risk by Dick et al. (7).

In conclusion, *C. lusitaniae* should be considered an opportunistic pathogen in both adults and children when isolated in the appropriate clinical setting, especially from patients with underlying malignancy undergoing cytotoxic therapy, with granulocytopenia receiving prolonged broad-spectrum antibiotic therapy, or with intravascular catheters. All isolates of *C. lusitaniae* should undergo susceptibility testing both before and during therapy, since the occurrence of amphotericin B resistance has been frequently reported. In addition, clinical isolates suspected of being *C. tropicalis* or *C. parapsilosis* should undergo biochemical testing with kits, such as the API 20C system, supplemented by additional assimilation and fermentation tests to ensure that misidentification does not occur. Amphotericin B and flucytosine are the only effective drugs for infections caused by *C. lusitaniae*, and a poor clinical response to either agent may be construed as indicative of a resistant isolate.

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