Nosocomial transmission of *Candida pelliculosa* fungemia in a pediatric intensive care unit and review of the literature

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Horizontal transmission of Candida species in the hospital environment and the fungemia rates have increased in the past decade. We describe a nosocomial cluster of fungemia caused by *Candida pelliculosa* (teleomorph *Pichia anomala*) in four infants hospitalized in the pediatric intensive care unit. Candida isolates had strictly related fingerprints, as generated by randomly amplified polymorphic DNA analysis using five different primer sets. The four babies were all treated successfully and recovered. All of the isolates were susceptible to the antifungals tested including amphotericin B, flucytosine, fluconazole, miconazole, micafungin, itraconazole, and voriconazole. Infection control procedures were adapted in the unit and no relapse was detected. In addition, 30 publications presenting 450 pediatric and 28 adult cases are reviewed.

Key words: Candida pelliculosa, Pichia anomala, fungemia, nosocomial, pediatric intensive care unit.

The incidence of neonatal candidiasis in low birth weight (LBW) infants is 7%–20%, and is associated with significant morbidity and mortality[1,2]. Previous epidemiologic outcome studies of neonatal candidiasis have reported crude mortality rates of 30%–60%, and increases in rates with decreasing birth weight[3,4].

Among Candida species pathogenic to humans, *Candida albicans* has been the species most often associated with neonatal infection. Recent reports, however, have suggested an increasing number of infections attributable to non-albicans species associated with common-source outbreaks[5-8] in pediatric ages.

Candida pelliculosa (teleomorph *Pichia anomala*-previously called *Hansenula anomala*-genbank anamorph *Candida beverwijkiae*) is a yeast frequently found in various fruits, tree exudates, soil, vegetables and other organic compounds[9]. It has occasionally been reported as the causative agent of nosocomial fungemia in both immunocompetent and immunocompromised pediatric patients[10-14].

Infant colonization with Candida spp. has been shown to occur either by horizontal transmission from nurses[15] or by cross-infection between infants through the hands of healthcare workers[16]. Preterm neonates were found to be colonized with Pichia (Hansenula) anomala in the hospital setting[15]. Nevertheless, direct evidence demonstrating that nosocomial disseminated Candida spp. infection may be linked to prior infant colonization is still lacking.

Here, we describe a horizontal transmission of *C. pelliculosa* fungemia in four neonates hospitalized in an intensive care unit of a Turkish tertiary care hospital.

Material and Methods

Cases and Identification of *Candida pelliculosa* strains

Four babies, including two premature and two

termed newborns hospitalized in the neonatal intensive care unit (NICU) showed signs of infection. Yeast colonies were obtained from blood cultures of the babies. Yeasts were identified according to germ tube production, corn meal agar morphology and carbohydrate assimilation profiles in ID32C kit (bioMerieux, France).

An active surveillance program is routinely performed for infection control in the NICU. After the second case of *C. pelliculosa* fungemia was diagnosed, some molecular epidemiological investigations were performed. Physicians and nursing staff of the ICU were screened for oral and hand carriage of Candida spp. Extensive sampling was undertaken from fomites and other environmental sources of the ward (floors, disinfectant solutions, multi-dose vials, infusion pumps, commercially prepared parenteral nutrition bags, and other medical equipment), and cultures were performed. Finally, compliance with standard infection control measures, including rigorous handwashing, was emphasized. Infusion sets were changed to a new one at the 48th hour (h) of insertion, instead of at 24 h. This misuse was abandoned.

In Vitro Susceptibility

Antifungal susceptibility testing for amphotericin B, flucytosine, fluconazole, miconazole, micafungin, itraconazole, and voriconazole was performed for each strain by colorimetric microdilution method using a commercially available kit, ASTY (Antifungal Susceptibility Testing of Yeasts, Kyokuto Pharmaceutical Industrial, Japan).

Acquisition of Genomic DNA

Genomic DNA was extracted according to Sugita et al.[17] The strains were grown on Sabouraud dextrose agar (SDA; Difco) for 48 h at 35°C. The cellular biomasses were separated by centrifugation at 14,000 x g and resuspended in 300 µl of lysing buffer (100 mM Tris HCl (pH 8.0); 30 mM EDTA (pH 8.0); and 0.5% sodium dodecyl sulfate) and boiled at 100°C for 15 minutes (min) in water bath. The nucleic acids obtained were transferred to 150 µl of phenol chloroform isoamyl alcohol (25:24:1) and then precipitated with absolute ethanol. The precipitate was centrifuged and washed twice with 70% ethanol, dried and resuspended in 30 µl of TE buffer (10mM Tris-HCl (pH 8.0), 1 mM EDTA (pH 8.0).

Randomly Amplified Polymorphic DNA (RAPD) Fingerprinting

All of the *C. pelliculosa* isolates were typed by RAPD. Five different primers were used and compared. M13 primer (5'-AGTCAGCCAAC-3'), RPO2 (5'-GCAATCCCCCA-3'), AP-1 (5'-AGTCAGCCAA-3'), OPE1 (5'-CCCAAGGTCC-3'), and RO8 (5'-GGATGTCGAA-3') were used for RAPD analysis. Briefly, approximately 10 ng Candida DNA was added to a 0.2 ml microfuge tube containing 20 pmol oligonucleotide primer, 250 µM each of dATP, dTTP, dCTP and dGTP, 3 mM $MgCl_2$, 2.5 U Taq DNA polymerase and 10X buffer in a final volume of 35 µl (all of the chemicals were obtained from Wako Nippon Gene, Japan). Amplification procedure was performed with an initial denaturation at 94°C for 1 min, followed by 35 cycles of 30 seconds (s) at 94°C, 30 s at 40°C for M13, 35°C for RPO2, 20°C for AP-1, 30°C for OPE3-RO8, and 30 s at 72°C, with a final extension at 72°C for 10 min in an thermal cycler (GeneAmp PCR System 9700, Applied Biosystems, USA). The products were separated in 1.5% (w/v) agarose gels containing 0.5 µg ethidium bromide ml^{-1} and viewed on a UV transluminator.

DNA Sequencing

DNA sequencing was additionally performed for the confirmation of identification of *C. pelliculosa*. The D1/D2 regions of 26S rDNA in the rRNA gene were sequenced directly from polymerase chain reaction (PCR) products using the primer pair ITS1 (GTCGTAACAAG GTTAACCTGCGG) and NL4 (GGT CCG TGT TTC AAG ACG G). The PCR products were sequenced using an ABI 310 DNA sequencer and a BigDye Terminator Cycle Sequencing Ready Reaction kit (Perkin-Elmer) according to the manufacturer's instructions. The sequence data were analyzed using the National Center for Biotechnology Information (Bethesda, MD, USA) BLAST system (available at http://www.ncbi.nlm.nih.gov/BLAST/).

Review of the Literature

PubMed service of the U.S. National Library of

Medicine and the National Institutes of Health (http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=pubmed) were screened using the key words of *Candida pelliculosa - Pichia anomala - Hansenula anomala – Candida beverwijkiae* case reports.

Results

Genetic analysis of four blood isolates derived from the four neonates demonstrated one genotype (Figs. 1, 2). In order to identify the source of infection and the route of transmission, the search for *C. pelliculosa* was extended to the medical personnel as well as to environmental surfaces. At the time of our investigation, we were unable to identify *C. pelliculosa* in any of the other clinical, surveillance, or environmental samples we tested. Horizontal transmission of *C. pelliculosa* between the babies was emphasized.

At the time the candidemia cases were detected, the four affected patients were in the same room. Their periods of hospitalization overlapped, and they were all cared for by NICU staff members. The clinical characteristics of the four patients are summarized in Table I. Outcomes of the babies were recovery. Isolates were susceptible to the seven antifungals tested. Minimal inhibitory concentrations (MICs) are mentioned in Table II.

The DNA sequences of all the isolates were completely matched to that of *C. pelliculosa* from the GenBank DNA database. Therefore, all the isolates were identified as a unique strain of C. pelliculosa. Clonal spread was confirmed by DNA sequencing results.

Thirty articles reported from 1986 to 2006 were reviewed. Articles were selected if they were presenting human infections, including case reports and outbreaks. Reviews, antifungal susceptibility data and epidemiological analysis were excluded. Among the 30 publications, 14 were pediatric cases, whereas 15 were adults. In one publication, both pediatric and adult cases were reported. A total of 478 patients were reported, including 450 children and 28 adults. All of the pediatric cases were fungemia, while four of the adult cases presented pneumonia, endocarditis, pancreatitis, or urinary tract infections. Other adult cases were also fungemia. The review of the literature is detailed in Table III.

Discussion

The increasing frequency of nosocomial infections in the neonatal ICU setting and high mortality rate associated with disseminated diseases have underscored the importance of understanding the molecular epidemiology of fungal infections[18]. Due to the ever increasing incidence and constant possibility of exogenous nosocomial acquisition of Candida infections, efforts to detect and prevent the cross-transmission of Candida spp. isolates are clearly warranted[19]. There are several reports of nosocomial cross-infections due to Candida spp. in the neonatal ICU setting[20-22]. As deep-seated infections due to *C. pelliculosa*, either as single cases or as outbreaks, have been reported rarely, our study contributes some important data to the literature.

The first report about *H. anomala* isolation from the lungs of infants was published in 1958 by Wang and Schwarz[24]. The first report about *C. pelliculosa* was published by de Montemayor and Gamboa in 1959[23]. In the literature, totally 30 publications, including 9 outbreak reports and 22 case reports were detected. In one publication, one pediatric case and four adult cases were reported. Among the 9 outbreak reports, 7 were pediatric cases while 2 were adults. Among the 22 case reports, 8 were pediatric cases, while 14 were adults. In all of these reports, a total of 478 patients were reviewed, including 450 of baby or young children, and 28 of adults. The literature review is detailed in Table III.

The predominance of young children with candidemia is noteworthy, as it is consistent with reports that infants are at particular risk of candidemia, for multiple reasons[25].

However, the reasons for the occurrence of the majority of *C. pelliculosa* fungemia cases in the pediatric rather than adult age groups should be evaluated with further studies. When the literature was evaluated carefully, it was seen that *C. pelliculosa* fungemia causes outbreaks in pediatric wards, while most of the adult cases were sporadic case reports (Table III).

Non-perinatal nosocomial transmission of *C. pelliculosa* suggests that the route of transmission is primarily from non-maternal sources, possibly via cross-contamination of the

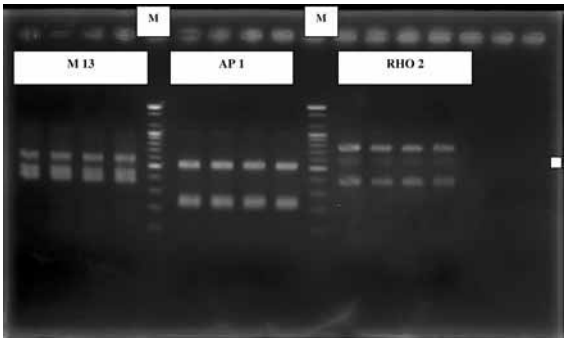

Fig. 1. Random amplified polymorphic DNA fingerprints of *Candida pelliculosa* clinical isolates. Lines 1-4 RAPD analysis using M13 primer, lines 6 to 9 RAPD analysis using AP1 primer, lines 11 to 14 RAPD analysis using RHO2 primer, lane M, lambda HaeIII molecular size marker (100 bp).

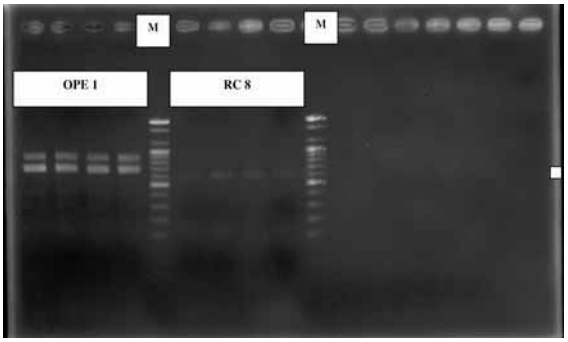

Fig. 2. Random amplified polymorphic DNA fingerprints of *Candida pelliculosa* clinical isolates. Lines 1-4 RAPD analysis using OPE1 primer, lines 5 to 8 RAPD analysis using RC8 primer, lines M, lambda HaeIII molecular size marker (100 bp).

Table I. Clinical Characteristics of Four Patients with *Candida pelliculosa* Fungemia

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age (gestational week)	24	29	38	37
Birth weight (g)7	50	790	3460	3240
Underlying disease	Prematurity, RDS, Intracranial hematoma	PDA,ASD, VSD,NEC	Pulmonary hypertension Intraparanchymal hematoma, ASD	Pyloric stenosis
Potential risk factors for candidemia				
CVC	Yes	Yes	Yes	Yes
Mechanic ventilation	Yes	Yes	Yes	No
TPN	Yes	Yes	Yes	No
Prior antibiotic usage	Ampicillin + amikacin / Meropenem + teicoplanin	Ampicillin + amikacin / Meropenem + teicoplanin	Meropenem + teicoplanin	Ampicillin + amikacin
Prior antifungal prophylaxis	No	No	No	No
Thoracal tube	Yes	No	No	No
Ventriculo-peritoneal shunt	No	No	Yes	No
Blood culture	*C. pelliculosa* (peripheral vein) + *Enteroccocus faecalis* (CVC)	*C. pelliculosa* (peripheral vein)	*C. pelliculosa* + CNS (peripheral vein)	*C. pelliculosa* (CVC)
Therapy				
Antifungal therapy	FL, AB + VO	FL, AB	AB	No
Catheter removal	Yes	Yes	Yes	Yes
Outcome				
Candidemia	Cleared	Cleared	Cleared	Cleared
Clinical	Recovery	Recovery	Recovery	Recovery

RDS: Respiratory distress syndrome. PDA: Patent ductus arteriosus. ASD: Atrial septal defect. VSD: Ventricular septal defect. NEC: Necrotizing enterocolitis. CVC: Central venous catheter. TPN: Total parenteral nutrition. FL: Fluconazole. AB: Amphotericin B. VO: Voriconazole.

Table II. Antifungal Susceptibility of the Strains

	AMP B	5-FC	FLCZ	MCZ	MCFG	ITCZ	VRCZ
Strain 1	0.25	0.125	16	4	0.25	2	0.25
Strain 2	0.25	0.125	32	4	0.25	0.5	1
Strain 3	0.25	0.125	32	2	0.125	0.5	0.5
Strain 4	0.25	0.125	16	2	0.25	0.5	0.5

AMP B: Amphotericin B. 5-FC: 5-Flucytosine. FLCZ: Fluconazole. MCZ: Miconazole. MCFG: Micafungin. ITCZ: Itraconazole. VRCZ: Voriconazole.

Table III. Review of the Literature

Pediatric cases		Adult cases		References
Case report	Outbreak	Case report	Outbreak	
	2 patients			Paula CR, et al. Med Mycol. 2006[14]
	17 patients			Pasqualotto AC, Infect Control Hosp Epidemiol. 2005[13]
1				Bakir M, Mycoses. 2004[12]
1			4 patients	Mestroni SC Rev Argent Microbiol. 2003[29]
		1*		Kane SL, Ann Pharmacother. 2002[30]
1				Hanzen J, Scand J Infect Dis. 2002[31]
			8 patients	Kalenic S, Eur J Epidemiol. 2001[32]
	8 patients			Aragão PA, Pediatr Infect Dis J. 2001[10]
	379 patients			Chakrabarti A, J Clin Microbiol. 2001[7]
1				Ma JS, J Microbiol Immunol Infect. 2000[33]
1				Wong AR, J Paediatr Child Health. 2000[34]
	24 patients			Thuler LC, Mycoses. 1997[11]
		1		Kunová A, Chemotherapy. 1996[35]
		1		Sumitomo M, Kansenshogaku Zasshi. 1996[36]
	4 patients			Yamada S, Scand J Infect Dis. 1995[37]
1				Goss G, Bone Marrow Transplant. 1994[38]
1				Alter SJ, Pediatr Infect Dis J. 1994[39]
		1		Hirasaki S, Intern Med. 1992[40]
1				Sekhon AS, Eur J Epidemiol. 1992[41]
		1*		Neumeister B, Mycoses. 1992[42]
		1		Salesa R, Mycoses. 1991[43]
		2 patients		López F, Enferm Infecc Microbiol Clin. 1990[44]
		1		Dickensheets DL, Rev Infect Dis. 1989[45]
		1		Muñoz P, Arch Intern Med. 1989[46]
		1*		Qadri SM, Mycopathologia. 1988[47]
		1		Haron E, Rev Infect Dis. 1988[48]
		2 patients		Klein AS, Arch Intern Med. 1988[49]
		1*		Nohinek B, Am J Med. 1987[50]
		1		Milstoc M, N Y State J Med. 1986[51]
	8 patients			Murphy N, Lancet. 1986[52]
Total cases	8 patients	442 patients	16 patients	12 patients	Total 30 publications

*: Infections other than fungemia (pneumonia, pancreatitis, urinary tract infection, endocarditis)

hands of healthcare workers or parents. Since patient screening was not carried out in our hospital at the admission, and the cluster was only investigated retrospectively, it is difficult to prove whether these patients became infected from a common source within the hospital environment or if the yeast was transmitted from the first patient to the others. Although the outbreak strain was not isolated from the hands of the ward personnel during our retrospective investigation, the transmission of *C. parapsilosis* between patients and staff would seem likely. Indeed, the nosocomial spread of fungal infections was stopped just after the standard infection control measures were reinforced in the ICU. Although no definitive source of the fungal strains could be found, this study reemphasizes why it is important for healthcare workers to wash their hands and follow other infection control procedures to prevent the nosocomial transmission of pathogens in the NICU environment.

In vitro testing showed a poor susceptibility of *C. pelliculosa* strains to fluconazole, confirming previously reported data [26]. Susceptibility to amphotericin B, flucytosine, miconazole, micafungin, itraconazole, and voriconazole was demonstrated with all of the isolates.

Molecular epidemiologic methods are required for the demonstration of clonal relationship between the isolates. The RAPD or arbitrarily primed PCR (AP-PCR) analysis is technically simple and often detects variations among Candida spp. isolates that are indiscriminative with other typing methods. RAPD is less time-consuming and easy to apply but the disadvantage of this method is its low reproducibility, although results have demonstrated the high discriminatory power and typing efficacy of this method [27,28].

The clinical importance of the genotyping and karyotyping of the Candida isolates is the strain characterization in order to identify hospital clusters. The genotyping of Candida isolates can provide important information for understanding and controlling the nosocomial spread of infections within a hospital. Different types of infections will clearly require different prophylactic approaches. We demonstrated that exogenous transmission occurred in our hematology unit between patients. During a one-week period, one genotype of *C. pelliculosa* was circulated among patients.

Our data demonstrate the utility of molecular biology-based typing methods for enhancing our understanding of the epidemiology of nosocomial *C. pelliculosa* infections. In conclusion, the genotypic pattern of this C. pelliculosa outbreak suggests a clonal outbreak, likely arising from an environmental source and distinct from sporadic infection.

At the time of our investigation, we were unable to identify *C. pelliculosa* in any of the other clinical or environmental samples tested. Since patient screening was not carried out at hospital admission, and the cluster was only investigated retrospectively, it is difficult to prove whether these patients became infected from a common source within the hospital environment or if the yeast was transmitted from the first patient to the others. Although the outbreak strain was not isolated from the hands of the ward personnel during our retrospective investigation, the transmission of *C. pelliculosa* between patients and staff would seem likely. Indeed, the nosocomial spread of fungal infections was stopped just after the standard infection control measures were reinforced in the NICU.

Investigation of an outbreak by molecular methods has a diagnostic value when the primary source can not be found. This study proves the importance of molecular approach to the suspected outbreaks in a hospital survey. Even though the source was not found in our case, reinforcing the standard infection control measures and enhancing the awareness among the NICU staff are important for terminating an outbreak.

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