J Microbiol Immunol Infect
2000;33:267-270

Neonatal fungemia caused by *Hansenula anomala*: a case report

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Received: January 21, 2000 Revised: March 31, 2000 Accepted: April 18, 2000

Hansenula anomala, an ascosporogenous yeast of the class *Ascomycetes*, is a free-living organism isolated from the environment. It is also a part of the normal or transient flora of the human throat and alimentary tract. It has been recognized as an opportunistic pathogen and its infection is very rare. A premature infant, a victim of right femoral osteomyelitis and right hip arthritis caused by oxacillin-resistant *Staphylococcus aureus*, was found to have developed *H. anomala* fungemia just before the initiation of the antimicrobial therapy with teicoplanin. Antifungal agents (fluconazole and amphotericin B) were prescribed for 10 days despite the absence of clinical sign of systemic fungal infection. His general condition remained good, with a subsequent sterile blood culture. The patient was discharged after completing 5 weeks of antimicrobial therapy, and he remained well during follow-up at our outpatient clinics. Here, we also review the risk factors, the clinical presentations, and the therapeutic strategies of *H. anomala* infection in the literature.

Key words: Fungemia, *Hansenula anomala*

The genus *Hansenula* belongs to the class *Ascomycetes*, order *Endomycetales*, family *Saccharomycetaceae*. *Pichia anomala* is a new name for *Hansenula anomala* and is identical in taxonomy [1]. To date, only two species of this genus, namely *H. anomala* and *Hansenula polymorpha*, have been implicated in human disease. *H. anomala* is an ascospore-forming yeast frequently found in various fruits, tree exudates, soil, fermenting vegetables and other organic substances [2, 3]. It represents the perfect stage of *Candida pelliculous* and grows well in a high-sugar medium. It can be identified by the production of ascospores and by its typical biochemical pattern. The asci can be elongated or globose and contain one to four hat- or helmet-shaped ascospores, which are characteristic for *H. anomala*. The yeast assimilates and ferments dextrose, maltose, sucrose, and galactose [2,4]. *H. anomala* was first discovered by Hansen in 1891. The first report of human infection caused by *H. anomala* was by Csillag *et al* who described an infant died from interstitial pneumonia in 1953. The yeast isolated from the infant's aspirate was later identified as being *H. anomala* by Wang and Schwarz in 1958. Thereafter, several reports have implicated *H. anomala* as a pathogen in pneumonia, endocarditis, fungemia, ventriculitis, urinary tract infection and oral mucosa infection [5-10].

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Case Report

A 20-day-old male baby was referred to our hospital with the chief complaint of right thigh swelling for 1 week. He had been born at a local clinic by cesarean section with a gestational age of 33 weeks and a birth weight of 2070 g. He had received phototherapy for hyperbilirubinemia and intravenous fluid for nutritional support. He had been relatively well until pus discharging from the insertion site of the intravenous catheter was noted on the eleventh day. He received local wound care and observation after septic work-up and removal of the intravenous catheter. Unfortunately, the right thigh swelling and redness developed 3 days later. There was no associated fever. The blood culture of the initial septic work-up yielded *Staphylococcus aureus*, and intravenous oxacillin therapy was then initiated. Oxacillin was continued for a week but the clinical response was poor. Therefore, he was transferred to our hospital for further evaluation and management.

On admission, physical examination disclosed right thigh swelling with redness and limited motion of the right hip joint. His vital signs, including body temperature, were within normal limits. His white blood cell count was 14,200/μL with 44% neutrophils, 47%

lymphocytes, and 9% monocytes. The hemoglobin concentration was 14 gm/dL and the platelet count was 349,000/μL. The C-reactive protein level was 3.74 mg/dL (normal range < 0.8 mg/dL). Radiographic evaluation showed widening of the right hip joint space and an osteolytic lesion with periosteal reaction over the right upper femur. An ultrasonographic study showed a hypoechoic lesion over his right upper thigh, which was compatible with subperiosteal abscess. Transcutaneous aspiration of the right hip joint was done and the pus culture revealed oxacillin-resistant *S. aureus*. Intravenous teicoplanin (6 mg/kg/day in single daily dose) was then initiated. Oral fluconazole (5 mg/kg/day in single daily dose) was also prescribed because a yeast-like organism was found in the blood culture on the third day of admission. The yeast grew well on Sabouraud dextrose agar (SDA) at 25 °C and 37 °C respectively. *Candida albicans* was excluded due to a negative germ tube test. Budding yeast cells with pseudohyphae were found on cornmeal-Tween 80 agar at 25 °C. Modified acid fast staining revealed helmet-shaped ascospores, which were typical for *H. anomala*. Assimilation and fermentation tests were also compatible with this diagnosis. Oral fluconazole was continued for 3 days and then shifted to intravenous amphotericin B (1 mg/kg in single daily dose) after *H. anomala* was identified. Computerized axial tomography of the right femur revealed poor resolution of the abscess after 1 week of antimicrobial therapy, and arthrotomy with drainage of the abscess was then performed. A blood culture was sterile 3 days after initiating amphotericin B therapy. Amphotericin B was continued for 1 week altogether. Intravenous teicoplanin was used for 5 weeks prior to his discharge from our ward in stable condition. He received regular rehabilitation in the out-patient clinic and recovered well with no residual handicap.

Discussion

Many fungi that were previously regarded as nonpathogenic for humans are now being reported with increasing frequency as the cause of a multitude of diseases. *Candida* spp. are the most common organisms involved in human fungal infections, although *Aspergillus* spp., *Cryptococcus* spp., and other fungi have also been implicated [11,12]. During the past decades, the progress in clinical medicine has improved the survival of many immunocompromised patients, including those with neoplasms, immunodeficiency, organ transplantation, and extreme prematurity. They are at a higher risk for fungal infection because of profound immunosuppression, prolonged hospital stays, vascular catheterization, administration of broad-spectrum antimicrobial agents, and extensive use of prophylactic antifungal drugs. All the above factors have also changed the spectrum of pathogens in favor of non-*Candida* species. The proportion of yeast other than *Candida* spp. (YOC) in fungemia reported from major cancer institutions varies from 1.5% to 32%. The new and emerging yeasts include *Malassezia furfur*, *Trichosporon* spp., *Blastoschizomyces capitus*, *Rhodotorula rubra*, *Saccharomyces cerevisiae*, *Clavispora lusitaniae*, *Cryptococcus laurentii*, and *H. anomala* [13].

H. anomala is rarely encountered as the cause of infections in clinical practice. A wide spectrum of infections can be seen, ranging from asymptomatic fungemia to severe disease. In a series of Taylor *et al*, *H. anom*ala represented only 1% of the causative agents of all the identified nosocomial fungemia [14]. The mechanism of pathogenesis is not yet well known, however, the killer toxin may play a role in the pathogenesis of *H. anomala* enteritis [15]. On the other hand, the killer toxin is also implicated in prevention and control of candidiasis, pneumocystosis and tuberculosis, based on its own antimicrobial activity. Nonetheless, it is strongly antigenic, toxic and cannot be used directly as a therapeutic agent. A new strategy using killer toxin-like anti-idiotypic antibodies mimicking the killer toxin activity has been developed recently [16,17]. The application of this technique in clinical use demands further clinical evaluation.

Very-low-birth-weight (< 1500 g), major surgery, central venous catheters, hyperalimentation, neutropenia, broad-spectrum antibiotics, corticosteroid and chemotherapy were ever reported as the major risk factors for *H. anomala* infection [6-10,18,19]. Murphy *et al* demonstrated the rectum, oropharynx, and skin as the most common sites for colonization in an outbreak of a neonatal intensive care unit. *H. anomala* was isolated from blood only once in four babies who were asymptomatic. These four babies remained well though they received no antifungal therapy [8]. This was the only paper we found which mentioned the management of asymptomatic *H. anomala* fungemia. It is important to distinguish between catheter-related transient fungemia and disseminated fungemia. The former is characterized by positive blood cultures without evidence of focal or disseminated disease, and it needs no treatment other than removing the catheter. When the fungemia persists or parenchymal disease develops, prompt initiation of appropriate antifungal therapy is usually successful. We did not repeat blood culture before the initiation of antifungal therapy, and that was the only shortcoming in this report. However,

meticulous technique for disinfection during sampling for the blood culture and the rarity of this organism being found in the clinical laboratory make contamination relatively impossible. There was no indwelling central venous catheter in our patient, however, his low birth weight with diminished cellular immunity was our main concern as an indication for antifungal therapy.

There are only limited data about the antifungal susceptibility test for *H. anomala* and these data show some discrepancy [2,5,6,9,10]. Amphotericin B with or without 5-flucytosine remains the drug of choice for *H. anomala* infections because of its *in vitro* and *in vivo* activity [5]. Satoshi *et al* reported an experience of successful treatment of *H. anomala* fungemia with fluconazole [6]. Nonetheless, Sherman *et al* emphasized the risk for emergence of fluconazole-resistant *H. anomala* infection in immunocompromised patients receiving fluconazole prophylaxis or therapy [9]. The application of the National Committee for Clinical Laboratory Standard (NCCLS) M27-A broth microdilution method is the present guideline for the susceptibility testing of common *Candida* spp. and *Cryptococcus neoformans*. This guideline can also be applied for a variety of emerging yeasts and yeast-like organisms, however, it may not be the most efficient and convenient procedure in clinical practice. Current data suggest the potential value of some commercial kits, such as the Sensititre YeastOne Colorimetric Antifungal Panel, in antifungal susceptibility testing of yeasts and yeast-like organisms, including *H. anomala* [20]. However, until further evidence of good correlation between *in vivo* and *in vitro* susceptibility data is obtained, caution should be exercised in applying the results of the minimal inhibitory concentration (MIC) determinations to the clinical practice [5].

Although the outcome of *H. anomala* infection is usually favorable, it can also cause severe and disseminated disease. The overall mortality rate was estimated as 12.5% in a recent review by Krcmery *et al* [13]. Early identification of this pathogen is crucial for improving the prognosis. Current routine methods for yeast identification may be insufficient for identifying the usual yeast within 2 days after isolation [21]. In comparison with the classical API 20C System, the RapID Yeast Plus System has been proven to be an accurate, rapid, and cost-effective tool in the clinical laboratory for the identification of common and certain new, emerging yeasts and yeast-like organisms, including *H. anomala* [22]. In conclusion, the potential of *H. anomala* as an opportunistic pathogen should be recognized, because the prognosis in compromised hosts may be poor without appropriate treatment.

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