Case Report / Olgu Sunumu

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Candida utilis: A Rare Cause of Septicemia in Two Immunocompetent Patients in the Pediatric Intensive Care Unit

Candida utilis: Çocuk Yoğun Bakım Ünitesinde İzlenen İki İmmünokompetan Hastada Nadir Bir Sepsis Etkeni

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Abstract

In recent years, an evident rise in the frequency of candidaemia caused by non-albicans Candida species has been reported. *Candida utilis* is a low-virulence fungus that is commonly used in the food processing industry. Only a few studies have reported invasive infection due to *C. utilis*. In this paper, we present two cases of clinically manifested candidaemia and sepsis caused by *C. utilis*. This was a retrospective study carried out at a tertiary intensive care center in Turkey. Two *C. utilis* were isolated from blood culture over a 6-month period. *C. utilis* fungemia has mainly been reported in immunocompromised patients, neonates, and following surgical intervention. The two cases discussed here did not have a defined immunodeficiency. Both patients had common risk factors such as prolonged stay in the pediatric intensive care unit and the presence of a central venous catheter. Our aim in reporting these cases is to highlight *C. utilis* as a probable cause of candidemia in hospitalized pediatric patients and can be mortal.

Keywords: Invasive fungal disease, *Candida utilis*, candidemia, sepsis, pediatric intensive care, children

Öz

Son yıllarda, albicans dışı Candida türlerinin neden olduğu kandidemi sıklığında belirgin bir artış bildirilmiştir. *Candida utilis*, gıda işleme endüstrisinde yaygın olarak kullanılan düşük virülanslı bir mantardır. Sadece birkaç çalışmada *C. utilis*'e bağlı invaziv enfeksiyon bildirilmiştir. Bu yazıda, *C. utilis*'in neden olduğu iki kandidemi/sepsis olgusunu sunuyoruz. Bu, Türkiye'de üçüncü basamak bir yoğun bakım merkezinde gerçekleştirilen geriye dönük bir çalışmadır. Altı aylık bir süre boyunca kan kültüründen iki *C. utilis* izole edildi. *C. utilis* fungemisi esas olarak bağışıklığı baskılanmış hastalarda, yenidoğanlarda ve cerrahi müdahaleyi takiben rapor edilmiştir. Burada tartışılan iki olguda tanımlanmış bir immün yetmezlik yoktu. Her iki hastada da çocuk yoğun bakım ünitesinde uzun süre kalma ve santral venöz kateter varlığı gibi ortak risk faktörleri vardı. Bu olguları bildirmekteki amacımız hastanede yatan çocuk hastalarda olası bir kandidemi nedeni olan ve ölümle sonuçlanabilen *C. utilis*'i vurgulamaktır.

Anahtar Kelimeler: İnvaziv fungal hastalık, *Candida utilis*, kandidemi, sepsis, çocuk yoğun bakım, çocuk

Introduction

Invasive fungal disease is a leading cause of death and morbidity in immunocompromised and hospitalized children. The incidence of candidaemia has been increasing during the past few decades.[1,2] Newborns and infants below the 3 months have an increased risk for candidaemia.[3] Here, we aimed to draw attention to this rare agent by discussing the characteristics of clinical findings and treatment of *Candida utilis* infections in pediatric patients.

Case Reports

Case 1: A 5-month-old male patient who had been coughing and wheezing for ten days and had been taking oral antibiotics for five days was admitted to the pediatric intensive

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care unit (PICU) due to pneumonia and respiratory distress. Regarding his medical history, he was born at 34 weeks, was hospitalized in neonatal intensive care for three months, and was diagnosed with bronchopulmonary dysplasia. On admission to PICU, he had a fever (axillary temperature 38.7 °C), oxygen saturation of 70%, a heart rate of 160/per minute, tachypnea, common crepitant rales, and drowsy consciousness. PRISM score was 28. We intubated the patient with cyanosis and carbon dioxide retention and placed them on a mechanical ventilator. We initiated empirical piperacillin tazobactam treatment. His echocardiography was normal, and pulmonary hypertension was not detected. According to the blood gas analysis, mechanical ventilator support was gradually increased so that the peak inspiratory pressure was 30 mmHg. Amikacin was started on the 5th day of his admission to the patient, who had a high fever. A furosemide infusion was started due to pretibial edema. He was extubated on the 12th day, and nasal high-flow oxygen was given. Due to peripheral vascular access problems, a central venous catheter has been inserted into the right jugular vein on the 15th day of hospitalization. liposomal amphotericin B (3 mg/kg per day i.v.) was started on the 23rd day because of the presence of a candida signal in the blood culture of the patient with resistant fever and thrombocytopenia (caspofungin was not available in our hospital at the time). Galactomannan antigen was negative. The patient, whose general condition worsened and oxygen saturation decreased to 70-75%, was re-intubated on the 27th day. Due to septic shock, we started an adrenaline infusion. Serum C-reactive protein (CRP) level was 96 mg/L and procalcitonin was 0.5 ng/mL. *Candia utilis* obtained in catheter blood culture (antifungal susceptibility MIC: fluconazole 1, caspofungin ≤0.12, micafungin ≤0.06, voriconazole ≤0.12, amphotericin B ≤0.25). He had full enteral nutrition and no need to use total parenteral nutrition. Ejection fraction 65%, good contraction, no thrombus or verruca in echocardiography. The central venous catheter was removed. The thorax computerized tomography examination revealed chronic changes and pneumonic infiltrations in the lower lobe of the left lung, which was performed due to a history of three previous hospitalizations for pneumonia. Serum immunoglobulin levels and T lymphocyte subgroups were in the normal range for age. After 10 days of liposomal amphotericin B treatment, the blood cultures showed no signs for microorganisms. Liposomal amphotericin B treatment had to be continued for another 15 days, for a total of 25 days of treatment. During the follow-up, the patient's septic findings regressed, and he was extubated on the 36th day of hospitalization, followed by discharge from the PICU on the 42nd day.

Case 2: A 4-month-old girl with no previous health problems, was admitted to the PICU after being hospitalized for 2 days with a diagnosis of pneumonia and undergoing intubation due to respiratory arrest. The patient has severe pediatric acute respiratory distress syndrome (pARDS) with an oxygen saturation of 70%, PaO_2/FiO_2 of 90, bilateral diffuse infiltration, and pulmonary edema on a chest X-ray. Prone position, high positive end-expiratory pressure (14 mmHg), and empirical piperacillin-tazobactam were started. An adrenaline infusion was started for hypotension, and its dose was titrated. We inserted a central venous catheter into the right jugular vein on the first day. The PRISM score was 35. Echocardiography revealed no pathology except for a small central muscular atrial septal defect. We provided early enteral feeding. Vancomycin was added to the treatment of the patient whose CRP elevation continued on the 6th day of his hospitalization, and her general condition was poor. No pathogen was detected in blood culture or a respiratory viral panel at admission. Severe acute respiratory syndrome-coronavirus-2 RNA test was negative on the nasopharyngeal swab by polymerase chain reaction. On the 11th day of hospitalization, her oxygenation improved, and ventilator support was reduced. After a successful spontaneous breathing test, we extubated the patient. However, the patient required re-intubation after 2 hours due to tachypnea and oxygen saturation not exceeding 80%. On the 15th day of hospitalization, a chest tube was placed in the right lung due to pneumothorax. On the 22nd day of hospitalization, caspofungin acetate (loading dose 70 mg/m^2, maintenance dose 50 mg/m^2 per day i.v.) was administered to the patient whose yeast signal in blood culture was detected. *C. utulis* have been reported in both catheter blood and endotracheal aspirate cultures (antifungal susceptibility MIC: fluconazole 1, caspofungin ≤0.12, micafungin ≤0.06, voriconazole ≤0.12, and amphotericin B ≤0.25). *C. utilis* have been reported in two blood cultures taken every 3 days. There was a bilateral ground-glass density appearance in the chest X-ray of the patient, and her oxygen saturation was 66%. In laboratory tests, respiratory acidosis (pH 7, PaO_2 60 mmHg, $PaCO_2$ 88 mmHg, lactate 4 mmol/L), creatinine 1.32 mg/dL, urea 178 mg/dL, thrombocytopenia (83.103/uL), CRP 42 mg/L, procalcitonin 0.6 ng/mL, liver enzymes, and electrolyte values were within the normal limit. We performed continuous veno-venous hemodialysis on the patient, who had edema throughout the body and inadequate urine output with a diuretic. However, our patient died due to candida septicemia and pARDS on the 28th day of her hospitalization.

Methods

The patients' blood cultures in a BACTEC 9050 system (Becton Dickinson) using BACTECPedsPlus/F culture vials. The isolates were identified using the ID 32 C yeast identification

method from BioMérieux, as well as by their morphology on cornmeal agar. *In vitro* antifungal susceptibility testing using the ATB FUNGUS 3 (bioMérieux) microdilution method have been used. Interpretation of the results based on the recommendations provided by the Clinical and Laboratory Standards Institute.

Discussion

Candida species are responsible for around 70-90% of invasive fungal infections and are the primary cause of fungal infections in patients referred to the PICU. Invasive candidiasis has a significant mortality rate, ranging from 40% to 60%. There are a substantial number of clinical trials about bloodstream infections (candidemia) caused by *Candida* spp. in the literature. There are at least 15 candida species that induce infections in humans, with five species accounting for over 90% of invasive infections: *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis,* and *C. krusei*. Based on these trials and studies on the epidemiological characteristics of candidemia, it has been found that non-albicans Candida species make up over 50% of the isolates in individuals with candidemia.[4,5]

Candida utilis is renowned for its fermentation capabilities in the food industry.[6] Infrequently, *C. utilis* causes fungemia. It is exceptionally rare to isolate it from superficial clinical specimens. The occurrence of it in the gastrointestinal system of hospitalized individuals is infrequent rare.[7,8] Alsina et al.[7] documented the occurrence of catheter-associated fungemia. Gaisne et al.[9] documented a case of *C. utilis* fungemia in a patient who had received a solid organ transplant. The fungemia was successfully managed with micafungin as a treatment. Another case was a 68-year-old individual afflicted with Alzheimer's disease who was admitted due to neurological problems and a persistent fever. However, it is worth noting that this patient did not exhibit neutropenia or have a central venous catheter (CVC).[10] The remaining three occurrences were fungemia associated with CVCs.[7,11,12]

In previously neutropenic or immunosuppressive patients, while candidemia is more common, diagnostic possibilities are also increased; it is now frequently encountered in individuals without an underlying disease. Mechanical ventilatotion, delays in enteral feeding, and the use of broad-spectrum antibiotics increase this possibility of candidemia in the PICU.[4,5] Additional factors that increase the likelihood of a condition include the use of antineoplastic drugs and the patient's impaired immune system.[2] Both of our hospitalized children in the critical care unit exhibited risk characteristics such as extended hospitalization in the PICU, CVC, and antibiotic medication. Our first patient, who was delivered preterm, required an extended period of hospitalization in the neonatal critical care unit. Both of our patients had early enteral feeding (within 24-48 hours) and did not have neutropenia. Lukić-Grlić et al.[13] documented three patients of clinically evident candidaemia caused by *C. utilis* who were admitted to the neonatal intensive care unit. The risk factors reported for three cases of newborns include antibiotic medication, total parenteral nutrition, anti-ulcer prophylaxis, CVC, receiving a surgical operation at delivery, and mechanical ventilation. All patients got better and no longer had any *C. utilis* in their blood after taking liposomal amphotericin B or caspofungin. The Infectious Diseases Society of America guidelines suggest using echinocandin drugs (such as caspofungin, micafungin, and anidulafungin) as the initial treatment for invasive candidiasis. If there is intolerance, limited availability, or resistance to existing antifungal drugs, the lipid formulation amphotericin B at a dosage of 3-5 mg/kg daily is an alternative. Fluconazole can be used as an alternative if the patient is not in severe condition and is unlikely to have a fluconazole-resistant *Candida* species.[5] In our first case, we administered liposomal amphotericin B, while in case 2, we used caspofungin. The *C. utilis* strain obtained from our patients showed minimal inhibitory concentrations of <0.25 µg/ml for amphotericin B and ≤0.12 µg/mL for caspofungin. We showed that *C. utilis* was susceptible to both medications. In our study, *C. utilis* was the single cause of the bloodstream infection in two cases. The duration of candidaemia in our patients was between 22 and 23 days. We obtained a sterile blood culture in our first case, but we did not have a sterile blood culture because we lost our second case on the 28th day of hospitalization. The limitation of this report is in the restricted number of cases and the retrospective assessment conducted inside a single center.

Conclusion

By presenting these cases, our intention is to point out *C. utilis*, a low-virulent Candida species, as a possible cause of candidaemia that can be fatal among hospitalized immunocompetent pediatric patients.

Ethics

Informed Consent: Retrospective study.

Authorship Contributions

Concept: E.K., T.E., Design: E.K., Data Collection E.K., Literature Search: E.K., Writing: E.K., T.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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