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Case Report

A case report of invasive glabrata candidiasis in extremely low birth weight premature twin newborns

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ABSTRACT

The incidence of invasive candidiasis (IC) in neonatal intensive care units (NICUs) has significantly increased. Although C. albicans is still the most common pathogen detected in IC cases (60-75%), the increase in the use of prophylactic antifungal therapies and empirical echinocandin has led to a shift in detected pathogens to non-albicans candida species such as C. glabrata (2-8%). In the past, C. glabrata was considered one of the relatively non-pathogenic saprophytes of the normal flora. However, mucosal and systemic C. glabrata infections have escalated with the increase in the survival rates of premature newborns, prolonged hospitalization, and the widespread use of immunosuppressives and broad-spectrum antibiotics and started to appear more frequently as an important nosocomial pathogen, especially with its natural resistance to the azole antifungals. In this article, we aimed to draw attention to the importance of C. glabrata in NICUs by presenting extremely low-birth-weight premature twins with severe clinical course.

Keywords: Extremely low birth weight, invasive candidiasis, Candida glabrata, sepsis

INTRODUCTION

Invasive candidiasis (IC) infection is an important cause of morbidity and mortality in low-birth-weight premature newborns.[1] Candida albicans is responsible for 60-75% of all cases, whereas Candida glabrata constitutes only 2-3% of candida infections in the neonatal period.[2-4] Definitive diagnosis of IC cases is made by demonstrating Candida species in the culture of sterile body fluid samples such as blood or cerebrospinal fluid (CSF). However, since the sensitivity of blood culture for IC cases is less than 50%, making a definitive diagnosis of Candida meningitis gets more difficult.[5] Normal neuroimaging and CSF findings do not exclude the diagnosis. Since C. glabrata is resistant to the azole group of antifungals, which are the first choice of empirical antifungal therapy when a fungal infection is suspected, this may create a challenge to the treatment.[6] This case report presents premature twin newborns with C. glabrata sepsis who were followed up and treated in the neonatal intensive care unit.

CASE PRESENTATION

A female newborn weighing 800 grams and a male newborn weighing 780 grams, delivered by C/S at the age of 25 1/7 weeks due to fetal distress, were transferred to the neonatal intensive care unit. In prenatal history, two courses of betamethasone and antibiotic treatment for premature rupture of membranes were administered. Both were treated with penicillin-gentamicin for 7 days with the diagnosis of early neonatal sepsis. The female newborn received three doses and the male newborn received

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two doses of surfactant therapy. On the 16th day of the follow-up, the female baby's general condition deteriorated and her activity decreased, immediately after her twin developed similar findings. Blood samples were obtained to evaluate these clinical changes, and laboratory tests showed thrombocytopenia and increased acute phase reactants. Based on these findings, late neonatal sepsis was considered in both twins. Lumbar puncture was also performed to exclude central nervous system involvement. Blood and CSF laboratory findings are shown in Table 1. In light of these findings, the infection was evaluated as a nosocomial infection by the infection committee, and they decided to start broad-spectrum empirical antibiotic treatment and to increase the antifungal treatment from prophylaxis dose to treatment dose. Vancomycin, meropenem, and fluconazole treatments were administered to both patients. At the 48th hour of the treatment, the microbiology laboratory presented the preliminary report that this pathogen could be fungi. Amphotericin B was added to the antifungal treatment. The same agent, Candida glabrata, was isolated from two consecutive blood cultures of the cases. CSF cultures were sterile. Abdominal and transfontanelle ultrasonography, echocardiography, and eye examinations were normal. After the first negative blood culture was obtained, antifungal treatment was continued for another 2 weeks and then discontinued. The female newborn was discharged on postnatal day 76, however, her twin died on postnatal day 136 while being followed up on mechanical ventilation with a tracheostomy, with the diagnosis of severe bronchopulmonary dysplasia and severe pulmonary hypertension.

DISCUSSION

The incidence of invasive candidiasis in neonatal intensive care units has escalated with the increase in the survival rates of extremely low birth weight premature newborns and prolonged hospitalization.[7,8] Although C. albicans is still the most common pathogen detected in IC cases (60-75%), the increase in the use of prophylactic antifungal therapies and empirical echinocandin has led to a shift in detected pathogens to non-albicans candida species such as C. tropicalis, C. parapsilosis, C. krusei and C. glabrata, which are more likely to be resistant to the azole group of antifungals.[9,10] Since this condition changed treatments and prognosis, identifying the type of the pathogen has become more important in cases with candidemia. C. glabrata as a

Table 1. Blood and CSF laboratory findings of patients

	Female Newborn	**Male Newborn**
Complete Blood Count Results	**WBC:** 18.66 x10^3/uL **Hb:** 9.7 g/dL **Thrombocyte:** 13 x10^3/uL	**WBC:** 24.99 x 10^3/uL **Hb:** 10.5 g/dL **Thrombocyte:** 109 x10^3/uL
CRP	1.89 mg/dl	2.39 mg/dL
CSF Results	**Glucose:** 70 mg/dL **Protein:** 189,00 mg/dL **Culture:** No growth.	**Glucose:** 65 mg/dL **Protein:** 187,00 mg/dL **Culture:** No growth.
Blood Culture	1. *Non-albicans Candida spp.* 2. *Candida Glabrata*	1. *Non-albicans Candida spp.* 2. *Candida Glabrata*
Urine Culture	No growth.	No growth.
Antifungal Sensitivity Results	***Candida Glabrata***	***Candida Glabrata***
Antifungal agent *Amphotericin B *Anidulafungin *Caspofungin *Fluconazole *Flucytosine *Itraconazole *Micafungin *Posaconazole *Voriconazole	**Resistant/MIC*** (1 µg/mL) Sensitive (0.06 µg/mL) Sensitive (0.06 µg/mL) (16 µg/mL) Sensitive (<=0.06 µg/mL) (0.5 µg/mL) Sensitive(<=0.008 µg/mL) (1 µg/mL) Sensitive (0.5 µg/mL)	**Resistant/MIC** (1 µg/mL) Sensitive (0.12 µg/mL) Sensitive (0.06 µg/mL) (16 µg/mL) Sensitive (<=0.06 µg/mL) (0.5 µg/mL) Sensitive (<=0.008 µg/mL) (1 µg/mL) Sensitive (0.25 µg/mL)

*MIC: minimum inhibitory concentration.

non-albicans Candida, which was isolated in our case, accounted for approximately 2-3% of IC cases.[2-4] In the study of Chen et al. published in 2022, it was reported that C. glabrata constitutes 7.9% of IC cases.[11] It is known that C. glabrata can be transmitted horizontally from the hospital environment as well as vertically from the mother.[12] As in other IC cases, C. glabrata cases usually present with sepsis findings. Since it can spread to other organs and systems by hematogenous and/or septic embolism, all cases should be carefully evaluated in detail.

C. glabrata has intrinsic resistance to conventional triazole antifungals such as fluconazole. It can also cross-react to new triazoles. In the study of Odds et al., the resistance rate of C. glabrata strains isolated from blood samples taken from all age groups to fluconazole was determined as 45%.[13] Malani et al. found that 60% of the isolated C. glabrata strains were resistant to fluconazole, 83% to itraconazole, and 44% to voriconazole for all age groups.[14] Similarly, the rate of resistance to fluconazole was found to be 33% by Lamp et al. in their study, which included only patients in tertiary NICUs. No amphotericin-resistant C. glabrata case was identified.[15] In this respect, antifungal susceptibility testing must be performed after the isolation of the pathogen. In our case, contrary to expectations, the isolated pathogen was not resistant to fluconazole. However, in light of the literature, when it was learned that the isolated microorganism was C. Glabrata, amphotericin B was administered in addition to the fluconazole treatment started after the preliminary report, considering the severe clinical condition of the patient. Besides, the fact that the isolated microorganism was sensitive to all antifungal agents led us to believe that this microorganism could have been from the patient's own flora or vertically transmitted rather than being a nosocomial infection. The American Infectious Diseases Society recommends that echinocandins should be used with extreme caution in newborn patients and only in cases of resistance to fluconazole or amphotericin B.[16] Although voriconazole is not widely used in newborns, it can be used in the step-down phase of the treatment in the presence of fluconazole-resistant voriconazole-sensitive pathogens. Since the active form of voriconazole is minimally excreted in the urine, it should not be preferred in cases with urinary candidiasis.[17,18] Although there is uncertainty about the optimal duration of treatment in candidiasis cases, according to the Infectious Diseases Society of America, in cases without end organ involvement, treatment should be completed in 3 weeks after the culture negativity and clinical improvement in the patient.[16] This duration is defined as 10-14 days after culture negativity in the Neonatal Infections Diagnosis and Treatment Guide of the Turkish Society of Neonatology.[19] In our case, candidiasis developed during the administration of fluconazole prophylaxis. In the presence of signs of sepsis, the dose of antifungal treatment was switched from prophylaxis to treatment dosage, and when the yeast signal was detected in the blood culture, the treatment was continued by adding Amphotericin B. In the study of Fridkin et al. involving 1997 newborns, the overall mortality in IC cases was 13%, while the mortality in C. glabrata cases was reported to be 21%.[2] Warris et al. reported that the mortality rate due to C. albicans was 13.6%, while the mortality rate due to C. glabrata was 14.2%.[4]

In the past, C. glabrata was considered one of the relatively non-pathogenic saprophytes of the normal flora, rarely causing serious infections. However, mucosal and systemic C. glabrata infections have escalated significantly with the increase in the survival rates of premature newborns, prolonged hospitalization, and the widespread use of immunosuppressive and broad-spectrum antibiotic treatments, and it has started to appear more frequently in clinical practice as an important nosocomial pathogen, especially with its natural resistance to the azole antifungals.

In conclusion, we aimed to draw attention to the importance of C. Glabrata, which was increased significantly in neonatal intensive care units, by presenting extremely low-birth-weight premature twins with severe clinical course.

Author contribution

Surgical and Medical Practices: EA, BGY, SB, MÖ, AK; Concept: EA, BGY; Design: EA, BGY; Data Collection or Processing: EA, BGY; Analysis or Interpretation: EA, BGY; Literature Search: EA, BGY, SB; Writing: EA, BGY, SB, MÖ, AK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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