

THE FIRST CASE OF STEPHANOASCUS CIFERRII INFECTION IN A NEWBORN AND REVIEW OF LITERATURE

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ABSTRACT

Intensive care unit patients have the risk for fungal infections, especially when broad-spectrum antibiotics and long-term indwelling catheters are used. We are here reporting a very rare fungus, *Stephanoascus ciferrii*, which caused cutaneous and systemic infections in a neonate, followed in Neonatal Intensive Care Unit. In contrast with

other few cases of *S. ciferrii*, the fungus presented here, was detected as more susceptible to antifungal agents such as amphotericin B, flucytosine, fluconazole, and voriconazole. Emergence of rare and unusual fungal agents should always be considered in high-risk patients with use of broad-spectrum antibiotics.

Keywords: Opportunistic fungal infection, fluconazole, *S. ciferrii*, newborn. *Nobel Med* 2015; 11(3): 97-100

BİR YENİDOĞANDA SAPTANAN İLK STEPHANOASCUS CİFERRİİ ENFEKSİYONU VE LİTERATÜRÜN GÖZDEN GEÇİRİLMESİ

ÖZET

Yoğun bakım hastaları, özellikle geniş spektrumlu antibiyotiklerin ve uzun dönem kalıcı kateterlerin kullanıldığı durumlarda fungal enfeksiyonlar açısından risk taşırlar. Bu raporda, yenidoğan yoğun bakım ünitesinde takip edilen bir yenidoğanda kütanöz ve sistemik enfeksiyona neden olan nadir bir fungal etken olan *Stephanoascus ciferrii* sunulmaktadır.

Literatürde bildirilen az sayıdaki *S. ciferrii* olgularının aksine burada sunulan *S. ciferrii*, amfoterisin B, flusitosin, flukonazol ve vorikonazol gibi antifungal ilaçlara daha duyarlı bulunmuştur. Geniş spektrumlu antibiyotiklerin kullanıldığı yüksek riskli hasta gruplarında nadir görülen mantar enfeksiyonlarının ortaya çıkabileceği her zaman akılda bulundurulmalıdır.

Anahtar kelimeler: Fırsatçı mantar enfeksiyonları, flukonazol, *S. ciferrii*, yenidoğan *Nobel Med* 2015; 11(3): 97-100

INTRODUCTION

Stephanoascus ciferrii is a very rare opportunistic fungal agent. It may cause both cutaneous and systemic infections especially in intensive care unit patients. It was first reported in 1965 as *Candida ciferrii* by Kreger van Rij and after 18S rDNA sequencing studies held by Ueda-Nishimura and Mikita in 2002, it has been named as *Stephanoascus ciferrii* as telemorph of *C. ciferrii*¹. Underlying immunosuppressive conditions and over use of broad-spectrum antibiotics are major causes for opportunistic fungal infections. Among these infections non-*C. albicans* species are generally associated with higher mortality when compared to *Candida albicans* species². As far as our review of the literature in English revealed, the case presented here is the first case of *S. ciferrii* isolated from a newborn patient.

CASE

Female newborn, born at 38 gestational weeks, weighting 3480 grams was admitted to Neonatal Intensive Care Unit (NICU) due to respiratory distress without antenatal diagnosis. At 18th hour of admittance the newborn was diagnosed as neonatal diaphragmatic hernia. Laboratory tests as supporting for the congenital diaphragmatic hernia; Arterial blood gas (ABG) measurements: pH (7.42), PaCO₂ (35 mmHg), PaO₂ (70 mmHg); Serum lactate levels (39 mg/dl) and serum electrolyte levels, ionized calcium and glucose were investigated and all tests were also pointed diaphragmatic hernia.

The patient was placed into an incubator, monitored and mechanically ventilated. Ampicillin 2x185 mg/ per day and gentamicin 1x15 mg/per day protocol was started. Because of persistent pulmonary pressure, nitrous oxide was added to treatment. After decrease in pulmonary pressure, the patient underwent Bochdalek Hernia Operation. Gentamicin was replaced with cefotaxime 2x200 mg/per day after surgery. At 5th day after operation, teicoplanin 1x27 mg/ per day was also added to antibiotic treatment because of surgical site infection caused by methicillin resistant coagulase negative staphylococcus. After emerge of septic symptoms and circulatory problems, cefotaxime was replaced with meropenem 3x160 mg and teicoplanin was replaced with vancomycin 3x60 mg/ per day. After the administration of new antibiotics clinical recovery was received in 48 hours. However, after infusion of meropenem, mucocutaneous oral lesions, vaginitis, and maculopapular rashes emerged indicating fungal infection. The patient's condition deteriorated further together with circulatory and respiratory problems suggesting septicemia. Umbilical catheter was pulled out. Catheter tip and blood culture

samples were collected for microbiological evaluation. Semi-quantitative method of Maki was used for catheter culture. Blood culture sample was analyzed with the Bact/Alert® 3D microbial detection systems (Biomérieux, France). Few inflammatory cells and yeast cells were detected at direct gram stain of catheter culture. Creamy-white, smooth round colonies were determined on sheep blood agar and chocolate agar after 18-hour incubation at 35°C. Also positive signal was received from Bact/Alert blood culture system at the 23rd hour of incubation. Yeast cells were seen at Gram stain of blood culture. The NICU was informed about the fungi detected. After isolation of fungi from both catheter and blood samples, identification and antifungal susceptibility tests of fungi were performed with VITEK 2® (Biomérieux, Marcy l'Etoile, France) automated system. Both of the samples were identified as *S. ciferrii*. According to susceptibility test results they were susceptible to amphotericin B (MIC ≤0.25µg/ml), flucytosine (MIC≤1µg/ml), fluconazole (MIC ≤1µg/ml) and voriconazole (MIC<0.12µg/ml). Additionally, API 20C AUX® (Biomérieux, Marcy l'Etoile, France) system was also used for identification of the fungi. Results from the API system enabled very good identification of *S. ciferrii*. Meropenem was discontinued and fluconazole 1x21 mg/per day was added. Clinical recovery was determined at 2nd day of the treatment. Antifungal treatment was continued for about 10 days. At postnatal 35th day the patient was discharged.

DISCUSSION

Fungal infections increasingly cause trouble especially in intensive care units with the advance of antimicrobial treatment and invasive instrumentations especially in immunocompromised patients.³ *Candida* species are most commonly isolated fungal agents in nosocomial fungal infections; also non-*C. albicans* species are emerging and should be always kept in mind as etiological agent in presence symptoms of fungal infections.⁴ Most isolated and studied non-*C. albicans* *Candida* species are *C. glabrata*, *C. parapsilosis*, *C. tropicalis*.⁵ When it comes to *S. ciferrii*, it is known to cause cutaneous lesions and onychomycosis. In a study about distribution and antifungal susceptibilities of *Candida* species causing candidemia, among 383 isolates, only one isolate was identified as *C. ciferrii*. It was resistant to amphotericin B and fluconazole. However clinical data was not available.⁶

There were three cases of clinically reported systemic infections of *S. ciferrii* with different patterns of antifungal susceptibilities. Systemic infections related to fluconazole-resistant yeasts are increasingly observed in immunocompromised patients receiving fluconazole as a prophylactic antifungal treatment. First one isolated

Table. Clinically important reported cases of <i>S. ciferrii</i> infections.				
	Gunsilius et al. 2001	Agin et al. 2011	Saha et al. 2013	Present case 2013
Diagnosis	Acute myeloid leukemia	Down Syndrome with cerebral palsy	Diabetic chronic obstructive pulmonary disease	Neonatal diaphragmatic hernia
Age	62	8	55	Newborn, 23 days
Clinical manifestation of fungal infection	Systemic mycosis, pulmonary infiltrations, cutaneous lesions	Candidemia	Pneumonia	Systemic mycosis, cutaneous lesions
Broad spectrum antibiotic usage	Yes	Yes	Yes	Yes
Outcome	Death	Death	Recovery	Recovery
Treatment	Amphotericin B	Amphotericin B then Fluconazole	Amphotericin B then Fluconazole	Fluconazole
Amphotericin B	Sensitive (MIC = 0.5 µg/ml)	Resistant (MIC > 1 µg/ml)	Sensitive (MIC ≤ 0.5 µg/ml)	Sensitive (MIC ≤ 0.25 µg/ml)
Flucytosine	Not available	Not available	Sensitive (MIC ≤ 1 µg/ml)	Sensitive (MIC ≤ 1 µg/ml)
Fluconazole	Resistant (MIC > 64 µg/ml)	Resistant (MIC ≥ 64 µg/ml)	Sensitive (MIC ≤ 1 µg/ml)	Sensitive (MIC ≤ 1 µg/ml)
Voriconazole	Not available	Sensitive (MIC ≤ 0.12 µg/ml)	Sensitive (MIC ≤ 1 µg/ml)	Sensitive (MIC < 0.12 µg/ml)
Method for antifungal susceptibility	Microdilution	Vitek 2	Vitek 2	Vitek 2

from 62-year old immunocompromised patient. It was resistant to fluconazole. Gunsilius et al. presented a case of invasive candidiasis caused by *C. ciferrii* in a patient with acute myeloid leukemia who suffered a relapse after autologous peripheral blood progenitor cell transplantation. The patient had erythematous skin papulae and spotted pulmonary infiltrations. The clinicians performed a skin biopsy which led to diagnosis of invasive candidiasis, emphasizing the diagnostic usefulness of this procedure. Identification of yeast species as *C. ciferrii* was followed by the in vitro susceptibility test which revealed its resistance to fluconazole. The case was the first one until that date with *C. ciferrii* as the causative agent of an invasive fungal infection in humans. Thus, they added another fungus to the list of flucanazole-resistant yeasts and suggested that isolated fungi should be further tested for in vitro susceptibility to allow the appropriate decision on antimycotic drugs.⁷

In the second case report, a rare candidemia case due to *C. ciferrii* in an 8-year-old boy with cerebral palsy and Down syndrome was presented by Agin et al. who isolated candida species resistant to amphotericin-B (MIC >1 µg/ml), fluconazole, (MIC ≥64 µg/ml), caspofungin (MIC ≥32 µg/ml), and anidulafungin (MIC ≥32 µg/ml) but sensitive to voriconazole (MIC ≤0.12 µg/ml).⁷ The third case in the literature by Saha et al. was a diabetic patient with chronic obstructive pulmonary disease who had pneumonia due to *S. ciferrii* sensitive to antifungal drugs. This particular

case was a 55-year-old female, suffering from moderate COPD for 2 years who was brought to the emergency room with progressive increase in dyspnea and cough with copious mucopurulent expectoration for 15 days and 10 days, respectively. Her peripheral oxygen saturation was 74% in room air during the admission and her arterial blood gas showed pH 7.43, PaO₂ 70 mmHg, PaCO₂ 36 mmHg, PaO₂ /FiO₂ 234, suggestive of acute lung injury. The patient had a known history of diabetes for 15 years. Upon her admission, samples were collected to perform blood culture, sputum for gram stain, Ziehl-Neelsen (Z-N) stain and pyogenic culture with sensitivity. Her chest X-ray showed bilateral pneumonia. Her laboratory findings were as follows: total leukocyte count 11,700/mm³, serum urea level 34 mg%, creatinine 0.7 mg%, sodium 138 mEq/L, and potassium 3.5 mEq/L. Sputum gram staining and Z-N staining were both negative. Computed tomographic scan of thorax was applied for further evaluation, which revealed left lower lobe collapse with consolidation along with patchy pulmonary infiltrations in the right middle and lower lobe. Fiber-optic bronchoscopy was carried out to know the cause of collapse, which showed patchy whitish lesion in the lateral wall of trachea just above the carina with a mucous plug. Bronchoalveolar lavage fluid (BAL) was taken from those segments with clearing of that mucous plug and BAL fluid was sent for cytological examination, gram staining, fungal staining, Z-N staining, malignant cells, mycobacterial culture, and fungal culture. The antimicrobial susceptibility test was performed by microbroth dilution method by

VITEK-2. Fungal staining of BAL and mucosal biopsy specimen showed yeast forms suggestive of *Candida* species. The fungal culture showed moderate growth of *C. ciferrii*. The clinicians managed the treatment by initiating intravenous liposomal amphotericin B (150 mg daily) then changed to oral fluconazole (150 mg daily) after 4 days, when drug sensitivity revealed that the strain was fluconazole sensitive. Following the administration of oral fluconazole 150 mg daily for 2 weeks the patient was discharged and at 6 weeks she had a follow-up chest X-ray examination featuring remarkable improvement.⁸ All previous patients, had risk factors for candidemia and underlying disease that impairs immune system of the patient. The neonate presented here, also had well-described risk factors for candidemia such as low birth weight, low gestational age, previous use of broad spectrum antibiotics, indwelling catheters, endotracheal intubation, previous bacteremia, respiratory disorders. Properties of the clinically important cases that were infected with *S. ciferrii* were given at Table.

Routine testing for antifungal susceptibility for *C. albicans* is not generally recommended due to uncommon resistance in these species. However, it is suggested that laboratories should perform routine

antifungal susceptibility testing against fluconazole for *C. glabrata* isolates from blood and sterile sites and for other *Candida* species that have failed to respond to antifungal therapy or in which azole resistance is strongly suspected. Especially, in case of failure to respond to initial antifungal therapy, susceptibility testing should be used to guide the management of fungal infections. When it comes to non-candidal species, because of the unpredictable susceptibility patterns, antifungal susceptibility test are of vital importance to determine the correct antifungal drug for the treatment.⁹ Although broth microdilution, standardized by the Clinical and Laboratory Standards Institute at 2008, is the reference method for antifungal susceptibility testing, increasing use of automated systems such as VITEK 2 have comparable results to reference method.¹⁰

As a result, *S. ciferrii* is a very rare cause of infection, together with other non-*albicans* species, should be kept in mind and antifungal treatment should be planned according to antifungal susceptibility test results.

* The authors declare that there are no conflicts of interest.



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