Case Report

Case report of a rare yeast *Cyberlindnera fabianii* fungemia in preterm twin neonates from North India: Diagnostic and therapeutic challenge

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ABSTRACT

Cyberlindnera fabianii infection has rarely been described in humans and only a few cases of human infections by this organism have been reported to date. Here, we present a case of premature twin neonates who were outborn and admitted for extremely low birth weight, early-onset sepsis, and patent ductus arteriosus. They were put on continuous positive airway pressure for 6 days and prolonged antibiotic course. Blood culture was positive for *Candida* sp. Antifungal drug fluconazole was added to the treatment regime which includes piperacillin-tazobactam and amikacin. Isolates were initially unidentified by conventional identification methods and showed reduced susceptibility to azoles. MALDI-TOF-MS identified the isolates as *C. fabianii.* Soon the neonates went into shock and cardiopulmonary arrest despite high ventilator support and died during treatment due to respiratory failure. This case report highlights *C. fabianii* as a rare fungal pathogen and emphasizes the importance of molecular methods such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) in its accurate identification.

Key words: Neonates, Fungemia, Prematurity, MALDI-TOF-MS, *Cyberlindnera fabianii*, Fluconazole

Candida fabianii (teleomorph *C. fabianii*) was first described in 1964. Since then, species have been variedly described under the genus *Hansenula* or *Pichia* [1]. A new genus *Lindnera* in 2008 was proposed by Kurtzman *et al*., to include several previously known taxa on the basis of phenotypic and phylogenetic differences that also included *C. fabianii* (teleomorph: *Lindnera fabianii*) [2]. Until now, *C. fabianii* has not been associated with invasive animal or human disease, except in one report on prostatitis and urinary tract infection [3].

Here, we describe the case of a preterm neonate who was admitted for extremely low birth weight (ELBW) and prematurity with patent ductus arteriosus (PDA) and put on immediate antibiotic therapy and supportive measures. Blood culture was positive for *Candida* spp. which was correctly identified by MALDI-TOF-MS as *C. fabianii.* Both the neonate went into shock and cardiopulmonary arrest despite high ventilator support and died during treatment due to respiratory failure. In this present era of molecular advancements in the diagnosis, it has now become easier to identify the rare pathogens by robust techniques such as MALDI-TOF-MS and treat the challenging cases with accurate, reliable, and faster microbiological aid in diagnosis. This case throws light on the rare pathogenic yeast which a clinician should consider and keep in mind at the time of diagnosis which could be challenging to treat.

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CASE REPORT

Outborn premature twin neonates (delivered at 35th week of gestation), who were 48-h old, admitted in the pediatric emergency department with ELBW which was 900 grams for twin 1 and 950 grams for twin 2, early-onset sepsis, PDA, and fairly low APGAR score (5 for both). The mother was a 27-year-old primigravida with a history of iron deficiency anemia.

On the date of admission, their hemogram revealed 400 leukocytes per mm^3 with 24% neutrophils and hemoglobin 14.5 g/dl for twin 1 and 500 leukocytes per mm^3 with 26% neutrophils hemoglobin 13.4 g/dl for twin 2 indicating that both neonates were neutropenic. Soon, the neonatal resuscitation was planned and the twin 1 was put on bubble continuous positive airway pressure for 6 days followed by the mechanical ventilation for 7 days and the twin 2, who had recurrent episodes of apnea,

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was put on the mechanical ventilation for 4 days. Both of them received i.v. fluids, i.v. antibiotics (piperacillin-tazobactam at a dose of 80 mg/kg/dose IV every 6 h and amikacin at a dose of 15 mg/kg IV q 24 h) and also received i.v. paracetamol for PDA.

Blood samples were collected from both the neonates from two different sites by heel prick of the right and left medial plantar surface and were sent for culture and sensitivity. Blood culture revealed the growth of *Candida* spp. in all the four biphasic blood culture bottles of both the neonates, for which fluconazole was started.

On day 16, twin 1 went into shock and was not maintaining saturation even with high ventilator support, and went into cardiopulmonary arrest. despite giving cardiopulmonary resuscitation the neonate, could not be revived and finally died due to respiratory failure. After 48 h of birth, twin 2 developed gastrointestinal hemorrhage due to disseminated intravascular coagulation and was desaturating, followed by bradycardia and could not be revived despite all the available measures.

Both the yeast species were found to be sensitive to fluconazole, voriconazole (MIC 0.5 μg ml^{-1}), and amphotericin B (MIC 0.25 μg ml^{-1}). The isolates were sent to the Department of Microbiology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, for confirmation of the species. Both the isolates were identified as *C. fabianii* (Figs. 1 and 2) by MALDI-TOF M S with a BRUKER value of 2.50 and 2.23

DISCUSSION

C. fabianii has rarely been described in humans and only a few cases of human infections by this organism have been reported to date [4,5]. Failure of the conventional methods to identify this *Candida* spp. led us to perform molecular identification of the yeast. It was eventually identified as *C. fabianii* (also known as *Lindnera fabianii* or *Pichia fabianii*). As commercial yeast identification and diagnostic kits (e.g., API 20CAUX, ID32C, and Vitek 2) used in routine practice have a poor ability to identify *C. fabianii*, this organism has also been misidentified as *Pichia anomala* or *Candida utilis* in other [6,7]. In 2013, Yun *et al*. reported a case of *C. fabianii* from the blood culture of a 47-year-old woman which was identified initially as *C. utilis* by Vitek 2. *C. fabianii* is pathogen of low and is the teleomorphic form of *C. fabianii*, which was described [8].

In recent years, MALDI TOF MS has proven a powerful technique that circumvents many challenges posed by other conventional techniques and is being adapted for rapid identification of fungi due to its high performance and less time requirement [9,10]. The technique relies on the generation of microorganism "protein fingerprints" that are compared to reference spectra in a well-characterized library. It has now reached a level at which the identification of complex mass spectra in databases has become much easier in a standardized fashion. Compared to biochemical procedures involving overnight growth, this is a highly time-saving procedure and can significantly speed up diagnostic processes. Furthermore, the technique is inexpensive and does not require experienced personnel.

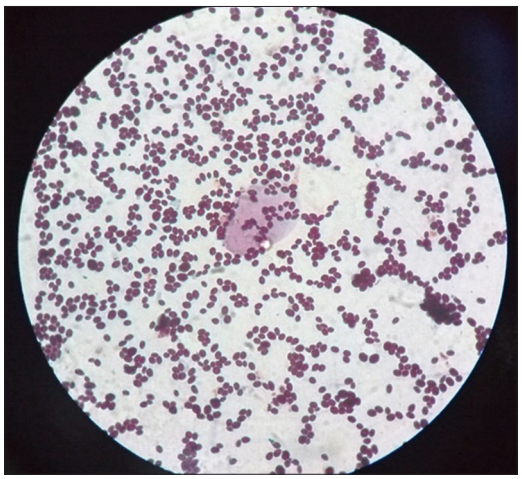

Figure 1: Gram stain image of *Cyberlindnera fabianii*

Figure 2: Purple color of yeast colonies on CHROM agar

Here, we present a case report that describes the isolation of *C. fabianii* from the blood culture of 48-h old ELBW premature twin neonates. Till now there are only five cases of *C. fabianii* fungemia have been reported worldwide which includes four adult patients [6,8] and three neonates [7,11,12]. To the best of our knowledge, in earlier cases, isolation of *C. fabianii* has only been reported from blood specimens and only infrequently. Risk factors associated with *Candida* infection are exposure to broad-spectrum antimicrobial agents, indwelling vascular catheters, prior surgery, and cancer chemotherapy. In this case report, the risk factors identified were ELBW, prematurity, indwelling catheters, and febrile neutropenia. As the isolated strain was sensitive to amphotericin B (MIC = 0.25 μg/ml) showing discordance from previous cases, one from China, in which *P. fabianii* isolated from the blood sample of a premature infant, had shown resistance to itraconazole and amphotericin B [12]. Another case report from Korea described clinical resistance of *L. fabianii* to amphotericin B, although the *in vitro* MIC value was 0.5 μg ml^{-1} [8] and one case report from India described in urine isolate that was resistant to amphotericin B (MIC >4 μg ml^{-1}). Thus, it is important to study antifungal susceptibility, along with speciation of the *Candida* isolates.

The limitations of our study were as follows: (i) It could not be confirmed whether *C. fabianii* was a true pathogen and causes

of mortality or an incidental finding, as a repeat sample was not available; (ii) the source of infection could not be traced. As the neonates were febrile at the time of admission, the infection was not acquired nosocomially from the present institution; however, it might have been acquired during the previous hospitalization.

CONCLUSION

To the best of our knowledge, we are reporting the first case of isolation of *C. fabianii* from a blood specimen from North India. We also emphasize the role of MALDI-TOF-MS in confirming the identity of uncommon fungal isolates, as correct identification is important for epidemiological purposes. Clinicians should consider the possibility of rare pathogenic yeast especially in neonates at the time of diagnosis which could be challenging to treat and may lead to fatal outcome.

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