Catheter-related Saccharomyces cerevisiae Fungemia Following Saccharomyces boulardii Probiotic Treatment: In a child in intensive care unit and review of the literature

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ABSTRACT

Although Saccharomyces boulardii is usually a non-pathogenic fungus, in rare occasions it can cause invasive infection in children. We present the case of an 8-year-old patient in pediatric surgical intensive care unit who developed S. cerevisiae fungemia following probiotic treatment containing S. boulardii. Caspofungin was not effective in this case and he was treated with amphotericin B. We want to emphasize that physicians should be careful about probiotic usage in critically ill patients.

1. Introduction

Saccharomyces boulardii, known as baker’s yeast, is a subtype of S. cerevisiae. Although S. boulardii is usually a non-pathogenic fungus, in rare occasions it can cause invasive infection in children. This fungus has been used in probiotics to prevent antibiotic-associated diarrhea and to treat recurrent Clostridium difficile associated diarrhea since 1991 [1]. However probiotic treatment is generally safe, many cases of fungemia with S. cerevisiae have been reported during the probiotic treatment in immunocompromised and critically ill patients.

Here, we report a pediatric case of catheter-related S. cerevisiae fungemia following S. boulardii probiotic treatment in pediatric surgical intensive care unit (ICU).

2. Case

An 8 years-old boy was admitted to pediatric surgical ICU with respiratory distress. The day of ICU admission was considered as day 0. Tracheostomy was planned. Due to the lack of peripheral venous line, a subclavian central venous catheter (CVC) was inserted. The patient’s medical history included cerebral palsy, mental retardation, sacral decubitus ulcer, swallowing dysfunction, gastrostomy, aspiration pneumonia, chronic lung disease, and long-term hospital stay. During his stay in the ICU, he had an episode of diarrhea and feeding intolerance that were thought to be related to formula (Day +7). The formula was changed, and probiotic containing S. boulardii (Reflor 250 mg sachet, Biocodex, Turkey) was offered once a day for five days. The probiotic diluted with water and administered via gastrostomy tube. Diarrhea resolved and the case was consulted with division of pediatric infectious diseases due to developed fever. The sacral decubitus ulcer had an appearance of being infected. After obtaining blood (both from the CVC and peripheral vein), urine and decubitus wound swab samples for culture, empirical meropenem and teicoplanin treatments were started (Day +19). Serratia marcescens and Enterococcus faecalis were isolated from wound swab, and it was determined that the isolates were susceptible to meropenem and teicoplanin, respectively. Despite broad-spectrum antibiotics, the fever had continued. S. cerevisiae was yielded in CVC blood culture. The strains were identified with Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) and the identification of the isolates was further confirmed using the technique called API ID 32 C (bioMérieux, France). Caspofungin (70 mg/m2 on the first day, followed by 50 mg/m2 once a day in the following days) was added the treatment empirically (Day +21). Despite antifungal therapy, the fever had resisted, and on the third day of caspofungin treatment, S. cerevisiae was detected for the second time in CVC blood culture (Day +24). The result of antifungal susceptibility test was obtained and the strain was susceptible to fluconazole, posaconazole, voriconazole, micafungin, caspofungin and amphotericin B with the Sensititre Yeast One (SYO; Trek Diagnostic Systems, UK) method. Although the strain was susceptible to in vitro
Probiotics are becoming increasingly available as food supplements and are widely used in the medicine industry. *Saccharomyces cerevisiae* var. *boulardii* was isolated by Henri Boulard in 1920 during a cholera outbreak and was used as a probiotic for the treatment of gastrointestinal diseases [2]. *S. boulardii* is yeast used worldwide and is often marketed as a dietary supplement. It has been tested for clinical efficacy in many yeast species has changed in light of molecular phylogenetic studies [5]. The results obtained in some studies show that *S. boulardii* is genetically very close or nearly identical to *S. cerevisiae*. These findings are also supported by some clinical studies, in which *S. cerevisiae* recovered from patients and *S. boulardii* strains isolated from probiotic preparations were proved to be genomically identical. With the use of molecular techniques *S. boulardii* has been classified within the species *S. cerevisiae* [2,4–7].

In a review of the literature including 60 cases of *S. cerevisiae* fungemia, we could not find any experience with caspofungin in the treatment of fungemia caused by *S. cerevisiae*. For these reasons, the caspofungin treatment was switched to liposomal amphotericin B (3 mg/kg/day). The CVC could be removed because peripheral venous access was established, and his fever resolved 72 h after the initiation of liposomal amphotericin B treatment (Day+27). Control blood cultures were negative, and the patient did not give good clinical response and the CVC withdrawal may be more important for patients such as our case. We do not know caspofungin treatment failed or not, because the CVC withdrawal could not be withdrawn. It is the limitation in this study.

### 3. Discussion

Probiotics are becoming increasingly available as food supplements and are widely used in the medicine industry. *Saccharomyces cerevisiae* var. *boulardii* was isolated by Henri Boulard in 1920 during a cholera outbreak and was used as a probiotic for the treatment of gastrointestinal diseases [2]. *S. boulardii* is yeast used worldwide and is often marketed as a dietary supplement. It has been tested for clinical efficacy and is often prescribed for the treatment of several types of diseases including enteral nutrition-related diarrhea, traveler’s diarrhea, acute adult diarrhea, antibiotic-associated diarrhea, *Helicobacter pylori* infections, HIV-related diarrhea, *Clostridium difficile* and *Salmonella typhi* infections, and Crohn’s disease [3,4].

Although *S. boulardii* was initially identified as a separate species of the *hemiascomycetes* genus *Saccharomyces*, in recent years, the classification of many yeast species has changed in light of molecular phylogenetic studies [5]. The results obtained in some studies show that *S. boulardii* is genetically very close or nearly identical to *S. cerevisiae*. For these reasons, the caspofungin treatment was switched to liposomal amphotericin B (3 mg/kg/day). The CVC could be removed because peripheral venous access was established, and his fever resolved 72 h after the initiation of liposomal amphotericin B treatment (Day+27). Control blood cultures were negative, and the patient did not give good clinical response and the CVC withdrawal may be more important for patients such as our case. We do not know caspofungin treatment failed or not, because the CVC withdrawal could not be withdrawn. It is the limitation in this study.

### 3.1. Review of the Literature about Pediatric Cases of *S. cerevisiae* Fungemia

*S. cerevisiae* fungemia cases have increased and some of these cases have been published. In our knowledge, there is not any literature review to identify previously reported pediatric cases of *S. cerevisiae*. We searched for “*S. cerevisiae*” and “fungemia” in the Pubmed database and found 15 suitable pediatric cases of *S. cerevisiae* fungemia [9–20]. Adult (> 18 years) cases and cases with insufficient clinical information were excluded from this review. The most important characteristics of cases are presented in Table 1. Gender was reported for 13 patients, where 8 (61.5%) patients were male. Ten (66.6%) patients were ≤ 1 year of age. All patients had underlying conditions and only one patient had no CVC. Thirteen patients received antifungal therapy (86.6%). The most commonly administered antifungal agent was amphotericin B (12 patients). One patient died and the mortality rate of this series was 28% [7].

| Case | Age | Sex | Underlying condition | IV catheter | ICU stay | Antifungal Therapy | Outcome | Reference |
|------|-----|-----|-----------------------|-------------|---------|-------------------|---------|-----------|
| 1    | < 1 | F   | Esophageal atresia, tracheoesophageal fistula | Yes         | Yes     | AmB               | Survived| 9         |
| 2    | < 1 | NR  | Acute myeloid leukemia | Yes         | NR      | AmB               | Survived| 10        |
| 3    | < 1 | M   | Congenital Cardiomyopathy | Yes         | NR      | L-Am B            | Survived| 11        |
| 4    | < 1 | F   | Intestinal atresia | Yes         | NR      | L-Am B            | Survived| 11        |
| 5    | < 1 | NR  | Abdominal surgery, respiratory failure | Yes         | NR      | AmB               | Survived| 9         |
| 6    | 1   | F   | Bronchopneumonia | Yes         | NR      | Flu               | Survived| 13        |
| 7    | 14  | M   | Burn | Yes         | Yes     | SFC, AmB          | Survived| 14        |
| 8    | 16  | M   | Self-inflicted fungemia, convulsion | No          | No      | NR                | Survived| 15        |
| 9    | 10  | F   | Cystic fibrosis, bowel obstruction, bilar cirrhosis | Yes         | No      | AmB               | Died    | 16        |
| 10   | < 1 | M   | Congenital malformation | Yes         | Yes     | AmB               | Survived| 16        |
| 11   | 7   | M   | Partial intestinal resection | Yes         | NR      | AmB               | Survived| 16        |
| 12   | 2   | M   | Small bowel resection, cystic fibrosis | Yes         | No      | AmB               | Survived| 17        |
| 13   | < 1 | F   | Premature birth | Yes         | Yes     | AmB               | Survived| 18        |
| 14   | < 1 | M   | Premature birth, ducus arteriosus, necrotizing enterocolitis | Yes         | Yes     | AmB, Flu          | Survived| 19        |
| 15   | < 1 | M   | Premature birth | Yes         | Yes     | L-AmB             | Survived| 20        |

M: male; F: female; AmB: amphotericin B, L-AmB: liposomal amphotericin B, Flu: fluconazole SFC: 5-fluorocytosine; NR: not reported

Fungemia caused by *S. cerevisiae* is rare in childhood and is predominantly reported in a history of probiotic use and central venous lines in place, as was in our case. The origin of the fungemia was thought to be either a digestive tract translocation or a contamination of the central venous line by the colonized hands of health care workers after the probiotic medications have been opened [8]. Fungemia is seen in median 10 days after probiotic treatment initiation in a study concerning 60 cases [7]. In our case, the first positive CVC culture with *S. cerevisiae* was seen 12 days after the first dose of the probiotic-containing *S. boulardii* was given.

The management of fungemia due to *S. cerevisiae* includes administration of antifungal agent and removal of infected foreign bodies, especially CVC. The antifungal agent of choice for treatment of *Saccharomyces* species has not been finally established, but amphotericin B and fluconazole seems to be preferable [7]. Although the patient received antifungal therapy with caspofungin, *S. cerevisiae* grew again in the second CVC blood culture and the patient recovered successfully with liposomal amphotericin B and removal of the CVC. In our patient, caspofungin could not treat the fungemia alone, which ended with liposomal amphotericin B and the removal of the CVC. Catheter withdrawal may be more important for patients such as our case. We do not know caspofungin treatment failed or not, because the CVC could not be withdrawn. It is the limitation in this study.
promised host. Physicians should be careful in the choice of antifungal agent and removal of the catheter as soon as possible for the effective treatment.

Conflict of interest

There are none.

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