Medical Mycology Case Reports 15 (2017) 33–35

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

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

Serkan Atıcı[a,*], Ahmet Soysal[a], Kıvılcım Karadeniz Cerit[b], Şerife Yılmaz[c], Burak Aksu[c], Gürsu Kıyan[b], Mustafa Bakır[a]

[a] Department of Pediatrics and Division of Pediatric Infectious Diseases, Medical School, Marmara University, Istanbul, Turkey
[b] Department of Pediatric Surgery, Medical School, Marmara University, Istanbul, Turkey
[c] Department of Microbiology, Medical School, Marmara University, Istanbul, Turkey

ARTICLE INFO

Keywords:
Saccharomyces cerevisiae
Saccharomyces boulardii
Fungemia
Probiotic treatment
Intensive care unit

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

* Corresponding author.

http://dx.doi.org/10.1016/j.mmcr.2017.02.002
Received 18 January 2017; Accepted 21 February 2017
Available online 22 February 2017

Table 1
Pediatric cases with fungemia caused by *Saccharomyces cerevisiae* in the literature.

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	–	Survived	12
6	1	F	Bronchopneumonia	Yes	NR	Flu	Survived	13
7	14	M	Burn	Yes	Yes	5FC, AmB	Survived	14
8	16	M	Self-inflicted fungemia, convulsion	No	No	NR	Survived	15
9	10	F	Cystic fibrosis, bowel obstruction, biliar 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, ductus 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 5FC: 5-fluorocytosine; NR: not reported

caspofungin, the patient did not give good clinical response and the same pathogen grew again under the caspofungin treatment. In our literature review, 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 venipuncture could be found (Day + 24). The patient was clinically stabilized, and his fever resolved 72 h after the initiation of liposomal amphotericin B treatment (Day + 27). Control blood cultures were sterile. No pathological fungal signs were found on eye examination, abdominal ultrasonography and echocardiography. The patient was successfully treated with liposomal amphotericin B for a course of 14 days (Day + 38).

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* diseases, 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*. 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,* it was found that the most consistent risk factor for fungemia was the use of probiotics containing *S. boulardii*. Almost all of the patients (93%) had a CVC, and 88% of the patients had received broad-spectrum antimicrobials. The fungemia was detected a median of 10 ± 62.3 days (range, 4–300 days) after the administration of the probiotic. The most commonly used antifungal therapies were amphotericin B (28 patients) and fluconazole (16 patients). The use of caspofungin was not detected in this large fungemia study. The overall mortality was 28% [7]. Fungemia caused by *S. cerevisiae* is rare in childhood and is predominantly reported in patients with 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.

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 found to be 6.6%.

We want to emphasize once again that physicians should be careful about probiotic usage. Clinicians should keep in mind that probiotic treatment could cause fungemia in immunocompetent patients with a history of long-term hospital stay, CVC applications, use of broad-spectrum antimicrobials, critically ill patient in ICUs, and immunocom-

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.

References

[1] J.B. Thygesen, H. Glerup, B. Tarp, *Saccharomyces boulardii* fungemia caused by treatment with a probioticum, BMJ Case Rep. (2012) 1–3.

[2] T.M. Batista, E.T. Marques Jr, G.R. Franco, B. Douradinha, Draft genome Sequence of the probiotic yeast *Saccharomyces cerevisiae var. boulardii* strain ATCC MYA-796, Genome Announc. 2 (2014) 1–2.

[3] T. Kelesidis, C. Pothoulakis, Efficacy and safety of the probiotic *Saccharomyces boulardii* for the prevention and therapy of gastrointestinal disorders, Ther. Adv. Gastroenterol. 5 (2012) 111–125.

[4] D. Czerucka, T. Piche, P. Rampal, Review article: yeast as probiotics – *Saccharomyces boulardii*, Aliment Pharm. Ther. 26 (2007) 767–778.

[5] L.V. McFarland, *Saccharomyces boulardii* is not *Saccharomyces cerevisiae*, Clin. Infect. Dis. 22 (1996) 200–201.

[6] G. Mitterdorfer, H.K. Mayer, W. Kneifel, H. Viernstein, Clustering of *Saccharomyces boulardii* strains within the species *S. cerevisiae* using molecular typing techniques, J. Appl Microbiol 93 (2002) 521–530.

[7] P. Munoz, E. Bouza, M. Cuenca-Estrella, J.M. Eiros, M.J. Perez, M. Sanchez-Somolinos, et al., *Saccharomyces cerevisiae* fungemia: an emerging infectious disease, Clin. Infect. Dis. 40 (2005) 1625–1634.

[8] R. Herbrecht, Y. Nivoix, *Saccharomyces cerevisiae* fungemia: an adverse effect of *Saccharomyces boulardii* probiotic administration, Clin. Infect. Dis. 40 (2005) 1635–1637.

[9] N. Belet, N. Dalgiç, S. Oncel, E. Ciftçi, E. Ince, H. Güriz, et al., Catheter-related fungemia caused by *Saccharomyces cerevisiae* in a newborn, Pedia. Infect. Dis. J. 24 (2005) 1125.

[10] S. Cesaro, P. Chinello, L. Rossi, L. Zanesco, *Saccharomyces cerevisiae* fungemia in a neutropenic patient treated with *Saccharomyces boulardii*, Support Care Cancer 8 (2000) 504–505.

[11] J. Perapoch, A.M. Planes, A. Querol, V. López, I. Martínez-Bendayán, R. Tormo, et al., Fungemia with *Saccharomyces cerevisiae* in two newborns, only one of whom had been treated with ultra-levura, Eur. J. Clin. Microbiol Infect. Dis. 19 (2000) 468–470.

[12] H. Nielsen, J. Stenderup, B. Bruun, Fungemia with *Saccharomycetaceae*: report of four cases and review of the literature, Scand. J. Infect. Dis. 22 (1990) 581–584.

[13] M. Pletincx, J. Legein, Y. Vandenplas, Fungemia with *Saccharomyces boulardii* in a 1-year-old girl with protracted diarrhea, J. Pedia. Gastroenterol. Nutr. 21 (1995) 113–115.

[14] M. Viggiano, C. Badetti, V. Bernini, M. Garabedian, J.C. Manelli, *Saccharomyces boulardii* fungemia in a patient with severe burns [in French], Ann. Fr. Anesth. Reanim. 14 (1995) 356–358.

[15] K.S. Fung, O. Scheel, D.J. Lyon, A.F. Cheng, J. Bendeck, Self-inflicted bacteraemia and fungaemia in Vietnamese migrants, Scand. J. Infect. Dis. 28 (1996) 83–85.

[16] N.F. Fiore, J.H. Conway, K.W. West, M.B. Kleiman, *Saccharomyces cerevisiae* infections in children, Pedia. Infect. Dis. J. 17 (1998) 1177–1179.

[17] C. Hennequin, C. Kauffmann-Lacroix, A. Jobert, J.P. Viard, C. Ricour, J.L. Jacquemin, et al., Possible role of catheters in *Saccharomyces boulardii* fungemia, Eur. J. Clin. Microbiol Infect. Dis. 19 (2000) 16–20.

[18] M.A. Ipson, C.L. Blanco, *Saccharomyces cerevisiae* sepsis in a 35-weekold premature infant: a case report, J. Perinatol. 21 (2001) 459–460.

[19] F. Ruiz-Esquide, M.C. Diaz, E. Wu, V. Silva, Verrucous endocarditis secondary to *Saccharomyces cerevisiae*: a case report [in Spanish], Rev. Med Chil. 130 (2002) 1165–1169.

[20] M.S. Lungarotti, D. Mezzetti, M. Radicioni, Methaemoglobinaemia with concurrent blood isolation of *Saccharomyces* and Candida, Arch. Dis. Child Fetal Neonatal Ed. 88 (2003) F446.