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Saccharomyces cerevisiae fungemia in a critically ill patient with acute cholangitis and long term probiotic use

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ABSTRACT

Saccharomyces cerevisiae has recently been used as an ingredient in probiotic supplements. Invasive Saccharomyces infection have been documented, and multiple predisposing risk factors have been identified including critical illness, ICU admission, antibiotics use, central venous catheters, probiotics use, and immunosuppression. We report a case of a 74-year-old man admitted for acute cholangitis taking a probiotic supplement containing the subtype Saccharomyces boulardii. He later developed S. cerevisiae fungemia that was successfully treated with Micafungin and Fluconazole.

1. Introduction

Saccharomyces cerevisiae, commonly known as 'baker's yeast' or 'sbrewer's yeast' has been used in baking and winemaking since ancient times. It is usually non-pathogenic and colonizes the skin and most of the mucosal surfaces. More recently, the subtype *S. boulardii* has become an ingredient in many probiotic supplements used in the treatment and prevention of diarrheal disorders. Invasive Saccharomyces infections have been described and are thought to be facilitated by the presence of predisposing factors, such as critical illness, ICU admission, antibiotics use, central venous catheters, probiotics use, and immunosuppression. Here, we report a case of Saccharomyces fungemia in a critically ill patient in the ICU who had been taking probiotics containing the subtype *S. boulardii* for several years.

2. Case

A 74-year-old man presented to the emergency department with abdominal pain, nausea, vomiting and chills for 1 day. The patient has a history of obstructive jaundice 7 years ago due to ampullary mass, for which he underwent ERCP with sphincterotomy and biliary stent placement. This was followed by Whipple's procedure when the biopsy showed concerns for adenocarcinoma. Additional significant past medical history included atrial fibrillation managed by anticoagulant therapy with Dabigatran, hypertension and coronary artery disease. On Day 0, the physical exam revealed normal vital signs and diffuse abdominal tenderness without any signs for an acute abdomen. His initial work-up was significant for WBCs of 11.7. The patient had markedly abnormal liver function test with ALP of 283, AST of 404, ALT of 499 and total bilirubin of 5.3. Lactic acid level was elevated at 3.4. A non-contrast CT scan of the abdomen and pelvis described new pneumobilia. On day 0, the patient was subsequently given intravenous fluids and was started on Piperacillin-Tazobactam 3.375 mg every 8 h for possible cholangitis. A gallbladder ultrasound was planned as well.

On day 1, he subsequently deteriorated with marked confusion, tachypnea and hypoxic respiratory failure requiring intubation. His course was further complicated by a fever of 40 C, atrial fibrillation with a rapid ventricular response, severe hypotension requiring a central line placement and pressor support. On day 1, the patient also had emergent percutaneous transhepatic cholangiography with biliary drain placement and was started on continuous renal replacement therapy for persistent severe metabolic acidosis. Blood cultures drawn on day 0 grew *Streptococcus bovis*, *Aeromonas hydrophila* and *Escherichia coli*. Cultures of the biliary drainage grew *E. coli* and *Streptococcus lutetiensis*. Repeat blood cultures on day 1 and day 2 later grew *E. coli* and *Saccharomyces cerevisiae* and *Saccharomyces cerevisiae* respectively. *Saccharomyces cerevisiae* was identified by Matrix Assisted Laser Desorption/Ionization (MALDI) mass spectrometry.

On Day 2, Micafungin 100 mg daily was started and maintained until Day 8. On Day 9, he switched to Fluconazole 200 mg daily until day 19 based on historical sensitivities. Eventually susceptibilities on the reported cultures were obtained.

A further review of the patient's history revealed long term use of probiotic supplement containing *Saccharomyces boulardii* for the past 7

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years, following his Whipple's procedure.

The rest of the patient's hospital course was remarkable for ventilator dependent respiratory failure requiring tracheostomy and percutaneous endoscopic gastrostomy tube placement, persistent renal failure on scheduled hemodialysis with the placement of long-term hemodialysis catheter and *C. difficile* associated diarrhea. The blood cultures from day 5 onward remained sterile other than one set growing *S. Epidermidis,* which was thought to be a contaminant.

3. Discussion

Saccharomyces cerevisiae is an ascomycetes yeast, historically used to ferment sugars to produce varieties of food and beverages, and more recently as an ingredient in probiotic supplements used in the treatment and prevention of various diarrheal disorders [1]. This single-cell microorganism is one of the most extensively studied eukaryotic model organisms and has served widely as a host for recombinant protein production [2]. It is a common colonizer of the skin, vaginal mucosa, and the digestive and respiratory tracts [1]. It is not clear whether digestive tract colonization is persistent or transient following the ingestion of yeast containing food [3].

Saccharomyces boulardii is a known ingredient in many probiotic supplements [1]. *S. boulardii* was thought once to be a separate species, but after genetic and molecular testing, it is now considered to be a subtype of *S. cerevisiae* [4]. Enhanced ability for pseudohyphal switching and better survival at acid pH are thought to be the reasons for *S. boulardii*'s success as a probiotic [5].

Invasive Saccharomyces cerevisiae infection have been identified over the past three decades with the microorganisms being recovered from blood, lungs, esophagi, peritoneal cavities, urinary tracts, and vaginas. Clinical and commercial strains are being identified with genotyping studies, and the contribution of commercial strains to the colonization and infection has been documented [6]. Predisposing risk factors are similar to those associated with invasive candidiasis. These include, indwelling center catheters, total parenteral nutrition, ICU admission, antibiotic use, and immunosuppression [7–10]. Multiple case reports demonstrate the association between the use of probiotics and invasive S. cerevisiae [11]. A literature review by Munoz et al. showed that in 90 case reports, 31% of patients were immunosuppressed, while 46% were labeled as critically ill [11]. Multiple case reports describe invasive *Saccharomyces cerevisiae* in hospitalized patients in beds near those taking probiotics [11]. These reports suggest a potential risk of colonization of materials within the hospital setting and the risk for transmission, if proper hygiene and sterility are not maintained. In our case report, our patient was taking probiotics for an extended period of time, likely leading to colonization and eventual translocation of the fungal pathogen during his acute illness.

Invasive infection is thought to be mainly through the invasion of the digestive tract and the colonization of central venous catheters [7]. It has been suggested that adhesins proteins, similar but weaker than those of *Candida albicans*, play a role in allowing *Saccharomyces cerevisiae* to cross compromised epithelial borders [12]. This mechanism has been the cornerstone of the pathophysiology of invasive infection in those with digestive tract disorders. A study in rat models have shown that complement pathway defects may also predispose hosts to invasive infection [13]. Probiotic therapy containing *Saccharomyces cerevisiae* and its subspecies, has been used in the treatment of patients with *C. difficile* colitis [14]. Clostridium difficile is known to colonize human mucosa and cause intestinal damage and inflammation through the release of exotoxins A and B [14]. Studies of the protease produced by *Saccharomyces cerevisiae* have shown the ability to inhibit toxin A and B produced by *Clostridium difficile* [14]. However, there have been reports that cases of *C. difficile* infection treated with probiotic supplement, have led to fungemia [8]. This suggests that even though *Saccharomyces cerevisiae* may play a role in the inhibition of the *C. difficile* exotoxins, the intestinal damage sustained may create a pathway for this yeast to translocate, resulting in an invasive infection.

Infection with Saccharomyces is usually non-specific and is clinically similar to infections caused by other microorganisms, including Candida. Like invasive candidiasis, fungemia with *S. cerevisiae* is by far the most common presentation, with a fever unresponsive to broad spectrum antibiotics being a commonly encountered clinical manifestation [11]. Cases describing invasive Saccharomyces with prosthetic valve endocarditis, peritonitis, cholecystitis, pneumonia, empyema, liver abscesses, and vaginitis, indistinguishable from those caused by *C. albican*, and UTI have been reported over the past three decades [6,11,15–17]. Fungemia with *S. cerevisiae* can have a transient, self-limited course without any further medical complication as described in a case report by Cohen et al. [18]. This is likely related to the low virulence of *S. cerevisiae* especially in immunocompetent hosts without any catheters or valvulopathy.

Diagnosis can be challenging, especially when the microorganism is recovered from a body site that is usually colonized with Saccharomyces in the absence of fungemia and with scarcity of symptoms. The presence of an underlying medical condition, along with a predisposing factor, usually aids with the diagnosis in such cases. In a review by Enache-Angoulvant et al. of 92 case reports of invasive Saccharomyces infection, all patients had at least one underlying medical condition facilitating invasive fungal infection [7]. The use of central venous catheters and prior use of antibiotics were the most encountered predisposing factors [7]. Invasive infection with *S. boulardii* was most likely to be found in patients with central venous catheters, digestive tract disease, ICU hospitalization, and those who are immunocompetent [7]. Many of these predisposing factors, including prior probiotic use, placement of central venous catheter and ICU admission, were present in our case and facilitated this invasive fungal infection.

The mainstay of therapy is the withdrawal of probiotic supplements, if taken, the removal of catheters, and the administration of antifungal agents. No drug of choice has been established yet, but S. cerevisiae has been consistently susceptible to Amphotericin B and Flucytosine [11]. A literature review by Munoz et al. reported a favorable response in 60% of 19 patients with invasive *S. cerevisiae* who received fluconazole alone, in contrast to a favorable response in 77.7% of 31 patients receiving amphotericin B [11]. The role of echinocandins has not yet been established and was not reported in the aforementioned study [11]. Multiple case reports show the successful eradication of *S. boulardii* from probiotic use with Caspofungin [8,19,20]. We were able to eradicate S. cerevisiae fungemia with Micafungin followed by Fluconazole.

A literature review by Enache-Angoulvant et al. reported the outcome in 84 cases of invasive *S. cerevisiae* infections with a favorable outcome in 68.7% of patients [7]. No significant difference in outcome between immunocompromised and immunocompetent hosts, with rates of favorable outcome of 65.5% and 73.8% respectively [7]. The only factor that appears to increase mortality is older age [11].

Invasive Saccharomyces infection due to the use of probiotic supplements containing *S. cerevisiae* or the subtype *S. boulardii* has been documented in patients with underlying predisposing risk factors and are mostly encountered in patients with immunosuppression, central venous catheters, antibiotic use, critical illness, and ICU hospitalization. These can infect the blood exclusively or co-infect other organs. Diagnosis can be challenging, given the non-specific presentation. Withdrawal of probiotic therapy, if given, and removal of central venous catheters in the presence of *S. cerevisiae* infection is of great importance. There has been no antifungal agent of choice so far to treat these infections, but *S. cerevisiae* has been consistently susceptible to Amphotericin B and Flucytosine. The role of echinocandins and to a lesser extent Fluconazole in invasive *S. cerevisiae* infection has not yet been established. We were able to eradicate *S. cerevisiae* fungemia with Micafungin and step-down therapy with Fluconazole (Tables 1 and 2).

Table 1
Culture Data.

Cultures		
Day	Location	Organisms Identified
Day 0	Blood	Aeromonas Hydrophila Escherichia Coli Streptococcus Bovis
Day 1	Biliary Fluid	Escherichia Coli Streptococcus Lutetienis
Day 1	Blood	Escherichia Coli Saccharomyces Cerevasiae
Day 2	Blood	Saccharomyces Cerevasiae

Table 2
Susceptibility Data on Saccharomyces Cerevasiae Isolate.

Antifungal	MIC (μg/mL)
5 - Fluorocytosine	< = 0.12
Amphoteracin B	< = 0.12
Anidulafungin	0.12
Caspofungin	< = 0.06
Fluconazole	16
Itraconazole	4
Micafungin	0.12
Posaconazole	1
Voriconazole	0.5

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Conflict of interest

There are no conflicts of interest.

References

[1] Valar Anoop, et al., Review of current methods for characterizing virulence and pathogenicity potential of industrial saccharomyces cerevisiae strains towards humans, FEMS Yeast Res. 15 (6) (2015), https://doi.org/10.1093/femsyr/fov057.
[2] Zihe Liu, Keith E.J. Tyo, José L. Martínez, Dina Petranovic, Jens Niel, Different expression systems for production of recombinant proteins in saccharomyces cerevisiae, Biotechnol. Bioeng. 109 (5) (2012) 1259–1268, https://doi.org/10.1002/bit.24409.
[3] L. Zerva, R.J. Hollis, M.A. Pfaller, In vitro susceptibility testing and DNA typing of saccharomyces cerevisiae clinical isolates, J. Clin. Microbiol. 34 (12) (1996) 3031–3034 (0095-1137/96/$04.0010).
[4] M.J. McCullough, et al., Species identification and virulence attributes of saccharomyces boulardii, J. Clin. Microbiol. 36 (9) (1998) 2613–2617 (doi:0095-1137/98/$04.0010).
[5] L. Edwards-Ingram, et al., Genotypic and physiological characterization of saccharomyces boulardii, the probiotic strain of saccharomyces cerevisiae, Appl. Environ. Microbiol. 73 (8) (2007) 2458–2467, https://doi.org/10.1128/aem.02201-06.
[6] P. Nyirjesy, et al., Saccharomyces cerevisiae vaginitis: transmission from yeast used in baking, Obstet. Gynecol. 86 (3) (1995) 326–329, https://doi.org/10.1016/0029-7844(95)00174-P.
[7] A. Enache-Angoulvant, C. Hennequin, Invasive saccharomyces infection: a comprehensive review, Clin. Infect. Dis. 41 (11) (2005) 1559–1568, https://doi.org/10.1086/497832.
[8] I. Santino, et al., Saccharomyces cerevisiae fungemia, a possible consequence of the treatment of clostridium difficile colitis with a probioticum, Int. J. Immunopathol. Pharmacol. 27 (1) (2014) 143–146, https://doi.org/10.1177/039463201402700120.
[9] J.B. Thygesen, et al., "Saccharomyces boulardii fungemia caused by treatment with a probioticum, Case Rep. 2012 (Mar 26) (2012) 1, https://doi.org/10.1136/bcr.06.2011.4412.
[10] Ky Popiel, et al., Invasive saccharomyces cerevisiae in a liver transplant patient: case report and review of infection in transplant recipients, Transplant. Infect. Dis. 17 (3) (2015) 435–441, https://doi.org/10.1111/tid.12384.
[11] Patricia Munoz, et al., Saccharomyces cerevisiae fungemia: an emerging infectious disease, Clin. Infect. Dis. 40 (11) (2015) 1625–1634, https://doi.org/10.1086/429916.
[12] Roberto Pérez-Torrado, Amparo Querol, Opportunistic strains of saccharomyces cerevisiae: a potential risk sold in food products, Front. Microbiol. 6 (2016), https://doi.org/10.3389/fmicb.2015.01522.
[13] Julie K. Byron, et al., Pathogenicity of saccharomyces cerevisiae in complement factor five-deficient mice, Infect. Immun. 63 (2) (1994) 478–485.
[14] I. Castagliuolo, et al., Saccharomyces boulardii protease inhibits clostridium difficile toxin a and b-induced effects in human colonic mucosa, Gastroenterology 114 (1998), https://doi.org/10.1016/s0016-5085(98)83862-6.
[15] J.N. Aucott, et al., Invasive infection with saccharomyces cerevisiae: report of three cases and review, Clin. Infect. Dis. 12 (3) (1990) 406–411, https://doi.org/10.1093/clinids/12.3.406.
[16] T. Katras, P.P. Hollier, P.E. Stanton, Calculous cholecystitis associated with saccharomyces F1cerevisiae, Inform. Med. 9 (1992) 38–39.
[17] R.H. Eng, et al., Saccharomyces cerevisiae infections in man, Sabouraudia 22 (5) (1984) 403–407.
[18] Lola Cohen, et al., Saccharomyces cerevisiae boulardii transient fungemia after intravenous self-inoculation, Med. Mycol. Case Rep. 2 (2013) 63–64.
[19] Serkan Atıcı, et al., Catheter-related saccharomyces cerevisiae fungemia following saccharomyces boulardii probiotic treatment: in a child in intensive care unit and review of the literature, Med. Mycol. Case Rep. 15 (2017) 33–35, https://doi.org/10.1016/j.mmcr.2017.02.002.
[20] Lolis Nikolaos, et al., Saccharomyces boulardii fungemia in an intensive care unit patient treated with caspofungin, Crit. Care 12 (2) (2008) 414, https://doi.org/10.1186/cc6843.