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Saccharomyces cerevisiae var. boulardii fungemia following probiotic treatment

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ABSTRACT

Probiotics are commonly prescribed as an adjuvant in the treatment of antibiotic-associated diarrhea caused by *Clostridium difficile*. We report the case of an immunocompromised 73-year-old patient on chemotherapy who developed *Saccharomyces cerevisiae* var. *boulardii* fungemia in a central venous catheter during treatment of antibiotic-associated pseudomembranous colitis with the probiotic *Saccharomyces cerevisiae* var. *boulardii*. Fungemia was resolved after interruption of probiotic administration without the need to replace the central venous line.

1. Introduction

Critical illness, especially in hospitalized patients, has been associated with gut microbial imbalance, possibly leading to increased susceptibility to infection, sepsis, and organ failure [1,2]. In these patients, the risk of complications linked to antibiotic-related dysbiosis, including diarrhea [3], underscores the importance of rational antibiotic and drug use.

Probiotics are commonly prescribed for the prevention or treatment of diarrhea and other systemic inflammatory processes. Nevertheless, the exact role of these agents in various clinical contexts has not been fully established, and their safety profile is still a matter of debate in certain populations [4]. In addition, clinical trials have failed to produce evidence of benefit from probiotic use [3,5]. In fact, the widespread use of probiotics has been associated with cases of fungemia in immunocompromised patients, with increasing incidence in the past years [6].

We report the case of an immunosuppressed patient on chemotherapy who developed *Saccharomyces cerevisiae* var. *boulardii* fungemia in a central venous catheter during treatment of pseudomembranous colitis with the probiotic *Saccharomyces cerevisiae* var. *boulardii*.

2. Case

A 73-year old female was admitted to a tertiary care hospital for surgical removal of frontal lobe glioblastoma multiforme. The procedure was uneventful, and after 10 days she was discharged on valproic acid. The patient was readmitted after 5 days with complaints of mild fever, excessive sleepiness, and dysphagia. Because a drug effect was considered, valproic acid was replaced with levetiracetam, without improvement. Magnetic resonance neuroimaging revealed a nodular lesion involving the corpus callosum. Given the patient's inability to swallow, the speech therapy team prescribed enteral nutrition via nasoenteric feeding tube for a short period of time. Urine and blood samples were collected for investigation of fever. Urine culture showed growth of *Proteus mirabilis* with a count $> 10^5$ colony forming units (CFU)/mL, treated with ciprofloxacin 500 mg, every 12 h, for 7 days. After 7 days, new samples were cultured for monitoring, with isolation of *Citrobacter freundii* ($> 10^5$ CFU/mL), which was subsequently treated with trimethoprim/sulfamethoxazole 800/160 mg during 7 days.

In the absence of further infection, oncologic treatment was started a month after admission including radiotherapy and chemotherapy with temozolomide (day 0). A control MRI performed after 20 days of treatment showed unsatisfactory response, with growth of the callosal lesion and deviation of the midline, without indication for neurosurgical treatment. Radiological examination revealed tetraparesis, with recurrence of dysphagia. Following reevaluation by the speech therapy team, the patient was again started on enteral diet via nasoenteric tube. Persistent low fever was treated with piperacillin/tazobactam 4.5 g every 6 h during 7 days to cover broad spectrum antimicrobial activity, while additional cultures were performed. In urine

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samples, culture again revealed growth of *Citrobacter freundii*, managed with a 7-day course of trimethoprim/sulfamethoxazole 800/160 mg. Neurological evaluation showed signs of intracranial hypertension, managed with ventriculoperitoneal shunt.

During the following days the patient developed profuse diarrhea (day +35). A diagnosis of antibiotic-associated colitis or infection by another opportunistic germ was considered. Stool analysis was performed, with prescription of an antiparasitic drug (albendazole 400 mg) and lyophilized *Saccharomyces boulardii* − 17-based probiotic (Floratil®, Merck) 100 mg capsule, 0.5×10^9 cells, every 12 h. Stool analysis was positive for fecal leukocytes and *Clostridium difficile* A and B toxins, leading to the prescription of metronidazole tablets 500 mg every 8 h. The continuation of fever led to the sampling of central catheter blood, with a preliminary result revealing yeast growth (day +36). Intravenous micafungin 100 mg was immediately started considering the primary suspicion of Candida infection. After yeast growth in Sabouraud agar, the culture was forwarded for identification through matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF), with confirmation of *Saccharomyces cerevisiae* var. *boulardii*. The minimal inhibitory concentration was determined using the E-test, showing sensitivity to amphotericin B, caspofungin, micafungin, and voriconazole. The patient was diagnosed with fungemia. Probiotic treatment was interrupted, with maintenance of antibiotic treatment with ampicillin/sulbactam 3 g, every 6 h, and metronidazole 400 mg every, 8 h, associated with micafungin 100 mg/day.

In the absence of neurological improvement, comfort measures were prioritized, while antimicrobial treatment was continued. Hyperthermia was no longer detected and control blood cultures were negative for yeast, despite the maintenance of the central venous line site.

3. Discussion

Saccharomyces boulardii is considered as a non-pathogenic yeast. It was initially identified in 1923 in tropical fruit (lychee and mangosteen) by French scientist Henri Boulard [7]. Its use as a probiotic has been studied for over 30 years, especially in the prevention and treatment of bacterial diarrhea. Tiago et al. [8] have described the mechanism of probiotic elimination of pathogenic bacteria, which would involve adhesion of bacteria onto the surface of *Saccharomyces cerevisiae* var. *boulardii*, preventing bacterial fixation on intestinal receptors. In addition, *Saccharomyces cerevisiae* var. *boulardii* seems to exert a protective effect against *C. difficile* infection, achieved by the production of proteases that are capable of neutralizing the A and B toxins, which are responsible for intestinal inflammation [9].

A meta-analysis on the use of probiotics for the prevention of antibiotic-associated diarrhea and CDI treatment revealed that *Saccharomyces cerevisiae* var. *boulardii* was the only effective choice [10]. However, more recent systematic review and meta-analysis concluded that there is insufficient evidence to support a recommendation for the combined use of probiotics and antibiotics to treat CDI [11,12]. The available studies are heterogeneous, having used different strains as well as variable probiotic doses, treatment durations, and administration modes (drinks or capsules, for example) [13].

The use of *Saccharomyces cerevisiae* var. *boulardii*-based probiotic as supplementary therapy in cases of infectious diarrhea is well-established in the literature and clinical routine, despite the inconsistent evidence of benefit. In healthy patients, studies show that probiotics are safe, without adverse effects [14,15]. However, in critically ill patients, with severe systemic gastrointestinal disease, admitted to intensive care units, in use of mechanical ventilation or central venous catheter, treated with broad spectrum antibiotics, or in individuals who are immunosuppressed as a result of other disorders or medication use, the risk of fungemia associated with probiotics, especially *Saccharomyces boulardii*, is high [16,17].

Immunosuppression related to critical illness and the handling of tubes and catheters for the administration of probiotics have been identified as risk factors for fungemia caused by *Saccharomyces*. Clinical practice guidelines [18] also recommend against the prescription of *Saccharomyces cerevisiae* var. *boulardii* probiotics to patients with severe or recurrent *Clostridium difficile* infection, especially in the presence of critical illness.

Many case reports of probiotic-related fungemia had been published but, despite that, those drugs are still widely prescribed and cases of fungemia keep on been diagnosed. Roy et al. [6] presented a series of seven cases of fungemia after consumption of probiotic containing *S. boulardii*, in which five of them were severely ill adults from ICU. Those patients were taking probiotic in order to prevent or to treat antibiotic-associated diarrhea and *S. cerevisiae* was isolated from blood of all those patients at least once; further clinical details were not available.

Lherm et al. [17] presented a series of seven patients who developed fungemia due to *Saccharomyces cerevisiae* var. *boulardii* probiotics. They were all intubated-ventilated, on enteral feeding, with central venous catheters and received broad-spectrum antibiotics at the time of the fungemia. Three of them were immunocompromised and had long stays in ICU. The fungemia occurred in the late course of the ICU stay and were associated with fever, but without significant change in leukocytosis. A worsening of respiratory, hemodynamic and neurologic statuses were observed in two cases. In all cases, normothermia was obtained after stopping the *S. boulardii* treatment and changing central venous catheters, while antifungal treatment was added in three patients.

In a case report from Santino et al. [19] an elderly man presented with fever and elevated inflammatory parameters (c-reactive protein greater than 3 mg/dL [normal range, 0.00–0.50] and procalcitonin level of 5.88 ng/mL [normal range < 0.05]) ten days after treating pseudomembranous colitis with antibiotic and probiotic treatment containing *Saccharomyces boulardii* var. *cerevisiae. S. cerevisiae* was isolated from both peripheral veins and indwelling catheter and antifungal treatment with caspofungin was initiated, resulting in diminished fever and improvement of the inflammatory biochemical parameters within 24 h.

In the present case report, the interpretation of fungemia as a result of *Saccharomyces cerevisiae* var. *boulardii* translocation resulted from the good clinical response, with control of fever, in addition to the evidence of fungal eradication in blood cultures despite the maintenance of the same central venous line.

After the present case, the medical protocol for indication and prescription of probiotics was reviewed in our institution, with the aim of minimizing the risk of fungemia. Considering the inconsistent evidence of benefit in patients with Clostridium difficile-diarrhea and the risk of fungemia in critically ill patients, caution advise related to the prescription of Floratil® was issued and the probiotic medication was discontinued.

Conflict of interest

The authors declares no conflicts of interests regarding publication of this paper.

Ethical form

This study received no funding, and there are no potential conflicts of interest to declare. We obtained written and signed consent to publish the case report from the patient.

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