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CASE REPORT

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Bloodstream infection by *Saccharomyces cerevisiae* in a COVID-19 patient receiving probiotic supplementation in the ICU in Brazil

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Abstract

Care-related infections (CRIs) have a negative impact on the morbidity and mortality of patients in intensive care. Among them, fungal infections (e.g. *Candida* spp. and *Aspergillus* spp.) have high mortality in critically ill patients, particularly those with acute respiratory distress syndrome (ARDS) and immunosuppression. Coronavirus disease 2019 (COVID-19) causes severe respiratory changes and deregulation of the immune system. Here, we describe a case of fungal infection in an intensive care unit (ICU) patient with COVID-19 caused by *Saccharomyces cerevisiae*, a yeast widely used in the baking and wine production industries. It is also used as a probiotic, both for prevention and as adjunctive therapy in patients with diarrhoea. The patient was admitted to the ICU with a diagnosis of COVID-19, respiratory failure, complications of ARDS and renal failure, and was being treated with antibiotics and vasoactive amines. Later, the patient had diarrhoea and, after supplementation with *Saccharomyces*, he developed a bloodstream infection with *Saccharomyces*. The patient died after 61 days of hospitalization due to thrombocytopenia and bleeding. This case report suggests avoiding the use of probiotics in intensive care patients under the administration of antibiotics and amines, and with damage to the intestinal mucosa and immunodeficiency caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), since these factors could favour the translocation of fungi.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had a huge impact on public health due to the rapid rate of transmissibility, as well as mortality. It also has a negative impact on care-related infections (CRIs) in critically ill patients [1]. Intensive care patients are susceptible to fungal infections, such as candidaemia related to the central venous catheter and pulmonary aspergillosis, which has already been described in patients with COVID-19 [2–5].

The genus *Saccharomyces* is a well-studied group of yeasts, and its most famous representative is *Saccharomyces cerevisiae*, which is widely used in baking and ethanol and wine production, as well as being used in the pharmaceutical industry to obtain lepirudin [6]. Another representative of the genus, *Saccharomyces boulardii*, which is described in the literature as genetically identical to *Saccharomyces cerevisiae*, has been used therapeutically in the treatment of disorders of the gastrointestinal tract [3, 7]. In humans, the genus *Saccharomyces* may be present as a colonizer of the gastrointestinal, respiratory and urinary mucosa [8], and also in patients with underlying diseases [3, 9, 10]. Although rare, reports of 'unusual' fungal infections have been increasing, with *S. cerevisiae* comprising 4% of fungi isolated in blood culture [3, 9–11]. Here we report the case of a patient with COVID-19 who received supplementation with *Saccharomyces*, due to diarrhoea, and developed fungaemia.

CASE REPORT

A Brazilian patient in his 70s, resident in the city of Rio de Janeiro, was transferred to the hospital's ICU on 6 May 2020 with a diagnosis of COVID-19 (CO-RADS 6) and acute respiratory distress syndrome (ARDS). The patient came from another hospital unit with a history of fever, cough, dyspnoea and use of ceftriaxone and azithromycin (administered from 4 May 2020 until 6 May 2020), with 2 days of right femoral vein and 1 day of orotracheal intubation on mechanical ventilation. In Brazil, during the pandemic, patients are initially treated in emergency hospitals and, subsequently, with the worsening of their health status, they are transferred to referral hospitals. On admission, the patient was sedated and attached to

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Keywords: COVID-19; coinfection; fungaemia; *Saccharomyces*; sepsis.

Abbreviations: ARDS, acute respiratory distress syndrome; CLSI, Clinical and Laboratory Standards Institute; COVID-19, coronavirus disease 2019; CRIs, care-related infections; FR, respiratory frequency; ICU, intensive care unit; PCV, pressure-controlled ventilation; VAC, flowing air volume.

Table 1. Laboratory tests, treatments and vital signs

	May 6–11	May 12–17	May 18–19	May 20	May 21
P/F ratio	357	255	261	305	298
Dialysis	No	Yes	Yes	Yes	Yes
Amines	Yes	Yes	Yes	Yes	Yes
Medication	Piperacillin/ tazobactam	Piperacillin Tazobactam Floratil Meropenem Vancomycin	Meropenem Vancomycin Fluconazole	Meropenem Vancomycin Fluconazole	Meropenem Vancomycin Fluconazole
Central venous catheter	Yes	Yes	Yes	Yes (exchanged)	Yes
Leukocytes (mm^3)	8600	11500	15390	15800	12540
Platelets (mm^3)	305000	310000	307000	312000	298000
Glucose (mg dl^{-1})	263	182	166	158	128
C-reactive protein (mg dl^{-1})	33.5	23.7	25.1	17.6	11.2
Maximum daily body temperature (°C)	37.2	38.5	38	37.9	36.8
Creatinine (mg dl^{-1})	1.5	4.7	2.2	1.9	2.3
PCR – SARS-CoV-2	Positive	–	–	–	–
Blood cultures	Negative	Negative	*Saccharomyces*	–	–

P/F ratio, ratio of partial pressure arterial oxygen (PaO_2 mmHg) and fraction of inspired oxygen (FiO_2); –, not tested. Normal values: P/F, >250; leukocytes, 4000–10000 mm^3; platelets, 200000–400000 mm^3; glucose, 60–99 mg dl^{-1}; creatinine, 0.6–1.3 mg dl^{-1}; C-reactive protein, <0.3 mg dl^{-1}.

a ventilatory prosthesis: pressure-controlled ventilation (PCV), 16 (normal values: ≤40); respiratory frequency (FR), 16 (12–16); fraction of inspired oxygen (FiO_2), 35% (variable to maintain arterial oxygen saturation at 93–98%); flowing air volume (VAC), 530 (6 ml kg^{-1}); inspiration to expiration ratio (I : E), 1:2 (1:2–1:3); and without the use of vasoactive amines. Examinations were as follows: arterial blood gas analysis (pH, 7.3; pO_2, 144; pCO_2, 40; SpO_2, 98; HCO_3, 23); glucose, 263 mg dl^{-1}; creatinine, 1.5 mg dl^{-1}; C-reactive protein, 33.5 mg dl^{-1}; leukocytes, 8600/mm^3; and platelets, 305000 mm^{-3} (Table 1). RT-PCR was COVID-19-positive; influenza A/B and respiratory syncytial virus were negative. Chest tomography showed 50% pulmonary involvement on the ground-glass imaging.

The antibiotic regimen was changed to piperacillin/tazobactam (administered for 12 days), and vasoactive amines were started (Table 1). Two days later, the right subclavian vein was punctured for haemodialysis. In the first 7 days of hospitalization, the blood count remained stable, and the nitrogenous slags, which went from 1.5 to 4.7 mg dl^{-1} after haemodialysis, remained at 2 mg dl^{-1}. On 12 May 2020, due to the appearance of watery diarrhoea for more than eight bowel movements/day for 3 days, the probiotic Floratil was administered, together with vancomycin and meropenem for 10 days (Table 1). The patient began to experience several daily peaks of fever of 38.5 °C and the need for an increase in vasoactive amines. Samples were collected for blood, urine and tracheal secretion on 18 May 2020, which revealed the growth of *S. cerevisiae* in three blood culture vials. Therefore, fluconazole was added to the antibiotic regimen and Floratil was suspended (Table 1). A sensitivity test for the fungus was performed with VITEK (bioMérieux) automated equipment [according to the Clinical and Laboratory Standards Institute (CLSI) guidelines], which showed growth inhibition with 2 µg ml^{-1} of fluconazole, which was maintained for 14 days. After 48 h of haemodynamic stabilization, the patient still had a fever, and so all of the central venous catheters were exchanged, which led to the resolution of the fever (Table 1). After 21 May 2020, the patient evolved with several episodes of sepsis of pulmonary origin associated with mechanical ventilation. Other blood cultures and tracheal secretions were analysed, revealing the growth of *Acinetobacter* spp. and *Stenotrophomonas maltophilia*, but not *S. cerevisiae*. Multiple antibiotic regimens were used (tigecycline, polymyxin b, sulfamethoxazole and trimethoprim) for 14 days. On July 2020 the patient died due to cardiopulmonary arrest and thrombocytopenia.

The patient was admitted to an ICU with a negative pressure environment solely with COVID-19 patients. He was treated by an exclusive medical and nursing team who had intensive physical and air contact precautionary training. According to medical records, no case of *Saccharomyces* fungaemia had been reported in the hospital, even though it has eight ICU units, one for liver and kidney transplant patients, and the practice of using probiotics with *Saccharomyces* is common in diarrhoea cases.

DISCUSSION

The definition commonly used for probiotics is live micro-organisms that are administered in adequate concentrations and that confer a benefit to the health of the host [12]. *S. cerevisiae* is a yeast that has been we have been aware of for a long time, with wide industrial use [3, 6, 13]. Despite being a germ distributed in nature and of low virulence for humans, it has been identified more frequently in recent decades with invasive infections, being a recognized agent in ~4% of positive blood cultures for fungi, including in immunocompetent individuals [3, 11]. Its first description as a pathogen occurred in 1958 (Reihersol and Hoel) in repeated sputum isolates from a patient with bronchopneumonia [10]. Its epidemiology is not yet fully known, being recognized as a transitory colonizer of the gastrointestinal mucosa (especially after eating contaminated food), the female genital tract and the respiratory tract [3, 9, 10, 13].

It is believed that *S. cerevisiae* entry into the human body is predominantly through the gastrointestinal tract [3, 5, 14, 15], but it can also occur via catheters contaminated by the hands of health professionals. This contamination can occur during the preparation of the probiotic capsules that are administered by nasogastric tube [5, 16]. As this preparation involves opening and handling the capsules, attention is needed, since the micro-organism would have the ability to colonize other surfaces. Further, its removal is difficult, even with hand washing, and this a possible source of contamination. The presence of *Saccharomyces* in sterile biological fluids indicates a gastrointestinal leakage or high concentration of the fungus, caused by gastrointestinal injury (diarrhoea, ulceration, intestinal surgery, haemodialysis, chemotherapy and/or ischaemia) [3, 9, 17].

The isolation of *Saccharomyces* in culture is simple, based on its morphology, growth characteristics and biochemical tests [9]. The subtype *S. boulardii* is described in the literature as being genetically identical to *S. cerevisiae* [3, 9], and routine differentiation by automation does not distinguish them, reporting only *S. cerevisia*e [3]. Thus, the identification of *S. cerevisiae* in the patient refers to *S. boulardii*, which is used in the administered probiotic (Floratil).

The risk factors for infection with *Saccharomyces* are similar to those for candidaemia, such as the use of catheters, parenteral nutrition, haemodialysis, use of broad-spectrum antibiotics, immunosuppression (HIV or neoplastic diseases) and transplantation [3, 9]. In addition to these, in *Saccharomyces* fungaemia, an isolated and exclusive risk factor consists of the previous administration of the probiotic *S. boulardii*, widely used in the treatment of diarrhoea, both prophylacticlly and as an adjunct, especially in association with the use of antibiotics [3, 9, 11]. In a study of 93 patients with infectious complications and the use of probiotics, fungaemia was the main infection (37.6%), with the genus *Saccharomyces* being the most frequent (50%), including contributing to mortality [18]. The most important clinical manifestation of *Saccharomyces* infection described is fungaemia in critical intensive care, immunocompromised, or HIV-positive patients, in addition to immunocompetent patients with endocarditis, liver abscess, pneumonia, vaginitis and esophagitis [3, 9, 14]. *Saccharomyces* fungaaemia after the use of probiotics is even more common in critically ill patients in the ICU than in patients with typical immunodeficiencies [19]. In this case report, the condition of a patient with diarrhoea under the administration of antibiotics and vasoactive amines could constitute a risk factor for increased intestinal permeability, as these conditions damage the mucosa and thus could allow fungal infection [15]. In addition, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is an aggravating factor, as it can invade enterocytes, cause dysbiosis and induce gastrointestinal symptoms, further injuring the intestinal mucosa. In fact, there is a prevalence of deaths in COVID-19 ICU patients that appears to be related to increased use of antibiotics and gut microbial dysbiosis [20]. Further, in severe COVID-19 disease, an increase in pro-inflammatory markers (IL-1, IL-6, TNF-α), lower IFN-N expression, and fewer CD4 and CD8 cells were observed, which would increase susceptibility to fungal and bacterial infections [21].

There is no consensus on the treatment of *Saccharomyces* infection, favouring the use of fluconazole, voriconazole, flucytosine, amphotericin b and even the association of amphotericin b with fluconazole [3, 9]. Other important measures are the removal of catheters and the suspension of the probiotic [5, 9, 13]. There are several studies on probiotic indications, but there is little evidence that determines its use, as in irritable bowel syndrome and as an adjunct in the treatment of *Helicobacter pylori* [22]. The evidence is moderate as to the indication for diarrhoea, as it has been shown to improve quality of life, and should therefore be used with caution in invasive diarrhoea. Further studies are needed for other indications, especially in critically ill patients [23, 24].

The case presented here in an ICU patient with COVID-19 is surprising since he was not known to be a typical immunocompromised case and was from the community. Even so, with the use of deep venous catheters and antibiotics, the patient developed a fungal infection with only *S. cerevisiae* after 6 days of using the probiotic. Treatment with fluconazole resulted in partial improvement of symptoms, but only with the subsequent removal of the catheters did the fever cease, raising the possibility of contamination by the fungus via central vascular catheters.

This case calls attention to an emerging germ, for which there have been increasing reports in recent decades concerning its infection being associated with the use of probiotics that are common in clinical practice and often considered innocuous. Based on this report, we suggest avoiding the use of probiotics in intensive care patients under the administration of antibiotics and amines, and with damage to the intestinal mucosa and immunodeficiency caused by SARS-CoV-2 virus, since these factors could favour the translocation of fungi. The use of probiotics is not free of complications, and we do not intend to discourage their use, but rather to discuss

the indications and necessary care for their use, especially in patients with risk factors.

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G.P.: conceptualization, formal analysis, methodology, writing – original draft. L.L., T.P. and A.A.: conceptualization, formal analysis, methodology. S.M.: writing – review and editing. L.M.: investigation, resources and validation.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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