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Reminder of important clinical lesson

Saccharomyces boulardii fungemia caused by treatment with a probioticum

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Summary

Saccharomyces cerevisiae, known as baker's yeast, is normally considered a non-pathogenic yeast. A genetically very similar subtype, *S boulardii*, is used in a probioticum (Sacchaflor) to prevent antibiotic-associated diarrhoea and in the treatment of recurrent *Clostridium difficile* associated diarrhoea. The authors present a case report of a 79-year-old woman with rheumatoid arthritis, who after a bowel resection developed *S boulardii* fungemia. Her postoperative course was complicated by nutritional problems, anaemia and several nosocomial infections including recurrent *C difficile* associated diarrhoea. The diarrhoea was treated with metronidazole, vancomycin and Sacchaflor. After 13 days of treatment, the patient developed fungemia with *S boulardii*. Treatment with Sacchaflor was immediately discontinued and the patient was successfully treated with amphotericin B. Fungemia is a rare, but a serious complication to treatment with probiotics. Accordingly, the authors find it important to remind the clinicians of this risk when prescribing probiotics especially to immunocompromised patients.

BACKGROUND

Saccharomyces boulardii is a subtype of *S cerevisiae*. Since 1991 *S boulardii* has been used in probiotics to prevent antibiotic-associated diarrhoea and to treat recurrent *Clostridium difficile* associated diarrhoea.[1] Probioticum has also been used in cases of ulcerative colitis and other inflammatory bowel conditions. Generally, treatment with probiotics is considered safe, but a few cases of fungemia with *S boulardii* have been reported in critically ill patients treated with probiotics.

Due to the seriousness of this complication, we find it important to remind the clinicians of this risk when they prescribe the probioticum especially to immunocompromised patients.

CASE PRESENTATION

A 79-year-old woman with rheumatoid arthritis was transferred from the surgical department after a bowel resection of one-metre ischemic distale ileum. Due to rheumatoid arthritis, the patient had previously been treated with the tumour necrosis factor-α inhibitor, adalimumab, but had not received any kind of immunosuppressive therapy within the past 17 months.

At the time of admission, she was debilitated with diarrhoea, nausea, vomiting and fever. She was undernourished with hypoalbuminemia, (serum albumin=0, 11 mmol/l), and anaemia (haemoglobin= 4, 1 mmol). Further, she had a nasogastric tube for nutrition and a central venous catheter (CVC) was established in order to supplement with parenteral nutrition. Due to anaemia, blood transfusions were indicated but because of the patient's religious beliefs the patient declined the offer of blood transfusions. Instead, she was treated with erythropoietin and iron supplementation.

The course was further complicated by the occurrence of universal colonisation of *Candida albicans*, but no Candida fungemia, recurrent urinary tract infections and recurrent *C difficile* associated diarrhoea. Due to the infections, the patient was treated with several types of broad-spectrum antibiotics including intravenous fluconazole.

The patient was suspected of having an inflammatory bowel disease (IBD), which in addition to the short bowel syndrome might have influenced her severe recurrent diarrhoea and nutritional problems. However, the diagnosis of IBD was never confirmed. The *C difficile* associated diarrhoea was treated with vancomycin, metronidazole and the probioticum, Sacchaflor. The probioticum was added due to recurrent *C difficile* associated diarrhoea in spite of prolonged treatment with metronidazole and/or vancomycin.[2 3] On this treatment, the diarrhoea ceased and the patient improved.

Yet, after 13 days of treatment with vancomycin, metronidazole and Sacchaflor, the patient developed fever and increasing inflammatory markers, but no sign of *C difficile* infection. *S boulardii* was identified in the blood cultures.

INVESTIGATIONS

S boulardii was isolated from blood cultures. During treatment with amphotericin B blood cultures were obtained every day until negative of *S boulardii*. For the rest of the treatment period blood cultures were examined two times a week.

Capsules of the probioticum, Sacchaflor, were obtained for culture and appeared positive with the same type of *S boulardii*, as identified in the blood cultures. The CVC was removed and culturing of the catheter tip turned out negative.

TREATMENT

Treatment with Sacchaflor was immediately discontinued, the CVC removed and the patient was treated with amphotericin B for 18 days.

OUTCOME AND FOLLOW-UP

Three days after initiation of amphotericin B therapy, the blood cultures were negative for *S boulardii*. The treatment continued for another 15 days. The patient improved and the inflammatory markers normalised within the first week.

Three weeks after the discontinuation of amphotericin B treatment, the patient was transferred to another department in order to optimise her nutrition. At this time she was afebrile and without diarrhoea.

However, the patient died 3 weeks later in a picture of septic shock, but no sign of fungemia.

DISCUSSION

The patient developed *S boulardii* fungemia as an adverse effect to treatment with the probioticum, Sacchaflor. According to the product information of Sacchaflor (PharmaForce Aps, Denmark) each capsule contains 5×10^9 *S boulardii* plus mannan oligosaccharides. The recommended dose is 1–2 capsules daily.[4] Our patient received one capsule a day corresponding to 280 mg.

The precautions stated in product information of the probioticum are pregnancy and children <1 year, but nothing about increased risk by treatment of critically ill or immunocompromised patients.[4]

Fungemia caused by *S cerevisiae* or *S boulardii* is rare. Previous studies have shown that routine investigations often fail to distinguish *S cerevisiae* from the subtype *S boulardii*. Some authors consider the two yeasts identical due to the genetically identity.[5–7]

Population-based studies suggest that *S cerevisiae* is responsible for 0.1%–3.6% of all episodes of fungemia.[6] Since 1991 a few cases of fungemia with Saccharomyces species have been reported.[1] This coincides with the time when the probioticum containing *S boulardii* was introduced at the market for treatment or prophylaxis of *C difficile* associated diarrhoea.[1] Fungemia by Saccharomyces species is mostly reported in patients treated with a probioticum, and who are critically ill or immunocompromised.[7 8] However, it has also been reported in patients not receiving treatment with the probioticum themselves, but who share room with probioticum treated patients.[9] *S boulardii* fungemia was reported in patients receiving high doses of probioticum, 1–3 g/d.[1] In current case the patient was treated with a low dose of 280 mg/day.[4]

A review of the literature concerning 60 cases of fungemia with *S cerevisiae* found, that the most consistent risk factor for *S cerevisiae* fungemia was the use of probiotics containing *S boulardii*. In order to differentiate *S cerevisiae* from *S boulardii* a PCR fingerprinting procedure was used. Moreover, in the studies included in the review a high mortality, up to 29, 5%, was reported for patients with fungemia caused by Saccharomyces species.[6]

According to previous studies, fungemia is seen in median 10 days after treatment initiation.[6] In our patient, the first positive blood culture with *S boulardii* was seen 13 days after the first dose of the probioticum was given.

Different theories concerning the main mechanisms of developing fungemia with *S cerevisiae* or *S boulardii* have been propounded.[1 8 9] One theory is that CVC may be contaminated from the hands of healthcare workers, when the probiotic capsules are opened and administered as a powder though nasogastric tubes. Accordingly, it has been demonstrated that when the probiotic capsules are opened, the powder with the yeast may persist on room surfaces after 2 h at a 1 metre distance and can be detected on the bare hands of the healthcare workers even after washing hands. Hence, the CVC of patients treated with probioticum as well as CVC of non-treated patients may be contaminated. Another route of transmission is by enteral translocation through the intestine of ingested microorganisms from probiotic capsules. This way of transmission has also been described to be in evidence for bacteria. Colonic ulceration may predispose to the translocation of the yeast through the intestine. Finally, debilitated patient are more susceptible to develop infections due to almost non-pathogenic microorganisms.

In our patient it is unlikely that the contamination occurred through the CVC as the culture of the catheter tip was negative. The patient had just undergone an intestine resection and may have had a leaky intestine predisposing for enteral translocation of *S boulardii*. Moreover, the patient may also have had an IBD although the diagnosis has never been decisively confirmed.

Most of the patients reported, who have developed a fungemia with *S cerevisiae* or *S boulardii*, were critically ill, were intubated, had a CVC in place, received intravenous alimentation and/or broad-spectrum antimicrobial therapy.[8] Our patient was not intubated but had the other risk factors for getting a fungemia with *S boulardii*.

S cerevisiae or *S boulardii* are unusual causes of fungemia, but should never be dismissed as non-pathogenic when detected in blood cultures and especially not, when recovered from critically ill and immunocompromised patients. Due to the high mortality, immediate treatment is important. The suggested treatment is interruption of probioticum therapy, removal of CVC and initiation of treatment with an antifungal agent as amphotericin B or according to sensitivity test.

The antifungal agent of choice for treatment of Saccharomyces species has not been finally established, but amphotericin B and fluconazole seems to be preferable.[6 10] In spite of ongoing treatment with fluconazole for 14 days due to colonisation with *C albicans* our patient still developed fungemia with *S boulardii*. Due to this, we chose to treat with amphotericin B. The subsequent sensitivity test showed sensitivity to amphotericin B, anidulafungin and voriconazole, but resistance to fluconazole, posaconazole and itraconazole.

This case illustrates, that clinicians must be cautious when prescribing probiotics to patients belonging to risk groups, that is, immunocompromised, critically ill patients or patients with severe IBD or similar bowel diseases. Therefore, we suggest that product information of *S boulardii* containing probiotics inform of these precautions and those guidelines for prescribing probiotics should be elaborated.

Learning points

- *S boulardii* might be a pathogenic microorganism.
- Clinicians should be aware that treatment with *S boulardii* containing probiotics might cause fungemia in severely ill and immunocompromised patients.
- The mortality for patients with fungemia caused by Saccharomyces species is high–up to 29, 5%.

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