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CASE REPORT

Successful treatment of liposomal amphotericin B refractory *Candida glabrata* fungaemia in a patient undergoing a stem cell transplantation

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ABSTRACT

Blood stream infections caused by *Candida glabrata* are difficult to manage. We describe a patient who underwent an allogeneic peripheral stem cell transplantation for acute myeloid leukaemia. The patient developed *C. glabrata* fungaemia that was refractory to liposomal amphotericin B therapy. After changing the therapy to caspofungin, blood cultures became sterile within two days and the patient recovered clinically. The patient died shortly after due to graft-versus-host disease and at autopsy there was no evidence of residual or persistent *Candida* infection. Caspofungin was effective in liposomal amphotericin-B refractory *C. glabrata* fungaemia and proved to rapidly clear the infection. Treatment options for candidaemia are discussed.

KEYWORDS

Candida glabrata, candidaemia, caspofungin, fungaemia

Stem cell transplant (SCT) recipients are at increased risk of developing opportunistic infections. Although the risk for fungaemia is low because prophylaxis is usually used with fluconazole, invasive infections due to *Candida glabrata* remain difficult to manage. *C. glabrata* is becoming increasingly prevalent in immunocompromised patients, and causes significant morbidity and mortality.[1,2] We report a patient with acute myeloid leukaemia who developed a fungaemia with *C. glabrata*, refractory to treatment with liposomal amphotericin B.

CASE REPORT

A 60-year-old female, with acute myeloid leukaemia in complete remission, was admitted for scheduled allogeneic peripheral SCT, following a preparative myeloablative regimen consisting of idarubicin, busulphan and cyclophosphamide. A subclavian catheter was inserted uneventfully on the day of admission. She received ciprofloxacin and valaciclovir as antimicrobial prophylaxis. The patient was colonised with *C. glabrata*, as cultures from the oral cavity as well as faeces were repeatedly positive, but no antifungal prophylaxis was initiated. During prior chemotherapy, she had not received antifungal therapy.

After the conditioning regimen, it was suspected that she had developed enterocolitis or typhlitis as she had continuous, but not voluminous, diarrhoea. Cultures of the stools remained positive for *C. glabrata*.

Three days before the SCT the patient developed fever up to 39.3°C On physical examination she was haemodynamically stable, had grade II mucositis of the mouth, normal breathing sounds and no cardiac murmur.[3] The abdomen revealed no abnormalities. At the extremities there were no special findings, especially no petechiae. Her prophylactic antibiotic therapy (ciprofloxacin) was discontinued and ceftazidime was empirically initiated because of febrile neutropenia as blood cultures remained sterile.

Eight days after SCT her peripheral blood showed signs of bone marrow repopulation and on day 11 her leucocyte count was above 0.5 x 10^9/l. At that time she had persistent fever, oral mucositis but no diarrhoea. She had peripheral oedema and was tachypnoeic. Her oxygen saturation was 92%. Because of the lack of clinical improvement and persistent mucositis with colonisation of *C. glabrata*,

fluconazole 800 mg once daily was started on the ninth day after SCT pre-emptively. Three blood cultures, taken eight days after transplantation, became positive for *C. glabrata* on day 15. Twelve prior blood cultures were sterile.
The central venous catheter was removed and antifungal therapy was switched to liposomal amphotericin B (Ambisome, 3 mg/kg/day). Despite liposomal amphotericin B treatment for twelve days, six out of ten blood cultures remained positive for *C. glabrata*.
As the patient's clinical condition worsened, liposomal amphotericin B was discontinued and intravenous caspofungin was initiated: 70 mg loading dose and 50 mg once daily maintenance dose. Extensive imaging, including magnetic resonance imaging of the brain, ultrasound, echocardiography and computed tomography scanning, revealed no localisation of *C. glabrata*. From two days after starting caspofungin, blood cultures remained sterile. Positive cultures from faeces and the oral cavity indicated persisting colonisation with *C. glabrata*.
After an initial improvement 20 days after transplantation, the patient developed symptoms of severe generalised graft-versus-host disease (GvHD) of the skin, liver and lungs resulting in respiratory insufficiency. On day 36 she died of respiratory insufficiency. At autopsy pulmonary GvHD was found, which was determined to be the cause of death. Blood cultures and cultures taken from internal organs were sterile and histology showed no evidence of invasive candidiasis.

DISCUSSION

Despite the relative increase in blood stream infections with nonalbicans *Candida* species, colonisation with *C. glabrata* rarely leads to invasive infection in haematology patients. If invasion occurs, this is mostly due to one of the many factors that are associated with increased risk of development of invasive infections in general.[4] The damage to the epithelium of the intestinal tract (mucosal barrier injury),[5] due to cytotoxic therapy and total body irradiation, predisposes to translocation of gut micro flora to the blood.[4] *Candida* species adhere avidly to synthetic catheters, making intravenous catheters another source of (persistent) fungaemia. In these cases removal of the intravascular catheters eliminates the source of *Candida*. But whether fungaemia originates from skin/catheter colonisation or from gastrointestinal colonisation has been subject of considerable debate.[6] A recent review by Nucci and Anaissie suggests a central role for the gut as the primary source of *Candida*.[6] In another study a clear-cut sequence of colonisation from stools followed by skin was observed, indicating the gut as the primary source of *Candida* colonisation. Nucci and Colombo also failed to find an association between presence of a central venous catheter and the occurrence of fungaemia.[7] Identification of the source is essential for implementation of preventive strategies. Finally, the depth and duration of neutropenia correlates well with the frequency of fungaemia, indicating a central role for neutrophils in the host defence against disseminated candidiasis.[8] But also in non-neutropenic patients, persistence of candidaemia occurs frequently.[9,10] In our patient, persistent intestinal colonisation with *C. glabrata* together with an impaired mucosal barrier after myeloablative therapy, probably predisposed to the development of fungaemia.

C. glabrata often has increased minimum inhibitory concentrations (MIC) of many azoles compared with other *Candida* species, such as *C. albicans*. In a recent survey, up to 8% of over 1400 *C. glabrata* cultures proved resistant to fluconazole.[11,12] In addition, *C. glabrata* has 4 to 40 times higher MIC values of amphotericin B compared with *C. albicans*.[13] Besides, in *in-vitro* studies Canton *et al.* have shown that the minimum fungicidal concentration (MFC) of amphotericin B against various *Candida* species can be substantially higher than their MICs.[13]

Ostrosky-Zeichner *et al.* investigated the effect of voriconazole in over 50 patients with candidaemia or invasive candidiasis, not responding to prior antifungal therapy.[14] Treatment with voriconazole resulted in an overall response rate for all *Candida* species of 56% and for *C. glabrata* of 38%. Patients in whom previous azole therapy failed had a response rate of 58%. Therefore voriconazole can be used as salvage therapy in candidaemia.

In the present case, *C. glabrata* fungaemia persisted despite treatment with liposomal amphotericin B. Therefore the treatment was changed to caspofungin, a relatively new antifungal drug belonging to the class of echinocandins.[15] Caspofungin is thought to exert antifungal activity by blocking cell wall synthesis by inhibition of the synthesis of 1,3-β-D-glucan, which is essential for structural integrity and osmotic stability of the yeast.[15,16] Since the target is the cell wall, which is absent in human eukaryotic cells, the drug has few side effects.
Several clinical trials comparing caspofungin with amphotericin B in the treatment of invasive fungaemia have recently been performed. Mora-Duarte *et al.* found that caspofungin was as effective as amphotericin B in treating invasive fungaemia, and that treatment with caspofungin resulted in significantly less side effects.[10]

In non-neutropenic patients as well as neutropenic patients, the first choice of treatment of candidaemia is intravenous fluconazole.[17] This does not account for blood stream infections with fluconazole-resistant micro-organisms such as *C. krusei* or organisms with a reduced

susceptibility to fluconazole such as *C. glabrata*. Then treatment with caspofungin, voriconazole or possibly liposomal amphotericin B should be considered.

Although our patient had persistent fungaemia, blood and tissue cultures remained sterile after switching antifungal therapy to caspofungin. She eventually died from pulmonary insufficiency and at autopsy histological examination and cultures indicated full recovery from the fungaemia. Therefore her death does not seem to be attributable to the fungaemia.

CONCLUSION

This case shows that in haematology patients with an impaired mucosal barrier, the gut is an important source of fungaemia. The change of antifungal therapy to caspofungin resulted in eradication of the yeast from the blood and tissues. With the availability of the echinocandins and the new azoles, in our view there is no place for (liposomal) amphotericin B in the initial treatment of candidaemia.

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