



Note

Candida norvegensis fungemia in a liver transplant recipient



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ABSTRACT

Background: The incidence of candidemia due to non-*Candida albicans* *Candida* species has been progressively increasing in recent years. The use of fluconazole as antifungal prophylaxis has been described as a risk factor for the development of infections by fluconazole resistant *Candida* strains. We report a case of *Candida norvegensis* bloodstream infection in a liver transplant recipient.

Case report: A 61-year-old man, who received a third liver allograft and became worse with the onset of ischemic cholangiopathy and recurrent episodes of cholangitis, was admitted to our hospital due to the development of intra-abdominal abscesses. He received multiple antibiotic schemes, and after 3 months he was discharged, maintaining parenteral antibiotic at home. While he was on fluconazole prophylaxis, a breakthrough candidemia due to *C. norvegensis* occurred. *In vitro* susceptibilities of the isolate to several antifungal agents were as follows: amphotericin B MIC 0.5 mg/l, flucytosine 64 mg/l, fluconazole 64 mg/l, itraconazole 4 mg/l, voriconazole 0.75 mg/l, and caspofungin 0.047 mg/l. He was treated with anidulafungin with resolution of candidemia.

Conclusions: The use of fluconazole for antifungal prophylaxis may lead to the emergence of fluconazole-resistant *Candida* infections, with *C. norvegensis* being a possible emerging pathogen in organ transplant recipients.

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Fungemia por *Candida norvegensis* en un receptor de trasplante hepático

RESUMEN

Antecedentes: En los últimos años ha aumentado la incidencia de candidemia causada por especies del género *Candida* distintas de *Candida albicans*. Se ha descrito el uso de profilaxis antifúngica con fluconazol como factor de riesgo para el desarrollo de infecciones por cepas de *Candida* resistentes a este antifúngico. Se describe un caso de fungemia por *Candida norvegensis* en un receptor de un trasplante hepático.

Caso clínico: Un varón de 61 años, receptor de un tercer trasplante hepático que se complica con una colangiopatía isquémica y episodios de colangitis de repetición, ingresó en nuestro hospital por presentar abscesos intraabdominales. Recibió múltiples esquemas antibióticos y, tras 3 meses de ingreso, se dio de alta manteniendo un tratamiento antibiótico parenteral en domicilio. Mientras recibía profilaxis con fluconazol, desarrolló una candidemia de brecha por *C. norvegensis*. Los valores de CMI *in vitro* del aislamiento para algunos antifúngicos fueron los siguientes: anfotericina B 0,5 mg/l, flucitosina 64 mg/l, fluconazol 64 mg/l, itraconazol 4 mg/l, voriconazol 0,75 mg/l y caspofungina 0,047 mg/l. El paciente recibió tratamiento con anidulafungina, con resolución de la candidemia.

Conclusiones: El uso de fluconazol como profilaxis antifúngica puede conllevar la aparición de infecciones por especies de *Candida* resistentes a este antifúngico, siendo *C. norvegensis* un posible patógeno emergente en pacientes receptores de un órgano sólido.

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Candida is the leading cause of invasive fungal infection in organ transplant recipients.²⁰ The main risk factors for invasive candidiasis in liver transplant recipients are previous use of broad spectrum antibiotics, the need of post-transplant dialysis and retransplantation.²⁷ Recent studies show a trend toward an increasing incidence of infections caused by non-*Candida albicans* *Candida* species, and this seems to be related to the use of prophylaxis with fluconazole.¹³ *Candida norvegensis* is an unusual pathogen, with high rates of fluconazole resistance, and it has been described as a potential pathogen in immunocompromised patients. Herein, we describe a case of *C. norvegensis* fungemia in a liver transplant patient under fluconazole prophylaxis successfully treated with anidulafungin.

Case report

In June 2008, a 61-year-old man underwent liver transplantation because of an end-stage liver disease caused by hepatitis C and B viruses coinfection and hepatocellular carcinoma. During the surgical procedure, hepatic artery thrombosis was found but it was not possible to completely recanalize the artery. Immunosuppressive scheme included tacrolimus, mofetil mycophenolate and prednisone. In February 2009 he was diagnosed with ischemic cholangiopathy. An arteriography did not show additional vascular complications. Since diagnosis the patient presented recurrent episodes of acute cholangitis. In April 2009, a hepaticojejunostomy was performed, but cholestasis persisted. Two months later the patient underwent a second liver transplantation. The postoperative course was complicated with surgical site bleeding, requiring liver packing and multiple blood transfusions. Because of the primary graft dysfunction, the patient received a third liver transplantation 7 days later. During the surgical procedure he developed hepatic artery thrombosis. In the post-transplant period he presented multiple episodes of acute cholangitis secondary to ischemic cholangiopathy.

In November 2009 he was admitted to the hospital because of *Escherichia coli* and *Enterococcus faecium* cholangitis. Initial treatment included meropenem, vancomycin, amikacin and prophylactic fluconazole (at a dose of 100 mg/d). During admission he developed multiple liver abscesses that required percutaneous drainage. Several blood cultures grew multidrug resistant *Pseudomonas aeruginosa*, *E. faecium*, *Enterococcus faecalis* and extended-spectrum betalactamase producing *E. coli*. He received multiple antibiotic regimens depending on the susceptibilities of the isolates (including vancomycin, ceftazidime, amikacin, metronidazole, fosfomycin, colistin, doripenem, meropenem, ampicillin, teicoplanin and piperacillin/tazobactam). In February 2010, as liver abscesses persisted, he was proposed to receive prolonged treatment with piperacillin/tazobactam plus amikacin in our outpatient parenteral antimicrobial therapy program. As broad-spectrum antibiotic therapy was administered, prophylactic fluconazole was maintained during outpatient antibiotic treatment.

Two weeks after hospital discharge, the fever reappeared and breakthrough candidemia due to *C. norvegensis* was diagnosed. Blood cultures were processed by the BACTEC 9240 system (Becton-Dickinson, MD, USA). The method used for the identification of the *Candida* strain was MALDI-TOF MS.^{16,25} The patient was hemodynamically stable and with good general status. Intravenous anidulafungin treatment (200 mg loading dose and thereafter 100 mg/d) was started in the first 36 h after the extraction of blood cultures and the patient was not readmitted to hospital. *In vitro* susceptibilities of the isolate to several antifungal agents, determined by CLSI microdilution method, were as follows: amphotericin B MIC 0.5 mg/l, flucytosine 64 mg/l, fluconazole 64 mg/l, itraconazole

4 mg/l; voriconazole 0.75 mg/l and caspofungin 0.047 mg/l, so the treatment with anidulafungin was maintained. The patient became afebrile and blood cultures performed 48 h after starting the antifungal treatment were negative. Anidulafungin was maintained for 14 days. After the resolution of candidemia the patient developed progressive ascites and peripheral edema and was readmitted to the hospital. Persistence of liver abscess was seen on abdominal ultrasonogram. Blood cultures were negative. Despite intravenous antibiotics, the patient's general condition worsened. He died 40 days after hospital admission due to end-stage liver disease and multiorgan failure.

Discussion

Candida is an increasing cause of bloodstream infections, being the fourth microorganism to be isolated frequently in blood cultures in the United States²⁹ and the seventh cause of nosocomial infection in our center.¹⁹ The increasing risk of invasive candidiasis may be explained by a rise in the use of invasive procedures, intravenous catheters, total parenteral nutrition and broad spectrum antibiotics.¹² Although *C. albicans* is the most common single species identified, the incidence of non-*C. albicans* candidemia has been progressively increasing.^{12,19}

Solid organ transplant recipients are at risk to develop invasive fungal infection due to a combination of aggressive surgery and requirement of immunosuppressive therapy. The incidence of fungal infection varies depending on the transplanted organ, being highest in small bowel transplantation (40–59%) and lowest in renal recipients (1–14%).^{9,20} Invasive candidiasis in organ transplant recipients is associated with candidemia in more than half of the episodes.²⁰ In our country, candidemia represents 8% of all cases of bloodstream infections in organ transplant recipients,¹⁷ with 46% of them caused by species with potential fluconazole resistance (*Candida krusei* and *Candida glabrata*).

C. norvegensis was first isolated in Norway from the sputum of three patients with asthma in 1954.⁶ The first described clinically relevant infection by this pathogen was in a renal transplant recipient who developed *C. norvegensis* peritonitis associated with the use of peritoneal dialysis.¹⁸ Since then, scarce cases of *C. norvegensis* infections have been described, most of them in patients with malignancies or HIV infection.^{11,14,26} A recent study reported that the rate of isolation of *C. norvegensis* has increased by 5–10-folds during the last 10 years.²⁴ In the same study the susceptibility of *C. norvegensis* to fluconazole and voriconazole was tested, with 41% of the isolates being resistant to fluconazole and 91.5% susceptible to voriconazole, although an increased percentage of voriconazole-resistant strains has been observed during the last years. Although the level of evidence is very low due to infrequent descriptions of infection in humans, amphotericin B has been considered the treatment of choice for *C. norvegensis* infections.¹⁵ However, the associated toxicity of amphotericin B could limit its use in solid organ transplant recipients. Several studies have demonstrated susceptibility of *C. norvegensis* to echinocandins.^{2,5,28} Although our patient died due to end-stage liver disease and other complications, *C. norvegensis* fungemia was successfully cleared with intravenous anidulafungin. In our patient, the *in vitro* susceptibility of *C. norvegensis* to echinocandins was tested only for caspofungin. When yeasts were isolated in blood cultures, and before having an identification of the species, a treatment with anidulafungin was prescribed because the patient was receiving fluconazole as prophylaxis. Although antifungal *in vitro* tests were not performed to establish the MIC value to anidulafungin, as the patient was doing well under this therapeutic regimen we maintained the same treatment. Previous reports have described that all three echinocandins have similar MICs against

the majority of *Candida* species.^{8,23} However, the MIC correlation between the three echinocandins has not been studied in *C. norvegensis*. In addition to the good response to treatment, we decided to maintain anidulafungin because while caspofungin decreases the concentration of tacrolimus, anidulafungin and micafungin have fewer interactions with immunosuppressants.⁸

Non-*C. albicans* candidal infections represent an emerging problem in immunosuppressed patients in general and in organ transplant recipients in particular. The broad use of fluconazole for antifungal prophylaxis may lead to an increase in fluconazole-resistant *Candida* infections,¹⁷ with *C. norvegensis* as a possible emerging pathogen in organ transplant recipients. In the case we report, the patient received fluconazole as prophylaxis due to the multiple history of abdominal surgery, the need for a central venous catheter, and the use of broad spectrum antibiotics during a long period of time, all of them being risk factors for the development of candidemia.³ There are some studies that have analyzed the efficacy of fluconazole prophylaxis in patients at high risk for invasive candidiasis, especially surgical and critically ill patients. The majority of them used a dose of 400 mg per day, but one study describes a reduction of invasive fungal infections using a dose of 100 mg per day.^{1,7,10,22} There are no studies comparing different doses of fluconazole for prophylaxis. European guidelines currently recommend the dose of 400 mg/day for prophylaxis in non-neutropenic adults.⁴ For antifungal prophylaxis in liver transplant patients at high risk of invasive candidiasis, the IDSA guidelines recommend fluconazole at a dose between 200 and 400 mg.²¹ However, the interaction of fluconazole with calcineurin inhibitors limits the safety of high-dose fluconazole prophylaxis in this subgroup of patients.

In conclusion, *C. norvegensis* must be taken into account as a possible emergent pathogen in organ transplant patients receiving prophylaxis with fluconazole.

Conflict of interest

Nothing to declare.

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