Invasive candidiasis due to *Candida norvegensis* in a liver transplant patient: case report and literature review

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Abstract

Candida norvegensis is an emerging fluconazole-resistant pathogen isolated in most cases from skin and mucous membranes of immunocompromized patients. Documented invasive candidiasis (IC) due to *C. norvegensis* has been rarely reported, thus the clinical features of patients at risk for this pathogen are poorly defined. We report a liver transplant patient who developed IC due to *C. norvegensis* and review other cases of *C. norvegensis* IC published in the literature.

Introduction

In recent years, there has been an increase in the incidence of invasive candidiasis (IC) and a shift toward non-*albicans Candida* species, some of them resistant to fluconazole.[1-3] Despite advances in the diagnostic and therapeutic management, the crude mortality associated with IC is as high as 40-50%.[3]

Among Candida species *C. krusei* is considered intrinsically resistant to fluconazole, whereas in *C. glabrata* the development of resistance of fluconazole is most related to antifungal exposure, especially in specific populations such as elderly patients, solid organ transplant (SOT) recipients, patients with neutropenia, patients receiving corticosteroids, and neonates.[2]

C. norvegensis is an emerging fluconazole-resistant species isolated in most cases from upper respiratory tract and wound specimens,[4] and uncommonly associated with documented IC.[5] Therefore, the clinical features of patients with *C. norvegensis* IC deserve to be fully described.

Here, we report a patient who developed an IC due to *C. norvegensis* after liver transplantation and review other cases of *C. norvegensis* IC published in the literature.

Case Report

A 47-year-old man, with history of HCV-related cirrhosis and hepatocarcinoma, was referred to our hospital for spontaneous bacterial peritonitis and partial portal vein thrombosis. After three months of hospitalization he underwent liver transplantation. The transplant procedure was uneventful, a duct-to-duct biliary anastomosis was done, antimicrobial prophylaxis was stopped within 24 hours after the surgical procedure, and no antifungal prophylaxis was administered. The patient was discharged on a standard immunosuppressive regimen with tacrolimus (3 mg every 12 hours), mycofenolate mofetil (500 mg every 12 hours) and prednisone (5 mg every 12 hours). After two weeks from discharge he was readmitted for fever, malaise and moderate hepatic dysfunction. We consider the date of readmission as day 0. A magnetic resonance cholangiography showed a biliary leak with bilioma and ascites. After obtaining blood cultures, empirical treatment with vancomycin, piperacillin/tazobactam and fluconazole was started. On the same day bilioma was drained percutaneously and a bile sample was sent to the laboratory for microbiological tests. Despite the antimicrobial therapy and the surgical procedure, the patient clinical conditions worsened and, on day 3, he was admitted to the intensive care unit (ICU) on septic shock. In the ICU, mechanical ventilation (MV) and inotropic support therapy were started; new blood cultures and tracheal aspirate were obtained and antimicrobial treatment was modified stopping vancomycin and piperacillin/tazobactam, and starting linezolid plus meropenem. Biochemical analysis showed an increase of the tacrolimus serum trough-levels up to 25 ng/mL, thus tacrolimus was temporally withdrawal; subsequently, fluconazole was stopped and anidulafungin was started. Chest x-ray showed bilateral pneumonia. Surgical drainage of the hepato-biliary ducts was performed. The microbiological tests collected on day 1 yielded *C. norvegensis* and *Enterococcus faecalis* from both blood cultures and bile specimens. Identification and susceptibility assay of *C. norvegensis* were performed using the automated Vitek2 system (bioMérieux, Inc. Durham NC, USA), the MICs of fluconazole and voriconazole resulted of 8 μg/mL and 0.25 μg/mL, respectively. Data regarding antifungal susceptibilities in *C. norvegensis* are scarce, however we made reference to the available EUCAST breakpoints, even though they are provided only for C. *albicans*, C. *tropicalis* and C. *parapsilosis*. Due to these considerations, we assumed that our strain was non susceptible to azoles as other non *albicans candida* species. We are aware that *C. norvegensis* and *C. incospicua* could be misidentified with traditional diagnostic procedures;[6] however, strain identification was later confirmed using a previously published molecular method.[7] We confirmed the definite taxonomic position of the strain with a direct polymerase chain reaction-sequencing method which analyzes a short sequence encompassing the hypervariable D2 region of the large subunit of the 25-28S ribosomal RNA (rRNA) gene.[7] Strain was submitted to Gen Bank and showed 100% omology with nucleotidic sequence previously deposited in Gen Bank. On day 6 bronchoaspirate and bile culture, collected at the admission in ICU, yielded extend-

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ed Spectrum β-Lactamases (ESBL) producing *Klebsiella pneumoniae.* In the following days, the clinical conditions of the patient improved with resolution of fever, achievement of hemodynamic stability and weaning from MV. The blood cultures drawn on day 5 after hospital admission were negative, whereas the cultures of bile became negative for *C. norvegensis* on day 7. Trans-esophageal echocardiography ruled out infective endocarditis, and the *fundus oculi* examination was negative for embolisms. Linezolid was stopped on day six, whereas meropenem and anidulafungin were continued up to 2 and 4 weeks, respectively. The bile tract was repaired with the implant of three stents by endoscopic procedure. Tacrolimus was re-started maintaining plasma trough-levels between 8 and 10 ng/mL. After one month of hospital stay, the patient was discharged on good health conditions and he remained asymptomatic during one year of follow-up.

Discussion

The strength of our case is the isolation of a very uncommon fluconazole resistant *Candida* species in a liver transplant patient with proven invasive candidiasis.

Candida norvegensis has been an unusual cause of infection in humans. It was first isolated in Norway from the sputum of three patients with asthma nearly 60 years ago.[4] The first report of a documented clinical infection appeared in 1990, when a case of IC in a renal transplant patient was described.[8] All isolates were resistant to fluconazole as two *C. norvegensis* strains isolated before 1940; it was therefore assumed that the fluconazole resistance is inherent.[4]

We performed a literature research on PubMed using as key word *Candida norvegensis* and as limit *English language*. Case reports and case series of IC due to *C. norvegensis* with enough information on the underlying conditions of patients, infection source, treatment and outcome were reviewed. *C. norvegensis* IC was defined by the isolation of *C. norvegensis* from blood cultures. Overall, eight manuscripts including 12 patients with invasive infection due to *C. norvegensis,* published during 1990-2013, were found (Table 1).[4,5,8-13] The underlying conditions included: hematological disease (7 patients), abdominal surgery (1 patient), solid tumor (1 patient), hemodialysis (1 patient), solid organ transplantation (1 patient), diabetes mellitus (1 patient). The most common clinical presentation was primary candidemia (6 patients out of 11);[9,4,11,13] in one case candidemia was considered related to central venous catheter infection;[5] abdomen and kidney/urinary tract were the most frequent infection source in secondary candidemia cases (4 patients out of 11).[4,8,10,12] Patients were treated with fluconazole (in 2 patients),[3] liposomal amphotericin B (in 2 patients),[10,11] amphotericin B plus flucytosine (in 1 patient),[8] liposomal amphotericin B followed by caspofungin (in 1 patient),[12] caspofungin (in 2 patients).[13] All the patients died but four. Among the four survivors, two were affected by an intra-abdominal abscess treated with antifungal therapy (liposomal amphotericin B followed by caspofungin and liposomal amphotericin B alone) associated to surgical drainage.[12,10] The other two patients were affected by primary candidemia.[13] Liver transplants recipients have the highest reported incidence of *Candida* infection and candidemia is the most frequent clinical manifestation of invasive candidiasis;[14] in these patients bloodstream infections (BSI) are frequently polymicrobial and associated to biliary complications, like biliary leakage as occurred in our patient.[15] We considered that in our patient *C. norvegensis* deep sited candidemia was the leading cause of the severe deterioration of the patient clinical conditions. Indeed, candidemia is a predictor of poor outcome in liver transplant receivers;[15] therefore, we decided to stop fluconazole, that could be ineffective, and to start a fungicidal agent as anidulafungin.

The review of the literature published from 1996 to 2013 shows that the high mortality of *C. norvegensis* infections could be mostly attributable to an inappropriate antifungal treatment and to a lack of infection source control.[4,5,8-13] Our case report, according to data from literature would suggest that *C. norvegensis* candidemia secondary to intrabdominal infection could have a better outcome if an antifungal treatment with echinocandins or amphotericin B is associated to a prompt surgical or percutaneous drainage of the infective focus.

Conclusions

In previous reports, mortality among patients with IC due to *C. norvegensis* was nearly 100%. Surgery and effective antifungal therapy seem to be together essential for a

Table 1. Literature cases of invasive candidiasis due to *C. norvegensis*.

Author, year	Patients	Underlying conditions	Infection source	Treatment	Outcome	MIC of fluconazole/ voriconazole
Nielsen *et al.*,[8] 1990	1	Renal transplant and peritoneal dialysis	Blood and abdomen	AmB plus flucytosine	Infection related death	Not available
Nielsen *et al.*,[5] 1996	1	Hematological disease	Blood and CVC	CVC removal	Infection related death	Not available
Bohme *et al.*,[9] 1996	1	Hematological disease	Blood	Not determined	Not determined	Not available
Sandven *et al.*,[4] 1997	3	Solid tumor (1 patient); hematological disease (2 patients)	Blood (2); blood and urine (1)	Fluconazole (2)	Infection related death (3)	Not available
Nolla-Salas *et al.*,[10] 2000	1	Abdominal surgery	Blood and abdomen	LAM-B plus surgery	Recovery	Not available
Kiraz *et al.*,[11] 2010	1	Hematological disease	Blood	LAM-B	Infection related death	128 µg/mL-1
Kurucu *et al.*,[12] 2011	1	Hematological disease	Blood and renal ball parenchima and fungus	LAM-B plus surgery followed by Caspofungin	Recovery	Fluconazole: 16 µg/mL; Voriconazole: 0.25 µg/mL
Guitard *et al.*[13] 2013	2	Hematological disease (1 patient); diabetes mellitus type 2 (1 patient); hemodialysis (1 patient)	Blood	Caspofungin	Recovery	Fluconazole: 16 µg/mL; Voriconazole: 0.25 µg/mL

AmB, amphotericin B; CVC, catheter related infection; LAM-B, liposomal amphotericin B.

favorable outcome in patients with intrabdominal abscesses, as observed in our patient and in those reported in literature.[10,12]

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