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.

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analysis showed an increase of the tacrolimus serum trough-levels up to 25 ng/mL, thus tacrolimus was temporarily withdrawn; subsequently, fluconazole was stopped and anidulafungin was started.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; however, strain identification was later confirmed using a previously published molecular method. 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. Strain was submitted to Gen Bank and showed 100% homology with nucleotide sequence previously deposited in Gen Bank. On day 6 bronchoaspirate and bile culture, collected at the admission in ICU, yielded extend-

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; however, strain identification was later confirmed using a previously published molecular method. 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. Strain was submitted to Gen Bank and showed 100% homology with nucleotide sequence previously deposited in Gen Bank. On day 6 bronchoaspirate and bile culture, collected at the admission in ICU, yielded extend-
ed Spectrum beta-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. The first report of a documented clinical infection appeared in 1990, when a case of IC in a renal transplant patient was described. All isolates were resistant to fluconazole as two *C. norvegensis* strains isolated before 1940; it was therefore assumed that the fluconazole resistance is inherent.

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). 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); in one case candidemia was considered related to central venous catheter infection; abdomen and kidney/urinary tract were the most frequent infection source in secondary candidemia cases (4 patients out of 11). Patients were treated with fluconazole (in 2 patients), liposomal amphotericin B (in 2 patients), amphotericin B plus flucytosine (in 1 patient), liposomal amphotericin B followed by caspofungin (in 1 patient), caspofungin (in 2 patients). 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. The other two patients were affected by primary candidemia. Liver transplant recipients have the highest reported incidence of *Candida* infection and candidemia is the most frequent clinical manifestation of invasive candidiasis in these patients bloodstream infections (BSI) are frequently polymicrobial and associated to biliary complications, like biliary leakage as occurred in our patient. 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; 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. *C. norvegensis* cases, 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., 2000 | 1        | Renal transplant and peritoneal dialysis      | Blood and abdomen                | AmB plus flucytosine          | Infection related death  | Not available                   |
| Nielsen et al., 2000 | 1        | Hematological disease                        | Blood and CVC                    | CVC removal                   | Infection related death  | Not available                   |
| Bohme et al., 2001   | 1        | Hematological disease                        | Blood                            | Not determined                | Not determined           | Not available                   |
| Sandven et al., 1997 | 3        | Solid tumor (1 patient); hemotological disease (2 patients) | Blood (2); blood and urine (1)  | Fluconazole (2)              | Infection related death (3) | Not available                   |
| Nolla-Salas et al., 2000 | 1   | Abdominal surgery                            | Blood and abdomen                | LAM-B plus surgery            | Recovery                 | Not available                   |
| Kizao et al., 2010   | 1        | Hematological disease                        | Blood                            | LAM-B                         | Infection related death  | 128 µg/mL-1                     |
| Kurucu et al., 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., 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.\textsuperscript{10,12}

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