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

Maria Musso,1 Maddalena Giannella,2 Mario Antonini,3 Eugenio Bordin,4 Giuseppe Maria Ettorre,5 Loretta Tessitore,6 Andrea Mariano,7 Giuseppe Maria Ettorre,5 Maria Musso,1 Maddalena Giannella,2

1Second Division of Infectious Diseases, National Institute for Infectious Diseases Lazzaro Spallanzani, Rome; 2Infectious Diseases Unit, Sant’Orsola Malpighi Hospital, Bologna; 3Intensive Care Unit and Anesthesia, National Institute for Infectious Diseases Lazzaro Spallanzani, Rome; 4Microbiology Unit, National Institute for Infectious Diseases Lazzaro Spallanzani, Rome; 5Transplant Surgical Unit, S. Camillo-Forlanini Hospital, Rome; 6Neurosurgical Intensive Care Unit, S. Camillo-Forlanini Hospital, Rome; 7First Division of Infectious Diseases, National Institute for Infectious Diseases Lazzaro Spallanzani, Rome, Italy

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), mycophenolate mofetil (500 mg every 12 hours) and prednisone (5 mg every 12 hours). After two weeks from discharge he was re-admitted 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 biloma 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 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. inopinata* 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 bronchospiration and bile culture, collected at the admission in ICU, yielded extend-
ed Spectrwm 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 embolism. 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 keyword 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 treatment (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 seated 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. 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.

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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients</th>
<th>Underlying conditions</th>
<th>Infection source</th>
<th>Treatment</th>
<th>Outcome</th>
<th>MIC of fluconazole/ voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nolla-Salas et al., 2000</td>
<td>1</td>
<td>Abdominal surgery</td>
<td>Blood and abdomen</td>
<td>LAM-B plus surgery</td>
<td>Recovery</td>
<td>Not available</td>
</tr>
<tr>
<td>Kaira et al., 2010</td>
<td>1</td>
<td>Hematological disease</td>
<td>Blood and renal ball parenchima and fungus</td>
<td>LAM-B plus surgery followed by Caspofungin</td>
<td>Recovery</td>
<td>Fluconazole: 16 ìg/mL; Voriconazole: 0.25 ìg/mL</td>
</tr>
<tr>
<td>Guitard et al., 2013</td>
<td>2</td>
<td>Hematological disease (1 patient); diabetes mellitus type 2 (1 patient); hemodialysis (1 patient)</td>
<td>Blood</td>
<td>Caspofungin</td>
<td>Recovery</td>
<td>Fluconazole: 16 ìg/mL; Voriconazole: 0.25 ìg/mL</td>
</tr>
</tbody>
</table>

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}

References