Case Report

Control of a *Candida glabrata* prosthetic endovascular infection with posaconazole

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A 63-year-old man with a history of cirrhosis of the liver developed *Candida glabrata* fungemia after undergoing transjugular intrahepatic portosystemic shunt (TIPS) placement. Treatment with oral fluconazole was initially effective, but when the patient became neutropenic, subsequent blood cultures grew *C. glabrata* and a thrombus developed, which partially occluded the stent. Despite treatment with fluconazole, blood cultures remained positive for *C. glabrata*. Treatment with posaconazole resulted in clinical improvement and the patient had only intermittently positive fungal cultures for 6 weeks. A CT scan showed resolution of the inferior vena cava thrombus. Subsequently, the patient developed hepatocellular carcinoma and hepatic encephalopathy and became noncompliant with posaconazole. Blood cultures again became positive for *C. glabrata*. The patient died a few weeks after the diagnosis of hepatocellular carcinoma, but the cause of death was believed to be worsening liver dysfunction, not *C. glabrata* infection. Posaconazole had controlled the infection for about 3 months prior to his death.

In conclusion, posaconazole may be a useful option in the management of prosthetic endovascular infections caused by *C. glabrata*.

Keywords *Candida glabrata*, infection, posaconazole, transjugular intrahepatic portosystemic shunt

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) placement is a treatment for portal hypertension that involves the placement of an intrahepatic, expandable metal stent between the portal and systemic circulations (Fig. 1) [1]. Early and late infectious complications of TIPS have been reported [2–5]. Early infections are insertion-related, due to bacterial seeding of the blood from the portal circulation or biliary tree [6].

Late infections ( >3 months after placement) are typically associated with thrombosis of the device and are more challenging to manage [4,5].

The pathogenesis of late infections is uncertain, but may be caused by portal bacteria/fungi seeding the pseudointima associated with the stent [5]. A stent infection should be suspected if a patient has sustained bacteremia/fungemia in the absence of an alternate source of infection [4]. Sanyal and Reddy [5] coined the terms ‘definite endotipsitis’ for continuous bacteremia concomitant with a thrombus and ‘probable endotipsitis’ for sustained bacteremia and fever with an apparently normal stent.

Most reported TIPS infections have been attributed to enteric bacteria [5,7–9]; however, three cases of TIPS infection caused by *Candida* species have been reported...
Two fatal cases involved Candida glabrata fungemia that was unsuccessfully managed with fluconazole/5-flucytosine and amphotericin B treatment regimens. Autopsies revealed that the TIPS were occluded with organized thrombi containing numerous yeast organisms [6,10]. A third case involved a patient with a thrombotic TIPS who was infected with fluconazole-sensitive Candida albicans [5]. The patient was successfully treated with amphotericin B for 6 weeks, followed by fluconazole for 3 months. We report here a severely immunocompromised patient with a TIPS infection caused by C. glabrata and successful suppressive treatment with posaconazole.

Case report

A 63-year-old man presented with a history of cirrhosis, esophageal varices and recent upper gastrointestinal bleeding. A TIPS was placed to manage portal hypertension and resultant recurrent gastrointestinal hemorrhages. During hospitalization after the procedure, the patient developed bacteremia due to Klebsiella pneumoniae and was treated with levofloxacin. One month after the TIPS placement, the patient returned to the hospital with a fever; blood cultures grew C. glabrata, methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecium. The minimum inhibitory concentration (MIC) of fluconazole against the C. glabrata isolate was 2 µg/ml [11]. The patient was treated with oral fluconazole (400 mg q.d. for a total of 72 days), intravenous (i.v.) vancomycin, and i.v. quinupristin/dalfopristin. Repeat blood cultures performed 6 days after admission were negative. However, after 2 weeks of antifungal therapy, the patient became neutropenic (absolute neutrophil count [ANC] = 200 cells/µl) and the quinupristin/dalfopristin was stopped. The patient was discharged on continued fluconazole therapy.

One month later, the patient was readmitted with fever and bacteremia due to K. pneumoniae. The patient was treated with 28 days of piperacillin-tazobactam and discharged on chronic suppressive therapy with oral levofloxacin. Ultrasonography of the TIPS on day 2 of this hospitalization showed a patent stent with good function.

Seven months after completing the course of fluconazole therapy, the patient was readmitted to the hospital with fever and neutropenia (ANC = 100 cells/µl). Multiple blood cultures during the following 6 days grew C. glabrata and oral fluconazole (400 mg q.d.) was initiated. A CT scan showed a partially occlusive thrombus extending from the stent into the suprahepatic inferior vena cava (IVC), ending near the right atrium. The clinical impression was definite C. glabrata endotipsitis. Because the patient continued to have positive blood cultures despite treatment with fluconazole, the patient’s therapy was changed to oral posaconazole (200 mg every 6 h) on day 6 of hospitalization. Susceptibility testing by the NCCLS M27-A2 microdilutional method [11] showed that the MIC of fluconazole, itraconazole, and posaconazole against the C. glabrata isolate were 16, 1 and 0.5 µg/ml, respectively. Three days after starting posaconazole therapy, an echocardiogram was obtained, which showed a large mobile echogenic mass (thrombus), 10 × 1.5 mm in size, extending from the TIPS into the IVC and right atrium (Fig. 2).

Therapeutic response to posaconazole therapy was evidenced by a series of negative blood cultures, improved clinical status, and resolution of the TIPS.
thrombus. Of 17 blood cultures performed during the first 32 days of therapy, nine were negative for all organisms. Although posaconazole was unable to consistently clear the blood cultures, the patient remained afebrile and the signs and symptoms of the infection were improved. Abdominal imaging on day 74 of posaconazole therapy showed the TIPS in place with resolution of the IVC thrombus (Fig. 3). However, a hepatic mass indicative of hepatocellular carcinoma was evident. The patient developed hepatic encephalopathy as a result of hepatocellular carcinoma-induced liver dysfunction and became noncompliant with posaconazole therapy. During the time that the patient did not receive posaconazole therapy, blood cultures became positive for C. glabrata. The patient died a few weeks after the diagnosis of hepatocellular carcinoma, but the cause of death was believed to be worsening liver dysfunction, not C. glabrata infection.

Discussion

This case demonstrates the difficulty in managing TIPS infections, especially those caused by fungus. Prophylaxis may have a role in prevention of early bacterial TIPS infections [6,8,12], but others have questioned the cost-effectiveness of this measure [3]. TIPS infections caused by fungi are very rare. There are no clinical efficacy data regarding the treatment of TIPS infections. Nevertheless, treatment should probably follow guidelines for endovascular infections involving prosthetic material, such as prosthetic valve endocarditis [4], but without removal of the device. In TIPS infections, surgical removal of the stent is not possible without transplantation, which is contraindicated in the setting of uncontrolled endovascular infection [8]. Perhaps thrombotic TIPS infections cannot be completely sterilized and the infection remains sequestered within the device [5,9]. Thus, after documented infection, suppressive antimicrobial therapy should be considered [7]. Similarly, in the case of documented TIPS infections due to fungus, suppressive antifungal therapy may be necessary.

Candida glabrata has emerged as the second most common cause of candidemia, after C. albicans [13,14]. In fact, in a recent multinational surveillance study (32 nations and 250 medical centers) that evaluated 6082 Candida species bloodstream infection isolates, C. glabrata was responsible for approximately 16% of all candidemias, whereas C. tropicalis and C. krusei were responsible for approximately 10 and 3% of all candidemias, respectively [15]. Although the prevalence of non-\textit{albicans} isolates varies geographically, it remains clear that infections caused by \textit{C. glabrata} are becoming increasingly common [16]. \textit{C. glabrata} is the most intrinsically resistant \textit{Candida} species to antifungal agents [17,18], which may account for the high mortality rate (49–83%) associated with infections caused by it [13,19]. The emergence of \textit{C. glabrata} as a nosocomial pathogen is promoted by fluconazole usage [13,18,19].

In this patient, secondary resistance of the \textit{C. glabrata} isolate to fluconazole occurred; the fluconazole MIC increased from 2 to 16 \(\mu g/ml\) (NCCLS breakpoint for fluconazole is 8 \(\mu g/ml\)) [17]. Secondary resistance of \textit{Candida} species to fluconazole has been reported many times [18,19] and may be responsible for the therapeutic failure observed in cases such as this. The mycologic outcome of this case corroborates the clinical relevance of \textit{in vitro} activity data that showed posaconazole and itraconazole to have 64-fold greater activity than that of fluconazole (MIC\textsubscript{90} 128 \(\mu g/ml\)) and equal activity against 60 clinical isolates of \textit{C. glabrata} (MIC\textsubscript{90} 2 \(\mu g/ml\)) [17].

In this case of fluconazole-resistant \textit{C. glabrata} infection of a prosthetic intravascular device in a cirrhotic patient, the anticipated goal of therapy was suppression of infection; eradication may not be possible. The utility of antifungal agents other than fluconazole in this setting was carefully considered. Itraconazole may be useful, but cross-resistance with fluconazole can occur [20]. Amphotericin B must be dosed at 1 mg/kg for optimal therapeutic efficacy against \textit{C. glabrata} and may have nephrotoxicity at this dosing level [21]. In a patient with cirrhosis, a nephrotoxic agent may precipitate hepatorenal syndrome [22]. This would be a concern even for the lipid formulations of amphotericin B, since the risk of nephrotoxicity is lessened, but not completely mollified. In a study of 601 isolates of \textit{C. glabrata}, 100 and
99.2% of the strains were susceptible to caspofungin and fluconazole, respectively [21]. However, the utility of caspofungin for long-term suppressive therapy is limited because of its high cost and requirement for ongoing venous access. The potential drawbacks of long-term fluconazole treatment are myelosuppression, hepatotoxicity, and the development of resistance when it is used as monotherapy [23]. In cases of fluconazole resistance, the extended spectrum triazoles voriconazole and posaconazole may be effective [24–26]. However, cross-resistance may occur, and thus susceptibility testing is recommended [21,24]. Both voriconazole and posaconazole are available in oral form and have low risk of renal or hepatic toxicity and thus were considered to be the most useful agents in this scenario.

Another potential approach to the treatment of refractory fungal infections is the use of combination therapy. Amphotericin B and fluconazole have been previously used as combination therapy for candidiasis [27]. However, as described above, neither of these agents would have a favorable safety profile for this patient. Amphotericin B has also been combined with azoles. There has been concern about antagonism between these two agents, but a recent clinical trial suggests that in candidemia the combination of fluconazole and amphotericin B results in an increased success rate compared to fluconazole alone [28]. In in vitro studies, terbinafine acts synergistically with azoles against C. glabrata [29]. Other in vitro data demonstrate that the combination of voriconazole with either terbinafine, amphotericin B, or 5-flucytosine results in either synergistic activity against the C. glabrata or an apparent decrease in the MIC of one or both drugs [30]. At the time this patient was treated, these data on combination regimens [amphotericin + fluconazole, terbinafine + azole, and voriconazole + (terbinafine or amphotericin B, or 5-flucytosine)] were not available, and so these regimens were not applied in this patient, but should be considered in cases of refractory candidiasis.

In conclusion, this case illustrates the efficacy of posaconazole in the management of a prosthetic endovascular infection with a fluconazole-resistant strain of C. glabrata in an immunocompromised patient with end-stage liver disease. Although intercurrent events make it difficult to assess overall clinical response, palliation of this patient’s condition with amelioration of fungemia and resolution of the TIPS thrombus was achieved with oral posaconazole when removal of the TIPS and more aggressive intervention were not possible.

References


