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Fungal Endotipsitis: A Case Report and Literature Review

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Abstract

Endotipsitis is a broad term used to describe sustained and clinically significant bacteremia or fungemia from a suspected vegetation or thrombus within the transjugular intrahepatic portosystemic shunt (TIPS) device. Endotipsitis is a rare infection in post-TIPS patients and given the diagnostic challenges, there is a need to establish formal diagnostic criteria. Bacterial causes of endotipsitis have been well documented in the literature, but few fungal-associated etiologies have been published to date. With this paucity of data, treatment strategies are lacking regarding the role of antifungal duration, the aggressiveness of medical therapy, and the role of liver transplantation. We present a case of *Candida*-associated endotipsitis and suggest a need for preferred management strategies in an effort to decrease the significant morbidity and mortality of the infection.

Keywords

Endotipsitis; Transjugular intrahepatic portosystemic shunt (TIPS); Fungal Infection; Candida; Cirrhosis

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Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is a commonly employed procedure for the decompression of elevated portal pressures in patients with refractory ascites or recurrent variceal bleeding. Despite the high frequency and efficacy of the TIPS procedure, bacterial or fungal infections of the device are a rare but serious complication.¹ The term “endotipsitis”, first proposed by Sanyal et al, is a broad term used to describe clinically significant, sustained bacteremia with definite or probable vegetation or thrombus within the TIPS prosthesis.¹ Here we report a case of endotipsitis with recurrent fungemia despite appropriate fungal coverage and aggressive medical therapy.

Case Presentation

A 47 year-old gentleman with Child-Pugh B alcoholic cirrhosis decompensated by ascites, hepatic encephalopathy, and variceal hemorrhage initially presented to our institution with massive hematemesis and hemodynamic instability. The patient received continuous octreotide and pantoprazole infusions, empiric spontaneous bacterial prophylaxis (SBP) with ceftriaxone, vasopressor support, and balloon tamponade due to uncontrolled hemorrhage. Upper endoscopy demonstrated 3 columns of large esophageal varices. Three bands were deployed with no further evidence of active bleeding.

The patient subsequently developed recurrent variceal hemorrhage refractory to band ligation 3 days later and underwent emergent TIPS placement. The procedure was performed without complication; however, within 24 hours of TIPS placement, the patient became febrile to 38.1° C. Blood cultures were positive for *Candida glabrata* [Table 1]. No obvious source could be identified from chest radiograph, urine culture, or paracentesis. Previous blood cultures prior to TIPS demonstrated no organisms suggesting that the post-TIPS course was immediately complicated by fungemia. A transesophageal echocardiogram (TEE) was unremarkable for any vegetation, and the patient responded to a 4-week treatment of anidulafungin with cleared cultures.

Four months later, the patient re-presented with increased abdominal girth, pain, fever, and hypotension. He was admitted to the intensive care unit and started on vasopressors for refractory shock. Paracentesis revealed culture negative SBP. Blood cultures were positive for *Candida glabrata* [Table 1]. Ceftriaxone and anidulafungin were initiated with cultures revealing sensitivity to anidulafungin. Subsequent paracenteses showed no SBP though blood cultures remained positive for *Candida*. A repeat TEE was unremarkable. Vancomycin and metronidazole were added for broader coverage in the setting of aspiration. Abdominal ultrasound with doppler studies revealed turbulent flow at the hepatic end of the TIPS device with increased peak systolic velocities concerning for in-stent stenosis. A whole body white blood cell scan with indium was attempted and showed vague right lower lung field pulmonary tracer; however the study was incomplete due to patient discomfort. Given persistent fungemia after 2 weeks, voriconazole was added to anidulafungin. Despite 23 days of anti-fungal therapy, the patient continued to have persistent fungemia and developed progressive respiratory failure before passing away. Family declined autopsy.

Discussion

This case highlights endotipsitis as an emerging prosthesis-associated infection in patients with portal hypertension. “Definite infection” is defined as clinically significant persistent bacteremia or fungemia along with vegetation or thrombi within the TIPS device. “Probable infection” is characterized by similar symptoms of fever and persistent bloodstream infection with no other identifiable source.¹ While rare and estimated to have an incidence of approximately 1%, the severity of endotipsitis necessitates an organized, standardized approach for medical therapy as removal of the TIPS device is only achievable through liver transplantation or autopsy.¹

Given the significant associated mortality, endotipsitis should be considered in any post-TIPS patients with recurrent bacteremia or fungemia despite appropriate antimicrobial therapy and negative workup for more common infectious etiologies (i.e. endocarditis). Although well-defined criteria exist for the diagnosis of endocarditis such as Duke’s criteria, presently there is no unified measure for the diagnosis or severity of endotipsitis. With limited anecdotal evidence available, a recent literature review performed by Navaratnam and colleagues found no predominant endotipsitis infections – though notably gram-positive organisms were more common among early-onset infections.² With no predominant infectious etiology identified and limited published case reports to date, managing patients with infection of the TIPS device remains a current clinical challenge and patients should be treated with empiric broad spectrum agents.

An interesting consideration remains regarding the potential for early prophylactic antibiotics post-TIPS placement. Some clinicians may propose prophylactic antibiotic therapy in an effort to prevent early bloodstream infections and to decrease mortality; however, Deibert and colleagues demonstrated that prophylactic antibiotics did not reduce the incidence of post-interventional infection.³ This study of 84 patients randomized to either treatment with or without cefotiam found no statistical significance in the rate of TIPS infection. Furthermore, concerns about prophylactic antibiotic treatment, especially in light of this negative randomized study, may predispose to the emergence of more drug-resistant pathogens.

Endotipsitis as a result of a fungal infection may also occur, as seen in our patient. Notably, *Candida* infections, as compared to bacterial infections, have been associated with the highest mortality (>60%).² Only six prior cases of *Candida* associated endotipsitis have been documented in the literature, of which only two responded to antifungal treatment [Table 2].⁴⁻⁸ While the role of prophylactic antibiotics has been studied in post-TIPS patients, no study has yet to evaluate prophylactic antifungal therapy in post-operative TIPS patients. Given the significantly higher mortality associated with *Candida* infections, there may be a role for antifungal therapy, though there are concerns for the development of drug-resistant organisms – specifically azole-resistant species.

A preferred treatment strategy for persistent bacterial or fungal endotipsitis is lacking given the limited data available. Though TIPS removal may be considered the “gold standard” for treatment of endotipsitis, the role of liver transplantation remains unclear in these patients,

as is the need for chronic suppressive antibiotic or antifungal therapy.⁹ Previous case reports have described liver transplantation in only four patients to date, none of which occurred in fungal-associated endotipsitis.^{2,9–12} In addition, there are many unanswered questions and concerns regarding the listing of patients with active infection, the opportunity for Model of End-stage Liver Disease (MELD) exception points, and the utilization of resources given the already significant mortality of endotipsitis itself. Despite the simplistic notion of TIPS removal, the feasibility and practicality of liver transplantation for patients with endotipsitis, fungal or bacterial, remain uncertain.

Ultimately, this case highlights that despite aggressive medical therapy and anti-fungal treatment, the prognosis of endotipsitis remains poor. While prophylactic antibiotic treatment appears to not reduce risk of bacterial endotipsitis, no study has yet to evaluate prophylactic antifungal therapy in post-operative TIPS patients. Given the lack of current data and the relative rarity of endotipsitis, more cases are needed to definitively comment on antibiotic and antifungal duration, aggressiveness of medical therapy, and the role of liver transplantation. Future studies are needed to establish treatment algorithms or preferred management strategies as endotipsitis remains an uncommon infection with significant morbidity and mortality.

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Table 1

Summary of Blood Culture Results From Initial Day of Positive Culture

	Day 0*	Day 1	Day 2	Day 3	Day 4	Day 126**	Day 132	Day 139	Day 152 Death
Blood Culture Result	Positive <i>Candida glabrata</i> 4 of 4 Bottles	Positive <i>Candida glabrata</i> 2 of 2 Bottles	No Growth	No Growth	No Growth	Positive <i>Candida glabrata</i> 4 of 4 Bottles	Positive <i>Candida glabrata</i> 2 of 2 Bottles	Positive <i>Candida glabrata</i> 2 of 2 Bottles	Positive <i>Candida glabrata</i> 2 of 2 Bottles
Treatment	Anidulafungin	Anidulafungin	Anidulafungin	Anidulafungin	Anidulafungin	Ceftriaxone, Anidulafungin	Vancomycin, Ceftriaxone, Metronidazole, Anidulafungin	Vancomycin, Ceftriaxone, Metronidazole, Voriconazole, Anidulafungin	Vancomycin, Ceftriaxone, Metronidazole, Voriconazole, Anidulafungin

* Fever within 24 hours of TIPS placement

** Fever and septic shock on second admission

Table 2

Published Reports of Fungal-associated TIPS Infections

Authors	Year of Study	Etiology of Liver Disease	Type of Fungal Infection	Treatment	Outcome
Schiano et al ⁴	1997	Alcohol	<i>Candida glabrata</i>	Fluconazole	Death
Darwin et al ⁵	1998	Cryptogenic	<i>Candida glabrata</i>	Amphotericin	Death
DeSimone et al ⁶	2000	Hepatitis B	<i>Candida albicans</i>	-	Cleared Fungemia
DeSimone et al ⁶	2000	Hepatitis C	<i>Candida albicans</i>	-	Death
Brickey et al ⁷	2005	Hepatitis C	<i>Candida glabrata</i>	Amphotericin	Cleared Fungemia
Anstead et al ⁸	2006	Alcohol	<i>Candida glabrata</i>	Posaconazole	Death
McCarty et al	2016	Alcohol	<i>Candida glabrata</i>	Anidulafungin and Voriconazole	Death