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Case report

Combination antifungal therapy for treatment of *Candida parapsilosis* prosthetic valve endocarditis and utility of T2Candida Panel®: A case series

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ABSTRACT

Although Candida species are common pathogens for nosocomial infections, Candida endocarditis is still considered a rare entity. Here, we report two cases of *Candida parapsilosis* endovascular infections in patients with prosthetic valves, both of which responded to combination antifungal therapy without surgical intervention. Additionally, T2 magnetic resonance (T2MR) was used to assess for resolution of invasive candidiasis. The first case is of an elderly man with *Candida parapsilosis* endovascular infection who responded to combination antifungal therapy with micafungin and fluconazole followed by suppressive therapy, without surgical intervention. The second case is of a middle-aged man with *Candida parapsilosis* prosthetic valve endocarditis who also responded to combination antifungal therapy with micafungin, flucytosine and fluconazole, without surgical intervention.

Introduction

Disseminated fungal infections are common in immunosuppressed patients, and increasingly becoming common in nosocomial blood stream infections, with Candida being the main causative species. Mortality associated with systemic candidiasis can be up to 40% [1,2]. Infective endocarditis (IE) with Candida species is more common in patients with prosthetic valves than native valves and treatment often includes surgical replacement of the infected valve [3,4]. We describe two patients with *Candida parapsilosis* prosthetic valve endocarditis, who were successfully treated with combination antifungal therapy as surgery was not an option due to comorbidities.

Case report 1

The first patient was a 69-year-old man with history of testicular cancer, chronic kidney disease, anemia, gangrenous gallbladder, status post cholecystectomy, hypertension, hyperlipidemia, type 2 diabetes mellitus, paroxysmal atrial fibrillation, heart failure with reduced ejection fraction and implantable cardioverter defibrillator (ICD), and aortic valve disease s/p mechanical aortic valve replacement who presented with fatigue, fever, diarrhea, and emesis. Upon presentation, he was febrile to 102.3 degrees Fahrenheit with a blood pressure of 93/43 mm Hg, heart rate of 64 bpm, and respiratory rate of 18 breaths/min. Physical exam was remarkable for metallic click, palpable liver edge and lower extremity edema. The initial white blood cell count was 10,100 cells/mm3, with 87% neutrophils. Blood cultures were sent and abdominal computed tomography (CT) scan revealed gallstones in the cystic duct, with panniculitis. He was treated with ciprofloxacin and metronidazole, and given his hemodynamic stability with rapid improvement in clinical symptoms and white blood cell count decreased to 5900 cells/mm^3, he was discharged without further antibiotics. Approximately five days after discharge, one blood culture grew *Candida parapsilosis* (amphothericin B minimal inhibitory concentration (MIC) 0.25 ug/mL, fluconazole MIC 1 ug/mL, micafungin MIC 1 ug/mL), and he was asked to return to the hospital. *Candida parapsilosis* was isolated on eight repeat serial sets of peripheral blood cultures. Since his electrocardiogram revealed a prolonged corrected QT interval (QTc) of 541 s and he was on therapy with amiodarone, azole antifungal therapy was deferred and he was initiated on liposomal amphotericin B at 5 mg/kg/day. However, shortly thereafter, he developed acute kidney injury, so therapy was changed to micafungin 150 mg intravenous (IV) daily. Repeat blood cultures continued to grow *Candida parapsilosis* 10 days after admission; combination antifungal therapy with micafungin 150 mg IV daily and fluconazole 400 mg orally daily was initiated

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on day 11 of admission. A trans esophageal echocardiogram (TEE) revealed fibrin stranding on the mechanical aortic valve. Blood cultures subsequently cleared on day 13 of admission and the electrocardiogram was monitored periodically for prolonged QT effect from fluconazole. Due to his multiple comorbidities, he was not deemed safe for surgical intervention. A peripherally inserted central catheter (PICC) was placed and the patient was discharged from the hospital to complete micafungin IV for 12 weeks plus fluconazole oral combination therapy. On follow up, six weeks after negative blood cultures, a T2Candida Panel® (T2 Biosystems, Lexington, Mass) was sent which still detected *Candida parapsilosis*; however, all repeat fungal blood cultures remained negative and the patient was overall improved. A repeat T2Candida Panel® was negative for any Candida species, 18 weeks after his blood cultures became negative, while on chronic suppression with fluconazole. One year later, the patient currently remains alive and doing well on oral fluconazole suppressive therapy at 200 mg daily.

Case report 2

The second patient was a 45-year-old man with history of bicuspid aortic valve disease who underwent a tissue aortic valve replacement at age 7. He had an episode of bacterial endocarditis at age 35 and underwent bovine aortic valve replacement with root reconstruction. He had another episode of bacterial endocarditis at age 42 and required bioprosthetic aortic valve replacement and also had a bioprosthetic mitral valve replacement. He had two more episodes of bacterial endocarditis and was treated with prolonged courses of antibiotics and was placed on chronic suppression with amoxicillin 500 mg orally three times per day. He presented with acute onset of pain in his left lower extremity and was diagnosed with a thrombus in his left popliteal artery. He underwent a left embolectomy and the pathology showed a thrombus with calcification and multiple fungal forms with pseudohyphae, which grew *Candida parapsilosis*, along with blood cultures and T2Candida Panel® positive for *Candida parapsilosis*. The *Candida parapsilosis* was sensitive to micafungin (MIC 0.5ug/ml), amphotericin B (MIC 0.25ug/ml), fluconazole (MIC 0.5ug/ml) and flucytosine (MIC 0.06ug/ml). He denied any recent central venous catheter, gastrointestinal symptoms, procedures, travel, intravenous drug use, and symptoms of thrush and was not on any immunosuppressive therapy. A TEE revealed trace aortic regurgitation and mild mitral regurgitation. Micafungin 150 mg IV daily in combination with fluconazole 600 mg (6 mg/kg) IV daily was started for suspected prosthetic valve endocarditis. CT aortogram of the chest revealed no thoracic aortic aneurysm or dissection or pseudoaneurysm, abdominal/pelvic CT revealed a normal aorta, and Indium WBC tagged study was negative. He continued to have positive blood cultures for *Candida parapsilosis* after 14 days of antifungal treatment. His treatment was then changed to liposomal amphotericin B 5 mg/kg IV daily, flucytosine 2500 mg orally every 6 h (25 mg/kg every 6 h) and fluconazole 400 mg orally daily. All subsequent blood cultures were negative. The patient refused surgical intervention at this time given his concern for possible complications as he had previously undergone three prior cardiac surgeries with extensive prosthetic material.

One week later he developed acute kidney injury and the liposomal amphotericin was changed to micafungin 150 mg IV daily. The fluconazole 400 mg orally daily was continued but the flucytosine was decreased to 2500 mg orally daily. His acute kidney injury resolved and the flucytosine was increased to 2500 mg PO every 8 h. An 18 F-Fluordeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography Angiography (PET/CTA) myocardial scan revealed activity on the aortic leaflets and right lateral wall of the ascending aorta 3 weeks after starting antifungal treatment. His blood cultures remained negative but the T2Candida Panel® completed two months after starting antifungal treatment was still positive for *Candida parapsilosis*. The micafungin was discontinued after 12 weeks and he was continued on flucytosine 2500 mg orally every 8 h and fluconazole 400 mg orally daily. Repeat T2Candida Panel® became negative five months after starting antifungal treatment. The patient was stable for one year but decided to discontinue his flucytosine, fluconazole and amoxicillin. He developed low grade fevers and repeat blood cultures were negative for bacteria but grew *Candida parapsilosis*. His T2Candida Panel® was positive for *Candida parapsilosis*. He was restarted on liposomal amphotericin B, flucytosine and fluconazole. His blood cultures became negative and his T2Candida Panel® was negative after two weeks of antifungal treatment. His TEE was unchanged and did not reveal any vegetations. His liposomal amphotericin B was discontinued after 6 weeks and he remains stable on flucytosine and fluconazole.

Discussion

In the United States, candidemia is the third or fourth most common cause of healthcare-associated bloodstream infections, and associated with up to 47% mortality. Along with the general increase in Candida infections, a concurrent increase in the incidence of Candida endocarditis has been observed which has a mortality rate of approximately 80% [1,2]. Cases of reported endocarditis have been evenly divided between *Candida albicans* and non-albicans Candida species [1]. However, there has been an increase of candidiasis caused by *Candida parapsilosis* worldwide, which may translate to a rising incidence of endocarditis specific to this species [3].

Cardiac valvular surgery has been reported as a major risk factor for Candida endocarditis, but other risk factors also include intravenous drug use, recipient of chemotherapy, prolonged presence of central venous catheters, and prior history of bacterial endocarditis [1]. *Candida parapsilosis* is a nosocomial pathogen and the associated infections are more closely related to the use of invasive devices and parenteral nutrition compared to all other Candida species combined. Specific characteristics responsible for their virulence in nosocomial settings include their frequent colonization of the subungual space and ability to proliferate in glucose-containing solutions, increasing their adherence to synthetic materials, thus enhancing the formation of biofilms [4]. Although our patients had histories of mechanical aortic valve replacement, we describe two cases of community-acquired *Candida parapsilosis* endocarditis in non-intravenous drug users, which is rarely reported in current medical literature.

According to guidelines, definitive therapy for cure of native and prosthetic valve Candida endocarditis in adults is the combination of valve replacement and a prolonged course of antifungal therapy [1]. Although complications of Candida endocarditis are similar to bacterial endocarditis, the major complication of large embolization to major vessels occurs in one quarter of this patient population which would favor definitive cure with surgery [1,5,6]. An additional consideration for definitive treatment is recurrence, usually attributed to an unresolved underlying condition or inappropriate antimicrobial therapy [7]. In a recent retrospective case-control study, Munoz et al identified fungemia due to *Candida parapsilosis* as an independent risk factor for recurrence (odds ratio 9.10; 95% confidence interval 1.33–62.00; $p = 0.02$) and approximately half were associated with endocarditis. The observed increased risk for recurrence may be contributed by the previously discussed pathophysiology of *Candida parapsilosis*. However, patients with Candida endocarditis may not be appropriate surgical candidates. A meta-analysis of Candida endocarditis by Steinbach et al previously showed that specifically for *Candida parapsilosis*,

success rates between medical antifungal combination therapy (63%) and combined medical/surgical therapy (67%) were similar. Combination antifungal therapy without surgical intervention appears to possibly approach the success observed with adjunctive surgery [2]. Therefore, optimal medical management by maximizing the pharmacodynamics effects of available antifungal therapy is essential to prevent recurrence and mortality.

Based on the limited data reported in the literature and clinical experience, lipid formulation amphotericin B, with or without flucytosine, OR high-dose echinocandin is recommended as initial therapy for prosthetic valve endocarditis. Chronic suppressive antifungal therapy with fluconazole is subsequently recommended to prevent recurrence [1]. The echinocandins are a newer class of antifungal agents with several advantages over amphotericin and the triazoles, including fungicidal activity, patient tolerability, and minimal drug interactions [5]. Furthermore, in vitro studies have previously reported that echinocandins maintain excellent activity in the presence of biofilms, a pharmacodynamic advantage over the older classes of antifungals [4,5,8]. Interestingly, all *Candida parapsilosis* fungemic patients who experienced recurrences previously received amphotericin B and fluconazole in the study by Munoz et al. Furthermore, MIC breakpoint criteria are only established for selected azoles and echinocandins excluding amphotericin B and flucytosine by the Clinical and Laboratory Standards Institute (CLSI) [9]. A consideration when using echinocandins is the higher in vitro MIC against *Candida parapsilosis* compared to other Candida species [4,10]. The clinical significance of this decreased susceptibility and correlation with clinical failure requires further study.

Upon revisiting the cases presented, both of our patients lacked the traditional risk factors for *Candida parapsilosis* endovascular infections and both developed acute kidney injury with amphotericin B, despite the liposomal formulation. Furthermore, both of our patients were not ideal candidates for valve surgery and so combination antifungal therapy was chosen to optimize the pharmacodynamics of the agents chosen. Echinocandin plus triazole antifungal therapy with or without flucytosine may be alternative regimens to consider for *Candida parapsilosis* endovascular infections when surgery is not feasible. In both of our patients, the MIC of fluconazole, micafungin, amphotericin B, and/or flucytosine for *Candida parapsilosis* appeared to be similarly low in comparison to the reported isolates surrounding endocarditis without surgical intervention [4,5,10]. This is an important observation to consider as our clinical success may have been influenced by the favorable MICs of the selected antifungal agents. Despite the favorable MICs and negative blood cultures and negative T2Candida Panel® our second patient relapsed after he discontinued his antifungal treatment. It is unlikely that either patient was cured, however, both are well controlled on suppressive antifungals. Rapid molecular diagnostics such as T2MR technology may help with prognosis of invasive candidiasis [11]. For both of our cases the T2Candida Panel® (T2 Biosystems) was utilized upon follow up to assess clearance of candidemia along with clinical symptoms. This T2MR nanodiagnostic panel for Candida qualitatively detects five species of Candida directly in whole blood without the need for blood cultures [12]. Although the T2Candida Panel® has been used to facilitate early detection and allow for targeted antifungal therapy, there is limited data on the utility of this test in assessing outcomes for deep-seated candidiasis [12]. A multicenter prospective clinical trial, designated the Serial Therapeutic and Antifungal Monitoring Protocol (STAMP) trial, was recently conducted in 31 patients to assess the performance of T2MR in monitoring candidemia clearance compared to blood culture. Based on the log-rank test, comparing the time to negative result distributions between the 2 surveillance methods, T2MR significantly outperformed blood cultures in monitoring the clearance of candidemia in patients receiving antifungal therapy (chi-square of 8.2, $p = 0.004$) [13]. However, clinical outcomes associated with incorporating T2MR monitoring into the management of known candidemia were not within the scope of this study. In both of our cases, the T2Candida Panel® was used to assess for presence of disease and continuation of antifungal therapy, despite negative blood cultures. In addition, our second patient had a 18 F-Fluordeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography Angiography (PET/CTA) myocardial scan which confirmed his diagnosis of endocarditis. This diagnostic tool has been reported to be useful in suspected cases of infectious endocarditis and implantable cardiac electronic device infections [14,15]. To our knowledge, this is the first report of using this diagnostic test in fungal prosthetic valve endocarditis. The successful use of combination antifungal therapy demonstrates the successful use of combination antifungal therapy and demonstrate the utility of this approach in a subset of patients who are not candidates for surgery. These cases also highlight the challenges with treatment of *Candida parapsilosis* prosthetic valve endocarditis.

Disclosures

All authors state that they have no conflicts of interest and nothing to disclose.

CRediT authorship contribution statement

Tania Ahuja: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Writing - original draft, Writing - review & editing. **Karen Fong**: Writing - original draft, Writing - review & editing. **Eddie Louie**: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Writing - original draft, Writing - review & editing.

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