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Case report

Candida tropicalis endocarditis successfully treated with AngioVac and micafungin followed by long-term isavuconazole suppression

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ABSTRACT

We provide a review of current literature of native valve *Candida tropicalis* endocarditis.

A 41-year old man presented with *C. tropicalis* candidemia complicated by superior vena cava mass and right main pulmonary artery thrombus. The patient achieved clinical and microbiologic cure with AngioVac of the mass and echinocandin for six weeks. Long-term suppression was challenging given the *C. tropicalis* strain was resistant to fluconazole, voriconazole and posaconazole. Additional susceptibilities were obtained and he remained relapse-free at 12 months with isavuconazole.

Introduction

Candida infective endocarditis (IE) is the most common form of fungal endocarditis (50 %) but accounts for only 2 % of all IE cases. *Candida* IE is seen in about 15 % of all candidemia cases. *Candida albicans* (44 %) is the causative species in most of the cases. Other common species include *C. parapsilosis* (27 %), *C. tropicalis* (10 %) and *C. glabrata* (6 %). Risk factors for *Candida* IE include history of prosthetic valve, cardiac implantable devices (pacemaker, defibrillator, left ventricular assist device), injection drug use, bacterial IE, chemotherapy, prolonged presence of central venous catheters, and renal replacement therapy. Clinical presentation is similar to bacterial IE but emboli to the large vessels are more frequent [1].

The incidence of *Candida* IE in renal replacement patients is 2.5 %. Incidence is higher in patients receiving hemodialysis (HD) compared to peritoneal dialysis. The risk is two fold higher in HD recipients with central venous catheters (CVC) compared with those with arteriovenous fistulas. In-patient mortality of CVC associated *Candida* IE is 22 % and 55 % at one year [2].

Since medical therapy alone has occasionally been curative, combination of antifungals and valve replacement are considered the cornerstone of treatment for *Candida* IE. Valve repair and vegetectomy are alternatives to the valve replacement. Currently, the need for surgery in all patients is being questioned as recent information suggests the outcome in patients treated with medical management alone may be similar to post valve replacement surgery. However, pending new information, the recommendations per Infectious Diseases Society of America (IDSA) for *Candida* IE include initial treatment with lipid formulation of amphotericin B (with or without flucytosine) or high-dose echinocandin. Azoles are not considered first line as they have decreased activity when compared with echinocandins against biofilms formed by Candida in vitro, and they penetrate poorly into vegetations. Long-term suppression with azoles is recommended to prevent relapses if valve surgery is not feasible [3].

Case

The patient, a 41-year old male with past medical history of hypertension and end stage renal disease on hemodialysis (HD) was transferred to our hospital for *Candida tropicalis* infective endocarditis. Ten months prior to the admission, he was admitted to an outside hospital with pulmonary septic emboli, respiratory failure, and renal failure resulting in renal replacement therapy with HD. A chest tunneled dialysis catheter and right arm atriovenous fistula was placed. Two sets of blood cultures and transesophageal echocardiogram (TEE) were negative. He was treated empirically with intravenous meropenem for six weeks for presumed endovascular infection. Six months prior to the admission, he noticed black tar substance in his dialysis catheter. The catheter was exchanged initially and subsequently removed a month later. Two weeks prior to admission, patient experienced intermittent fever, anorexia, nausea and vomiting. Blood cultures

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were drawn at the dialysis center and found to be positive for *C. tropicalis.* TEE showed a large mobile 2 cm superior vena cava (SVC) mass attached to the right atrium and possible an aortic root abscess (Fig. 1). The vegetation appeared to be attached to the fibrous cast left from the previous dialysis catheter.

The patient was transferred to our facility for cardiovascular surgery evaluation. On arrival, patient complained of fever, chills, sweats, neck and back pain. He had no history of injection drug use, immunosuppressive therapy and no indwelling hardware. His vitals showed temperature 101.1 °F, blood pressure 123/71, heart rate 98/min, respiratory rate 18/min, and oxygen saturation 92 % at room air. He appeared uncomfortable and had bilateral rales on lung auscultation. A 3/6 systolic murmur was best heard in the left sternal border, most prominent at 2nd and 5th intercostal space. No spinal tenderness to palpation was appreciated. Chest CT showed multiple bilateral septic emboli and large right main pulmonary artery thrombus (Fig. 2). Patient was initially started on intravenous (IV) amphotericin B but developed severe back pain so antifungal was changed to IV micafungin 150 mg once a day. Patient was evaluated by cardiovascular surgery but was not considered a valve replacement candidate due to lack of valve vegetation on cardiac CT scan. Ophthalmologic exam was negative for endopthalmitis. CT scan of the abdomen and pelvis and MRI of the vertebral spine showed no infection.

Repeat blood cultures were positive for *C. tropicalis* with following mean inhibitory concentrations (MIC): micafungin 0.016 mg/L, fluconazole ≥256 mg/L, itraconazole ≥16 mg/L, voriconazole ≥8 mg/l and posaconazole ≥8 mg/L. Additional susceptibilities were requested for isavuconazole. The patient underwent right pulmonary thrombectomy. The thrombus culture was positive for *C. tropicalis.* Interventional radiologist performed an AngioVac procedure and removed 75 % of the SVC mass. While inpatient, IV micafungin 150 mg once a day was continued and post AngioVac blood cultures were negative. He improved clinically and refused any indwelling catheter. On discharge from the hospital, IV micafungin was switched to 200 mg on dialysis days to complete 6 weeks course. Post six weeks of IV micafungin, TEE showed resolution of the cardiac mass. Isavuconazole MIC was 0.03 mg/l and he was switched to oral isavuconazle for long-term suppression. At one-year follow-up, patient was clinically stable.

Methods

We conducted a Pubmed based search for *Candida tropicalis* endocarditis, which yielded 47 results. Post application of 'Adult: age 19+' filter, the results were narrowed to 26 articles. Case reports with prosthetic valve (4) or cardiac device (4) or polymicrobial infections (2) or different *Candida* species (2) or basic science articles (2) were excluded. Twelve remaining case reports of native valve *C. tropicalis* IE are summarized briefly in Table 1 [4–15].

Discussion

We present a case of central venous catheter associated native valve *Candida tropicalis* endocarditis successfully treated with AngioVac of the vegetation along with intravenous echinocandin for 6 weeks followed by oral isavuconazole for suppression. Only two prior cases of native valve *C. tropicalis* achieved microbiologic cure without valve replacement. Unfortunately on long-term follow up, these two patient died (Table 1). We found four cases of *Candida* endocarditis treated successfully with AngioVac procedures. Jones et al. described a case of *C. albicans* cardioverter-defibrilattor lead vegetation treated with AngioVac aspiration of a

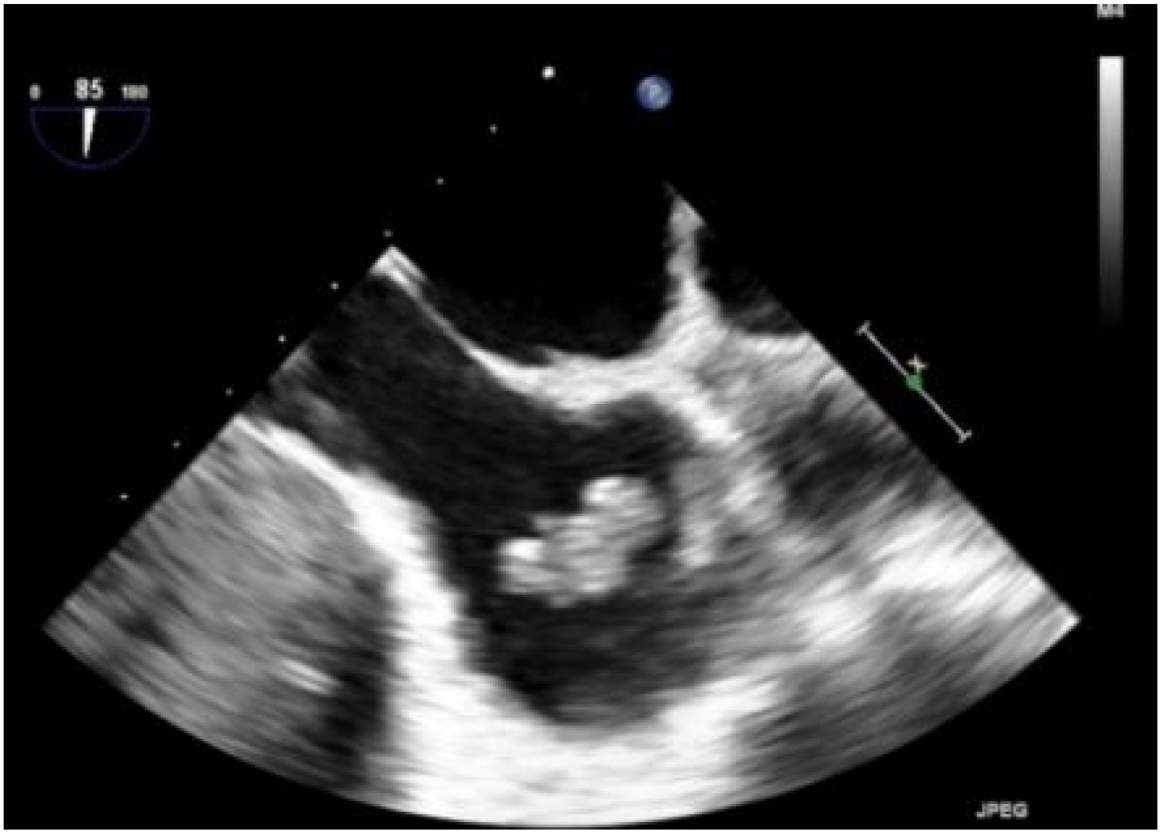

Fig. 1. Transesophageal Echocardiogram: Large mobile superior vena cava mass.

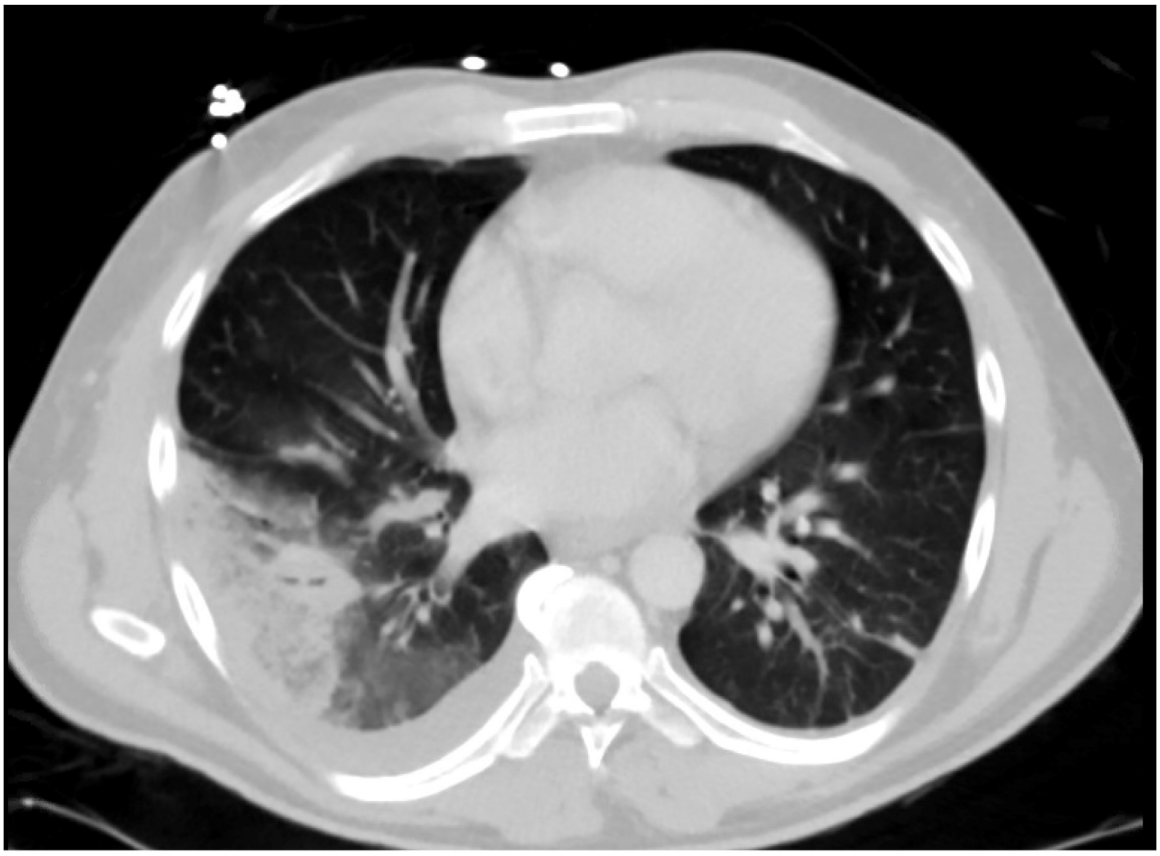

Fig. 2. Multiple pulmonary septic emboli and Right main pulmonary artery thrombus.

Table 1
Outcomes of Native Valve *Candida tropicalis* Endocarditis.

Reference	Risk Factor	Native Valve Infection	Valve replacement	Treatment	Outcome
[4]	Pancreatitis	Tricuspid	Yes TVR	Amphotericin B + flucytosine x 2 weeks followed by flucytosine x 4 weeks followed by long term oral fluconazole	Cured
[5]	IDU, Burns, CVC	Aortic, Mitral	Yes AVR, MVR	Micafungin x 3 weeks switched to Amphotericin B x 8 weeks	Cured
[6]		Mitral	Yes MVR	IV Fluconazole x 7 weeks	Cured
[7]		Aortic	No	Amphotericin B switched to Caspofungin	Cured Later died of refractory heart failure
[8]	TURP/ Candiduria	Aortic	No	Amphotericin B + flucytosine	Failure: death prior to valve surgery
[9]	TPN	Tricuspid	Yes TVR	Amphotericin B + flucytosine	Cured
[10]		Aortic	No	IV Fluconazole x 7 weeks	Cured Later died of *Staphylococcus aureus* sepsis
[11]	Pancreatitis, TPN	Mitral	Yes MVR	Miconazole switched to Amphotericin B + fluconazole	Cured Stable at 10 month follow-up
[12]	IHSS	Mitral	No	Amphotericin B x 8 weeks	Failure: Died of *Pseudomonas* bacteremia
[13]	HL on chemotherapy		No	None	Failed: Autopsy diagnosis
[14]	Recent hospitalization for CVA	Mitral	Yes MVR	Amphotericin B	Failure: Died 20 days pos-op
[15]	RA, recent gastrectomy	Right Atrial vegetation	No	None	Failed: Autopsy diagnosis

Aortic valve replacement-AVR; Cerebrovascular accident-CVA; Hodgkin's Lymphoma (HL); Idiopathic Hypertrophic Subortic Stenosis-IHSS; Injection drug use-IDU; Mitral valve replacement-MVR; Rheumatoid Arthritis-RA; Total parenteral nutrition-TPN; Transurethral resection of the prostate-TURP; TVR-Tricuspid valve replacement.

large right atrial vegetation and laser sheath lead extraction [16]. Talebi et al, Tanaka et al, and Kalotericuset et al. each successfully treated a fungal tricuspid valve vegetation with an AngioVac procedure [17–19].

Per IDSA guidelines, clinically stable patients with susceptible *Candida*isolates who have cleared *Candida*from the bloodstream, can be changed to oral fluconazole to complete the treatment. Based on susceptibilities, other azole options could be voriconazole or posaconazole. There is no mention of isavuconazole in the guidelines due to lack of data. There has only been one significant human randomized, double blind, multicenter, non-inferiority candidemia study, which evaluated the role of initial isavuconazole versus caspofungin. Patients were assigned to either IV isavuconazole followed by oral isavuconazole or IV caspofungin followed by oral voriconazole as initial therapies for candidemia and other invasive candidiasis. There were total of 67 patients with invasive candidiasis (29 in the isavuconazole arm and 38 in the caspofungin arms) with response rates of 34.5 % for isavuconazole and 65.8 % for caspofungin. Isavuconazole was favored as the oral step-down therapy when compared to voriconazole. While the failure of voriconazole was 15 %, it was reported at only 5.8 % for isavuconazole. Given the performance of oral isavuconazole as a step-down therapy in this study, it is potentially a reasonable treatment option for fluconazole-resistant isolates [20].

In our case, fluconazole, voriconazole and posaconazole showed resistance to *C. tropicalis* so we chose isavuconazole based on the susceptibilities. There is no human data suggesting that in-vitro resistance lead to poor clinical outcomes. In a Taiwanese study, Chen et al. showed 16.9 % patients infected with fluconazole non-susceptible *C. tropicalis* had cross-resistance to itraconazole, voriconazole, and posaconazole even though 55.2 % of patients were azole naïve [21]. In an in-vitro study, Paul et al. found that 4 out of 9 fluconazole induced resistant isolates with MICs $\geq$ 128 mg/l also developed cross-resistance to other azoles including posaconazole, voriconazole and itraconazole but the resistance was not long lasting. Isavuconazole was not tested in this study [22].

Our case adds to the growing evidence that right-sided *Candida* endocarditis patients who are not surgical candidates can be managed successfully with an AngioVac procedure. The patient was treated with intravenous echinocandin for six weeks as he had idiosyncratic reaction to amphotericin B. For long-term suppression, fluconazole is the most commonly used azole and alternatives are voriconazole and posaconazole. The patient was suppressed with isavuconazole due to resistance to other azoles. It shows the importance of requesting susceptibilities to all azoles. We need more studies, which include isavuconazole, to understand the correlation between in-vitro azole resistance to *C tropicalis* and its clinical implications and outcomes.

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None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contribution

Kirsten K Prabhudas-Strycker: Writing the case report and providing the figures

Saira Butt: Writing and editing the Introduction, Methods and Discussion and the physician in charge of the patient care at the hospital and clinic follow up.

Madhukanth Reddy: Reviewing the article and the physician in charge of the patient care at the hospital.

Declaration of Competing Interest

None.

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