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Scedosporium apiosermum infection of the "Native" valve: Fungal endocarditis in an orthotopic heart transplant recipient

Meredith E. Clement [a,*], Eileen K. Maziarz [a], Jacob N. Schroder [b], Chetan B. Patel [c], John R. Perfect [a]

[a] Division of Infectious Diseases, Duke University Medical Center, Durham, NC USA
[b] Division of Cardiovascular and Thoracic Surgery, Duke University Medical Center, Durham, NC, USA
[c] Division of Cardiology, Duke University Medical Center, Durham, NC, USA

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ABSTRACT

Scedosporium apiospermum is an increasingly appreciated pathogen in immunosuppressed patients. We present a case of *S. apiospermum* endocarditis in a 70-year-old male who had undergone orthotopic heart transplant. Echocardiogram demonstrated a 1.4 cm tricuspid valve vegetation. He underwent valve replacement, complicated by fatal massive post-operative haemorrhage. Valve cultures grew *S. apiospermum*. To our knowledge, our case is the first reported instance of endocarditis caused by *S. apiospermum* in a recipient of a cardiac transplant.

1. Introduction

Scedosporium apiospermum is a filamentous saprophytic mould found ubiquitously throughout the environment. Historically regarded as the anamorph (asexual form) of *Pseudallescheria boydii*, more recent molecular-based work has proposed the two as distinct species [1]. It was first named *Monosporium apiospermum* by Saccardo in 1911 as a cause of mycetoma [2], a chronic subcutaneous infection acquired by direct inoculation. In recent years, however, the organism has become an emerging pathogen in immunocompromised populations, specifically in the setting of hematopoietic and solid organ transplantation, chronic corticosteroid use, and haematologic malignancy. *S. apiospermum* is well known to cause respiratory tract infection, which occurs via inhalation of spores, though this organism can disseminate and has a predilection for the central nervous system. It is notorious for causing meningitis after near drowning episodes [3], and this fungus can produce adventitial forms in tissue and release yeast-like forms into circulation, which likely allows for isolation in blood cultures [4]. It has rarely been shown to cause infective endocarditis. Our case represents one of the few reported cases of *S. apiospermum* endocarditis, and the first reported case of endocarditis due to this organism in a heart transplant recipient. Furthermore, this case demonstrates the potential for immunocompromised patients to develop a sequence of infections due to opportunistic mycoses.

2. Case

A 70-year-old male with chronic kidney disease, anemia, and insulin-dependant diabetes underwent orthotopic heart transplant for ischaemic heart disease at our institution in September 2011. Post-operative course was complicated by invasive pulmonary aspergillosis one year after transplant, at which time biopsy of a large paratracheal mass showed septate hyphae and bronchoalveolar lavage fluid grew *Aspergillus fumigatus*. The patient was initially treated with combination antifungal therapy including micafungin and voriconazole for over 5 weeks and was thereafter transitioned to voriconazole monotherapy upon discharge. Surgical resection was considered but ultimately not pursued as it was thought to carry unacceptably high mortality risk. His immunosuppressive regimen was minimized in the setting of infection and he was maintained on tacrolimus monotherapy without significant allograft rejection on surveillance endomyocardial biopsies. Over the ensuing two years, surveillance computed tomography (CT) scans demonstrated probable improvement in disease burden. During this time, the patient was hospitalized five times for weight loss and failure to thrive, and

* Corresponding author.

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required placement of a feeding tube for supplemental nutrition. In follow-up he had therapeutic voriconazole levels (trough levels 1.5–3.1 μg/mL) but developed periositis (with elevated fluoride levels) and hepatotoxicity while on voriconazole, and ultimately this medication was stopped after 21 months of therapy. Six weeks after discontinuation he reported increased appetite and had gained 23 pounds. He had no known exposure to any fresh water settings of contamination and no persistent catheters *in situ*.

In July 2014 (three months after stopping voriconazole and three years after transplant), he presented to an outside hospital with left knee pain after a fall, accompanied by confusion, generalized weakness, and fevers. Head CT was negative for masses or other acute process. He was transferred to our hospital the following day. On presentation he had a large left knee effusion and underwent arthrocentesis with cell count of 32,000 nucleated cells (90% neutrophils). His vital signs were normal without hypoxia or fevers. On hospital day 4, we were notified by the outside hospital that his blood cultures were growing mould, and he was started on posaconazole, 300 mg intravenously for two doses, then 300 mg oral daily thereafter (voriconazole was avoided due to concern over previous long-term use and side effects). On hospital day 8, he began having fevers and was taken for surgical drainage of his knee with demonstration of purulent, bloody fluid. Blood and synovial cultures from our hospital eventually grew *Scedosporium apiospermum*, identified by standard mycologic criteria (sequencing not performed). He developed an increasing oxygen requirement, and on hospital day 9 underwent CT scan of his chest that showed pulmonary nodules and diffuse ground glass opacities concerning for fungal infection. Terbinafine 250 mg oral daily was added for possible synergy with the triazole [5,6]. On hospital day 11, echocardiogram was performed, demonstrating a 1.4 cm vegetation on the tricuspid valve (see Fig. 1). Given surgical indications of congestive heart failure with valvular dysfunction and presumed mould infection of the valve, he was taken to the operating room and underwent tricuspid valve replacement. Despite the high risk of this necessary procedure, the patient survived surgery but required extracorporeal membrane oxygenation (ECMO) cannulation and suffered massive post-operative haemorrhage while on anti-coagulation. The patient's family ultimately decided to pursue comfort measures and he expired following surgery, on his 12th hospital day. Tricuspid valve pathology revealed acute fungal endocarditis with large amounts of fungal organisms and focal leaflet destruction (see Fig. 2). Cultures from the tricuspid valve grew *S. apiospermum*. Antifungal susceptibility testing was performed using M38-A2 Clinical and Laboratory Standards Institute's methods for broth dilution. Results ultimately returned as follows: Voriconazole MIC 0.5 μg/mL, Posaconazole 1 μg/mL, Terbinafine > 2 μg/mL. Post-mortem examination was declined by the patient's family.

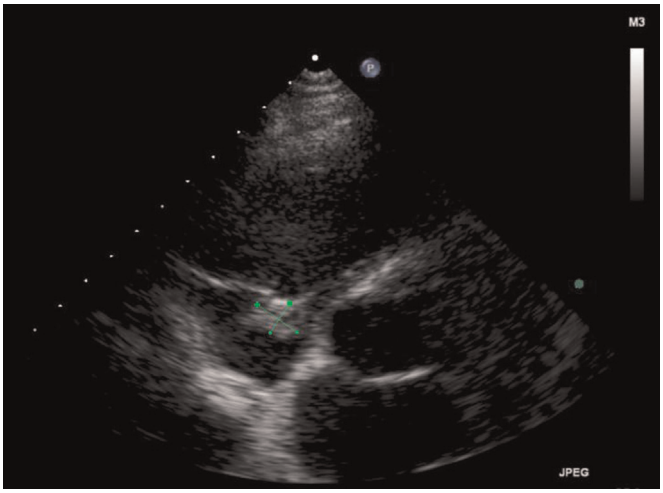

Fig. 1. 1.4 cm tricuspid valve vegetation, transthoracic echocardiogram.

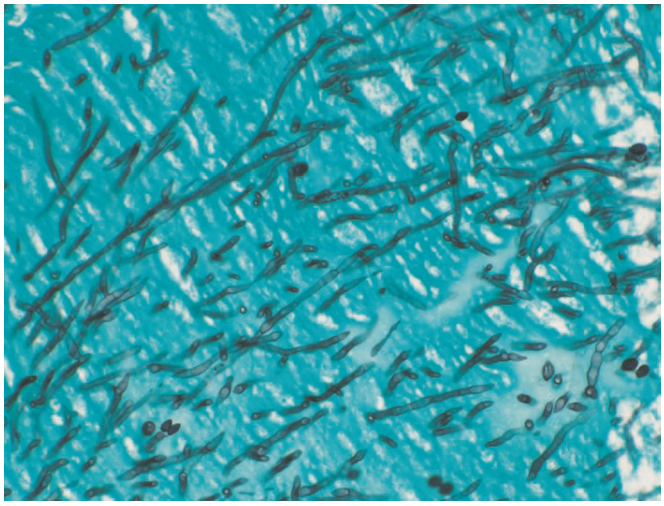

Fig. 2. Tricuspid valve, Grocott's methanamine silver stain.

3. Discussion

We report a case of fungal endocarditis caused by *S.apiospermum* in a patient following orthotopic heart transplant (OHT). Our case is unique in several respects. First, although *Scedosporium* species have emerged as important agents of opportunistic infection in immunocompromised hosts and can invade normal endocardium as demonstrated in a recent case of *Scedosporium* (Lomentspora) *prolificans* endocarditis in a leukaemic patient undergoing chemotherapy [7], this fungus is an extremely rare cause of fungal endocarditis. Most previously documented cases of endocarditis due to this mould are associated with cardiac or intravascular devices [8], which our patient did not have in either the pre- or post-transplant periods. Second, it is an especially rare cause of endocarditis in solid organ transplant recipients [9]. One case has previously been reported in a liver transplant recipient and another in a patient following kidney transplantation; both patients died from infectious complications [10,11]. To our knowledge, this is the first reported case of endocarditis caused by *S. apiospermum* in a recipient of a cardiac transplant. It has been our experience in rabbit models of endocarditis that even slight damage to valve or endocardium and then concomitant fungemia will uniformly produce fungal endocarditis [12]. In our patient with multiple right-sided endocardial biopsies for transplant rejection assessment, we hypothesize that the biopsy procedures may have produced a nidus for fungemia to seed the tricuspid valve. This possible risk factor will need to be further studied for clarity in future cases.

Besides endocarditis, a variety of other infections caused by *S. apiospermum* in OHT patients including non-healing cutaneous nodules and ulcers, brain abscess, sternal wound infection, and pneumonia with empyema have been reported [13–18]. Invasive fungal infection (IFI) with *Aspergillus* species and other hyalohyphomycetes are important to accurately identify because of variable susceptibility to antifungal agents and their particularly aggressive course. There is no substitute for accurate identification of these moulds; by pairing morphologic characteristics with newer technologies including sequence identification and Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF), greater precision in identification of invasive fungi is increasingly possible.

These infections have high mortality rates, estimated at 57% at 90 days in one study [19]. Among patients with *S. apiospermum* endocarditis, associated mortality is 100%, and we must do better.

Our patient had been diagnosed with invasive aspergillosis two years prior to his infection with *S. apiospermum*. In another case report, a cardiac transplant patient had also suffered invasive aspergillosis prior to infection with *S. apiospermum* [16]. These types of cases raise the question of whether additional predisposing factors beyond immunosuppressive therapy, such as genetic susceptibility to filamentous fungi, play a role in disease appearance. The investigation of genetic susceptibility to fungal infections is in its infancy stages outside of primary immunodeficiency syndromes, but our case emphasizes the potential for immune defects to be uncovered when the patient already has certain other immune functions blocked. In fact, immunologic profiles associated with increased susceptibility to IFIs have been suggested as a means to assess those at particular risk after transplant [20]. Our case highlights a patient who suffered two serious invasive fungal infections, including one very rare cause of fungal endocarditis, which appeared shortly after stopping treatment for the other previously recognized infection.

An alternative pathophysiological explanation for this case is that the patient suffered co-infection with two hyaline moulds initially, with long-term voriconazole therapy serving as a prophylactic agent against the *Scedosporium* and the second episode representing reactivation of a suppressed *Scedosporium* infection for two years. We believe this is less likely in part due to the MIC of the blood *S. apiospermum* isolate to voriconazole. Whether a second *de novo* infection or reactivation of previous infection, it is clear from this case that immune defects persist in SOT recipients and documented mould infections need to be treated aggressively and for an extended period of time with close follow-up when antifungal drugs are discontinued.

In conclusion, mortality in the setting of mould endocarditis is high. We felt surgery was essential for cure and also attempted to treat aggressively with at least two antifungal agents. Unfortunately, the patient did not survive. However, we feel that the two principles above—aggressive surgical and medical management—gave the patient the best chance of surviving an episode of mould endocarditis, a rare and deadly entity requiring the skill of both surgical and medical teams to impact outcome.

Conflict of interest

There are none.

Disclosures

Dr. Perfect has research grants and sits on advisory committees for Merck and Astellas.

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