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A Case of Catastrophic *Aspergillus* Endocarditis

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INTRODUCTION

Aspergillus endocarditis accounts for less than 5% of infective endocarditis cases, but it has a high mortality and diagnosis is often elusive.[1,2] Previous case reviews have suggested the mortality rate of *Aspergillus* endocarditis to be between 62-68%, with the most common species identified as *Aspergillus fumigatus*.[2-4] Those populations often affected are patients who are immunosuppressed, on long-term antibiotic therapy, or have prosthetic heart valves.[5,6] Previous valvular surgery has been reported in 35-50% of patients with *Aspergillus* endocarditis.[2,7] Additionally, blood cultures are rarely positive for *Aspergillus* species, making the diagnosis difficult.[2,3] Complications of *Aspergillus* endocarditis include peripheral emboli, mycotic abscesses, endophthalmitis, and aneurysms.[2,7]

A case of *Aspergillus* prosthetic valve endocarditis with a timely diagnosis is presented, but the patient was not a surgical candidate and had complications with progression of his infection despite a prolonged course of antifungal therapy.

CASE REPORT

A 69-year-old male with a past medical history of hyperlipidemia, hypertension, and bioprosthetic mitral valve replacement (one year prior to presentation) presented as a transfer to our institution with a left parietal hemorrhage after having been admitted two weeks prior for a left middle cerebral artery stroke treated with thrombectomy. He was sedated, intubated, and underwent placement of an external ventricular drain. Per the family, the patient was doing well since the first stroke. He had reported mild fatigue and a headache the night prior to presentation. He was on warfarin, aspirin, and rosuvastatin at home. He worked as an attorney in a rural town in Kansas, raised horses, and had no recent history of travel.

Initial physical exam was significant for a III/IV holosystolic murmur at the apex, but he did not have any other peripheral stigmata of endocarditis. Transesophageal echocardiogram (TEE) during stroke workup demonstrated three mobile echodensities on the posterior mitral valve leaflet: the largest measuring 6 mm x 18 mm (Figure 1). These mobile echodensities were not present on the transthoracic echocardiogram (TTE) completed during the previous hospitalization. He originally was started empirically on cefepime (2 g IV every eight hours), gentamicin (80 mg IV every eight hours), and vancomycin (1250 mg IV twice daily). Lab work revealed an *Aspergillus* galactomannan antigen of 0.899 (normal < 0.500) and 1,3-β-D-glucan greater than 500 pg/mL (normal < 80 pg/mL). The Karius® cell-free DNA plasma quantitative test returned positive for *Aspergillus fumigatus*. Liposomal amphotericin B (3 mg/kg IV every 24 hours) and voriconazole (360 mg per oral twice daily) were added to his antimicrobial regimen. On day six of hospitalization, his fungal blood cultures grew *Aspergillus fumigatus*, susceptible to amphotericin, micafungin, isavuconazole, and voriconazole. He developed right eye fungal endophthalmitis, which was treated with intravitreal voriconazole (100 mcg). After discussion with the cardiothoracic surgery service, valve repair surgery was deferred at the time due to his recent hemorrhagic stroke preventing use of anticoagulation. The plan was to complete a six to eight week course of combined antifungal therapy and re-evaluate.

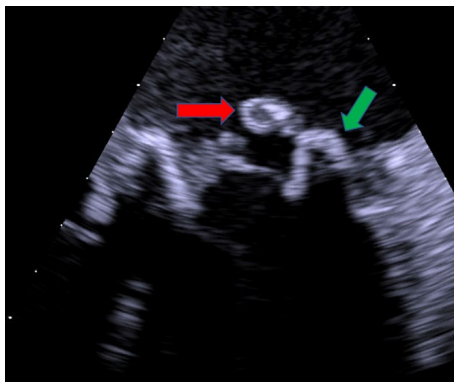

Figure 1. 2D Transesophageal echocardiogram showed a large mobile echodensity (red arrow) attached to the posterior leaflet of the bioprosthetic mitral valve (green arrow).

After 21 days of treatment with liposomal amphotericin B and voriconazole, the patient was switched from voriconazole to isavuconazole (372 mg daily) due to a prolonged QTc (0.55 sec). Isavuconazole levels were confirmed to be therapeutic. On day 33 of admission, he was discharged to inpatient rehabilitation. He then transitioned to a skilled nursing facility. After 50 days of treatment, amphotericin B was switched to micafungin (150 mg IV daily) due to the patient developing renal insufficiency (creatinine increased by 0.34 mg/dL). The plan was to continue micafungin and isavuconazole until an appointment with the cardiothoracic surgery service three weeks later to discuss valve replacement.

Two weeks after the switch to micafungin, the patient returned to the emergency department with gradually worsening generalized weakness and failure to thrive. He also had a white blood cell count elevation of 14.3 K/UL. Computed tomography (CT) scan demonstrated splenic infarcts with associated splenic abscess and wedge-shaped renal infarcts likely from septic emboli (Figure 2).

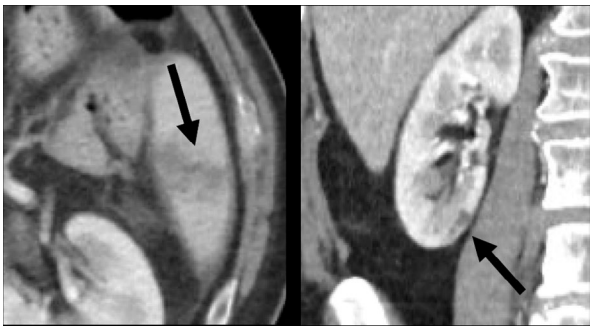

Figure 2. Computed tomography scan of abdomen/pelvis with contrast showed a 3.1 cm x 1.9 cm well-defined fluid collection in spleen (left arrow) and a wedge-shaped cortical hypodensity in right kidney (right arrow).

The patient was continued on micafungin and isavuconazole. Vancomycin (1250 mg IV) and cefepime (2 g IV every eight hours) were added. The abscesses were not amenable to drainage per interventional radiology. The next day he became hypotensive requiring vasopressor initiation and was transferred to the Intensive Care Unit. A repeat TTE demonstrated a persistent mobile echodensity attached to the mitral valve leaflets. Serum 1,3-β-D-glucan was greater than 500 pg/mL and galactomannan antigen was 5.863. The cardiothoracic surgeon met with the family, and they decided to not pursue surgical intervention. His hospital course was complicated by acute embolic occlusions in the lower extremities treated with thrombectomy, worsening hypoxemia requiring intubation and mechanical ventilation, and increased vasopressor requirements. On day seven of that admission, he was transitioned to comfort measures and died shortly after that.

DISCUSSION

This patient represented a case of severe *Aspergillus* endocarditis that ultimately led to his death despite completing a 10-week course of appropriate combined antifungal therapy. The Infectious Disease Society of America (IDSA) guidelines for *Aspergillus* endocarditis recommend early surgical intervention with antifungal therapy (voriconazole or liposomal amphotericin B) followed by lifelong suppressive antifungal therapy. However, there only is low-moderate quality of evidence for this recommendation, and many patients with this disease are not appropriate candidates for high-risk surgery.[3]

One of the unique aspects of this case was the use of Karius® cell-free DNA technology to identify the organism in addition to a fungal culture growing *Aspergillus fumigatus*. The Karius® test detects microbial cell-free DNA (mcfDNA) circulating in the bloodstream from 1,250 clinically relevant organisms. This microbial cell-free DNA technology may be a novel way to diagnose fungemia given the high frequency of negative blood cultures. Reviews have found blood cultures resulting as negative in at least 96% of *Aspergillus* endocarditis cases.[2,5] A previously published analytical and clinical validation study for the Karius® test showed a 93.7% agreement with blood culture in a cohort of 350 patients.[8] In other examples, authors of two case reports used the test to diagnose central nervous system aspergillosis and pulmonary aspergillosis, but neither had infective endocarditis.[9,10] As shown in our patient, the Karius® test was a useful tool for diagnosis, but the clinical utility of the test was somewhat disputed. A recent retrospective study explored the diagnostic benefit of the test in clinical settings and demonstrated overall limited real-world clinical impact.[11] For now, the gold standard for diagnosis of *Aspergillus* endocarditis remains histological with tissue culture confirmation. Fortunately, our patient also had a positive blood culture for *Aspergillus fumigatus*, which helped to guide therapy with our ability to obtain antifungal susceptibilities.

As far as treatment for *Aspergillus* endocarditis, early surgical intervention is considered crucial particularly in cases with prosthetic valve endocarditis.[3,7] In our review of current literature, only four patients with *Aspergillus* endocarditis have survived without surgical intervention, and three of them were infants or children.[12-15] Higher mortality rates exist for immunosuppressed patients and for patients with mitral valve involvement.[2] However, it was important to remember that like our patient, many patients initially are not surgical candidates and medical treatment in the form of antifungal therapy is the only option. Most recent literature suggested the use of combined antifungal therapy, but even with this mortality remained high.[5] Additionally, long-term use of antifungal agents is challenging due to the various toxicities.

Unfortunately, it is not always possible to complete early surgical intervention for patients with *Aspergillus* endocarditis as the guidelines suggest.[3] Like our patient, most patients also develop complications, such as emboli, later in the course of the disease, further complicating the ability to perform surgery.[2] This case illustrated that prolonged combined antifungal therapy alone for *Aspergillus* endocarditis was ineffective, and it was important to complete valve replacement surgery at some point during the treatment process to optimize the chance of survival. Newer diagnostic modalities, such as the use of cell-free DNA technology, can assist in making the diagnosis. Further research, ideally with multi-center involvement, is needed to optimize our approach to antifungal therapy regimens and duration of treatment in *Aspergillus* endocarditis, particularly in cases where surgical debridement is not feasible or able to be performed in a timely manner.

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