Aspergillus fumigatus endocarditis in a splenectomized patient with no risk factors

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ABSTRACT

Aspergillus endocarditis is a rare cause of culture-negative fungal endocarditis, after Candida endocarditis. Typical risk factors include intravenous drug use, immunosuppression, prior cardiac surgery or presence of prosthetic heart valves, hematopoietic stem cell or solid organ transplantation. Common presentations include signs and symptoms consistent with endocarditis but with negative bacterial blood cultures. Here, we present a case report of a 49-year-old male without known risk factors for fungal endocarditis who presented with a stroke and found to have Aspergillus endocarditis. Despite surgical intervention and antifungal treatment, the outcome was fatal. This underscores the difficulty in diagnosing Aspergillus endocarditis and its poor prognosis, necessitating the need for early diagnosis and intervention.

Introduction

Aspergillus sp. is a mold that is ubiquitous worldwide and found in soil, water, food and air, and is particularly common in decaying vegetation. Associated syndromes can range from colonization such as fungal ball, to allergic responses such as allergic bronchopulmonary aspergillosis, to semi-invasive or invasive infections such as pulmonary aspergillosis. In rare cases, in the presence of risk factors such as intravenous drug use, immunocompromised patients or prosthetic heart valves, invasive aspergillosis can present as infective endocarditis as well, the most common species involved being Aspergillus fumigatus.

Case report

A 49-year-old otherwise healthy male sustained a motor vehicle accident causing splenic laceration, traumatic brain injury, multiple rib fractures and pelvic fracture, and required a series of 14 intraabdominal, transthoracic and intracranial surgeries within a span of two months. Computed tomography (CT) chest noted an isolated 6 mm right lower lobe pulmonary nodule. He never smoked cigarettes but smoked marijuana. He eventually needed splenectomy, tracheostomy and gastrostomy tube placement, and long term rehabilitation. During this hospitalization, he did not receive any prolonged antibiotic treatment and only received one week of antibiotic therapy. He initially received vancomycin and piperacillin-tazobactam that was later switched to cefepime for suspected ventilator acquired pneumonia with endotracheal aspirate culture growing Acinetobacter baumannii. He was not discharged on any antibiotic regimen. Six months post-hospital discharge, he was sent to the emergency department of a local hospital for sudden altered mentation and inability to follow commands. He was noted to have right facial droop and right arm weakness. Significant lab results showed elevated white blood cell count of 18,800/mm³ with 86.5 % neutrophils with remainder blood work being unremarkable. Electrocardiography showed sinus tachycardia but no other conduction abnormalities or ischemic changes. Magnetic resonance imaging (MRI) brain demonstrated subacute left middle cerebral artery distribution ischemic stroke in the insular cortex and portion of the frontoparietal cortex. Transthoracic echocardiogram demonstrated 1.2 cm × 1.3 cm vegetation in the anterior leaflet of native mitral valve but with normal left ventricular function and no regional wall motion abnormality consistent with endocarditis. Three sets of blood cultures were negative. He was transferred to our facility for cardiac surgery evaluation. Cardiac surgery did not recommend any immediate surgical intervention. He was discharged with a left upper extremity PICC line to complete a total of six weeks of intravenous vancomycin, ciprofloxacin and ampicillin/sulbactam treating for culture-negative mitral valve endocarditis. Repeat echocardiogram was recommended prior to finishing the course of antibiotics. At the time of hospital discharge, he was noted to

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be alert, awake, could speak in full sentences and moderate resolution of right-sided hemiparesis.

Three days following hospital discharge, he presented again to the local ED with altered sensorium and leukocytosis at 28,000/mm³, with otherwise unremarkable blood work. He was transferred back to our facility where repeat MRI brain showed increased restricted diffusion in the periphery of prior stroke distribution, presumably an evolution of prior stroke, but no new lesions. He was continued on vancomycin, gentamicin and ceftriaxone. Repeat transthoracic and transesophageal echocardiogram demonstrated enlarged mitral valve vegetation of the size 2.1 cm × 2.2 cm. Repeat blood cultures were drawn as well as Bartonella and Coxiella antibodies were sent that later returned negative. The patient underwent mitral valve replacement with placement of bioprosthetic valve the following day. Intra-operative findings were described as “extensive replacement of entire mitral valve with what appeared to be fungus with vegetation extending into both papillary muscles requiring extensive debridement” (Fig. 1). Postoperatively, he was started on liposomal amphotericin B dosed at 5 mg/kg/day. Histopathology of the valve specimen showed acute-angle branching septate hyphae, suspected to be a mold (Fig. 2). Tissue fungal culture grew Aspergillus fumigatus (Fig. 3). Post-operatively, he developed shocked liver with aspartate transaminase 3555 U/L and alanine transaminase 2141 U/L. He developed postoperative fevers and persistently elevated white blood cell count. His respiratory status worsened with development of left-sided empyema, which was drained with pleural fluid culture eventually growing Aspergillus fumigatus. Repeat MRI brain showed development of right parietal leptomeningeal enhancement compatible with meningitis and new extensive bilateral cerebral ring enhancing lesions consistent with small abscesses, likely embolic in nature. Further evaluation for extent of aspergillosis was done and several non-healing fractures in the pelvic area were noted. One of them had the largest lucency in right iliac bone which was aspirated under CT-guidance but returned negative for the fungal infection. Patient’s family eventually decided to pursue hospice care and shortly thereafter, the patient expired.

Discussion

Aspergillus is a saprophytic sporulating mold, with most species reproducing asexually but a sexual form has been identified for some pathogenic species, including Aspergillus fumigatus. A distinguishing characteristic of Aspergillus fumigatus is its ability to grow at 500°C. Each conidial head produces several conidia which upon disturbance by environment or strong air releases them into air, and their small size keeps them suspended in air and virtually all humans inhale it at some point in their lifetime [1].

Aspergillus fumigatus is the most frequent species associated with invasive infections. Patients with prolonged and profound immunosuppression are at high risk for invasive aspergillosis. Factors associated with poor host pulmonary defense mechanisms predispose to enlargement and germination of inhaled conidia resulting in maturation into hyphal with subsequent vascular invasion and eventual dissemination. Despite its nature of vascular invasion and that Aspergillus fumigatus can grow in BACTEC culture vials. For unclear reasons, blood culture of patients with invasive aspergillosis is frequently negative [2].

More commonly, the invasive aspergillosis involves the lungs and rarely causes endocarditis. Most cases of Aspergillus endocarditis have been reported to affect prosthetic valves. There is paucity of literature about infections affecting native valves. Reported risk factors for Aspergillus endocarditis include intravenous drug use, immunosuppression, prior cardiac surgery or prosthetic heart valves, hematopoietic stem cell or solid organ transplantation. Kalokhe et al. published a review of 53 cases of Aspergillus endocarditis reported between 1950 and 2010, of which 50 cases were left-sided endocarditis and in 11 cases, diagnosis was established post-mortem [3]. In 2016, another series of 14 case reports of Aspergillus fumigatus endocarditis was published where except for one case with positive blood culture, all had negative blood cultures [4]. All published reports had variable outcomes regardless of surgical intervention.

Aspergillus endocarditis is difficult to diagnose particularly in patients who do not have traditional risk factors for this infection such as our case. In the case presented above, after going through several surgeries including splenectomy and acute illness after the accident, the patient was in a relative immunocompromised state. Perhaps, Aspergillus fumigatus invasive infection occurred. Source could also have been an undiagnosed pelvic infection given open fracture contaminated from the environment. A biopsy of one of the non-healing fractures of right ilium was performed that was negative for fungal growth but sensitivity of this is low. Another possibility is respiratory colonization with Aspergillus fumigatus or subclinical infection given the presence of pulmonary nodules. Development of empyema with positive pleural fluid culture may support this but fungal pulmonary septic emboli cannot be ruled

Fig. 1. Excised fungating lesion of the mitral valve.

Fig. 2. Acute-angle branching septate hyphae as seen under 100× magnifications on Gomori methenamine silver (GMS) staining.

Fig. 3. Fungal culture growth in microbiology laboratory.
out either although that would require lesions on tricuspid/pulmonary valve which was not noted in his case. In any case, the suspicion for Aspergillus endocarditis was low and diagnosis was established intraoperatively. It is unclear if his asplenia contributed to his risk of invasive aspergillosis. Mehrtra et al. presented a case report of chronic pulmonary aspergillosis in a splenectomized patient but no definitive evidence of increased risk of Aspergillosis in patients undergoing splenectomy [5] and no conclusive evidence on our review of literature too. At least 2 case reports of Aspergillus endocarditis did not have definite risk factors for this infection [6,7]. Variable presentations of Aspergillus endocarditis have also been reported [8,9].

Molecular diagnosis of Aspergillus infection utilizes serum galactomannan assay that has been shown to be an accurate marker for diagnosis of invasive aspergillosis in certain patient subpopulation, and was noted to be having 78.4 % sensitivity, 87.5 % specificity, 27% positive predictive value and 98.6% negative predictive value [10]. Some case reports have utilized this combined with Aspergillus PCR testing with not much significant additional benefit [11]. Other fungal markers of infection such as beta-D glucan although sensitive, they are not specific for Aspergillus [11].

A review of 270 cases of fungal endocarditis between 1965–1995, showed recurrence rate of 30% of cases despite improved diagnostic technology and treatment options [12]. Surgical intervention remains the corner stone of treatment of fungal endocarditis including Aspergillus endocarditis. Fungal endocarditis has been a “standalone indication” for surgical intervention due to bulky nature of vegetations and subsequent increased risk of relapse and emboli [2]. In 2012 UK guidelines, Aspergillus endocarditis has a separate category where “surgical valve replacement is mandatory for survival”. Most case reports on Aspergillus endocarditis have documented the use of amphotericin B but the liposomal formulation of amphotericin B has less nephrotoxic potential and more propensity to work on biofilms, which can be somewhat beneficial particularly in cases where surgery is not feasible. With the landmark trial published in 2002, voriconazole emerged as a primary choice of fungicidal drug against Aspergillus endocarditis [13]. Current IDSA guidelines recommend voriconazole or lipid formulation Amphotericin B as the initial therapy for Aspergillus endocarditis and consideration for lifelong antifungal therapy after surgical replacement [14]. Even with surgery, the long term survival is limited. Mortality rates have approached 96% in patients with Aspergillus endocarditis treated only with medical therapy.

**Declaration of Competing Interest**

There were no conflicts of interest in preparation of this case report.

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**CRediT authorship contribution statement**

Aggarwal Abhimanyu: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. Hogan Karen: Data curation, Formal analysis, Writing - review & editing. Paez Armando: Data curation, Formal analysis, Writing - review & editing, Supervision.