CASE REPORT

Aspergillus fumigatus Infective Endocarditis in a Native Valve with Bilateral Endogenous Endophthalmitis: A Case Report

Asalaysa Bushyakanist, M.D.[1], Somnuek Sungkanuparph, M.D.[2]

[1]Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

[2]Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand.

ABSTRACT

Fungal endocarditis is rare and has poor prognosis. *Aspergillus* species are the second most frequent pathogens of invasive fungal infection. We report a case of 69-year-old man with a history of complete treatment of pulmonary tuberculosis who presented with left-side blurred vision for 3 days. Shortly thereafter, he subsequently developed blurred vision of the right eye and a high fever. Physical examination revealed evidence of a newly documented heart murmur. Transthoracic echocardiogram revealed a large hypermobile isoechoic mass attached to aortic valve leaflet, 1.5 × 1.7 cm in size, severe aortic regurgitation, and moderate mitral valve regurgitation. He had no known risk factors for fungal endocarditis. He underwent phacoemulsification with pars plana vitrectomy bilaterally and Bentall operation with mitral valve replacement. Gram and Gomerimethenamine silver stains of the aortic valvular tissues showed few septate hyphae. The aortic valve tissue for cultures and molecular identification, based on the 18s ribosomal RNA gene, were positive for *Aspergillus fumigatus*. Tissue histopathology was consistent with Aspergillus endocarditis. Intravenous amphotericin B was then administered. However, he developed multi-organ failure and died 6 days after the surgery. Despite the lack of well described risk factors, fungal endocarditis should still be considered in the patients with large sized vegetations, and negative blood cultures. Early recognition and prompt medical and surgical treatment remains crucial. (*J Infect Dis Antimicrob Agents 2018;35:33-40.*)

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INTRODUCTION

Fungal endocarditis is rare and has poor prognosis. The prevalence of fungal endocarditis is between 1% and 10% of all infective endocarditis.[1,2] Among these, *Aspergillus* species have been reported as the second most frequent

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Corresponding author: Asalaysa Bushyakanist, M.D., Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand.

E-mail: asalaysa@gmail.com

pathogens accounting for approximately 20% to 25%.[2,3] *Aspergillus* species are saprotrophic fungi that are found in soil, water, food, air and grow on decaying vegetation. *Aspergillus* species causes a broad spectrum of diseases in all human body sites, ranging from noninvasive to invasive diseases. Aspergillus endocarditis is one of serious forms of invasive disease and can occur mostly in prosthetic heart valves.[3] Known risk factors for fungal endocarditis include intravenous drug abuse, prosthetic heart valve, prior history of endocarditis, prolonged antibiotic therapy, prolonged indwelling central venous catheter, neutropenia, parenteral nutrition, and diabetes mellitus.[2] We herein report a case of Aspergillus endocarditis in an adult with no known risk factors of fungal endocarditis.

CASE REPORT

A 69-year-old male, and previous wicker maker presented with left-side blurred vision for 3 days. He reported to be a heavy smoker and drinker but had been sober for 20 years. He had no history of intravenous drug use and had not been treated with corticosteroids or other immunosuppressive agents for any medical conditions prior to this admission. He denied any significant medical condition except that at 7 months prior, he was diagnosed with smear-negative pulmonary tuberculosis when he visited an outside hospital with symptoms of chronic cough and prolonged fever. A six-month-course regimen was completed a month prior to this illness. Initially, the patient had a low-grade fever and myalgias which limited his daily living activities for 4 days. Three days prior to admission, he developed painful blurred vision in the left eye and witnessed redness of the affected area. He visited hospital A and was treated with an unknown topical agent but no improvement at day 3 of treatment. Due to ongoing symptoms, he was sent to hospital B for further care. At hospital B, he was noted to have a temperature of 39°C and his visual acuity was 20/70, with pinhole 20/30-1 in right eye, and hand movement in left eye. A diagnosis of acute panuveitis of the left eye was made and he was hospitalized for further investigation and treatment. Prednisolone eye drops, neomycin/polymyxin/dexamethasone eye drops, and 1% atropine eye drops were given. One day after admission, fever remained and he developed dyspnea at rest with sputum production. Ceftriaxone was begun for presumptive diagnosis of bacterial pneumonia and switched to cefoperazone/sulbactam and clarithromycin the following day. Despite treatment, his condition continued to deteriorate in terms of respiration and new development of painless blurred vision in right eye and redness 3 days later. Just prior to his last transfer to our hospital, high-grade fever still remained and he was able to count fingers only with the right eye and visual acuity testing demonstrated 5/200 in the left eye.

Upon arrival, physical examination showed blood pressure of 140/60 mmHg, pulses of 120/min, temperature of 38.8°C, and respiration rate of 22/min. He was alert, awake, and able to follow verbal commands. He was able to perform finger counting only at half a foot with the right eye and at 3 feet with the left eye on visual acuity testing. Fundoscopic examination displayed signs of inflammation consistent with vitritis in both eyes and yellowish-whitish material infiltration noticed in the retina of the left eye. Grade 1/6 diastolic rumbling murmurs were identified at left upper parasternal border area. No evidence of peripheral

stigmata of endocarditis was found on physical examination, namely Osler nodes, Janeway lesions, purpura, and conjunctival hemorrhages. Apart from these findings, fine crackles were heard over the left lung zone.

Initial laboratory investigations were conducted which included complete blood count that showed white blood cell count of 14,000 cells/mm^3, hemoglobin of 11 g/dL, platelet count of 130,000 cells/mm^3, random plasma glucose of 103 mg/dL, HbA1C of 5.76%, and negative anti-HIV antibody. Three sets of aerobic blood cultures were drawn which no bacterial growth identified at all until day 5 of admission. A transthoracic echocardiogram demonstrated a large hypermobile isoechoic mass attached to aortic valve leaflet, 1.5×1.7 cm in size, severe aortic regurgitation, and moderate mitral valve regurgitation (Figure 1). He was still receiving intravenous ceftazidime and vancomycin while all aforementioned tests were being obtained and he underwent surgery for his eyes on the first day of admission. Antibiotics were changed to intravenous ampicillin, cloxacillin and gentamicin after echocardiogram.

He underwent phacoemulsification with 23 gauge parsplanavitrectomy of both eyes and Bentall operation with mitral valve replacement. Intraoperative findings revealed findings consistent with endophthalmitis of both eyes and active infective endocarditis at aortic valve with huge vegetation, 1.5 cm in size, adhered to the left cusp region resulting in severe aortic regurgitation, peri-annular abscess and large penetrating hole at the left-right commissure, markedly inflamed surrounding tissue, and moderate-severe mitral regurgitation secondary to ruptured A3 chordae. Vitreous fluid from both eyes was sent for microbiological testings with all negative results (Gram and Gomerimethenamine stains (GMS), aerobic, mycobacterial, and fungal cultures). Gram stain and GMS of aortic valve demonstrated

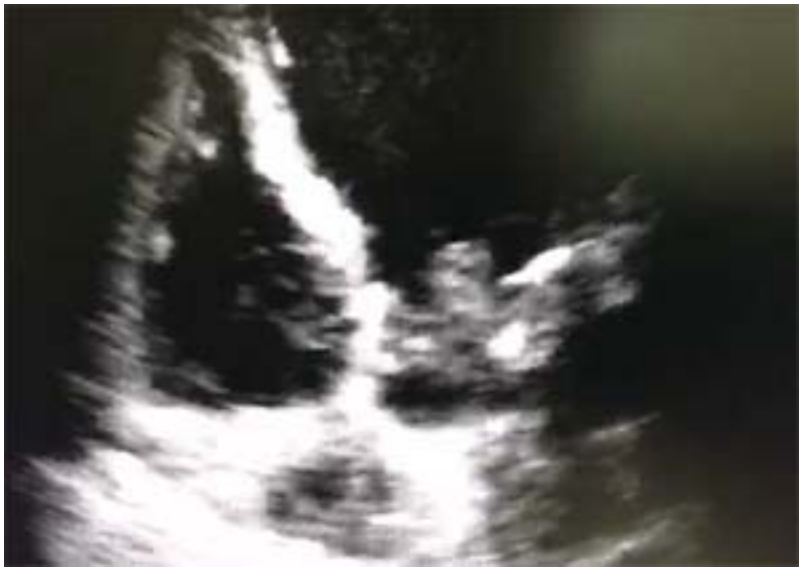

Figure 1. Transthoracic echocardiogram: aortic valve: 1.5×1.7 cm hypermobile isoechoic mass attached to aortic valve leaflet.

few septate hyphae (Figure 2).

In addition to systemic antibiotics, intravenous amphotericin B deoxycholate at a dose of 1 mg/kg/day was promptly administered after fungal identification on obtained specimens. Serum galactomannan antigen assay by ELISA was drawn at day 3 of antifungal therapy and yielded negative results (index = 0.36, positive reference cut-off: index ≥ 0.5). Three days later, aortic valve tissue aerobic and fungal cultures grew fungal colonies which later were identified as *Aspergillus fumigatus*. Similar to stated microbiological tests, molecular identification based on 18s ribosomal RNA gene, was positive for the same organism. Tissue histopathology confirmed the diagnosis of fungal endocarditis and were determined as fungal elements compatible with *Aspergillus* spp., as shown in Figure 3.

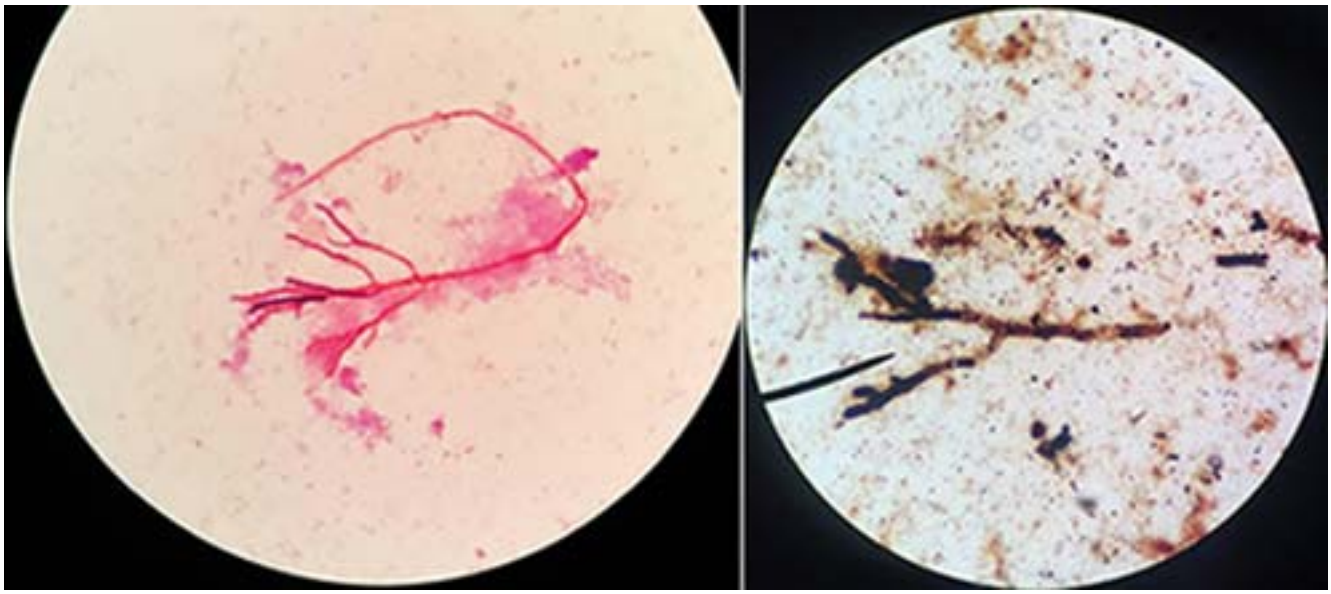

Figure 2. Aortic tissue Gram stain & Gomorimethenamine silver stain: few septate hyphae.

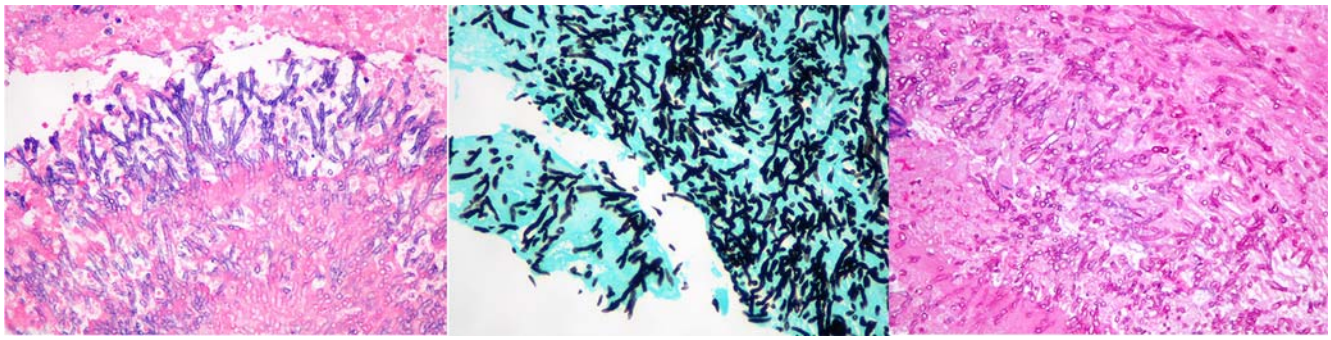

Figure 3. Aortic valve tissue histopathology (from left to right): Hematoxylin and eosin stain, Gomorimethenamine silver stain and Periodic acid - Schiff stain: consistent with fungal endocarditis.

After the surgeries, he developed multi-organ failure described as respiratory failure, acute kidney injury, and severe electrolyte disturbances. Renal replacement therapy was not provided as per family's desire. Vasopressive agents were needed for hemodynamic stabilization and he died on day 6 after the procedures.

DISCUSSION

Aspergillus species have the ability to cause severe invasive infections in almost every major organ system. Aspergillus endocarditis is an uncommon fungal infection in immunocompetent patients, but a life threatening condition once it occurs. The proportion of fungal endocarditis caused by Aspergillus was 24% to 28% between 1965 and 1995.[1,5] In a recent review of fungal endocarditis between 1995 and 2000, this proportion was 18%.[1] The most common species implicated in fungal infective endocarditis is *A. fulmigatus* (54%), followed by *A. terreus* (18%), *A. niger* (7%), and *A. flavus* (7%).[1,4-5] The frequency of invasive aspergillosis in developing countries is expected to be high, even though the disease is under-reported.[6] A few series reported *A. flavus* to be the exclusive agent or several times more common than *A. fumigatus*.[7,8] Prolonged environmental contamination of *A. flavus* may lead to increased frequency of *A. flavus* infections.[6-8] The pathogen of the first reported case of native valve endocarditis in Thailand was *A. flavus*.[9] However, the most common species of invasive aspergillosis in Thailand (67% to 69% of cases) is *A. fumigatus*.[10,11] Known risk factors for fungal endocarditis include intravenous drug abuse, prosthetic heart valve, previous history of endocarditis, prolonged antibiotic therapy, prolonged indwelling central venous catheter, neutropenia, parenteral nutrition, and diabetes mellitus.[2] Apart from these classic risk factors, a previous review by Chakrabarti and colleagues found that other factors such as critically ill patients admitted in intensive care units, patients with pre-existing lung diseases (emphysema, chronic obstructive pulmonary disease, healed tuberculosis cavity), and patients with liver failure are also determined to be associated with invasive aspergillosis in developing countries.[6] Our patient did not share such risk factors but he only had a history of complete treatment of smear-negative pulmonary tuberculosis for a month before this admission and he was a heavy drinker, although he had been sober for 20 years. He might have been exposed to Aspergillus conidia in his previous work place and prolonged colonization of the organism in conjunction with unrecognized chronic lung condition, might have posed a risk of fungal endocarditis development in this patient even though there was no solid evidence in history and chest radiographs.

Clinical manifestations of Aspergillus endocarditis are non-specific including fever, new or changing pattern of pre-existing heart murmur, emboli, focal or general neurological symptoms or signs and cardiac failure. Some of the cases had respiratory symptoms such as dyspnea or hemoptysis.[2-4,12] Previous review by Yuan, et al found that all patients had fever early in their clinical presentations.[3] Embolic phenomenon can involve any part of the body. Diagnosis is difficult because up to one-third of the patients may not have any of classic signs of endocarditis and the blood cultures are also negative in over 50% of patients with Aspergillus endocarditis.[2-4,13] The time from the first symptom to hospital admission ranged from one day to one year.[5] In most cases, Aspergillus

endocarditis is diagnosed by tissue culture, galactomannan antigen assay, or post-mortem examination. Serum galactomannan has been validated for the diagnosis of invasive aspergillosis in neutropenic patients but not for diagnosis of Aspergillus endocarditis, despite positive results in 44% of Aspergillus endocarditis.[4,12-15] According to the collected data from 1995 to 2000, Pierotti and colleagues observed that the pathogens were mostly identified by blood culture (46.5%), specimens from intracardiac sites (25.2%), or both (28.3%).[1]

The most common site for fungal vegetation is at aortic valve. All of the fungal vegetations are described as large size.[12] In a previous review, vegetations were demonstrated in 83 of 102 patients (81.4%), described as large in 42 patients (50.6%) and mobile in 16 patients (19.3%). Transthoracic echocardiography (TTE) identified 88.9% of vegetations in patients with native valve endocarditis (NVE) and transesophageal echocardiography (TEE) identified 92.0% of vegetations in patients with NVE. Large vegetation was common in cases of NVE.[1] According to the review, the large vegetation seemed to increase the sensitivity of TTE and prompted a consideration of fungal infection in the setting of culture-negative endocarditis.[5]

We concluded that our patient had fungal endocarditis because the diagnosis of bilateral endogenous endophthalmitis was suspected and he had presumably new cardiac murmurs. TTE demonstrated large hypermobile vegetations. Therefore, in a patient with large vegetation, with suspected embolic events and negative blood cultures, clinical diagnosis of fungal endocarditis was concluded.

Fungal endocarditis necessitates an aggressive treatment strategy given high mortality. This may be in part because of the immunocompromised status of the hosts, delay in diagnosis, and rapidity of embolization.[4] Surgical replacement of an infected valve is mandatory in almost all patients with fungal endocarditis and a fungicidal agent should be initiated as soon as possible.[2] Clinical response following antifungal therapy may vary depending on several factors, including the immune status of the host and the extent of infection at the time of diagnosis.[16] Voriconazole is both the first-line for induction and long-term suppression therapy for treatment of Aspergillus endocarditis. Amphotericin B is the second-line but may be used as a first-line agent if there is intolerance to azoles.[2-3,17-18] Several guidelines have consistently recommended surgery as first-line treatment in patients with fungal endocarditis.[3,17-20] A combination of medical therapy and valve replacement are essential in attempting to improve clinical outcomes, as neither alone has a significant influence on patients consequences.[21-22] The optimal duration of antifungal therapy is difficult to determine. However, most authors recommend lifelong suppressive therapy.[2,4]

In conclusion, Aspergillus endocarditis is an uncommon fungal infection in immunocompetent patients and has high morbidity and mortality. Fungal endocarditis should be considered in the patients with large vegetations, suspected emboli, and negative aerobic blood cultures even without classical risk factors. Early diagnosis and combination treatment with valve replacement and antifungal therapy may improve the unsatisfactory prognosis of the patients.

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