

LETHAL *ASPERGILLUS* ENDOCARDITIS AFTER HEART TRANSPLANTATION

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We report a case of a 21-year-old male who died from lethal *Aspergillus* endocarditis 3 months after heart transplantation. He underwent heart transplantation in other country. He was treated with hemodialysis for acute renal failure due to cyclosporine and then transferred to our hospital. When he complained high fever, follow-up echocardiography showed a large mobile echogenic mass attached to posterior mitral valve leaflet. The result of serum *Aspergillus galactomannan* antigen assay was positive. He was empirically treated with intravenous amphotericin B and antibiotics. However, he was rapidly deteriorated and died on hospital day 3.

KEY WORDS : Endocarditis · Heart transplantation.

INTRODUCTION

Infection remains as the leading cause of morbidity and mortality after organ transplantation.¹⁾ Among them, fungal infections carry the risk of higher mortality. *Candida* and *Aspergillus* species are the most common fungi that cause diseases in transplant recipients.²⁾ Especially, *Aspergillus* most frequently causes pneumonia and is the opportunistic pathogen in heart transplant recipients.³⁾ Although invasive aspergillosis (IA) is a serious disease in heart transplant recipients, little is known regarding this infection due to limited experience. Here, we report a lethal case of *Aspergillus* endocarditis in a 21-year-old male who rapidly deteriorated and died despite prompt intravenous amphotericin B and antibiotics.

CASE

A 21-year-old male suffering from severe dilated cardiomyopathy after doxorubicin-based chemotherapy due to lymphoma underwent heart transplantation in an university hospital of other country on September 20th, 2006. He was diagnosed with complete remission of lymphoma after eight cycles of CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) in 2000. The deceased donor was a 55-yr-old man without known cardiac disease. According to the medical records, his initial immunosuppressive regimen

consisted of cyclosporine, mycophenolate mofetil, and prednisolone. On day 37, he had a seizure attack, followed by renal impairment due to cyclosporine. He underwent hemodialysis 3 times a week for 3 weeks. And then, cyclosporine was changed to FK506. When he was transferred to our hospital, maintenance immunosuppression consisted of 2 mg of FK506 (target blood trough level 10-20 ng/ml), 2.0 gm of mycophenolate mofetil, and 10 mg of prednisolone. On admission, he complained of general weakness. All laboratory findings were in normal range except for elevated BUN/Cr level (83.3/2.2 mg/dL). After hydration with intravenous fluids and reduction of FK506 dosage (1.5 mg/day), the level of BUN/Cr was normalized. Echocardiography showed unremarkable with normal left ventricular systolic and diastolic function. There was no evidence of lymphoma recurrence on abdominal sonography, computed tomography, and laboratory data, which was confirmed by a hematologist. He was discharged 2 weeks later with clinical improvement. However, he was re-admitted 4 days later with fever, vomiting, and tachypnea. The leukocyte count was $19.5 \times 10^3/\mu\text{L}$ with 83.9% neutrophils, and a mild thrombocytopenia of $110 \times 10^3/\mu\text{L}$. On physical examination, body temperature was 38.6 °C and respiratory rate was 40 rate per min. Clear breathing sounds were noted and he had high blood pressure

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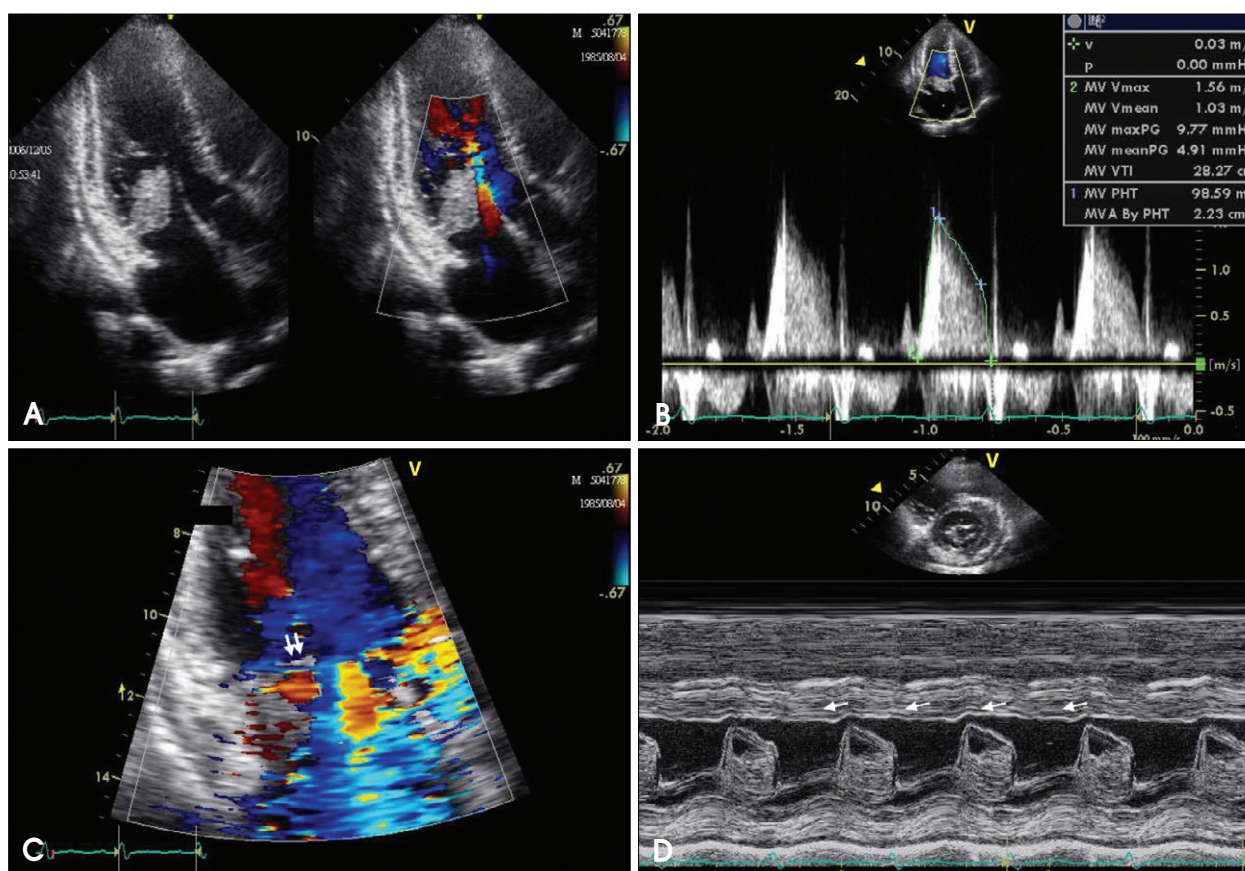


Fig. 1. A: Two dimensional echocardiography showing large (3 x 2 cm sized) mobile homogenous echogenic mass attached at posterior mitral leaflet (left). Color Doppler echocardiography revealed large echogenic mass obstructing mitral valve flow during diastole (right). B: Continuous wave Doppler echocardiography showed increased mitral inflow velocity (peak velocity=1.56 m/sec and peak pressure gradient=9.77 mmHg), suggesting of mitral inflow obstruction. C: Color Doppler echocardiography revealed mitral regurgitation (arrows) due to perforation of posterior mitral leaflet during systole. D: M-mode echocardiography showed the mitral orifice is filled with increased echodensity (arrows) representing protruding mass.

(150/100 mmHg). Mid-diastolic heart murmurs (Grade III/VI) and pansystolic murmurs (Grade IV/VI) at the apex were audible. There was no ankle edema. Chest radiography showed mild cardiomegaly and no evidence of pulmonary edema or pneumonia in both lung fields. Follow-up two dimensional echocardiography showed a large (3 × 2 cm sized) mobile homogenous echogenic mass attached to the posterior mitral valve leaflet with normal left ventricular function. Color Doppler echocardiography revealed a large echogenic mass obstructing mitral valve flow during diastole as well as mitral regurgitation due to perforation of posterior mitral leaflet during systole (Fig. 1). Empirical intravenous antibiotic treatment with meropenem, vancomycin and amphotericin B was started after sets of blood culture were drawn. The result of serial blood cultures were negative for aerobic, anaerobic bacteria and fungi. However, the serum *Aspergillus galactomannan* antigen assay showed strong positive (6.17, cut-off optical density index is 1.5). The blood trough level of FK506 was 11.2 ng/ml. The patient died of

septic shock with hepatic and renal failure on hospital day 3. We could not perform autopsy for pathologic confirmation, because the patient's family declined.

DISCUSSION

Invasive aspergillosis (IA) is the most common invasive fungal infection in heart transplant recipients, affecting 1-14%.²⁾ *Aspergillus* species can result in a variety of clinical syndromes, including sinusitis, pneumonia, brain abscess, endomyocarditis, and disseminated disease in heart transplant recipient.³⁾ Pulmonary aspergillosis is associated with a mean mortality rate of approximately 50% in heart transplantation.^{2,3)} The mortality rate is highest with cerebral aspergillosis (mean 99%), irrespective of the underlying condition. Overall mortality rate of IA in this population ranges from 53% to 78%.^{2,3)} Early clinical recognition of this complication is difficult and laboratory data are not specific or sensitive enough. Accordingly, antifungal therapy is frequently initiated too late and some cases are only diagnosed after death. Thus,

aggressive diagnostic and therapeutic approaches are required when suggestive lesions are found in high-risk heart transplant patients such as concomitant CMV disease, re-operation, and post-transplant hemodialysis.⁸⁾ Although IA is a serious disease in heart transplantation, little is known regarding natural history of this infection due to limited experience. Several case reports and clinical experiences of invasive pulmonary aspergillosis were reported.⁴⁾ Few reports regarding *Aspergillus* endocarditis were reported in heart transplant recipients.^{5,6)}

In this patient, intravenous amphotericin B was empirically administered within 24 hrs when a large echogenic mass attached at posterior mitral valve leaflet was found. However, intravenous amphotericin B may not be sufficient to treat established fungal foci. Galactomannan, which is released during growth of hyphae, is a major constituent of *Aspergillus* cell walls.⁷⁾ The serum galactomannan assay by sandwich enzyme linked immunosorbent assay permits detection of antigenemia in some patients an average of five to eight days before the presence of clinical signs, an abnormal chest X-ray, or positive cultures. The galactomannan assay showed sensitivity ranges from 61 to 71 percent with a specificity of 89 to 93 percent for IA.⁷⁾ Although we did not perform pathologic diagnosis for aspergillosis, our results strongly suggested endomyocardial seeding of *Aspergillus* species.

Surgical removal including valve replacement is the treatment of choice for *Aspergillus* endocarditis but would not have been possible in our patient due to poor clinical conditions. Recent study reported that post-heart transplant hemodialysis, cytomegalo virus (CMV) disease, re-operation and other episodes of aspergillosis in the ward close to the transplantation date were major risk factors for IA in this population.⁸⁾ Other risk factors that have been reported include prolonged neutropenia, neutrophil function deficits, corticosteroid therapy, and graft-versus-host disease.⁹⁾ Singh et al. reported that patients requiring hemodialysis had a 14% incidence of IA, and this risk was completely abolished when prophylaxis, with a lipid preparation of amphotericin B, was administered during the time renal replacement therapy was required. However, no impact on the mortality rate was achieved.¹⁰⁾ In this patient, antifungal prophylaxis during hemodialysis was not done in other country. Sherman-Weber S et al. reported that *S. aureus* was the most common pathogen

causing infective endocarditis (40% of post-heart transplant endocarditis) and followed by *Aspergillus fumigatus* (30% of cases).⁵⁾ Interestingly, *Aspergillus fumigatus* endocarditis following heart transplant had antecedent CMV viremia. This finding suggests that patients with *Aspergillus fumigatus* infection had heightened immunosuppression prior to infective endocarditis.¹⁾ The frequent association of CMV infection with IA has been interpreted as CMV being a risk factor for invasive fungal disease. Unfortunately, pre-transplant antibody IgM or IgG for CMV was not examined and ganciclovir prophylaxis was not given because of impaired renal function in other country.

In conclusion, this case represents a lethal outcome of fungal infectious disease following heart transplantation. Although a prompt approach and aggressive treatment is paramount for management of IA, our case shows that *Aspergillus* endocarditis has a higher mortality when surgery would not have been possible in poor clinical condition.

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