Overcoming Double Jeopardy: Successful Orthotopic Heart Transplant in a Recipient with Bacterial and Fungal Infections

Paopat Munthananuchat[1], Bundit Naratreekoon[1], Narongrit Kantathut[1], Piya Samankatiwat[1], Akeatit Trirattanapikul[1], and Teerapat Yingchoncharoen[1]

[1]Mahidol University Faculty of Medicine Ramathibodi Hospital

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Introduction

Heart transplantation is considered an important treatment option for advance heart failure patient who do not respond to medical therapy. However, before surgery, contraindications for heart transplantation should be evaluated. These contraindications may include fixed pulmonary hypertension, active cancer, HIV infection, or active infections with unstable conditions.(1)

Infection is a significant concern for patients undergoing heart transplantation include pre- and post-operative period, as it may lead to the risk of severe infections in these patients. In fact, infections are the second leading cause of death after graft rejection within the first 30 days following heart transplantation and the leading cause of death beyond 30 days post transplantation.(2)

Bacterial infections are significant concern for patients undergoing heart transplantation. According to a study, the incidence of bacterial infections in these patients can be as high as 43.6%. Common causes of infection include pneumonia, bloodstream infections due to the placement of central venous catheters, and infections associated with the use of ventricular assist devices. In the past, the mortality rate from invasive pulmonary aspergillosis in heart transplant patients was as high as 66.7%. However, advancements in medical treatments, including antifungal medications, adjustment of immunosuppressive therapy, and improved surgical techniques, have improve survival in these patients.(3,4)

As a result, current medical guidelines recommend treating fungal infections until symptoms, radiological findings, and laboratory tests show improvement before proceeding with heart transplantation. However, there are no specific recommendations for the optimal duration of treatment before emergency heart transplantation or in cases where the patient's condition requires urgent surgery.(5)

History of presentation

A previously healthy 16-year-old man presented with gradually worsening dyspnea on exertion for over 5 months. As the dyspnea progressed, he had a low-grade fever for 2 days and was initially diagnosed with congestive heart failure and acute respiratory failure at general hospital. Despite having treated with mechanical ventilator support for 4 days, patient's condition did not improve, leading to a development of cardiogenic shock. In consequence, he was immediately transferred to our hospital for further management.

On admission, the patient had 36.0°C of body temperature with a heart rate of 130 beats per minute, an oxygen saturation level of 92%, and a blood pressure was 85/50 mmHg. Physical examination showed engorge neck vein, fine crepitation on both lower lung zones, normal heart sounds without murmur, and cold extremities with delayed capillary refill. Initial transthoracic echocardiogram revealed left ventricular dilatation with ejection fraction of 10%. Acute myocarditis was suspected and underwent the insertion of venoarterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pump (IABP) to

stabilize hemodynamics. Furthermore, an atrial septostomy procedure was performed to alleviate the pressure on the left ventricle. After 4 days of intensive treatment with mechanical circulatory support, A decision of bridge to orthotopic heart transplant was made.

Transthoracic echocardiogram after VA-ECMO placement revealed severe left ventricular dilation with left ventricular ejection fraction of 19% by biplane method, global wall hypokinesia, right ventricular systolic dysfunction, complete aortic valve closure, mild to moderate secondary mitral regurgitation, and other valves were not significant dysfunction. After adequate decongestion, chest X-ray showed persistent pulmonary infiltration in the right middle lung zone (Figure 1). On the 9^{th} day, the VA-ECMO was switched to biventricular assist device (BiVAD). The patient was then listed for urgent orthotopic heart transplant.

Past Medical History

The patient had no significant medical history.

Differential diagnosis

Differential diagnosis on acute heart failure includes lymphocytic myocarditis, viral myocarditis, and decompensated dilated cardiomyopathy. Regarding the persistent infiltration observed in the right middle lung zone, various conditions can be considered in the differential diagnosis. These include localized pulmonary edema, pulmonary infection such as bacterial pneumonia, pulmonary tuberculosis, or fungal infection.

Investigations

A comprehensive workup of acute myocarditis conducted included viral infection, *Mycoplasma pneumoniae* infection, and toxin screening. All test results were negative. Additionally, an endomyocardial biopsy was performed, and the pathological findings revealed mild interstitial fibrosis and no pathological evidence of acute myocarditis (Figure 2).

Further investigation for persistent infiltration in the right middle lung zone was performed. A chest CT scan could not be performed due to the unstable condition and mechanical circulatory support. As an alternative, a lateral plain chest X-ray was done, which indicated a suspected lesion in the superior segment of the right lower lobe (RLL). The finding of bronchoalveolar lavage (BAL) through fiberoptic bronchoscopy was old blood streak with mild mucosal swelling at distal right bronchus intermedius (Figure 3). Separate BAL samples were collected from the superior segment and posterior segment of the RLL and were sent for aerobe culture, cryptococcal antigen, and*Aspergillus* galactomannan antigen. The aerobe culture of the BAL fluid showed *Trichosporon asahii* and trimethoprim-sulfamethoxazole resistant *Stenotrophomonas maltophilia* . Additionally, the *Aspergillus* galactomannan antigen and cryptococcal antigen test were positive from BAL fluid from the superior segment of the RLL. Upon discussing the result of the BAL fluid cryptococcal antigen, an additional serum cryptococcal antigen test was performed which came back negative. This raised suspicion of a false positive cryptococcal antigen due to cross-reaction with*Trichosporon asahii* .(6) Considering the overall test results, the patient was diagnosed with probable invasive pulmonary aspergillosis (IPA) in conjunction with *Stenotrophomonas maltophilia*ventilator-associated pneumonia (VAP).

Management

During the initial diagnosis of cardiogenic shock, hemodynamic stability was maintained through using mechanical circulatory support. Medical management involved the administration of inotropic drugs. The antibiotics and antiviral prescribed included ceftriaxone, azithromycin, doxycycline, and oseltamivir to cover potential causes of myocarditis. After the VA-ECMO insertion, the dosage of inotropic drugs could be gradually reduced while still maintaining adequate hemodynamics.

On the 10^{th} day after BiVAD insertion, the patient's hemodynamics deteriorated even though BiVAD function remains normal and there were no mechanical complications on echocardiogram found. Higher vasopressor doses were required to maintain mean arterial pressure. Persistent pulmonary infiltration raised suspicion of VAP with septic shock. Empiric antibiotics were administered, including meropenem, vancomycin, levofloxacin, trimethoprim-sulfamethoxazole, and colistin. After the BAL results came back. Antibiotics were changed

to meropenem, tigecycline, levofloxacin, and voriconazole. Fortunately, after implementing intensive management, the patient's hemodynamics improved within 24 hours. This positive response led to an urgent orthotopic heart transplant. However, due to active VAP with septic shock within the past 24 hours as well as the diagnosis of probable IPA, a lower immunosuppressive regimen was chosen for this patient.

After the 20^{th} day, the patient underwent orthotopic heart transplant. The explanted heart's pathological examination revealed dilated cardiomyopathy without a specific etiology, leading to the diagnosis of idiopathic dilated cardiomyopathy (Figure 4).

Following the successful transplant, the overall clinical condition showed improvement, enabling the removal of all mechanical circulatory support and the discontinuation of antibiotics within 7 days. Voriconazole was continued to treat probable IPA, in addition to immunosuppressive drugs such as tacrolimus, mycophenolic acid, and prednisolone.

Discussion

IPA was a significant cause of morbidity and mortality among heart and other solid organ transplant recipients.(3) The active infection raised concerns about the transplant timing.

In this case, the timeline is demonstrated in Figure 5. The decision to proceed with orthotopic heart transplant in the presence of active infection required careful consideration by a multidisciplinary team. During the perioperative and postoperative periods, the team had to weigh the risks and benefits of the transplant simultaneously with an ongoing infection. The decision was well made to minimize the risk of exacerbating the infection or compromising the patient's post-transplant outcome and the potential consequences of delaying the transplant.

Follow-up

The chest's CT scans were performed on the 2^{nd} and 6^{th} week after initiating voriconazole treatment, which revealed a gradual improvement in the consolidation observed in the right lower lobe (Figure 6). To monitor for rejection, serial endomyocardial biopsies were performed and all pathological results did not show any significant concerns.

Conclusion

We demonstrated that controlled infection within a 24-hour period and the presence of probable IPA may not necessarily be a contraindication for orthotopic heart transplant. However, the decision should be carefully weighed on an individual basis and should not be extended to general practice.

Learning Objectives

To recognize the appropriate timing of orthotopic heart transplant in the setting of active infection.

To understand the appropriate preoperative and postoperative management of invasive pulmonary aspergillosis in orthotopic heart transplant patient.

Author contributions

All authors contributed to editing of the manuscript and provided direct patient care.

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Figure Legends

Figure 1: [Comparison of chest X ray finding on the 1st day and 9th day of admission.

(A) and (B) On the 9th day of admission, after adequate decongestion, the follow up chest X-ray revealed persistent pulmonary infiltration right middle lung zone (yellow arrow).]

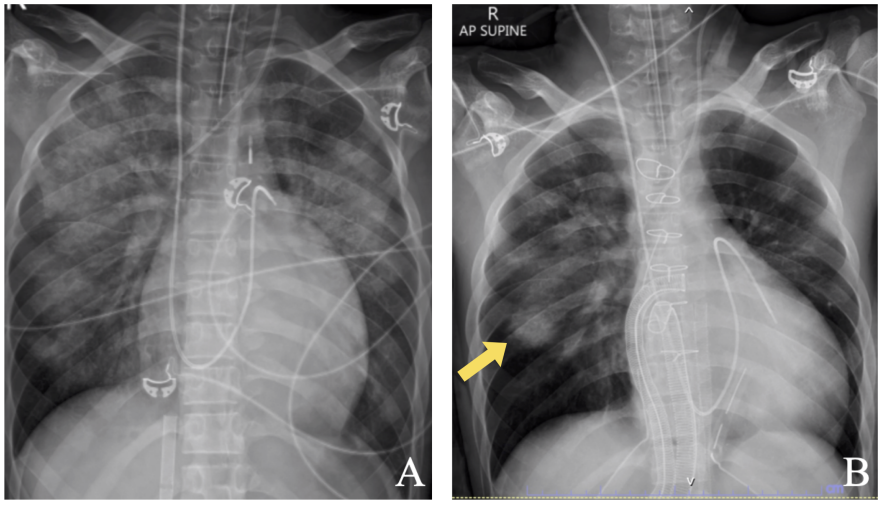

Figure 2: [Pathological findings from endomyocardial biopsy on the 9th day of admission. (A) The black arrows indicate mild interstitial fibrosis. (B) The yellow arrow indicates vacuolar degeneration.]

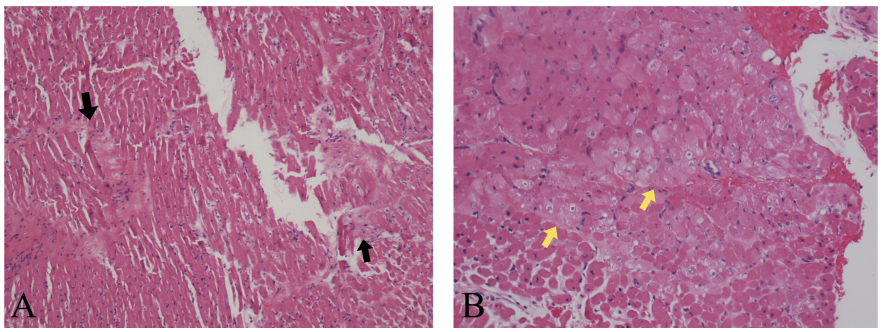

Figure 3: [Plain AP and lateral chest X ray and bronchoscopic finding. (A) and (B) Comparison

of chest X ray views indicating a suspected superior segment of right lower lobe lesion (yellow arrows). (C) Bronchoscopic finding reveal blood streak on bronchus intermedius (red arrow).]

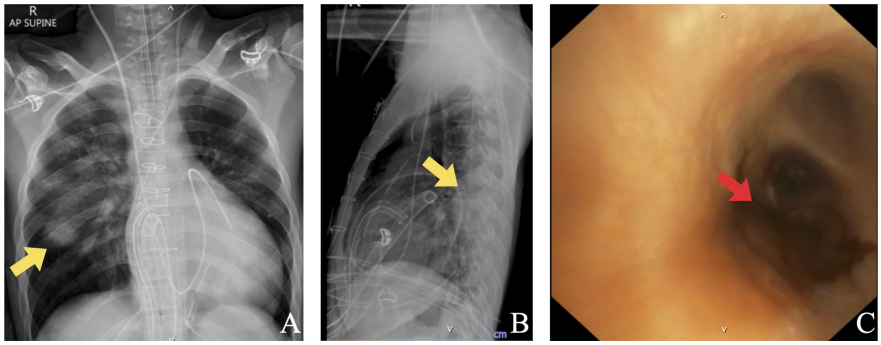

Figure 4: [**Pathology of the explanted heart.** (A) Gross pathology showed biventricular dilatation with no significant ischemia or fibrosis that are consistent with dilated cardiomyopathy. (B) Microscopic finding revealed myocyte hypertrophy (yellow arrows) and vacuolar degeneration (black arrows).]

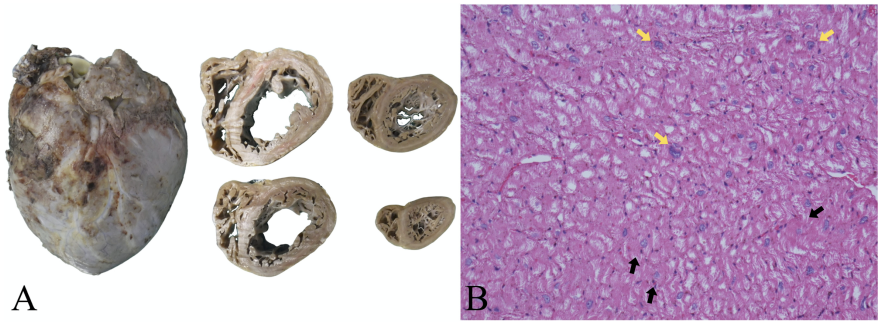

Figure 5: [**Timeline of admission.** Created with BioRender.com.]

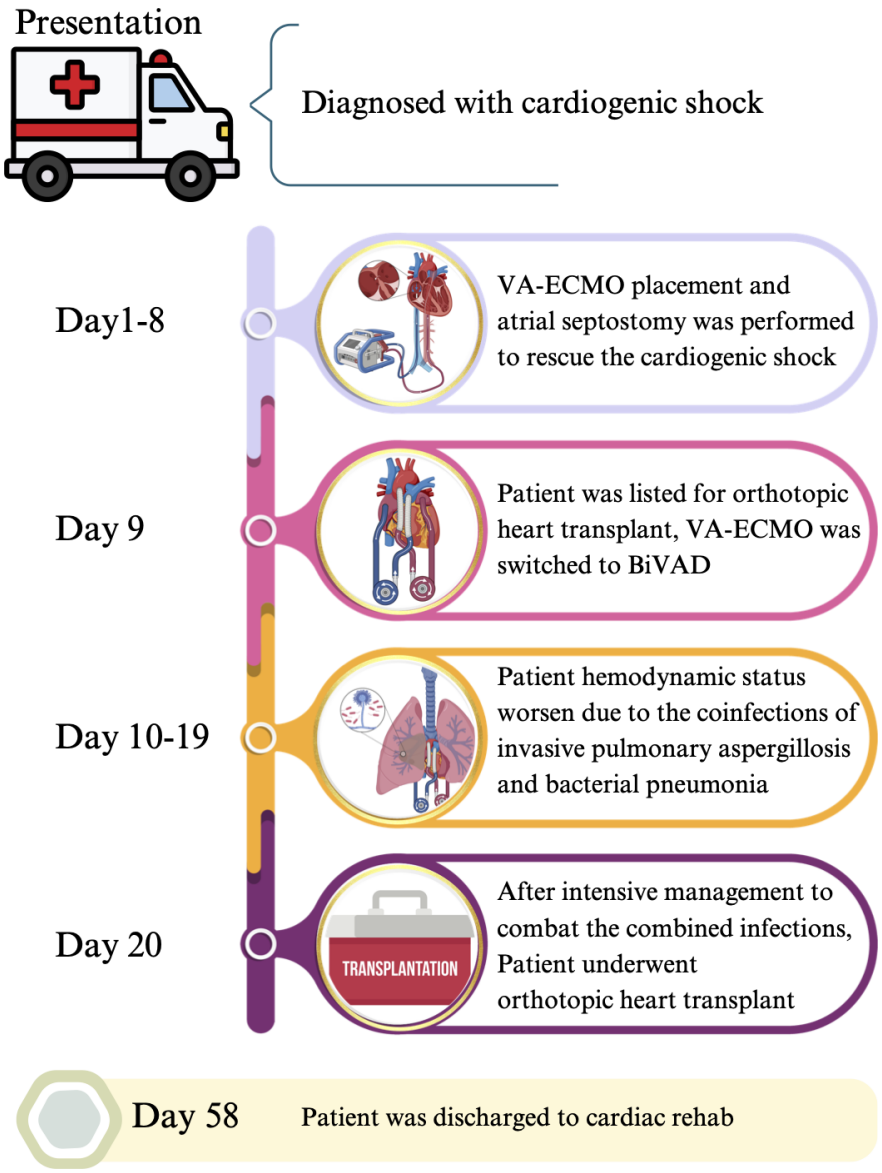

Figure 6: [Comparison of computed tomography scan of the chest showed improvement at 6th week after voriconazole treatment.]