Sepsis and mediastinitis after heart transplantation: donor-transmitted *Klebsiella* infection

Kalp nakli sonrası sepsis ve mediastinit: Donör kaynaklı Klebsiella enfeksiyonu

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Early diagnosis and treatment of infection following heart transplantation is a determinant factor for the prognosis. However, it may easily be overlooked because of vague clinical signs and non-specific laboratory findings as a result of immunosuppression in these patients. Herein, we present a case of donor-transmitted bacterial infection after heart transplantation and its consequences.

Key words: Donor-transmitted infection; heart transplantation; mediastinitis; sepsis.

Kalp nakli sonrası enfeksiyonların erken tanı ve tedavisi prognoz için belirleyici bir faktördür. Ancak bu olgularda tanı, immün süpresyon kaynaklı müphem klinik belirtiler ve belirli bir özellik göstermeyen laboratuvar bulguları nedeniyle kolayca atlanabilir. Bu yazıda, kalp nakli sonrasında donör kaynaklı bakteriyel enfeksiyon gelişen bir olgu ve bu klinik tablonun sonuçları sunuldu.

Anahtar sözcükler: Donör kaynaklı enfeksiyon; kalp nakli; mediastinit; sepsis.

Infection is a serious complication and a major cause of mortality and morbidity within one year after heart transplantation (HTx).[1] The use of immunosuppressive drug combinations to hinder acute rejection compromises the recipient's immune system; thus, the recipient becomes prone to infections caused by bacteria, viruses, fungi, and protozoa. The main sources for early (< one month) postoperative infection after HTx are technical or nasocomial factors.[2] However, donor-transmitted bacterial infections constitute a rare but important cause of early postoperative infection after HTx.[3] Herein, we present a case with donor-transmitted *Klebsiella pneumoniae (K. pneumoniae)* infection, which led to mediastinitis and sepsis and also discuss the consequences associated with this type of infection.

CASE REPORT

A 51-year-old male patient suffering from end-stage heart failure was admitted to our center on May 16, 2011. He had a history of ischemic cardiomyopathy that began in 2008. At admission, he had dyspnea at rest, orthopnea, signs of volume overload (ascites, pretibial edema, jugular venous distension, and rales), and mild-to-moderate hepatic and renal dysfunction. Intravenous (i.v.) inotropes and diuretic therapy were initiated immediately, and he was placed on the list for an emergency heart transplant.

Nine days later, a 35-year-old male donor who had been declared brain dead because of post-traumatic intracranial bleeding became available. The donor had good cardiac functions and no clinical and/or laboratory signs of infection, so the heart was harvested for transplantation. Because the donor had undergone several cranial operations and a 10-day intensive care unit (ICU) stay, our team obtained blood and deep tracheal aspiration samples for culture.

The patient underwent orthotopic HTx and ascending aorta replacement using a Dacron tube graft (cardiac ischemia: 245 minutes). One gram of cefazolin sodium i.v. was given every six hours

during the first 48 hours as a perioperative antibiotic prophylaxis. Methylprednisolone (500 mg i.v. before general anesthesia, 500 mg before declamping, 125 mg every eight hours) was then given on postoperative day 0 (POD 0) followed by oral prednisone [1 mg/kg/twice a day (bid) tapered daily], cyclosporine A (3-8 mg/kg/day bid, C_0: 250-350 ng/mL) and mycophenolate mofetil (MMF) (1 g/day bid). He was transferred to the ICU with low-dose inotropes and nitric oxide (NO) after the operation. Transthoracic echocardiography (TTE) on POD 1 revealed normal left (LV) and right ventricular (RV) functions [LV ejection fraction (EF): 60%], cardiac chamber dimensions (LV end-diastolic diameter: 44 mm, LV end-systolic diameter: 22 mm, RV end-diastolic diameter: 28 mm, left atrium: 26 mm, and right atrium: 38 mm) and a systolic pulmonary artery pressure (SPAP) of 30 mmHg, and the patient was extubated 36 hours after the operation.

Three hours after the extubation, multidrug-resistant, carbapenemase-producing *K. pneumoniae* was isolated in the donor blood cultures. Despite the lack of any symptoms or findings suggestive of an infection, the immunosuppressive therapy was diminished (MMF from 1 g/day to 0.25 g/day; cyclosporin-A ceased), and a combination of colistin, levofloxacine, and amikacin was started after sampling the recipient's blood for culture. The same pathogen was isolated two days later. Acute renal failure requiring renal replacement therapy (RRT) was detected after the initiation of the antibiotics, and on POD 13, sternal dehiscence and purulent drainage were observed as the initial signs of infection, despite the use of antibiotics. The patient's body temperature along with the C-reactive protein (CRP), and procalcitonin levels were normal, and the leukocyte count ranged from 10,700-28,000/mL. Surgical revision was performed on POD 15. The heart and major vasculature were covered by a purulent, adherent suppurative layer, but the sternum was free of infection. The debris was partially removed; however, the heart was still indistinguishable (Figure 1). A continuous negative aspiration system was implemented, and the sternum was then rewired. After revision, the patient required vasoconstrictors for three days because of septic shock. As the septic shock resolved, his hemodynamics stabilized, and the end-organ functions began to improve. A percutaneous tracheostomy was performed on POD 22, and transthoracic echocardiography on POD 24 showed biatrial and RV dilatation along with moderate pericardial effusion, but the LV dimensions and functions were normal. In addition,

the RV systolic functions were slightly depressed, and moderate tricuspid regurgitation and pulmonary hypertension (SPAP: 64 mmHg) were also noted. This was attributed to the progressive renal dysfunction and volume overload, so the RRT was continued until the urine output recovered. Mycophenolate mofetil was added to the prednisolone, and the tracheostomy was removed on POD 38. As the volume overload resolved, the patient was transferred to a ward on POD 45, where he started an active rehabilitation program. A cardiac biopsy on POD 50 revealed grade 1 cellular rejection but no humoral rejection. On POD 54, we demonstrated that all of the cardiac chamber dimensions and functions had returned to baseline values, but the SPAP remained high (44 mmHg) on TTE. A dense, massive echogenic shell surrounding the heart was also discovered. The antibiotics were then discontinued on POD 60, and everolimus was added to the immunosuppressive therapy.

The patient was finally discharged from the hospital 10 weeks after the HTx with no cardiac symptoms and no signs of infection. However, he had moderate renal

Figure 1. Intraoperative view of the mediastinum at surgical revision from the anesthesiologist's site. The sternum was intact; however, the pericardium, heart, and major vasculature were covered with purulent and necrotic material. Extensive resection was not possible since the epicardial layer was indistinguishable, suggesting that the donor heart was the source of the infection. Please note the two epicardial pacing wires on the left hand side of the picture.

failure and a segmental wall motion abnormality on both ventricles, although his systolic and diastolic dimensions were normal. The echogenic shell around the heart was still visible on TTE, but there were no signs of restriction and/or constriction. In the follow-up, the patient recovered well via a rehabilitation program. He was capable of doing his daily activities at home but complained of swelling in his legs and abdomen, which was suggestive of progressive RV dilatation and systolic dysfunction. Five months after the HTx, he was readmitted to the hospital with signs of biventricular heart failure. The TTE showed biatrial and RV dilatation along with biventricular systolic and diastolic dysfunction. An analysis of the ventricular myocardial velocity, strain, and strain rate were indicative of both myocardial and pericardial restriction. There was no pericardial effusion, but the dense, massive echogenic shell surrounding the heart still existed. Furthermore, there were still no signs or symptoms of infection, and a cardiac biopsy ruled out rejection as the source of the problems.

Unfortunately, the patient died in the ICU six months after the HTx because of cardiorenal syndrome.

DISCUSSION

Mediastinitis is a serious infection that is associated with high morbidity and mortality after open heart surgery. The in-hospital mortality for patients with mediastinitis was reported to be between 20% and 40% three decades ago,[4] and it remains high despite an increase in experience, more advanced techniques, and evolving technology.[5,6] Furthermore, Braxton et al.[7] showed that mediastinitis was associated with increased long-term mortality (3% vs. 7% at 30 days, 5% vs. 22% at one year, and 11% vs. 35% at four years) with an hazard ratio of 3.09 (95% CI= 2.28 to 4.19, p<0.0001) in 15,000 consecutive patients who underwent coronary artery bypass grafting (CABG).

Such a complication may be more challenging for both the physician and patient after HTx when immunosuppression is indicated. By its very definition, this act suppresses the ability of the recipient's immune system to fight off acute and chronic rejection, rendering the recipient prone to infections. Furthermore, immunosuppression may obscure the symptoms of systemic infection, such as fever, purulent drainage, and pain, and the results of laboratory findings, including the elevation of inflammatory markers and leukocytosis, thus possibly delaying the diagnosis and initiation of antibiotics.

Although rarely reported, donor-transmitted bacterial infection is a serious complication after HTx.[3] However, the use of hearts from infected donors has been advocated by some centers to enlarge the donor pool.[8,9] The International Society for Heart and Lung Transplantation Guidelines recommend the use of hearts from infected donors if the infection is community-acquired and the donor's death occurs within 96 hours, if repeat blood cultures before the organ procurement are negative, if pathogen-specific antimicrobial therapy is administered to the donor, if the donor's myocardial function is normal, and if there is no evidence of endocarditis via direct inspection of the donor heart (Class 2a, C).[10] Nevertheless, these recommendations fail to cover all situations in the clinical practice, and an undetected, and thus untreated, donor bloodstream infection may occur, as it did in our patient.[11] We recovered the heart since there was no sign of infection. The prior blood cultures were negative, but as a precaution, we took one more sample for a blood culture during the cardiectomy. The positive result of this culture on POD 2 urged us to diminish the immunosuppression and initiate antibiotics for this resistant, gram-negative pathogen, even when there were no signs or evidence of infection. This was probably the turning point in our treatment because we succeeded in achieving a full recovery from the infection.

Nevertheless, aggressive treatment of such an infection may have a high cost. Our patient experienced septic shock after the sternal revision which required a high dose of inotropes and vasoconstrictors. Together with the aminoglycosides and colistin, his renal functions deteriorated, and RRT was indicated in the early postoperative period. His creatinine clearance, as calculated by the Cockroft-Gault formula, decreased to 15-20 mL/minute during the antibiotic therapy, but it partially recovered (up to 45 mL/minute) after the cessation of the antibiotics before his discharge. Despite the lack of rejection, the dense shell surrounding the heart, a sequela of the mediastinitis, led to progressive systolic and diastolic allograft dysfunction and eventually created a vicious cycle together with persistent renal dysfunction during the follow-up. Unfortunately, the patient, who survived the mediastinitis in the early stages after the HTx, died because of cardiorenal syndrome at the postoperative sixth month.

Conclusion

Donor-transmitted infections may result in disastrous complications, and prior donor screening may not be sufficient to hinder transmission. Furthermore, routine blood cultures performed at the donor cardiectomy could help identify donor-borne

pathogens well before any clinical or laboratory signs occur in the recipient since they may be obscured by immunosuppression. Because of the potential risks, the use of infected donors should be reassessed carefully before the recovery of organs.

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