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The First Successful Heart-Lung Transplantation in the Baltic Countries

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Summary. *Successful heart-lung complex transplantation was performed to a 48-year-old man. During the postoperative period, M. tuberculosis infection was diagnosed, and the treatment subsequently started. One year after, the patient was urgently hospitalized due to myocardial infarction. However, despite best efforts, the patient died.*

Antituberculosis treatment is recommended to all the patients with confirmed active tuberculosis. Treatment of tuberculosis in transplant recipients is similar to that of the general population, with the exclusion of rifamycins in the treatment regimen and longer duration of treatment.

Introduction

The first successful heart-lung transplantation in the Baltic countries was performed in Lithuania on October 28, 2009. In the same year, 87 operations of such a type were recorded by the International Society of Heart and Lung Transplantation globally (1). Lung-heart complex transplantations are usually required because of the following reasons: congenital heart defects (35.9%), idiopathic pulmonary hypertension (27.5%), and cystic fibrosis (14.3%) (1). Postoperative mortality is relatively high due to the size and complexity of such operations. The first 12 months after heart-lung complex transplantation are the most important, since 75% of transplant recipients survive the first 3 months and only 68% the first year (1). Prognoses for patients who survive the first year improve significantly. The most common causes of death during the first 12 months are infection (34.9%), of which 0.4% is cytomegalovirus, and failure of the transplanted graft (21.7%) (1). One of the most dangerous infections is tuberculosis (TB), as it occurs 20–74 times more frequently in transplant recipients compared with the general population (2). Furthermore, mortality rates are increased by 31% as well (3). The highest risk of developing the infection is during the first year after transplantation (1) due to high doses of immunosuppressive medications in this period. On average, the disease develops 9 months after transplantation, and in 3 out of 4 cases, it is pulmonary (4). It is very important to diagnose this infection in time, although this is quite difficult due to a superinfection, which can conceal the symptoms of TB and may even develop into atypical forms of the disease (5).

Based on international research and experience, anti-TB treatment is recommended to all the recipients who have a confirmed diagnosis. Treatment of tuberculosis in transplant recipients is similar to that of the general population, with the exception (6) of the treatment regimen because of the interaction between rifamycins and immunosuppressors of calcineurin inhibitors (cyclosporine and tacrolimus) (7) and the duration of treatment.

Clinical Case

A 45-year-old man was diagnosed with idiopathic pulmonary arterial hypertension in 2005. On October 28, 2009, the patient underwent heart-lung transplantation due to the failing heart and lungs. In accordance with the lung-heart transplantation protocol, immunosuppression for the patient was maintained with cyclosporine (250 mg/day), mycophenolate mofetil (3 g/day), and prednisolone (15 mg/day) in order to prevent acute or chronic rejection. On February 2, 2010, as required by the protocol, the patient underwent a heart and lung biopsy, and no acute rejection was documented (A0B0). Biopsies were repeated every few months. As the patient was coughing and expectoration was observed, bronchoalveolar lavage specimens were taken to test

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for the *M. tuberculosis* bacteria complex. One month later, *M. tuberculosis* growth was observed in the BACTEC culture system. The diagnosis of TB was confirmed, and the treatment with a combination of 4 anti-TB drugs, i.e., rifampicin (0.6 g/day), isoniazid (0.3 g/day), pyrazinamide (2 g/day), and ethambutol (0.4 g/day), was initiated. Two weeks later, rifampicin was replaced with ofloxacin (800 mg/day) for the reason that a therapeutic dose of cyclosporine could not be achieved while using rifampicin. Daily tests for cyclosporine showed that its concentration in the blood was varying from 43 to 237 *m*g/L, while the rifampicin dose was not varied.

After 7 months, the patient was hospitalized in the Department of Pulmonology and Immunology for a detailed examination due to the deteriorating lung function and a manifestation of airway limitation. Spirometry showed a rapid decline in forced expiratory volume in 1 second (FEV_1): on May 24, FEV_1 was 2.37 L (63% of the predicted), while, on June 28, it was 1.22 L (33% of the predicted). Computed tomography of the chest revealed structural changes in the lungs: at the top of both lungs, more on the right, small fibrotic scar lesions were observed, and low-density (0.2 to 0.4 cm) centrilobular foci were found. The interlobular septa were thicker in the basal region; the peribronchovascular interstitium was brightened. Considering the results of the above examinations, chronic lung rejection, namely bronchiolitis obliterans syndrome (BOS), was confirmed. Recent data suggests replacing cyclosporine with tacrolimus for patients with BOS, as it is associated with an improvement in functional capacity and oxygenation (8). For this reason, a decision to replace cyclosporine with tacrolimus (7 mg/day) was made. Azithromycin (500 mg 3 times per week) was also prescribed.

On October 4, 2010, the patient was hospitalized once again due to severe chest pain in the epigastric area, radiating toward the back, and shortness of breath. Echocardiography showed an ST-segment elevation in the anterior leads. The level of troponin I was 18.1 μg/L. Echocardiography revealed negative dynamics and a significantly reduced systolic function of the left ventricle: the ejection fraction was decreased from 55% to 20%, and the right ventricle was expanded and hypokinetic. Coronary angiography showed 99% stenosis of the proximal left anterior descending coronary artery and a complete occlusion of the middle left anterior descending coronary artery and the first diagonal artery. Percutaneous transluminal coronary angioplasty and stenting of the left anterior descending coronary artery were successfully performed. Anti-ischemic therapy was initiated, and antiplatelet agents were administered. On October 7, 2010, the patient suddenly became unresponsive and stopped breathing. Resuscitation was attempted, though without success, and the patient was pronounced dead. The postmortem autopsy revealed the cause of death to be progressive heart and respiratory failure, which, in turn, was a result of a large-scale myocardial infarction. The postmortem examination also confirmed the TB infection and the presence of BOS, thus, showing that morphological and clinical diagnoses matched.

Discussion

Infection is one of the main causes of death in patients who undergo heart-lung transplantation. TB is one of the most common infections (1). It typically develops in one of the following 3 ways, which are important to understand in order to identify the source of the infection in time and to administer appropriate treatment and prevention (6, 7):

1. Latent infection, when *M. tuberculosis* persists in the recipient due to the previous infection with these bacteria.

2. Transmission of the infection via the donated organ, when the donor's organ or tissues are infected with *M. tuberculosis*. It is a potential source of infection in the recipient. The lungs are infected most often.

3. De novo TB infection. Patients, due to aggressive immunosuppressive treatment, are at a greater risk of acquiring TB when they encounter a carrier of the infection.

In the first 2 cases, patients are at the highest risk of reactivation during the early postoperative period, when the doses of immunosuppressants are highest. Later activation can occur if the dose of immunosuppressants is increased, for example, due to beginning organ rejection. In our clinical case, no decision to reduce the dose of immunosuppressive drugs was taken because chronic rejection of the lungs (obliterative bronchiolitis) was developing; however, this decision did not have any negative impact on the patient's health and life.

Early diagnosis and treatment of TB depend on morbidity from this infection in a particular country. If morbidity in a region is high (>100 per 100 000 population), anti-TB treatment may be initiated even without positive diagnostic results. Prompt treatment can be initiated in patients with latent tuberculosis and those who develop clinical symptoms of weight loss, fever, and sweating during the postoperative period (6). If morbidity is average (20–100 per 100 000 population), like in Lithuania, all patients waiting for organ transplantation should undergo testing for a specific immune system response to *M. tuberculosis* (8). Therefore, in Lithuania, for the treatment of latent tuberculosis, isoniazid and rifampicin are given for 3 months (9); when active tuberculosis is diagnosed (micro-

biologically or/and morphologically), all pretransplant patients and transplant recipients are treated with anti-TB drugs.

Treatment of TB in patients who have undergone organ transplantation differs in 2 aspects when compared with the general population. First, since rifampicin has an effect on the metabolism of immunosuppressive drugs, which belong to the group of calcineurin inhibitors (cyclosporine and tacrolimus), it has to be replaced with other drugs (10). Otherwise, the likelihood of organ rejection is highly increased. In case rifampicin is not replaced with another drug, the concentration of cyclosporine or tacrolimus should be carefully monitored and, if needed, the dose has to be increased, even up to 3 to 5 times (11). The second aspect is related to the duration of treatment and the higher frequency of side effects when administering anti-TB drugs to such patients.

In patients without suspicion or evidence of resistance to isoniazid or with localized, nonsevere forms of TB, it is advisable to avoid the use of rifamycins. Isoniazid and ethambutol (or pyrazinamide) are recommended for 12–18 months; addition of a third drug, such as pyrazinamide or levofloxacin, may reduce this period to 12 months. In severe or disseminated forms of TB or evidence of resistance to isoniazid, addition of rifampicin to the anti-TB treatment regimen and complete treatment with isoniazid and rifampicin for at least 9 months should be considered. In multidrug-resistant TB, 4–6 drugs including injectable antimicrobials (streptomycin, amikacin, kanamycin, or capreomycin), linezolid, or other second-line drugs should be administered during induction treatment (11, 12).

The duration of treatment after the first 2 months of treatment is controversial, especially if rifampicin has not been used during the first 2 months. The optimal duration of anti-TB treatment in transplant recipients has not been assessed. Because transplant recipients are actively immunosuppressed, it is reasonable to use a prolonged course of treatment (even up to 18–24 months), especially in those with cavitary lung disease, disseminated or extrapulmonary involvement, or evidence of persistently positive cultures after 2 months of treatment.

Conclusions

Based on international research and experience, anti-tuberculosis treatment is recommended to all the recipients who have a confirmed diagnosis of active tuberculosis. This treatment should differ from the standard approach applicable to the general population: it should be less aggressive and continue longer.

Statement of Conflict of Interest

The authors state no conflict of interest.

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