Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Case report

A case of diffuse panbronchiolitis, associated with severe pulmonary hypertension, managed with bilateral lung transplantation from a brain-dead donor

Yasutaka Onishi, M.D.[a,*], *Tetsuji Kawamura, M.D.*[a], *Akie Morimoto, M.D.*[a], *Yasuharu Nakahara, M.D.*[a], *Yoshiro Mochizuki, M.D.*[a], *Kentaroh Miyoshi, M.D.*[b], *Takahiro Oto, M.D.*[b]

[a]*Department of Respiratory Medicine, National Hospital Organization, Himeji Medical Center, Honnmachi 68, Himeji City 670-8520, Hyogo, Japan*

[b]*Department of Thoracic Surgery, Okayama University Hospital, 2-5-1, Shikata-cho, Kita-ku, Okayama 700-8558, Japan*

ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form
2 March 2015
Accepted 4 March 2015
Available online 27 May 2015

Keywords:
Diffuse panbronchiolitis
Brain-dead donor
Lung transplantation
Chronic sinusitis
Pulmonary hypertension

ABSTRACT

Diffuse panbronchiolitis (DPB) is a chronic respiratory disease that mainly involves the respiratory bronchioles, and has historically been associated with a very poor prognosis. The development of long-term low dose macrolide therapy in the 1980s has dramatically improved the prognosis of DPB. Nevertheless, some cases are resistant to macrolide therapy, and ultimately develop severe respiratory failure and pulmonary hypertension; in such cases lung transplantation is a viable treatment option. Here we report the case of a 40-year-old patient with a 20-year history of DPB, who underwent bilateral lung transplantation due to severe respiratory failure with pulmonary hypertension.

1. Introduction

Diffuse panbronchiolitis (DPB) is an extremely intractable chronic respiratory disease that was first reported in Japan in the 1960s. In the 1980s, Kudo et al. found that long-term administration of low dose macrolides dramatically improved its prognosis [1]. However, some cases are refractory to this treatment, necessitating lung transplantation [2]. We report

*Corresponding author. Tel.: +81 79 225 3211; fax: +81 79 223 8310.
E-mail addresses: yonishi@hmj-net.hosp.go.jp (Y. Onishi), kawa-t@hmj-net.hosp.go.jp (T. Kawamura), a.morimoto@hmj-net.hosp.go.jp (A. Morimoto), nakahary@hmj-net.hosp.go.jp (Y. Nakahara), mochi@hmj-net.hosp.go.jp (Y. Mochizuki), kentarohmiyoshi@yahoo.co.jp (K. Miyoshi), oto@md.okayama-u.ac.jp (T. Oto).

http://dx.doi.org/10.1016/j.resinv.2015.03.001
2212-5345/

here a case of a 40-year-old patient with DPB, who underwent bilateral lung transplantation from a brain-dead donor due to severe respiratory failure with pulmonary hypertension, 20 years after the onset of her disease.

2. Case presentation

The patient was a 40-year-old woman who was diagnosed with chronic sinusitis in childhood, and started to experience coughing with sputum at junior high school age. At 20 years of age, she visited our hospital complaining of increased amount of sputum and was diagnosed with DPB. Administration of erythromycin at a dose of 400 mg/day was initiated. Her signs and symptoms improved temporarily, but gradually deteriorated, in spite of a change from erythromycin to clarithromycin (200 mg/day).

Thereafter, mucoid type *Pseudomonas aeruginosa* (*P. aeruginosa*) was detected in sputum specimens, and she had repeated episodes of pneumonia. Subsequent exertional dyspnea was consistent with Modified British Medical Research Council (mMRC) grade 4, and was so aggravated that she could not sleep in the supine position. Right heart catheterization revealed severe pulmonary hypertension, as evidenced by a pulmonary arterial pressure of 93/34 (mean 62) mmHg, mean pulmonary capillary wedge pressure of 15 mmHg, mean right atrial pressure of 12 mmHg, cardiac output of 8.4 L/min, and pulmonary vascular resistance of 448 dyn/s/cm^5. The patient was referred to the National Hospital Organization Okayama Medical Center, where she was treated with bosentan, sildenafil, and home oxygen therapy. Unfortunately, this regimen did not result in sufficient clinical improvement, and we therefore consulted the Department of Thoracic Surgery, Okayama University Hospital regarding her suitability for lung transplantation. She was registered on the Japan Organ Transplant Network at 40 years of age. She was admitted to our hospital 6 months after registration with headaches, worsened dyspnea, fever, and increased sputum.

Results of the physical examination on admission included height 134.9 cm; body weight 51.2 kg; body temperature 37.3 °C; blood pressure 122/60 mmHg; pulse rate 122/min, regular; normal heart sounds; coarse crackles bilaterally, over all lung regions; SpO_2 86% (FiO_2: 0.32); clubbed fingers; and bilateral pedal edema. The results of laboratory investigations on admission included leukocytosis, an elevated CRP, and hypoxemia (Table 1). Chest X-ray on admission showed multiple nodular shadows in the bilateral and lower lung fields, and reduced translucency in the left middle and lower lung fields. Chest computed tomography showed multiple centrilobular nodules, cystic shadows, and multiple infiltrative shadows. Cardiac ultrasonography showed a tricuspid regurgitation pressure of 55 mmHg. Pulmonary function tests showed severe mixed ventilatory impairment (%VC, 34.3%; FEV_1/FVC, 47.5%; %FEV_1, 16.7%) and small airway obstruction ($\dot{V}50$, 2.9%; $\dot{V}25$, 2.1%).

The patient's clinical course is illustrated in Fig. 1. On re-presentation she was treated for bacterial pneumonia with meropenem (MEPM). Since drug-resistant *P. aeruginosa* was detected in the sputum, MEPM was changed to a combination of tazobactam/piperacillin and tobramycin. The bacterial pneumonia improved, and she was discharged. However, she suffered recurrent episodes of bacterial pneumonia, and her respiratory condition worsened such that she presented with orthopnea. A year after her registration on the Japan Organ Transplant Network, she received a bilateral lung transplantation from a brain-dead donor at Okayama University Hospital. She was discharged on postoperative day 88 and has received ongoing immunosuppressive therapy, including prednisolone, tacrolimus, and mycophenolate mofetil. To date, she has not experienced rejection, or a recurrence of DPB.

After the transplantation, her pulmonary function was remarkably improved, with the exception of a persistent restrictive ventilatory defect, likely due to muscle weakness as shown (Fig. 2). Tricuspid valve regurgitation pressure also recovered to 29 mmHg, despite the discontinuation of bosentan and sildenafil, and she was able to walk 400 m in the 6 min walk test (Fig. 2).

Histopathologic examination of the recipient's lungs (Fig. 3) showed peribronchiolar inflammation and bronchiolar dilation throughout the lung fields, compatible with typical DPB. Bronchiectasis and bronchiolectasis were predominant in the lower lobes. The peribronchiolar regions showed infiltration with lymphocytes and plasma cells, and the formation of lymph follicles. However, fibrosis in this case was minimal, compared with that usually observed in the terminal stage of DPB. Additionally, the pulmonary arteries and veins were not substantially affected, and there was no evidence of plexiform lesions or pulmonary artery thrombosis.

3. Discussion

DPB was first reported as a new disease entity in Japan in the 1960s, and it is characterized by diffuse involvement in the peribronchiolar region. Patients with DPB expectorate a large amount of sputum, experience gradually progressive dyspnea, and often die from respiratory failure. In Japan in the 1970s DPB was not uncommon, with an incidence of 1.12 per 100,000, and a prevalence of 13.78 per 100,000. In addition to improvements in poor prognosis, associated with better nutrition and the administration of low dose macrolide therapy, the incidence had decreased to almost 0% by the 2000s [3]. However, a double-blind trial performed by a study group of the Health and Welfare Ministry in 1990 suggested that not all patients benefit from such therapy; of treated patients, 24.2% were unchanged in their condition, and 6.1% deteriorated, even after long-term low dose erythromycin [4]. Poor outcomes in the majority of DPB cases may be attributable to respiratory tract infection and/or right heart failure due to pulmonary hypertension. Therefore, in cases like the present one, where the patient's condition worsened despite low dose macrolide therapy, lung transplantation is the final treatment option available [2].

We considered that the severe pulmonary hypertension in the present case was caused by vasoconstriction of pulmonary vessels triggered by severe hypoxemia, because the pulmonary arteries and veins were not significantly affected on histopathological examination. However, it is possible that the administration of bosentan, sildenafil, and home oxygen