Bilateral lung transplantation (BLTx) in a 9-year-old girl with bronchopulmonary dysplasia with pulmonary hypertension

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Abstract

Background Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease that occurs in premature infants and the prognosis is variable depending on the comorbidities including fibrosis, emphysema, or pulmonary hypertension (PH). We present a case of a 9-year-old girl who developed PH associated with severe BPD (BPD-PH) and underwent bilateral lung transplantation (BLTx). Case description A 9-year-old girl admitted to our department to undergo BLTx. She was born at 23 weeks and 4 days gestation with a weight of 507 grams. She received ventilation for the first 2 months and required further respiratory care due to repetitive, severe respiratory infections. She was diagnosed with BPD-PH at 6 months of age and oral administration of pulmonary vasodilators were initiated. She was registered as a lung transplant candidate at 4 years of age after the life-threatening exacerbation. Chest computed tomography (CT) revealed severe lung conditions with ground-glass opacities and emphysematous low-density areas in the upper and lower lobes. BLTx from a brain-dead male donor was performed. The pathological findings of her resected lung revealed saccular, hypoplastic lung with alveolar repair/regeneration and medial hypertrophy and muscularization of peripheral arteries. The postoperative course was mostly uneventful. She was free from oxygen administration and showed no signs of PH after 6 months of the surgery. Conclusion This is the first case report of BLTx in a pediatric, irreversible BPH-PH patient with detailed pathohistological findings and clinical examination. Lung transplantation is one of the treatment options for severe BPD-PH.

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Abstract

Background

Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease that occurs in premature infants and the prognosis is variable depending on the comorbidities including fibrosis, emphysema, or pulmonary hypertension (PH). We present a case of a 9-year-old girl who developed PH associated with severe BPD (BPD-PH) and underwent bilateral lung transplantation (BLTx).

Case description

A 9-year-old girl admitted to our department to undergo BLTx. She was born at 23 weeks and 4 days gestation with a weight of 507 grams. She received ventilation for the first 2 months and required further respiratory care due to repetitive, severe respiratory infections. She was diagnosed with BPD-PH at 6 months of age and oral administration of pulmonary vasodilators were initiated. She was registered as a lung transplant candidate at 4 years of age after the life-threatening exacerbation. Chest computed tomography (CT) revealed severe lung conditions with ground-glass opacities and emphysematous low-density areas in the upper and lower lobes. BLTx from a brain-dead male donor was performed. The pathological findings of her resected lung revealed saccular, hypoplastic lung with alveolar repair/regeneration and medial hypertrophy and muscularization of peripheral arteries. The postoperative course was mostly uneventful. She was free from oxygen administration and showed no signs of PH after 6 months of the surgery.

Conclusion

This is the first case report of BLTx in a pediatric, irreversible BPD-PH patient with detailed pathohistological findings and clinical examination. Lung transplantation is one of the treatment options for severe BPD-PH.

Introduction

Bronchopulmonary dysplasia (BPD), a chronic respiratory disease in premature infants, occurs due to inflammation, oxygen supplementation, and prolonged mechanical ventilation. Patients with severe BPD usually are discharged from the neonatal care unit with home oxygen therapy or tracheostomy with a ventilator. Eighty percent of the patients show "reversible" BPD with improving respiratory status within 2 years after birth while 20% show "irreversible" BPD with complicated comorbidities including pulmonary hypertension (PH)[1] . Patients with severe BPD require further respiratory support with increased risks of morbidity and mortality. It remains unclear whether this different prognosis of severe BPD depends on aberrant lung development with mismatched vascular/epithelial formation, or the postnatal lung insults, such as repetitive infection, ventilation, hypo/hyperoxia, or drug treatments owing to the lack of pathological findings with a detailed clinical course. Here, we present a case of a 9-year-old girl who developed PH associated with severe BPD (BPD-PH) and underwent bilateral lung transplantation (BLTx). The pathological findings of her lung revealed saccular, hypoplastic lung with alveolar repair/regeneration and medial hypertrophy and muscularization of peripheral arteries. This is the first case report of BLTx in a pediatric, irreversible BPD-PH patient with detailed pathohistological findings and clinical examination including right heart catheterization.

Case description

A 9-year-old girl was admitted to our department for bilateral lung transplantation (BLTx). Her chest radiograph showed ground-glass opacities (Figure 1). The patient was born at 23 weeks and 4 days of gestation with a weight of 507 grams. She received mechanical ventilation for the first 2 months and required further respiratory care with tracheostomy due to repetitive and severe respiratory infections. She was diagnosed with BPD-PH at 6 months of age using transthoracic echocardiography. The oral administration

of sildenafil, a phosphodiesterase-5 inhibitor, and beraprost, a prostacyclin analogue, was initiated. At 2 years and 6 months of age, right heart catheterization (RHC) showed an elevated mean pulmonary arterial pressure (mPAP) of 49 mmHg, a pulmonary capillary wedge pressure (PCWP) of 12 mmHg, and a high pulmonary vascular resistance (Rp) of 13 wood units. Pulmonary angiography (PAG) revealed hypoplastic pulmonary arteries and dilated main pulmonary artery (Figure 2A). At 4 years of age, she experienced transient cardiopulmonary arrest (CPA) caused by the exacerbation of PH with severe respiratory infection. RHC revealed rapid aggravation of PH, mPAP of 70 mmHg, PCWP of 8 mmHg, and Rp of 22 wood units with hypoplastic pulmonary arteries by PAG (Figure 2B). Subsequently, she was listed as a candidate for lung transplantation at that time. An endothelin receptor antagonist was added to the treatment regimen and her respiratory condition was again gradually stabilized for the following years with familial support to prevent respiratory infections. Nevertheless, a follow-up RHC at 8 years old demonstrated PH with mPAP of 32 mmHg, PCWP of 8 mmHg, and Rp of 8 wood units with hypoplastic pulmonary arteries by PAG (Figure 2C). Chest computed tomography (CT) revealed severe lung conditions with ground-glass opacities and emphysematous low-density areas in the upper and lower lobes (Figure 2D). In addition, pulmonary perfusion scintigraphy revealed low blood flow in the bilateral lower lobes (Figure 2E). When she was 9 years and 7 months, the lungs from a brain-dead male donor under 6 years of age were donated.

On admission, she weighed 21.6 kg (-1.5 standard deviation; SD), was 113.5 cm (-3.2 SD) tall, and her oxygen saturation was 95% with 3L/min of oxygen supplementation through a tracheostomy. BLTx was performed and the immediate postoperative course was mostly uneventful. After experiencing a high fever due to adenovirus (serotype 1) and methicillin resistant staphylococcus aureus (MRSA) infection during the first month, her respiratory status was improved and showed no signs of PH and pulmonary arterial hypoplasia after 6 months of the surgery (Figure 2F). She was free from oxygen supplementation when she was discharged from our department. Figure 2G shows lung growth by CT-based lung volumetric analysis from 1 years old to 10 years old, before and after BLTx. Figure 2H depicts the lung volume divided by height, showing that the lung volume/height increased after the CPA episode and reached a plateau thereafter.

We performed a detailed pathological examination of the patient's lungs extracted during the surgery. Macroscopically, emphysema-like cystic changes of up to 2 cm and patchy mild solid appearance were observed in several areas (Figure 3A). The emphysema-like areas demonstrated dilated alveolar spaces with thin distracted alveolar septa without apparent epithelial injury or repair such as fibrosis (Figure 3B, C). In contrast, the solid areas showed thickened alveolar walls with fibrosis, chronic inflammatory cell infiltration, foreign body reaction and hypertrophic smooth muscle, suggesting chronic epithelial injury and repair (Figure 3D, E). In addition, the muscularization of the peripheral arteries and mild medial hypertrophy, compatible with Heath-Edwards classification Grade 1 PH, were observed especially in the area showing fibrosis (Figure 3F). In addition, capillary proliferation was observed in the alveolar septa (Figure 3G). No apparent occlusion of veins or venules was detected. With the above findings, we histologically diagnosed the patient's lung with pulmonary hypoplasia and BPD-PH. Furthermore, the lung demonstrated hypoplastic alveoli resembling a saccular-stage lung, in which the radial alveolar count was only 3-4 (normal range: >5-6 after birth) and only a few alveolar entrance rings were formed (Figure 4). There was no mismatch in the development of the airway and blood vessels.

Discussion

In our case, along with the premature lungs at the canalicular stage of lung

development, prolonged ventilation and repetitive respiratory infections may cause BPD-PH. We treated the patient with multiple pulmonary vasodilators which enabled her to survive over the long waiting time until the BLTx procedure. The use of pulmonary vasodilators for BPD-PH has long been a controversial issue. Recently, the Pediatric Pulmonary Hypertension Network stated consensus recommendations for the use of pulmonary vasodilators for BPD-PH[2]. Nitric oxide, a strong pulmonary vasodilator, is reported to attenuate pulmonary fibrosis by preserving the epithelial phenotype[3]. We previously reported that both pulmonary fibrosis and PH due to ATP-binding cassette A3 (ABCA3)-mediated combined pulmonary fibrosis and emphysema were ameliorated with the use of pulmonary vasodilators[4]. We speculated that for our

patient, the pulmonary vasodilators played a role in improving her pulmonary fibrosis as well as PH which bridges a long waiting time between listing and LTx in Japan[5]. Furthermore, LTx will be one of the options for pediatric patients with severe BPD-PH as reported recently for adult patients with BPD-PH [6].

Pulmonary hypoplasia due to premature development of the lung is one of the causes of pediatric PH[7]. Pulmonary angiography revealed hypoplastic peripheral pulmonary arteries and a dilated main pulmonary artery (Figure 2A-C). Additionally, pulmonary perfusion scintigraphy showed reduced pulmonary blood flow in the bilateral lower lungs (Figure 2E). Capillary proliferation shown in pathological findings (Figure 3G) can be explained as a compensatory response for hypoplastic vascular bed[8]. It is also possible that treatment with pulmonary vasodilators promoted vascular growth[9]. On the other hand, chest CT showed a combination of fibrotic areas and emphysematous low-density areas with several distinct bullae at the upper and lower lobes. Along with the above mechanisms, lung parenchymal destruction and interstitial inflammation or fibrosis cause PH due to reduction of the vascular bed and subsequent hypoxic pulmonary vasoconstriction. Notably, CT-based lung volume estimation showed that the lung volume had been constantly growing (Figure 2G), and that after the CPA episode, the lung volume/height ratio had expanded and subsequently plateaued until BLTx (Figure 2H). We speculate that the high positive airway pressure ventilation during CPA resuscitation caused the exacerbation of emphysematous changes in the patient's vulnerable lungs.

The pathological findings revealed that pulmonary hypoplasia due to ceased lung development at the saccular stage led to BPD-PH. In addition, there were various irreversible changes in the lungs, including emphysema-like cystic changes, which may be due to the fragility associated with extension because there was no evidence of epithelial injury like adult chronic obstructive pulmonary disease. As described above, CT-based lung volume estimation also supports these findings. In contrast, the fibrotic changes with chronic epithelial injury and alveolar repair may be due to repetitive inflammation such as infection, hypo/hyperoxia, or ventilation-associated lung injury.

Conclusion

To the best of our knowledge, this is the first case report of BLTx in a pediatric, irreversible BPD-PH patient with detailed pathohistological findings and clinical examination, including right heart catheterization and CT-based lung volume estimation. Lung transplantation is one of the treatment options for severe BPD-PH. Pulmonary vasodilators might improve both PH and fibrosis due to BPD.

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