

Pediatric case report: successful bilateral lung transplantation performed to treat an 8-year-old girl with pulmonary interstitial fibrosis due to surfactant protein (SP)-C gene mutation

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To the Editor: Pediatric lung transplantation is a highly specialized therapy for end stage pulmonary disease in children, and is performed in only a handful of transplant centers around the world. In the past decade, about 100 cases of pediatric lung transplantation have been performed annually all over the world. Most centers perform 1 to 4 pediatric lung transplantations annually, with only five centers performing more than five per year. Since 2007, our team has performed lung transplantations in 12 pediatric patients, among whom 11 were over 10 years old.

Indications for pediatric lung transplantation vary by age, ranging from primary lung pathologies and cystic fibrosis to congenital heart disease with pulmonary vascular anomalies or pulmonary hypertension. In children over the age of 5 years, cystic fibrosis is the most common indication. In infants, the most common indications are pulmonary hypertension of all forms (37%, including primary pulmonary arterial hypertension and congenital heart disease) and surfactant disorders (30%).^[1,2] In our center, 7 out of 12 patients received lung transplantation because of pulmonary hypertension.

Mutations of the surfactant protein (SP)-C gene (*SFTPC*) have been associated with neonatal respiratory distress syndrome (RDS) and childhood interstitial lung disease (ILD). If accurate diagnosis and proper management are delayed, irreversible respiratory failure demanding lung transplantation may ensue.

In this report, we describe a rare case of successful bilateral lung transplantation performed to treat an 8-year-old girl with pulmonary interstitial fibrosis due to the *SFTPC* mutation. To our knowledge, this is the first successful pediatric bilateral lung transplantation recipient younger than 10 years old in the mainland of China.

The girl was admitted to our hospital due to chronic tachypnea, cough, and poor nutritional status in July 2019. She developed symptoms when she was 9 months old. At that time, she was diagnosed with severe pneumonia and pneumothorax. During her hospitalization, she was intubated because of respiratory failure. She was discharged after intensive care, but subsequently had gradually worsening symptoms of cough, tachypnea, and failure to thrive. In the past few years, her symptoms had been aggravated with recurrent respiratory tract infections. Despite inpatient treatment with antibiotics and combined use of oral prednisolone, her symptoms worsened. Also, the patient did not respond to the long-term oxygen therapy.

In July 2019, she was referred to our hospital for a chance of lung transplantation. The girl showed poor nutritional status, with height of 110 cm and weight of 18.4 kg (body mass index: 15.2 kg/m²). Clinically, her 6-min walking test result was 230 m, while minimal pulse oxygen saturation (SO₂) was 90% (oxygen flow rate 2.5 L/min). Initial venous blood gas analysis showed pH 7.38, partial pressure of carbon dioxide 50.1 mmHg, partial pressure of oxygen 53 mmHg, and SO₂ 86%. A chest computed tomography (CT) scan showed pulmonary interstitial fibrosis with pulmonary infections and emphysema.

Genetic analysis was performed for relevant genes including *ABCA3*, *SFTPC*, and *STAT3*. The genetic analysis revealed a novel heterozygous c.218T>C, chr8-22020609*1p.173T, a kind of autosomal dominant mutation of *SFTPC*. However, the same mutation was not found in her parents.

After detailed discussion with the family, she was listed on Chinese Network for Organ Sharing as a lung transplantation candidate on July 31th, 2019. Within two months, she underwent successful bilateral lung transplantation

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DOI:

10.1097/CM9.0000000000001053

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Chinese Medical Journal 2021;134(4)

Received: 22-03-2020 Edited by: Pei-Fang Wei

from the donor who was a 15-year-old boy. The patient was weaned off mechanical ventilation 1 day after lung transplantation. She was transferred from the intensive care unit to the general ward 3 days post-lung transplantation. She was discharged 20 days post-lung transplantation without acute complications. Immunosuppressive drugs including tacrolimus, mycophenolate mofetil, and methylprednisolone were administered. The donated lungs have good recruitment in the little girl's chest, as can be seen from the comparison between chest CT scans before and after the operation [Figure 1A and 1B]. After lung transplantation, the 8-year-old girl, for the first time in her life, was not coughing all day. She was running freely without any respiratory symptoms and gained weight to reach the standard of her age.

There are many reported cases of *SFTPC* mutations associated with RDS, childhood ILD, or adult ILD. This case is unique in that the patient developed respiratory failure symptoms at 9 months of age and needed mechanical ventilation. She continued to have respiratory symptoms and showed acute aggravation with respiratory

infection. The typical course of our case originally raised suspicion for a surfactant mutation abnormality of *SFTPC*.

The patient has been suffering from ILD and respiratory failure since birth. She cannot live without portable oxygen. That is why she and her parents made their decision to receive lung transplantation to relieve her symptoms. Although other measures have been used, size matching in lung transplantation is usually based on the ratio of donor to recipient predicted total lung capacity (TLC). Primarily based on adult data, the International Society for Heart and Lung Transplantation guidelines on lung transplant size suggest an acceptable donor size match of 75% to 125% of recipient TLC,^[3,4] while others have suggested adjustments to this size range based on recipient lung pathology or measures of actual chest dimensions.^[5] Donor-recipient size matching in lung transplantation by CT lung volume may be a reasonable approach because size matching is an anatomical issue.^[6]

There are no specific guidelines regarding size matching in pediatric patients. So it may cause difficulty to choose the

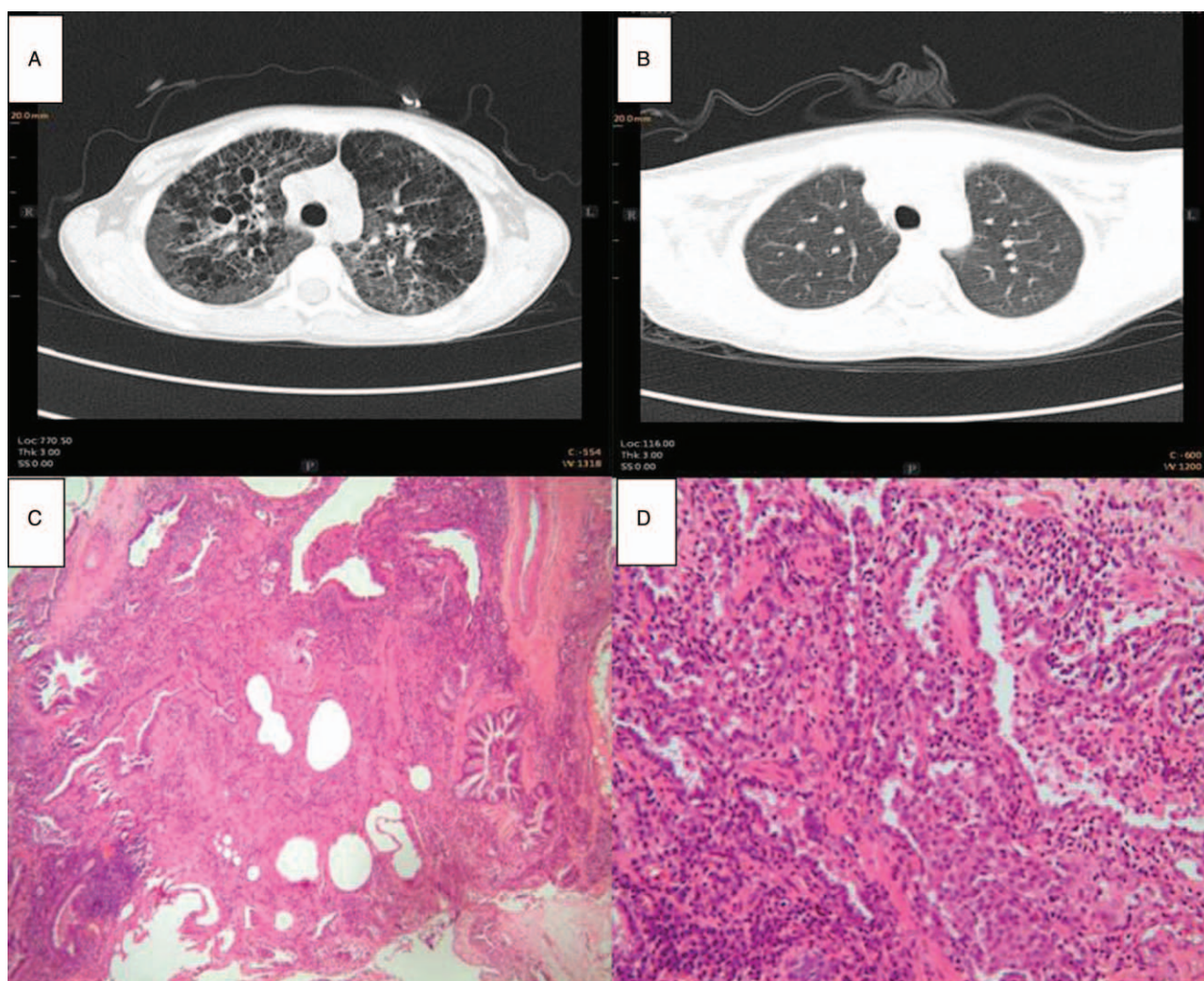


Figure 1: (A) Chest CT scan before the operation; (B) Chest CT scan 3 months after the operation; (C and D) Pathological results: chronic pulmonary interstitial fibrosis along with destruction and collapse of pulmonary alveoli (hematoxylin and eosin staining; C, original magnification $\times 40$; D, original magnification $\times 200$). CT: Computed tomography.

proper donor. In our report, the recipient is 8 years old, with height of 110 cm and weight of 18.4 kg. However, the donor is 15 years old, with height of 165 cm and weight of 70 kg. Initially, we planned to perform lobar lung transplantation, considering that the huge mismatch may lead to anastomotic challenges.^[7] During the operation, we found that the disparity between donor and recipient was not as large as anticipated. After anatomic resection of the left pulmonary lingular segment and the right middle lobe, the size matched perfectly, without causing much anastomotic difficulty. We chose the clamshell incision and used 4 h to finish the bilateral lung transplantation. The post-operative pathological result showed chronic pulmonary interstitial fibrosis along with destruction and collapse of pulmonary alveoli [Figure 1C and 1D].

A multi-disciplinary team of pediatric pulmonologists, thoracic surgeons, organ transplantation team, and infectious disease specialists were closely monitoring this patient for possible complications. She was discharged from the hospital 20 days after the surgery benefiting from the enhanced recovery after surgery. In addition, rehabilitation therapist played an important role in the recovery.

The limitation to our case report is that we cannot yet anticipate the long-term outcome of this patient. Despite the advances described above as well as a gradual improvement in long-term post-transplant survival, patients receiving lung transplantation continue to suffer from less than ideal long-term outcomes, even in pediatric patients. Overall survival after lung transplantation is comparable between pediatric and adult transplant recipients, with median survival of 5.4 and 5.9 years, respectively, for those who received transplantation between 1990 and 2015. Within the pediatric age group, post-transplantation survival is better for patients aged <12 years than for patients aged 12 to 17 years (median survival of 6.5 to 8.2 and 4.8 years, respectively).

This case is about cadaveric lung transplantation (CLT), but living-donor lobar lung transplantation (LDLLT) has been successfully used in lung transplantation. There was no significant difference in patient survival between CLT and LDLLT. Between 1998 and 2015, 55 children underwent lung transplantation at nine lung transplantation centers in Japan.^[8] It is worth noting that only seven children received CLT, and all others received LDLLT. LDLLT is often the only realistic option for very ill patients especially for children.

Chronic lung allograft dysfunction (CLAD) manifested as bronchiolitis obliterans (BO) is the most common cause of graft failure and death beyond the first year of lung transplantation. Retransplantation can significantly improve the overall survival rate in pediatric patients with CLAD, with a 1-year survival rate of 91.7% and a 5-year

survival rate of 80.2%.^[9] A deep understanding of BO is achieved, however, with further insight into the adverse early impact of neutrophils and monocytes, followed by a cascade that leads to recruitment of immune mediators, graft injury, fibrosis, and graft loss. In conclusion, pediatric lung transplantation is promising and worth our continuous efforts.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's guardians have given consent for her images and other clinical information to be reported in the article. The guardians understand that her name and initials will not be published and due efforts will be made to conceal the identity of the patients, although anonymity cannot be guaranteed.

Conflicts of interest

None.

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How to cite this article: Liu F, Jin YL, Li HX, Chen Y, Wu B, Shi LZ, Chen JY. Pediatric case report: successful bilateral lung transplantation performed to treat an 8-year-old girl with pulmonary interstitial fibrosis due to surfactant protein (SP)-C gene mutation. *Chin Med J* 2021;134:498–500. doi: 10.1097/CM9.0000000000001053