Successful Single-Lung Transplantation for Multicentric Castleman Disease

Yuki Morimura, MD,* Fengshi Chen, MD, PhD,* Tomoaki Kinjo, MD, Aya Miyagawa-Hayashino, MD, PhD, Takeshi Kubo, MD, Tetsu Yamada, MD, Masaaki Sato, MD, PhD, Akihiro Aoyama, MD, PhD, and Hiroshi Date, MD, PhD

Departments of Thoracic Surgery, Diagnostic Pathology and Diagnostic Radiology, Kyoto University, Kyoto, Japan

We report a rare case of multicentric Castleman disease treated successfully with single-lung transplantation. A 12-year-old patient developed increasing dyspnea. Elevated serum interleukin-6 (177.0 pg/mL) and immunoglobulin G (IgG; 13,900 mg/dL) levels were observed. Steroid therapy was effective but the respiratory condition gradually deteriorated. He underwent single-lung transplantation at 36 years of age. Preoperative interleukin-6 and IgG levels were 0.3 pg/mL and 5,260 mg/dL, respectively. After 6 months he is alive without symptoms. Postoperative IgG levels were restored to normal limits (1,624 mg/dL) and interleukin-6 levels remained within normal limits (1.4 pg/mL). Overinflation of the native left lung also improved. [Ann Thorac Surg 2014;98:e63–5] © 2014 by The Society of Thoracic Surgeons

Castleman disease, also known as angiofollicular mediastinal lymph node hyperplasia or benign giant lymph node hyperplasia, is a rare atypical lymphoproliferative disorder characterized by hyperplasia of the lymphoid follicles [1, 2]. Although Castleman disease is localized in a majority of the cases, a proliferative type known as multicentric Castleman disease (MCD) has been recognized based on clinical and histologic features [3, 4]. Clinical symptoms associated with MCD include fever, fatigue, and hypergammaglobulinemia. An occasional lung parenchymal involvement has been observed, although this has not been well clarified. Here, we report a rare case of MCD with severe respiratory insufficiency treated successfully with a cadaveric single-lung transplant.

A 12-year-old Japanese boy was admitted to a regional hospital with a 3-month history of fever, abnormal shadow on chest radiography, and peripheral lymphadenopathy. Laboratory tests revealed elevated levels of serum protein (9.8 g/dL) and immunoglobulin G (IgG) (5,469 mg/dL). After open lung biopsy, he was diagnosed with MCD. His symptoms resolved without any treatment and he completed all follow-up visits. However, after 5 years, he was readmitted with exacerbation of dyspnea. Laboratory tests revealed elevated levels of serum protein and IgG (Table 1). The serum interleukin (IL)-6 level was elevated to 177.0 pg/mL. Methylprednisolone pulse therapy was initiated at a dose of 1,000 mg/day for 3 consecutive days, followed by oral methylprednisolone (starting dose 40 mg/day, which was gradually tapered to 7.5 mg/day over several weeks), along with 50 mg/day of mizoribine. His symptoms were controlled with treatment but his respiratory function continued to gradually decline. At 34 years of age, he was listed for cadaveric lung transplantation. At this time, he required 3 L/minute of oxygen therapy at home throughout the day. His total serum protein level was 9.2 g/dL, IgG level was 5,260 mg/dL, and IL-6 level was 0.3 pg/mL. Based on these data, the MCD state was considered to be stable. Preoperative chest radiography and computed tomography (CT) demonstrated numerous thin-walled cysts in both lungs. The lung parenchyma in the upper lobes was almost entirely replaced with these cystic structures, and only a minimal amount of functioning lung tissue remained. In the lower lobes, cystic changes were observed predominantly along the pulmonary arteries, bronchi, and veins (Figs 1A and 2A-B). At 36 years of age, he underwent cadaveric right single-lung transplantation. Histologic examination of the extracted right lung showed an extensive infiltration of small lymphocytes with variable numbers of plasma cells in the peribronchovascular interstitium and alveolar septa (Fig 3A). A prominent interstitial lymphoid infiltrate was detected predominantly in the middle and lower lobes rather than the upper lobe. In addition to thickening of the bronchovascular interstitium and alveolar wall, cystic enlargement of the alveolar walls was observed, predominantly in the upper lobe (Fig 3B). These findings were consistent with plasma cell-type Castleman disease. Postoperative immunosuppression included a triple drug regimen (tacrolimus, prednisolone, and mycophenolate mofetil). The postoperative recovery was uneventful.

<table>
<thead>
<tr>
<th>Event</th>
<th>Second Admission</th>
<th>Assessment for LT</th>
<th>6 Months After LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>17</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>IgG (mg/dL)</td>
<td>13,900</td>
<td>5,260</td>
<td>1,498</td>
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<td>IL-6 (pg/mL)</td>
<td>177</td>
<td>0.3</td>
<td>1.4</td>
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<tr>
<td>FVC (L)</td>
<td>2.02</td>
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<td>FEV1 (L)</td>
<td>1.67</td>
<td>0.44</td>
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<tr>
<td>%FEV1</td>
<td>82.7%</td>
<td>32.6%</td>
<td>71.1%</td>
</tr>
</tbody>
</table>

FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IgG = immunoglobulin G; IL-6 = interleukin-6; LT = lung transplantation.
without any infection or rejection. The patient has survived for 6 months, without any oxygen supplementation. The 6-month postoperative chest CT showed no signs of recurrent MCD in the graft or exacerbation of pulmonary manifestations of MCD in the native lung. Interestingly, chest radiography revealed that over-inflation of the left native lung had improved (Fig 1B). His serum total protein and IgG levels decreased within the normal limits (6.5 g/dL and 1,624 mg/dL, respectively), and serum IL-6 levels also remained within the normal limits (1.4 pg/mL).

Comment
We report a rare case of MCD with severe lung involvement treated with single-lung transplantation. To date, only 1 case of MCD with bronchiolitis obliterans treated with bilateral live-donor lobar lung transplantation has been reported [5].

Notably, the patient’s preoperative serum IgG levels remained high despite the clinically stable MCD state with normalized serum IL-6 levels. Furthermore, after right single-lung transplantation, the total serum protein and IgG levels returned to within normal limits, although the diseased left lung was still present. We speculated that this finding might be related to the postoperative immunosuppressive therapy. Ohsumi and colleagues reported that posttransplant immunoglobulin levels were significantly lower than pretransplant levels [6]. They also presumed that this phenomenon was an effect of immunosuppressive therapy. In addition, this phenomenon also suggests immunosuppression as a potential treatment option in the management of refractory Castleman disease.

Hyperinflation of the native lung is a known complication of single-lung transplantation for patients with emphysema. However, overinflation of the left native lung was improved on radiologic examination after right single-lung transplantation in the present...
The true mechanism of this phenomenon is unclear, but it could not be explained only by the replacement of the diseased native right lung with a healthy donor lung. Similar to the postoperative normalization of total serum protein and IgG levels, it might be attributed to some undetermined effect of postoperative immunosuppression.

It is generally difficult to determine an indication for lung transplantation in MCD, as it is a potentially systemic disease. However, when the clinical symptoms of MCD are controlled as in the current patient, he was clinically stable with well-controlled serum marker levels during a long-term clinical course. Thus, lung transplantation is an effective treatment for MCD patients with severe lung involvement. Because of the severe donor shortage in Japan we chose single-lung transplantation for this patient, but we consequently found single-lung transplantation is also effective when a diseased hemi-lateral lung is present.

In conclusion, a rare case of MCD with end-stage respiratory failure was treated successfully with single-lung transplantation. Postoperatively, IgG levels restored to normal limits and interleukin-6 levels remained within normal limits. Furthermore, overinflation of the native left lung also improved.

References

Fig 3. Pathology of the explanted native right lung. (A) The upper lobe showed cystic enlargement of the alveolar walls and interstitial infiltration of lymphocytes and plasma cells (hematoxylin and eosin staining, original magnification: 20×). (B) The lower lobe showed a densely cellular appearance of the alveolar septa and peribronchial interstitium (hematoxylin and eosin staining, original magnification: 40×).