

Successful Lung Transplantation in a Patient with Myasthenia Gravis

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A 47-year-old man with myasthenia gravis (MG) was admitted for a lung transplant. He had bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation due to acute myeloid leukemia. MG developed after stem cell transplantation. Bilateral sequential lung transplantations and a total thymectomy were performed. The patient underwent right diaphragmatic plication simultaneously due to preoperatively diagnosed right diaphragmatic paralysis. A tracheostomy was performed and bilevel positive airway pressure (BiPAP) was applied on postoperative days 8 and 9, respectively. The patient was transferred to the general ward on postoperative day 12, successfully weaned off BiPAP on postoperative day 18, and finally discharged on postoperative day 62.

Key words: 1. Bronchiolitis obliterans
2. Lung transplantation
3. Myasthenia gravis
4. Plication
5. Thymectomy

Case report

A 46-year-old man was admitted for a bilateral lung transplant. The patient had a history of acute myeloid leukemia (AML) and received allogeneic hematopoietic stem cell transplantation (HSCT) in 1999. He experienced graft-versus-host disease (GVHD) and recurrent pneumonia, including cytomegalovirus (CMV) pneumonia and bacterial pneumonia. Although the AML was in complete remission, the patient had been followed up for bronchiolitis obliterans (BO). He had been treated with home oxygen therapy. A pulmonary function test revealed a forced vital capacity (FVC) of 1.33 L (27%), a forced expiratory

volume in the first second of expiration (FEV₁) of 1.05 L (29%), a FEV₁/FVC ratio of 79%, and a forced expiratory flow between 25% and 75% (FEF_{25%-75%}) of 0.98 L/sec (26%). The diffusing capacity of the lungs for carbon monoxide was 6.2 mL/mm Hg per minute (26%). The partial pressure of oxygen upon arterial blood gas analysis (performed while the patient was breathing room air) was 63.1 mm Hg, and the partial pressure of carbon dioxide was 54.4 mm Hg.

The patient's respiratory symptoms were aggravated due to myasthenia gravis (MG). He developed right ptosis and diplopia and was diagnosed with ocular MG in 2004, based on a positive Jolly test and

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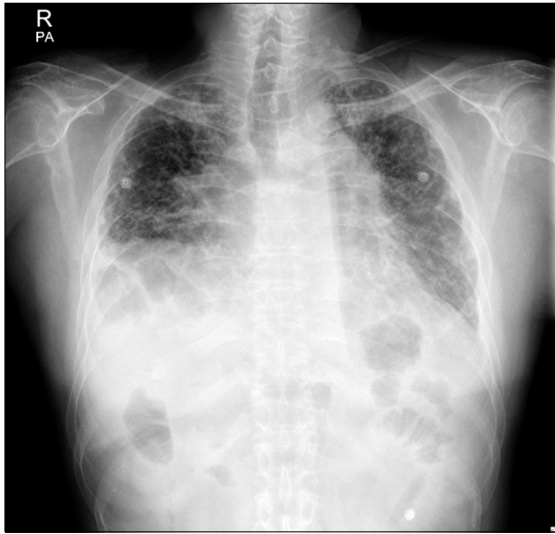


Fig. 1. Preoperative chest X-ray showing bilateral diffuse reticular opacities and right diaphragm elevation.

an elevated level of acetylcholine receptor antibody (Ach-R-Ab, 7.67 nmol/L). He started pyridostigmine therapy, and visual symptoms were controlled. In 2013, the patient was readmitted for pneumonia. He was diagnosed with generalized MG and presented with generalized weakness and dyspnea. His Ach-R-Ab serum level remained elevated, at 7.63 nmol/L. Six sessions of plasmapheresis were performed and added to the steroid therapy. In 2014, tacrolimus was started at 3 mg once daily and continued until early 2016 when he developed tacrolimus-induced chronic kidney disease. Computed tomography findings showed no thymoma or thymic hyperplasia. The patient had an elevated right diaphragm. Based on serial X-ray follow-ups, the right thoracic cavity was shown to decrease in size after the CMV pneumonia (Fig. 1). A fluoroscopy-guided examination confirmed the right diaphragmatic paralysis. Given the presence of BO, generalized MG without thymoma, and diaphragmatic paralysis, his respiratory function deteriorated. Thus, we decided to perform bilateral sequential lung transplantations.

The bilateral sequential lung transplantations were performed using cardiopulmonary bypass support and via a clamshell thoracotomy. Subsequently, a total thymectomy was conducted laterally from phrenic nerve to phrenic nerve to prevent MG recurrence and save pulmonary function. Dense adhesion in both pleural cavities was detected; thus, adhesiolysis was

conducted. Right diaphragm plication was then performed due to the elevated diaphragm. The ischemic time for the bilateral sequential lung transplantations was 5 hours 9 minutes. After an initial infusion of Simulect, tacrolimus, mycophenolate mofetil, and steroids were used as immunosuppressive drugs after the lung transplantation. The tacrolimus level was titrated based on the daily serum level, with a targeted therapeutic range of 11–12 ng/mL, and renal function was cautiously monitored. The patient had difficulty weaning off mechanical ventilation support; he had respiratory muscle weakness and no generalized MG symptoms postoperatively. On postoperative day 8, we decided to perform tracheostomy and administered pyridostigmine at an initial dose of 30 mg every 8 hours per day for the newly developed subjective generalized weakness. On postoperative day 9, bilevel positive airway pressure (BiPAP) was applied. The patient was transferred to the general ward on postoperative day 12. He was then weaned from BiPAP on postoperative day 18 without complications. Pyridostigmine was also discontinued due to an improvement in generalized symptoms and pyridostigmine-induced gastrointestinal adverse effects on postoperative day 18. The level of Ach-R-Ab decreased from 1.4 to 0.03 nmol/L postoperatively. The patient underwent a routine postoperative rehabilitation program, including extremity stretching, deep breathing, standing on one leg, and ambulation. The patient was discharged on postoperative day 62. The patient underwent a follow-up pulmonary function test 8 months postoperatively. The results showed improvement (FVC, 1.75 L [38%]; FEV₁, 1.53 L [44%]; FEV₁/FVC, 88%; and FEF_{25%-75%}, 0.98 L/sec [26%]) but still presented a severely restrictive pattern. The patient was followed up monthly, and the last chest X-ray taken 8 months postoperatively showed a left-sided pleural effusion and no sign of right diaphragm elevation (Fig. 2). The patient was prescribed with 5 mg of prednisolone daily, 1.25 mg of tacrolimus twice daily, and 500 mg of mycophenolate mofetil twice daily. There were no MG events after discharge.

Discussion

BO is a complication of allogeneic HSCT. The overall prevalence of BO is approximately 5.5%, with

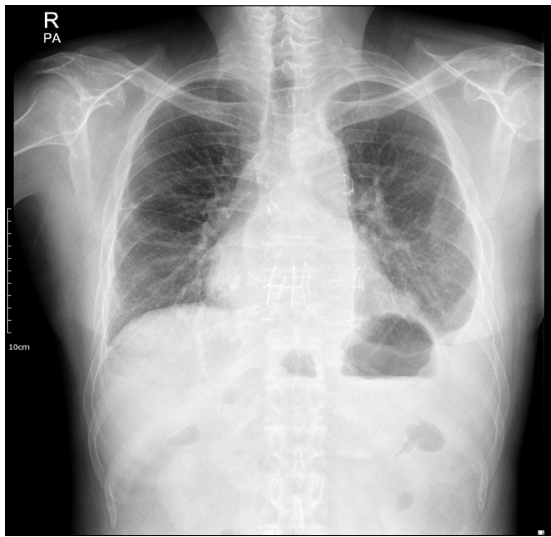


Fig. 2. Follow-up chest X-ray taken 8 months postoperatively. The patient exhibited a lowered right diaphragm. Left pleural effusion was detected.

10% of patients surviving at least 1 year after transplant and 16% of all patients developing chronic GVHD [1]. The prognosis of BO is poor, with an overall survival rate of 44% at 2 years and 13% at 5 years. Lung transplantation is regarded as the last salvage treatment for BO [1].

The development of MG after allogeneic HSCT, with or without chronic GVHD, has been reported in a few cases [2]. In the current case, MG developed after HSCT. Generalized MG can be treated with both surgical and medical treatments. For medical therapy, immunosuppression is the mainstay of treatment for MG. Eighty-two percent of patients with MG received immunosuppressant for at least 1 year [3]. Thymectomy is another treatment modality of MG. Patients who underwent a thymectomy even without evidence of thymoma required lower dose of steroids or immunosuppressants and showed lower rate of hospitalization or exacerbation than those who had been treated by medication alone [4]. Thymectomy can be easily conducted during lung transplantation because a clamshell thoracotomy allows for good exposure of the mediastinum. The International Society for Heart and Lung Transplantation developed a consensus document for the selection of lung transplant candidates in 2014. According to the guidelines, lung transplantation is contraindicated in patients with severely limited functional status and poor re-

habilitation potential; however, no indication or contraindication for patients with MG was included [5].

The current case is the first report of lung transplantation in a patient with MG. To control MG symptoms, the patient was treated with immunosuppressants and pyridostigmine preoperatively (50 mg of prednisone every other day for 2.5 years, 3 mg of tacrolimus daily for 3 years, and 90 mg of pyridostigmine 4 times daily). The patient underwent plasmapheresis 6 times because of respiratory failure and an elevated Ach-R-Ab serum level (7.63 nmol/L). Additional plasmapheresis was not necessary, because no other respiratory failure occurred and the Ach-R-Ab serum level lowered after plasmapheresis and maintained under 1.4 nmol/L. After a lung transplantation, immunosuppressants are required to prevent rejection and treat MG. However, few differences in immunosuppressant doses have been reported in the literature. Three milligrams of tacrolimus per day was recommended for MG treatment instead of titrating the dosage based on the serum level [6]. The tacrolimus dose is adjusted to maintain a target rough concentration of 5–15 ng/mL [7] in lung-transplantation patients (the target rough concentration used in our center is 11–12 ng/mL during the immediate postoperative period). In this case, since the patient experienced tacrolimus-induced chronic kidney disease preoperatively based on the MG therapeutic dose, the tacrolimus dose was adjusted based on the serum level. The patient is currently taking 1.25 mg of tacrolimus twice daily and 5 mg of prednisolone once daily. The dosage of pyridostigmine can be adjusted based on the clinical symptoms. The patient was administered pyridostigmine on postoperative day 8, due to the suspicion of generalized weakness from MG. However, the required dose of pyridostigmine was less than that of the preoperative therapeutic dose (90 mg 4 times daily to 30 mg 3 times daily). Pyridostigmine was also discontinued due to an improvement of the patient's generalized symptoms and a pyridostigmine-induced gastrointestinal adverse effect on postoperative day 18. The patient was weaned from BiPAP on postoperative day 18 without complications.

Patients with MG who are rather young, whose symptoms can be well controlled by medication, and whose activities are not restricted can be candidates for lung transplantation. Consequently, this patient

with BO and MG underwent bilateral sequential lung transplantations successfully.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Chien JW, Duncan S, Williams KM, Pavletic SZ. *Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation-an increasingly recognized manifestation of chronic graft-versus-host disease*. Biol Blood Marrow Transplant 2010;16(1 Suppl):S106-14.
2. Zaja F, Barillari G, Russo D, Silvestri F, Fanin R, Bacarani M. *Myasthenia gravis after allogeneic bone marrow transplantation: a case report and a review of the literature*. Acta Neurol Scand 1997;96:256-9.
3. Sanders DB, Evoli A. *Immunosuppressive therapies in myasthenia gravis*. Autoimmunity 2010;43:428-35.
4. Wolfe GI, Kaminski HJ, Aban IB, et al. *Randomized trial of thymectomy in myasthenia gravis*. N Engl J Med 2016;375: 511-22.
5. Weill D, Benden C, Corris PA, et al. *A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation*. J Heart Lung Transplant 2015;34:1-15.
6. Cruz JL, Wolff ML, Vanderman AJ, Brown JN. *The emerging role of tacrolimus in myasthenia gravis*. Ther Adv Neurol Disord 2015;8:92-103.
7. Scheffert JL, Raza K. *Immunosuppression in lung transplantation*. J Thorac Dis 2014;6:1039-53.