

## Recurrent Lung Cancer in the Mediastinum Noticed after a Living-Donor Lobar Lung Transplantation

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**We describe a case of lung cancer in a living-donor lobar lung transplantation (LDLLT) recipient that was identified because of a recurrence in the mediastinum. The patient was a 55-year-old woman who had undergone bilateral LDLLT for nonspecific interstitial pneumonia. She developed dyspnea upon exertion at 15 months after transplantation and was diagnosed as suffering from chronic rejection. A computed tomography scan also revealed enlarged mediastinal lymph nodes (LNs) that were subsequently confirmed as poorly differentiated squamous cell carcinomas. Retrospectively, a small tumor was found in the explanted right lung tissue, the microscopic findings of which were similar to those of the mediastinal lesion. A whole body examination revealed no other lesions; thus we resected the LNs and subsequently irradiated the mediastinum. Recurrent disease appeared in her transplanted lungs 10 months after resection of the LNs, and she died of pneumonia with chronic rejection 2 years and 7 months after transplantation. (Ann Thorac Cardiovasc Surg 2009; 15: 119–122)**

**Key words:** lung cancer, lung transplantation, immunosuppression, living-donor lobar lung transplantation

### Introduction

Lung transplantation is a commonly employed therapy in the treatment of patients with various end-stage lung diseases, including smoking-related chronic obstructive pulmonary disease (COPD) and idiopathic interstitial pneumonia (IIP). With the increasing number of cases and the improvement of clinical outcomes after lung transplantation, neoplasms in recipients have become one complication of lung transplantation.<sup>1)</sup> The bronchogenic

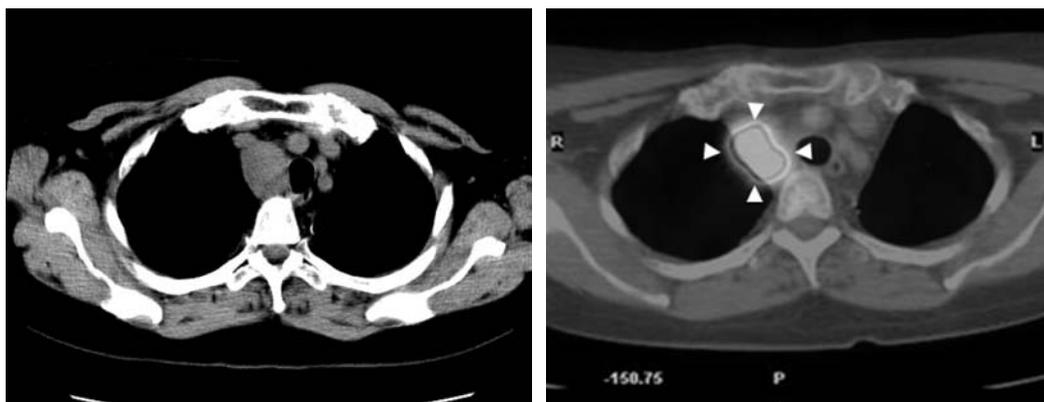
carcinomas in patients who have undergone lung transplantation can originate within either the recipient's organ or the donor's.<sup>2–5)</sup> Most types in recipients are lung cancers that have occurred in the retained native lungs of recipients following a single lung transplantation.<sup>6)</sup> Although lung cancer is the leading cause of death from cancer worldwide and has an unfavorable prognosis,<sup>7)</sup> one of the characteristics of lung cancer in transplanted patients is an even more dismal clinical outcome and an aggressive disease because of the patient's immunosuppressed status, compared with the outcomes of non-transplanted patients.

We introduced living-donor lobar lung transplantation (LDLLT) at Okayama University Hospital in October 1998<sup>8)</sup> and as of September 2007 we had performed 59 cases of lung transplantation, consisting of 47 cases of living-donor transplantation and 12 of cadaveric.<sup>9)</sup> In our series of lung transplantations, we experienced one female recipient who had undetected cancer in the native lung at the time of the transplantation, but she was subsequently diagnosed with it when metastatic mediastinal lymph nodes (LNs) were detected.

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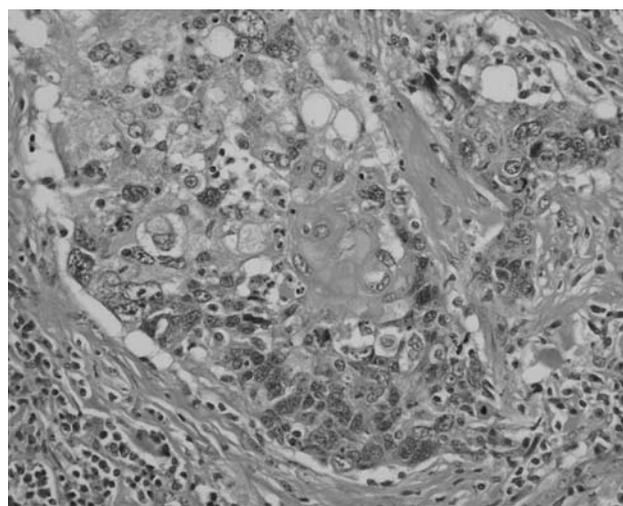
**Fig. 1.** Image exam.

- A:** A computed tomography (CT) scan of the chest shows that enlarged LNs were detected in the mediastinum. An enhanced CT is unavailable because of allergy to contrast material.
- B:** A positron emission tomography CT scan (PET-CT) shows the 2-deoxy-2-[F-18] fluoro-D-glucose uptake in mediastinum lymph nodes (arrowheads).

A | B

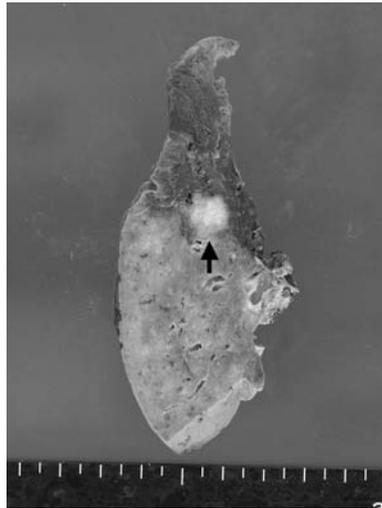
## Case Report

The patient was a 55-year-old woman with no history of smoking. She had undergone bilateral LDLLT for non-specific interstitial pneumonia (NSIP). The donors were her two sons, who also had no history of smoking. Post-operative immunosuppression was a triple drug therapy consisting of cyclosporine, azathioprine, and prednisone. Her postoperative course was relatively uneventful except that she required reparation for sternal dehiscence. The patient had been routinely followed at an outpatient clinic. She complained of dyspnea on exertion at 15 months after transplantation, which was assumed to be caused by acute rejection based on imaging and blood exams. She was treated with methylprednisolone (500 mg/day for 3 days), and cyclosporine and azathioprine were changed to tacrolimus and mycophenolate mofetil to augment immunosuppression. At that time, a computed tomography (CT) examination of the chest showed swollen LNs in the upper mediastinum (Fig. 1). We suspected a posttransplantation lymphoproliferative disease. A mediastinoscopy was performed, and a poorly differentiated squamous cell carcinoma was diagnosed by pathological examination (Fig. 2). We could not detect any other abnormal lesions by means of imaging examinations, including a positron emission tomography CT (PET-CT) scan (Fig. 1). We reinvestigated the native lung tissue that had been explanted at transplantation. We found a poorly differentiated squamous cell carcinoma (13 mm in diameter) in the explanted right upper lobe (Fig. 3) and a metastatic LN in the hilum of the explanted

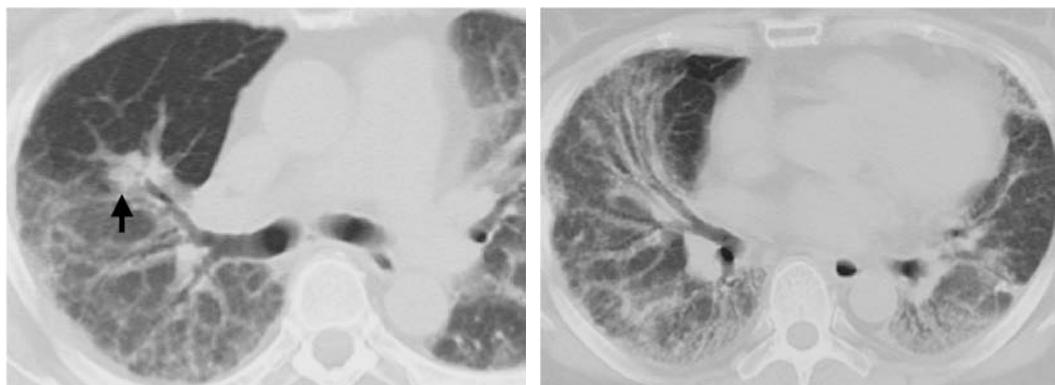


**Fig. 2.** Microscopic finding of biopsied mediastinal lymph node. Biopsied lymph node shows a poorly differentiated squamous cell carcinoma revealing keratinization, cytologic atypia, and pleomorphism.

right lung. A retrospective review of pretransplant CT scans revealed a pulmonary nodule that was thought to be a primary lesion (Fig. 4). We concluded that the mediastinal lesion was metastatic LN from lung cancer in the explanted native lung. Regarding therapy, dissection of the mediastinal and cervical LNs was performed through a median sternotomy and neck incision 16 months after transplantation. The postoperative course was uneventful, and radiation on the mediastinum with 46 Gy was subsequently performed. Two years after transplantation, the patient developed dyspnea with mild fever. Examinations



**Fig. 3.** Tumor in the explanted right lung.  
A tumor 13 mm in size exists in the right upper lobe (arrow).



**Fig. 4.** CT scan findings 1 month before transplantation.  
A: A CT scan shows a nodule with an irregular margin in the right upper lobe (arrow).  
B: A CT scan shows extensive bilateral areas of ground-glass opacities superimposed reticulation and traction bronchiectasis, which represent severe fibrosis.

A | B

showed chronic rejection and the recurrence of lung cancer as multiple nodules in the implanted lung tissue. She died of pneumonia with chronic rejection 2 years and 7 months after transplantation.

## Discussion

According to international guidelines for the selection of lung transplant candidates, lung transplantation is basically contraindicated for patients with active malignancy within the past two years.<sup>10)</sup> On the other hand, Garver et al. reported a challenging attempt at lung transplantation to save patients with bronchioloalveolar carcinoma (BAC), which is known to occur less frequently in distant and lymph node metastases.<sup>11)</sup> Further, de Perrot et al. conducted an international survey to examine the out-

comes of patients having lung cancer at the time of transplantation. These studies suggest that lung transplantation can be indicated for patients with stage I lung cancer or with advanced multifocal BAC.<sup>12)</sup>

COPD and IIP are not only lung diseases requiring lung transplantation, but they are also well-known risk factors for lung cancer. Although the patient presented here had no history of smoking, she did have end-stage NSIP, which is also a risk factor for lung cancer. Two factors are responsible for delaying her diagnosis and treatment. The tumor was difficult to identify on the CT exam because the NSIP produced unspecific background findings (Fig. 4). Moreover, although we usually slice the explanted lung tissue in widths of approximately 15 mm for examination, the nodule—which had a diameter of 13 mm—happened to escape the cut surface. Careful preop-

erative examination and examination of the explanted specimens are critical for the diagnosis of lung cancer existing in recipient lungs, especially in patients with a high risk of lung cancer.

Regarding the treatment for recurrent lung cancer in the mediastinal LNs, we chose a surgical approach because standard systemic chemotherapy would augment the immunosuppressive state, increasing the risk of a fatal infection. Indeed, this patient was thought to require more aggressive immunosuppression to prevent further rejection. Furthermore, a whole body examination including PET-CT revealed no evidence of metastatic lesions except for the mediastinal LNs at 16 months after transplantation. Unfortunately, the patient developed recurrent disease at 10 months after resection of the metastatic LNs. Malignant tumors in transplant recipients, including lung cancer among lung transplant recipients, are generally more aggressive than those in nontransplanted patients.<sup>2,13</sup> One reason for this is the impairment of the cell-mediated immune system by immunosuppressants,<sup>14</sup> especially since lung and heart transplants require more intense immunosuppressive regimens than those used for other solid organ transplantations.<sup>15</sup> Moreover, previous studies have demonstrated that immunosuppressants, such as cyclosporine and tacrolimus, can promote cancer progression through a direct cellular effect involving TGF- $\beta$  production, an effect that occurs independently of the effects of these drugs on the host's immune cells.<sup>16,17</sup> Because of these points, the strategy for treating solid tumors in LDLLT recipients might be a difficult matter. Early detection of a malignant tumor is one of the most important issues in the management of recipients during the follow-up period after transplantation.

Our case is the first report describing the clinical course of an unsuspected advanced lung cancer in an LDLLT recipient. The difficulties involved in the diagnosis and treatment of lung cancer should be kept in mind before and after LDLLT transplantation.

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