Late sequelae of lobectomy for primary lung cancer: fibrobullous changes in ipsilateral residual lobes

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Abstract

Background: Late complications after lobectomy for primary lung cancer are rare. Progressive fibrobullous changes in the ipsilateral residual lobes were observed in some of the long-surviving patients after lobectomy for lung cancer. We report clinical details of this late complication. **Methods:** Between 1975 and 1997, we selected 39 patients (35 males and 4 females) from a total of 1321 patients who underwent lobectomy for primary lung cancer. **Results:** The incidence rate of this complication was 3%; this increased to 5.6% in patients who had survived for 5 years or more. A chest roentgenogram revealed fibrobullous changes on an average of 2.5 years (range 3 months–6 years) after lobectomy; these changes progressed throughout the ipsilateral lobes over several years. Ten patients (26%) required continuous oxygen therapy. The fibrobullous lungs of 21 (54%) patients were infected with nontuberculous mycobacterium, aspergillus, methicillin-resistant *Staphylococcus aureus*, and unidentified bacteria in 5, 4, 1, and 11 patients, respectively. Twenty-four patients died of the following causes: cancer (8, 33%), respiratory failure and chronic infections related to this complication (10, 42%), and other diseases (6, 25%). Three patients underwent successful surgical intervention for treating chronic infection of the destroyed lungs (omentopexy 1, completion pneumonectomy 2). **Conclusions:** Fibrobullous lung should be recognized as an important late complication that develops in lung cancer patients after lobectomy.

1. Introduction

Fibrobullous changes in the lung parenchyma have been observed as sequelae of acute lung injury, severe pulmonary infections, drug/chemical intake, aspiration/inhalation of toxic agents, and so on [1]. In lung cancer patients, these changes are observed after aggressive chemoradiation therapy [2]. We have previously reported 15 lung cancer patients who had late fibrobullous changes of residual lobes after lobectomy without above-mentioned causes. We also mentioned that recurrent infections in the fibrobullous lobes resulted in lung abscess, fungal infection, and finally in the destruction of the ipsilateral residual lung in the following patients [3]. Lobectomy with mediastinal lymph node dissection is the most frequently used surgical method, and approximately 80% of the patients undergo pulmonary resectional therapy for primary lung cancer [4]. Lobectomy is generally well tolerated, usually leaving sufficient lung volume to fill the pleural void left resection, and avoiding some of the short-

term and late complications of pneumonectomy. This procedure is safe, and there have hardly been any complaints during the perioperative period. Late complications that are directly related to the operative method are rare after re-expansion of the residual lobes [5]. We regard fibrobullous changes in the residual lobes as being a significant late complication that occurs after lobectomy for primary lung cancer. In this study, we reviewed the clinical details of patients with fibrobullous lung after lobectomy.

2. Patients and methods

Between January 1975 and December 1997, 1321 pulmonary lobectomies for primary lung cancer were undertaken at National Kinki-chuo Chest Medical Center. We retrospectively reviewed the clinical records and radiological images of 1321 patients and selected 39 patients based on the following criteria: we included patients whose radiological findings showed a smooth and clear lung margin (Figs. 1A and 2A) that changed to an irregular thick and infiltrative pleural shadow on a chest roentgenogram (Fig. 1B) and in whom small bullous and fibrous changes

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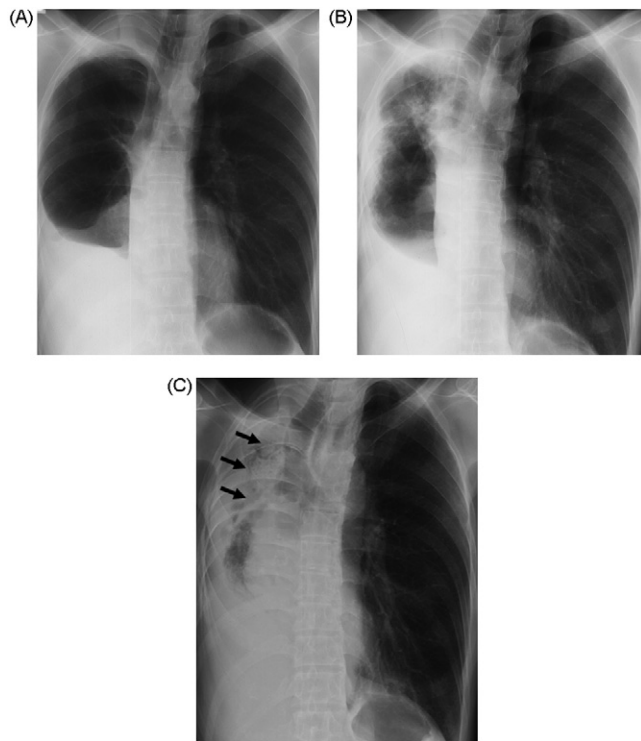*E-mail address:* h-tanaka@kch.hosp.go.jp (H. Tanaka).

Fig. 1. The chest roentgenogram reveals a smooth and clear lung margin (A) that changed to an irregular one with thickness and infiltration (B). These changes progressed throughout the residual lung and were followed by scarring and retraction of the residual lung and large cavity formation. Finally, total destruction of the residual lung, overinflation of the contralateral lung, and a mediastinal shift occurred (C). The case presented here shows fungal infection in the large cavity 13 years after lobectomy (C, arrows).

were observed in a peripheral lung lesion upon chest-computed tomography (Fig. 2B and C). These changes frequently occurred at the apex of the re-expanded residual lobes and progressed throughout the ipsilateral lung with scarification, lung retraction, and excavated alterations (Figs. 1C and 2D). At the early phase, all 39 patients had no symptoms and showed no marked changes in their blood biochemical analysis data. Radiographic changes were the only significant clinical findings. The fibrobullous change progressed and caused respiratory symptoms. Moreover, chronic or recurrent infection frequently occurred in the affected lobes and resulted in lung abscess, fungal infection, and finally in the complete destruction of the ipsilateral residual lung within several years (Fig. 1C). We excluded patients with causes resulting to late sequential changes, such as chemotherapy or radiation therapy and major postoperative complications including persistent air leakage, residual space, empyema, and severe pulmonary infection. We reviewed the radiological findings, patient background, clinical course, and outcome in the selected patients.

3. Results

3.1. Patient background

Of the 39 selected patients, 35 (90%) were male and 4 (10%) were female. The mean age at lobectomy was 62 years (range

43—78 years). All 35 males were heavy smokers, and their mean Brinkman index (cigarettes per day $\times$ years) was 1020 (range 640—2280). Persistent smoking patients were three (8%) after operation. Underlying pulmonary disease was detected in 27 patients (69%). Old tuberculosis was observed in 9; pneumococcosis, 8; emphysemas, 8; lung fibrosis, 3; and old pleurisy, 3. Lobectomy was performed on the right side in 22 (56%) patients and on the left side in 17 (44%) patients. The upper lobes were resected in 17 patients (6 right and 11 left); lower lobes, 14 (8 right and 6 left); middle lobe, 1; upper and middle lobes, 2; and lower and middle lobes, 5. All patients underwent mediastinal lymph node dissection.

Pathological typing of lung cancer revealed squamous cell carcinomas in 22 (56%) patients, adenocarcinomas in 14 (36%) patients, and other non-small cell lung cancers in 3 (8%) patients. The mean tumor diameter was 3.3 cm (range 1—7.4 cm). All tumors except one were located in the peripheral lung area. Pathological staging of all the patients resulted in TNM as stage 1 ($n = 27$, 69%), stage 2 ($n = 9$, 23%), and stage 3A ($n = 3$, 8%) diseases.

The postoperative course was uneventful in 27 (69%) patients. The chest tube was removed within 7 postoperative days when re-expansion of residual lobe was complete with no air leak and pleural effusion was less than 150 cc total per day. If the air leak persisted over 14 postoperative days, chemical pleurodesis was indicated. Prolonged air leak was observed in 12 (31%) patients, and chemical pleurodesis was performed in 11 (28%) patients. All patients showed sufficient lung inflation with no residual space, and they were followed up for 9.5 years on an average (range 1—23 years). One patient died of tumor recurrence 1 year after surgery, and the overall 5-year survival rate was 85%.

3.2. Incidence rate of fibrobullous changes after lobectomy for lung cancer

During the same period, 149 patients underwent pneumonectomy, 100 segmentectomy, and 83 wedge resection. Fibrobullous changes were not observed in these patients. Therefore, the incidence rate of this complication was 3% in the 1321 patients who underwent lobectomy, and this increased to 5.6% in patients who survived for 5 years or more after the operation.

3.3. Clinical course and outcome of fibrobullous lung

The initial fibrobullous changes appeared on the chest roentgenogram on an average of 2 years (range 3 months—6 years) after lobectomy. The fibrobullous changes progressed and caused the following symptoms: the fibrobullous lungs of 20 (51%) patients were infected by the following organisms: nontuberculous mycobacterium in 5 patients (4 patients with *Mycobacterium avium* and 1 with *Mycobacterium kansasii*); aspergillus, 3; methicillin-resistant *Staphylococcus aureus*, 1; and unidentified bacteria, 11. Chronic and recurrent infections accelerated fibrobullous changes throughout the ipsilateral residual lobes, and these infections were refractory to medical treatment. Contralateral spillage of infectious materials caused chronic respiratory deficiency. Twelve (31%) patients required continuous oxygen therapy, and 10 died of respiratory failure with chronic infection. Three
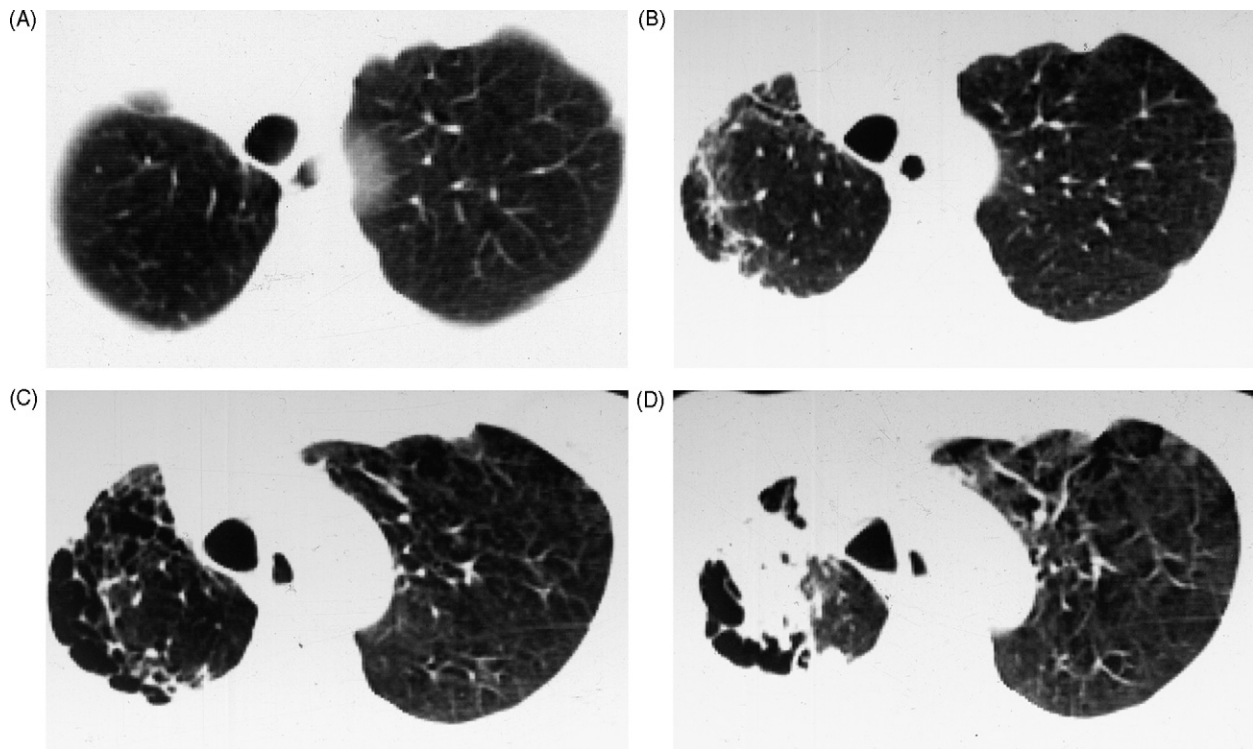
Fig. 2. The computed tomographic scan showed a smooth and clear lung margin 2 years after right upper lobectomy (A). Small bullous and fibrous changes occurred at the apex of the re-expanded residual lobe 4 years after the lobectomy (B) and progressed throughout the ipsilateral lung with scarification, lung retraction, and excavated alterations (C; 6 years and D; 7 years after the lobectomy).

patients had hemoptysis, purulent sputum, chronic fever, and body weight loss. Careful staging based on bronchoscopy, computed tomographic scan, brain magnetic resonance imaging, and other clinical examinations showed no evidence of recurrent or metastatic disease. The contralateral lungs of the patients were intact. We selected two-stage operations. Omentopexy was performed 8 months after open drainage of a large cavity with *Mycobacterium kansasii* infection in one patient; this patient died of tumor relapse 3 years after the procedure. Two patients with aspergilloma underwent a cavernostomy following a completion pneumonectomy, and each of these showed satisfactory results. Histological findings of these two resected lungs revealed no specific findings but only chronic infectious inflammatory changes such as diffuse pulmonary fibrosis, bronchiectasis, micro-abscesses, and fungal cavity formation.

The mean follow-up period from the appearance of the fibrobullous changes was 4 years (range 5 months–19.5 years). Fifteen patients survived. Eight patients died of tumor recurrence. Ten patients died of respiratory failure due to chronic infection related to fibrobullous lung and they had underlying pulmonary disease. Six patients died of some other type of cancer or nonrespiratory disease. Thirteen asymptomatic patients were carefully observed in our outpatient clinic.

4. Comment

Lobectomy with mediastinal lymph node dissection is safe, and there have hardly been any complaints during the perioperative period. The mortality rate of this procedure in a recently reported large patient series was 1.2–4% [4,6]. Respiratory system involvement and cardiac complication are the most commonly encountered postoperative complications after lobectomy for lung cancer. Early complications that are directly related to the procedure include prolonged air leaks, pleural effusion, empyema, postoperative hemorrhage, bronchial stump leaks, pulmonary emboli, and wound infections, which occur in the perioperative period and rarely in the late period after re-expansion of the residual lungs [7]. In our hospital, postoperative patients are followed in the outpatient clinic for 5 years or more after the operation. Fibrobullous lung occurred in 3% of our patients who had undergone lobectomy. Moreover, in patients who had survived for 5 years or more after lobectomy, the incidence rate increased to 5.6%. Our mean follow-up was 9.5 years, and 10 years follow-up is the minimum to find this complication. With regard to the cause of death in 24 patients, 8 (33%) died of recurrent cancer, while 16 (67%) died due to non-lung cancer related reasons. Of these 16 patients, respiratory failure with chronic infections related to fibrobullous lung occurred in 10 patients (62.5%). We suggest that fibrobullous lung should be recognized as a significant late complication that is directly related to lobectomy for lung cancer.

Fibrobullous changes in the lung parenchyma are observed in interstitial pneumonitis and the chronic phase (fibrotic phase) of acute lung injury, which are usually diffuse and bilateral [1]. In lung cancer patients, these changes are observed after aggressive chemoradiation therapy [2]. Chemical pleurodesis may have a physiopathological role

of acute lung damage leading to fibrobullous changes. However, acute lung damage after pleurodesis was not observed in our patients. The fibrobullous changes appeared on average of 1.4 years in 11 patients with pleurodesis and 1.8 years in 28 patients without pleurodesis. There was no significant difference and the relationship between chemical pleurodesis and fibrobullous changes was unclear in our series. The characteristic findings of the cases reported in this study are as follows: (1) there was no history of acute lung injury and chemoradiation therapy for lung cancer; (2) radiographic change was the only clinical finding at early phase; (3) fibrobullous changes presented at the only operative site (unilateral) and were not observed after limited resection such as a segmentectomy and wedge resection. Diagnosis of fibrobullous lung was defined with the above-mentioned radiological and clinical findings. These findings suggest that fibrobullous lung is directly related to lobectomy. Approximately 90% of the patients in this study were heavy smokers whose Brickman index was more than 1000 and in whom emphysematous or fibrous pulmonary diseases coexisted. Persistent smoking patients were only three (8%). We speculate that re-expansion (compensatory overinflation) of the residual lobes might lead to progression of coexisting fibro-emphysematous changes. This process might be similar to the so-called compensatory emphysema caused by traction of distal air space.

Surgical treatment is indicated when the fibrobullous lung complaint is concurrent with massive hemoptysis, chronic and recurrent infection, lung abscess, and cavitary infection. If the residual lobes are entirely destroyed, surgical indication is the same as that of unilateral destroyed lung [8,9]. In routine clinical examinations, it is necessary to confirm that no recurrent or metastatic disease has occurred. Patients with nutritional disorders, septic conditions, and respiratory deficiency due to chronic infections and contralateral spillage of infectious materials may inadvertently be missing out on surgical therapy. In our series, three patients underwent two-stage operations due to their poor condition. The first operation was an open-window thoracostomy for draining a large lung abscess and the fungal cavity. Once the septic conditions and nutritional status had improved, the second operation was successful. Such a two-stage surgical procedure establishes a safe and effective strategy for treatment of empyema [10]. In patients who have been cured of their lung cancer, surgical therapy can prevent the equally dreadful complications of fibrobullous lung. In an asymptomatic patient, careful follow-up is important so that opportunities for surgical treatment are not missed.

In conclusion, fibrobullous lung should be recognized as a late sequela of lobectomy for primary lung cancer. When the secondary infections occur in infected lobes, surgical treatment is occasionally necessary and might resolve this complication.

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