Original Article

Treatment of secondary pneumothorax with interstitial lung disease: the surgical indications at the start of treatment is important

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Background: Secondary pneumothorax with interstitial lung disease (ILD) is often difficult to treat in comparison to primary pneumothorax. The purpose of this study was to analyze the actual management and outcome, and to find the most effective treatment.

Methods: Among 180 patients with pneumothorax caused by ILD, who were managed between January 2000 and April 2021, 129 patients were included. Fifty-one patients with observation only were excluded. In the present study, a patient was considered to be cured if their chest tube could be removed.

Results: The managements included chest tube drainage alone (n=41), pleurodesis (n=67), bronchoscopic treatment (n=14), and surgery (include overlapping cases) (n=25). The mean number of pleurodesis treatments was 2.4 (range, 1–9), and the most frequently used agent was blood-patch. All patients who received bronchoscopic treatment underwent bronchial occlusion with silicon spigots. The surgical procedures included bullectomy (n=20), lung cyst ligation (n=3), pleural covering with oxidized cellulose sheet (n=1), and spraying of fibrin glue alone (n=1). One hundred patients (77.5%) were curatively treated, 27 patients (20.9%) died, and 2 patients were transferred without chest tube removal. Among 25 patients who received surgery [including 6 patients with performance status (PS) ≥2], 24 patients (96.0%) were cured, and 1 patient died due to an acute exacerbation of ILD after surgery. The univariate analysis revealed that PS ≥2 and >3 pleurodesis treatments were significant non-curative factors, while steroid treatment before the development of pneumothorax was not.

Conclusions: The outcomes of surgery for pneumothorax in patients with ILD were good, and it is desirable to consider the surgical indications.

Keywords: Secondary pneumothorax; interstitial lung disease (ILD); surgery; pleurodesis; treatment

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Introduction

Interstitial lung disease (ILD) is a chronically progressive respiratory disease with a poor prognosis (1-4). Secondary pneumothorax may occur during the clinical course of ILD; the frequency is reported 12.9–20.2% (5). In addition, the onset of pneumothorax is significantly associated with poor outcomes (6). The most important reason for this is the limitation of treatment options due to the patient's underlying diseases, progressive respiratory dysfunction, and poor performance status (PS) (7). The British Thoracic Society (BTS) guidelines recommend surgical intervention for such patients when an air leak persists for 48 hours (8). However, ILD patients with pneumothorax are often considered—especially by internal medicine physicians—to not be good candidates for surgical treatment, and several treatment options, including pleurodesis and endoscopic intervention are performed in combination (9). The management of these pneumothorax patients is still controversial. The purpose of this study was to analyze the actual managements and outcomes of such patients, and to find the most effective treatment. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1851/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Seirei Mikatahara General Hospital (No. 20-54, approval date: December 14, 2020). Patient information was obtained from a database, and the requirement for informed consent from each patient was waived due to the retrospective nature of the study. Among the 180 patients with secondary pneumothorax caused by ILD who were managed between January 2000 and April 2021, 129 patients were included, 51 patients treated with observation only were excluded. In the present study, a patient was considered to be cured if their chest tube could be removed.

Clinical diagnosis of ILD

The diagnosis of ILD was performed by expert diagnostic radiologists and physicians according to thin-section computed tomography (CT) findings. In addition, the clinical course, such as the exacerbation of reticular shadows on CT over time, also assisted in the diagnosis. A few patients were diagnosed based on the pathological examination of surgical specimens (n=11, 8.5%), and transbronchial lung biopsy with bronchoscopy (n=5, 3.9%).

The degree of pneumothorax

The size of pneumothorax was evaluated by chest roentgenography and CT. According to the BTS guidelines, it was determined whether a >2-cm space between the lung margin and the chest wall (at the level of the hilum) was present (8). The degree of pneumothorax was defined as follows: grade 1 pneumothorax was defined as the absence of a >2-cm space between the lung margin and the chest wall, and the collapse of the lung at the level of the clavicle on chest X-ray; grade 2 pneumothorax was defined with the presence of a space of a >2-cm space, without tension pneumothorax; grade 3 pneumothorax, was defined as tension pneumothorax.

Treatment process

All treatments for pneumothorax were performed by physicians and surgeons (respiratory specialists). In principle, when the patient had grade 2 or 3 pneumothorax, thoracic drainage was indicated. One or two chest tubes were inserted as needed for thoracic drainage, and double lumens as well as single lumens were selected according to the patient's condition. Pleurodesis was performed via the chest tube at the bedside; sclerosing agents, such as minocycline, OK-432 (a pulverized product of heat-killed Streptococcus pyogenes), blood patch, 50% glucose, and talc, were used at the discretion of each physician. Bronchoscopic treatment was bronchial occlusion with silicon spigots [endobronchial Watanabe spigots (EWSs)]. The surgical indication was comprehensively determined by thoracic surgeons based on the patients' PS, cardiopulmonary function, and comorbidities. Surgery was mainly performed under general anesthesia. On the other hand, surgery under local anesthesia was selected for patients who are unable to tolerate general anesthesia.

Prognostic factors

Age, smoking index, degree of pneumothorax, autoimmune disease, PS, administration of steroids, dose of steroids, number of pleurodesis treatments were included as prognostic factors, and their effect on treatment was analyzed.

Table 1 Patient characteristics at the onset of pneumothorax

Characteristic	N (%)
Patients	129
Sex	
Male	116 (89.9)
Female	13 (10.1)
Median age, years (range)	73 (50–90)
Median smoking index (range)	800 (0–3,060)
Laterality	
Right	65 (50.4)
Left	57 (44.2)
Both sides	7 (5.4)
Degree of pneumothorax[†]	
1	6 (4.7)
2	95 (73.6)
3	28 (21.7)
ECOG PS score	
0	83 (64.3)
1	14 (10.9)
2	6 (4.7)
3	9 (7.0)
4	4 (3.1)
Unknown	13 (10.0)
Cause of ILD	
IPF	28 (21.7)
CPFE	23 (17.8)
Autoimmunity	20 (15.5)
Organizing pneumonia	5 (3.9)
NSIP	4 (3.1)
Drug-induced	4 (3.1)
Chronic hypersensitivity pneumonitis	3 (2.3)
Idiopathic pulmonary upper-lobe fibrosis	2 (1.6)
Pneumoconiosis	2 (1.6)
Unknown	38 (29.4)
Administration of steroids	
Yes	51 (39.5)
No	78 (60.5)
Dose of steroids (n=51)	
≤5 mg	7 (13.7)
5–≤10 mg	10 (19.6)
10–≤20 mg	13 (25.5)
>20 mg	5 (9.8)
Steroid pulse therapy	16 (31.4)

[†], in bilateral cases, the degree on the higher side was used. ECOG, Eastern Cooperative Oncology Group; PS, performance status; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; NSIP, nonspecific interstitial pneumonia.

Statistical analysis

Fisher's exact test was used to compare categorical variables, while Student's *t*-test or the Mann-Whitney U test were used for continuous variables. P values of <0.05 were considered statistically significant. All statistical analyses were performed using the StatView software program (SAS Institute Inc., Cary, NC, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (10).

Results

Patient characteristics

The characteristics of the 129 patients [male, n=116; female, n=13; median age, 73 years (range, 50–90 years)] are shown in *Table 1*. The median smoking index was 800 (range, 0–3,060). The laterality of pneumothorax was as follows: right (n=65), left (n=57), and bilateral (n=7). The degree of pneumothorax was as follows: grade 1 (n=6), grade 2 (n=95), and grade 3 (n=28). The PS at the onset of pneumothorax was as follows: PS 0 (n=83), PS 1 (n=14), PS 2 (n=6), PS 3 (n=9), and PS 4 (n=4). The causes of ILD were very diverse, and included idiopathic pulmonary fibrosis (IPF) (n=28), combined pulmonary fibrosis and emphysema (CPFE) (n=23), autoimmunity (n=20), organizing pneumonia (n=5), nonspecific interstitial pneumonia (NSIP) (n=4), drug-induced (n=4), other (n=7), and unknown (n=38). Regarding the administration and dose of steroids at the onset of pneumothorax, 51 patients (39.5%) had received steroid treatment [dose: ≤5 mg (n=7); 5–≤10 mg (n=10); 10–≤20 mg (n=13); >20 mg (n=5); steroid pulse therapy (n=16)].

Table 2 Treatments for secondary pneumothorax in patients with ILD

Treatment	N	Cure[†]	%[‡]
Only thoracic drainage	41	30	73.2
Pleurodesis	67[§]	50	74.6
Blood-patch	55	43	78.2
Minocycline	36	24	66.7
OK-432	35	31	88.6
50% glucose	10	8	80.0
Talc	3	2	66.7
Bronchoscopic treatment[¶]	14[§]	11	78.6
Surgery	25[§]	24	96.0
Bullectomy	20	20	100
Lung cyst ligation	3	2	66.7
Pleural covering	1	1	100
Spraying fibrin glue	1	1	100
Combined treatment	16	13	81.3
Pleurodesis + bronchoscopic treatment	7	5	71.4
Pleurodesis + surgery	5	4	80.0
Pleurodesis + surgery + bronchoscopic treatment	2	2	100
Surgery + bronchoscopic treatment	2	2	100

[†], a patient was considered to be cured if their chest tube could be removed; [‡], number of curatively treated patients divided by the number of patients who received these treatments; [§], number of times the treatment was performed (including overlapping cases); [¶], bronchoscopic treatment was performed using EWSs. ILD, interstitial lung disease; EWSs, endobronchial Watanabe spigots.

Treatment

The details of the treatments are shown in *Table 2*. The treatments included: thoracic drainage with chest tube alone (n=41), pleurodesis (n=67), bronchoscopic treatment (n=14), and surgery (n=25). The surgically treated cases included overlapping cases, with 16 patients receiving combined treatment.

The mean number of pleurodesis treatments was 2.4 times (range, 1–9). Blood-patch, which was used 55 times, was the most frequently used agent. Minocycline was used 36 times, OK-432 was used 35 times, 50% glucose was used 10 times, and talc was used 3 times. The most common doses were 50 mL for blood-patch, 100 mg for minocycline, and 5 units for OK-432. Bronchoscopic treatment was bronchial occlusion with EWSs in all patients. Surgery was also performed for patients with a poor PS (6 patients had a PS of ≥2). The surgical procedures included bullectomy (n=20), lung cyst ligation (n=3), pleural covering with oxidized cellulose sheet (n=1), and spraying of fibrin glue alone (n=1).

Outcomes

One hundred patients (77.5%) were cured. Among these curatively treated patients, the median drainage period was 16 days (range, 4–180 days). Among the 29 patients who were not curatively treated, 27 (20.9%) died, and 2 were transferred without chest tube removal. The causes of death were as follows: respiratory failure (n=9), bacterial pneumonia (n=8), an acute exacerbation of ILD (n=5), empyema (n=4), and lung cancer (n=1).

Regarding the outcomes of pleurodesis, 34 (81.0%) of the 42 patients who received 1–2 pleurodesis treatments were cured; however, only 15 (62.5%) of the 25 patients who received ≥3 pleurodesis treatments were cured. No critical complications, including acute exacerbations of

Table 3 Analysis of non-curative factors

Variable	Univariate		Multivariate†	
	HR‡ (95% CI)	P value	HR (95% CI)	P value
Age	1.06 (1.00–1.13)	0.060	–	–
Smoking index	0.61 (0.32–1.19)	0.146	–	–
Autoimmune disease (absence *vs.* presence)	1.08 (0.36–3.21)	0.891	–	–
PS 0–1 *vs.* PS ≥2	4.05 (1.39–11.9)	0.011	2.93 (0.62–13.9)	0.177
Steroids (none *vs.* administration)	1.78 (0.76–4.14)	0.183	–	–
Steroids (≤10 *vs.* >10 mg)	2.62 (0.62–11.0)	0.190	–	–
Pleurodesis (1–2 *vs.* ≥3 times)	2.06 (1.62–6.89)	0.048	1.89 (0.51–7.05)	0.341

†, variables with P<0.05 on univariate analysis were selected for inclusion in multivariate analysis; ‡, the HR was calculated as the risk of the latter compared to the former. HR, hazard ratio; CI, confidence interval; PS, performance status.

ILD occurred in association with pleurodesis. Among the 67 patients who received pleurodesis, 14 patients (20.9%) required additional treatment due to continuous air leak: bronchoscopic treatment (n=7), surgery (n=5), and surgery and bronchoscopic treatment (n=2). In addition, when examining 53 patients who received pleurodesis alone, 34 patients (64.2%) were cured and had no recurrence, while 13 patients (24.5%) died during the clinical course [cause of death: respiratory failure (n=7), bacterial pneumonia (n=3), empyema (n=2), and lung cancer (n=1)]; 6 patients (11.3%) developed recurrent pneumothorax after discharge, despite being initially cured. On the other hand, of the 14 patients who received combined treatment including pleurodesis, only 1 patient (7.1%) developed recurrent pneumothorax.

Regarding the outcomes of bronchoscopic treatment, treatment was effective (air leak stopped or decreased) in 4 patients (28.6%) and was ineffective in 10 patients. The bronchi involved in the air leak were able to be identified by a bronchial occlusion test using a balloon catheter in all 4 patients in whom treatment was effective; in contrast, identification was impossible for the 10 patients in whom treatment was ineffective. In the 4 cases in which bronchoscopic treatment was effective, the number of treatments before the effect was 1 (n=1), 2 (n=2), and 4 (n=1). No critical complications occurred in association with bronchoscopic treatment.

Regarding the outcomes of surgery, among the 25 patients who received surgery, 24 (96.0%) were cured. Operative death within 30 days after surgery occurred in 1 patient (4.0%) due to an acute exacerbation of ILD (death occurred on the 1st day after surgery). During the observation period, none of these patients developed recurrent pneumothorax.

Analysis of prognostic factors

The univariate and multivariate analyses are shown in *Table 3*. In the univariate analysis, PS ≥2 and ≥3 pleurodesis treatments were identified as significant non-curative factors, while steroid treatment (administration and dose) before the development of pneumothorax was not. On the other hand, the multivariate analysis did not identify any significant factors.

Discussion

Secondary pneumothorax due to ILD is difficult to treat and is associated with poor outcomes (1-4,11). This is because of treatment options are limited due to the patient's underlying diseases, progressive respiratory dysfunction, and poor PS (7). Unfortunately, secondary pneumothorax often occurs during the clinical course of ILD; the frequency is reported to be 12.9–20.2% (5). Thus, while it is often experienced in the clinical setting, these patients are very difficult to treat. While quite a few cases can be curatively treated with thoracic drainage alone, only 31.8% of the patients in the present study could be managed in this way, and many patients required additional treatment.

Pleurodesis via a chest tube may be the treatment that is most frequently performed in clinical practice, as was observed in this study. When performing pleurodesis, the focus is on which sclerosing agent to use and how much. Of the many sclerosing agents, talc is considered to be the most effective and is widely used based on BTS guidelines (8,11,12). The author previously reported the efficacy of talc pleurodesis for secondary pneumothorax in elderly patients

with persistent air leak (13). However, talc may cause an acute exacerbation of ILD or acute respiratory distress syndrome (14,15). Thus, talc pleurodesis for pneumothorax patients with ILD should be cautiously indicated (13). Excluding talc, blood-patch has been reported to be safe and effective for pneumothorax patients with ILD (7). In the present study, blood-patch was the most frequently used agent, with 50 mL being the most popular dose. In addition, minocycline, OK-432, and 50% glucose were selected as sclerosing agents for chemical pleurodesis (16). In this study, they were used by each physician, and there was no evidence to support the superiority of any of the agents. Among patients who received pleurodesis, 64.2% were cured, 24.5% died during the clinical course, and 11.3% developed recurrent pneumothorax after discharge following curative treatment. Fortunately, no critical complications occurred after pleurodesis. From these results, we consider that pleurodesis can be performed easily but that the outcome is not sufficient.

All bronchoscopic treatments were performed using EWSs. An EWS is a type of silicon bronchial blocker, and its clinical effectiveness for achieving endoscopic bronchial occlusion in patients with prolonged air leak has been reported (17). When performing this procedure, the identification of bronchus at which the air leak has occurred is most important. There are some methods for identifying bronchi, including—but not limited to—a bronchial occlusion test using a balloon catheter, indocyanine green injection via a chest tube, and thoracography (17-19). The authors applied different identification methods; however, in many cases of secondary pneumothorax with ILD, several bronchi were involved in the air leak, and the success rate was low. Because excessive bronchial occlusion may cause atelectasis and reduce the pulmonary function, it should not be performed blindly. Appropriate patient selection for bronchoscopic treatment is needed. In addition, in the present study, the bronchi involved in the air leak were only able to be identified by a bronchial occlusion test using a balloon catheter in the patients for whom treatment was effective.

Surgery was associated with very good outcomes, of the 25 patients who received surgery, 24 patients (96.0%) were cured and no recurrence of pneumothorax was observed in the curatively treated patients. Patients with secondary pneumothorax generally have a poor PS, large numbers of comorbidities, and surgery is often considered high-risk in such cases. Thus, there tends to be a bias toward the provision of non-surgical treatment. However, the results of the present study strongly demonstrated the usefulness of surgery. At the start of treatment for secondary pneumothorax, it is important for physicians to consult with thoracic surgeons to discuss the possibility of surgery. The patient's general condition may worsen during repeated thoracic drainage and pleurodesis treatments. Deterioration of the PS, lower body mass index and a poor nutrition status have been reported as risk factors for the acute exacerbation of ILD after surgery (20). Thus, efforts are required to avoid missing the chance to perform surgical treatment due to delayed consultation. In addition, successful video-assisted thoracic surgery under local anesthesia has been reported (21,22). In patients who are unable to tolerate general anesthesia, surgery under local anesthesia may be useful. In this study, in one patient was successful treated by spraying fibrin glue under local anesthesia.

Regarding prognostic factors, the univariate analysis identified PS ≥2 and ≥3 pleurodesis treatment as significant non-curative factors. However, the multivariate analysis revealed no significant factors. The reason for this is considered to involve the existence of complex confounding factors due to the diversity of the patient background. Moreover, it is notable that steroid treatment (administration and dose) before the development of pneumothorax was not a significant non-curative factor. Thus, we considered that there was no need to delay surgery for a long time due to the use of steroids.

The present study was associated with some limitations. First, the present study was retrospective in nature and was performed in a single-center. However, to our knowledge, this study examined the largest number of patients among reports investigating the treatments and outcomes of secondary pneumothorax in patients with ILD. Second, because this study was retrospective, a biopsy to define the exact sub-classification of ILD was not performed for all patients, and data on the pulmonary function before treatment were missing. Third, there were a bias with regard to patient selection for treatment, especially the choice of surgical or non-surgical treatment. However, the outcomes of surgery were favorable, in other words, the selection of secondary pneumothorax patients who are able to tolerate surgery is most important. Then, thoracic surgeons should perform appropriate surgery for each patient.

Conclusions

We examined the treatments and outcomes of secondary pneumothorax caused by ILD. To our knowledge, among

previous reports on this topic, this study examined the largest number of patients. The mortality was high. However, the outcomes of surgery were good, and would be desirable for surgeons and physicians to discuss the surgical indications at the start of treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1851/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1851/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Seirei Mikatahara General Hospital (No. 20-54, approval date: December 14, 2020). Patient information was obtained from a database, and the requirement for informed consent from each patient was waived due to the retrospective nature of the study.

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