Shinshu Med J, 65(3) : 163～170, 2017

Outcomes of Surgically Treated Pneumothorax in Patients with Interstitial Pneumonia

Kentaro MIURA[1)]*, Ryoichi KONDO[1)] and Yoshiaki KITAGUCHI[2)]

1) *Department of Thoracic Surgery, National Hospital Organization Matsumoto Medical Center*
2) *First Department of Internal Medicine, Shinshu University School of Medicine*

Background : Pneumothorax with interstitial pneumonia (IP) is a refractory and life-threatening disease. The aim of the study was to clarify the benefits of surgical treatment of initial-onset pneumothorax in patients with IP.

Methods : The medical records of 37 patients with IP who developed initial-onset pneumothorax were retrospectively reviewed. Two groups of patients were analyzed : a surgical treatment group (n = 20) and a non-surgical treatment group (n = 17). The clinical characteristics of the two groups were compared. Risk factors for respiratory complications in hospital were assessed by univariate and multivariate logistic regression analyses.

Results : A Respiratory complications in hospital in the surgical treatment group included two patients who developed bacterial pneumonia ; however, no patient developed acute exacerbation of IP. The location of air leakage was determined during surgery in 19 of the 20 (95 %) patients. Air leakage developed from the bulla in 18 patients and from a crack of the lung parenchyma in one patient. Univariate and multivariate logistic regression analyses showed that surgery was independently associated with a significantly lower risk of respiratory complications in hospital (hazard ratio [HR] = 0.115, p = 0.022).

Conclusion : Surgical treatment yielded relatively better results than non-surgical treatment in patients with IP who develop initial-onset pneumothorax. Surgical treatment should be considered for IP patients who develop pneumothorax. *Shinshu Med J 65 : 163—170, 2017*

(Received for publication December 13, 2016 ; accepted in revised form February 1, 2017)

Key words : pneumothorax, interstitial pneumonia, acute exacerbation, surgical treatment

Abbreviations : IP, interstitial pneumonia ; ISDs, immunosuppressive drugs ; ECOG, Eastern Cooperative Oncology Group ; PS, performance status ; KL-6, serum Krebs von den Lungen-6 ; LTOT, long-term oxygen therapy ; CT, computed tomography ; VATS, video-assisted thoracic surgery ; IIP, idiopathic interstitial pneumonia

I Introduction

Pneumothorax with interstitial pneumonia (IP) is a life-threatening condition, with a frequency of 3.7 %-7.6 %[1)]. Because patients with pneumothorax with IP have hard lungs and poor compliance, and because they often use steroids or immunosuppressive drugs (ISDs), this condition is often refractory to treatment. Treatment of these patients is difficult and their morbidity and mortality rates are high[2)]. As excursive continuation of chest tube drainage carries a risk of empyema, surgery or pleurodesis is considered for some patients. However, these aggressive treatments may result in the acute exacerbation of IP, and decision on timing is difficult. Although studies have reported the effectiveness of pleurodesis in patients with pneumothorax with IP[3)-8)], fewer studies have assessed the effectiveness of surgical operations[9)10)]. Relatively little is known about the comparative safety and effectiveness of surgical treatment and non-surgical conservative treatment of pneumothorax with IP. This study there-

* Corresponding author : Kentaro Miura
Department of Thoracic Surgery, Shinshu University Hospital, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : kmiura@shinshu-u.ac.jp

fore analyzed the benefits of surgical treatment in these patients, with the goal of optimizing strategies for the management of pneumothorax with IP.

Ⅱ Materials and Methods

A Selection of patients and variables

The medical records of all patients with initial-onset pneumothorax with IP, who were seen at National Hospital Organization Matsumoto Medical Center from January 2000 to December 2013, were retrospectively reviewed. Clinical data recorded included patient age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS), serum Krebs von den Lungen-6 (KL-6) concentrations, receipt of long-term oxygen therapy (LTOT), regular treatment with steroids and/or ISDs, history of pulmonary fungus disease, and classification of IP. The patients were categorized into two groups, those treated surgically and those treated non-surgically, with the latter including patients who underwent pleurodesis or chest tube drainage. Clinical outcomes and in-hospital complications were compared in the two groups. The relationships between respiratory complications in hospital and patient demographic and clinical characteristics were evaluated. This study was approved by the institutional research ethics committee of National Hospital Organization Matsumoto Medical Center in August 9, 2016 (approval number 28-13).

B Methods of treatment

All of the included patients were admitted to hospital just after onset of pneumothorax, with chest tube drainage performed immediately upon admission.

Surgical treatment was performed via thoracotomy or video-assisted thoracic surgery (VATS). Failing lesions were treated by bulla resection using stapling instruments, suture repair, heat ablation using a ball chip for electrocoagulation, and ligation. Fibrin glue was used to repair lesions in all patients. A single-lumen chest drainage tube was inserted and continually suctioned at -10 cmH_2O pressure. Prior to removal of the chest draining tube, a 12-hour clamp test was performed and non-collapse of the lungs was assessed by chest X-ray.

Pleurodesis was performed by injecting picibanil (OK-432) into the chest drainage tube, followed by clamping of the tube for approximately 30–60 minutes and release of the clamp.

C Respiratory complications in hospital

Bacterial pneumonia and exacerbations of IP in hospital were diagnosed and distinguished by chest computed tomography (CT) and by clinical indications of inflammation, including white blood cell count and serum concentration of C-reactive protein. Sputum culture was used to diagnose some patients.

D Statistical analysis

The distribution of numerical data in the two groups was assessed with Bartlett's test. Normally distributed variables were compared using parametric Student's t-tests, whereas non-normally distributed variables were compared using nonparametric Mann-Whitney U-tests. Categorical variables were compared by chi-squared tests. Univariate and multivariate logistic regression analyses were performed to identify risk factors for in-hospital respiratory complications. Variables with P-values < 0.05 on univariate analyses were included in the multivariate model. All statistical analyses were performed using SPSS version 23 software (Chicago, IL, USA), with P-values < 0.05 considered statistically significant.

Ⅲ Results

A Clinical features of the patients

From January 2000 to December 2013, 37 patients admitted to the National Hospital Organization Matsumoto Medical Center, Matsumoto, Japan, experienced first episodes of pneumothorax with IP ; **Table 1** shows their demographic and clinical characteristics. Of these 37 patients, 33 (89.2 %) experienced idiopathic interstitial pneumonia (IIP), three (8.1 %) developed rheumatoid arthritis-related IP, and one (2.7 %) developed drug-induced IP. Serum KL-6 concentrations were elevated in 17 patients (45.9 %) just before the onset of pneumothorax, 17 (45.9 %) received LTOT and 18 (48.6 %) were regularly treated with steroids and/or ISDs. Twenty patients (54.1 %) un-

Table 1　Clinical features of all included patients

Variables	Number n = 37
Age (mean ± SD)	70.9 ± 8.8
Gender, male/female	31/6
ECOG Performance Status	
0/1/2/3/4	7/11/7/9/3
Smoking history, +/−	13/24
Serum KL-6 at diagnosis, higher than the normal range (≧500 U/ml)/normal	17/20
LTOT, +/−	17/20
Regular treatment with steroid and/or ISDs, +/−	18/19
History of pulmonary fungus diseases, +/−	11/26
Classification of IP	
IIP	33
Others (Rheumatism/Drug-induced)	4(3/1)
Operation/Pleurodesis/Drainage only	20/5/12

Abbreviations : ECOG, Eastern Cooperative Oncology Group ; KL6, Krebs von den Lungen-6 ; LTOT, long-term oxygen therapy ; ISDs, immunosuppressive drugs ; IP, interstitial pneumonia ; IIP, idiopathic interstitial pneumonia.

Table 2　Clinical characteristics of patients in the surgical and non-surgical treatment groups

	Surgical treatment Yes (n = 20)	No (n = 17)	p-value
Age (mean ± SD)	71.2 ± 8.5	70.8 ± 9.2	0.9
Gender, male/female	17/3	14/3	0.83
ECOG Performance Status			
0/1/2/3/4	5/8/3/4/0	2/3/4/5/3	0.15
Smoking history, +/−	7/13	6/11	0.99
Serum KL-6 at diagnosis (mean ± SD)	784.4 ± 399.1	616.6 ± 467.0	0.31
LTOT, +/−	12/8	5/12	0.06
Regular treatment with steroid and/or ISDs, +/−	7/13	6/11	0.99
History of pulmonary fungus diseases, +/−	3/17	7/10	0.07
Classification of IP, IIP/Others	17/3	16/1	0.37
Respiratory complicatio n in hospital, +/−	2/18	10/7	<0.01
Bacterial pneumonia	2	7	
IP exacerbation	0	3	
Death in hospital, +/−	0/20	8/9	<0.01
Respiratory failure caused by pneumonia	0	8	

Abbreviations : ECOG, Eastern Cooperative Oncology Group ; KL-6, Krebs von den Lungen-6 ; LTOT, long-term oxygen therapy ; ISDs, immunosuppressive drugs ; IP, interstitial pneumonia ; IIP, idiopathic interstitial pneumonia.

derwent surgical treatment and 17 (45.9 %) were treated non-surgically ; of the latter, five patients underwent pleurodesis, and the remaining 12 underwent only chest tube drainage.

B　Comparative clinical features of the surgical and non-surgical treatment groups

Table 2 shows the clinical features of the surgically and non-surgically treated groups. The rates of in-hospital complications ($p<0.01$) and deaths ($p<0.01$) were significantly higher in the non-surgical than in the surgical treatment group. Two surgically treated patients developed bacterial pneumonia as respiratory complications, whereas 10 non-surgically treated patients developed respiratory complications, with

Table 3　Detailed clinical records of patients who experienced respiratory complications in hospital

	Therapy	Respiratory complication	Age	Gender	ECOG PS	Fungus	Classification of IP	Smoking	KL-6	Steroid/ ISD	Death in hospital	Total duration of drainage (days)
1	Operation	Pneumonia	77	M	3	0	IIP	never	400	−	−	28
2	Operation	Pneumonia	87	M	2	0	IIP	never	553	−	−	15
3	Drainage only	Pneumonia	74	F	3	1	IIP	never	333	−	+	4
4	Drainage only	Pneumonia	76	M	2	0	IIP	never	392	Steroid	+	95
5	Drainage only	Pneumonia	66	M	4	1	IIP	never	480	Steroid	+	30
6	Drainage only	IP exacerbation	56	M	0	1	IIP	former	747	−	−	30
7	Drainage only	IP exacerbation	63	M	3	1	IIP	never	2180	−	+	35※
8	Drainage only	Pneumonia	68	F	4	0	IIP	never	unknown	−	+	23
9	Drainage only	Pneumonia	56	M	2	1	IIP	former	396	Steroid	+	21§
10	Pleurodesis	Pneumonia	79	M	4	0	IIP	former	450	ISD	+	47
11	Pleurodesis	Pneumonia	75	M	3	0	IIP	never	587	Steroid	+	30
12	Pleurodesis	IP exacerbation	77	M	1	0	IIP	former	510	−	−	20

Abbreviations : IP, interstitial pneumonia ; ECOG, Eastern Cooperative Oncology Group ; IIP, idiopathic interstitial pneumonia ; KL-6, Krebs von den Lungen-6 ; ISDs, immunosuppressive drugs

※ Bilateral pneumothorax

§ Recurrence of pneumothorax and reinsertion of a chest drainage tube.

Table 4　Clinical features of the surgical treatment group

Variables	Number
Duration from onset of pneumothorax to the operation, mean days (range)	23.0 (8-60)
VATS/Thoracotomy, n	13/7
Operation methods	
Bulla resection, n	10
Sutural repair, n	5
Ablation only, n	4
Ligation, n	1
Operation time , minutes (mean ± standard deviation of the mean)	63.0 ± 17.8
Location of air leakage, bulla/crack/unknown, n	18/1/1
Durations of drainage after operation, mean days (range)	4.7 (2-21)
Recurrence within 30 days, n (%)	2 (10 %)
Respiratory complication after operation, n (%)	2 (10 %)
Bacterial pneumonia, n	2

Abbreviations : VATS, video-assisted thoracic surgery ; IP, interstitial pneumonia

eight of the latter group dying of respiratory complications. **Table 3** shows the detailed clinical records of patients with in-hospital respiratory complications. Of the five patients who underwent pleurodesis, three (60 %) responded and were cured. However, bacterial pneumonia developed in two patients and IP became exacerbated in one patient. Two patients who underwent pleurodesis died of respiratory failure caused by bacterial pneumonia in hospital.

C　Clinical features of the surgical treatment group

Table 4 shows the clinical features of the surgical treatment group. The mean time from diagnosis of pneumothorax to surgery was 23 days (range, 8-60 days) and the mean operation time was 63.0 minutes. The chest drainage tube was removed an average 4.7 days after surgery. Only one patient experienced prolonged air leakage, requiring 21 days for tube removal. The location of air leakage was detected intraoperatively in 19 (95 %) patients, occurring from the bulla in 18 patients and from a crack of the lung parenchyma in one. Treatments included bulla resection in 10 patients, fistula closure by manual suturing in five, bulla ablation and application of absorbable seats and fibrin spray in four, and bulla

Table 5 Univariate and multivariate analyses of the relationships between in-hospital respiratory complications and patient demographic and clinical characteristics

Variable	HR	95 % CI	p-value
Univariate analysis			
Age years	1.004	0.927-1.087	0.92
Gender Male	0.952	0.149-6.099	0.96
ECOG PS Grade2-4	2.607	1.272-5.341	0.009
Smoking history yes	1.125	0.263-4.804	0.87
Serum KL-6 at diagnosis higher than the normal range (≧500 U/ml)	1.292	0.322-5.19	0.72
LTOT yes	2.167	0.516-9.09	0.29
Regular treatment with steroid and/or ISDs yes	1.517	0.378-6.09	0.56
History of pulmonary fungus diseases yes	0.35	0.077-1.583	0.17
Surgical treatment yes	0.078	0.013-0.048	0.002
Multivariate analysis			
ECOG PS Grade2-4	2.167	0.989-4.748	0.053
Surgical treatment yes	0.115	0.018-0.735	0.022

Abbreviations : ECOG, Eastern Cooperative Oncology Group ; KL6, Krebs von den Lungen-6 ; LTOT, long-term oxygen therapy ; ISDs, immunosuppressive drugs

ligation in one. Two patients experienced recurrence of pneumothorax within 30 days after surgery ; one patient underwent repeat surgery, and the other patient underwent repeat chest tube drainage. These two patients were finally cured. The patient who underwent repeat surgery experienced air leakage from a new location, a crack in the lung parenchyma near the staple line of the first operation.

Postoperative complications included bacterial pneumonia in two patients. One had undergone bulla resection and developed bacterial pneumonia during chest tube drainage 3 days after the operation. The other patient had undergone ligation of the bulla and developed bacterial pneumonia after removal of the chest drainage tube 5 days after the operation. These two patients were cured using antibiotic therapy. No patient experienced acute exacerbation of IP after surgery. All of the patients were discharged from the hospital.

D Relationships between respiratory complications in hospital and patient backgrounds

Table 5 shows univariate and multivariate logistic regression analyses of factors associated with the risk of respiratory complications in hospital. Univariate logistic regression analysis showed that lower ECOG PS (hazard ratio [HR] = 2.607, 95 % confidence interval [CI] 1.272-4.804, p = 0.009) and surgery (HR = 0.078, 95 % CI 0.013-0.048, p = 0.002) were significantly associated with a lower risk of in-hospital respiratory complications. Interestingly, age, sex, smoking history, serum KL-6 levels, administration of LTOT, regular treatment with steroids and/or ISDs, and history of pulmonary fungal disease were not significantly associated with a risk of respiratory complica-

tions in hospital. Lower ECOG PS and surgical treatment were included in the multivariate analysis, which showed that surgery was independently associated with a lower risk of in-hospital respiratory complications (HR = 0.115, 95 % CI 0.018-0.735, p = 0.022). Because no surgically treated patient had an ECOG PS of 4, sub-analyses were performed to examine the relationship between respiratory complications in hospital and the clinical characteristics of the 34 surgically and non-surgically treated patients with ECOG PS of 0-3 (n = 34), an analysis that yielded similar results (data not shown).

Ⅳ Discussion

The present study found that all of the surgically treated patients with pneumothorax with IP were cured and discharged. Univariate logistic regression analysis showed that age, sex, smoking history, serum KL-6 levels, administration of LTOT, regular treatment with steroids and/or ISDs, and history of pulmonary fungal disease were not associated with a risk of respiratory complications in hospital. Multivariate logistic regression analysis showed that surgical treatment was independently associated with a lower risk of respiratory complications in hospital, suggesting the effectiveness of surgical treatment in patients with pneumothorax with IP.

None of the surgically treated patients in the present study experienced acute exacerbations of IP. In contrast, acute exacerbation of IP has been reported in 13.5 %-15 % of patients surgically treated for lung cancer under general anesthesia[11)-13)], with these patients having a mortality rate of 80 %[11)]. Factors associated with acute exacerbation of IP include preoperative serum KL-6, lactate dehydrogenase, and C-reactive protein concentrations, duration of surgery, and exposure to high oxygen concentrations[12)-14)]. In our institution, we attempt to shorten the duration of surgery and the duration of exposure to high oxygen concentrations by shortening one-lung ventilation. Furthermore, to rapidly detect the location of air leakage, we change video-assisted thoracic surgery to small-incision thoracotomy under direct view.

We found that almost all air leakages in patients with pneumothorax from IP were caused by puncture of the bulla. Therefore, preoperative chest CT may predict the location of air leakage. Preoperative determination of air leakage may affect the placement of the surgical wound or ports, as well as shortening the operation time. Two of our surgically treated patients experienced recurrence of pneumothorax within 30 days after surgery. Both of these patients had undergone bulla resection using an auto suture stapler. One of these two patients underwent repeat surgery, resulting in a new air leak near the staple line from the first operation. Because lungs with IP are hard, they can be easily cracked by the auto suture stapler. Use of fibrin glue and wide covering of the staple line with absorbable material may prevent such incidents[15)].

Another issue is related to the timing of surgery in patients with pneumothorax with IP. One study recommended that if air leakage is prolonged for 48 hours, surgery should be considered in patients with secondary spontaneous pneumothorax[16)]. Although six of our patients were cured by chest tube drainage alone, this required an average of 14 days (range, 9-30 days). Prolonged continuation of chest tube drainage carries the risks of empyema and malnutrition, as well as gradually worsening the general condition of patients. Because conservative non-surgical methods require a longer treatment duration to cure pneumothorax with IP, additional therapy, such as surgical treatment or pleurodesis, should be considered before patient conditions worsen.

Generally, chemical pleurodesis is ineffective in patients with deflated lungs, and may result in acute exacerbation of IP[17)]. In contrast, blood-patch pleurodesis has been reported safe and effective in such patients[8)]. Autologous blood-patch pleurodesis showed a cure rate of 72.7 %, with respiratory complications, in patients with pneumothorax with IP. However, 50 % of cured patients experienced recurrence of pneumothorax[8)]. Pleurodesis may be considered first-line therapy prior to surgery for patients with poor general condition and/or poor PS.

Previous results have suggested that patients with

air leakage for over 48 hours be considered for surgery before developing acute exacerbation of IP or other respiratory complications. However, surgery was successful in some patients when performed >48 hours after initial development of air leakage, up to 60 days in this study. These findings suggest that the optimal timing of surgery should be assessed in each individual patient.

This study had several limitations. First, this was a single-center, retrospective study of uncontrolled design. Furthermore, there was no standard to determine whether or not to perform surgery. Additional prospective studies with larger sample sizes are required to confirm the present results. Second, there was a potential for selection bias. National Hospital Organization Matsumoto Medical Center is a major hospital with a department of thoracic surgery, and may have more patients with very severe respiratory diseases than other general hospitals. Third, we did not investigate long-term patient prognosis.

In conclusion, surgical treatment should be considered in patients with pneumothorax with IP before their general condition worsens owing to prolonged continuation of chest tube drainage.

Conflicts of interest : none declared.

References

1) Franquet T, Gimenez A, Cremades R, Domingo P, Plaza V : Spontaneous pneumothorax and pneumomediastinum in IPF. Eur Radio 1 : 108-113, 2000
2) Marshall MB, Deeb ME, Bleier JI, Kucharrczuk JC, Friedberg JS, Kaiser LR, Shrager JB : Suction vs water seal after pulmonary resection : a randomized prospective study. Chest 3 : 831-835, 2002
3) Goldszer RC, Bennett J, VanCampen J, Rudnitzky J : Intrapleural tetracycline for spontaneous pneumothorax. JAMA 7 : 724-725, 1979
4) Macoviak JA, Stephenson LW, Ochs R, Edmunds LH : Tetracycline pleurodesis during active pulmonary-pleural air leak for prevention of recurrent pneumothorax. Chest 1 : 78-81, 1982
5) Almind M, Lange P, Viskum K : Spontaneous pneumothorax : comparison of simple drainage, talc pleurodesis, and tetracycline pleurodesis. Thorax 8 : 627-630, 1989
6) Almassi GH, Haasler GB : Chemical pleurodesis in the presence of persistent air leak. Ann Thorac Surg 5 : 786-787, 1989
7) Kennedy L, Sahn SA : Talc pleurodesis for the treatment of pneumothorax and pleural effusion. Chest 4 : 1215-1222, 1994
8) Aihara K, Handa T, Nagai S, Tanizawa K, Watanabe K, Harada Y, Chihara Y, Hitomi T, Oga T, Tsuboi T, Chin K, Mishima M : Efficacy of blood-patch pleurodesis for secondary spontaneous pneumothorax in interstitial lung disease. Intern Med 11 : 1157-1162, 2011
9) Schoenenberger RA, Haefeli WE, Weiss P, Ritz RF : Timing of invasive procedures in therapy for primary and secondary spontaneous pneumothorax. Arch Surg 6 : 764-766, 1991
10) Nakajima J, Takamoto S, Murakawa T, Fukami T, Yoshida Y, Kusakabe M : Outcomes of thoracoscopic management of secondary pneumothorax in patients with COPD and interstitial pulmonary fibrosis. Surg Endosc 7 : 1536-1540, 2009
11) Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T : Acute exacerbation of idiopathic pulmonary fibrosis : frequency and clinical features. Eur Respir J 1 : 143-150, 2006
12) Shintani Y, Ohta M, Iwasaki T, Ikeda N, Tomita E, Kawahara K, Ohno Y : Predictive factors for postoperative acute exacerbation of interstitial pneumonia combined with lung cancer. Gen Thorac Cardiovasc Surg 4 : 182-185, 2010
13) Mizuno Y, Iwata H, Shirahashi K, Takamochi K, Oh S, Suzuki K, Takemura H : The importance of intraoperative fluid balance for the prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmo-

nary resection for primary lung cancer. Eur J Cardiothorac Surg 41 : 161–165, 2012

14) Sakamoto S, Homma S, Mun M, Fujii T, Kurosaki A, Yoshimura K : Acute exacerbation of idiopathic interstitial pneumonia following lung surgery in 3 of 68 consecutive patients : a retrospective study. Intern Med 2 : 77–85, 2011

15) Sakamoto K, Takei H, Nishii T, Miehara T, Omori T, Tajiri M, Imada T, Takanashi Y : Staple line coverage with absorbable mesh after thoracoscopicbullectomy for spontaneous pneumothorax. Surg Endosc 3 : 478–481, 2004

16) MacDuff A, Arnold A, Harvey J : Management of spontaneous pneumothorax : British Thoracic Society Pleural Disease Guideline 2010. Thorax Suppl 2 : ii18–31, 2010

17) Brant A, Eaton T : Serious complications with talc slurry pleurodesis. Respirology 3 : 181–185, 2001

（2016．12．13 received ; 2017．2．1 accepted）