Subclinical idiopathic pulmonary fibrosis is also a risk factor of postoperative acute respiratory distress syndrome following thoracic surgery

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Received 2 April 2008; received in revised form 11 July 2008; accepted 16 July 2008; Available online 21 August 2008

Abstract

Objective: Postoperative acute interstitial pneumonia is a subset of post-surgical acute respiratory distress syndrome (ARDS) and is responsible for one third of in-hospital deaths following lung resection in patients with primary lung cancer. We evaluated the usefulness of computed tomography (CT) for detection of interstitial pneumonia (IP) as a risk factor of postoperative ARDS.

Methods: Preoperative chest CT of patients who underwent thoracotomy for primary lung cancer was reviewed retrospectively and IP findings in the chest CT were detected.

Results: A total of 1148 patients with primary lung cancer underwent thoracotomy. Fifteen patients (1.3%) developed postoperative ARDS. Eleven of these 15 patients died of ARDS. Three of 41 patients who received induction therapy developed postoperative ARDS. Induction therapy was a risk factor of postoperative ARDS (p < 0.01). Eleven out of the 15 patients who developed postoperative ARDS had IP findings (10: localized, 1: diffuse) in their chest CT. Two of three patients who had postoperative ARDS after induction therapy also had IP findings. Chest CTs of 834 patients were retrospectively analyzed; 91 patients (10.9%) had IP-findings (diffuse 1.8%, localized 9.1%). Postoperative ARDS occurred in 8.8% of IP-positive patients, and in 0.4% of IP-negative patients (p < 0.001).

Conclusion: Detection of IP by chest CT is useful for the selection of high-risk patients who may have postoperative ARDS following thoracotomy.

Keywords: Usual interstitial pneumonia; Acute interstitial pneumonia; Lung cancer

1. Introduction

Post-surgical pneumonia is one of the life-threatening complications following surgery for patients with lung cancer [1]. We have previously reported [2] that acute interstitial pneumonia (AIP) is a subset of post-surgical acute respiratory distress syndrome (ARDS) that is responsible for approximately 30% of hospital deaths following lung resection. Given this high mortality rate, we believe it is important to elucidate the mechanism of postoperative ARDS.

Although it has been known that an acute exacerbation of idiopathic pulmonary fibrosis (IPF) sometimes occurs following surgery, chemotherapy, or radiotherapy, patients who develop ARDS following lung resection are not always thought to have IPF prior to surgery. Localized, not diffuse, usual interstitial pneumonia (UIP) lesions have recently been reported in some cases to progress to IPF or acute exacerbation [3]. Moreover, patients with these lesions are not always recognized to have IPF because the lesions are localized, symptomless and not detectable except via chest computed tomography (CT). There is a possibility that some parts of postoperative ARDS may be an acute exacerbation of IPF that was mostly not recognized as IPF prior to surgery because of symptomless and localized UIP change.

In this study, we investigated (1) whether patients who had ARDS following lung resection due to primary lung cancer had UIP (especially localized UIP), (2) whether detection of IP, which reflects pathological UIP, in chest CT is useful for the selection of high-risk patients who may develop postoperative ARDS after thoracotomy.

2. Materials and methods

A total of 1148 patients who underwent lung resection due to primary lung cancer from January 1996 through March 2008 in our institution and relative hospitals were investigated retrospectively. IP findings of preoperative chest CT scans, which reflect pathological UIP, were double-checked by both a pulmonologist and a radiologist.
The criteria for identifying IP on a chest CT scan in the current study were (1) honeycomb formation, (2) reticular shadow, and (3) ground-glass opacity [4—6]. Curvilinear shadow and dependent density, which indicate the gravitational effect, were excluded from these diagnostic criteria. Shadow that did not exceed the dependent area was excluded unless it accompanied a honeycomb formation. A cyst with a thin wall was also excluded when differential diagnosis from the emphysematous change was difficult. The conditions used in preoperative CT scans included a slice thickness of 10 mm, window width of 2000, and −700 window level. The images of thin slice CT scans were also referred when available. IP findings in chest CT scan were surveyed in whole lung, unrelated to the cancer localization. The extent of IP findings was categorized into two groups; diffuse UIP and localized UIP. The lesion of the former lesion has a diffuse extent, and that of the latter has a subpleural and localized extent. The same examination was conducted in a control population of 275 healthy participants who received a chest CT detection survey in the institutions during the same period.

We defined subclinical IPF as following; (1) not diagnosed as IPF prior to admission for lung cancer, (2) symptomless, (3) localized IP findings positive in chest CT.

The occurrence of ARDS in patients who received chemotherapy or chemoradiotherapy before surgery was also analyzed retrospectively. When patients had an episode of ARDS, the pathological detection of UIP in the resected lungs was performed. The diagnosis of postoperative ARDS was made from clinical symptoms, chest radiograph, CT scan, biochemical tests such as lactate dehydrogenase (LDH) levels, and autopsy. Pneumonia was excluded from postoperative ARDS when bacteria were proven in the airway.

Values are expressed as means ± SD. Statistical analysis was performed using a chi-square test for comparison of variables, and differences were considered significant when \( p < 0.05 \).

### 3. Results

Fifteen patients (1.3%) developed ARDS following lung resection (Fig. 1). One case was thought to have IPF due to diffuse IP findings in CT scan. Fourteen cases were not thought to have IPF before surgery (Table 1). The preoperative lung function tests of 14 patients showed almost normal findings. The %VC, FEV1, FEV1% and %DLCO were 110.0 ± 29.2 (%), 2390 ± 430 (ml), 69.5 ± 12.6 (%) and 69.2 ± 19.1 (%), respectively. Arterial blood gas analysis showed normal values. \( \text{Po}_2, \text{PaCO}_2 \) and pH were 82.7 ± 4.3 (Torr), 40.4 ± 1.0 (Torr) and 7.41 ± 0.01, respectively. In addition, patient serum biochemistry did not show any abnormal findings.

Forty-one patients in this series received induction chemotherapy or chemoradiotherapy preoperatively, in 16 patients and in 25 patients, respectively. Three (6.3%) in 41 patients with induction therapy developed postoperative ARDS after lung resection; one in chemotherapy and two in chemoradiotherapy. Twelve (1.1%) in 1107 patients who did not receive induction therapy had ARDS (Table 2). The incidence (6.3%) of postoperative ARDS in patients with induction therapy was significantly higher than that (1.1%) of the patient without induction therapy (\( p < 0.01 \)).

Retrospective interpretation of preoperative chest CT revealed that 9 out of the 12 patients had localized IP findings that were not recognized prior to surgery (Fig. 2). Two of three patients who received induction therapy and developed ARDS also had IP findings in chest CT. Total 11 out of the 15 patients who developed postoperative ARDS had IP findings in preoperative chest CT. Pathological examination also revealed fibrotic lesions in the resected lungs (Fig. 3).

Although steroid pulse therapy was employed to treat ARDS, 11 of the 15 patients died. All patients showed the appearance of reticular or ground-glass shadows on chest X-ray films. Serum LDH levels were higher than normal ranges at the onset of ARDS in all cases. There was no relationship between the date of onset and death. All drugs, such as antibiotics, were changed after the onset of ARDS to prevent the possibility of drug-induced interstitial pneumonia from developing. None of the drugs utilized to treat patients in some cases were identified as allergens in drug-stimulation tests.

In 834 of the 1148 patients, preoperative chest CT films stored in the institutes were reviewed to detect IP findings. IP findings were observed in 91 (10.9%) of the 834 patients (Table 2). Most of IP findings were located in bilateral dorsal subpleural area. Fifteen patients (1.8%) had diffuse IP shadow (clinically diagnosed IPF), whereas 76 patients (9.1%) had only localized IP findings in the chest CT (subclinical IPF). There was no relationship between resected lobe and location of IP findings in the patients with postoperative ARDS. Since 11 of the 15 patients with postoperative ARDS had IP finding in their chest CT, the occurrence rate of postoperative ARDS from IP finding positives was 11/1148 (1.0%) in all patients. This value (1.0%) was 8.8% of IP finding positives (10.9% of 834 cases). Four patients (0.35% of 1148 cases) who were negative for IP prior to thoracotomy did, however, develop postoperative ARDS; this value (0.35%) was 0.4% of all negative IP findings (79.6% of 834 cases). The occurrence rate (8.8%) of ARDS from IP finding positives was significantly higher than that (0.4%) of IP finding negatives (\( p < 0.001 \)).
Ninety-seven percent of patients with IP findings were smokers, with a smoking index (average number of cigarettes per day times years of smoking) of 992/431. All patients with postoperative ARDS were smokers, with a smoking index average of 1015/498. There was no significant difference between these patients. Nor was there any significant difference in the age between patients with IP finding and patients with postoperative ARDS, 70.4/5.7 and 69.5/6.8, respectively.

Eight of the 275 healthy participants (male: 225, female: 50, age: 53.0/9.5) had IP findings in their chest CT (2.9%). The occurrence rate (11.9%) of the IP finding in patients with lung cancer was significantly higher than that (2.9%) of the healthy participants ($p < 0.001$).

### 4. Discussion

In our retrospective study, postoperative ARDS occurred in 1.3% of patients who underwent thoracotomy. Seventy-three percent of patients with ARDS died. ARDS following thoracotomy is an important postoperative complication with a high mortality. ARDS occurred in 8.8% of patients who had IP findings in their preoperative chest CT, and occurred in 0.4% of patients who were negative for IP. Furthermore, 73% of patients with postoperative ARDS had IP findings in their chest CT. These data suggest that some parts of postoperative ARDS may be an acute exacerbation of IPF, and that the detection of IP findings in a chest CT may be important in identifying high-risk patients who may develop postoperative ARDS following thoracotomy.

### Table 1

Patient characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Operation</th>
<th>Induction therapy</th>
<th>UIP findings</th>
<th>Pattern</th>
<th>Smoking index</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>(−)</td>
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<td>2</td>
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<tr>
<td>3</td>
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<td>(−)</td>
<td>(−)</td>
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<td>1125</td>
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<tr>
<td>4</td>
<td>78</td>
<td>Male</td>
<td>RUL</td>
<td>(−)</td>
<td>(−)</td>
<td>Localized</td>
<td>1000</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>Male</td>
<td>RPn</td>
<td>(−)</td>
<td>(−)</td>
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<td>6</td>
<td>72</td>
<td>Male</td>
<td>LLL</td>
<td>CRT</td>
<td>(+)</td>
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<td>520</td>
</tr>
<tr>
<td>7</td>
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<td>Male</td>
<td>LPh</td>
<td>(−)</td>
<td>(+)</td>
<td>Localized</td>
<td>720</td>
</tr>
<tr>
<td>8</td>
<td>71</td>
<td>Male</td>
<td>RMLL</td>
<td>(−)</td>
<td>(+)</td>
<td>Localized</td>
<td>1020</td>
</tr>
<tr>
<td>9</td>
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<td>Male</td>
<td>RPn</td>
<td>(−)</td>
<td>(−)</td>
<td>Localized</td>
<td>800</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
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<td>1140</td>
</tr>
<tr>
<td>11</td>
<td>80</td>
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<td>LUD</td>
<td>(−)</td>
<td>(−)</td>
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<tr>
<td>12</td>
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<td>RLL</td>
<td>(−)</td>
<td>(−)</td>
<td>Localized</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>Male</td>
<td>RUL</td>
<td>(−)</td>
<td>(+)</td>
<td>Diffuse</td>
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</tr>
<tr>
<td>14</td>
<td>52</td>
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<td>RMLL</td>
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<td>(−)</td>
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<td>Died, 107 POD</td>
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<tr>
<td>15</td>
<td>71</td>
<td>Female</td>
<td>RUL</td>
<td>(−)</td>
<td>(−)</td>
<td>NA</td>
<td>Died, 29 POD</td>
</tr>
</tbody>
</table>

RUL: right upper lobectomy. RLL: right lower lobectomy. RPn: right pneumonectomy. LLL: left lower lobectomy. LPh: left pneumonectomy. RMLL: right middle and lower lobectomy. LUD: left upper divisionectomy. CT: chemotherapy. CRT: chemoradiotherapy. NA: smoker, but smoking index not available. POD: postoperative date.

### Table 2

Incidence of ARDS

<table>
<thead>
<tr>
<th>Induction therapy (+)</th>
<th>ARDS (+)</th>
<th>ARDS (−)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CT/CRT)</td>
<td>3</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>(IP+/IP−)</td>
<td>(1/2)</td>
<td>(2/1)</td>
<td></td>
</tr>
<tr>
<td>Induction therapy (−)</td>
<td>12</td>
<td>1095</td>
<td>1107</td>
</tr>
<tr>
<td>IP (+)</td>
<td>11 (8.8%)</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>IP (−)</td>
<td>4 (0.4%)</td>
<td>739</td>
<td>743</td>
</tr>
</tbody>
</table>

CT: chemotherapy. CRT: chemoradiotherapy.

* Value is the incidence of ARDS in total 1148 patients.

Fig. 2. Chest CT shows honeycomb findings in the subpleural space (within 1 cm from pleura), defined as localized IP findings in this study.

Fig. 3. Pathological examination of a case, diagnosed as IP finding positive, shows a fibrous lesion in the subpleural space (HE stain, ×100).
Three of 41 patients with induction therapy developed postoperative ARDS. Induction therapy was also a risk factor of postoperative ARDS. Two (67%) of the three patients who developed postoperative ARDS had IP findings in chest CT. Because the incidence of positive IP findings in patients with operated lung cancer was 10.9%, patients with IP findings may be more susceptible to postoperative ARDS after the combination of induction therapy and surgery than patients without IP findings.

Pathological findings of both acute exacerbation of IPF and ARDS show the same diffuse alveolar damage in the final phase of severe cases. In this point of view, it is difficult to distinguish acute exacerbation of IPF apart from postoperative ARDS. However, the incidence of postoperative ARDS in patients with IP findings was much higher than that of patients without IP findings. A patient with IPF sometimes develops an acute exacerbation following surgery. Patients with IP findings were more susceptible to postoperative ARDS because of surgical stress than patients without IP findings. These data suggest that some parts of postoperative ARDS may be an acute exacerbation of IPF.

However, patients with postoperative ARDS in the current study were not always clinically diagnosed with IPF before surgery, because they had normal lung function, no symptoms, and the extent of IP lesions in these patients were localized, not diffuse. Localized IP findings were not detectable by chest X-ray film, but rather by chest CT in patients who underwent this procedure. This localized type of IP (subclinical IPF) has not drawn attention as being a risk factor of acute exacerbation. This study also indicates that an acute exacerbation following surgery may occur even in a patient with subclinical IPF (localized UIP).

Drug-induced interstitial pneumonia may also occur in a patient given drugs during the perioperative period. Since no drugs were identified as the allergen, drug-induced interstitial pneumonia could be ruled out as the diagnosis in our study. Drug-induced interstitial pneumonia is also known to respond well to steroid therapy when the inducing drug has been removed from the therapy regimen, whereas steroid pulse therapy in the present cases failed to improve postoperative ARDS.

In the current study, 91 of 834 patients (10.9%) had IP findings in their chest CT. Several reports have described that pathological UIP lesions have been observed in 6.3 — 10.8% of resected lungs or in cadavers with lung cancer [3,7,8]. Matsubara et al. [9] also reported that a third of patients with lung cancer had subclinical fibrotic lesions that were detected in their chest CT. Because IP findings in chest CT include not only UIP but also non-specific interstitial pneumonia, the detection rate of IP findings in this study is reasonable.

The IP finding positives in healthy participants (2.9%) were less than that of patients with lung cancer (10.9%). Although we cannot state exact differences because the average age of the subjects was different, it seemed to be related to the fact that UIP is a risk factor for lung cancer. It may be important to follow up healthy participants with IP findings as a high-risk group for lung cancer.

In conclusion, detection of IP findings by chest CT is useful in identifying high-risk patients who may develop postoperative ARDS following thoracotomy. Localized UIP is also a risk factor for acute exacerbation of IPF. Some parts of postoperative ARDS are an acute exacerbation of subclinical IPF.

References