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Risk Factors for Postoperative Acute Exacerbation of Idiopathic Interstitial Pneumonia Following Surgery for Primary Lung Cancer

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Abstract

Objective: Postoperative acute exacerbation of idiopathic interstitial pneumonia (IIP) is a serious complication in patients with lung cancer. This study was aimed to investigate risk factors for postoperative acute exacerbation of IIP in surgery for primary lung cancer. Method: We evaluated retrospectively 37 IIP patients combined with primary lung cancer who underwent lung resection for lung cancer from January 2006 and March 2010. Preoperative and perioperative clinical data were collected and analyzed. Results: Ten of 37 patients (27.0%) developed acute exacerbation of IIP after surgery for primary lung cancer and five patients (13.5%) died of progressive respiratory failure. There was no significant difference in preoperative clinical factors between acute exacerbation (AE) group and non-acute exacerbation (non-AE) group. In perioperative factors, the duration of anesthesia is significantly longer in AE group than in non-AE group. Conclusion: These data suggest that it is unable to predict postoperative acute exacerbation of IIP from preoperative clinical data. Perioperative and postoperative management might be important to prevent acute exacerbation of IIP combined lung cancer.

Keywords

Postoperative Acute Exacerbation, Idiopathic Interstitial Pneumonia, Lung Cancer

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1. Introduction

Acute lung injury/Acute respiratory distress syndrome (ALI/ARDS) is the most serious postoperative complication in lung cancer patients [1]. Idiopathic interstitial pneumonia (IIP) is associated with an increased risk of lung cancer [2]. Mortality and morbidity have been reported to be high in patients with interstitial pneumonia who underwent lung surgery [3]. Seventy-three percents of postoperative ARDS patients had interstitial pneumonia (IP) finding on preoperative thoracic computed tomography (CT) [4]. On the contrary, postoperative ARDS occurred in 4% - 30% of IP-positive patients [5]-[8]. Less than 1% of IP negative patients with primary lung cancer by chest CT were reported to have postoperative ARDS [4]. Therefore, postoperative ARDS in IP patients with lung cancer is probably due to acute exacerbation of IP. Precise risk factors for postoperative acute exacerbation of IIP associated with primary lung cancer are uncertain. To identify the risk factors for acute exacerbation of IIP and to prevent ARDS, we retrospectively analyzed preoperative and perioperative clinical data of IIP patients combined with lung cancer following thoracic surgery.

2. Materials and Methods

Thirty-seven consecutive IIP patients combined with primary lung cancer undergone lung resection at Nippon Medical School Hospital between January 2006 and March 2010 were enrolled in this study. Preoperative and perioperative clinical data of those patients were collected and analyzed retrospectively. Smoking index was calculated as follows: daily number of cigarettes × years. Idiopathic interstitial pneumonia was defined according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria [9] [10]. The definition of acute exacerbation was as described previously with minor modifications [11]: (1) exacerbation of dyspnea within a 1 month post operation, (2) newly developing pulmonary ground glass opacity or consolidation on high-resolution (HR) CT of the thorax, (3) deterioration of hypoxemia (PaO_2 > 10 Torr compared with preoperative stable state), (4) absence of infection, pneumothorax, congestive heart failure, pulmonary thromboembolism, as causes of acute worsening. Histopathological examination was performed using resected lung specimen to evaluate interstitial pneumonia. Informed consent was obtained from all patients and the study protocol was approved by the local ethics committee at Nippon Medical School.

Statistical analysis was performed using Statview 5.0 software (SAS institute Inc. Cary, NC, USA). All data were expressed as the mean ± standard deviation (SD). The statistical analysis of differences among the groups was done by χ^2 test and T-test. A $p < 0.05$ was considered statistically significant.

3. Results

Table 1 shows the clinical profile of the study population. The median age was 72 years (range, 57 - 95). Thirty-one patients were male and 6were female. Thirty-three patients were current or ex-smokers and 4 patients were never smokers. Histopathological types of lung cancer were squamous cell carcinoma (20 patients) and adenocarcinoma (12 patients). Characteristics of patients with postoperative acute exacerbation are listed in **Table 2**. Postoperative acute exacerbation of IP was diagnosed in 10 (27.0%) of 37 patients. The pathological stages of all 10 patients with postoperative acute exacerbation were IIIA. All patients were treated with steroid-pulse therapy and five patients (13.5%) died of progressive respiratory failure at post operated day (POD) 60 on average (range, 18 - 137). Acute exacerbation of IIP occurred within a median of 5.3 day (range, 1 - 12) after operation and all exacerbations occurred within 2 weeks. There were no significant differences in preoperative factors such as gender, age, smoking history, laboratory data, blood gas analysis and pulmonary function test between acute exacerbation (AE) group and non-acute exacerbation (non-AE) group (**Table 3**). Perioperative factors between AE and non-AE group were analyzed in **Table 4**. Only duration of anesthesia in AE groups (444 ± 70 min) was significantly longer than in non-AE group (354 ± 89 min, $p = 0.010$). Although duration of surgery, total bleeding and total fluid intake were tended to be lower in non-AE group, there was not significant difference between both groups. In order to evaluate interstitial pneumonia, histopathological examination was performed using resected lung specimen. There was no significant difference between both groups in pathological finding of fibroblastic focus (FF), a typical finding of usual interstitial pneumonia (UIP) (**Table 4**).

4. Discussion

The prognosis of IIP patients combined with lung cancer has been reported to be poor [3]. Although localized

Table 1. Characteristics of patients with idiopathic interstitial.

Patients (n)	37
Male/Female	31/6
Ages (years)	72 ± 7 (57 - 95)
Smoking index	990 ± 607 (4 never smokers)
Histology (Ad/Sq/others)	11/20/6

Ad: adenocarcinoma; Sq: squamous cell carcinoma. Smoking index: daily number of cigarettes × years.

Table 2. Characteristics of patients with postoperative acute exacerbation.

Pt	age/sex	histolog/p-stage/operation	duration to AE (days)	therapy	prognosis
1	76/F	Ad/IIIA/LLL	1	mPSL pulse·sivelestat	improved
2	78/F	Sq/IIIA/RLL	8	mPSL pulse·sivelestat·PMX	Dead POD44
3	70/M	Sq/IIIA/LUL	2	mPSL pulse·sivelestat·PMX	improved
4	95/M	Ad/IIIA/RLL	2	mPSL pulse·sivelestat·CPA	Dead POD18
5	67/M	Sq/IIIA/RLL	3	mPSL pulse·sivelestat	improved
6	68/M	Sq/IIIA/LLL	11	mPSL pulse·sivelestat	Dead POD49
7	68/M	Sq/IIIA/RPn	7	mPSL pulse·sivelestat	Dead POD137
8	70/M	Sq/IIIA/RUL	12	mPSL pulse·sivelestat	improved
9	73/M	Sq/IIIA/RLL	4	mPSL pulse·sivelestat	improved
10	75/M	Ad/IIIA/LUML	3	mPSL pulse	Dead POD74

Ad: adenocarcinoma; Sq: squamous cell carcinoma; AE: acute exacerbation; LLL: left lower lobectomy; RLL: right lower lobectomy; RPn: right pneumonectomy; LUML: left upper middle lobectomy; mPSL: methylprednisolone; CPA: cyclophosphamide ; PMX: polymyxin B immobilized fiver column; POD: post operated day.

Table 3. Comparison of preoperative data between AE and non-AE group.

	AE group (n = 10)	non-AE group (n = 27)	p value
Ages (years)	74 ± 8	71 ± 7	0.236
Male/Female	9/1	22/5	0.903
Smoking index	1080 ± 620	957 ± 637	0.602
Serum markers			
WBC(/μl)	7110 ± 1314	6911 ± 1641	0.733
LDH (IU/l)	218 ± 56	201 ± 52	0.381
CRP (mg/dl)	1.0 ± 2.4	0.8 ± 1.5	0.757
KL-6 (U/ml)	802 ± 549	682 ± 299	0.449
SP-D(ng/ml)	137 ± 88	140 ± 106	0.964
Pulmonary function test			
%VC (%)	99 ± 22	95 ± 17	0.571
FEV1(L)	2.2 ± 0.5	2.1 ± 0.4	0.886
FEV1% (%)	72 ± 11	75 ± 10	0.501
Blood gas analysis			
PaO_2 (Torr)	89 ± 14	86 ± 9	0.358
$AaDO_2$ (Torr)	14 ± 11	15 ± 10	0.813

WBC: white blood cell; LDH: lactatedehydrogenase; CRP: C-reactive protein; KL-6: Kerb von den Lungen-6; SP-D: surfactant protein D. VC: vital capacity; FEV1: forced expiratory volume in 1 second; PaO_2: arterial oxygen tension; $AaDO_2$: alveolar-arterial oxygen gradient.

Table 4. Comparison between perioperative data and findings of FF between AE and non-AE group.

	AE group (n = 10)	non-AE group (n = 27)	p value
Perioperative factors			
Duration of surgery (min)	290 ± 45	243 ± 81	0.096
Duration of anesthesia (min)	444 ± 70	354 ± 89	0.011
Bleeding(ml)	851 ± 1096	451 ± 392	0.106
MaxPaO_2 (Torr)	293 ± 110	228 ± 131	0.217
Fluid intake(ml)	3850 ± 1342	3171 ± 1478	0.256
Administration of steroid (n)	5	14	0.787
Pathological FF findings (n)	5	14	0.787

FF: fibroblast focus.

lung cancer should be resected if the patient can tolerate surgical procedure, postoperative acute exacerbation of IIP is the most serious complication after lung resection [1]. Our data suggest that it is difficult to predict post-operative of IIP from preoperative clinical data. Duration of anesthesia was the only different factor in between AE and non-AE groups in the present study. Perioperative and postoperative management may be important to prevent postoperative acute exacerbation.

Several risk factors have been reported on postoperative acute exacerbation of IIP combined with primary lung cancer. Shintani *et al.* recently reported that percent vital capacity (%VC) and serum lactate dehydrogenase (LDH) were predictive factors for acute exacerbation of interstitial pneumonia combined with lung cancer [12]. In the present study, there were not significant differences in both pulmonary function tests and serum markers for interstitial pneumonia between AE and non-AE groups. Serum LDH and Kerb von den Lungen-6 (KL-6), markers for interstitial pneumonia, levels were not only elevated in interstitial pneumonias but also elevated in lung cancers [13] [14]. Izumi *et al.* also reported that deceased %VC might be a predictive factor of outcome in patients with interstitial pneumonia undergoing lung resection for cancer [15]. Although VC correlates with the extent of lung fibrosis and pathophysiologic severity [16], reduced VC may occur in chronic obstructive lung disease. A combination of obstructive and restrictive lung disease frequently occurs in heavy cigarette smokers who have interstitial pneumonia [17]. In the present study, thirty-three (89.1%) of 37 patients were cigarette smokers. It is difficult to determine disability is primary due to interstitial pneumonia or emphysema. Pathologically both emphysematous and fibrosis changes were found in 3 of 10 patients with postoperative acute exacerbation in the present study.

We have previously reported that abundant FF in the tissue specimens were possibly one of the predictive factors in the postoperative exacerbation of IIP [18]. However, Titto *et al.* have reported that the number of FF cannot be a predictor of acute exacerbation [19]. Pathological findings of FF were not different between in AE and non-AE groups in the present study.

Even in cases without IIP, ALI/ARDS has been serious complications post surgery for lung cancer. Jeon *et al.* have reported that large tidal volume and high airway pressure during one-lung ventilation were associated with an increased risk of postoperative ALI/ARDS in primary lung cancer patients [20]. Shilling *et al.* compared bronchoalveolar lavage fluid of the lung received mechanical ventilation with high (10 mg/kg) and low (5 mg/kg) tidal volume when undergoing open thoracic surgery. Ventilation with low tidal volume significantly decreased alveolar pro-inflammatory tumor necrosis factor (TNF)-α and soluble intracellular adhesion molecule (ICAM)-1 and increased anti-inflammatory interleukin (IL)-10 levels compared to high tidal volume ventilation [21]. Over-ventilation of the lung units can induce inflammatory responses and may contribute to the development of lung injury. In the present study, longer anesthesia, that is to say, longer ventilation, may cause over-ventilation and induce acute exacerbation of IIP.

ALI has reported to be occurred more often after pneumonectomy than after lobar or lesser resections. Blood flow to the remaining lung increased as a result of lung amputation, excessive intravascular volume and surgical

stress responses. Hemodynamic shear stress can physically injure capillary endothelium, allowing protein-rich fluid to fill the interstitial and alveolar space [22]. Similarly, excessive perioperative intravascular volume may cause postoperative lung injury. In the present study, we found no significant differences in the incidence of acute exacerbation of IIP about lesser resections or intravascular volume.

In order to prevent postoperative acute exacerbation of IIP, perioperative administration of steroid has been evaluated [23] [24]. We could not demonstrate the efficacy of perioperative steroid in the present study.

Licker *et al.* distinguished secondary ALI caused by bronchopneumonia, inhalation of gastric contents, broncho-pulmonary fistula, and thromboembolism from primary ALI that was unknown cause. Primary ALI usually occurred within 3 days and secondary occurred after 4 days post operation [25]. Compared with secondary ALI, primary ALI has reported to be associated with less mortality. In the present study, patients with acute exacerbation after 4 or later days post operation had higher mortality rate than patients occurred within 3 days (75% vs. 33%). Postoperative management may be an important factor to prevent acute exacerbation of IIP.

The present study has some limitations. First, the sample size was small. Second, the retrospective design means that medication regimens for AE group and data collection were not systematically implemented.

5. Conclusion

In conclusion, it is difficult to predict postoperative acute exacerbation of IIP combined with primary lung cancer. Perioperative and postoperative managements are important to prevent acute exacerbation of IIP. Further clinical studies will be needed to find risk factors and prevent acute exacerbation of IIP combined with primary lung cancer.

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Abbreviations

IIP: Idiopathic Interstitial Pneumonia
AE: Acute Exacerbation
ALI: Acute Lung Injury
ARDS: Acute Respiratory Distress Syndrome
CT: Computed Tomography
HRCT: High-Resolution (HR)
CT; POD: Post Operated Day
FF: Fibroblastic Focus
VC: Vital Capacity
KL-6: Kerb Von Den Lungen-6
LDH: Lactate Dehydrogenase