Subpleural Honeycombing on High Resolution Computed Tomography is Risk Factor for Fatal Pneumonitis

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GENERAL THORACIC

Background. **Postoperative interstitial pneumonitis is a life-threatening complication after lung cancer surgery. We conducted this study to identify risk factors for postoperative interstitial pneumonitis in patients with no clinical evidence of interstitial lung disease.**

Methods. **We retrospectively studied patients who underwent lung cancer resection. The characteristics of patients were analyzed by reviewing their clinical and surgical records and preoperative chest high-resolution computed tomographic scans. Postoperative interstitial pneumonitis was defined as acute severe hypoxemia accompanied by radiographic diffuse interstitial infiltrates of the lung with no apparent cause within a few weeks after surgery.**

Results. **From 2002 through 2005, 651 patients were evaluated, operated on, and managed by the same team. Postoperative interstitial pneumonia developed in 7 patients (7 of 651, 1.1%). Five of these patients had local, but not diffuse, dorsal subpleural honeycombing occupying three or more segments in both lower lobes on high-resolution computed tomography (CT honeycombing). During the same period, 46 patients had CT honeycombing. The incidence of postoperative interstitial pneumonia was 10.9% (5 of 46) among patients with CT honeycombing and 0.3% (2 of 605) among those without CT honeycombing. Four of the 7 (57%) patients with postoperative interstitial pneumonia died of respiratory failure. Mortality among the patients who had postoperative interstitial pneumonia as well as CT honeycombing was 80% (4 of 5); in contrast, none of the patients without CT honeycombing died. Multivariate analyses showed that the presence of CT honeycombing and prolonged operation time were significant risk factors.**

Conclusions. **Subpleural honeycombing on high-resolution computed tomography is a significant predictor of postoperative interstitial pneumonia in asymptomatic patients who undergo resection for lung cancer.**

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Recent improvements in patient-selection criteria, operative techniques, and postoperative management have contributed to lower mortality from lung cancer surgery. In 1983 the Lung Cancer Study Group reported a mortality rate of 3.7% [1]. In 1999 an analysis of data from a Japanese lung cancer registry estimated that mortality had decreased to 0.9% [2]. Respiratory complications frequently occur after lung cancer resection and about half of all postoperative deaths are attributed to interstitial pneumonia (IP) [3]. Of course, apparent interstitial lung disease (ILD), including idiopathic pulmonary fibrosis (IPF), is an important risk factor for postoperative IP as well as for poor outcomes in patients with lung cancer [4, 5]. The treatment strategy for patients who have lung cancer with apparent ILD must therefore be decided more judiciously than usual [5, 6]. On the other hand, postoperative IP sometimes occurs unexpectedly in patients without apparent ILD who have acute lung injury-acute respiratory distress syndrome (ALI/ARDS) accompanied by bilateral reticular infiltrations on chest radiography. In many such patients, ILD is not diagnosed preoperatively because their clinical signs and symptoms are atypical of ILD; ie, focal (not diffuse) fibrotic changes on computed tomography (CT) of the chest with no apparent symptoms [7]. High-resolution computed tomography (HR-CT) has been shown to delineate the anatomy of the lungs more clearly than conventional CT. Using HR-CT, it can be easier to check focal fibrosis of the lung and exclude gravitational effect. It is difficult to estimate the incidence of serious but infrequent complications by a multiinstitutional analysis because preoperative evaluations of CT findings as well as operative procedures and postoperative management differ among hospitals. Intraoperative management by anesthesiologists also has a considerable influence on postoperative ALI [8]. To exclude these potential biases, we conducted this study to identify risk factors for postoperative IP in patients with no clinical evidence of ILD before surgical resection who were treated in a single center.

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Abbreviations and Acronyms

ALI = acute lung injury
ARDS = acute respiratory distress syndrome
CT = computed tomography
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
HE = hematoxylin-eosin stain
HR-CT = high-resolution computed tomographic
HU = Hounsfield unit
ICU = intensive care unit
ILD = interstitial lung disease
IP = interstitial pneumonia
IPF = idiopathic pulmonary fibrosis
LDH = lactate dehydrogenase
Lob. = lobectomy
NSIP = nonspecific interstitial pneumonia
Pao_2 = arterial oxygen tension
Pneu. = pneumonectomy
Sub. = sublober resection
UIP = usual interstitial pneumonia

Patients and Methods

Our institutional Internal Review Board approved this retrospective study. From January 2002 through December 2005, a total of 651 patients underwent resection of primary lung cancer at Kanagawa Cancer Center. Patients with apparent ILD or obstructive pneumonia before operation were excluded from this study. All patients were closely evaluated by a single team of pulmonologists, radiologists, medical oncologist, and thoracic surgeons together. Surgery and postoperative management were performed by the same surgical team in all patients. After operation, patients were admitted to the intensive care unit for only that day, transfusion was performed at the speed of 1.25 $mL \cdot kg^{-1} \cdot hour^{-1}$, and an oxygen mask (40%) was set in until next morning. From the next day of operation, patients started to walk by themselves with support. In our routine daily check-up of postoperative patients, Spo_2 (oxygen saturation as measured by pulse oximetry) and body weight were checked at least twice a day, and chest X-ray was undertaken on postoperative days 0, 1, 4, and 7. Laboratory values were checked on postoperative days 1, 4, and 7. Cefazolin (1.0 g) was used just before operation to postoperative day 1 twice a day. When we noted a patient with Spo_2 less than 93 in room air and infiltrating shadow on chest X-ray, a chest CT was immediately undertaken. Sputum culture was examined or bronchofiberscopy performed to exclude aspiration and bacterial infection.

No patient was given a diagnosis of ILD preoperatively and had no clinical symptoms such as breathlessness, presence of crackles, or finger clubbing except caused by lung cancer. We retrospectively studied patients in whom IP developed postoperatively by reviewing their clinical characteristics (age, sex, smoking history, arterial oxygen tension, % forced vital capacity, forced expiratory volume in 1 second %, coexisting heart disease, tumor-nodes-metastasis stage), surgical records (operation time, blood loss, operative procedure, blood transfusion), and preoperative HR-CT scans of the chest. Postoperative IP was diagnosed on the basis of acute hypoxia-like ALI-ARDS, an arterial oxygen tension to fraction of inspired oxygen ratio of less than 300 with bilateral infiltrations on chest radiography, and the involvement of both lungs. Patients who had ALI-ARDS caused by bacterial pneumonia or aspiration were excluded. An ultrasound cardiogram was performed to rule out acute heart failure.

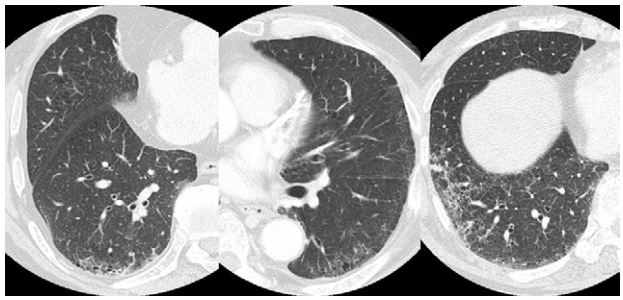

Fig 1. Preoperative high-resolution computed tomographic films of computed tomographic honeycombing in three patients. Focal, not diffuse subpleural dorsal honeycombing with focal fibrotic changes can be seen.

Both lungs were examined by HR-CT. The conditions of HR-CT were a slice thickness of 3 mm or thinner using the mediastinal (level, 40 Hounsfield unit [HU]; width, 400 HU) and lung (level, 600 HU; width, 1,600 HU) window settings. The HR-CT scans were double-checked by a pulmonologist and a radiologist. We assumed that subpleural localized CT honeycombing may be a predictor of subclinical ILD. The criteria for CT honeycombing in this study were dorsal and focal (not diffuse) subpleural honeycomb formation with or without fibrotic changes occupying three or more segments in both lower lobes (CT honeycombing), without any physical symptoms (Fig 1). Curvilinear shadows and dependent densities indicating gravitational effects were excluded. All patients in whom apparent ILD had been previously diagnosed were excluded. Lung specimens from all patients in whom ALI-ARDS developed during the study period were histopathologically examined to confirm the presence or absence of ILD findings.

Each variable was tested by the χ^2 test, Fisher exact test, and Student t test. Logistic-regression analysis was used for multivariate analysis, performed with Stat View for Windows (version 5.0; SAS Institute Inc, Cary, NC). The p values of less than 0.05 were considered to indicate statistical significance.

Results

Postoperative IP developed in 7 patients (7 of 651, 1.1%). Four of these patients (4 of 7, 57%) died of respiratory failure. Table 1 shows the clinical characteristics of the patients with postoperative IP. All 7 patients were men, with an average age of 66.5 years (62 to 73). All were smokers, and the average smoking index (cigarettes/day ×