A clinicopathological study of resected pulmonary nodules with focal pure ground-glass opacity

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Abstract

Objective: Pulmonary lesions with focal ground-glass opacity (GGO) have been detected increasingly by low-dose helical computed tomography (CT). However, the strategy of treatment for focal pure GGO lesions is still undecided. This study evaluates clinicopathological characteristics of resected pulmonary nodules with focal pure ground-glass opacity. Methods: Between January 1997 and December 2005, 26 patients (35 lesions) with pure GGO lesions underwent pulmonary resection. The data on patient age, lesion size, pathology, carcinoembryonic antigen (CEA) level and palpability of the tumor in the resected specimen were evaluated. Results: The histological diagnosis was bronchioloalveolar carcinoma (BAC) in 10 patients (12 lesions), atypical adenomatous hyperplasia (AAH) in 15 patients (22 lesions), and focal scar in 1 patient (1 lesion). There were no significant differences in age, sex, tumor size, and CEA level between the patients with BAC, AAH, and focal scar. However, the lesions >10 mm in size were all BAC. Palpability of the tumor in the resected specimen was significantly more frequent in BAC cases than in AAH cases (p < 0.01). For BAC, lobectomy was performed for four lesions, and limited resection for eight. None of the BACs showed lymphatic or vascular invasion upon pathological examination. At the median follow-up point of 44 months (range: 4—84 months), no recurrences were observed. Conclusions: BAC and AAH cannot be discriminated by their size. In the resected specimen, BAC lesions are more frequently palpable than AAH lesions. Thoracoscopic surgery is recommended for focal pure GGO after repeated CT even if the GGO lesion is small. Partial resection is a sufficient treatment for pure GGO.

Keywords: Ground-glass opacity; Lung cancer; Atypical adenomatous hyperplasia; Bronchioloalveolar carcinoma

1. Introduction

Pulmonary lesions with focal ground-glass opacity (GGO) [1] have been detected increasingly by low-dose helical computed tomography (CT) [2]. Some reports have suggested that focal GGO lesions with a solid component (mixed GGO) are significantly likely to be malignant [3,4] and that thoracoscopic resection is recommended. However, the treatment of focal pure GGO lesions is still controversial. Precise details of the natural history of focal pure GGO are still largely unclear. A number of differential diagnoses are possible, including inflammatory disease, focal scar, atypical adenomatous hyperplasia (AAH), and bronchioloalveolar carcinoma (BAC). As BAC grows very slowly [5], differential diagnosis remains difficult with follow-up CT. BAC without fibrotic scarring could be considered early adenocarcinoma of the lung [6,7], early detection and treatment of lung cancer has the possibility to reduce the mortality of lung cancer patients [8]. When the surgery is performed for the treatment of GGO, it is sometimes difficult to localize such a small nodule. But no report demonstrates the intraoperative findings and palpability of the focal pure GGO. Carcinoembryonic antigen (CEA) level is a useful tumor marker for non-small cell lung cancer correlated with tumor progression [9,10], and a study demonstrates that CEA is associated with the formation of GGO [11].

The purpose of the present study is to evaluate the pathologic and clinical characteristics (age, sex CEA level, tumor size, and palpability of the tumor in the resected specimen) of focal pure GGO lesions.

2. Materials and methods

Between January 1997 and December 2005, we encountered 32 patients with 41 focal pure GGO lesions less than 20 mm in size on CT examination. Of the 32 patients, GGO was detected on helical CT screening for lung cancer in 10 patients. In the remaining 22 patients, GGO was unexpectedly identified on the CT scan for other reasons. All the patients underwent repeated CT scan after more than 3 months. Two lesions in two patients were found to have dimished and four patients (with four lesions) refused...
surgical intervention and continued to be followed up by CT. Therefore, a total of 26 patients (with 35 lesions) underwent pulmonary resection. Before surgical resection, the nodules were marked with lipiodol under CT guidance when they were not located in the lobe for which lobectomy was planned [12]. Briefly, we measure the shortest distance from the GGO lesion to the thoracic wall and select the injection site by CT. The site for marker injection was marked on the skin, and the angle and depth of the needle required to reach the GGO lesion are determined. After local anesthesia of the thoracic wall, a 23-gauge needle was introduced from the point marked on the skin to the nodule, according to the angle and depth measured by CT. We injected 0.4 mL of lipiodol with one shot. The presence of the injected materials was confirmed by CT just after marking. During the operation, we identified the GGO lesion with the aid of the fluoroscopy, and then resected with an endostapler. Wedge resection of the lung containing focal-pure GGO was performed. If we could palpate the tumor in the resected specimen, we examine the frozen-section specimen immediately. If the tumor was confirmed as malignant, lobectomy was performed until September 2002. Since October 2003, if the tumor was confirmed as Noguchi type A or B [6] with a resection margin greater than 1 cm by frozen-section specimen, no additional surgery was required. If the margin was not sufficient, additional margin was resected. If we could not palpate the tumor during the surgery, the resected specimen was histologically diagnosed by a routine pathologic examination after the operation.

The acquisition variables used on the CT scanner (ProSeed SA, General Electrical Medical System, Milwaukee, WI, USA) were as follows: high voltage (120 kV), tube load 160 mA, window level 500 Hounsfield units (HU), window width–1500 HU, and a 512 × 512 matrix corresponding to a pixel size of about 0.6 mm. Air calibration was conducted every morning before using the phantom. All lesions were subjected to helical scanning using sections 1 mm thick during one breath hold with maximum inspiration. Each tumor was scanned with at least three slices. Pure GGO was defined as a hazy increase in lung attenuation without obscuring the underlying bronchial or vascular structures [1]. The data on patient age, tumor size, pathology, carcinoembryonic antigen (CEA) level and palpability of the tumor in the resected specimen were collected and analyzed. Three thoracic surgeons judged the palpability of the resected lung including the GGO lesion.

All data were expressed as mean ± standard deviation (SD). The differences in mean and SD values between the groups were analyzed using two-tailed Student’s t-test. Between-group differences at p < 0.05 were regarded as significant.

3. Results

The histological diagnosis was BAC in 10 patients (12 lesions), AAH in 15 patients (22 lesions), and focal scar in 1 patient (1 lesion) (Fig. 1). Twenty-one patients had one GGO lesion, one had two lesions, and four had three lesions. There were no significant differences in age, sex, or CEA level between the patients with BAC, AAH, and focal scar (Table 1). The mean maximum tumor diameter was 8 ± 4 mm (range: 4–16 mm) for BAC and 6 ± 3 mm (range: 2–10 mm) for AAH. There were no significant differences in tumor size between BAC and AAH. However, both of the only two lesions >10 mm in size were BAC. All lesions were discovered initially by CT and were not identified on chest X-ray films. Nine of the 12 BAC lesions were palpable after lung resection. However, none of the 22 AAH lesions was palpable. BAC tumors were palpable significantly more frequently than AAH lesions (p < 0.01) (Table 2). The palpability of the tumor in the resected specimen of focal pure GGO lesions and their size were also evaluated, but there was no significant difference in palpability between lesions classified on the basis of size as ≥10 mm or <10 mm (p = 0.41) (Table 3). Lobectomy was performed for four BAC lesions, and limited resection was performed for eight. None of the BACs showed lymphatic or vascular invasion upon pathological examination. After a median follow-up period of 44 months (range: 4–84 months), no recurrences had been observed.

4. Discussion

Recently, lung cancer screening using low-dose helical CT has been reported to be effective for detecting small lung

Fig. 1. High-resolution computed tomography of focal pure ground-glass opacity (GGO). (A) Bronchioloalveolar carcinoma (B) Atypical adenomatous hyperplasia.
cancers [8,13], thus increasing the expectation that a much larger number of GGO lesions will be found. Although several studies have demonstrated relationships between the CT appearance of peripheral pulmonary nodules and pathologic results [5,14,15], the diagnosis of GGO still remains difficult.

In the present study, we examined 35 focal pure GGO lesions, and there were no significant differences in lesion size between BAC and AAH. However, both of the only two pure GGO lesions measuring >10 mm were BAC. An important finding in our study is that pure GGO >10 mm in diameter had a high possibility of malignancy. We also evaluated patient age and CEA level, but there were no differences in these parameters between AAH and BAC.

We also demonstrated that palpability of GGO lesion in the resected specimen was higher in BAC than in AAH. To our knowledge, this is the first report to describe the palpability of focal pure GGO. Among the nine GGO lesions >10 mm in size, five were not palpable. Therefore, before thoracoscopic biopsy, marking of GGO should be performed even if the size is >10 mm. Why is BAC much more palpable than AAH? Both AAH and BAC usually appear as GGO lesions on CT due to the combined effects of reduction of alveolar air spaces, increased cellular components with alveolar cuboidal cell hyperplasia, thickening of alveolar septa, and partial filling of the alveolar air spaces by the tumor cells [16]. AAH usually has significantly more air spaces and fewer cell components than BAC, and this explains why BAC has higher palpability. If a GGO lesion is not palpable, it is difficult to obtain a specimen for intraoperative frozen microscopic examination. Several studies have shown that limited resection may be sufficient for pure GGO lesions [3,17]. Therefore, we think it unnecessary to carry out intraoperative microscopic examination of pure GGO when the surgical margin is sufficient.

Hill [18] noted that in cases of unresected clinical stage I BAC, the disease progressed to a more advanced stage, typically within 2 years. Although BAC shows slow progression, it may eventually reach an advanced stage. Kakinuma et al. [19] followed up eight cases of pure GGO with CT and surgery, and found that one of the lesions showed transformation to mixed GGO with an invasive component. They also considered that lesion stability or a reduction in size over a 2-year period does not necessarily indicate a benign nature. Wallace et al. [20] reported that CT-guided percutaneous fine-needle biopsy yielded high rates of diagnostic accuracy for pulmonary nodules less than 1 cm in diameter. However, it is difficult to differentiate BAC from AAH with such a small specimen. Even if a pure GGO is small, thoracoscopic limited resection is recommended after repeated CT.

Only a few studies have made a pathological comparison of pure GGO, probably because of the difficulty in removing such minute nodules. Several methods have been reported for the localization of small pulmonary nodules [21–23]. In the present study, we were able to remove pure GGO lesions easily using the lipiodol marking technique. We therefore believe that GGO lesions should be diagnosed by thoracoscopic biopsy with preoperative lipiodol marking.

In conclusion, thoracoscopic wedge resection for focal pure GGO is a valid procedure. Detections of GGO lesions had increased strikingly since lung cancer screening with low dose helical CT. Although the natural history of focal GGO remains unclear, AAH is probably precursor lesion of BAC [24], and thoracoscopic resection is recommended after an interval of several months even if the GGO lesion is small.

References


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Table 1

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<td>CEA</td>
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<td>Age (years)</td>
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BAC: bronchioloalveolar carcinoma; AAH: atypical adenomatous hyperplasia; CEA: carcinoembryonic antigen.

Table 2

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Table 3

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<td>Non-palpable</td>
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Size of focal pure ground-glass opacity.


