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CHEST

Asbestosis and other pulmonary fibrosis in asbestos-exposed workers: high-resolution CT features with pathological correlations

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Abstract

Objective The purpose was to identify distinguishing CT features of pathologically diagnosed asbestosis, and correlate diagnostic confidence with asbestos body burden.

Methods Thirty-three workers (mean age at CT: 73 years) with clinical diagnoses of asbestosis, who were autopsied (n=30) or underwent lobectomy (n=3), were collected. Two radiologists independently scored high-resolution CT images for various CT findings and the likelihood of asbestosis was scored. Two pathologists reviewed the pathology specimens and scored the confidence of their diagnoses. Asbestos body count was correlated with CT and pathology scores.

Results Pathologically, 15 cases were diagnosed as asbestosis and 18 cases with various lung fibroses other than asbestosis. On CT, only the score of the subpleural curvilinear lines was significantly higher in asbestosis (p=0.03). Accuracy of CT diagnosis of asbestosis with a high confidence ranged from 0.73 to 0.79. Asbestos body count positively correlated with CT likelihood of asbestosis (r=0.503, p=0.003), and with the confidence level of pathological diagnosis (r=0.637, p<0.001).

Conclusions Subpleural curvilinear lines were the only clue for the diagnosis of asbestosis. However, this was complicated by other lung fibrosis, especially at low asbestos body burden.

Key points

- *Various patterns of pulmonary fibrosis occurred in asbestos-exposed workers.*
- *The fibre burden in lungs paralleled confident CT diagnosis of asbestosis.*
- *The fibre burden in lungs paralleled confident pathological diagnosis of asbestosis.*
- *Subpleural curvilinear lines were an important CT finding favouring asbestosis.*

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Keywords Computed tomography, radiography · Asbestos · Pulmonary fibrosis · Asbestosis · Chronic interstitial pneumonia

Introduction

Asbestosis is suspected when diffuse lung fibrosis is identified in patients with clinical evidence of vast amounts of asbestos exposure. However, it is not only asbestosis that presents with diffuse lung fibrosis in such patients, but also idiopathic pulmonary fibrosis (IPF), and this is the important differential diagnosis. Pathologically, asbestosis is characterized by the fibrosis of alveolar walls adjacent to the respiratory bronchioles, which extend to involve the surrounding lung in the centrifugal direction [1]. In contrast, usual interstitial pneumonia (UIP), which is the pathologic counterpart of IPF, begins at the periphery of the secondary pulmonary lobule and progresses in the centripetal direction. These anatomical differences of lung fibrosis could be appreciated by high-resolution computed tomography (CT) images to some extent; however, the story is not straightforward. There are three studies that dealt with the imaging differences between asbestosis and IPF; they have yielded conflicting results [2–4]. Two reports found some important differences that facilitated the diagnosis; however, the other report found no differences between asbestosis and IPF. The drawback of these previous researches is that the diagnosis was made clinically without pathological diagnosis, and the IPF patients were not always exposed to asbestos.

In this retrospective study, we collected high-resolution CT and lung tissue obtained from autopsy or lobectomy from a nationwide network that cares for asbestos-exposed patients in our country. The purpose of this study was to find CT differences between asbestosis and other pulmonary fibrosis (non-asbestosis) in asbestos-exposed workers based on pathological diagnosis, and to elucidate diagnostic feasibility of computed tomography and pathology in comparison to the degree of asbestos exposure.

Materials and methods

This retrospective study was approved by the institutional review boards of the six participating hospitals. Informed consent from the patients who were alive was obtained; it was waived for deceased patients.

Patients

We collected cases of possible asbestosis from the nationwide hospital network that cares for asbestos workers. Those cases with a pathologic specimen (either lobectomy or autopsy) were identified, and the CT images, during life and pathology specimens, were collected. Patients were followed up for pulmonary fibrosis with known occupational asbestos exposure. Fifty-six cases were collected from six hospitals. Twenty-three cases were excluded because of the lack of high-resolution CT or absence of lung fibrosis on CT and pathological analysis. Thus, 33 patients (31 men, two women, mean age at CT: 73 years) who underwent chest CT between May 2000 and July 2011 were enrolled in the study group. Sixteen patients, in whom subsequent pathological diagnosis revealed four asbestosis and 12 non-asbestosis, as described below, were included in the previous study [5]. Thirty cases underwent autopsy, and three cases had lobectomies for lung cancer (two from right lower lobe, and one from left upper lobe). The interval between CT scan and autopsy ranged from 1 month to 68 months (mean=16 months). In the autopsied cases, those CT images were avoided that showed complications such as pneumonia, acute exacerbation of chronic interstitial pneumonia or advanced lung cancer. Only those images of patients in stable condition were evaluated. For lobectomy cases, CT images were obtained within 2 months of lobectomy. Occupational histories included: asbestos-manufacturer (n=9), shipyard workers (n=8), asbestos-spraying (n=4), repairing boiler (n=2), insulation worker (n=2), plumbing (n=2), and others (n=5). Working years ranged from 10 to 42 years (mean=24 years).

High-resolution CT technique

CT images were obtained by various CT systems. Patients were imaged in the supine position. Lung window images were provided with 1–2 mm thickness with 10 mm intervals of the whole lung in all but one case, in which lung and mediastinal window images were provided with 3 mm thickness without gap. Additional contiguous images with 5–7 mm thickness of the whole lung were also available in most cases. Images were provided with the DICOM format and reviewed on monitors.

Image analysis

Two radiologists (K. A. and K. K., with 24 and 20 years of experience, respectively) independently reviewed the images without knowledge of pathological diagnosis and occupational history, but with knowledge of age and sex of the patient. Disagreements about the presence or absence of each CT finding were resolved by the decision of the third radiologist (H. A., 22 years of experience).

CT images for lung disease were scored by the nearest of 10 % of the cross-sectional area in each zone. The zone consisted of upper, middle and lower; the tracheal carina and the confluence of inferior pulmonary vein served as the boundaries. The extent of ground-glass opacity, reticulation,

honeycombing, consolidation and emphysema were scored. The presence of dot-like opacity [6], subpleural curvilinear line [7, 8], parenchymal band and mosaic perfusion were evaluated (score range, 0–6). The coarseness of fibrosis was scored as: 0=ground-glass opacity only, 1=ground-glass opacity with reticulation, 2=honeycomb cysts less than 5 mm, 3=honeycomb cysts more than 5 mm (score range, 0–18) [3]. If no interstitial opacity was identified in the zone, the zone was excluded for scoring coarseness. The number of segments with traction bronchiectasis was scored in the upper, middle/lingual and lower lobes (score range, 0–18).

The pleural disease, comprising both pleural plaque and diffuse pleural thickening, was scored in each zone by the maximum extent compared to the circumference of hemithorax at the level of tracheal carina as: 1=less than one-quarter, 2=more than one-quarter and less than one-half, 3=more than one-half and less than three-quarters, 4=more than three quarters (score range, 0–24). The presence of diffuse pleural thickening and rounded atelectasis were also evaluated. Pleural calcification was not evaluated.

CT scores determined by the two radiologists were averaged, which yielded the final scores.

Finally, the likelihood of asbestosis was given to each case on a four-point scale: 0=not asbestosis, 1=possible asbestosis, 2=probable asbestosis, 3=definite asbestosis. The summation of the two scores provided the CT-asbestosis score. The CT diagnosis of asbestosis was made based on the previous report [2, 4]. The presence of subpleural dot-like opacity, subpleural curvilinear lines only a few millimetres from the pleural surface, subpleural consolidation without traction bronchiectasis (atelectatic induration) [8], and mosaic perfusion were CT findings favouring asbestosis, while extensive honeycomb cysts, severe traction bronchiectasis with architectural distortion, absence of pleural disease were regarded as favouring an alternative diagnosis. In the case with conflicting CT findings, the diagnosis and confidence level depended on the experience of each reviewer.

Pathological diagnosis

Two pulmonary pathologists (K. H. and K. O., with 31 and 34 years of experience, respectively) independently reviewed the same tissue specimens without knowledge of occupational history, made diagnoses and suggested a confidence level for each case based on the recently published criteria of asbestosis [1]. It should be noted that fibrosis in asbestosis is accompanied by very little inflammation, and fibroblastic foci are infrequent [1]. In early asbestosis, the fibrosing process is limited to the walls of alveoli immediately around the bronchioles. In the advanced stage, however, a variety of morphologic patterns may be seen, such as UIP, nonspecific interstitial pneumonia (NSIP), and even an unclassifiable pattern can be identified [1]. The pathological diagnosis was scored on a three-point scale: 0=fibrosis other than asbestosis, 1=possible asbestosis, 2=definite asbestosis. The summation of the score given by each pathologist provided the pathological asbestosis score. Because the pathological specimens were obtained from autopsy or lobectomy, we reviewed multiple specimens from different sites. In the autopsy cases, several samples were obtained from different lobes. In 16 cases, we re-excised the specimen in order to correlate with CT findings and confirm the diagnosis.

Asbestos body count

Asbestos body count was performed by experienced technicians in one of the institutions participating in this study. The method of counting asbestos bodies is detailed elsewhere [9]. Briefly, one specimen was sampled from each lobe and trimmed so that the weight of the wet lung totalled to between 1 and 2 g. In the autopsy cases, specimens were sampled from each lobe, excluding the heavily damaged ones. In regard to the lobectomy cases, one sample was excised, avoiding the tumour. The specimens were mixed and allowed to react with laboratory bleach. The digested solution was centrifuged two times, followed by filtering through the membrane filter. The filter was then fixed on the glass slide, and the ferruginous bodies were counted using polarized light microscopy.

Statistical analysis

Agreement of CT scores were evaluated by single determination standard deviation [10]. Agreement of CT and pathological scores were calculated by weighted kappa statistics. The difference in CT scores between asbestosis and non-asbestosis were evaluated by a non-parametric test (IBM SPSS Statistics ver. 22, Tokyo, Japan). The correlations of asbestos body count and CT/pathological scores were evaluated with the Spearman rank correlation coefficient. A value of $p<0.05$ was considered significant.

Results

The inter-observer agreement of pathological diagnosis was excellent (weighted kappa, 0.80). Each pathologist diagnosed 14 and 12 cases as definite asbestosis, one and five cases as possible asbestosis, and 18 and 16 cases as non-asbestosis, respectively. When the pathological asbestosis score of 2 or more was considered asbestosis, there were 15 asbestosis and 18 non-asbestosis cases. Non-asbestosis cases included UIP (n=5), chronic interstitial pneumonia that cannot be classified in the current classification (unclassifiable) (n=4) and mixed dust fibrosis (n=2) (Fig. 1). In two cases where one pathologist suggested an asbestosis (score 1), the other pathologist made the diagnosis of UIP and NSIP, respectively (Fig. 2).

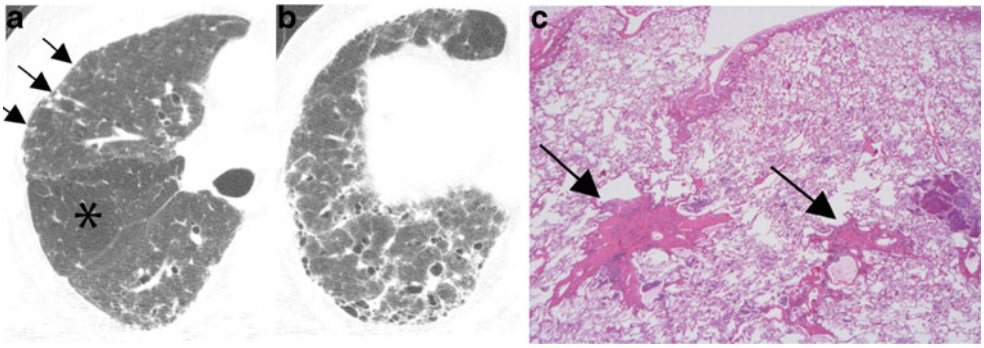

Fig. 1 A 72-year-old previous asbestos textile male worker with mixed dust fibrosis. **a**. HRCT of right upper lobe shows multiple subpleural dot-like opacities that are relatively well defined and show high density in spite of their small size. Note that there is a lower attenuation area indicating mosaic perfusion (*asterisk*). **b**. HRCT of right lower lobe shows septal line thickening and subpleural ground-glass opacity with traction bronchiectasis resembling UIP. **c**. Low-power view of pathological specimen obtained from right upper lobe corresponding to *a* shows centrilobular stellate fibrosis typical of mixed dust fibrosis, which differs from asbestosis. Multiple asbestos bodies were identified in the specimen (not shown). The asbestos body count was 67,406/g (dry lung)

In these cases, asbestos body count was low (263,480/g and 86,560/g, respectively). In the other five cases, pathological diagnosis was either UIP, NSIP or unclassifiable pattern, and they were discordant.

In terms of CT scores, there were good inter-observer agreements with a single determination standard deviation. They were less than 5 % for all the parenchymal opacities, 2.7 for traction bronchiectasis, 1.2 for both dot-like and subpleural curvilinear opacities, 0.5 for coarseness, and less than 2 for others including pleural diseases. The inter-observer agreement in the diagnosis of asbestosis by two radiologists was 0.56 by weighted kappa statistics. Each radiologist diagnosed 19 and 16 cases as asbestosis, respectively. With a CT score of 2 or more considered as a high likelihood of asbestosis (i.e., probable and definite asbestosis) and the pathological diagnosis as a gold standard, sensitivity, specificity and accuracy by two radiologists were 0.67, 0.78, 0.73 and 0.73, 0.83, 0.79, respectively.

The mean asbestos body count was 1,464,711 and 98,745 for asbestosis and non-asbestosis, respectively ($p<0.001$) (Table 1). Age and work period were comparable between the two groups. Among the various CT findings, only the scores for subpleural curvilinear lines were significantly different between asbestosis and non-asbestosis (2.9 and 1.7, respectively, $p=0.03$) (Table 1) (Fig. 3). They were equally identified in each lung zones (summation of scores in all patients were 20, 23 and 23, in the upper, middle and lower lung zones, respectively). The other CT scores showed no significant differences between the two groups. The frequencies of CT findings considered important in the diagnosis of asbestosis from previous study are indicated in Table 2 [2]. Again, the prevalence of subpleural curvilinear lines was significantly higher in asbestosis than in non-asbestosis (86.7 % vs. 50 %, $p=0.034$). Honeycombing was observed less frequently in asbestosis than in non-asbestosis; however, the difference was not significant (40 % vs. 66.7 %, $p=0.17$). The other CT findings were observed in the comparable frequencies in both groups. Of note, two patients with asbestosis did not show pleural plaque. The likelihood of asbestosis by CT was significantly higher for pathologically diagnosed asbestosis than for pathologically diagnosed non-asbestosis (mean=3.5 vs. 1.0; $p<0.001$).

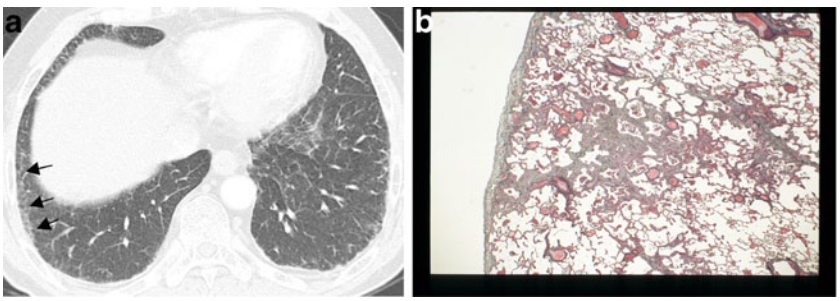

Fig. 2 A 60-year-old male carpenter with lung cancer and pulmonary fibrosis other than asbestosis. **a**. HRCT at lower lobes before right lower lobe resection shows peripheral ground-glass and fine reticular opacities without obvious traction bronchiectasis. Note there are coalescent dot-like opacities in the midst of ground-glass opacity of right lung base, simulating subpleural curvilinear line (*arrows*). **b**. Pathological specimen (Elastic-Goldner stain) obtained from the right lung base corresponding CT image in *a* shows subpleural fibrosis as well as fibrosis in the centrilobular area. No linear fibrosis corresponding to that of CT image was observed. Asbestos body was identified (not shown) and one pathologist suggested possible asbestosis, while the other diagnosed fibrotic NSIP. Asbestos body count was 86,560/g (dry lung)

Table 1 Patients' demographics, asbestos body count and CT scores of asbestosis vs. non-asbestosis

	Asbestosis (n=15)		Non-Asbestosis (n=18)		*p* Value
	Mean	SD	Mean	SD	
CT-Asbestosis Score	3.5	1.7	1.0	1.5	**0**
Asbestos Body	1,464,711	1,974,822	98,745	174,492	**0**
Age at CT	74	5	72	8	0.274
Work Period (years)	24	11	29	15	0.35
Ground-Glass Opacity	10.1	6.1	9.7	6.2	0.682
Reticular Opacity	9.4	6.0	10.8	6.5	0.464
Honeycombing	4.9	6.3	6.2	7.3	0.656
Coarseness	1.8	0.5	1.8	0.7	0.985
Consolidation	9.3	10.5	4.1	3.8	0.135
Emphysema	4.0	4.4	11.8	17.9	0.117
Dot-Like Opacity	4.4	1.4	3.8	2.1	0.58
Subpleural Curvilinear Lines	2.9	1.7	1.7	1.6	**0.04**
Septal Lines	4.5	2.0	4.9	1.3	0.656
Parenchymal Band	1.9	2.3	1.8	2.1	0.957
Traction Bronchiectasis	13.5	6.5	12.2	6.3	0.486
Bronchial Wall Thickening	4.7	1.9	3.9	1.9	0.117
Mosaic Perfusion	0.5	1.1	0.2	0.7	0.656
Pleural Plaque	7.5	5.3	7.5	4.0	0.929
Diffuse Pleural Thickening	1.1	1.2	1.1	1.5	0.817

p values less than 0.05 were indicated with bold

We found a significant positive correlation between asbestos body count and CT-asbestosis score (r=0.503, $p=0.003$) and between asbestos body count and pathological asbestosis score (r=0.637, $p<0.001$) (Figs. 4 and 5). CT-asbestosis score and pathological asbestosis score also showed a significant positive correlation (r=0.656, $p<0.001$).

Discussion

There have been a few reports discussing the imaging differences of asbestosis and chronic interstitial pneumonia, especially IPF [2–4]. Akira et al. reported the significant differences of CT findings between asbestosis and IPF [2]. In their report, subpleural dot-like opacities and subpleural curvilinear lines were the relatively specific CT findings of asbestosis seen in 81 % and 69 % of cases as opposed to 25 % and 28 % in IPF, respectively. Other highly specific CT findings included parenchymal band and mosaic perfusion in 48 % and 49 %, compared to 4 % and 11 % in IPF. Notably, honeycombing, the hallmark of UIP pattern, was seen in only 34 % of asbestosis patients as compared to 76 % in IPF. The paucity of honeycombing in asbestosis has also been suggested by pathologists [8, 11]. Al-Jarad et al., in their earlier comparison of CT findings between asbestosis and IPF, gained

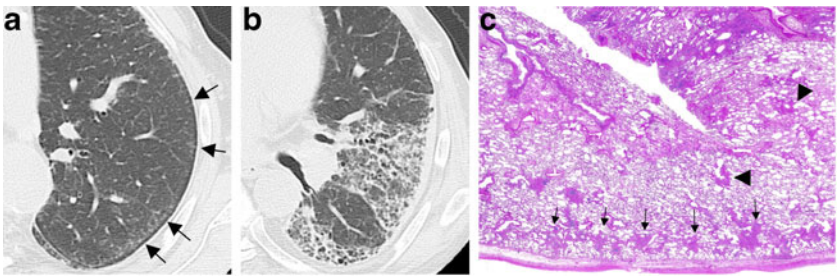

Fig. 3 A 76-year-old previous asbestos insulation male worker with asbestosis. **a**. HRCT of left upper lobe shows a typical subpleural curvilinear line. Note that the line is formed by the coalescence of dot-like opacities and is identified along the lateral chest wall as well as in the dependent lung. **b**. HRCT of the left lower lobe shows ground-glass opacity with fine reticulation and strong traction bronchiectasis in segmental distribution, precluding the diagnosis of idiopathic pulmonary fibrosis. **c**. Low-power view of pathological specimen shows alveolar wall fibrosis of respiratory bronchioles typical of asbestosis in the subpleural area (*arrows*), which corresponds to subpleural curvilinear lines. Note that there are alveolar wall fibroses adjacent to respiratory bronchioles in the more inner side of the lung (*arrowheads*) (Hematoxylin-eosin staining). Asbestos body count was 2,711,807/g (dry lung)

Table 2 Frequencies of CT findings in asbestosis and non-asbestosis

	Asbestosis (n=15)	Non-asbestosis (n=18)	*p* Value
Subpleural Dot-like Opacity	15 (100)	16 (88.9)	0.489
Subpleural Curvilinear Lines	13 (86.7)	9 (50)	**0.034**
Honeycomb Lung	6 (40)	12 (66.7)	0.17
Mosaic Perfusion	2 (13.3)	2 (11.1)	1
Parenchymal Band	8 (53.3)	5 (27.8)	0.169
Pleural Plaque	13 (86.7)	17 (94.4)	0.579
Diffuse Pleural Thickening	6 (40)	5 (27.8)	0.488

Note: The numbers indicate how many cases, with percentage in parentheses

the qualitative impression that fibrosis of IPF was more distorting than that of asbestosis [4]. Copley et al., however, reported no significant differences between asbestosis and IPF, and concluded that clinically diagnosed asbestosis closely resembled biopsy-confirmed IPF [3]. No pathological confirmation was obtained in these three reports, and the discrepancy is considered to be due to the selection bias of their asbestosis cases. In the era of strict asbestos regulation, cases with radiological pleural plaque and pulmonary fibrosis do not necessarily equal asbestosis, because pleural plaque occurs at much lower exposure levels, and lung fibrosis other than asbestosis can be incidental. Furthermore, several epidemiological studies have shown that workers exposed to various kinds of dust including smoking are more inclined to have IPF than those without such exposure [12–15].

Our asbestos-exposed workers were pathologically confirmed for lung fibrosis by either autopsy or surgical lobectomy. Our study confirmed the significance of subpleural curvilinear line as the sole high-resolution CT difference between asbestosis and other chronic interstitial pneumonia. Other imaging findings considered important in discriminating asbestosis from IPF in previous study did not differ in our series [2]. One reason is that non-asbestosis cases in our series included workers exposed to asbestos and other kinds of dust, and their lung conditions were complicated with various kinds of lung fibrosis. Non-asbestosis cases included not only IPF, but also mixed dust fibrosis and chronic interstitial pneumonia of unclassifiable histopathology. Mixed dust fibrosis and some unclassifiable interstitial pneumonia were airway-centred, and on that point, resembled asbestosis. This is an important difference from the previous reports, and at the same time, made differentiation by imaging difficult. Coexistence of various kinds of fibrosis in dust-exposed

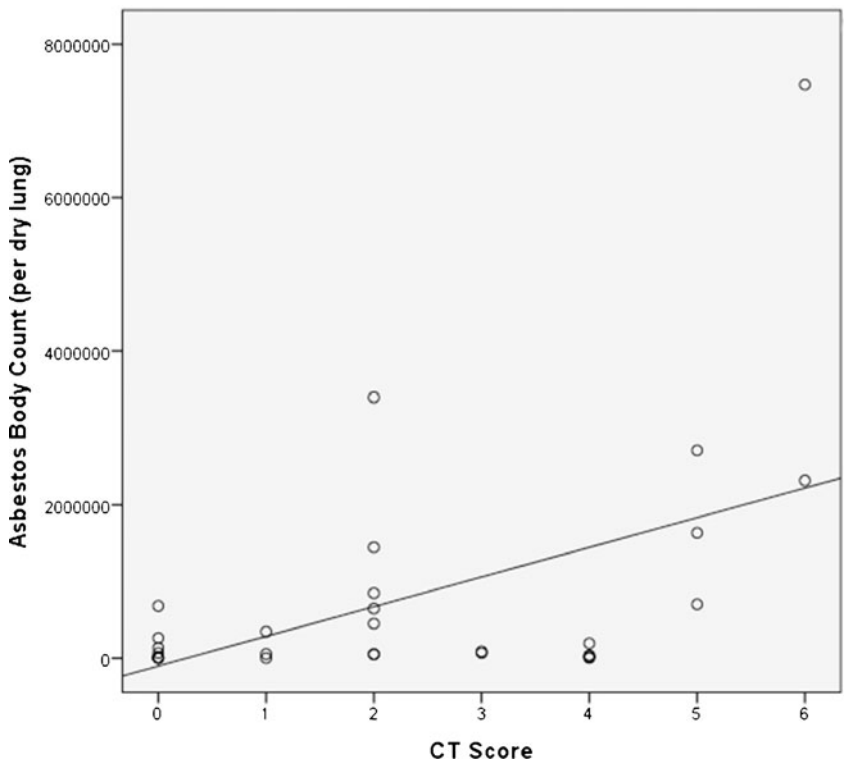

Fig. 4 Scattered plot of asbestos body burden in lungs against CT score. There was a significant positive correlation between asbestos body count and CT-asbestosis score (r=0.503, *p*=0.003)

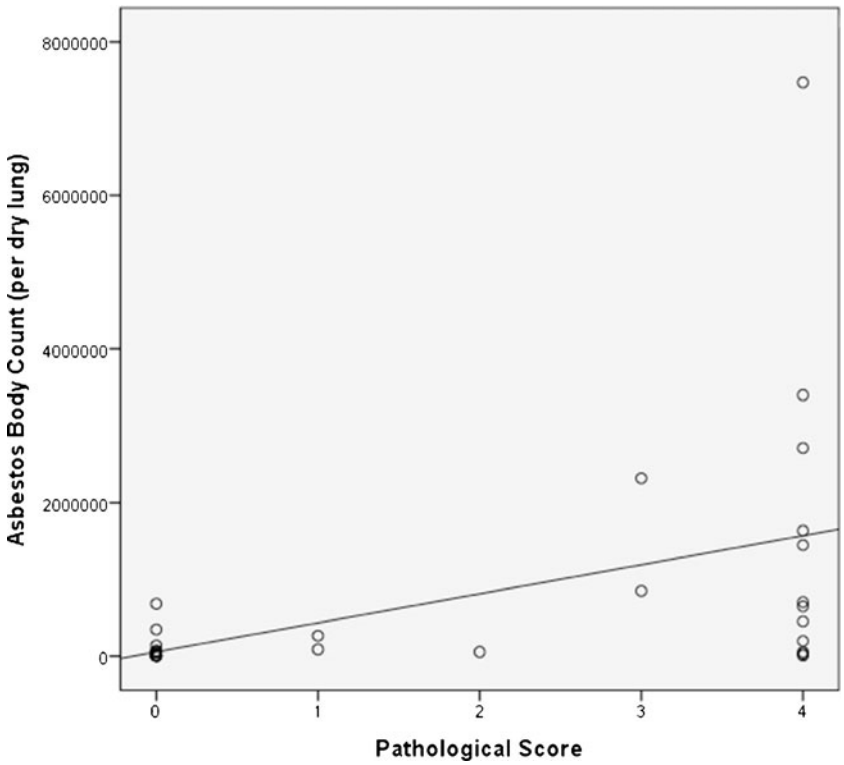

Fig. 5 Scattered plot of asbestos body burden in lungs against pathological score. There was a significant positive correlation between asbestos body count and pathological asbestosis score ($r=0.637$, $p<0.001$)

patients was one of the problems in the pathological diagnosis of these patients; this was indicated by the fact that discordant pathological diagnoses were made in seven of 18 non-asbestosis cases, and this must have been reflected in the CT diagnosis as well.

Interesting observations were obtained in our series that found significant positive correlations of likelihood of asbestosis on CT, pathology and quantity of asbestos bodies; in other words, the more asbestos bodies in the lungs, the more the radiographic and pathological appearance of asbestosis becomes obvious. Asbestosis is a pneumoconiosis, creating a dose-response relationship, and thus the associated lung fibrosis is the direct consequence of deposited asbestos fibres. It is quite expected that the greater the fibre burden in the lungs, the more easily the patient will develop asbestosis. Our results indicate that while lungs with heavily deposited asbestos show typical appearance of asbestosis, lungs with a lesser degree of deposition may show rather atypical radiographic findings or may be complicated with other kinds of lung fibrosis that can obscure the typical findings of asbestosis, if any, resulting in atypical CT findings.

There are several limitations in our study. First, CT images were obtained in supine position, which might cause difficulty in the analyses of ground-glass opacity and subpleural curvilinear lines. Our two radiologists are well-experienced chest radiologists, and the inter-observer agreements were 4.9 and 1.2 for ground-glass opacity and subpleural curvilinear lines by single determination standard deviation, respectively. Subpleural curvilinear lines were observed as often in the upper lobes as in lower lobes, and they were not only in the dependent, but also in the lateral zone of the lungs (Fig. 3). We suppose that some inaccuracy remains in the evaluation of these findings; however, it is not so big as to alter our conclusion. Second, the series included a total of 33 cases, 15 asbestosis and 18 non-asbestosis, which is rather small in number. Third, our series included only patients with pathological diagnosis, mostly autopsy, which could be the selection bias. Fourth, the interval between CT imaging and pathology diagnosis was long, with a mean of 16 months. However, interval progression of lung fibrosis in our series is indolent and the pathology diagnosis could not change. Finally, we did not count the number of asbestos fibres, but rather counted only asbestos bodies. It has been reported that rare cases showing significant numbers of asbestos fibres with small asbestos body counts have been found [16]. While such cases could possibly be found in our series, we assume that such cases are rare and might not affect the results.

In summary, in a series of 33 asbestos-exposed patients with pathologically confirmed pulmonary fibrosis, more than half were not asbestosis and included various kinds of fibrosis, which was often discordant between pathologists. We found subpleural curvilinear lines to be the sole CT finding that differed between asbestosis and non-asbestosis cases. The CT likelihood and pathological confidence of asbestosis paralleled the asbestos body count. These findings may indicate the difficulty of discriminating asbestosis from other

types of lung fibrosis in the era of low asbestos exposure. Careful enquiry of working conditions as well as detailed observation of HRCT are mandatory.

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