Asbestos-Related Diffuse Pleural Thickening

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Key Words
Asbestos · Pleural thickening · Medical Research Council dyspnea scale · Respiratory function test · Pleural plaques · Blunted costophrenic angle · Imaging

Abstract
Background: The clinical features of asbestos-related diffuse pleural thickening (DPT) remain unclear. Objectives: To clarify the association between radiological findings of DPT and respiratory function. Methods: Medical data from patients with asbestos-related DPT were collected, including their history of occupational or neighborhood asbestos exposure, initial symptoms, modified Medical Research Council dyspnea grade, smoking history, radiological findings, and respiratory function test results. Results: There were 106 DPT patients between 2005 and 2010 [i.e. 103 men (97.2%) and 3 women (2.8%)]. The median age at diagnosis was 69 years (range 46–88). Patient occupations related to asbestos exposure included: asbestos product manufacturing (n = 17); the shipbuilding industry (n = 14); the construction industry (n = 13); heat insulation work (n = 12); plumbing, asbestos spraying, and electrical work (n = 7 each), and transportation and demolition work (n = 4 each). The median duration of asbestos exposure was 25 years (range 2–54), and the median latency period before the onset of DPT was 46 years (range 25–66). Involvement of the costophrenic angle (CPA) was also negatively correlated with the percent vital capacity (%VC; r = −0.448, p < 0.01). Pleural thickness and the craniocaudal and horizontal extension of pleural thickening, as determined by chest computed tomography (CT), were also negatively correlated with %VC (r = −0.226, p < 0.05; r = −0.409, p < 0.01, and r = −0.408, p < 0.01, respectively). Conclusions: DPT develops after a long latency period following occupational asbestos exposure and causes marked respiratory dysfunction. The extension of DPT should be evaluated by chest CT, and chest X-ray would be important for the evaluation of the involvement of the CPA.

Introduction

Asbestos-related pleural diseases include malignant pleural mesothelioma, benign asbestos pleural effusion (BAPE), and diffuse pleural thickening (DPT) [1]. DPT often develops after the onset of BAPE [2, 3]; however,
some patients develop DPT in the absence of BAPE. Asbestos-related DPT is considered to be a consequence of asbestos-induced inflammation of the visceral pleura, which leads to adhesion to the parietal pleura [4]; however, the actual pathogenesis is unknown.

DPT is not precisely defined in radiological terms [5]. McLoud et al. [6] described DPT on chest X-ray as a smooth, noninterrupted pleural density extending over at least one fourth of the chest wall with or without involvement of the costophrenic angle (CPA). However, these criteria are somewhat ambiguous. In addition, radiological differentiation between DPT and pleural plaques is often difficult. The revised 2000 International Labour Organization Classification of Radiographs of Pneumocœlioses provides a criterion for the differentiation between pleural plaques and DPT, in which involvement of the CPA should be demonstrated for DPT [7]. However, the validity of this criterion is still controversial. Some studies have examined the characteristics and natural history of DPT [2, 5, 6, 8–10]. One of the main limitations of these earlier studies is that the definitions used for DPT varied; a significant proportion of the studies included patients with pleural plaques, BAPE, and malignant pleural mesothelioma, mainly due to the difficulty of making differential diagnoses based on chest X-rays without computed tomography (CT) images.

In this study, we investigated the clinical features of DPT. Our main purpose was to clarify the association between DPT and asbestos exposure. In addition, we focused on the association between radiological findings and respiratory function. For this purpose, we analyzed the extension of DPT on chest CT images in detail using our own scoring methods, and we examined its association with impaired respiratory function.

**Methods**

**Patients**

All of the subjects diagnosed with DPT at each of the researchers’ institution were extracted. Medical data from those patients were collected and analyzed retrospectively. Inclusion criteria were a history of occupational or neighborhood asbestos exposure and pleural thickening >5 mm on chest X-ray extending for more than half of the lateral thoracic wall (LTW) in patients with unilateral DPT or for more than a quarter of the LTW in patients with bilateral DPT. The medical information we collected included the initial symptoms, the modified Medical Research Council (mMRC) dyspnea grade, the smoking history, radiological findings, and respiratory function test results. Information about the history of asbestos exposure and the mMRC dyspnea grade was also collected at the diagnosis. The respiratory function test was based on the official statement of the American Thoracic Society [11]. To examine the association between radiological findings and respiratory function, chest images and the results of respiratory function tests undergone within a year were extracted. This study was approved by the Japan Labour Health and Welfare Organization and the institutional review boards of each institution.

**Radiological Analyses**

The chest X-ray findings we examined included the craniocaudal extension of pleural thickening and the involvement of the CPA. Craniocaudal extension was classified and scored as 0 (none), 1 (total length up to one quarter of the projection of the LTW), 2 (total length exceeding one quarter and up to one half of the projection of the LTW), or 3 (total length exceeding one half of the projection of the LTW) in accordance with the International Labour Organization classification [7]. The involvement of the CPA was also determined and classified into 3 categories: 0 (no involvement), 1 (CPA ≤90°), or 2 (CPA >90°) (fig. 1).

The thickness of the pleura and the craniocaudal extension were also determined by chest CT. The thickness of the pleura was determined and scored as 0 (none), 1 (<3 mm), 2 (3–5 mm), 3 (5–10 mm), or 4 (>10 mm). To assess the craniocaudal extension of pleural thickening, the thorax was divided into 5 zones according to the upper border of the aortic arch, the tracheal bifurcation, the inflow portion of the left inferior pulmonary vein to the heart,
and the upper border of the diaphragm (fig. 2). The number of involved zones was scored as 0–5. The horizontal extension was determined in the most involved zone and scored as 0 (no involvement), 1 (less than a quarter of the outer perimeter of the thorax), 2 (between a quarter and half of the outer perimeter of the thorax), or 3 (more than half of the outer perimeter of the thorax). The total scores in individual cases were calculated as the sum of both sides of the pleura. Other items that were analyzed by chest CT included pleural plaques, crow’s feet signs (defined as fibrous strands with accompanying pleural circumscribed thickening), fibrotic changes, and emphysematous findings.

For all of the radiological analyses, the researchers were divided in 2 groups, both of which comprised at least 1 radiation and 2 respiratory specialists. The radiological findings were analyzed independently by each group. In cases in which the results differed between the 2 groups, 2 radiologists (K.K. and F.S.) and the chairman (T.K.) discussed to reach a final agreement.

Respiratory Function Test
Respiratory function tests were performed in clinical practice. The data included the percent vital capacity (%VC) and the forced expiratory volume percentage in 1 s (FEV1). The ratio of FEV1 to forced vital capacity (FVC) was also calculated as FEV1/FVC. Blood gas data such as PaO2 and PaCO2 were also extracted. The data closest in time to when the chest CT was performed were used for the analyses.

Statistical Analysis
Pearson’s rank correlation coefficient was calculated for the correlation between respiratory function and radiological findings. Cohen’s kappa coefficient (κ) was calculated for intergroup agreement [12]. These calculations were performed with SPSS 11.0 software (SPSS, Inc., Chicago, Ill., USA).

Results
Patient Characteristics
We collected and analyzed data from 106 patients diagnosed with DPT between August 1993 and November 2011 (103 men and 3 women). The median age (range) was 70 years (46–88). There were 25 (24.0%) current and 64 (61.6%) former smokers; 15 (14.4%) of the patients had never smoked, while the smoking status of 2 patients was unknown. Forty-five (42.5%) patients had been diagnosed with DPT during a routine medical checkup, and 56 (52.8%) patients had visited a medical institution for subjective complaints, including dyspnea in 45 cases, cough in 38, sputum in 6, chest pain in 5, fever in 3, and weight loss, anorexia, and chest discomfort in 1 patient each. The mMRC dyspnea grade was determined in 96 cases. Fourteen patients (14.6%) were grade 0; 25 (24.0%) were grade 1; 34 (35.4%) were grade 2, and 23 (24.0%) were grade 3 or 4. Fifty-three patients (50.0%) had a medical history of BAPE.

Asbestos-Related DPT

Asbestos Exposure History
The occupational categories associated with asbestos exposure are shown in table 1. The median duration of exposure was 25 years (range 2–54), and the median period of latency from the first exposure to the onset of
DPT was 47 years (range 25–66). There were no patients in whom neighborhood asbestos exposure was suspected.

**Radiological Features**

The characteristic radiological findings are summarized in table 2. Asbestosis, defined as a profusion rate >1 based on ILO criteria [7], was present in 7 patients (6.6%).

The craniocaudal extension of pleural thickening, the involvement of the CPA scored on chest X-ray, the thickness of the pleura, the craniocaudal extension of pleural thickening, and the horizontal extension scored on chest CT are shown in figure 3. Cohen’s κ for these parameters were 0.206, 0.431, 0.441, 0.843, and 0.565, respectively.

**Respiratory Function Test**

The median (range) values for %VC and FEV₁/FVC were 54.3% (17.3–99.4) and 79.7% (37.9–100.0), respectively. The median (range) PaO₂ and PaCO₂ values were 81.0 mm Hg (52.4–94.8) and 42.7 mm Hg (22.3–73.2), respectively. Constrictive respiratory dysfunction (%VC <80) was found in 96 patients (91.0%), and obstructive respiratory dysfunction (FEV₁/FVC <70) was found in 29 patients (28%). Mixed respiratory dysfunction was found in 25 patients (24.0%).

We next analyzed the correlation between %VC and the extension of DPT as measured on radiological images. The craniocaudal extension of pleural thickening as determined and scored on chest X-ray was negatively correlated with %VC (r = −0.483, p < 0.01), and involvement of the CPA was also negatively correlated with %VC (r = −0.448, p < 0.01) (fig. 4). In the 52 cases in which the involvement of the CPA was scored as 2, the %VC tended to be lower in cases with bilateral involvement (a score of 1 on each side) than in cases with unilateral involvement (a score of 2 on one side and 0 on the other). However, this difference was not statistically significant (p = 0.078). The thickness of the pleura (fig. 5a) and the craniocaudal (fig. 5b) and horizontal (fig. 5c) extension of pleural thickening, as determined...
on chest CT, were also negatively correlated with %VC 
(r = –0.226, p < 0.05; r = –0.409, p < 0.01; and r = –0.408, 
p < 0.01, respectively).

Discussion

In the current study, we retrospectively analyzed 106 patients with DPT. We extracted all of the patients diagnosed with DPT in the participating institutions. A limitation of this retrospective study is that we could not determine the initial cohort, e.g. all of the subjects with asbestos exposure. The occupational categories in which the exposed patients had been employed, e.g. asbestos product manufacturing and shipbuilding, were associated with relatively high levels of asbestos. The median duration of asbestos exposure was 25 years, and the median period of latency from the first exposure to the onset of DPT was 47 years. Gibbs and Pooley [13] reported that, among the asbestos-related diseases, pulmonary asbestosis and lung cancer are associated with high levels of asbestos exposure, while malignant mesothelioma and DPT may develop after lower levels of exposure. Gibbs et al. [14] reported that >5 million asbestos fibers per gram of lung tissue were detected in 12 out of 13 patients with DPT. Our results provide support for these previous findings and suggest that DPT can develop after moderate-to-high levels of exposure to asbestos, because the occupational category of the subjects in the current study included those of relatively high levels of asbestos exposure, such as asbestos product manufacturing and shipbuilding. The median latency period between asbestos exposure and DPT development in the present study was similar to that observed for malignant mesothelioma and lung cancer in our previous reports [15–17] and that for DPT in another report by Kee et al. [18].

The prevalence of asbestos-related DPT is reported to range from 1.1 to 24.1% [3, 6, 19–21]. One of the reasons for this wide range could be variations in the diagnostic criteria for chest X-rays. Most patients, including ours, were originally diagnosed by chest X-ray based on dimension criteria; however, it is usually difficult to make a diagnosis or to evaluate DPT based solely on a chest X-ray. One of the purposes of the current study was to validate the utility of chest X-rays and CT to evaluate DPT. For this purpose, 2 independent researcher groups evaluated the presence or absence of pleural plaques, crow’s feet signs, fibrotic changes, and emphysematous changes. Substantial κ were calculated for calcified pleural plaques, emphysematous changes, and crow’s feet signs. More moderate coefficients were calculated for noncalcified plaques, fibrotic changes, and the involvement of the CPA, while the coefficients were low for the extension of DPT as determined by chest X-ray. These results indicate that the evaluation of DPT extension by chest X-ray is subjective and has a lower reliability, although the involvement of the CPA can be evaluated by chest X-ray.

Radiological differentiation between pleural plaques and DPT is often controversial [22]; however, this differentiation was not a critical issue in the current study because we focused on crow’s feet and pleuraparenchymal fibrous strands [23] as indicators of the involvement of the visceral pleura and not of the plaques. In addition, a considerable number of patients in the current study had calcified plaques, possibly due to the long latency period since the initial asbestos exposure. These findings make it easier to differentiate pleural plaques from DPT.

The most common pattern of respiratory dysfunction in DPT is constrictive respiratory dysfunction [24, 25]. Therefore, in the current study, we investigated the main factors associated with %VC. We found that the mMRC dyspnea grade was the most important factor associated with an impaired %VC. DPT patients have been reported to complain of dyspnea on exertion relative to the amount of conserved respiratory function [4, 26]. When the visceral and parietal pleura conglutinate, the movement of the diaphragm may be impaired, particularly in cases in which the CPA is involved. This could lead to inhibition

Fig. 4. The correlation between %VC and involvement of the CPA is shown by the correlation coefficient (r) and the regression line.
of ventilation and to dyspnea on exertion. We evaluated the degree of dyspnea using the mMRC scale, but the mMRC scale is subjective; thus, more objective tools are necessary for the evaluation of DPT.

Among the radiological factors that we investigated, involvement of the CPA and craniocaudal and horizontal extension of pleural thickening were negatively correlated with %VC. Previous reports have described a correlation between involvement of the CPA and a reduced %VC [24, 27, 28]. In the current study, we demonstrated that the degree of involvement of the CPA was associated with a reduced %VC. In addition, bilateral involvement of the CPA tended to be associated with a reduced %VC. Craniocaudal and horizontal extension of pleural thickening was also associated with a reduced %VC, but this association was not strong. It is important that the extension of DPT was correlated with a reduced %VC when it was evaluated by chest X-ray and CT, but evaluation of the extension of DPT by chest X-ray is subjective, as described above. Therefore, we suggest that the extension of DPT should be evaluated by chest CT, which is a more accurate diagnostic method.

The pathogenic mechanisms of DPT are speculated to be as follows: (1) pulmonary asbestosis that spreads to the visceral and parietal pleura, (2) DPT that develops as a consequence of BAPE, and (3) DPT that develops independently of asbestosis or BAPE. In our study, 38 patients (35.5%) had some fibrotic changes, but asbestosis, defined as a profusion rate >1, was present in only 7 patients (6.6%). This rate is lower than that observed in a previous

Fig. 5. Correlation between %VC and thickness of the pleura (a) and craniocaudal (b) and horizontal (c) extension of pleural thickening as determined by chest CT. The correlation is shown by the correlation coefficient (r) and the regression line.
The effect of smoking should be considered in conjunction with the respiratory embarrassment caused by inhalation of dust, such as asbestos [29, 30]. Finkelstein and Vingilis [31] reported that smokers had a 2.9-fold greater risk of DPT development compared to nonsmokers. In fact, the majority of patients in our study had smoked, and about 30% of the total cases demonstrated mixed ventilatory impairment. Cotes and King [24] reported that DPT patients demonstrated no significant changes in %FEV, but Kilburn and Warshaw [28] reported that some DPT cases had obstructive ventilatory impairment. The association between smoking and ventilatory impairment in DPT should be clarified in a future study.

In conclusion, we analyzed the clinical features of asbestos-related DPT and focused in particular on respiratory embarrassment. The mMRC dyspnea scale, the involvement of the CPA on chest X-ray, and the extension of pleural thickening on CT may be useful for evaluation of this disease.

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References