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Original Article

Pilot Analysis of Asbestos-induced Diffuse Pleural Thickening with Respiratory Compromise

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We investigated the clinical features of asbestos-induced diffuse pleural thickening (DPT) with severe respiratory compromise. We conducted a retrospective study of consecutive subjects with asbestos-induced DPT. Medical data such as initial symptoms, radiological findings, respiratory function test results, and clinical course were collected and analyzed. There were 24 patients between 2003 and 2012. All were men, and the median age at the development of DPT was 74 years. The top occupational category associated with asbestos exposure was dockyard workers. The median duration of asbestos exposure was 35.0 years, and the median latency from first exposure to the onset of DPT was 49.0 years. There were no significant differences in respiratory function test results between the higher and lower Brinkman index groups or between unilateral and bilateral DPT. Thirteen patients had a history of benign asbestos pleural effusion (BAPE), and the median duration from pleural fluid accumulation to DPT with severe respiratory compromise was 28.4 months. DPT with severe respiratory compromise can develop after a long latency following occupational asbestos exposure and a history of BAPE.

Key words: asbestos, pleural thickening, MRC dyspnea scale, respiratory function test, costophrenic angle

Asbestos-related health problems remain a major public health concern. Asbestos-related pleural diseases include malignant pleural mesothelioma (MPM), benign asbestos pleural effusion (BAPE), and diffuse pleural thickening (DPT) [1]; cases of these diseases will continue to be seen in the next several decades due to past industrial asbestos use. Asbestos-induced DPT is considered to be a consequence of asbestos-induced inflammation of the visceral pleura, which leads to adhesion to the parietal pleura. However, the actual pathogenesis is still unknown and the radiological definition of DPT is ambiguous. McLoud *et al.* described DPT on chest X-rays as a smooth, uninterrupted pleural density extending over at least one-quarter of the chest wall, with or without involvement of the costophrenic angle (CPA) [2]. Yates *et al.* also proposed a definition of DPT based on dimensional criteria, in which DPT is characterized by pleural thickening of ≥ 5 mm that extends over more than one-quarter of the chest wall, with or without obliteration of the CPA [3].

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Several studies have examined the characteristics of DPT [2, 4–7]. A major limitation of these earlier studies is that their definitions of DPT varied; as such, some studies may have included patients with pleural plaques, BAPE, and MPM, mainly due to the difficulty of confirming a diagnosis of DPT based on chest X-ray without computed tomography (CT) images.

DPT often induces significant impairment of lung function [8]. In Japan, patients with DPT are provided worker's compensation or given financial relief by the Act on Asbestos Health Damage Relief if they present severe respiratory compromise. We recently retrospectively analyzed the clinical features and radiological findings of DPT, and we reported that some of the radiological findings, such as the involvement of CPA and pleural thickness and the craniocaudal and horizontal extension of pleural thickening (as determined by chest CT) were correlated with impaired respiratory function in patients with DPT [9]. There are few reports concerning the features of DPT in patients with severe respiratory compromise, however.

The objectives of the present retrospective analysis, which was conducted in a single region of Japan, were to clarify the clinical features of DPT patients with severe respiratory compromise, including the clinical course. We focused on the association between BAPE and DPT. We also investigated clinical issues associated with the diagnosis, evaluation, and handling of compensation for DPT.

Materials and Methods

Subjects. The consecutive subjects diagnosed as having asbestos-induced DPT in Okayama Rosai Hospital (Okayama, Japan) between 2003 and 2012 were identified. The inclusion criteria were a history of occupational asbestos exposure, pleural thickening >5 mm on chest X-ray extending for more than one-half of the lateral thoracic wall (LTW) in patients with unilateral DPT or more than one-quarter of the LTW in patients with bilateral DPT, and impaired respiratory function (defined below). The subjects had to have been followed up for at least 6 months after the diagnosis of DPT. Medical data from these patients were collected and analyzed retrospectively. The medical information included age, gender, initial symptoms, modified Medical Research Council (mMRC) dyspnea grade, smoking history, radiological findings, respiratory function test results, and the clinical course. Former smoker was defined as those quitted smoking for more than 6 months. Information about the history of asbestos exposure was also collected. In some patients who changed to local hospitals or clinics, we made inquiries about their information at outcome at the relevant medical institutions.

This study was done according to Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Education, Culture, Sports, Science and Technology and the Japanese Ministry of Health, Labour and Welfare. This study was approved by the ethics committee of the Japan Labour Health and Welfare Organization and the institutional review board of Okayama Rosai Hospital.

Respiratory function test. Respiratory function tests were performed in clinical settings based on the guidelines set forth in the Official Statement of the American Thoracic Society [10]. The data obtained included the percentage of vital capacity (%VC) and the forced expiratory volume percentage in 1 sec (FEV1). Blood gas data such as PaO_2 (the partial pressure of O_2 in arterial blood) and $PaCO_2$ (the partial pressure of carbon dioxide in arterial blood) were also extracted. The data obtained closest in time to when the chest CT was performed were used for the analyses. Impaired respiratory function was defined as (1) %VC $<60\%$ or (2) %VC 60–80%, FEV1 $\leq$ 70%, and FEV1/forced vital capacity (FVC) $<50\%$ or PaO_2 on arterial blood gas test ≤ 60 Torr.

Statistical analysis. Comparisons between groups were performed using a nonparametric analysis with the Wilcoxon rank-sum test. The latency period of DPT was calculated as the time between the first exposure to asbestos and the onset of DPT. In the patients with a history of BAPE, the period from the detection of pleural effusion to the onset of DPT and the development of severe respiratory impairment were calculated. Correlations were examined in a regression analysis. The software package used for the statistical analyses was JMP 10.0.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. A total of 24 patients were analyzed retrospectively. The patients' demo-

graphic details are listed in Table 1. All of the patients were men, and the median age at the diagnosis of DPT was 74 years. More than 90% of the patients smoked, and the Brinkman index was ≥ 600 in 14 (58.3%) of the patients. Fifteen patients had visited a clinic or a hospital with symptoms, 5 had an abnormal shadow on a chest X-ray at a medical checkup, and 4 were diagnosed with DPT while receiving medical treatment for other diseases. The mMRC dyspnea grade at the diagnosis of DPT was 1 in 3 patients, 2 in 15 patients, 3 in 3 patients, and 4 in 3 patients.

Occupational asbestos exposure history. Occupational categories associated with asbestos exposure are listed in Table 2 and included dockyard, construction, and heating trade work and more. The median (range) duration of asbestos exposure was 35.0 (3.0–50.0) years. The median (range) latency period since the first exposure to the onset of DPT was 49.0 (37.0–64.0) years.

Radiological findings. Unilateral DPT was found in the thorax in 6 cases and bilateral DPT was found in 18 cases at the time of diagnosis. In the 6 cases with unilateral DPT, DPT was found in the right thorax in 4 cases and in the left thorax in 2 cases. Radiographic findings associated with DPT are listed in Table 3. All of the cases showed CPA involvement on chest X-ray. Pleural plaques were detected in most of the patients. Pulmonary asbestosis was diagnosed in 3 (12.5%) cases, and the profusion rate according to the International Labour Organization criteria [11] was 1 in 2 cases and 3 in one case. Rounded atelectasis was detected in 18 (75.0%) cases on chest CT. Crow's feet signs, defined as fibrous strands with accompanying circumscribed pleural thickening, was detected in all cases on chest CT.

Respiratory function test. The median (range) value of %VC was 51.4% (31.2–70.7%); the %VC was < 60% in 22 (91.7%) patients. The median (range) value for FEV1 was 82.9% (47.7–100%). Eighteen (75.0%) patients showed restrictive ventilatory impairment, and 6 (25.0%) showed combined restrictive and obstructive ventilatory impairment. Blood gas data were available in 23 cases, and the median (range) values for PaO_2 and $PaCO_2$ were 78.9 (53–86) Torr and 43.3 (35.8–56.5) Torr, respectively.

We then examined the association between respiratory function and smoking history. First, we compared %VC and FEV1 between lower (< 600) and higher (≥ 600) Brinkman index groups ($n = 10$ and 14, respectively). Never-smokers were included in lower Brinkman index group. The median values for %VC in the lower (< 600) and higher (≥ 600) Brinkman index groups were 50.9% and 51.4%, respectively. The median values for FEV1 in the lower (< 600) and higher (≥ 600) Brinkman index groups were 71.7% and 85.4%, respectively. There

Table 1 Demographics of the study population ($n = 24$)

Characteristics		No. of patients (%)
Median age (range)		74 (63–92) years
Gender	Male	24 (100.0%)
Smoking	Never	6 (25.0%)
	Former	16 (66.7%)
	Present	2 (8.3%)
Initial symptom	Cough	14 (56.0%)
	Chest pain	3 (12.0%)
	Sputum	1 (4.0%)
mMRC* grade	0/1/2/3/4	0/3/15/3/3

*modified Medical Research Council.

Table 2 Occupational category of asbestos exposure ($n = 24$)

Occupation	No. of patients
Dockyards	7
Construction	4
Heating trade	3
Demolition work	2
Asbestos product industry	2
Furnace installation	1
Electric work	1
Painting	1
Plumbing	1
Welding	1
Shipman	1

Table 3 Radiographic findings associated with DPT

Findings	No. of patients (%)
Asbestosis	3 (12.5%)
Pleural plaques (X-ray)	14 (58.3%)
Pleural plaque (CT*)	22 (91.7%)
Rounded atelectasis	18 (75.0%)
Crow's feet sign	24 (100.0%)
Costophrenic angle involvement	24 (100.0%)

*Computed tomography. DPT: diffuse pleural thickening.

were no significant differences in %VC ($p = 0.5780$) and FEV1 ($p = 0.5387$) between the 2 Brinkman index groups (Fig. 1). We also compared the %VC and FEV1 values between lower (< 400) and higher (≥ 400) Brinkman index groups ($n = 6$ and 18, respectively). The median values for %VC in the lower (< 400) and higher (≥ 400) Brinkman index groups were 56.3% and 50.1%, respectively. The median values for FEV1 in the lower (< 400) and higher (≥ 400) Brinkman index groups were 68.1% and 86.4%, respectively. There were no significant differences in %VC ($p = 0.5709$) and FEV1 ($p = 0.0773$) between these 2 Brinkman index groups.

We next examined the association between respiratory function and unilateral or bilateral DPT. The median values for %VC in the unilateral ($n = 6$) and bilateral ($n = 18$) DPT cases were 53.3% and 51.4%, respectively. The median values for FEV1 in the unilateral and bilateral DPT cases were 67.7% and 84.4%, respectively. There were no significant differences in %VC ($p = 0.7642$) or FEV1 ($p = 0.3014$) between the cases of unilateral and bilateral DPT.

We compared respiratory function between 2 groups: those with longer asbestos exposure (≥ 30 years: $n = 16$) and those with shorter asbestos exposure (< 30 years: $n = 8$). The median VC values in the longer- and shorter-exposure groups were 48.4% and 54.2%, respectively. The median FEV1 values in the longer- and shorter-exposure groups were 76.4% (41.3–70.7%) and 85.4%, respectively. The longer-exposure group showed more impaired respiratory function, although the difference was not significant ($p = 0.3123$ for %VC and $p = 0.4813$ for FEV1).

Clinical course of DPT. Thirteen patients had a medical history of BAPE that preceded the diagnosis of DPT. The date of the accumulation of pleural effusion was identified based on their medical records, except in one case. The median (range) duration from the accumulation of pleural effusion to the development of DPT was 28.4 (8.9–255.3) months. The median duration from the accumulation of pleural effusion to the development of impaired respiratory function was 35.1 (2.8–255.3) months. We examined the correlation between the duration from the fluid accumulation to the onset of DPT and the duration of asbestos exposure using a regression analysis, but there was no significant correlation ($r = 0.09$). In 2 of the 6 cases with unilateral DPT, the DPT had progressed to the other side of the thorax in 3.2 and 18.7 months, respectively. At the time of the analysis, 15 patients were alive and 9 patients had died. Of the 9 patients who had died, 4 died of respiratory failure, and 1 died of lung cancer. The other 4 patients died of unknown causes. There was no patient who developed MPM.

Discussion

We retrospectively analyzed the characteristic features of asbestos-induced DPT. We focused in particular on DPT cases with severe respiratory compromise. The criteria that we applied are those used for worker's compensation and the Act on Asbestos Health Damage Relief in Japan. The top

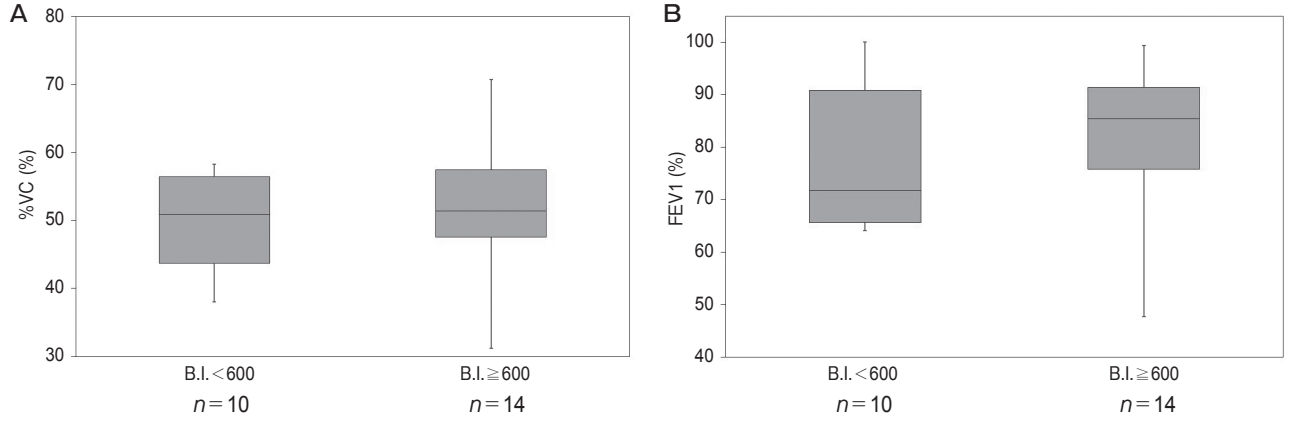

Fig. 1 Comparison of the percentage of vital capacity (%VC) (**A**) and the forced expiratory volume percentage in 1 sec (FEV1) (**B**), between the groups with lower and higher Brinkman index values.

occupational category in which the patients had been exposed to asbestos was dockyard workers, as there is a dockyard facility in the suburbs of the Okayama area. The median duration of asbestos exposure was 35 years, and the median latency period for the development of DPT from the first asbestos exposure was 49.0 years. These results are similar to those of our previous study [9] and those from other groups [7, 12]. The results of the present study confirm that DPT can develop after long latency periods following occupational asbestos exposure.

Making a diagnosis of DPT is challenging. In the present study, we defined DPT as pleural thickening of > 5 mm on a posteroanterior chest X-ray, extending for more than one-half of the LTW in the patients with unilateral DPT, or over more than one-quarter of the LTW in the patients with bilateral DPT. These definitions were made based on dimensional criteria [3], because these are the criteria that are applied when making a diagnosis for the certification of worker's compensation or the Act on Asbestos Health Damage Relief in Japan. However, these criteria are based on chest X-rays and are ambiguous and subjective.

Ameille *et al.* reported that obliteration of the CPA was a far more reliable sign than dimensional criteria in the characterization of DPT [13]. Accordingly, the revised International Labor Office (ILO) Classification of Radiographs of Pneumoconiosis provided clearer criteria, in which involvement of the CPA had to be demonstrated for DPT [11]. We recently reported that the involvement of the CPA was negatively correlated with %VC [9]. This finding supports the use of CPA involvement not only for making a diagnosis of DPT, but also for assessing the severity of DPT. There is still room for discussion regarding the most relevant radiological diagnostic criteria for DPT.

Our present findings demonstrated that breathlessness, cough, and chest pain were the most frequent symptoms of DPT; this finding was similar to that of Yates *et al.* [3]. Moreover, 75.0% of the patients showed restrictive ventilatory impairment, and 25.0% of the patients showed combined ventilatory impairment. The characteristic features of DPT with respect to respiratory function testing are a restrictive ventilator defect, decreased compliance, a reduction in total lung capacity, and impairment of gas transfer [8]. We suggest that the obstructive ventilatory impairment demonstrated in some of the patients in our study may be due to a history of smoking, although we could find no clear association between respiratory function and smoking history.

Unilateral DPT has been reported to cause less severe ventilatory impairment than bilateral DPT [8]. However, there were no differences in ventilatory impairment between the patients with unilateral or bilateral DPT in the present study and in our previous study [9]. However, caution should be used when drawing conclusions from these results, since the sample size was small. In the present study, FEV1 in unilateral DPT was lower than that in bilateral DPT. In fact, among 6 cases with unilateral DPT, there were 3 cases with mild pulmonary emphysema, 1 case with asbestosis, and 1 case with pulmonary emphysema and bronchial asthma. We consider that these concomitant diseases contributed to lower FEV1 in unilateral DPT.

Severe respiratory compromise is the key factor for approval for worker's compensation, and thus the most appropriate method for assessing respiratory impairment associated with DPT should be investigated further.

In the present study, we focused on the sequence of DPT and BAPE (also known as asbestos pleuritis). Epler *et al.* advocated the following diagnostic criteria for BAPE: (1) previous asbestos exposure, (2) determination of pleural effusion by chest X-ray or thoracentesis, and (3) absence of other causes of effusion [4]. We examined the patients' history of pleural fluid accumulation based on the medical information available and their subsequent clinical courses. We found that 54.2% of the 24 DPT cases had a history of pleural fluid accumulation, and they subsequently developed DPT at a median of 28.4 months. In addition, these patients developed severe respiratory compromise at a median of 35.1 months following the episode of pleural fluid accumulation. In a previous report, 40% of DPT cases were preceded by the development of pleural effusion [7]. However, in the present study, there were some cases in which it was difficult to determine the radiological change from BAPE to DPT, especially in patients with BAPE in the organizing stage. Diagnostic criteria for differentiating between BAPE in the organizing stage and DPT would be of critical importance with respect to

worker's compensation in Japan.

Our present findings demonstrated that the main cause of death was respiratory failure. Karjalainen *et al.* reported that asbestos-induced benign pleural disease raised the risk of MPM, but the risk of lung cancer was only slightly elevated [14]. In our study, only one of the 24 patients died of lung cancer and there were no patients with MPM. Associations between DPT and MPM or lung cancer should be clarified in a large-scale, long-term study.

In conclusion, our results indicate that DPT can develop after a long latency period following occupational asbestos exposure and a history of BAPE. Radiological diagnostic criteria that are suitable for practical use and appropriate methods for assessing respiratory impairment due to DPT should be established. Clinical, pathological, and temporal alterations that occur in the transition from BAPE to DPT should be clarified, and the association between DPT and MPM or lung cancer should be examined in large-scale, long-term prospective studies.

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