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Original Article

A retrospective study on radiological findings of diffuse pleural thickening with benign asbestos pleural effusion in Japanese cases

Takumi KISHIMOTO[1]*, Katsuya KATO[2], Kazuto ASHIZAWA[3], Yasuyuki KURIHARA[4], Takeshi TOKUYAMA[5] and Fumikazu SAKAI[6]

[1]Research and Training Center for Asbestos-Related Diseases Okayama, Japan
[2]Department of Radiology, Kawasaki General Medical Center, Japan
[3]Department of Clinical Oncology, Nagasaki University Hospital, Japan
[4]Department of Radiology, St. Luke's International Hospital, Japan
[5]Department of Internal Medicine, Saiseikai Chuwa Hospital, Japan
[6]Department of Diagnostic Radiology, Saitama Medical University, Japan

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Abstract: The requirement for compensation for diffuse pleural thickening in benign asbestos pleural effusion include five computed tomography findings of organized pleural effusion: [1] heterogeneity in the pleural effusion, [2] declined chest capacity, [3] "crow's feet" sign at the pleura, [4] immobilization of effusion volume, and [5] air in the effusion. Pleural effusion is diagnosed as organized, immobilized, and in the state of diffuse pleural thickening if at least three of these items are fulfilled, ([1] and [3] compulsory + one of the remaining items). This retrospective study investigated whether the requirement to confirm no organized pleural effusion changes after a follow-up of >3 months were available for cases fulfilling three of the five items; i.e., the confirmation of only [2] with [1] and [3]. Of 302 cases recognized by the Japanese laws, 105 cases with diffuse pleural thickening with organized effusion were enrolled. The number of subjects who fulfilled the diagnostic requirement for organized pleural effusion was confirmed. Eight subjects had a full score of 5 points, 82 subjects scored 4 points, and only 15 subjects scored 3 points. Furthermore, no changes were observed in the organized pleural effusion volume after a follow-up of >3 months.

Key words: Benign asbestos pleural effusion, Diffuse pleural thickening, Organized pleural effusion, Heterogeneity in the pleural effusion, Crow's feet sign, Diagnostic criteria

Introduction

Diffuse pleural thickening is the pleural fibrosis (lesion of the visceral pleura, resulting in adhesion to the parietal pleura) over a wide area involving at least one lung lobe. Unlike mesothelioma or pleural plaque, diffuse pleural thickening occurs secondarily to diseases other than asbestos exposure, such as rheumatism and tuberculous pleurisy. Thus, it is important to differentiate whether it is caused by asbestos exposure or other diseases[1)].

*To whom correspondence should be addressed.
E-mail address: nakisimt@okayamah.johas.go.jp

In Japan, it is a target disease of the Worker's Accident Compensation Law and the Act on Asbestos Health Damage Relief. The requirement for compensation and Asbestos Health Damage Relief are as follows:

(1) Unilateral lesion with area >1/2 of the whole chest and bilateral lesion with area >1/4 of the whole chest

(2) An occupational asbestos exposure history of >3 years

(3) Complicated with a marked respiratory functional disorder

Benign asbestos pleural effusion (BAPE) is known as a factor of diffuse pleural thickening[2, 3], but in many diffuse pleural thickening cases, BAPE has been reported to continue and organization remains[3]. The Act on Asbestos Health Damage Relief of the Ministry of the Environment do not approve BAPE.

In 2017, the Act on Asbestos Health Damage Relief of the Ministry of the Environment set the requirement as chest computed tomography (CT) images for the development of diffuse pleural thickening in BAPE to determine diffuse pleural thickening. In other words, the five CT findings of organized pleural effusion, preventing lung re-expansion in diffuse pleural thickening, are as follows: [1] heterogeneity in the pleural effusion (high absorption of the pleural effusion), [2] declined chest capacity, [3] presence of the "crow's feet" sign in the pleural effusion site[4], [4] immobilization of the pleural effusion volume, and [5] presence of air in the pleural effusion. If at least three of the above items are fulfilled, with [1] and [3] being compulsory along with one of the remaining items, the pleural effusion can be diagnosed to be organized, immobilized, and in the state of diffuse pleural thickening. For approximately 3 months, we followed-up cases that fulfilled three of the five items, i.e., confirmation of [2] in addition to [1] and [3], and confirmed no changes in the state of organized pleural effusion.

In this study, of the previously approved cases, those whose clinical course could be examined using chest CT images were selected, and the availability of the requirement of three items of five chest CT finding was retrospectively evaluated.

Subjects and Methods

A total of 302 cases were recognized by the Worker's Accident Compensation Law and the Act on Asbestos Health Damage Relief (January 2020) in Japan with a history of occupational asbestos exposure of >3 years, pleural thickening of unilateral lesions that covered >1/2 of one side in the chest and bilateral lesions that covered >1/4 of two sides of the chest, and a marked respiratory functional disorder. Of these, 105 cases with organized pleural effusion who could be followed-up using chest CT images were included. Moreover, 57 cases without pleural effusion and 140 cases who could not be followed-up using chest CT images were excluded. Written informed consent was obtained from all patients in the study. This study was approved by the relevant center of our institute (Approval number #2) on May 14, 2020.

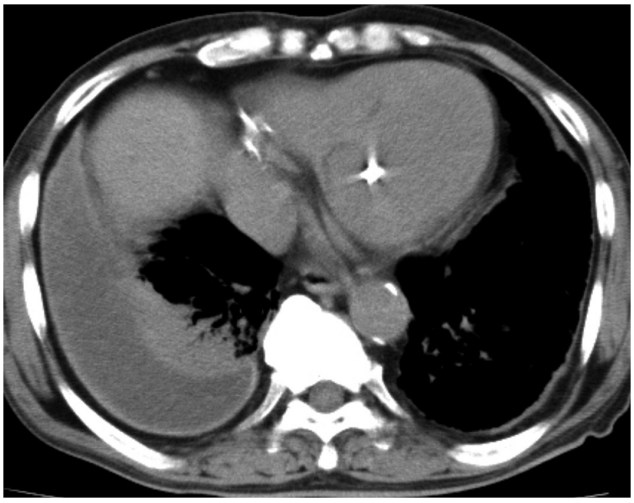

Fig. 1. A cross-sectional chest computed tomography (CT) image showing heterogeneity in the pleural effusion. The right pleural effusion has a high absorption value with heterogeneity. A small quantity of pleural effusion with heterogeneity was also observed in the left side.

The chest X-ray and CT images that demonstrated the clinical course of these 105 patients were obtained. These images were interpreted by six specialists, including four chest radiologists and two pulmonologists.

The findings for organized pleural effusion in chest CT are as follows: [1] heterogeneity in the pleural effusion (high absorption of the pleural effusion) (Fig. 1), [2] declined chest capacity (Fig. 2), [3] presence of the "crow's feet" sign in the pleural effusion site[4] (Fig. 3), [4] immobilization of the pleural effusion volume, and [5] presence of air in the pleural effusion (Fig. 4). The availability of these findings for organized pleural effusion was evaluated with organization having a score of ≥3 points.

Furthermore, we examined the fluctuation in the pleural effusion of the subjects by evaluating their chest CT images at the onset of pleural effusion, organization of pleural effusion, immobilization with changes in the organized pleural effusion, and identifying their eligibility as per the diagnostic requirement following immobilization, diagnosis, and application.

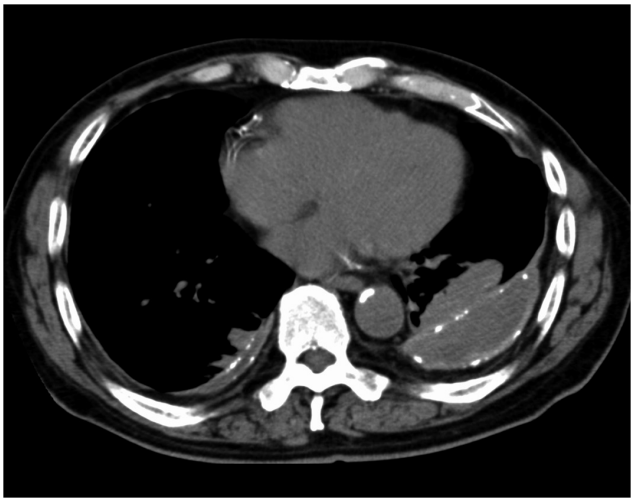

Fig. 2. A cross-sectional chest computed tomography (CT) image showing a decline in chest capacity. A slightly heterogenous pleural effusion with the tendency to be encapsulated was observed in both sides, and the left chest is smaller than the right chest.

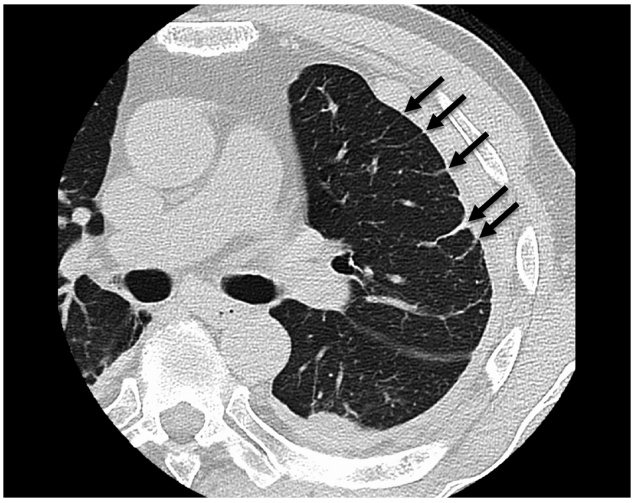

Fig. 3. A cross-sectional chest computed tomography (CT) image showing the presence of the "crow's feet" sign in the pleural effusion site.

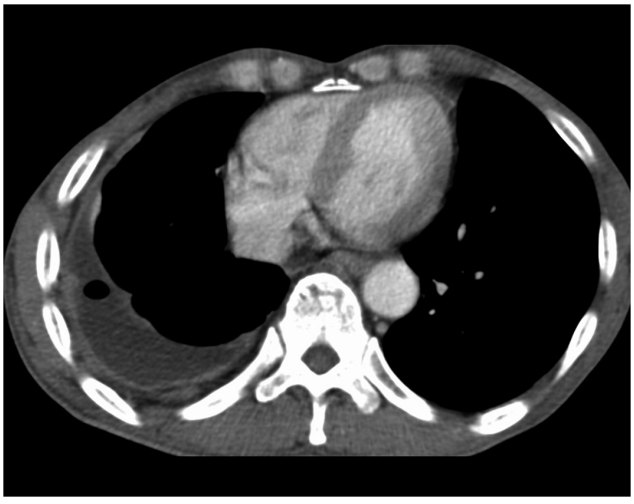

Fig. 4. A cross-sectional chest computed tomography (CT) image showing the presence of air in the pleural effusion. The right pleural effusion tends to be encapsulated, the interior is slightly heterogenous, and the pleural effusion contains the air trapped by the septation due to the fibrin nets formed inside.

Results

In this study, 105 male subjects presented with diffuse pleural thickening and organized pleural effusion, aged 53–93 years at diagnosis with a mean age of 72.8 ± 6.2 years and median age of 73 years.

Based on the chest CT images, approximately the same number of subjects presented with unilateral diffuse pleural thickening and bilateral diffuse pleural thickening (51.6% and 48.4%, respectively). Among the subjects, 92.9% had pleural plaque and calcification was observed in 90.9% of them. Moreover, 32.6% of the subjects had pulmonary fibrosis as a complication; however, no typical asbestosis was observed (≥type I) as stipulated by the pneumoconiosis law. On the other hand, round atelectasis showing fibrosis of the visceral pleura was observed in 69.5% of the subjects.

We calculated the number of subjects who met the five findings for organized pleural effusion. Eight subjects (7.6%) had a full score of 5 points, 82 subjects (78.1%) scored 4 points, and only 15 subjects (14.3%) scored 3 points (Table 1). The two findings of [1] heterogeneity in the pleural effusion and [3] the presence of the "crow's feet" sign in the pleural effusion site were observed in all 105 subjects. [2] Declined chest capacity was observed in 93 subjects (88.6%). In addition, [4] immobilization of the pleural effusion volume was observed in 101 subjects (96.2%). The three subjects who did not show immobilization of the pleural effusion volume scored >3 points with [5] the presence of air in the pleural effusion.

The confirmation period for pleural effusion organization was <3 months in 9.5% of the subjects. Despite having 3 points, most of the 15 subjects who took a period of ≥3 months to develop organization showed no changes in the pleural effusion volume in the follow-up period of 7–12 months. In certain subjects, organization took up to 108.4 months to be confirmed. For such subjects, although they were diagnosed with BAPE, pleural mesothelioma was not confirmed and they were not followed-up. Therefore, it took a long time for them to be recognized. The median observation period of the course of pleural effusion organization was 11.3 months (17.6 ± 19.3 months) (Fig. 5). Once

Table 1. Evaluation of the five diagnostic criteria for organized pleural effusion

Points	Number of cases	(%)
1 point	0 cases	(0.0%)
2 points	0 cases	(0.0%)
3 points	15 cases	(14.3%)
4 points	82 cases	(78.1%)
5 points	8 cases	(7.6%)

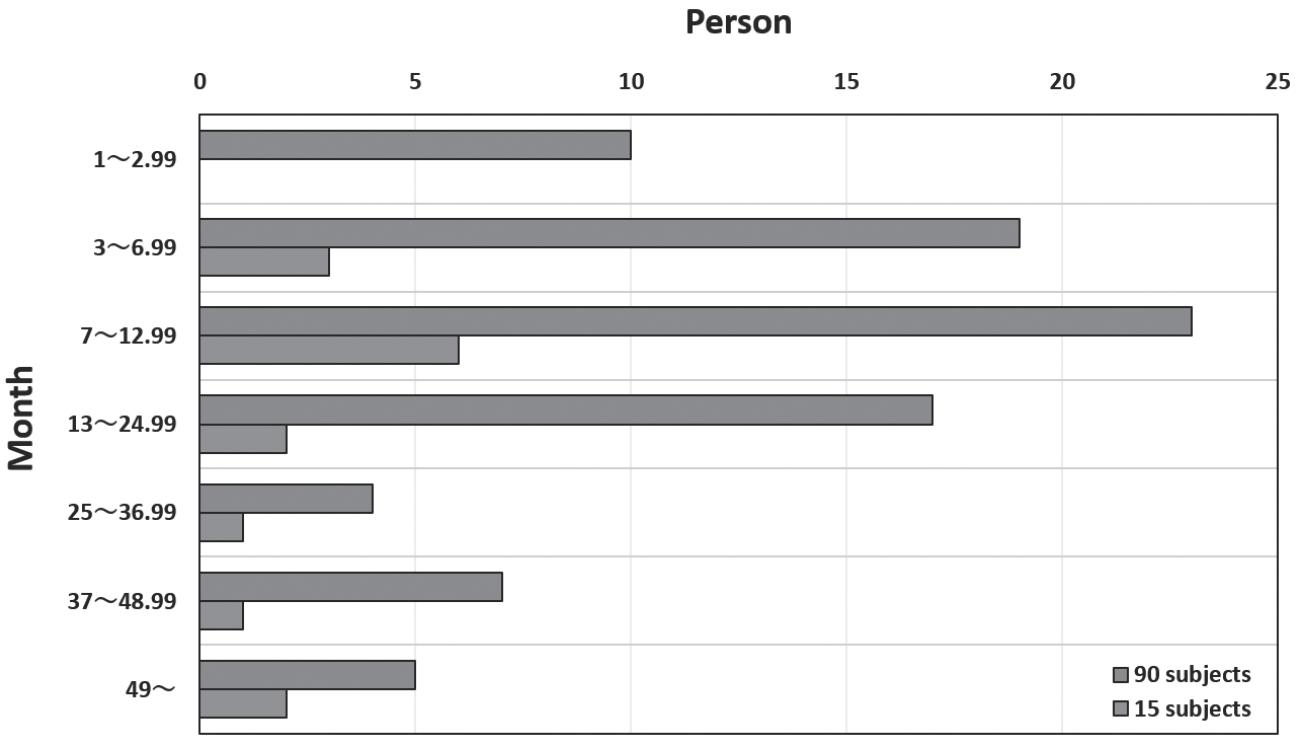

Fig. 5. Observation period following the confirmation of pleural effusion organization on chest computed tomography (CT) images. The confirmation period of organization in all 105 subjects and 15 subjects recognized by 3 points is shown. The observation period varies greatly depending on the subject.

organization was confirmed, the lung capacity did not become greater than that at the confirmation period in any case of relapsed BAPE. However, after an approximate 3-month follow-up on the organization, because the chest shrank although the organized pleural effusion volume decreased, the % vital capacity (VC) that had once dropped to <60% did not exceed 60% again any subject.

Although %VC is an indicator of restrictive ventilatory defect showing a significant respiratory functional disorder, it was 17.3%–70.3% with a mean of 43.8% ± 11.9% (median = 43.2%). Of 102 subjects whose %VC was measured, 95 subjects (93.1%) had a %VC of <60% and seven subjects (6.7%) had >60%. Thirty subjects (29.4%) had a recognized %VC of 50%–59.9%, whereas 29 subjects (28.4%) had a recognized %VC of 30%–39.9%, demonstrating bimodality (Fig. 6). The seven subjects that were not recognized by %VC were recognized by the Worker's Accident Compensation Law. Five subjects had a forced expiratory volume in one second/forced VC ratio of <70% and a forced expiratory volume in one second of <50%; one subject exceeded the alveolar-arterial oxygen difference ($AaDO_2$) threshold value, and one subject had a partial pressure of oxygen in the arterial blood (PaO_2) of <60 Torr.

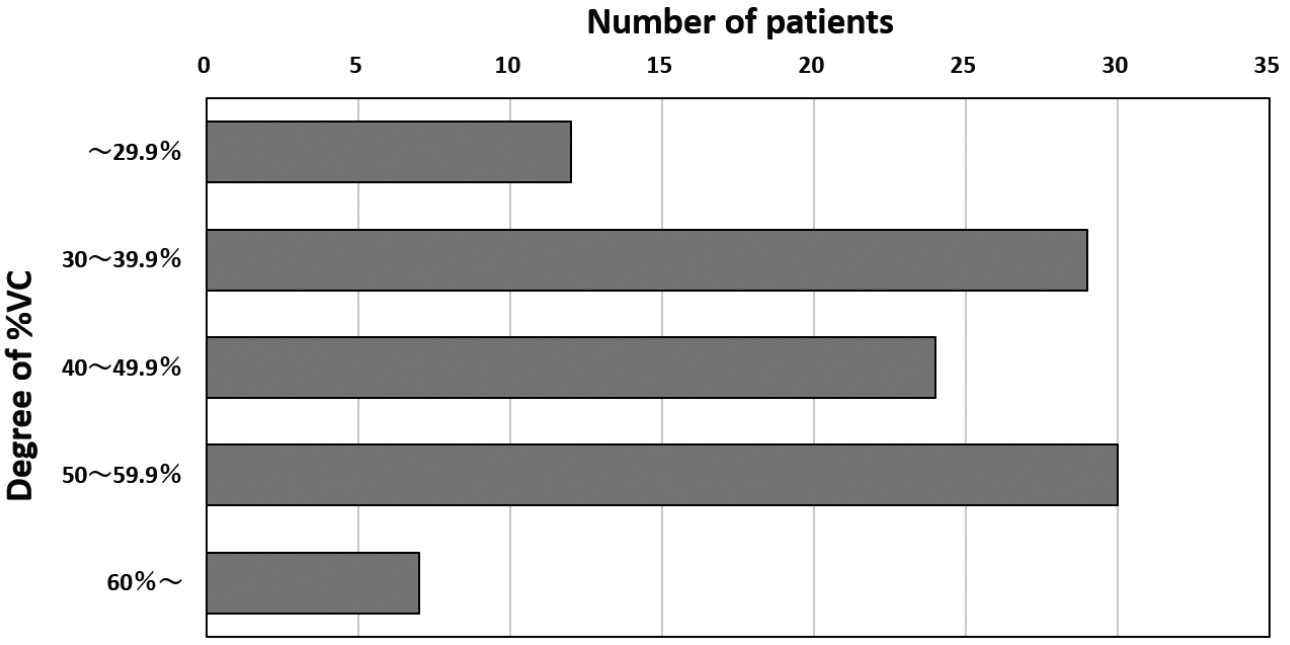

Fig. 6. The number of cases by the degree of %vital capacity (VC) in significant respiratory dysfunction in the respiratory function test.

Discussion

Benign asbestos pleural effusion that occurs due to asbestos exposure is an inflammatory disease of the visceral pleura caused by asbestos fibers, and because diffuse pleural thickening develops after BAPE, many studies have reported diffuse pleural thickening caused by BAPE[2, 3].

This is a retrospective study on 105 subjects (34.8%) who were diagnosed with at least BAPE and had clinical course with the onset of pleural effusion organization. They were selected out of 302 patients with diffuse pleural thickening in Japan. Yates *et al.*[5] have reported that the transition rate from BAPE to diffuse pleural thickening was 30% in 64 cases, which is consistent with the results of our study (34.7%). However, our study was a mega study including 302 patients in Japan.

Of the five chest CT findings indicating that pleural effusion is organized without disappearing and lung re-expansion is hindered and irreversible according to the Act on Asbestos Health Damage Relief 2017, [1] heterogeneity in the pleural effusion (high absorption of the pleural effusion) and [3] presence of the "crow's feet" sign in the pleural effusion site are the two findings showing pleural effusion organization and fibrosis of the visceral pleura; these are crucial image findings of the development of diffuse pleural thickening in BAPE. Furthermore, these findings were observed in all 105 subjects.

On the other hand, [2] declined chest capacity was observed in 93 subjects (88.8%); however, in the case of bilateral lesions, it is difficult to capture the declined chest capacity as laterality, and the findings are inconsistent for all cases. Thus, although declined chest capacity is observed, [4] the immobilization of the pleural effusion should be confirmed. However, it is difficult to determine immobilization by investigating at one time point, so pleural effusion immobilization can be determined by observing its course through CT images. Organized pleural effusion is said to be immobilized if it remains unchanged for approximately 3 months; although many cases required approximately 18 months (mean, 17.6 ± 19.3 months; median, 11.3 months), the dispersion was large. In particular, 9.5% of the subjects were diagnosed with organized pleural effusion in approximately 3 months, in accordance with the requirement of the Act on Asbestos Health Damage Relief of the Ministry of the Environment. Although [5] the presence of air in the pleural effusion was not observed in eight cases, it is an important finding that indicates immobilization.

In certain subjects, pleural effusion decreased and lung capacity increased after organization; however, when the long-term course was observed using chest CT images, no lung re-expansion due to pleural adhesion and almost no recovery in lung capacity were observed in most subjects. Therefore, the 3-month follow-up after the confirmation of pleural effusion organization was considered available. Subjects in whom the confirmation of pleural effusion im-

mobilization took some time were followed-up while still being diagnosed with BAPE despite the complication of significant respiratory functional disorder, left uncared for despite the diagnosis of BAPE, not recognized after the development of diffuse pleural thickening, and not provided long-term treatment despite exertional dyspnea.

In an ideal scenario, the appropriate pleural effusion observation period must be determined in a prospective study, but the temporal examination from BAPE to diffuse pleural thickening could be done in only a limited number of cases. In particular, because BAPE is not a target disease according to the Act on Asbestos Health Damage Relief of the Ministry of the Environment, its confirmation is difficult, but we need to confirm whether 3 months follow up of organized pleural effusion is suitable or not, using cases followed-up of BAPE approved by the Worker's Accident Compensation Law. Therefore, in the actual prospective evaluation, it is necessary to recommend and request a chest CT examination simultaneously with chest X-ray images, and it may also be necessary to supplement the periods if the chest CT images are not captured with chest X-ray images in a retrospective study.

In certain cases, as BAPE often relapses, and although pleural mesothelioma was ruled out using thoracoscopic pleural biopsy, follow-ups revealed the development of diffuse pleural thickening and significant respiratory dysfunction; thus, it is necessary to perform thorough follow-ups instead of leaving the patients uncared for without reexamination because it is not a malignant tumor.

In addition, approximately half the subjects presented with unilateral lesions and the other half with bilateral lesions. In the study by Jeebun *et al.*[6], 80% of the subjects presented with unilateral lesions initially, but a 2-year follow-up revealed that in 24% of their subjects, pleural effusion accumulated in the opposite side and bilateral diffuse pleural thickening developed. In the current study, certain subjects initially presented with unilateral lesions but no significant respiratory dysfunction. They were inevitably followed-up due to the accumulation of pleural effusion in the opposite side, and eventually a respiratory dysfunction developed due to the bilateral diffuse pleural thickening, and it took a long time for some subjects to be diagnosed, although the number was small. The results of our previous study showed more cases of diffuse pleural thickening with organized pleural effusion than without pleural effusion. To that end, it is necessary to determine the requirement for organized pleural effusion and to identify diffuse pleural thickening for optimal outcomes.

On the other hand, based on the results of the respiratory function test performed to evaluate respiratory dysfunction, 95.2% of the marked respiratory dysfunctions were recognized as restrictive defects with a %VC of <60%. In terms of the degree of %VC, a similar number of subjects with severe dysfunction and a %VC of <40% and subjects with relatively mild dysfunction with a %VC slightly <60% was observed. It was suggested that this difference in degree greatly affected the prognosis. However, based on the diagnostic criteria of the Worker's Accident Compensation Law, cases with a forced expiratory volume in one second/forced VC ratio of <70% and a forced expiratory volume in one second of <50% were also identified, and two cases were recognized based on this criterion, whereas 3 cases were recognized based on the criteria of the arterial blood gas analyses results exceeding the $AaDO_2$ threshold value or PaO_2 <60 Torr.

The criteria for compensation and Asbestos Health Damage Relief in Japan do not consider the dullness of costophrenic angles, which is a British criterion, but according to Fonseka *et al.*[7], even without the dullness of costophrenic angels, %VC reduced to 79.5% in unilateral diffuse pleural thickening and 66.7% in bilateral cases, leading to a respiratory compromise within the range of diffuse pleural thickening, which is the Japanese criterion. In addition, Singh *et al.*[8] reported that the movements of the diaphragm and lower pleura greatly affected the respiratory function of diffuse pleural thickening patients. Therefore, we believed that it was not necessarily crucial to assess the dullness of costophrenic angles. The mechanism of diffuse pleural thickening, a fibrosis of the visceral pleura, is believed to involve proliferation of subpleural fibroblasts induced by BAPE, and this fibrosis presumably consists of an interaction between inflammatory and epipleural mesothelial cells[9].

BAPE is the important factor to approve asbestos-induced diffuse pleural thickening, therefore it is essential to diagnose organized pleural effusion to prevent re-expansion of lung for many cases. We want to assess this requirement of the diffuse pleural thickening with BAPE by the Act on Asbestos Health Damage Relief of the Ministry of the Environment and grope the better Japanese criteria including the dullness of costophrenic angles for the diffuse pleural thickening with BAPE.

We hope that many patients will be diagnosed based on this requirement for compensation and Asbestos Health Damage Relief for organized pleural effusion stipulated in the 2017 Revision of Points to Note regarding Materials Pertaining to Medical Judgment under the Act on Asbestos Health Damage Relief of the Ministry of the Environment.

Declarations of Interest

None.

Institution at Which the Work was Performed

Research and Training Center for Asbestos-Related Diseases, Okayama, Japan

Institution and Ethics Approval and Informed Consent

Written informed consent was obtained from all patients in this study. Research and Training Center for Asbestos-Related Diseases granted approval for this study (Approval number #2) on May 14, 2020.

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Data Statement

The data of this study are not publicly available, as we may use the data in future research.

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