3. Diagnostic Tools for ARDs

3- B ~ E. Asbestos-Related Respiratory Diseases

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Summary

For the pulmonary diseases arising from asbestos there are benign lesions from asbestosis and malignant tumors from lung cancer. On the other hand, as pleural diseases there are malignant pleural mesothelioma, nonmalignant benign asbestos pleural effusion, and diffuse pleural thickening, and pleural plaque as a clinical condition. Aside from benign asbestos pleural effusion there are four diseases targeted by workmen's compensation and the Act on Asbestos Health Damage Relief (Asbestos Relief Act). Forming the basis for diagnosis of benign asbestos pleural effusion is difficult, and because these diseases are candidates for workmen's compensation, physicians specializing in respiratory diseases must well recognize the diagnostic criteria. This paper focuses on the diagnosis of these diseases.

I. ASBESTOSIS

Asbestosis is one type of pneumoconiosis that results from exposure to high levels of asbestosis, and becomes diffuse pulmonary fibrosis, which begins peribronchiolar.

1) Diagnosis and Clinical Findings

The diagnosis criteria are given hereafter. 1) Occupational asbestos exposure; 2) presence of irregular opacities mainly in the lower lung field in chest roentgenogram; 3) decreased forced vital capacity based on respiratory function test (restrictive respiratory functional disorder); 4) crepitations are audible during inhalation in both lung bases; and 5) other similar diseases and diseases with causes other than asbestos are excluded [1].

In particular, 1, 2, and 5 are required for the diagnosis of asbestosis. In the lung field, minute linear and reticular opacities progress upwards in both lower lung fields, and due to the accompanying decrease in pneumatization, the lower lung field becomes smaller. Furthermore, as the minute linear reticular shadow becomes coarse, the boundary of the heart shadow becomes blurred (shaggy heart), and honeycombing may manifest in the middle and lower lung fields (Figs. 1 and 2). However, compared to Idiopathic Pulmonary Fibrosis and Usual Interstitial Pneumonia (IPF/UIP) the frequency of honeycombing is low. It is more often atypical, and the frequency of traction bronchiectasis is also low. It is thought that at present, early confirmation of lesions based on high resolution CT (HRCT) is useful in diagnosis. In other words, there are pleural lesions such as subpleural dots, curvilinear lines, and branching opacity, and images of central respiratory tract fibrosis such as interlobular septum hyperplasia (Fig. 3) and parenchymal (transpulmonary) band that are associated with findings of lung parenchyma lesions [2,3]. On the other hand, when there are extremely high levels of asbestos exposure, stenosis and obstruction of the lumen of the respiratory bronchiole occur, collapse of the peripheral air occurs, atelectasis of the lobular unit emerges, and collapse type fibrosis occurs. This type of asbestosis is referred to as a hardening

type of atelectasis. This is an image of typical asbestosis.

In order to diagnose asbestosis using the pneumoconiosis method, a PR1/0 or greater in the standard film of pneumoconiosis is required. Pleura lesions such as diffuse pleural thickening or pleural plaque often appear and are accompanied by calcification.

Entrusted by the Ministry of the Environment, a panel of more than three specialists on asbestos associated diseases investigated cases diagnosed as asbestosis at Rosai hospitals all over the country. The targets of the investigation were 119 cases that were diagnosed with asbestosis of higher than PR1/0. Based on gender, there were 109 male cases (92%) and 10 female cases (8%) ranging in age from 52-89 with the average of 73±6.6 yrs. (median value of 74 years). The reasons for seeking medical consultation were the presentation of symptoms, 40 cases (34%); consultation based on health examination, 60 cases (50%); and other reasons, 19 cases (16%). The most common motivation was consultation based on regular health examination.

By December 31, 2008, 35 of the 119 patients died. The causes of death were 12 cases of respiratory failure due to asbestosis, 7 cases of lung cancer, and 2 cases of mesothelioma. Other 14 cases are unknown. There were 86 smokers (72%) and the average value for the Brinkman index was 710. Based on chest roentgenogram, there were 61 cases of PR1 pneumoconiosis, 40 PR2 cases, and 18 PR3 cases.

Based on occupation, there were 34 patients from the asbestos product manufacturing industry; 18 patients in plumbing, insulation, and thermal insulation work; 18 patients involved in asbestos handling work on board a ship; 14 patients involved in asbestos spraying work; and most were exposed to medium or higher levels of asbestos.

The asbestos exposure period was from 2 – 59 years (average of 26.2 years), and the initial exposure age was 13-60 years old with the average of 22.9 years old. The period of time from initial exposure to diagnosis was an average of 45.4 years, and that from the end of the exposure period to diagnosis was 21.4 years. There was a poor prognosis for the time period from the day of diagnosis to the day of death, 1 month – 18.7 years and the mean value of 1.7 years (average 3.4 years) [4].

2) Differential Diagnosis

Pathological changes in the pleura such as pleural plaque, diffuse pleural thickening, and hyperplasia of the visceral pleura that accompanies lung parenchyma with a band like shadow are useful in differentiating asbestosis from idiopathic interstitial pneumonia. However, there is a more than a 5% chance that asbestosis will not combine with pleural plaque. There are cases in which calcified pleura plaque is present and even though there are findings of fibrosis in the lungs, they are not diagnosable asbestosis. Cases in which fibrosis is accompanied by chronic interstitial pneumonia or pulmonary emphysema are not uncommon, so it is important to listen to the detailed occupational history and ask if there was exposure to a high concentration of asbestos. In other words, we should take special note of pulmonary fibrosis with pleural plaque when the case is not asbestosis. The reason for this is that pleural plaque occurs even at exposure to low concentrations of asbestos, but also in many cases it occurs in combination with asbestosis at exposure to high concentrations of asbestos. Therefore, the occurrence of pleural plaque is not a sufficient condition for the diagnosis of asbestosis.

II. Asbestos Related Lung Cancer

Up to now, the definition of asbestos related lung cancer was asbestosis complicated with primary lung cancer, and it was thought that fibrosis of the lung is important to the carcinogenesis mechanism. However, recently there have been asbestos related lung cancer cases that were not compli-

cated with asbestosis, and it is thought that asbestos itself is important to the emergence of lung cancer.

1) Diagnosis

As stated above, asbestosis combined with lung cancer is also considered globally as asbestos related lung cancer, and as for the carcinogenesis of lung cancer, an exposure related relationship has been identified in that as the degree of exposure to asbestos increases the risk of lung cancer becomes higher. On the other hand, based on the Helsinki criteria [5] the chance that lung cancer will manifest becomes double if the level of exposure to asbestos is 25 asbestos fiber/ml* year (exposure level * number of years). If workers engage in work that involves exposure to high concentrations of asbestos such as asbestos spraying work and insulation work for a period of one year or in work that involves exposure to moderate levels of asbestos such as shipbuilding or construction work for 10 years, it is said that lung cancer will appear. So, from the initial exposure to asbestos to the emergence of lung cancer there are at least ten years, and almost a 30 - 40 year incubation period is needed. In general, when compared to cases of lung cancer without asbestosis, the age at the onset of asbestosis combined with lung cancer is later.

There is no characteristic feature for the site of the origin of lung cancer that results from exposure to asbestos or the histopathological type, the case is similar to that for general type lung cancer. The largest factor in the emergence of lung cancer is smoking, and if the patient was exposed to both cigarette smoke and asbestos, the risk of lung cancer becomes high due to a synergistic effect. In the case of exposure to asbestos alone, however, the risk of lung cancer is 5.2 times greater and the incidence of lung cancer for mixed exposure to asbestos and cigarette smoke is reported to be 53.2 times greater [6].

As the definition of lung cancer without asbestosis in terms of the criteria for authorizing injury

compensation in Japan, confirmation of the presence of pleural plaque or the presence of a pathological sample of an asbestos body accompanied by occupational exposure to asbestos for a period of more than 10 years are required (Appendix 1). On the other hand, the Act on Asbestos Health Damage Relief (Asbestos Relief Act) sets the criteria for asbestos related lung cancer as having the exposure level that doubles the incidence of the standardized lung cancer. In other words, a case with higher than PR 1 asbestosis showing pulmonary fibrosis findings according to the Pneumoconiosis Act together with pleural plaque confirmed based on chest image or the number of intrapulmonary asbestos bodies with the dry lung weight of more than 5,000 bodies/g or bronchoalveolar lavage fluid with the concentration of greater than 5 bodies/ml, or the presence of asbestos fibers in the dry lung weight of greater than 2,000,000 (fiber which is longer than 5μ) or more than 5,000,000 (fiber which is longer than 1μ) is required (Appendix 2) [5].

III. PLEURAL MESOTHELIOMA

Mesothelioma is a malignant tumor that originates from mesothelial cells or has the tendency to differentiate from the mesothelium, and occurs in the pleura, peritoneum, pericardium, or tunica vaginalis testis. Approximately 80% of mesothelioma cases originate in the pleura, and approximately 80% occur due to exposure to asbestos; however, SV40 virus, irradiation, and heredity were also reported as other causes, but the frequency of these is low.

1) Diagnosis

The chief complaints as symptoms are dyspnea and chest pain for pleural mesothelioma, and a sense of abdomen distension and stomachache for peritoneal mesothelioma. Based on chest images, more than 80% of pleural mesothelioma cases were accompanied by pleural effusion. In a typical example, based on chest CT, we find a mass shadow projecting into the pleural cavity, diffusion of 1-cm thick, tuberous pleural thickening (Fig. 4), or hyperplasia of the interlobar pleura. However, in the case of a relatively early lesion, these characteristic findings may not pre-

sent themselves, and there are many cases that are diagnosed as unidentified pleurisy or tuberculous pleurisy. MRI has superior capability compared to other methods in terms of detailed detection of invasion in the chest wall or diaphragm. Because FDG - PET is useful in differentiating tumors and inflammatory lesions, it is used to differentiate diffuse pleural thickening due to asbestos exposure; however, false positives are a problem. Also, cases of early lesion or lymph node metastases of mesothelioma give false negatives and, at best, are considered reference findings.

Based on pleural fluid examination, in cases with more than 100,000 ng/ml of hyaluronic acid, the chance of pleural mesothelioma is high, but the positive rate is around 40% and the sarcoma type does not present at a high frequency. Also, since most cases have a low carcinoembryonic antigen (CEA) level, CEA is useful in differentiating carcinomatous pleurisy, etc., due to lung cancer [7]. Measuring the soluble mesothelin related peptides (SMRP) is reported to be useful in foreign journals, and can be used in differential diagnosis and evaluating the effects of treatment for lung cancer [8].

To reach a diagnosis, cytodiagnosis or a tissue diagnosis is required. The diagnosis rate for cytodiagnosis is around 40% and the diagnosis rate for sarcoma type mesothelioma is particularly low, so the immunohistochemical technique is essential for diagnosis. The diagnosis rate for methods for tissue diagnoses such as ultrasound or CT guided needle biopsy is not poor, but in order to increase the diagnosis rate video-assisted thoracoscopic biopsy is recommended. Based on thoracoscopic findings, there are two types of characteristics of malignant mesothelioma that can be observed by the naked eye: multiple eminence and non-specific hyperplasia. If we use thoracoscopy, macroscopic observation becomes possible. From the subtle differences in color of the difficult-to-diagnose comparatively-early-stage lesions we can detect neoplastic lesions that are too difficult to detect even if we make full use of the imaging technology.

For the histological type of mesothelioma, there are three types: carcinoma that resembles epithe-

lial mesothelioma, sarcoma from sarcomatoid mesothelioma, and a mixture of these, a two phase type, in which one of the types comprises more than 10%. Then in the diagnosis, the immunohistochemical staining technique used in the histopathology of the tumor is useful. Diagnosis confirms that there are more than two kinds of mesothelioma that match the positive and negative markers for epithelial mesothelioma shown in Appendix 3 [8]. However, in the case of sarcomatoid mesothelioma, it is required that low molecular keratin (AE1/AE3 or CAM5.2), calretinin, and epithelial membrane antigen (EMA) show positive, but smooth muscle actin, desmin, s-100, CD34, etc. in which true sarcoma shows positive must show negative. If these tests are not conducted, it is easy for them to be confused with other diseases and the probability for misdiagnoses becomes high [9].

2) Differential Diagnosis

a. Pseudomesotheliomatous carcinoma primary lung cancer or pleomorphic carcinoma

Among the types of cases of lung cancer in which a primary tumor does not present in the lung, lung cancer immediately under the pleura infiltrates the pleura, and the lung cancer progresses in a similar manner to pleural mesothelioma. This type of case of lung cancer is referred to as pseudomesotheliomatous carcinoma [10]. In this case, since we cannot differentiate it from the pleural mesothelioma based on images, pathological diagnosis using the tumor tissue is required. Also, there is tumorigenesis, but the pleura contacting the tumorigenesis shows pleomorphic carcinoma, which is referred to as carcinosarcoma, and differential diagnosis must be performed comprehensively using image based findings and histopathological findings together.

b. Fibrous pleurisy (benign asbestos pleural effusion)

Based on images, neoplastic pleural thickening is not observed, but since the histology based on biopsy resembles that of desmoplastic mesothelioma pathological differentiation is required.

c. Chest wall tumor

Based on images, since the origin of the tumorigenesis is on the chest wall there is a strong tendency to destroy ribs. Most tumors are histologically diagnosed as sarcoma, but since the possibility of pleural mesothelioma cannot be denied, immunostaining is performed on biopsied tumor tissue and differential diagnosis is conducted.

IV. Benign Pleural Effusion

Among asbestos based nonmalignant pleura lesions, inflammatory changes in visceral pleura that accompany pleural effusions are called benign asbestos pleural effusions.

1) Diagnosis

Diagnosis criteria should satisfy the following four conditions: 1) A history of exposure to asbestos, 2) a chest roentgenogram or confirmation of pleural effusion through puncture biopsy to confirm the presence of a pleural effusion, 3) there is no cause other than asbestos exposure for the pleural effusion, and 4) within three years of confirmation of pleural effusion there are no malignant tumors [11]. Here, this benign means that the tumor is not diagnosed as malignant but in the clinical course we cannot necessarily say it is benign. Hillerdal *et al*. [12] reported that it is best to do a follow-up one year after when detailed clinical course is observed based on imaging such as chest CT. Up to now, new diagnostic criteria have not been indicated; however, we proposed a tentative clinical plan [13] (Appendix 4). There are two theories for the occurrence mechanism of pleural effusion. One based on external stimulation from asbestos fibers or pleural fibrosis indicates that the excretory pore of the parietopleural pleura becomes occluded, and the other is the adjuvant effect from asbestos fiber based on autoimmune theory.

2) Differential Diagnosis

Since this is diagnosis by exclusion, we must exclude every disease that can cause pleural effu-

sion. There are cases of pleural effusion where puncture biopsy yields very low amounts of fluid to cases in which more than 1000 ml are removed and removal must be repeated. The exudate of the pleural effusion often contains blood, and cellular analysis shows that lymphocytes are predominant. The hyaluronic acid concentration in the pleural effusion is 100,000 ng/ml or less in many cases. In the case that the hyaluronic acid concentration exceeds 100,000 ng/ml, even if there is no neoplastic pleural thickening based on imaging, in order to exclude pleural mesothelioma detailed examination such as thoracoscopy should be performed. Also, the adenine deaminase (ADA) and CEA levels should not be high [14].

From macroscopic findings based on thoracoscopy, the surface of the parietal pleura is smooth in many cases, and protrudent lesions that are evident in pleural mesothelioma are not found. For a case of refractory pleural effusion where exposure to asbestos is evident, thoracoscopy should definitely be performed. If pleural mesothelioma can be excluded, benign asbestos pleural effusion can be diagnosed making it possible to apply for injury compensation. For this disease careful follow-up is required not only regarding the development of mesothelioma but also in regard to the transition to diffuse pleural thickening.

As for the form of treatment, for a case where there is large volume accumulation of pleural effusion, sustained aspiration may be required, but it may remit spontaneously even without treatment. In addition, internal use of a small dose of steroids (prednisolone 20 mg/day) for one week may be effective [14]. The prognosis for pleural effusions for all cases is not necessarily good with the median value of 9.6 years for the survival period.

V. Diffuse Pleural Thickening

There are two types of pleural thickening due to asbestos: pleural plaque, which is localized pleural thickening, and diffuse pleural thickening. Diffuse pleural thickening is a visceral pleura lesion

that spreads widely either unilaterally or bilaterally. The thickness ranges widely from less than 1 mm to more than 1 cm, and since the lesion reaches the parietal pleura, both pleura often adhere to each other.

There are three categories for the origin of diffuse pleural thickening from asbestos exposure: Asbestosis extends from the visceral pleura to the parietal pleura, benign asbestos pleural effusion is involved as a preceding lesion, and neither asbestosis nor benign asbestos pleural effusion is the origin.

1) Diagnosis

Based on basic chest X-ray the degree of spread is more than one half in the case of one side or more than one fourth in the case for both sides. The standard thickness is greater than 5 mm (Fig. 5), but this is not a strict standard. Differentiation diagnosis of pleural plaque due to parietal pleural lesion is needed [15]. The Pneumoconiosis Act states that significant impaired pulmonary function is recognized when the degree of spread and thickness satisfy the worker accident compensation standard in Japan and there was occupational exposure to asbestos for more than 3 years.

Since the case shown in Fig. 6 is visceral pleura hyperplasia, based on the image, circular atelectasis or crow's feet sign is apparent in the lung parenchyma. It is rare to see this type of irregular thick hyperplasia as we would find in pleural mesothelioma. It presents as flat and smooth. However, if this progresses the affected side of the lungs will narrow similarly to the case of pleural mesothelioma. Pathologically, this is a case of diffuse pleural fibrosis, where fibrous tissue with few cell components is thinly distributed.

Among the pleural lesions, 9-22% of these lesions result from asbestos exposure. There are other cases of a collagen disease nature, chemical nature, infective pleurisy nature, and unidentified na-

ture, so it is important to obtain a detailed occupational history.

2) Differential Diagnosis

a. Differentiating pleural mesothelioma particularly from the desmoplasia type of mesothelioma is necessary. In the case of mesothelioma, the advancement of conditions is fast and eventually neoplastic hyperplasia will present.

b. Because pleural plaque is a clinical condition of the parietal pleura, there is no adhesion to the visceral pleura and there are no consecutive findings of lung parenchyma. Furthermore, no significant impaired pulmonary function develops.

VI. PLEURAL PLAQUE (PLEURAL THICKENING)

By being exposed to asbestos, a flat and irregular protrusion is formed under the mesothelium of the parietal pleura and is accompanied by hyperplasia. Histopathologically, the cell components show scarce fibrous lesions. The most common sites for pleural plaque to originate are the anterior chest wall, the sixth to eighth dorsal costal cartilage, lateral thorax, side of the of vertebra body, and the upper bifurcatio tracheae (Figs. 7 and 8). Also, calcification often occurs in the convexity of the diaphragm. On the other hand, it does not occur in the costodiaphragmatic recess or the apex area.

Even if exposure to low concentrations of asbestos occurs, it is still an indicator of asbestos exposure. From the first exposure pleural plaque will present in at least 15 years, and after 20 years partial calcification will occur. Asbestos bodies detected from inside the lungs and lung cancer from asbestos are important findings in terms of receiving authorization for accident or relief compensation. To reach a diagnosis, it is possible to use chest X-rays, but chest CT imaging has a higher rate of detection [16]. Especially in regard to examination, detection of pleural plaque,

since it is a high risk factor for mesothelioma, and lung cancer requires careful follow up. On the other hand, thin pleural plaque that cannot be detected even using chest CT can be macroscopically observed in the case of thoracoscopy, operation, or autopsy, and a photo image is useful as evidence of asbestos exposure.

In terms of differential diagnosis, there are changes to the pleura such as intercostal veins, calcification after tuberculous pleurisy, extrapleural fat, and post pneumonia. Also, we can differentiate diffuse pleural thickening based on the presence or absence of visceral pleura lesions, but in the case of plaque without calcification differentiation becomes difficult. We should take careful note when pleural mesothelioma shows only localized lesions (Fig. 9) because differentiation is difficult and video assisted thoracoscopic biopsy is required. In general, there are no rapid changes in the condition of pleural plaque, and there is no chance of developing respiratory functional disorders such as dyspnea.

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Appendixes

Appendix 1. Authorization criteria for asbestos lung cancer based on worker's compensation insurance law (injury compensation)

The two items below are applicable to primary lung cancer occurring in a worker exposed to asbestos.

A) Higher than type 1 asbestos findings are determined from chest roentgenogram images based on the Pneumoconiosis Act

B) Medical findings 1) and 2) below are obtained and the term of occupational exposure to asbestos is more than 10 years.

However, from among the published medical findings in 2) below, if the number of asbestos particles or fibers in the lung is more than a fixed quantity (per gram of dry lung weight, 5,000 or more particles, more than 2 million fibers that are more than 5 μm long, or more than 5 million asbestos fibers that are more than 1 μm long, or 5 particle/ml of asbestos particles in bronchoalveolar lavage fluid) but does not meet the requirement for occupational exposure to asbestos for the period of 10 years, it is still considered that the requirement is satisfied.

1) Patient has pleural plaque (pleural thickening) based on chest X-ray examination, chest computed tomography, etc.

2) Patient has intrapulmonary asbestos particles or asbestos fibers

Appendix 2. Authorization criteria for asbestos lung cancer based on Asbestos Relief Act

1) Chest image findings

Presence of pleural plaque based on chest X-rays or CT, presence of irregularly shaped shadows

of greater than PR1 as determined by the Pneumoconiosis Act based on chest X-rays, and proof of fibrosis lesion in the lung based on CT.

2) Number of asbestos particles

There are more than 5,000 asbestos particles, more than 2 million (more than 5 μm long), or 5 million (more than 1 μm long) asbestos fibers per gram of dry lung weight. Alternatively, there are more than 5 asbestos particles/ml in the bronchoalveolar lavage.

Appendix 3. Immune tissue staining marker for epithelial mesothelioma

Positive marker;

calretinin, D2-40, cytokeratin 5/6, WT-1, thrombomodulin

Negative marker;

CEA ,TTF-1, Ber-EP4, MOC-31

Appendix 4. Benign asbestos pleural effusion criteria (2007 Ministry of Health, Labour and Welfare Research Group development plan)

1) History of asbestos exposure

2) Presence of pleural effusion confirmed based on pleural effusion puncture

3) Based on the investigation results below, we may exclude other diseases that present pleural effusion

- Pleural effusion exudate
- Pleural effusion ADA value of less than 50 U/L
- Pleural effusion CEA value less than the maximum normal serum value
- A hyaluronic acid value of less than 100,000 ng/ml
- Cytopathologic examination of pleural fluid: Negative

- In the classification of pleural effusion cells, the class of mesothelial cells represents less than 5%
- There are no pleura lesions that are suspected to be a malignant tumor in chest CT (in addition, for observation of pleura findings contrast radiographic CT is desirable)
- We can exclude other diseases through observation of pleura lesions based on thoracoscopy and pleural biopsy. However, in cases in which thoracoscopy is not possible, malignant tumors and other diseases can be excluded in the follow-up examination for one year.

Figures

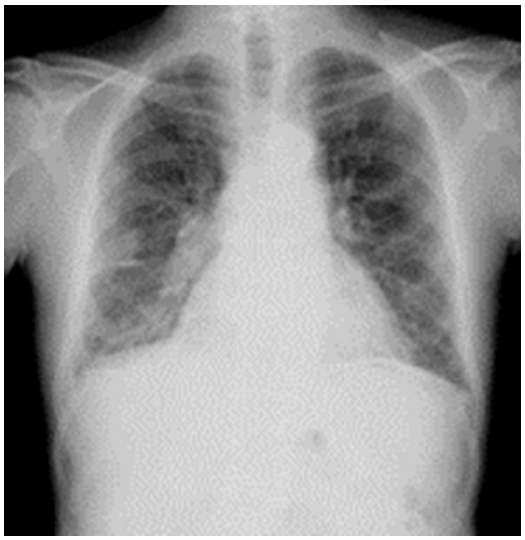

Fig. 1 Front view chest photograph of asbestosis case indicating irregular opacities mainly in both lower lung areas. This case is PR2 type asbestosis with calcified pleural plaque.

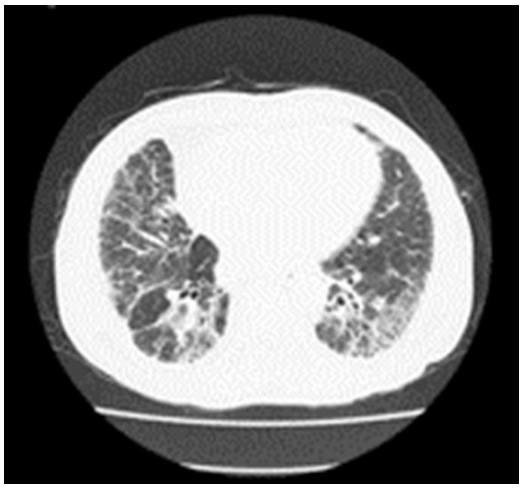

Fig. 2 Chest CT showing lung field conditions of the same case. Ground glass shadows and parenchymal band are identified with partial honeycombing accompanied by findings of fibrosis in the lung.

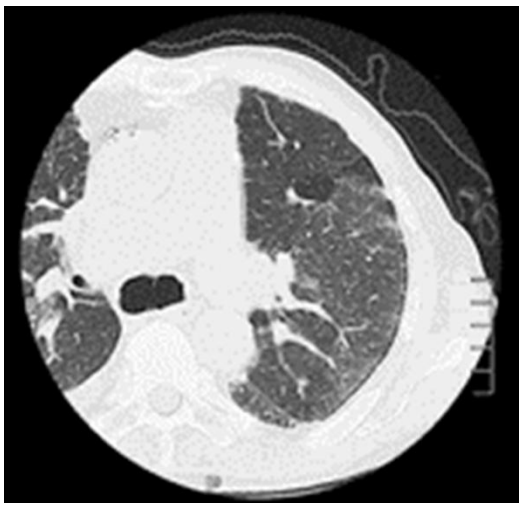

Fig. 3 HRCT showing fibrosis as comparatively light areas. Along with subpleural dots and subpleural curvilinear lines a mosaic pattern is observed.

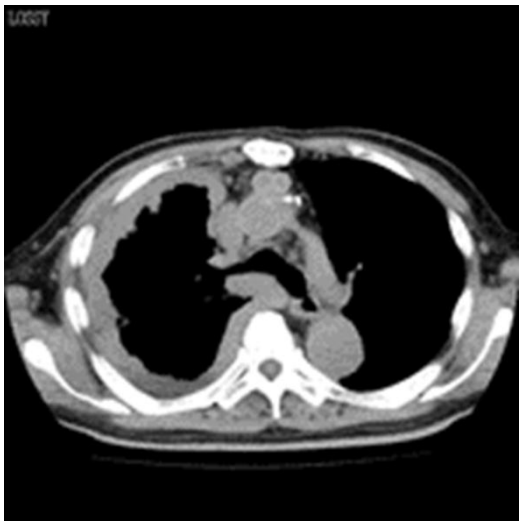

Fig. 4 In the chest CT mediastinal window of this pleural mesothelioma case, the right pleura diffusely presents with irregular hyperplasia and covers the unilateral pleura (pleural rind). Then the right thorax narrows.

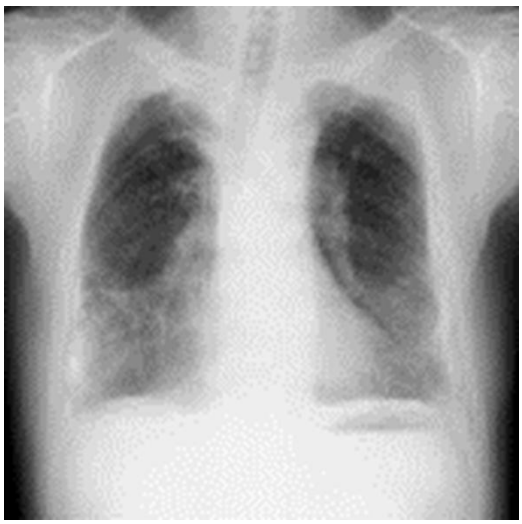

Fig. 5　In the chest X-ray findings of this case of diffuse pleural thickening. In addition, both side apex areas are observed to have decreased air content due to hyperplasia and calcified pleura plaque.

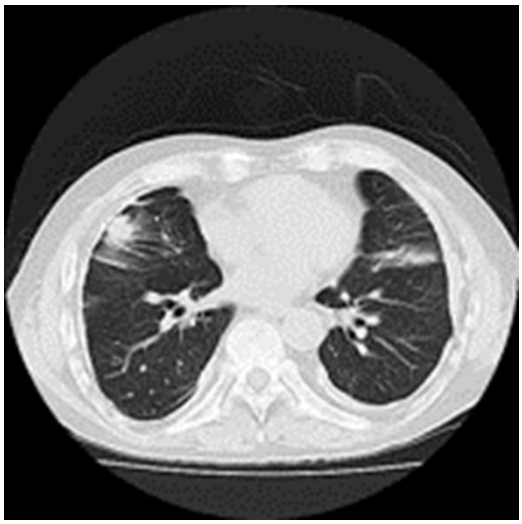

Fig. 6　Chest CT showing lung conditions of the same case. Both pleura show diffuse hyperplasia without irregularity accompanied by visceral pleura lesions in the right lung field with round atelectasis.

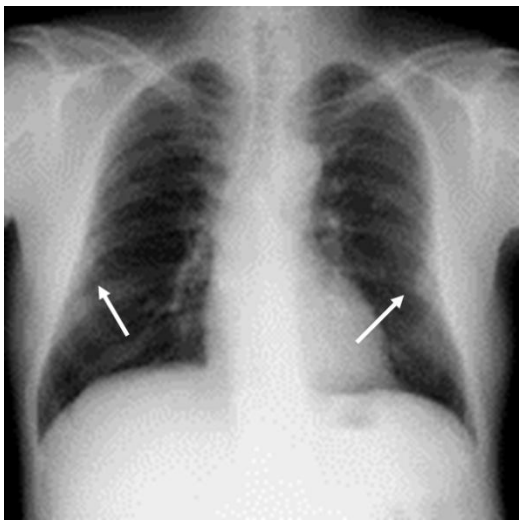

Fig. 7 Chest roentgenogram showing noncalcified pleural plaque that is symmetrical to both chest walls (arrow).

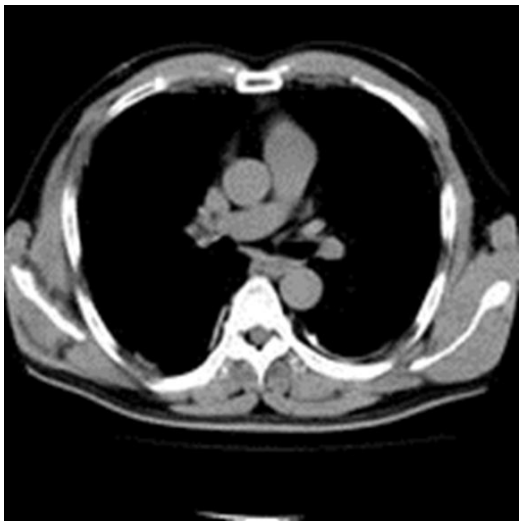

Fig. 8 Chest CT showing lung conditions of the same case. This is a typical case of pleural plaque accompanied by partial calcification.

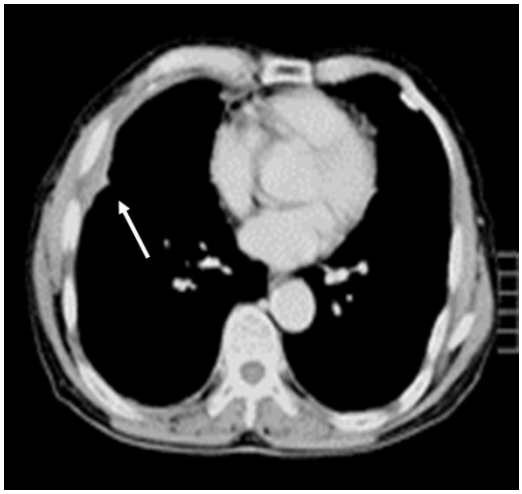

Fig. 9 Chest CT of the pleural mesothelioma case only indicating irregular protrusion to a portion of the right pleura. On the other hand, left pleura shows typical pleural plaque.

3-F. Pathology of Mesothelioma

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Introduction

Mesothelioma is a peculiar type of malignancy, which is highly related to asbestos-exposure, because 80 to 90% of the patients with mesothelioma have a history of occupational and/or environmental exposure to asbestos. Also, it is known that mesothelioma is a highly aggressive malignancy, and average survival of the patients has been reported to be only 13 months[1)]. Effective treatments including chemotherapy and radiotherapy have not been established so far, therefore, we have to diagnose it at the earlier stage when the radical surgery including pleuro-pneumonectomy can be performed.

The incidence of mesothelioma is lower rather than those of lung cancer[2)], so the clinicians as well as pathologists have fewer experience of diagnosis, especially at the earlier stage. When a small amount of pleurisy or ascites is found clinically with no significant thickening of pleura or peritoneum by the imagings, the diagnosis of mesothelioma is very difficult. Even if the biopsy specimen consisted of a small piece of tissue can be taken, its pathological diagnosis has so many difficulties, therefore, the comprehensive judgement including clinical examination, X-P or CT imaging as well as pathological findings can be led to an accurate diagnosis of mesothelioma[3)].
So in this article, the pathology of mesothelioma is presented on the basis of knowledges presented in the articles previously published. The aim is to achieve a good understanding on mesothelioma for many pathologists and clinicians.

Gross features

Mesothelioma is a malignancy located in the pleura, the peritoneum, the pericardium and the tunica vaginalis, all of which is normally lined by mesothelial cells.

In most of the mesothelioma, diffuse spread along the cavity is characteristic. In the case of pleura, it is supposed that there are small nodules in the parietal pleura at the intial stage and immediately tumor begins to spread along the pleural surface, and as the result diffuse pleural thickening associated with adhesion between parietal and visceral pleura is induced. Finally, mesothelioma encloses lung parenchyma, which is a classical gross feature of mesothelioma.

Occasionally (probably a few percent) mesothelioma forms a localized tumor with no diffuse spread pattern[4]. Mesothelioma chiefly extends in the pleural cavity, however sometimes it invades mainly to the chest wall, and as the result, it resembles to chest wall tumor. Those cases are unusual as mesothelioma, and have difficulties to diagnose mesothelioma on the basis of gross features, because the possibility that the tumor derives from chest wall (soft tissue or bone) or lung cannot be excluded[5].

In the case of peritoneum, most of mesothelioma show diffuse thickening of the peritoneum or disseminated small nodules in the peritoneum, and rarely a large nodule may be noticed.

Histological features

Mesothelial cell primarily has a potential of differentiation to an epithelioid cell lined at the serosal surface as well as a mesenchymal-spindle cell presented under the serosal lining. Therefore, mesothelioma has many histological subtypes, including carcinoma-like (epithelioid) tumor or sarcoma-like tumor (sarcomatoid) tumor, or mixed epithelioid and sarcomatoid tumor[6]. The histological classification of mesothelioma is shown in Table 1.

Epithelioid mesothelioma shows papillo-tubular pattern of mesothelial cell like-atypical cells in

the differentiated type, but in the less-differentiated type, solid growth of atypical epithelioid cells is dominant. Sometimes, the tumor cells produce abundant mucin in the cytoplasm and the mucin-pool background is prominent. This mucin is positive by alcian-blue stain and is digested by hyaluronidase, so those findings indicate this mucin is rich for hyaluronic acid. In the former time, this has been to be considered a diagnostic feature for mesothelioma, but in the present time, it is well known this is not a specific finding of mesothelioma[7].

Sarcomatoid mesothelioma shows a proliferation of spindle-shaped cells. Among these cells, collagen fibers exist more or less. Sometimes polygonal or anaplastic cells with abundant cytoplasm, which look like-epithelioid cell, are present. The differentiation between less-differentiated epithelioid mesothelioma and sarcomatoid mesothelioma is occasionally difficult. Also, by the H&E specimen only, the differentiation between sarcomatoid mesothelioma and true sarcoma is very difficult.

In desmoplastic mesothelioma, tumor consists of extensive fibro-collagenous tissue with occasional storiform pattern[8]. Tumor cells are scanty and associated with no significant cellular atypia in most of areas, however, highly-cellular areas with atypical cells are noted somewhere in the tumor. By examining small biopsy specimen, the diagnosis of desmoplastic mesothelioma is difficult. In those cases, the diagnosis by imaging, especially CT, can help and support the diagnosis of desmoplastic mesothelioma. The CT imaging shows diffuse pleural thickening associated with reduction of the affected pleural cavity. In the peritoneum, the case of desmoplastic mesothelioma is very rare[9].

Biphasic mesothelioma is diagnosed based on the mixed features of epithelioid and sarcomatoid mesothelioma. The fact that at least 10% of the total area shows another histology of mesothelioma is necessary for the diagnosis of biphasic mesothelioma as a general rule[6]. The proportion

of three major types is as follows; epithelioid mesothelioma, about 60%, sarcomatoid mesothelioma including several percent of desmoplastic mesothelioma, about 20%, and biphasic mesothelioma, about 20%.

Except for three major types mentioned above, many histological variants are known[6]. Lymphohistiocytoid mesothelioma is consisted of large histiocytoid cell with some features of mesothelial cells, associated with lymphocytic infiltration[10]. Deciduoid mesothelioma is consisted of large cells with abundant eosinophilic cytoplasm and centrally located-round nucleus like decidual cells[11]. The case purely consisted of deciduoid cells are very few, while, in most of the cases, the part of tumor shows this particular feature. Anaplastic mesothelioma has a character of nuclear pleomorphism with irregular cellular shape. These unusual type of mesothelioma necessiate a confirmation of phenotype as a mesothelial cell in tumor cells using immunohistochemistry.

On the other hand, well differentiation papillary mesothelioma(WDPM) shows papillary structures with fibrovascular core. The lining cells are well-differentiated with no significant atypia, therefore, the differential diagnosis from reactive mesothelioid hyperplasia is necessary. WDPM was originally reported in the pleura, and the recent cases reported in the articles include peritoneal cases[12]. The histological criteria of WDPM remains to be obscure, and the clinicopathological analysis of WDPM should be done using real WDPM cases.

Differential diagnosis

It is important to rember that there are many diseases to be differentiated when mesothelioma is diagnosed. Table 2 shows the list of other tumors or lesions which have to be differentiated.

In the pleura, the invasion of adenocarcinoma of the lung is common, occasionally associated with severe desmoplasia. Even if the primary carcinoma is small beneath the visceral pleura, a

broad extention along the pleura occurs. This type of tumor is called as pseudomesotheliomatous adenocarcinoma (or carcinoma)[13]. Also, lung carcinomas with sarcomatoid features are common, which are called as sarcomatoid carcinoma or pleomorphic carcinoma in the WHO classification. To make this diagnosis, the primary focus showing adenocarcinoma or squamous cell carcinoma has to be detected in the lung parenchyma. These differentiation should be based on the observation of H&E specimen, however, immunohistochemistry using specific antibodies, mentioned below, is very useful[14].

In the peritoneum, ovarian or peritoneal serous carcinoma is difficult to be differentiated[3]. On the basis of knowledges of embryology, the ovarian surface cell is very closed to mesothelial cell with common origin of coelomic epithelium[16]. So, immunohistochemistry for differentiation is necessary to ascertain phenotype of tumor cells[15].

Various types of sarcoma have to be differentiated from sarcomatoid mesothelioma in the peritoneum as well as pleura, although sarcomatoid mesothelioma of peritoneum is very rare[9].

For the dicision of treatment, the differentiation between benign lesion and mesothelioma is very important. In the pleura, misdiagnosis of desmoplastic mesothelioma occur very often[3]. Fibrous pleuritis sometimes shows diffuse pleural thickening and the histological examination on small pieces of tissue cannot be denied to be malignant. The important criteria about the differentiation is shown in the Table 3. The clinicians should give an abundant and perpendicularly-deep specimen to the pathologists. Among some criteria, zonation pattern is most important[16]. In fibrous pleuritis, superficial area (pleural surface-side) shows relatively higher cellularity. The spindle cells (fibroblastic cells) have mild to moderate nuclear atypia, and capillaries perpendicular to pleural surface are common. Also, inflammatory cells, mainly lymphocyte are mixed. However, the cellularity in the deep area (chest wall-side), is low with no

atypia among spindle cells. In general, collagen fibers run parallel to the surface. On the other hand, desmoplastic mesothelioma shows no uniformity in the running of collagen fibers, and it does haphazardly or forms a storiform-like pattern.

Useful immunohistochemistry for the differential diagnosis

As mentioned above, the diagnosis as mesothelioma is very difficult because of the differentiation from many malignancies and lesions. Many antibodies with higher specificity for a mesothelial cell have been developed, as well as many antibodies for detection of lung cancer, sarcoma or other malignancy. However, there is no single antibody, which can be definitely diagnosed as mesothelioma, therefore, the comprehensive judgement by the results using the combination of antibodies including positive or negative markers is required in general[3)]. The list of useful antibodies is shown in Table 4.

Among the markers for differentiation to mesothelial cell, calretinin is the most reliable, when the nucleus is strongly positive and the cytoplasm is weakly positive. The case with only cytoplasmic positivity is doubtful for mesothelioma[17)]. In the cytoplasmic membrane of mesothelial cell, D2-40, thrombomodulin or EMA is positive[18)], but in the case of less- differentiated epithelioid mesothelioma and sarcomatoid mesothelioma those markers are weakly-positive or negative. In spite of the degree of differentiation, the positivity of cytokeratin (CAM5.2 or AE1/AE3) is well preserved, even if in the case of sarcomatoid mesothelioma. It is very often that cytokeratin is only a positive marker in sarcomatoid mesothelioma[19)]. In those cases, many negative markers, which are specific for each of sarcoma, such as CD31 for endothelial marker, desmin for myogenic marker, and S-100 for nerve-sheath cell marker, have to be examined[20)].

The immunohistochemistry is useful for the differentiation between benign lesions and mesothelioma[21)]. Table 5 shows useful markers for differentiation between reactive mesothelial hyperplasia and epithelioid mesothelioma with no invasion. These findings are not uniform, and

therefore, comprehensive judgement is necessary. The antibody for differentiation between fibrous pleuritis and desmoplastic mesothelioma is limited. In the cases with fibrous pleuritis, desmin as well as cytokeratin is mostly positive in fibroblastic cells[22]. It is supposed that those spindle cells show the character of myofibroblastic cells as well as the phenotype of mesothelial cell[23]. On the other hand, desmin is negative in the desmoplastic mesothelioma, although α-smooth muscle actin (SMA) as well as cytokeratin are positive in tumor cells.

Conclusion

The pathological diagnosis as mesothelioma is very difficult, because many other malignancies or lesions should be differentiated. The immunohistochemistry using many antibodies as positive or negative markers of mesothelioma is useful, however the single result of immunohistochemistry is not enough to make an accurate diagnosis and the comprehensive judgement of the results is necessary.

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Table 1. Histological classification of mesothelioma

1. Epithelioid mesothelioma
2. Sarcomatoid mesothelioma
(1) Desmoplastic mesothelioma
3. Biphasic mesothelioma
4. Variants
(1) Lymphohistiocytoid mesothelioma
(2) Deciduoid mesothelioma
(3) Anaplastic mesothelioma
(4) Well differentiated papillary mesothelioma
(5) Others

Table 2. Differential diagnosis of mesothelioma

1. Epithelioid mesothelioma

   In the case of pleura:

   1) Adenocarcinoma of lung with invasion to pleura

   2) Metastatic adenocarcinoma involving pleura

   (ex:renal cell carcinoma)

   3) Reactive mesothelial hyperplasia

   In the case of peritoneum:

   1) Serous papillary adenocarcinoma of ovary

   2) Serous surface papillary adenocarcinoma of peritoneum

   3) Metastatic (disseminated) adenocarcinoma involving peritoneum

2. Sarcomatoid mesothelioma

   In the case of pleura:

   1) Sarcomatoid carcinoma of lung with invasion to pleura

   2) Sarcoma, pleura, lung or chest wall primary

   In the case of peritoneum:

   1) Sarcoma, peritoneum, GI tract or abdominal wall primary

3. Desmoplastic mesothelioma

   In the case of pleura:

   1) Fibrous pleuritis

4. Biphasic mesothelioma

   In the case of pleura:

   1) Carcinosarcoma or pulmonary blastoma of lung with invasion to pleura

   2) Biphasic synovial sarcoma, pleura primary or metastatic

   In the case of peritoneum:

   1) Carcinosarcoma of ovary or uterus with invasion to peritoneum

Table 3. The criteria for differentiation between fibrous pleuritis and desmoplastic mesothelioma

Findings	Fibrous pleuritis	Desmoplastic mesothelioma
Zonation pattern	Present	Absent
Capillary pattern	Rich, long perpendicular to pleural surface	Poor
Cellular atypia	Present in only superficial zone	Present in occasional cellular area
Collagen pattern	Parallel to the surface	Not parallel, occasional storiform pattern
Invasion to adipose tissue	Absent	Present
Inflammatory reaction in border to adipose tissue	Occasionally present	Absent

Table 4. Antibodies used in the immunohistochemistry for the differential diagnosis

Type of mesothelioma	Positive markers	Negative markers
		-In the case of pleura-
Epithelioid type	Calretinin (N*)	CEA (C)
	WT1 (N)	TTF-1 (N)
	D2-40 (M*)	NapsinA (C)
	Thrombomodulin (M)	Surfactant apoprotein A (C)
	EMA (M)	Ber-EP4 (M)
	CAM5.2 (C*)	MOC31 (M)
	AE1/AE3 (C)	-In the case of peritoneum-
		ER (N)
		Ber-EP4 (M)
		MOC31 (M)
Sarcomatoid type	CAM5.2 (C)	CD34
	AE1/AE3 (C)	CD31
	D2-40 (M)	Factor VIII
	WT-1 (N)	Desmin
	Calretinin (N)	h-caldesmon
		MyoD1
		Myogenin
		S-100
		Others (specific for each sarcoma)

*Location of positive findings

N: in the nucleus

M: in the cytoplasmic membrane

C: in the cytoplasm

Table 5. The markers (antibodies used in immunohistochemistry) useful for the differential diagnosis between reactive mesothelioma hyperplasia and epithelioid mesothelioma with no invasion

	Reactive mesothelial hyperplasia	Epithelioid mesothelioma with no invasion
Desmin	+	-
EMA	-	+
p53	-	+ or -
Glut-1	-	+
IMP3	-	+ or -
p16	+	-
CD146	-	+