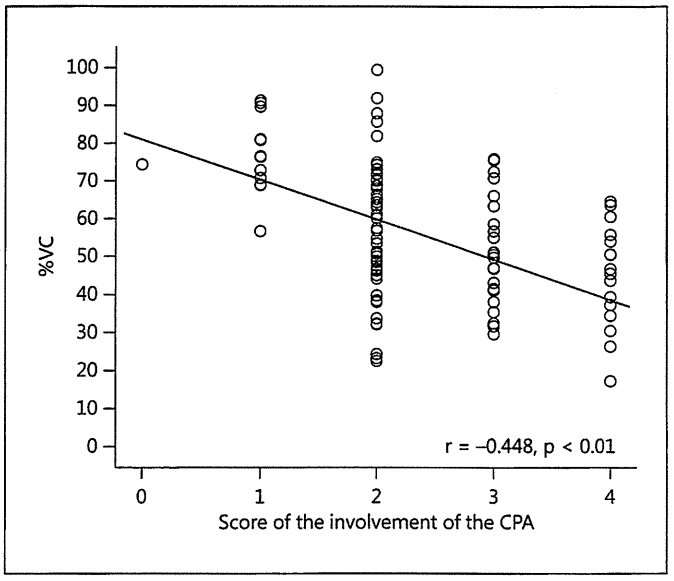

Fig. 4. The correlation between %VC and involvement of the CPA is shown by the correlation coefficient (r) and the regression line.

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 pleuroparenchymal 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

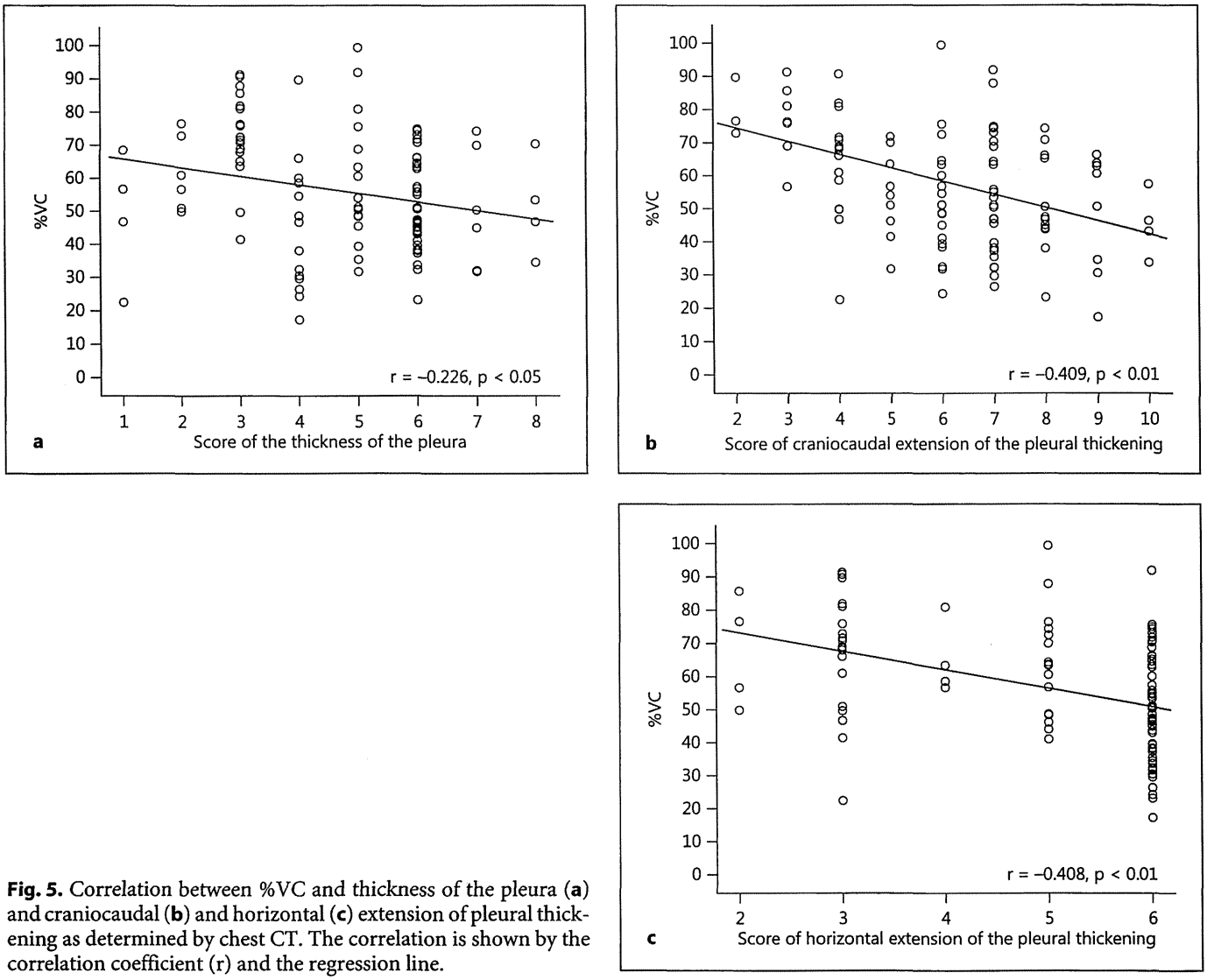

Fig. 5. Correlation between %VC and thickness of the pleura (**a**) and craniocaudal (**b**) and horizontal (**c**) extension of pleural thickening as determined by chest CT. The correlation is shown by the correlation coefficient (r) and the regression line.

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

report by McLoud et al. [6]. These results suggest that there is no obvious association between DPT and asbestosis. On the other hand, previous studies reported that a considerable number of patients with BAPE subsequently developed DPT [2, 3]. In the current study, half of the patients had a history of BAPE, and involvement of the CPA was shown in most of the cases with a history of BAPE. Thus, we believe that there is no direct association between asbestosis and DPT, but there is a strong link between BAPE and DPT.

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.

Acknowledgements

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Financial Disclosure and Conflicts of Interest

All authors have no financial/nonfinancial disclosures.

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Phrenic Nerve Paralysis as the Initial Presentation in Pleural Sarcomatoid Mesothelioma

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Key Words
Malignant pleural mesothelioma · Localized sarcomatoid mesothelioma · Phrenic nerve paralysis · Immunohistological examination

Abstract
A 74-year-old man was referred to our hospital because of persistent cough. A chest radiograph revealed an elevation of the right diaphragm. Computed tomography (CT) images revealed a small nodule localized on the right mediastinum. Five months later, the nodule had grown and was diagnosed as malignant pleural mesothelioma (MPM) by a CT-guided needle biopsy. The patient underwent combined chemotherapy, but the disease progressed rapidly and he passed away. On autopsy, microscopic findings and immunohistological examinations supported the diagnosis of sarcomatoid mesothelioma. Therefore, we diagnosed this rare case as localized sarcomatoid MPM showing phrenic nerve paralysis as an initial presentation.

Introduction

Malignant pleural mesothelioma (MPM) is a disease with poor prognosis. The median survival period is 7.7 months [1], and only an extrapleural pneumonectomy at an early stage can cure the disease. However, early detection of MPM is usually difficult, because its symptoms are nonspecific. In this study, we report a case of sarcomatoid MPM initially presenting as phrenic nerve paralysis.

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Case Report

A 74-year-old man was referred to our hospital because of persistent cough in October 2011. He had a history of prostate enlargement and gastric ulcer. He worked in the shipyard and had been exposed to asbestos for several years during his early twenties. He previously smoked 20 cigarettes per day for 24 years until he stopped smoking at the age of 44 years. A chest radiograph revealed an elevation of the right diaphragm (fig. 1a). Computed tomography (CT) images revealed a small nodule localized on the right mediastinum adjacent to the pericardial cavity (fig. 1b). Five months later, the nodule had developed into a massive tumor (fig. 1c). Finally, MPM was pathologically diagnosed by a CT-guided needle biopsy. The patient underwent combined chemotherapy with carboplatin and pemetrexed, but the disease progressed rapidly and caused superior vena cava syndrome. The patient then underwent palliative thoracic irradiation, but he passed away in June 2012. His family provided consent to conduct an autopsy.

On autopsy, a whitish solid tumor was detected on the right side of the mediastinum, and the tumor had infiltrated the parietal pleura, diaphragm, pericardial cavity, and aorta. The tumor had adhered strongly to the right upper lobe of the lung. Microscopically, the tumor consisted of spindle-shaped cells and collagen fibers, and had necrotic areas (fig. 2). Immunohistochemical examination revealed that the tumor cells were positive for calretinin, Wilms' tumor protein (WT-1), D2-40 and cytokeratin (AE1/AE3 and CAM 5.2), and negative for carcinoembryonic antigen (CEA) and thyroid transcription factor (TTF-1) (fig. 3). Diagnosis of sarcomatoid MPM was confirmed on the basis of these findings.

Discussion

MPM is classified into 2 types: diffused and localized. Localized MPM is uncommon and presents as a microscopic tumor characterized by a sharp circumscription of the serosal membrane without any evidence of diffused spread [2]. In the present case, a small localized tumor on the right chest wall was detected in October 2011. We suspected that the right phrenic nerve was involved with the tumor resulting in right phrenic nerve paralysis. At the beginning of the course, the lesion was localized. To our knowledge, this is the first report of MPM presenting phrenic nerve paralysis as an initial manifestation.

In order to confirm the diagnosis of sarcomatoid MPM, it is essential to distinguish it from lung sarcomatoid carcinoma (LSC). LSC is defined as an epithelial carcinoma consisting of spindle- or polygonal-shaped tumor cells, and is often a combination of the characteristics of adenocarcinoma or squamous cell carcinoma. It is difficult to differentiate sarcomatoid MPM from LSC; however, immunohistochemistry has proven to be useful in this regard [3]. Takeshima et al. [4] reported that the well-known mesothelial marker D2-40 was useful in differentiating sarcomatoid MPM from the sarcomatoid component of LSC. In our case, tumor cells were positive for both mesenchymal and epithelial markers, including D2-40, and negative for CEA and TTF-1. In addition, the radiological findings in the current case indicated that the primary lesion was apparently not in the lung. Therefore, a final diagnosis of MPM could be ascertained.

In conclusion, we report here a case of localized sarcomatoid MPM showing phrenic nerve paralysis as an initial presentation. It is important to perform immunohistochemical examination with sufficient materials to diagnose sarcomatoid MPM.

Disclosure Statement

The authors state that they have no conflict of interest.

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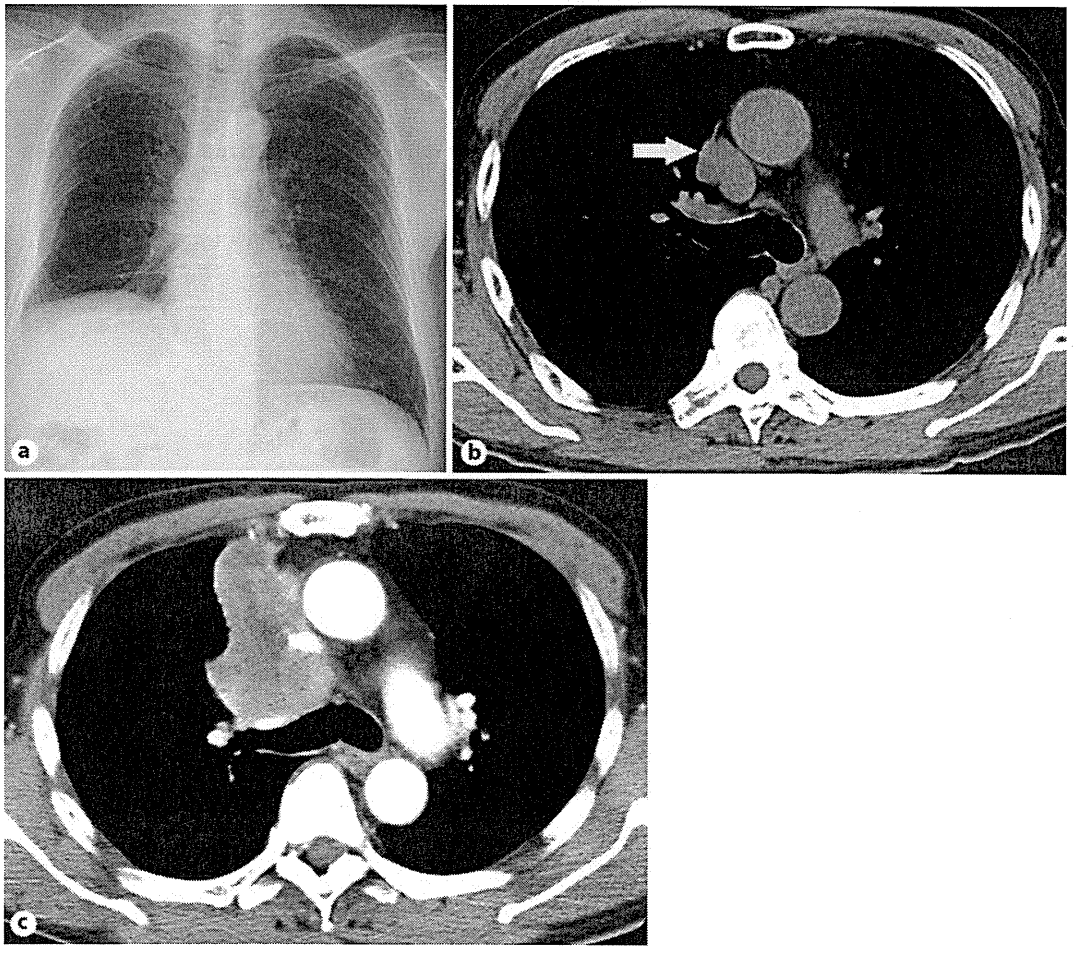

Fig. 1. A chest radiograph taken in October 2011 revealed elevation of the right diaphragm (**a**). CT images revealed a small nodule localized on the right mediastinum adjacent to the pericardial cavity (**b**). The nodule had developed into a massive tumor in March 2012 (**c**).

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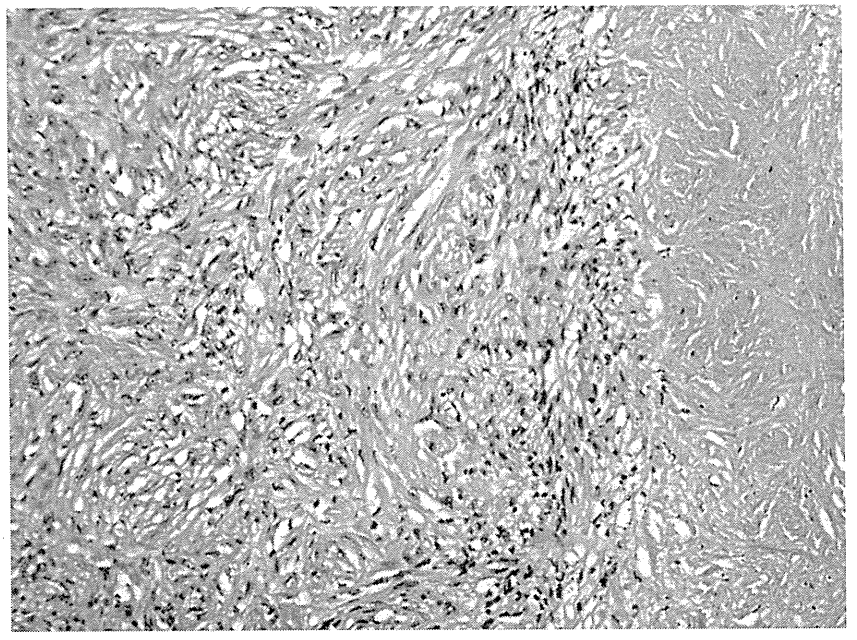

Fig. 2. During autopsy, histopathology of the mediastinal tumor revealed proliferation of spindle-shaped cells and collagen fibers with necrotic areas (hematoxylin and eosin stain).

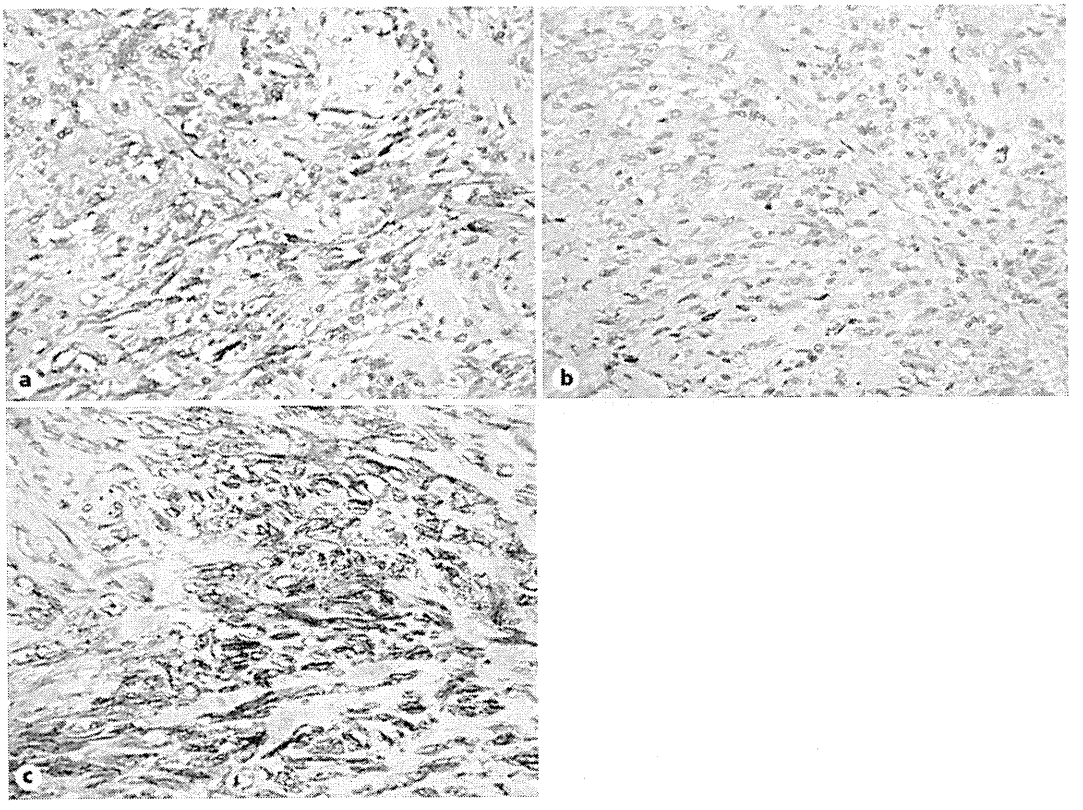

Fig. 3. Immunohistology revealed positive staining for calretinin (**a**), WT-1 (**b**), and D2-40 (**c**).

（肺癌．2014;54:767-771）

ORIGINAL ARTICLE

胸膜中皮腫を中心とした胸水ヒアルロン酸に関する症例調査

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Clinical Investigation of Hyaluronic Acid in Pleural Effusion

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ABSTRACT —— ***Objective.*** We evaluated the usefulness of assessing the hyaluronic acid (HA) level in pleural fluid for the differential diagnosis of malignant pleural mesothelioma (MPM). ***Methods.*** The data regarding the pleural fluid HA concentration were retrospectively collected from Rosai Hospitals and related facilities in Japan. ***Results.*** A total of 860 cases were examined, which included 139 cases of MPM, 76 of benign asbestos pleurisy (BAP), 324 of lung cancer (LC), 74 of other malignant conditions (OMC), 120 of infectious pleuritis (IP), 11 of collagen diseases (CD) and 116 cases had other conditions. The median (range) HA concentrations in the pleural fluid were 76,650 (211-33,000,000) ng/ml in the MPM cases, 28,000 (165-152,000) ng/ml in the BAP, 19,000 (800-134,000) ng/ml in the LC, 12,200 (900-157,200) ng/ml in the OMC, 23,400 (900-230,000) ng/ml in the IP, 17,800 (9,000-80,800) ng/ml in the CD and 11,575 (23-90,000) ng/ml in patients with other diseases. The HA levels were significantly higher in MPM cases than in the patients with other diseases. The receiver operating characteristics (ROC) analysis revealed an area under the ROC curve value of 0.818 (95% confidence interval, 0.772-0.864) for the differential diagnosis of MPM. With a cut-off value of 100,000 ng/ml, the sensitivity was 44.5% and the specificity was 98.2%. These results indicate that MPM should be strongly suspected in cases with an elevated concentration of pleural fluid HA. ***Conclusion.*** The pleural fluid HA concentrations might be useful for the differential diagnosis of MPM.

(*JJLC.* 2014;54:767-771)

KEY WORDS —— Asbestos, Hyaluronic acid, Mesothelioma, Pleural effusion, Tumor marker

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要旨 —— **目的．** 胸膜中皮腫の鑑別診断における胸水ヒアルロン酸の有用性を明らかにする．**方法．** 診療録より胸水ヒアルロン酸濃度を抽出し比較検討を行った．**結果．** 計860例分の胸水ヒアルロン酸濃度が抽出された．疾患の内訳は胸膜中皮腫139例，良性石綿胸水76例，肺癌324例，他臓器の悪性腫瘍74例，感染性胸膜炎120例，膠原病11例，その他116例であり，ヒアルロン酸濃度の中央値は胸膜中皮腫76,650 ng/ml，良性石綿胸水28,000 ng/ml，肺癌19,000 ng/ml，他臓器の悪性腫瘍12,200 ng/ml，感染性胸膜炎23,400 ng/ml，膠原病17,800 ng/ml，その他11,575 ng/mlであった．胸膜中皮腫における胸水ヒアルロン酸濃度はその他の疾患に比べ有意に高

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値であり，カットオフ値を 100,000 ng/ml としたところ，胸膜中皮腫の診断における感度は 44.5%，特異度は 98.2% であった．**結論**．胸水中のヒアルロン酸濃度は，胸膜中皮腫の鑑別診断の一助となり得る．

索引用語 —— アスベスト，ヒアルロン酸，中皮腫，胸水，腫瘍マーカー

緒　言

胸膜中皮腫は胸膜の中皮細胞由来の予後不良な悪性腫瘍であり，[1] 石綿ばく露との関連が深い．[2,3] 胸膜中皮腫の確定診断は腫瘍組織からの生検組織を用いた病理診断に基づく．腫瘍組織を得るための最も有用な検査は胸腔鏡検査であり，中皮腫診断におけるゴールド・スタンダードといえる．胸腔鏡検査は，特に局所麻酔下にて施行される場合比較的侵襲は少ないものの，高齢者や合併症を有する患者の場合は本検査の適応から除外されるケースがしばしば見られる．このように，臨床的に胸膜中皮腫が疑われるものの確定診断が得られない，という症例は少なくない．

胸膜中皮腫においては診断時にその 70% 以上の症例で胸水貯留を呈する．[4] 胸水は臨床現場において比較的容易に採取することが可能であり，鑑別診断において重要な意味合いを持つが，胸水細胞診にて中皮腫の確定診断に達する症例は少なく，中皮腫のうち約 30% にとどまるといわれている．[5]

いわゆる分子生物学的マーカーは，各種の悪性腫瘍において高発現している分子の総称であり，その一部はある種の悪性腫瘍の補助診断や治療効果のモニタリングに臨床応用されている．胸膜中皮腫においてもこれまでにいくつかの分子マーカーが着目され，診断のための有用性について検討されている．なかでもヒアルロン酸は，以前より胸膜中皮腫の胸水中に高濃度で存在することが知られており，[6-8] 細胞外マトリクスの主成分として中皮腫細胞の移動や発育に重要な役割を果たしている．Pettersson らの報告では，カットオフ値を 100,000 ng/ml とした場合，胸膜中皮腫では 73% が陽性，炎症性胸膜炎で 23% が陽性であったが，その他の悪性腫瘍や心不全では 1 例も陽性例は認められなかったと報告している．[6] 悪性中皮腫以外でも，ウイルス性胸膜炎や関節リウマチ患者の胸水中のヒアルロン酸濃度が高値を呈するとの報告がある．[7] この他，頻度は低いものの癌性胸膜炎，良性石綿胸水，心不全でも同様の報告がある．[8] われわれはこれまでに，単一施設における後ろ向きの検討を行い他疾患との鑑別，および胸膜中皮腫の診断における胸水ヒアルロン酸の有用性について検討した．[9] 本研究では，多施設より胸膜中皮腫症例や他の胸水貯留症例を収集し，胸水ヒアルロン酸濃度を胸膜中皮腫診断の指標として用いる意義について検証した．

研究対象，方法

2001 年 8 月から 2010 年 10 月までの間に，全国各労災病院および本研究における研究協力施設において，胸水貯留をきたし，診断目的にて胸水採取を行われた症例を後ろ向きに集積し，診療録より胸水中のヒアルロン酸濃度を抽出した．ヒアルロン酸濃度は各施設より委託された外部検査施設においてラテックス凝集法にて測定されていた．これらの症例を胸膜中皮腫，良性石綿胸水，肺癌，胸膜中皮腫と肺癌以外の悪性腫瘍，感染性胸膜炎，膠原病，その他の疾患に分類し比較検討した．また可能な限り carcinoembryonic antigen（CEA），アデノシンデアミナーゼ（ADA）値についてもデータを収集した．データの収集に当たっては，厚生労働省の「疫学研究に関する倫理指針」を遵守し，労働者健康福祉機構が定める倫理審査手順に沿って同機構が妥当性の評価を行った．統計学的手法としては，多群間の比較には Kruskal-Wallis 検定を用い，独立した 2 群間の比較には Mann-Whitney 検定を用いた．

結　果

上記の期間中に胸水中のヒアルロン酸濃度が測定され，本研究のために集積された症例は 860 例であった．各施設における疾患別の症例集積数を Table 1 に示す．疾患群毎の内訳は，胸膜中皮腫 139 例，良性石綿胸水 76 例，肺癌 324 例，他臓器の悪性腫瘍の胸腔内転移 74 例，感染性胸膜炎 120 例，膠原病 11 例，その他の疾患 116 例である．その他の疾患の大半はうっ血性心不全，肝硬変が占めた．

胸水中のヒアルロン酸濃度の中央値（範囲）は，胸膜中皮腫 76,650 ng/ml（211～33,000,000 ng/ml），良性石綿胸水 28,000 ng/ml（165～152,000 ng/ml），肺癌 19,000 ng/ml（800～134,000 ng/ml），他臓器の悪性腫瘍の胸腔内転移 12,200 ng/ml（900～157,200 ng/ml），感染性胸膜炎 23,400 ng/ml（900～230,000 ng/ml），膠原病 17,800 ng/ml（9,000～80,800 ng/ml），その他の疾患では 11,575 ng/ml（23～90,000 ng/ml）であった（Figure 1）．胸膜中皮腫とそれ以外の疾患において Kruskal-Wallis 検定を用いて比較したところ，明らかな有意差が認められた（$P<0.001$）．Mann-Whitney 検定を用いた 2 群間の比較では，胸膜中

Table 1. The Numbers of Cases Collected at Each Facility

	n	Disease						
		MPM*	BAPE†	LC‡	OMC§	IP‖	CD¶	Others
Okayama Rosai Hospital	336	51	45	81	22	69	6	62
Yamaguchi-Ube Medical Center	183	27	15	88	10	23	5	15
Shikoku Cancer Center	160	12	3	92	32	5	0	16
Kagawa Rosai Hospital	109	5	9	42	9	23	0	21
Hokkaido University Hospital	32	10	0	20	1	0	0	1
Kanto Rosai Hospital	6	6	0	0	0	0	0	0
Tokyo Rosai Hospital	6	5	1	0	0	0	0	0
Chiba Rosai Hospital	5	5	0	0	0	0	0	0
Asahi Rosai Hospital	5	3	2	0	0	0	0	0
Tohoku Rosai Hospital	4	4	0	0	0	0	0	0
Hokkaido Chuo Rosai Hospital	3	3	0	0	0	0	0	0
Toyama Rosai Hospital	3	3	0	0	0	0	0	0
Yamaguchi Rosai Hospital	3	3	0	0	0	0	0	0
Nagasaki Rosai Hospital	3	2	1	0	0	0	0	0
Kashima Rosai Hospital	1	0	0	0	0	0	0	1
Hamamatsu Rosai Hospital	1	0	0	1	0	0	0	0
Total	860	139	76	324	74	120	11	116

*malignant pleural mesothelioma, †benign asbestos pleural effusion, ‡lung cancer, §other malignant condition, ‖infectious pleuritis, ¶collagen disease.

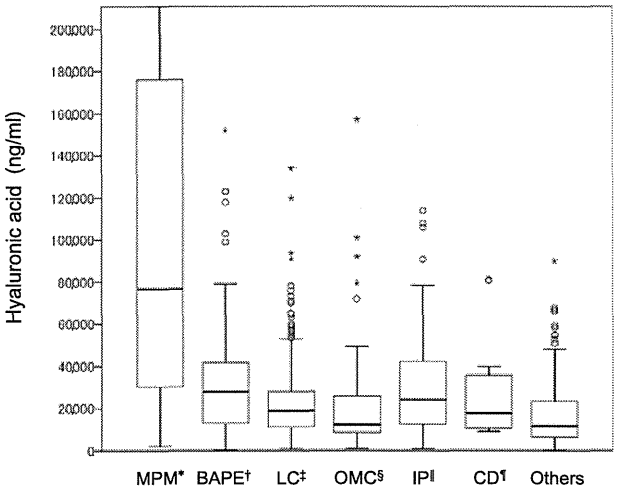

Figure 1. Comparison of the hyaluronic acid concentrations in pleural fluid. *malignant pleural mesothelioma, †benign asbestos pleural effusion, ‡lung cancer, §other malignant condition, ‖infectious pleuritis, ¶collagen disease.

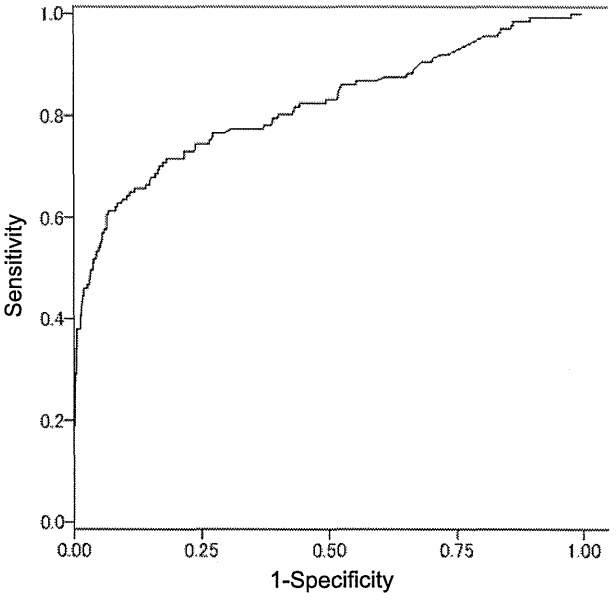

Figure 2. The results of the receiver operating characteristics analysis of the use of the hyaluronic acid concentration for the differential diagnosis of malignant pleural mesothelioma.

皮腫と他の疾患群の間には明らかな有意差が認められた．次に胸膜中皮腫とそれ以外の症例について，receiver operating characteristics（ROC）曲線を作成し検討したところ，area under the ROC curve（AUC）値は0.818（95%信頼区間0.772～0.864）であった（Figure 2）．Youden's index[10]を用いて得られた最適のカットオフ値は59,650 ng/mlであり，その際の胸膜中皮腫の診断における感度は61.3%，特異度は93.1%であった．またカットオフ値を100,000 ng/ml, 150,000 ng/ml, 200,000 ng/mlとした場合の感度はそれぞれ44.5%，29.2%，22.6%であり，特異度はそれぞれ98.2%，99.6%，99.9%であった．

胸水中のヒアルロン酸濃度が100,000 ng/ml以上で

Table 2. The Features of the Cases Other Than Malignant Pleural Mesothelioma with a Hyaluronic Acid Concentration More Than 100,000 ng/ml

Case	Disease	Hyaluronic acid (ng/ml)	CEA[§] (ng/ml)	ADA[¶] (IU/l)
1	Pharyngeal cancer	101,000	83.1	15.6
2	BAPE*	103,000	0.9	30.2
3	Pleuritis	106,000	2.2	16.9
4	Tbc[†]	108,000	3.2	123.4
5	Tbc	114,000	1.8	114.5
6	BAPE	118,000	1.5	13.6
7	LC[‡]	120,000	2.1	16.1
8	BAPE	123,000	3.1	17.7
9	BAPE	123,000	0.9	18.7
10	LC	134,000	13979.4	149.0
11	BAPE	152,000	0.9	21.5
12	Renal cancer	157,200	ND[‖]	32.3
13	Pyothorax	230,000	4.8	ND

*benign asbestos pleural effusion, [†]tuberculous pleuritis, [‡]lung cancer, [§]carcinoembryonic antigen, [‖]not determined, [¶]adenosine deaminase.

あった症例は860例中74例で，全体の8.6%であった．これらの74例のうち61例（82.4%）は胸膜中皮腫であり，胸膜中皮腫以外で100,000 ng/ml以上であった例はTable 2に示す13例（全体の1.5%）であり，内訳は良性石綿胸水が5例，結核性胸膜炎が2例，肺癌が2例，咽頭癌，腎癌の胸腔内転移がそれぞれ1例ずつ，結核以外の感染性胸膜炎が2例（膿胸の1例を含む）であった．このうち，結核性胸膜炎の2例は，Table 2に示すように胸水中のADA値がそれぞれ123.4 IU/l，114.5 IU/lと著明な高値を呈しており，またいずれの症例においても発熱などの感染症状に加え，PCR法による胸水中の遺伝子検索にて結核菌の存在が証明されていた．また肺癌の2例は胸水細胞診において疑義の余地なく肺癌と診断されていた．このうち1例はTable 2に示すように胸水中のCEA値が著明な高値を呈していた．腎癌の症例についても臨床経過より診断には疑義の余地はなかった．感染性胸膜炎と診断されている2例は，いずれも発熱などの感染症状や炎症反応などを呈し，特に膿胸の症例は特異的な胸水の性状などから臨床診断に疑義の余地は見られなかった．それ以外の咽頭癌の1例と良性石綿胸水の5例については臨床経過や画像を含めた検査所見からの診断は困難であり，診断の確定には胸腔鏡下胸膜生検を要した．

考　察

われわれは最近，岡山労災病院における胸膜中皮腫並びに他の疾患における胸水中のヒアルロン酸濃度を中心に解析した．その結果，1)胸水中のヒアルロン酸濃度が100,000 ng/mlを上回る場合，その大半の症例は胸膜中皮腫であること，2)中皮腫以外の疾患である場合，他の臨床徴候，画像所見，あるいは胸水の性状や抗酸菌を含む細菌学的な検討を加えることで，肺癌や結核性胸膜炎を含めた感染性胸膜炎の大半は臨床診断が可能であること，3)良性石綿胸水において胸水中のヒアルロン酸濃度が100,000 ng/mlを上回る症例が散見されること，を報告した.[9] ただその際の検討では特に胸膜中皮腫以外の疾患の症例集積数は十分とはいえず，多施設，多症例における検討が必要と思われた．本研究では前述の岡山労災病院のデータに加え全国の各労災病院，および北海道大学病院，国立病院機構四国がんセンター，国立病院機構山口宇部医療センターを中心にデータを加え，860例に及ぶデータが集積された．各施設の特徴を反映して疾患の分布に多少の違いがあるものの，ある程度実臨床を反映した疾患の分布といえると思われる．その結果今回の検討でも，胸膜中皮腫では他の胸水を呈する疾患に比べ明らかにヒアルロン酸濃度は高値を呈しており，胸膜中皮腫の診断マーカーとしての有用性が改めて示唆された．実臨床において胸膜中皮腫を強く疑う目安の数値とされている100,000 ng/mlをカットオフ値とした場合，胸膜中皮腫の診断における感度は44.5%，特異度は98.2%に達していた．このことから，胸水ヒアルロン酸濃度が高値である場合，まず胸膜中皮腫を念頭に置く必要があることが改めて示されたと考える．

胸膜中皮腫の確定診断は病理診断によるものであり，胸腔鏡などの検査により十分量の腫瘍組織を元に各種の免疫組織学的検索を踏まえた上で診断されるべきであるが，胸膜中皮腫患者の多くは過去の石綿ばく露から30年から40年に及ぶ潜伏期間を経て発症することが多い

ため，高齢であることが多く，合併症などのため侵襲を伴う検査が見送られるケースが少なからずある．今回の検討において，胸水ヒアルロン酸濃度が100,000 ng/ml以上であった場合，胸膜中皮腫である確率は74例のうち61例で82.4%である．このカットオフ値で，ヒアルロン酸値のみで中皮腫と診断した場合，13例が偽陽性，つまり中皮腫でないのに中皮腫と診断されることとなる．しかしTable 2に示したこれらの症例のうち，約半数は発熱などの臨床徴候や検査所見，画像所見より臨床診断が比較的容易になされている．ただこれらの症例を除く下咽頭癌の1例と良性石綿胸水の5例については，臨床経過や画像を含めた検査所見からの診断は困難であり，診断の確定には胸腔鏡下胸膜生検を要した．なおこれらの良性石綿胸水の5例は，その後の経過観察においても胸膜中皮腫の発症は認められていない．この結果より，胸水中のヒアルロン酸濃度に一般臨床において通常施行されうる検査所見を加えることにより，大半の症例は臨床診断に到達しうるといえる．具体的には，発熱などの感染症状の有無，血液検査における白血球数，CRP値などの炎症所見の有無，画像所見，さらには胸水の性状，細胞診に加え一般細菌や抗酸菌の塗抹，培養，および結核菌群核酸同定（PCR法）などがあげられる．さらに他の胸水マーカーとしてCEA，ADAなどもその一助となり得る．たとえばTable 2に示した咽頭癌の1例と肺癌の2例のうちの1例では胸水CEA値が著明な高値を呈しており，胸膜中皮腫以外の疾患を示唆する所見といえる．またADAは結核性胸膜炎において高値を呈することが多く，一般的に40 IU/*l*を上回る場合は結核性胸膜炎である可能性が高いといわれているが，[11,12] 今回の検討ではそれ以外の疾患群においても40 IU/*l*を上回る症例も散見されており，鑑別診断には慎重である必要がある．

これまで述べてきたように，胸水中のヒアルロン酸濃度は胸膜中皮腫の鑑別診断において有用である．実臨床における有用性のみならず，石綿健康被害救済制度などの運用において，高齢や合併症など何らかの理由により病理診断が得られていないものの胸水中のヒアルロン酸濃度が高値を呈する症例において，1)胸膜の腫瘍性肥厚，不整な肥厚など画像的に胸膜中皮腫として矛盾しないこと，2)発熱や炎症反応など，明らかに感染症を疑わせる所見がないこと，3)CEAやADAが極端な高値でないことなどを確認し，さらに臨床経過などを十分吟味し胸膜中皮腫を認定していくことも考慮すべきと思われる．ただ本来は胸膜中皮腫の診断は病理診断によるものであり，胸腔鏡などの検査により十分量の腫瘍組織を元に各種の免疫組織学的検索を踏まえた上で診断されるべきである．

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CASE REPORT

Simultaneous occurrence of bilateral malignant pleural mesothelioma

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Abstract A 59-year-old man was referred to our hospital because of left pleural effusion detected at a regular medical checkup. A chest X-ray showed left pleural effusion. A thoracoscopic pleural biopsy specimen from the left side gave a pathological diagnosis of malignant pleural mesothelioma (MPM), epithelioid type. Then thoracoscopic exploration of the right pleura was performed because of fluorodeoxyglucose accumulation along the right dorsal pleura. Thoracoscopic exploration of the right indicated no visible tumor formation, but a pleural biopsy specimen revealed epithelioid MPM. In this case, MPM in each thorax was confined to the parietal pleura and was classified as stage I. We therefore suggest that MPM may develop simultaneously in both thoraxes.

Keywords Mesothelioma · Asbestos · Thoracoscopy · PET

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor highly associated with asbestos exposure [1]. MPM often progresses from one side of the thorax to the other during the clinical course of the disease [2]. We present an unusual case of MPM that was considered to consist of simultaneous occurrence in both thoraxes.

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Case report

A 59-year-old man was referred to our hospital because of left pleural effusion detected at a regular medical checkup. He had smoked a bit and was exposed to asbestos for 28 years while working in the construction industry. A chest X-ray showed left pleural effusion. Computed tomography (CT) demonstrated no irregular pleural thickening or tumor on either side of the pleura, and fluorodeoxyglucose positron emission tomography (PET) showed a mild accumulation of fluorodeoxyglucose (FDG) along the right dorsal pleura, with a standardized uptake value (SUV) of 1.9 (Fig. 1). The hyaluronic acid level in the fluid was 130430 ng/mL, and cytological examination revealed MPM cells. A thoracoscopic pleural biopsy specimen from the left revealed atypical mesothelial cells with invasion into adjacent fat layers. Immunohistochemical analyses demonstrated that the tumor cells were positive for calretinin, Wilms' tumor 1, and CAM5.2, and negative for carcinoembryonic antigen and thyroid transcription factor 1 (Fig. 2). Based on these findings, the patient was diagnosed with MPM, epithelioid type.

Extrapleural pneumonectomy was planned, but prior to the operation, thoracoscopic exploration of the right pleura was undergone because of FDG accumulation along the right dorsal pleura. Thoracoscopic exploration of the right indicated no visible tumor formation, but a pleural biopsy specimen revealed that enlarged atypical mesothelial cells had formed a pseudoglandular structure and had partially

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invaded adjacent fat layers. These observations confirmed the diagnosis of epithelioid MPM. Fluorescence in situ hybridization demonstrated no homozygous deletion of p16 in either specimen. CT and PET demonstrated no mediastinal lymphadenopathy or distant metastasis. The patient has been treated with systemic chemotherapy consisting of cisplatin and pemetrexed.

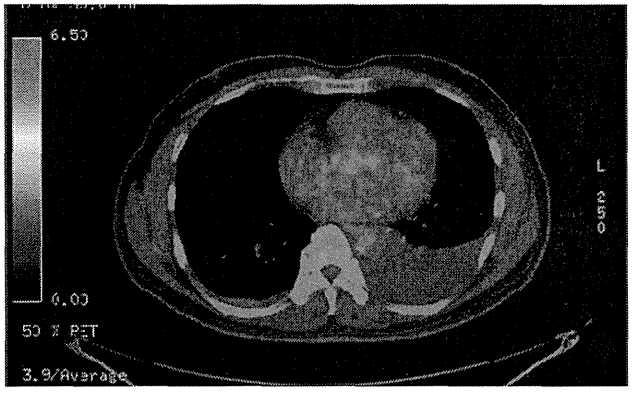

Fig. 1 PET–CT revealed left pleural effusion and mild accumulation of fluorodeoxyglucose along the right dorsal pleura

Discussion

In the current case, thoracoscopic exploration revealed MPM in both sides of the pleura. MPM often progresses from one side of the pleura to the other in the advanced stage of the disease. However, in this case, each lesion was confined to the parietal pleura and was classified as stage I based on TNM classification by the International Mesothelioma Interest Group. We therefore suggest that MPM developed simultaneously in both thoraxes, although the tumor cells exhibited similar characteristics upon immunohistochemistry and fluorescence in situ hybridization. In this case, CT did not demonstrate irregular pleural thickening or tumor, but fluorodeoxyglucose accumulation suggested disease involvement, and thoracoscopic exploration provided the diagnosis of MPM. Duysinx et al. [3] reported that PET may play a role in differentiating benign and malignant pleural diseases. In our case, PET showed an accumulation of FDG only on the right side, and SUV was fairly low. We have no clear explanation, but we suggest that the amount of tumor on the left is very limited, and it is very small even on the right side, which is why PET showed an accumulation only on the right side with low SUV. The current case demonstrates the utility of PET–CT

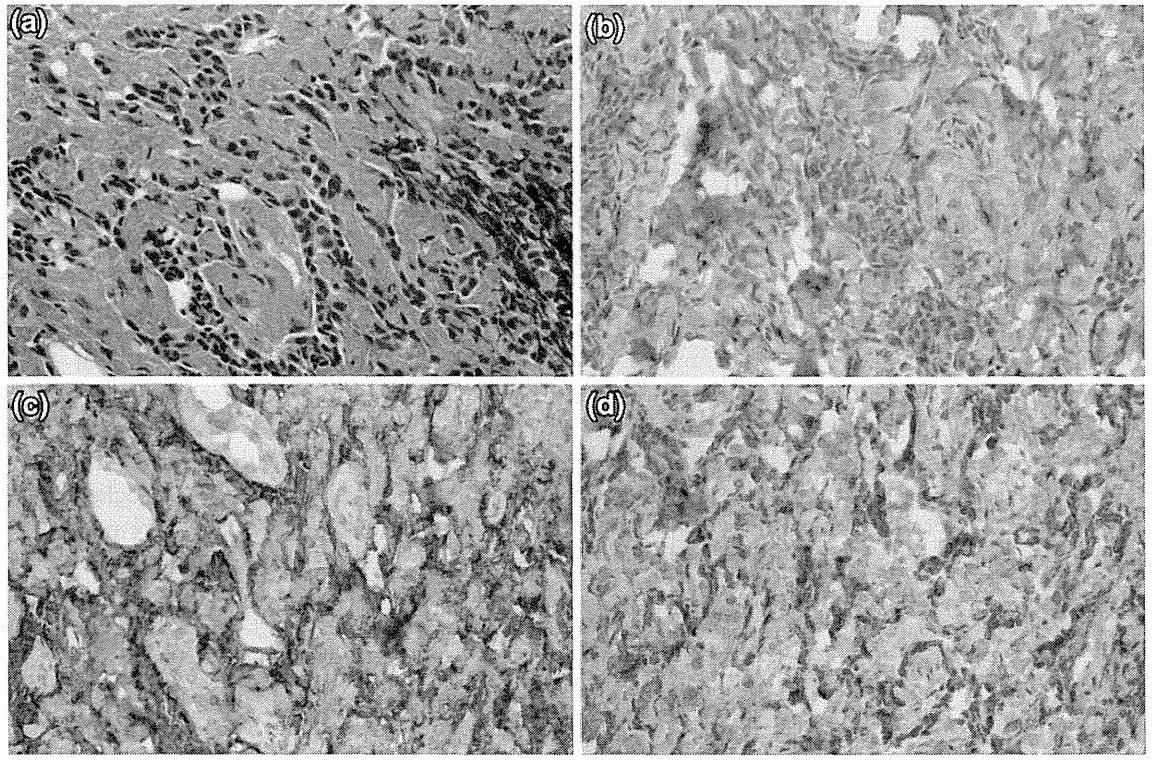

Fig. 2 **a** Microscopic examination of the biopsy specimen showed atypical mesothelial cells consistent with malignant mesothelioma (hematoxylin and eosin stain, ×40). Immunohistochemical analysis indicated positive expression of **b** calretinin (×40), **c** D2-40 (×40), and **d** CAM5.2 (×40)

and thoracoscopic exploration for early detection of MPM. Clinical phase I or II MPM cases may be candidates for extrapleural pneumonectomy, but bilateral onset rendered this technique unsuitable in this case. The clinical implications of less-invasive surgical procedures such as pleural decortication [4] may merit consideration in such situations.

In conclusion, we reported an unusual case of MPM considered as a simultaneous occurrence of bilateral thoraxes.

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Conflict of interest None declared.

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Extrapulmonary small cell carcinoma mimicking malignant pleural mesothelioma

We report a case with a history of occupational asbestos exposure in which malignant pleural mesothelioma (MPM) was suspected clinically and diagnosed postmortem as pleural involvement of extrapulmonary small cell carcinoma (SCC). An 85-year-old man with a 65 pack-year history of smoking was referred to our hospital in June 2011. The patient had been exposed to asbestos in the iron production industry over the course of 30 years, and an irregular thickening of the right pleura was observed on chest CT at a medical check-up. The patient had a history of chronic hepatitis C and had been undergone transurethral resection for urothelial bladder cancer five times since 2006. Chest CT revealed neoplastic thickening of the right pleura, which had grown over 6 months (figure 1). The CT scan demonstrated bilateral pleural plaques, but no mass-like lesion in other organs, including the lungs, or mediastinal lymphadenopathy. The patient was suspected as having MPM and scheduled for thoracoscopic pleural biopsy, but his general condition worsened rapidly and he died due to pneumonia in August 2011. Autopsy revealed multiple tumours on the right chest wall, as well as multiple tumours in the bilateral lung, liver, pancreas and prostate, which were not detected in the CT scan in July 2011. H&E staining revealed similar histology for the tumours on the lung and pleura; the tumour cells were small with an increased cytoplasm to nucleus ratio. Immunohistochemical analysis revealed that these tumour cells were positive for CD56 (figure 2) but negative for chromogranin, synaptophysin, thyroid transcription factor (TTF)-1 and calretinin. Based on these findings, the patient was diagnosed with SCC.

In addition, transitional cell carcinoma was detected in the bladder by postmortem microscopic analysis, suggesting residual or recurrent bladder cancer. The patient was considered as having extrapulmonary SCC because no mass-like lesion was found in the lung antemortem, and detailed pathological examination revealed that the SCC component was detected in

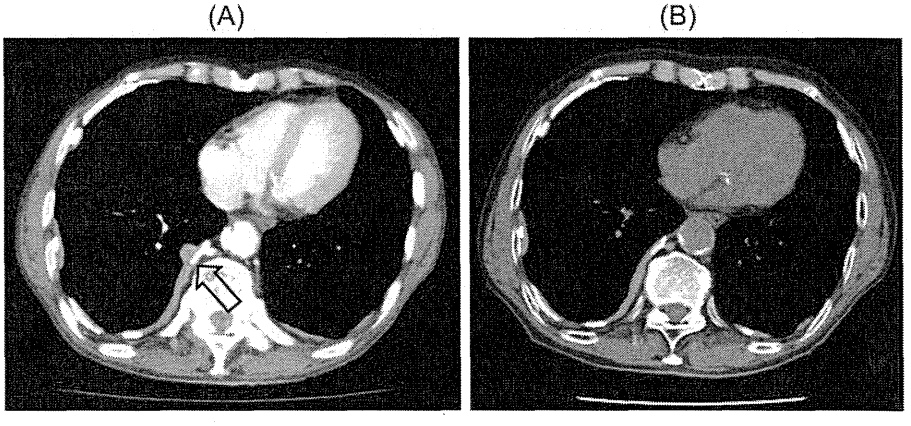

Figure 1 (A) Chest CT at initial presentation revealed neoplastic thickening of the right pleura. (B) The neoplastic lesion was not detected in the CT scan 6 months prior.

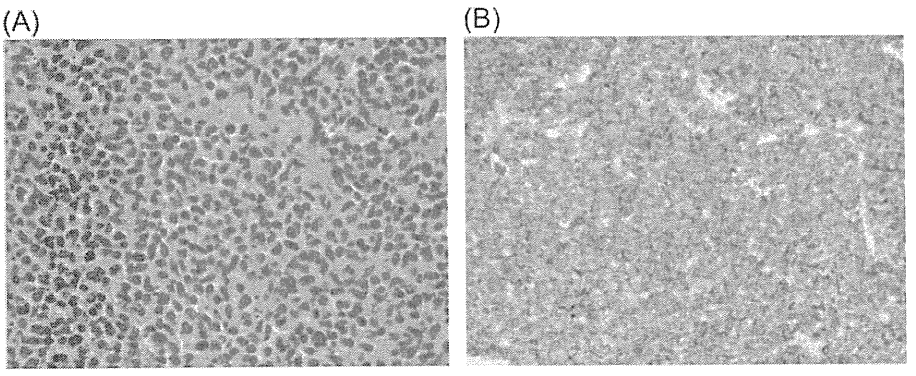

Figure 2 Pathological findings for the pleural tumour. (A) H&E staining revealed that the tumour cells were small with an increased cytoplasm to nucleus ratio. (B) Immunohistochemical analysis revealed that these tumour cells were positive for CD56.

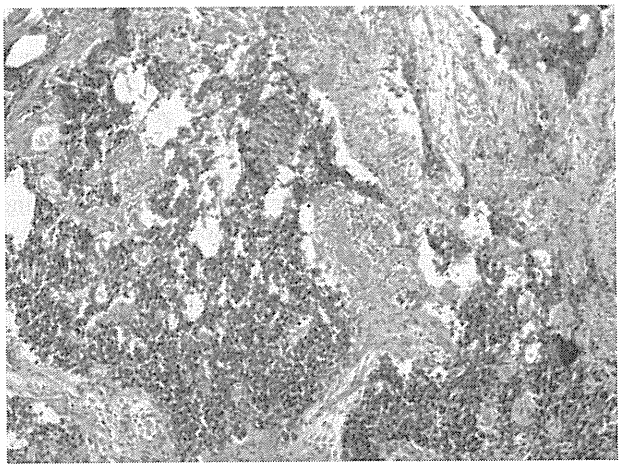

Figure 3 The small cell carcinoma component was detected in the resected bladder specimen in 2006.

the bladder specimen resected in 2006 (figure 3). The bladder specimen was partially positive for CD56, and negative for chromogranin and synaptophysin. Finally, the patient was diagnosed with recurrence of SCC originating in the bladder.

The current case was clinically suspected as MPM because the patient had a history of occupational asbestos exposure and the CT scan demonstrated neoplastic pleural thickening. Autopsy gave the postmortem diagnosis of SCC. We think that the SCC in the current case was extrapulmonary in origin based on the following. First, neoplastic pleural thickening was the initial finding without any evidence of the lesions in other organs, including the lung. Second, the cancer cells were TTF-1-negative. TTF-1 has been reported to be present in pulmonary SCC, but not in extrapulmonary SCC, though there is another report that a large number of extrapulmonary SCC express TTF-1.[1]

Extrapulmonary SCC is uncommon but occurs at various sites.[2] In the current case, postmortem macroscopic analysis revealed tumours in the lung, pleura, liver and pancreas. At the time of the autopsy, we thought that the pleura was the origin because the neoplastic pleural thickening was the initial clinical finding, though primary SCC of the pleura is quite rare and only a few cases have been reported.[3 4] Ultimately, we determined that the SCC in the current case was a recurrence of SCC of the bladder because detailed pathological examination of the bladder resected in 2006 revealed the SCC component. SCC of the bladder is also quite rare, accounting for less than 1% of all bladder tumours[5] and often coexists with another tumour component, such as urothelial carcinoma,[6] as in the present case.

In patients with irregular pleural thickening, especially those with a history of asbestos exposure, MPM is the most common neoplasm. However, extrapulmonary SCC should be noted as a differential diagnosis.

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Contributors KN treated the patient and drafted the paper. NF treated the patient and drafted and revised the paper. MA, YF, KO and SO contributed to the data monitoring and drafted and revised the paper. KH first found the CT finding of the patient and analysed the patient data. KK analysed the radiological images of the patients. HT and KT contributed to the pathological examination of the patients. TK finally approved the work to be published.

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Patient consent Obtained.

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III. 最近注目されている職業関連疾患

アスベスト関連疾患

岸本卓巳

Asbestos-related diseases

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Abstract

Asbestosis shows peribronchiolar fibrosis with numerous asbestos bodies. Subpleural dots and curvilinear lines in HRCT are good indicators for the diagnosis of asbestosis. Asbestos-related lung cancer in Japanese Compensation System means lung cancer with asbestosis. Furthermore, pleural plaques and the content of asbestos bodies in the lung tissues with the term of occupational asbestos exposure are good indicators. Mesothelioma induced also by the low dense exposure to asbestos. For the definite diagnosis of mesothelioma, we need histological examination using biopsy and immunochemical staining for positive and negative markers. Benign asbestos pleurisy is diagnosed by cytological and biochemical examinations of pleural effusions and pleural biopsy. Diffuse pleural thickening depends on the extent of radiological findings and impairment of pulmonary function with occupational asbestos exposure.

Key words: asbestosis, asbestos-related lung cancer, mesothelioma, benign asbestos pleurisy, diffuse pleural thickening

はじめに

アスベストは単一の鉱物名ではなく，アスペクト比3以上の繊維性ケイ酸塩からなる鉱物の総称であり，蛇紋石族のクリソタイルと角閃石族のクロシドライト，アモサイト，アンソフィライト，トレモライト，アクチノライトがある．アスベストの特性として耐熱性・抗張性・化学的安定性に富み，防音性・断熱性・電気絶縁性も高いため，各種工業製品に使用されてきた[1]．しかし，中皮腫や肺癌の発がん性が明らかとなったため，日本では2006年に輸入，製造，販売などが全面禁止となった．

アスベスト曝露によって生じる疾患としては，肺病変としての石綿肺(アスベスト肺)と肺癌，および胸膜疾患である．胸膜疾患には悪性腫瘍の中皮腫と，非悪性疾患の良性石綿胸水(アスベスト胸膜炎)，びまん性胸膜肥厚がある．中皮腫は胸膜のみならず，腹膜，心膜，精巣鞘膜にも発生する．

アスベスト関連疾患の最も重要な点は，アスベスト曝露を確認することである．アスベスト曝露を示す医学的所見として胸膜プラーク，石綿小体(アスベスト小体)および石綿繊維(アス

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表1 労災補償における石綿肺癌認定基準

1) 第1型以上の石綿肺がある
2) 画像あるいは肉眼的に胸膜プラークが検出され，職業性石綿曝露が10年以上ある
3) 病理組織標本上に石綿小体または石綿繊維が検出され，職業性石綿曝露が1年以上ある
4) 肺乾燥重量1gあたり5,000本以上の石綿小体あるいは200万本以上(5μm超)の石綿繊維，500万本以上(1μm超)の石綿繊維を検出する，もしくは気管支肺胞洗浄液1mL中5本以上の石綿小体を検出し，職業性石綿曝露が1年以上ある
5) びまん性胸膜肥厚(胸部レントゲンの肥厚範囲が認定基準を満たす＝片側の場合は片側胸郭の1/2以上，両側の場合は両側胸郭の1/4以上)を認めるとともに著しい呼吸障害を認める
6) 胸部レントゲン上で胸膜プラークを検出するまたは胸部CT上片側1/4以上の広範な胸膜プラークがあり，職業性石綿曝露が1年以上である
7) 石綿紡績，石綿吹付け，石綿セメント製造の職業性石綿曝露が5年以上ある

ベスト繊維)がある．

1. 石綿肺(アスベスト肺)

1) 診　　断

石綿肺はじん肺の一種で，アスベスト高濃度曝露によって発生する．早期には自覚症状は出現しないが，病期が進行すると労作時呼吸困難，空咳がみられる．

診断には①職業性アスベスト曝露歴があること，②胸部X線で下肺野を中心にした不整形陰影を認めること，③肺機能検査で肺活量が低下すること，④両側肺底部に吸気時(中期から終期)に捻髪音を聴取すること，そして，⑤他の類似疾患やアスベスト以外の原因物質による疾患を除外することが必須である[2]．

このように，石綿肺の診断は必ずしも容易でなく，しばしば特発性間質性肺炎(IPF/UIP)，膠原病や薬剤性，感染症などによる間質性肺炎との鑑別が必要になる．石綿肺の比較的軽度な部位にはhigh resolution CT(HRCT)上細気管支周囲からの線維化を示すsubpleural dotsやcurvilinear linesを認めることから他疾患との鑑別に有用である[3]．病理組織学的には細気管支周囲から始まるびまん性肺線維症であるため，石綿小体を含む小葉中心性の線維化病変が小葉辺縁に進展する像が認められる．しかし，病期が進行すると蜂窩肺を形成して，慢性間質性肺炎と鑑別が難しいこともある．

2) 治療方法

対症療法として，鎮咳剤，気管支拡張剤を使用することがあるが，呼吸不全をきたした際には在宅酸素療法導入が必須である．

2. アスベスト由来の原発性肺癌(石綿肺癌)

アスベスト由来の肺癌の発がんには，曝露量が多くなるほど肺癌リスクが高くなるという量一応反応関係が知られている．また，臨床的にはアスベスト曝露によって生じる肺癌の発生部位や病理組織型などには，一般の肺癌と相違はないといわれている．従来，アスベスト肺癌の定義は石綿肺に合併した肺癌であり，肺の線維化が発がんメカニズム上重要であると考えられていたが，最近では石綿肺を合併しないアスベスト肺癌の存在も明らかとなり，アスベスト自体が肺癌発生に重要であると考えられている．石綿肺を伴わない肺癌の場合には，アスベスト曝露によって発生する胸膜プラークの存在や顕微鏡下に病理組織標本上に石綿小体を検出すれば，アスベスト曝露の目安になる．また，喫煙はアスベストとは独立した肺癌発生の危険因子となることが知られており，喫煙者であるアスベスト曝露者では相乗的に肺癌発生頻度が増加する[4]．そのため，アスベストによる肺癌発生を防止するためには禁煙が必須である．

1) 診　　断

平成24(2012)年に改訂された日本の労災補償上のアスベスト肺癌認定基準を表1に示す．日本のアスベスト肺癌認定基準は肺癌発生頻度を2倍にするとした1997年のヘルシンキクラ