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CASE REPORT

An Autopsy Case of Pleural Mesothelioma with Miliary Pulmonary Metastases

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ABSTRACT —— ***Background.*** Pleural mesothelioma is difficult to diagnose at an early stage and has a poor prognosis. This tumor may occasionally metastasize to other organs in the terminal stage. However, intrapulmonary miliary metastases are rare. We herein report a case of epithelioid pleural mesothelioma that presented with miliary metastases during chest imaging and an autopsy. ***Case.*** The patient was a 92-year-old woman without a history of asbestos exposure. The initial sign of mesothelioma was left pleural effusion. The patient lived for one year after the definitive diagnosis without specific treatment other than pleurodesis. Two months prior to death, chest radiography and computed tomography showed intrapulmonary miliary metastases. An autopsy confirmed this pattern of metastasis. The reason for the occurrence of miliary metastases remains unclear. However, the invasive characteristics of the tumor were speculated based on the histological and immunohistochemical findings. For example, a homozygous deletion of p16, which is related to a poor prognosis, was noted. In addition, the mesothelioma possessed micropapillary components, which indicated its aggressive characteristic. Thus, we speculated that these invasive characteristics contributed to hematogenous metastasis and lymphangitic spread and ultimately resulted in miliary metastases. ***Conclusion.*** We presented a case of epithelioid pleural mesothelioma with a rare metastatic pattern. We speculate that the pathogenesis of intrapulmonary miliary metastasis was related to the aggressive behavior, characterized by p16 deletion or micropapillary components.

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KEY WORDS —— Epithelioid pleural mesothelioma, Miliary metastasis, Chest X-ray findings, p16 deletion, Micropapillary component

INTRODUCTION

Pleural mesothelioma is difficult to diagnose at an early stage and has a poor prognosis with limited treatment options. Pleural mesothelioma may occasionally metastasize to other organs, such as the liver, spleen, thyroid gland, brain, and lymph nodes, in the terminal stage.[1] However, intrapulmonary miliary metastases are uncommon.

Infectious diseases, such as tuberculosis, or metastatic tumors are known to present with miliary shadows on chest radiography. Among malignancies, thyroid cancer, various sarcomas, and some types of lung adenocarcinoma cause miliary intrapulmonary metastases,[2] but little is known about mesothelioma. There have been no reports on miliary intrapulmonary metastases of pleural mesothelioma since the 13 cases reviewed by Tsukamoto et al.,[3] and this pattern was named "miliary mesothelioma" by Huncharek.[4]

We herein report an elderly woman with epithelioid pleural mesothelioma (EPM) who exhibited a rare metastatic pattern.

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CASE

A 92-year-old-woman visited our hospital after being diagnosed with left pleural effusion by a regional doctor. She had no specific medical history, no history of smoking, and had never been employed. Neither her family employment history nor regional environment indicated asbestos exposure.

Table 1. Immunohistochemical Examinations Performed for the Biopsy and Autopsy Specimens

	biopsy specimen	autopsy specimen
Carletinin	+	+
WT-1	+	+
D2-40	+	+
CAM5.2	+	+
EMA	+	+
Vimentin	NE	+
GLUT-1	+	NE
CD146	±	NE
TTF-1	−	−
NapsinA	NE	−
CEA	− *	−
Desmin	NE	−
MOC31	−	−
Thrombomodulin	NE	−
BAP-1	lost	NE

All results were diagnostic for mesothelioma.

+ : positive, − : negative, ± : partially positive, NE: not examined, WT-1: Wilms tumor 1, EMA: epithelial membrane antigen, GLUT-1: glucose transporter 1, CD: cluster of differentiation, TTF-1: thyroid transcription factor-1, CEA: carcinoembryonic antigen, BAP-1: BRCA-1 associated protein 1.

* For CEA, few cells showed very faint staining.

Chest radiography performed at the first visit showed a small amount of left pleural effusion. Despite a needle biopsy and several attempts at analyzing the pleural effusion, a definitive diagnosis could not be made. Six months later, a thoracoscopic examination was performed under local anesthesia. Upon inspection, the parietal pleura was irregularly lined with disseminated tumors. A histological examination of the specimen revealed a malignant lesion containing epithelioid mesothelial cells with atypia. Immunohistochemical studies were positive for calretinin, Wilms tumor 1, and D2-40 and negative for thyroid transcription factor-1 and carcinoembryonic antigen (Table 1). Based on these results, the definitive diagnosis of pleural mesothelioma, epithelioid, cT1aN0M0 stage 1A, low grade (nuclear grade 1 and 2 without necrosis) was made. In addition, we observed micropapillary components upon microscopic inspection (Figure 1).

After confirming the diagnosis, the treatment options were discussed, and after pleurodesis, best supportive care was chosen according to her age and wishes. Two months before her death, multiple granular shadows had developed on chest radiography (Figure 2). Computed tomography revealed numerous tiny nodules less than 2 mm in diameter randomly scattered throughout both lungs (Figure 3). The sputum specimens did not include acid-fast bacilli, but mesothelioma cells were detected on cytology. The patient weakened and died suddenly at home, approximately one and a half years after her first visit. An autopsy was performed.

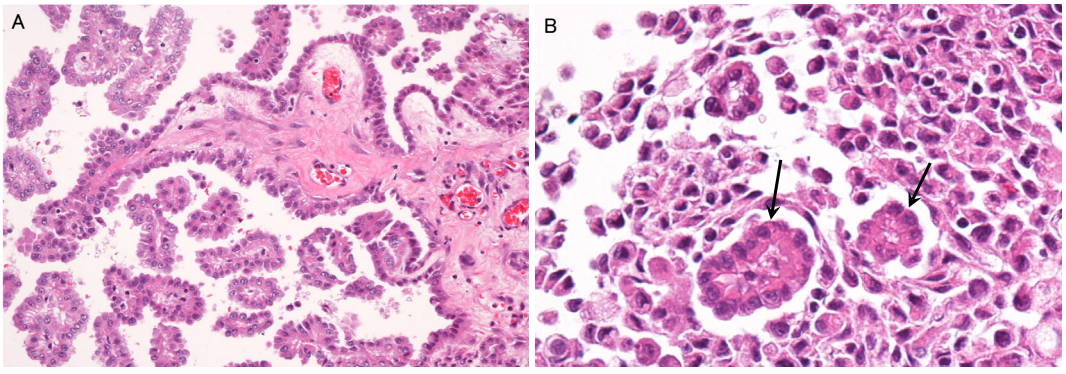

Figure 1. Pathological images of biopsied pleura sampled by a thoracoscopic examination under local anesthesia. **A.** Epithelioid mesothelioma cells with atypia revealed single and multilayered papillary structures. Hematoxylin and Eosin (HE) staining (×100). **B.** Other parts of the specimen had a micropapillary component characterized by the lack of interstitium in the center of the cell circle (arrows). HE staining (×400).

Autopsy findings

Upon inspection, the left lung was encapsulated by a white, hard tumor, approximately 1 cm in thickness. Numerous tiny, white nodules were observed in the lung parenchyma. Metastases were identified at the hilar node and thoracic vertebral bone. Upon a microscopic examination, multiple randomly distributed nodular lesions, measuring up to 2.5 mm in diameter, were observed in both lungs. Remarkably, the EPM exhibited two metastatic patterns: hematogenous metastasis and lymphangitic spread (Figure 4A-4C). As seen in the biopsy specimen, the tumor contained micropapillary components (Figure 4D). Additional fluorescence *in situ* hybridization was performed on the biopsy specimen. In 98% of the tumor cells, the homozygous deletion of p16/CDKN2A was detected (Figure 5a). Immunohistochemical staining for BRCA-1 associated protein 1 was also examined, which confirmed the loss of expression in nuclei (Figure 5b).

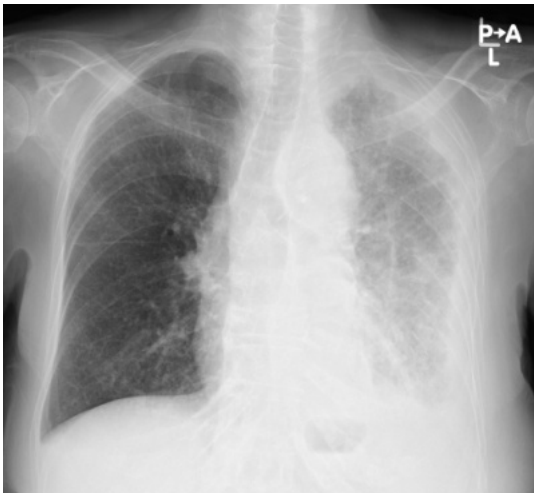

Figure 2. Chest X-ray image obtained two months prior to the death of the patient. The left lung was encapsulated by thickened mesothelioma tissue; however, multiple tiny nodules are clearly present in the lung field. The right lung also contained numerous tiny nodules.

DISCUSSION

We reported an elderly woman with EPM complicated by intrapulmonary miliary metastases. Metastasis occurs at the terminal stage in most cases of mesothelioma.[1,5] According to Tsukamoto et al., only 13 cases of pleural mesothelioma were reported to be complicated by miliary intrapulmonary metastases,[3] making this the 14th such reported case. There is no ambiguity regarding our diagnosis of EPM, as it is robustly supported by the immunohistochemical findings (Table 1). In addition, the homozygous deletion of p16/CDKN2A is an important marker for the diagnosis of EPM and the prediction of a poor prognosis.[6] Hida et al. reported a case of EPM with miliary pulmonary metastases with the same clinical features as ours (i.e. marked lymphovascular involvement along the bronchovascular tissue suggesting both hematogenous and lymphangitic spread) based on detailed histological observations.[7] They further reported the homozygous deletion of p16 in 93% of the tumor cells, consistent with our case.

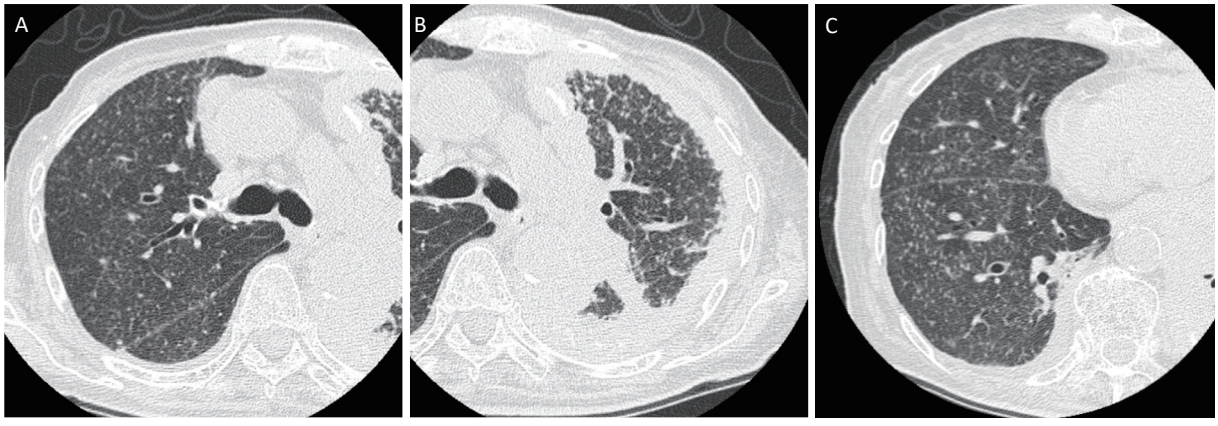

Figure 3. Computed tomography imaging 40 days prior to the death of the patient. **A.** Right lung at the level of the first carina. **B.** Left lung at the level of the first carina. The left lung was encapsulated by thickened mesothelioma tissue and contained some interlobular thickening that might indicate lymphangitic spread. **C.** Right lung at the lung base. All of these images reveal numerous tiny metastatic nodules with a random distribution.

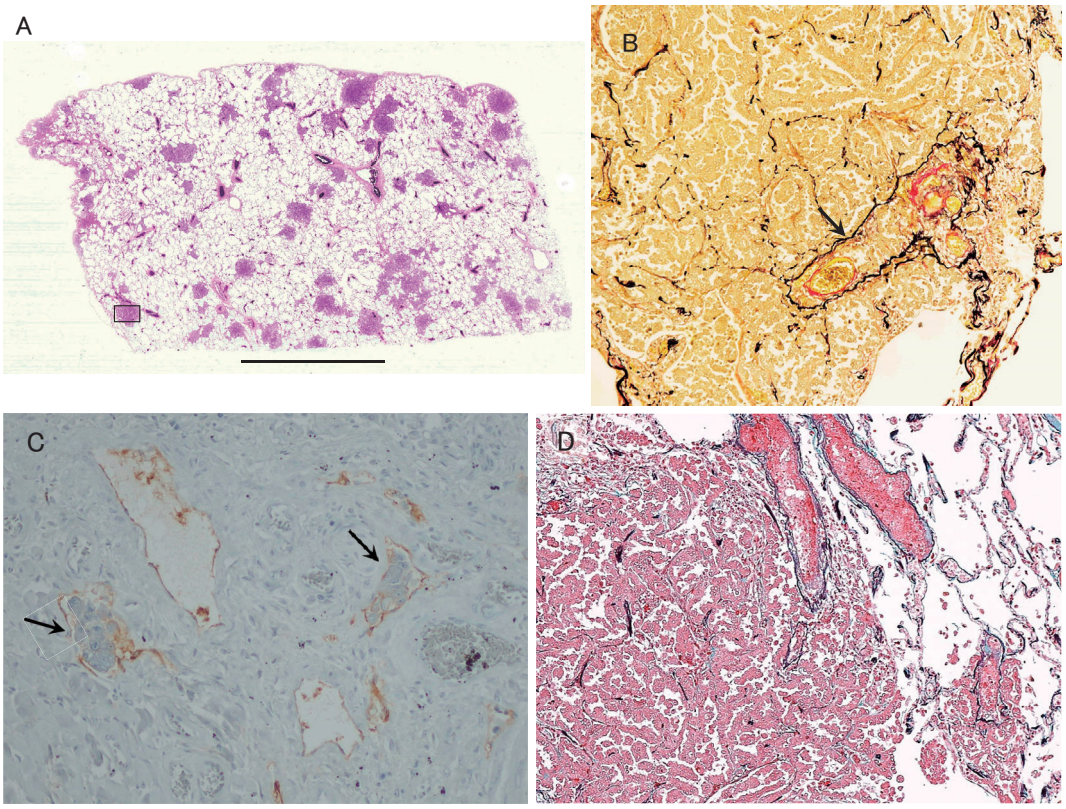

Figure 4. Results of a histological examination of the autopsied right lung. Histological findings at the opposite side (right lung) of the malignant mesothelioma. **A.** Several nodular lesions (up to 2.5 mm in size) were observed in the lung tissue with random distribution. Bar 1 cm. Hematoxylin and Eosin (HE) staining, panoramic view. **B.** Histology was suggestive of hematogenous metastasis. A venule (arrow) can be observed in the nodule showing papillary growth. The lumen was filled with tumor cells, and the residual lumen was narrowed. The tumor may have spread from this area to the surrounding lung. Inset of (**A**). Elastica van Gieson staining (×100). **C.** Tumor cells were found in the lymphatic vessels (arrows) as revealed by immunohistochemical staining for D2-40 (×400). **D.** Papillary/micropapillary structures were also evident in the metastatic focus in the right lung, as seen in the biopsy specimen. Elastica-Masson-Goldner staining (×100).

In general, there are three possible mechanisms associated with pulmonary metastasis: hematogenous, lymphatic and aerogenous spread. In both aerogenous and lymphatic spread, metastatic foci may not be randomly distributed, and these two mechanisms cannot explain the miliary mesothelioma for this case. However, when hematogenous spread occurs, it can result in multiple randomly distributed lesions.[8] The proof of hematogenous dissemination lies in the detection of circulating tumor cells (CTCs) in the peripheral blood of patients with EPM. Yoneda et al. reported that CTCs were detected in approximately 40% of EPM cases, which correlates with a poor prognosis.[9] Our patient's blood sample was not evaluated for the presence of CTCs; therefore, the true mechanism underlying the hematogenous dissemination is unclear.

Some types of EPM are aggressive in nature. Mogi et al. described how an invasive micropapillary component identified by a histological examination may be indicative of pulmonary metastasis. They reported that micropapillary components are associated with a poor prognosis due to lymphatic invasion or metastasis in several types of cancer, including mesothelioma.[10] In their series, 34 mesothelioma patients were reviewed with a focus on the micropapillary component. Two out of 21 EPM cases showed a micropapillary component. Kadota et al. also investigated EPM by focusing on the histologic subtype.[11] In their series, a micropapillary component was reported in 20 out of 232 patients. We identified the micropapillary component in our patient's

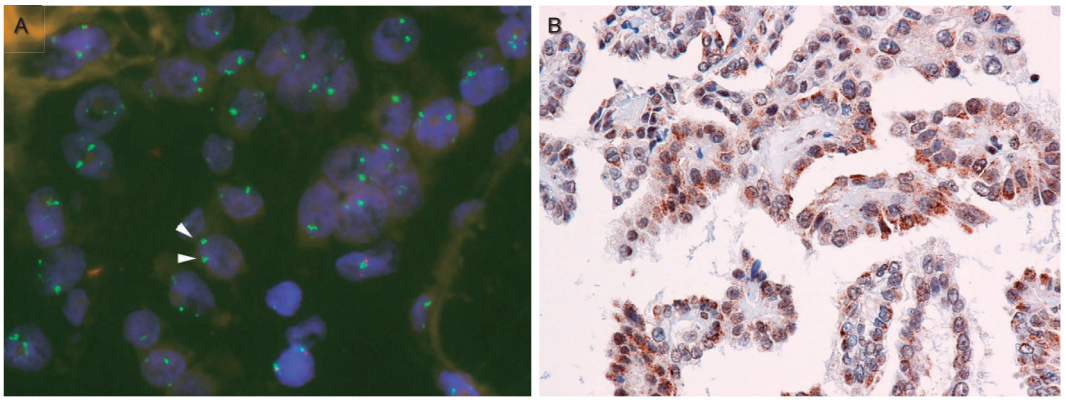

Figure 5. Epithelioid pleural mesothelioma confirmation after additional investigations of the biopsy specimen, obtained by a thoracoscopic examination under local anesthesia (Investigation and photos are courtesy of LSI Medience Co., Ltd.). **A.** Fluorescence *in situ* hybridization of p16/CDKN2A. Green spots indicate the marker of the centromere, and red spots indicate the marker of 9p21, the location of the p16 gene. Most tumor cells contain pairs of green spots, without a red spot, indicating homozygous deletion of the p16 gene (representative cell with arrowheads). **B.** Immunohistochemical staining for BRCA-1-associated protein 1. Loss of expression for nuclei is evident. The cytoplasm is weakly stained and not positively expressed (×400).

specimen through a pathological examination (Figure 1B, 4D), and this was consistent with the aggressive behavior of the tumor.

Images of this case (Figure 2, 3) show that the nodules are relatively uniform in size and randomly distributed, similar to observations in miliary tuberculosis. It is known that the presence of a micropapillary component predisposes a lesion to lead to lymphatic metastasis.[10] However, our findings are not suggestive of lymphangitic spread, as seen in the images. If we assume that hematogenous dissemination occurred initially, the tumor cells remained in the pulmonary small vessels and then invaded the lymphatic tissue surrounding them. This resulted in the formation of a tumor nodule, which aids in explaining the pathological features of this case, i.e. the hematogenous metastasis with lymphangitic spread.[8]

In recent years, a nuclear grading system has been used to predict the prognosis of EPM.[12,13] In our case, invasive characteristics were observed pathologically, even though the lesion was considered a low-grade one. Our case highlights the difficulty in predicting miliary metastases by the grading system.

CONCLUSION

We reported an elderly woman with miliary mesothelioma. Organ metastasis commonly occurs in mesothelioma, but a miliary pattern is uncommon. In our case, tumor cells with invasive characteristics, represented by p16 deletion or micropapillary components, may have caused hematogenous dissemination and lymphangitic spread, leading to miliary mesothelioma.

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