—Case Reports—

Cytological Assessment of Desmoplastic Malignant Pleural Mesothelioma in an Autopsy Case

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Introduction: Desmoplastic malignant pleural mesothelioma (DMPM) is a sarcoma-type mesothelioma, comprising approximately 5% of malignant pleural mesotheliomas. Although effusion cytology is commonly used as the primary diagnostic approach for mesothelioma, it may not be useful for DMPM because of the presence of desmoplasia and bland cellular atypia. We report a case, and previously undescribed cytological features, of DMPM that was diagnosed during autopsy.

Case Presentation: A man in his 60s with a history of occupational asbestos exposure was referred to our hospital with right chest pain. A chest CT scan showed right pleural effusion. Thirteen months later, the patient died of respiratory failure. During autopsy, scrape-imprint smears were prepared and cytology of pleural effusions was performed. The scrape-imprint smear samples showed spindle cells with mild nuclear atypia and grooves with fibrous stroma. Pleural effusion cytology revealed spindle cells with mild nuclear atypia, as well as grooves with loose epithelial connections. Histological examination of the right pleura showed spindle cells proliferating with dense collagen fibers, as seen in the cytological samples, thus indicating a diagnosis of DMPM, which was confirmed by fluorescence *in situ* hybridization.

Conclusion: Cytological procedures such as pleural effusion cytology and scrape-imprinting cytology may help in diagnosing rare tumors such as DMPM. (J Nippon Med Sch 2022; 89: 616–622)

Key words: fluorescence *in situ* hybridization, autopsy, cytology, desmoplastic malignant pleural mesothelioma, immunohistochemistry

Introduction

Desmoplastic malignant pleural mesothelioma (DMPM) is a sarcoma-type malignant pleural mesothelioma (MPM). DMPM is a rare tumor that accounts for only 5% of MPM diagnoses in Japan. Prognosis is poor; median survival is 3.8 months[1]. Effusion cytology is the primary diagnostic approach for MPM, since most patients with MPM initially present with pleural effusion. However, cytological diagnosis of DMPM is challenging because tumor cells scarcely exfoliate into pleural effusion because of the presence of desmoplasia. Furthermore, histological diagnosis of DMPM is difficult because bland nuclear atypia mimics fibrous pleurisy.

Autopsy cytology is a rapid, inexpensive diagnostic tool that prospectively assists pathologists, clinicians, and the patient's family. Autopsy cytology can play an ancillary role in diagnosing rare diseases with ambiguous histological features and can also be used for educational

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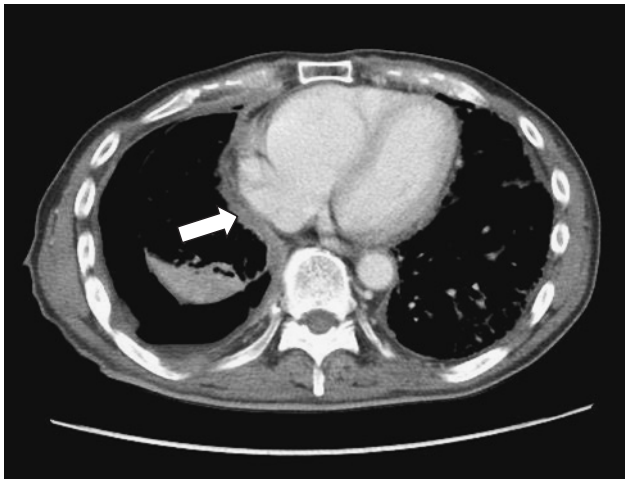

Fig. 1 Chest computed tomography scan on admission. Thickening of the right pleura with effusion was observed (arrow).

purposes. We report a case of DMPM that was ultimately diagnosed during autopsy aided by postmortem cytology. Cytological features of DMPM, ie, the presence of spindle cells with mild atypia and nuclear grooves, are described here for the first time.

Case Report

Clinical History

A man in his 60s presented to our hospital for treatment of right chest pain. He was a retired carpenter with a history of asbestos exposure. A chest CT scan showed right pleural effusion (**Fig. 1**), and hyaluronic acid (HA) concentration in the pleural fluid was 58,405 mg/mL. A right thoracoscopy revealed that the parietal pleura was speckled with white nodules. Cytology of the pleural effusion showed only a small number of atypical cells with pale cytoplasm in the inflamed background. There were no findings suggesting a neoplasm, including mesothelioma. The patient underwent video-assisted thoracoscopic surgery (VATS) biopsy for diagnosis. A parietal pleural biopsy revealed increased collagen fibers with inflammatory cells, predominantly comprising lymphocytes. However, these were classified as "indeterminate"; ie, no apparent mesothelioma cells were identified. The cause of the patient's refractory pleural effusion was considered to be pleurodesis, and supportive care to maintain respiratory function was provided. Thirteen months after his first presentation, the patient died of respiratory failure. An autopsy was performed after obtaining the consent of his family.

Autopsy Findings

The autopsy revealed right parietal pleural thickening

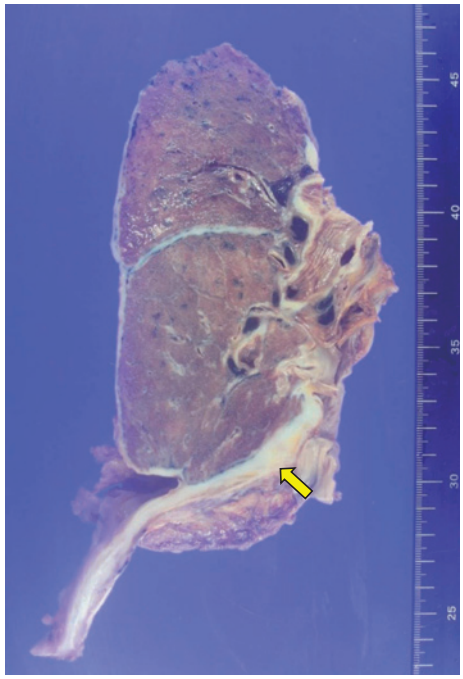

Fig. 2 Macroscopic findings of the right lung at autopsy. Right parietal pleura was thickened (arrow).

and adherence to the surrounding tissue (**Fig. 2**) but no findings indicating lymph node metastases or distant metastases. Two samples (15 × 7 mm and 10 × 10 mm) were collected from the disseminated lesion in the right pleura, and a scrape-imprint smear was collected by scraping a cut surface of the samples. Smear samples were fixed immediately in 95% ethanol for 30 minutes and then subjected to Papanicolaou staining. The scrape-imprint smear samples showed spindle cells with fibrous stroma. The cells had fusiform or round nuclei with mild atypia (shown in **Fig. 3a**), and some exhibited nuclear grooves (**Fig. 3b**). Pleural effusion cytology revealed loosely connected cells with thick, light green cytoplasm (**Fig. 3c**) and round or fusiform nuclei and nuclear grooves (**Fig. 3d**). These autopsy cytological features suggested a diagnosis of mesothelioma, and DMPM was included in the differential diagnosis.

Histological samples (3 cm and 2 cm) were obtained from the right pleura, independently from the samples for the scrape-imprint smear. Histological analysis showed spindle cells proliferating in a short storiform pattern with dense collagen fibers. The spindle cells accounted for more than 50% of the tumor (**Fig. 3e**), and some exhibited nuclear grooves (**Fig. 3f**), as seen in the cytological samples. Asbestos bodies were not present in the parietal pleura or the lung. Immunohistochemical (IHC) analysis (**Table 1**)[2–18] showed that the tumor cells were positive for cytokeratin AE1/AE3 (**Fig. 3g**), α-

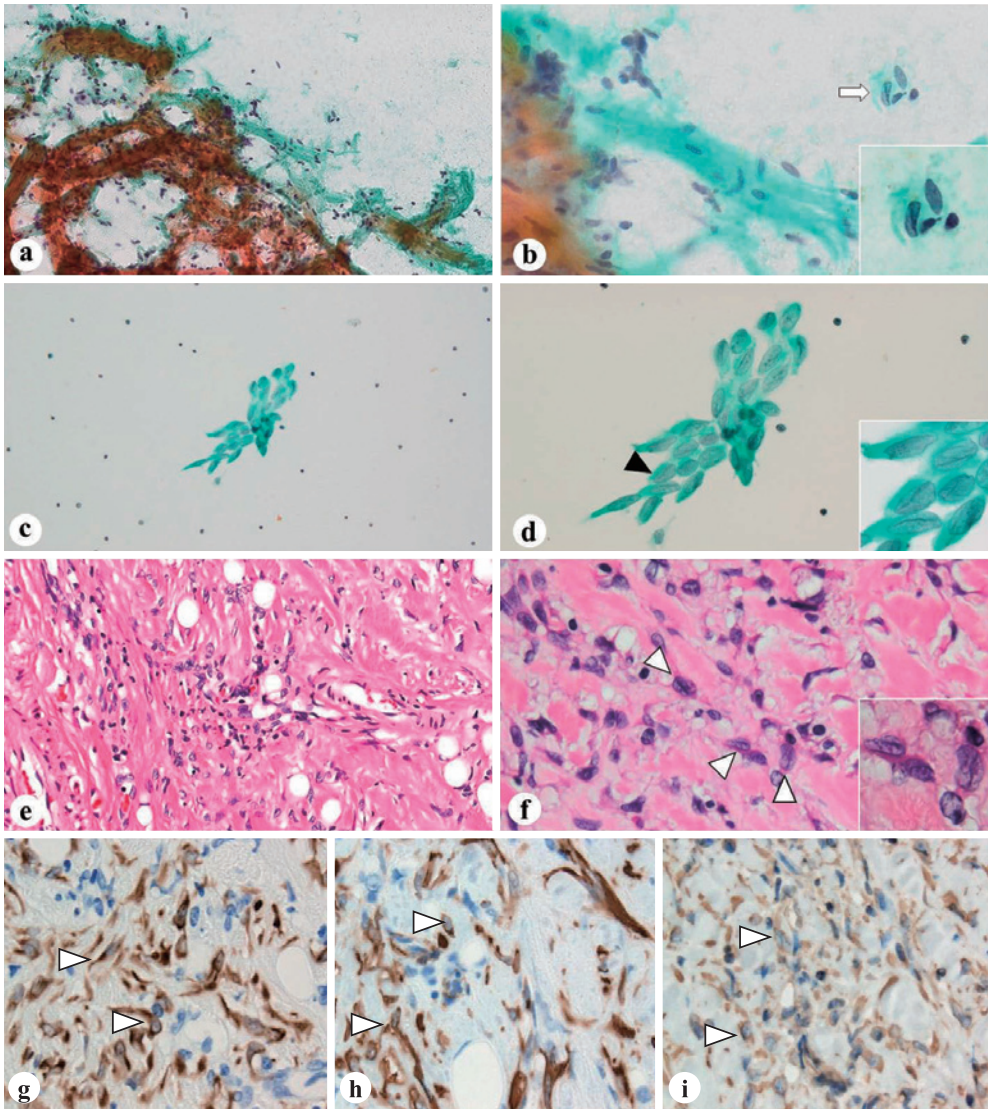

Fig. 3 Cytological and histological findings of DMPM in scrape-imprint smear (a, b), pleural effusion (c, d), and histological sections (e, f). (a) Cytological findings of the right pleural scrape-imprint smear. Spindle cells with mild nuclear atypia proliferating with fibrous stroma, stained with Papanicolaou stain (Pap), ×200. (b) A few cells exhibited nuclear grooves (arrow), ×400. Inset: Higher-power view of nuclear grooves. (c) Cytological findings of the patient's pleural effusion. Atypical spindle cells formed rough epithelioid clusters stained with Pap, ×200. (d) Many cells exhibited nuclear grooves and green cytoplasm (arrowhead), ×400. Inset: Higher magnification of nuclear grooves. (e) Histological findings of the right pleural tissue. More than 50% of the tumor in dense collagen fibers was DMPM cells. Hematoxylin and eosin stain (H&E), ×200. (f) Some cells exhibit nuclear grooves (arrowheads), ×400. Inset: Higher-power view of the nuclear grooves.
On immunohistochemistry, the tumor cells were positive for cytokeratin AE1/AE3 (g), α-smooth muscle actin (α-SMA) (h), and vimentin (i). ×600.

smooth muscle actin (α-SMA) (**Fig. 3h**), vimentin (**Fig. 3i**), CAM5.2, calretinin, glucose transporter 1 (GLUT 1), and developmental protein with EGF-like domains (HEG1). The tumor cells were negative for S-100, CD34, myogenin, desmin, carcinoembryonic antigen (CEA), thyroid transcription factor 1 (TTF-1), napsin A, epithelial cell adhesion molecule antibody clone number Ber-EP4 (BerEP4), anti-epithelial cell adhesion molecule monoclonal antibody, clone number-31 (MOC31), p63, and p40. In the fluorescence *in situ* hybridization (FISH) analysis, homozygous loss of the cyclin-dependent kinase inhibitor 2A (*CDKN2A)/p16* gene was observed in 50.4% of cells (**Fig. 4**). These cytohistological and IHC findings were consistent with a diagnosis of DMPM.

Table 1 Immunohistochemical profile of mesothelioma [2-18] in comparison with the present case

	Epithelioid type		Sarcomatoid type (including DMPM)	Present case
	Pleural mesothelioma	Peritoneal mesothelioma		
Calretinin	+	+	−/+	+
WT-1	+	+	−/+	−
D2-40	+	+	−/+	−
EMA	+	+	−/+	−
GLUT-1	+	−/+	−/+	+
HEG1	+	+	−/+	+
IMP3	+	+	−/+	−
CD146	+	+	−/+	−
AE1/AE3	+	+	+	+
CAM5.2	+	+	+	+
Vimentin	−/+	+	+	+
α-SMA	−	−	+	+
S-100	−	−	−	−
CD34	−	−	−	−
Myogenin	−	−	−	−
Desmin	−	−	−	−
BerEP4	−	−	−	−
MOC31	−/+	−	−	−
p63	−	−	−	−
p40	−	−	−	−
CEA	−	−	−	−
TTF-1	−	−	−	−
Napsin A	−	−	−	−

α-SMA, α-smooth muscle actin; BerEP4, epithelial cell adhesion molecule antibody, clone BerEP4; CEA, carcinoembryonic antigen; DMPM, desmoplastic malignant pleural mesothelioma; EMA, epithelial membrane antigen; GLUT1, glucose transporter 1; HEG1, heart development protein with EGF like domains 1; IMP3, insulin-like growth factor II mRNA-binding protein-3; MOC31, anti-epithelial cell adhesion molecule monoclonal antibody, clone number-31; TTF-1, thyroid transcription factor 1; WT-1, Wilms' tumor 1.

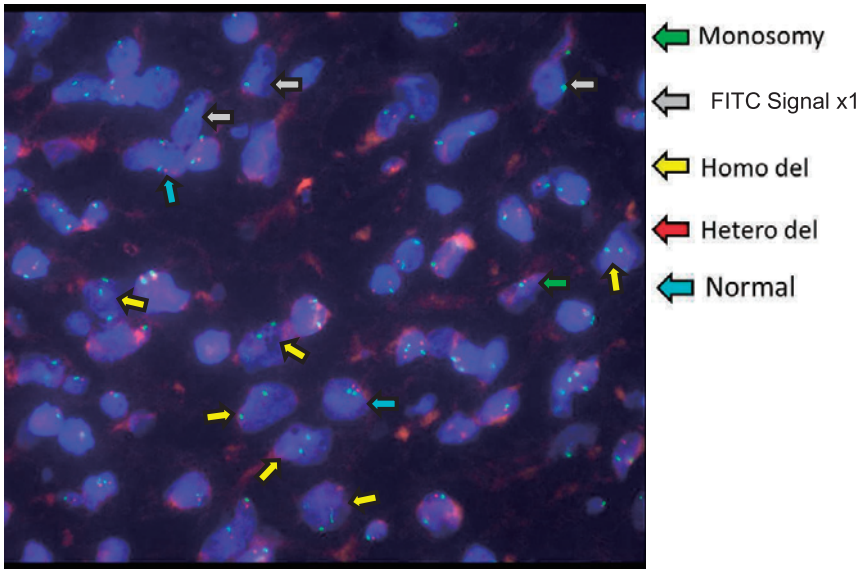

Fig. 4 Fluorescence *in situ* hybridization (FISH) of the *CDKN2A/p16* gene. Homozygous loss of the *CDKN2A/p16* gene is observed in 50.4% of the tumor cells.

Table 2 Cytological features of MPM subtypes

	Epithelioid	Sarcomatoid	DMPM
Cellularity	++	+	+/−~−
Cytoplasm	++	+/−~−	+/−~−
Microvilli	++	−	−
Nuclear atypia	+	++	+/−

MPM, malignant pleural mesothelioma; DMPM, desmoplastic malignant pleural mesothelioma.

Discussion

DMPM is a rare tumor that accounts for 5% of malignant pleural mesotheliomas. Because of its rarity and desmoplastic characteristics, only histological findings have been reported, and cytological characteristics are unclear. In the present case, a scrape-imprint smear from the right pleura showed abundant atypical spindle cells and nuclear grooves with fibrous stroma. Similar findings were seen in tumor cells from the right pleural tissue. Histological examination revealed that spindle cells accounted for more than 50% of the tumor in dense collagen fibers, indicating a diagnosis of DMPM, which was confirmed by FISH showing homozygous loss of the *CDKN2A/p16* gene. To our knowledge, this is the first report of the cytological features of DMPM.

High concentrations of HA in MPM have been reported. When the cutoff value for HA in pleural fluid was set at 100,000 mg/mL, sensitivity was 73-93% and specificity was 90-100%[19,20]. However, aggressive, sarcomatoid-type MPM is associated with lower HA concentrations[20,21]. In the present case, the HA concentration in pleural fluid was 58,405 mg/mL, which was insufficient for diagnosis of MPM.

Cytologic identification of MPM and its subtypes in effusion can be challenging because of the lack of well-established cytological criteria. The epithelioid type appears to be very cellular—multiple atypical mesothelial cells are arranged in three-dimensional structures with morulae or papillae. The abundant cytoplasm is eosinophilic, and the periphery is fuzzy because of the action of HA on the microvilli. In addition, the cytoplasm of engulfed cells exhibits a hump-like cytoplasmic structure[22]. Cellularity is lower for the sarcomatoid type than for the epithelial type. Tumor cells appear alone, with moderate or marked nuclear pleomorphism and irregular chromatin and prominent nucleoli. The desmoplastic type is rare in pleural effusion, but discohesive fusiform cells are sometimes present, as is a surrounding fibrous stroma. Nuclear atypia and nucleoli are less prominent than in the sarcomatoid types. **Table 2** shows the cytological features of the MPM subtypes.

During hospitalization, pleural effusion cytology was used to identify tumor cells that may have exfoliated into the effusion. However, the sample was insufficient to provide significant information, perhaps because their desmoplastic characteristics make DMPM cells rare in pleural effusion. At autopsy, clusters of atypical spindle cells with a reduced connection and high nuclear-cytoplasmic ratio were identified in pleural effusion. Notably, these tumor cells had many nuclear grooves. These cytological characteristics are not unique to DMPM; previous studies have reported nuclear grooves in other types of MPM, such as the microcystic types and adenomatoid types[23,24]. Although these are not characteristics specific to DMPM, they assist in diagnosis.

In this case, the pleural scrape-imprint smear cytology from the autopsy was a diagnostic key. Autopsy cytology is a quick, inexpensive diagnostic tool that provides rapid guidance for pathologists and the family of the deceased patient. This technique can yield a tentative diagnosis before the final histological diagnosis and can also be used for educational purposes. Scrape-imprint cytology is a combination of the scrape and imprint methods. Scraping allows for collection of many tumor cells, especially from stroma-rich tumors, and the imprint method enables detailed visualization of cytological features. Thus, we believe that a combination of scrape and imprint methods is useful for cytological diagnosis of stroma-rich tumors, such as DMPM.

p16 FISH is a useful assay in the diagnosis of several mesothelioma types. For instance, homozygous deletion of *p16* is present in up to 80% of patients, and in 90-100% of DMPM patients[25–27]. In particular, detection by FISH of homozygous deletion of *p16* in an effusion smear or pleural tissue can confirm an MPM diagnosis (positive predictive value, 100%)[26,28]. If enough cells can be collected from effusion samples, FISH should be performed to confirm a histological diagnosis of DMPM.

Currently, cytological diagnosis alone is not recommended for diagnosis. However, as the disease pro-

gresses and the pleura thickens, clinicians usually perform a pleural biopsy. Scrape-imprint cytology is useful to confirm the appearance of tumor cells, allowing a tentative diagnosis. If cytological features strongly suggest DMPM, IHC and/or FISH are highly recommended. The present findings indicate that as many cells as possible cells should be collected by centrifuging all the fluid for further analysis. Even if it is not possible to collect cells from the tumor itself, collecting cells from pleural and ascitic fluid can predict the histological type, and cell block-IHC and FISH can be performed. Even when definitive diagnosis is challenging, it is possible to collect a variety of information that will be useful for subsequent treatment strategies.

In conclusion, this is to our knowledge the first report of rare cytology findings for DMPM in an autopsy. Scrape-imprint smear and pleural effusion cytology revealed spindle cells with mild nuclear atypia and grooves with fibrous stroma. Cytological procedures during autopsy can be a rapid and convenient tool for diagnosing rare tumors such as DMPM.

Statement of Ethics: Written informed consent was obtained from the patient and his family. All procedures performed in studies involving human participants were in accordance with institutional ethical standards and the Declaration of Helsinki.

Author Contributions: Y. K., S. Kure., H. K., S. Kunugi, and M. O. conceived the presented idea. Y. K., K. K., and K. T. made and screened the cytological specimen, and all authors assessed the cytological and histological findings. N. M. and R. O. supervised the work. Y. K. and S. Kure drafted the manuscript. All authors discussed the results and contributed to the final manuscript.

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Conflict of Interest: None declared.

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