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Pseudomesotheliomatous Carcinoma with a High Pleural Hyaluronic Acid Concentration Arising from a Primary Esophageal Squamous Cell Carcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 65
Final Diagnosis: Esophageal squamous cell carcinoma
Symptoms: Low grade fever • persistent productive cough
Medication: —
Clinical Procedure: Upper gastrointestinal endoscopy
Specialty: Oncology

Objective: Rare disease
Background: Pseudomesotheliomatous carcinomas are rare tumors that develop like malignant pleural mesothelioma (MPM). These tumors have similar features, and thus pseudomesotheliomatous carcinomas can sometimes be misdiagnosed as MPM. Most pseudomesotheliomatous carcinomas develop from primary lung cancers, although there have been some reports involving other malignancies; however, there has been no report describing a pseudomesotheliomatous carcinoma developing from an esophageal squamous cell carcinoma (ESCC). To the best of our knowledge, this is the first case report describing pseudomesotheliomatous carcinoma originating from primary ESCC.

Case Report: A 65-year-old man was admitted to our hospital because of persistent cough and right chest pain. Radiological examination suggested MPM, and a high concentration of pleural hyaluronic acid was also observed. Cytological examination of pleural effusion confirmed metastatic squamous cell carcinoma, and ESCC was confirmed by upper-gastrointestinal endoscopy. The patient received cisplatin and 5-FU combination chemotherapy as first-line treatment, and docetaxel chemotherapy as second-line treatment. However, the patient's condition deteriorated, and he died 6 months after the diagnosis was established. We performed an autopsy and found that ESCC had invaded the lung, pleura, peritoneum, liver, stomach, ureter, bladder, spine, and lymph nodes.

Conclusions: We demonstrated that primary ESCC can give rise to a pseudomesotheliomatous carcinoma. This report describes the clinical features and outcome of such a patient, with an emphasis on differential diagnosis of MPM.

MeSH Keywords: Esophageal Neoplasms • Hyaluronic Acid • Mesothelioma

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Background

A malignant pleural mesothelioma (MPM) originates from mesothelial cells in the pleura and extends invasively along the pleural surface; this is radiologically characterized by pleural thickening, multiple pleural plaques, and pleural effusion with high concentration of hyaluronic acid. However, these features are not specific to MPM. Pseudomesotheliomatous carcinomas are rare tumors that resemble MPM in clinical, radiological, and pathological features. They constitute approximately 6% of all pleural malignancies; most cases originate from lung cancer, particularly adenocarcinoma; pseudomesotheliomatous progression rarely occurs with pleural metastasis from other sites of the body such as the pancreas, bladder, and renal or parotid gland [1]. However, there have been no reported cases of pseudomesotheliomatous carcinoma originating from the esophagus. Here, we present a rare case of a Japanese man who died from pseudomesotheliomatous carcinoma that originated from an esophageal squamous cell carcinoma (ESCC), and we discuss the clinical characteristics and differential diagnosis of this case, especially with respect to MPM.

Case Report

A 65-year-old man visited a local clinic in May 2015 because of persistent cough and low fever. He had been experiencing these symptoms for 2 weeks. His medical history included appendicitis at the age of 18 years; his familial medical history was unremarkable. He had a 68-pack-year history of smoking and had worked for a construction company, which means that he had had occupational asbestos exposure. Initially, a doctor at the clinic prescribed him antibiotics, suspecting bacterial pleuritis. However, his symptoms did not improve, and he gradually started experiencing right chest pain. Therefore, he was admitted to the emergency department of our hospital. On admission, his vital status was as follows: consciousness, clear; height, 163 cm; body weight, 48 kg; body mass index, 18.1 kg/m²; body temperature, 37.2°C; blood pressure, 116/76 mmHg; pulse, 77 beats/min and regular; and SpO₂, 98% (room air). There were no palpable lymph nodes. Cardiac sounds were clear. Breathing sounds were reduced in the right lower lung field. He did not have abdominal hepatosplenomegaly or

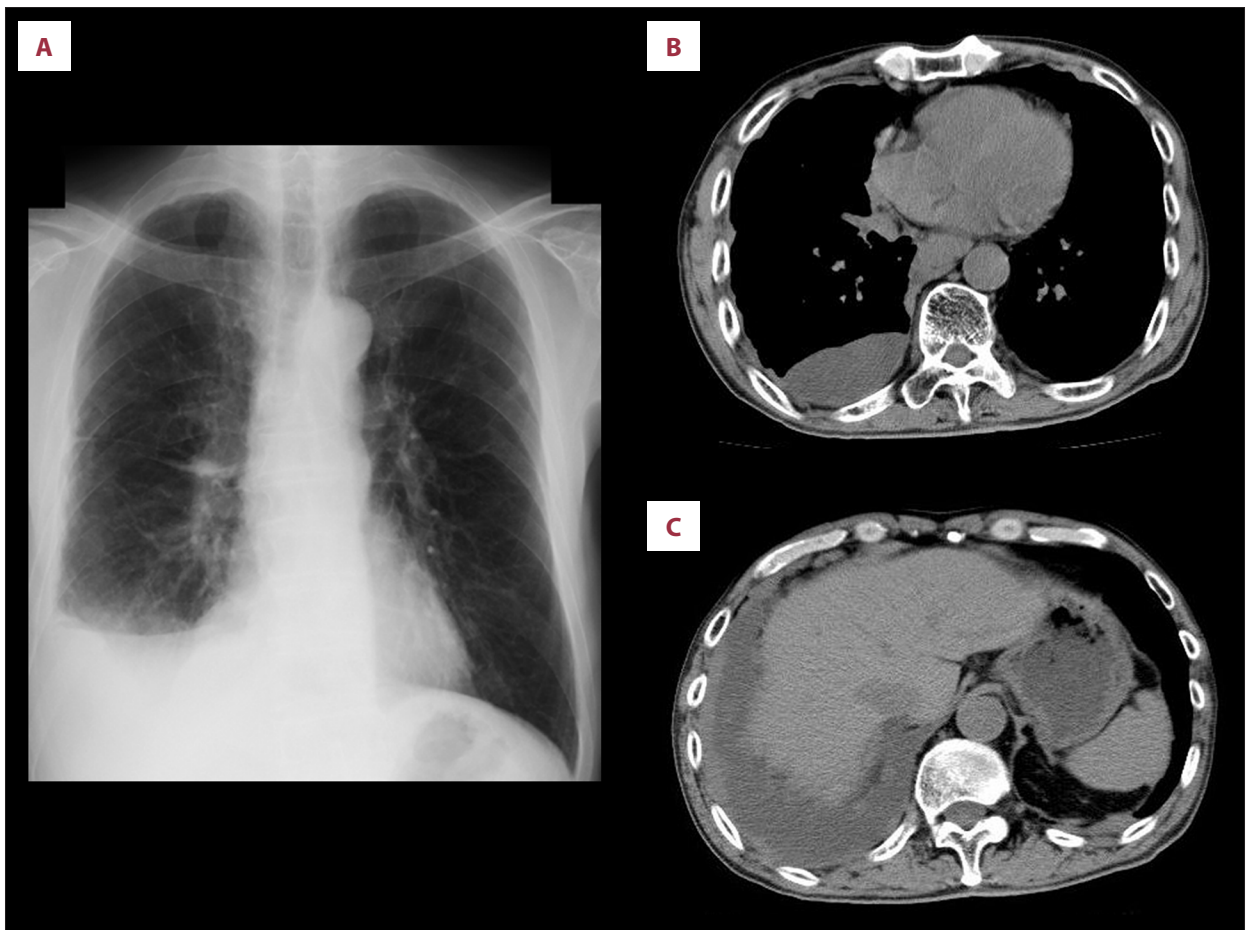


Figure 1. Chest radiograph and chest CT scans on admission. (A) Chest radiograph showing right pleural effusion. (B, C) Chest CT showing right pleural effusion, pleural nodules, pleural thickening, and a mass at the lower thoracic esophagus. CT – computed tomography.

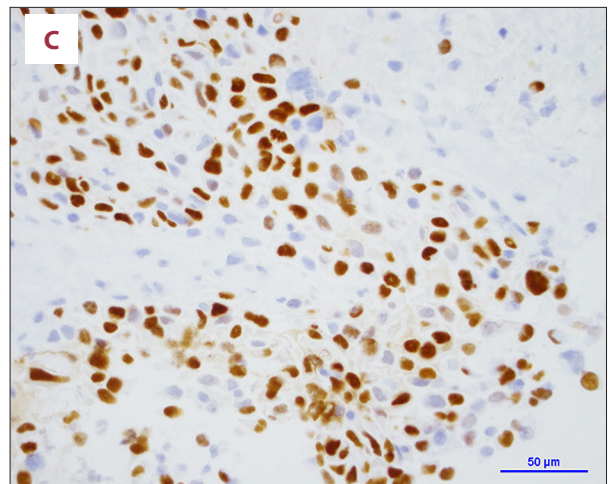
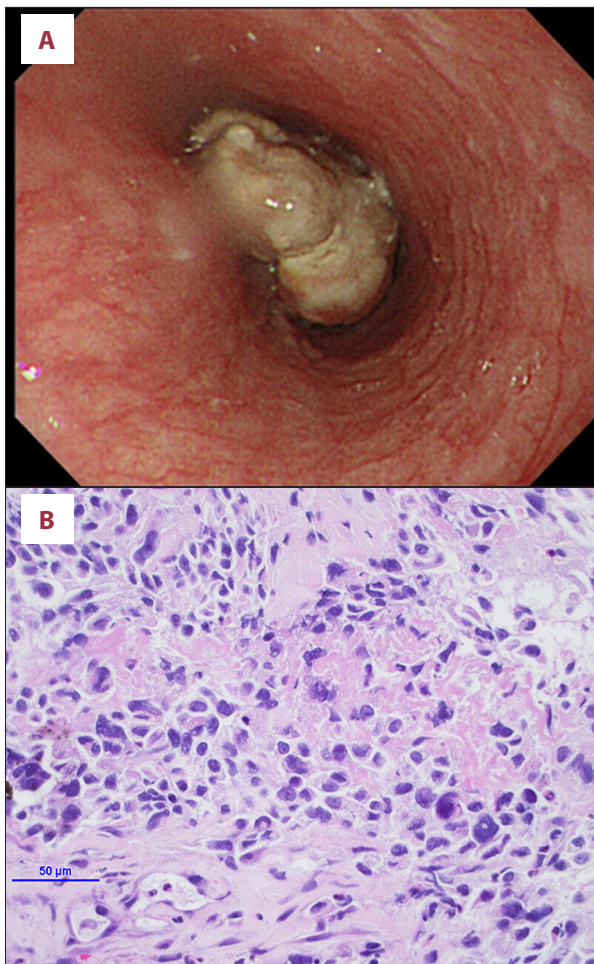


Figure 2. Results of upper gastrointestinal endoscopy and biopsy ($\times 400$). (A) Endoscopy results showing a tumor at the lower thoracic esophagus. (B) Hematoxylin and eosin staining of the biopsy specimen showing loosely cohesive carcinoma cells without intercellular bridges, keratinization, or glandular differentiation, indicating a poorly differentiated carcinoma. (C) Immunohistochemical staining showing p63-expressing cells.

edema of either lower limb. Blood testing revealed mild anemia (11.0 g/dL), an increased C-reactive protein level (7.8 mg/dL), and decreased total protein and albumin levels (6.1 g/dL and 2.7 g/dL, respectively). Tumor markers related to lung cancer, such as carcinoembryonic antigen, squamous cell carcinoma antigen, and CYFRA, showed negative expression levels (1.4 ng/mL, 0.5 mg/mL, and <1.0 ng/mL, respectively). Tests for general and acid-fast bacteria and cytological examination using sputum smears showed negative results. Chest radiography showed right pleural effusion. Chest computed tomography (CT) revealed no nodules in the lung, multiple nodules on the bilateral pleural membrane, enlargement of the mediastinal lymph nodes, and a nodule that seemed to be connected with the pleura at the lower thoracic esophagus in addition to the existing pleural effusion (Figure 1A–1C). Based on these results, the patient was urgently hospitalized for further examination. First, we examined the pleural effusion by thoracentesis, as we suspected MPM because of his past occupation and presence of pleural effusion and multiple pleural nodules. The pleural effusion was bloody and non-viscous; glycoprotein and lactate dehydrogenase levels in the pleural fluid were 4.1g/dL and 291IU/L, respectively, which indicated an exudative pattern.

The white blood cell count was 3075/ μ L and cell fractions were 80.3% lymphocytes and 12% neutrophils. The pleural fluid had a high hyaluronic acid (HA) concentration of 168 mg/L, which was also suggestive of MPM. Culturing of general and acid-fast bacteria showed negative results. Cytological examination demonstrated metastatic squamous cell carcinoma. Next, we performed an upper-gastrointestinal endoscopy. A tumor was found in the lower esophagus; biopsy showed a poorly differentiated squamous cell carcinoma of type 1 (Figure 2A–2C). Immunohistochemical analysis of specimens from the esophageal tissue and cell block of pleural effusion showed that they positively expressed p63 and p40 and negatively expressed calretinin and D2-40 (Figure 3A–3D). These histopathological findings were also consistent with the diagnosis of ESCC. He received cisplatin and 5-FU combination chemotherapy as first-line treatment and docetaxel chemotherapy as second-line treatment. However, these treatments did not result in any symptomatic or radiographic improvement; new metastases to the liver, bone, and peritoneum were detected during his follow-up CT examination. Finally, he died in November, 6 months after he was first admitted.

We performed an autopsy (Figure 4A–4C), which revealed that the primary ESCC was mainly in the mucosa and submucosal layers of the esophagus. There was no fibrosis, scarring, or adhesion with the surrounding organs. There was no evidence that the primary ESCC had directly infiltrated the chest wall. Regarding the lungs, tumor invasion was extensively observed in the pleura. On the mediastinal side, tumor invasion along

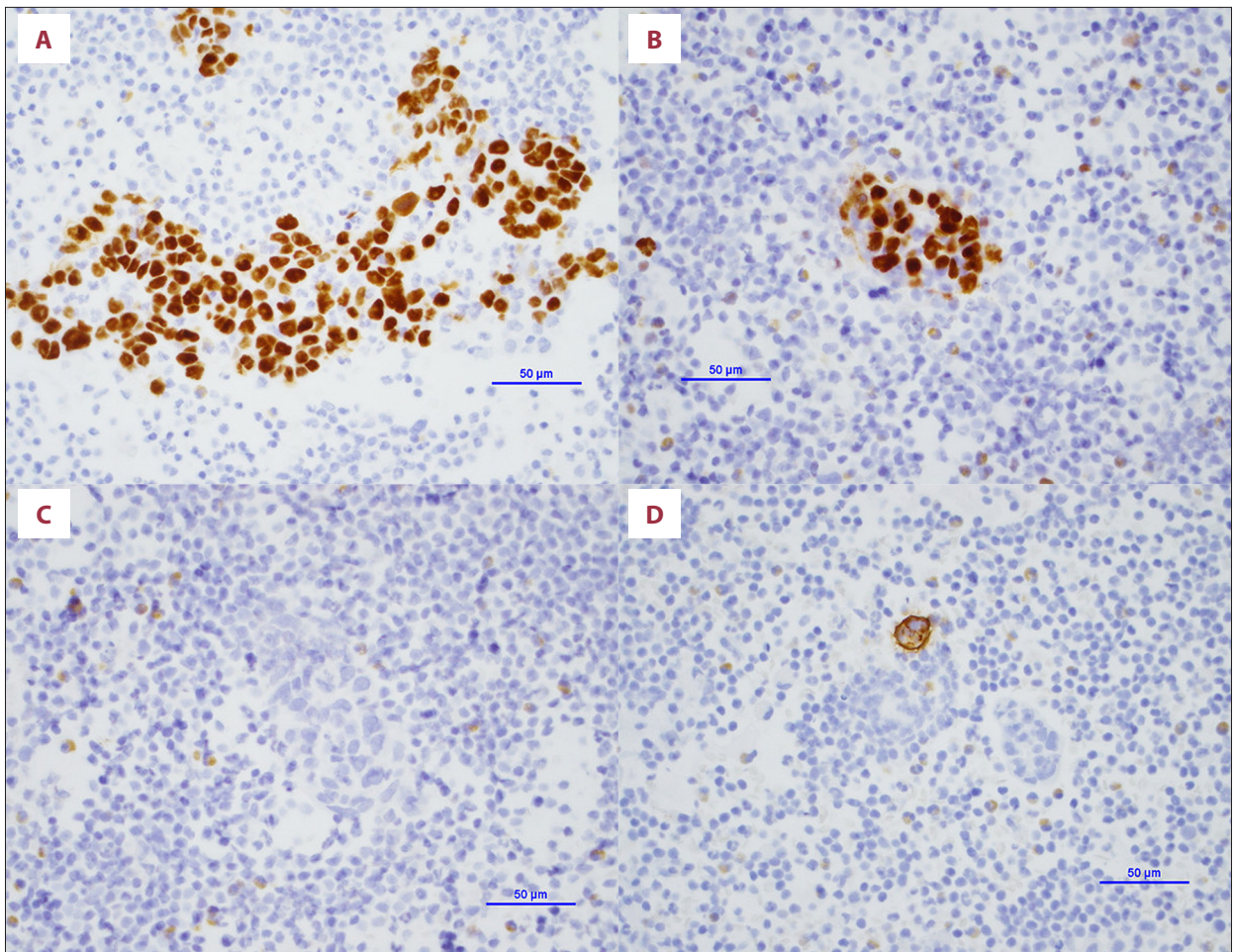


Figure 3. Pathological view of tumor cells on the cell block of pleural effusion (×400). Immunohistochemical staining revealing the expression of: (A) p40 and (B) p63. Negative immunohistochemical staining for: (C) calretinin and (D) D2-40.

the pleura and interlobular pleura was observed; however, on the peripheral side, pleural adhesions were too strong to enable clean peeling of the pleura. These findings were considered to be consistent with pseudomesotheliomatous carcinoma. Moreover, ESCC had invaded the lung, pleura, peritoneum, liver, stomach, ureter, bladder, spine, and lymph nodes. All of the metastases, including multiple pleural nodules, had originated from the ESCC. No signs suggestive of lung asbestosis, such as asbestos corpuscles, were detected.

Discussion

Pseudomesotheliomatous carcinoma was first reported by Harwood et al. in 1976 [2]. The term “pseudomesotheliomatous carcinoma” refers to rare tumors that mimic MPM radiologically and clinically but differ from MPM histopathologically. Most pseudomesotheliomatous carcinomas originate from lung cancer although some cases have been reported in which they have metastasized to the pleura from other sites of the body.

Therefore, the term “pseudomesotheliomatous carcinoma” is used not only for lung cancer, but also for other tumors that mimic MPM. Differentiating between MPM and pseudomesotheliomatous carcinoma is difficult in many cases. Regarding the clinical features, pseudomesotheliomatous tumors are mostly found in elderly men, especially those aged 50–70 years. Most of these patients are heavy smokers, and asbestos exposure is a well-known etiological factor for pseudomesotheliomatous tumors (68–76%) [1,3]. However, since these features are common to MPM, it is difficult to distinguish between these 2 conditions clinically. Cytological differentiation is also considered to be difficult. The detection rate of MPM by performing thoracentesis is not very high (26–82%) [4–7]. Kobayashi et al. reported that among 7 pseudomesotheliomatous carcinoma cases, only 2 could be distinguished from MPM by performing thoracentesis and the remaining 5 cases required biopsy or autopsy [8]. However, different histochemical and immunohistochemical methods have been suggested to help the differential diagnosis of MPM and other carcinomas, especially adenocarcinoma [9,10]. MPM tumor cells show

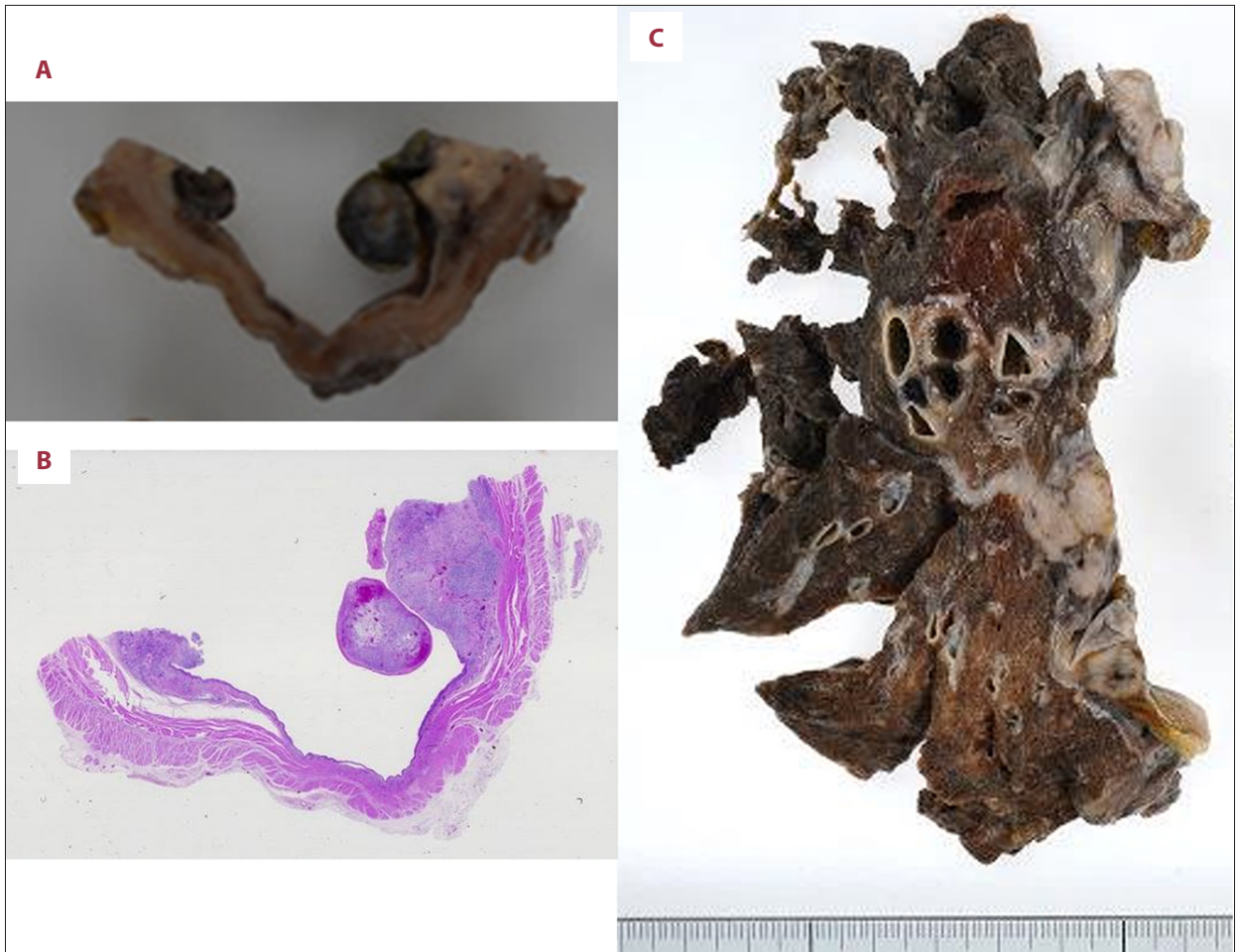


Figure 4. Autopsy findings. (A, B) Serial sections of the esophagus. A specimen strip cut out from the esophagus in the minor axis direction. (A) There was a remnant of cancer showing projecting development. (B) Magnified view of the esophagus showing a 1-cm exophytic tumor (hematoxylin-eosin staining; Loupe image $\times 1$ magnification). Some of the tumor had invaded the proper muscular layer; however, the structure of the wall was not destroyed. There was no rupture or scarring of the muscular layer. (C) Sagittal section of the right lung showing tumor invasion along the pleura and interlobular pleura, causing widespread adhesion of the pleura.

positive expression of vimentin, D2-40, and calretinin, while primary lung adenocarcinomas show positive expression of TTF-1 [11]. In squamous cell carcinoma, the diagnostic utility of immunohistochemistry in distinguishing between MPM and squamous carcinomas includes calretinin (positive mesothelioma marker) and p63 (negative mesothelioma marker) [12].

In the present case, although we fortunately could diagnose metastatic squamous cell carcinoma by performing thoracentesis, we initially suspected MPM due to his past occupation, pleural effusion, pleural thickening, and multiple pleural nodules. With respect to CT imaging, Metintas et al. reported that the CT findings of “rind-like pleural involvement”, “mediastinal pleural involvement”, and “pleural thickness of more than 1 cm” were independent findings for differentiating MPM from metastatic pleural disease [13]. Although these findings were recognized in this case,

the final diagnosis was not MPM. Accurate discrimination of MPM from metastatic pleural disease based only on CT imaging findings is considered to be difficult. In addition, his pleural HA level was extremely high, at 168 mg/L. Previous studies have demonstrated that a high concentration of HA in pleural effusion is suggestive of MPM. The cut-off level for HA concentration between MPM and other diseases is approximately 100 mg/L [14]. Several studies reported that with the cut-off value of 100 mg/L, the sensitivity and specificity of MPM detection were 36.8–44.0% and 96.5–98.7%, respectively [15,16]. Contrastingly, there have been some reports of malignancies, rheumatoid arthritis, and complicated parapneumonic effusion in which the pleural fluid HA concentration exceeds 100 mg/L [17–19]. However, there has been no report on high pleural fluid HA concentration in a case of ESCC; to the best of our knowledge, this is the first case report on this topic in the literature.

The treatment method for pseudomesotheliomatous carcinoma depends on the origin of a given tumor; however, these carcinomas have a poor prognosis, with a median patient survival of approximately 8 months [1]. Our patient survived for only approximately 6 months after the diagnosis was established, despite receiving standard chemotherapy.

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Conclusions

In the present case, ESCC diffusely metastasized to the pleura, causing pleural effusion accompanied with high HA concentration, which manifested with mesothelioma-like findings. Although pseudomesotheliomatous tumors are rare malignancies, ESCC should be suspected as the primary tumor for pseudomesotheliomatous carcinoma.

Conflict of interest

None.