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CASE REPORT

# A Patient with Pulmonary Spindle Cell Carcinoma

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***ABSTRACT*** —— ***Background.*** Pulmonary spindle cell carcinoma is a rare lung cancer which was first classified in 1999 by the World Health Organization (WHO). ***Case.*** A 70-year-old man was admitted to our hospital because of bloody sputum, right-side chest and back pain, and an abnormal lung shadow. He was originally given a diagnosis of poorly differentiated non-small cell lung carcinoma based on cytology. The tumor had invaded the bones, and the patient received radiotherapy and chemotherapy, both of which were ineffective. The cancer progressed and he died 5 months later. An autopsy revealed that the cancer was sarcomatoid carcinoma (subgroup, spindle cell carcinoma) according to the 2004 WHO classification of tumors. It was difficult to distinguish the carcinoma from sarcomatoid mesothelioma by pathological examination alone. Initial chest computed tomography had showed a lung mass that led to the diagnosis of sarcomatoid carcinoma. The cause directly leading to his death was respiratory failure caused by diffuse alveolar damage. ***Conclusion.*** Pulmonary spindle cell carcinoma is believed to have a poor prognosis and is sometimes difficult to distinguish from sarcomatoid mesothelioma. Additional study of cases is needed to confirm this disease entity and to develop better treatments.

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***KEY WORDS*** —— Sarcomatoid carcinoma, Spindle cell carcinoma, Immunohistochemistry, Lung, Sarcomatoid mesothelioma

## BACKGROUND

Sarcomatoid carcinomas are a group of poorly differentiated non-small cell lung carcinomas that contain a component of sarcoma or sarcoma-like (spindle and/or giant cell) differentiation.[1] Five subgroups representing a morphological continuum are currently recognized: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma. These tumors are rare, accounting for only approximately 0.3-1.3% of all lung malignancies.[1] Spindle cell carcinoma is defined as non-small cell carcinoma consisting of only spindle-shaped tumor cells with cohesive nests and irregular fascicles of overtly malignant cells featuring nuclear hyperchromasia and distinct nucleoli. It was reported that among 37 cases of sarcomatoid carcinoma of the lung, only 1 case was spindle cell carcinoma without recognizable carcinomatous elements.[2] Rossi et al. found 10 cases of spindle cell carcinoma among 75 cases of sarcomatoid carcinoma,[3] and Fishback et al. reported that 9.4% of patients had pure spindle cell carcinomas.[4] We report a case of rapidly progressing case of pulmonary spindle cell carcinoma, who was resistant to chemotherapy and radiotherapy.

## CASE

A 70-year-old man presented at a cardiovascular clinic complaining of bloody sputum and right-side chest and back pain, which had deteriorated over 2 weeks. He had undergone aortic valve replacement surgery for aortic regurgitation 13 years previously. He was given a diagnosis of hyperlipidemia and gout 14 years previously,

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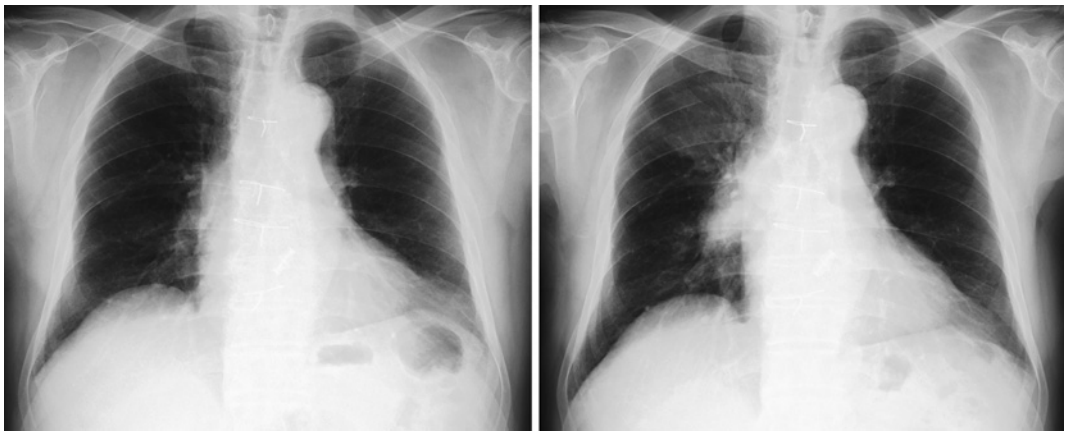


**Figure 1.** A chest radiograph 6 months before admission showed no abnormalities in the lung (**A**). A chest radiograph on admission showed a right-side hilar mass and ill-defined infiltrate in the right upper lung field (**B**).

**Table 1.** Laboratory Tests on Admission

| | On Admission | Reference Range | | On Admission | Reference Range |
|---|---|---|---|---|---|
| White cells (per $mm^3$) | 10670 | (3400-8800) | Potassium (mmol/*l*) | 4.2 | (3.4-4.9) |
| Differential count (%) | | | Chloride (mmol/*l*) | 96 | (98-108) |
| Neutrophils | 91 | (16-60) | Calcium (mg/dl) | 8.9 | (8.6-10.8) |
| Lymphocytes | 5 | (18-50) | Lactate dehydrogenase (U/*l*) | 193 | (106-220) |
| Monocytes | 3 | (1-10) | Alanine aminotransferase (U/*l*) | 36 | (8-40) |
| Eosinophils | 1 | (1-7) | Aspartate aminotransferase (U/*l*) | 67 | (5-35) |
| Basophils | 0 | (0-2) | Alkaline phosphatase | 421 | (100-340) |
| Atypical lymphocytes | 0 | | Bilirubin Total (mg/dl) | 0.8 | (0.3-1.10) |
| Hemoglobin (g/dl) | 11.7 | (13.2-17.2) | Conjugated (mg/dl) | 0.21 | (0-0.3) |
| Hematocrit (%) | 34.8 | (39.2-49.2) | Glucose (mg/dl) | 254 | (60-110) |
| Platelet count ($\times 10^4$ per $mm^3$) | 32.6 | (11.8-36.4) | Hemoglobin A1c (%) | 8.6 | (4.3-5.8) |
| Erythrocyte sedimentation rate (mm/hr) | 110 | (2-10) | Total cholesterol (mg/dl) | 137 | (130-220) |
| Prothrombin time (sec) | 17.2 | | Amylase (U/*l*) | 72 | (35-120) |
| International normalized ratio | 1.99 | | C-reactive protein (mg/dl) | 22.4 | (< = 0.5) |
| Partial thromboplastin time (sec) | 37.7 | | | | |
| Total protein (g/dl) | 6.3 | (6.8-8.2) | Carcinoembryonic antigen (ng/ml) | 2.2 | (<5) |
| Albumin (g/dl) | 2.9 | (3.7-5.2) | Carbohydrate antigen 19-9 (ng/ml) | 13.4 | (<37) |
| Urea nitrogen (mg/dl) | 17 | (5-22) | Sialyl lewis X antigen (U/ml) | 24 | (< = 38) |
| Creatinine (mg/dl) | 0.74 | (0.6-1.3) | Squamous cell carcinoma antigen (ng/ml) | 0.7 | (< = 1.5) |
| Sodium (mmol/*l*) | 134 | (134-146) | Soluble cytokeratin 19 fragments (ng/ml) | 1.1 | (< = 3.5) |
| | | | Neuron specific enolase (ng/ml) | 11 | (< = 10) |

diabetes mellitus 12 years previously, and hypertension 8 years previously. He was not a smoker but could have inhaled small particles, because he had been a teacher who had written on blackboards with chalk. As chest radiography revealed abnormalities that were not present 6 months previously (Figure 1A), he was referred to our hospital. On physical examination, his lungs were clear on auscultation, but lung sounds were reduced in intensity in the right lung field. There was no peripheral edema. His temperature was 36.0℃, his pulse was regular at 100 beats per minute, and oxygen saturation by pulse oximeter ($SpO_2$) was 95% breathing room air. Laboratory findings (Table 1) showed severe inflammation (C-reactive protein, 22.4 mg/dl), but tumor markers were within the normal range. Chest radiography revealed a mass lesion in the right hilum and abnormal densities in the right upper lung field (Figure 1B). A chest computed tomography (CT) scan revealed a 4×3-

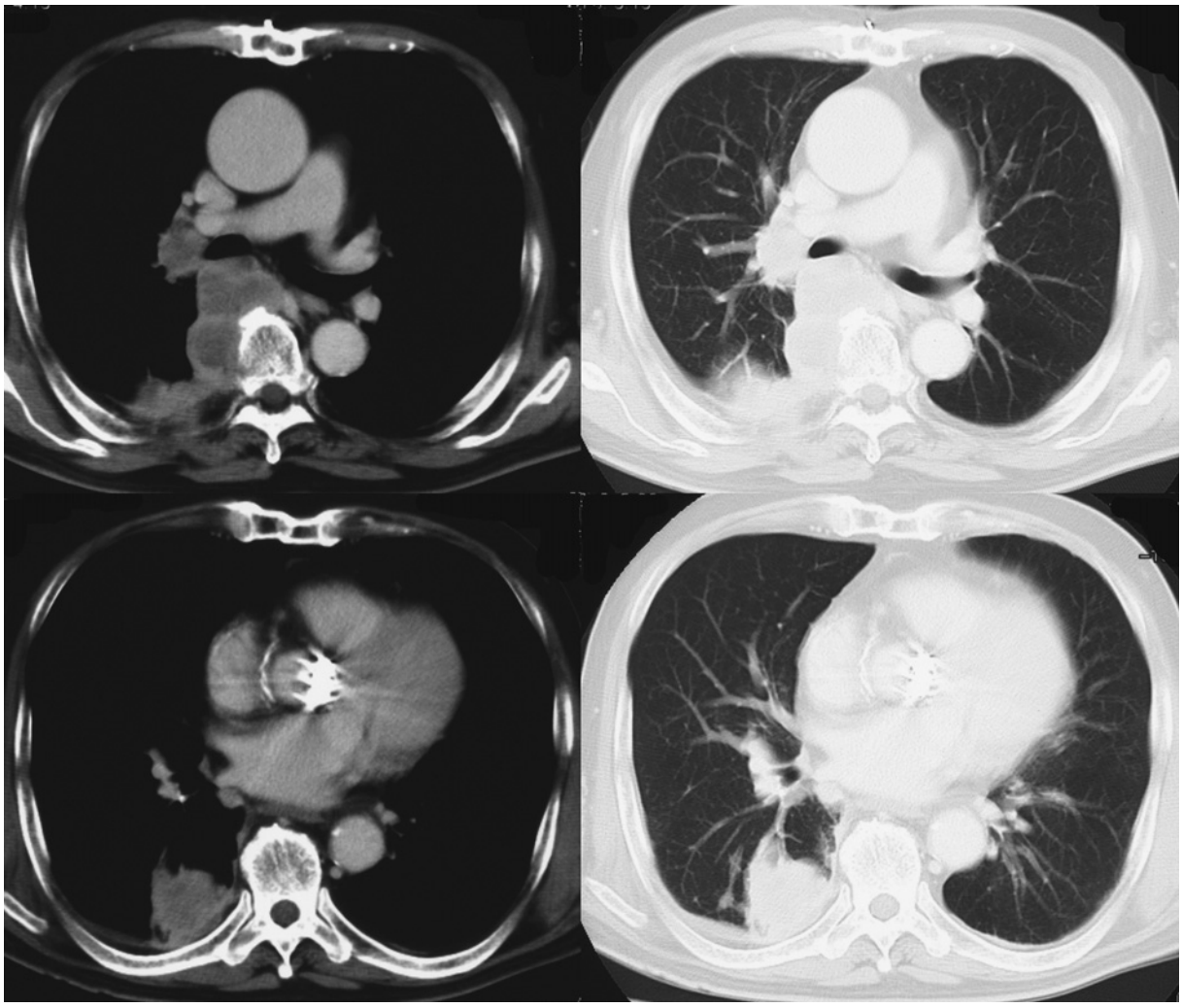

**Figure 2.** Computed tomography of the chest. An axial image revealed a low density mass extending into the ribs, vertebra, upper lung, spine, hilar lymph node, and mediastinal lymph nodes.

cm mass at the superior segment in the right lower lobe of the lung (Figure 2). The center of the mass showed low density on CT and the mass had invaded the upper lung, spine, ribs, and had spread into the hilar and mediastinal lymph nodes (Figure 2). Magnetic resonance imaging also revealed pleural and vertebral invasion (Figure 3). Bone scintigraphy showed rib metastasis. A bronchoscopy was performed, and curette cytology and transbronchial lymph node aspiration cytology specimens were obtained (Figure 4). He was given a diagnosis of poorly differentiated non-small cell lung carcinoma, cT4N2M1, stage IV, performance status 1. We tried to treat him with a combination chemotherapy using carboplatin and paclitaxel, but it was stopped because he developed an anaphylactic reaction to the paclitaxel. He underwent radiotherapy for bone involvement (30 Gy for the sixth thoracic vertebra, 39 Gy for the eleventh thoracic vertebra, and 30 Gy for the right fifth rib). Chemotherapy (two cycles of carboplatin plus vinorelbine and one cycle of carboplatin plus gemcitabine) was ineffective, and the clinical response was progressive disease (PD) according to the criteria. The cancer progressed, and he died of respiratory failure due to acute respiratory distress syndrome (ARDS) 5 months after admission. The autopsy results showed that the direct cause of death was diffuse alveolar damage (DAD) in the organizing stage, which confirmed the clinical diagnosis. Gross examination of the lungs at autopsy (Figure 5) showed that the ivory-white 5-cm tumor with a cavity was located at the superior segment in the right lower lobe. The tumor had spread into the pleural space, including the major and minor fissures, and encased the

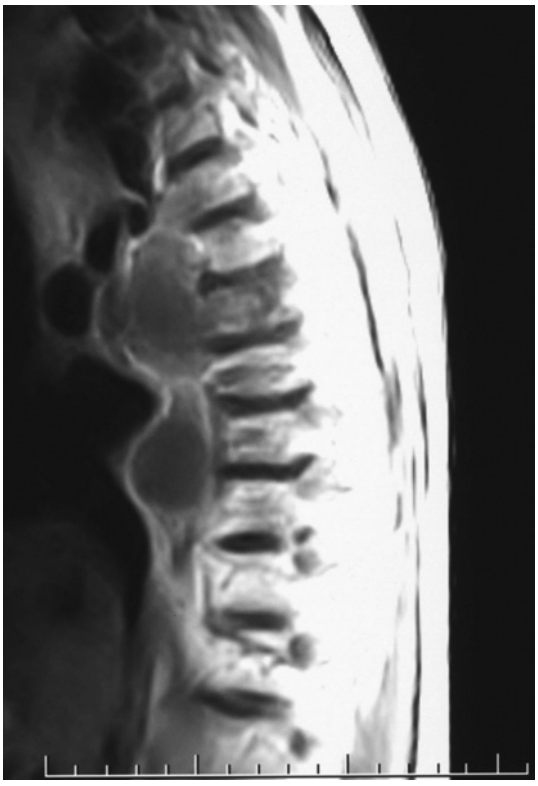

**Figure 3.** Magnetic resonance imaging of the chest. A sagittal image revealed the mass extending into the vertebra.

entire lung. Metastases were observed in the mediastinal lymph nodes, bones, and lungs. Sections taken from various portions of the tumor showed only spindle cells arranged in an interlacing fascicular pattern. Transitions to adenocarcinoma, squamous cell, giant cell, or large cell carcinoma were not seen (Figure 6). Immunohistochemical staining for epithelial markers including cytokeratins (CAM5.2 and AE1/AE3) were positive (Figure 7), whereas immunohistochemical staining for lung adenocarcinoma markers (TTF-1 and napsin-A) were negative (Figure 7). Immunohistochemical staining for calretinin, WT1, D2-40, keratins 5 and 6, which are mesothelioma markers, were focally positive (Figure 8).

Immunohistochemical staining for SMA, desmin, S-100, HHF35, and CD34, which are mesenchymal tumor markers, were negative, suggesting that the tumor was unlikely to be a sarcoma. Distinguishing sarcomatoid carcinoma of the lung from a secondary invasion of the pleura can be exceedingly difficult.[1] A wide immunophenotypic overlap exists among sarcomatoid mesotheliomas, sarcoma, and sarcomatoid carcinomas; therefore, immunostaining does not reliably differentiate these possibilities.[1,3,5,6] In such cases, gross and clinical features may be helpful. For sarcomatoid tumors involving the pleural lining, clinicopathological data, especially in-

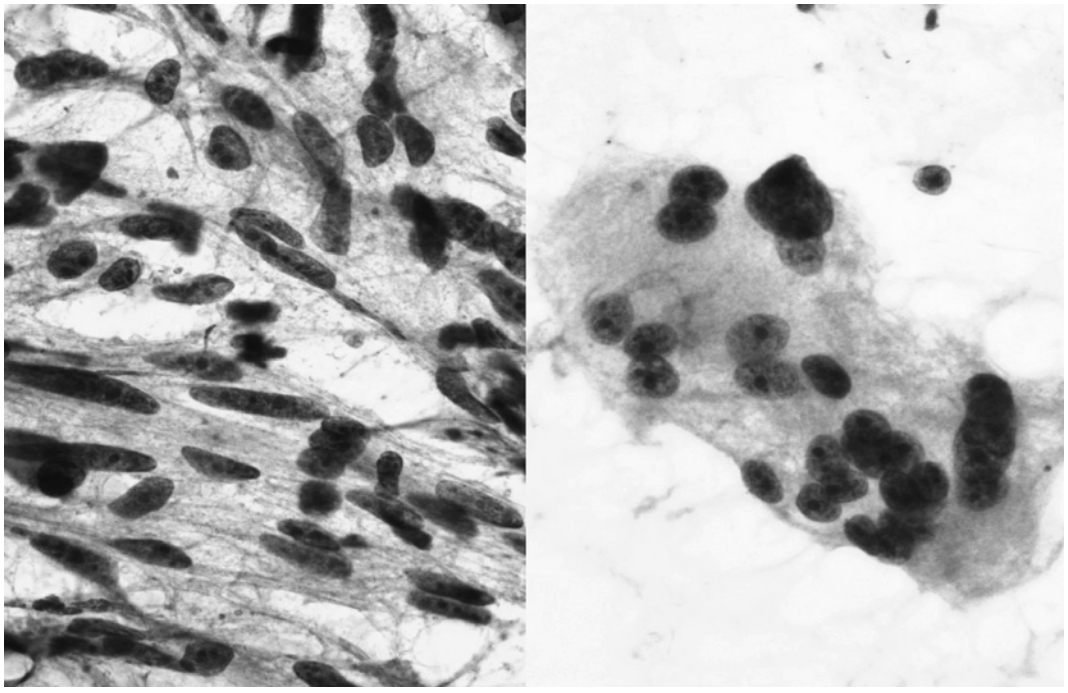

**Figure 4.** Curettage cytology and transbronchial lymph node aspiration cytology.

formation about the gross appearance of the tumor (i.e., localized vs. diffuse pleural-based mass), should be noted and carefully correlated with microscopic and immunohistochemical findings.[1,5] In the present case, it was difficult to distinguish sarcomatoid mesothelioma by pathological examination only, but the initial chest CT indicated a lung mass and showed limited spread to the pleura (Figure 2); therefore, we believed that this case was sarcomatoid carcinoma (subgroup, spindle cell carcinoma) of the lung invading the pleura, and not sarcomatoid mesothelioma.

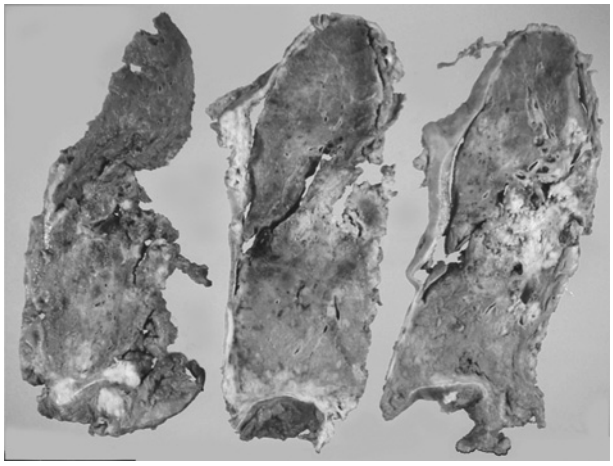

**Figure 5.** Gross image of the lung at autopsy showing that the ivory-white 5-cm tumor with a cavity located at the superior segment in the right lower lobe of the lung. The tumor had spread into the pleural space, including major and minor fissures, and encased the entire lung.

## DISCUSSION

In the second edition of the WHO histological classification of lung tumors, spindle cell carcinoma is classified as a variant of squamous cell carcinoma, and giant cell carcinoma is classified as a variant of large cell carcinoma.[7] Since the third edition was released in 1999, spindle cell carcinoma has been classified as a sarcomatoid carcinoma, which is a carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements.[8] In the current 2004 edition, spindle cell carcinoma is classified as a subgroup of sarcomatoid carcinomas.[1]

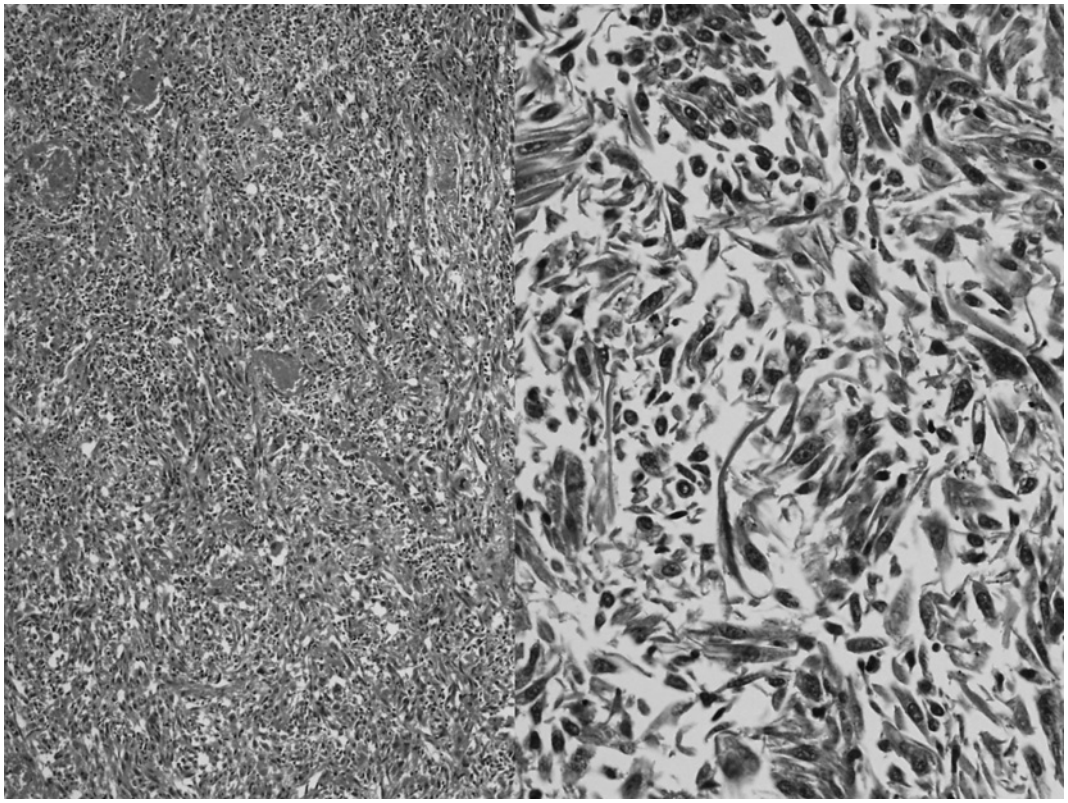

**Figure 6.** Sections taken from various portions of the tumor showed a monophasic spindle cell type with an interlacing fascicular pattern.

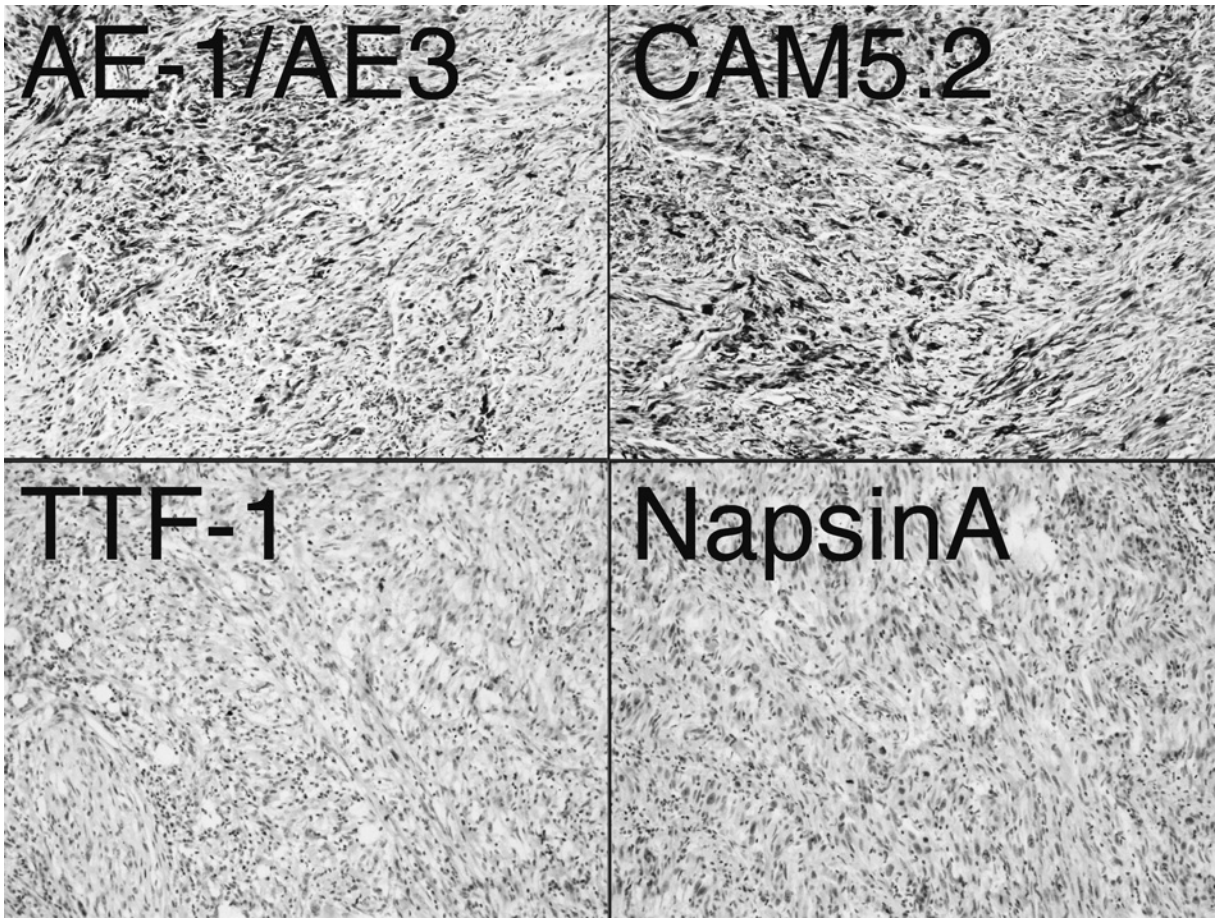


**Figure 7.** Immunohistochemical staining for cytokeratin multi (AE1/AE3), cytokeratin (CAM5.2), transcription termination factor (TTF)-1, and napsin-A.

Many investigators believe that carcinoma cells change into neoplastic spindle cells and giant cells and that these cells are still carcinoma cells because the transition to spindle cells is occasionally recognized.[2] Molecular studies have established that the epithelial and sarcomatoid components of pleomorphic carcinoma have identical molecular profiles, including equivalent patterns of acquired allelic loss,[9] p53 mutation profile,[10] and X chromosome inactivation.[11] A high percentage of pleomorphic carcinomas are reported to have a CYP1A12 variant.[12] The molecular profiles of these tumors are similar to those of other non-small cell tumors. Beta-catenin mutations are seen in blastomas.[13]

In our case, only spindle cells, but not carcinomatous areas, were evident at the time of death. Chemotherapy and radiotherapy may have been effective against the carcinomatous components and that insensitive sarcomatoid area that remained. Although some authors believe that irradiation causes sarcomatous or anaplastic changes in carcinomas, it would be unlikely that all of the carcinoma components had changed into sarcomatous components in the present case.

The differential diagnosis of spindle cell carcinoma includes true sarcomas, such as malignant fibrous histiocytoma (MFH), a very rare neoplasm. It was difficult to distinguish primary MFH of the lung from spindle cell carcinoma by examining hematoxylin and eosin sections because there was no evidence of epithelial differentiation. In our case the tumor was not diagnosed as a sarcoma, because the immunohistochemical staining for epithelial markers was positive, whereas that for markers of mesenchymal neoplasms was negative. It was difficult to differentiate the carcinoma from sarcomatoid mesothelioma by pathological examination. Both sarcomatoid carcinoma and sarcomatoid mesothelioma were compatible with the results of the immunohistochemical staining, and the differentiation between sarcomatoid mesothelioma from sarcomatoid carcinoma of the lung

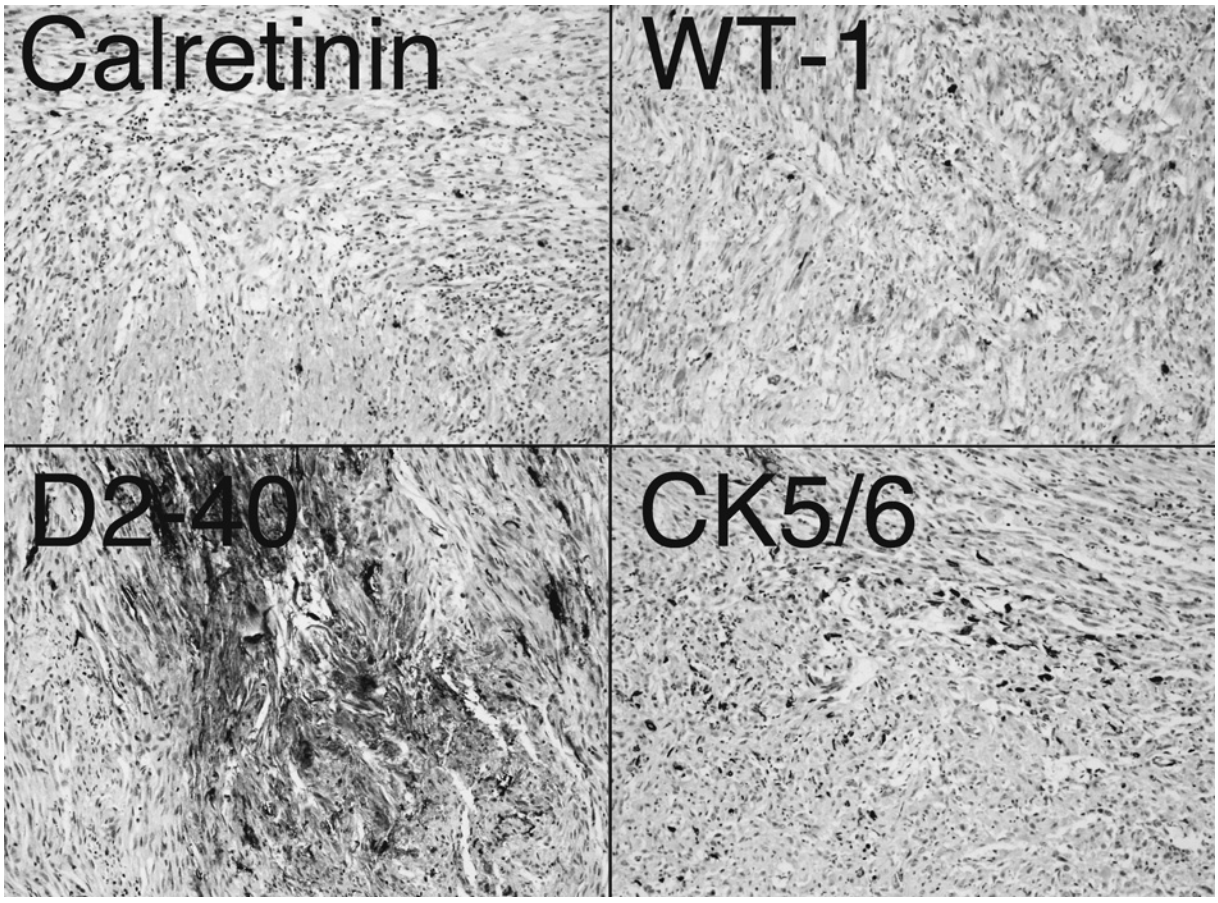


**Figure 8.** Immunohistochemical staining for calretinin, Wilms' tumor suppressor (WT1), D2-40, and keratins 5 and 6 (CK5/6).

that secondarily invades the pleura can be exceedingly difficult.[1] Furthermore, immunostaining does not reliably distinguish these possibilities.[1]

In such cases, gross and clinical features may be helpful.[1] The patient had no history of prior asbestos exposure, which is present in more than 90% of pleural mesotheliomas in men from most industrialized countries.[1] Moreover, there were no asbestos fibers on pathological examination at autopsy. On admission the patient had a 4×3-cm mass at the superior segment in the right lower lung lobe, which is typically absent in mesothelioma, and this finding lead to the diagnosis of sarcomatoid carcinoma.

The average age at diagnosis in patients with sarcomatoid carcinoma is 60 years, and the men to women ratio is almost 4:1.[1] The factors implicated in the etiology of sarcomatoid carcinomas are similar to those involved in conventional histological types. Tobacco smoking is a major factor and more than 90% of patients with pleomorphic carcinoma are heavy cigarette smokers.[1] Some cases may be related to asbestos exposure.[1] Sarcomatoid carcinomas can arise in the central or peripheral lung, but a predilection for the upper lobes has been reported. Peripheral tumors grow to large sizes, and patients often present with chest pain due to pleural or chest wall invasion.[1] A case report[14] showed extensive F-18 fluorodeoxyglucose uptake in spindle cell carcinoma of the lung.

Sarcomatoid carcinomas may have worse outcome than conventional non-small cell carcinomas,[1,3] and half of patients who presenting with stage I disease have a 5-year survival rate of only 20%, and adjuvant chemotherapy and radiotherapy do not appear helpful. In contrast, Nakajima et al.[2] showed that there was no apparent difference in biological behavior between sarcomatoid carcinoma and ordinary lung carcinoma.

Our case was very characteristic of sarcomatoid carcinoma in terms of symptoms, radiographic findings, poor response to chemotherapy and radiotherapy, and rapid progression.

A case report described a patient with an unresectable pulmonary spindle cell carcinoma who, showing no response to conventional treatment with combined modality therapy, chose to medicate herself with daily doses of germanium obtained from a health food store.[15] She noted prompt symptomatic improvement and remained clinically and radiographically free of disease 42 months after starting her alternative therapy. Because sarcomatoid carcinoma has a poor response to chemotherapy and radiotherapy, rapid progression, and poor prognosis, we need to seek better treatments for this rare cancer.

## CONCLUSION

We reported a patient with aggressive lung pulmonary spindle cell carcinoma that was aggressive and resistant to chemotherapy and radiotherapy. Additional case studies are needed to clarify this disease entity and establish better treatments.

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