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An Autopsy Case of Rapidly Progressing Spindle Cell Carcinoma of the Lung Accompanied with Intratumor Hemorrhage

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, 74
Final Diagnosis: Spindle cell carcinoma of the lung
Symptoms: —
Medication: Pemetrexed • carboplatin
Clinical Procedure: Biopsy and autopsy
Specialty: Oncology

Objective: Rare disease

Background: Spindle cell carcinoma (SPCC) of the lung is a subset of sarcomatoid carcinoma. Its clinical features are unclear because of its rarity. Here, we report an autopsy case of SPCC and review CT findings and chemotherapeutic regimens based on previous reports of this disease. To our knowledge, this is the first reported case of pemetrexed used to treat SPCC.

Case Report: A 74-year-old Japanese male presented with dyspnea and contrast-enhanced computed tomography (CT) showed abundant left pleural effusion and a mass in lower lobe of the left lung. By the tumor biopsy, he was diagnosed for SPCC of the lung, cT3N0M1a, stage IV. The tumor was resistant to chemotherapy with carboplatin and pemetrexed, and rapidly progressed. Autopsy revealed abundant hemorrhage within the tumor, which apparently reflects a low-density area in CT.

Conclusions: Present case and the accumulation of cases indicate that low-density areas in CT and rapid tumor progression may be common SPCC findings.

MeSH Keywords: Tomography, X-Ray Computed • Carcinoma • Antineoplastic Agents

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/894443

Background

Sarcomatoid carcinoma of the lung is a subset of lung cancer, defined by the World Health Organization (WHO) in 2004 as including five histological subtypes: giant cell carcinoma, pleomorphic carcinoma, carcinosarcoma, pulmonary blastoma, and spindle cell carcinoma (SPCC) [1,2]. Sarcomatoid carcinoma is rare, comprising approximately 1% of all lung malignancies. About 75% of sarcomatoid carcinoma of the lung cases are pleomorphic carcinoma; spindle cell carcinoma reportedly accounts for 9.4% [1,3]. Because the clinical features of SPCC are unclear because of its rarity, the accumulation of the case reports is important. We here report an autopsy case of SPCC, which was seen as a mass with an internal low-density area in computed tomography (CT); it was resistant to chemotherapy consisting of carboplatin and pemetrexed; and rapidly progressed, with hemorrhage within the tumor. In addition, we review CT finings and chemotherapeutic regimens based on the previous reports of SPCC.

Case Report

A 74-year-old Japanese male presented with dyspnea for two weeks. He had an 84-pack-year smoking history and had worked for the construction industry for 40 years. Also, he received gastrectomy and treated with doxifluridine because of gastric cancer at 54-year-old. Then, he had been in good condition without any comorbidities. Contrast-enhanced (CE)-CT showed abundant left pleural effusion and a mass of ~85 mm in lower lobe of the left lung. The mass had a little enhancement and showed an internal low-density area, and focal thickening outside the mass at the left pleura (Figure 1A). Interestingly, the border with the internal low-density areas inside the mass and pleural effusion was indistinct in a part. ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) showed abnormal FDG accumulation in the mass and thickening pleura; no other abnormal sites were shown. The magnetic resonance imaging (MRI) of the head showed no metastasis. Tumor markers for the lung cancer were carcinoembryonic antigen (CEA): 9.4 ng/mL, which was a little high; other tumor markers, including sialyl Lewis Xi antigen, squamous cell carcinoma antigen, cytokeratin 19 fragment, neuron specific enolase and pro-gastrin releasing peptide, were within normal limits. Respiratory function test showed restrictive impairment: the vital capacity of the predicted value (%VC) was 51.6%, and forced expiratory volume in 1 second divided by forced vital capacity (FEV1/FVC ratio) was 79.5%. Performance Status defined by Eastern Cooperative Oncology Group was grade 2. Oxygen saturation of arterial blood measured by pulse oximeter (SpO2) was 92% at room air.

Though the obtained pleural fluid was bloody and exudative, cytology did not reveal obvious malignant cells. Thoracentesis was performed twice more, but the results were same. A bronchoscopy showed upper and lower bronchus of the left lung were oppressed and a transbronchial lung biopsy was performed, but the sample showed no malignant findings. The tumor biopsy used with thoracoscope finally detected the malignant lesion from thickening left parietal pleura outside of the mass. The obtained specimen contained a sarcomatoid lesion which consisted of spindle-shaped tumor cells.

Based on immunohistochemical findings, we diagnosed the non-small cell lung cancer including sarcomatoid carcinoma, with pleural dissemination, cT3N0M1a (PLE), Stage IV by the 7th Union for International Cancer Control (UICC) criteria. After drainage of the pleural fluid and pleurodesis used with picibanil and minocycline, chemotherapy was started within two weeks after thoracoscopic examination. The chemotherapy regimen was carboplatin (AUC 5, day 1) and pemetrexed (500 mg/m^2, day 1). However, CE-CT taken 15 days after chemotherapy was initiated showed a progressive lesion with large internal low-density area (Figure 1B). In addition, SpO2 decreased gradually for 3 days before death and finally went down below 80% under inhalation of 15 L/min of oxygen. The patient died of respiratory failure 19 days after starting the first cycle of chemotherapy. No hemoptysis was observed during the diagnostic and treatment process.

On autopsy, the tumor was found to occupy almost all of left thoracic cavity and invaded to the pulmonary artery and vein. Inside of the mass was abundant hemorrhage, which was thought to have been the low-density area seen in the CE-CT (Figure 2A). The solid compartment of the left lung consisted of disarrayed malignant spindle cells surrounded by myxoid interstitial tissue with propagated collagen fibers (Figure 2B) and tumor cells invaded blood vessels. No epithelial component was contained. Immunohistochemical staining showed the malignant cells to be positive for cytokeratin AE1/AE3 and negative for CEA, smooth muscle actin, synaptophysin, chromogranin-A, calretinin, thyroid transcription facter-1, Napsin-A, p63, desmin, S-100 protein, and bcl-2. Tumor cells were also positive for Ki67 (index 50%) (Figure 2C). There was no distant metastatic lesion. According to the above results, the definite diagnosis was SPCC of the left lung, pT4N0M1a. In addition, no anti-tumor efficacy of chemotherapy such as apoptotic cells was observed.

Discussion

In the present case, the tumor was resistant to chemotherapy consisting of carboplatin and pemetrexed, and rapidly progressed with hemorrhage within the tumor. We searched case

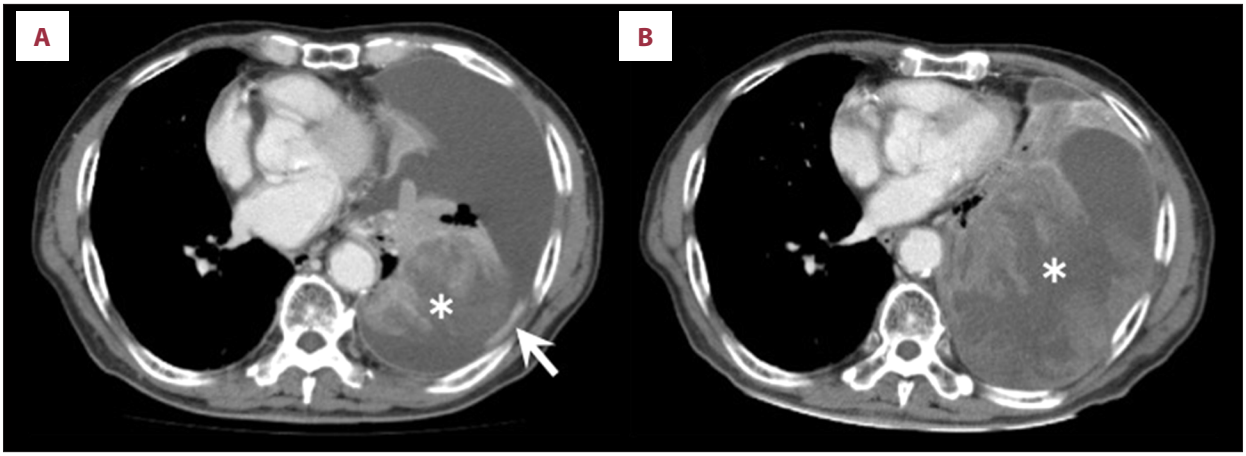

Figure 1. Contrast-enhanced computed tomography (CE-CT). (**A**) CT at hospitalization shows abundant left pleural fluid and ~85-mm mass in lower left lobe with an internal low-density area (asterisk), and thickening left pleura outside of the mass (arrow). (**B**) CT at 15 days after chemotherapy shows progressive lesion with large internal low-density area (asterisk), which was thought to be hemorrhage or mucous fluid.

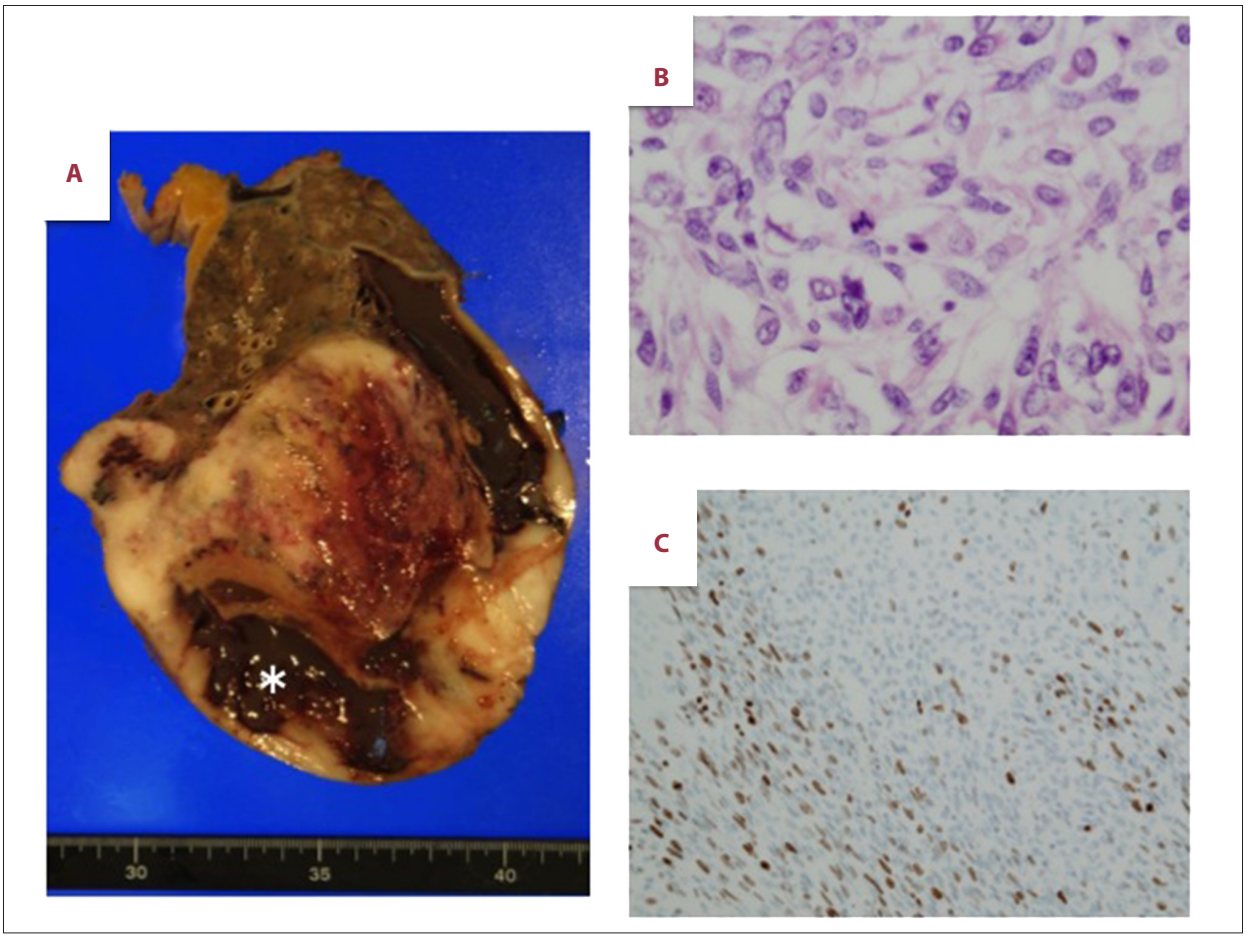

Figure 2. Autopsy findings. (**A**) Macroscopic autopsy findings. The tumor occupied almost all of the left thoracic cavity; inside of the mass was abundant hemorrhage (asterisk), which was thought to reflect the low-density area seen in the CE-CT. (**B**) Microscopic autopsy findings. The solid tumor tissue in the left lung consisted of disarrayed malignant spindle cells surrounded by myxoid interstitial tissue with propagated collagen fiber (hematoxylin and eosin staining ×100). (**C**) Immunohistochemical staining (×200) shows Ki67^{+} malignant cells (index 50%).

Table 1. Characterization of reported cases of spindle cell carcinoma of the lung.

Case No.	Ref No.	Age (yrs)	Sex	Smoking history (pack-year)	TNM stage	Location in lung field	Central low density in CT	Pathological findings inside the tumor
1	4	70	M	Never	cT4N2M1, IV	Peripheral	Yes	ND
2	5	53	M	75	cT3N1M1, IV	Peripheral	Yes	ND
3	6	47	F	ND	cT4N?M?, IIIA or greater	Central	Yes	ND
4	7	65	M	125	cT4N2M0, IIIB	Central	ND	Necrosis And Hemorrhage
5	14	59	F	Never	cT4N3M1, IV	Peripheral	ND	ND
6	2	43	F	83	cT3N0M0, IIB	Peripheral	Yes	ND
7	8	73	F	ND	cT2N0M0, IB	Peripheral	ND	Degenerative necrosis
8	9	31	M	ND	cT2N0M0, IB	ND	ND	Hemorrhage
9	9	43	F	ND	cT1N0M0, IA	Peripheral	ND	ND
10	12	68	M	83	pT3N0M0, IIB	Peripheral	Cavity	ND
11	13	70	M	170	cT2N0M0, IB	Peripheral	ND	ND
12	Present case	74	M	84	cT3N0M1, IV	Peripheral	Yes	Hemorrhage

ND – not described.

reports of SPCC from the literature and have summarized the clinical features of 12 reported patients, including the present case in Table 1. Their age range was 31–74 years; four patients were younger than 50 years old. Seven patients were male and five were female.

In general, it has been reported that smoking habit is associated with development of sarcomatoid carcinoma [1]. Smoking history was described in eight of 12 SPCC patients (Table 1). Of which, Two patients were never smokers, suggesting that smoking habit is not always associated with SPCC carcinogenesis, unlike other types of sarcomatoid carcinomas. However, more patients are needed to clarify the effect of smoking on the SPCC carcinogenesis.

Imaging signs for SPCC are unclear because of its rarity. The present case showed a big tumor, the inside of which consisted of a low-density area with indistinct border to pleural effusion in CE-CT, which was found to be abundant hemorrhage in autopsy. Several case reports of SPCC also present low-density areas within the tumors (Table 1) [2,4–6]. Also, in several cases, though low-density areas in CT were not described, specimens obtained by operation or autopsy showed hemorrhage and/or necrosis within the tumor [7–9]. In addition, in 9 of the 12 cases, the tumor was located at the lung periphery. In pleomorphic carcinoma, most patients (>50%) show low-density areas within the tumor in CT, which reflect hemorrhage, necrosis and myxoid degeneration, as confirmed by pathology [10,11]. In addition, sarcomatoid carcinoma is frequently reported to show areas of hemorrhage and necrosis, and occasionally shows cavitation [1,3]. Also, most sarcomatoid carcinomas arise peripherally and rapidly progress to aggressively invade adjacent structures such as the chest wall or the pleura [2,3,10,12].

The above reports, image findings for SPCC in the lung, indicate that it appears with an internal low-density area in CT, locates at periphery of the lung and rapidly progresses. These characteristics might be useful distinguishing SPCC from other carcinomas, such as adenocarcinoma, squamous cell carcinoma and large-cell carcinoma, in which these findings are shown less frequently. In present case, the Ki67 index was approximately 50%, which implied rapid progression, leading to vulnerability of neovessels. In addition, autopsy of present case showed tumor cell invasion to blood vessels. Thus, tumor rapid progression and angioinvasivity might lead to diathesis to easily bleed.

The prognosis and treatment of SPCC of the lung is also unclear [2]. Standard treatment of inoperable sarcomatoid carcinoma cases (including SPCC) has not been established, and many cases have been treated with chemotherapeutic regimens for non-small cell lung carcinoma. We selected pemetrexed because it is a relatively recent developed drug compared to paclitaxel, docetaxel, vinorelbine, or gemcitabine, and

Table 2. Therapeutic efficacy in reported cases of spindle cell carcinoma of the lung.

Case No.	Reference	Surgery	Chemotherapy	Other therapy	Effecacy	Outcome
1	4	–	CBDCA + PTX + VNR + GEM	None	PD	Died after 5 months
2	5	–	CBDCA + PTX	None	PD	Died after 2 months
3	6	–	VP-16 + IFO, CDDP + PTX, ADR + IFO + DTIC	RT, germanium*	Chemotherapy: PD germanium*: CR	CR for 4 years
4	7	–	CDDP + VNR	None	PD	Died after 5 months
5	14	–	CBDCA + PTX	RT	SD	Died after 6 months
6	2	+	Adjuvant CDDP + GEM	None	ND	Relapsed 8 months after operation
7	8	+	Adjuvant uracil-tegafur	None	ND	CR for 11 months
8	9	+	Performed, regimens unclear	RT	ND	Relapsed and died 12 months after operation
9	9	+	None	None	ND	CR for 3 years
10	12	+	Adjuvant S-1 + Krestin	None	ND	Died after 6 months
11	13	+	None	None	ND	Died after 5 months
12	Present case	–	CBDCA + PEM	None	PD	Died after 2 months

ND – not described; CBDCA – carboplatin; PTX – paclitaxel, VNR – vinorelbine; GEM – gemcitabine; VP-16 – etoposide; IFO – ifosfamide; CDDP – cicplatin; ADR – doxorubicin; DTIC – dacarbazine; S-1 – tegafur/gimeracil/oteracil; PEM – pemetrexed; RT – radiotherapy; PD – progressive disease; SD – stable disease; CR – complete response. * Bis-betacarboxyethygermanium sesquioxide.

has a greater anti-cancer efficacy for a subset of non-small cell lung carcinoma. To our knowledge, the present case is the first report of SPCC treated with pemetrexed. Previous case reports of SPCC (Table 2) show some patients with operable cases living a long time [8,9] and other operable cases dying and/or relapsing within a year after surgery [2,9,12,13]. In inoperable cases [4–7,14], platinum-based chemotherapy or chemoradiotherapy was selected according to non-small cell lung carcinoma regimens (Table 2). However, the efficacy was poor and the patients died within 6 months. Interestingly, oral bis-betacarboxyethygermanium sesquioxide got complete response for four years, even after chemoradiotherapy [6]. More patients are needed to confirm the efficacy of bis-betacarboxyethygermanium sesquioxide for SPCC. Sugano et al. reported that the chemotherapy consisted of carboplatin, paclitaxel, and bevacizumab gave a partial response to inoperable sarcomatoid carcinoma of the lung [15]. Although bevacizumab might be a treatment option for sarcomatoid carcinoma, including SPCC, intratumor hemorrhage should be watched carefully for deterioration.

Conclusions

We report an autopsy case of SPCC resistant to chemotherapy with carboplatin and pemetrexed. The low-density area shown by CT had reflected significant intratumor hemorrhage, which may be a common finding in SPCC.

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