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A Case of Pulmonary Pleomorphic Carcinoma Discovered During Optional Low-dose Computed Tomography Screening and Resected at the Early Stage

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Abstract

Pulmonary pleomorphic carcinoma (PPC) is a subgroup of non-small cell lung cancer that contains both epithelial and mesenchymal (sarcomatoid) components. Because of its rarity and aggressiveness, there are few reports describing the early stage of PPC. In this report, we describe a case of PPC detected as a small shadow during optional low-dose computed tomography (CT) screening that was completely resected at the early stage after follow-up.

During a health check-up for a 64-year-old man at our institution, optional low-dose chest CT screening revealed a small ground-glass opacity-like shadow in the peripheral area of the upper lobe of the right lung. Afterwards, the lesion was monitored using standard-dose CT. Although no remarkable changes had been observed up to 12 months, it had become enlarged by the 18-month follow-up. Further examinations did not provide a definitive diagnosis, so a surgical operation was performed for both diagnosis and treatment purposes. As the intraoperative rapid pathologic diagnosis revealed malignancy, a typical right upper lobectomy and mediastinal lymph node dissection were performed. Microscopic images of the tumor showed both epithelial and sarcomatoid components. The pathological diagnosis obtained using permanent sections was PPC resected completely at stage IA.

Keywords Pulmonary pleomorphic carcinoma, lung cancer, low-dose computed tomography

Pulmonary pleomorphic carcinoma (PPC) is a subgroup of non-small cell lung cancer (NSCLC) that contains both epithelial and mesenchymal (sarcomatoid) components. Owing to its rarity and aggressiveness, there have been few reports describing the early stage of PPC. This report describes a case of PPC detected as a small shadow during optional low-dose computed tomography (CT) screening that was completely resected at the early stage after follow-up.

This report was approved by the Ethics Committee of Seirei Social Welfare Community, and general informed consent was obtained from the patient.

Case Report

A 64-year-old man with diabetes, hyperlipidemia, and prostatomegaly underwent a health check-up during a visit to our institution. He had history of smoking 45 packs of cigarettes a year, but was symptom free.

Optional low-dose chest computed tomography (CT) screening revealed a ground-glass opacity (GGO)-like shadow with a diameter of 7–8 mm in the peripheral area of the upper lobe of the right lung (**Fig. 1**). It had been difficult to detect the shadow on a chest radiograph.

The lesion was monitored using standard-dose helical CT after 3, 6, 12, and 18 months. Although the shadow was GGO-like on low-dose CT and the 5-mm slice of standard-dose CT, it was solid on the 2.5-mm slice of standard-dose CT (**Fig. 1**). Up to 12 months, there had been no remarkable change in the shadow but after 18 months, its diameter had increased to approximately 1 cm.

Further examinations were performed, but a definitive diagnosis could not be obtained. The results of the QuantiFERON-TB test (Japan BCG Laboratory, Tokyo), cryptococcal antigen test, aspergillus antigen test, and serum β-D-glucan level were normal. Serum levels of common tumor markers of lung cancer - carcinoembry-

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onic antigen (CEA), Cytokeratin-19 fragments (CYFRA), and pro-gastrin-releasing peptide (pro-GRP) - were all within normal limits (**Table 1**). The SCC antigen level was slightly high, but this is common for smokers. In bronchoscopy that was performed, there were no findings that could lead to a definitive diagnosis. In fluorodeoxyglucose positron emission tomography (FGD-PET), the SUVmax (value = 3.1) indicated weak uptake by the lesion. A whole body search using FGD-PET and magnetic resonance imaging (MRI) of the brain did not reveal any additional lesions.

Surgery for both diagnosis and treatment purposes was performed. Initially, only the tumor and surrounding lung parenchyma were resected for intraoperative rapid pathologic diagnosis (**Fig.2a**, **2b**). As the resected tumor tissue showed malignancy, a typical right upper lobec-

Table 1. Tumor Markers

CEA (carcinoembryonic antigen)	2.1	ng/mL (≤5.0)
SCC (squamous cell carcinoma antigen)	2.0 ↑	ng/mL (<1.5)
CYFRA (cytokeratin 19 fragment)	1.0	ng/mL (<3.5)
ProGRP (pro-gastrin-releasing peptide)	33.5	ng/mL (<81.0)

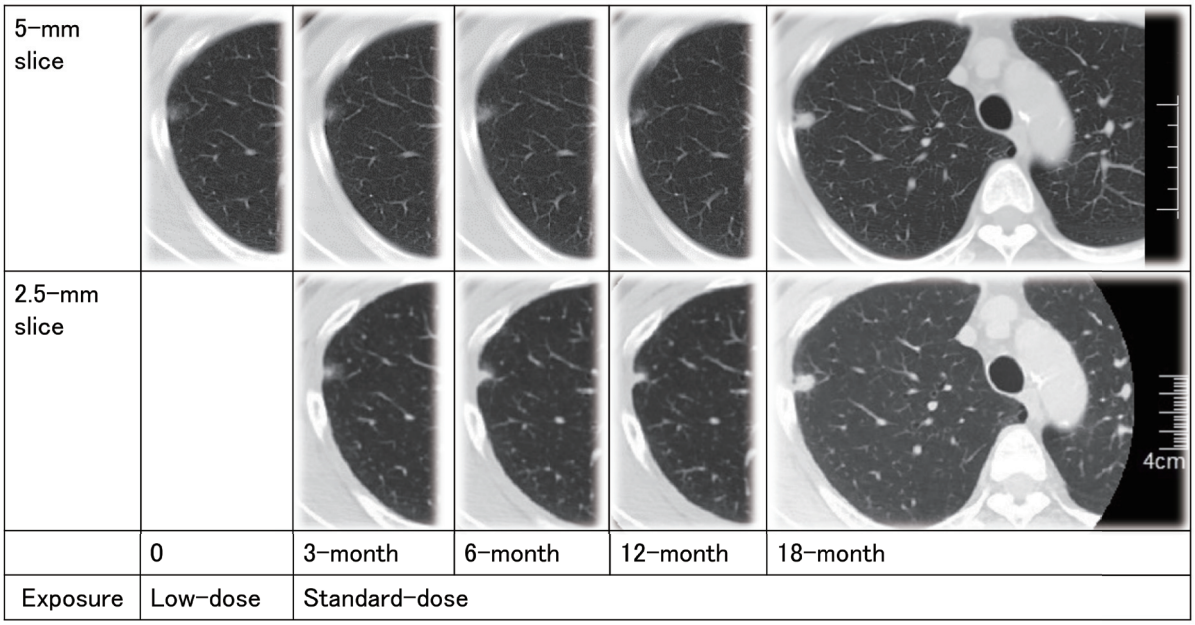

Fig.1. Computed Tomography (CT) Findings

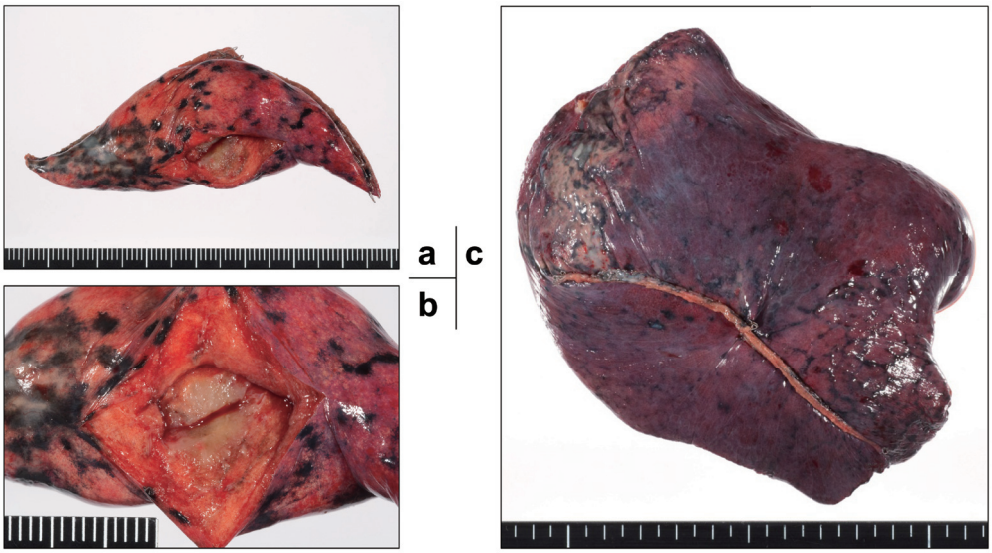

Fig.2. Resected Specimens
(a) Specimen from partially resected lung. (b) Cut surface of tumor. (c) Right upper lobe resected after partial resection.

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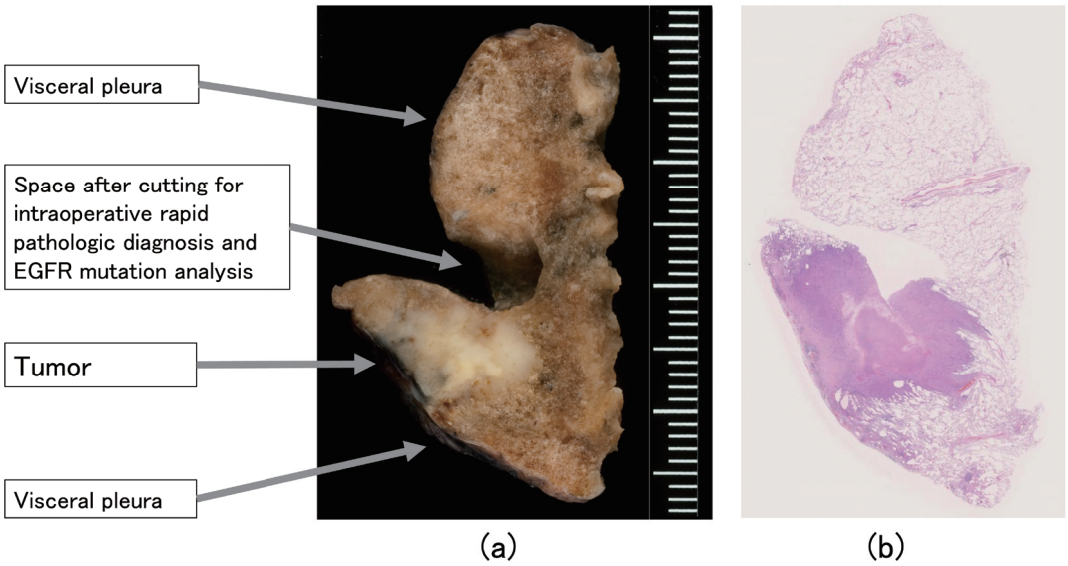

Fig. 3. Macroscopic Findings
(a) Formalin fixed. (b) Hematoxylin and eosin (HE) staining

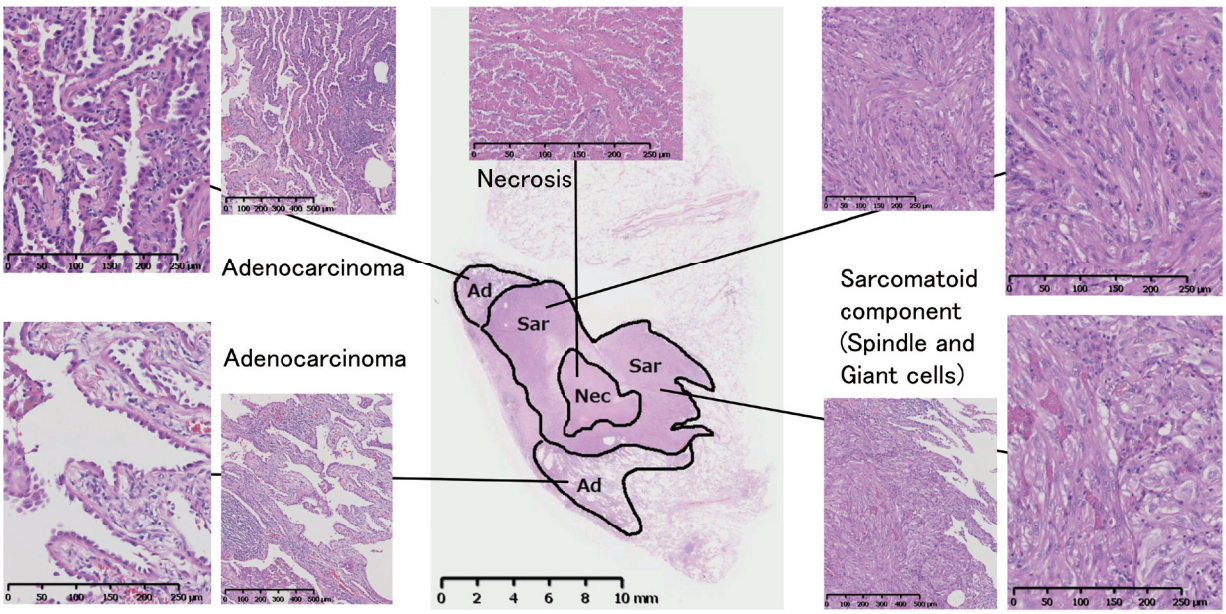

Fig. 4. Microscopic Features (HE staining)
Nec: Necrosis, Sar: Sarcomatoid component, Ad: Adenocarcinoma.

tomy and mediastinal lymph node dissection were performed sequentially (**Fig. 2c**). The operation concluded without any major problems.

The gross features of formalin-fixed tissue are shown in **Fig. 3a**. The tumor was solid, yellowish-white, without cavitation, relatively well-circumscribed, and approximately 1.6 x 1 x 1 cm in size.

Microscopic images showed a three-layered structure (**Fig. 3b**, **Fig. 4**). The central area revealed necrosis, the middle layer consisted of a sarcomatoid component (spindle cells and giant cells), and the outer area contained an adenocarcinoma (**Fig. 4**). The central necrosis consisted of non-specific necrotic tissue and neither caseous necrosis nor cavity formation were observed. Most of the sarcomatoid component was occupied by spindle cells, and giant cells had a scattered distribution. The sarcomatoid component accounted for approximately 80% of the whole area of the tumor. The adenocarcinoma was well to moderately differentiated. Inflammatory fibrous tissue was observed between it and the visceral pleura. These pathological findings gave the impression that the sarcomatoid component was infiltrating the adenocarci-

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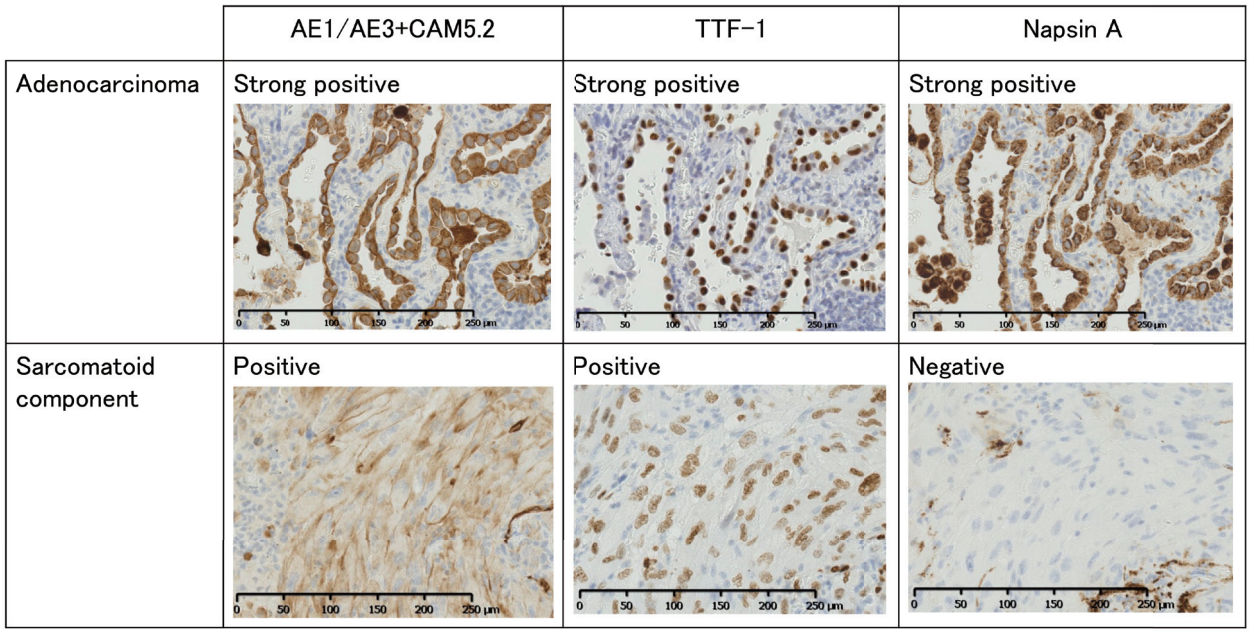

Fig.5. Immunohistochemical Study

noma towards the outside.

Immunostaining showed that the adenocarcinoma was strongly positive for all pan-epithelial markers (AE1/AE3 + CAM5.2), thyroid transcription factor-1 (TTF-1), and Napsin A (**Fig.5**). This staining pattern is commonly found in lung adenocarcinomas. The spindle cells were positive for pan-epithelial markers and TTF-1, but negative for Napsin A, indicating that the spindle cells were partially epithelial in character. If the spindle cells had been completely mesenchymal, the reactions for all these antibodies would have been weak or negative.

From these histopathological findings, a final diagnosis of "pleomorphic carcinoma (80%) with adenocarcinoma (20%)" was made. The TNM classification at the time of the diagnosis was pT1aN0M0, stage IA (according to the current TNM classification 8th edition, pT1bN0M0, stage IA2)[1,2]. The tumor was negative for pleural invasion, pleural dissemination, pulmonary metastasis, and lymph duct invasion, but positive for invasion into the vein. The EGFR gene had a wild-type phenotype.

The patient remains recurrence-free at 4 years after the surgery.

Discussion

PPC is a subgroup of NSCLC that contains both epithelial and mesenchymal (sarcomatoid) components[3–5]. PPC is defined as "a poorly differentiated non-small cell carcinoma namely a squamous cell carcinoma, adenocarcinoma, or undifferentiated non-small cell carcinoma that contains at least 10% spindle and/or giant cells or a carcinoma consisting only of spindle and giant cells"[3].

PPC was first defined in the World Health Organization classification of 1999. In the revised third edition of 2004, PPC was classified under "Sarcomatoid carcinoma"[4]. Currently, in the fourth edition of 2015, pleomorphic carcinoma and the other four types that had been classified under "Sarcomatoid carcinoma" are listed independently[3].

PPC tends to occur in elderly men with a history of smoking and resides in a peripheral location in the upper lobe of the lung[5–15]. In this case report, the patient was a 64-year-old male smoker, and the lesion was located in the periphery of the right upper lobe. All the features of this case were similar to those generally characteristic of PPC.

According to the literature, PPC is rare, accounting for 0.4–3.9% of resected lung cancers[6–10] and therefore, there are few reports of PPC. In addition, due to its aggressiveness, there are even fewer reports describing PPC at the early stage and its behavior[3–5]. In the present case, the lesion was discovered at an early stage in optional low-dose CT screening, and the early stage and behavior were monitored during the follow-up period. There were no remarkable changes in the lesion up to 12 months but it had become enlarged by the 18-month follow-up. So, why was its progression like this?

Currently, the major hypothesis for the histogenesis of PPC is the "divergent hypothesis", i.e., both the epithelial and sarcomatoid components originate from a single clone[3–5]. In this regard, the phenomenon of an epithelial cell converting to a mesenchymal cell in a malignant tumor has been described as "epithelial-to-mesenchymal transition (EMT)"[16]. Also, when EMT occurs, the epithelial cell becomes spindle-shaped, and intracellular

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junctions are decreased[16], which raises the question: does "divergence" in PPC indicate EMT?

Applying the divergent hypothesis to the current case, the lesion might have been pure adenocarcinoma during the period when the CT shadow was stable. Then, part of the adenocarcinoma could have converted to sarcomatoid tissue, and the sarcomatoid component might have proliferated rapidly, which could be the reason that the CT shadow became enlarged later on.

The microscopic features support the above assumptions. The three-layered structure, i.e. central necrosis, middle sarcomatoid component and outer epithelial component, seems to indicate the process of the sarcomatoid component infiltrating the initial epithelial component towards the outside. The central necrosis probably occurred with the rapid increase of the sarcomatoid component.

In the immunohistochemical examination, spindle cells were positive for pan-epithelial markers and TTF-1, but negative for Napsin A, which indicates that the spindle cells were partly epithelial in character and supports the possibility that they were derived from adenocarcinoma.

In the present case, the tumor consisted of a combination of epithelial and sarcomatoid components with the adenocarcinoma as the epithelial component and spindle and giant cells as the sarcomatoid component. To date, various combinations of epithelial and sarcomatoid components have been reported, among them adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other types as epithelial components; and spindle cells only, giant cells only, or both spindle and giant cells as sarcomatoid components. According to the literature, the rate of adenocarcinoma as the epithelial component of PPC was 24–73%, and that of both spindle and giant cells as the sarcomatoid component was 16–57%[6–13].

If the surgery in our case had been performed later, how might the lesion have progressed? The sarcomatoid component might have infiltrated deeper into the adenocarcinoma, and finally, the whole tumor might have consisted of the sarcomatoid component only. The last part of the definition of PPC mentioned above has the statement "or a carcinoma consisting of only of spindle and giant cells" so lung cancer consisting of only a sarcomatoid component is clearly PPC. Apart from a few studies, the rate of this type among all PPCs has been reported to be 0–22%[6–14]. PPC consisting only of a sarcomatoid component may be formed when the progress of this component is faster and completely infiltrates the epithelial component.

The prognosis of PPC is generally poorer compared with that of other NSCLC because metastasis or recurrence is more frequent and most chemotherapies and radiotherapies are ineffective[4,5,7,8]. According to the literature, the 5-year survival rate of patients with PPC was 20–48%[7,8,10,12,13,15], and the median survival was 8–19 months[6–8,11]. Yuki *et al.* reported that subtype according to epithelial or sarcomatoid components did not affect prognosis[12]. As EMT plays an important role in the metastatic mechanism of a malignant tumor[16] and influences its sensitivity to chemoradiotherapy[17], if "divergence" in PPC does indicate EMT, it would be natural for PPC to be more aggressive, highly resistant to chemoradiotherapy, and have a poorer prognosis.

Similar to the other types of NSCLC, disease stage and lymph node metastasis have been reported as prognostic factors of PPC, considering tumor progression[6,10,11,13]. Therefore, the treatment strategy in the present case was early detection and resection.

Conflict of Interest

The authors have no conflict of interest to declare.

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