

Stromal micropapillary predominant lung adenocarcinoma: A rare histological phenotype with poor prognosis

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Abstract

An extremely rare case of stromal micropapillary predominant lung adenocarcinoma is presented in this study. A 70-year-old woman visited our hospital because of an abnormal shadow on chest X-ray. Chest computed tomography revealed a nodule in the left lower lobe and a mass in the left upper lobe. She underwent an exploratory thoracotomy owing to the suspicion of advanced lung cancer. Pathological examination of the left lower lobe nodule revealed tumour cells with more than half the tumour cells showing stromal micropapillary pattern (SMP), consisting of tumour cells invading the fibrotic stroma. In general, micropapillary adenocarcinomas in the lung form an arogenous micropapillary pattern (AMP), in which tumour cells float in alveolar spaces. Because the prognosis of SMP lung adenocarcinomas is known to be worse than that of AMP lung adenocarcinomas and have a high frequency of epidermal growth factor receptor mutations, the discrimination of SMP from AMP is important for both pathologists and clinicians.

Introduction

Micropapillary adenocarcinoma of the lung is a relatively rare subtype of adenocarcinoma and is known to be associated with a poor prognosis [1]. In general, micropapillary lung adenocarcinomas form an arogenous micropapillary pattern (AMP), in which tumour cells float in alveolar spaces. Recently, a lung adenocarcinoma exhibiting a stromal micropapillary pattern (SMP), consisting of tumour cells invading the fibrotic stroma, has been reported to be a rare phenotype of micropapillary lung adenocarcinoma and to be associated with a significantly poorer prognosis than AMP [2]. We report a rare case of SMP lung adenocarcinoma, which is valuable in terms of differentiating SMP from AMP.

Case Report

A 70-year-old woman visited our hospital because of an abnormal shadow on chest X-ray. Chest computed

tomography revealed a nodule measuring 2.7×1.5 cm with a cavity in the left lower lobe and a mass measuring 4.1×2.4 cm in the left upper lobe (Fig. 1A, B). The serum carcinoembryonic antigen level was high as 42.2 ng/mL (normal value < 5.0 ng/mL). Because bronchoscopic biopsy failed to confirm the diagnosis, she underwent an exploratory thoracotomy owing to the suspicion of advanced lung cancer. The nodule in the left lower lobe was localized at a peripheral portion and was extracted by wedge resection. The mass in the left upper lobe macroscopically showed extra-pleural invasion and was accompanied by numerous disseminated lesions. Because the mass was too large to perform wedge resection, the disseminated lesions were biopsied.

Pathological examination of the left lower lobe nodule revealed that approximately 70% of the tumour was occupied by micropapillary tufts lacking a central fibrovascular core, surrounded by clear spaces, and invading the fibrotic stroma (Fig. 2A, B). The lepidic adenocarcinoma

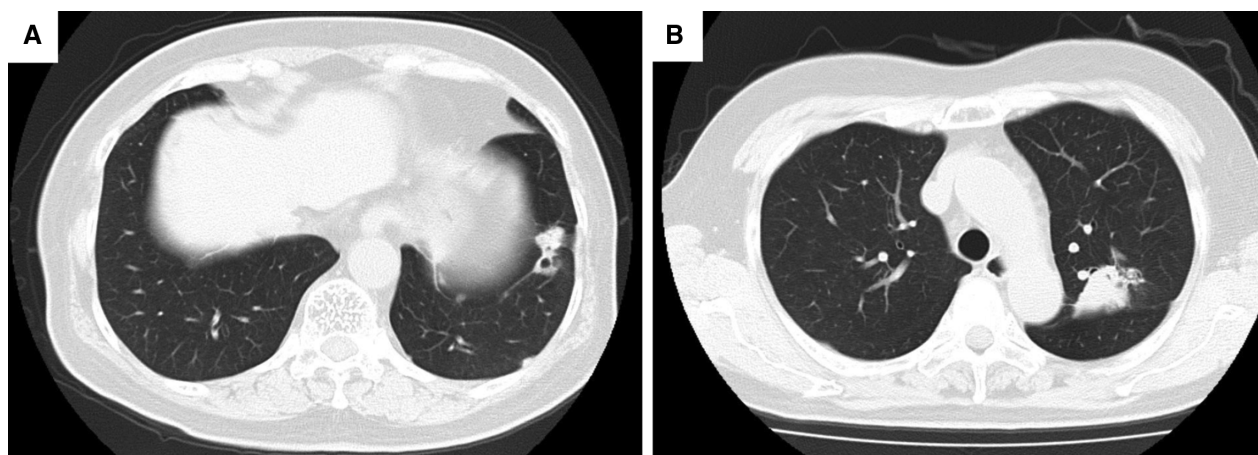


Figure 1. Computed tomography of the chest revealed (A) a nodule measuring 2.7 × 1.5 cm with a cavity in the left lower lobe and (B) a second mass measuring 4.1 × 2.4 cm in the left upper lobe.

accounted for approximately 30% of the tumour. There was a scar tissue in the central portion of the tumour, suggesting this lesion to be the primary site. Immunohistochemical examination of the micropapillary lesion revealed that thyroid transcription factor-1 (TTF-1) and Napsin-A were strongly expressed in the nuclei and cytoplasm of the tumour cells, while these were negative in the tissue surrounding the tumour tufts (Fig. 2C, D). Mucin 1 (MUC1) was expressed in the outer surface of the tumour tufts, displaying an inside-out pattern (Fig. 2E). D2-40 was negative in the surrounding tissue, indicating that the tumour cells were external to the lymphatic vessels. Although vascular and pleural invasion were not observed, lymphatic invasion was evident in some areas (Fig. 2F). These findings confirmed the diagnosis of primary stromal micropapillary predominant lung adenocarcinoma (T1bNXM0). Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement were both negative.

The tumour cells of the disseminated lesion displayed adenocarcinoma with an acinar pattern, which was different from the left lower lobe tumour. The dissemination was presumed to be derived from the left upper lobe tumour (T2aNXM1a), which exhibited extra-pleural invasion on intraoperative findings. Thus, the tumours in left lower and upper lobes were suspected to be synchronous primary carcinomas. The patient was treated with chemotherapy, including cisplatin, pemetrexed, and bevacizumab, which resulted in partial response of the residual left upper lobe tumour.

Discussion

An extremely rare case of stromal micropapillary predominant lung adenocarcinoma is presented in this study.

Because the prognosis of SMP lung adenocarcinomas is known to be worse than that of AMP lung adenocarcinomas, the discrimination of SMP from AMP is important for both pathologists and clinicians.

Micropapillary predominant adenocarcinoma is a relatively rare subgroup, newly classified by the WHO in 2015 [3]. The micropapillary pattern itself is known to be a poor prognostic factor even in early stages without lymph node metastasis because it is frequently associated with lymphatic invasion. The 5-year survival rate of stage IA micropapillary pattern-positive lung adenocarcinomas was significantly lower than that of micropapillary pattern-negative lung adenocarcinomas (77.6% vs. 98.1%) [1].

Micropapillary adenocarcinomas are also found in other organs such as the breast, colon, and urinary duct. Typically, micropapillary adenocarcinomas in other organs, except for the lungs, show SMP, in which tumour cells invade the fibrotic stroma. In contrast, typical micropapillary adenocarcinoma of the lung shows AMP, in which tumour cells float in alveolar spaces. The present case is extremely rare because micropapillary adenocarcinoma of the lung presented with SMP, which is usually observed in adenocarcinomas of other organs.

Stromal micropapillary lung adenocarcinoma was initially reported by Kuroda *et al.* as “lung micropapillary carcinoma of breast type” [4]. According to Ohe, lung adenocarcinomas with the SMP component account for 3.4% of lung adenocarcinomas (19/559 cases) [2]. The important features include a significantly worse prognosis than that of AMP and a higher rate of EGFR mutation (74%) than that of the whole population of micropapillary predominant lung adenocarcinomas in Japanese individuals (40.1%) [5]. SMP is a rare feature expected with AMP in micropapillary lung adenocarcinoma and should be

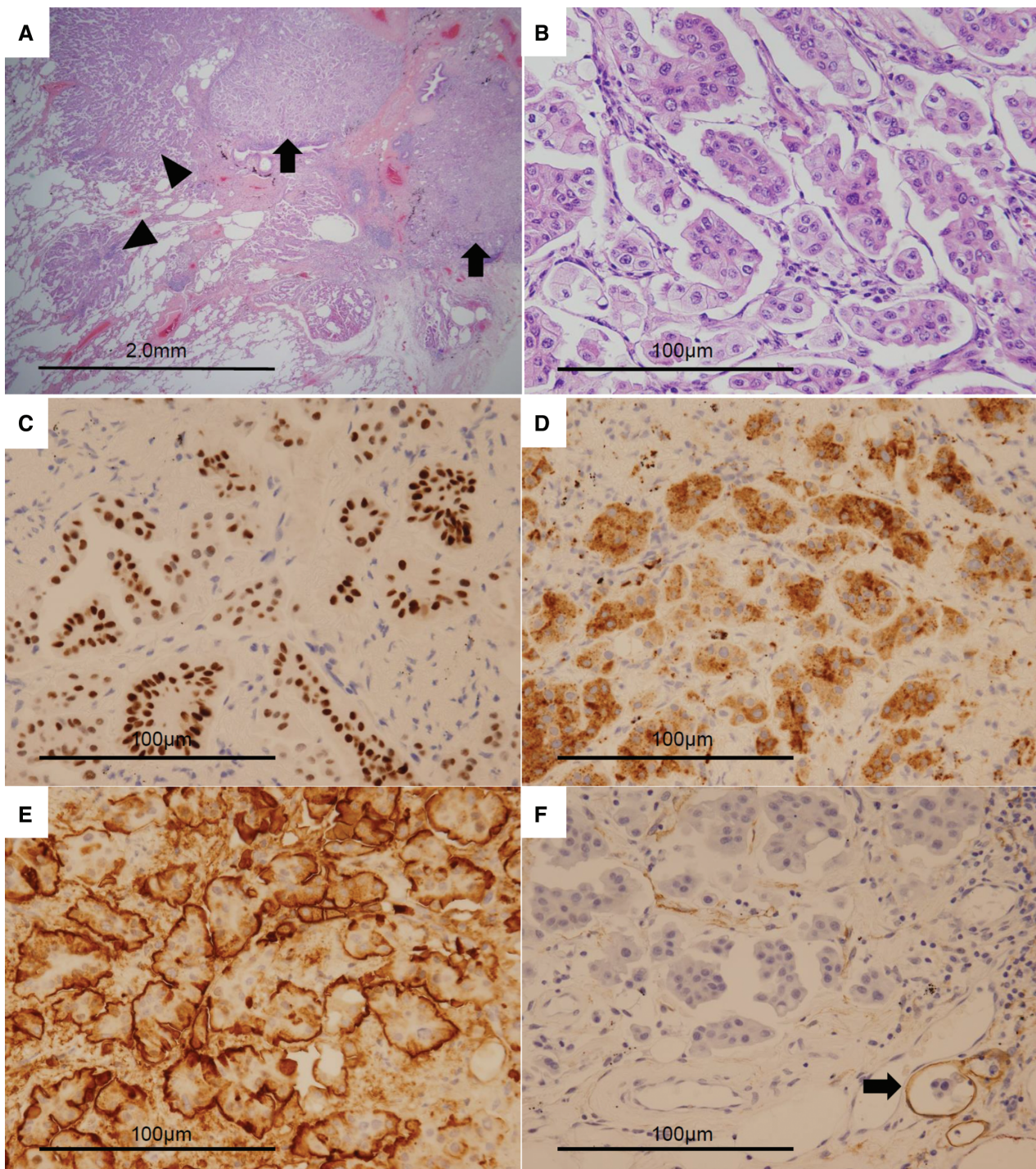


Figure 2. (A) Haematoxylin and eosin staining revealed approximately 70% of the tumour with stromal micropapillary pattern (SMP) component (arrow) and the rest comprised lepidic adenocarcinoma in the peripheral portion (arrowhead). (B) In the SMP component, the tumour presented micropapillary tufts lacking a central fibrovascular core, which were surrounded by clear spaces and invading fibrotic stroma. (C) TTF-1 and (D) Napsin-A were strongly expressed in the nuclei and cytoplasm of the tumour cell, while the tissue surrounding the tumour tufts was negative. (E) MUC1 was expressed in the outer surface of tumour tufts, exhibiting an inside-out pattern. (F) D2-40 was negative for the surrounding tissue; however, lymphatic invasion was evident in some areas (arrow).

mentioned in pathological diagnosis. In the present case, although the residual left upper lobe tumour showed a good response to cytotoxic chemotherapy, the resected SMP adenocarcinoma of the left lower lobe must be carefully followed up for lymph node recurrence because it is presumed to have a potentiality of poor prognosis.

The distinction between SMP and AMP is not described by the current WHO classification of micropapillary adenocarcinomas. However, because SMP adenocarcinomas are associated with a relatively worse prognosis than AMP adenocarcinomas and have a high frequency of EGFR mutations, pathologists and clinicians should be able to clearly distinguish SMP from AMP for diagnosis. Although EGFR mutation in the present case was negative, this may provide more opportunity for patients with SMP lung adenocarcinoma to receive meticulous treatment options, particularly including the proper use of EGFR tyrosine kinase inhibitors.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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