CASE REPORT

Micropapillary structure of lung adenocarcinoma and spread through air space (STAS) in thick-section histology

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Abstract

The patient was a 61-year-old woman, a current smoker, who presented with a solid spiculated mass in right lower lobe of the lung detected by chest computed tomography. The diagnosis of adenocarcinoma was made by aspiration cytology. Right lower lobectomy was performed, and the diagnosis of acinar predominant lung adenocarcinoma was confirmed on histology. The histology also showed isolated intra-alveolar micropapillary clusters of malignant cells around the main tumor, additionally involving lung segments beyond the main tumor. We examined 150 μm thick-sections, stained with hematoxylin and eosin, which showed these intra-alveolar cancer cell clusters in three-dimensions. This method of tissue examination confirmed that these were metastatic intra-alveolar micropapillary clusters with spread through air spaces and were not due to direct extension from the main tumor mass. In the lung, "spread through air spaces" (STAS) has been recently described as an important prognostic indicator in adenocarcinoma of the lung. In this case, tumor cells were found as micropapillary structures, cell nests, and single cells within air spaces and beyond the edge of the main tumor. Because of their association with poorer prognosis, it is important to recognize the micropapillary variant of primary lung adenocarcinoma and to identify STAS. We would recommend the use of thick-section histology in evaluation of STAS in adenocarcinoma of the lung.

Key words

Lung, Lung adenocarcinoma, Micropapillary, Spread through air spaces, Aerogenous metastasis, Three-dimensional pathology

1 Introduction

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer death worldwide [1], with adenocarcinoma as the most common histologic subtype of lung cancer [2, 3]. Recently, the WHO classification of adenocarcinoma was modified due to the recognition of poor prognostic subtypes, especially, micropapillary

subtype [2, 4, 5]. In the lung, tumor metastasis occurs not just by vascular and lymphatic spread but also by STAS [6-9]. This form of intra-alveolar metastatic spread has recently been identified as a prognostic indicator in primary adenocarcinoma of the lung, which should be included in routine diagnostic reporting [7, 9].

We reviewed one case of acinar predominant lung adenocarcinoma with conspicuous STAS of micropapillary clusters of malignant cells, which were undetectable by chest computed tomography (CT) imaging.

2 Case presentation

The patient was a 61-year-old woman, a current smoker (37 pack-year), and was found with abnormalities on chest x-ray and CT. The CT showed a solid spiculated mass (32 mm × 27 mm) in right lower lobe of the lung, segments 8 and 9, with no evidence of metastasis, and the diagnosis of adenocarcinoma was made by aspiration cytology. Right lower lobectomy was performed, and the diagnosis of acinar predominant lung adenocarcinoma was confirmed on histology (see Figure 1A). The histology also showed isolated intra-alveolar micropapillary clusters of malignant cells floating with a small amount of mucin inside the main tumor (see Figure 1B). Those micropapillary clusters without mucus pool were also seen in the normal air space distant from the main tumor. In the areas of STAS, there was no lepidic growth of carcinoma as seen in cases of mucinous adenocarcinoma, previously called "mucinous bronchioloalveolar adenocarcinoma". There were no tumor cells in those normal alveoli and no definite findings suggestive of lymphatic and hematogenous metastasis. The cells of those micropapillary clusters showed identical characteristics with the main tumor cells in immunohistochemistry: positive for cytokeratin (clone; AE1/3, Dako, Glostrup, Denmark) and p53 (clone; DO-7, Leica Biosystems, Melbourne, Australia) (see Figure 1C-D).

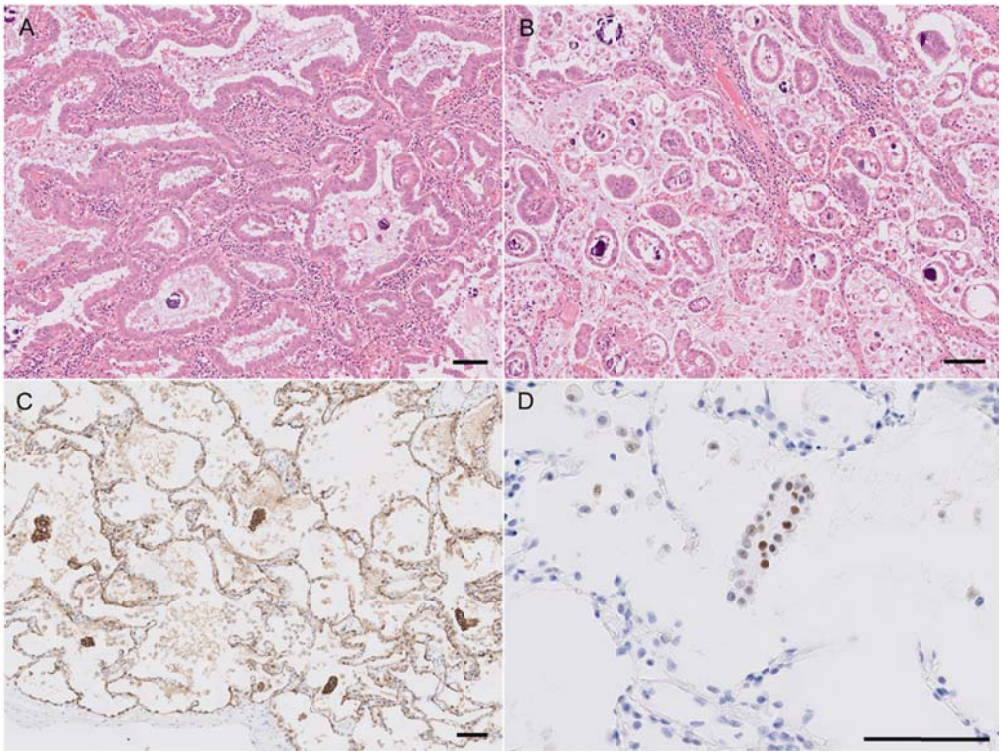

Figure 1. Histology of lung adenocarcinoma of this case. Acinar subtype was predominant (A). Areas of micropapillary subtype were also found (B). Some clusters were seen to have a psammoma body in their core. Micropapillary cancer cell clusters in normal lung parenchyma showed identical characteristics with the main tumor cells in immunohistochemistry: positive for cytokeratin (C) and p53 (D). The length of the internal scales is 100 μm.

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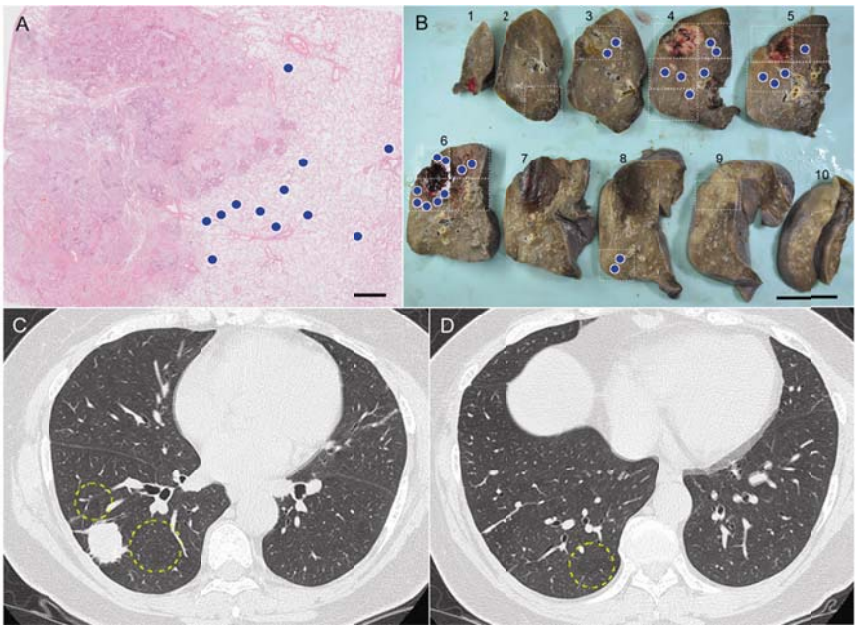

Figure 2. Spread of the micropapillary cancer cell cluster in the normal lung parenchyma. The floating micropapillary clusters were widely seen around the main tumor (blue dots, A, the length of the internal scale is 2 mm). The foci of spread were dotted on the gross cutting image (blue dots, B, the length of the internal scale is 5 cm). The number shows the order of the lung slice from upper part of the lobe to base. Micropapillary clusters were also found in the different segment of the same lobe, segment 10, in slice 8. White squares show the area where tissue blocks were processed. The chest CT showed no definite abnormality in the areas where micropapillary clusters was seen in histology (yellow circles, C and D). A is from slice 3. C and D are at the same level with slice 4 and slice 8, respectively.

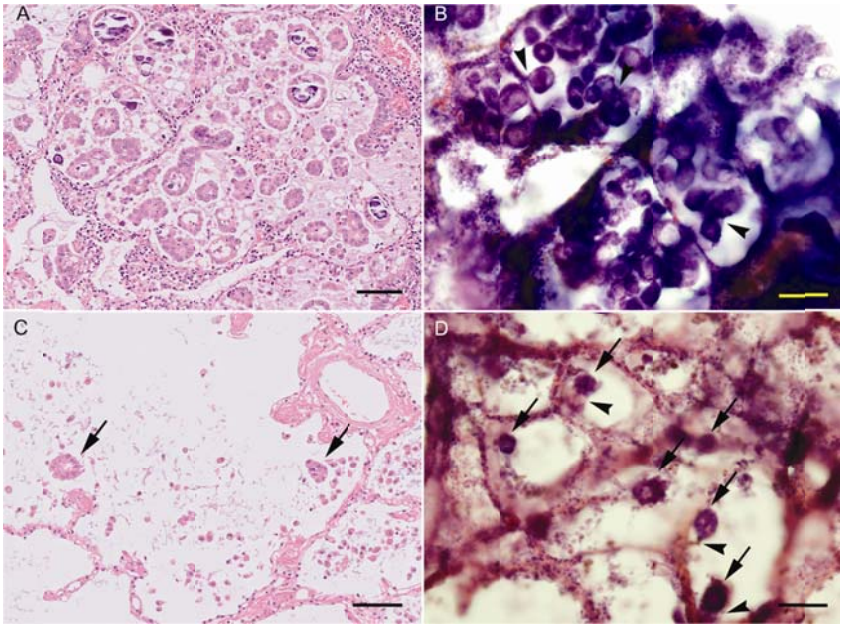

Figure 3. Image of ordinary histological slides and thick-sliced slides. A and B are from the same part of the lung adenocarcinoma. C and D are from the same part of the normal parenchyma where micropapillary clusters were seen. Through observation of the thick-sections, spherical cell clusters identical with the micropapillary clusters in the ordinary histological slide were found (arrows). Connections were occasionally seen among the clusters or between the cluster and alveolar wall (arrowheads). The length of the internal scales is 100 μm.

The floating micropapillary clusters were widely seen around the main tumor (see Figure 2A). Hematoxylin and eosin (H&E) slides of 17 blocks from the lobectomy lung were carefully examined, and the foci of STAS were also found in a different segment of the same lobe, segment 10 (see Figure 2B). The chest CT showed no definite abnormality in the areas where micropapillary clusters was seen in histology (see Figure 2C-D).

We observed the three-dimensional structure of floating cancer cell clusters with 150 μm thick-sections. Through observation of the thick-sections, we found spherical cell clusters identical with the micropapillary clusters in the ordinary H&E slide. The clusters were gathering into grape-like structure inside the main tumor area and also disseminated in normal lung area. Some of these clusters were floating independently and some were adhered each other, to the main tumor, or to the normal alveolar wall (see Figure 3A-D). In this case, tumor cells clusters were easy to distinguish from airspace macrophages due to the absence of brown pigmentation and dense feature of clustering (see Figure 4).

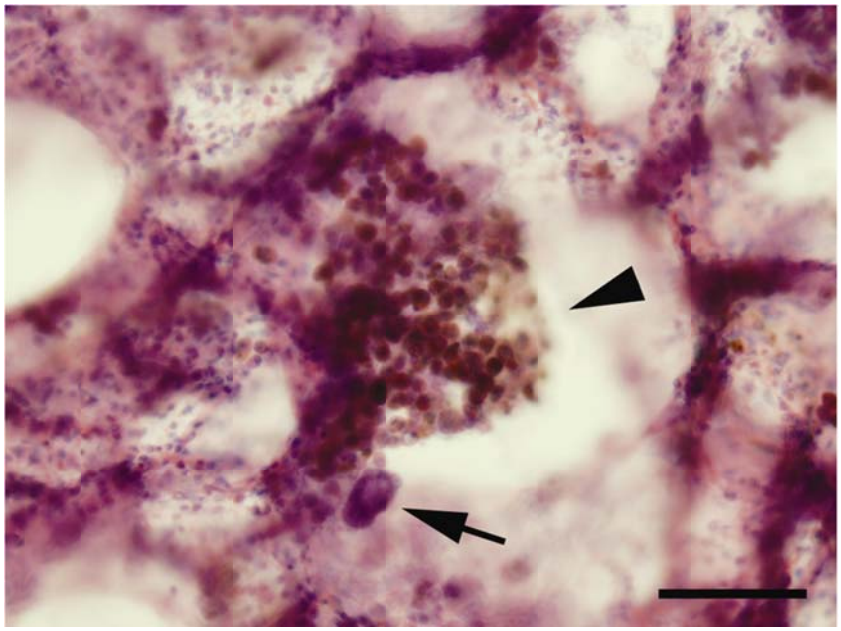

Figure 4. Cluster of cancer cell (arrow) and airspace macrophages (arrowhead). In this case, micropapillary clusters of malignant cells were easy to distinguish from airspace macrophages due to absence of brown pigmentation and dense feature of clustering. The length of the internal scale is 100 μm.

3 Discussion

We experienced a case of acinar predominant lung adenocarcinoma showing extensive STAS of micropapillary clusters of malignant cells. Through the observation of the thick-sections, we found that micropapillary structure of lung adenocarcinoma showed 4 different variations: floating independently in the airspace; attached with the main tumor; attached with other clusters; attached with the normal alveolar wall distant from the tumor. Previous studies suggested that STAS may be seen as ground-glass opacity on chest CT imaging [6, 10]. However, in this case, abnormality was not observed in the area with STAS, which may be indicating the limitation of current CT imaging.

This case suggests that judgement of micropapillary proportion may not be simple, and pathologists should carefully evaluate for the dominancy of micropapillary subtype in cases of adenocarcinoma. Since micropapillary clusters that seem detached from the main tumor can be a branching of the main tumor, the judgement as to whether micropapillaries are truly floating or not may be critical.

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Considering the association between STAS and the prognosis, it is important to recognize the micropapillary variant of primary lung adenocarcinoma and to identify STAS. We would recommend the use of thick-section histology in evaluation of STAS in adenocarcinoma of the lung.

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