CASE REPORT

"Real" Tumor-Spread Through Air Spaces of Lung Adenocarcinoma Presented Intrapulmonary Metastases Through Bronchiole Air Spaces: A Case Report

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ABSTRACT

Here, we report a rare case of lung adenocarcinoma with intrapulmonary metastases that have "spread through air spaces" (STAS) by means of the alveoli and bronchioles. The peripheral intrapulmonary metastases were exhibiting pure ground-glass nodules along the bronchioles on computed tomography. The primary pathologic diagnosis was micropapillary adenocarcinoma with prominent tumor STAS. Histopathologic examination revealed that the cancer cells in the bronchioles around the primary tumor revealed micropapillary clusters on the mucosal surface or in the air spaces and reached peripheral intrapulmonary metastatic nodules. Notably, no vascular and stromal invasion was observed. The pathologic findings suggest that cancer cells are viable in the airspace of the bronchioles and alveoli and may support the significance of STAS as a pattern of airborne metastasis.

Keywords: Lung adenocarcinoma; Tumor-spread through air spaces (STAS); Micropapillary adenocarcinoma; Case report

Introduction

Tumor-spread through air spaces (STAS) is a new invasion concept that was introduced by the WHO classification of lung cancer in 2015.[1,2] It is defined as "micropapillary clusters, solid nests, or single cells spreading within air spaces beyond the edge of the main tumor."[1]

STAS is an essential clinical concept because it can be an independent predictor of recurrence or prognosis in lung cancer.[2] In contrast, whether STAS is a real metastatic finding or a kind of artifact during the cutting and processing of resected lung specimens remains controversial.[3]

We report a rare case of lung micropapillary adenocarcinoma with intrapulmonary metastasis This case can

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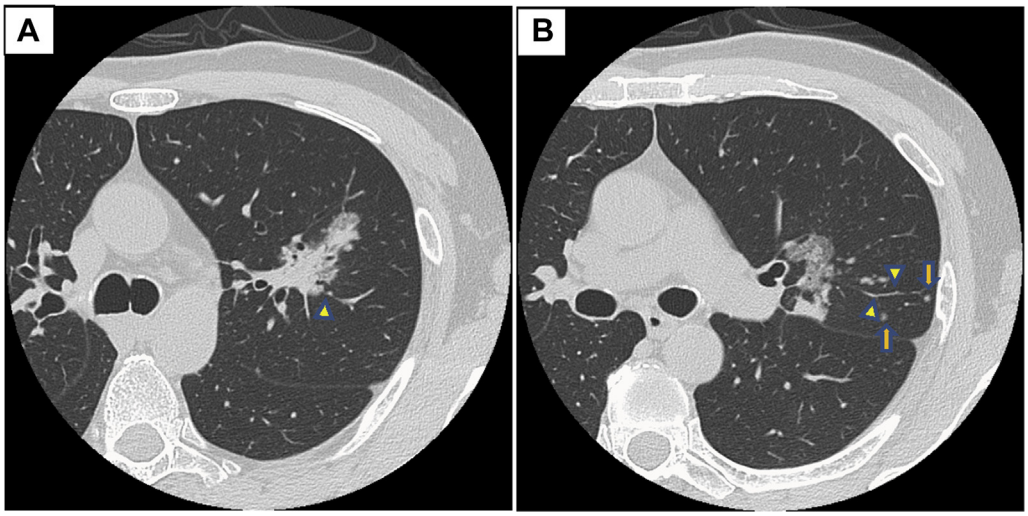

Figure 1. Computed tomography illustrating an irregular-shaped, solid nodule with ground-glass opacity in the left upper lobe of the lung (*A*) and metastatic small solid nodules (*B*, orange arrow). Grainy appearance along the bronchioles is observed (*B*, yellow arrowhead). The bronchioles, with the grainy appearance, reached the intrapulmonary metastatic tumors.

provide clarity on the controversial subject of independent aerogenous metastatic capacity.

Case Presentation

A 59-year-old man visited our hospital with an abnormal lung shadow detected at the routine medical screening. Thin-section computed tomography (CT) revealed a 4.6 cm irregular-shaped part-solid tumor in the left lung (Fig. 1*A*). Several ground-glass nodules (GGNs) were on the primary lesion's distal side, suggesting intrapulmonary metastases. Interestingly, the bronchioles between the primary tumor and peripheral GGN presented with skipping lesions within the same lobe (Fig. 1*B*). He underwent left upper lobectomy with lymph node dissection. The pathologic diagnosis was invasive micropapillary adenocarcinoma with many intrapulmonary metastatic nodules, pT3N0M0 stage IIB (Figs. 2*A, D* and *E* and 3).

Microscopic examination revealed many STAS tumor cells in the alveolar air spaces (Fig. 2*B* and *C*) and scattered STAS tumor cells in the bronchioles (Fig. 3*A–C*), which formed floating cancer cell clusters or single cells. The bronchioles with STAS reached the intrapulmonary metastatic tumors (Fig. 2*B*). The cancer cells in the bronchioles grew in a micropapillary fashion on the mucosa surface and had a discontinuous skipping distribution (Fig. 3*B*). There was no submucosal stromal invasion of the STAS-positive bronchioles (Fig. 3*C*). No lymphovascular invasion was observed.

Biomarker test results were positive for *EGFR* mutation (L858R and S768I), negative for *ALK* fusion, and no programmed death-ligand 1 expression. The patient received standard adjuvant chemotherapy with cisplatin and vinorelbine. After 9 months, he started treatment with a third-generation EGFR tyrosine kinase inhibitor (osimertinib) for postoperative lung recurrence. He is alive with the disease for 26 months after the operation.

Discussion

We report a unique STAS-positive case of micropapillary lung adenocarcinoma with intrapulmonary metastases. The metastases presented as multiple GGNs on CT and skipping cancer cell clusters along the bronchioles that spread by means of air spaces on the microscopy. On the basis of pathologic findings, the diagnosis was intrapulmonary metastases by means of air spaces, specifically the bronchioles.

The novelty of this report is centered around three points. First, we observed that STAS occurred in both the alveoli and bronchioles, which presented as intrapulmonary metastasis with skipping cancer cell nests in the bronchioles. The "air space" in STAS is practically synonymous with alveolar and cancer cells, given that STAS involving the bronchioles are rare. In our case, cancer cells formed skipping nests in the bronchioles near the intrapulmonary metastases, and cancer cell clusters were floating in the bronchioles and surrounding alveoli (Fig. 3*D*). It is unlikely to be a continuous superficial spreading from the primary tumor on the basis of the ratio of the longitudinal distance between the nearest skipping focus (>2.7 mm) and the diameter of the involved bronchiole (0.5 mm) (Supplementary Fig. 1). It was revealed that the "air spaces" involved in STAS were both the alveoli and bronchioles; pathologic examination confirmed this. The absence of lymphovascular invasion also supports the independent metastatic

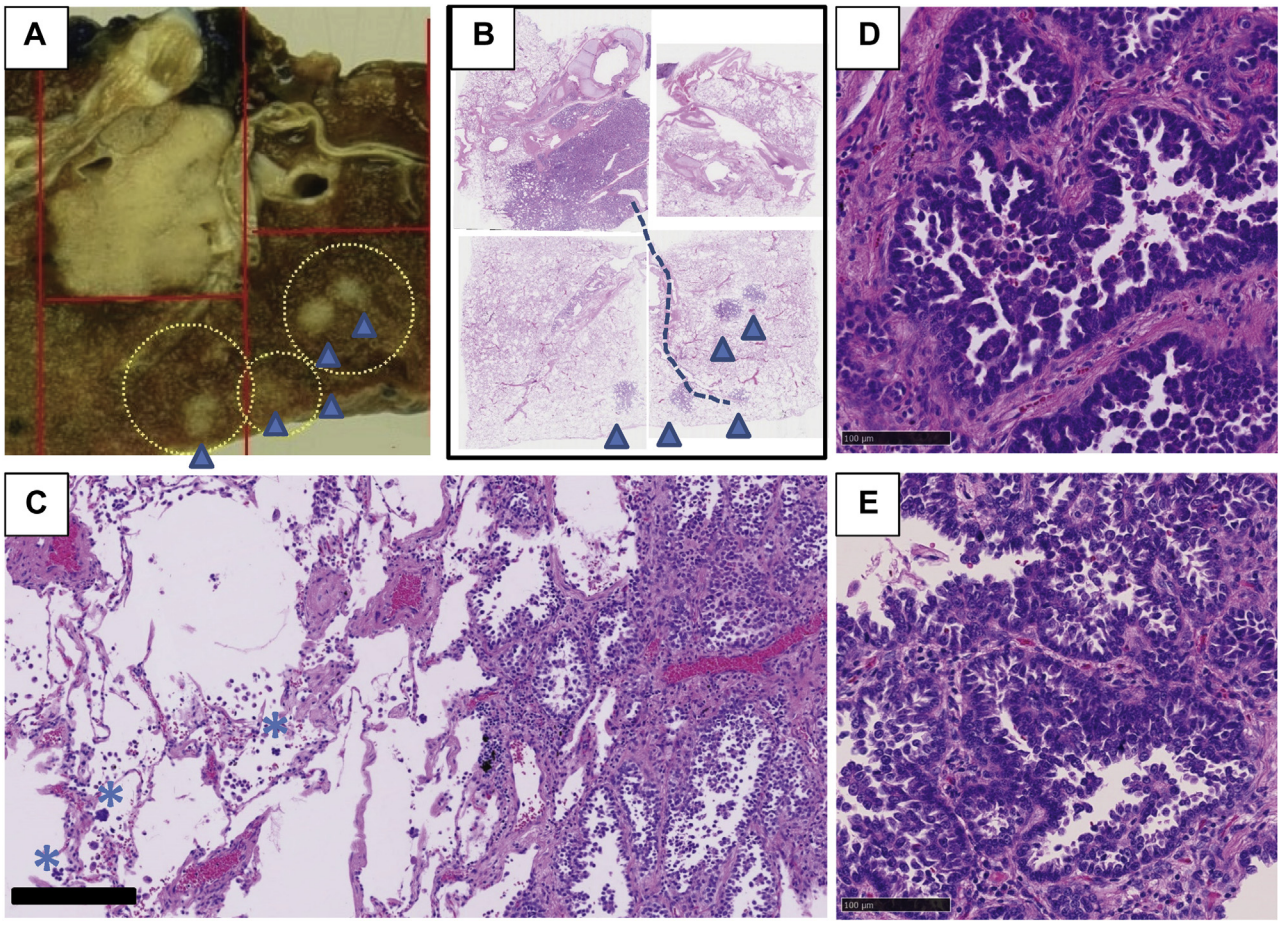

Figure 2. Pathologic images of resected lung adenocarcinoma. (*A*) Macroscopic view and corresponding tiled *(B)* low-power microscopic view of the main tumor and metastatic tumors (blue triangle). Micropapillary adenocarcinoma involves bronchioles in the main tumor and reached the metastatic nodules through the bronchiole (*B*, dotted line). (*C)* Many STAS tumor cells in the alveolar air spaces are seen (blue asterisk). The (*D*) primary and (*E*) metastatic adenocarcinomas reveal similar histology with abundant micropapillary clusters. (*B-E*: HE stains, bar = 250 μm [*C*], 100 μm [*D*, *E*]). HE, hematoxylin and eosin; STAS, spread through air spaces.

capacity of STAS tumor cells. Given that STAS occurs with lymphovascular invasion, there is a debate on whether STAS is a real metastatic pattern. Independent aerogenous metastasis in our case suggests the survival and metastatic potency of cancer cells on the bronchiolar and alveolar surfaces by means of air space spread. These findings can endorse the significance of STAS and aerogenous metastasis as a pattern of metastasis. Multiple cancer cell lesions are differentiated from multiple cancerizations by field cancerization. Field cancerization is a known phenomenon in smoking-associated cancer, such as squamous cell carcinoma and small cell carcinoma.[4] Our patient had a nonsmoker adenocarcinoma. In addition, intrabronchial lesions were micropapillary adenocarcinoma, not atypical adenomatous hyperplasia or adenocarcinoma in situ. It is unlikely that a continuum exists between the precursor lesions in the field cancerization of the lung.[4] We concluded that it was an intrabronchial airborne spread. Bronchiolar STAS was differentiated from field cancerization of the lung by the following: (1) tumor cells were found only in the restricted sublobules between the primary tumor and peripheral metastatic tumors; (2) tumor cells were highly atypical with no less atypical precursor lesions; (3) tumor cells revealed an abrupt in situ pattern on the bronchiolar surfaces; and (4) absence of stromal or intravascular cancer cells in the involved bronchioles.

Second, transbronchial metastasis of nonmucinous adenocarcinoma, which presented as skipping nests in the bronchus away from the primary lesion, was observed; this is a rare finding. Intrapulmonary metastasis of invasive mucinous adenocarcinoma (formerly called mucinous bronchoalveolar carcinoma) occurs owing to pneumatic spread with mucus.[5] However, few studies have reported aerogenous metastasis in micropapillary adenocarcinoma without mucus. In our case, skipping cancer cell nests were observed in the bronchus away from the primary lesion without mucinous stroma

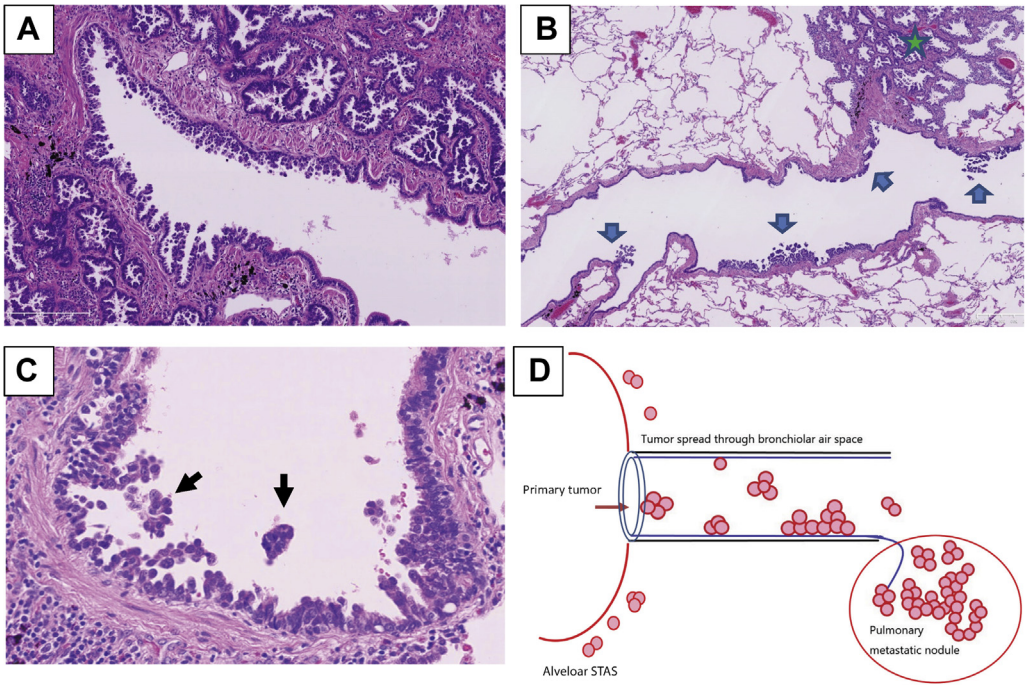

Figure 3. Representative images of tumors that spread through "bronchiolar" air spaces (bronchiolar STAS). (*A*) The primary tumor is micropapillary adenocarcinoma with many STAS tumor cells both in the alveoli and bronchiolar air spaces. (*B*) Low-power view of the intrapulmonary metastatic nodule (star) and bronchiole between the main tumor and the accessory nodule. Many skipping cancer cell clusters are noted along the bronchioles (blue arrow). (*C*) High power view: The STAS tumor cells (black arrow) and in situ clusters form micropapillary structures on the mucosal surface. There was no stromal invasion or lymphovascular invasion. (*D*) Schema of cancer spreading pathway in this case. Cancer cells from the primary tumor formed a skipping nest in the bronchiole near the intrapulmonary metastases, and cancer cell clusters were also floating in the surrounding alveoli. STAS, spread through air space.

around the tumor cells. This report supports the theory mentioned above that nonmucinous pathologic subtypes have the potential for aerogenous spread.

Finally, multiple intrapulmonary metastases presented as GGN on CT. The presence of multiple GGN makes distinguishing intrapulmonary metastasis from multiple primary lung cancer on radiology challenging.[6] In this case, we suspected low grade lung cancer at first because the primary tumor was a part-solid nodule with a clear boundary between normal lung tissue. Moreover, multiple GGN in the periphery of the primary tumor was suspected not to be intrapulmonary metastases. The pathologic diagnosis revealed micropapillary adenocarcinoma, which has a higher malignancy potential and poor prognosis than tumors with the lepidic pattern. This pathologic finding supported the presence of intrapulmonary metastases. Moreover, surgery is rarely performed in patients with intrapulmonary metastasis. Thus, this is a rare case of multiple GGN with pathologic evidence of intrapulmonary metastasis.

Conclusions

This case is a vivid example of STAS-positive lung micropapillary adenocarcinoma with intrapulmonary metastases detected as multiple GGN on CT. It proves the metastatic potential of STAS and independent aerogenous metastasis.

CRediT Authorship Contribution Statement

Sawako Kaku: Investigation, Validation, Writing - original draft, Visualization.

Noriko Motoi: Conceptualization, Methodology, Writing - review & editing, Visualization, Supervision, Project administration.

Hirokazu Watanabe: Writing - review & editing.

Yukihiro Yoshida, Shun-ichi Watanabe: Resources, Data curation.

Masahiko Kusumoto: Resources, Data curation, Writing - review & editing.

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The patient involved in this case report gave his informed consent authorizing the use and disclosure of his health information.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO*

Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100273.

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