Journal of
Pulmonary & Respiratory Medicine

Othman et al., J Pulm Respir Med 2016, 6:6
DOI: 10.4172/2161-105X.1000384

Case Report Open Access

Spread through Air Spaces Detected in Frozen Sections of Lung Adenocarcinoma is a Sign of Air Space Invasion: A Case Report

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Abstract

A 70-year-old non-smoking woman was found to have 23 mm sized lung adenocarcinoma. Intraoperative frozen sections were performed which confirmed the diagnosis of adenocarcinoma. Surgical material revealed presence of tumor nests spreading through airspaces (STAS) as far as 9 mm from the edge of the main tumor. Based on the presence of STAS, resection of the remaining left upper lobe was performed after the first operation, and no residual tumor or STAS was detected. A retrospective review of the frozen sections showed the presence of STAS. This report indicates that evaluation of STAS at the time of surgery may help improve the clinical course of a patient undergoing limited resection.

Keywords: Pulmonary neoplasm; Non-small cell carcinoma; Computed tomography; Surgery; Pathology

Introduction

Lung cancer is one of the most common cancers worldwide [1,2] and it has been reported to be the leading cause of cancer death in men and women in the Unites States and Europe [1-4]. Although 25% of lung cancer cases are detected in the early stage, lung cancer has one of the highest mortality rates among malignancies [5]. Limited resection after confirming negative margins in frozen sections has been increasingly used to treat patients with peripheral lung cancer, and this approach is beneficial for preserving pulmonary function [6]. However, it has been reported that about 20% to 25% of patients treated with limited resection experience recurrence despite negative margins [7-9]. Thus, features that can predict poor prognosis in early lung adenocarcinoma are of clinical interest.

Recently, Onozato et al. [10] focused on the extra-tumor area to identify indications of poor prognosis of Stage I to II lung adenocarcinomas. The authors analyzed 261 patients and found that the presence of viable tumor islands in extratumoral alveoli doubled the recurrence risk, which led to a poor five-year survival rate (presence of tumor islands vs. absence of tumor islands, 44.6% *vs*. 74.4%). A previous study [11] performed three-dimensional reconstruction from paraffin embedded sections, and the findings suggested that tumor islands physically interconnected with the main solid tumor. In 2015, Kadota et al. [12] performed a study in 411 patients and named this condition as spread through air spaces (STAS). STAS was defined as the spread of lung cancer cells into air spaces in the lung parenchyma adjacent to the main tumor, including carcinoma cells forming micropapillary structures, solid nests, or single cells spreading within air spaces in the lung parenchyma beyond the edge of the main tumor [12]. On reviewing paraffin-embedded lung specimens, the authors found STAS in as high as 38% of stage I lung adenocarcinoma cases, and the risk of distant and loco-regional recurrence was higher in the STAS-positive group than in the STAS-negative group [12]. Based on these previous studies, it has been suggested that invasion of lung adenocarcinoma not only involves adjacent blood vessels, pleura, or stroma, but also involves STAS [12-14].

Frozen sections have enabled clinicians to obtain information regarding the pathological type of tumor and its solid margin, and this helps determine the type of resection required during surgery. The findings of the above-mentioned studies suggest that if STAS could be detected in frozen sections during surgery for early cancer, the clinical course of the patient might benefit and a two-stage curative resection might be avoided. However, detection of STAS in frozen tissue has not been reported previously. Here, we report a case in which STAS was detected in frozen sections.

Case Description

A 70-year-old non-smoking woman was found to have an abnormal chest radiograph during a medical examination. Chest computed tomography (CT) revealed a part-solid ground-glass nodule measuring 16 mm in the left upper lobe. The nodule increased in size to 23 mm on subsequent chest CT (Figure 1A). Early lung cancer was strongly suspected, and segmentectomy for segments 1 and 2 was performed. Intraoperative frozen sections confirmed the diagnosis of adenocarcinoma. The paraffin embedded surgical specimen showed adenocarcinoma (papillary predominant) with the presence of minor micropapillary components, and STAS, which was noted as far as 9 mm from the edge of the main tumor (Figure 1B). Based on the presence of STAS, resection of the remaining left upper lobe was performed after the first operation, and no residual tumor or STAS was detected. A retrospective review of the frozen sections showed the presence of STAS (Figure 1C and 1D). The patient has been well without any sign of recurrence.

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Received October 29, 2016; **Accepted** December 30, 2016; **Published** December 31, 2016

Citation: Othman NB, Akazawa Y, Kitamura Y, Hashisako M, Tsuchiya T, et al. (2016) Spread through Air Spaces Detected in Frozen Sections of Lung Adenocarcinoma is a Sign of Air Space Invasion: A Case Report. J Pulm Respir Med 6: 384. doi: 10.4172/2161-105X.1000384

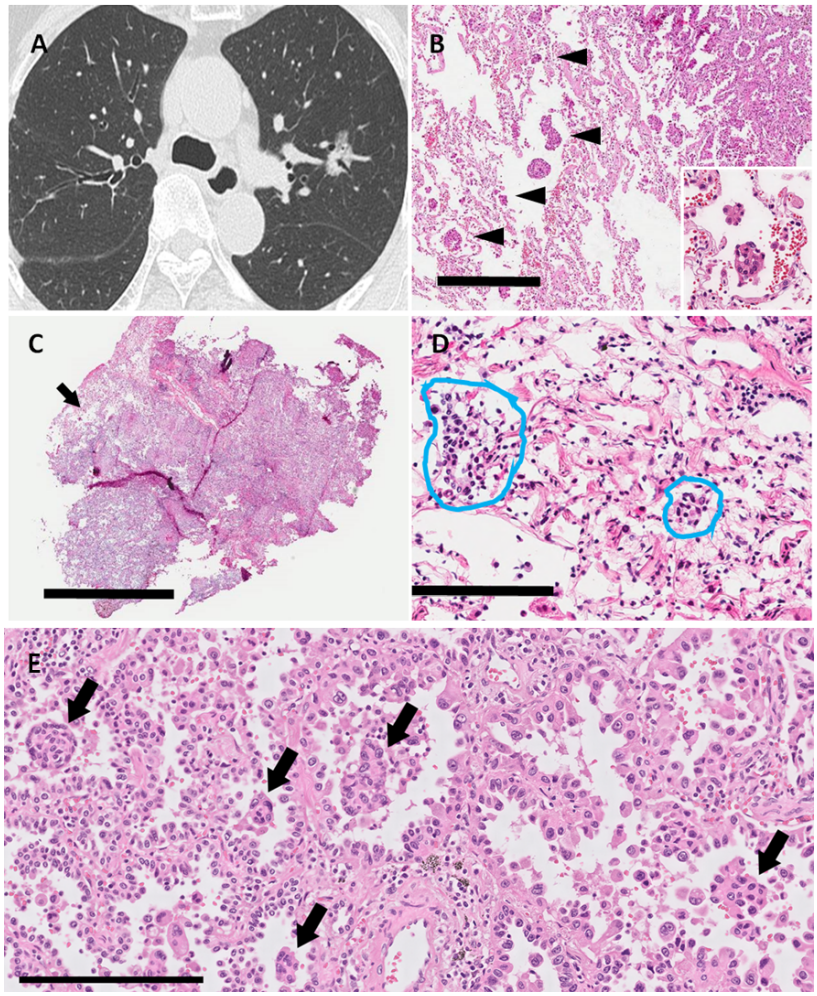

Figure 1: A) A chest computed tomography image showing a 23 mm × 15 mm nodule in the lower lobe of the left lung. B) A stained surgical specimen indicating invasive adenocarcinoma (papillary predominant) with the presence of spread through air spaces (STAS) (arrowheads; scale bar=50 μm). C) Low magnification view of the frozen section. The area with STAS is indicated with an arrow (scale bar=2 mm). D) High magnification view of the frozen section showing foci of STAS (enclosed by solid lines; scale bar=200 μm). E) The center of the tumor of the removed cancer shows papillary pattern with airspace floating tumor nests (arrows; scale bar=200 μm).

Discussion

Although the pathophysiology of STAS is not well known at present, it may show close relationship with the one of micropapillary structure [15]. Overall survival has been reported to be significantly worse in cases of STAS-positive tumors than in cases of STAS-negative tumors [12,16]. Additionally, STAS-positive tumors have been shown to be associated with a significantly high risk of loco-regional and distant recurrence in patients undergoing limited resection, whereas no significance risk was noted in patients undergoing lobectomy for STAS-positive tumors [12].

In the present report, we showed that STAS can be identified in frozen sections if the sections are properly examined. Currently, frozen sections of lung cancer are used for assessing the marginal status, assessing the lymph node status, and tumor typing. To our knowledge, no report has assessed STAS in frozen sections. The present case suggests that tumor margins should be included in frozen sections to assess the presence of STAS if limited resection is considered for small-sized lung cancer. The identification of STAS in frozen sections can be challenging owing to the possible presence of processing artifacts and the sampling area. As differentiation of tumor cells from macrophages can be difficult, especially in case of single discohesive tumor cells spread in air spaces, the sections should be carefully assessed. The chance of identifying STAS may increase with the preparation of multiple specimen sections, including the non-tumor area, rather than with the preparation of only a single section. Our case suggests that pathologists should consider assessing the presence of STAS in frozen sections to avoid additional surgery after the initial treatment. However, further prospective studies are required to elucidate the benefits of assessing the presence of STAS in frozen sections.

Conclusion

We reported the identification of STAS in intraoperative frozen sections. The evaluation of STAS at the time of surgery would help improve the clinical course of a patient undergoing limited resection, as additional resection can be considered if STAS is identified. We suggest that further studies should be performed to examine the clinical importance of identifying STAS in frozen sections.

Clinical practice points

- Spread through air spaces (STAS) is a pattern of invasion that

is newly recognized in lung tumors, and it is most commonly seen in invasive adenocarcinoma with papillary or micropapillary predominant patterns.

• The presence of STAS has been shown to indicate a high risk of recurrence, especially in patients treated with segmentectomy. However, assessment of STAS has not been performed in frozen tissues during surgeries.

• We report a case of invasive adenocarcinoma in a 72-year-old woman who initially underwent segmentectomy for lung adenocarcinoma in the left upper lobe. The presence of STAS was detected in paraffin-embedded surgical material, and she later underwent left upper lobe resection. Retrospectively, STAS was also detected in frozen section slides.

• The present case indicates that in some cases, STAS is detectable not only in paraffin-embedded tissue, but also in frozen sections, and pathologists should pay attention to the presence of STAS to ensure appropriate therapeutic strategies for patients with lung carcinomas.

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