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An anaplastic lymphoma kinase-positive lung cancer microlesion: A case report

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ABSTRACT

Anaplastic lymphoma kinase (ALK)-positive lung cancers are generally diagnosed at an advanced clinical stage. Herein, we report a case of an ALK-positive lung cancer patient who had a microlesion of this tumor type. The patient was a 51-year-old woman without a smoking history. Computed tomography performed during a lung cancer screening program showed a 7 × 5-mm subpleural nodule with an irregular border in the right lower lobe. The background lung parenchyma was almost normal. Serum tumor marker levels were not elevated. Histological assessment showed destructive growth in the center of the lesion, as confirmed using Victoria blue-hematoxylin and eosin staining and immunostaining for CD34 and D2-40; however, at the other site, the tumor mainly showed intra-alveolar growth with minor lepidic growth. The tumor cells were positive for thyroid transcription factor-1 and ALK. Fluorescent in situ hybridization of the tumor revealed an *ALK* gene spilt. Accordingly, the tumor was diagnosed as ALK-positive lung cancer. ALK-positive lung cancer presents diverse histological architectures in the early phase.

1. Introduction

Aberrant expression of anaplastic lymphoma kinase (ALK) due to rearrangement of the *ALK* gene causes a specific type of adenocarcinoma of the lung, namely, ALK-positive lung cancer [1]. Clinically, ALK-positive lung cancers are aggressive, and currently, most patients are diagnosed with locally advanced or metastatic disease [2]. Therefore, a microlesion of ALK-positive lung cancer has not been fully described histopathologically. It is important to characterize the microlesions of this tumor type in order to make the diagnosis and to determine the appropriate treatment regimen. Here, we report a case of ALK-positive lung cancer showing a microlesion of this tumor type and describe its histopathological characteristics.

2. Case report

The patient was a 51-year-old asymptomatic woman without a history of smoking. Computed tomography (CT) performed during a lung cancer screening program revealed a 7 × 5-mm subpleural nodule with an irregular border in the right lower lobe (Fig. 1). The background lung parenchyma was almost normal. Levels of serum tumor markers, including carcinoembryonic antigen, sialyl SSEA-1 antigen, squamous cell carcinoma antigen, cytokeratin 19 fragment, and pro-gastrin-releasing peptide, were within the normal limits. The results of other laboratory studies were almost normal. The patient was diagnosed with early-phase lung cancer. CT-guided tumor marking was performed. Subsequently, video-assisted thoracic wedge resection of the tumor was performed. Macroscopic examination of the resected specimen revealed localized indentation of the visceral pleura (Fig. 2a). On the cut surface of the specimen, a tan-white tumor (diameter, 5 × 4 mm) was adjacent to the pleura, and the visceral pleura retracted towards the lesion (Fig. 2b). The surgical margin was macroscopically negative. Microscopically, the tumor showed a nodular growth pattern without capsulation at a low magnification (Fig. 3a). The center of the tumor showed densely intra-alveolar growth (Fig. 3b). Peripherally, the tumor had lepidic growth along the alveolar wall (Fig. 3c). Elastic fibers of the alveolar wall were diminished in the center of the tumor, but were observed at the periphery with Victoria blue-hematoxylin and eosin staining. Transition from an alveolar-preserved area to an alveolar-destructive area was also evident (Fig. 3d). Immunostaining for CD34 (Fig. 3e) and D2-40 (Fig. 3f) showed the same results. At the center of the alveolar-destructive area, the tumor cells had high nuclear atypia (Fig. 3g). The tumor cells were positive for thyroid transcription factor-1 (TTF-1) (Fig. 4a), ALK (Fig. 4b), E-cadherin, cytokeratin (CK) 7, epithelial membrane antigen, napsin A, β-catenin, MSH2, MLH1, and MUC1. The cells were also sporadically positive for p53. The Ki-67 mitotic index was 8% (Fig. 4c). The tumor

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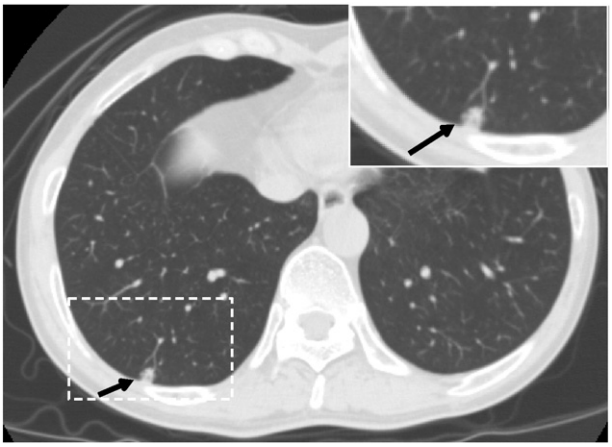

Fig. 1. Preoperative computed tomography (CT) findings. A 7 × 5-mm subpleural nodule with an irregular border in the right lower lobe (arrow) is seen. The background lung parenchyma is almost normal. The area enclosed by the dotted line is highlighted in the inset.

cells were negative for CK20, p63, p40, MUC2, MUC5AC, and MUC6. Furthermore, fluorescent in situ hybridization of the tumor revealed an *ALK* gene split (Fig. 4d). Based on these results, we diagnosed the tumor as a microlesion of ALK-positive lung cancer. The postoperative course was uneventful without any adjuvant therapy. One year after surgery, the patient was doing well without any signs of recurrence.

3. Discussion

We present a case of a very small lesion of ALK-positive lung cancer. Aberrant expression of ALK due to rearrangement of the *ALK* gene is known to cause specific types of adenocarcinomas of the lung, namely, ALK-positive lung cancer [1]. This type of lung cancer accounts for 6.7% of non-small lung cancers [1]. ALK-positive lung cancer exhibits certain histology, such as an acinar pattern with prominent mucin production, a mixed papillary pattern, and a solid pattern with signet-ring cells [3–9]. This type of lung tumor is thought to be derived from cells of the terminal respiratory unit because of positive reactivity for TTF-1 [10]. However, clinically, ALK-positive lung cancers are aggressive, and currently, most patients are diagnosed with locally advanced or metastatic disease [2]. Therefore, the reported histopathological features of ALK-positive lung cancer are based on data from advanced stage patients [1,3–9]. The average size of ALK-positive lung cancer from previous reports was larger than 2 cm (Table 1). On the other hand, the lesion in our case was less than 1 cm in diameter (0.7 × 0.5 mm on CT and 0.5 × 0.4 cm on macroscopic examination). Therefore, the ALK-positive lung cancer microlesion in this case is an important contribution considering the known information about ALK-positive lung cancer.

ALK-positive lung cancer could exhibit diverse histological architecture in the early phase. On the basis of information given in previous reports, ALK-positive lung cancer shows diverse histological patterns, including lepidic predominant, acinar predominant, papillary predominant, and solid predominant patterns. However, these histological characteristics were observed in relatively advanced lesions [3–9]. In our patient, the tumor showed destructive growth (Fig. 3d–f) with highly atypical nuclei (Fig. 3g) in the cells in the center of the tumor. However, these findings were seen in a small part of the tumor. The tumor mainly showed intra-alveolar growth (Fig. 3b) with minor lepidic growth at the periphery (Fig. 3c). It is notable that the microlesion of ALK-positive lung cancer in our case showed such diverse histological architecture in the early phase.

A small non-mucinous bronchioloalveolar carcinoma with ALK immunoreactivity was previously reported [11]. The authors retrospectively collected 49 adenocarcinoma samples from patients who were younger than 50 years of age to confirm the frequency of ALK-positive lung adenocarcinoma in young patients at their hospital [11]. They found three ALK-positive adenocarcinomas, and one of them measured 8 × 6 mm and was located adjacent to the pleura. The histological appearance was identical to that of bronchioloalveolar carcinoma, showing lepidic growth along the alveolar wall [11]. These findings differ from our case; in our case, the tumor size was smaller than that previously reported [11]. In contrast to the bronchioloalveolar pattern observed in the previous study [11], our case showed diverse histological architecture, including alveolar wall destruction with highly atypical cells (Fig. 3d–g), intra-alveolar growth (Fig. 3b), and lepidic growth along the alveolar wall (Fig. 3c). Therefore, the early histopathogenesis of ALK-positive lung cancer needs to be elucidated.

When small lung cancer lesions exhibit a diverse histological appearance, investigation for ALK immunoreactivity and/or performing fluorescent in situ hybridization for *ALK* translocation are recommended for diagnosing ALK-positive lung cancer. Similar to advanced stage disease [7], early phase ALK-positive lung cancer could present with diverse histological architecture; in turn, this diverse histological architecture could be helpful in predicting ALK-positive lung cancer. Whether ALK-positive cancer will metastasize in the early phase is not well understood. Therefore, characterization of this tumor in the early phase is required to reveal its natural course. Furthermore,

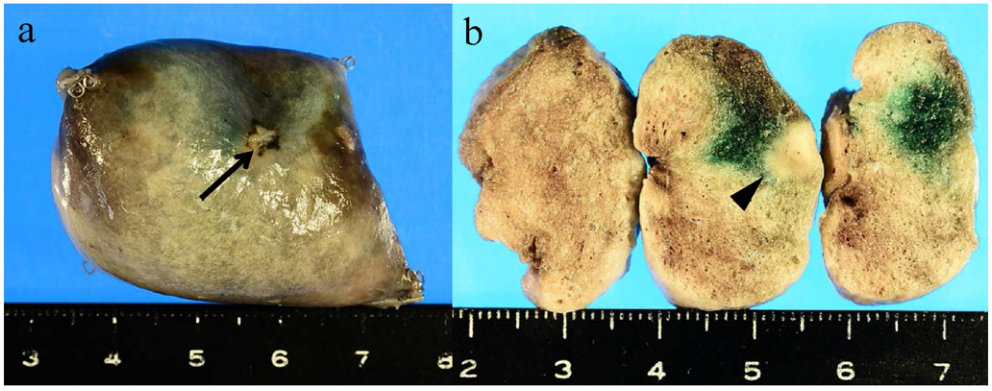

Fig. 2. Resected lung tumor specimen. Macroscopic examination of the resected specimen reveals localized indentation of the visceral pleura (arrow) (a). On the cut surface of the specimen, a tan-white tumor (diameter, 5 × 4 mm) (arrowhead) is adjacent to the pleura, and the visceral pleura retracted towards the lesion (b). The surgical margin is macroscopically negative.