**CASE REPORT**

**Clonally-related primary ALK rearranged adenocarcinoma and associated metastatic lesions**

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**Abstract**

ALK rearrangement is a driver gene in non-small cell lung cancer (NSCLC). ALK-positive tumors are sensitive to ALK-tyrosine kinase inhibitors (TKIs). The detection of key driver genes is crucial to enable personalized treatment. Different histomorphological patterns have different driver genes. Herein, we report the case of a 42-year-old male patient diagnosed with adenocarcinoma with different histotypes in the primary lung site (mucinous type) and lymph node metastasis (solid type), of the same genotype, both presenting with ALK rearrangement but negative for EGFR mutation. This histological heterogeneity did not necessarily indicate a genomic difference. Genomic analysis may be a supplement to the histological features of ALK-rearranged tumors. These gene alterations could aid the choice of an appropriate TKI and predict therapeutic response.

**Introduction**

Lung cancer has the highest incidence and mortality worldwide. ALK and EML4 gene rearrangements occur in 2–7% of patients with non-small cell lung cancer (NSCLC). Some studies have shown that young, never/light smokers with adenocarcinoma are most likely to harbor EML4-ALK gene rearrangements; while morphological histologic features have also been reported. ALK-positive primary adenocarcinomas are associated with solid, micropapillary, papillary-predominant, and mucinous histologic patterns. A previous study indicated that a distinguishing morphological feature of ALK-positive metastatic lung tumors was the presence of signet ring cells. These findings allow pathologists to identify cases that merit molecular identification and detect suitable patients for targeted therapy. Lung cancer is a highly heterogeneous disease with respect to morphology and gene status; however, few reports have shown that there are different histomorphologies between primary and metastatic tumors with consistent genetic results in NSCLC. In the current study we report the case of a 42-year-old male...
patient with locally advanced NSCLC. We discuss whether or not the different histopathologies from primary lesions and paired metastatic lymph nodes were clonally related based on molecular analysis.

**Case report**

In 2009, a 42-year-old non-smoking male presented to our hospital for the evaluation of a right lung nodule detected during physical examination. He underwent radical resection of the right lung, and the postoperative pathological report revealed a mucoid adenocarcinoma of the inferior lobe of the right lung (3.5 × 3.0 cm), but no positive lymph nodes (0 of 29; T2aN0M0 stage I). The patient relapsed in 2015. A computed tomography (CT) scan revealed a mass in the superior lobe of the right lung and mediastinal lymph node enlargement. He underwent resection of the residual right lung. Postoperative pathological evaluation and hematoxylin and eosin staining showed different histomorphologies in the primary lung site (mucinous type) (Fig 1a) and the fourth group of lymph node metastases (solid type, T2N2M0 stage III) (Fig 1b). Immunohistochemistry indicated a pulmonary origin of both tumors: TTF-1 and Napsin A were positive, and CK 5/6 and P63 were negative. We simultaneously detected ALK and EGFR gene status by reverse transcription-PCR (Amoy, Xiamen, China) in two tumor tissue specimens. The results indicated a positive EML4-ALK rearrangement in tissues and wild EGFR (Fig 2). The patient received adjuvant chemotherapy and achieved stable disease.

**Discussion**

The heterogeneity of lung cancer is considered a major limitation for precise diagnosis and successful treatment. The heterogeneity includes morphological features and genetic disorders. Metastasis involves the spread of the primary tumor to a locally distant site or via the circulatory system. The different morphological patterns leading to distinction in molecular status are unclear. These differences may influence the tumor microenvironment and potentially reflect the therapeutic effects of target drugs.

This is the third reported case involving an ALK-positive NSCLC patient with different histomorphologies but the same genotype. Yoshida et al. explored a large number of surgically resected ALK-rearranged lung cancers and compared the histological findings with ALK-negative tumors. They found that the histomorphologies of the metastatic tumors were largely similar to the primary site in ALK-positive patients, except for a case in which the primary tumor lacked signet-ring cells but the solid signet-ring cell pattern predominated in metastases. Zhao et al. reported a case with different histomorphologies in primary sites and metastases, but the same genotype was present with an ALK rearrangement. The present case also showed that the ALK status between the primary lung cancer and the corresponding metastatic lymph node tumor were consistent; however, the morphological features were different.

Hou et al. explored the status of ALK rearrangements between primary tumors and paired metastatic lymph nodes in 101 patients with lung adenocarcinomas. The concordance rate of ALK rearrangements between primary tumors and paired metastatic lymph nodes was 98%. Only two patients with ALK rearrangements in the primary tumors did not exhibit ALK gene fusions on paired metastatic lymph nodes. Gao et al. evaluated the ALK gene in 78 paired specimens (primary tumor site and paired metastatic lymph nodes); 98.7% of the patients had concordant ALK rearrangements. However, these studies did not further analyze the histological classification between primary

![Figure 1](image-url)  
*Figure 1* Hematoxylin and eosin staining revealed: (a) primary lung site (mucinous type) (×200) and (b) lymph node metastasis (solid type) (×200).
and metastatic lymph nodes. Few reports have simultaneously explored the intra-tumor heterogeneity in histomorphology and molecular subtype between primary and paired metastatic tumors.

For patients with ALK rearrangements, we consider that the primary lesion and metastatic tumor might be from the same clone or originate from the same genetic origin, because there were morphological changes during the process of metastasis within the microenvironment. Zhong et al. examined whether or not there was a driver gene alteration within histologically heterogeneous primary lung cancers. They found that rare intra-tumoral heterogeneity of EML4-ALK alterations within histologically heterogeneous primary lung adenocarcinomas existed. The intra-tumor heterogeneity was caused by genetic alterations and the influence of the tumor microenvironment, both potentially reflecting on the variability of morphological features. Thus, although the presence of primary and metastatic lesions in morphology was different, no discrepancies in EML4-ALK rearrangements existed. In patients with lung adenocarcinoma, the appearance of driver genes may be regarded as an early circumstance of tumor development. As in our case, an EML4-ALK rearrangement might be a molecular alteration that occurs in the early phase and is transferred to the lymph nodes. None of the histological morphological indicators determined the status of ALK gene rearrangements, and histomorphology should not replace confirmatory molecular detection.

We have presented a case of lung adenocarcinoma with different histological types between the primary and metastatic lymph node tumors, but both with ALK rearrangements. This case suggests that gene detection is important to apply precise treatment for lung cancer patients. Further exploration of the relationship between this distinct histomorphology and the feature of driver genes in lung cancer is warranted. Comparative molecular analysis could be of value to better understand the potential role of gene alterations in the development of the pathogenesis underlying lung cancer.

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**Disclosure**

No authors report any conflict of interest.

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