Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

CASE REPORT

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

You-cai Zhu[1*], Yun-te Deng[2*], Wen-xian Wang[3], Chun-wei Xu[4], Wu Zhuang[5] & Kai-qi Du[1]

1 Chest Disease Diagnosis and Treatment Center, Zhejiang Rongjun Hospital, Jiaxing, China
2 Department of Pathology, Tongji University Affiliated Shanghai East Hospital, Shanghai, China
3 Department of Chemotherapy, Zhejiang Cancer Hospital, Hangzhou, China
4 Department of Pathology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, China
5 Department of Medical Thoracic Oncology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, China

Keywords
ALK; histology; metastasis; non-small-cell lung cancer.

Correspondence
Wen-xian Wang, Department of Chemotherapy, Zhejiang Cancer Hospital, No. 1 Banshan East Street, Gongshu District, Hangzhou, Zhejiang 310022, China.
Tel: +86 10 8812 2188
Fax: +86 10 8812 2004
Email: helen-0407@163.com

Chun-wei Xu, Department of Pathology, Fujian Cancer Hospital, Fujian Medical University, No. 420, Fuma Road, Fuzhou, Fujian Province 350014, China.
Tel: +86 591 8366 0063
Fax: +86 591 6275 2890
Email: xuchunweibbb@163.com

*These authors contributed equally to the study.

Received: 28 February 2018;
Accepted: 28 March 2018.

doi: 10.1111/1759-7714.12648

Thoracic Cancer **9** (2018) 881–884

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 histomorphologies 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).[1] Some studies have shown that young, never/light smokers with adenocarcinoma are most likely to harbor *EML4-ALK* gene rearrangements;[2,3] while morphological histologic features have also been reported.[4,5] *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.[6] 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; $T_{2a}N_0M_0$ 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, $T_2N_2M_0$ 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.[7] 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.[5] 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.[5] Zhao *et al.* reported a case with different histomorphologies in primary sites and metastases, but the same genotype was present with an *ALK* rearrangement.[6] 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.[8] 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.[9] However, these studies did not further analyze the histological classification between primary

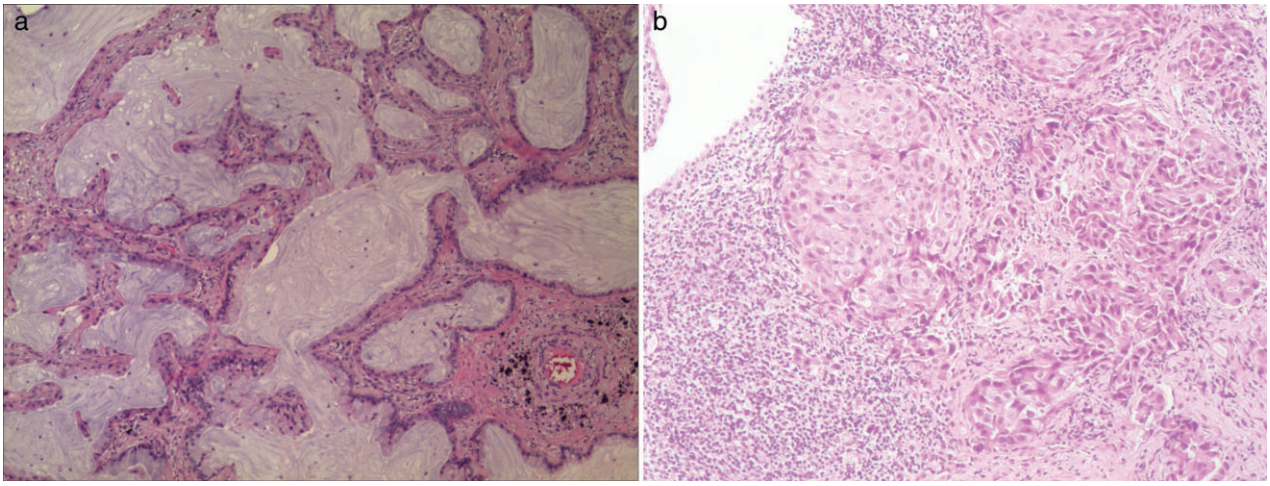

Figure 1 Hematoxylin and eosin staining revealed: (**a**) primary lung site (mucinous type) (×200) and (**b**) lymph node metastasis (solid type) (×200).

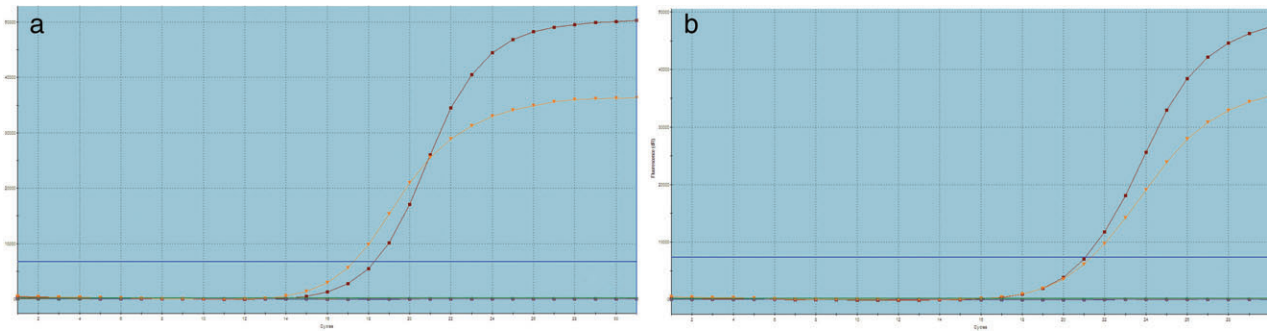

Figure 2 Schema shows (**a**) primary and (**b**) metastatic tumors with *ALK* gene positive drivers by reverse transcription-PCR. Orange, dark red, and green represent the sample, and positive and negative controls, respectively.

and metastatic lymph nodes.[8,9] 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.[10] Zhong *et al.* examined whether or not there was a driver gene alteration within histologically heterogeneous primary lung cancers.[11] They found that rare intra-tumoral heterogeneity of *EML4-ALK* alterations within histologically heterogeneous primary lung adenocarcinomas existed.[11] 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.[12] 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.[13] 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.

Acknowledgments

This work was supported by Zhejiang Province of China (2013KYB051), the Zhejiang Administration of Traditional Chinese Medicine Foundation (2013ZQ005), the Science and Technology Planning Project of Zhejiang Province (2015C33194), and the National Clinical Key Specialty Construction Program (2013).

Disclosure

No authors report any conflict of interest.

References

1 Ettinger DS, Wood DE, Akerley W *et al.* National comprehensive cancer network. Non-small Cell Lung Cancer, version 6.2015. *J Natl Compr Canc Netw* 2015; **13**: 515–24.
2 Shaw AT, Yeap BY, Mino-Kenudson M *et al.* Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009; **27**: 4247–53.
3 Chen G, Chen X, Zhang Y *et al.* A large, single-center, real-world study of clinicopathological characteristics and treatment in advanced ALK-positive non-small-cell lung cancer. *Cancer Med* 2017; **6**: 953–61.
4 Nishino M, Klepeis VE, Yeap BY *et al.* Histologic and cytomorphologic features of ALK-rearranged lung adenocarcinomas. *Mod Pathol* 2012; **25**: 1462–72.
5 Yoshida A, Tsuta K, Nakamura H *et al.* Comprehensive histologic analysis of ALK-rearranged lung carcinomas. *Am J Surg Pathol* 2011; **35**: 1226–34.
6 Zhao J, Zhou J, Chen Z *et al.* Different histopathology but the same clonality: ALK rearrangement in a patient with metastatic non-small-cell lung cancer. *Int J Clin Exp Pathol* 2015; **8**: 3344–8.
7 Woodhouse EC, Chuaqui RF, Liotta LA. General mechanisms of metastasis. *Cancer* 1997; **80** (8 Suppl): 1529–37.

8 Hou L, Ren S, Su B *et al*. High concordance of ALK rearrangement between primary tumor and paired metastatic lymph node in patients with lung adenocarcinoma. *J Thorac Dis* 2016; **8**: 1103–11.
9 Gao Q, Ma H, Wang B, Yao Y, Zhou J, Zhou J. Comparison of ALK status between primary and corresponding lymph node metastatic tumors in lung cancer patients. *Oncotarget* 2017; **8**: 108840–7.
10 Fidler IJ, Kripke ML. Metastasis results from preexisting variant cells within a malignant tumor. *Science* 1977; **197**: 893–5.
11 Zhong WZ, Su J, Xu FP *et al*. Rare discrepancies in a driver gene alteration within histologically heterogeneous primary lung cancers. *Lung Cancer* 2015; **90**: 205–11.
12 Nassar A, Radhakrishnan A, Cabrero IA, Cotsonis GA, Cohen C. Intratumoral heterogeneity of immunohistochemical marker expression in breast carcinoma: A tissue microarray-based study. *Appl Immunohistochem Mol Morphol* 2010; **18**: 433–41.
13 Tuveson DA, Neoptolemos JP. Understanding metastasis in pancreatic cancer: A call for new clinical approaches. *Cell* 2012; **148**: 21–3.

