Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

CASE REPORT

Molecular characteristics of multifocal invasive mucinous adenocarcinoma of the lung: Report of a rare case

Yan Tian[1], Wenqi Zheng[2], Huijing Ge[3], Yufei Wang[3], Nashunbayaer Zha[3], Shaojun Huang[3] & Zhanlin Guo[3]

1 Department of Hyperbaric Oxygen, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China
2 Laboratory of Surgery, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China
3 Department of Thoracic Surgery, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China

Keywords
Invasive mucinous adenocarcinoma; lung cancer; targeted therapy; thoracoscopic.

Correspondence
Zhanlin Guo, Department of Thoracic Surgery, The Affiliated Hospital of Inner Mongolia Medical University, 1 Tongdaobei Road, Hohhot, Inner Mongolia 010050, China.
Tel: +86 47 1345 2489
Fax: +86 187 0471 0099
Email: nmggzl@163.com

Received: 7 June 2017;
Accepted: 22 July 2017.

doi: 10.1111/1759-7714.12495

Thoracic Cancer **8** (2017) 710–713

Abstract

Invasive mucinous adenocarcinoma (IMA) is an uncommon entity in the lung, with a poor prognosis. Multifocal IMA of the lung is even more unusual, and there is little experience with effective treatments. Herein, we present a case of multifocal IMA diagnosed in a 36 year-old man by video-assisted thoracoscopic surgery. A right middle lobe and a nodule in the right upper lobe were resected, as were mediastinal lymph nodes, leaving behind an autonomous right lower lobe nodule. To explore the feasibility of molecular treatment, next-generation sequencing of genetic mutations was performed after four cycles of chemotherapy (pemetrexed + cisplatin). Ultimately, a *KIAA1468-RET* fusion gene was detected at a disproportionate level (~67.3%), indicating that targeted therapy may be efficacious in treating this disease.

Introduction

Invasive mucinous adenocarcinoma (IMA) is uncommon in the lung, accounting for 2–10% of primary lung adenocarcinomas.[1] Compared to other variants of lung adenocarcinoma, cases of IMA carry a poorer prognosis.[2] A number of studies have linked IMA and *KRAS* mutations,[3–5] and a lower prevalence of *EGFR* mutations and a higher prevalence of *KRAS*, *ALK*, and *HER2* mutations were recently reported in conjunction with IMA, as opposed to other invasive adenocarcinomas.[6] To the best of our knowledge, reports of an association between IMA and *RET* fusion genes are rare.

Case report

On May 19, 2015, a 36-year-old Chinese man was admitted complaining of dyspnea and chest discomfort that had lasted approximately two months, unaccompanied by hemoptysis or low-grade fever. No pertinent signs emerged during physical examination. The patient had generally enjoyed good health and had no history of smoking. All pulmonary function tests, as well as cranial magnetic resonance imaging, bone scan, and abdominal ultrasound, showed no obvious abnormalities. Serum levels of carcinoembryonic antigen, squamous cell carcinoma antigen, and neuron-specific enolase were also within normal reference ranges.

Subsequently, a CT scan revealed a sizeable mass (diameter 9 cm) within the middle lobe of the right lung. Its border at the upper lobe was poorly demarcated, and two small nodules in the right upper and lower lobes were also identified (Fig 1). A benign condition was considered, because the largest mass was ill defined and had not changed in size after two months of observation. Although fibrobronchoscopy was performed on two occasions, the bronchial lumen was devoid of lesions or external impingement, and no malignancy was identified in exfoliative cytology. Results of a positron emission tomography-computed tomography (PET-CT) scan were also compatible with a benign process of the right middle lobe (standardized update value 1.4). The nodules of the right upper and lower lobes failed to abnormally retain concentrated tracer, and no metastases were encountered in regional lymph nodes or in other areas of the body.

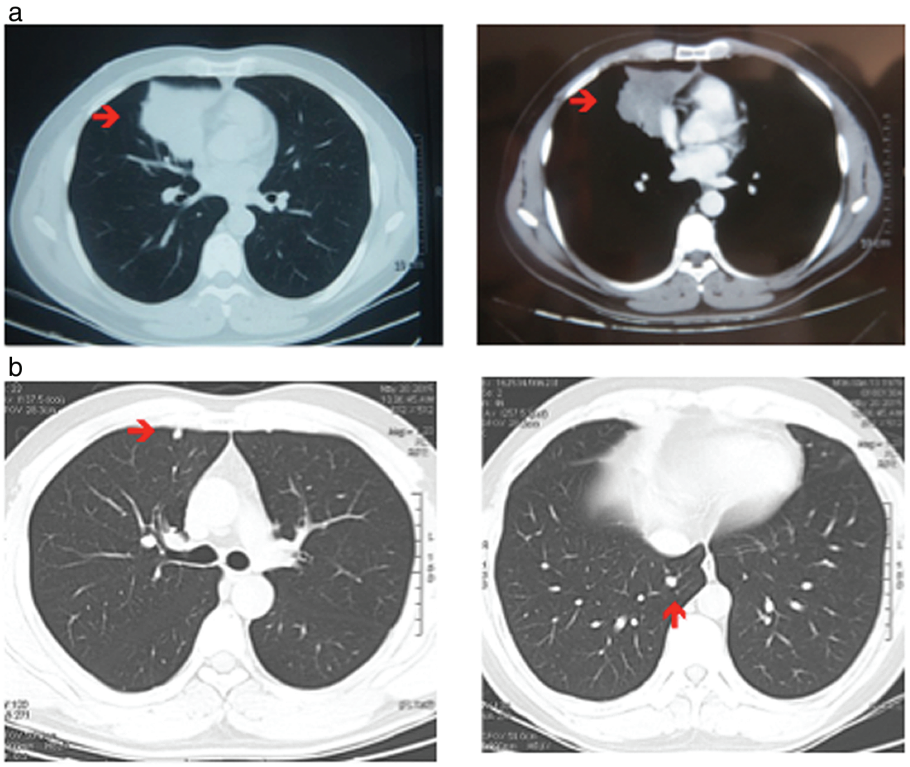

Figure 1 A chest computed tomography scan shows (**a**) a 9 cm diameter mass in the middle lobe of the right lung (boundary with the upper lobe unclear); and (**b**) small nodules in the upper and lower lobes of the right lung (arrows).

The middle lobe of the right lung and the small nodule in the right upper lobe were resected during video-assisted thoracoscopy on June 3, 2015. The mediastinal lymph nodes were also removed, leaving the separate lower lobe nodule intact. Upon examination, the growths were rich in mucus and highly gelatinous. Microscopic sections confirmed IMA at both the middle and upper lobe sites of involvement and in subcarinal lymph nodes (hematoxylin and eosin staining) (Fig 2a). Subsequent *EGFR* genetic testing (genes 18, 19, 20, and 21) was negative. The same was true of *EML4-ALK* genetic fusion testing.

Because the right lower lobe lesion remained unchanged after four chemotherapeutic cycles of pemetrexed/cisplatin (Fig 2b), the molecular structure of the tumor was explored. Profiling of genetic mutations via next-generation sequencing (OncoScreen TM 295 genes, Burning Rock Dx, Guangzhou, China) (Table S1) revealed a high proportion (~67.3%) of *KIAA1468-RET* fusion gene (Table S2). No other tumor-related somatic mutations were detected. The patient has survived for 20 months postoperatively, free of tumor recurrence or metastasis.

Discussion

The *RET* gene is a proto-oncogene located in the pericentromeric region of chromosome 10q11.2, which encodes a single-pass transmembrane, RTK. *RET* rearrangement is newly recognized as an oncogenic mutation in adenocarcinoma of the lung. The *RET* gene encodes a receptor tyrosine kinase that is critical in neural crest development,[7] binding with its ligand (i.e. extracellular signaling molecules of the glial cell line-derived neurotropic factor family)[8] to activate downstream pathways. Mutated *RET* genes are visible in a variety of cancers, such as hereditary medullary thyroid carcinoma of multiple endocrine neoplasia, but are seldom seen in normal lung tissue.[9,10] To date, over seven *RET* fusion partner genes have been identified: *KIF5B*, the most common fusion partner gene with more than 10 variations; *CCDC6*; *CUX1*; *TRIM33*; *NCOA4*; *KIAA1468*; and *KIAA1217*. The RET tyrosine kinase in particular is preserved in all fusions and each RET partner protein contains a coiled-coil domain, which is believed to promote ligand-independent dimerization and constitutive activation of RET. Therefore, *KIAA1468-RET*, which was detected in our case, is preserved in the RET tyrosine kinase. This phenomenon has been documented in close succession by several sources, all conceding that the *RET* fusion gene is a new key virulence mutation in lung cancer.[10–13] Cumulative data at present indicate that ~1.3% of patients with lung cancer harbor *RET* fusion genes, and nearly all corresponding tumors are adenocarcinomas.[14] Although the current National Comprehensive Cancer Network guidelines (2014) clearly advise testing for *RET* fusion in patients with lung

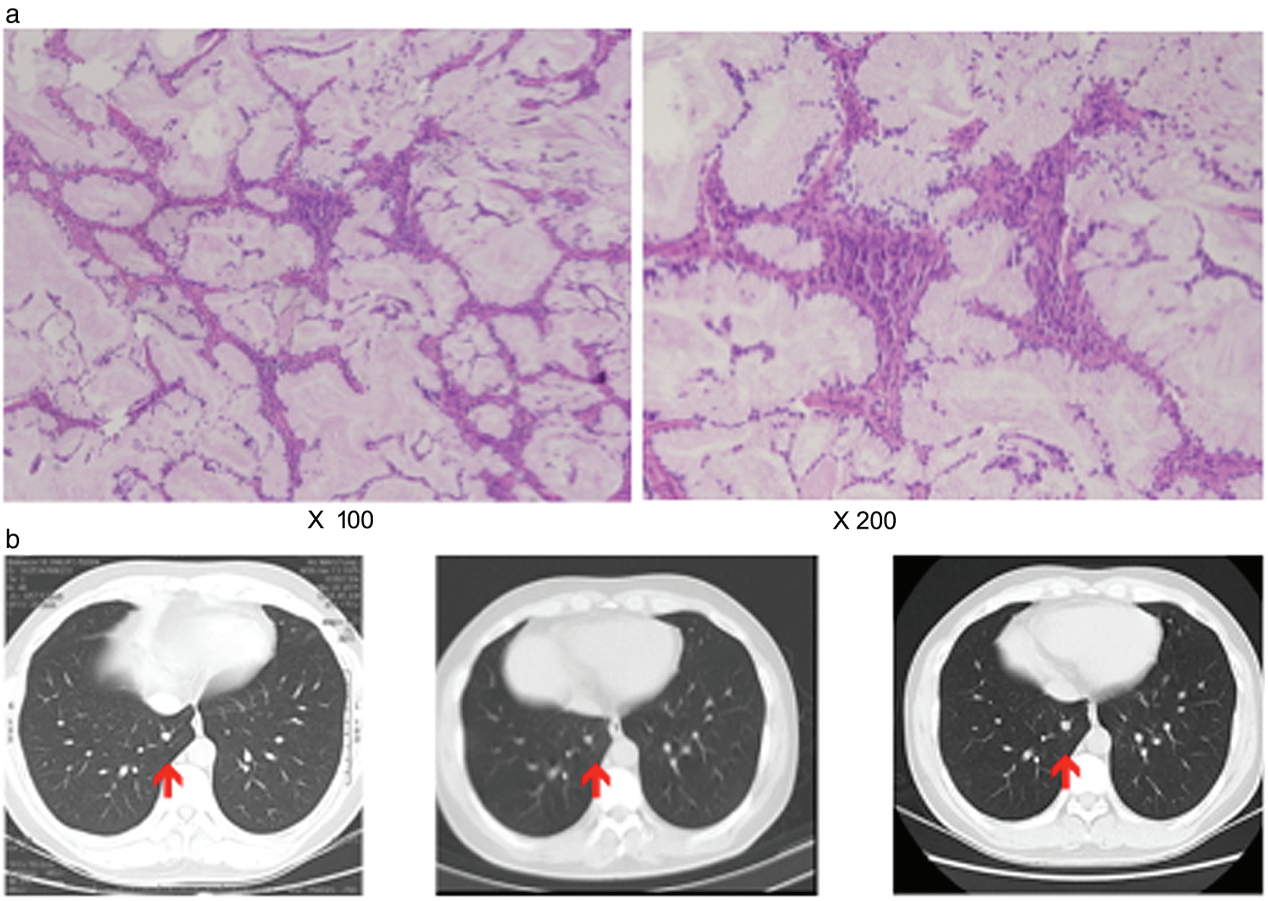

Figure 2 (**a**) Hematoxylin and eosin stained sections of the tumor: copious mucus production fills the alveolar spaces. (**b**) Serial computed tomography scans of the chest show that the size of the lower lobe lesion was essentially unchanged during chemotherapy. The diameter of this lesion was 5 mm on May 20, 2015, October 13, 2015, and June 16, 2016 (left to right, marked by arrows).

cancer,[15] there are no targeted therapies directed specifically at *RET* as yet. Nevertheless, the following multi-targeted agents may variably inhibit *RET* kinase activity: vandetanib (inhibiting *VEGFR-2/3*, *EGFR*, and *RET*); sorafenib (inhibiting *VEGFR-1/2, KIT, RET, CRAF,* and mutated *BRAF*); sunitinib (inhibiting *VEGFR-2, KIT, RET,* and *PDGFR* alpha); and cabozantinib (inhibiting *VEGFR-2, KIT, RET, MET, PLT-1/3/4, TIE-2* and *AXL*).[16,17] No clinical trials for molecular subtypes of *RET* fusion have been completed, but research is ongoing.

Our patient was satisfied with the surgery undertaken (i.e. resected right middle lobe, upper lobe nodule, and mediastinal lymph nodes), which confirmed IMA in both lobes of the lung and in the subcarinal nodes (pathologic stage T4N2M0). However, the residual disease in the right lower lobe proved refractory to chemotherapy, with no prospect of further surgical removal, radiation, or other options.

It is well known that targeted therapy may significantly prolong survival in patients with adenocarcinoma of the lung. Given current diagnostic guidelines, most clinicians are inclined to test for *EGFR* and *ALK* only, despite the fact that there are few targeted therapies focusing on *EGFR* or *ALK*. The results of both *EGFR* and *ALK* testing were negative in our patient, but next-generation sequencing is capable of distinguishing more actionable genomic alterations than standard diagnostic methods.[18] As genetic testing assumes greater importance in the clinical guidance of targeted therapy, the *RET* gene may increasingly become a potential target, enabling breakthrough treatments for patients with IMA of the lung.

Acknowledgments

This study was supported by grants from the Wu Jieping Medical Foundation (No.320.6750.143 20) and the National Natural Science Foundation of China (No. 81760528).

Disclosure

No authors report any conflict of interest.

References

1 Li S, Choi YL, Gong Z *et al.* Comprehensive characterization of oncogenic drivers in Asian lung adenocarcinoma. *J Thorac Oncol* 2016; **11**: 2129–40.
2 Zhang Y, Sun Y, Xiang J, Zhang Y, Hu H, Chen H. A clinicopathologic prediction model for postoperative recurrence in stage IA non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2014; **148**: 1193–9.
3 Tsuta K, Kawago M, Inoue E *et al.* The utility of the proposed IASLC/ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations. *Lung Cancer* 2013; **81**: 371–6.
4 Yoshizawa A, Sumiyoshi S, Sonobe M *et al.* Validation of the IASLC/ATS/ERS lung adenocarcinoma classification for prognosis and association with EGFR and KRAS gene mutations: Analysis of 440 Japanese patients. *J Thorac Oncol* 2013; **8**: 52–61.
5 Wislez M, Antoine M, Baudrin L *et al.* Non-mucinous and mucinous subtypes of adenocarcinoma with bronchioloalveolar carcinoma features differ by biomarker expression and in the response to gefitinib. *Lung Cancer* 2010; **68**: 185–91.
6 Hu H, Pan Y, Li Y *et al.* Oncogenic mutations are associated with histological subtypes but do not have an independent prognostic value in lung adenocarcinoma. *Onco Targets Ther* 2014; **7**: 1423–37.
7 Eng C. RET proto-oncogene in the development of human cancer. *J Clin Oncol* 1999; **17**: 380–93.
8 Kaczmarczyk M, Loniewska B, Kuprjanowicz A *et al.* Association between RET (rs1800860) and GFRA1 (rs45568534, rs8192663, rs181595401, rs7090693, and rs2694770) variants and kidney size in healthy newborns. *Genet Test Mol Biomarkers* 2016; **20**: 624–8.
9 Wang Y, Du LL, Hou SH *et al.* [RET pro-oncogene and medullary thyroid carcinoma]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2016; **51**: 873–6. (In Chinese.)
10 Wang R, Hu H, Pan Y *et al.* RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. *J Clin Oncol* 2012; **30**: 4352–9.
11 Kohno T, Ichikawa H, Totoki Y *et al.* KIF5B-RET fusions in lung adenocarcinoma. *Nat Med* 2012; **18**: 375–7.
12 Takeuchi K, Soda M, Togashi Y *et al.* RET, ROS1 and ALK fusions in lung cancer. *Nat Med* 2012; **18**: 378–81.
13 Drilon A, Wang L, Hasanovic A *et al.* Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov* 2013; **3**: 630–5.
14 Tsuta K, Kohno T, Yoshida A *et al.* RET-rearranged non-small-cell lung carcinoma: A clinicopathological and molecular analysis. *Br J Cancer* 2014; **110**: 1571–8.
15 Leduc C, Besse B. [Targeted therapies in non-small cell lung cancer in 2014.]. *Rev Mal Respir* 2015; **32**: 182–92. (In French.)
16 Dabir S, Babakoohi S, Kluge A *et al.* RET mutation and expression in small-cell lung cancer. *J Thorac Oncol* 2014; **9**: 1316–23.
17 Kodama T, Tsukaguchi T, Satoh Y *et al.* Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. *Mol Cancer Ther* 2014; **13**: 2910–8.
18 Muller M. Harnessing the power of next-generation sequencing. *Genet Test Mol Biomarkers* 2017; **21**: 1–2.

Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1 The detected 295 genes by next generation sequencing (OncoScreen TM 295 genes, Burning Rock Dx, Guangzhou, China).

Table S2 Next generation sequencing (OncoScreen TM 295 genes, Burning Rock Dx, Guangzhou, China): high proportion (~67.3%) of *KIAA1468-RET* fusion gene detected.

