CASE REPORT

The case of double primary lung adenocarcinomas with an *EGFR* mutation and *ALK* translocation successfully treated with alectinib at the post-surgical recurrence

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Abstract : A 36-year-old male was found two nodules in the right lower lobe of the lung. After the surgical resection, both lesions were diagnosed as invasive adenocarcinomas. One lesion was primarily lepidic growth component with EGFR-L858R mutation, and the other was micropapillary component with *ALK* translocation accompanying mediastinal lymphnode metastases. While he experienced disease recurrence, the disease was controlled by an ALK inhibitor, given based on the findings of surgical specimens. This is the first case who had two simultaneous lung cancers with *EGFR* mutation and *ALK* translocation in each respective lesion, and was successfully treated with ALK inhibitor at the post-surgical recurrence. J. Med. Invest. 64 : 305-307, August, 2017

Keywords **:** *EGFR mutation, EML4-ALK, double cancers, alectinib*

INTRODUCTION

Mutated *EGFR* and translocations in *ALK* are major drug targets in non-small cell lung cancer (NSCLC). In general, these two oncogenic drivers exist exclusively (1). Here we present to the best of our knowledge the first patient who had two simultaneous lung cancers with *EGFR* mutation and *ALK* translocation in each respective lesion, and was successfully treated with ALK inhibitor alectinib at the post-surgical recurrence.

CASE REPORT

A 36-year-old male, who was 8-pack year current smoker with no significant previous medical history, was found to have right lung opacity on a chest radiograph during a health examination. A computed tomography chest scan revealed two nodules in the right lower lobe, a 2.6 cm lesion in S8/9 with a cavity and ground glass opacity, and a solid and lobulated 2.1 cm lesion in S9. The maximum standard uptake value (SUVmax) of S8/9 and S9 lesions by FDG-PET scan was 1.9 and 15.3, respectively (Fig. 1). No significant accumulation was detected elsewhere. Each lesion was diagnosed as cT1bN0M0 (cStage IA) and a thoracoscopic right lower lobectomy with mediastinal lymphadenectomy was performed. Histological examination revealed the right S8/9 lesion to be invasive adenocarcinoma primarily with a lepidic growth component and the S9 lesion as invasive papillary adenocarcinoma with a micropapillary component. Mediastinal (#7, 4/6) and right hilar lymph node (#11, 1/6) metastases were detected.

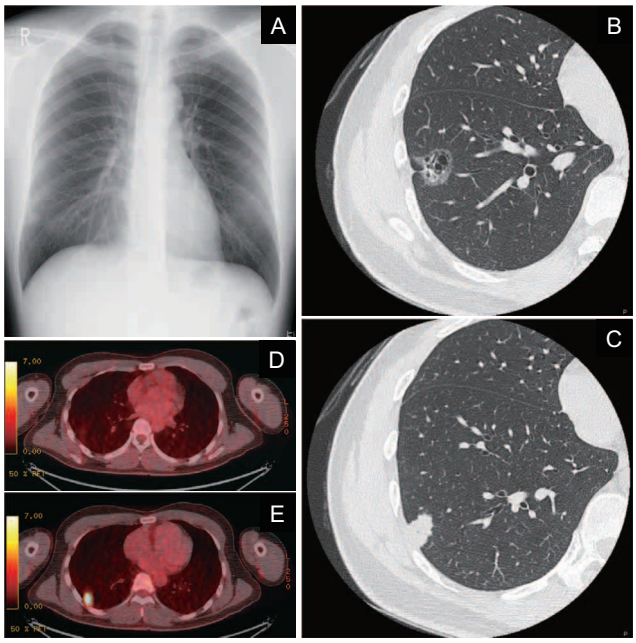

Figure 1. Radiographical appearance of the two lung lesions. (A) Chest radiograph showing the opacity in the right lower field. (B) Chest CT scan showing right lung lesions in S8/9. (C) Chest CT scan showing right lung lesions in S9. (D) FDG-PET scan showing low accumulation in the S8/9 lesion. (E) FDG-PET scan showing high accumulation in the S9 lesion.

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An *EGFR*-L858R mutation was detected by PCR-Invader assay in the S8/9, but not S9 lesion. FISH analyses for *ALK* and *EML4* revealed that cells from the S9, but not S8/9 lesion, had an *EML4-ALK* fusion (Fig. 2). Analysis with 5'-RACE using corresponding formalin-fixed paraffin-embedded tissue (2) further revealed the S9 tumor to have *EML4-ALK* E13 ; A20 (variant 1). Immunohistochemistry with specific antibodies for L858R mutant EGFR, and ALK showed that the S8/9, but not S9 lesion, was positive for *EGFR*-L858R. The S9, but not S8/9 lesion, was positive for ALK (Fig. 3), consistent with genetic results. Mediastinal and right hilar lymph node metastases were positive for ALK, but not EGFR-L858R (Fig. 3).

Therefore, we diagnosed that this patient had double lung cancers consisting of an *EGFR*-L858R mutation positive lesion (pT1bN0 M0, pStage IA) and an *EML4-ALK* translocation positive lesion (pT2aN2M0, pStage IIIA). Treatment with adjuvant chemotherapy consisting of 4 cycles of cisplatin and vinorelbin was given. Ten months after the completion of the adjuvant chemotherapy, the multiple bone metastases, associated with small volume of right pleural effusion, pericardial effusion, and elevated level of serum carcinoembryonic antigen (CEA), were detected by FDG-PET scan (Fig. 4). Re-biopsy could not be performed because there were no lesions for safe biopsy. We diagnosed the patient had recurrence of EML4-ALK lung cancer component, since EML4-ALK positive tumor cells invaded the mediastinal and right hilar lymph nodes.

The patient was treated with an ALK inhibitor alectinib (300 mg twice a day) (3). FDG-PET and CT scan taken 3 months after the initiation of alectinib revealed that accumulation in multiple bone lesions, right pleural effusion, and pericardial effusion disappeared (Fig. 4). Elevated level of CEA was improved with in normal limit by the treatment. Alectinib treatment is continued for longer than 17 months.

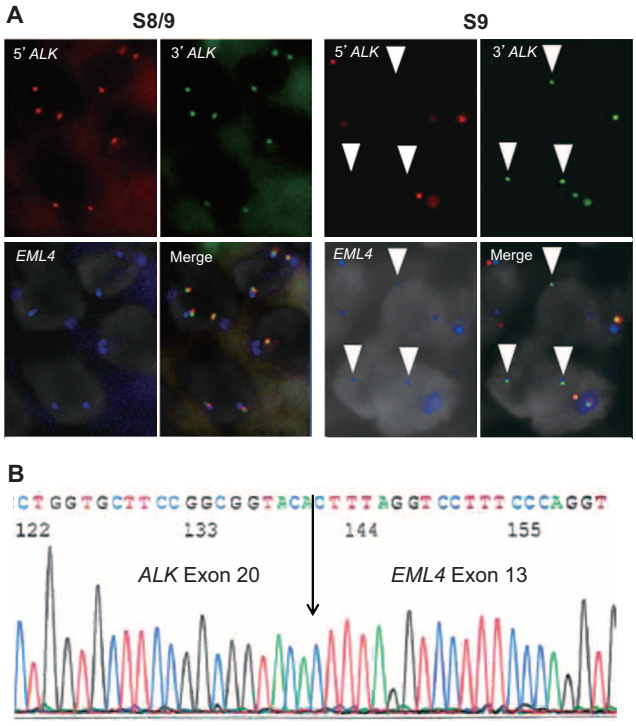

Figure 2. Detection of *EML4-ALK* in tumor cells in the S9 lesion. (A) FISH analyses for *ALK* and *EML4* revealed tumor cells in the S9 lesion, but not the S8/9 lesion, had an *EML4-ALK* fusion gene (5'*ALK*, red ; 3'*ALK*, green ; *EML4*, blue). Arrowheads indicate the rearranged *EML4-ALK* allele. (B) Sequence of the junction between *EML4* exon 13 and *ALK* exon 20 in the S9 lesion, with an arrow indicating the junction.

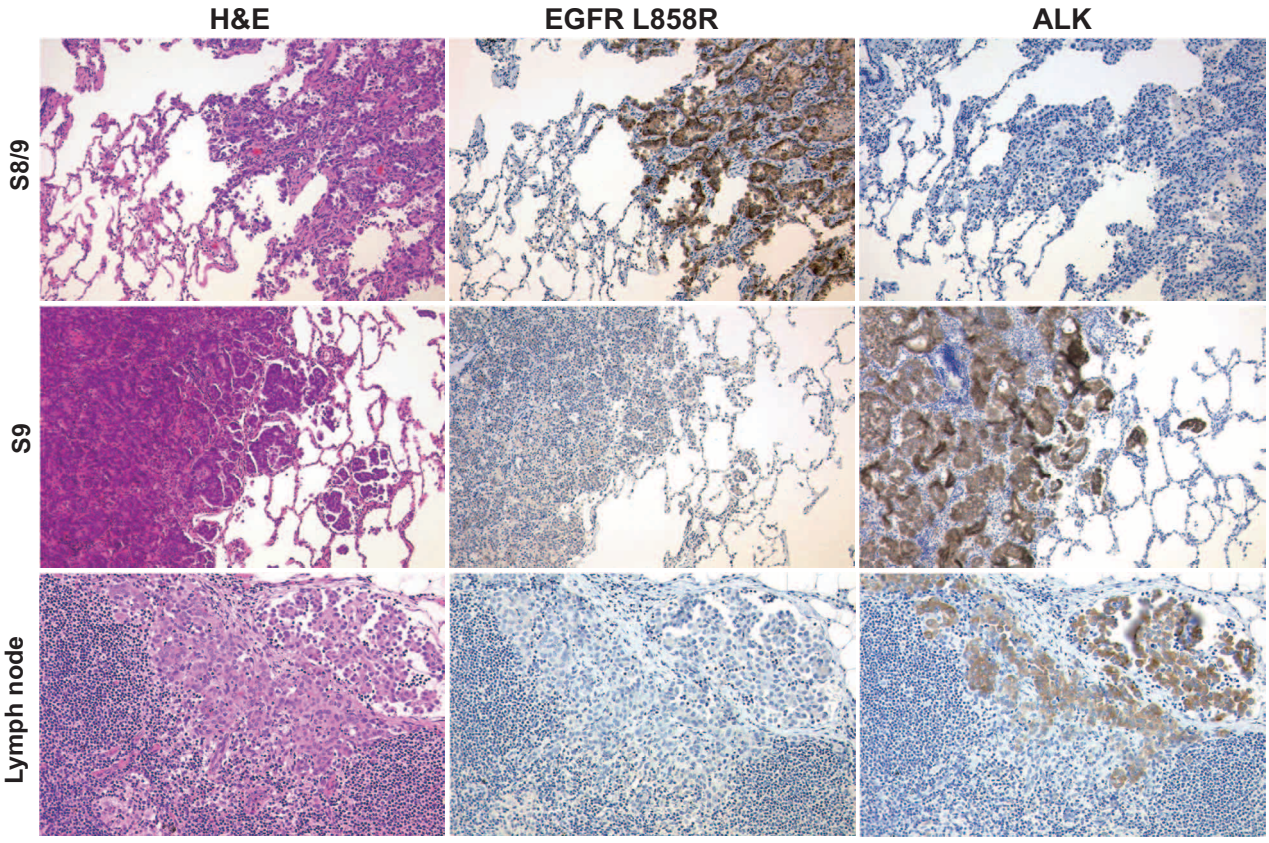

Figure 3. Histological findings of the two lung lesions. H&E staining and immunohistochemistry with anti-L858R mutant EGFR specific antibody and anti-ALK antibody of lung lesions (S8/9 and S9) and mediastinal lymphnode metastasis are shown (10× objective).

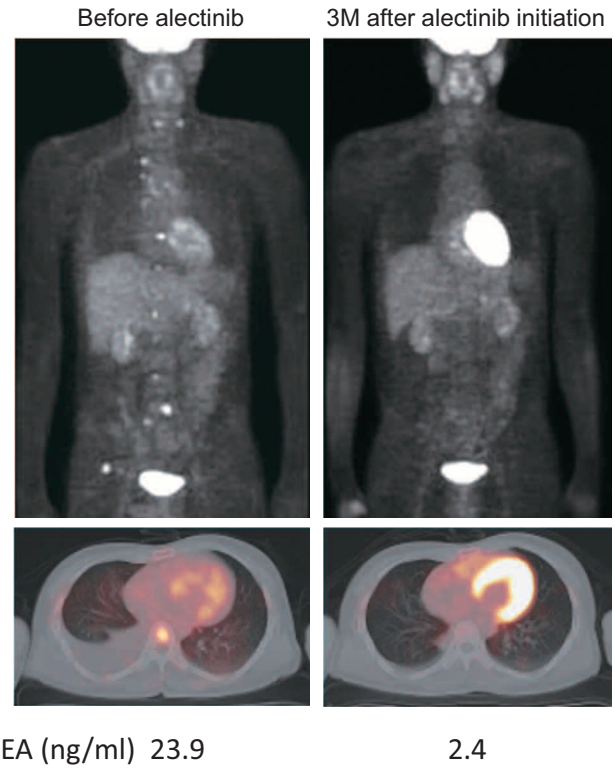

Figure 4. Effect of ALK inhibitor alectinib at the post-surgical recurrence. FDG-PET scan before and 3 months after the initiation of alectinib treatment (300 mg twice a day).

DISCUSSION

Three case reports (4-6) describe lung cancer patients with concomitant *EGFR* mutation and *ALK* translocation. However, it is unclear from these reports whether two tumors, each with one genetic alteration developed simultaneously, or a single tumor acquired both oncogenic drivers during its development. In our case, it is clear that two different lesions with different oncogenic drivers developed independently, because the microscopic appearance (lepidic vs papillary) and oncogenic drivers (*EGFR* mutation vs *ALK* translocation) were quite different in the surgically resected two tumors. This further indicates that double cancers with different oncogenic drivers can occur even in a young individual.

Recent clinical trials show the possibility of molecular diagnosis utilizing liquid biopsy specimens. However, it is still challenging in the clinical practice. Since our case did not have lesion for safe re-biopsy at the disease recurrence, we could not perform re-biopsy for assessing *EGFR* mutation and *ALK* translocation. We alternatively diagnosed that *EML4-ALK* component developed recurrent disease, because *EML4-ALK* component metastasized mediastinal and hiller lymph nodes at the surgical resection for double primary tumors. As the result, recurrent disease was dramatically diminished by alectinib treatment and controlled longer than 17 months. Our case also informed the importance of intensive molecular pathological diagnosis of surgical specimens for precision medicine by targeted drugs for recurrent disease.

CONFLICT OF INTERESTS-DISCLOSURE

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REFERENCES

1. Inamura K, Takeuchi K, Togashi Y, Hatano S, Ninomiya H, Motoi N, Mun MY, Sakao Y, Okumura S, Nakagawa K, Soda M, Choi YL, Mano H, Ishikawa Y : EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. Mod Pathol 22 : 508-515, 2009
2. Togashi Y, Soda M, Sakata S, Sugawara E, Hatano S, Asaka R, Nakajima T, Mano H, Takeuchi K : KLC1-ALK : a novel fusion in lung cancer identified using a formalin-fixed paraffin-embedded tissue only. PLoS One 7 : e31323, 2012
3. Seto T, Kiura K, Nishio M, Nakagawa K, Maemondo M, Inoue A, Hida T, Yamamoto N, Yoshioka H, Harada M, Ohe Y, Nogami N, Takeuchi K, Shimada T, Tanaka T, Tamura T : CH 5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study) : a single-arm, open-label, phase 1-2 study. Lancet Oncol 14 : 590-598, 2013
4. Toyokawa G, Taguchi K, Ohba T, Morodomi Y, Takenaka T, Hirai F, Yamaguchi M, Seto T, Takenoyama M, Sugio K, Ichinose Y : First case of combined small-cell lung cancer with adenocarcinoma harboring EML4-ALK fusion and an exon 19 EGFR mutation in each histological component. J Thorac Oncol 7 : e39-41, 2012
5. Miyanaga A, Shimizu K, Noro R, Seike M, Kitamura K, Kosaihira S, Minegishi Y, Shukuya T, Yoshimura A, Kawamoto M, Tsuchiya S, Hagiwara K, Soda M, Takeuchi K, Yamamoto N, Mano H, Ishikawa Y, Gemma A : Activity of EGFR-tyrosine kinase and ALK inhibitors for EML4-ALK-rearranged non-small-cell lung cancer harbored coexisting EGFR mutation. BMC Cancer 13 : 262, 2013
6. Chiari R, Duranti S, Ludovini V, Bellezza G, Pireddu A, Minotti V, Bennati C, Crinò L : Long-term response to gefitinib and crizotinib in lung adenocarcinoma harboring both epidermal growth factor receptor mutation and EML4-ALK fusion gene. J Clin Oncol 32 : e30-32, 2014