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Long-term complete response in a patient with postoperative recurrent *ALK*-rearranged lung adenocarcinoma treated with crizotinib: A case report

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Abstract. Anaplastic lymphoma kinase *(ALK)* gene rearrangements are identified in approximately 5% of patients with non-small cell lung cancer (NSCLC). Despite initial dramatic responses to ALK inhibitors, the majority of patients relapse within 1 year, owing to the development of resistance. Herein we present a case of variant type 2 *ALK*-rearranged lung adenocarcinoma recurrence with multiple lung metastasis that maintained complete response over 5 years with crizotinib, which is the first approved ALK inhibitor. The efficacy of crizotinib may vary among ALK fusion variants and thus, variant type may represent an important factor in guiding the treatment strategy for *ALK*-rearranged lung adenocarcinoma.

Introduction

Anaplastic lymphoma kinase *(ALK)* gene rearrangements are found in approximately 5% of non-small cell lung cancer (NSCLC) patients, and are enriched in patients with adenocarcinoma histology, patients with tumors of young onset, and never or light-smokers (1,2). Several ALK tyrosine kinase inhibitors (TKIs), such as crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib have been developed for *ALK*-positive NSCLC (3-7), and crizotinib was the first multi-targeted ALK-TKI to be approved. Despite initial dramatic responses to crizotinib, the majority of patients show relapse within 12 months because of the development of resistance (3). Only a few cases have shown long-lasting response to crizotinib, especially over 5 years. Here we experienced a very rare case of *ALK*-positive lung adenocarcinoma with postoperative recurrence that maintained complete response with crizotinib for over 5 years.

Case report

A 60-year-old male smoker with a right upper lobe lung tumor was referred to our hospital for operation (Fig. 1A). The patient had a medical history of controlled hypertension and hyperlipidemia. Transbronchial biopsy showed histology of adenocarcinoma. Radical right upper lobectomy with mediastinal lymph node dissection was performed. Pathological examination revealed moderately differentiated adenocarcinoma with acinar and solid component with cribriform pattern (Fig. 1B-D). Micropapillary component was identified within the acinar component and signet-ring cells were present in the solid component. The tumor was 7-cm in diameter and pleural invasion to superficial pleural connective tissue, vessel invasion, and lymphatic invasion were detected. Metastasis to hilar node was present, and the final pathological stage was IIB according to the 7th edition of tumor, node, and metastasis (TNM) classification. As postoperative adjuvant therapy, the patient was administered three cycles of carboplatin and S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) followed by one year of tegafur-uracil (UFT; Taiho Pharmaceutical). One year after the operation, multiple small nodules were detected by computed tomography (CT) and follow-up CT scan showed that nodules continued to grow (Fig. 2A). At one year and 8 months after the operation, thoracoscopic resection of a nodule in the right lower lobe was performed for pathological diagnosis. Pathological examination of the lung nodule revealed identical histology as the initial surgical specimen (i.e., adenocarcinoma with solid tumor with acinar

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Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; TNM, tumor, node, and metastasis; CT, computed tomography; EML4, echinoderm microtubule-associated protein-like 4; PFS, progression-free survival

Key words: crizotinib, anaplastic lymphoma kinase, non-small cell lung cancer, lung adenocarcinoma, post-operative recurrence

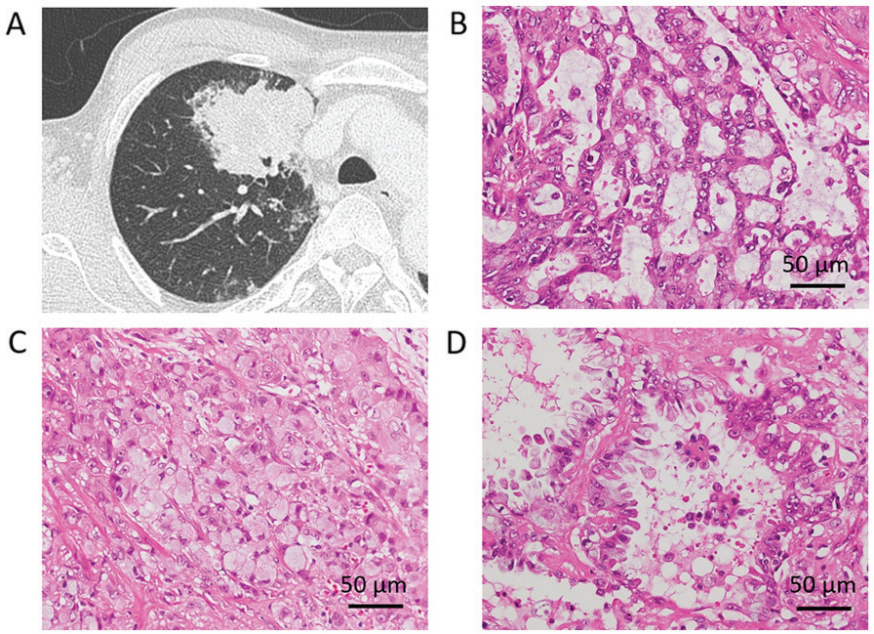

Figure 1. Radiologic appearance and photomicrographs of initial adenocarcinoma. (A) Computed tomography image of solid tumor in right upper lobe. (B) Mucinous cribriform component. (C) Signet cell component. (D) Micropapillary component. Scale bar, 50 μm.

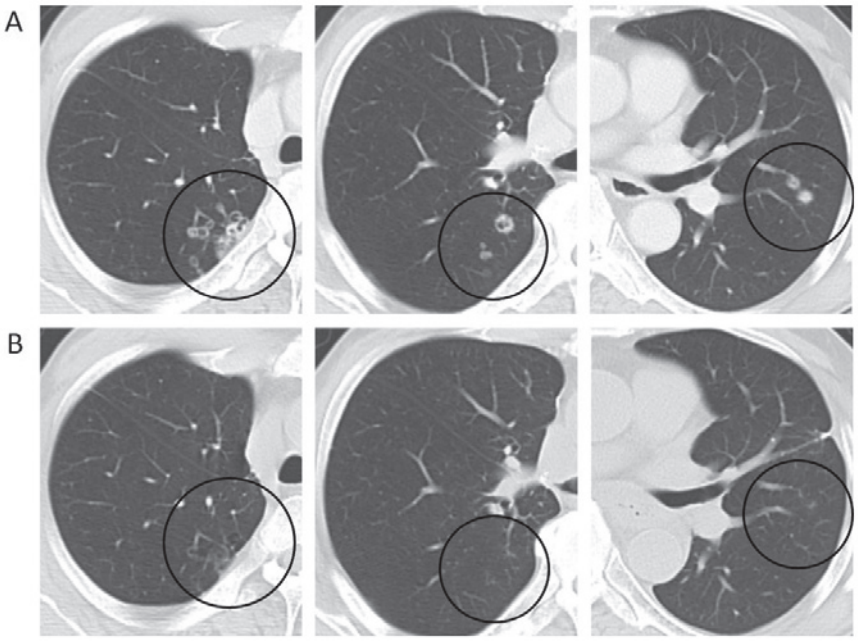

Figure 2. Radiologic appearance before and after the crizotinib treatment. (A) Computed tomography image revealed multiple small nodules in bilateral lung. (B) All small nodules disappeared following treatment with crizotinib.

and micropapillary components). Lung cancer recurrence was diagnosed, and all other nodules detected by CT were also considered to be recurrent lesions. Magnetic resonance imaging of brain and 18F-fluorodeoxyglucose positron emission tomography revealed there was no other metastasis than multiple lung metastases. Immunohistochemical analysis of the initial surgical specimen using a commercial assay showed that tumor cells were positive for ALK and fluorescence in situ hybridization confirmed the presence of *ALK* gene rearrangement with a positive cell rate of 62%. Analysis of the initial surgical specimen by next-generation sequencing assay using FusionPlex (Archer, Boulder, CO, US) revealed a variant type 2 of *echinoderm microtubule-associated protein-like 4 (EML4)-ALK* rearrangement [exon 20 of *EML4* fused to exon 20 of *ALK* (E20;A20)].

As the first-line treatment, crizotinib was administered twice daily (250 mg) and the size of multiple nodules remarkably decreased on follow-up CT after a month. Complete response was confirmed after 4 months (Fig. 2B) and was maintained over 5 years after the first administration of crizotinib. Grade 1 photopsia and diarrhea were the only adverse events observed.

Discussion

We present here a case of *ALK*-rearranged lung adenocarcinoma with postoperative multiple pulmonary metastases that showed complete response to crizotinib over a period of 5 years. The majority of patients treated with crizotinib have a relapse within 1 year (3). Clinical trials of crizotinib revealed that progression-free survival (PFS) was 10.9 months after first line treatment (3) and 7.7 months in patients who had received one prior platinum-based regimen (8). Rangachari *et al* (9), reported two cases of advanced lung adenocarcinoma with a PFS exceeding 5 years with crizotinib as first-line treatment. To the best of our knowledge, the current case is the third reported case of long-lasting PFS by crizotinib treatment exceeding 5 years. In addition, the current case is the first case depicting long-term complete response to crizotinib after postoperative recurrence. The previous report by Rangachari *et al* (9), does not include clinical and pathological details of the two cases with long-lasting PFS, and thus it is difficult to discuss the clinicopathological tendencies of these cases.

Several variants of the *EML4-ALK* fusion have been previously reported (10-12). The most frequent variants are variant 1 (33%), in which exon 13 of *EML4* is fused to exon 20 of *ALK* (E13;A20); variant 3a/b (29%), in which exon 6a or 6b of *EML4* is fused to exon 20 of *ALK* (E6a/b;A20); and variant 2 (9%), in which exon 20 of *EML4* is fused to exon 20 of *ALK* (E20;A20) (11). Other minor variants have also been reported. Recent studies have suggested that the response to crizotinib differs according to the *ALK* rearrangement variant (13-18) (Table I). Li *et al* (13), reported that patients with variant 2 had a longer PFS compared with patients with other variants. These clinical results are supported by *in vitro* studies in which Ba/F3 cells expressing variant 2 had higher sensitivity to crizotinib compared with cells expressing other variants (15,19). The results of these studies are consistent with our case, since our patient also had variant 2 fusion and achieved long PFS with crizotinib. However, such clinical differences in response or PFS vary amongst reports (13-18). Because the previous clinical studies were performed in small cohorts (Table I), a definitive conclusion has not yet been established.

In the treatment of *EGFR* mutated lung cancer, EGFR-TKIs sometimes maintain a good response for a long time. Lin *et al* analyzed patients with *EGFR* mutation treated with EGFR-TKIs and found that 14.6% of patients were 5-year survivors (20). The absence of extrathoracic metastasis was a significant factor associated with prolonged overall survival (20). In our case, the patient had multiple metastatic nodules, but these were limited to pulmonary metastases. Thus, similar to *EGFR* mutated lung cancer, absence of extrathoracic metastasis may also be a factor related to long-lasting CR for patients with *ALK* rearrangement.

In conclusion, here we presented a very rare case of variant type 2 *ALK*-rearranged lung adenocarcinoma that maintained complete response with crizotinib over 5 years. The efficacy of crizotinib may vary among ALK fusion variants, indicating that ALK variant type may represent an important factor in guiding the treatment strategy for *ALK*-rearranged lung adenocarcinoma. A large cohort analysis is required for further study.

Table I. Different of efficacy of crizotinib among *ALK* fusion variants.

First author (Ref. no.)	Total case	Variant 1			Variant 2			Variant 3a/b		
		Case	ORR	PFS	Case	ORR	PFS	Case	ORR	PFS
Lei *et al* (18)	61	22	73%	11.0 m	[a]non-v1/3a/b; n=21 ORR 81%, PFS 7.4 m		18	56%	10.9 m	
Cha *et al* (17)	32	10	30%	x	2	100%	x	8	50%	x
Yoshida *et al* (16)	35	19	74%	11.0 m	[a]non-v1; n=16 ORR 63%, PFS 4.2 m					
Woo *et al* (15)	51	[a]non-v3a/b; n=24, ORR 83%, 2-year PFSR: 76%						20	75%	2-year PFSR 26.4%
McLeer-Florin *et al* (14)	18	v1/2; n=6, ORR 60%, PFS 314 d						8	63%	192 d
Li *et al* (13)	60	14	46%	10.7 m	9	67%	18.5 m	20	65%	7.9 m

[a]including several types of variant. ORR, overall response rate; PFS, progression free survival; PFSR, progression free survival rate; m, months; d, days; n, number; x, data not shown.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contribution

TK designed the study. TK, TY, EY, SN, KiS, KT, RO, AM, KeS wrote the manuscript. KT, TY, EY, SN, KT, RO, KiS, AM, and KeS have contributed to the clinical management of the patient. AY and JH analyzed pathological findings. YY performed the next-generation sequencing assay. All authors critically reviewed the manuscript and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval for this study was obtained from Gunma University Hospital Ethics Committee. The patient provided written informed consent.

Patient consent for publication

Written informed consent was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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