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SHORT REPORT

Leptomeningeal recurrence after long-term alectinib therapy for non-small cell lung cancer harboring an EML4-ALK fusion protein

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Summary

The recent approval of anaplastic lymphoma kinase (ALK) inhibitors for the treatment of *ALK*-rearranged non-small cell lung cancer (NSCLC) has dramatically transformed cancer therapy. However, leptomeningeal metastases (LM) are frequent and often devastating complications of *ALK*-rearranged NSCLC, and treatment against LM remains challenging. Herein we report a case of a 19-year-old male diagnosed with *ALK*-rearranged NSCLC with LM. He experienced heavy treatment before introduction of alectinib therapy, which continued for approximately 5.5 years with marked efficacy. However, he experienced recurrence of a bulbar metastasis after discontinuation of alectinib. Reintroduction of standard-dose alectinib therapy resolved the lesion again. Our findings suggest that ALK-tyrosine kinase inhibitor therapy should be continued in patients showing a long-term complete response, unless intolerable toxicities are present, and that rechallenge treatment with alectinib may represent a therapeutic option for central nervous system metastases.

Keywords Non-small cell lung cancer · Leptomeningeal metastases · Anaplastic lymphoma kinase inhibitor · Alectinib

Introduction

Alectinib, a second-generation anaplastic lymphoma kinase (ALK) inhibitor, shows promising efficacy against *ALK*-positive non-small cell lung cancer (NSCLC), including leptomeningeal metastases (LM), management of which remains difficult for physicians [1, 2]. Herein we report a case of a young patient diagnosed with *ALK*-rearranged NSCLC with LM who received dramatic and durable benefits of alectinib therapy for more than five years, and also experienced successful alectinib therapy in a rechallenge setting after recurrence following cessation of alectinib.

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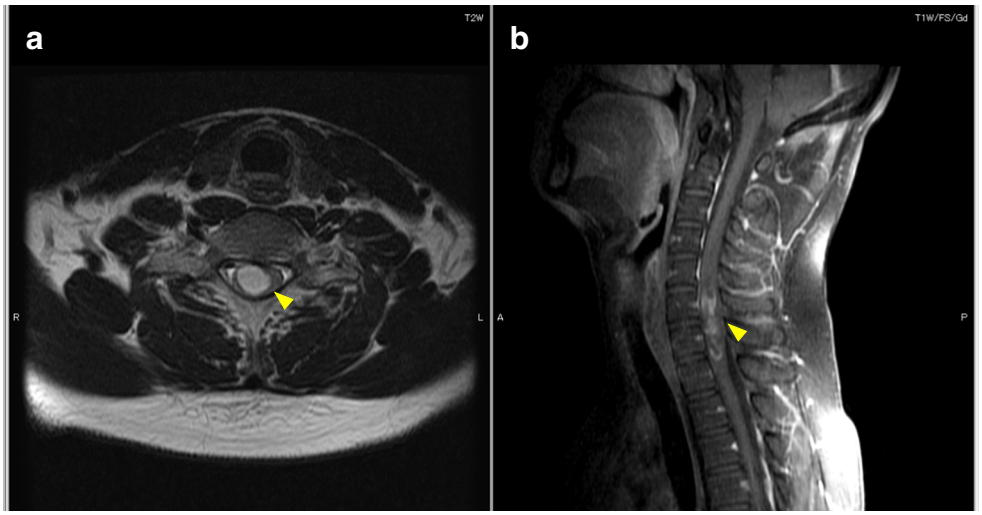

Fig. 1 Magnetic resonance imaging showing spinal cord metastasis (arrowheads). **a** Lesion in the transverse plane view of a T2-weighted image. **b** Lesion in the sagittal plane view of a gadolinium-enhanced T1 image

Case report

A 19-year-old male first visited Shizuoka Cancer Center in 2003 and was diagnosed with NSCLC at stage IIIA (cT2N2M0). He underwent a left lower lobectomy in August 2003, and adenocarcinoma with *EGFR* mutation negative status was pathologically diagnosed. However, the patient experienced recurrence with a cerebellar brain metastasis 2 years later. Stereotactic radiosurgery followed by 4 cycles of chemotherapy with cisplatin and gemcitabine was performed, and multiple brain metastases subsequently developed. Following whole brain radiotherapy (40 Gy/20 fr), the patient received chemotherapy with docetaxel for 36 cycles. However, a spinal cord lesion was identified by magnetic resonance imaging (MRI) in September 2009 (Fig. 1). The lesion was resected and confirmed as metastasis from the lung adenocarcinoma, and mutational analysis revealed positive *ALK* expression (Fig. 2). The patient received irradiation for the spinal cord lesion (40 Gy/20 fr), followed by 10 cycles of pemetrexed. The patient's carcinoembryonic antigen (CEA) level was found to be elevated 6 fold compared with baseline with glowing pulmonary hilar lymph node metastasis by computed tomography. The patient enrolled in a clinical trial and commenced treatment with alectinib in March 2011. The metastases subsequently shrank and CEA level normalized in a complete response. Alectinib therapy continued for approximately 5.5 years with marked efficacy and minimal toxicity, after which the patient chose to discontinue therapy in October

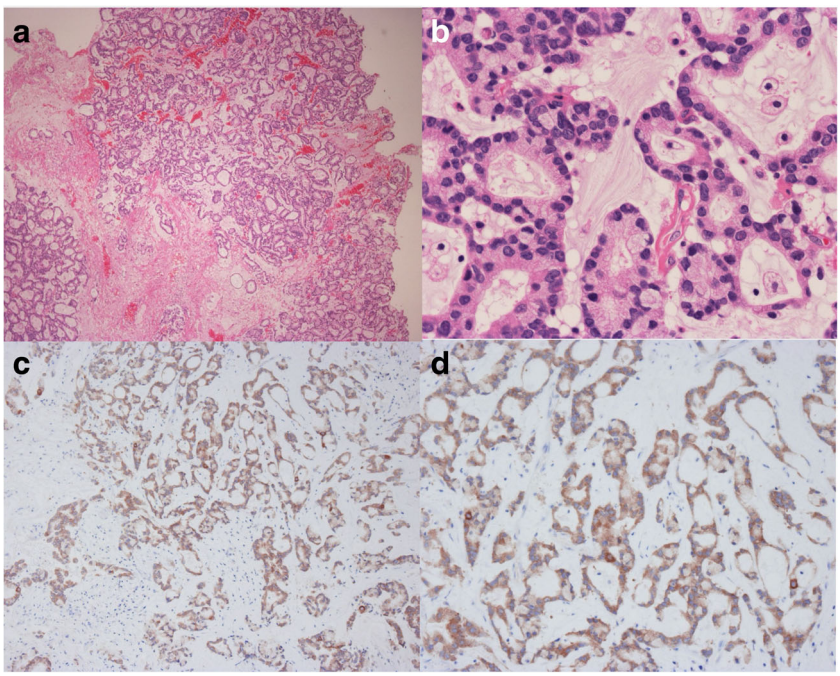

Fig. 2 Surgical specimen from brain. **a** Hematoxylin and eosin (HE) staining revealed adenocarcinoma with an acinar pattern (*arrows*) in a low-power field. **b** HE staining in a high-power field. **c** Immunohistochemical staining revealed that the tumor cells were positive for ALK. **d** ALK staining in a high-power field

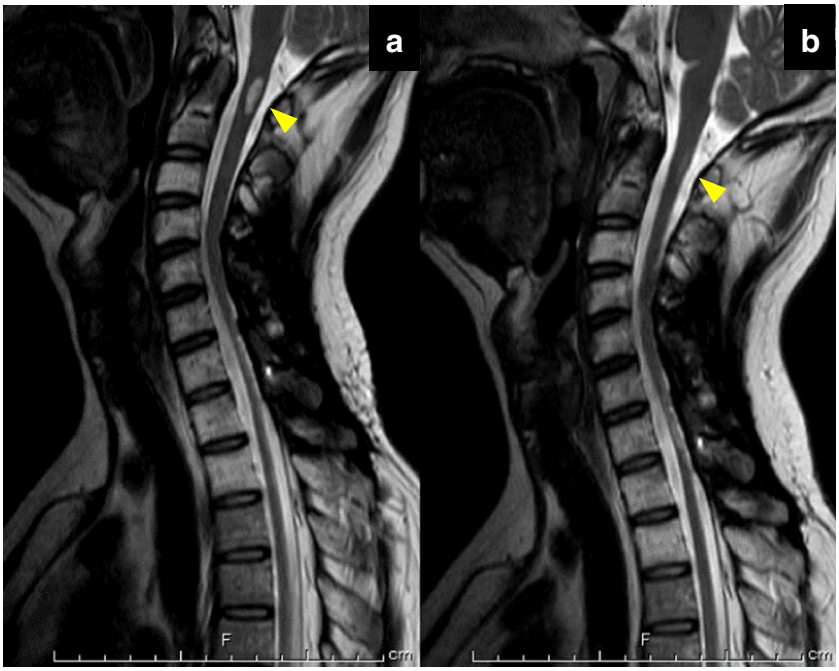

Fig. 3 Magnetic resonance imaging showing a new bulbar lesion after alectinib discontinuation (**a**; sagittal plane view of T2-weighted image). Four months after alectinib rechallenge therapy, the lesion had disappeared (**b**; sagittal plane view of T2-weighted image). Arrowheads indicate metastatic lesions

2016. However, a bulbar metastasis was identified by MRI in May 2017 (Fig. 3a) and alectinib therapy was reintroduced. Four months later, the lesion had resolved (Fig. 3b). The patient continues to receive outpatient follow-up with no new recurrences.

Discussion

Herein we describe a case of *ALK*-rearranged NSCLC with LM, showing long survival arising from alectinib therapy in particular. LM are frequent and often devastating complications of *ALK*-rearranged NSCLC, but their optimal management remains unclear because affected patients are generally excluded from clinical trials. Preclinical studies have shown that, unlike crizotinib and ceritinib, alectinib is not a substrate of P-glycoprotein and can thus penetrate the blood–brain barrier at a high rate to demonstrate clinical efficacy against central nervous system (CNS) lesions [3, 4]. In the present case, the patient responded strongly to alectinib therapy but nevertheless experienced recurrence after treatment cessation. Fortunately, he was successfully treated following the reintroduction of standard-dose alectinib therapy. Among the few cases of standard-dose alectinib rechallenge treatment reported to date, some showed that alectinib dose escalation was effective for recurrence with standard dose alectinib [5].

In summary, we have described rechallenge treatment with alectinib in a patient with *ALK*-positive NSCLC. Our findings suggest that ALK-tyrosine kinase inhibitor therapy should be continued in patients showing a long-term complete response, unless intolerable toxicities are present, and that rechallenge treatment with alectinib may represent a therapeutic option for CNS metastases.

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Compliance with ethical standards

Conflict of interest Haruyasu Murakami has received honoraria from Boehringer Ingelheim, Pfizer, Chugai Pharma, Taiho Pharmaceutical, AstraZeneca, Eli Lilly, Ono Pharmaceutical, Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme, and a grant from AstraZeneca. Haruki Kobayashi has received honoraria from MSD K.K. and Taiho Pharmaceutical. Kazuhisa Nakashima has received honoraria from Chugai Pharma, Boeringer Ingelheim and Novartis Pharma. Shota Omori has received honoraria from MSD K.K. Kazushige Wakuda has received honoraria from AstraZeneca, Chugai Pharmaceutical, Boeringer Ingelheim, Eli Lilly, Taiho Pharmaceutical, Ono Pharmaceutical, and a grant from AstraZeneca. Akira Ono has received honoraria from Chugai Pharmaceutical, Taiho Pharmaceutical, Ono Pharmaceutical, and grants from Chugai Pharma and Taiho Pharmaceutical. Hirotsugu Kenmotsu has received honoraria from AstraZeneca, Chugai Pharmaceutical, Bristol-Myers, Boeringer Ingelheim, Eli Lilly, Kyowa Hakko Kirin, MSD K.K., Novartis Pharma, and grants from AstraZeneca, Chugai Pharmaceutical and Boehringer Ingelheim. Tateaki Naito has received honoraria from Ono Pharmaceutical. Masahiro Endo has received honoraria from AstraZeneca and Ono Pharmaceutical. Toshiaki Takahashi has received honoraria from Eli Lilly, AstraZeneca, Chugai Pharma, MSD, Ono Pharmaceutical, Novartis Pharma, Roche Diagnostics, and grants from Eli Lilly, AstraZeneca, Chugai Pharma, MSD, and Ono Pharmaceutical. For the remaining authors no conflicts of interest are declared.

Ethical approval All procedures performed on the patient were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

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