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CASE REPORT

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Successful treatment of refractory brain metastases from ALK-positive lung cancer with lorlatinib

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Abstract

A 44-year-old woman with ALK-positive advanced adenocarcinoma of the lung was treated with crizotinib, and the lung lesions disappeared. The patient was treated with alectinib and chemotherapy, but brain metastases worsened; therefore, we performed an ALK resistance gene mutation test using plasma samples. Since no ALK resistance gene mutations were detected, we speculated that ALK inhibitors failed to achieve therapeutic effects due to poor transport to the central nervous system. Therefore, we switched to lorlatinib, and found a reduction in brain metastases. In ALK-positive advanced lung cancer, plasma-based resistance gene testing may be useful for treatment decisions.

KEYWORDS

ALK-positive lung cancer, highly sensitive PCR, rebiopsy

INTRODUCTION

The ALK fusion gene is one of the driver gene mutations in lung cancer, and ALK-positive lung cancer is found in approximately 3%–5% of non-small cell lung cancers (NSCLC).[1] In the J-ALEX and ALEX studies, alectinib showed better results than crizotinib.[2,3] Alectinib has also been shown to be effective in crizotinib-resistant patients.[4,5]

The mechanisms of ALK inhibitor resistance development are as follows: (1) mutations in the ALK kinase region, (2) ALK gene amplification, (3) the emergence of bypass pathways such as KRAS and EGFR activation, and (4) pharmacokinetic resistance related to poor transport of the drug to the central nervous system through the blood–brain barrier. The mutations that develop in the ALK kinase region vary greatly depending on the ALK inhibitor used, with the most common being L1196M with crizotinib, G1202R and l1171T/N/S with alectinib, and G1202R with crizotinib.[6] Alectinib has been shown in clinical trials to be effective against tumors with L1196M and C1156Y mutations, which are resistant to crizotinib,[7,8] and ceritinib has been reported to be effective against tumors with L1196M, l1171T/N/S, and V1180L mutations.[9] Lorlatinib, a third-generation ALK inhibitor, was developed to treat lung cancer resistant to ALK inhibitors. G1202R and G1202del mutations are representative of resistance gene mutations to first- and second-generation ALK inhibitors, and lorlatinib has been shown to be effective against tumors with these mutations.[10] In addition, lorlatinib has good drug transport to the central nervous system and has shown good efficacy against brain metastases.[11] Here, we report the case of a patient with ALK-positive lung cancer with refractory brain metastases that responded well to lorlatinib.

CASE REPORT

A 44-year-old woman was diagnosed with ALK-positive lung adenocarcinoma cT2aN3M1b stage IV (brain metastasis) in May 201X (Figure 1). After γ knife therapy for brain metastases, oral crizotinib (500 mg/day) was started in August 201X. Although the lung lesions were reduced by crizotinib, new brain metastases appeared in January 201X + 1, and repeated γ-knife therapy was performed for brain metastases. In February 201X + 2, head MRI showed a worsening of brain metastases and spinal cord tumors. (Figure 2a–c) After changing the anticancer drug therapy

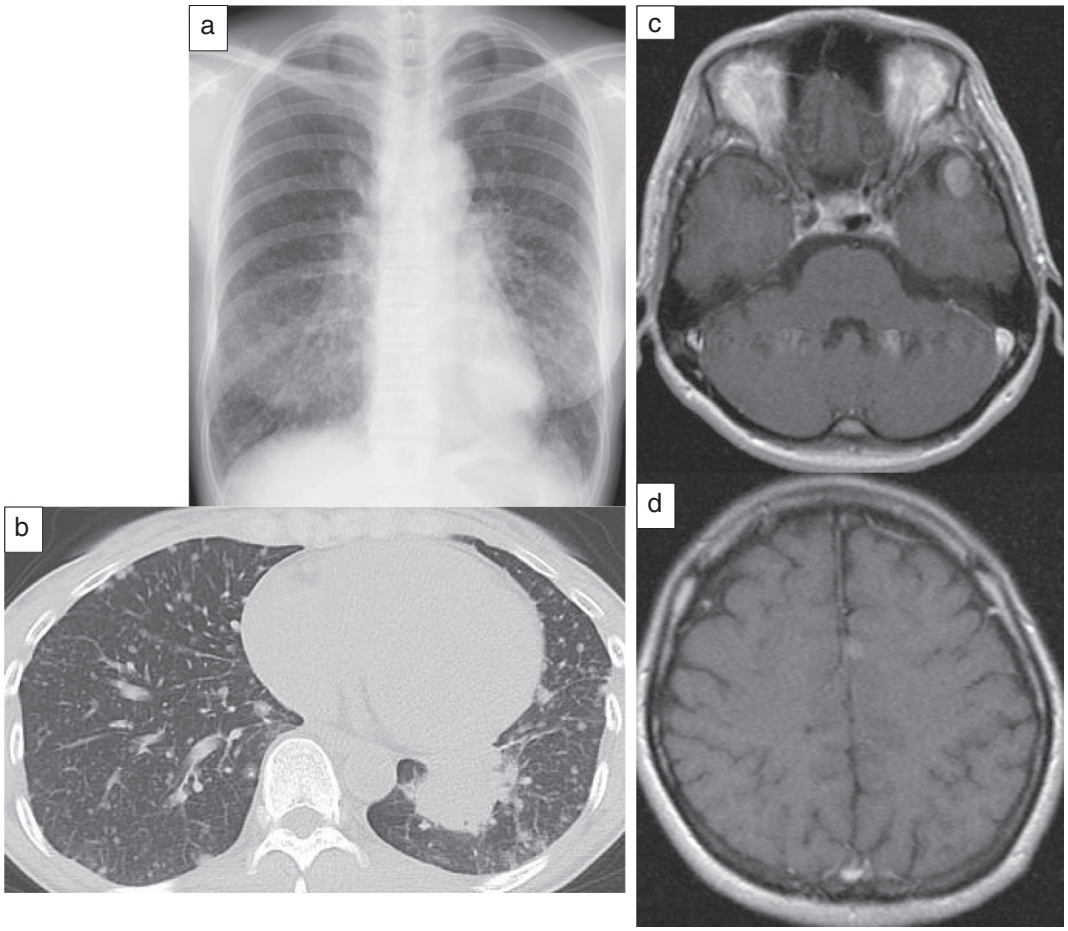

FIGURE 1 (a) Chest x-ray at the first visit showing bilateral small granular shadows. (b) Chest computed tomography (CT) at the first visit showing a mass in the left lower lobe and bilateral small granular shadows. (c, d) Contrast-enhanced (CE) brain magnetic resonance imaging (MRI) showed a mass in the frontal and temporal lobes

to alectinib, brain metastases and spinal cord tumors shrank(Figure 2d–f). In February 201X + 3, brain metastases and spinal cord tumors were shown to have worsened, and whole-brain irradiation and radiation to the cervical spinal cord were performed. Alectinib was discontinued, and the patient was switched to carboplatin + pemetrexed + bevacizumab. However, a new brain metastasis appeared, and because the patient was experiencing severe chemotherapy-induced fatigue, alectinib administration was challenged after March 201X + 4. However, the brain metastasis worsened despite repeated γ-knife therapy. Therefore, she was switched to lorlatinib in March 201X + 5. Before lorlatinib administration, ALK gene PCR was performed using plasma samples.

We assayed the presence of *ALK* mutations on circulating cell-free DNA of the patient. Extraction was carried out with 7 ml plasma using a QIAamp circulating nucleic acid kit (Qiagen). Determination of *ALK* mutational status was carried out using a Veriti Thermal Cycler (Thermo Fisher Science).

Primers and probes were designed for the detection of *ALK* resistance gene mutations ALK1151Tins, ALKL1152R, ALKC1156Y, ALKI1171T, ALKF11174L, ALKV1180L, ALKL1196M, ALKG1202R ALKS1206Y, ALKG1269A, and ALKL1198F, and analyzed using QuantaSoft analysis Pro software.

In the ALK gene test, no resistance gene mutation was detected in the plasma samples (Table 1).

No new brain metastases were observed after lorlatinib treatment. Lung lesions had disappeared after treatment with crizotinib, and no new lesions were observed (Figure 2g,h) The clinical course is shown in Figure 3.

DISCUSSION

First, we suspected that the failure of alectinib to control brain metastases was due to resistance to alectinib caused by secondary genetic mutations. ALK resistance gene mutations were analyzed by highly sensitive PCR using plasma samples from the patient, but only wild-type ALK was found; that is, no ALK resistance gene mutations were found. We hypothesized that the reason why the brain metastases in this patient were refractory to alectinib may be a difficulty in alectinib

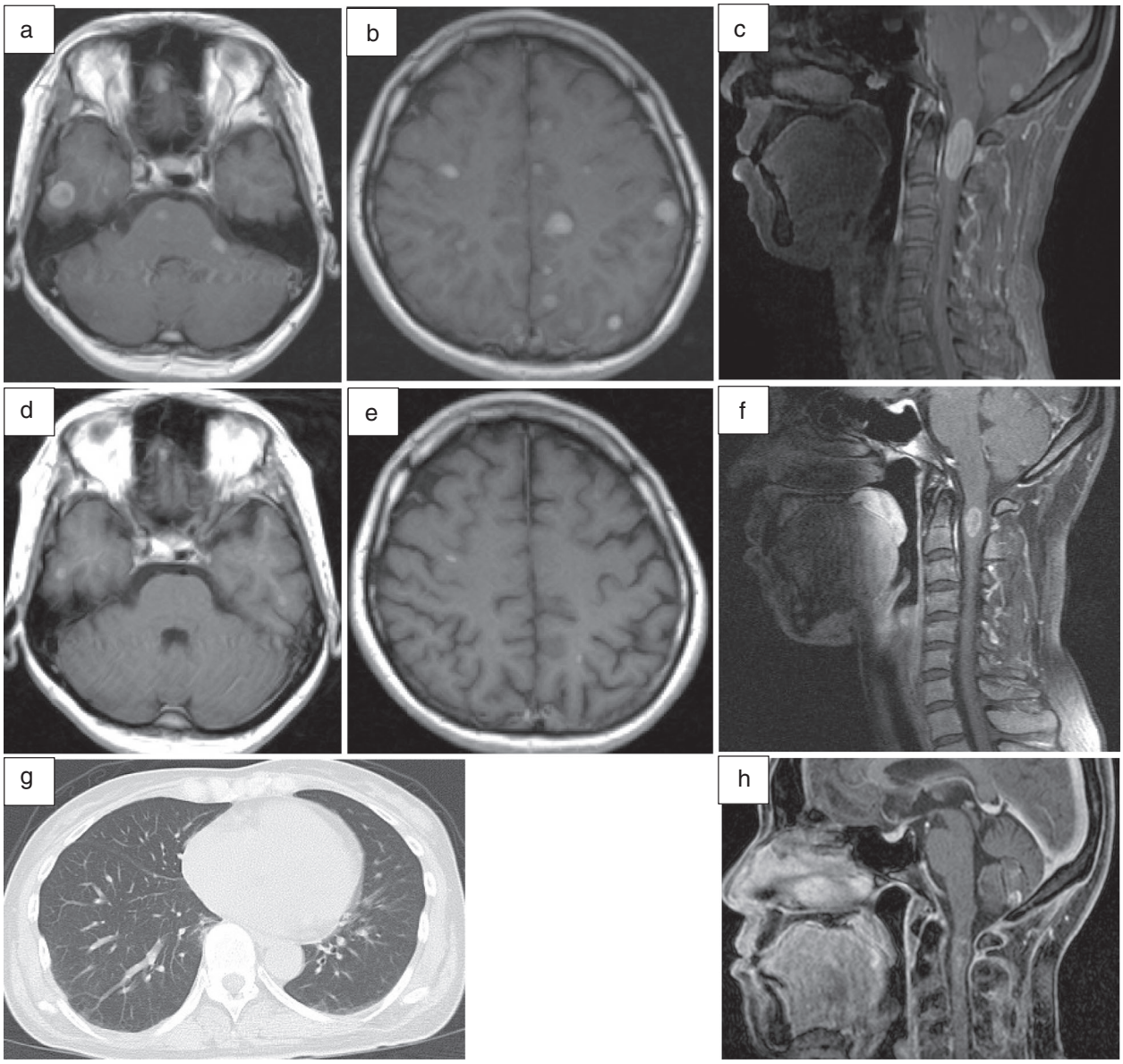

FIGURE 2 (a–c) Contrast-enhanced (CE) brain magnetic resonance imaging (MRI) showed disease progression of the brain metastases and an intramedullary tumor. (d–f) Brain MRI showed a reduction of the brain metastases and intramedullary tumor. (g) Chest CT showed an improvement in the lung shadows. (h) CE brain MRI showed an improvement in the brain metastases and intramedullary tumor

reaching the brain metastases. In contrast to crizotinib, alectinib is a drug that is highly bioavailable to the brain because it is not affected by the P-glycoprotein involved in drug efflux. In addition, alectinib has been reported to have good results against brain metastases in clinical trials. The approved dose of alectinib in Japan is 600 mg/bodyweight, which is less than the 1200 mg/bodyweight in international clinical trials. Therefore, it is suspected that the concentration of alectinib in the brain was not sufficient in this patient. Lorlatinib is a modified version of crizotinib with improved efficacy against tumors with ALK resistance gene mutations such as C1156Y and better brain transferability. Good brain transport has been reported for lorlatinib in basic research. In this patient, brain metastases were significantly reduced by lorlatinib, suggesting that lorlatinib may be more effective than alectinib in the approved capacity in Japan.

In this case, brain metastases worsened during treatment with alectinib and the lung lesion did not worsen; therefore, we did not perform a lung biopsy and an ALK gene test was performed using plasma samples. High-sensitivity PCR-based genetic testing of plasma is useful when rebiopsy is not possible. In the treatment of lung cancer, the status of genetic abnormalities is constantly changing; therefore, we should actively perform genetic testing using rebiopsy or highly sensitive PCR using plasma samples when lung cancer worsens, and plan the next treatment strategy based on the results of genetic testing.

TABLE 1 Results of the ALK polymerase chain reaction test with blood plasma

Assay	Target	Copies/ 20 µl Well	Accepted droplets	Fractional abundance	Poisson fractional abundance max	Poisson fractional abundance min	Total copies/ 20 µl well
ALK L1152R	L1152R	0.00	11085	0.00	0.00	0.00	508.52
	L1152wt	508.52	11085	-	-	-	
ALK C1156Y	C1156Y	0.00	11479	0.00	0.00	0.00	419.83
	C1156wt	419.83	11479	-	-	-	
ALK I1171T	I1171T	0.00	14013	0.00	0.00	0.00	648.60
	I1171wt	648.60	14013	-	-	-	
ALK F1174L	F1174L	0.00	12558	0.00	0.00	0.00	511.41
	F1174wt	511.41	12558	-	-	-	
ALK V1180L	V1180L	0.00	11166	0.00	0.00	0.00	580.27
	V1180wt	580.27	11166	-	-	-	
ALK L1196M	L1196M	0.00	10068	0.00	0.00	0.00	586.85
	L1196wt	586.85	10068	-	-	-	
ALK G1202R	G1202R	0.00	11236	0.00	0.00	0.00	589.49
	G1202wt	589.49	11236	-	-	-	
ALK S1206Y	S1206Y	0.00	10364	0.00	0.00	0.00	600.14
	S1206wt	600.14	10364	-	-	-	
ALK G1269A	G1269A	0.00	13145	0.00	0.00	0.00	611.09
	G1269wt	611.09	13145	-	-	-	
ALK T1151ins	T1151ins	0.00	12425	0.00	0.00	0.00	476.32
	T1151wt	476.32	12425	-	-	-	
ALK L1198F	L1198F	0.00	11164	0.00	0.00	0.00	448.96
	L1198wt	448.96	11164	-	-	-	

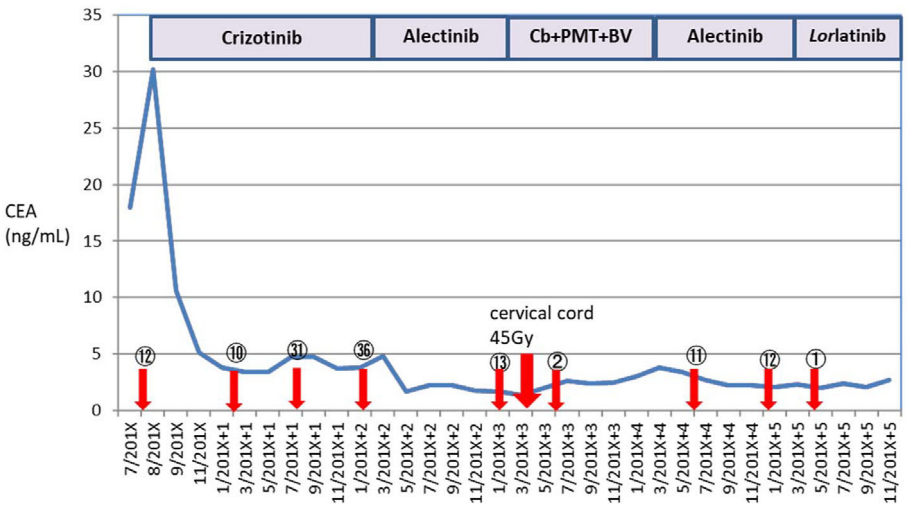

FIGURE 3 History of treatment. ↓shows the number of γ knife therapy cycles

CONFLICT OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

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REFERENCES

1. Wong DW, Leung EL, So KK, Tam IY, Sihoe AD, Cheng L, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancer from nosmokers with wild-type EGFR and KRAS. Cancer. 2009;115:1723–33.
2. Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer(J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017;390(10089):29–39.

3. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377(9):829–38.
4. Ou SH, Ahn JS, De Petris L, Govindan R, Yang J, Hughes B, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. J Clin Oncol. 2016;34(7):661–8.
5. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol. 2016; 17(2):234–42.
6. Gainor JF, Dardaei L, Yoda S, Friboulet L, Leshchiner I, Katayama R, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in *ALK*-rearranged lung cancer. Cancer Diccov. 2016;6:1118–33.
7. Seto T, Kiura K, Nishio M, Nakagawa K, Maemondo M, Inoue A, et al. CH5424802 (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. 2013;14(7):590–8.
8. Tamura T, Kiura K, Seto T, Nakagawa K, Maemondo M, Inoue A, et al. Three-year follow-up of an Alectinib phase I/II study in ALK-positive non-SmallCell lung cancer: AF-001JP. J Clin Oncol. 2017;35: 1515–21.
9. Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. NEJM. 2014; 370(13):1189–97.
10. Shaw AT, Solomon BJ, Besse B, Bauer TM, Lin CC, Soo RA, et al. *ALK* resistance mutations and efficacy of Lorlatinib in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer. J Clin Oncol. 2019;37(16):1370–9.
11. Bauer TM, Shaw AT, Johnson ML, Navarro A, Gainor JF, Thurm H, et al. Brain penetration of Lorlatinib: cumulative incidences of CNS and non-CNS progression with Lorlatinib in patients with previously treated ALK-positive non-small-cell lung cancer. Target Oncol. 2020;15(1):55–65.

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