Case Reports in Oncology

Case Rep Oncol 2023;16:1558–1567
DOI: 10.1159/000534549
Received: March 18, 2023
Accepted: September 21, 2023
Published online: December 12, 2023

Case Report

Entrectinib Response to ROS1-Fusion-Positive Non-Small-Cell Lung Cancer That Progressed on Crizotinib with Leptomeningeal Metastasis: A Case Report

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Keywords
Entrectinib · ROS1 · Crizotinib · Leptomeningeal metastasis · Non-small-cell lung cancer

Abstract
Introduction: C-ros oncogene 1 (ROS1) translocation is an oncogenic driver-mutation identified in 1–2% of non-small-cell lung cancer (NSCLC) cases. Although crizotinib, a tyrosine kinase inhibitor (TKI) against ALK/ROS1, is known to be effective against ROS1-fusion-positive NSCLC, such cases sometimes progress with brain metastases. The most frequently reported crizotinib-resistance mutation is ROS1 G2032R, and some studies have found that even newly developed ROS1 TKIs, such as entrectinib and lorlatinib, show a decreased efficacy against it. The optimal therapies for ROS1-fusion-positive NSCLC and how such cases can be sequenced have not yet been established. ***Case Presentation:*** We herein report a patient with ROS1-fusion-positive NSCLC diagnosed at 34 years old. Crizotinib was started at the diagnosis and switched after 25 months to cisplatin/pemetrexed/bevacizumab once the disease progressed with multiple brain metastases that were resistant to stereotactic radiation therapy. The cytotoxic chemotherapy stabilized the patient's condition for 17 months until he developed leptomeningeal metastasis (LM). He underwent lumboperitoneal shunting and whole-brain radiotherapy, followed by crizotinib re-administration. Despite crizotinib treatment, his neurological symptoms, such as double vision, headache, weakness in the legs, and walking difficulties, progressed. Eventually, subsequent entrectinib treatment was initiated, which resolved all of the symptoms mentioned above. Regrettably, liquid next-generation

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sequencing had failed to detect the resistance mechanism due to minimal ctDNA in this case. ***Conclusion:*** These findings imply that sequential entrectinib administration may be effective in patients with disease progression limited to central nervous system metastases during crizotinib administration.

Introduction

The treatment of non-small-cell lung cancer (NSCLC) has progressed significantly over the last 2 decades, from the approval of gefitinib, the first epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), in 2002, to the advent of precision medicine combining genetic profiling and molecular targeted therapy. Currently, there are seven oncoprotein-targeted therapies, EGFR, ALK, C-ros oncogene 1 (ROS1), BRAF, MET, RET, and KRAS that are approved in Japan, all of which are key cancer drugs. Despite the remarkable response in tumor shrinkage brought by TKIs, relapse due to acquired resistance is inevitable in almost all cases, and research to elucidate the resistance mechanism and new drugs to overcome resistance has been actively conducted [1].

Crizotinib and entrectinib are ROS1 TKIs and can be used as first-line treatment for ROS1-rearranged NSCLC [2]. The difference between these drugs is that entrectinib is a weak substrate with P-glycoprotein (P-gp) with a favorable brain distribution, whereas crizotinib is not [3]. P-gp is an essential efflux transporter located at the blood-brain barrier, and it transports out many drugs that are strong substrates of P-gp, leading to poor central nervous system (CNS) efficacy [4]. For that reason, the brain is a common first site of progression in NSCLC patients with ROS1 translocation who are taking crizotinib [5].

In general, the presence of a crizotinib resistance gene decreases the efficacy of entrectinib, as the two drugs share the same resistance gene (G2032R) [6]. However, there might be some clinical scenarios in which entrectinib remains effective even after progressive disease (PD) on crizotinib.

We herein report a case of ROS1-rearranged NSCLC that developed leptomeningeal metastasis (LM) despite crizotinib treatment. Furthermore, entrectinib elicited a significant response and completely resolved the neurological symptoms.

Case Presentation

A 34-year-old man presented to the respiratory department with a cough and breathlessness in October 2018. Investigations, including computed tomography (CT) and fluorodeoxyglucose-positron emission tomography, demonstrated widespread bilateral lung changes, most prominent within the lower lobe, consistent with primary lung cancer and metastatic spread. Associated hilar mediastinal and para-aortic lymphadenopathy were also noted, as were multiple bone and left adrenal metastases. Therefore, the final staging was cT4N3M1c (stage IVB), and a CT-guided biopsy revealed lung adenocarcinoma (TTF1+, CK7+, CK20-, CDX2-).

The patient developed significant back pain with associated leg weakness shortly after undergoing the above investigations and was emergently admitted to the hospital. Spinal magnetic resonance imaging (MRI) confirmed a solitary lumbar spine metastasis with no evidence of spinal cord compression. His pain was attributed to the bone lesion as well as to

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his abdominal lymphadenopathy, so he underwent palliative radiotherapy (20 Gy in 5 fractions) with an excellent clinical response. Molecular analysis showed that the tumor had an ROS1 translocation (immunohistochemistry strongly positive with a confirmatory fluorescence in situ hybridization [FISH] result). There was no evidence of an EGFR mutation or ALK translocation. PD-L1 was weakly positive (1–49%).

Following detection of the ROS1 translocation, he was started on crizotinib (500 mg a day) in November 2018. Although a complete response was achieved and sustained, a brain MRI revealed multiple asymptomatic brain metastasis in July 2020, which were treated with stereotactic radiation therapy (SRT). Two new lesions were detected on the cerebellum and cerebrum in October 2020, necessitating additional SRT. Subsequently, SRT was also added to the right parietal lobe and pons lesions in October 2020 and January 2021, respectively.

When we needed to administer a third round of SRT to his brain metastasis in January 2021, we concluded that the progression was due to acquired resistance to crizotinib and switched to cytotoxic chemotherapy of cisplatin/pemetrexed/bevacizumab. The chemotherapy stabilized his condition well with a good partial response (PR) until he started complaining of dizziness, tinnitus, light headache, and blurred vision in June 2022. MRI only showed the two known metastases on the cerebellum and cerebrum without any signs of leptomeningeal enhancement or enlargement of the ventricles (Fig. 1). A cerebrospinal fluid examination showed a normal protein concentration (32.2 mg/dL) and normal glucose concentration (53.0 mg/dL) but slightly elevated opening pressure (25 cmH_2O). The ophthalmologist he was referred to for his blurred vision confirmed that he had optic disc edema bilaterally. Although the initial CSF cytology only showed a few atypical cells, repeated testing eventually revealed positive with obvious signs of malignancy (Fig. 2a, b). As a result, we diagnosed him with LM. The progression only occurred on the CNS, whereas the whole body CT/positron emission tomography-scan did not show any changes from previous examinations.

While performing these tests, his neurological symptoms became exacerbated, and he became unable to walk. Eventually, lumboperitoneal shunting and whole-brain radiotherapy (30 Gy in 15 fr) with systemic steroid therapy were performed, which resulted in mild improvement in the dizziness and headache. Crizotinib was re-administered in August 2022 after liquid next-generation sequencing (NGS)-Based FoundationOne CDx failed to detect the presence of ROS1 fusion due to minimal ctDNA.

Finally, entrectinib 600 mg daily was initiated in October 2022 because crizotinib retreatment did not bring the expected efficacy, and he remained wheelchair-bound. By the end of December 2022, his symptoms had completely disappeared, and he was once more totally ambulatory. Both lactate dehydrogenase (LDH) and sialyl SSEA-1 antigen (SLX), known as tumor markers because of the concordance with his disease burden, have decreased significantly since entrectinib was introduced (Fig. 3, 4). The head MRI showed the metastatic site on the right basis pontis had become smaller (Fig. 5). Even though the dosage of entrectinib was reduced from 600 mg to 400 mg in January 2023 due to lower leg edema, bilateral pleural effusion, and mood swings, his symptoms of LM have not recurred. In addition, imaging studies including whole body CT and head MRI have had no significant sign of progression until now.

Discussion and Conclusion

ROS1 is a driver oncogene located on chromosome 6q22, and its translocation accounts for 1–2% of all NSCLC cases [2, 7]. ROS1-rearranged NSCLC is sensitive to ROS1 TKIs, such as crizotinib and entrectinib. Both agents are equally effective for NSCLC and are approved as

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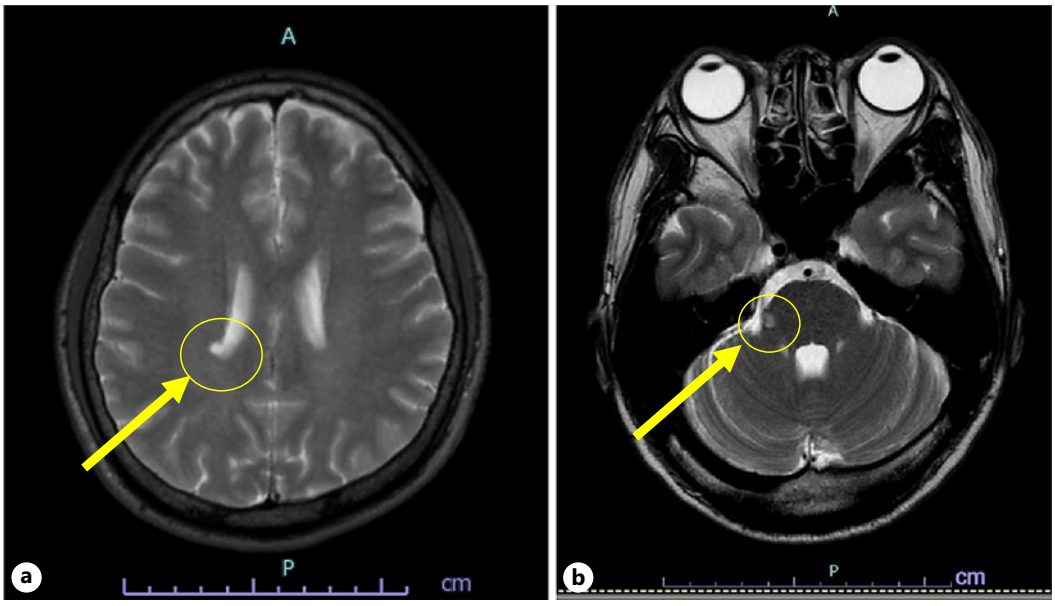

Fig. 1. T2-weighted MRI only shows pretreated metastasis lesion without any signs of leptomeningeal enhancement or enlargement of the ventricles. **a** 6 mm metastasis by the central part of lateral ventricle. **b** 5 mm nodule on the right basis pontis.

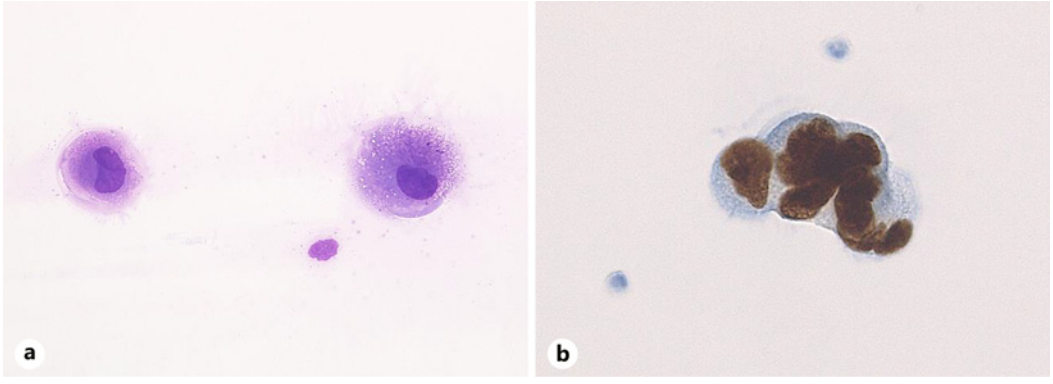

Fig. 2. a CSF cytology (Giemsa staining) showing atypical cells (×400). **b** CSF cytology (TTF-1 staining) showing TTF-1 positive (×400).

first-line therapies for ROS1-positive NSCLC by the United States Food and Drug Administration (FDA), Japan Pharmaceuticals, Medical Devices Agency (PMDA), and European Medicines Agency (EMA) [8].

Entrectinib has been evaluated in two phase I trials (ALKA-372-001 and STARTRK-1) and one phase II trial (STARTRK-2). The integrated analysis of these 3 trials showed that entrectinib is a potent ROS1-TKI with an objective response ratio of 67% (n = 108, 95% confidence interval [CI]: 59.3–74.3%), a duration of response of 15.7 months (95% CI: 13.9–28.6 months), and a median progression-free survival of 15.7 months (95% CI: 11.0–21.1 months) [9]. Entrectinib was also well-tolerated with a manageable safety profile. In these prospective trials, only 18 patients with CNS-only progression after crizotinib were included in total. A partial response (PR) and stable disease (SD) were achieved in 2 patients

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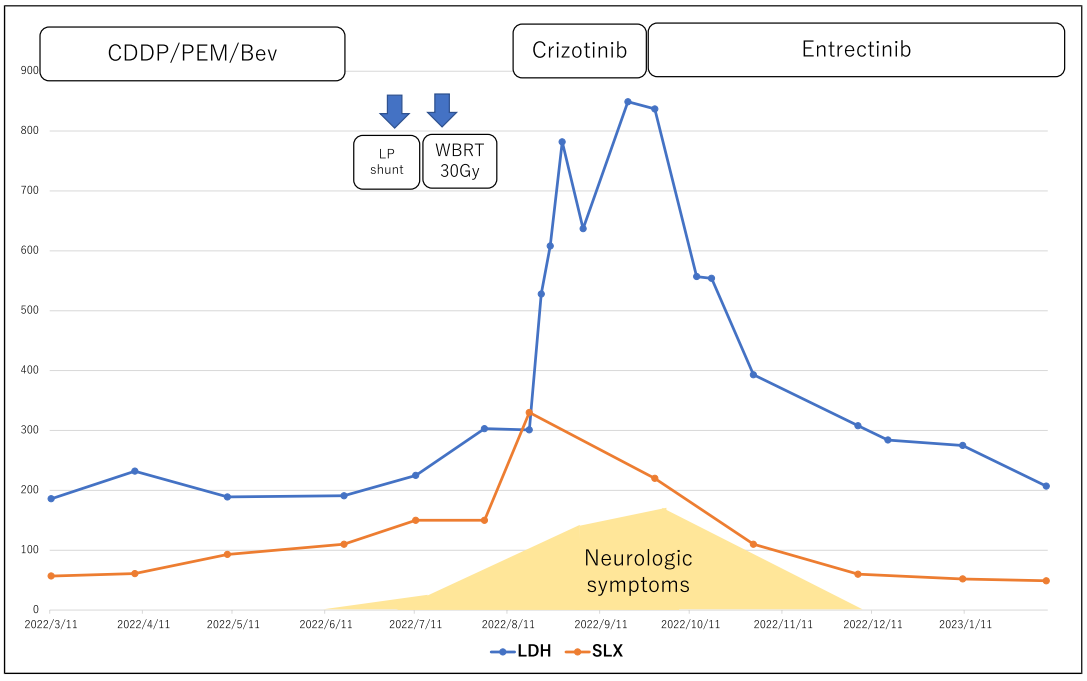

Fig. 3. Treatment course and tumor markers.

(11%) and 4 patients (22%), respectively. The median progression-free survival was 4.7 months (95% CI: 2.9–43.5 months), and the 12-month overall survival (OS) rate was 69% (95% CI: 46–92%), although the OS data remained immature, since some patients withdrew their consent during the study [10]. Due to the rarity of this driver mutation, it is difficult to wait for a prospective study to be conducted to evaluate how effective entrectinib is in a post-crizotinib setting. To our knowledge, the number of case reports written in English concerning entrectinib's efficacy is limited, especially for ROS1-fusion carcinomas, and this is the fourth case ever reported where entrectinib was administered after crizotinib (Table 1) [11–21].

Brain metastasis is found in 30–40% of stage IV ROS1-positive NSCLC cases at the diagnosis [5, 22]. The CNS is also a common first site of progression in those on crizotinib [5]. LM is a devastating form of CNS metastasis, accounting for approximately 5% of malignant tumors. Treatment options for LM for NSCLC require a multidisciplinary approach consisting of ventricular shunt placement, radiation therapy, and systemic or intrathecal chemotherapy. Regardless, the presence of LM is often explained as the final event for the patient, and hardly any effective treatment existed previously until immunotherapy and CNS-penetrating molecular-targeted therapies were developed [23]. Indeed, the median OS of NSCLC patients with LM has been reported to be as short as 3.6–11 months [24, 25]. P-gp, an important protein that actively transports drugs out of the blood-brain barrier, causes poor CNS efficacy [4]. Entrectinib is a weak P-gp substrate [3], in contrast to many other TKIs, including crizotinib. Therefore, entrectinib is an ideal ROS1-TKI against CNS metastases, including LM. In the present case, entrectinib was administered following crizotinib after disease progression, resulting in the amelioration of symptoms of LM derived from NSCLC.

Current methods of genetic screening in clinical practice are shifting from FISH break-apart assays and IHC assays to polymerase chain reaction and NGS panels. NGS can detect mutations, including resistance secondary mutations in the ROS1 kinase domain, which occurs in 50–60% of cases receiving first-line treatment with an ROS1-TKI. How the TKIs should be sequenced for ROS1-fusion-positive NSCLC is of great significance, but has not been

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October 2018	**Symptoms** :	Cough and breathlessness
	Diagnosis :	cT4N3M1c (stage IVB) lung cancer
	Symptoms :	Back pain and leg weakness
		MRI revealed a solitary lumbar spine metastasis
		ROS1 translocation was detected
November 2018	**Treatment** :	Crizotinib started
		Complete response was achieved
July 2020		Multiple asymptomatic brain metastasis was revealed
	Treatment :	Stereotactic radiation therapy started
October 2020		Two new lesions were detected on the cerebellum and cerebrum
January 2021	**Treatment** :	Switching from crizotinib to cytotoxic chemotherapy of cisplatin/pemetrexed/bevacizumab
June 2022	**Symptoms** :	Dizziness, tinnitus, light headache, and blurred vision
		CSF cytology showed obvious signs of malignancy / **Diagnosis** : leptomeningeal metastasis
	Treatment :	Lumboperitoneal shunting and whole-brain radiotherapy with systemic steroid therapy were performed
August 2022	**Treatment** :	Crizotinib was re-administered
October 2022	**Treatment** :	Entrectinib was initiated
December 2022		The patient's symptoms had completely disappeared

Fig. 4. A timeline summarizing the main events.

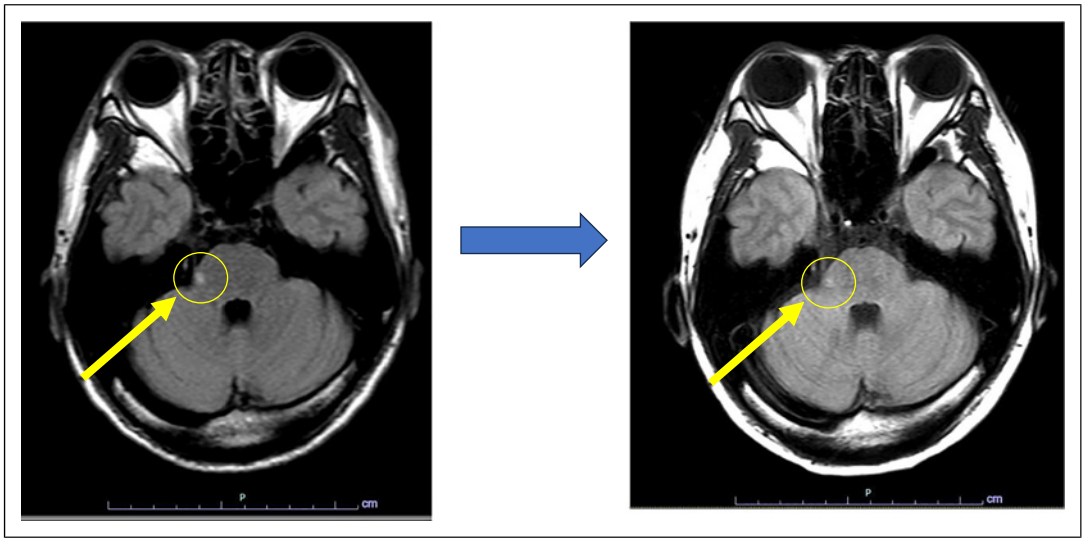

Fig. 5. The FLAIR MRI shows the metastatic site on the right basis pontis has become smaller once entrectinib was initiated.

established yet. ROS1 resistance mutations in those who experience progression on crizotinib treatment were well researched in a single-institutional retrospective report, which identified G2032R (41%), D2033N (6%), and S1986F (6%) in the population [22]. Other resistance mechanisms include EGFR and BRAF bypass mechanisms, downstream signaling mutations such as KRAS/PI3KCA, and conversion to SCLC and Sq. There is a possibility that entrectinib is less effective after PD with crizotinib, except for CNS-only progression like in our case study, because the IC_{50} of entrectinib is reported to be high with respect to the on-target G2032R mutation [6]. While lorlatinib is a subsequent therapy that can be administered for ROS1-positive NSCLC, as determined in the NCCN guideline, one case report also suggests its lack of

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Table 1. Case reports on entrectinib's efficacy for ROS1-fusion carcinomas

Case	Age	Sex	Country	Type of tumor	Brain metastasis	Treatment line	Entrectinib dosage	Response	Adverse event	Reference
1	51	Female	UK	NSCLC	Yes	1st	600 mg once daily →reduced to 400 mg	Good response	Myocarditis	Fonseca et al. [11] (2021)
2	22	Female	Turkey	NSCLC	No	1st	600 mg once daily	PR	Grade 2 dyspepsia, weight gain	Taban et al. [12] (2022)
3	40s	Female	Japan	NSCLC	No	2nd	600 mg once daily	CR	Generalized erythema	Tsuda et al. [13] (2022)
4	85	Female	Japan	NSCLC	Yes	2nd	400 mg once daily	Tumor shrinkage with a marginal response		Tanimura et al. [14] (2021)
5	38	Female	Japan	NSCLC	Yes	4th	Not mentioned	Good response		Hashiguchi et al. [15] (2021)
6	60	Female	USA	NSCLC	Yes	1st	600 mg once daily →reduced to 400 mg	Good response	Dizziness, gait instability, diarrhea	Sehgal et al. [16] (2020)
7	22	Female	USA	NSCLC	Yes	2nd	600 mg once daily →increased to 800 mg	Decrease in disease burden in the brain		Dimou et al. [17] (2019)
8	74	Female	Japan	NSCLC	No	1st	600 mg once daily →reduced to 400 mg	PR	Heart failure	Otsu et al. [18] (2022)
9	50	Female	USA	Nodular infiltrating papillary thyroid carcinoma	Yes	2nd	Not mentioned	SD		Liu et al. [19] (2017)
10	62	Female	France	NSCLC	No	1st	600 mg once daily	PR		Mayr et al. [20] (2020)
11	Infant		Austria	Infantile hemispheric high-grade glioma	primary lesion	2nd	400 mg once daily	SD		Facchinetti et al. [21] (2021)

NSCLC, non-small-cell lung cancer; CR, complete response; PR, partial response; SD, stable disease.

efficacy against ROS1 G2032R [26]. Conversely, the resistance mechanism after entrectinib is vastly different from that of crizotinib. In addition to on-target G2032R and L2026M mutations, KRAS and BRAF mutations, MET amplification, IGF-1R activation are also described. One paper published in Thoracic Cancer in 2022, specifically showed that MET amplification is associated with entrectinib resistance in vivo [27]. In fact, cell proliferation was suppressed when the ROS1/MET inhibitor, crozotinib, and the MET-selective inhibitor, capmatinib, were administered to entrectinib-resistant cell-lines. In other words, even if one ROS1 TKI fails, it might be meaningful to sequence to other approved TKIs.

In the present case, ROS1 translocation was initially identified by FISH and IHC assays but could not be re-confirmed by a liquid NGS panel (Foundation One Liquid CDx) that was repeated on progression. The inability to reconfirm is probably due to the very small amount of circulating tumor DNA in his blood. The CSF was not accepted to NGS testing because the number of malignant cells in the CSF was too minute to make a cell-block, as well, the liquid NGS was indicated for blood only. It may be difficult to identify a mutation by blood-based NGS if the lesion is limited to the brain. Regardless of whether the tumor had an ROS1-G2032R mutation in our case, entrectinib might have still been effective because the progression was limited to the CNS. Of the three previously reported cases in whom entrectinib was administered after crizotinib treatment, two switched due to CNS progression and one due to crizotinib-induced interstitial lung disease. Entrectinib showed a great response to all three CNS-progressed cases, including our patient.

We therefore propose that sequential entrectinib administration may be effective in patients who have disease progression limited to CNS metastases during crizotinib administration. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534549).

Statement of Ethics

This case report was reviewed and approved at yokohama municipal citizen's hospital Ethics Committee. Reference number; 23-03-04. Written informed consent was obtained from our patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest in association with the present study.

Funding Sources

There is no source of funding for this report.

Author Contributions

Dr. Sawada: conceptualization, investigation, and writing.

Dr. Taniguchi: conceptualization, and drafting/revising.

Dr. Iizuka, Dr. Ikeda, Dr. Aga, Dr. Hamakawa, Dr. Miyazaki, Dr. Misumi, Dr. Agemi, Dr. Nakamura, Dr. Maeda, Dr. Shimokawa, and Dr. Okamoto: supervision.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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