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Case Report

Effect of the First-Line Therapy with Osimertinib for a Metastatic Choroidal Tumor in Advanced-Stage Lung Cancer: A Case Report

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Keywords
Metastatic choroidal tumor · Osimertinib · Lung cancer

Abstract
Although the advent of molecular-targeted drugs has improved the prognosis of various cancers, the long-term prognosis and side effects as the first-line therapy for metastatic choroidal tumors remain unclear. We describe a case in which the first-line therapy of osimertinib has shown long-term successful and minimum side effect responses for metastatic choroidal tumors in a patient with advanced-stage lung cancer. The patient was a 62-year-old man who complained of foggy vision and visual field defects in his left eye for 1 month. When he visited his local doctor, a serous retinal detachment was noted in the left eye, and he was referred to our hospital for further examination. The patient had no history of systemic disease. A fundus examination of his left eye showed a slightly elevated choroidal lesion along with the superior retinal vascular arcade. Optical coherence tomography showed a serous retinal detachment around the lesion. Fluorescein angiography showed that the site of the lesion had spotty and mottled hyperfluorescence in the early phase and ring hypofluorescence in the late phase. We suspected a metastatic choroidal tumor and performed a whole-body computed tomography scan, which indicated lung cancer and metastasis to the left iliac bone. The patient was referred to the department of respiratory medicine of our hospital, and after a thorough examination, a diagnosis of lung adenocarcinoma (stage IV-B, epidermal growth factor receptor [*EGFR*] gene mutation positive) was made. Treatment with osimertinib was initiated, and shrinkage of the primary tumor was observed. The elevated choroidal lesion and serous retinal detachment resolved after 2 months of treatment, and no recurrence was observed during the 20 months of treatment. The use of osimertinib as primary treatment for EGFR

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mutation-positive lung cancer was found to significantly reduce the size of metastatic choroidal tumors and to have a relatively long-lasting antitumor effect without serious ocular complications.

Introduction

Metastatic uveal tumors are thought to develop hematogenously. The choroid accounts for approximately 88% of metastases in the uvea, followed by the iris (9%) and ciliary body (2%) [1]. Lung cancer is the most common primary tumor causing choroidal metastasis in men and the second most common cause of cancer in women in Japanese population. Non-small cell lung cancer (NSCLC) accounts for approximately 84% of lung cancers and adenocarcinomas are the most common histological entity [2]. Among patients with NSCLC, epidermal growth factor receptor (*EGFR*) mutations are found in 30–40% of Asian patients and 5–20% of Caucasian patients [3]. Choroidal metastases occur in 0.2–7% of patients with NSCLC. A recent report showed a prevalence of 8.4% of choroidal metastases in patients with *EGFR*-mutant NSCLC [4].

In the cases of advanced or metastatic NSCLC with mutations (exon 19 deletion or L858R point mutation) in the *EGFR* gene that confers sensitivity to tyrosine kinase inhibitors (TKIs), treatment with EGFR-TKIs is recommended [5]. In particular, osimertinib, a third-generation EGFR-TKI that selectively inhibits both EGFR-TKI-sensitizing and *EGFR* T790M-resistant mutations, has been shown to improve overall survival and central nervous system efficacy over the first-generation EGFR-TKIs in untreated patients with advanced-stage NSCLC [5, 6].

Systemic administration of EGFR-TKIs has been reported to be effective for choroidal metastases in *EGFR*-mutant NSCLC, and the efficacy of osimertinib has recently been reported [4, 7–11]. An attempt to use osimertinib as the first-line drug for choroidal metastasis in *EGFR*-mutant NSCLC is also under investigation. However, the long-term prognosis and complications are still unclear as there have been very few reported cases, and it is important to accumulate case series. In this study, we report a case of metastatic *EGFR*-mutant lung adenocarcinoma that was discovered by ophthalmologist. The patient was treated with osimertinib as the first-line therapy and maintained the resolution of the primary tumor and choroidal tumor without severe side effects for more than 1 year.

Case Presentation

A 62-year-old man was presented to a local ophthalmology clinic with foggy vision and partial visual field loss in the left eye. The patient had been visiting this clinic regularly for several years for primary angle-closure glaucoma which was controlled with glaucoma eye drops. Symptoms in the left eye developed for 1 month and gradually worsened. At the time of his last visit to the clinic, his intraocular pressure was within the normal range, and the anterior segment findings were also normal, but an exudative retinal detachment was observed at the posterior pole of the left eye. The patient was referred to our hospital for a further examination. He had smoked for 30 years, from age 20 to 50, and quit smoking at the age of 50. The patient was not taking any specific oral medications. There were no systemic symptoms such as cough, phlegm, or dyspnea. The patient's father had a history

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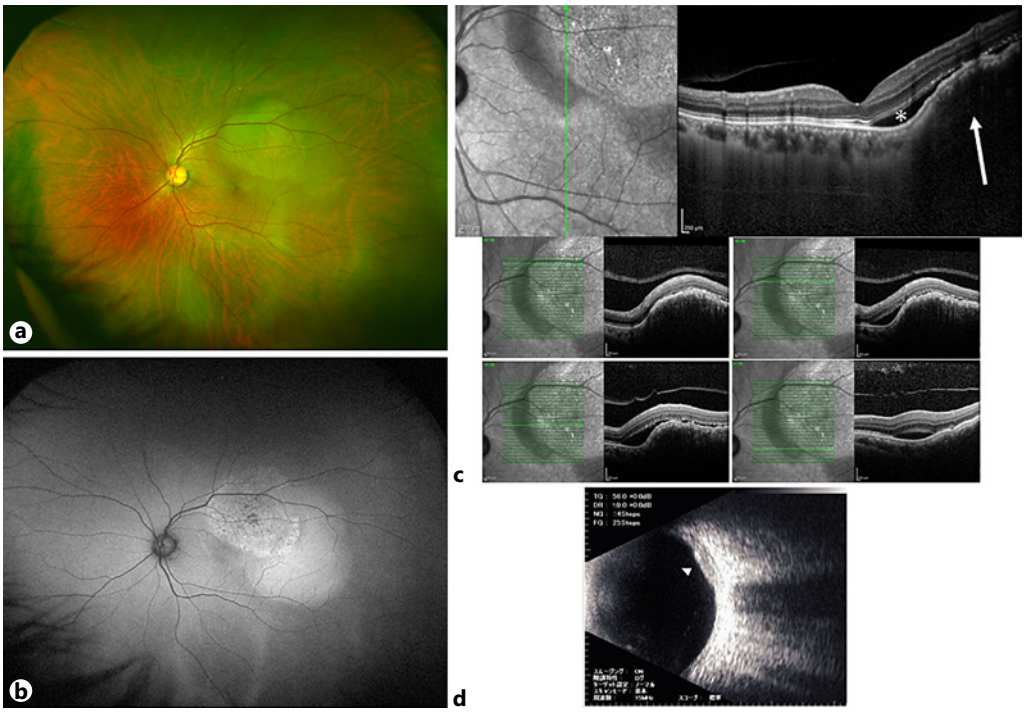

Fig. 1. a Widefield fundus photography showed a yellow-white elevated lesion with exudative retinal detachment around the superior vessel in the left eye. **b** Fundus autofluorescence showed granular and partially hypofluorescent at the protuberant lesion area and hyperfluorescent at the area of exudative retinal detachment. **c** Optical coherence tomography showed a choroidal mass lesion with a mildly irregular anterior surface (arrow) and subretinal fluid (*). **d** B-mode ultrasonography revealed a flattened, elevated lesion with medium-to-high reflectivity (arrowhead).

of *EGFR* mutation-positive lung cancer that was treated with gefitinib. At the time of the initial visit to our hospital, the visual acuity was 1.0 in the right eye and 1.2 in the left eye. The intraocular pressure was 12 mm Hg in the right eye and 14 mm Hg in the left eye. Slit-lamp examination showed shallow anterior chamber in both eyes. Anterior segment optical coherence tomography (AS-OCT) imaging showed anterior chamber depth of the right eye was 1.95 mm and anterior chamber depth of the left eye was 1.99 mm. Lens opacity was mild. Fundus examination revealed enlarged optic disc cupping in both eyes and a yellowish-white elevated lesion with exudative retinal detachment around the superior arcade vessels in the left eye (shown in Fig. 1a). Fundus autofluorescence showed granular and partial hypofluorescence in the protuberant lesion and hyperfluorescence in the area of exudative retinal detachment (shown in Fig. 1b). OCT revealed a choroidal mass lesion with mildly irregular anterior surface-associated subretinal fluid (shown in Fig. 1c). B-mode ultrasonography revealed a slightly elevated lesion with medium-to-high reflectivity (shown in Fig. 1d). Fluorescein angiography showed early spotty and mottled hyperfluorescence in the lesion, late fluorescence leakage from the retinal pigment epithelium, and ring hypofluorescence along the border of the lesion (shown in Fig. 2a, b). By indocyanine green angiography, the choroidal lesion was fluorescently blocked, and no obvious abnormal vessels were observed. The central area was consistently hypofluorescent from the early to late stage, but the surrounding area became hyperfluorescent and formed a halo in the late stage (shown in Fig. 2c, d). Based on his smoking history, his family's history of lung cancer, and ophthalmological findings, we

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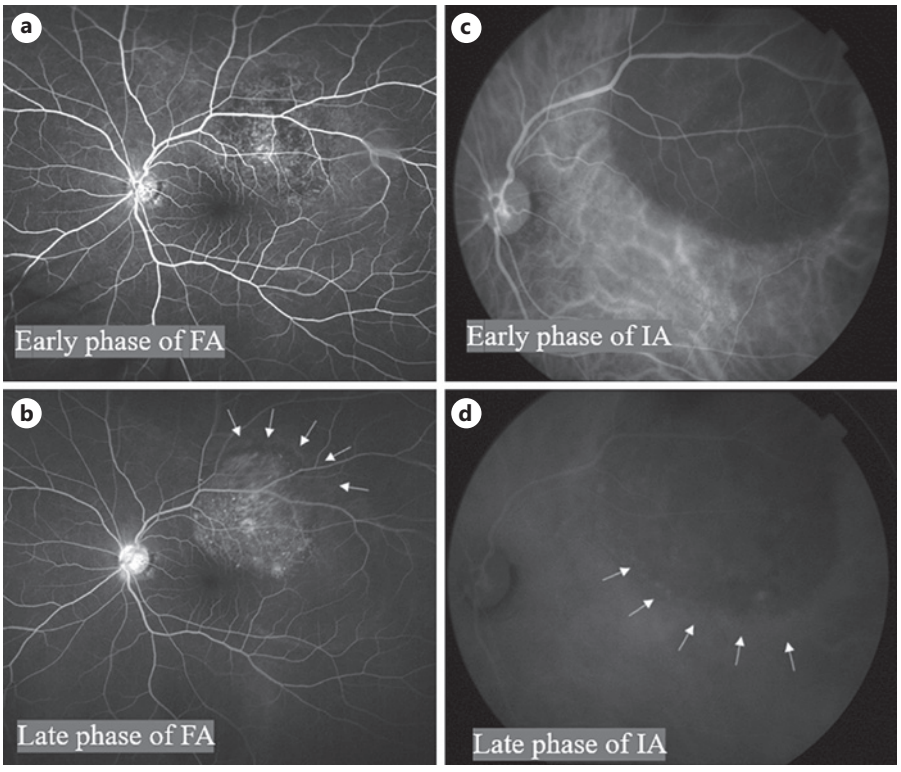

Fig. 2. a, **b** Fluorescein angiography showed early spotty and mottled hyperfluorescence in the left eye lesion area, late fluorescence leakage from the retinal pigment epithelium, and ring hypofluorescence along the border of the lesion (arrow). **c**, **d** Indocyanine-green angiography showed a consistent hypofluorescence from the early to late stages in the lesion area. However, the surrounding area gradually became hyperfluorescent and formed a halo in the late stage (arrow).

considered the possibility of a metastatic choroidal tumor and decided to conduct a thorough systemic examination for searching a tumor. Blood test results showed elevated blood calcium levels (10.9 mg/dL) and elevated tumor markers (carcinoembryonic antigen: 20.7 ng/mL, cytokeratin 19 fragment: 2.4 ng/mL, carbohydrate antigen 19–9: 130.0 U/mL). A chest radiograph showed an abnormal shadow in the right lower lung lobe, and a whole-body computed tomography scan revealed a right lower lobe lung tumor, pleural dissemination, pleural effusion, and metastasis to the left iliac bone (shown in Fig. 3a–c). We diagnosed a metastatic choroidal tumor of the left eye from advanced-stage lung cancer and consulted a respiratory physician who diagnosed as the stage IV-B lung adenocarcinoma with *EGFR* mutation (exon 19 deletion: c.2239_2248delTTAAGAGAA-GinsC). Systemic chemotherapy with osimertinib (80 mg/day) was initiated. Two months after the systemic therapy, fundus findings, OCT imaging, and B-mode ultrasonography revealed the complete disappearance of the left choroidal lesion and subretinal fluid (shown in Fig. 4a–d). Furthermore, after 6 months of treatment with osimertinib, the right lower lobe lung cancer shrank to a maximum diameter of 15 mm, and pleural effusion decreased (shown in Fig. 4e, f). Systemic treatment with osimertinib has been continued, and there has been no recurrence of the choroidal tumor in 20 months. Acneiform rash and stomatitis, which were thought to be the side effects of osimertinib, were observed but resolved with symptomatic treatment. Currently, no other side effects or serious complications have been noted.

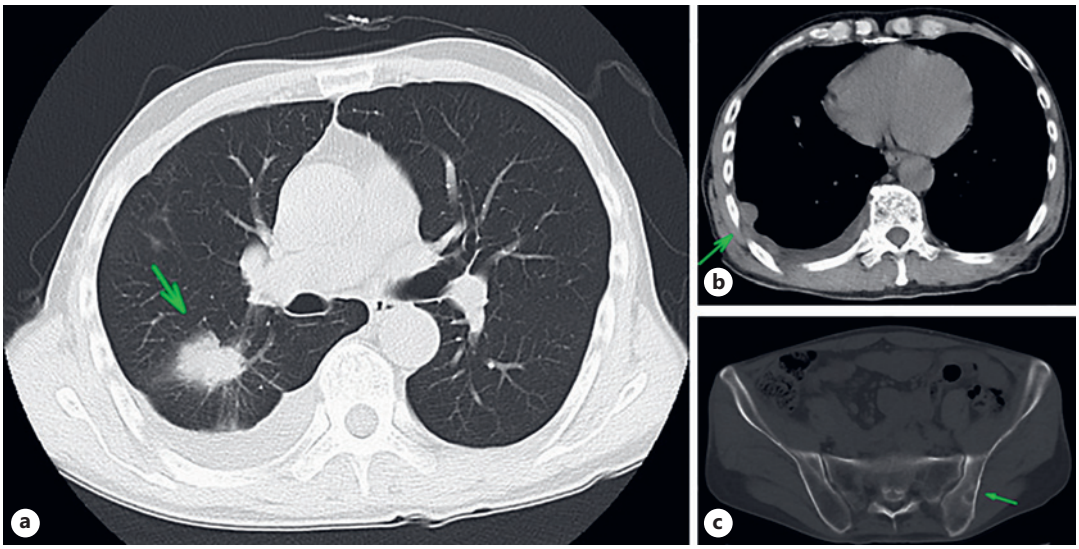

Fig. 3. a–c A whole-body computed tomography scan revealed a right lower lobe lung tumor, pleural dissemination, pleural effusion, and metastasis to the left iliac bone (arrow).

Discussion/Conclusion

This case highlights the relatively long-term effect of the first-line therapy with osimertinib for choroidal metastases in *EGFR* mutation-positive NSCLC. Also, this case suggests the importance of early checkups of systemic diseases including lung cancer, in patients with choroidal tumors. It has been reported that approximately 35% of ocular metastasis are discovered before the diagnosis of lung cancer, as the present case [12]. It has been also reported that metastatic uveal lung cancer has a poor prognosis, with an average of 18.4 months from diagnosis to death [13]. However, the advent of osimertinib for *EGFR* mutation-positive lung cancer, which is particularly common in Asian patients, significantly improved the prognosis of the underlying disease and choroidal tumor. Ophthalmologists are responsible for providing treatment as soon as these conditions are detected.

Molecule-targeted therapy is a good option when the primary tumor contains drug-sensitive genes. TKIs, which are the leading molecular therapies, are widely used in patients with advanced NSCLC with *EGFR* mutations. Osimertinib, a third-generation *EGFR*-TKI developed for patients with the T790M mutation who have acquired resistance to TKIs, is more effective than other TKIs. In addition to the T790M mutation, efficacy against deletion mutations in exon 19 and point mutations in exon 21 (L858R) has also been noted [14]. Previous reports showed osimertinib showed a higher median overall survival of 38.6 months for untreated patients with NSCLC compared to those treated with EGFR-TKIs, gefitinib, and erlotinib (31.8 months) [5]. Major adverse events included rash, acne, diarrhea, and dry skin. The incidence of fatal adverse events is approximately 2%, with reports of pneumonia, respiratory tract infection, cerebral infarction, myocardial infarction, pulmonary embolism, and enteritis [14].

A notable feature of osimertinib is its potential to effectively cross the blood-brain and blood-eye barriers. Previous studies found that the osimertinib group had a 58% progression-free survival rate at 18 months, while the comparator group had a rate of 40% in patients with central nervous system metastases (HR, 0.48; 95% CI, 0.26–0.86) [5, 15]. Even though a clear mechanism is currently unknown, osimertinib is suggested to inhibit the progression of

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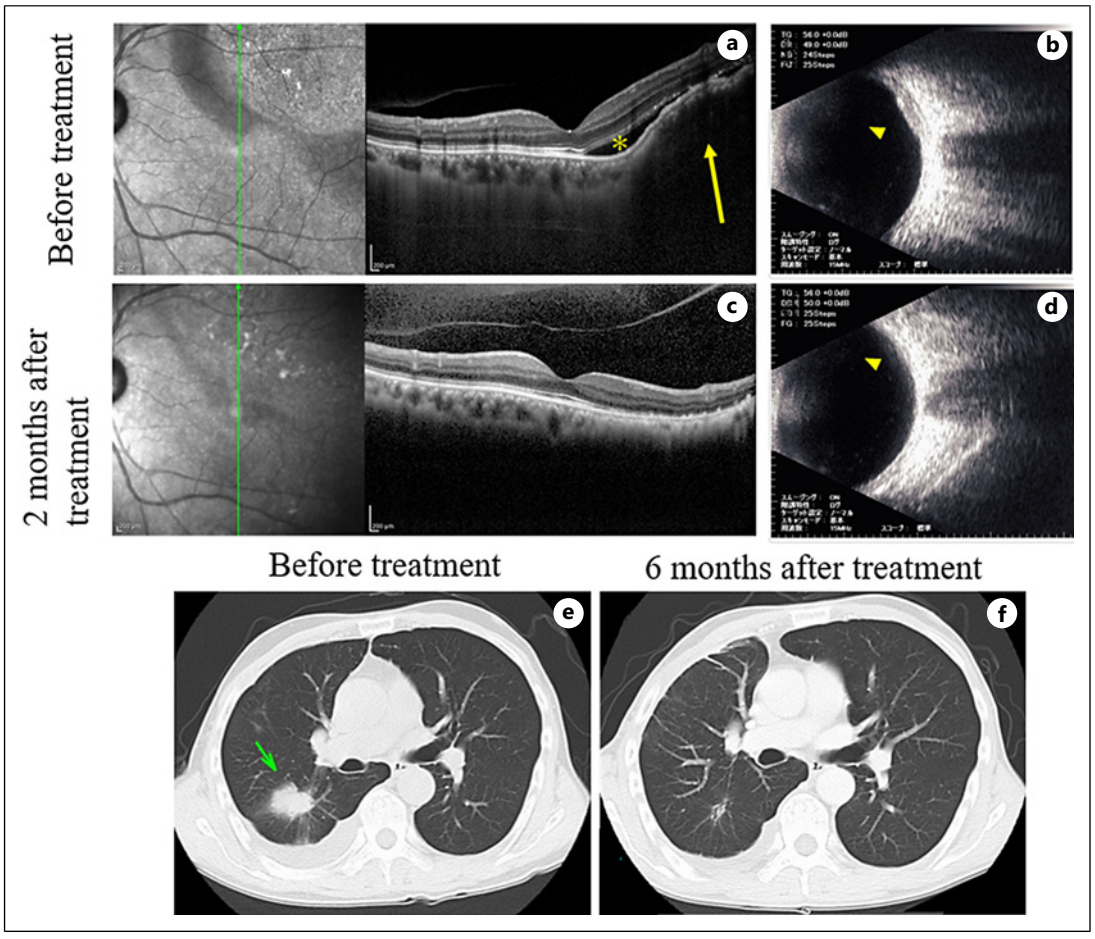

Fig. 4. a–d Two months after osimertinib therapy, fundus findings, optical coherence tomography, and B-mode ultrasonography revealed a left choroidal lesion, and subretinal fluid was almost completely gone. **e**, **f** The right lower lobe lung cancer had shrunk to about 15 mm in maximum diameter and decreased pleural effusion after 6 months of treatment with osimertinib.

central nervous system lesions and is more likely to cross the blood-brain and blood-ocular barriers than other drugs, making it a better choice for treating metastatic choroidal tumors.

The case reports on the efficacy of osimertinib in metastatic choroidal tumors of primary NSCLC are summarized in Table 1. Previously, osimertinib was often reported as a second-line therapy [4, 7, 8, 11], but since the FLAURA trial, osimertinib has been used as a first-line therapy. However, few reports have demonstrated the efficacy of osimertinib as a first-line therapy for metastatic choroidal tumors [9, 10]. Field et al. [9] found that choroidal metastases in a patient with NSCLC and exon 19 *EGFR* and *TP53* mutations resolved completely after 3 months of the first-line therapy with osimertinib. They reported complete resolution within 3 months and maintenance for 17 months. In many cases, osimertinib has been associated with a reduction in choroidal lesions and improvement in symptoms such as visual disturbances, brain metastases, and metastatic disease [4, 7–9]. The reported side effects were within the control limits [8].

In this case, osimertinib was used as the primary treatment without concomitant therapy, and relatively long-term responses, such as reduction of choroidal lesions, maintenance of visual acuity, and shrinkage of the primary tumor, were achieved. Side effects were also within control.

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Table 1. A summary of reported cases of NSCLC primary metastatic choroidal tumors treated with osimertinib

	This case	Bouchez et al. [4] 2020	Mariachiara et al. [7] 2018	Keshwani et al. [8] 2017	Field et al. [9] 2022	N Vu et al. [10] 2022
Sex	Male	Male:1, Female:3	Female	Female	Male	Male
Age (y.o.)	62	45–50 (1/4), 50–55 (2/4), 60–65 (1/4)	54	41	68	63
Race	Asian (Japanese)	Moroccan (1/4), Caucasian (3/4)	Caucasian	Unknown	Unknown	Asian
Smoking history	+	+ (3/4)	Unknown	–	+	–
Initial symptoms	Foggy vision, visual field defect	Eye pain, foggy vision	Foggy vision, visual field defect	Foggy vision	–	Blurry vision
Systemic metastasis	Bone	Brain	Bone, brain	Brain, lymph nodes	Brain, liver, bone, lymph nodes	Bone, brain, lymph nodes
Combined therapy	–	Pemetrexed/platinum Chemotherapy	Chemotherapy, radiation	Gamma knife therapy, radiation	–	–
EGFR gene mutation	Exon 19 deletion	Exon 19 deletion (2/4) Exon 21 mutation (2/4) T790M mutation (4/4)	Exon 19 deletion T790M mutation	T790M mutation	Exon 19 deletion	Unknown
Treatment with other EGFR-TKIs	–	Afatinib (2/4) Erlotinib (1/4) Afatinib+Erlotinib (1/4)	Gefitinib, Erlotinib	Erlotinib	–	–
Adverse effects	Acneiform rash and stomatitis	Unknown	Unknown	Acneiform rash and skin dryness	Unknown	Unknown
Period of remission (months)	20	Unknown	5	8	17	9

However, several issues need to be addressed. First, the long-term prognosis and safety of osimertinib therapy for metastatic choroidal tumors remain unclear. Second, the long-term use of osimertinib may lead to drug resistance, which may reduce its efficacy, and there is no established treatment for recurrent choroidal tumor. Patients should be informed of the possibility of additional treatment, such as radiation therapy or anti-VEGF therapy because there is a risk of inadequate efficacy due to drug resistance in the future.

In conclusion, in patients with metastatic choroidal tumors in NSCLC with exon 19 *EGFR* mutations, osimertinib may not only be effective against the primary tumor but may also shrink the choroidal tumor and improve vision. If osimertinib is used instead of radiation therapy to treat ocular lesions, it may be beneficial and have fewer local ocular side effects. But reports on the long-term prognosis and safety of osimertinib as a first-line therapy for metastatic choroidal tumors are limited, and further case studies are needed. 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/10.1159/000531255).

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

Y.K. and T.B. contributed to the design of the work. I.U. and Y.K. have drafted the work, and H.Y. and T.B. have substantively revised it. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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