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Case Report

A Case of Binocular Metastatic Choroidal Tumor Originating from Pulmonary Adenocarcinoma Successfully Treated with Molecular Target Therapy

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Keywords
Metastatic choroid tumors · Lung adenocarcinoma · Bevacizumab

Abstract
The occurrence of ocular metastasis from lung cancer is uncommon. In our current case, we report on a 64-year-old male patient found to have metastatic lesions in both choroids after being diagnosed with lung adenocarcinoma. As the patient was found to have a mutation in the epidermal growth factor receptor (EGFR), he was treated with the EGFR tyrosine kinase inhibitor (EGFR TKI), afatinib. However, the treatment response suggested the presence of a progressive disease. Thus, due to cancerous meningitis, the patient's treatment was changed from afatinib to erlotinib, in addition to adding bevacizumab. Although the general condition of the patient did not change, improvement was noted for the choroidal metastasis. Moreover, the drug change also resulted in an improvement of the visual power of both eyes. Therefore, the results for this patient suggest that systemic administration of erlotinib and bevacizumab may be an effective treatment that leads to morphological and functional improvement in choroidal metastasis cases.

Introduction

Although rare, metastatic choroid tumors are the most common type of intraocular malignancy. The frequency of intraocular metastasis in all patients dying of cancer was reported to be approximately 12% [1]. Lung and breast cancers are two of the predominant tumors that metastasize to the eye [2, 3]. Among the ocular metastases, the choroid is the most commonly affected site [2]. The prognosis for patients with ocular metastases remains unsatisfactory. For

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these patients, life expectancy is reported to be between 2 and 48 months (median 6–9 months) [4, 5]. Radiotherapy remains the main type of treatment, as this has been shown to help the majority of patients maintain good vision for as long as they are alive [1]. The development of molecular targeted therapies, such as humanized anti-vascular endothelial growth factor, bevacizumab, and EGFR TKI, has improved the survival rate of patients with advanced lung adenocarcinoma, without substantially increasing the toxicity [6]. In our current case, while choroidal metastasis was found, the disease was progressive and ultimately the patient's life could not be saved. However, after treatment of the patient with afatinib followed by switching to bevacizumab and erlotinib, there was improvement in the ocular lesions. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530130).

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The patient was a 64-year-old male smoker. A year and a half prior to his initial presentation at our hospital, he had been diagnosed with EGFR-positive lung adenocarcinoma stage IVB. The following year, based on the previous findings for afatinib administration, it was decided to start the patient on afatinib 20 mg [7]. Subsequently, the patient became aware of deterioration in his binocular vision, and in June of the same year, he was referred to our hospital.

At his first visit, his best corrected visual acuity in the right eye was 20/32, while in the left eye it was 20/40. Slit-lamp examination revealed mild inflammation of the anterior chamber of his left eye. His pupils were of normal size and responded to light, and his intraocular pressure was within the normal range. His eye movements were normal for all gazes. His fundus examination revealed multiple yellowish-white lesions in the posterior poles of both eyes (Fig. 1).

Fluorescein angiography (FA) showed low fluorescence during the early stages followed by high fluorescence with leakage during the late stages, which was associated with surface pinpoints (Fig. 2). Indocyanine green fluorescence fundus angiography (IA) showed low fluorescence with marginal alignment that was consistent with the tumor in all phases (Fig. 3). Optical coherence tomography (OCT) showed serous retinal detachment and retinal pigment epithelium (RPE) malformation in both eyes (Fig. 4).

In addition, although B-scan ultrasonography, head CT, and head MRI showed no organic lesions, choroidal metastasis from lung adenocarcinoma was clinically diagnosed based on the characteristic findings observed for the FA and IA and OCT images.

Metastasis to the meninges was also observed, and thus, EGFR TKI was changed from afatinib to erlotinib 150 mg/day. In addition, bevacizumab 640 mg was added, with 2 courses of treatment performed starting from August 2019.

An ophthalmic examination in October of the same year in conjunction with OCT showed complete elimination of the serous retinal detachment in both eyes (Fig. 5). Best corrected visual acuity at this examination was 20/28 in both eyes.

However, in November of the same year, due to a poor general condition, the patient was switched to palliative medicine. After the treatment was stopped, the patient slipped into a coma and died shortly after.

Discussion

The choroid is a major site for the development of metastasis within the eye due to its abundant arterial supply and its favorable microenvironment for the seeding of cancer cells. According to the literature, the incidence of ocular metastases from lung cancer is about 2–7%

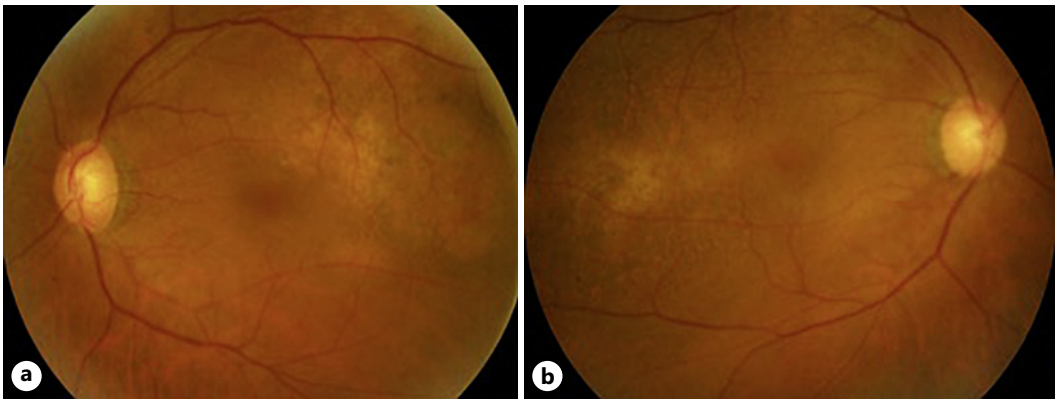

Fig. 1. The fundus photo revealed multiple yellowish-white lesions in the posterior poles of both eyes.

[8, 9]. In most cases (66–97%), diagnosis of a systemic cancer is established before the detection of any choroidal metastasis [10]. In contrast to that observed in patients with breast cancer, patients with lung cancer generally have poorer outcomes and lower survival rates. This is believed to be responsible for the much lower percentage of choroidal metastasis that is found as compared to lung cancer [11].

Differential diagnosis of choroidal metastasis includes amelanotic choroidal melanoma, choroidal osteoma, choroidal hemangioma, posterior scleritis, and other rare lesions. Metastatic tumors usually have a creamy-yellow appearance. During the early phases of FA, they are hypofluorescent. However, during the late phases, they become progressively hyperfluorescent [12].

Although it was not completely clear in our current case, the B-scan ultrasound showed an echogenic subretinal mass with diffuse, ill-defined borders. Overlying retinal detachment is common and sound attenuation in the lesion is usually found to be moderate [13]. OCT has provided additional useful information in the evaluation of the RPE and retina. There are many characteristic features of choroidal metastasis, such as the presence of subretinal fluid and the marked irregularity of the RPE, with thickening and gross undulation [14].

Choroidal metastases are usually treated in a palliative way with radiotherapy, enucleation, or transpapillary thermotherapy. In a few reported cases, it has actually been shown that there was a partial or complete response of the choroidal metastases to chemotherapy alone or to chemotherapy associated with targeted therapy. Despite limited published data regarding its use, bevacizumab, which is a monoclonal antibody that is used against the vascular endothelial growth factor (VEGF), is a promising new therapeutic option when used systemically [15] or intravitreally [16–18]. Thus, this may be an acceptable alternative to the conventional modalities.

Since the meningeal carcinomatosis was complicated, the treatment was changed to erlotinib, which has good cerebrospinal fluid transfer. Furthermore, systemic administration of bevacizumab was added in order to inhibit the angiogenesis and vascular hyperpermeability and to suppress the cerebral edema and peritumoral edema [19–22].

Solid tumor growth and metastasis are dependent on the development of new blood vessels (neovascularization). Thus, inhibition of tumor-induced angiogenesis should be able to prevent the growth of solid tumors and reduce the development of metastases. VEGF and human epidermal growth factor receptor (HER-1/EGFR) have been identified as key molecular targets for therapy in lung adenocarcinoma [23]. Bevacizumab, which is a humanized anti-vascular endothelial growth factor monoclonal antibody, and erlotinib, which is a reversible, orally available, highly selective EGFR tyrosine kinase inhibitor

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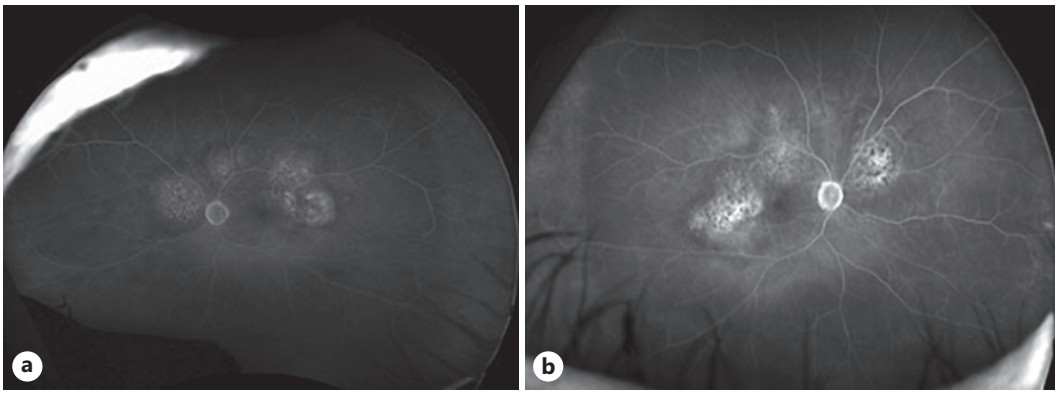

Fig. 2. FA showed low fluorescence in the early stages followed by high fluorescence with leakage in the late stages, which was associated with surface pinpoints.

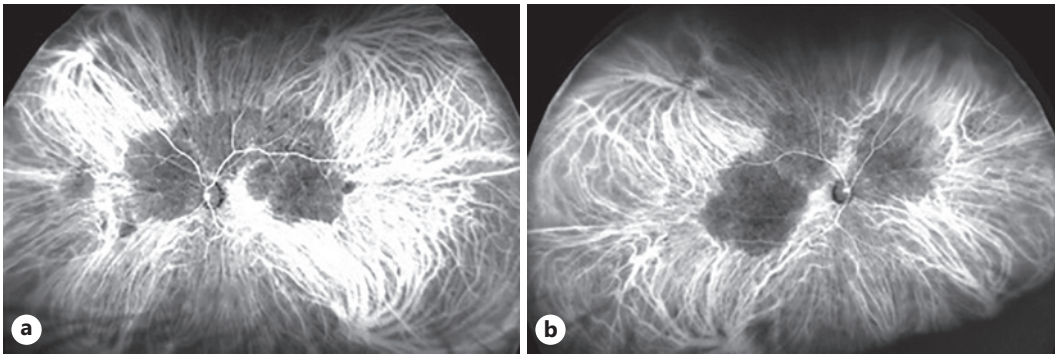

Fig. 3. IA showed low fluorescence with marginal alignment consistent with the tumor in all phases.

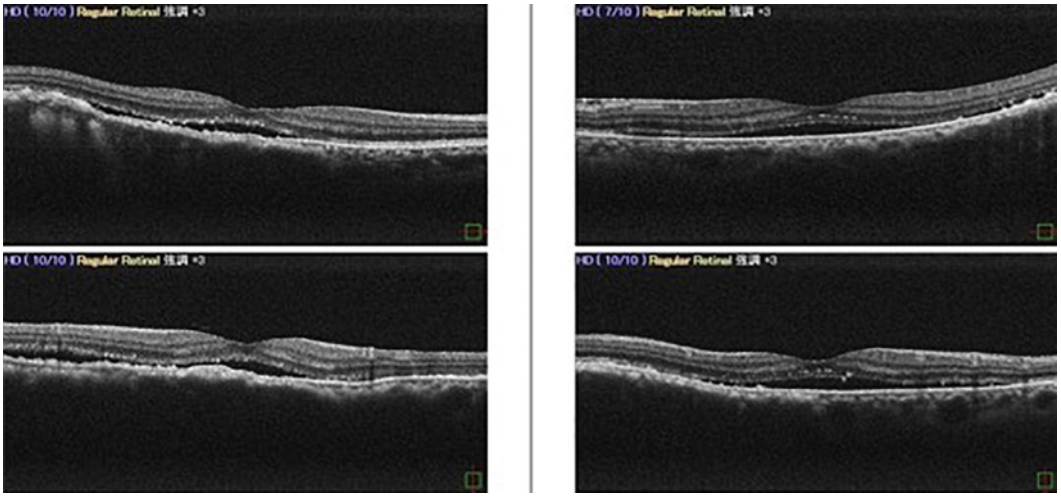

Fig. 4. OCT showed serous retinal detachment and retinal pigment epithelium malformation in both eyes.

(EGFR TKI), have both been demonstrated to have encouraging results with regard to the treatment of lung adenocarcinoma [19–22, 24, 25]. HER-1/EGFR and VEGF share common downstream signaling pathways. Erlotinib inhibits tumor cell growth and blocks the synthesis of angiogenic proteins by tumor cells, including VEGF. Bevacizumab inhibits

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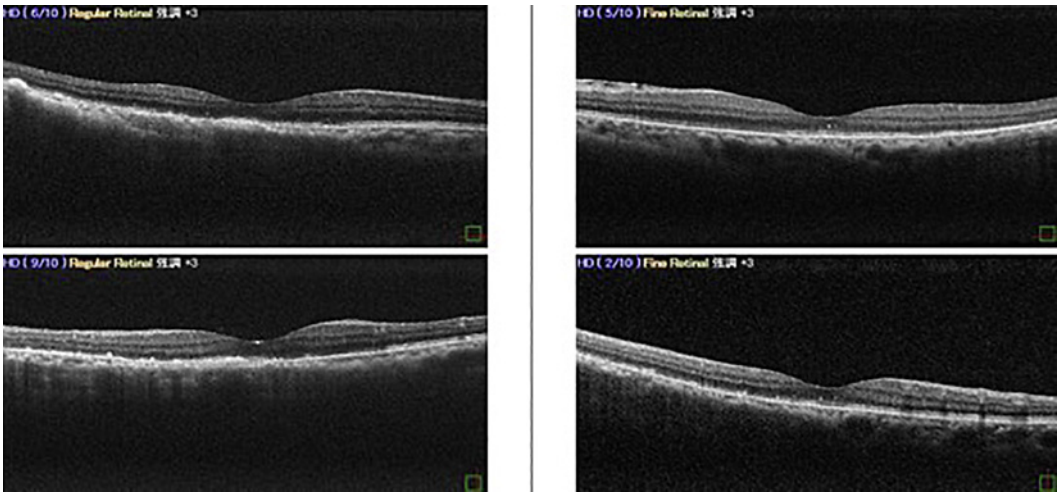

Fig. 5. After treatment, OCT showed complete elimination of the serous retinal detachment in both eyes.

endothelial cells from responding to the angiogenic protein VEGF. VEGF is downregulated by HER-1/EGFR inhibition [26], and thus, blockade of VEGF may also inhibit HER-1/EGFR autocrine signaling [27]. Therefore, by combining these drugs in order to block these 2 receptors, this may confer additional clinical benefits, as was demonstrated in our current patient.

Ocular effects have been reported with topical administration of bevacizumab [28]. On the other hand, systemic administration of bevacizumab facilitates access to the choroid, which is rich in blood flow because the choroidal vessels are fenestrated and there is no blood-retinal barrier and maintenance of sufficient bevacizumab concentration around the choroidal tumor leads to tumor shrinkage [29]. In this patient, the patient's general condition was poor, and it was difficult to maintain a posture for vitreous injection, and it seemed difficult to perform multiple vitreous injections. In this case, systemic administration of bevacizumab was suitable and demonstrated its efficacy.

Conclusion

In conclusion, the present case report demonstrates the efficacy of systemic bevacizumab therapy in combination with erlotinib for the treatment of choroid metastasis. Use of this treatment resulted in morphological and functional improvements in the choroidal metastatic tumor. Therefore, selection of systemic administration of bevacizumab with intravitreal injections may be a beneficial therapeutic approach. This is likely due to the greater potential to produce effective chemotherapeutic concentrations around the metastasis site via the rich choroidal blood supply, which is within the systemic circulation and not protected by the blood-retina barrier. In addition, the results for our current case showed that systemic administration of bevacizumab also contributes to the improvement of choroidal metastasis when the systemic condition is poor, and normally a time when it is difficult to maintain the system for vitreous injection.

Statement of Ethics

Written informed consent was obtained from the patient' wife and son (patient's wife and sons are allowed to give consent on behalf of the patient) for publication of this case report and any accompanying images. The research was conducted in accordance with the tenets of the Declaration of Helsinki. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Masataka Yamaoka, Tsutomu Igarashi, Naka Shiratori, Keiki Miyadera, Teppei Sugano, and Rintaro Noro examined and treated the patient. Masataka Yamaoka, Tsutomu Igarashi, and Rintaro Noro contributed to the writing of the manuscript. Hiroshi Takahashi provided critical manuscript revisions.

Data Availability Statement

All data analyzed during this case report are included in the manuscript. Further inquiries can be directed to the corresponding author.

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