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Successful response to first-line treatment with osimertinib for choroidal metastasis from EGFR-mutated non-small-cell lung cancer

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ABSTRACT

Purpose: Describe the use of osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, as the first-line treatment in a patient with choroidal and central nervous system metastases from EGFR-mutated non-small cell lung cancer.

Observations: A 68-year-old man presented with an amelanotic choroidal lesion in the left eye concerning for choroidal metastasis. Systemic evaluation identified widely metastatic adenocarcinoma of the lung with EGFR exon 19 mutation. Within one month of initiating treatment with osimertinib, there was complete resolution of the subretinal fluid over the choroidal lesion and decreased thickness of the lesion. At follow-up after three months of treatment, the lesion was clinically involuted. Positron emission tomography at two months and magnetic resonance imaging of the brain at three months showed significant interval decrease in size and activity of the primary right lung lesion, central nervous system lesions, and other metastatic sites with no new metastatic lesions. After 17 months of follow up, the lesion remained involuted.

Conclusions and Importance: Osimertinib may be considered as a first-line treatment option in patients with choroidal metastases from an EGFR-mutated non-small cell lung cancer.

1. Introduction

Choroidal metastasis, the most common intraocular malignancy in adults, classically presents as single or multiple yellow-to-white amelanotic lesions in the posterior pole.[1] They tend to have an apical height less than that of choroidal melanomas, and medium-to-high reflectivity on standardized ultrasonography.[2] These features can help distinguish metastatic lesions from primary choroidal melanomas, which are more vascular, often more heavily pigmented, and have low reflectivity and internal vascularity on ultrasound.[3]

Breast cancer is the most common cause of choroidal metastases.[4] Lung cancer is the most common cause of choroidal metastasis in men and the second most common cause in women.[4] Non-small cell lung cancer (NSCLC) which includes the histologic sub-types adenocarcinoma and squamous cell carcinoma accounts for approximately 85% of lung cancers.[5] Among patients with NSCLC, epidermal growth factor receptor (EGFR) mutations are found in 30–40% of Asian patients and 5–20% of Caucasian patients.[6] It has been reported that the prevalence of choroidal metastases ranges from 0.2 to 7% in cases with NSCLC[7,8] with a recent case series showing the prevalence to be 8.4% in NSCLC cases with an EGFR mutation.[9]

Tyrosine kinase inhibitors (TKIs) targeting the EGFR pathway have become the gold standard of treatment for EGFR-mutated NSCLC. First and second generation EGFR-TKIs, such as gefitinib, erlotinib, or afatinib, have shown efficacy in treating choroidal metastasis,[9–11] but an *EGFR* T790 M resistance mutation can occur that limits the systemic efficacy of these treatments.[12] Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI–sensitizing and *EGFR* T790 M resistance mutations and has been shown to have improved overall survival over first generation EGFR-TKIs in previously untreated advanced stage NSCLC patients, as well as improved efficacy in the CNS.[13] While external beam radiation has historically been the gold standard for the treatment of choroidal metastases, osimertinib has been used with efficacy as a post-first-line and as a second/third-line treatment to successfully treat choroidal metastases,[9,14] prompting the suggestion to consider its use as a first-line therapy.[9] Here we describe a complete response of choroidal metastasis to osimertinib as the first-line treatment in a patient with EGFR-mutated lung adenocarcinoma.

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2. Case report

A 68-year-old man with a history of hypertension was referred for evaluation of a new choroidal lesion in the left eye discovered during a routine eye examination. The lesion was not present in fundus photographs taken two years prior. The patient denied any new visual symptoms or other medical issues and was up to date on his preventative health examinations, including colonoscopy and prostate specific antigen (PSA) screenings. He did report 15 pounds of weight loss over the last year, which he stated was intentional. He was a former smoker between the ages of 15 and 35-years-old but had not smoked in over 30 years. Family history was remarkable for prostate cancer in his father.

On examination, visual acuity was 20/20 + 2 in the right eye and 20/15 in the left eye. Intraocular pressure was normal in each eye. Anterior segment examination was unremarkable. Dilated funduscopic examination in the right eye was unremarkable. In the left eye, there was a 7.5x6.0x < 1 mm amelanotic choroidal lesion centered just below the inferotemporal arcade with overlying subretinal fluid that extended inferior to the lesion (Fig. 1A), as well as mild retinal pigment epithelial changes over the surface of the lesion. No lipofuscin or drusen was visualized and no other lesions were seen on scleral depressed examination. Optical coherence tomography (OCT) over the lesion showed a "lumpy-bumpy" choroidal lesion with extensive overlying subretinal fluid (Fig. 1B). Standardized echography of the left eye revealed an irregular mass with high internal reflectivity (though less reliable in the setting of a small lesion), no vascularity, and less than 1 mm in thickness (note that the A-scan echo thickness includes both the lesion and the retina that is shallowly detached over the surface) (figure 1C and D). The exam and imaging findings were highly concerning for a choroidal metastasis from an unknown primary malignancy, and the patient was referred to the hematology-oncology service for evaluation.

Initial positron emission tomography (PET) scan showed a central hypermetabolic mass-like lesion of the lower lobe of the right lung, as well as multiple hypermetabolic lesions in the intrathoracic lymph nodes, bilateral lungs, right pleura, liver, as well as multiple lytic bone lesions, including in the spine and iliac crest, all concerning for metastatic cancer (Fig. 2A). Magnetic resonance imaging (MRI) of the brain showed numerous intracranial enhancing lesions with the largest lesion in the right temporal lobe, measuring 9.5 mm in diameter (Fig. 2B). A right-sided thoracentesis was performed for diagnostic and molecular studies that showed a thyroid transcription factor-1 (TTF-1) positive adenocarcinoma consistent with a primary of pulmonary origin. The tumor harbored both an EGFR mutation on exon 19 (E746_A750del) and a TP53 mutation (R248W).

Two and a half weeks from the initial ophthalmology exam, repeat examination showed the lesion had increased from 7.5x6.0 × 1.1mm to 8.5x6.5 × 1.1mm with subtle extension at the inferior and nasal margins. The patient was evaluated by the radiation oncology service, and an extensive discussion of options was held. Whole brain radiation with irradiation of the orbits at the time of treatment was considered, but given the extensive disease burden and associated morbidity with whole brain radiation, the decision was made to proceed with an initial trial of systemic targeted therapy for primary-treatment of all lesions. Treatment with osimertinib was initiated.

After one month of treatment, there was complete resolution of the subretinal fluid over the surface of the choroidal lesion with decreased thickness of the choroidal infiltrate, indicating a therapeutic response. After three months of treatment, the lesion further involuted with decreased thickness on OCT and the overlying subretinal fluid remained resolved (Fig. 3A and B). Follow-up PET scan after two months of treatment demonstrated a robust therapeutic response with significant interval decrease in size and activity of the right lung lesion, decreased metastatic disease burden in the liver and lymph nodes, and no evidence of any new lesions. Follow-up MRI of the brain after three months of treatment showed significant decrease in the size of numerous intracranial lesions without any interval growth or appearance of new lesions. The choroidal lesion remained involuted at his most recent follow-up, 17 months following presentation.

3. Discussion

Traditionally, external beam radiation therapy has been the treatment of choice for choroidal metastases due to the limited response to traditional chemotherapeutics. In the setting of NSCLC, there have been reports of a response to systemic chemotherapy, particularly with the use of the agents pemetrexed and cisplastin for adenocarcinoma.[15] However, many of these patients succumbed to their systemic metastasis within a short period of time and the long term-efficacy is not known.[15]

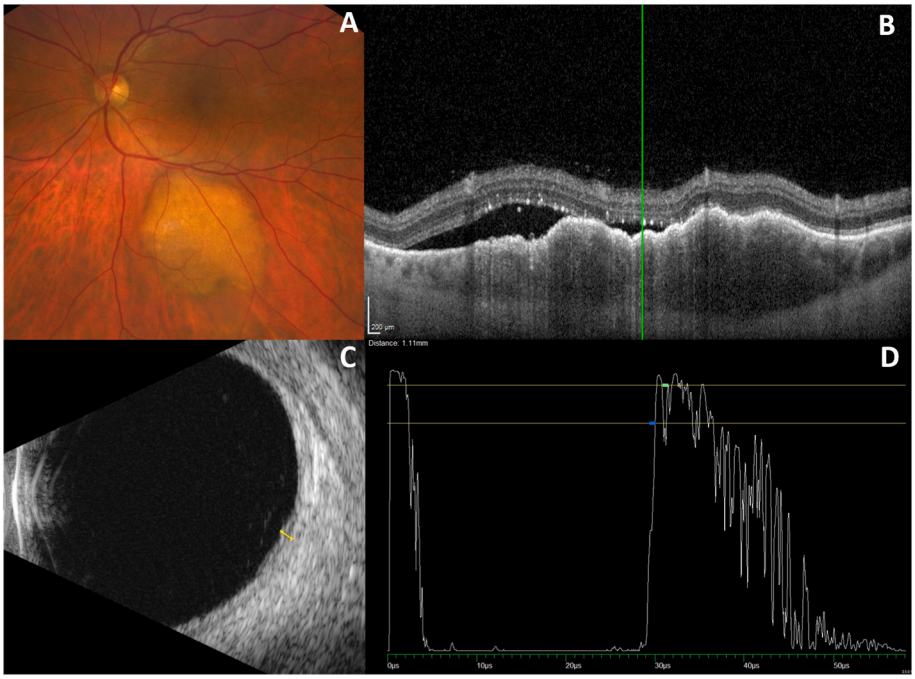

Fig. 1. Images of the choroidal lesion at presentation. (A) Color fundus photograph showing an amelanotic choroidal lesion with overlying retinal pigment epithelial changes and subretinal fluid centered just below the inferotemporal arcade. (B) Optical coherence tomography (OCT) over the lesion showing a "lumpy-bumpy" choroidal infiltrate with overlying subretinal fluid. (C) B-scan echography (T4PE) shows a small elevated choroidal lesion in the posterior pole. (D) Standardized A-scan over the lesion shows high internal reflectivity (though less reliable in the setting of a small lesion). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

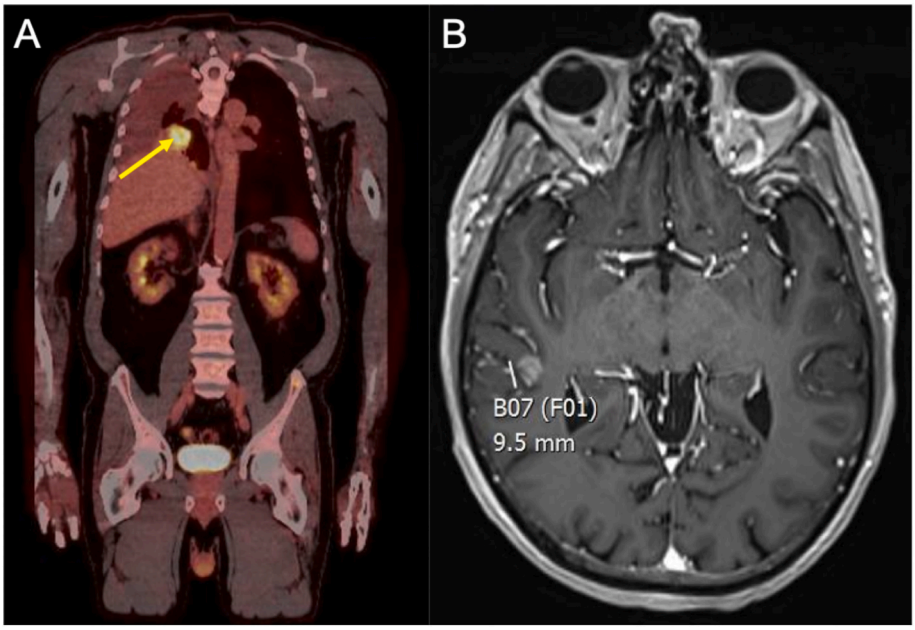

Fig. 2. Systemic imaging at presentation. (A) PET scan shows a right lower lobe hypermetabolic mass (yellow arrow) in addition to multiple hypermetabolic lesions in the lymph nodes, lungs, right pleura, liver, and bones (all lesions not visible in section shown). (B) MRI brain at presentation shows numerous ring enhancing and focally enhancing intracranial lesions with the largest in the right temporal lobe measuring 9.5 mm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

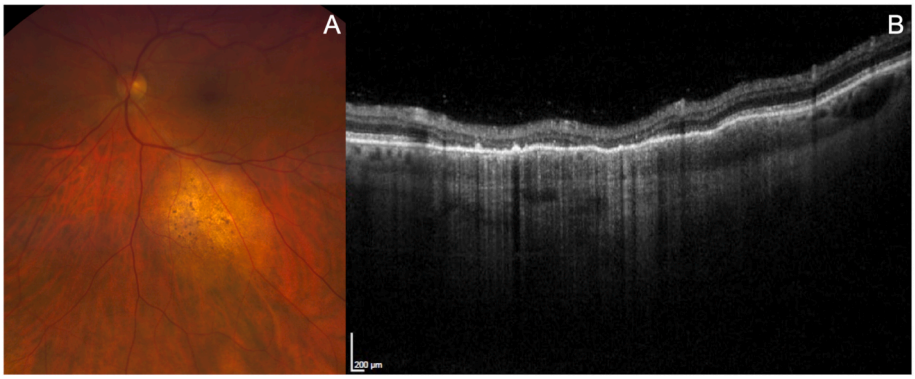

Fig. 3. Images of the lesion four months following treatment. (A) Color fundus photography shows an atrophic chorioretinal lesion with increased retinal pigment epithelial changes compared to presentation. (B) Optical coherence tomography over the lesion shows near resolution of the choroidal infiltrate and resolved subretinal fluid over the lesion. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The development of targeted systemic therapies offers an alternative approach to management. Specifically, in the case of EGFR-mutated NSCLC, treatment with first generation and second generation EGFR-TKIs has shown improved efficacy and survival compared to treatment with cytotoxic chemotherapy, including objective and sustained responses in cases with choroidal metastases.[9–11] However, in some cases, patients developed a T790 M mutation in EGFR that made them resistant to treatment with first and second generation EGFR-TKIs. Osimertinib, an oral, third-generation, irreversible EGFR-TKI selectively inhibits both EGFR-TKI–sensitizing and *EGFR* T790 M resistance mutations and has been shown to have improved overall survival over first generation EGFR-TKIs and improved efficacy in the CNS.[13]

There are several reports describing the effects of osimertinib on choroidal metastases from EGFR-mutated NSCLC.[9,14,16] The first published case describes a patient who was initially found to have metastatic NSCLC with a deletion in exon 19 treated with two first-generation EGFR-TKIs (gefitinib and erlotinib) who presented with new visual symptoms and was found to have a lesion concerning for a choroidal metastasis in the right eye. Subsequent biopsy of the primary lesion showed that the tumor had developed an EGFR T790 M resistance mutation and thus the patient was subsequently started on osimertinib. Significant regression of the lesion was seen following 14 days of treatment with even more pronounced regression at 4 months, improved visual acuity, and no evidence of additional metastatic disease.[14] This is similar to a report by Dall'Olio et al. who describe a patient with choroidal metastasis from NSCLC with progression of disease on gefitinib but whose choroidal metastasis responded dramatically to osimertimib.[17] Two additional patients who had an EGFR T790 M resistance mutation did not initially respond to treatment with erlotinib but showed an objective response of the choroidal metastases with osimertinib. The other three patients had all been initially treated with first or second generation EGFR-TKIs with improvement in visual symptoms and objective regression of the lesions, and all received post-first-line treatment with osimertinib based on the discovery of the EGFR T790 resistance mutation.

Despite these promising findings, the question of how to treat choroidal metastases is a complicated one and has to be carefully considered in the context of the patient's symptoms, cancer-subtype, available treatment options, prognosis, patient goals, and metastatic disease burden. In the case of EGFR-mutated NSCLC, with improving systemic targeted therapies and longer overall survival rates, the chance of a durable systemic response may lead to deferring radiation treatment, sparing the patient from multiple radiotherapy visits and the risk for radiation retinopathy. From a quality of life standpoint, the

challenge arises when patients fail the targeted therapy and lose vision in the last months of their life. It is encouraging that our patient developed an excellent response, however, the long-term durability of this therapy will require further follow up.

4. Conclusion

Osimertinib showed significant and rapid activity as a first line treatment of a choroidal metastasis in a patient with NSCLC that harbored an EGFR 19 deletion mutation. This replaced the need for initial treatment with external beam radiation and resulted in complete resolution of the metastasis in 3 months and was sustained at 17 months. Future work should address the durability of this response over time.

Disclosures

The authors have conflicts of interest to declare.

Statement of ethics

The subject gave written informed consent for publication of this case. The IRB at the University of Iowa determined that this report does not meet the regulatory definition of human subjects research and did not require formal IRB review since it is a single case report.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

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All listed authors meet the ICMJE criteria.
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