A Rare Differential Diagnosis of Neovascular Age-Related Macular Degeneration: Choroidal Metastasis

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ABSTRACT

We present the case of 80-year-old patient with choroidal metastasis that was initially misdiagnosed as neovascular age-related macular degeneration (n-AMD) because of the presence of subretinal fluid. He received four intravitreal ranibizumab injections within six months before he was referred to our retina clinic due to unresponsiveness. A clinical diagnosis of choroidal metastasis from an advanced pulmonary adenocarcinoma was made with an interdisciplinary approach. Three doses of intravitreal aflibercept (AFL) were administered with 9 concurrent cycles of systemic chemotherapy over 13 months. Visual acuity improved from 20/125 to 20/63; complete resolution of the mass was obtained with residual pigmentary and atrophic changes. This regression was sustained during follow-up period, even though the systemic disease progressed. This is the first report of successful combination therapy of intravitreal AFL and systemic chemotherapy. Despite being rare, choroidal metastasis should be considered as a differential diagnosis of n-AMD.

Keywords: Aflibercept, choroidal metastasis, drug therapy; combination, non-small-cell lung cancer

INTRODUCTION

The uvea is the most common structure for ocular metastasis. Eighty-eight percent of metastases within the uvea are found in the choroid owing to its rich blood supply, followed by the iris (9%) and ciliary body (2%). Breast cancer is the leading cancer that metastasizes to the choroid occuring in approximately 50% of patients, followed by lung cancer which ranges from 20% to 29% of cases.[1-2]

The treatment of choroidal metastasis is affected by the illness and patients' various characteristics. Systemic chemotherapy, immunotherapy, hormone therapy, or whole eye radiotherapy are preferred if metastases are multifocal and bilateral. Plaque radiotherapy, transpupillary radiotherapy or photodynamic therapy are the preference for solitary metastases. Observation is also acceptable if the patient is preterminal and finally enucleation for blind painful eyes.[3] Herein, we report a case of choroidal metastasis successfully treated with a combination of systemic chemotherapy and aflibercept (AFL) injections. Additionally, we also emphasize a rare differential diagnosis of n-AMD.

CASE REPORT

A causacian male aged 80-year with history of smoking cessation 30 years previously (87 packyears), presented with symptoms of progressive visual loss from his right eye. The patient was diagnosed with n-AMD because of the presence of subretinal fluid and received four intravitreal ranibizumab injections within six months before he was referred to our retina clinic due to unresponsiveness (**Figure 1**). Another prominent sign was weight loss, he had lost more than 5 percent of his body weight (12 kilograms) and there was a history of cancer in his family. On examination, best-corrected visual acuity (BCVA) was 20/125 in the right eye and 20/25 in the left eye. The anterior segment examination was unremarkable, there was no relative afferent pupillary defect and the vitreous was clear in both eyes. Dilated fundus examination showed a solitary juxtapapillary yellowish mass with unclear borders and extensive subretinal fluid in the right eye. On fluorescein angiography, the mass had a hypofluorescent pattern in early arterial phases, and became progressively hyperfluorescent in late venous phases, containing dilated retinal capillaries with a pin-point leakage at the tumor border **(Figure 2)**. Optical coherence tomography (OCT)

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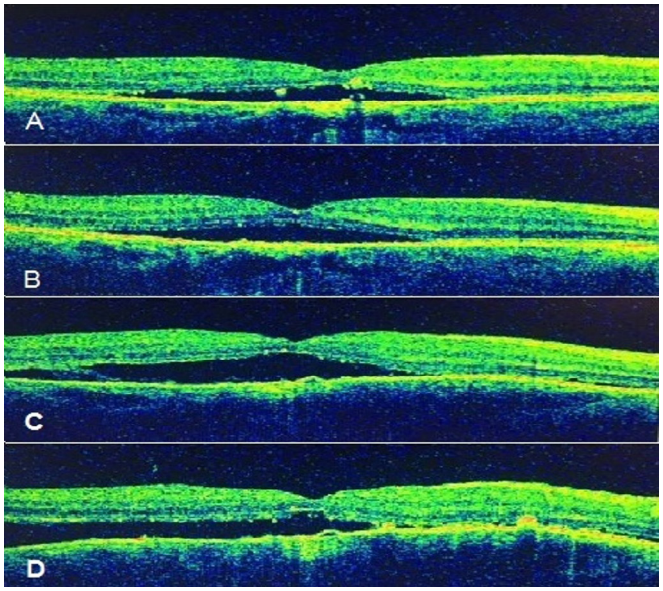

Figure 1: *Consecutive horizontal foveal spectral-domain OCT images of the right eye.*

*(**A-D**) The course of treatment with 4 intravitreal ranibizumab injections in the former center. Further progression and replacing of the subretinal fluid, and increase of undulation and thickening of the retinal pigment epithelium with hiperintense irregularities in the photoreceptor layer can be seen in the course of time.*

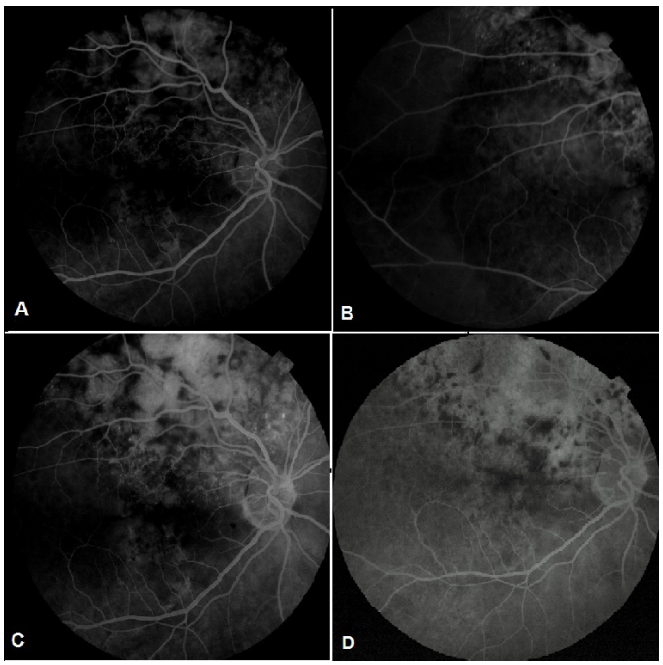

Figure 2: *Fluorescein angiography findings of the choroidal metastasis.*

***(A-B)** Typical early hypofluorescent pattern due to blockage by the mass in active lesions **(C)** Late hyperfluoresence containing dilated retinal capillaries with a pin-point leakage at the tumor border is visible in active lesions **(D)** Common window defects showing pigmentary and atrophic changes in passive lesions.*

was characteristic such as the presence of subretinal fluid and notable irregularity of the RPE with thickening and gross undulation (**Figure 3**). The left fundus showed no evidence of tumor.

The patient was subsequently referred to the internal medicine department with the suspicion of lung cancer and choroidal metastasis.Imaging methods revealed a pulmonary mass in the left upper lobe and malignant pleural thickening with multiple swollen mediastinal lymph nodes in addition to metastatic lesions. A transbronchial biopsy confirmed the diagnosis of stage IV lung adenocarcinoma with an epidermal growth factor receptor (EGFR) mutation (exon 19).After informed consent was obtained, systemic chemotherapy with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) was performed with an additional local treatment of AFL every 4 weeks.

At the end of 6 cycles of systemic therapy and 3 intravitreal doses of AFL, complete resolution of the mass was obtained with residual pigmentary and atrophic changes. (**Figure 4**) BCVA improved to 20/63 and no more local therapy was applied, but his chemotherapy cycles continued until the end of the schedule. The patient experienced no systemic or ocular toxicity. Tumor regression was sustained with the preservation of visual acuity after thirteen months follow-up even though the systemic disease progressed.

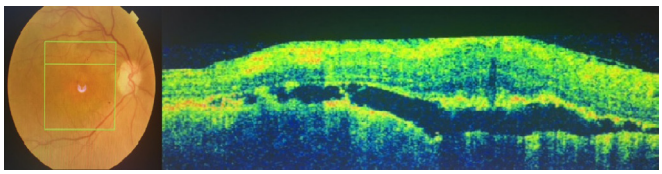

Figure 3: *Fundus photo and optical coherence tomography image of the right eye before treatment.*

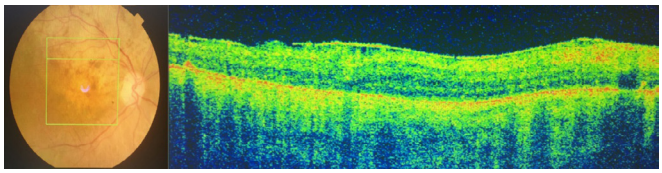

Figure 4: *Fundus photo and optical coherence tomography image of the same section at the end of the combined therapy.*

DISCUSSION

Choroidal metastases which are typically yellow in color (in 95% of lesions), plateau-shaped and associated with subretinal fluid generally involve the post-equatorial region of the fundus.The most common presenting symptoms are blurred vision (70-81%), flashes and floaters (5-12%) and pain (5-14%). Nevertheless, 9-11% of patients may present

with no symptoms and metastases are detected during routine ocular examinations.[1,3-5] The differential diagnosis of choroidal metastasis includes choroidal amelanotic melanoma, choroidal osteoma, choroidal hemangioma, posterior scleritis, central serous retinopathy, AMD and other rare lesions.Our patient who had characteristic features of choroidal metastasis was misdiagnosed as having n-AMD because most ophthalmologists tend to prefer the diagnosis of n-AMD in the presence of subretinal fluid in older patients and OCT is the most common tool used by the ophthalmologists during follow-up.This brief delay hindered recognition of the systemic disease and allowed the eye involvement to progress.

Radiotherapy is regarded as the standard treatment for choroidal metastases and has a high rate of lesion regression ranging from 85% to 93% of cases with external beam radiotherapy. Radiotherapy-induced complications such as cataracts, exposure keratopathy, iris neovascularization, radiation retinopathy, and papillopathy have been reported in 12% of cases.[6] Plaque brachytherapy is a more focused therapy that allows the delivery of radiation directly to the choroid which regresses metastases in up to 94% of patients with fewer ocular complications. Nevertheless, the main disadvantage is that surgical procedures are needed to place and remove the plaque.

There are some reports about regression of choroidal metastases from lung primary cancer after chemotherapy alone or observation. In a previous study, twenty-two patients suffering from lung cancer treated with chemotherapy alone with 68% regression of choroidal metastasis and 15 eyes managed with observation alone with 20% regression.[4] Intravitreal bevacizumab or ranibizumab, monoclonal antibodies that target vascular epithelial growth factor (anti-VEGF) are promising new therapeutic alternatives to ocular radiation though their use in this indication is off-label.[7-8] Anti-VEGF therapy can be suitable for metastatic lesions since they spread and colonize distant sites through angiogenesis.[9] Another available anti-VEGF agent, aflibercept (AFL), binds to more isoforms of the VEGF-receptor, has a stronger binding affinity for VEGF, also binds VEGF-B and placental growth factor beside VEGF-A.[10] Systemic chemotherapy was performed with additional weekly administrations of local AFL therapy due to its powerful pharmaceutic properties compared with other anti-VEGF agents.Similarly, injections have typically been administered every 1-3 months depending on tumor response in previous reports. As described by Maudgil et al.[11], our patient was not cured with ranibizumab alone when he was treated as having n-AMD in the former center. It is controversial AFL changed the response so markedly by comparison with ranibizumab. If ranibizumab treatment continued with the chemotherapy, this regimen may be curative for the lesions. So we cannot argue a superiority between the ranibizumab and AFL in the absence a comparative case series.

In summary, our case resulted in morphologic and functional improvements in a choroidal metastatic tumor with a combination therapy of intravitreal AFL and systemic chemotherapy with no ocular and systemic toxicity. Furthermore, choroidal metastases should be considered as a differential diagnosis of n-AMD in older patients despite being rare.

Conflict of Interests

None of the authors has any proprietary, commercial, or financial interest in any of the products mentioned.

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