Case Report

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Intravitreal aflibercept combined with transpupillary thermotherapy in the treatment of refractory macular edema due to primary uveal melanoma

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Abstract:

We reported a 74 year old Asian female with a uveal tumor with subretinal fluid (SRF) and cystoid macula edema. Since she declined biopsy, multimodal imaging study was performed, including fundus photography, ultrasonography, optical coherence tomography, fluorescein angiography, and magnetic resonance imaging. Uveal melanoma was diagnosed. However, despite aggressive treatment with TTT and three adjuvant intravitreal bevacizumab doses, SRF, and cystoid macula edema were persistent. Therefore, aflibercept was administered, resulting in anatomical and functional improvement within 1 month, which lasted for 12 months. Aflibercept offered great efficacy in improving refractory macular edema in this case of primary uveal melanoma. Multimodal imaging can provide us with more diagnostic clues in differentiating the nature of intraocular tumors.

Keywords:

Aflibercept, cystoid macula edema, multimodal image, subretinal fluid, uveal melanoma

Introduction

Choroidal melanoma, arising from melanocytes, is suggested being the most common primary intraocular malignant tumor, making up 72%–80% of all cases of ocular melanoma.[1] Even though various treatments have been attempted and local disease control rate is improving, around 50% of cases will experience metastasis.[1] Previous reports have showed that systemic metastases result in a 5-year mortality rate of approximately 20%–30% and 15-year mortality rate of 45%, among patients diagnosed with primary uveal melanoma.[2] On multivariate analysis, tumor distance to foveola and the presence of subretinal fluid (SRF) maybe predictive of both worsening final visual acuity.[3]

Since elevated levels of vascular endothelial growth factor have been found in both choroidal melanoma and secondary choroidal neovascularization (CNV),[4] Bevacizumab (Avastin; Genentech, Inc.), an anti-vascular endothelium growth factor (VEGF) agent with off-label intravitreal, has been reported as an adjuvant therapy for the treatment of choroidal melanoma, hemangioma, and metastases, especially when retinal edema is present.[4]

Aflibercept (Eylea; Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA) is another anti-VEGF agent, which has revealed promising effect in cases of bevacizumab-resistant postradiation cystoid macular edema (CME).[5] Thus, here, we present a case of primary uveal melanoma with bevacizumab-resistant

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CME and demonstrate the role of aflibercept as a potential therapy.

Case Report

A 74-year-old Asian female presented after suffering painless progressive blurry vision in her right eye for 6 months. Her past ocular, medical, and surgical histories were unremarkable. Best-corrected visual acuities (BCVA) were 20/200 in her right eye and 20/20 in her left eye. The pupils and confrontation visual fields were normal. Pneumo-tonometer revealed right eye pressure at the level of 13 and 16 mmHg in her left eye. Extraocular movement was intact bilaterally. Examination of anterior segment demonstrated 1+ nuclear sclerosis OU without signs of inflammation. In fundus examination, a dome-shaped subretinal mass without obvious pigmentation at the temporal side [Figure 1a] was found in her right eye. The vessels and periphery appeared normal. The left eye was unremarkable.

Since the patient strongly declined biopsy, multimodal imaging studying was performed. Ultrasonography of the right eye revealed a dome-shaped mass with medium-to-high homogeneous reflectivity and a high height-to-base ratio [Figure 1b]. The base of the dome was 5.1 mm wide, and the thickness was 4.9 mm. Optical coherence tomography (OCT) showed significant SRF and marked CME [Figure 1c]. Fluorescein angiography (FA) revealed early hypofluorescence and late heterogeneous hyperfluorescence [Figure 1d]. A choroidal tumor was suspected, so an oncologist was consulted to rule out systemic malignancy. Orbit magnetic resonance imaging showed a moderately high T1 signal [Figure 1e] and moderately low T2 signal mass lesion [Figure 1f]. Enhancement with gadolinium contrast was noted [Figure 1g]. Compared to the T1-weighted image, the T2 FLAIR image showed more conspicuous hyperintensity and a better-delineated lesion margin. Taking the magnetic resonance imaging (MRI), ultrasound, and OCT findings, primary choroidal melanoma with secondary CME and SRF was suspected.

After discussing the diagnosis with the patient, transpupillary thermotherapy (TTT) (3 mm spot size, 250–300 mW, 60 s, 5 spots) with concurrent 3 consecutive weekly intravitreal injections of 4 mg bevacizumab (IVB) were given for tumor control and suspected occult CNV. Unfortunately, observed anatomical and functional response was both minimal. BCVA was 20/100 in the right eye and OCT still demonstrated persistent SRF and CME. FA and indocyanine green angiography (ICGA) were done for further evaluation, which revealed simultaneous fluorescence of the retinal and choroidal vasculature.

Photodynamic therapy (PDT) was suggested but was refused by the patient. Since no benefit was observed after treatment with both TTT and IVB, aflibercept was considered. Confluent TTT (3 mm spot size, 250–300 mW, 60 s, 5 spots) with two weekly 4 mg aflibercept injections were performed. Thereafter, CME and SRF markedly subsided [Figure 2a]. BCVA showed mark improvement to 20/25 in her right eye. Since then, the macula has remained fluid-free for 12 months [Figure 2b]; however, the mass has persisted [Figure 2c, d]. No adverse events have been reported to date.

Discussion

We presented a 74-year-old relatively healthy woman with choroidal tumor with SRF and CME. No evidence

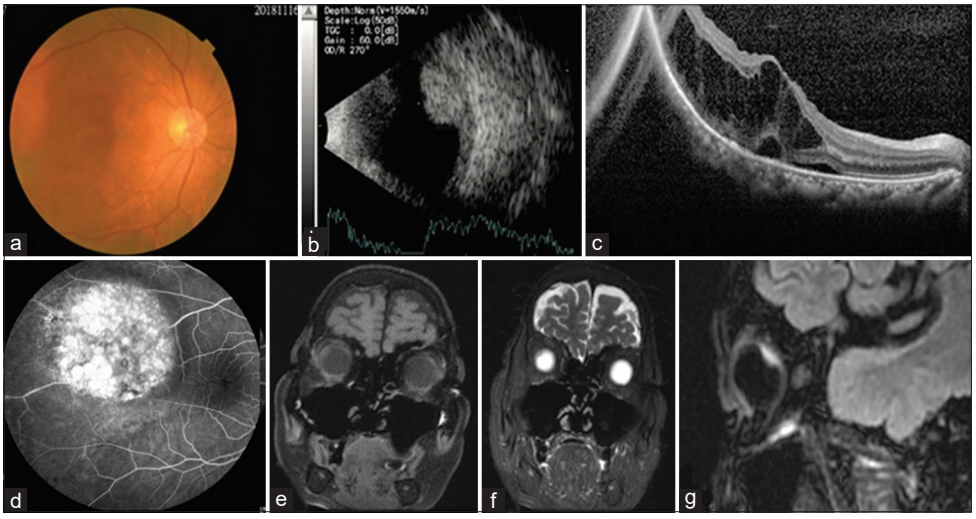

Figure 1: (a) Color fundus, (b) b-scan ultrasonography, (c) optical coherence tomography, (d) fluorescent angiography, late phase, (e) T1 moderately hyperintense signal, (f) T2 moderately hypointense signal, (g) T2 FLAIR more conspicuous hyperintensity and better delineated lesion margin

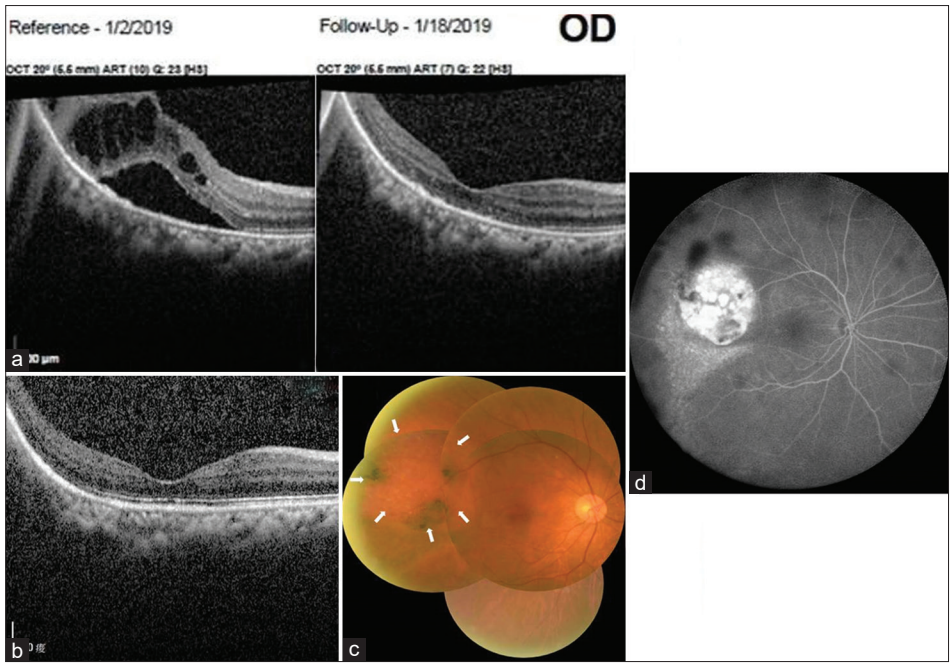

Figure 2: (a) 16 days after aflibercept injections, marked resolution of cystoid macular edema (CME) and subretinal fluid (SRF) was noted, (b) optical coherence tomography 12 months after aflibercept injections, with no demonstrated recurrence of CME and SRF, (c) color fundus photography 12 months after aflibercept injections, with tumor stable in size, (d) FAG of 12 months after aflibercept injections

of metastasis was found at presentation. The differential diagnosis included choroidal nevus, choroidal hemangioma, lymphoid tumor (benign and malignant), choroidal melanoma, and choroidal metastasis. Multimodal imaging offered strong diagnostic power in this circumstance when pathology was unavailable. Fundus photography revealed a dome- or mushroom-like shape lesion with various degree of pigmentation. B-scan showed low-to-medium/medium-to-high internal reflectivity. FA revealed mottled hyperfluorescence in the arterial phase and diffuse staining in later phases. ICGA demonstrated intrinsic choroidal vasculature in early phase, faded out in late phase, and double circulation pattern. MRI revealed a T1 hyperintense, T2 hypointense, and T2 FLAIR hyperintense gadolinium contrast-enhancing lesion.

The tumor size, OCT, FA, ICGA, and MRI findings were all compatible with choroidal melanoma. Still, there were atypical features that made a diagnosis inconclusive, including less pigmentation of the tumor, hypoautofluorescence on AF, and relatively higher internal reflectivity on B-scan. These findings made choroidal metastasis another possible etiology. However, no systemic malignancies were found after multiple referrals to the oncologists.

The presence of SRF and especially CME is uncommon in choroidal melanoma. Estimates of rates of choroidal melanoma-associated CNV in one retrospectively reviewed study is around 6%,[5] if one considers SRF to be a marker of CNV.

In the therapies of uveal melanoma, both global-preserving local treatment (surgery, laser photocoagulation and radiation therapy) and enucleation were all played a role. In the 1970s, eye-saving procedures gradually replaced prompt enucleation. Treatment with plaque brachytherapy for primary choroidal melanomas is considered the first-line therapy in the United States. In Collaborative Ocular Melanoma Study Group study, randomized control trials for either enucleation or brachytherapy revealed relatively similar survival in cases with medium-sized uveal melanomas.[6] Verteporfin PDT is also an effective alternative. A main drawback of PDT is its financial burden and not covered by the national health insurance in Taiwan.

In small-to-medium uveal melanoma, TTT is another available choice as a primary therapy, however it demonstrates variable efficacy. Furthermore, TTT may paradoxically result in complications of macula edema (6%–9%) even as the melanoma regresses.[3] The optimal outcomes depend highly on prudent patient selection. TTT with simultaneous brachytherapy may improve chance of globe preservation, diseases-free interval and local control rates in one study but showed no difference in other analysis.[2]

Previous studies suggested TTT performed in melanoma more than 4 mm in height might be associated with higher recurrences.[7] The rationale of choosing TTT in this case was the unavailability of brachytherapy, financial burden of PDT, and relatively fair vision that does not warrant surgical resection and enucleation. We

have discussed the treatment option of radiotherapy to the patient and her family. We all agreed to refer for radiotherapy if the tumor progressed or other complications occurred after TTT.

Nevertheless, TTT offers a safe, convenient, and affordable option with few side effects. TTT has been established as an optional treatment for small choroidal melanomas.[8] Lin and Tsai also reported TTT combined with intravitreal bevacizumab as a cost-reducing and time-saving treatment option for patients with choroidal metastases.[9] Although TTT was not the most effective treatment in choroidal melanoma, it stabilized tumor size, retained vision, and resulted in no metastasis after more than 1 year in this case.

Regarding metastatic progression, the overexpression of growth factor receptors is clinically critical in choroidal melanoma. Besides VEGF receptors, insulin growth factor receptor 1 and epidermal growth factor receptor may also play an important role in cell proliferation and survival.[10] Some hypothesis suggested in the environment with high VEGF, choroidal capillaries may turn into VEGF-dependent.[4] Bevacizumab, a full-length recombinant humanized antibody against all isoforms of VEGF-A, was the first Food and Drug Administration (FDA)-approved biologic therapy designed to inhibit tumor angiogenesis. In most settings, efficacious use of intravitreal bevacizumab combined it with either plaque radiotherapy or TTT. When using as monotherapy, the effect of local control and tumor inhibition was not observed in clinical settings.[4]

Aflibercept is a new anti-VEGF that has been FDA approved for several conditions, including neovascular AMD, diabetic ME, and other causes of CNV. First approved in November 2011, it consists of the Fc portion of the human immunoglobulin G and extracellular domains of human VEGF receptors 1 and 2 to form its VEGF-binding portions. Acting like a "VEGF trap," aflibercept binds not only VEGF-A but also VEGF-B and placental growth factor (PlGF). Compared with bevacizumab, which only inhibits VEGF-A, aflibercept serves as a better candidate to regress neovascularization in tumor and choriocapillaris.[11]

In our patient, CME and SRF persisted despite treatment with TTT and three consecutive intravitreal injections of bevacizumab. After switching to 4 mg aflibercept, anatomical and functional improvements were achieved, and no recurrence was noted in 12 months.

The precise mechanism for the visual acuity and anatomical improvement with aflibercept compared to bevacizumab is speculative. In previous reports, aflibercept binds VEGF-A with affinity 100-times stronger than bevacizumab.[12] The more sustained and greater inhibition may be thus an explanation for less frequent injections and more effective in the long-term control. Another mechanism worth mentioning is PlGF blockage. PlGF is known as a key in ocular inflammation and cystoids macula edema due to its implication in a series of local factors, including thromboplastin, factor III and CD142.[12] Monocyte chemotaxis is also another pathological pathway.[13] Finally, VEGF-B, bound by aflibercept but not bevacizumab, also contributes to the formation of CME.[12] Of note, tumor size monitoring, including MRI and oncologist referral, was crucial to ensure there was no tumor progression or metastasis.

Khan *et al*. reported intravitreal aflibercept as rescue therapy for postradiation CME.[5] To our knowledge, this is the first case report describing the administration of aflibercept combined with TTT as a therapy for resistant CME and SRF in primary choroidal melanoma.

Multimodal imaging offered strong diagnostic power in a circumstance when pathology was unavailable. Intravitreal aflibercept may serve as a valid choice in the context of choroidal melanoma with persistent SRF and CME. In our present case, significant anatomical and functional improvements were observed and maintained for 1 year. Further randomized control trials with longer follow-up periods would serve to clarify best clinical practices when dealing with persistent SRF and CME.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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