Acute Exudative Polymorphous Paraneoplastic Vitelliform Maculopathy Managed With Intravitreal Aflibercept

Kaan Gündüz, MD; Gökçen Çöndü, MD; Carol L. Shields, MD

ABSTRACT: The authors report on two patients with bilateral acute exudative polymorphous paraneoplastic vitelliform maculopathy (AEPPVM) treated with intravitreal aflibercept (Eylea; Regeneron, Tarrytown, NY [marketed locally in Turkey by Bayer]). Underlying malignancy had been treated in each case, including breast carcinoma in one case and colon carcinoma in the other case. A macular vitelliform lesion was noted in the right eye and atrophic retinal pigment epithelial (RPE) changes were noted in the left eye of each case. Enhanced depth imaging optical coherence tomography (EDI-OCT) of the vitelliform lesion showed sensorineural retinal detachment, highly reflective subretinal material, ellipsoid loss in the right eye, and photoreceptor loss in both eyes of each patient. In both cases, the right eye with a vitelliform macular lesion was treated with intravitreal aflibercept (2.0 mg/0.05 mL) at monthly intervals for the first three injections and at bimonthly intervals for the following injections. Case 1 received a total of six injections and visual acuity (VA) increased from 20/70 to 20/50 at 10 months’ follow-up. EDI-OCT showed slight gradual resolution of subretinal vitelliform material. Case 2 received three injections and VA increased from 20/100 to 20/40 at 4 months’ follow-up with a decrease in the subretinal vitelliform deposit and intraretinal edema on EDI-OCT. Intravitreal aflibercept may control progression of APPVME in newly diagnosed cases by decreasing vascular leakage and stabilizing RPE function.

INTRODUCTION

Acute exudative polymorphous paraneoplastic vitelliform maculopathy (AEPPVM) is a rarely seen paraneoplastic retinopathy affecting primarily the retinal pigment epithelium (RPE). Previous terms used in this condition included paraneoplastic vitelliform maculopathy, melanoma-associated retinopathy syndrome variant, and vitelliform maculopathy with skin melanoma. The term AEPPVM has been used for a specific paraneoplastic retinal finding with carcinoma,1 as well as cutaneous and uveal melanoma.2 In this report, we describe two patients with systemic cancer and AEPPVM who were treated with intravitreal aflibercept (Eylea; Regeneron, Tarrytown, NY [marketed locally in Turkey by Bayer]). This is a HIPPA-compliant, institutional review board-approved, interventional case series performed in accordance with The Declaration of Helsinki.

CASE REPORTS

Case 1

A 66-year-old woman diagnosed with breast carcinoma 6 years previously and treated with bilateral mastectomy, chemotherapy, and radiotherapy experienced nyctalopia and photopsia for 6 months. Later, she noticed vision decrease in the right eye. By history, the left eye had also demonstrated similar symptoms approximately 2 years ago.

Ocular examination at referral to us revealed best-corrected visual acuities (BCVAs) of 20/70 in the right eye and counting fingers at 1 meter in the left eye. The intraocular pressure (IOP) was 18 mm Hg in both eyes. Anterior segment examination revealed mild nuclear cataract in both eyes. Funduscopically, there was a vitelliform subretinal collection measuring 1.0 mm × 1.0 mm in diameter in the right subfoveal region (Figure 1A). In the left eye, there was a 0.5 mm × 0.5 mm round area of RPE atrophy in the

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From the Department of Ophthalmology, Ankara University Faculty of Medicine, Ankara, Turkey (KG, GC); and Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia (CLS).

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Address correspondence to Kaan Gündüz, MD, Professor of Ophthalmology, Farya Is Merkezi 8/50, Ufuk Universitesi Cad, Cukurambar Sogutozu, Ankara, Turkey; email: drkaangunduz@gmail.com.

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foveal center without vitelliform deposit, probably representing sequela of once-active AEPPVM (Figure 2A). The vitreous was clear in both eyes.

Enhanced depth imaging optical coherence tomography (EDI-OCT) showed sensorineural retinal detachment with highly reflective subretinal material, ellipsoid loss, and photoreceptor loss in the right eye (Figure 1B). The left eye had dispersed high-reflective intraretinal dots, RPE atrophy, and reverse shadowing on EDI-OCT (Figure 2B). Fundus autofluorescence (FAF) showed irregular patchy hyperautofluorescence in the fovea of both eyes corresponding to the intraretinal collection of lipofuscin. The left eye probably had resolving left-over lipofuscin (Figures 1C and 2C). Fluorescein angiography (FA) demonstrated isofluorescence in the early venous and mid phases with minor, late hyperfluorescence in the foveal region in the right eye (Figure 1D). The left eye demonstrated hyperfluorescence in the macula starting in the late venous phase and becoming more prominent in the late phase with no leakage, consistent with retinal pigment epithelial atrophy and window defect (Figure 2D). Other diagnostic findings, including electro-oculogram (EOG) and electroretinogram (ERG), were normal.

Based on the diagnosis of previous systemic cancer and current ocular findings, a diagnosis of AEPPVM was made. Serum analysis for antibody detection was not performed per patient preference due to cost. Systemic evaluation for metastasis was negative. A decision was made to treat the right eye with intravitreal aflibercept (2.0 mg/0.05 mL) monthly for the first three injections and then once every 2 months thereafter. A total of six injections were made and visual acuity increased to 20/50 at 10-month follow-up. OCT showed slight resolution of the subretinal highly reflective material (Figure 1E). The left eye remained stable.

Figure 1. Case 1, right eye. (A) Fundus photograph shows a 1.0 mm × 1.0 mm-sized vitelliform lesion in the fovea. (B) Enhanced depth imaging optical coherence tomography (EDI-OCT) shows sensorial retinal detachment, highly reflective material (probably lipofuscin) under the outer retina, ellipsoid loss, and photoreceptor loss. (C) Fundus autofluorescence demonstrates irregular patchy hyperautofluorescence in the fovea corresponding to the intraretinal collection of lipofuscin. (D) Late-phase fluorescein angiogram demonstrates minor hyperfluorescence in the foveal region. (E) EDI-OCT after six intravitreal aflibercept injections shows slight resolution of subretinal highly reflective material.
Case 2

A 51-year-old woman diagnosed with colon carcinoma and treated by surgery, chemotherapy, and radiotherapy 2 years previously had decreased vision for 3 months before being referred to our practice. BCVAs were 20/100 and 20/400 in the right and left eyes, respectively. The IOP was 12 mm Hg in both eyes. Anterior segment examination revealed mild nuclear sclerosis in both eyes. There were a few pigmented vitreous cells in both eyes. Funduscopically, there was a 0.5 mm × 0.5 mm sized subretinal vitelliform deposit in the foveola and multiple areas of RPE atrophy in the macular area of the right eye (Figure 3A). In the left eye, there was an ill-defined area of RPE atrophy in the fovea and multiple atrophic spots in the macular area reminiscent of inactive AEPPVM (Figure 4A).

FA demonstrated mild hyperfluorescence in the macula in the late phase in the right eye and a window defect in the left eye (Figures 3B and 4B). FAF showed pinpoint/patchy hyperautofluorescence in the macular vitelliform lesions (Figures 3C and 4C). The right eye had sensorineural retinal detachment, highly reflective subretinal material, intraretinal ede-
ma, inner segment/outer segment (IS/OS), and photoreceptor loss on EDI-OCT (Figure 3B). The left eye demonstrated highly reflective subretinal material, IS/OS loss, and photoreceptor loss on EDI-OCT (Figure 4D).

Systemic evaluation for metastasis was negative. No systemic antibody testing could be done due to financial reasons. The right eye was treated with intravitreal aflibercept (2.0 mg/0.05 mL) at monthly intervals.
intervals. After three monthly injections, the visual acuity increased to 20/40 at 4-month follow-up. The EDI-OCT showed marked regression of subretinal lipofuscin collection and intraretinal edema (Figure 3E). The visual acuity and EDI-OCT of the left eye remained stable.

DISCUSSION

Paraneoplastic retinopathy is characterized by autoantibodies against a focus of cancer that cross-reacts with retinal or RPE antigens, resulting in retinal damage. Cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) are the two well-known examples of paraneoplastic retinopathy. Both CAR and MAR syndromes are associated with normal retinal appearance with subtle RPE changes initially. In contrast to these two paraneoplastic entities, AEPPVM is characterized by vitelliform lesions associated with sensory detachment in the macula that looks like the vitelliform changes seen in Best’s disease.

Acute exudative polymorphous paraneoplastic vitelliform maculopathy has been reported in cases with cutaneous melanoma, choroidal melanoma, breast cancer, pulmonary adenocarcinoma, and multiple myeloma. In AEPPVM cases, antibodies against the RPE proteins including recoverin, peroxiredoxin 3, carbonic anhydrase 2, bestrophin 1, and interphotoreceptor-retinoid binding protein have been reported in the literature. These anti-cancer antibodies can cross react with the RPE antigens in genetically predisposed patients. Impaired phagocytic function of the RPE results in bilateral accumulation of lipofuscin in and under the neural retina. There may also be subretinal fluid in the affected inflamed area. However, the presence of these antibodies does not always provide unequivocal evidence for paraneoplastic retinopathy.
On occasion, individuals without clinical evidence of retinopathy may have these antibodies, and, in some cases of presumed paraneoplastic retinopathy, the antibodies cannot be identified with current techniques. In one report, it was estimated that up to 35% of retinal antibodies are not detected in patients with presumed CAR.  

The initial symptoms in AEPPVM may be nystagmus and photophobia followed by decreased vision, as in our Case 1. However, visual acuity may be normal at initial diagnosis of AEPPVM. Anterior segment examination is usually normal in these patients. Funduscopically, white or yellow vitelliform lesions in the macular area are seen. The vitelliform lesions can be unilateral or bilateral. The vitelliform lesions are observed to represent accumulations of lipofuscin under serous retinal detachment on OCT. FAF usually demonstrates increased intrinsic autofluorescence due to the accumulation of lipofuscin. FA usually shows normal microcirculation and vessel anatomy. Hyperfluorescent areas corresponding to sensorineurral retinal detachments may be seen in the late phases. Usually there is no dye leakage. There may be intervening areas of hypofluorescence from the dense subretinal material. The ERG and EOG are usually normal. Our cases had clinical, OCT, FAF, FA, and electroretinographic findings conforming to the reported findings alluded to above.

Differential diagnosis of AEPPVM include acute exudative polymorphous vitelliform maculopathy (AEPVM), adult-onset Best’s disease and central serous chorioretinopathy, and drug toxicity such as seen with MEK (mitogen-activated protein kinase [MAPK] kinase) inhibition. Acute exudative polymorphous vitelliform maculopathy (AEPVM), also known as adult-onset vitelliform maculopathy, adult foveo-macular vitelliform dystrophy or adult-onset Best’s disease, is a rare disease with onset between the forth and fifth decades of life, and mostly affecting females. The patients classically present with bilateral, round, and discrete yellow lesions that are in or near the macula, resulting in disturbances in central vision. However, the patients usually maintain relatively good vision until late. The disease rarely progresses to development of choroidal neovascular membranes or areas of geographic atrophy. There may be associated cuticular drusen. FA usually reveals central hyperfluorescence with a hypofluorescent surrounding rim due to RPE atrophy. Usually there is late leakage. Unlike AEPVM, vision derangement is more likely to occur in cases with AEPPVM as in the left eyes of our two cases. Furthermore, there is usually less late fluorescence and leakage on FA in AEPPVM compared to AEPVM and central serous chorioretinopathy. MEK inhibitors such as binimetinib which are more commonly used in the treatment of systemic cancer may be associated with a central serous-like retinopathy with subretinal fluid in some patients. Further differential diagnosis of AEPVM may include CAR and MAR syndromes which are characterized by optic atrophy, vascular narrowing and marked RPE changes in the later stages.

AEPPVM can occur before or after the diagnosis of primary cancer. Al-Dahmash et al. reported that the mean interval between the diagnosis of malignancy and onset of AEPPVM was 42 months in their series of five patients affected with cutaneous melanoma, uveal melanoma, lung carcinoma, and breast carcinoma. In our two cases, the diagnosis of systemic malignancy heralded ocular findings by a period of 66 months and 20 months. Ocular findings of AEPPVM can also precede the diagnosis of systemic tumor in which case the diagnosis of paraneoplastic vitelliform maculopathy may be difficult until other signs of metastatic disease appear.

There is little information regarding treatment and outcome of this disorder because most patients die of their underlying malignancy within months after diagnosis. Review of the literature shows different treatments including oral corticosteroids, intravitreal dexamethasone implant, and systemic chemotherapy have been tried in cases with AEPPVM with variable success. Spontaneous resolution of subretinal fluid and visual recovery has also been documented.

In our cases with AEPPVM, the primary cancers seemed to have been successfully treated and there was no evidence of systemic metastasis. Therefore, we elected to treat these cases with intravitreal anti-VEGF agent aflibercept. Intravitreal anti-VEGF treatment has previously been used in cases with AEPVM. Aflibercept is a recombinant, high-affinity, VEGF-binding fusion protein blocking all isomers of VEGF-A, VEGF-B, and placental growth factor. We speculate intravitreal aflibercept may prevent vascular leakage and stabilize RPE function in newly diagnosed cases of AEPPVM. There has been no prior report on treatment of paraneoplastic vitelliform maculopathy with intravitreal anti-VEGF agents. Based on the good short-term results obtained in our two patients, we believe that anti-VEGF treatment could be considered as a therapeutic alternative for these patients.

REFERENCES


