High-Resolution OCT Imaging of RPE Degeneration in Bilateral Diffuse Uveal Melanocytic Proliferation

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ABSTRACT

Bilateral diffuse uveal melanocytic proliferation is a rare paraneoplastic syndrome that presents with bilateral progressive loss of vision. A 70-year-old woman presented with a 3-month history of progressive, bilateral vision loss. The patient had bilateral, diffuse, shallow, subretinal fluid with patchy, reddish-brown lesions at the level of the retinal pigment epithelium (RPE) that showed significant early hyperfluorescence on fluorescein angiography and a corresponding loss of autofluorescence. Optical coherence tomography of both eyes revealed complete RPE and inner segment/outer segment junction loss with adjacent areas of thickening at the level of the RPE. Bilateral diffuse uveal melanocytic proliferation was diagnosed based on these clinical findings, and a systemic evaluation for malignancy revealed metastatic endometrial adenocarcinoma. Both autofluorescence and optical coherence tomography demonstrated unique imaging characteristics that correlated with the reported histopathology of bilateral diffuse uveal melanocytic proliferation. [Ophthalmic Surg Lasers Imaging 2010;41:S96-S100.]

INTRODUCTION

Initially described by Machemer in 1966,1 bilateral diffuse uveal melanocytic proliferation is a rare paraneoplastic syndrome that causes severe loss of vision in patients with an extraocular, frequently occult, malignancy.2 Visual symptoms frequently precede other manifestations of the malignancy.2 Gass et al.3 described five cardinal ocular signs: multiple, round or oval, subtle, red patches at the level of the retinal pigment epithelium (RPE) in the posterior fundus; a striking pattern of multifocal areas of early hyperfluorescence corresponding with these patches; development of multiple, slightly elevated, pigmented and nonpigmented uveal melanocytic tumors, as well as evidence of diffuse thickening of the uveal tract; exudative retinal detachment; and rapid progression of cataracts. Other findings may include dilated episcleral vessels, shallow anterior chamber, glaucoma, and iris and ciliary body cysts.4,5

The most common underlying malignancy is ovarian carcinoma in women and lung or pancreatic adenocarcinoma in men, which is usually fatal within 1 to 2 years.2 The exact mechanism between the malignancy and ocular changes is not clearly understood. However, bilateral diffuse congenital choroidal uveal melanocytosis has been suggested as a possible preexisting condition in patients with bilateral diffuse uveal melanocytic proliferation.3,6

Histopathology of affected eyes demonstrates a diffuse proliferation of pigmented and nonpigmented spindle-shaped melanocytes in the uveal tract and extensive destruction of the RPE and the outer retina.3,7 We present the first high-resolution optical coherence tomography (OCT) study of the retina demonstrating ablation of the inner segment/outer segment (IS/OS) junction, focal loss of RPE with adjacent thickening, and subretinal fluid in a patient with bilateral diffuse uveal melanocytic proliferation.
CASE REPORT

A 70-year-old woman presented with a 3-month history of progressive, bilateral vision loss. Her medical history was significant for breast and uterine cancer, which were treated 12 and 2 years prior to presentation, respectively. The best-corrected visual acuity was 20/400 in the right eye and 20/200 in the left eye. The anterior segment examination of both eyes revealed pigment on the corneal endothelium and 3+ nuclear sclerotic cataracts with posterior subcapsular opacifications.

Funduscopic examination was significant for diffuse shallow subretinal fluid with patchy, reddish-brown lesions at the level of the RPE bilaterally (Figs. 1A and 1B). These patches demonstrated complete loss of fundus autofluorescence (Spectralis; Heidelberg Engineering, Inc., Vista, CA) (Figs. 1C and 1D) and corresponding early hyperfluorescence on fluorescein angiography (Spectralis) (Figs. 1E and 1F). Spectral domain OCT (Cirrus HD-OCT software version 3.0.0.64; Carl Zeiss Meditec Inc., Dublin, CA) revealed subfoveal fluid (Fig. 2), complete loss of the IS/OS junction, and patchy absence of the RPE adjacent to significant RPE thickening. B-scan ultrasonography (I3 System-ABD; Innovative Imaging, Inc., Sacramento, CA) revealed a hypoechoic mass in the vitreous adjacent to the macula.

Figure 1. Composite color photographs of the right (A) and left (B) eyes show multiple, nummular, red patches at the level of retinal pigment epithelium. Complete loss of autofluorescence was seen in multiple areas in the right (C) and left (D) eyes. Fluorescein angiography of the right (E) and left (F) eyes demonstrates early hyperfluorescence corresponding with red patches seen in color photographs.
to, CA) demonstrated posterior choroidal thickening around the posterior poles of both eyes (Fig. 3).

Based on these findings, a diagnosis of bilateral diffuse uveal melanocytic proliferation was made and a systemic evaluation was undertaken to identify a new underlying malignancy. Positron emission tomography scan was positive for fluorodeoxyglucose activity in pelvic lymph nodes. Lymph node biopsy was performed and pathology revealed metastatic endometrial adenocarcinoma.

Due to patient request and lack of viable treatment options, 1.25 mg of the vascular endothelial growth factor inhibitor bevacizumab (Genentech, San Francisco, CA) was injected off-label into the vitreous of the right eye. Repeat evaluation 1 month after the anti-vascular endothelial growth factor treatment showed no improvement in visual acuity or resolution of the subretinal fluid.

**DISCUSSION**

Bilateral diffuse uveal melanocytic proliferation is a rare paraneoplastic syndrome that presents with bilateral progressive loss of vision in patients with an extraocular, frequently occult, malignancy. Gass et al. described five cardinal ocular signs: multiple, round or oval, subtle, red patches at the level of the RPE in the posterior fundus; a striking pattern of multifocal areas of early hyperfluorescence corresponding with these patches; development of multiple, slightly elevated, pigmented and nonpigmented uveal melanocytic tumors, as well as evidence of diffuse thickening of the uveal tract; exudative retinal detachment; and rapid progression of cataracts.

Histologically, hypopigmented, spindle and epithelioid melanocytes infiltrate the uveal tract, leading to significant patches of thickening in the choroid. These cells demonstrate a wide spectrum of atypia.
but rarely contain mitotic figures. The RPE and photoreceptors overlying the area of choroidal thickening undergo extensive destruction, whereas the choriocapillaris is largely unaffected. The etiology is poorly understood.

This patient exhibited clinically apparent bilateral, multiple, ovoid, reddish-brown lesions of the posterior fundus, subretinal fluid, choroidal thickening on ultrasound, and dense cataracts in association with a known history of uterine adenocarcinoma, which match many of the clinical criteria put forth by previous reports. On imaging, the lesions corresponded with early hyperfluorescence without late leakage or pooling on fluorescein angiography and complete loss of fundus autofluorescence, similar to the findings reported by Wu et al.8

The transmitted fluorescence from the RPE window defects on fluorescein angiography supports the persistence of the choriocapillaris in addition to RPE destruction reported on histopathology.3,7 Corresponding fundus autofluorescence, which measures accumulated lipofuscin within the lysosomes of RPE cells, was completely devoid and further corroborates the absence of RPE.

Despite subretinal fluid, neither leakage nor pooling was appreciated in later phase fluorescein angiography, which suggests a diffuse, relatively slowly progressive accumulation of fluid. The pockets of fluid were primarily focused over RPE loss. Thus, the loss of RPE may play a role in the accumulation of the fluid.

This is the first report to describe the unique high-resolution OCT characteristics of bilateral diffuse uveal melanocytic proliferation, which include complete IS/OS junction ablation, patchy RPE absence, and subretinal fluid. Immediately adjacent to each lesion was significant thickening at the level of the RPE that was clinically visualized as yellowish honeycombing and contained marked hypofluorescence on fluorescein angiography and mild hyperreflectance on autofluorescence. Again, the IS/OS junction and RPE ablation observed on OCT supports the pathologic description of marked outer retinal and RPE destruction.

No effective treatment exists for bilateral diffuse uveal melanocytic proliferation. Discovery of specific treatments is hindered by the poor understanding of the pathogenesis of melanocytic proliferation and the mechanism of RPE and outer retinal degeneration. Although some investigators have reported temporary improvement of vision with chemotherapy, radiation, or corticosteroids,9-12 these treatments are generally ineffective in preventing the progressive nature of this disorder. In this report, the subretinal fluid was not affected by the off-label use of bevacizumab, which would suggest that vascular endothelial growth factor does not play a role in the pathogenesis. Future treatments may include specific targeting of unknown paraneoplastic factors.

REFERENCES


