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Wet age-related macular degeneration refractory to aflibercept but responsive to systemic everolimus

A 69-year-old Caucasian woman with a history of metastatic breast cancer had been receiving injections of aflibercept every 4−8 weeks for wet age-related macular degeneration in her right eye for the past 4 years. Despite the regular frequency of the aflibercept injections, her optical coherence tomography had always demonstrated significant levels of intraretinal fluid (Fig. 1). It was decided in the past to maintain her schedule of aflibercept in order to maintain her baseline level of vision of 20/60. Her left eye had some drusen and a visual acuity of 20/30.

The patient developed pleural effusions secondary to her metastatic breast cancer, which prompted her oncologist to start her on systemic everolimus. Three weeks later, at her scheduled visit with her retina specialist, it was noted that the amount of intraretinal fluid had decreased. Aflibercept was administered at this visit. At the following visit, 2 months after starting everolimus, her optical coherence tomography was almost absent of any intraretinal fluid for the first time since she first started receiving the injections (Fig. 1). Her vision improved from her baseline of 20/60 to 20/40. Therefore, after discussing with the patient, it was decided to defer her aflibercept.

Unfortunately, the patient's pleural effusions were not responding to the everolimus, and after 3 months on the medication, she was switched to etoposide. She was seen by her retina specialist a month later, and the level of intraretinal fluid had returned to baseline (Fig. 1). After a discussion with the patient, it was decided to restart the aflibercept. Despite this, her vision returned to its baseline of 20/60 at the next visit.

Discussion

Age-related macular degeneration (AMD) is the leading cause of vision loss in patients over the age of 65 years in developed countries.[1] The advent of intravitreal antiangiogenesis therapy has greatly benefited the treatment of the wet form of AMD.[2–4] However, 10%−17% of patients do not respond.[5,6]

Everolimus is an inhibitor of the mechanistic/mammalian target of rapamycin (mTOR). mTOR serves as the core of protein complexes that are involved in the regulation of direct protein synthesis, cell growth, and cell proliferation. Because mTOR is also integral in allowing lymphocytes to enter the S phase, everolimus is also effectively a T-cell inhibitor.

Part of the pathophysiology of wet AMD is thought to involve the immune system. Indeed, there are associations between AMD and complement factor H,[7] and with high temperature serine protease (HTRA-1)[8]—which is thought to regulate tumor necrosis factor-beta and cleaves fibronectin. Fas ligand has also been shown to play a role in the inhibition of angiogenesis in the retinal pigment epithelium.[9] Indeed, systemic immunosuppression, specifically sirolimus, has been shown to inhibit choroidal neovascularization in animal models.[10] However, intravitreal corticosteroids have been shown to not be effective in treating wet AMD.[11] A small pilot study did seem to suggest that systemic immunosuppression could decrease the number of anti-vascular endothelial growth factor injections needed.[12]

Everolimus is a derivative of sirolimus—both are mTOR inhibitors. In the Study Assessing double-masKed Uveitis tREAtrement 1 study, patients with uveitis were randomized to 44, 440, and 880 mcg of intravitreal sirolimus.[13] The primary outcome was the control of inflammation—the 440 and 880 mcg groups were the intervention arms and compared with the 44 mcg group, which was the minimal dose calculated to have any therapeutic effect according to regression models. Although the

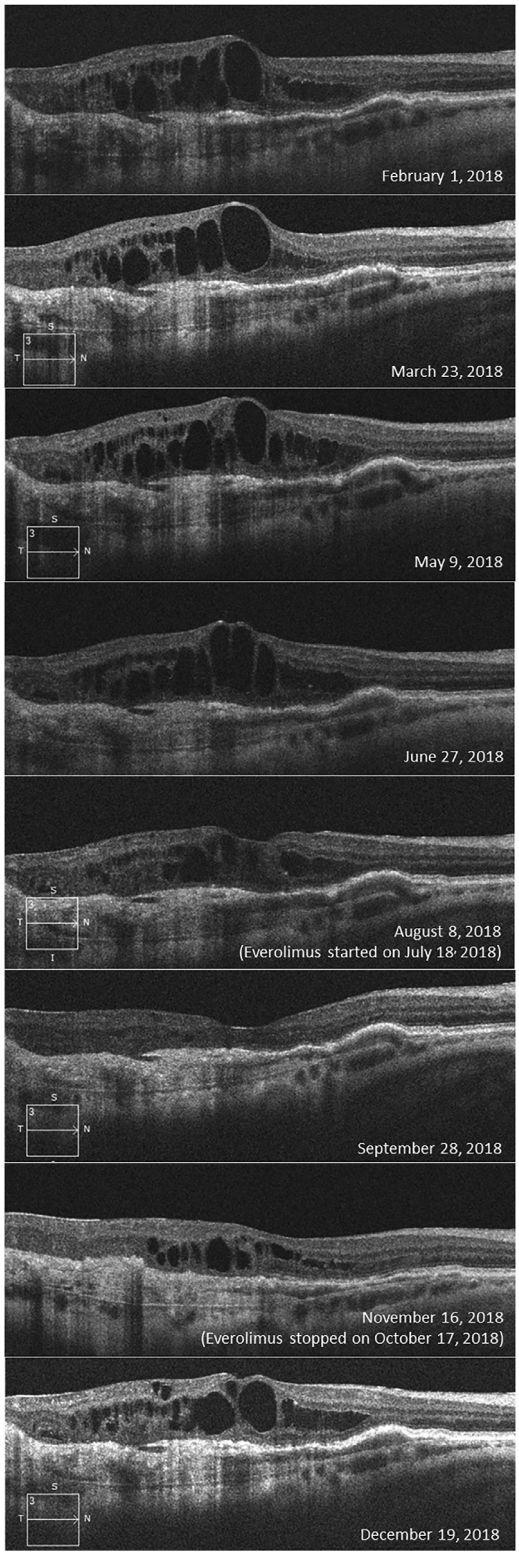

Fig. 1—Optical coherence tomography of the right eye over 11 months. The intraretinal fluid is present despite regular aflibercept and only resolves under everolimus. However, after the everolimus is stopped, the intraretinal fluid reappears. The patient received an injection of aflibercept during all visits except for September 28, 2018, when the injection was deferred due to the minimal intraretinal fluid.

440 and 880 mcg groups showed the best control of inflammation, all 3 groups showed similar reductions in macular edema—in around half of the patients. Subconjunctival and intravitreal sirolimus has also been shown to decrease diabetic macular edema.[14]

To the best of our knowledge, this is the first documented case of wet age-related macular degeneration that has responded to everolimus. Causality is supported by the temporal relationship between the initiation of everolimus with the near resolution of intraretinal fluid and the subsequent cessation of everolimus with the return of intraretinal fluid. More research, such as with a pilot study, would help further characterize the effect of everolimus on wet AMD and possibly open up a new avenue of therapy.

Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

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Fundus autofluorescence of bilateral ora serrata pearls

Ora serrata pearls (OSPs) were first described in 1967 by Lonn et al as idiopathic drusen-like deposits located at the furthest extent of the retina.[1] Using energy dispersive x-ray spectroscopy, it was recently noted that these brilliant anterior lesions are composed of calcium phosphate also found in dystrophic calcification of drusen.[2] Herein, we report a case of bilateral OSPs imaged with wide-field color fundus photography and fundus autofluorescence (FAF).

Case Presentation

A 32-year-old Caucasian woman with severe myopia was referred to the Stein Eye Institute for retinal evaluation of lattice degeneration. The patient was asymptomatic. A complete ophthalmologic evaluation was performed, and the following was recorded: best corrected visual acuity, intraocular pressure, and results of anterior segment and dilated fundus examination. Multimodal imaging, including wide-field color fundus photography and FAF (Optos PLC, Dunfermline, Scotland, UK) and spectral domain optical coherence tomography (SD-OCT, Heidelberg Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) of the macula, was performed and the findings were analyzed.

Best corrected visual acuity measured 20/25 in the right eye and 20/20 in the left eye. Anterior slit-lamp examination findings were normal in both eyes. Intraocular pressure was 15 and 18 mm Hg in the right and left eye, respectively. Fundus examination showed perivascular lattice degeneration along the inferotemporal vascular arcade in the left eye. Of note, multiple OSPs were bilaterally identified in the far temporal peripheral quadrant (left eye greater than the right eye) and appeared as multiple refractile or glistening nummular white-yellow lesions (Fig. 1). On wide-field FAF, the pearls displayed a round, intensely hyperautofluorescent pattern with well-defined borders (Fig. 2). Macular SD-OCT was unremarkable in both eyes.

Discussion

In the early evolution of these deposits, OSPs may be dark and difficult to detect as they can be initially small and hidden under the retinal pigment epithelium (RPE).[1] In later stages, the characteristic opalescent pearl appearance may develop with attenuation and loss of overlying RPE cells. In our case, the pearls were readily identified as small, discrete white-yellow nodules indicative of a later stage lesion lacking overlying RPE (Fig. 1). The clinical presentation was consistent with the original description of OSPs with regard to bilaterality and peripheral retinal location.[1] Evaluation with SD-OCT was technically limited given the peripheral location.

In our case the OSPs illustrated a very interesting pattern on FAF displaying a uniformly bright and homogenous autofluorescence. This is in contrast to macular drusen associated with age-related macular degeneration in which there is a more variable pattern of autofluorescence depending on their type and localization.[3] We believe that the characteristic hyperautofluorescence of the OSPs is related to their composition, because calcium phosphate has intrinsic hyperautofluorescent properties.[4]

OSPs have been evaluated with various analyses, including light microscopic histopathologic evaluation with staining, polarized microscopy, and scanning electron microscopy, and various reports have failed to identify any evidence of lipid composition unlike typical hard or soft macular drusen; instead, OSPs have been shown to be comprising acidic carbohydrates and calcium phosphate and have been linked to dystrophic calcification of drusen and defined as drusen-like structures.[1,2]

There are only 2 reports of spectral domain OCT through OSP, and findings of schisis and retinal atrophy were described, but no evidence of actual drusen deposition was noted.[5,6]