OCT-BASED INTERPRETATION OF THE VITREOMACULAR INTERFACE AND INDICATIONS FOR PHARMACOLOGIC VITREOLYSIS

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Purpose: To review the role of optical coherence tomography (OCT) in diagnosis and management of vitreomacular disease and the impact of OCT on potential uses of ocriplasmin, a new pharmacologic vitreolysis agent recently approved by the U.S. Food and Drug Administration for the treatment of symptomatic vitreomacular adhesion.

Methods: Analysis of current literature regarding OCT in diagnosis and management of vitreomacular interface disease.

Results: Posterior vitreous detachment is typically a nonpathologic age-related event. Anomalous posterior vitreous detachment emerges when the vitreous cortex fails to cleanly detach from the macula, optic nerve, or other adherent sites. Focal vitreomacular adhesion is a nonpathologic anatomical designation associated with perifoveal posterior vitreous detachment but normal retinal morphology on OCT. Vitreomacular traction is a pathologic consequence of persistent vitreous attachment with structural disturbance of the macular retina visible on OCT. Full-thickness macular holes are foveal defects continuous through all retinal layers to the retinal pigment epithelium. Vitreomacular traction and macular hole with focal vitreomacular adhesion are indications for pharmacologic vitreolysis.

Conclusion: Noninvasive high-resolution OCT imaging has transformed the understanding of vitreomacular interface disease. Careful evaluation of the vitreomacular interface with OCT has increased in importance with the introduction of ocriplasmin for vitreomacular adhesion associated with symptomatic anatomical retinal changes.

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Our understanding of the vitreoretinal interface (VRI) has been transformed with the advent of optical coherence tomography (OCT) imaging. Previous imaging technologies had logistical obstacles and limited analytic capabilities that often challenged the physician’s ability to precisely diagnose and manage the full spectrum of VRI diseases. Optical coherence tomography allows noninvasive capture of high-resolution images with detailed examination of vitreoretinal anatomy (Figure 1).1,2 Advances in VRI imaging technology using newer spectral domain OCT have further improved the efficiency and accuracy with which pathologic VRI conditions are identified and treated.3 Recent interest in the role of OCT in VRI diagnosis and treatment has increased since the introduction of ocriplasmin, a pharmacologic vitreolysis agent with demonstrated efficacy in vitreomacular traction (VMT) including full-thickness macular holes (FTMHS).4,5 Ocriplasmin was approved by the U.S. Food and Drug Administration in October 2012 for the treatment of patients with symptomatic vitreomacular adhesion (VMA) and by the European Medicines Agency for the treatment of patients with VMT, including when associated with macular hole of diameter ≤400 μm.

Vitreoretinal Adhesion

The vitreous gel has an outer cortex of dense collagen (primarily Type II) that is attached to the internal limiting membrane (ILM; primarily Type IV collagen). Attachment between the vitreous gel and the retina is typically complete from birth through young adulthood (Figure 2).
As the eye ages, the vitreous gel liquefies in a process called synchysis and ultimately collapses, a process called syneresis. At this time, the vitreous cortex normally detaches from the retina as liquid enters the inter-vening space (posterior vitreous detachment [PVD]). Posterior vitreous detachment is an age-related event detected in half of the subjects at 50 years of age and almost all the subjects aged 80 years or older (Figure 2).8

Other than seeing floaters, most patients experience PVD without any significant problems; however, if vitreoretinal adhesion has not sufficiently weakened, a subset of patients will develop pathologic consequences known as anomalous PVD.9,10

This occurs at the sites of strong adherence: the vitreous base, the optic disk, and the macula (Figure 2) in a focal and sheet-like pattern.6,11,12 Persistent attachment and traction near the vitreous base can lead to retinal tears and subsequent retinal detachment.13 Persistent attachment to the optic disk, called vitreopapillary adhesion, can lead to visual loss, particularly in patients with diabetes, and neovascularization of the disk that can hemorrhage under the forces of vitreopapillary adhesion.14–16 Focal VMA occurs when the perifoveal vitreous cortex adheres to the macula after detaching from the surrounding retina.17,18 This situation typically is asymptomatic, nonpathologic, and causes no discernible retinal changes. Alternatively, VMA can lead to VMT if the forces of attachment are great enough to cause anatomical disturbance of the macular architecture.19,20 By definition, VMT is always pathologic and symptomatic. Therefore, the term “symptomatic VMA” is most accurately referred to as VMT, with or without concurrent macular hole. Symptoms commonly associated with VMT include metamorphopsia, blurred vision, and difficulties with daily vision-related tasks such as reading. Asymptomatic VMA is not an indication for the treatment with occlusion or any active intervention and is a normal transient phase in the course of PVD (Figure 2).

Vitreoretinal Pathologies

Epiretinal Membranes, Vitreoschisis, and Macular Schisis

Anomalous PVD can lead to a variety of pathologic conditions (Figure 3), such as VMT and macular hole.22 Unresolved VMA has also been reported to aggravate concomitant retinal conditions, such as diabetic macular edema or age-related macular degeneration. Broad areas of VMA (defined as >1,500 μm by OCT) are thought to be a potential causative factor in the development of vitreous or retinal splitting. In the former case, PVD often leaves remnants of the vitreous cortex on the ILM surface that can be focal or

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broad and serve as scaffolding for epiretinal membrane (ERM) formation. These vitreous remnants are often prominent sheets that result from splitting of the posterior vitreous cortex, known as vitreoschisis, which has been identified in half of the eyes with macular hole or macular pucker.23–32

Splitting of the retina can result in lamellar macular holes (see below). Vitreopapillary adhesion is found in nearly all full-thickness and lamellar macular holes and vitreomaculopathies with intraretinal cysts.15,16

Although the mere presence of an ERM is usually asymptomatic (sometimes referred to as cellophane maculopathy), growth of an ERM as a result of hyalocyte and other cell proliferation with contraction of the membrane can distort underlying retinal layers to create macular pucker resulting in decreased visual acuity.

Vitreomacular Traction, Lamellar Holes, and Macular Holes

Because focal VMA is rarely symptomatic and, by definition, not associated with changes in retinal anatomy on OCT (Figure 4C), it is often first discovered during routine OCT evaluation of middle-aged or elderly patients.17,18

Figure 4 illustrates the range of pathologic outcomes that can develop from unresolved focal VMA. Focal VMA can exert tractional forces that pull on the inner retina to distort the retinal surface. Once focal VMA is associated with retinal changes on OCT, the anatomical finding is defined as VMT (Figure 4, D and E).19,20,33 Figure 4E shows an example of VMT in which the fovea contour is abnormally raised and associated with focal attachment of the vitreous cortex. Similar VMT morphology is often discovered in
VMA is present on the FTMH edge.\textsuperscript{43,44} An FTMH without focal VMA often seems cystic and elevated at the surface edges where the traction has broken the ILM (Figure 4). Multiple line scans, with at least 2 obtained at perpendicular angles, must be analyzed to conclusively determine whether an operculum has been fully released from the edges of a macular hole (Figure 5).

Full-thickness macular holes can be categorized into 3 groups based on the response to therapy according to the narrowest linear width of the hole (excluding the inner retinal surface).\textsuperscript{45,46} An FTMH is categorized as small if the narrowest linear width is \(\leq 250\) \(\mu\)m (Figure 4G), medium if \(>250\) \(\mu\)m but \(\leq 400\) \(\mu\)m (Figure 4H), and large if \(>400\) \(\mu\)m (Figure 4I). Strong evidence exists that size of the hole is the most important determinant of anatomical success rate of the surgical intervention and likelihood of spontaneous closure.\textsuperscript{43–49} This is apparently also true for pharmacologic vitreolysis with ocriplasmin.

Nonsurgical treatment options now exist for patients who have FTMH with focal VMA, especially if the smallest width is \(<400\) \(\mu\)m. Pharmacologic vitreolysis proximity to the broken edges of the inner retina. B. Second scan of the same eye taken at 90\(^\circ\) to that shown in (A) revealed that the FTMH was indeed associated with focal VMA and that the operculum was attached (arrow).
with agents such as ocriplasmin can facilitate FTMH closure by resolving associated focal VMT. Combined data from the ocriplasmin Phase 3 clinical trial program showed that a single ocriplasmin injection resulted in higher rates of FTMH closure (40.6%) at postinjection Day 28 versus placebo (10.6%).36 Closure rates varied according to the FTMH width at baseline. In the ocriplasmin treatment group, postinjection Day 28 closure rates were higher in patients with small FTMH at baseline (58.3%) versus those with medium (36.8%) or large macular holes (0%).

Both VMT and FTMH with focal VMA are sometimes referred to as "symptomatic VMA," which is an indication for pharmacologic vitreolysis.36,50,51 Ocriplasmin was approved by the U.S. Food and Drug Administration for the treatment of patients with symptomatic VMA and has been submitted to the European Medicines Agency for approval to treat VMT, including when associated with small macular hole.

Broad Vitreomacular Adhesion and Tractional Macular Thickening

Instances of VMA that occur over broad areas (>1,500 μm) can cause thickening and schisis-like separation of underlying retinal layers.52,53 Tractional macular thickening seems as anterior–posterior stretching of the retina with intraretinal fluid and numerous vertical elements stretching between retinal layers that have separated (Figure 6). Mechanisms underlying tractional macular thickening are diverse, vary from case to case, and can involve ERM and vitreous traction.54–56 This is seen especially in eyes with pathologic myopia and posterior staphyloma.

Epiretinal Membrane and Macular Pucker

An ERM can form regardless of whether PVD has progressed to completion or not, in the absence or presence of VMA-associated pathologies, or often as a secondary consequence of concomitant disease or ocular surgery.57 Causes of ERM formation are incompletely understood but may involve vitreous cortex remnants that are left on the inner retina surface after PVD and thought to serve as stimulus for cellular proliferation.58 Optical coherence tomography studies detected vitreoschisis, sheets of cortical remnants, in nearly half of the eyes with macular pucker.23,27 These sheets contain hyalocytes, which promote cell proliferation and membrane contraction, which can lead to macular pucker.59

Residual reactive fibrous tissue from FTMH closure or chronic VMT may also have a contributing role.57 Epiretinal membranes adhere to the ILM and can cause retinal edema that can dramatically distort the fovea on OCT (Figure 7A). Epiretinal membranes can also exert centripetal tractional forces that pull underlying retina inward toward the ERM center to create a folded or wrinkled retinal morphology called macular pucker (Figure 7, B and C).60,61 Macular pucker is usually symptomatic and associated with decreased visual acuity and metamorphopsia.62

Pseudohole refers to a clinical condition in which the macula is covered by an ERM that has a centrally positioned opening over the foveal depression. A pseudohole usually appears as a round or oval-shaped window by standard ophthalmoscopic techniques and can be mistaken for an FTMH. These conditions are now easily distinguished by OCT scan on which a pseudohole can be identified as an ERM with a central opening above retinal tissue that is intact or incompletely torn (Figure 7D).53,54 General and reading visual acuity are usually only slightly affected, although reports of metamorphopsia are common. This finding is consistent with the observation that pseudohole is often associated with distorted fovea morphology (Figure 7D). Pseudohole treatment options are similar to those for macular pucker and include surgical membrane peeling.

Various degrees of ERM are often observed in association with VMT in the same eye.33,58 Concomitant presence of ERM with VMT can affect treatment outcomes, including those with pharmacologic vitreolysis. Indeed, studies have detected that 40% of the macular holes have eccentric macular pucker.27 Phase 3 data from the ocriplasmin clinical trial program showed that patients with isolated VMT at baseline experienced greater rates of VMT resolution after ocriplasmin treatment versus patients who had VMT with ERM at baseline. Of cases with isolated VMT or FTMH, 37.4% had VMT resolution at postinjection Day 28 versus 8.7% of the eyes that had VMT or FTMH with ERM at baseline.36 It is important to emphasize that cases of isolated ERM without associated VMT have never been investigated for treatment with a pharmacologic vitreolysis agent.

Fig. 6. Macular thickening with schisis-like separation of the retinal layers and concomitant ERM. Optical coherence tomography showing macular thickening with separation of the retinal layers. The internal limiting membrane is broken and associated with an ERM. There is a horizontal separation between the outer nuclear and outer plexiform layers, with multiple vertical elements stretching between the layers across the space.
References


