Natural History and Pathogenesis of Vitreomacular Traction

Recent pharmacologic and surgical developments provide ophthalmologists more options for treating vitreomacular traction.

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In order to better understand the diseases of the vitreoretinal interface, it is imperative to understand the normal sequence of events in healthy eyes with evolving posterior vitreous detachment (PVD). Posterior vitreous detachment is a chronic, age-related event, and its early stages are detected in half of the population older than 50 years, in more than two-thirds of those 65 years and older, and in almost 100% of the population older than 80 years.[1]

AGE-RELATED CHANGES AND VITREOUS BIOCHEMISTRY

There are significant structural changes in an aging vitreous that may result in PVD. Between the ages of 70 and 90 years, the collagen concentration of the vitreous gel is significantly greater than at ages 15 to 20.[2] As an individual ages, the volume of the vitreous gel decreases, thereby increasing the concentration of collagen deposits. This process results in a transition from clear vitreous in youth (the result of a homogeneous distribution of collagen and hyaluronic acid) to a fibrous structure in adults. Over time, the vitreous fibers thicken and twist, and the vitreous liquefies in a process called syneresis. Fluid-filled pockets are initially formed in front of the macula, and these eventually coalesce and enlarge into the central vitreous cavity.

Syneresis predisposes patients to PVD, but it is not sufficient to precipitate complete vitreous detachment. Physiologic PVD results from progressive syneresis occurring simultaneously with progressive weakening of the adhesion between the posterior vitreous cortex and the internal limiting membrane (ILM), allowing liquid vitreous to dissect a plane at the vitreoretinal interface.[3,4]

Complications of PVD can be caused by an imbalance between the vitreous liquefaction and the weakness of the vitreoretinal adhesion.[5] Any condition (ie, thickening of the posterior hyaloid or ILM) that precipitates vitreous liquefaction or increases the strength of the VMA can prevent the smooth and shallow separation of the vitreoretinal interface. Conditions that induce vitreous liquefaction are high myopia, ocular inflammatory diseases, trauma, and retinal vascular diseases such as diabetic retinopathy and retinal vein occlusion.[6]

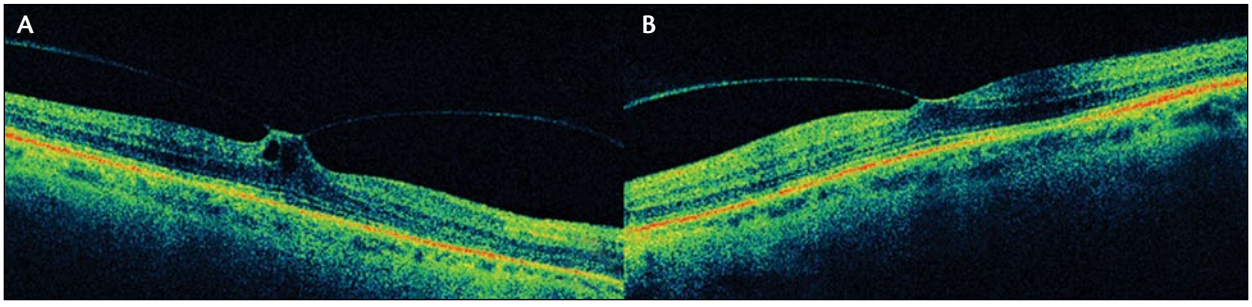

Figure 1. High-definition optical coherence tomography (HD-OCT) images of vitreomacular traction (VMT) based on the morphology of the vitreomacular adhesion (VMA): (A) V-shaped VMT and (B) J-shaped VMT.

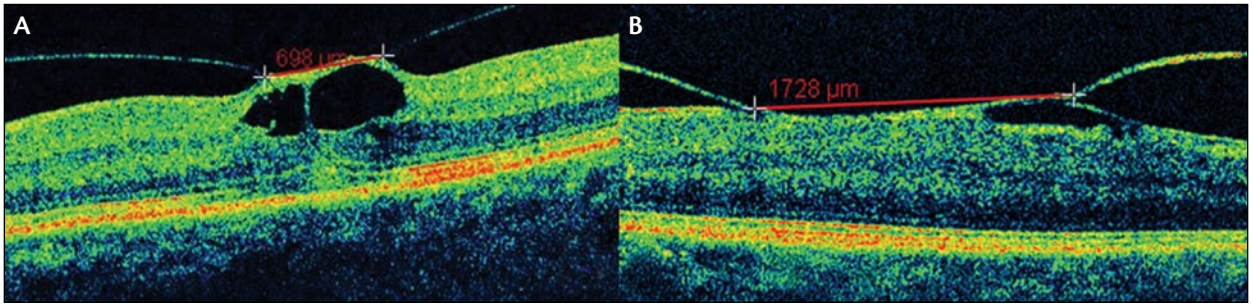

Figure 2. HD-OCT images of VMT classified based on the diameter of the VMA: (A) focal VMT and (B) broad VMT.

Idiopathic VMT occurs in men and women of any age or race.[7] Women may be more susceptible to early PVD because premature vitreous liquefaction is associated with declining postmenopausal estrogen levels. For these patients, the use of estrogen-replacement therapy is associated with a reduced risk of macular hole (MH) development.[8]

The particular pattern of PVD is based on gravitational effects. PVD begins in the perifoveal region and takes months or years to extend to the superior and temporal midperiphery. In its later stages, PVD affects the fovea, inferior midperiphery, and optic disc, resulting in a Weiss ring and a complete nonpathologic PVD.[3,9] In many instances, the PVD process occurs without patients reporting symptoms; however, some patients report flashes or floaters for a period of time. These patients may experience the traction effects of an incomplete detachment that results in a variety of visual changes, determined in part by the size and strength of the residual VMA.[3]

Regions with stronger VMA due to thin ILM include: the peripapillary retina, the areas along major vessels, enclosed ora bays, retinal tufts, points of degenerative remodeling, the vitreous base, the central 500 µm of the fovea, and the foveal margin, which is about 1500 µm in diameter.[3] Persistent VMA at such points allows static and dynamic traction forces to act over time, leading to VMT.[10-12]

PATHOGENESIS OF VMT

With the advent of optical coherence tomography (OCT), especially spectral-domain (SD) OCT, ophthalmologists can better assess the vitreoretinal interface. Noninvasive imaging examinations allow investigators to study disease processes that were previously undetectable by biomicroscopy, which resulted in frequent underdiagnosis of many diseases.[13] HD-OCT and SD-OCT further enhance the capacity to identify the morphologic changes of vitreoretinal diseases, allowing better comprehension of the physiopathology of several macular diseases.[14] SD-OCT has introduced novel ways of staging eyes with PVD through better evaluation of the tractional forces at the vitreoretinal interface,[12,15,16] as well as their involvement in the development of certain macular conditions.[16,17]

CLASSIFICATION OF VMA

VMT is defined as the result of abnormal and incomplete PVD with persistent attachment to the macular area, leading to tractional anatomic changes and usually resulting in reduced or distorted vision. Both VMA and VMT can be classified as either focal or broad (depending on the diameter of vitreous attachment) and as concurrent or isolated (depending on the presence of other ocular diseases).[18]

Different anatomic presentations of VMT have been described. Each configuration has unique implications concerning anatomic and functional outcomes. Although several classification systems of this syndrome have been proposed,[14,19-21] there is currently no consensus for classifying VMT. Based on morphologic findings on OCT images, however, the pattern of VMA can be divided into 2 shapes: J-shaped and V-shaped (Figure 1), the latter of

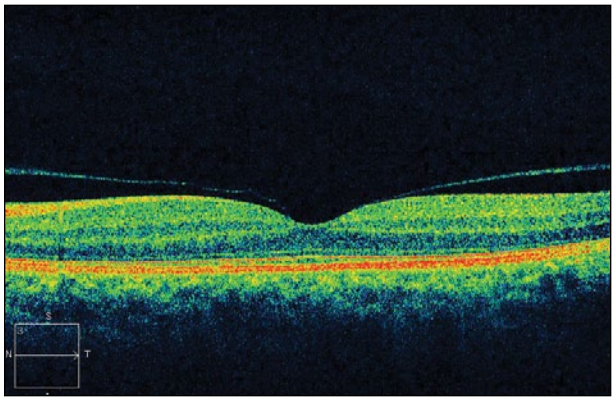

Figure 3. VMA in an asymptomatic patient, without any evidence of traction effects.

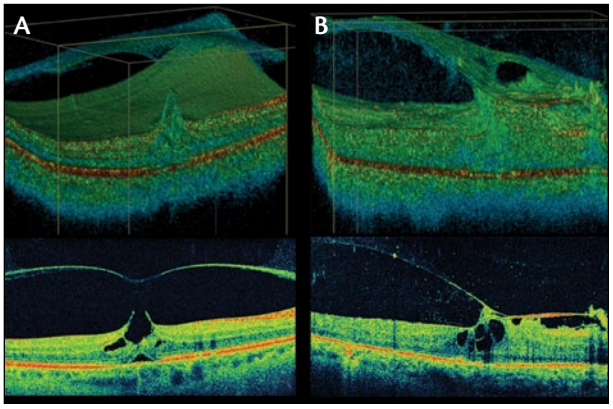

Figure 4. Macular changes associated with specific VMT types. SD-OCT images of a focal VMT show intraretinal cysts and subfoveal retinal detachment (A). SD-OCT images of broad-VMT show degenerative retinal changes, associated epiretinal membranes (ERM), and retinal thickening (B).

which is associated with better surgical outcomes.[19,20] Based on the concept that the diameter of the vitreomacular attachment is inversely related to macular morbidity and foveal deformation, a distinct classification has also been proposed: focal adhesion (≤1500 µm) and broad adhesion (>1500 µm) (Figure 2).[14,22] Studies have demonstrated that classification based on the diameter of the adhesion (focal or broad) and not on the adhesion morphology (V- or J-shaped) more accurately reflects the specific macular changes and may better predict postoperative anatomic and functional outcomes.[23-25]

Recently, the International Vitreomacular Traction Study Group proposed a classification of VMA, VMT, and MH based on findings from SD-OCT imaging.[18] VMA, a partial vitreofoveal separation without retinal abnormalities, is characterized by an elevation of the cortical vitreous above the retinal surface, with an acute angle between the vitreous and the inner retinal surface (Figure 3). This is a normal development during the natural course of PVD, but one that can progress to complete separation; the only symptoms usually reported are floaters. It is important to remember that the anatomic definition of VMA has been dissociated from symptomatology and, like VMT, may be subclassified by size of the adhesion as either focal (≤1500 µm) or broad (>1500 µm).

Patients with VMA may have other associated macular abnormalities such as age-related macular degeneration, retinal vein occlusion, or diabetic macular edema. In these patients, VMA should be termed "concurrent VMA"; the term "isolated VMA" should be reserved for cases in which no ocular disease is present.[18]

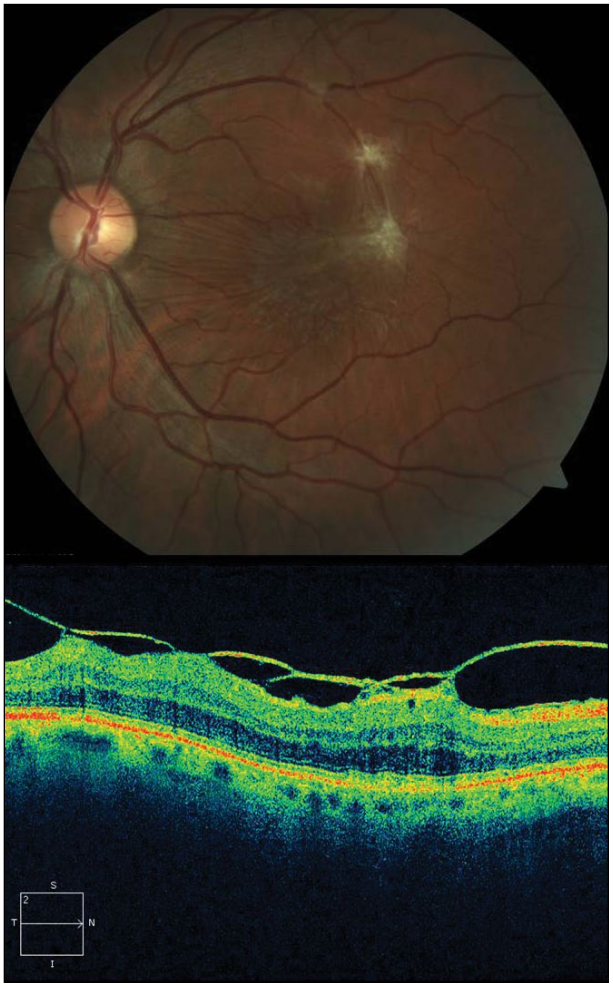

Figure 5. Fundus photograph and SD-OCT image of a patient with multiple areas of VMT associated with an ERM.

ASSOCIATED MACULOPATHIES

Until recently, VMT was considered an isolated pathology. It is now believed to assume a contributory role in a wide spectrum of macular diseases, including MH, cystoid macular edema (CME), ERM, diabetic retinopathy, and age-related macular degeneration.[3,17,26] Recognition of the role of VMT in such macular diseases is imperative for proper diagnosis and management. However, it remains uncertain why patients with VMT have distinct maculopathies and which macular configurations will benefit from expectant, surgical, or enzymatic treatment.[3,27-29]

Specific macular diseases are associated with specific VMT types. The diameter of the VMA is inversely related to macular morbidity and foveal deformation: The narrower the vitreomacular attachment, the greater its tractional force on the macula. Diffuse VMA may distribute the tractional forces beyond the border of the foveal region.[14] Based

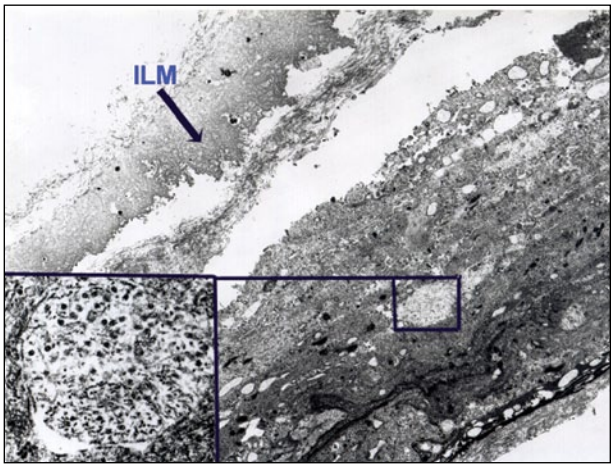

Figure 6. ERM and ILM analyzed by transmission electron microscopy (×3800 magnification). The matrix around the surface is composed of moderate amounts of native collagen fibrils (inset, ×24 000 magnification).

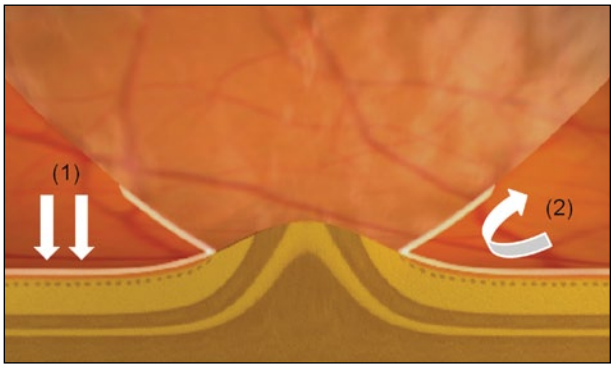

Figure 7. Proposed mechanism of ERM proliferation in VMT, according to Johnson[15] and Chang et al.[21] After development of a partial posterior vitreous detachment, small splits within the ILM may form, allowing glial cells to gain access to the superficial retina, which serves as a scaffold for ERM proliferation (left, indicated by double arrow). These cells also proliferate on the detached hyaloid face (right arrow), strongly anchoring the vitreous to the macula.

on this physical theory, focal VMT may lead to MH, tractional CME, and foveal retinal detachment, and broad VMT may be related to ERM, diffuse retinal thickening, and poor recovery of foveal depression (Figure 4).[24]

ERM

The ERM may play an important role in chronic VMT, mainly in broad adhesions (Figure 5).[14,21,24] Partial PVD with vitreoretinal traction can cause small splits in the ILM, allowing glial cells to gain access to the superficial retina. In these eyes, epiretinal fibroglial membranes, collagen, astrocytes, and myofibroblasts may proliferate from the retinal surface to the back surface of the detached posterior vitreous (Figure 6). This configuration strengthens the VMA and prolongs the duration of VMT by preventing spontaneous separation. Furthermore, the proliferative epiretinal fibroglial membranes increase the tangential traction by thickening and tightening the detached posterior hyaloid and anchoring the posterior hyaloid to the surrounding retinal surface, thus enhancing the anteroposterior traction caused by the VMT adhesion (Figure 7).[14,21]

MH AND TRACTIONAL CME

Eyes with tractional CME and eyes with early-stage idiopathic MH share structural qualities.[15] The smaller the area of foveal adhesions, the greater the force exerted on the macula, in turn causing more intense morphologic abnormalities.[22] This condition of focal adhesion, known as *vitreofoveal traction*, induces MH and CME.[9,30-32] The strong effect of narrow bands of adhesion can lead to this variant of VMT, called *tractional CME*.

Symptoms of tractional CME must be distinguished from symptoms of other inflammatory diseases such as postoperative pseudophakia, retinal vascular diseases, or uveitic CME, which generally exhibits capillary leakage on fluorescein angiography. Tractional CME is not linked with inflammatory aspects and shows only minimal, if any, leakage (Figure 8).[15] It has yet to be determined why vitreofoveal traction leads to MH in some cases and tractional CME without hole formation develops in other cases.[15]

TREATMENT

Many patients with VMT maintain good visual acuity with mild metamorphopsia and require no treatment. Some cases resolve spontaneously with complete PVD, generally with anatomic and functional outcomes similar to surgery.[33] However, other cases have poor or worsening visual acuity and require treatment. Several investigators have reported the results of surgery to treat VMT, with visual acuity improvement in 44% to 78% of cases.[19,20,34,35]

Despite resolution of posterior hyaloid traction, improved signs and symptoms are not always achieved. Specific preoperative VMT patterns as seen on OCT might predict postoperative improvements in visual acuity.[19,20,25] Patients with focal VMT adhesion and a V-shaped pattern usually have lower preoperative visual acuity than those with broad adhesion and a J-shaped pattern. However, the final visual acuity is similar between groups, so the magnitude of visual acuity improvement appears to be better in focal cases. The greater magnitude of visual acuity improvement in focal cases may also

contrast with the poor vision in patients with broad VMT who experience degenerative macular changes due to the chronic nature of broad VMT, longer symptom duration, and prolonged macular thickening usually related to the presence of an ERM.[23]

It is important to consider some aspects of the vitreoretinal surgical anatomy. The use of vital dyes to stain preretinal tissues during surgery allows visualization of the thin, transparent tissues in the vitreoretinal interface: the ILM (brilliant blue), the ERM (trypan blue), and the vitreous posterior surface (triamcinolone acetonide).[36,37] Lutein crystals with brilliant blue is another vital dye recently available as an adjuvant for chromovitrectomy, for the better visualization of the vitreous and the ILM.[38]

Until recently, vitrectomy was the only treatment for VMT; however, the introduction of medical agents to induce a PVD expands management options. Ocriplasmin (Jetrea, ThromboGenics), approved by the US Food and Drug Administration for the treatment of symptomatic VMA, is a recombinant product that shares the catalytic properties of human plasmin. In clinical trials, the magnitude of clinical effect was modest overall but varied substantially depending on baseline characteristics. Presence of a full-thickness MH, VMT diameter less than 1500 µm (focal VMT), phakic lens status, absence of ERM, and patient age younger than 65 years were baseline characteristics that predicted treatment success.[23,29,30] The primary endpoint of a particular group study was the resolution of VMA at day 28. In that study, 26.5% of eyes treated with ocriplasmin had release of VMA at day 28 compared with 10.1% of control eyes.[27] Ocriplasmin had a favorable safety profile, and many of the reported adverse events, including vitreous floaters and photopsia, were linked to the release of the vitreous. There were more cases of blurred vision in the treatment group than in the control group, and those cases

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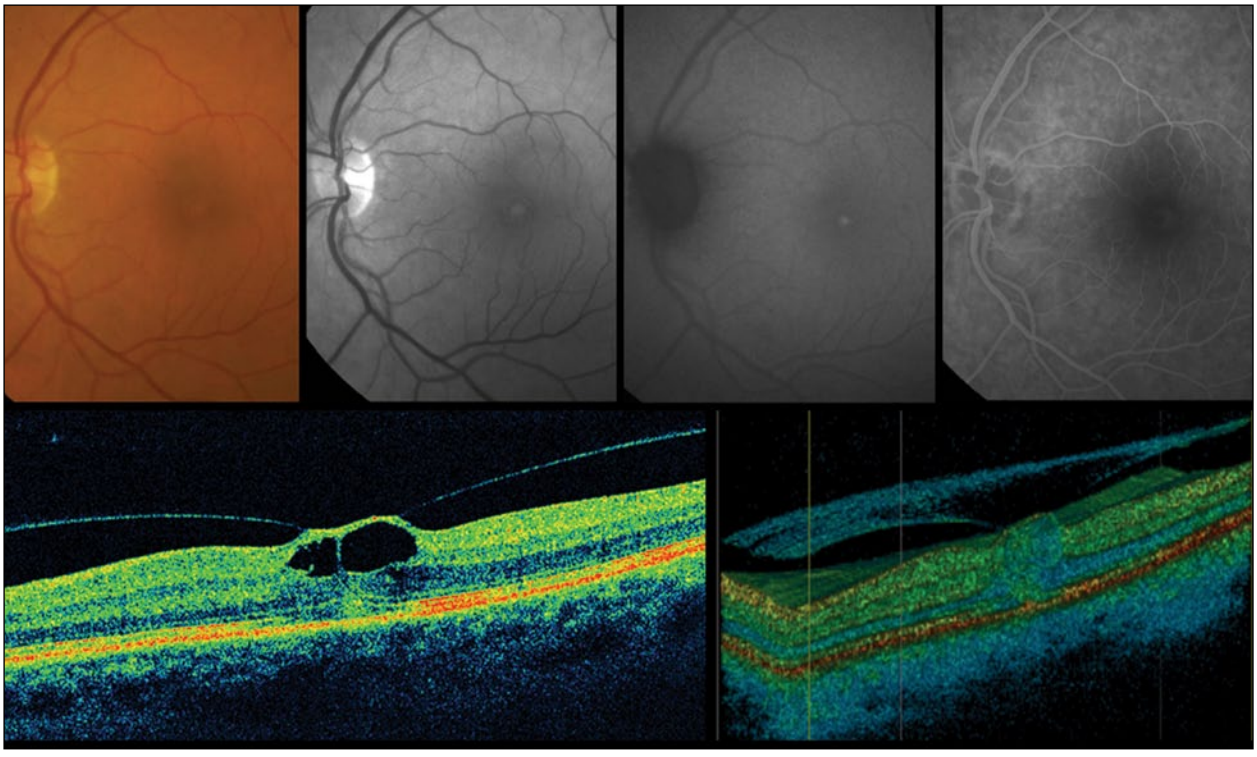

Figure 8. Fundus photograph, red-free image, fundus autofluorescence, and fluorescein angiogram (top) of a patient with tractional cystoid macular edema. The fundus photograph shows a yellow spot that corresponds to the hyperautofluorescent pattern on the autofluorescence image. A corresponding midphase fluorescein angiogram shows minimal leakage from the retinal capillaries. SD-OCT (bottom) shows focal VMA with a perifoveal vitreous detachment causing tractional cystoid foveal edema.

were often transient, possibly suggesting the aggravated VMT that occurs before release of the VMA.[27] Ocriplasmin injection is also linked to adverse events unrelated to vitreous detachment, including cataract, increased intraocular pressure, and conjunctival hemorrhage.[39] Decline in visual acuity postinjection seems to be an acute, transient visual dysfunction that resolves in some patients. Although its mechanism of action is not fully understood, it is possible that ocriplasmin may have a diffuse enzymatic effect on photoreceptors or the retinal pigment epithelium that is not limited to areas of VMA, and the rod photoreceptors may be more susceptible than cone photoreceptors to this effect; additionally, zonular dehiscences were also reported, resulting in the possibility of lens displacement into the vitreous cavity during cataract surgery.[40,41] It is appropriate to consider the full spectrum of the ocriplasmin risks when evaluating treatment options. ■

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