Vitreous in Age-Related Macular Degeneration

III.G.

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Outline

Keywords
Vitreous • Anomalous posterior vitreous detachment Vitreoschisis • Exudative age-related macular degeneration Choroidal neovascularization • Vitreo-macular adhesion Vitreo-papillary adhesion • Traction • Vascular endothelial growth factor • Optical coherence tomography • Ultrasound

Key Concepts

1. Anomalous posterior vitreous detachment (assessed by ultrasound) and adhesion of the posterior vitreous (visualized by optical coherence tomography) are significantly correlated to exudative AMD with 100 % co-localization of vitreo-macular adhesion and choroidal neovascularization, often located extrafoveally. Vitreo-papillary adhesion and vitreoschisis are additional morphological changes providing further evidence of an association if not a role for anomalous posterior vitreous detachment in exudative AMD.
2. Vitreo-macular adhesion/traction might promote the development of choroidal neovascularization by low-grade inflammation. Furthermore, the attached posterior vitreous might prevent normal diffusion of oxygen (causing hypoxia) or clearing of vascular endothelial growth factor and other proangiogenic cytokines.
3. Whereas the morphological findings in neovascular AMD are uncontested, the interpretation of these changes regarding their impact on the course of the disease and the role in the etiology of exudative AMD are controversial. The favorable effect of vitrectomy and spontaneous posterior vitreous detachment on the activity of neovascular lesions and the significant correlation of vitreo-macular adherence and the response to pharmacotherapy indicate there is not only a pathogenic role for vitreous but also an influence of vitreo-macular adhesion/traction on the effect of modern anti-VEGF therapy.

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I. History

Due to the increasing importance of age-related macular degeneration (AMD) in the modern western world an enormous number of scientific papers have been published concerning the epidemiology, pathogenesis, morphology, and therapy of this disease. All these articles mainly concentrated on changes of the posterior part of the retina, as AMD is a disease of the chorioretinal interface, specifically the retinal pigment epithelium - Bruch's membrane - choriocapillaris complex. In the past, only a few studies examined the relationship of the posterior vitreous cortex to the retina and changes at the vitreo-macular interface in eyes suffering from AMD. Weber-Krause et al. conducted a study based on B-scan ultrasound and reported a higher incidence of incomplete posterior vitreous detachment (PVD) in eyes with AMD compared to age-matched controls [1]. Similarly, Ondes et al. found that complete PVD was more frequent in eyes without AMD compared to eyes with AMD [2]. Neither study specifically evaluated the vitreo-macular relationship in AMD, although it was implicit that anomalous PVD may play a role, as it does in other conditions [see chapter III.B. Anomalous PVD and vitreoschisis].

Interest was drawn to the vitreo-macular interface in AMD by Professor Susanne Binder [3] who performed pars plana vitrectomy, subretinal membrane removal, and transplantation of a suspension of retinal pigment epithelial cells in cases of neovascular AMD. She reported very strong adherences of the posterior vitreous in the macular region with an incidence of attached posterior vitreous of 83 % in 66 eyes of patients with a mean age of 77.8 years; in contrast to publications concerning age-related changes of the vitreous report an increasing incidence of PVD with age, reaching 63 % in the eighth decade of healthy or not selected cases [4]. The development of optical coherence tomography (OCT) enabled us to get a more detailed insight on the changes of the vitreo-macular interface in AMD. In exudative AMD, eyes treated with photodynamic therapy had central vitreo-macular adherences surrounded by shallow detachment of the posterior vitreous. The interest aroused by these observations led to clinical studies, whose basis and findings will be presented in detail in this chapter [5].

II. Epidemiology of Vitreo-Macular Adhesion in AMD

A. Posterior Vitreous Detachment (PVD) in AMD Study

Although OCT provides more detailed information concerning localized adherences of the posterior vitreous, ultrasound is still needed to diagnose PVD. With OCT, only 1 mm anterior to the retina can be examined; a total vitreous detachment and localized detachments in the periphery can only be detected by ultrasound. Furthermore, the posterior vitreous cortex and the inner limiting membrane cannot be differentiated by OCT; therefore, a total attached vitreous cannot be diagnosed by OCT. Thus, the comparative study of PVD in AMD [5] employed both ultrasound and OCT, to examine the incidence of posterior vitreous detachment and central adherences (Figure III.G-1).

A consecutive series of eyes at our institution with exudative AMD (50 eyes), nonexudative AMD (57 eyes), and age-matched controls (56 eyes) was assembled. Of the 50 eyes with exudative AMD 34 % had a complete PVD, as compared to 71.9 % with nonexudative AMD ($p=0.00002$) and 60.7 % control eyes ($p=0.014$). In contrast, partial PVD was significantly more frequent in eyes with exudative AMD (30 %) than in eyes with nonexudative AMD (12.3 %, $p=0.02$) and control eyes (5.4 %, $p=0.003$). These results indicate a high percentage of anomalous PVD in eyes with exudative AMD. Another sign of anomalous PVD in exudative AMD were central adherences surrounded by shallow detachments visualized by OCT. These adherences were significantly more frequent in exudative AMD (36 %) than in nonexudative AMD (7 %) or controls (11 %), $p<0.0001$ and 0.002, respectively (Figure III.G-1 presents plots of US and OCT results). Therefore, anomalous PVD seemed to play an important role in the etiology of exudative AMD. However, a number of confounding factors might influence the development of exudative AMD, among others genetic and environmental factors. To properly evaluate the importance of anomalous PVD in exudative AMD, such factors should be excluded. This could be achieved by examining patients with exudative AMD only in one eye and nonexudative or no AMD in the fellow eye. In the PVD in AMD study, both eyes of a patient were included, 40 % of the patients with neovascular AMD had this diagnosis only in one eye, 28 % had non-neovascular AMD, and 12 % no AMD in the fellow eye. 22.2 % of the patients showed different behavior of the posterior vitreous cortex in each eyes, and half of these patients had different diagnosis in each eye: neovascular AMD in one eye, which means that 36 % of the patients with neovascular AMD presented with different status of the posterior vitreous and different diagnosis concerning both eyes.

B. Vitreous in Unilateral Exudative AMD Study

To address the issue of confounding genetic and environmental factors, a collaborative multicenter study was conducted with the Department of Ophthalmology of the Rudolf Foundation Hospital, with Jerry Sebag, Founding

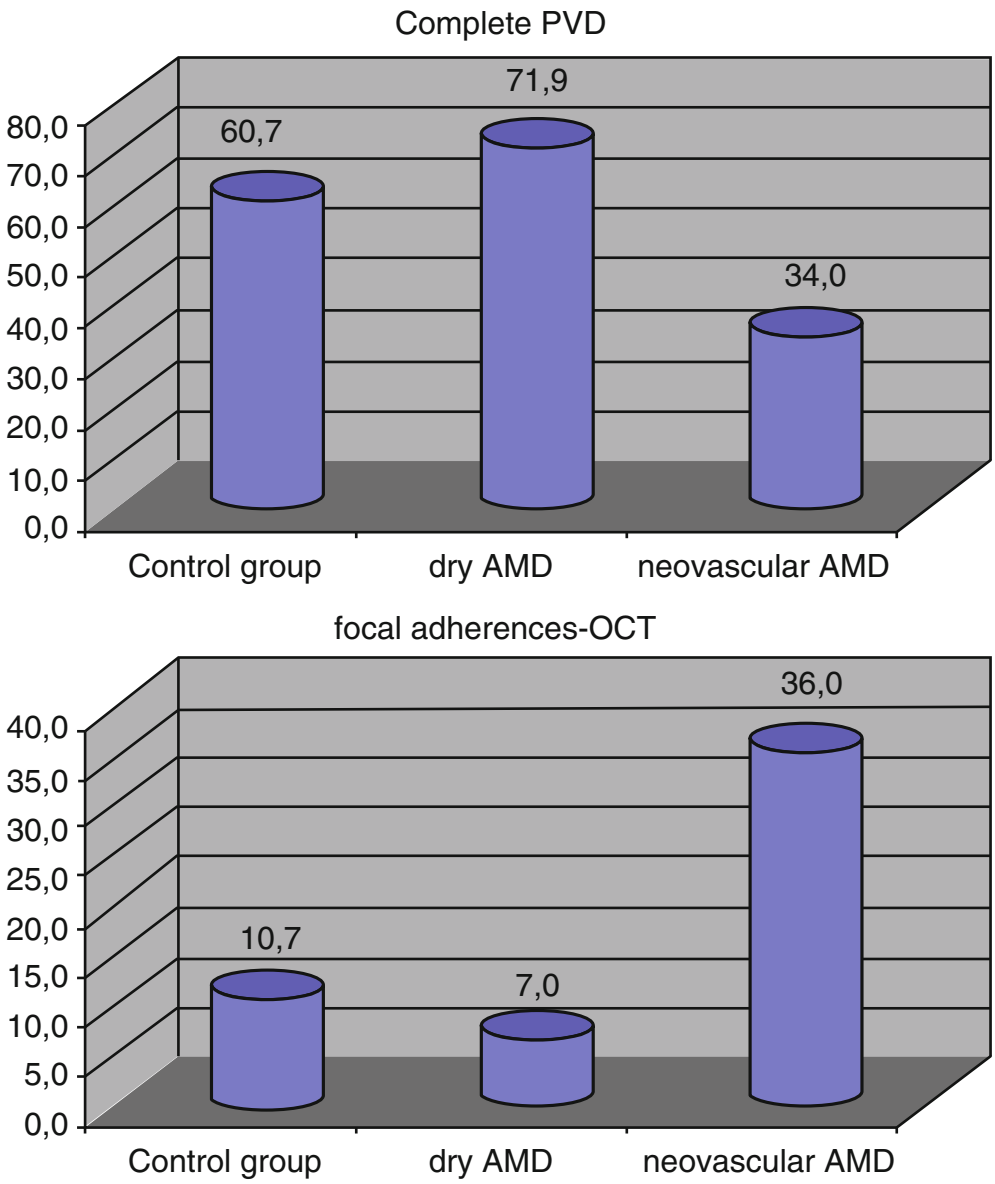

Figure III.G-1 The plots in the upper part show the incidence of complete PVD (significantly higher in dry AMD and controls than in neovascular AMD, and in the lower part the plots show that the incidence of localized adherences of the posterior vitreous is significantly higher in neovascular AMD than in the other groups

Director of the VMR Institute in Huntington Beach and Lawrence Yanuzzi's group in New York [6]. This study included 39 patients with exudative AMD in one eye and nonexudative AMD in the fellow eye. Eyes with active exudative AMD confirmed the results of the PVD in AMD study, as they had significantly less frequent PVD ($p = 0.002$) and more frequent vitreo-macular adhesion ($p = 0.008$). When including only eyes with end-stage exudative AMD, PVD was more frequent in exudative AMD, but failed to be significant. To exclude another possible factor, which might have influenced the incidence of PVD, the status of the lens was evaluated. However, the number of pseudophakic eyes was not significantly different between the groups.

A Korean group headed by Sung Jun Lee retrospectively analyzed the records of 251 patients with unilateral exudative AMD [7]. This study was based on Stratus OCT, and therefore only the status of the vitreo-macular interface was evaluated. Vitreo-macular adhesions were found in 22.3 % of the patients: 18.7 % in eyes with exudative AMD, only 2.4 % in fellow eyes, and 1.2 % in both eyes. In comparison to the data of the PVD in AMD study, vitreo-macular adherences were found less frequently in the Korean study. However, they were present almost exclusively in eyes with neovascular AMD (83 %). Including a larger number of patients, classification of the lesions was possible: classic lesions in 38 % and occult lesions in 62 % of the vitreo-macular adhesion group, and in 38.3 and 61.7 %, respectively, in the eyes without vitreo-macular adhesions. Furthermore, the localization of the choroidal neovascularization did not reveal any influence on the presence of vitreo-macular adherences.

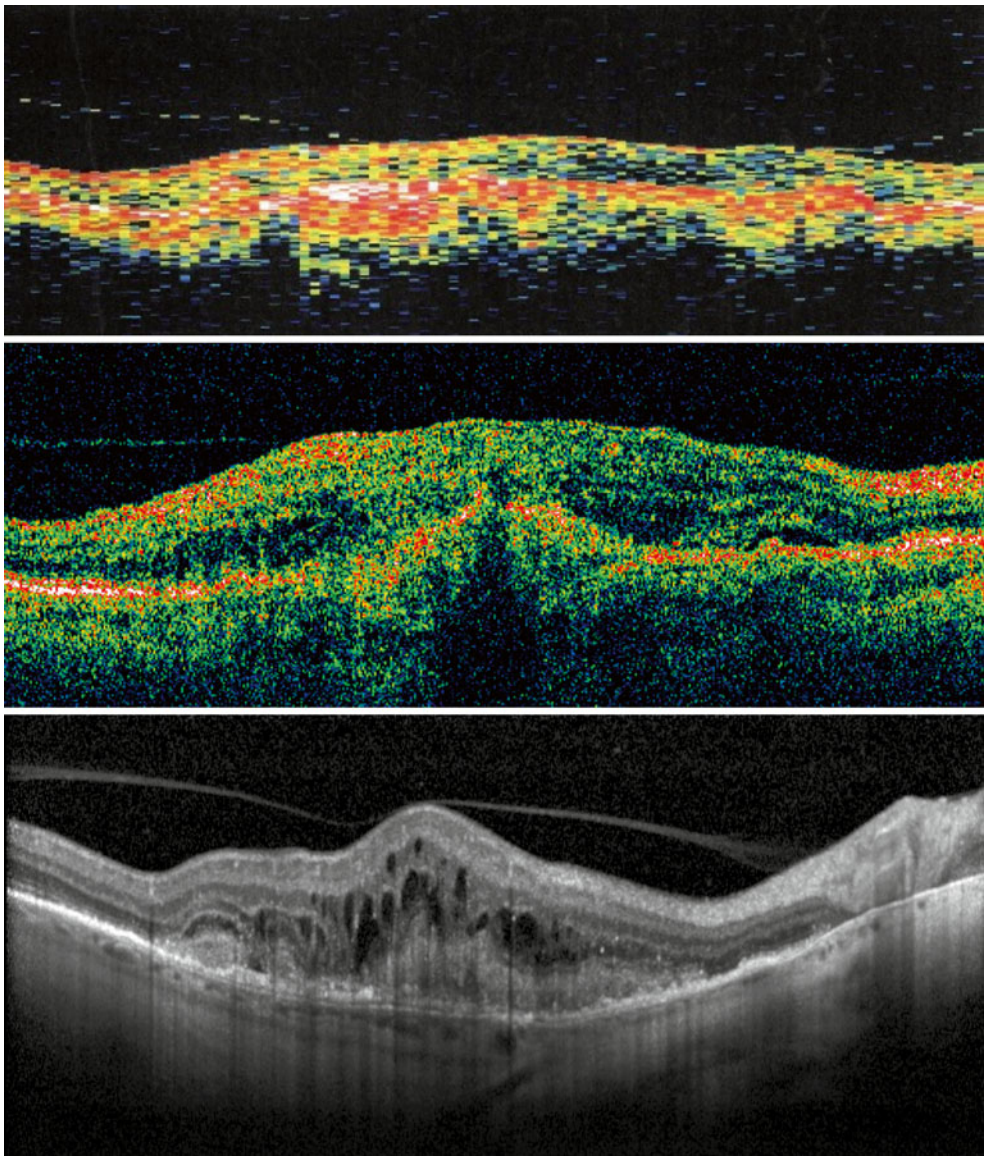

Figure III.G-2 Comparison of different generations of OCT. *First line*: OCT of the first generation; *Second line*: time domain OCT (Stratus OCT); *Third line*: spectral domain OCT (Spectralis OCT)

III. Morphology of Vitreo-Macular Adhesion in AMD

A. Imaging

As previously mentioned, ultrasound is indispensible in diagnosing PVD. Resolution of structure at the vitreo-macular interface, however, is not very good. Our understanding of the morphology of the vitreo-macular interface in AMD has benefited greatly from OCT imaging. Spectral domain imaging technology has several advantages compared to time domain OCT. In addition to enhancing resolution, the increased scan velocity considerably improved the evaluation of AMD cases. In Stratus OCT, only 6 (most frequently radial) lines were possible, and in SD OCT, the posterior pole is scanned by a raster of parallel lines. Different machines are on the market, all of them offering higher resolution and increased scan density. We have our own experiences with two of these machines, the Cirrus OCT (Carl Zeiss Meditec, Dublin, California) and the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), both offering special advantages. The Cirrus OCT provides 128 raster scans of very good quality within seconds. The built-in software offers among other tools retinal thickness maps, tissue layer images of the inner limiting membrane, and the retinal pigment epithelium. Furthermore, slabs of different height can be determined. The most prominent advantage of the Spectralis OCT is the eye tracker. A second light source provides that the images are recorded on the correct place and on identical locations in repeated examinations. The course of changes over time of retinal pathologies (such as vitreo-macular adhesions) can therefore be visualized more accurately. Averaging of up to 100 identical scans provides extremely high-quality single scans almost without any disturbing noise. The single scans can be recorded with a length of 8 mm, giving the possibility to record the fovea and the rim of the optic disc in one scan. Figure III.G-2

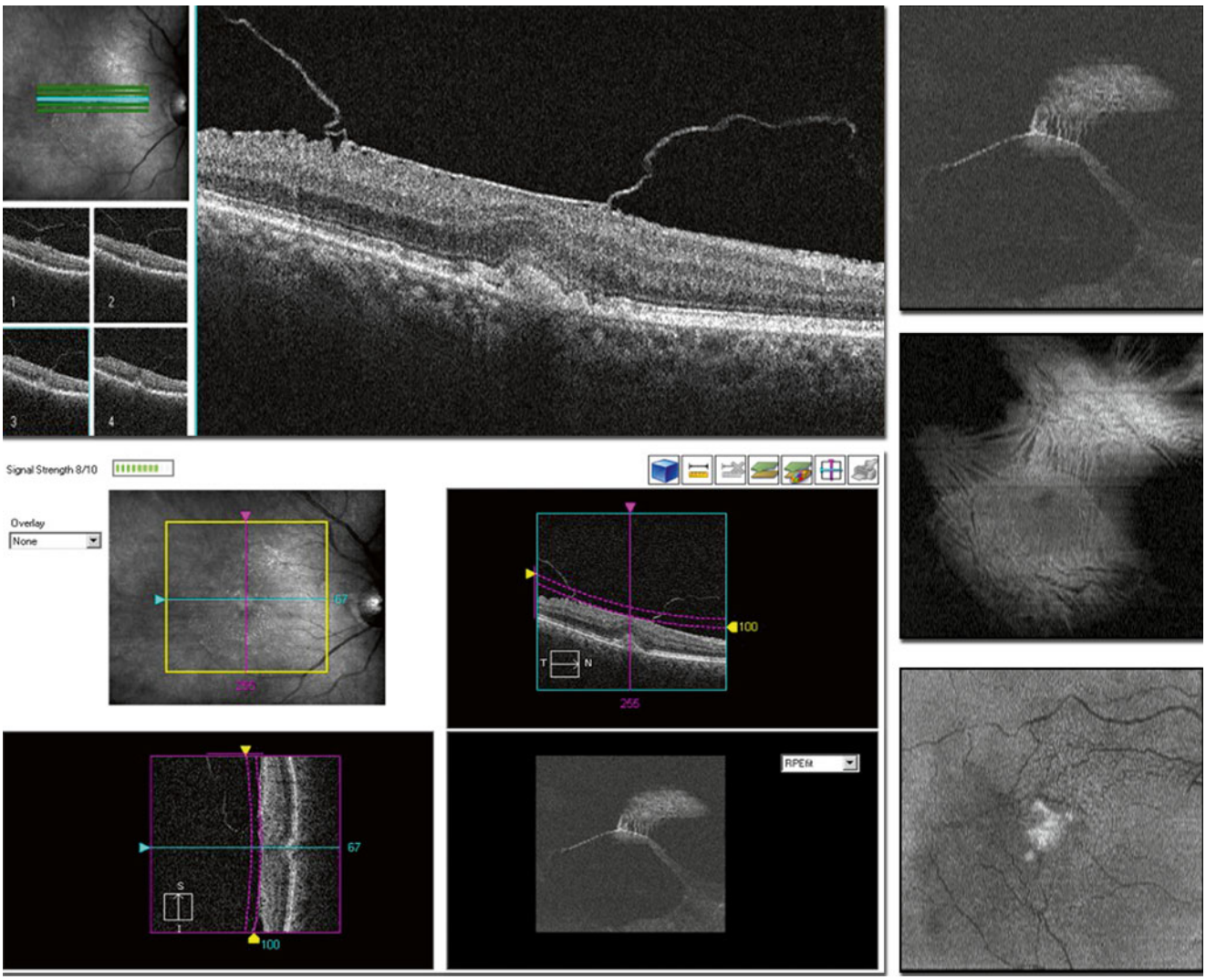

Figure III.G-3 Instrument OCT review. Review of OCT data directly on the instrument (Carl Zeiss Meditec® HD-OCT™). *Top left*: B-mode scan review. *Bottom and right*: Virtual C-mode scan review using an RPE-fit slab set at 10 µ which is slowly moved from *top to bottom* showing the three-dimensional structure of the lesion as well as the correlation between vitreo-retinal traction and the choroidal neovascularization

presents images of a neovascular AMD case recorded with 3 generations of OCT (see below and chapter III.E. Vitreo-papillary Adhesion and Traction].

1. Three-Dimensional OCT

When ascertaining the relationship between choroidal neovascularization and vitreo-retinal adhesion/traction, it is important to understand the three-dimensional structures of the traction as they relate to the location of the neovascularization. It is also necessary to be able to visualize subtle structures of the vitreo-retinal interface. This can be done in several ways. First of all, it is possible to manually scrub through the B-mode scans of a data set in order to find anatomical relationships (Figure III.G-3, Videos III.G-1 and III.G-2). This is time consuming and difficult. Secondly, it is possible to create virtual C-mode scans. On the Cirrus HD™ OCT, this is achieved by creating an RPE-fit slab of approximately 100 micron thickness and slowly scrubbing through the virtual C-mode scans in the *Z*-axis (Figure III.G-3, Videos III.G-1 and III.G-2). This can be very helpful, but is also time consuming and difficult. With both these methods, it is difficult to mentally visualize the three-dimensional correlations between the different areas of the lesions. The third method would be to use three-dimensional visualization. This method is hardly used either clinically or for research purposes because the three-dimensional rendering systems available on commercial OCT equipment do not visualize the data in a useful way as they lack ray-traced shading. This leads to very washed-out, indistinct structures, especially when looking at subtle and small structures of the vitreo-retinal interface. Additionally, structures above the interface inside the vitreous itself tend to be lost due to bad signal-to-noise ratio as the conventional noise reduction algorithms such as tracked averaging are prohibitively time consuming when dealing with large data sets. In order to have a viable method of analyzing these structures, new three-dimensional visualization systems needed to be developed.

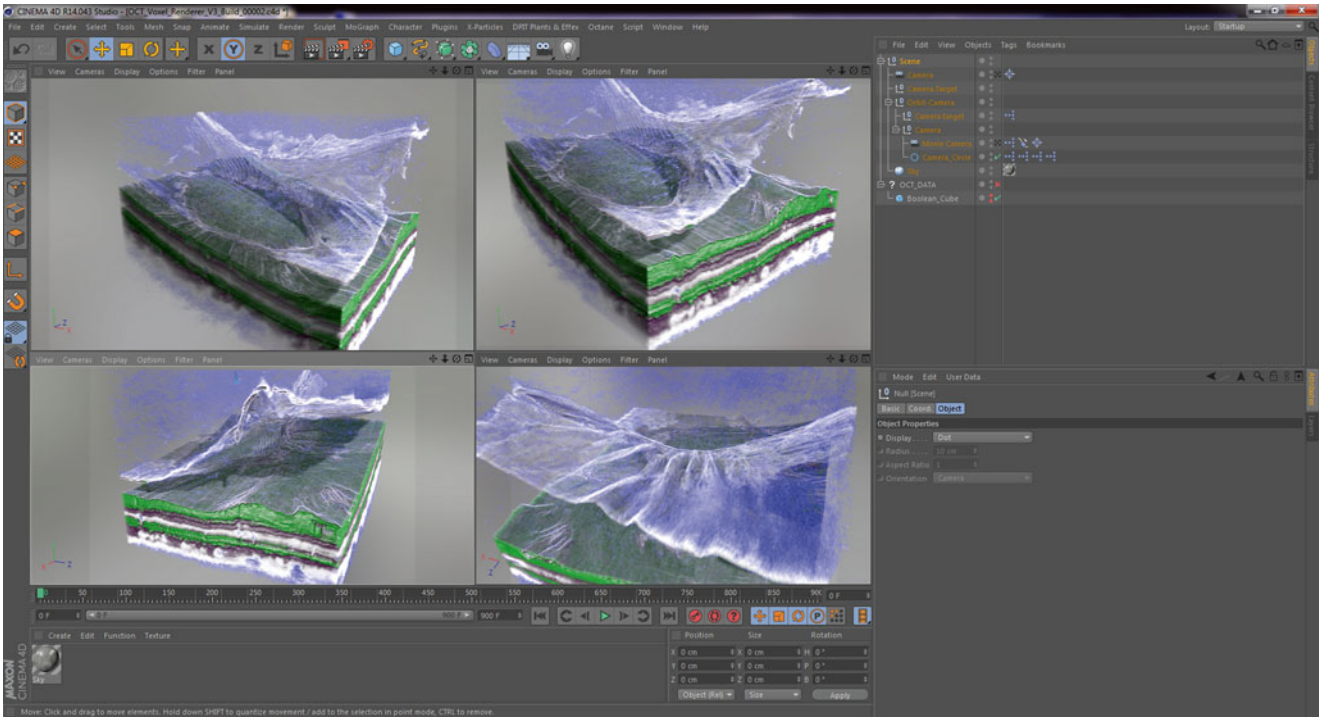

Figure III.G-4 3D voxel-based OCT rendering. Voxel-based 3D visualization of OCT data using a custom-built plug-in for Maxon® Cinema 4D™. This real-time *screenshot* of the interface shows how the visualization utilizes ray-traced shading to achieve an increased contrast which in turn results in an increased visibility of the vitreous traction forces

With the goal of enhancing the clarity of subtle structures of the vitreo-retinal interface, two different 3D visualization systems were designed, each having different strengths and weaknesses. Both of them employ ray-traced shading which enhances small structures by throwing a shadow from the light source or light sources onto the data behind or below the illuminated structure, making the structure stand out from its surroundings and thereby increasing the contrast of the visualization. The first system (Figure III.G-4, Videos III.G-3 and III.G-4) is voxel based and has the advantage of being usable on almost any computer graphics card (including conventional laptop graphics cards). It also has relatively low preprocessing time and can if necessary use unprocessed raw data directly from the Cirrus OCT™. Additionally, the look-up table range and values can be interactively adjusted during visualization in order to adjust the coloring to specific data sets. The disadvantage is that the visualization becomes diffuse at extreme zoom levels. The second system (Figure III.G-5, Videos III.G-5, III.G-6, and III.G-7) is based on triangle-mesh representation of the data. This requires full nonplanar segmentation of the data, and a large amount of preprocessing is therefore necessary. A second drawback with this method is that it can only be rendered on CUDA (*Compute Unified Device Architecture*)-based graphics cards. This limits the usability of the system to computers running Nvidia™ graphics processor units (GPU). Although the examples shown in this chapter are created from Cirrus HD™ data sets, any OCT data that has a dense enough scan pattern of approximately 50 micron or less between each B-mode scan, can be used for this type of visualization system.

In order to achieve the first, voxel-based, visualization system (Figure III.G-4), the raw OCT data sets (512×128 macular cube or 200×200 macular cubes) are exported to ImageJ™ in which they are converted into a file format readable by imaging and rendering programs. As the raw data sets we were using did not contain Z-alignment, this had to be added in postprocessing. The data was imported into Adobe After Effects™ where Z-alignment and noise reduction were performed (Figure III.G-6). The noise reduction was based on a temporal filter, which samples empty noise over several frames and removes an averaged noise from the entire set. This increases the signal-to-noise ratio in the vitreous significantly without affecting the detail of actual structure, as this is not averaged (Figure III.G-6). This noise-corrected data is imported into Cinema 4D™ and rendered using a custom-made plug-in which renders the data as voxels with ray-traced shading and a single customizable light source direction.

The second, triangle-mesh-based visualization system (Figure III.G-5) gathers and preprocesses the data similarly to the first method, but before the data is exported to Cinema

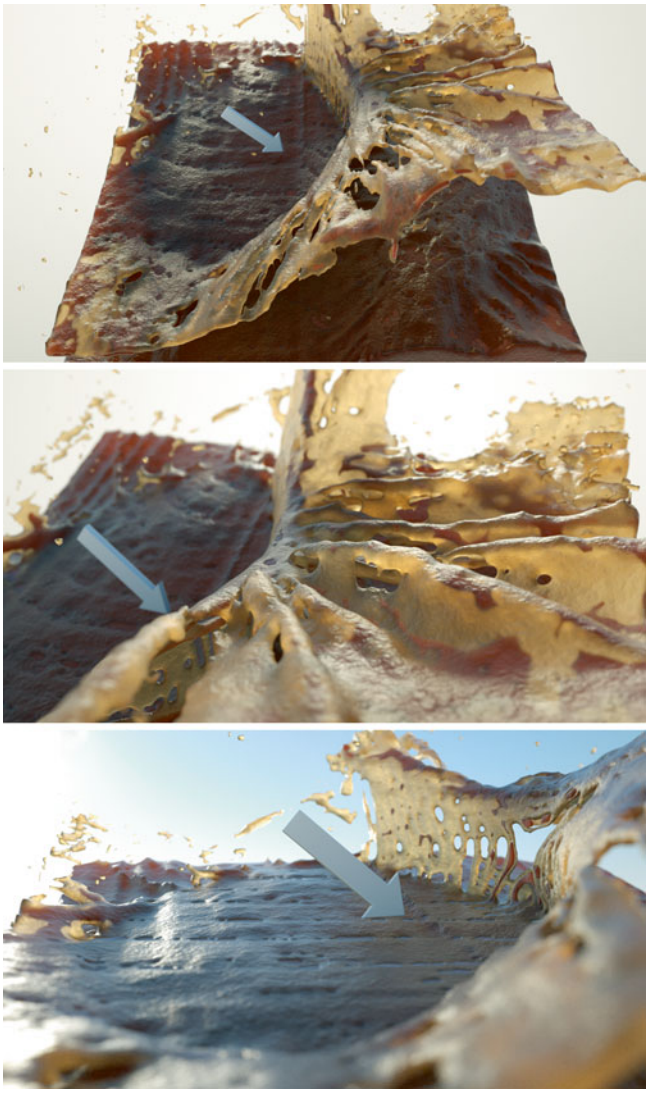

Figure III.G-5 3D mesh-based OCT rendering. Graphics processor (CUDA) based real-time visualization of triangle-meshed OCT data from within Maxon® Cinema 4d™ using the Otoy® Octane Render™. Clearly visible are the traction force lines which orient to a point on the adhesion (*arrow*) under which the choroidal neovascularization is located

4D™, it is converted into intensity range threshold-based particle clouds in Realflow™ (Figure III.G-6). These particle clouds are used to create triangle meshes of the retinal structures corresponding to the intensity ranges. These meshes are exported to Cinema 4D™ and rendered using a CUDA GPU. The benefit in rendering over the CUDA GPU instead of the central processing unit (CPU) on the computer's motherboard is the possibility of accessing its massive parallel computing capabilities. This means that instead of the 8 computing cores that a traditional computer chip accesses, GPU-based computing can access 1024 CUDA cores simultaneously on a single graphics chip. If two graphics chips are used in parallel, the number of cores accessed increases to 2048. This leads to an exponential increase in the computing speed. This rendering speed increase makes photorealistic rendering in real-time possible. It is even possible to render using multiple freely configurable light sources as well as HDRI (high dynamic range image)-based lighting and automatic depth of field (DOF). The photorealistic rendering and full control of lighting and shading in real time make it possible to visualize very small and subtle structures at the vitreo-retinal interface.

These two methods are very helpful in a research situation, but at this time are too cumbersome to be used effectively in a clinical setting. The transfer of data between the different postprocessing programs needs to be automated. The Z-alignment, noise reduction and the point cloud segmentation need to be moved away from CPU computing towards GPU computing in order to increase processing speed. As computing technology improves this type of data visualization will become an important aid in understanding the three-dimensional relationships between vitreous and age-related macular degeneration. Videos showing the different visualization methods as well as several clinical examples are accessible in the online section of this book.

B. Vitreo-Macular Adhesion

Focal adherences of the posterior vitreous to the anterior retina surrounded by a shallow vitreous detachment were identified even by time domain OCT. More posterior in the same scans were morphological changes due to neovascular AMD, like fusiform thickening of the retinal pigment epithelium/choriocapillaris band, detachment of the retinal pigment epithelium, and intra- or subretinal fluid. Therefore, correlations between the localization of adherences and the neovascular complex were determined. Simultaneously recorded video images in Cirrus OCT (in Stratus OCT, the video images were taken at the end of the examination) or even more accurate in Spectralis OCT (due to the eye tracker) allowed for exact localization of the changes on the retinal surface and at the retinal pigment epithelium within the posterior pole. However, the correlation between the localization of adherences and neovascular complex in 100 % was confirmed with the help of SD-OCT presented in Figure III.G-7 [8]. Of the CNV lesions with vitreo-macular adherences, adhesions were located in the fovea in 43.3 % and juxtafoveally in 56.7 %. The high incidence of juxtafoveal adhesions may be related to the high percentage of lesions with retinal angiomatous proliferation (88 % of the juxtafoveal lesions). This type of neovascular lesion begins characteristically juxta- or extrafoveally. Whether it does so by proliferation of retinal capillaries or by choroidal vessel

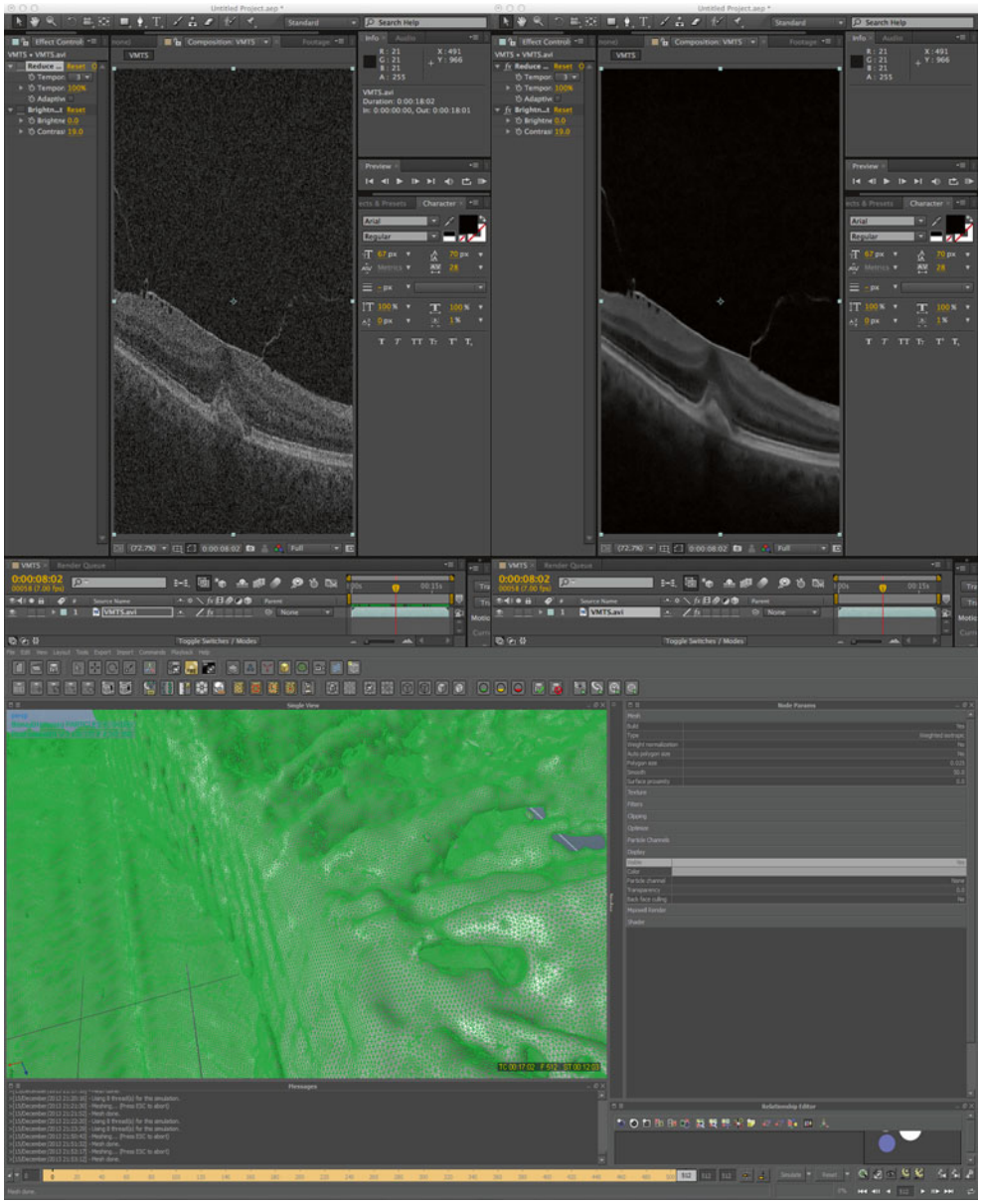

Figure III.G-6 Preprocessing for 3D visualization. *Top*: Adobe® After Effects™ Z-alignment and temporal noise reduction. *Bottom*: Nextlimit® Realflow™ particle cloud formation and triangle meshing

penetration through Bruch's membrane and retinal pigment epithelium is still under discussion [9–11]. The juxtafoveal position of vitreo-macular adhesion in RAP lesions further confirms the correlation between the origin of the neovascularization and the adhesion of the posterior vitreous cortex. In early lesions, this correlation can be demonstrated very well, especially in the 3D animations (Videos III.G-1, III.G-3, III.G-4, III.G-5, and III.G-6). Visualization of the retina in slabs of 100 µm height shows very well the area of adhesion and corresponding neovascularization in the deeper layers. In more advanced lesions, the size of the adhesion is usually smaller than the size of the entire lesion, and the distance of the center of the adhesion and of the neovascular lesion correlates very well as was reported by Mojana et al. [12]. The course of a vitreomacular adhesion over time is presented in Figure III.G-8.

1. Adhesion Versus Traction

Initial studies (PVD in AMD study (see above) and others) were conducted using time domain (Stratus) OCT evaluations that were able to identify vitreo-macular adhesion. However, differentiating between adhesion and traction was not possible without doubt, although traction was suspected in a high percentage of the cases. Sharp angulation of the posterior vitreous cortex present at the site of adhesion or a localized deformation of the retinal profile indicating traction could be detected definitively only with the help of spectral domain imaging. The incidence of vitreo-macular traction was 73.3 % in eyes with neovascular AMD presenting with vitreo-macular adhesion [8]. With the help of 3D animated images, traction lines could be visualized as directed towards the neovascularization. In early lesions with small neovascular membranes, it was even more obvious that

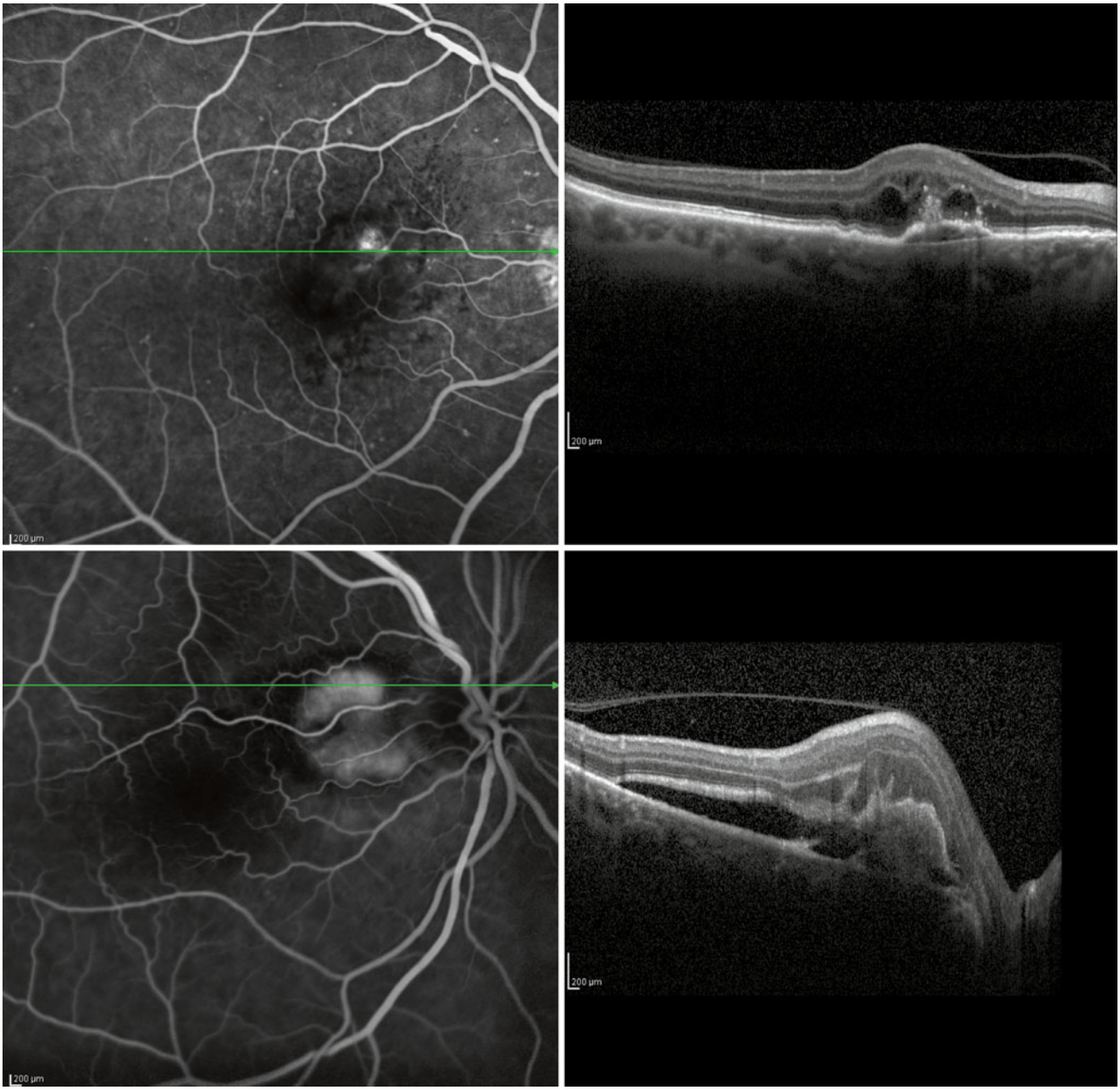

Figure III.G-7 The localization of the vitreo-macular adhesion corresponds to the localization of the choroidal neovascularization even in cases with juxta- or extrafoveal location. In the *upper panel*, a lesion with retinal angiomatous proliferation localized in the supero-nasal fovea is presented, and in the *lower panel*, a juxtapapillary lesion is shown

the traction forces were directed to the origin of the neovascular membrane. These results of our own studies and examinations were confirmed also by Mojana et al., who found an incidence of traction in 60 % of the cases with vitreo-macular adherences [12].

C. Vitreopapillary Adhesion/Traction

Vitreo-papillary adhesion (VPA) has been shown to be present in 87.5 % of full-thickness macular holes and 80 % of macular pucker cases with intraretinal cysts [13, 14]. Based on these studies, it was proposed that VPA alters the vector of vitreo-macular traction forces inducing macular holes and tractional cystoid spaces [see chapter III.E. Vitreo-papillary adhesion and traction]. This might also be a factor in the pathogenesis of exudative AMD. Indeed, in AMD studies, the use of Spectralis OCT has enabled observation of the foveal region and the rim of the optic disk in one single 8 mm scan of high quality in clinical practice. In a retrospective study of exudative AMD, vitreo-papillary adhesion was identified in 83 % of the cases with

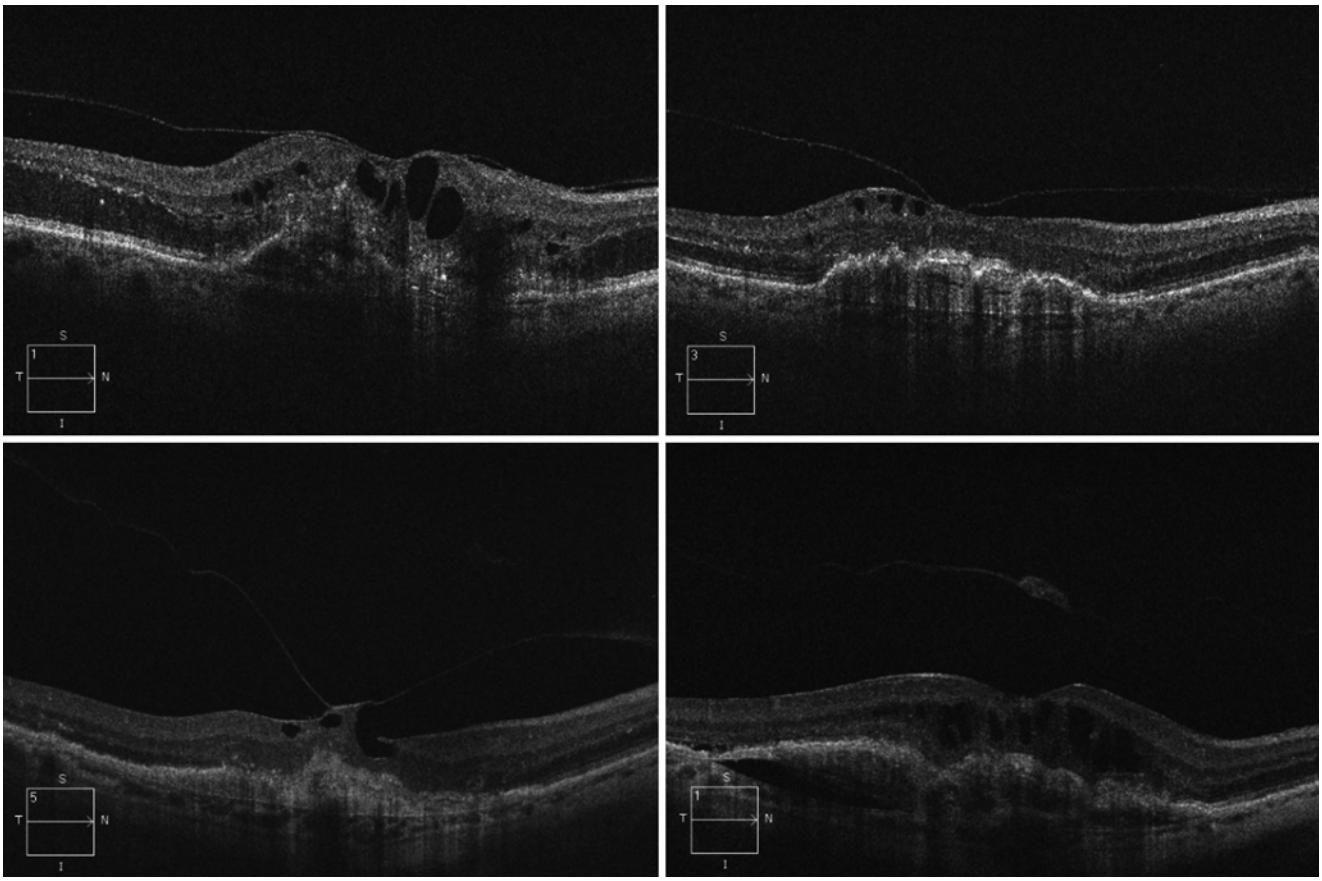

Figure III.G-8 The course of a very tight adherence is presented. At baseline (*upper left*), the vitreo-macular adhesion is broad; at month 6 (*upper right*), it is more localized; after 2 years, traction is obvious with incipient macular hole; and 6 months later, the pseudo-operculum and the detached posterior vitreous cortex are seen

vitreo-macular adhesion [8]. In the remaining 17 %, the scans failed to show the optic disk in spite of the length of the scan. However, vitreo-papillary adhesions were also detected in the PVD in AMD study with Stratus OCT in nearly 60 % of the eyes with vitreo-macular adhesion, because radial lines through the optic disk were part of the study protocol (unpublished data). Obviously, the focal adherences in AMD cases are in the areas where vitreous is naturally more firmly attached, such as the optic disc and fovea. Vitreo-papillary traction is known to be present also in other diagnoses like proliferative diabetic vitreo-retinopathy and macular hole [13, 14]. In diabetic cases, it has been demonstrated that vitreo-papillary traction can cause possibly reversible damage to the anterior optic nerve combined with a decrease of distance acuity [see chapter III.L. Proliferative diabetic vitreo-retinopathy]. Whether vitreo-papillary adhesion might contribute to a worse outcome of cases of AMD with vitreo-macular adhesion/traction has to be further explored.

1. Vitreoschisis

Anomalous PVD in exudative AMD may not only manifest as vitreo-macular and vitreo-papillary adhesions but also as vitreoschisis, a split of the posterior vitreous cortex [15, 16]. While the incidence of vitreoschisis in AMD is not as high as vitreo-macular adhesion/traction, only 8 % in exudative AMD [8], there was more frequent vitreoschisis in cases of combined vitreo-papillary and vitreo-macular adhesion where a second layer was noted only adherent at the optic disk. Figure III.G-9 demonstrates splitting of the posterior vitreous. Like vitreo-papillary traction, vitreoschisis is apparent also in other cases associated with anomalous PVD like macular hole, macular pucker, or proliferative diabetic vitreo-retinopathy [see chapter III.B. Anomalous PVD and vitreoschisis].

IV. Role of Vitreous in Conversion from Dry to Exudative AMD

The AREDS study defined the risk of dry AMD cases converting to either geographic atrophy or choroidal neovascularization based on the number and size of drusen and the presence of pigment changes. In the PVD in AMD study (see above), the dry AMD cases were classified according to the AREDS classification [17, 18]. We found

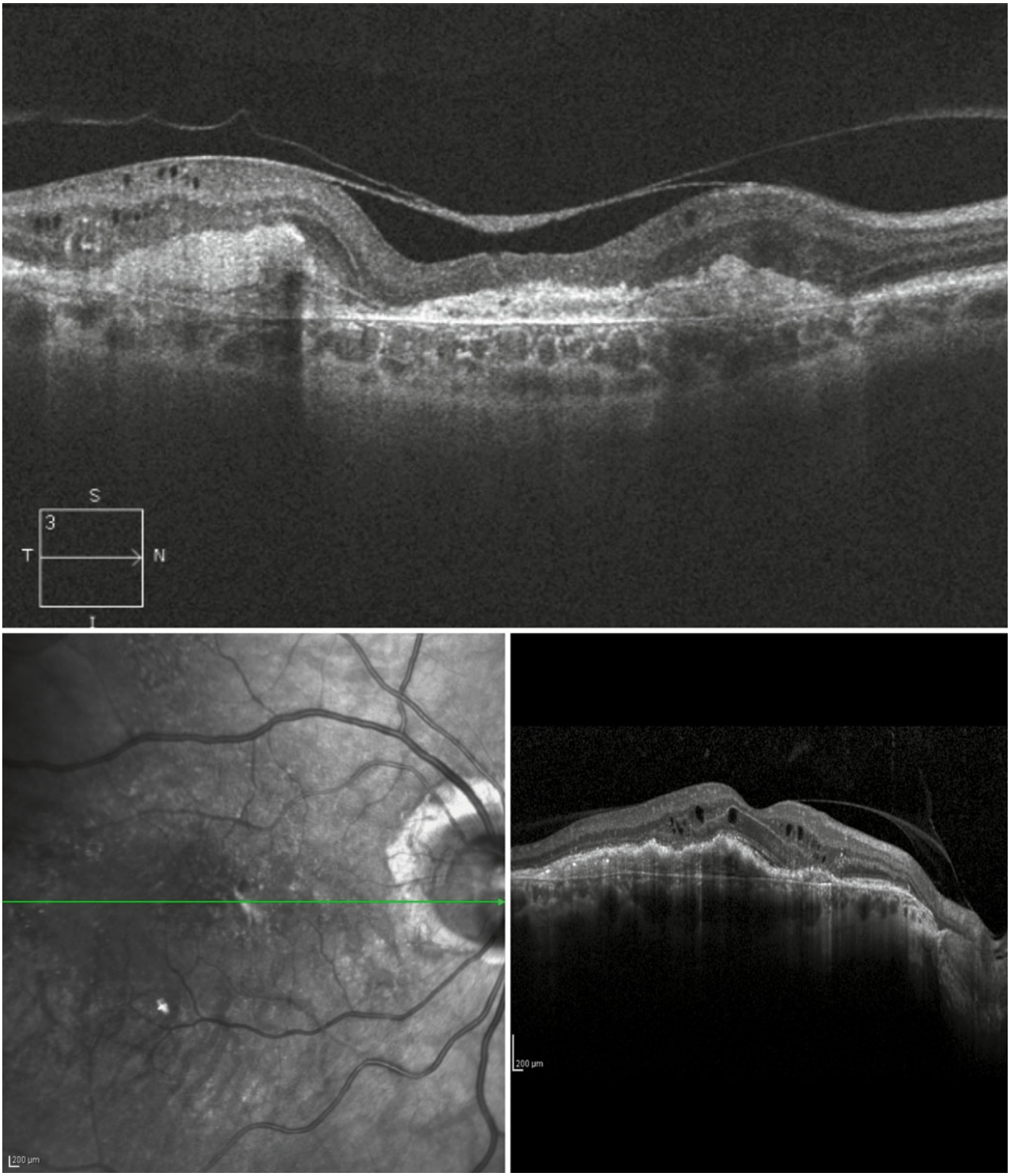

Figure III.G-9 In AMD cases, the posterior vitreous cortex is frequently not a single membrane, but vitreoschisis occurs frequently (in the *upper image* in the foveal region, in the *lower image* peripapillary)

a significant correlation between the AREDS risk to develop CNV in dry AMD and an attached posterior vitreous (odds ratio = 0.065, 95 %-CI for odds ratio = [0.012, 0.362], *p*-value = 0.00178). Six of 57 eyes (10.5 %) with dry AMD developed exudative AMD (3 eyes AREDS III, 1 eye AREDS II, 2 eyes AREDS I), and after 2 years, in five of these six eyes, the vitreous was attached (extension of the PVD in AMD study) [5]. Central adhesion sur-

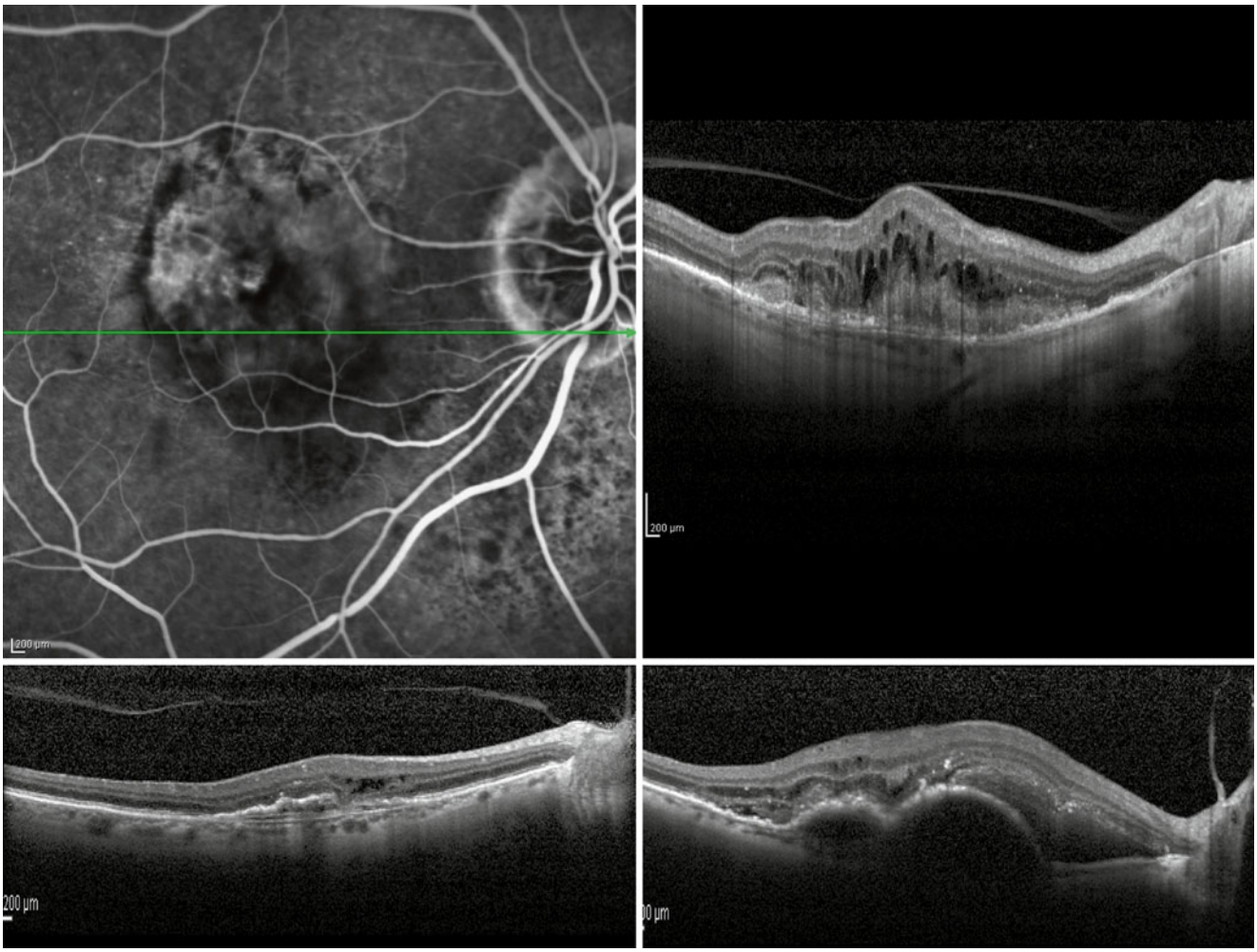

Figure III.G-10 Different stages of vitreo-macular and vitreo-papillary adherences are presented. In the *upper image*, foveal and papillary adherences are shown, and in the *lower images*, only vitreo-papillary adhesions are visible in the foveal region since the vitreous is already detached

rounded by elevation of the posterior vitreous cortex on OCT was more frequent in high-risk nonexudative AMD though not significant (p-value = 0.670).

In a prospective study conducted at the Medical University of Vienna, the risk to develop exudative AMD in high-risk dry AMD cases was examined. This study was based on SD OCT findings only and did not find a significant influence of vitreo-macular adhesions to develop choroidal neovascularization within a 4-year observation period [19]. However, ultrasound examinations were not performed, and to evaluate the influence of vitreo-macular adhesions, the number of participants was not high enough. We therefore initiated a prospective study to evaluate the risk of developing neovascular AMD in dry AMD cases and calculated that a study population of 320 is mandatory. At present, the results of this study are not yet available.

V. Impact of Vitreous on Treatment of Exudative AMD

A. Spontaneous PVD

In our studies of vitreo-macular adhesion/traction (see above), the status of the posterior vitreous remained unchanged in the majority of eyes (76.7 %) up to 1 year later, in spite of anti-VEGF treatment [8]. In 10 %, a PVD occurred with release of vitreo-macular adhesion. Figure III.G-11 shows the impact of posterior vitreous on the course of the disease in three examples. This was associated with an increase in visual acuity and regression of the neovascular lesion. In contrast, an incidence of nearly 25 % of PVD was found within three months of intravitreal injections for various other conditions (including AMD). The impact on the activity of the disease and the visual acuity are not available [20].

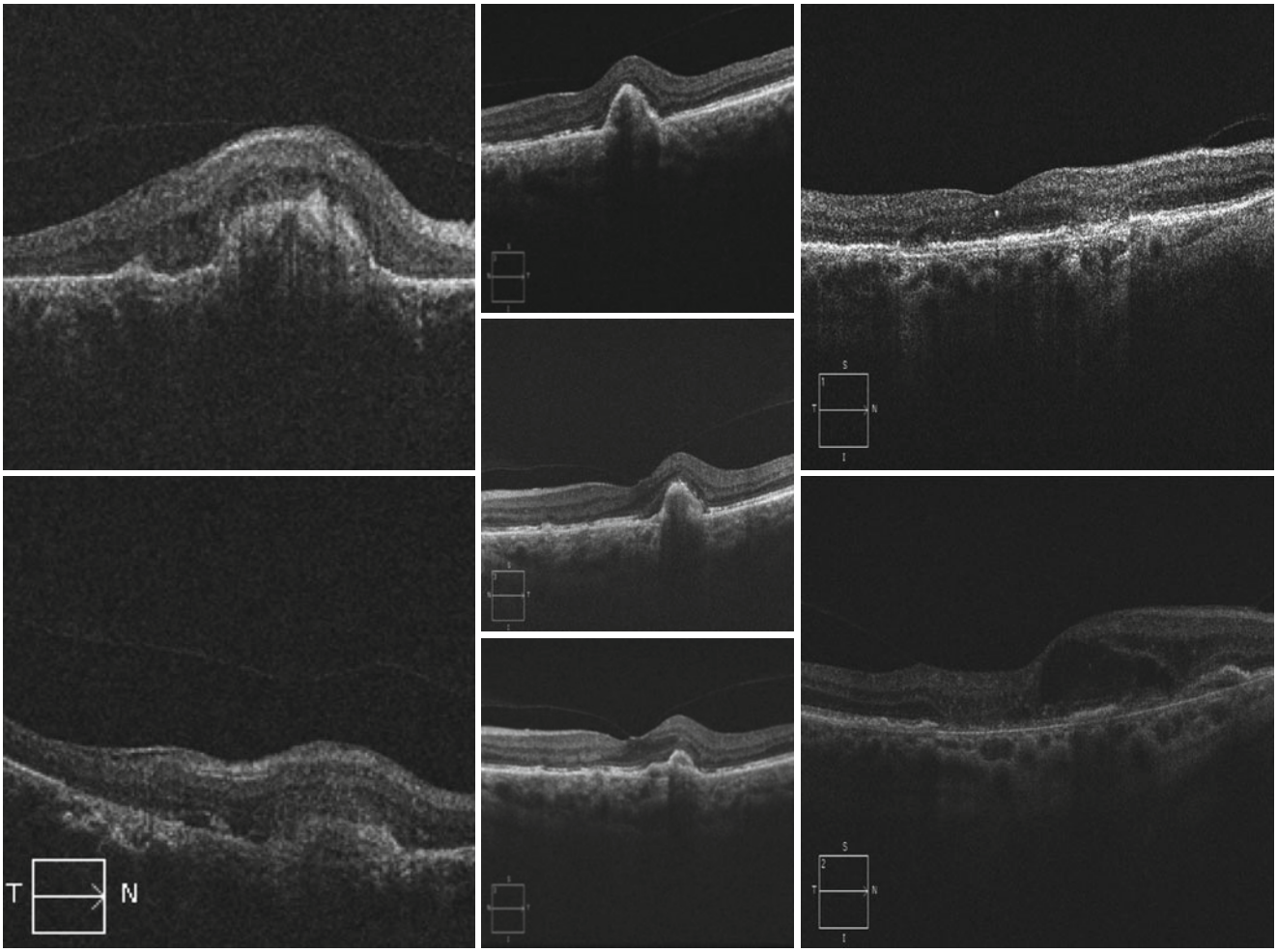

Figure III.G-11 The course of vitreo-retinal adherences in relation to anti-VEGF treatment is shown. At the *left side*, spontaneous vitreous detachment occurred, and distance visual acuity improved by two lines. In the *middle*, the adherences remained unchanged, and distance visual acuity improved by one line. At the *right*, vitreo-macular traction increased, and distance visual acuity decreased by four lines

B. Nonresponders

Modern therapy of neovascular AMD consists of intravitreal injection of inhibitors of vascular endothelial growth factor (VEGF). Pegaptanib (Macugen) and ranibizumab (Lucentis) are approved for the therapy of exudative AMD. A third substance bevacizumab (Avastin) is frequently used off-label for treatment in the eye. The effect of Avastin has been shown in comparative studies to be non-inferior to Lucentis [21–23]. Macugen, the first substance approved, provided less favorable results. Whereas the effect of these substances was the subject of many publications, there is little information concerning nonresponders in the literature.

In a retrospective evaluation of 287 patients who completed a 12-month examination, we evaluated distance acuity, retinal thickness measured with OCT, and lesion size at baseline, months 3 and 12. Usually there is a steep increase of distance acuity and decrease of retinal thickness in the first 3 months of therapy, and thereafter the success is maintained. Therefore, we evaluated the cases at month 3 and declared patients exhibiting a loss of ≥3 lines distance acuity and/or an increase of retinal thickness and/or lesion size as nonresponders. Vitreo-macular adhesion was present in 12.94 % of responders and 29.17 % of nonresponders. Besides distance acuity at baseline, vitreo-macular adhesion was the only factor significantly associated with nonresponders. Demographic data, the presence of blood, fibrosis, and the type lesion did not reveal a significant influence. Delayed response occurred overall in only 10 %. One of these cases was an eye with vitreo-macular adherence, which exhibited a spontaneous PVD [24]. Another study compared the outcome of anti-VEGF therapy of eyes with and without vitreo-macular adhesions and found a significantly better outcome of lesions without adherences [25]. A possible bias by including lesions of different composition could not be excluded in this study, because lesion type and composition were not evaluated.

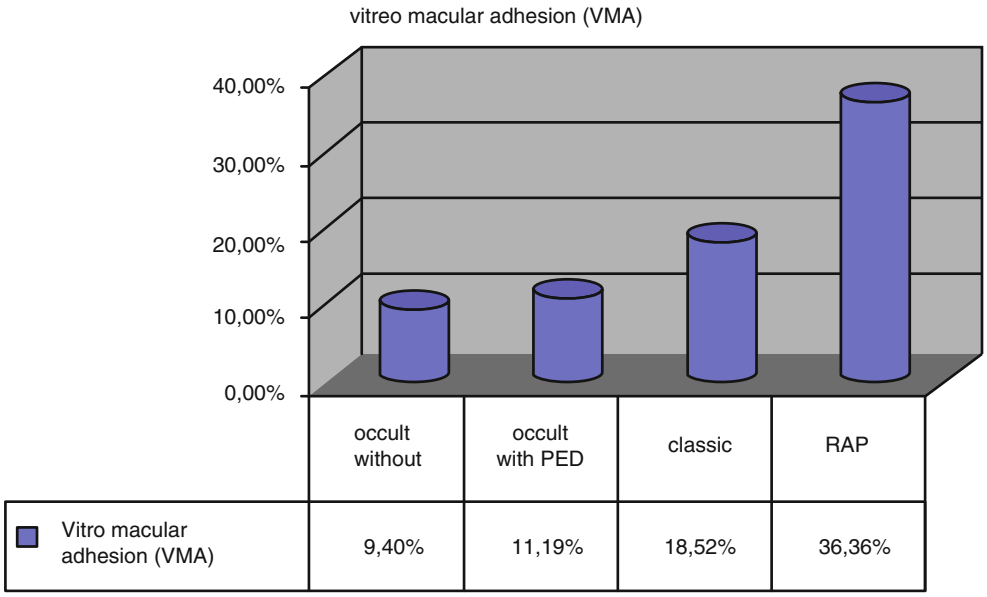

Figure III.G-12 The incidence of vitreo-macular adhesion was higher in classic lesions and especially in lesions with retinal angiomatous proliferation

There are different hypotheses, why lesions with vitreo-macular adhesion might have a worse response to therapy. Mechanical traction during eye movements may potentiate low-grade inflammation [26, 27]. Another possible explanation is the persistence of retinal edema due to traction on the retina. Since retinal edema promotes hypoxia and hypoxia causes VEGF production, it might explain the nonresponse in these cases. It is also plausible that vitreo-macular adhesion/traction prevents flattening of the retinal pigment epithelium (RPE) in cases of RPE detachment or cause tears of the RPE, a feared complication of RPE detachment. Similar processes might be responsible for recurrences in eyes treated by photodynamic therapy exhibiting vitreo-macular adhesion/traction.

C. Polypoidal Choroidal Vasculopathy and Retinal Angiomatous Proliferation

Until recently, the only available therapies of exudative AMD were argon laser photocoagulation and photodynamic therapy. The success of these therapies was related much to the lesion type and composition. In modern anti-VEGF therapy, the lesion type does not play as important a role. However, in clinical practice, some lesion types, like polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP), are thought to have a worse outcome than other lesions [28, 29]. Concerning PCV, a higher incidence of PVD was found than in typical exudative AMD, and vitreo-macular adhesions tended to be more frequent in eyes without PCV. Therefore, worse outcome in eyes with PCV seems to be not associated with changes at the vitreo-macular interface [30]. In the nonresponder study, the incidence distribution of vitreo-macular adhesion was quite different between different lesion types. Occult lesions without and with detachment of the RPE had a low incidence of vitreo- macular adhesion (9.4 and 11.2 %, respectively). Vitreo-macular adhesion was more frequent in classic lesions (18.5 %) and most frequent in RAP lesions (36.4 %), results presented in Figure III.G-12. The incidence of nonresponders was higher in the RAP group, but did not reach statistical significance in contrast to the incidence of vitreo-macular adhesion. The association of RAP lesions and vitreo-macular adhesion was also seen in another of our studies where 50 % of the lesions with vitreo-macular adhesion were RAP lesions [8].

D. Vitrectomy

Further evidence of the important role of an adherent posterior vitreous in exudative AMD is provided by the influence of vitrectomy. There are two studies reporting a higher incidence of AMD (geographic atrophy and choroidal neovascularization) in non-vitrectomized eyes compared to the fellow eyes which underwent pars plana vitrectomy for different reasons other than AMD [31, 32]. The first experiences of the effect of vitrectomy on an already established neovascular AMD originate from as early as 2000 [33]. Regression of choroidal neovascularization was achieved in 6 of 12 cases with attached posterior vitreous and an active neovascular lesion. In a series of 54 eyes with vitreous hemorrhage and exudative AMD, regression of choroidal neovascularization was observed in 74 % following pars plana vitrectomy [34]. Furthermore, in eyes with unsuccessfully treated exudative AMD (PDT

or anti-VEGF) and vitreo-macular traction, vitrectomy and release of traction were accompanied by regression of the neovascular membrane, albeit in some cases only transient [12, 35, 36]. The favorable effect of pars plana vitrectomy is not only based on the mechanical removal of vitreo-macular adhesion/traction but also an increase of oxygenation after vitrectomy, verified in eyes with retinal vein occlusion and diabetic retinopathy [37, 38]. The better diffusion and availability of oxygen after vitrectomy have also been demonstrated in animals and also in humans [39] [see chapter IV.B. Oxygen in vitreo-retinal physiology and pathology].

E. Pharmacologic Vitreolysis

Pharmacologic vitreolysis is a term used for the intravitreal application of pharmacologic agents to induce posterior vitreous detachment (vitreo-retinal separation and vitreous liquefaction) [40, 41; see chapter VI.A. Pharmacologic vitreolysis]. Concerning age-related macular degeneration, results after pharmacologic vitreolysis are rare so far. In 4 of 4 eyes with vitreo-macular adhesion that were nonresponsive to anti-VEGF treatment, a PVD was achieved by intravitreal injection of 0.3 mL of 100 % perfluoropropane [42]. In nearly 70 % of 27 eyes, a PVD occurred after intravitreally applied tissue plasminogen activator, significantly more frequent than after intravitreal bevacizumab injection [43]. There are a series of studies ongoing using ocriplasmin in various diagnoses [44]. Combined therapy of intravitreally applied ocriplasmin and anti-VEGF might be favorable especially in nonresponders with an attached posterior vitreous cortex.

VI. The Putative Role of Vitreous in the Pathogenesis of AMD

Considering the importance of AMD, especially exudative AMD, there are understandably many studies that have been performed to identify the pathogenesis of this disease. Currently, a multifactorial etiology is suspected. A series of contributing factors have been identified, such as genetic, aging, and environmental factors [45]. Morphological changes at the vitreo-macular interface of exudative AMD, summarized as anomalous PVD, have been proven in a series of studies, but are still only associations. While the aforementioned findings regarding the impact of vitreous on AMD, especially therapy, are highly suggestive, these are not studies that prove causation. Possibly, anomalous PVD and neovascular AMD are caused by a third, up to now unknown, factor. It is also plausible that the developing neovascularization promotes vitreo-macular adhesion, possibly by localized inflammation or by exudation containing fibrin from new vessels [46]. Certainly, this might strengthen localized adherences between the posterior vitreous and the anterior retina. However, this theory cannot explain why normal age-related PVD did not occur before choroidal neovascularization developed. Furthermore, the size of the adherences is much smaller than the area occupied by the retinal or subretinal fluid exudation [12]. In our opinion, it is more plausible that an anomalous PVD influences the development and/or progression of exudative AMD, perhaps by traction, hypoxia, and/or low-grade inflammation.

A. Traction

Traction has been detected in more than 73 % of exudative AMD eyes with vitreo-macular adhesion [8]. 3D animation visualized the direction of the traction forces from the vitreous towards the retina more specifically towards the choroidal neovascular complex. In these cases, the traction forces are directed from anterior to posterior. But also in eyes with completely attached posterior vitreous, traction forces might be present between areas of loose or tighter adherences [26, 27]. During eye movements, tangential traction forces may act, further exaggerated by vitreo-papillary adhesion, as seen in other vitreo-maculopathies. This thesis is supported by cases presenting first with flat adherences and a more tangential vector of traction. In the course of the disease, the elevation of the posterior vitreous increases, and traction in an anterior posterior direction becomes more prominent [8].

Different pathogenic consequences of traction in the development of neovascular AMD can be imagined. When the anterior part of the retina is pulled apart, the hydrostatic pressure in the posterior retina decreases, and fluid and blood cells might enter the area of lower pressure leading to focal edema [26, 27, 47]. The same mechanism might also be responsible for the deceased responsiveness of neovascular lesions to treatment. Furthermore, the traction forces might cause chronic low-grade inflammation, further contributing to the neovascular stimulus. Lastly, the distortion of structures in the outer retina could prevent the normal supply of nutrients and oxygen (see below).

B. Low-Grade Inflammation

The traction forces might cause chronic low-grade inflammation. Even, when the traction is not yet visible by currently available imaging technologies, the steady stimulus caused by localized tighter vitreo-macular adhesion could be responsible for low-grade inflammation. The importance of inflammation in the development of neovascular AMD

was supported by histopathological examinations of excised neovascular membranes containing inflammatory cells [27]. The findings of examinations of the composition of drusen suggested that activation of the complement system and resultant release of inflammatory mediators play an important role in the etiology of exudative AMD. This was further supported by genetic studies especially of polymorphisms of the complement regulating factor H. The good response of neovascular lesions to anti-inflammatory therapy is additional evidence of the importance of inflammation [48].

C. Barrier Function

1. Hypoxia

Hypoxia is one of the most prominent drivers of angiogenesis and therefore promoters of exudative AMD. The outer two-thirds of the retina are supplied by oxygen and nutrients by the choroidal vasculature, the inner third by the retinal vessels. Oxygen diffuses through the structures of the outer retina and is consumed by the photoreceptors. The partial pressure of O_2 (PO_2) decreases almost linearly with distance from the choriocapillaris to the inner portion of the photoreceptors, where it reaches values of 0 [47]. Thickening of Bruch's membrane, large drusen, and detachment of the retinal pigment epithelium might all increase the distance between choriocapillaris and the photoreceptors and cause hypoxia at the level of the photoreceptors. Vitreous traction might cause localized ischemia and prevent support of the photoreceptors with oxygen. Furthermore, the attached posterior vitreous might prevent oxygen diffusion to the metabolically active cells. Due to the viscous nature of vitreous gel, diffusion of oxygen and other molecules is much slower than in saline solution. In cases of abnormal tissue at the vitreo-macular interface, inadequate diffusion of oxygen might occur comparable to inadequate diffusion through the thickened Bruch's membrane causing hypoxia.

Further support to the theory that the attached vitreous plays an important role concerning the diffusion of oxygen to the retina was provided by studies measuring the PO_2 before and after vitrectomy. They found an increased PO_2 after vitrectomy compared to values before vitrectomy preretinal and in the mid-vitreous cavity [35, 36]. Similar examinations were performed before and after pharmacologic vitreolysis with ocriplasmin in rats and guinea pigs [49]. After PVD, there were increased values of PO_2 compared to controls with attached vitreous as well as a faster increase of PO_2 after exposure of 100 % oxygen by face mask. Obviously, oxygen is distributed faster when vitreous is detached. Interestingly, the increase of PO_2 failed to appear when only liquefaction (by injection of hyaluronidase) of the vitreous occurred without syneresis and PVD.

2. Macular Cytokine Load

Vascular endothelial growth factor (VEGF) is an important angiogenic growth factor also causing hyperpermeability. It has been detected in excised neovascular membranes, and its importance in causing neovascularization in and beneath the macula and other locations in the eye and the whole body in vivo and in vitro has been proven [50, 51]. The production of VEGF and other growth factors is regulated by oxygen. Hypoxia increases the upregulation of VEGF, which causes neovascularization and retinal edema. Retinal edema increases the distance between choriocapillaris and photoreceptors and therefore also increases hypoxia, resulting in a vicious circle [47]. Posterior vitreous attachment can increase local levels of VEGF and cytokines by preventing egress anteriorly. Due to the large size of the VEGF molecule, diffusion might be considerably slowed by the high density of collagen in the posterior vitreous cortex. Vitreous detachment and also vitrectomy can facilitate a higher clearance rate of these substances from the macula [39]. Besides these physiological considerations, VEGF might also be bound by age-altered vitreous collagen fibrils in the posterior vitreous cortex.

Abbreviations

3D	Three-Dimensional
AMD	Age-Related Macular Degeneration
AREDS	Age-Related Eye Disease Study
CNV	Choroidal Neovascularization
CPU	Central Processing Unit
CUDA	Compute Unified Device Architecture
DOF	Depth of Field
GPU	Graphics Processor Units
HDRI	High Dynamic Range Image
mm	Millimeter
OCT	Optical Coherence Tomography
PCV	Polypoidal Choroidal Vasculopathy
PDT	Photodynamic Therapy
PO2	Partial Pressure of Oxygen
PVD	Posterior Vitreous Detachment
PVR	Proliferative Vitreo-Retinopathy
RAP	Retinal Angiomatous Proliferation
RPE	Retinal Pigment Epithelium
SD	Spectral Domain
US	Ultrasonography
VEGF	Vascular Endothelial Growth Factor
VPA	Vitreo-Papillary Adhesion
µm	Micron

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