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MAJOR REVIEW

Evaluation of Age-related Macular Degeneration With Optical Coherence Tomography

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Abstract. Age-related macular degeneration (AMD) is the leading cause of severe visual loss in people aged 50 years or older in the developed world. In recent years, major advances have been made in the treatment of AMD, with the introduction of anti-angiogenic agents, offering the first hope of significant visual recovery for patients with neovascular AMD. In line with these advances, a new imaging modality—optical coherence tomography (OCT)—has emerged as an essential adjunct for the diagnosis and monitoring of patients with AMD. The ability to accurately interpret OCT images is thus a prerequisite for both retina specialists and comprehensive ophthalmologists. Despite this, the relatively recent introduction of OCT and the absence of formal training, coupled with rapid evolution of the technology, may make such interpretation difficult. These problems are compounded by the phenotypically heterogeneous nature of AMD and its complex morphology as visualized using OCT. We address these issues by summarizing the current understanding of OCT image interpretation in patients with AMD and describe how OCT can best be applied in clinical practice. (**Surv Ophthalmol 57**:389–414, 2012. © 2012 Elsevier Inc. All rights reserved.)

Key words. age-related macular degeneration • choroidal neovascularization • cystoid macular edema • drusen • geographic atrophy • optical coherence tomography • pigment epithelium detachment • polypoidal choroidal vasculopathy • retinal angiomatous proliferation • subretinal fluid

I. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in people aged 50 years or older in the developed world.[21,180] Several groups have proposed classification systems of AMD.[16,24,41,129,239] We will follow the "International" classification system, though we recognize that classification systems are likely to continue to evolve as new technologies emerge.[16] The clinical hallmark of "early" AMD is the deposition of acellular, polymorphous material—termed drusen—between the retinal pigment epithelium (RPE) and Bruch's membrane.[9,103,256] Focal retinal pigmentary abnormalities are also commonly seen in patients with early AMD. Patients with early AMD are frequently asymptomatic; the development of "late" AMD, however, is typically associated with visual loss.[93] In one form of late AMD, alterations in

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the RPE accumulate, resulting in the loss of large areas of RPE and outer retina, a phenomenon termed geographic atrophy (GA).[42] In the other form of late AMD, the accumulation of drusen and RPE abnormalities results in growth of abnormal blood vessels from the choroid. This process, termed choroidal neovascularization (CNV), is the pathognomonic feature of "neovascular" or "wet" AMD.[94] Growth of abnormal blood vessels originating in the retina has also been identified in a distinct subset of patients with neovascular AMD—such lesions are commonly referred to as "retinal angiomatous proliferation" (RAP).[249]

In recent years, major advances have been made in the treatment of AMD.[22,213] The development of anti-angiogenic agents such as ranibizumab and bevacizumab (Lucentis and Avastin, respectively; Genentech, South San Francisco, CA), has offered the first hope of significant visual improvement for patients that develop neovascular AMD.[25,159,195,238] Advances have also been made in our understanding of GA pathophysiology, with many potential therapeutic agents being evaluated in preliminary clinical trials.[257] In line with these advances, a new imaging modality—optical coherence tomography (OCT)—has emerged as an essential adjunct for the diagnosis and monitoring of patients with AMD.[26,44,115]

OCT, first described by Huang et al in 1991, allows high-resolution cross-sectional (tomographic) images of the neurosensory retina and deeper structures to be obtained in a non-invasive manner.[96] OCT works by measuring the properties of light waves reflected from and scattered by tissue (analogous to measurement of sound waves in ultrasonography). As the wavelength of light is much shorter than that of sound, OCT produces images with much higher resolution than that of ultrasound. Utilization of light instead of sound presents a number of technical challenges, however—in particular, the speed of light exceeds that of sound by a factor of 150,000, making direct measurement of optical "echoes" impossible. In OCT systems, this hurdle is overcome through the use of a technique called interferometry.[199] In *interferometry*, a beam of light is divided into a measuring beam and a reference beam. The reconvergence of light reflected from the tissue of interest and light reflected from a reference path produces characteristic patterns of interference that are dependent on the mismatch between the reflected waves. Because the time delay and amplitude of one of the waves (i.e., the reference path) is known, the time delay and intensity of light returning from the sample tissue may then be extracted from the interference pattern.

Commercially available OCT systems are now capable of obtaining retinal images with an axial resolution of approximately 3–8 μm, and a transverse resolution of approximately 15–20 μm; thus OCT is often dubbed in vivo "clinical biopsy".[123,127] OCT has been widely adopted for the management of vitreoretinal disorders, and nowhere more so than for the evaluation of AMD, a change driven in large part by the need for frequent anti-angiogenic therapy in patients with neovascular AMD.[26] The ability to accurately interpret OCT images is thus critical for retina specialists and important for comprehensive ophthalmologists. Despite this, the relatively recent introduction of OCT and, as a result, the relative absence of formal training, coupled with rapid evolution of the technology, may make OCT image interpretation difficult. These problems are compounded by the phenotypically heterogeneous nature of AMD and its complex morphology as visualized using OCT.[105] Therefore, we summarize the current understanding of OCT image interpretation in patients with AMD, and describe how OCT can best be applied to the management of these patients in clinical practice.

II. Optical Coherence Tomography Image Interpretation in Normal Eyes

A. QUALITATIVE IMAGE ANALYSIS

Light waves traveling through tissue can be reflected, scattered, or absorbed at each tissue interface; as a result, the multi-layered structure of the retina is particularly amenable to assessment using OCT (Figs. 1 and 2).[199] Care must be taken when making assumptions about the correlation between OCT images and retinal histological sections, however, as the strength of backscattered light is related to its angle of incidence on the area of interest. Therefore, structures running obliquely in the retina, such as Henle's fiber layer, are often not well visualized or appear variably on standard OCT images.[152,176]

On OCT scans presented in false color, "hotter" colors denote stronger reflectivity and "cooler" colors denote weaker reflectively. Thus, highly reflective tissue is reddish-white, whereas hyporeflective tissue is bluish-black. Alternatively, images can be shown in 256 shades of gray, corresponding to different optical reflectivities. (Figs. 1 and 2).[19,199] On most OCT scans, the first hyperreflective layer detected is the internal limiting membrane (ILM) at the vitreoretinal interface. In a subset of the population, the posterior hyaloid may be seen as a thin hyperreflective layer above the ILM. Within the retina, the retinal nerve fiber layer and both the inner and outer plexiform layers are seen as

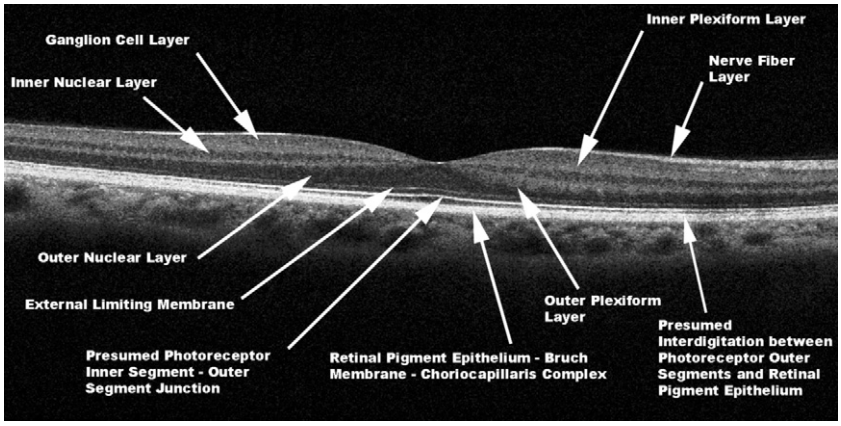

Fig. 1. Cross-sectional image of the neurosensory retina produced using spectral domain optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec). The high axial resolution offered by OCT is well-suited to providing information regarding the multi-layered structure of the retina. On grayscale OCT images, structures are represented in 256 shades of gray, corresponding to different optical reflectivities. Alternatively, on OCT false-color B-scans, highly reflective tissue is red-to-white in color, and hyporeflective tissue is blue-to-black in color.

hyperreflective, whereas the ganglion cell layer and both the inner and outer nuclear layers are hyporeflective. By varying the measurement beam angle, two aspects of the outer plexiform layer may be alternately seen: 1) a thin hyperreflective layer corresponding to the photoreceptor synapses, and 2) a thicker hyperreflective layer corresponding to photoreceptor axonal extensions (Henle's fiber layer) enveloped by the outer cytoplasm of Muller cells.[152,176] Finally, retinal vessels may sometimes be seen on OCT images as circular hyperreflective foci located in the inner retina, with a vertically oriented zone of "shadowing" or reduced reflectivity extending into the deeper layers.

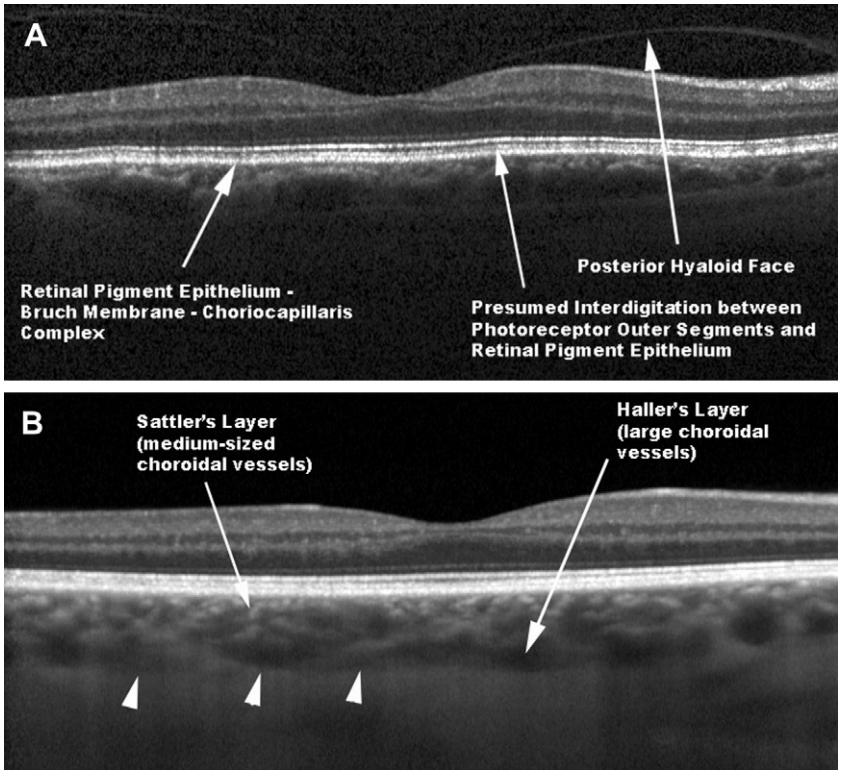

Fig. 2. *A*: On high-quality spectral domain optical coherence tomography (OCT) images (in this case, produced using Spectralis; Heidelberg Engineering), additional features of the vitreoretinal interface and outer retina are often seen. *B*: Use of "enhanced depth imaging" scanning protocols also allows greatly improved visualization of choroidal structures (in this case, again produced using Spectralis). The choroidal-scleral junction can often be clearly delineated (*arrowheads*).

Correlation of OCT images with the microstructure of the outer retina is less well understood than that of the inner retina (Figs. 1 and 2).[72,229] The first continuous strongly hyperreflective line seen in the outer retina is commonly designated as the junction of the inner and outer segments of the photoreceptors (IS–OS junction), although it may also represent the "ellipsoid," a dense aggregation of mitochondria located in the apical region of the photoreceptor inner segment. A faint hyperreflective line is often seen above this and is thought to represent the external limiting membrane (ELM). Beneath the IS–OS junction, the interdigitations of the photoreceptor outer segments and apical microvilli of the RPE may be visible with high-resolution OCT systems (in some high quality images, separate bands corresponding to the rod and cone interdigitations may also be seen). Finally, a wide, hyperreflective line corresponding to the RPE–Bruch's membrane–choriocapillaris complex lies at the outermost extent of these tissue layers. Using spectral domain OCT with B-scan averaging, zero-delay optimization, or longer-wavelength light sources, larger choroidal vessels, the suprachoroidal space, and the choroidal-scleral junction may also be seen in good quality images (Fig. 2).[226]

B. QUANTITATIVE IMAGE ANALYSIS

Since their introduction, OCT systems have been revolutionary in their attempts to obtain quantitative data of clinical significance from images in an automated fashion.[89,90] In particular, the high axial resolution offered by OCT is well suited to the objective, accurate measurement of retinal thickness. Stratus OCT (Carl Zeiss Meditec, Dublin, CA), the first widely adopted OCT system, uses image processing techniques to automatically detect the inner and outer retinal boundaries on OCT B-scans (segmentation) and thus provide measurements of retinal thickness.[199] Using these techniques, it is possible to measure retinal thickness at multiple locations and to construct retinal thickness maps approximately corresponding to the Early Treatment of Diabetic Retinopathy Study (ETDRS) subfields. (For historical reasons concerning disk diameter size, the ETDRS grid is actually slightly larger than the OCT grid typically used.) Caution is required, however, as errors in automated measurements are known to occur, and these errors are often severe in macular disorders with complex morphology (e.g., neovascular AMD), that alters the ability of segmentation algorithms to detect normal boundaries.[68,110,118,120,136,139,183,190,203] Newer OCT systems offer considerably improved image acquisition speed, as well as improved sensitivity and axial resolution.[112,127] These changes have facilitated improved accuracy in retinal segmentation; further improvements in image processing algorithms are still required before segmentation errors can be eliminated entirely, however.[69,85,121,136,155]

III. Retinal Imaging with Spectral Domain Technology

The newer generation of commercial OCT systems is often described as "spectral domain" or "Fourier domain" OCT. Spectral domain OCT systems use spectral interferometry and a mathematical function called Fourier transformation to assess interference patterns as a function of frequency. In older "time domain" systems, such as Stratus OCT, these patterns are assessed as a function of time.[30,244] Thus, light scattered from different depths within the tissue can be measured simultaneously, and images can be acquired 50-100 times more quickly than in time domain systems (typically over 20,000 A-scans per second).[112,127]

Currently available commercial OCT devices include the Cirrus HD-OCT (Carl Zeiss Meditec), 3D OCT-2000 (Topcon Medical Systems, Tokyo, Japan), Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), RTVue-100 (Optovue Corporation, Fremont, CA), Spectral OCT/SLO (Opko Instrumentation/OTI, Canada), SOCT Copernicus HR (Canon/Optopol, Inc, Tokyo, Japan), Retinascan RS3000 (Nidek, Tokyo, Japan), and 3D SDOCT (Bioptigen, Durham, NC).[112,127] In addition to their increased speed and sensitivity, many of these instruments offer incremental improvements in axial resolution through the use of improved light sources.[44]

Each of the recently introduced commercial spectral domain OCT systems is capable of acquiring sizable image sets over short time periods. As a result, new methods of utilizing these image sets have evolved, significantly enhancing the evaluation of AMD and other vitreoretinal disorders.[123]

A. RASTER SCANNING

The high speed of spectral domain OCT facilitates greater sampling of the macular area via the use of dense raster scanning protocols.[212,230,245] Raster scans consist of a rectangular pattern of horizontal line scans that run in parallel across the macula (e.g., 128 OCT B-scans, with each B-scan consisting of 512 A-scans) (Fig. 3). The greater retinal sampling density of spectral domain raster scans may facilitate early detection of morphologic changes in AMD, as well as allowing these changes to be more accurately followed over time.[114,126]

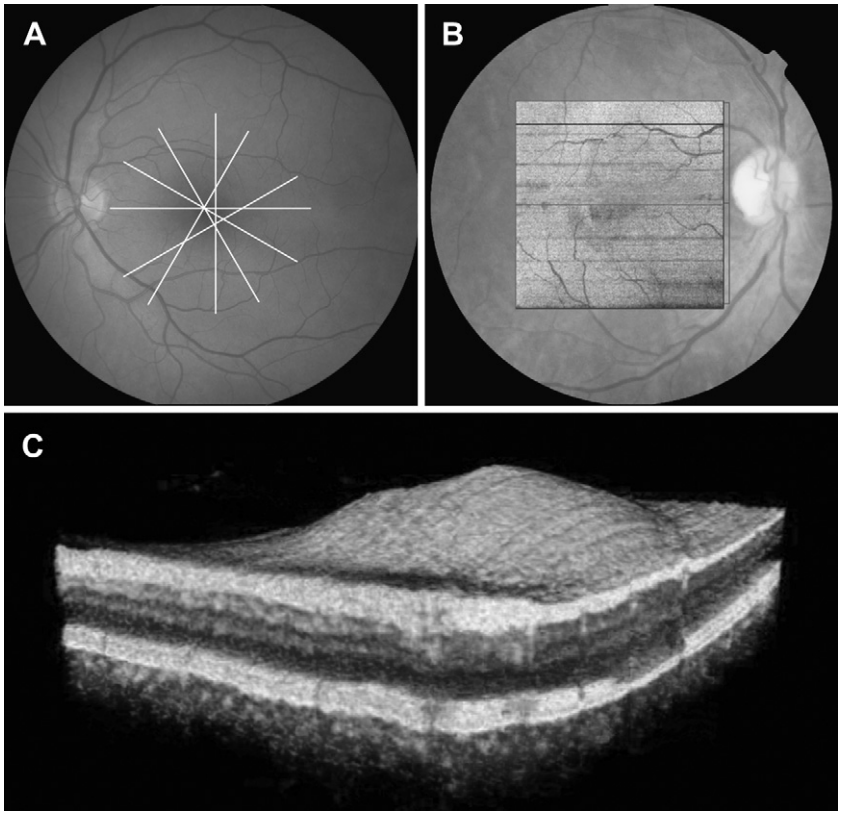

Fig. 3. *A*: Conventional time domain optical coherence tomography (OCT) scanning protocol (Stratus OCT; Carl Zeiss Meditec) showing sparse coverage from radial line B-scans. *B*: Spectral domain OCT data projected onto a fundus image showing dense coverage of the macular area by using a raster scanning protocol (i.e., a rectangular pattern of horizontal line scans that run in parallel) (3D-OCT 1000; Topcon Medical Systems, Japan). *C*: Volumetric rendering of the macular region in a patient examined with 3D-OCT 1000 (Topcon Medical Systems). Rendering is the processing of OCT images to make them appear solid and three-dimensional, and allows visualization of the retina from any direction, including from below.

When dense raster scanning is performed, spectral domain OCT systems have the ability to perform volumetric rendering of the OCT images (*rendering* is the processing of OCT images to make them appear solid and three-dimensional).[212] Volumetric rendering allows enhanced visualization of the retina that may be useful when AMD is associated with other pathologies such as epiretinal membrane, or vitreomacular traction (Fig. 3).[132]

B. OCT FUNDUS IMAGES

Another important feature of spectral domain OCT is the ability to generate "OCT fundus images" that mimic the images obtained from standard fundus photography.[212,245] These images are generated from the raster scan OCT data by summing the intensity of pixels in the axial direction, resulting in a pixel brightness value for each axial scan position. OCT fundus images show a direct view of the macula in which the retinal vascular arcades may be clearly visible and spatially consistent with the vasculature on color photographic and angiographic, images.[44] OCT fundus images are useful in the clinical setting as they can facilitate registration of any point on an OCT image with a corresponding point on the retinal surface. OCT fundus images also permit the acquisition of images in the same location over time, although this is not always possible in the setting of severe disease, where the vascular pattern and other landmarks may be less apparent, or in patients with poor fixation. In the context of AMD, use of OCT fundus images is of particular value for the quantitative monitoring of patients with GA (see section V).[153,253]

C. REAL-TIME EYE MOTION TRACKING AND B-SCAN AVERAGING

Although it is possible to generate large 3D data stacks with spectral domain OCT, motion artifacts such as vertical microsaccades remain a problem when high sampling density is required. Many spectral domain OCT systems address this problem by sacrificing sampling density along one axis of the raster scan; however, one of the commercially

available OCT instruments (Spectralis, Heidelberg Engineering, Germany) also provides real-time eye motion tracking with the potential for longer acquisition times and higher density data sets.[49,91,102] The rapid scanning of spectral domain OCT also allows multiple B-scans to be averaged (particularly in the context of real-time eye-motion tracking), which reduces speckle noise and allows detailed visualization of fine structures. This feature may be of particular use for the evaluation of sub-RPE and choroidal structure in patients with AMD.[205,224,226]

IV. Features of Early Age-Related Macular Degeneration on Optical Coherence Tomography

A. DRUSEN

Until the advent of high-speed spectral domain technology, evaluation of drusen with OCT was often difficult as motion artifacts commonly resulted in apparent undulation of the RPE, mimicking the appearance of drusen.[88,185,194] On spectral domain OCT, small and intermediate-size drusen may be more clearly seen as discrete areas of RPE elevation with variable reflectivity, reflecting the variable composition of the underlying material.[73,125] In larger drusen, or drusenoid pigment epithelium detachment (PED), greater elevation of the RPE may be seen, often dome-shaped, with a hypo- or medium-reflective material separating the RPE from the underlying Bruch's membrane (Fig. 4).[194,221,225] Larger drusen may often become confluent, resulting in a large lateral dimension, but no single broad-domed lesion. A recent study using OCT suggests that large confluent drusen may sometimes be accompanied by fluid accumulation under the retina in the absence of CNV (Fig. 5). This fluid is seen in the depression between drusen and does not exceed their peaks.[221] Thus, the mechanism involved may involve mechanical strain on outer retinal layers produced by the bridging of the drusen. Although confirmatory studies are required, recognition of this feature may allow some patients with AMD to avoid unnecessary treatment with anti-angiogenic therapies. Alternatively, these patients may have subclinical CNV warranting more careful follow-up.

On OCT, drusen are often accompanied by changes in the overlying neurosensory retina. These may be seen as disruption of the IS–OS junction and ELM, as well as significant thinning of the outer nuclear layer.[73,217] These findings are consistent with previous histopathologic studies demonstrating photoreceptor loss in patients with drusen.[40,106] In subjects with extensive drusen, apparent thickening of the photoreceptor outer segments may also sometimes be seen, possibly representing incomplete phagocytosis of photoreceptor outer segments.[53] Finally, drusen may often be associated with a diffuse hyperreflective haze at the inner boundary of the outer nuclear layer, although the origin and significance of this finding remains uncertain.[217] These hyperreflective regions are now believed to represent portions of Henle's fiber layer that become visible because of the change in the angle of incidence of the OCT beam relative to the topological change produced by the drusen.

OCT has also proven useful for the assessment of a variety of conditions characterized by variant forms of drusen—as opposed to the "typical" drusen of AMD, which are seen as deposits between the RPE and the inner collagenous portion of Bruch's membrane.[225] In particular, attention has focused

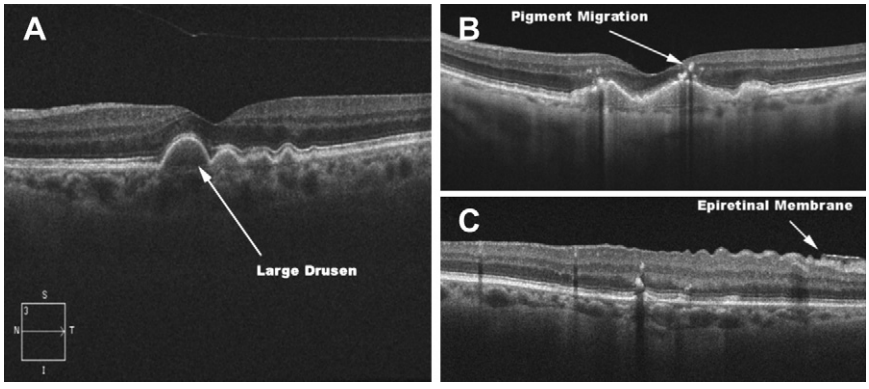

Fig. 4. *A*: On optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec), large drusen are typically seen as dome-shaped elevations of the retinal pigment epithelium (RPE), with a hypo- or medium-reflective material separating the RPE from the underlying Bruch's membrane. *(B* and *C)*: intraretinal pigment clumping and migration may be seen as discrete foci of hyperreflectivity with underlying shadowing, most commonly in the outer nuclear layer or attached to areas of elevated RPE overlying drusen. Epiretinal membranes (ERMs) are often seen on OCT as hyperreflective bands anterior to the inner retinal surface, with distortion of the underlying anatomy.

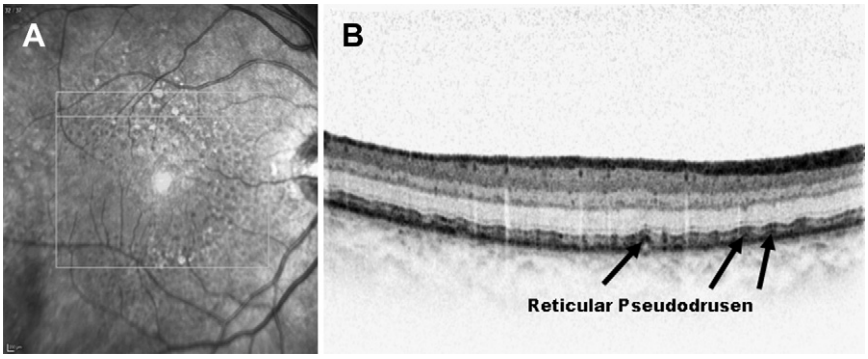

Fig. 5. Using optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering), reticular pseudodrusen can be seen as multiple areas of granular hyperreflectivity between the retinal pigment epithelium (RPE) and photoreceptor inner segment-outer segment (IS-OS) junctions *(A)* and *(B)*.

on the use of OCT for evaluation of so-called "reticular pseudodrusen" (Fig. 6).[12,36,84,130,197] Reticular pseudodrusen were first described by Mimoun et al in 1990 as a peculiar yellowish pattern in the fundus of AMD patients, best seen with blue light.[164] In 1991 the same entity, an ill-defined network of broad interlacing ribbons, was termed "reticular drusen" in the Wisconsin age-related maculopathy grading system.[129] Using this system, the Beaver Dam Eye Study identified reticular drusen as a major risk factor for the development of advanced AMD.[130] With the advent of spectral domain OCT, improved characterization of "reticular pseudodrusen/drusen" is now possible, and it appears that these drusen correspond to granular hyperreflective material between the RPE and the IS–OS junctions (i.e., they occur in the subretinal space). As a result, the term "subretinal drusenoid deposits" has been suggested as a clarification of the existing nomenclature; furthermore, such deposits may also be accompanied by acquired vitelliform lesions.[216,222,259,261,262]

Another important drusen variant occurring in AMD is that of "basal laminar" drusen, first

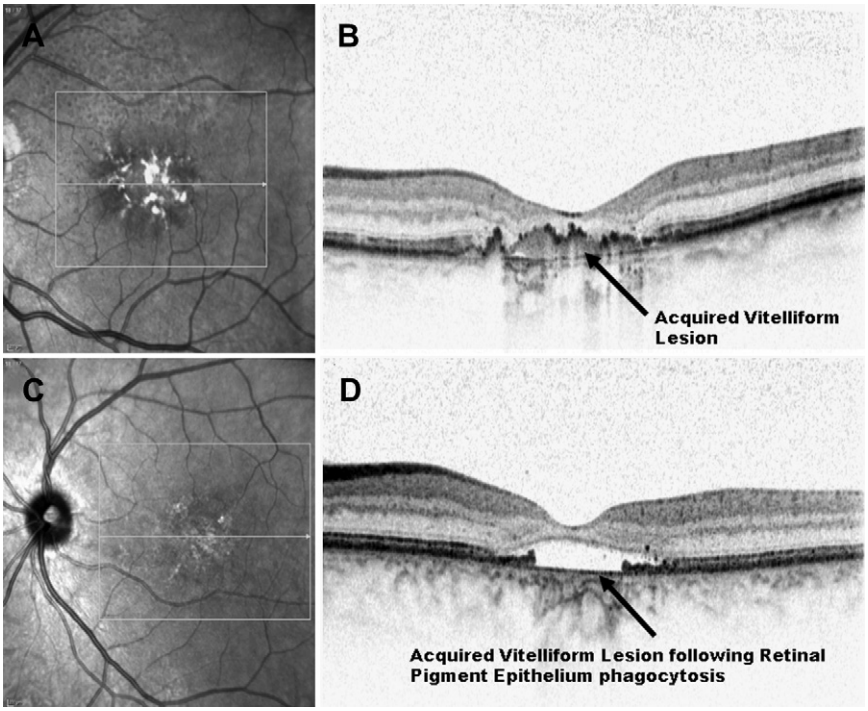

Fig. 6. Acquired vitelliform lesions are believed to occur as a result of retinal pigment epithelium (RPE) dysfunction leading to impaired turnover of photoreceptor outer segments and may be localized to the subretinal space using optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering) *(A* and *B)*: RPE phagocytosis of the subretinal material may lead to resolution of the lesion; in the process, acquired vitelliform lesions may be seen to contain subretinal fluid on OCT *(C* and *D)*.

described by Gass in 1974.[43,65] Basal laminar drusen are seen as numerous, small, round, uniformly sized, yellow, sub-RPE lesions that show early hyperfluorescence on fluorescein angiography resulting in a "starry night" appearance, as opposed to typical drusen seen in AMD that may fluoresce later in the angiogram. Basal laminar drusen were originally thought to constitute focal nodular thickening of the RPE basement membrane,[66] although recent histopathologic analysis suggests that their features are indistinguishable from those of typical drusen.[198] Therefore, the descriptor "cuticular" drusen has now been widely adopted. On OCT, cuticular drusen are seen as a saw-tooth elevation of the RPE with rippling (and occasional disruption) of the overlying IS–OS junction and ELM.[52,148,225] When cuticular drusen occur in the context of typical findings of early AMD (i.e., large drusen and pigmentary abnormalities), they may sometimes be associated with acquired vitelliform lesions—clinically apparent yellowish material that localize on OCT to the subretinal space and mimic the appearance of CNV on fluorescein angiography (Fig. 5).[61] Acquired vitelliform lesions are believed to occur as a result of RPE dysfunction leading to impaired photoreceptor outer segment turnover. RPE phagocytosis of the subretinal material may lead to resolution of the lesion. In the process, acquired vitelliform lesions may be seen to contain subretinal fluid on OCT.[61] Thus, awareness and recognition of this feature, particularly given the fluorescein angiographic findings, is important for the appropriate management of patients with AMD.

Numerous cross-sectional and prospective epidemiologic studies have demonstrated that drusen diameter and area are a significant risk factor for progression to advanced AMD; manual analysis of drusen on color fundus photographs shows only moderate correlation between graders in the context of a dedicated reading center, however, and is not practical in clinical practice. Therefore, efforts are underway to use spectral domain OCT for automated detection and quantification of drusen.[59,79,211,255] By assessing drusen size, area, and volume in this manner, it may be possible to identify patients at high risk of disease progression. With the introduction of pathway-based therapies for early AMD, it may then be possible to institute appropriate prophylactic interventions.

B. RETINAL PIGMENT EPITHELIUM ABNORMALITIES

In response to various stimuli, RPE cells are capable of hypertrophy, proliferation, and, in many cases, intraretinal migration (this has been well described on histopathology for a variety of retinal degenerative disorders). Such changes are commonly seen in AMD and can often be visualized using OCT (Fig. 4).[92] For example, focal areas of RPE loss or depigmentation may be seen on OCT images as increased reflectivity of the underlying choroidal vessels. Furthermore, pigment clumping and migration may be seen as discrete foci of hyperreflectivity with underlying shadowing, most commonly in the outer nuclear layer or attached to areas of elevated RPE overlying drusen.[73,92] Color fundus photography established that RPE abnormalities are associated with increased risk of disease progression in AMD; OCT may allow improved characterization and tracking of such changes. Thus, the recent AREDS 2 trial has incorporated an ancillary, spectral domain OCT study evaluating RPE abnormalities over time with a view to identifying early risk factors for disease progression.[217,A]

V. Features of Geographic Atrophy on Optical Coherence Tomography

In GA, confluent areas of RPE atrophy are accompanied by loss of the overlying photoreceptors and varying degrees of choriocapillaris loss seen on fluorescein angiography. These changes are often preceded by dehydration and calcification of local drusen.[43,94,232] On OCT, GA appears as areas of sharply demarcated choroidal hyperreflectivity from loss of the overlying RPE (atrophy from causes other than AMD [e.g., from confluent laser photocoagulation] may have a similar appearance) (Fig. 7).[246] Associated retinal atrophy is seen as thinning or loss of the outer nuclear layer and the absence of ELM and IS–OS junctions.[53,214] On OCT islands of preserved outer retina may sometimes be identified in areas of GA, as can regressing drusenoid material, seen as hyperreflective plaques at the level of the RPE.[53] GA may sometimes be foveal-sparing. Preliminary OCT evidence suggests that mild retinal swelling in areas of foveal sparing may represent a pre-apoptotic stage of neuronal cellular elements indicative of imminent atrophy.[215] GA may also be associated with the presence of small cyst-like spaces in the inner nuclear layer in the absence of macular edema.[35]

In the junctional zone surrounding GA, the ELM and IS–OS junctions may be seen to taper off, and the outer plexiform layer can be seen to approach Bruch's membrane, suggesting that photoreceptor loss often extends beyond the margins of GA lesions.[14,54] OCT studies have also demonstrated a variety of dynamic changes in the zones surrounding GA, including pigment migration and alterations in drusen height (both increases and decreases).[54,56]

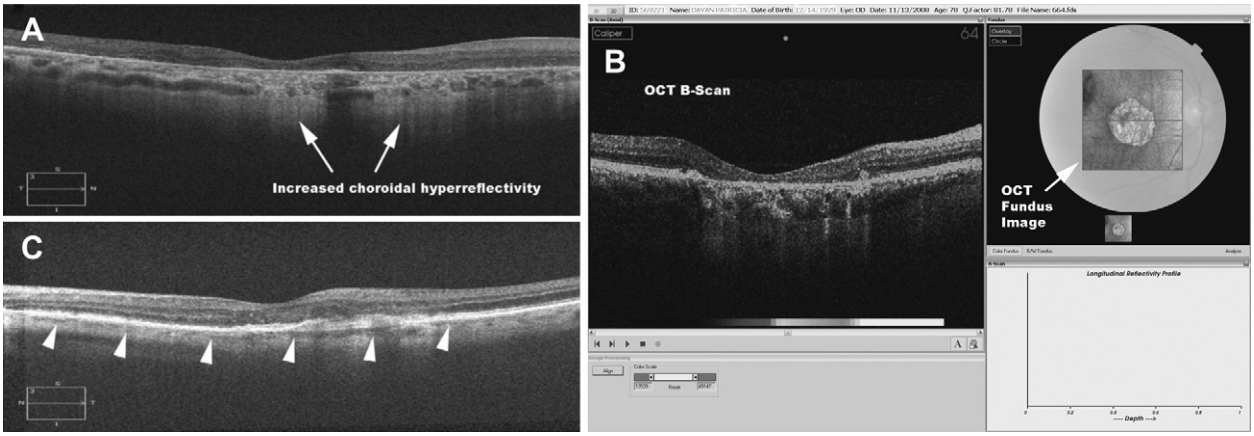

Fig. 7. *A*: On optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec), geographic atrophy (GA) appears as areas of sharply demarcated choroidal hyperreflectivity due to loss of the overlying retinal pigment epithelium (RPE). *B*: Standard output of 3D-OCT 1000 (Topcon Medical Systems). An OCT fundus image displaying evidence of geographic atrophy is seen superimposed on the standard color photographic image. Geographic atrophy is often well demarcated on OCT fundus images as a result of the increased choroidal light reflections that occur in this disorder. *C*: Using spectral domain OCT (in this case, Cirrus HD-OCT), an age-related decline in subfoveal choroidal thickness ("age-related choroidal atrophy") has recently been demonstrated (*arrowheads*).

Evaluation of these junctional zones may thus provide insight into the pathogenesis of GA and the relative roles of RPE and photoreceptors in the initiation and propagation of this condition. In a recent study using spectral domain OCT, patients with a rapidly progressing form of GA exhibited a characteristic separation of the RPE–Bruch's membrane complex in these borders zones.[55]

The OCT fundus images provided by spectral domain OCT devices show an increased total signal in areas where GA is apparent on clinical examination (Fig. 7). As a result, it is possible to manually quantify areas of GA by registering these images to fundus photographs and delineating the GA boundaries with imaging software.[20,153,218,253,254] This approach may allow more accurate and reproducible measurements of GA progression in future clinical trials of this disorder.

A. AGE-RELATED CHOROIDAL ATROPHY

Prior to the advent of OCT, evaluation of choroidal structure in patients with non-neovascular AMD was limited; with the use of "enhanced depth" OCT imaging protocols, however, it is now possible to visualize the cross-sectional structure of the choroid and to measure its thicknesses.[226] Using this technique, an age-related decline in subfoveal choroidal thickness has recently been demonstrated (Fig. 7).[158] A subset of elderly patients have also been identified with choroidal thinning greater than that of any expected age-related decline. Many of these patients demonstrate posterior pole features typical of AMD.[223] Further work is required to determine whether this "age-related choroidal atrophy" represents a distinct clinical entity or an AMD subtype.

VI. Features of Neovascular Age-Related Macular Degeneration on Optical Coherence Tomography

In neovascular AMD abnormal blood vessels develop from the choroidal circulation, pass anteriorly through breaks in Bruch's membrane, and then proliferate in the sub-RPE or subretinal space.[82] As the CNV lesion proliferates, the structural immaturity of its vessels commonly results in fluid exudation and hemorrhage, leading to the formation of pathologic "compartments" between the RPE and Bruch's membrane (PED) and between the neurosensory retina and the RPE (serous retinal detachment).[4,119] In addition, neovascular invasion may result in significant degradation and remodeling of the retinal extracellular space, as well as the incursion of cellular components such as fibroblasts. These changes ultimately result in disciform scar formation with loss of the RPE and overlying photoreceptors and significant disorganization of the overlying retinal architecture.[74–76] Awareness of this basic schema greatly facilitates assessment of disease activity using OCT in patients with neovascular AMD.

A. FIBROVASCULAR PIGMENT EPITHELIUM DETACHMENT

Growth of the choroidal neovascular membrane in the sub-RPE space produces an irregularly

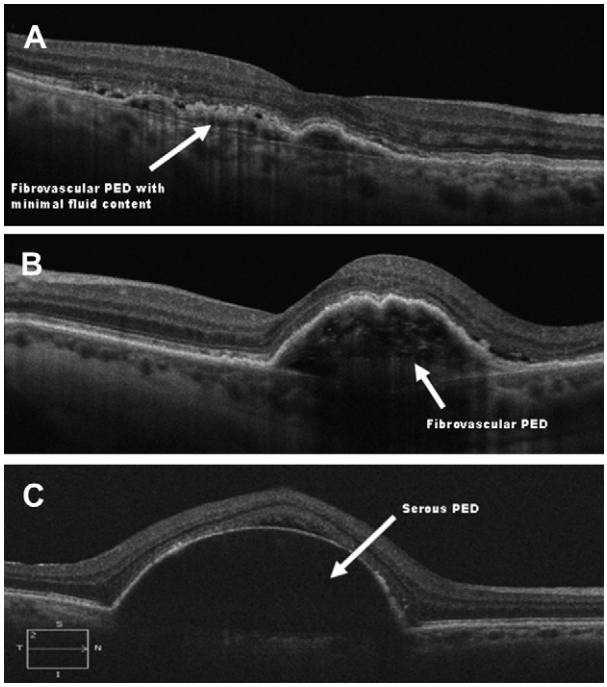

Fig. 8. On optical coherence tomography (OCT), pigment epithelium detachments (PEDs) appear as broad elevations of the retinal pigment epithelium (RPE) band relative to Bruch's membrane (Cirrus HD-OCT; Carl Zeiss Meditec). Fibrovascular PEDs may be accompanied by variable quantities of serous exudation and/or hemorrhage, with the slope of the PED varying according to fluid content *(A, B)*. Using spectral domain OCT, many fibrovascular PEDs appear to be filled with solid layers of material of medium reflectivity, separated by hyporeflective clefts *(B)*. Serous PEDs are seen on OCT as areas of smooth, sharply demarcated, dome-shaped RPE elevation, typically overlying a homogenously hyporeflective space. Bruch's membrane is often visible as a thin hyperreflective line at the outer aspect of the PED *(C)*.

elevated lesion visible on clinical examination, termed a "fibrovascular PED". On fluorescein angiography, fibrovascular PEDs are associated with stippled or granular hyperfluorescence that appears in the late frames.[1] On OCT, PEDs appear as broad elevations of the RPE band relative to Bruch's membrane.[37,154] Fibrovascular PEDs may be accompanied by variable quantities of serous exudation and/or hemorrhage; as a result, the slope of the PED may vary depending on its fluid content (Fig. 8). The detailed structural characteristics and precise mechanisms of PED formation have not been completely resolved, in part due to the relative inability of conventional OCT devices to visualize the areas underneath the highly reflective RPE. Recent studies have utilized "enhanced depth" spectral domain OCT imaging to aid visualization of the sub-RPE space.[63,100,101,158,160,161,226] Using this method, many fibrovascular PEDs appear to be filled with solid layers of material of medium reflectivity,[224] separated by hyporeflective clefts — a finding consistent with previous histopathologic reports (Fig. 8).[76,78]

B. SEROUS PIGMENT EPITHELIUM DETACHMENT

Patients with AMD may develop a so-called "serous PED," an area of smooth, sharply demarcated, dome-shaped RPE elevation that can be easily seen on clinical examination. On fluorescein angiography serous PEDs are associated with intense, early fluorescence that typically, but not always, has a distinct border. Controversy exists regarding the pathophysiology of serous PEDs in AMD; broadly speaking, however, they may be categorized as *vascular* or *avascular*.[94,258] On OCT in an avascular serous PED, dome-shaped elevation of the RPE can typically be seen overlying a homogenously hyporeflective space, with Bruch's membrane often visible as a thin hyperreflective line at the outer aspect of the PED.[17,105] Vascularized serous PEDs are thought to occur when growth of a CNV lesion in the sub-RPE space is associated with profuse exudation, creating a serous fluid compartment. The OCT appearance of such PEDs is often similar to that of their avascular counterparts; in some cases, however, small collections of solid material (the apparent fibrovascular proliferation) can be seen adherent to the outer surface of the RPE (Fig. 8 [also seen later in Fig. 15]). Following treatment with anti-angiogenic agents, these supposed areas of sub-RPE CNV can be seen to contract and separate from the RPE, with flattening of the PED that may be associated with RPE tear formation in a minority of cases.[224] Using "enhanced depth" OCT, it may sometimes also be possible to identify the point at which a new vessel growing from the choroid penetrates Bruch's membrane and enters the sub-RPE space. As OCT image quality and analysis techniques continue to improve, the identification of such a feature in patients with drusen may allow early initiation of treatment and improved outcomes. In vascularized PEDs, there is often also a notch in the contour of the PED as identified using fluorescein angiography. Using OCT RPE segmentation algorithms, these notches can often be appreciated on the RPE contour maps; thus, examining the OCT B-scans that run through this area can often reveal the fibrovascular tissue.[7]

C. HEMORRHAGIC PIGMENT EPITHELIUM DETACHMENT

Frank hemorrhage from proliferating blood vessels in the sub-RPE space may also result in the

formation of a hemorrhagic PED. As in serous PEDs, elevation of the RPE on OCT is often dome-shaped, although the slope of such elevations is often more acute in the context of profuse bleeding. In addition, Bruch's membrane is less commonly seen in hemorrhagic PEDs, where there is often dramatic posterior shadowing below the RPE.[17,105] Hemorrhagic PEDs often occur as a result of tears in the RPE. On OCT such tears are typically seen as an area of discontinuity in a large hemorrhagic PED.

D. RETINAL ANGIOMATOUS PROLIFERATION

Although neovascular AMD is predominantly a disorder of the choroidal vasculature, the retinal circulation may also be involved in some patients, and retino-choroidal anastomoses may form in advanced disease.[77] In 2001 Yannuzzi et al suggested that the initial event in the development of retino-choroidal anastomosis was intraretinal neovascularization and coined the term RAP.[249] Conversely, Gass et al suggested that the initial event in retinal involvement was the development of occult anastomosis at the site of a sub-RPE CNV lesion.[67] A recent histopathologic study has provided evidence supportive of an intraretinal origin for the neovascular process in these patients.[169] Recent OCT studies, however, suggest that the earliest change visible in these patients is the development of fibrovascular PED—a feature more consistent with the Gass et al theory of occult chorio-retinal anastomosis.[38,60,188] Thus, retinal involvement in neovascular AMD may incorporate both sub-RPE and intraretinal origins ("the expanded spectrum of RAP").[60] On OCT, active RAP lesions have a characteristic appearance, typified by frank CME overlying a PED and accompanied by subretinal fluid (Fig. 9).[137,235] Querques et al have described a focal funnel shaped defect in the RPE of such cases and termed it the "kissing sign". In their study this defect was seen in association with an intraretinal hyperreflective lesion, presumably representative of intraretinal neovascular invasion.[188] In some advanced cases, the use of dense raster scanning with spectral domain OCT may allow the actual retino-choroidal

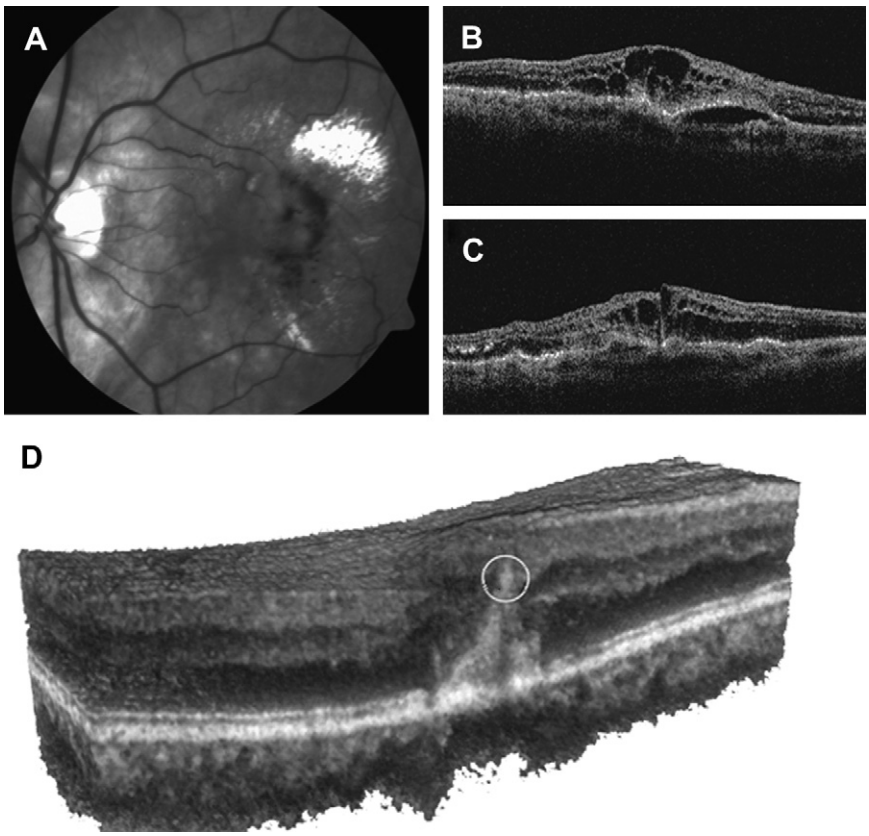

Fig. 9. On fundus photography, retinal angiomatous proliferation (RAP) lesions are typically associated with focal areas of intraretinal hemorrhage, right-angled venules, and circinate collection of hard exudates (*A*). On optical coherence tomography (OCT) (Stratus OCT; Carl Zeiss Meditec), active RAP lesions are typified by frank cystoid macular edema overlying a fibrovascular PED and associated with subretinal fluid (*B*). Volumetric rending of OCT raster scans can often highlight the intraretinal component of these lesions (3D-OCT 1000; Topcon Medical Systems) (*C*).

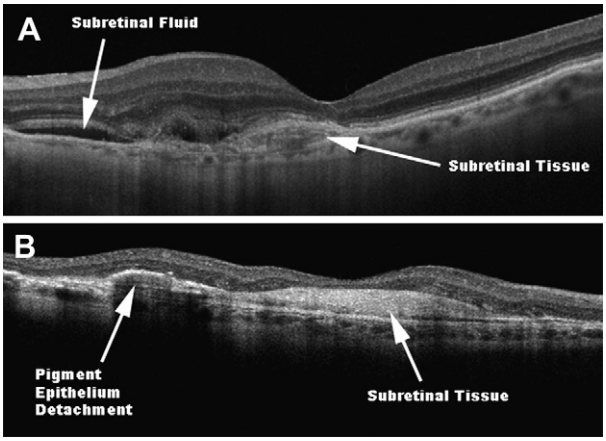

Fig. 10. On optical coherence tomography (OCT), fibrovascular tissue in the subretinal space often appears as an amorphous lesion of mediumto high- reflectivity above the RPE (*A*); with increased scarring, it may be seen as a more well-demarcated, highly hyperreflective lesion (Cirrus HD-OCT; Carl Zeiss Meditec) (*B*). Invasion of fibrovascular tissue is often accompanied by profuse leakage from its immature blood vessels that appears on OCT images as areas of hyporeflective space between the neurosensory retina and the RPE (Spectralis; Heidelberg Engineering).

anastomosis to be seen as a discrete hyperreflective area extending through the retina (Fig. 9).

E. SUBRETINAL HYPERREFLECTIVE MATERIAL / DISCIFORM SCARS

In many cases of neovascular AMD, vessels from the choroidal neovascular complex may pass directly into the subretinal space after their initial penetration of Bruch's membrane.[82] In these initial growth phases, the CNV membrane is often highly vascular and appears on OCT as an amorphous lesion of medium- to high- reflectivity above the RPE (Fig. 10).[105,116] As the CNV lesion becomes less active over time, the vascular component typically regresses, while the fibrous component increases, resulting in disciform scar formation that appears on OCT as a well demarcated highly hyperreflective lesion. Scar formation may be associated with loss of the overlying photoreceptor layer and irreversible reduction in visual acuity. This may often be seen on OCT as disruption of the IS–OS junction and ELM.[87,143,174,210] Hemorrhage, lipid, or thick fibrin may also appear as hyperreflective material in the subretinal space, but should not be mistaken for the fibrovascular lesion.[105] In some patients contraction of a disciform scar may result in the appearance of choroidal folds radiating from the lesion.[162] Such folds appear on OCT as undulations of the RPE without evidence of separation from Bruch's membrane.

F. SEROUS RETINAL DETACHMENT / SUBRETINAL FLUID

As the choroidal neovascular membrane grows, it is often accompanied by profuse leakage from its immature blood vessels. Consequently, pockets of fluid commonly accumulate between the neurosensory retina and the RPE. These areas may be seen on OCT as hyporeflective spaces (Fig. 10).[105] CNV lesions growing in the subretinal space are often associated with the greatest volume of subretinal fluid; sub-RPE lesions may also result in subretinal fluid when there is sufficient dysfunction of the outer blood–retinal barrier, however.[117] When fluid exudation is serous in nature, subretinal fluid pockets are seen on OCT as homogenous hyporeflective spaces. When the exudate contains fibrin or red blood cells, the area of subretinal fluid may by sparsely hyperreflective.[113,248] Profuse fibrinous exudation in neovascular AMD, seen after PDT or in particularly active classic CNV lesions, may result in the formation of distinct subretinal fluid compartments separated by fibrinous membranes. These compartments may sometimes be seen on FA as areas of loculated fluid, that is, compartmentalized spaces anterior to the CNV lesion, that demonstrate late phase pooling on fluorescein angiography.[23]

Spectral domain OCT allows enhanced visualization of the subretinal space and assessment of the optical density of subretinal fluid compartments and may have value for the differentiation of macular disorders associated with subretinal accumulation.[3] Increasing clinical use of OCT has also highlighted that the identification of subretinal fluid in patients with a typical picture of dry AMD is not always indicative of underlying CNV and may sometimes occur in conjunction with large confluent drusen or in acquired vitelliform lesions (see previous discussion).[61,221] Therefore, it is important to consider the full clinical picture and not reach a diagnosis based on a single OCT feature.

G. INTRARETINAL FLUID

Disruption of the ELM–photoreceptor complex in the outer retina by the active CNV membrane may result in the accumulation of fluid in the neurosensory retina. Increased local production of vascular endothelial growth factor may also result in hyperpermeability of normal retinal vessels.[43] Initially this fluid collection manifests as diffuse thickening of the outer nuclear layer.[111] Severe outer nuclear layer swelling may sometimes be mistaken for subretinal fluid. The distinction can usually be made by the presence of an intact IS–OS junction at the outer aspect of outer nuclear layer thickening. With more severe fluid exudation,

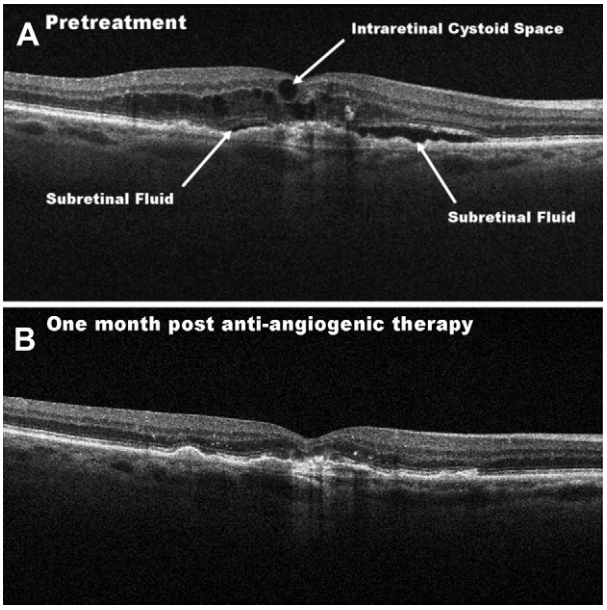

Fig. 11. Accumulation of fluid within the retina may lead to diffuse retinal thickening and/or the formation of intraretinal cystoid spaces (Cirrus HD-OCT; Carl Zeiss Meditec) (*A*). Treatment with anti-angiogenic agents often leads to cessation of choroidal neovascular leakage with consequent resolution of these cystoid spaces (*B*).

cystoid spaces may form and can be seen on OCT as round or oval hyporeflective areas (Fig. 11).[111,234] Larger cystoid spaces often contain tissue septae and may involve all layers of the retina.

Treatment with anti-angiogenic agents often leads to cessation of CNV leakage with consequent resolution of these cystoid spaces (Fig. 11). In severe cases, however, cystoid spaces may persist even in the absence of leakage, and these areas have been termed "cystoid macular degeneration".[97,107] Furthermore, when monitoring patients following treatment for neovascular AMD, the recurrence of intra- or subretinal fluid must be differentiated from that of "outer retinal tubulation"—a recently described, novel, OCT finding.[260] Outer retinal tubulations are branching tubular structures that appear as round or ovoid hyporeflective spaces with hyperreflective borders in the outer nuclear layer, commonly overlying areas of PED or subretinal fibrosis (Fig. 12). They are most often seen in patients with advanced neovascular or atrophic AMD, but also in other disorders. They may represent a rearrangement of photoreceptors in response to injury.[260]

Profuse intraretinal fluid exudation is often associated with the precipitation of lipid exudations, both in neovascular AMD and in other disorders, particularly diabetic maculopathy.[18,105,124] On OCT lipid exudates appear as discrete hyperreflective foci. These foci are commonly seen in the outer retina, but may be scattered throughout all retinal layers and in some cases may cluster to form confluent plaques, particularly in patients with retinal angiomatous proliferation (see subsequent discussion). Framme et al have recently described "small dense particles" on OCT in the outer retina of patients receiving treatment for neovascular AMD[57]; Lima et al have described similar hyperreflective foci that they characterize as "intraretinal crystalline deposits".[150] Although the origin of these findings is unclear, they may represent subclinical lipid exudates, small foci of intraretinal pigment migration, or degenerated Muller cell elements.

H. ABNORMALITIES OF THE VITREOMACULAR INTERFACE

Retinal imaging with OCT allows detailed evaluation of the structural features of the vitreomacular interface (Fig. 13).[165] On OCT vitreomacular traction may be seen when a thickened, taut, posterior hyaloid causes deformation of the inner retinal surface, which may often be accompanied by cystoid macular edema (CME).[28] Epiretinal membranes are often seen on OCT as hyperreflective bands anterior to the inner retinal surface, with distortion of the underlying anatomy.[146] In recent years it has been

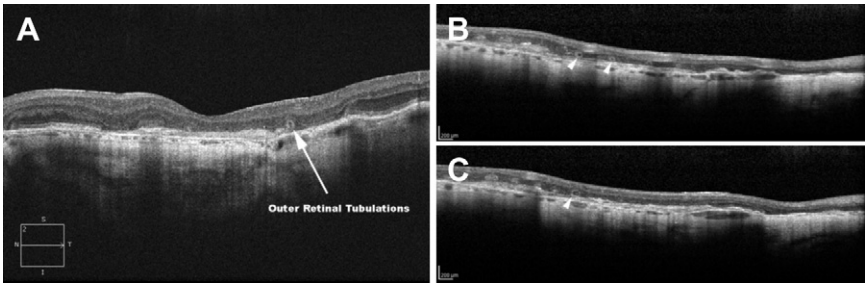

Fig. 12. Outer retinal tubulations are branching tubular structures that appear on optical coherence tomography (OCT) as round or ovoid hyporeflective spaces with hyperreflective borders in the outer nuclear layer (commonly overlying areas of PED or subretinal fibrosis) (*A*: Cirrus HD-OCT, Carl Zeiss Meditec; *B, C*: *arrowheads*, Spectralis Heidelberg Engineering).

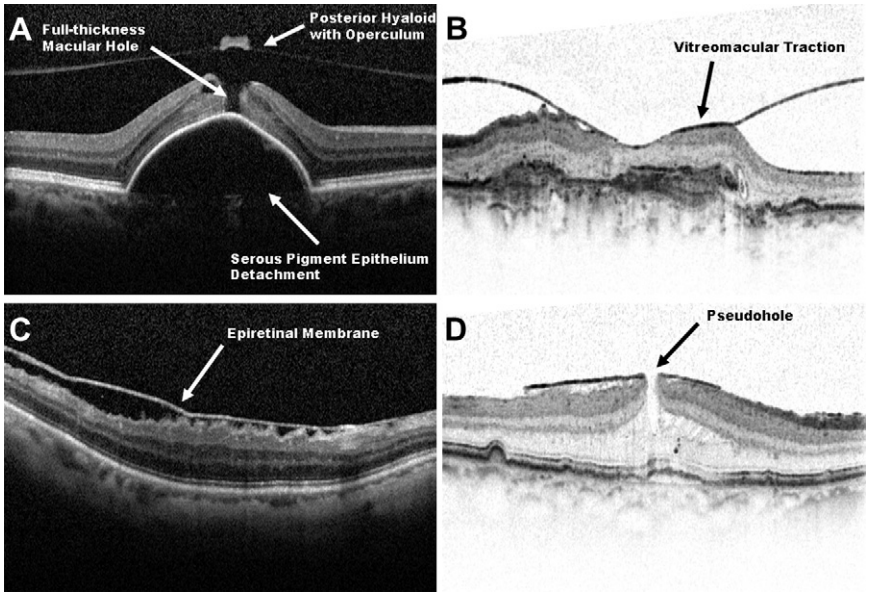

Fig. 13. On optical coherence tomography (OCT), vitreomacular traction may be seen when a thickened, taut, posterior hyaloid causes deformation of the inner retinal surface, occasionally leading to formation of a full-thickness macular hole (*A, B*). Epiretinal membranes are often seen on OCT as hyperreflective bands anterior to the inner retinal surface, with distortion of the underlying anatomy (*C*) and pseudohole formation (*D*).

suggested that abnormalities of this interface may play a role in CNV pathogenesis. A number of studies, using both time domain and spectral domain OCT, have reported a higher prevalence of vitreomacular adhesion in patients with neovascular AMD.[135,144,168,172,193] Further study is required to confirm this association and to determine whether it has any clinical implications.[138,145,196]

I. RETINAL PIGMENT EPITHELIUM TEARS

RPE tears, a well-described complication of neovascular AMD, have achieved a new prominence with the introduction of new pharmacotherapies for this disorder.[29] On OCT, RPE tears are typically seen as an area of discontinuity in a large PED, with the free edge of the RPE often curled under the PED creating a corrugated appearance (Fig. 14).[71] Adjacent to the tear, increased reflectivity from the choroidal vessels can usually be seen, the result of reduced attenuation of the signal from the absent RPE. The overlying retina is typically intact, but may be separated from the area of atrophy by subretinal fluid.[184] OCT-derived measurements of PED height or irregular contour of the PED surface may allow prediction of risk for RPE tear occurrence in anti-angiogenic therapy.[27,31,147] Subsequently the greatest linear dimension of the tear measured on fluorescein angiography may provide prognostic information.[207] In the long term, the area of the tear is usually covered by disciform scar formation and the visual outcome may be poor if the fovea is involved.[95]

VII. Features of Neovascular Age-related Macular Degeneration Variants using Optical Coherence Tomography

A. POLYPOIDAL CHOROIDAL VASCULOPATHY

In 1990 Yannuzzi et al suggested the term "idiopathic polypoidal choroidal vasculopathy" (PCV) for a disorder characterized by multiple serosanguineous PEDs, commonly seen in black and Asian populations, and previously described as the "posterior uveal bleeding syndrome."[131,251] This disorder was initially felt to be a distinct entity with its own risk factors and clinical course; the disease spectrum has been greatly expanded, however, with many authorities now considering PCV to be an important form of neovascular AMD.[34] On indocyanine green (ICG) angiography, PCV appears as a branching vascular network below the RPE that ends in reddish-orange polypoidal lesions and is often associated with serosanguineous PEDs.[39] Freund et al suggest that the polyps in polypoidal choroidal vasculopathy originate from long-standing type 1 (sub-RPE) neovascular tissue rather than from the choroidal circulation.[62] They hypothesize that differences in the structure of the RPE monolayer in Asian and black patients relative to white patients render the RPE somewhat resistant to penetration by underlying neovascular tissue.

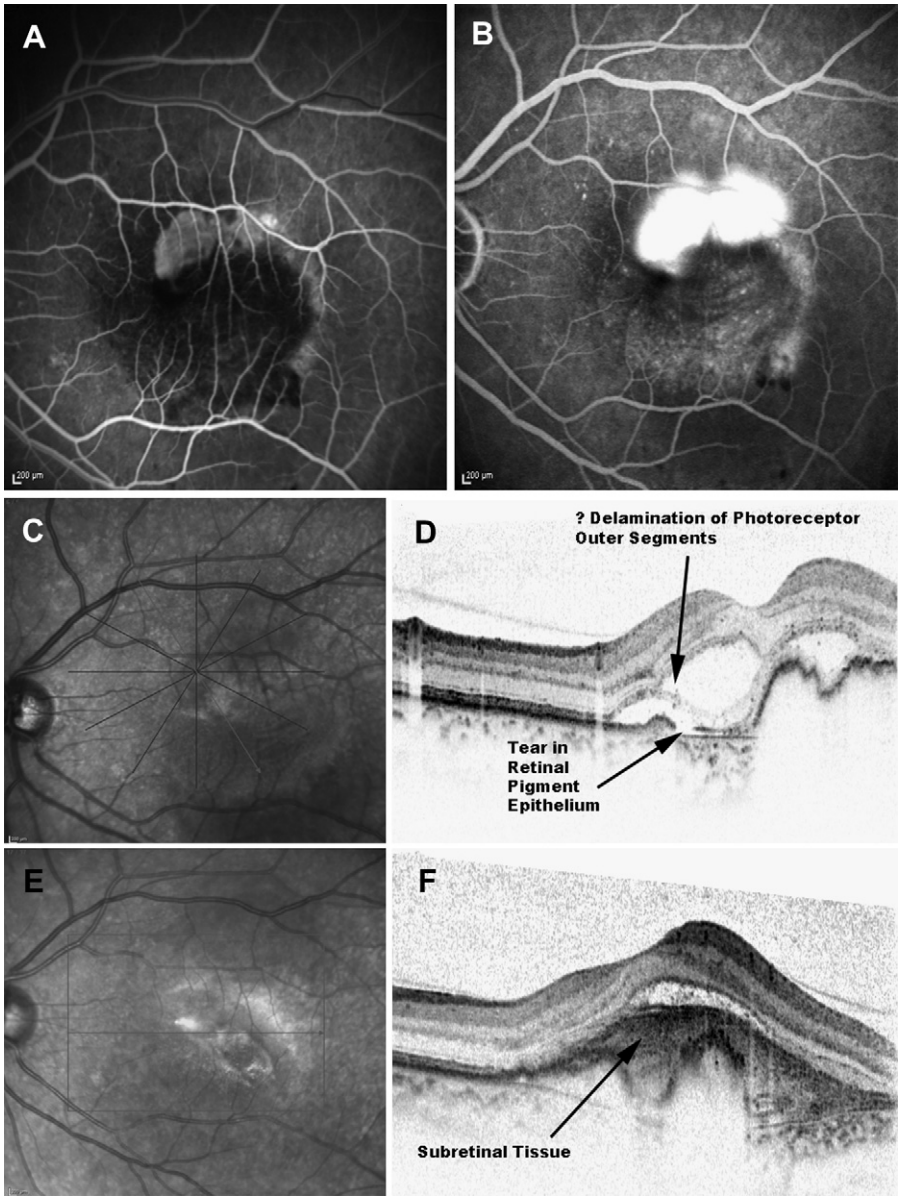

Fig. 14. Tears in the retinal pigment epithelium (RPE) are a well-described complication of neovascular AMD (*A, B*). On OCT, RPE tears are typically seen as an area of discontinuity in a large pigment epithelium detachment (PED) (Spectralis; Heidelberg Engineering) (*C, D*); with time, a disciform scar may form (*E, F*).

As a result, CNV lesions in these populations often demonstrate slow lateral growth with eventual development of saccular dilatations (polyps) and finally to fluid exudation and hemorrhage.

On Stratus OCT, and more recently with spectral domain OCT, the branching vascular network appears as a shallow elevation of the RPE, while the polypoidal lesions appear as sharper protuberances.[2,98,99,175,177,204,209,237] As the exudative complications of these lesions evolve, large serosanguineous PEDs develop adjacent to the polypoidal bulges, creating tomographic notches. With continued exudation, these polypoidal lesions remain adherent to the RPE and are lifted away from Bruch's membrane (Fig. 15).[237] ICG angiography is still considered necessary for the diagnosis of PCV, although OCT is likely to play a greater role as the technology improves and the awareness of this disorder grows.[231]

B. PERIPAPILLARY AND PERIPHERAL CHOROIDAL NEOVASCULARIZATION

In patients with AMD, CNV lesions may sometimes occur in a peripapillary location, that is, contiguous with the optic disc.[15,108,151] As a result the OCT appearance of such patients may differ from that of patients with subfoveal CNV. The natural history

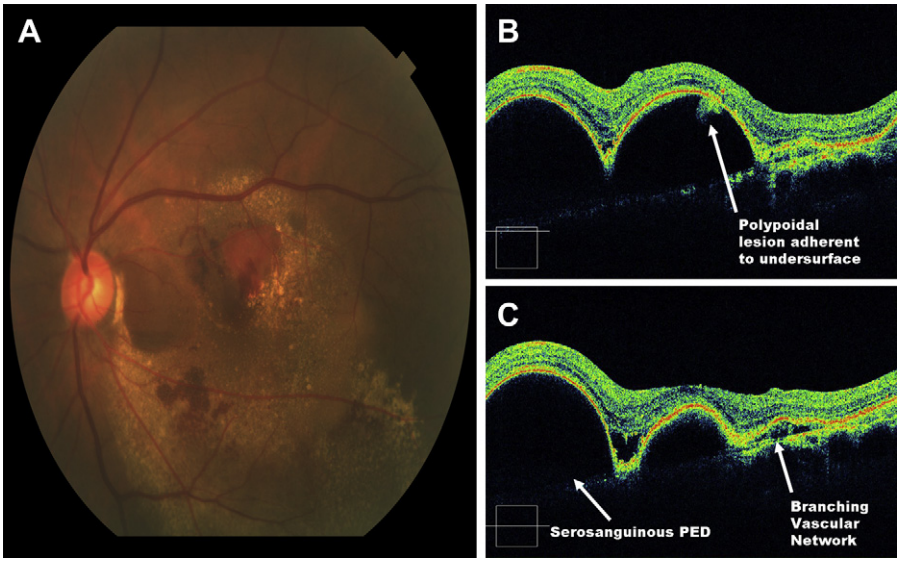

Fig. 15. Polypoidal choroidal vasculopathy (PCV) is associated with a branching vascular network and polypoidal lesions (*A*). On optical coherence tomography (OCT), branching vascular networks are associated with shallow elevations of the retinal pigment epithelium (RPE), while polypoidal lesions appear as sharper protuberances (Cirrus HD-OCT; Carl Zeiss Meditec) *(B, C)*. As the exudative complications of these lesions evolve, large serosanguineous pigment epithelium detachments (PEDs) develop adjacent to the polypoidal bulges, creating a tomographic notch. With continued exudation, these polypoidal lesions remain adherent to the RPE and are lifted away from Bruch's membrane (*B*).

of such lesions may be highly variable.[8,51] In many cases the outer retina and RPE may appear flat at the foveal center; in patients presenting with visual symptoms, however, subretinal fluid is typically seen encroaching from the nasal aspect of the OCT B-scan. OCT image sets are typically centered on the fovea. In patients with putative peripapillary CNV, it may prove more informative to obtain scan patterns centered on the optic disk as such images may better illustrate the presence of hyperreflective tissue in the subretinal space corresponding to CNV and subretinal hemorrhage. Similarly, a minority of patients with AMD may develop CNV lesions outside the posterior pole. Such peripheral CNV is sometimes termed "peripheral exudative hemorrhagic chorioretinopathy," and its manifestations may be seen on OCT when subretinal fluid and lipid exudates encroach on the posterior pole.[43,157,220,236]

VIII. Clinical Applications of Optical Coherence Tomography in Age-related Macular Degeneration

A. DIAGNOSIS AND INITIATION OF THERAPY

Traditionally, fluorescein angiography (FA) has been required for the diagnosis of neovascular AMD;[1,22] with the advent of OCT, however, some question this dogma.[206,233] In elderly patients complaining of acute or subacute unilateral visual loss, the combination of biomicroscopic (e.g., drusen, macular hemorrhage, subretinal fibrosis) and tomographic (e.g., PED, subretinal hyperreflective material, subretinal fluid) findings often allows a diagnosis of neovascular AMD to be made with confidence. This is particularly the case with the advent of spectral domain OCT, given that areas of focal macular pathology are less likely to be missed on raster scanning of the macula.[114] Despite this, clinical studies have not yet adequately addressed this issue, and FA is still regarded by most retinal specialists as mandatory on initial assessment.[22,86] In particular, FA may be useful for the exclusion of other macular disease that can mimic the features of neovascular AMD (e.g., retinal macroaneurysms resulting in submacular hemorrhage, central serous chorioretinopathy resulting in subretinal and sub-RPE fluid, and acquired vitelliform lesions where there is progressive staining of vitelliform-like material).[22] Fluorescein angiography can also highlight those cases where CNV is present but caused by other etiologies (e.g., pathologic myopia, inflammatory disorders, trauma). Such etiologies may respond differently to anti-angiogenic therapy and may benefit from alternative or supplementary treatments regimens.[22] Finally, ICG angiography may also be useful for the assessment of selected cases[231]—for example, in the context of substantial submacular hemorrhage where the presence or extent of underlying CNV is unclear[133,191] or where polypoidal choroidal vasculopathy is suspected.[228]

B. ROLE IN ANTI-ANGIOGENIC RETREATMENT PROTOCOLS

In 2006 the MARINA and ANCHOR phase III clinical trials demonstrated that treatment with ranibizumab was capable of improving visual acuity in many patients with neovascular AMD.[25,195] In parallel with this, use of OCT had become widespread among retinal specialists for the management of neovascular AMD.[58,182] Consequently, OCT measurements were soon adopted as anatomic outcome parameters and as a means of guiding retreatment in clinical trials.[192] In the PrONTO study an OCT-guided variable dosing regimen was assessed for the treatment of neovascular AMD with ranibizumab.[64] Ranibizumab retreatment was performed, in part, based on OCT criteria: a loss of five letters of visual acuity in conjunction with fluid on OCT, an increase of OCT central retinal thickness of at least 100 μm, or the persistence of fluid on OCT one month after previous treatment. In the second year of this study, these criteria were amended so that any qualitative OCT changes suggestive of recurrent fluid in the macula (e.g., the appearance of retinal cysts or subretinal fluid or enlargement of a PED) were indications for retreatment.[142] The results suggest that results similar to the MARINA and ANCHOR trials could be obtained with fewer injections; the small, open-label nature of this study and significant differences in the trial design limit the conclusions that can be drawn, however. More recently, the results of the ABC trial, a double-masked, randomized, controlled trial of bevacizumab for neovascular AMD provided level I evidence for the use of an OCT-guided variable dosing regimen, following three loading treatments with six weekly study visits. In this study the retreatment criteria adopted did not result in any loss of mean visual acuity during the period after the loading phase to the end of the study.[181,238] Similarly, in the large, multicenter CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) study, the efficacies of ranibizumab and bevacizumab were compared using both OCT-guided and fixed, monthly retreatment strategies.[159] Although fixed monthly retreatment led to greater mean visual acuity gain, the differences were not significant for the ranibizumab groups and were inconclusive for the bevacizumab groups. Although the results from the ABC and CATT reports are encouraging, both studies have only reported their findings after approximately one year of follow up. With longer follow-up, the SUSTAIN and HORIZON studies suggest that the chance of substantial visual acuity gain decrease with retreatments that occur less than monthly, whether they be determined on a reduced frequency, fixed dosing schedule or when retreatment decisions are influenced by imaging parameters such as OCT or fluorescein angiography.[22,166]

Although there is a relative lack of evidence from clinical trials, a wide variety of other retreatment regimens, often tailored to healthcare system-specific logistical factors, have been adopted worldwide.[26] In an attempt to minimize both the number of intravitreal injections required and the number of office visits, a "treat and extend" approach has recently been described.[45,46,83,178] In this method monthly injections with ranibizumab are provided until all signs of exudation have resolved on OCT. The treatment interval is then sequentially lengthened by one to two weeks as long as there are no signs of recurrent exudation. When recurrent exudation is detected on a follow-up visit, the treatment interval is reduced to the prior interval. Thus, treatment is rendered at every visit but the time between visits is individualized based on a given patient's response to treatment.

C. TERMINATION OF ANTI-ANGIOGENIC THERAPY

Although there is a considerable body of work documenting the natural history of untreated neovascular AMD,[219,247] the duration of disease activity in patients receiving anti-angiogenic therapy is less clear.[166] Thus, careful monitoring of patients with neovascular AMD using OCT is required over extended time periods. Although unproven, reduction in the frequency of follow-up may be justified when the disease has been quiescent for a protracted period. On occasion termination of treatment for situations other than lack of disease activity may also be required. For example, treatment may be deferred or terminated in situations where further visual improvement appears unlikely (e.g., severe RPE tears involving the foveal center or in the context of significant co-existing geographic atrophy or subfoveal scar formation).[10,11,166] Many of these features are well demonstrated using OCT.

D. CORRELATIONS WITH VISUAL ACUITY

Many clinical trials have demonstrated substantial changes in retinal thickness in response to anti-angiogenic therapies[109,119,202,227]; these studies have failed to find any statistically significant correlation between OCT-derived retinal thickness and visual acuity, however.[170,227] This failure may be due, at least in part, to the frequent inaccuracy of retinal thickness measurements provided by OCT image analysis software.[203] In addition, the older Stratus OCT systems typically ued in such trials use

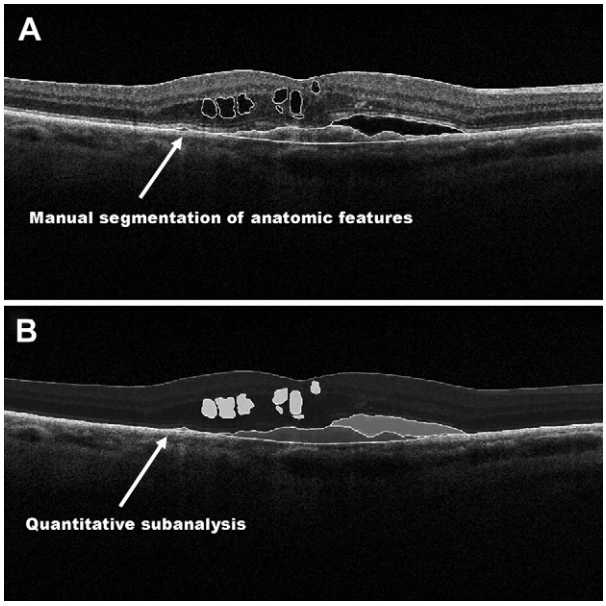

Fig. 16. Optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec) B-scan of an eye demonstrating intraretinal cystoid spaces, subretinal fluid, and pigment epithelium detachment (PED). The clinically relevant boundaries (internal limiting membrane, outer photoreceptor border, retinal pigment epithelium [RPE], and the estimated normal position of the RPE layer [*A*]) are manually graded using custom software (in this case, "OCTOR" software, Doheny Image Reading Center, www.diesel.la), which then computes the volumes of the spaces (retina, subretinal fluid, and PED) defined by these boundaries (*B*).

the presumed IS–OS junction, rather than the RPE, as their outer retinal boundary.[140,189] Manual segmentation of OCT images allows accurate measurement of retinal thickness, as well as allowing quantification of any morphologic space of interest (e.g., intraretinal cysts, subretinal hyperreflective material, subretinal fluid, or PED) (Fig. 16).[104,201] Using this approach, modest correlations have been found between the volume of subretinal hyperreflective material, the thickness of the neurosensory retina, and visual acuity in patients newly diagnosed with neovascular AMD.[117,122] Manual grading has also shown that, for patients receiving ranibizumab, "regression" of any initially gained reductions in retinal thickness is strongly associated with deterioration in visual acuity.[115] Manual segmentation has usually been performed using custom software, although OCT image analysis software from certain vendors has begun to offer this (e.g., Stratus OCT v5.0). Spectral domain OCT may allow more accurate quantification of retinal pathology, although manual grading of these images may not be feasible for large studies.[3,4,47,128,243]

E. CORRELATION WITH FLUORESCEIN ANGIOGRAPHY

CNV lesions in neovascular AMD are commonly described as "classic" or "occult," depending on their leakage characteristics on FA.[13] Classic CNV is believed to correspond to fibrovascular proliferation in the subretinal space, whereas occult CNV is believed to correspond to fibrovascular proliferation beneath the RPE.[80,81,141] This classification may have clinical significance in terms of disease progression over time and impact on visual function. A number of studies have examined the relationship between OCT findings and fluorescein angiography in neovascular AMD.[6,70,134,149,156,179,200,208] In these studies classic lesions are associated with significantly greater volumes of subretinal hyperreflective material than occult lesions, while occult lesions are more commonly associated with PED. These are first steps towards development of hybrid OCT-FA classifications systems for neovascular AMD. Such systems may allow clinicians to identify those patients most likely to respond to any given therapeutic intervention and thus improve clinical outcomes.[62]

IX. Future Directions and Conclusion

OCT has clearly revolutionized the assessment of patients with AMD and other macular disorders; nevertheless, the full potential of OCT for chorioretinal imaging remains to be realized. Current commercial OCT systems, based on spectral domain technology, allow dense scanning of the macula with high axial resolution;[112] as with older systems based on time domain technology, however, the transverse resolution of spectral domain OCT is limited by the optics of the eye.[44] As a result OCT platforms in current clinical practice do not permit visualization of individual cells. In addition, the functional data provided by spectral domain OCT remains rudimentary at best. Better image analysis software is also required to facilitate accurate measurement of OCT-derived morphologic parameters. Future OCT technologies will likely address these limitations. Doppler OCT systems allow measurement of retinal blood flow by the assessment of light reflectivity changes in retinal blood vessels over short time periods.[240–242] "Swept-source" OCT systems allow significant increases in imaging sensitivity and speed (>300,000 A-scans per second) through the use of a tunable laser,[32,33] and polarization-sensitive OCT may prove to encode more RPE specific information than conventional fundus autofluorescence imaging.[5,163,167,186] "Long-wavelength" OCT systems using 1,060 nm rather than ~850 nm allow improved penetration of incident light facilitating

visualization of areas underlying the RPE.[48,187,252] Finally, the use of adaptive optics, namely, the application of a computer-controlled deformable mirror to adjust for distortions in the ocular media, in OCT devices may increase the transverse resolution of OCT systems and provide cellular level detail.[50,171]

In conclusion, the diagnosis and management of AMD and other macular disorders has always been driven in large part by advances in ocular imaging.[250] The advent of fundus fluorescein angiography in the 1960s, and the subsequent pioneering work by Gass, provided the first insights into AMD pathophysiology and highlighted the central role of CNV. The insights provided by this work formed the basis of early attempts at treatment for this disorder with methods such as laser photocoagulation and ultimately provided the rationale for the use of anti-angiogenic therapies such as ranibizumab (Lucentis; Genentech). Three decades after the first description of fundus fluorescein angiography,[173] the introduction of OCT and its application to retinal imaging has led to similarly profound changes in the management of patients with AMD.[96] With the continued rapid development of new technologies, it appears likely that OCT will provide further insights into the pathophysiology and treatment of AMD.

X. Method of Literature Search

References for this review were identified through a comprehensive literature search of the electronic MEDLINE database (1966–2011) using the Pubmed search service. Further articles, abstracts, and textbook references generated from reviewing the bibliographies of the initial search were selectively included. To ensure the up-to-date nature of our review article, current issues of *Archives of Ophthalmology, Surveys of Ophthalmology, American Journal of Ophthalmology, Ophthalmology, British Journal of Ophthalmology, RETINA, Acta Ophthalmologica, Eye, Graefe's Archive for Clinical and Experimental Ophthalmology,* and *Investigative Ophthalmology and Visual Sciences* were regularly reviewed throughout the period of writing. The following key words, and combinations thereof, were used to perform the initial search: *age-related macular degeneration, choroidal neovascularization, cystoid macular edema, drusen, Fourier domain, geographic atrophy, optical coherence tomography, pigment epithelium detachment, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, spectral domain,* and *subretinal fluid.*

XI. Disclosure

Dr Sadda is a co-inventor of Doheny intellectual property related to optical coherence tomography that has been licensed by Topcon Medical Systems, and is a member of the scientific advisory board for Heidelberg Engineering. Dr Sadda also receives research support from Carl Zeiss Meditec, Optos, and Optovue, Inc. He also served as a consultant for Genentech, Inc. and Allergan, Inc. Dr Tufail has been on advisory boards for Novartis, Pfizer, GSK, Thrombogenics, Bayer, and Allergan. Dr Patel has received travel grants from Novartis UK and is a member of the Allergan European Retina Panel. Drs Keane and Tufail have received a proportion of their funding from the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology. The views expressed in the publication are those of the authors and not necessarily those of the Department of Health.

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Other Cited Material

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