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OCT Biomarkers for AMD

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Abstract

Age-related Macular Degeneration (AMD) is an acquired retina disease that can potentially cause significant central visual impairment. Optical coherence tomography (OCT) applied to the study of retinal pathologies has revolutionized the understanding and management of AMD, especially with the technology of full-depth imaging (FDI) Spectral Domain (SD) OCT. With the increasing amount of data from several important studies using SD-OCT and OCT-angiography (OCT-A) we can now better classify and more accurately decode AMD. The purpose of this chapter is to describe the most important AMD biomarkers recently discovered using SD OCT. Understanding AMD phenotype is very important to define prognosis and individualized forms of treatment and follow up. Biomarkers on OCT have been crucial for a better understanding of AMD.

Keywords: AMD, phenotyping, OCT

1. Introduction

Age-related Macular Degeneration (AMD) is an acquired retina disease that can potentially cause significant central visual impairment. Advanced forms of the disease may present as areas of retinal pigment epithelium (RPE) loss, subretinal/sub-RPE hemorrhage or serous fluid, as well as subretinal fibrosis. Severely affected areas may have no visual function, since loss of RPE is associated with photoreceptor collapse.

When OCT (Optical Coherence Tomography) was not available yet, several studies proposed classifications using a wide variety of parameters for AMD grading systems [1–3]. In order to facilitate data comparison among those studies and develop a core grading system using color stereoscopic fundus photography, the International Age-Related Maculopathy Epidemiological Study Group compiled the results of a series of meetings among groups involved in the epidemiological analysis of Age-Related Maculopathy (ARM) [4].

Also The Macular Photocoagulation Study Group contributed significantly to AMD grading, to the understanding of natural history of subfoveal neovascularization as well as to the effectiveness of laser photocoagulation on juxtafoveal neovascularizations [5].

OCT applied to the study of retinal pathologies has revolutionized the understanding and management of AMD, especially with the technology of full-depth imaging (FDI) Spectral Domain (SD) OCT. With the increasing amount of data from several important studies using SD-OCT and OCT-angiography (OCT-A) we can now better classify and more accurately decode AMD.

The purpose of this chapter is to describe the most important AMD biomarkers recently discovered using SD OCT.

2. Cuticular Drusen

Cuticular drusen were first described by Gass in 1977 and consist of a subtype of drusen characterized by being much more numerous than small hard drusen [6]. They frequently coalesce revealing a diffuse appearance. On fluorescein angiography (FA), they are seen as a starry-sky fluorescence pattern that is most evident during the early arteriovenous phase. Some authors suggested that cuticular drusen are often initially visible in the peripheral or midperipheral retina, where the rod-to-cone ratio is the highest [7, 8]. On fundus autofluorescence (FAF), the lesions have a central hypoautofluorescent area with a rim of hyperautofluorescence. The central hypoautofluorescent area corresponds to the area of central hyperfluorescence on FA.

Based on studies with light microscopy and transmission electron microscopy, the location of cuticular drusen was determined to be at the same of hard small drusen and soft drusen: between the inner collagenous layer of the Bruch's membrane and the basal lamina of the RPE [9, 10]. Cuticular drusen are small with steep sides and contain a dense hyalinized component that is identical to hard drusen. This contrasts with soft drusen, which are larger and have sloping sides.

On B-Scan SD-OCT, cuticular drusen are located beneath the RPE and imprint the area below with a pattern of hyperreflectivity alternated with hyporefectivity, providing an aspect similar to a barcode sign. This aspect is due to the thinning of the RPE at the apex of the drusen and thickening at the base of the drusen. On SD-OCT, the height of drusen did not correlate with the area of hyperfluorescence on FA or hypoautofluorescence on FAF (**Figure 1**).

Figure 1. Cuticular drusen. Type 1 (green arrowhead): Shallow elevations of the RPE and basal laminar band. Type 2 (red arrowhead): Triangular shape resulting in a saw-tooth appearance and hyporefective internal contents. Type 3 (yellow arrowhead): Mound-shaped elevations of the RPE and basal laminar band with hyporefective internal contents.

The morphological features of cuticular drusen seen on SD OCT B-scans can be categorized into 3 patterns:

1. Type 1 (33%): characterized by shallow elevations of the RPE
2. Type 2 (49%) with a triangular shape, resulting in a saw-tooth appearance, and hyporreflective internal contents
3. Type 3 pattern (18%) characterized by broad, mound-shaped elevations of the RPE with hyporreflective internal contents [11].

Near infra-red (NIR) images showed variable reflectivity patterns of cuticular drusen: hyporreflective centers with a surrounding hyperreflective margin in 53.9%, diffuse hyperreflectivity in 15.2%, heterogeneous reflectivity in 3.9%, and a combination of these patterns in 27.0%. These variations of aspects demonstrate that the accurate detection of the cuticular drusen phenotype requires the integration of data from more than one imaging method [11].

In a very extensive multimodal analysis, cuticular drusen were shown to be involved in the formation of: RPE clumping, large drusen, vitelliform lesions and subretinal neovascular membranes [11]. In the entire cohort of this study, new pigmentary RPE abnormalities were identified in 47.5% of eyes, large drusen in 45.4%, drusen resorption in 58.3% and drusen coalescence in 70.8%.

Acquired vitelliform lesions (AVL) involving the central macula were seen in 24.2% of the eyes in the study. However, visual acuity in eyes with AVLs was not significantly different from that in eyes without AVLs [11].

Geographic atrophy (GA) was identified in the macula of 25% of the eyes. The frequency of atrophy in patients older than 60 years was significantly greater than in those that were 60 years-old or younger (42.9% vs. 9.4%; $p < 0.001$). Visual acuity (VA) in eyes with atrophy was significantly worse than in those without atrophy (0.32 vs. 0.14 logMAR; $p < 0.001$) [11].

Twelve percent of the cases were complicated by choroidal neovascularization. The frequency of neovascularization in patients older than 60 years was significantly higher than in those that were 60 years-old or younger (19.6% vs. 6.2%; $p < 0.014$). The vast majority of cases (76.7%) were of type 1 neovascularization, while 9 cases were a mixture of type 1 and 2 lesions. There were no cases of type 3 macular neovascularization [11–13].

3. Reticular Drusen

Reticular pseudodrusen are multiple yellowish-white lesions arranged in a reticular network pattern. A distinction between conventional drusen and pseudodrusen was first made in 1990 by Mimoun et al. [14]. More recently the knowledge on pseudodrusen, more accurately called subretinal drusenoid deposits (SDDs), has expanded.

Reticular pseudodrusen have an increased visibility in blue light. On FAF imaging, reticular drusen are shown as numerous spots of reduced autofluorescence, with brighter lines in-between. SDDs frequently spares the fovea and usually are distributed at the superior macula, which has the highest rod-photoreceptor density [15]. Such topographic characteristic is probably related to a rod-photoreceptor association [16–18].

The fluorescein angiographic findings of subretinal drusenoid deposits are subtle, ranging from no demonstrable change to minimal hypofluorescence.

On NIR photography, reticular drusen are hyporreflective lesions, most of them with a lighter center, on a hyperreflective background. The area superior to the fovea, which has the highest rod-photoreceptor density, is the most commonly involved. The fovea, however, is typically spared [15].

The reticular pattern may not be needed for diagnosis, but most studies have required at least five reticular pseudodrusen lesions and multiple imaging modalities for confirmation of the diagnosis.

Histologic evaluation of these deposits revealed aggregation of material in the subretinal space between photoreceptors and the RPE. SDDs contain some proteins that are common to soft drusen but differ in lipid composition. There is a decrease in the number of photoreceptor nuclei above the deposits. These deposits are interconnected, forming a branching pattern [19].

SDDs contain some proteins that are common to soft drusen but differ in lipid composition.

On OCT scans, these lesions are shown as collections of granular hyperreflective deposits located between the RPE layer and the ellipsoid zone (**Figure 2**). These deposits are more commonly seen in older eyes with thinner choroids. Currently, it was shown that retinal thinning in early AMD with reticular pseudodrusen was accompanied by choroidal and retinal vascular loss, which suggests that eyes with reticular pseudodrusen may have limited compliance with changes in ocular perfusion pressure at the level of choroidal and retinal vasculature [20].

OCT has been used to classify SDD into three subtypes [21]:

1. Type 1: characterized by the presence of hyperreflective material between the RPE and the Inner/outer segment junction or ellipsoid zone (EZ). There is no elevation or breach of the EZ
2. Type 2: characterized by hyperreflective material that accumulates and forms a mound over the RPE, with distortion of overlying EZ
3. Type 3 characterized by hyperreflective material that has a conical configuration which perforates the EZ and reaches the outer retina.

Figure 2.

Reticular drusen. The pink arrowhead indicates a stage 1 lesion where diffuse hyperreflective material between the RPE and ellipsoid layer without elevation of the ellipsoid layer. The red arrowhead indicates a stage 2 lesion with increased accumulation of hyperreflective material and distortion of the ellipsoid layer. The yellow arrowhead indicates a stage 3 lesion that has a characteristic conical shape and has punctured through the ellipsoid layer.

Many studies reported that SDDs are strong independent risk factors for late AMD. GA and type 3 neovascularization are particularly associated with SDD. Outer retinal atrophy develops in eyes with regression of SDD, a newly recognized form of late AMD [19, 22].

4. Calcified soft Drusen

This type of drusen originates from classical drusen that had their colloidal content mineralized along time. While classical drusen have a hyperreflective content due to the presence of colloid, calcified drusen have hyporreflective nodules that correspond to hydroxyapatite crystals [23].

Calcified drusen have a glistening appearance due to calcium-containing spherules and a depigmentation area around them. They present with reduced autofluorescence. On OCT, they appear as hyperreflective dots on a hyporreflective base, and they can cause shadowing of deeper structures (**Figure 3**). Refractile deposits within drusen may indicate a higher rate of GA development.

There are three calcified structures associated with advanced AMD: 1) small hyperreflective dots within drusen; [2] heterogeneous internal reflectivity within drusen (HIRD) and 3) hyperreflective lines near the Bruch's membrane. The composition of HIRD and the reason of its hyporreflectivity was not determined yet [24].

5. Subclinical Neovascular membranes

Subclinical neovascular membranes are membranes that are not exuding. Therefore, this is an important biomarker either for an exudative form or for the atrophic form of the disease.

Analyzing the NIR, B Scans and OCT-A, a neovascular complex can be observed without exudation and it is providing an elevated but shallow contour of the pigmented epithelium (**Figure 4**). The initial nomenclature of this type of membrane was quiescent neovascular membrane but more recently terminology for this finding is Shallow Irregular RPE Elevation (SIRE) [25, 26].

Figure 3.
Calcified small drusen (white arrowheads). In this OCT-B scan, it is possible to identify a hyperreflective sheath with a hyporreflective content. There may be hyperreflective dots inside the lesions.

Figure 4. SIRE. Superiorly, en face OCT-A slabs show subretinal neovascular complexes. Inferiorly, the OCT-B scan demonstrates a SIRE with the presence of heterogeneous material beneath the RPE. Additionally, it is possible to note the absence of intraretinal or subretinal fluid.

The baseline prevalence of this type of neovascularization in patients with AMD was around 13 to 14%. Exudative shift at 12 months had a prevalence of 6.8% among patients without Non-Exudative Macular Neovascularization (NE-MNV) and of 21.1% among patients with NE-MNV. Exudative shift at 24 months had a prevalence of 6.3% among patients without NE-MNV and of 34.5% among patients with NE-MNV. Therefore, it is recommendable a very close follow-up of the patients identified with SIRE [25, 26].

6. Hyperreflective foci

A concept that came to light with SD-OCTs, that we did not have previously with angiography or retinography, is intraretinal hyperreflective foci (HRF). HRF are well-circumscribed, discrete lesions with an equal or superior reflectivity compared to the RPE band on OCT (**Figure 5**). They are usually associated with hyperpigmentation on color fundus photography. There is an important specific spatial correlation of HRF with the apex of drusen [27] and/or SDD [28]. Additionally, there is an association between HRF overlying drusen and increased risk of atrophy at that location. HRF in eyes with intermediate AMD could be the result of migration of activated RPE cells into the inner retinal layers, as proposed by in vivo OCT study [29].

Figure 5.
Hyperreflective foci are observed in the inner (pink arrowhead) and outer retina (orange arrowhead).

Its development is triggered by a process of gliosis and phagocytosis of the Muller cells, followed by accumulation of decomposed cells in hyperreflective deposits, such as the mechanism observed in MacTel. The debris can be located at the external limiting membrane, external nuclear layer and the plexiform layer. They are biomarkers of poor prognosis, because they reveal that Muller Cells are losing their structure and will collapse [30].

Among patients classified as having intermediate AMD, the choriocapillaris flow deficit is apparently worse in eyes with HRF and is commonly located directly below HRF [31]. The amount of HRF was correlated with EZ normalized reflectivity and drusen volume (DV), that are well-defined markers of photoreceptor damage and AMD progression, respectively. Nassisi et al. [32] evaluated the correlation between HRF quantity and progression to advanced AMD after 1 year. He concluded that the area of HRF measured by en face OCT in eyes with intermediate AMD was highly correlated with development of atrophy [33, 34].

7. Acquired Vitelliform lesion

AVLs are deposits of melanosomes, melanolipofuscin, lipofuscin and outer segment debris located between the RPE and the photoreceptor layer (**Figure 6**). Their pathophysiology may be related to paraneoplastic, toxic, degenerative and vitreoretinal interface disorders of the macula.

AVL were correlated with SDD and cuticular drusen in the past and can occur in conjunction with large drusen. The same dysfunctional processes that lead to drusen formation, or parallel processes, could be related to AVL formation [35].

On fundus exam and SD-OCT, AVLs manifests as yellowish deposits between the EZ or external limiting membrane (ELM) and RPE. On FAF, they appear as areas of hyperautofluorescence that corresponded to the sites where vitelliform material was seen on SD-OCT and fundus exam. In some cases with pseudohypopyon, on FAF it is possible to identify a hypoautofluorescent top portion and a hyperautofluorescent inferior portion. On FA, there is early

Figure 6.

Acquired Vitelliform lesion: OCT B-scan detects an accumulation of hyperreflective material between the ellipsoid layer and the RPE. This material (white arrowhead) is located above soft drusen, with discrete thinning of the overlying outer retinal layers.

hypofluorescence with a halo of hyperfluorescence. A progressive late staining of the lesion was noted during the exam. On red-free imaging studies, AVLs manifest with a slight hyperchromia of the material [36].

The lifecycle of an AVL is characterized by a phase of growth followed resorption and, over time, it can lead to complications as foveal atrophy and choroidal neovascularization (type 1 in 8% of cases). These complications are frequent and can impair central vision. There is a decrease in visual acuity from 0,3 to 0,5 logMAR (2 to 3 lines on log scale) in 7 years. Development of neovascular complexes occurs during the collapse phase of the AVL life cycle, after the AVL peak volume was reached. Type 1 choroidal neovascularization occurs in nearly 10% of cases. The risk of neovascularization and the decline in best corrected visual acuity (BCVA) are both significantly greater among eyes with AMD. Foveal atrophy was the characteristic most significantly associated with final BCVA and with change in BCVA from baseline. The development of neovascularization was not predictive of long-term visual outcomes [37].

8. Drusenoid PED

A drusenoid pigment epithelial detachment (PED) is a large elevation of the RPE that is formed from the coalescence of drusen and colloid material. It is a hallmark feature of AMD and a known precursor of GA. It may be distinguished from hemorrhagic and serous PEDs by its appearance on clinical exam and angiography (**Figure 7**). Drusenoid PEDs have an accelerated growth rate of 0,022 mm³/month. Additionally, its rate of collapse is 10 times faster: 0,199 mm³/month, similarly to the observed in AVL. The onset of intraretinal hyperreflective foci and AVL usually precedes its collapse.

Features such as maximal height, volume and diameter of drusenoid PEDs were inversely correlated with visual acuity and directly correlated with the rate of collapse [38].

Figure 7.
Drusenoid PED. In this OCT-B scan, it is possible to note a lesion that has an internal homogenous and mild hyperreflectivity. The lesion is delimited by the Bruch's membrane at its base.

9. Macular neovascularization

In the exudative form of AMD, the local production of vascular endothelial growth factor (VEGF) promotes the growth of choroidal neovascularization. These lesions were initially classified in: classic, occult, and variations (predominantly classic and minimally classic) based on their characteristics on FA.

Gass proposed [39] that the location of the neovascular membrane could be important to predict response to treatment and after the advent of OCT, an alternative classification was suggested:

9.1 Type 1

In this type the vessels are located in the sub-RPE space (**Figure 8**). It is the most common type of neovascularization in AMD. On FA, these lesions are depicted as occult or poorly defined CNV (choroidal neovascularization). Other FA terminologies are used to describe type 1 neovascular complex: vascularized RPE, vascularized PED or stippled hyperfluorescence. On indocyanine green angiography (ICG-A), this neovascular membrane appears as an area of low-intensity hyperfluorescence, known as plaque. On SD-OCT, it is possible to determine its location on a space bounded inferiorly by the hyperreflective remnants of Bruch membrane and superiorly by the hyperreflective RPE band. A new finding of the type 1 neovascularization was described by Spaide [40] recently. It was observed that when the RPE becomes elevated due to sub-RPE exudation, the neovessels adhere to the basal surface of the RPE. On Enhanced Depth Imaging (EDI) OCT, this is described as a hyperreflective material (supposed to be the neovascularization) lining the undersurface of the elevated RPE. This pattern may explain the vulnerability of type 1 neovascularization to RPE tears. This subgroup also includes polypoidal vasculopathy, which was recently renamed as aneurysmal type 1 neovascularization.

Figure 8.
Type 1 neovascularization, also known as aneurysmal type 1 subretinal neovascular membrane. Inferiorly, OCT-B scan demonstrates PED with shallow subretinal fluid and intraretinal cystic degeneration. Superiorly, OCT-A slabs detect a branch vascular network ending in an aneurysm formation (yellow circle) located between the RPE and the Bruch's membrane.

9.2 Type 2

It consists of a neovascular membrane that has perforated the RPE/Bruch membrane complex and is growing in the space between the neurosensory retina and the RPE [40]. On FA, these new vessels are commonly described as being classic or having a well-defined contour (**Figure 9**). Due to the attenuation of the choroidal fluorescence by the interjacent RPE promoting the formation of a dark background, the new vessels appear to fluoresce intensely. On the other hand, on ICG-A it may be challenging to identify the neovascular complex due to the intense hyperfluorescence of the background choroidal circulation. It is common to detect type 2 neovascularization along with type 1 vessels in exudative AMD. It is also possible that a type 2 neovascular complex regresses and turns into a type 1.

On OCT, it is possible to detect a disorganization of the overlying inner/outer segment junction in conjunction with intraretinal cystic spaces. Additionally, this exam identifies intraretinal rather than subretinal fluid.

9.3 Type 3

Type 3 neovascularization is the recent terminology for what once was known as Retinal Angiomatous Proliferation (RAP) and consists of an intraretinal neovascularization. Notable discussions happened regarding whether the origin of this neovascular complex was from the retinal circulation (as Yanuzzi suggested) or from the choroidal circulation (as suggested by Gass). Some studies support the

Figure 9.
Type 2 neovascularization. En face OCT-A projection images of the neovascular complex with vessels both in the outer retina and the choriocapillaris (pink circles). Inferiorly, an OCT-B scan demonstrates the neovascular complex (arrowhead) located between the RPE and the neurosensory retina.

Figure 10.
Type 3 neovascularization. On the left, en face OCT-A slabs show the vascular lesion (pink circles) in the superficial and deep segments of the retina. The OCT-B scan, on the left, demonstrates the presence of intraretinal fluid, caused by the vascular lesion before treatment with anti-VEGF (arrowhead). On the right, en face OCT-A slabs still show the vascular lesion (orange circle), although the OCT-B scan, on the right, demonstrates resolution of fluid after the first injection of anti-VEGF (this type of neovascularization tends to respond well to treatment with anti-VEGF).

theory that the origin of this neovascular complex can be from either circulation and may arise from both circulations at the same time as a Retinal-Choroidal Anastomosis (RCA) (**Figure 10**).

On OCT, it is characterized by large amounts of intraretinal fluid as well as a thin choroid. In this aspect it differs from types 1 and 2 neovascularization that have an associated thickened choroid. Another differential aspect, is that type 3 neovascularization leads more often to retinal atrophy due to damage to the external retina caused by its intraretinal origin and the thinner choroid [39, 41].

10. Outer retina atrophy

Geographic Atrophy (GA) is a late-stage disease manifestation of non-neovascular AMD that generally progresses to severe central vision loss. It has traditionally been defined on color fundus photography as a sharply delineated circular or oval area of hypopigmentation or depigmentation in which choroidal vessels are visible. The size required for a lesion to be classified as GA varies with different studies, ranging from 175 μm to 430 μm in diameter.

Autofluorescence of these areas indicate them as hypoautofluorescent lesions, that may have a hyperautofluorescent rim, which is linked to acute suffering of the RPE. Atrophic areas typically demonstrate a late well-defined hyperfluorescence.

On OCT, as drusen regress, the overlying retinal layers undergo characteristic changes, while progressing to atrophy, that can be captured on OCT imaging. These changes, referred to as nascent GA in previous reports, include subsidence of the inner nuclear layer (INL) and outer plexiform layer (OPL), a hyporeflective wedge-shaped band within the Henle fiber layer (HFL), often accompanied by RPE disturbance, and increased signal hypertransmission into the choroid [42].

OCT-A shows significant impairment on the choriocapillaris flow in the zone immediately surrounding GA lesions. OCT-A seems to be able to give us information about the progression of atrophy, since the flow at the choriocapillary layer is diminished in the perifoveal region if compared to the parafoveal regions [43].

Previous studies have identified characteristic fundus features that are associated with a high risk for progression to GA [44]. Features related to a greater chance of developing GA are: large drusen volume, calcified drusen, intraretinal hyperreflective foci and SDD.

Spaide was one of the first to describe that outer retina atrophy could result from regression of SDD [45]. The outcomes of this study showed that, 43% of patients would eventually develop choroidal neovascularization after a period of two years and 43% would develop regression of SDD. Patients that had regression of SDD, had a decrease in the photoreceptor length, decrease in choroidal thickness and loss of ellipsoid band.

A score was proposed to better follow patients [28]. Among the scoring factors, there are: hyporeflective drusen, hyperreflective intraretinal foci, subretinal drusenoid deposits, and volume of large drusen. In order to generate the score, one point was assigned to each feature present in the study eye. The fellow eye was scored in a similar fashion. By adding the scores from both eyes, the total score (TS) is calculated. Category I is defined as a TS of 0, 1 or 2. Category II is defined as a TS of 3 or 4. Category III corresponds to a TS of 7 or 8. According to this score, in category I there was 0% chance to develop retinal atrophy; in category II there was a chance of 14,3%; in category III there was a chance of 47,5% and in category IV the chance was of 73%. The results allowed to conclude that patients in category I could be safely seen every 12 months, whereas patients in category II, III and IV could be seen every 6, 4 and 3 months, respectively [28, 43].

10.1 Classification of outer retina and RPE atrophy

GA usually is characterized by RPE atrophy and recently received the term RPE and outer retina atrophy (RORA). When there is a photoreceptor loss without RPE atrophy, the term proposed is outer retina atrophy (ORA). ORA also occurs in eyes after regression of reticular pseudodrusen. SD-OCT is characterized by thinning of the outer retina, including the ELM and the inner segment of the EZ band and decreased choroidal thickness. ORA increases the risk for progression to RORA or macular neovascularization [44].

Figure 11.
cRORA. The green arrow in the red-free image, on the left, shows the location where the OCT B-scan, on the right, was taken. This scan demonstrates an area greater than 250μm in diameter with choroidal hypertransmission due to absence of the RPE layer and overlying outer retinal thinning and loss of photoreceptors.

Figure 12.
iRORA. OCT-B scan demonstrates choroidal heterogeneous hypertransmission (pink arrowhead), subsidence of the INL and OPL (green arrowhead) as well as RPE attenuation and overlying photoreceptor disruption (red arrowhead).

Along several meetings, experts proposed a classification according to OCT findings and four terms were described: cRORA, complete RPE and outer retina atrophy; iRORA, incomplete RPE and outer retina atrophy; cORA, complete outer retinal atrophy and iORA, incomplete outer retinal atrophy (**Figures 11–14**) [46].

iRORA is defined on OCT by the following criteria: (1) a region of signal hypertransmission into the choroid, (2) a corresponding zone of attenuation or disruption of the RPE, with or without persistence of basal laminar deposits, and (3)

Figure 13.
cORA. OCT-B scan demonstrates thinning of the outer retina with loss of visibility of the ELM, EZ, IZ (interdigitation zone) (red arrowhead). It is possible to note regressing reticular pseudodrusen (yellow arrowhead).

Figure 14.
iORA. OCT-B scan demonstrates thinning of the outer retina where intermittent areas of EZ and ELM can still be identified (arrowhead). It is also possible to note an uninjured RPE layer.

evidence of overlying photoreceptor degeneration (subsidence of the INL and OPL, presence of a hyporeflective wedge in the Henle fiber layer (HFL), thinning of the outer nuclear layer (ONL), disruption of the external limiting membrane (ELM), or disintegration of the EZ), and when these criteria do not meet the definition of cRORA. A minimum size to determine that a lesion is iRORA was not proposed. iRORA progresses into cRORA over a variable period, from months to years. If each of the areas of RPE change and hypertransmission has a diameter of at least 250 μm on the OCT B-scan, in addition to evidence of photoreceptor loss, then they qualify as cRORA.

En face OCT allows to observe a hyperreflective contour that is the ELM descent. On FAF, this border is hyperautofluorescent. Studies have confirmed histologically that the descent ELM is an important biomarker for the development of a complete atrophy of the RPE and outer retina. Increase of ELM reflectivity also was found as possible biomarker for severe photoreceptor loss and gliosis [47–53].

Understanding AMD phenotype is very important to define prognosis and individualized forms of treatment and follow up. Biomarkers on OCT have been crucial for a better understanding of AMD.

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References

- [1] Bressler, N. M., Bressler, S. B., West, S. K., Fine, S. L., & Taylor, H. R. (1989). The grading and prevalence of macular degeneration in Chesapeake Bay watermen. *Archives of ophthalmology (Chicago, Ill. : 1960)*, 107(6), 847–852. <https://doi.org/10.1001/archophth.1989.01070010869032>
- [2] Gregor, Z., Bird, A. C., & Chisholm, I. H. (1977). Senile disciform macular degeneration in the second eye. The British journal of ophthalmology, 61(2), 141–147. <https://doi.org/10.1136/bjo.61.2.141>
- [3] Klein, R., Klein, B. E., & Linton, K. L. (1992). Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology*, 99(6), 933–943. [https://doi.org/10.1016/s0161-6420\(92\)31871-8](https://doi.org/10.1016/s0161-6420(92)31871-8)
- [4] Bird, A. C., Bressler, N. M., Bressler, S. B., Chisholm, I. H., Coscas, G., Davis, M. D., de Jong, P. T., Klaver, C. C., Klein, B. E., & Klein, R. (1995). An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Survey of ophthalmology*, 39(5), 367–374. [https://doi.org/10.1016/s0039-6257\(05\)80092-x](https://doi.org/10.1016/s0039-6257(05)80092-x)
- [5] Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group. (1991). *Archives of ophthalmology (Chicago, Ill. : 1960)*, 109(9), 1220–1231. <https://doi.org/10.1001/archophth.1991.01080090044025>
- [6] Gass JDM. Stereoscopic Atlas of Macular Diseases. Diagnosis and Treatment. 2nd ed. St. Louis: C.V. Mosby; 1977:46-50
- [7] Boon, C. J., van de Ven, J. P., Hoyng, C. B., den Hollander, A. I., & Klevering, B. J. (2013). Cuticular drusen: stars in the sky. *Progress in retinal and eye research*, 37, 90–113. <https://doi.org/10.1016/j.preteyeres.2013.08.003>
- [8] Boon, C. J., Klevering, B. J., Hoyng, C. B., Zonneveld-Vrieling, M. N., Nabuurs, S. B., Blokland, E., Cremers, F. P., & den Hollander, A. I. (2008). Basal laminar drusen caused by compound heterozygous variants in the CFH gene. *American journal of human genetics*, 82(2), 516–523. <https://doi.org/10.1016/j.ajhg.2007.11.007>
- [9] Russell, S. R., Mullins, R. F., Schneider, B. L., & Hageman, G. S. (2000). Location, substructure, and composition of basal laminar drusen compared with drusen associated with aging and age-related macular degeneration. *American journal of ophthalmology*, 129(2), 205–214. [https://doi.org/10.1016/s0002-9394\(99\)00345-1](https://doi.org/10.1016/s0002-9394(99)00345-1)
- [10] Spaide, R. F., & Curcio, C. A. (2010). Drusen characterization with multimodal imaging. *Retina (Philadelphia, Pa.)*, 30(9), 1441–1454. <https://doi.org/10.1097/IAE.0b013e3181ee5ce8>
- [11] Balaratnasingam, C., Cherepanoff, S., Dolz-Marco, R., Killingsworth, M., Chen, F. K., Mendis, R., Mrejen, S., Too, L. K., Gal-Or, O., Curcio, C. A., Freund, K. B., & Yannuzzi, L. A. (2018). Cuticular Drusen: Clinical Phenotypes and Natural History Defined Using Multimodal Imaging. *Ophthalmology*, 125(1), 100–118. <https://doi.org/10.1016/j.ophtha.2017.08.033>
- [12] Tan, C. S., Heussen, F., & Sadda, S. R. (2013). Peripheral autofluorescence and clinical findings in neovascular and non-neovascular age-related macular degeneration. *Ophthalmology*, 120(6), 1271–1277. <https://doi.org/10.1016/j.ophtha.2012.12.002>
- [13] Domalpally A, Clemons TE, Danis RP, et al. (2017) Peripheral retinal

changes associated with age-related macular degeneration in the Age-Related Eye Disease Study 2: Age-Related Eye Disease Study 2 report number 12 by the Age-Related Eye Disease Study 2 Optos PEripheral RetinA (OPERA) Study Research Group. *Ophthalmology*, 124:479-487.

[14] Mimoun, G., Soubrane, G., & Coscas, G. (1990). Les drusen maculaires [Macular drusen]. *Journal francais d'ophtalmologie*, 13(10), 511-530.

[15] Klein, R., Meuer, S. M., Knudtson, M. D., Iyengar, S. K., & Klein, B. E. (2008). The epidemiology of retinal reticular drusen. *American journal of ophthalmology*, 145(2), 317-326.

[16] Curcio, C. A., Messinger, J. D., Sloan, K. R., McGwin, G., Medeiros, N. E., & Spaide, R. F. (2013). Subretinal drusenoid deposits in non-neovascular age-related macular degeneration: morphology, prevalence, topography, and biogenesis model. *Retina (Philadelphia, Pa.)*, 33(2), 265-276. <https://doi.org/10.1097/IAE.0b013e31827e25e0>

[17] Curcio, C. A., Sloan, K. R., Kalina, R. E., & Hendrickson, A. E. (1990). Human photoreceptor topography. *The Journal of comparative neurology*, 292(4), 497-523. <https://doi.org/10.1002/cne.902920402>

[18] Zarubina, A. V., Neely, D. C., Clark, M. E., Huisinigh, C. E., Samuels, B. C., Zhang, Y., McGwin, G., Jr, Owsley, C., & Curcio, C. A. (2016). Prevalence of Subretinal Drusenoid Deposits in Older Persons with and without Age-Related Macular Degeneration, by Multimodal Imaging. *Ophthalmology*, 123(5), 1090-1100. <https://doi.org/10.1016/j.ophtha.2015.12.034>

[19] Zweifel, S. A., Spaide, R. F., Curcio, C. A., Malek, G., & Imamura, Y. (2010). Reticular pseudodrusen are subretinal

drusenoid deposits. *Ophthalmology*, 117(2), 303-12.e1. <https://doi.org/10.1016/j.ophtha.2009.07.014>

[20] Ahn, S. M., Lee, S. Y., Hwang, S. Y., Kim, S. W., Oh, J., & Yun, C. (2018). Retinal vascular flow and choroidal thickness in eyes with early age-related macular degeneration with reticular pseudodrusen. *BMC ophthalmology*, 18(1), 184. <https://doi.org/10.1186/s12886-018-0866-3>

[21] Zweifel, S. A., Imamura, Y., Spaide, T. C., Fujiwara, T., & Spaide, R. F. (2010). Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. *Ophthalmology*, 117(9), 1775-1781. <https://doi.org/10.1016/j.ophtha.2010.01.027>

[22] Spaide, R. F., Ooto, S., & Curcio, C. A. (2018). Subretinal drusenoid deposits AKA pseudodrusen. *Survey of ophthalmology*, 63(6), 782-815. <https://doi.org/10.1016/j.survophtha.2018.05.005>

[23] Pilgrim, M. G., Lengyel, I., Lanzirotti, A., Newville, M., Fearn, S., Emri, E., Knowles, J. C., Messinger, J. D., Read, R. W., Guidry, C., & Curcio, C. A. (2017). Subretinal Pigment Epithelial Deposition of Drusen Components Including Hydroxyapatite in a Primary Cell Culture Model. *Investigative ophthalmology & visual science*, 58(2), 708-719. <https://doi.org/10.1167/iovs.16-21060>

[24] Tan, A. C. S., Pilgrim, M. G., Fearn, S., Bertazzo, S., Tsolaki, E., Morrell, A. P., Li, M., Messinger, J. D., Dolz-Marco, R., Lei, J., Nittala, M. G., Sadda, S. R., Lengyel, I., Freund, K. B., & Curcio, C. A. (2018). Calcified nodules in retinal drusen are associated with disease progression in age-related macular degeneration. *Science Translational Medicine*, 10(466), [eaat4544]. <https://doi.org/10.1126/scitranslmed.aat4544>

[25] de Oliveira Dias, J. R., Zhang, Q., Garcia, J., Zheng, F., Motulsky, E. H.,

- Roisman, L., Miller, A., Chen, C. L., Kubach, S., de Sisternes, L., Durbin, M. K., Feuer, W., Wang, R. K., Gregori, G., & Rosenfeld, P. J. (2018). Natural History of Subclinical Neovascularization in Nonexudative Age-Related Macular Degeneration Using Swept-Source OCT Angiography. *Ophthalmology*, 125(2), 255–266. <https://doi.org/10.1016/j.ophtha.2017.08.030>
- [26] Yang, J., Zhang, Q., Motulsky, E. H., Thulliez, M., Shi, Y., Lyu, C., de Sisternes, L., Durbin, M. K., Feuer, W., Wang, R. K., Gregori, G., & Rosenfeld, P. J. (2019). Two-Year Risk of Exudation in Eyes with Nonexudative Age-Related Macular Degeneration and Subclinical Neovascularization Detected with Swept Source Optical Coherence Tomography Angiography. *American journal of ophthalmology*, 208, 1–11. <https://doi.org/10.1016/j.ajo.2019.06.017>
- [27] Folgar, F. A., Chow, J. H., Farsiu, S., Wong, W. T., Schuman, S. G., O'Connell, R. V., Winter, K. P., Chew, E. Y., Hwang, T. S., Srivastava, S. K., Harrington, M. W., Clemons, T. E., & Toth, C. A. (2012). Spatial correlation between hyperpigmentary changes on color fundus photography and hyperreflective foci on SDOCT in intermediate AMD. *Investigative ophthalmology & visual science*, 53(8), 4626–4633. <https://doi.org/10.1167/iovs.12-9813>
- [28] Lei, J., Balasubramanian, S., Abdelfattah, N. S., Nittala, M. G., & Sadda, S. R. (2017). Proposal of a simple optical coherence tomography-based scoring system for progression of age-related macular degeneration. *Graefes archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*, 255(8), 1551–1558. <https://doi.org/10.1007/s00417-017-3693-y>
- [29] Ho, J., Witkin, A. J., Liu, J., Chen, Y., Fujimoto, J. G., Schuman, J. S., & Duker, J. S. (2011). Documentation of intraretinal retinal pigment epithelium migration via high-speed ultrahigh-resolution optical coherence tomography. *Ophthalmology*, 118(4), 687–693. <https://doi.org/10.1016/j.ophtha.2010.08.010>
- [30] Echols, B. S., Clark, M. E., Swain, T. A., Chen, L., Kar, D., Zhang, Y., Sloan, K. R., McGwin, G., Jr, Singireddy, R., Mays, C., Kilpatrick, D., Crosson, J. N., Owsley, C., & Curcio, C. A. (2020). Hyperreflective Foci and Specks Are Associated with Delayed Rod-Mediated Dark Adaptation in Nonneovascular Age-Related Macular Degeneration. *Ophthalmology. Retina*, 4(11), 1059–1068. <https://doi.org/10.1016/j.oret.2020.05.001>
- [31] Tiosano, L., Byon, I., Alagorie, A. R., Ji, Y. S., & Sadda, S. R. (2020). Choriocapillaris flow deficit associated with intraretinal hyperreflective foci in intermediate age-related macular degeneration. *Graefes archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*, 258(11), 2353–2362. <https://doi.org/10.1007/s00417-020-04837-y>
- [32] Nassisi, M., Fan, W., Shi, Y., Lei, J., Borrelli, E., Ip, M., & Sadda, S. R. (2018). Quantity of Intraretinal Hyperreflective Foci in Patients With Intermediate Age-Related Macular Degeneration Correlates With 1-Year Progression. *Investigative ophthalmology & visual science*, 59(8), 3431–3439. <https://doi.org/10.1167/iovs.18-24143>
- [33] Ouyang, Y., Heussen, F. M., Hariri, A., Keane, P. A., & Sadda, S. R. (2013). Optical coherence tomography-based observation of the natural history of drusenoid lesion in eyes with dry age-related macular degeneration. *Ophthalmology*, 120(12), 2656–2665. <https://doi.org/10.1016/j.ophtha.2013.05.029>

- [34] Leuschen, J. N., Schuman, S. G., Winter, K. P., McCall, M. N., Wong, W. T., Chew, E. Y., Hwang, T., Srivastava, S., Sarin, N., Clemons, T., Harrington, M., & Toth, C. A. (2013). Spectral-domain optical coherence tomography characteristics of intermediate age-related macular degeneration. *Ophthalmology*, 120(1), 140–150. <https://doi.org/10.1016/j.ophtha.2012.07.004>
- [35] Lima, L. H., Laud, K., Freund, K. B., Yannuzzi, L. A., & Spaide, R. F. (2012). Acquired vitelliform lesion associated with large drusen. *Retina* (Philadelphia, Pa.), 32(4), 647–651. <https://doi.org/10.1097/IAE.0b013e31823fb847>
- [36] Bastos, R. R., Ferreira, C. S., Brandão, E., Falcão-Reis, F., Carneiro, A. (2016). Multimodal Image Analysis in Acquired Vitelliform Lesions and Adult-Onset Foveomacular Vitelliform Dystrophy, *Journal of Ophthalmology*, vol. 2016, Article ID 6037537, 6 pages, 2016. <https://doi.org/10.1155/2016/6037537>
- [37] Balaratnasingam, C., Hoang, Q. V., Inoue, M., Curcio, C. A., Dolz-Marco, R., Yannuzzi, N. A., Dhrami-Gavazi, E., Yannuzzi, L. A., & Freund, K. B. (2016). Clinical Characteristics, Choroidal Neovascularization, and Predictors of Visual Outcomes in Acquired Vitelliform Lesions. *American journal of ophthalmology*, 172, 28–38. <https://doi.org/10.1016/j.ajo.2016.09.008>
- [38] Balaratnasingam, C., Yannuzzi, L. A., Curcio, C. A., Morgan, W. H., Querques, G., Capuano, V., Souied, E., Jung, J., & Freund, K. B. (2016). Associations Between Retinal Pigment Epithelium and Drusen Volume Changes During the Lifecycle of Large Drusenoid Pigment Epithelial Detachments. *Investigative ophthalmology & visual science*, 57(13), 5479–5489. <https://doi.org/10.1167/iovs.16-19816>
- [39] Freund, K. B., Zweifel, S. A., & Engelbert, M. (2010). Do we need a new classification for choroidal neovascularization in age-related macular degeneration?. *Retina* (Philadelphia, Pa.), 30(9), 1333–1349. <https://doi.org/10.1097/IAE.0b013e3181e7976b>
- [40] Spaide, R. F., Jaffe, G. J., Sarraf, D., Freund, K. B., Sadda, S. R., Staurengi, G., Waheed, N. K., Chakravarthy, U., Rosenfeld, P. J., Holz, F. G., Souied, E. H., Cohen, S. Y., Querques, G., Ohno-Matsui, K., Boyer, D., Gaudric, A., Blodi, B., Bauman, C. R., Li, X., Coscas, G. J., ... Fujimoto, J. (2020). Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. *Ophthalmology*, 127(5), 616–636. <https://doi.org/10.1016/j.ophtha.2019.11.004>
- [41] Nagiel, A., Sarraf, D., Sadda, S. R., Spaide, R. F., Jung, J. J., Bhavsar, K. V., Ameri, H., Querques, G., & Freund, K. B. (2015). Type 3 neovascularization: evolution, association with pigment epithelial detachment, and treatment response as revealed by spectral domain optical coherence tomography. *Retina* (Philadelphia, Pa.), 35(4), 638–647. <https://doi.org/10.1097/IAE.0000000000000488>
- [42] Schaal, K. B., Gregori, G., & Rosenfeld, P. J. (2017). En Face Optical Coherence Tomography Imaging for the Detection of Nascent Geographic Atrophy. *American journal of ophthalmology*, 174, 145–154. <https://doi.org/10.1016/j.ajo.2016.11.002>
- [43] Nassisi, M., Shi, Y., Fan, W., Borrelli, E., Uji, A., Ip, M. S., & Sadda, S. R. (2019). Choriocapillaris impairment around the atrophic lesions in patients with geographic atrophy: a swept-source optical coherence tomography angiography study. *The British journal of ophthalmology*, 103(7), 911–917. <https://doi.org/10.1136/bjophthalmol-2018-312643>

- [44] Age-Related Eye Disease Study Research Group (2001). The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. *American journal of ophthalmology*, 132(5), 668–681. [https://doi.org/10.1016/s0002-9394\(01\)01218-1](https://doi.org/10.1016/s0002-9394(01)01218-1)
- [45] Spaide R. F. (2013). Outer retinal atrophy after regression of subretinal drusenoid deposits as a newly recognized form of late age-related macular degeneration. *Retina (Philadelphia, Pa.)*, 33(9), 1800–1808. <https://doi.org/10.1097/IAE.0b013e31829c3765>
- [46] Sadda, S. R., Guymer, R., Holz, F. G., Schmitz-Valckenberg, S., Curcio, C. A., Bird, A. C., Blodi, B. A., Bottoni, F., Chakravarthy, U., Chew, E. Y., Csaky, K., Danis, R. P., Fleckenstein, M., Freund, K. B., Grunwald, J., Hoyng, C. B., Jaffe, G. J., Liakopoulos, S., Monés, J. M., Pauleikhoff, D., ... Staurenghi, G. (2018). Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3. *Ophthalmology*, 125(4), 537–548. <https://doi.org/10.1016/j.ophtha.2017.09.028>
- [47] Sarks S. H. (1976). Ageing and degeneration in the macular region: a clinico-pathological study. *The British journal of ophthalmology*, 60(5), 324–341. <https://doi.org/10.1136/bjo.60.5.324>
- [48] Sarks, J. P., Sarks, S. H., & Killingsworth, M. C. (1988). Evolution of geographic atrophy of the retinal pigment epithelium. *Eye (London, England)*, 2 (Pt 5), 552–577. <https://doi.org/10.1038/eye.1988.106>
- [49] Zanzottera, E. C., Ach, T., Huisinigh, C., Messinger, J. D., Spaide, R. F., & Curcio, C. A. (2016). VISUALIZING RETINAL PIGMENT EPITHELIUM PHENOTYPES IN THE TRANSITION TO GEOGRAPHIC ATROPHY IN AGE-RELATED MACULAR DEGENERATION. *Retina (Philadelphia, Pa.)*, 36 Suppl 1(Suppl 1), S12–S25. <https://doi.org/10.1097/IAE.0000000000001276>
- [50] Li, M., Dolz-Marco, R., Huisinigh, C., Messinger, J. D., Feist, R. M., Ferrara, D., Freund, K. B., & Curcio, C. A. (2019). CLINICOPATHOLOGIC CORRELATION OF GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION. *Retina (Philadelphia, Pa.)*, 39(4), 802–816. <https://doi.org/10.1097/IAE.0000000000002461>
- [51] Dolz-Marco, R., Balaratnasingam, C., Messinger, J. D., Li, M., Ferrara, D., Freund, K. B., & Curcio, C. A. (2018). The Border of Macular Atrophy in Age-Related Macular Degeneration: A Clinicopathologic Correlation. *American journal of ophthalmology*, 193, 166–177. <https://doi.org/10.1016/j.ajo.2018.06.020>
- [52] Li, M., Dolz-Marco, R., Messinger, J. D., Ferrara, D., Freund, K. B., & Curcio, C. A. (2021). Neurodegeneration, gliosis, and resolution of haemorrhage in neovascular age-related macular degeneration, a clinicopathologic correlation. *Eye (London, England)*, 35(2), 548–558. <https://doi.org/10.1038/s41433-020-0896-y>
- [53] Garrity, S. T., Sarraf, D., Freund, K. B., & Sadda, S. R. (2018). Multimodal Imaging of Nonneovascular Age-Related Macular Degeneration. *Investigative ophthalmology & visual science*, 59(4), AMD48–AMD64. <https://doi.org/10.1167/iovs.18-24158>