

Morphologic Changes in Patients with Geographic Atrophy Assessed with a Novel Spectral OCT–SLO Combination

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PURPOSE. To investigate the appearance of geographic atrophy in high-resolution optical coherence tomography (OCT) images, the fundus autofluorescence (FAF) pattern, and infrared images simultaneously recorded with a novel combined OCT-scanning laser ophthalmology (SLO) system.

METHODS. Patients aged over 50 years with geographic atrophy secondary to dry age-related macular degeneration (ARMD) were assessed in a prospective cross-sectional study by means of simultaneous spectral OCT-SLO (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). The integrity of the retinal layers was analyzed in the apparently normal areas, the junctional zone between the normal retina and the geographic atrophy, and the atrophic area. The presence and integrity of the external limiting membrane, the photoreceptor inner segments, the outer segments, and the retinal pigment epithelium were assessed.

RESULTS. Fifty-two eyes of 52 patients (28 women, 24 men) aged 51 to 92 years were examined. Retinal layer alterations were documented, not only in atrophic zones, but also in junctional zones surrounding the geographic atrophy. Disintegration of the retinal layers began in the RPE and adjacent retinal layers, such as the photoreceptor inner and outer segments and external limiting membrane.

CONCLUSIONS. Novel imaging modalities will provide further valuable insight into ARMD pathogenesis. The key to understanding the morphologic change lies in *in vivo* depiction of retinal layers by spectral OCT technology in combination with other imaging modalities such as FAF. (*Invest Ophthalmol Vis Sci.* 2008;49:3095–3099) DOI:10.1167/iovs.07-1460

Geographic atrophy (GA) is a frequent cause of severe visual loss in patients with age-related macular degeneration (ARMD).^{1–4} The pathogenic mechanism underlying the atrophic process remains putative. However, the data indicate the involvement of not only the retinal pigment epithelial (RPE) but also the outer neurosensory retinal layer and the choriocapillaris.⁴

Lipofuscin accumulates in RPE cells within the lysosomal compartment^{5–7} with age, but controversy still exists with regard to the effects of lipofuscin on RPE cell function. Results in recent studies have implied that lipofuscin and A2E may

interfere with healthy RPE cell function, including lysosomal degradation.^{8–10} Fundus spectrometric studies by Delori et al.¹¹ and Dorey et al.¹² showed that fundus autofluorescence (FAF) *in vivo* is mainly derived from the lipofuscin in the RPE. The advent of scanning laser ophthalmology (SLO) made possible easy, noninvasive imaging of FAF and its spatial distribution over the whole retina.^{13,14} Abnormal FAF patterns in the junctional zone of GA have been demonstrated by SLO in patients with ARMD.^{13–15}

For a better understanding of the morphologic and structural pathogenic mechanisms underlying the atrophic processes, detailed imaging is very important.¹⁶ Tomographic retinal imaging is provided by optical coherence tomography (OCT), which was introduced into the clinical routine during the past decade as a noninvasive means of assessing the posterior pole of the human eye.¹⁷ OCT allows for the analysis of retinal morphology and the assessment of structural change within the retina. OCT is an evolving technology. Current advances—for example, the introduction of Fourier analysis (spectral OCT)—have made both high resolution and fast scanning speed possible.¹⁸ High resolution allows for differentiation of as much as 11 structural characteristics within the retina.^{18,19} SLO is used for generating high-resolution digital images of the fundus.²⁰ The recorded images can be used for assessment of topographic detail and tracking of pathologic changes.^{13,14,20,21} Both imaging modalities have so far been considered complementary.²² However, it is the combination of both devices (spectral OCT and SLO) that seems to offer profound insights and may be valuable for follow-up examinations.

In this study, we investigated the appearance of GA in high-resolution OCT images, the FAF pattern, and infrared images simultaneously recorded with a novel combined OCT-SLO system.

MATERIALS AND METHODS

Patients aged 50 years or more with GA secondary to dry ARMD have been included into this prospective cross-sectional study. Inclusion criteria included clear media to allow FAF imaging and a total area of GA larger than 0.5 mm². Only one eye of each patient was included in the study. If both eyes qualified for the study, the eye with the better visual acuity (VA) was used. Exclusion criteria included any history of retinal surgery, laser photocoagulation, or other retinal diseases in the study eye, including diabetic retinopathy or hereditary retinal dystrophies, and refractive error of more than 3 D. Fluorescein angiography was performed only if there were fundoscopic signs indicative of exudative ARMD in addition to GA. Such eyes were excluded from the study. All subjects underwent FAF, infrared (IR), and simultaneous spectral OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) imaging. In addition, we performed a comprehensive ocular examination with best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, binocular ophthalmoscopy color fundus photography (FF 450 plus; Carl Zeiss Meditec, Jena, Germany), and fluorescein angiography using the Hei-

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Submitted for publication November 14, 2007; revised March 13, 2008; accepted May 9, 2008.

Disclosure: U.E.K. Wolf-Schnurrbusch, None; V. Enzmann, None; C.K. Brinkmann, None; S. Wolf, None

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delberg Retina Angiograph (HRA, Heidelberg Engineering). In addition, ARMD risk factors (e.g., sex, family history, and status of smoking) were assessed with a standardized questionnaire.

The Spectralis HRA+OCT combines high-resolution spectral domain OCT with an SLO. The system allows for simultaneous OCT scans with FAF imaging, infrared imaging, blue light reflectance imaging, fluorescein angiography, or indocyanine green (ICG) angiography. The instrument uses broadband 870-nm super luminescent diode (SLD) for the OCT channel. The retina is scanned at 40,000 A-scans per second, crating highly detailed images of the structure of the retina. The OCT optical depth resolution is 7 μm , the digital depth resolution, 3.5 μm . The combination of high-resolution scanning laser retinal images and spectral domain OCT allows for real-time tracking of eye movements and real-time averaging of scanning laser images and OCT scans, reducing speckle noise of the OCT images. Twenty-five OCT scans were averaged to reduce speckle noise by a factor five.

Before examination, the pupil of the study eye was dilated with drops containing 0.5% tropicamide and 2.5% phenylephrine. We obtained two spectral OCT scans in cross-hair fashion centered on the fovea. Thereafter, combined FAF images and spectral OCT images were recorded.

The spectral OCT images were graded as follows: The integrity of the retinal layers was analyzed in the areas with apparently normal retina, the junctional zone between the normal retina and the geographic atrophy, and within the atrophic area. Especially, the presence and integrity of the external limiting membrane (ELM), the photoreceptor inner segment (IS), the outer segment (OS), and the retinal pigment epithelium (RPE) was assessed. The presence of a third hyperreflective layer just above the RPE and the below the IS/OS complex was noted. In addition, integrity of the inner retinal layers, foveal depression, and presence of intraretinal fluid accumulation were evaluated (Fig. 1).

FAF images were classified according to Holz et al.¹⁵ as follows: group 1, GA without any abnormal FAF outside the area of atrophy; group 2, GA with a *continuous band* at the margin with variable peripheral extension; group 3, GA with a *diffusely increased* FAF at the entire posterior pole; and group 4, GA surrounded from *small focal spots* of increased FAF in the junctional zone.

All images were assessed by two independent graders from the Bern Photographic Reading Center (BPRC) in blinded fashion. In case of discrepancies between the two observers, the differences were discussed, and a third observer was asked to arbitrate.

The research adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Informed consent was obtained from each subject after explanation of the nature and possible risks of the study.

RESULTS

Fifty-two eyes of 52 patients (28 women, 24 men) aged 51 to 92 years (mean: 72.4 ± 6.3 years) with uni- or multifocal GA

(unifocal: 16 eyes; multifocal 36 eyes) due to dry ARMD were included in this prospective cross-sectional study.

In areas with apparently normal retina the integrity of all inner and outer retinal layers was seen in spectral OCT in all eyes (52/52, 100%). The display of these defined structures in the OCT is due to high resolution of distinct retinal interfaces and intensity and contrast are comparable to those shown in Figure 1. Especially the ELM, photoreceptor IS and OS, and RPE, as well as a third hyperreflective layer just above the RPE, were present.

In the junctional zone between the normal retina and the area of GA, alterations in the layer structure were found in all eyes (Fig. 2). The inner retinal layers were normal in most eyes (49/52, 94%), whereas the outer retinal layers showed structural alteration in all eyes (52/52). Such structural alteration is seen as a partial loss of defined boundaries between the layers. Especially, the ELM was damaged and partly destroyed in the junctional zone. The integrity of photoreceptor IS and OS was not preserved, and the RPE showed rarefactions and thinning and an increased optical reflectivity. In most cases (41/52) we found some high reflective material on the level of the RPE in the junctional zone, possibly caused by RPE hypertrophy²³ and/or phagocytosed melanin by RPE/macrophages.²⁴ A third hyperreflective layer just above the RPE was present in 2 (4%) of 52 eyes.

In the areas of GA, the integrity of inner retinal layers was preserved in most eyes (40/52, 78%), but the outer retinal layers showed severe structural alteration in all 52 eyes, characterized by a complete loss of defined boundaries between the layers. The ELM, IS, OS, and a third hyperreflective layer just above the RPE were not detectable. Corresponding to the areas of GA on the SLO channel, the spectral OCT scan showed well-defined areas of extensive thinning of the RPE in all eyes. An increased optical reflectivity from the choroid due to increased penetration of the light through the atrophic RPE was also observed in all GA areas.

The fovea was not affected by GA in 20 (38%) of 52 eyes. In these eyes, a normal foveal depression was present. The inner and outer retinal layers were distinguishable in the fovea but showed irregularities (for examples, see Fig. 2).

In 32 (62%) of 52 eyes the fovea was included in the area of GA, but in 12 of these 32 eyes a foveal depression could be detected (Fig. 3). Severe alterations in inner retinal structures were observed in 3 of the 32 eyes. The outer retinal structures were destroyed in all eyes, and the ELM was not detectable in those areas.

There was a marked spatial correspondence between the absence of FAF and RPE atrophy seen in spectral OCT. Similarly, the absence of FAF corresponded spatially with areas of GA on fundus photographs (color and infrared images; Fig. 4).

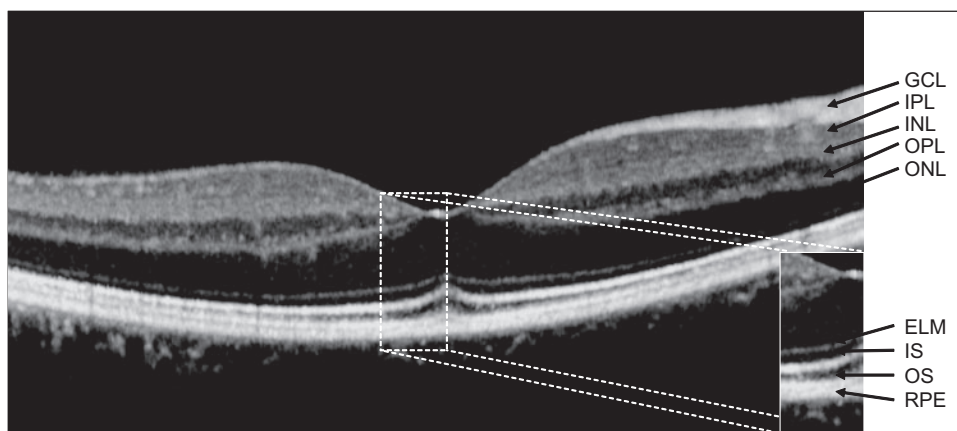


FIGURE 1. Normal retina as imaged by HRA+OCT. *Arrows:* the ganglion cell layer (GCL), the inner plexiform layer (IPL), the inner nuclear layer (INL), the outer plexiform layer (OPL), and outer nuclear layer (ONL). *Inset:* appearance of the ELM, the photoreceptor IS and OS, and the RPE. Please note the appearance of the choroid and the pluglike structure in the center of the fovea formed by Henle's fibers.

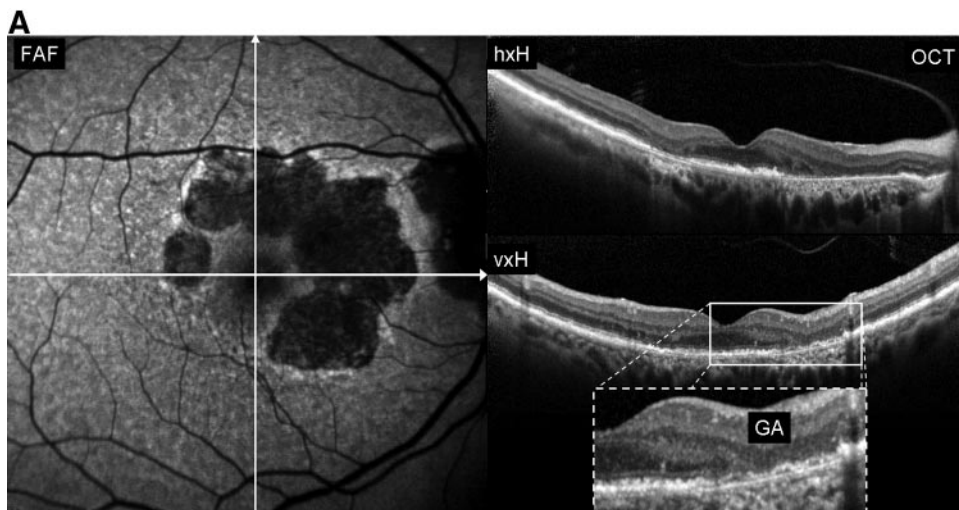
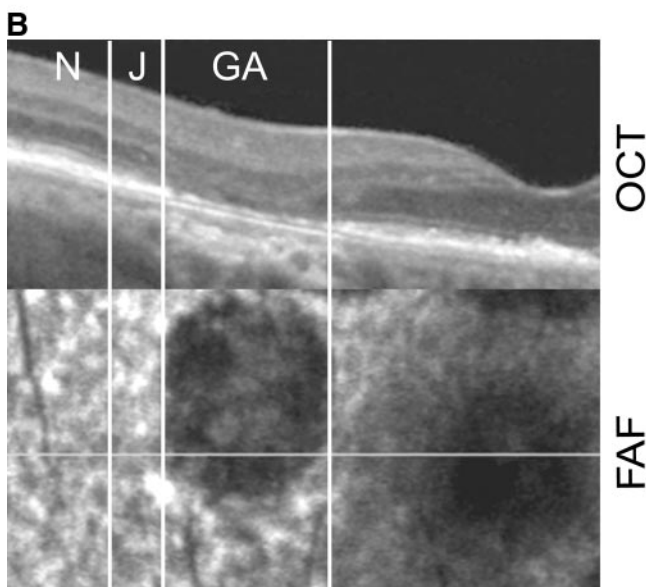


FIGURE 2. (A) FAF and spectral OCT images from an 80-year-old woman (BCVA 20/40). FAF showed a *small continuous band* at the margin with variable peripheral extension. The vertical (vxH) and the horizontal (hxH) scans on OCT showed a nearly normal-shaped fovea. In the foveal area, the ELM and the photoreceptor layers were preserved, whereas in the adjacent atrophic area the ELM was not visible (see magnification from the vxH scan). Please note the lack of photoreceptor body reflex as well the thinned RPE reflex in the atrophic area (see magnification). Outside the atrophic area pseudoreticular drusen were visible. The RPE in this area appeared to be thickened. (B) In the GA area, the inner retinal layer structure was normal, and the outer retinal layers showed structural alteration. The ELM was not detectable in the GA area. Outside the GA the retinal layer structure appeared normal (N). In the junctional zone (J) alterations between the layer structures were found.



However, the borders of the GA in funduscopy and on fundus photographs were not as well defined as in spectral OCT and FAF.

Using the FAF images we grouped the patterns of GA as follows: A total of 8 (15%) 52 eyes showed GA without visible abnormal FAF outside the area of atrophy (group 1).

All other 44 (85%) of 52 patients presented different forms of abnormal FAF patterns surrounding the area of GA. FAF with a *small continuous band* at the margin with variable peripheral extension was noted in a majority of these eyes (30/44, 68%) and included in group 2 (Fig. 2). FAF with a *diffusely increased* autofluorescence at the entire posterior pole (group 3) was seen in 8/44 (18%) eyes (Fig. 3), and FAF with *small focal spots* of increased autofluorescence in the junctional zone (group 4) was observed in 6 (14%) of 44 eyes.

Looking at the junctional zone with an abnormal FAF pattern (groups 2-4) we noted quantitative differences: Most alteration in the retinal layer structure in the junctional zone was seen in the patients of group 2. These changes were relatively homogenous and corresponded with the width of the continuous band at the margin of the GA. In group 4 (FAF with *small focal spots* of increased autofluorescence in the junctional zone) the structural layer irregularities seen on spectral OCT corre-

sponded pixel to pixel with the focal spots of increased autofluorescence seen on the simultaneous FAF image. In group 3 (FAF with a *diffusely increased* FAF at the entire posterior pole) only a few alterations were noted in the retinal layer structure by spectral OCT. The areas showed irregular borders and corresponded pixel to pixel to the areas with diffusely increased FAF.

BCVA (ETDRS) of all study eyes was 64.2 ± 8.7 letters (approximately 20/68; logMAR -0.53). Letter scores ranged from counting fingers scoring 0 letters up to 90 letters.

We found significant differences between the best corrected VA depending on areas of GA and the configuration of the fovea. The mean VA letter score of all eyes with a normal foveal depression and without atrophic changes at the fovea (A, $n = 20$) was significantly higher compared to the eyes without a normal foveal depression and with GA involving the foveal region (B, $n = 32$; mean VA letter score_A: 82.1 ± 9.1 letters (20/32; logMAR -0.2) vs. mean VA letter score_B: 45.4 ± 8.2 letters (20/160; logMAR -0.9 ; $P < 0.01$).

Neither the age of the patients, nor the presence of additional ARMD risk factors (e.g., sex, family history, status of smoking) revealed significant differences among the groups 1 to 4.

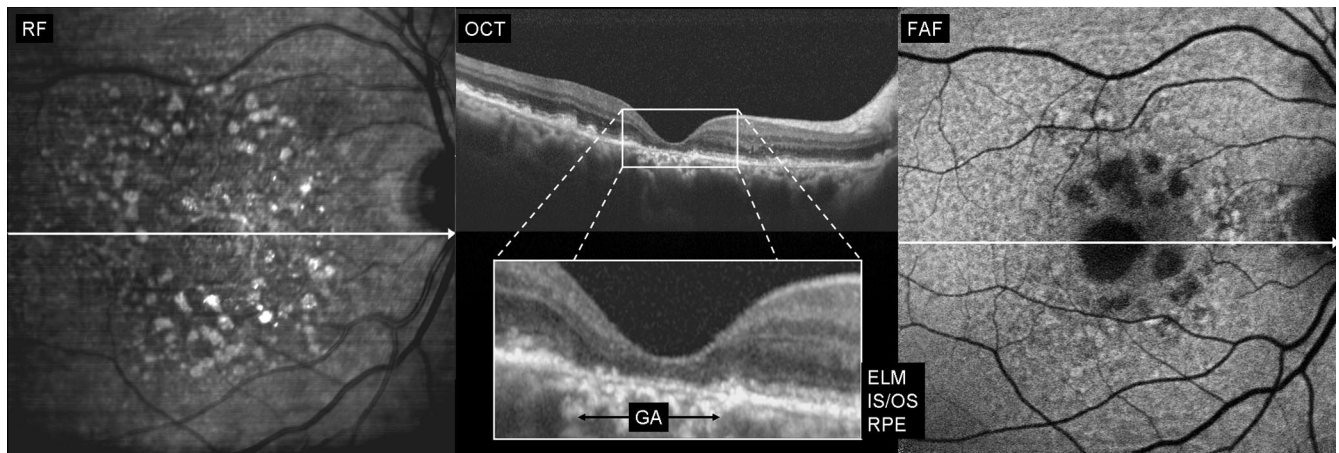


FIGURE 3. Red-free (RF), OCT, and FAF images from a 76-year-old woman (BCVA 20/200). The area of GA included the fovea, but a foveal depression was seen. However, the foveal depression appeared not to be normal. On the horizontal OCT scan small, well-defined atrophic patches were found. In areas of GA (see magnification of the fovea) the inner retinal layer structure was present, but the outer retinal layer showed structural alteration, and the ELM was not detectable. OCT demonstrated increased penetration of light through the atrophic region, which was most significant nasal to the fovea leading to enhanced reflectivity from the choroids. FAF revealed GA with *diffusely increased* FAF at the entire posterior pole.

DISCUSSION

In the work of Drexler et al.¹⁹ ultrahigh-resolution OCT (UHR-OCT) was used to describe images of several selected patients with different macular diseases. They found that UHR-OCT can enhance visualization of intraretinal morphologic features and could be used to evaluate the integrity of each retinal layer.

In our study, the inner and outer retinal layers were normal on high-resolution spectral OCT scans in areas with apparently normal retina, seen in fundus photography and FAF. The ELM, the photoreceptor IS and OS, and the RPE were especially visible in all eyes.

The junctional zone between normal retina and GA revealed alterations in the layer structure in all eyes. There were differences between the integrity of inner and outer retinal layers in the examined eyes. Although the integrity of the inner retinal layer was present in most cases, the outer retinal layers showed alteration in all eyes. The ELM seemed to have particularly disintegrated in the junctional zone. These outer layer alterations could be related to swelling of damaged RPE cells. One trigger for this may be an increased accumulation of lipofuscin and/or melanin in the junctional zone of eyes with GA, as demonstrated previously,^{25,26} and it may be consistent with

the findings of highly reflective material in the junctional zone of our patients. In our study, there was no remnant of the ELM in areas of GA. Since this analysis was not planned, we are not able to quantify sensitivity and specificity for these changes. However, the absence of ELM seems to be a good predictor of alterations in the outer retinal layer structure. On the other hand, inner retinal layers remained intact in most eyes. Disintegration and loss of defined boundaries of the inner retinal layers may take more time because these layers are less vulnerable, in that they are not as dependent on the function of an intact RPE. However, these changes may develop over time due to neural remodeling initialized by the deafferented inner retina after the loss of the outer retina.²⁷ Cytokines/growth factors released during the disease process could have similar effects.²⁸

UHR-OCT offers improved visualization of smaller structures¹⁹ in the retinal layers. The pixel-to-pixel correspondence between the spectral OCT image and the FAF (or red-free image) makes it easier to find “small lesions” on the FAF image and to analyze them on OCT. This method may help to correlate OCT findings in an accurate way or to observe small lesions longitudinally.

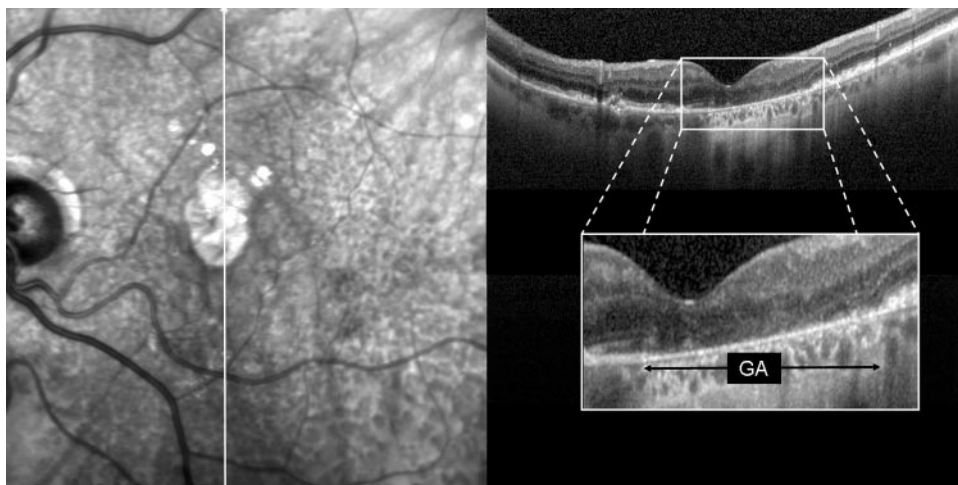


FIGURE 4. Near IR and OCT images from an 85-year-old man (BCVA 20/200). The area of GA included the fovea, but a foveal depression was seen. On the vertical OCT scan the atrophic area showed a loss of the reflexes from the ELM and OS/IS. The RPE reflex (see magnification of the fovea) was significantly thinner than in the adjacent nonatrophic areas. OCT demonstrated increased penetration of light through the atrophic region, with increase visibility of choroidal structures.

We categorized the FAF images according to the classification from Holz et al.¹⁵ In general, most patients with GA due to dry ARMD show abnormal FAF patterns outside the GA. In our study we also noticed differences in the retinal layer alterations related to certain FAF patterns. Various patterns of FAF in the junctional zone of GA may reflect the heterogeneity of the underlying disease mechanisms. When a small, continuous band at the margin of the GA was detected on FAF, we observed extensive, relatively homogenous alterations in the outer retinal layers. These alterations corresponded with the width of the *continuous band* in the FAF at the margin of the GA.

The structural alterations in the group with *small focal spots* of increased FAF in the junctional zone are very confined. They corresponded pixel to pixel to the focal spots of increased FAF seen in the simultaneous FAF image of the HRA+OCT. In the group with FAF with a *diffusely increased* FAF at the entire posterior pole, only a few alterations in the retinal layer structure were observed.

As in many samples of multimodal imaging^{16,29} the combined spectral OCT-SLO system seems to offer unique perspectives and insights to retinal disease. High resolution is derived from broadband light sources and high-speed acquisition from Fourier spectral analysis. OCT thus achieves unprecedented morphologic assessment with less motion or noise artifact. In addition to histologic studies and OCT images, examination with the SLO provides information on spatial distribution of retinal diseases. Especially, variations in lipofuscin-mediated pathogenic processes can be appreciated in FAF. In our opinion the pixel-to-pixel correspondence between both modalities is relevant for analyzing the topographic variation in lipofuscin accumulation (e.g., spots of increased FAF). The high resolution of the corresponding imaging modalities allows for an allocation of OCT-scans in any desired position on the SLO image. This may increase our knowledge of the structure and pathogenic mechanisms in the outer neurosensory retina layer, the RPE layer, and the choriocapillaris, which are involved in the pathophysiological processes resulting in GA. In addition, the structural findings using HRA+OCT may be useful in detecting a treatment effect early in clinical trials for GA.

References

- Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology*. 1999;106(9):1768-1779.
- Maguire P, Vine AK. Geographic atrophy of the retinal pigment epithelium. *Am J Ophthalmol*. 1986;102:621-625.
- Holz F, Wolfensberger T, Piquet B, et al. Bilateral macular drusen in age-related macular degeneration. *Ophthalmology*. 1994;101:1522-1528.
- Holz FG, Bellman C, Staudt S, Schutt F, Volcker HE. Fundus autofluorescence and development of geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2001;42(5):1051-1056.
- Bermann M, Schutt F, Holz FG, Kopitz J. Does A2E, a retinoid component of lipofuscin and inhibitor of lysosomal degradative functions, directly affect the activity of lysosomal hydrolases? *Exp Eye Res*. 2001;72(2):191-195.
- Weiter JJ, Delori FC, Wing GL, Fitch KA. Retinal pigment epithelial lipofuscin and melanin and choroidal melanin in human eyes. *Invest Ophthalmol Vis Sci*. 1986;27:145-152.
- Kennedy CJ, Rakoczy PE, Constable JJ. Lipofuscin of the retinal pigment epithelium: a review. *Eye*. 1995;9:763-771.
- Eldred GE, Lasky MR. Retinal age pigments generated by self-assembling lysomotropic detergents. *Nature*. 1993;361:724-726.
- Boulton M, Marshall J. Effects of increasing numbers of phagocytic inclusions on human RPE cells in culture: a model of aging. *Br J Ophthalmol*. 1986;70:808-815.
- Boulton M, Dayhaw-Barker P. The role of the retinal pigment epithelium: topographical variation and ageing changes. *Eye*. 2001;15:384-389.
- Delori FC, Dorey CK, Staurenghi G, Arend O, Gorger DG, Weiter JJ. In vivo fluorescence of the ocular fundus exhibits retinal pigment epithelium lipofuscin characteristics. *Invest Ophthalmol Vis Sci*. 1995;36:718-729.
- Dorey CK, Staurenghi G, Delori FC. *Lipofuscin in Aged and AMD Eyes*. New York: Plenum Press; 1993.
- von Rückmann A, Fitzke F, Bird A. Fundus autofluorescence in age-related macular disease imaged with a scanning laser ophthalmoscope. *Invest Ophthalmol Vis Sci*. 1997;38(2):478-486.
- Solbach U, Keilhauer C, Knabben H, Wolf S. Imaging of retinal autofluorescence in patients with age-related macular degeneration. *Retina*. 1997;17(5):385-389.
- Holz FG, Bellmann C, Margaritidis M, Schutt F, Otto TP, Volcker HE. Patterns of increased in vivo fundus autofluorescence in the junctional zone of geographic atrophy of the retinal pigment epithelium associated with age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 1999;237(2):145-152.
- Bernardes R, Lobo C, Cunha-Vaz JG. Multimodal macula mapping: a new approach to study diseases of the macula. *Surv Ophthalmol*. 2002;47(6):580-589.
- Puliafito CA, Hee MR, Lin CP, et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995;102:217-229.
- Ruggeri M, Wehbe H, Jiao S, et al. In vivo three-dimensional high-resolution imaging of rodent retina with spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2007;48(4):1808-1814.
- Drexler W, Sattmann H, Hermann B, et al. Enhanced visualization of macular pathology with the use of ultrahigh-resolution optical coherence tomography. *Arch Ophthalmol*. 2003;121(5):695-706.
- Webb RH, Hughes GW, Delori FC. Confocal scanning laser ophthalmoscope. *Appl Optics*. 1987;26:1492-1499.
- Sharp PF, Manivannan A. The scanning laser ophthalmoscope. *Phys Med Biol*. 1997;42(5):951-966.
- Sharp PF, Manivannan A, Xu H, Forrester JV. The scanning laser ophthalmoscope: a review of its role in bioscience and medicine. *Phys Med Biol*. 2004;49(7):1085-1096.
- Rakoczy P, Zhang D, Robertson T, et al. Progressive age-related changes similar to age-related macular degeneration in a transgenic mouse model. *Am J Pathol*. 2002;161(4):1515-1524.
- Crafoord S, Kopp ED, Seregard S, Alverer PV. Cellular migration into neural retina following implantation of melanin granules in the subretinal space. *Graefes Arch Clin Exp Ophthalmol*. 2000;238(8):682-689.
- Sarks SH. Drusen patterns predisposing to geographic atrophy of the retinal pigment epithelium. *Aust J Ophthalmol*. 1982;10(2):91-97.
- Green WR, Enger C. Age-related macular degeneration histopathologic studies. *Ophthalmology*. 1993;100:1519-1535.
- Marc R, Jones B, Watt C, Strettoi E. Neural remodeling in retinal degeneration. *Prog Retin Eye Res*. 2003;22:607-655.
- Wiedemann P. Growth factors in retinal diseases: proliferative retinopathy, proliferative diabetic retinopathy, and retinal degeneration. *Surv Ophthalmol*. 1992;36(2):373-384.
- Podoleanu AG, Dobre GM, Cucu RG, et al. Combined multiplanar optical coherence tomography and confocal scanning ophthalmoscopy. *J Biomed Opt*. 2004;9(1):86-93.