

Evaluating Age-related Macular Degeneration With Ultra-widefield Fundus Autofluorescence

Patterns in the periphery may offer prognostic clues regarding progression.

BY SRINIVAS R. SADDA, MD

Approximately 2 million Americans currently have advanced age-related macular degeneration (AMD), and the disease remains the leading cause of blindness among older adults in the United States and other developed countries, with a global prevalence estimated at more than 40 million.¹ As new therapeutic approaches to AMD are developed, improved outcomes will depend on our ability to detect retinal pathology as early as possible and understand the prognostic value of what we are seeing. The more readily we can identify which patients are likely to progress to advanced non-neovascular or neovascular disease, the better opportunity we will have to slow or prevent associated vision loss.

With this objective in mind, we have recently begun to evaluate the utility of Optos ultra-widefield (UWF) retinal imaging, specifically the potential role of UWF peripheral fundus autofluorescence (FAF), in classifying AMD. Our findings to date have confirmed that a substantial amount of pathology can be detected in the periphery (that is, outside the central 30°) with autofluorescence, underscoring the potential relevance of these findings to disease progression and revealing distinct pathologic patterns that we have been able to correlate with clinical features of AMD.²

FAF IN AMD

The use of FAF to examine the retinal pigment epithelium (RPE) and neurosensory retina is well established; this imaging modality can detect retinal pathology related to AMD that may not be visible with ophthalmoscopy. These findings have also been shown to have prognostic value, even helping to predict which eyes are at greater risk for progression to advanced disease.³

FAF reflects the lipofuscin content, and therefore the relative health, of the photoreceptors and RPE (the primary

site of lipofuscin accumulation). Accumulation of lipofuscin, which is associated with the disease process in AMD, increases autofluorescence. Conversely, areas of atrophy in later stages of disease create regions that do not autofluoresce. Because of technological limitations, most FAF imaging in AMD has been performed around the posterior pole. Now however, ultra-widefield retinal imaging systems from Optos permit noncontact, single-shot imaging of approximately 200° of the retina (the optomap), and 2 Optos devices incorporate UWF FAF capabilities.

To explore the utility of this new modality in the evaluation of AMD, we designed a study to examine the frequency and pattern of autofluorescence abnormalities in eyes with AMD and to determine what these patterns could tell us about the stage and expected course of the disease.

EVALUATING UWF FAF

This study enrolled 124 consecutive patients from my retina clinic at the Doheny Eye Institute, including 105 patients with diagnosed AMD and 19 patients with no disease. Patients were imaged using the Optos 200Tx, and both color and FAF images were taken. A total of 238 eyes (119 patients) were considered gradable, including eyes with non-neovascular AMD (114), neovascular AMD (86), and no diagnosed retinal disease (38).

Optos V2 Vantage Pro Review software was used to review the images, which were graded separately by 2 independent, masked graders from the Doheny Image Reading Center using a standard protocol. The color images were reviewed for the presence of peripheral pigmentary abnormalities, including drusen, RPE depigmentation, hyperpigmentation or hyperplasia, and atrophy; nonpigmentary features were also noted. Grading of the UWF FAF images was based on increase or decrease of

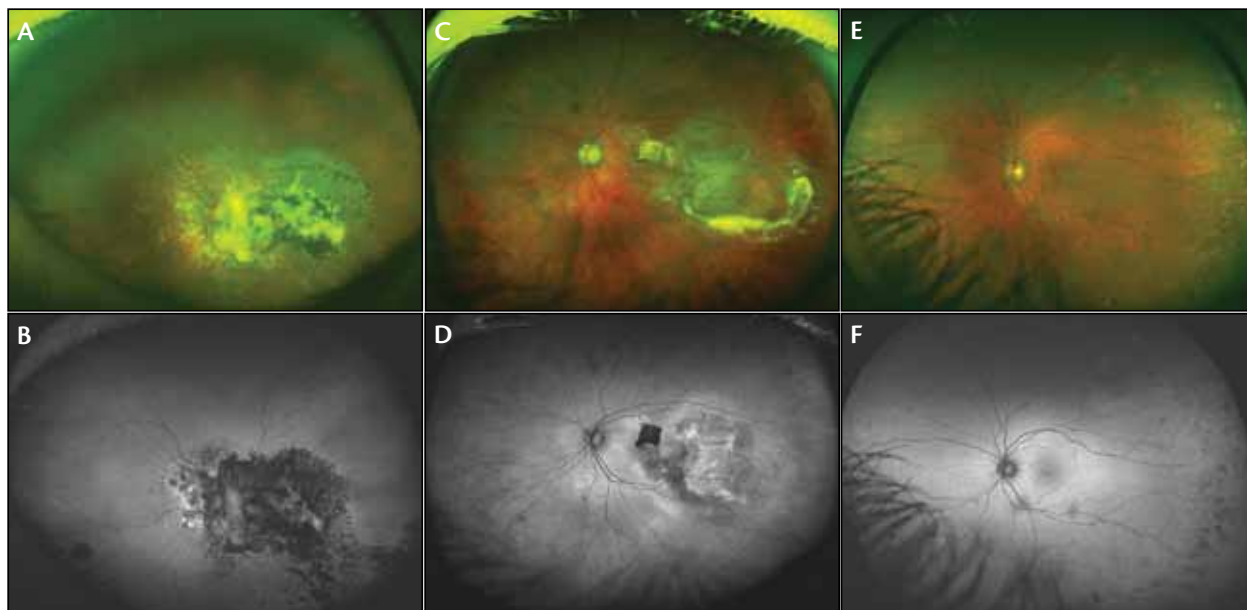


Figure 1. Color and autofluorescence photographs showing FAF abnormalities and associated clinical features. Color fundus image shows peripheral drusen (A). FAF shows increased granular autofluorescence corresponding to the drusen (B). Color fundus image shows areas of RPE depigmentation (C) and FAF reveals a large area of mottled decreased autofluorescence (D). Color fundus shows areas of RPE atrophy (E) and FAF shows areas of nummular decreased autofluorescence.

autofluorescence compared with the background of the image. In cases of disagreement between the 2 graders, we re-reviewed the images to form a consensus, and a third party provided a tie-breaking assessment if needed.

KEY FINDINGS

We identified peripheral FAF abnormalities in 69% of all eyes imaged. These abnormalities were identified in 86% of eyes with neovascular AMD, 73% of eyes with non-neovascular AMD, and 18% of normal eyes. The higher frequency observed in neovascular AMD was statistically significant. There was a 90% concordance rate in FAF patterns between both eyes. Peripheral FAF abnormalities were more frequent among women than men (77% vs 51%) and increased in frequency with age. Patients 75 years old or less had a frequency of FAF abnormalities of 36%, whereas patients 76 to 79 years old had a rate of more than 80%. Multivariate and subgroup analyses confirmed that AMD type, female sex, and older age were risk factors for peripheral FAF abnormalities.

Evaluation of these images allowed us to propose a classification system for AMD based on 3 distinct FAF patterns: granular, mottled, and nummular. Granular was defined as small, discrete areas of increased hyper-autofluorescence; mottled as areas of uneven or irregular decreased autofluorescence; and nummular as small to medium areas of discrete, uniformly decreased autofluorescence. We observed granular FAF patterns in 110

eyes (46%), nummular in 43 eyes (18%), and mottled in 81 eyes (34%). About 30% of eyes exhibited a secondary abnormality, but none had all 3 patterns.

These peripheral UWF FAF patterns were strongly correlated with clinical features of the disease. Ninety-six percent of the eyes with abnormal peripheral FAF also had abnormalities evident in UWF color images. There were also correlations between the pathologic patterns detected by the 2 modalities, with granular FAF most commonly associated with peripheral drusen, nummular FAF with atrophic patches consistent with cobblestone degeneration, and mottled FAF with RPE depigmentation. Figures 1A-F show examples of the ultra-widefield images.

THE RELEVANCE OF PATTERNS IN THE PERIPHERY AND NEXT STEPS

Our findings suggest that UWF FAF imaging could play a key role in the management of AMD and raise a number of intriguing questions for further investigation. In our study, the use of UWF imaging, both color and FAF, detected a significant amount of pathology in the peripheral retinas of eyes with AMD—abnormalities that would have been missed with conventional imaging. The prospect that these abnormalities may appear earlier in the periphery adds to the appeal of UWF FAF. The frequency of observed abnormal peripheral FAF patterns

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was highest in eyes with neovascular AMD, suggesting that detecting these patterns in non-neovascular AMD could be predictive of progression, as has been established previously with FAF patterns in the central retina. Data supportive of this hypothesis may be generated by the inclusion of UWF FAF imaging in an AREDS 2 substudy, but additional longitudinal, prospective studies will be necessary to confirm the relationship between these observations and the risk of conversion to more advanced disease. Such studies would benefit from a larger cohort of age-matched normals than we were able to include in our preliminary investigation.

In addition to its prognostic value, UWF FAF could expand our understanding of the contribution of genetics to AMD. Research with conventional imaging techniques has suggested that the high degree of observed pattern symmetry between the 2 eyes of individuals with AMD is evidence of genetic determinants in the etiology of the disease.⁴ Peripheral FAF patterns may be useful in refining phenotyping in AMD and produce further insights into the contribution of genetic risk factors.

Finally, the high correlation between the 3 principal abnormal peripheral FAF patterns we identified and specific clinical findings evident in color images points to the potential value of the higher-contrast FAF imaging for facilitating earlier identification of pathology associated with AMD. Further refinement and validation of the classification system we have proposed based on these peripheral FAF pattern types, along with the efficiency and ease-of-use of non-contact, high-resolution UWF FAF imaging, could make this approach an important component of AMD management. Because Optos systems are the only ones capable of both UWF color and FAF imaging, and because these devices also produce the widest field of view to sample the far edges of the retinal periphery, they provide a unique platform for ongoing work in this area. ■

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