Dear Editor:

I read with interest the article by Wu et al.1 on the characterization of the pathologic changes preceding the development of drusen-associated atrophy in eyes with age-related macular degeneration (AMD) using spectral-domain optical coherence tomography (SD OCT). The authors identified “subsidence of the outer plexiform layer (OPL) and inner nuclear layer (INL),” and “development of a hyporeflective wedge-shaped band within the limits of the OPL,” as the SD OCT features unique of drusen-associated atrophy.1 These features portend the development of drusen-associated atrophy, and were termed “nascent geographic atrophy [GA].” Using SD OCT, the authors detected 20 areas of drusen-associated atrophy. In 5 areas, only the subsidence of the OPL and INL was present (without development of a hyporeflective wedge-shaped band within the limits of the OPL).

The authors point out the current lack of sensitive and specific structural biomarkers of the early stages of AMD, which can be used to monitor progression and severity of disease. Therefore, considering the urgent need to identify robust markers of disease state and risk of progression (which develop within a predictable and clinically relevant time frame), the authors believe that nascent GA could be used as an earlier, surrogate endpoint for interventional trials targeting the early stages of AMD.

I have concerns regarding the specificity of “subsidence of the OPL and INL” as a marker of disease state and risk of progression to GA. We recently described on SD OCT a small, localized retinal pigment epithelium (RPE) elevation, characterized by a focal disruption of the RPE and photoreceptors, and by the OPL that makes contact with the RPE (Fig 1, available at www.aaojournal.org), as the precursors of type 3 neovascularization.2 Interestingly, the morphological features preceding the development of type 3 neovascularization (Fig 1, available at www.aaojournal.org), were similar to drusen-associated atrophy. The precursor lesion of type 3 neovascularization progresses over time to focal atrophy (visualized on SD OCT as the OPL that progressively makes contact with a disrupted RPE). This focal atrophy as precursor of type 3 neovascularization is in agreement with the recent study of McBain et al. reporting on the occurrence of high rates of RPE atrophy at presentation.

We recently showed how type 3 neovascularization typically arises within a zone of outer retinal thinning (both the OPL and the deep capillary plexus move closer to the RPE), where hypoxia-associated with increased levels of vascular endothelial growth factor are brought about by a combination of factors, including the presence of a drusenoid pigment epithelial detachment.3 Therefore, although I agree with the authors on the sensitivity of the reported SD OCT features, I wish to advise against specificity by considering them as a marker of drusen-associated atrophy (i.e., progression to GA—nonneovascular AMD), because these SD OCT features may also (not infrequently) be considered as a marker of progression to type 3 neovascularization (i.e., neovascular AMD).

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References