Splitting the Lumps: The Importance of Phenotyping Drusen
Robyn H. Guymer, MBBS, PhD - Melbourne, Australia

Age-related macular degeneration (AMD) is currently defined by the presence of drusen, and as such, many retinal drusen phenotypes are lumped in the catch-all disease AMD. There is no doubt AMD is a heterogeneous disease, and to date as many as 34 different gene loci have been identified as contributing to the AMD phenotype. However, now more than ever, we need to be “splitters” rather than “lumpers,” as we enter an era where there will be specific treatments to slow progression of early stages of AMD toward vision-threatening complications. If we are unable to ensure that homogeneous disease phenotypes are being included in intervention trials, we run the risk of missing potentially effective treatments because an intervention may be specific for one disease pathologic process and not another. Any efficacy signal may be lost in the noise created by the potpourri of drusen-associated speculated treatments to slow progression of early stages of AMD toward vision-threatening complications. If we are unable to ensure that homogeneous disease phenotypes are being included in intervention trials, we run the risk of missing potentially effective treatments because an intervention may be specific for one disease pathologic process and not another. Any efficacy signal may be lost in the noise created by the potpourri of drusen-associated diseases.

With the use of only clinical acumen and color photography, outstanding clinicians, epitomized by Donald Gass, enabled certain drusen phenotypes—such as dominantly inherited malattia leventinese, Doyné’s honeycomb dystrophy, and Sorsby’s fundus dystrophy—to be identified as different from AMD and subsequently to have had their associated specific genetic mutations identified, offering the real possibility of targeted intervention. However, we now practice in an era where there have been tremendous advances in retinal imaging such that we are assisted greatly by information provided by multimodal imaging (MMI) tools to subclassify drusen phenotypes further. The hope is that armed with the additional information provided, we will identify new characteristics that better define already known subsets of drusen-associated diseases or that help to define new drusen phenotypes. Multimodal imaging already has been highly significant in shedding new light on the clinical entity of reticular pseudodrusen (RPD) (also referred to as subretinal drusenoid deposits) and in appreciating their importance as a distinct phenotype of drusen. In recognition of the rapidly changing imaging capabilities and essential information gathered using MMI, the Classification of Atrophy Meeting group recently published recommendations in Ophthalmology for MMI in AMD.

In this issue of Ophthalmology, Balaratnasingam et al (see page 100) report on their use of state-of-the-art MMI, including spectral-domain OCT and ultrawide-field imaging, to provide new insight into the cuticular drusen phenotype by conducting a retrospective, observational study on a large cohort. They also further defined the life cycle and associated histologic features of this phenotype by investigating a number of pathologic specimens in comparison with tissue exhibiting hard and soft drusen. Gass first described cuticular drusen in 1997 as an uncommon distinct druse subtype, with small, round drusen measuring 25 to 75 µm and consistent with basal laminar drusen. He described this distinct form as being identified best by the “starry-sky” or “Milky Way” fluorescence pattern most evident during the arteriovenous phase of fluorescein angiography. However, as with RPD, this distinct phenotype is also found in eyes that appear also to have typical AMD-associated drusen. Gass identified this in his first description, stating that people older than 50 years of age with cuticular drusen could demonstrate the appearance of regular large drusen indistinguishable from AMD. Indeed, without the benefit of fluorescein angiography, it can sometimes be difficult to identify the presence of cuticular drusen when typical AMD-related drusen also are clearly present. Balaratnasingam et al point out that the typical sawtooth pattern described with cuticular drusen was not seen in all eyes that demonstrated the characteristic starry-sky fluorescence angiographic pattern, with some cases resembling soft drusen and others being barely discernible on OCT. Therefore, as was demonstrated to be the case for RPD, accurate detection of cuticular drusen requires data from more than one imaging method. The best way to handle these seemingly mixed clinical phenotypes is currently not clear. Whether someone with RPD alone should be included in a definition of AMD is problematic because the current nomenclature requires drusen to be present. Similarly, whether cuticular drusen should be considered a simple variant on AMD or a distinct disease with specific pathophysiologic pathways, which in some cases can coexist with AMD, remains to be determined. However, either way, identifying at least that an eye contains drusen with a cuticular phenotype is likely to be important as we begin interventions that target specific pathways.

Balaratnasingam et al also demonstrate the strength of working collaboratively across clinics, in this case, across 3 continents, to enable collection of a large cohort of persons with a rare disease with, in many cases, long follow-up. This is a great example of collective strength, which we have also seen in the Machet consortium, where a combined multinational longitudinal natural history study revealed new phenotypical appearances when MMI was used to better define another rare retinal disease, macular telangiectasia type 2.

By accruing a large cohort to follow up longitudinally, Balaratnasingam et al provide insight into the typical presenting characteristics and natural history of patients with a cuticular drusen phenotype. It should be acknowledged that the cohort was identified in specific retinal practices, potentially biasing the results toward...
older and more symptomatic patients and those who also had features more typical of an AMD phenotype, because they may be more likely to be seen in these practices and included in the cohort. Also, we do not know about potential recruits who might not have had the opportunity to have undergone all the MMI studies that this cohort underwent to help in their diagnosis. Importantly, however, the authors indicate that although the OCT location, appearance, and histologic results, which localized cuticular drusen to the same anatomic plane as small hard drusen (between the basal lamina of the retinal pigment epithelium and the inner collagenous layer of Bruch’s membrane) more closely resemble hard drusen than soft drusen, the manifestations were more like those seen with AMD-associated large drusen. The authors report 25% of the cohort demonstrating geographic atrophy and 12% demonstrating choroidal neovascularization in eyes with more than 5 years of follow-up. Therefore, one important message from the study is that although cuticular drusen have an appearance more closely resembling hard drusen, their macular vision-threatening complications are more comparable with those of AMD-associated large drusen. This is important because often people first seek treatment with a cuticular drusen phenotype at a younger age than typically seen with AMD and as such have a longer life ahead of them in which to show progression. The prognosis deserves to be more circumspect than if dealing with someone who manifests only typical small, hard drusen.

It is reasonable to assume that there will be different interventions for different drusen phenotypes because the causes and pathogenic pathways leading to a common clinical appearance are likely to be different. Recent clinical trials suggesting potential interventions, such as the report of reduction in large drusen in AMD after lipid-targeted treatment and the subthreshold laser treatments that seem to reduce drusen load, each may act in an entirely different manner and be effective in different subgroups to reduce drusen load, if proven to be useful in future studies. It will be a major setback if we lose a signal of efficacy by studying a treatment on a diverse range of drusen diseases, some of which may not respond.

Ultimately, we await genetic clues to differentiate definitively the various drusen phenotypes, delivering us personalized diagnosis and with that, personalized treatments chosen based on specific knowledge. However, while we wait for this to become a reality, novel interventions that may slow progression of the AMD phenotype to vision-threatening complications will be arriving at our doorstep. Therefore, it behooves us, as clinicians, to be as careful and diligent as we can when phenotyping our patients with drusen and to take advantage of available imaging resources to phenotype our patients as completely as possible as part of our normal practice. This will be of utmost importance in a research trial setting to ensure that we do not squander the opportunity to identify a new treatment that could provide enormous benefits, not only to typical AMD drusen patients, but also to those with other drusen phenotypes.

References


Footnotes and Financial Disclosures

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Correspondence:
Robyn H. Guymer, MBBS, PhD, Center for Eye Research Australia, 32 Gisborne Street, East Melbourne 3002, Australia. E-mail: rh.guymer@unimelb.edu.au.