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Drusen, an Old but New Frontier

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Early in the education of ophthalmologists the student is introduced to the concept of drusen. The material is presented in an efficient unquestioning manner: drusen are formed by material under the retinal pigment epithelium (RPE). This material seems to have varying composition, which may have clinically recognizable correlates.[1-4] Classification systems are presented such as dividing drusen into hard or soft, or as small intermediate, or large.[5-9] Each of the classification systems builds on the underlying educational principles of the location and physical characteristics of drusen.

In 1990 Mimoun, Soubrane, and Coscas described an unusual type of drusen, “les pseudo-drusen visibles en lumière bleue”, recognizing these drusen were different from previously described forms.[10] These drusen were later called reticular pseudodrusen. Reticular is derived from the Latin reticulum, or little net, and curiously was used to describe the arrangement of dot-like spots. The International Classification system did not recognize either a reticular pattern of drusen or specifically reticular pseudodrusen.[5] Reticular pseudodrusen appear to have been classified as a type of soft drusen by the Wisconsin Reading Center under the term reticular soft drusen.[7,11] This expression highlighted the reticular pattern, but simultaneously implied reticular pseudodrusen were a form of soft drusen, which are not best seen with blue light. Reticular pseudodrusen were classified as “early” soft drusen in the Blue Mountains Eye studies.[8]

In 1995 Arnold and associates[12] examined a series of 100 patients with reticular pseudodrusen as seen with “red-free” light or with a scanning laser ophthalmoscope (SLO), although the type of SLO was not mentioned. Of these patients 2/3rd had choroidal neovascularization (CNV) in one or both eyes. In this paper one eye came to histopathologic examination; however, the retina was absent in the published pictures. The choroid was thin and showed fibrotic changes, loss of choroidal vessels, and a reduction of choroidal melanocytes. Although a specific correlate was not found, the authors thought the pseudodrusen were the same size as the remaining choroidal veins and attributed pseudodrusen to thinning of the choroid.[12] They did not explain how tubular choroidal vessels would produce a picture resembling drusen. In 1997 Cohen and coworkers reported two series of patients in one paper,[13] the first was 100 eyes with newly diagnosed CNV and 24% of those had reticular pseudodrusen as diagnosed by blue light photography, although the actual diagnostic criteria was not stated. In the second series, 100 consecutive patients with reticular pseudodrusen were examined and these represented 8% of all cases referred to their imaging and laser center.[13] Smith and colleagues used multimodal imaging employing color photography, infrared and autofluorescence imaging, and indocyanine angiography to evaluate 65 eyes of 42 patients.[14] They concluded that reticular pseudodrusen were a manifestation of reticular macular disease, a new term, and autofluorescence, infrared imaging, and indocyanine green angiography suggested this disease involved the retinal pigment epithelium and choriocapillaris while the photographic patterns

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implicated the inner choroid. No imaging with optical coherence tomography (OCT) was reported in this series.[14]

Multimodal imaging using high resolution spectral domain (SD) OCT provided new information concerning both the diagnosis and pathologic changes associated with reticular pseudodrusen. Using image correlations among the blue channel of color photographs, infrared imaging, and autofluorescence imaging the pseudodrusen were found to correlate to depositions of material above the RPE.[15] This material formed mounds or conical projections. In some patients these accumulations mimicked, to a certain extent, ordinary soft drusen, except they had a slightly bluer appearance. The SD-OCT reflectance of these deposits was similar to that seen in soft drusen. In other eyes the deposits, particularly those with more conical configurations, looked similar to cuticular drusen.

In a histopathologic study of geographic atrophy accumulations of membranous debris, a hallmark of soft drusen, was found below and *above* the RPE by Sarks and associates.[16] Later investigators characterized the accumulations above the RPE and analyzed the composition of these accumulations.[17] The material, termed subretinal drusenoid deposits, showed aggregations of membranous debris. The deposits unesterified cholesterol, apoE, complement factor H, and vitronectin, but did not show opsins, which are molecules associated with photoreceptors, glial fibrillary acid protein (associated with Muller cells) or cellular retinal binding protein (Muller cells or RPE).[17] The location of the material and its shape was strikingly similar to the OCT findings of pseudodrusen. The link was made. The accumulation of material seen with SD-OCT appeared to be the same material examined by histologic means.

Examination of 153 consecutive patients with the diagnosis of age-related macular degeneration (AMD) revealed 131 with late AMD in at least 1 eye.[18] Subretinal drusenoid deposits were diagnosed in a much larger proportion of patients using SD-OCT than by examining the blue channel of color photographs. The associations of ocular risk factors were determined by using a case-control study and both soft drusen and subretinal drusenoid deposits were found to be independently associated with late AMD. Subretinal drusenoid deposits showed a lower, but still significant odds ratio for late AMD as compared with soft drusen. Although we can estimate odds ratios with this study design, we can't estimate risk. To do this a cohort study would be needed.

Although mechanisms of drusen formation are hardly known for typical drusen, they have a substrate, Bruch's membrane, and a consistency with past educational foundations in retinal diseases. Drusen occurring in the subretinal space imply a substrate is not particularly necessary. There have been a variety of potential factors leading to accumulation of material. One suggestion has been a “loss of polarity” of RPE cells, but how this occurs or what it precisely means has yet to be specified. RPE cells ordinarily phagocytize material at their apical surface, and it could be hypothesized the accumulation of the subretinal deposits could reflect a global abnormality of phagocytosis through the loss of polarity. However the material doesn't seem to have opsins and is hypoautofluorescent, which implies an absence of retinoids. The material as seen in the limited number of specimens so far is not associated with accumulations of unphagocytized outer segments. This implies something more specific is abnormal. For cholesterol and potentially other lipids, such as phospholipids, to accumulate there may be an abnormality of lipid transport in the subretinal space. The turnover of polyunsaturated fatty acids is rapid; phagocytized outer segments, which have docosahexanoic acid are processed by the RPE and these lipids are shuttled through the subretinal space back to the inner segments of the photoreceptors. Interestingly another lipid transport cycle is concurrently operating.[19, 20] It is estimated that the total pool of cholesterol in the retina turns over every 6-7 days.[19] The RPE appears to secrete HDL-like particles that transport cholesterol and potentially other lipids in the subretinal space that aide in lipid transport in the outer retina.[19] Cholesterol analogues

administered via LDL by intravenous injection in rats can be observed in outer segments of the photoreceptors 4 hours after injection. These HDL-like particles have been proposed to transport lipids back to the RPE where they are phagocytized through actions of scavenger receptor receptors.[19] A2E interferes with various aspects of cholesterol metabolism in RPE cells.[21] Interruption of lipid cycling, particularly of reverse cholesterol transport,[22] could allow for the accumulation of cholesterol laden material at the apical surface of the RPE cells. A third mechanism has also been proposed,[15] there is potential for inflammation to play a role in subretinal drusen formation. Complement has been found in subretinal drusenoid deposits, the subretinal space contains cellular debris as well as inflammatory cells. It is possible that inflammation could provide nucleation sites for deposition of drusenoid material. None of these mechanisms are mutually exclusive and all of them may be operating simultaneously.

The finding of drusen in the subretinal space that are risk factors for the development of late AMD expands the universe of ideas to consider. A principle consideration would be how to image and classify drusen more accurately. An accompanying article in this issue describes various types of drusen and how their location and composition affects their imaging characteristics. Late AMD and models thereof almost exclusively focused on Bruch's membrane, even though a significant proportion of CNV occurs in the subretinal space. Why would soft drusen be an ocular risk factor for Type 2 CNV? Whatever factors are deposited in the plane of the soft drusen would not seem to be germane if the CNV grows on the other side of the RPE. Retinal vascular contribution to neovascularization has been seen in retinal angiomatous proliferation and in cases of retinochoroidal anastomosis; do these patients have subretinal drusenoid deposits as a risk factor? Animal models studied so far poorly replicate what happens in AMD, now these same models would need to replicate what happens in the subretinal space. In the short term it is likely that we will have to depend on human pathologic and human OCT studies to answer AMD questions. Finally the way we teach basic ophthalmologic knowledge should be re-examined. Science is not a core of accepted unchanging information surrounded by a periphery of partially known new ideas suitable for more research. Indoctrination involves passing on basic doctrines and the recipient is expected not to question these doctrines. Education, on the other hand, strives to pass on knowledge and the skills necessary to question, even the most basic underlying assumptions.

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