Reticular Pseudodrusen Are Subretinal Drusenoid Deposits

Sandrine A. Zweifel, MD,[1,2] Richard F. Spaide, MD,[2] Christine A. Curcio, PhD,[3] Goldis Malek, PhD,[4] Yutaka Imamura, MD[1,2]

Purpose: To characterize reticular pseudodrusen, a potential risk factor for late age-related macular degeneration.

Design: Retrospective, observational case series.

Participants: Fifty-eight eyes of 33 patients with pseudodrusen (20 female).

Methods: Consecutive patients with reticular pseudodrusen, diagnosed by their typical appearance and distribution using ophthalmoscopy, the blue channel of color fundus photographs, and near infrared images. The patients were imaged by spectral domain optical coherence tomography (SD OCT), and correlations were made between the near infrared images and the SD OCT images. The SD OCT findings in patients with pseudodrusen were compared with previously reported histologic findings of subretinal drusenoid deposits. The histologic specimens were reevaluated with the additional knowledge of the clinical information.

Main Outcome Measures: Spectral domain optical coherence tomography and histologic characteristics of pseudodrusen.

Results: The mean age of the 33 patients was 81.7 years. The correlating SD OCT scans showed collections of granular hyperreflective material above the retinal pigment epithelium (RPE), in the subretinal space located primarily between the RPE and the boundary between the inner and outer segments of the photoreceptors (IS/OS boundary). In a more advanced stage, this material formed small mounds that broke through the IS/OS boundary. There were no correlates to the deposits seen under the RPE or in the choroid. These findings were similar in character to previously reported histologic characterization of subretinal drusenoid deposits, which had identified the presence of membranous debris, unesterified cholesterol, and complement within the deposits.

Conclusions: Pseudodrusen seen by clinical examination may be subretinal drusenoid deposits seen by histologic examination. This unexpected location suggests that potential pathophysiologic mechanisms on both sides of the RPE need to be taken into account in theories related to the development of age-related macular degeneration.

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Reticular pseudodrusen were first described by Mimoun et al[1] in 1990 as a peculiar yellowish pattern in the fundus of patients with age-related macular degeneration (AMD). They named the structures "les pseudo-drusen visibles en lumière bleue" because of their enhanced visibility when viewed using blue light. Arnold et al[2] stated the reticular pseudodrusen were easily visualized with a scanning laser ophthalmoscope, and seemed to be associated with late AMD. They further postulated that the appearance arose from structures in the choroid. They performed histologic examination in 1 eye, but only of the choroid, and did not find any visible correlates to the pseudodrusen, although the patient did have a markedly thin choroid.[2] Descriptions and photographs used to illustrate reticular pseudodrusen vary substantially from publication to publication,[2–9] with some authorities classifying reticular pseudodrusen as being no different from ordinary soft drusen material arranged in a reticular (derived from the Latin word "reticulum," which means net) pattern.[8,9] This raises an important question "What are pseudodrusen?"

The Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) is capable of imaging the fundus with near infrared light using scanning laser ophthalmoscopy and can simultaneously perform spectral domain optical coherence tomography (SD OCT) with point-to-point correlation between the 2 imaging modalities. To investigate the characteristics of pseudodrusen, we performed a retrospective review of images from patients with a reticular pseudodrusen appearance. Rudolf et al[10] previously identified 3 eye bank eyes that appear to have deposition consistent with what is described in the patients in this series. The eyes were found to have subretinal deposition of drusenoid material that had many characteristics of soft drusen, which ordinarily are found on the inner portion of Bruch's membrane. At the time, this described material had no known clinical correlate. Later collaboration revealed that pseudodrusen seen by SD OCT corresponded to the material seen as subretinal drusenoid deposits. This realization lead to additional histologic investigation as detailed below.

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Materials and Methods

This was a retrospective study of consecutive patients with the clinical diagnosis of reticular pseudodrusen. These patients were examined in a private retinal referral practice in which nearly all examined patients have OCT imaging, and all were seen in a 2-month period starting at the beginning of January 2009. The study had institutional review board approval through the Western Institutional Review Board and complied with the Health Insurance Portability and Accountability Act of 1996. Although the presence of pseudodrusen can be readily suspected by simple ophthalmoscopy, the diagnosis of reticular pseudodrusen in this study was based on the possible presence of 2 features: The pseudodrusen were more easily identified in the blue channel of the color photograph or were evident in the near-infrared photograph taken with the scanning laser ophthalmoscope, the Heidelberg Spectralis, or both. A reticular pattern, per se, was not a criterion used to establish the diagnosis. Patients who met these criteria independently of the underlying disease, such as neovascular AMD, dry AMD, branch retinal vein occlusion, and central retinal vein occlusion, were included in this study.

The original description of pseudodrusen referred to their increased visibility in blue light. A functional equivalent is to look at the blue channel of a color photograph, which by the additive color theory contains the same information (for derivation see Appendix 1, available at http://aaojournal.org). To examine the blue channel of the color photograph, high-resolution digital color fundus photographs taken with a Topcon ImageNet camera (Topcon America, Paramus, NJ) were viewed in Topcon ImageNet (version 2.55, Topcon America) or Photoshop (Photoshop CS3, Adobe System Inc., San Jose, CA). In the Topcon ImageNet program the commands Utilities>RGB channels were selected. The 3 principal channels (red, green, and blue) comprising the color image were then displayed along with the original color photograph. In Photoshop, the "Channels Palette" was selected and the command "Split Channels" was used. The individual color channels were then displayed individually.

The SD OCT scans of the eyes were obtained with the Heidelberg Spectralis (version 1.6.1) as viewed with the contained Heidelberg software (Spectralis Viewing Module 4.0.0.0; Heidelberg Engineering). The scanning protocol for the patients varied with the underlying disease because the pseudodrusen were usually an incidental finding. The area of pathology in the posterior pole was imaged using sections each comprising up to 100 averaged scans. The point-to point correlation feature of the Heidelberg Spectralis was used to find corresponding pathology between the near-infrared image and the SD OCT image. The pathology observed was scored using a defined grading system of 3 stages based on their cross-sectional appearance. Stage 1 was defined as diffuse deposition of granular hyperreflective material between the retinal pigment epithelium (RPE) and the boundary between the inner segments (IS) and outer segments (OS) of the photoreceptors (the IS/OS boundary). Stage 2 was considered to be mounds of accumulated material sufficient to alter the contour of the IS/OS boundary. In stage 3 the material was thicker, adopted a conical appearance, and broke through the IS/OS boundary (Fig 1). To determine the proportion of each of the stages, drusen were sampled as follows. A table of random numbers was generated in Microsoft Excel (Microsoft Corporation, Redmond, WA) using the Rand() function. These random numbers range from 0 to 0.999+. The scan line for each eye was selected at random. A reticule was constructed that divided any given scan line into 10 regions labeled 0 to 9. The most significant digit of the random number was read first, which indicated the region in the reticule in which the drusen were to be counted. If the total number of drusen read was less than 10, the next most non-repeating significant digit was used. If 5 significant digits were used, a new scan line was selected at random and the process was continued until at least 10 drusen were counted.

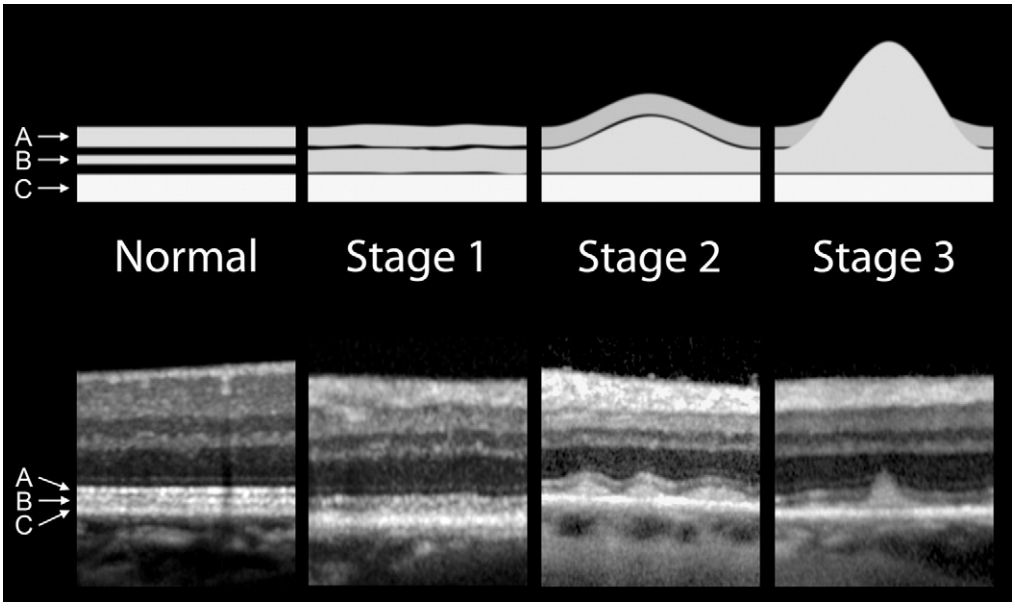

Figure 1. The top row shows schematic drawings with the stages of subretinal drusenoid deposition. Along each column is 1 representative OCT image of the respective stage. The top grey line in the schematic represents the IS/OS boundary (**A**), the middle line represents the line formed by the interdigitation of the photoreceptor outer segments and the apical processes of the RPE (**B**), and the bottom line represents the RPE (**C**). Stage 1 was defined as diffuse deposition of granular hyperreflective material between the RPE and the boundary between the IS and OS of the photoreceptors. Stage 2 was considered to be mounds of accumulated material sufficient to alter the contour of the IS/OS boundary. The representative case shows 3 mounds side by side. In stage 3, the material adopted a conical appearance and broke through the IS/OS boundary. IS = inner segments; OCT = optical coherence tomography; OS = outer segments; RPE = retinal pigment epithelium.