Cuticular Drusen

Clinical Phenotypes and Natural History Defined Using Multimodal Imaging

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**Purpose:** To define the range and life cycles of cuticular drusen phenotypes using multimodal imaging and to review the histologic characteristics of cuticular drusen.

**Design:** Retrospective, observational cohort study and experimental laboratory study.

**Participants:** Two hundred forty eyes of 120 clinic patients with a cuticular drusen phenotype and 4 human donor eyes with cuticular drusen (n = 2), soft drusen (n = 1), and hard drusen (n = 1).

**Methods:** We performed a retrospective review of clinical and multimodal imaging data of patients with a cuticular drusen phenotype. Patients had undergone imaging with various combinations of color photography, fluorescein angiography, indocyanine green angiography, near-infrared reflectance, fundus autofluorescence, high-resolution OCT, and ultrawide-field imaging. Human donor eyes underwent processing for high-resolution light and electron microscopy.

**Main Outcome Measures:** Appearance of cuticular drusen in multimodal imaging and the topography of a cuticular drusen distribution; age-dependent variations in cuticular drusen phenotypes, including the occurrence of retinal pigment epithelium (RPE) abnormalities, choroidal neovascularization, acquired vitelliform lesions (AVLs), and geographic atrophy (GA); and ultrastructural and staining characteristics of druse subtypes.

**Results:** The mean age of patients at the first visit was 57.9 ± 13.4 years. Drusen and RPE changes were seen in the peripheral retina, anterior to the vortex veins, in 21.8% of eyes. Of eyes with more than 5 years of follow-up, cuticular drusen disappeared from view in 58.3% of eyes, drusen coalescence was seen in 70.8% of eyes, and new RPE pigmentedary changes developed in 56.2% of eyes. Retinal pigment epithelium abnormalities, AVLs, neovascularization, and GA occurred at a frequency of 47.5%, 24.2%, 12.5%, and 25%, respectively, and were significantly more common in patients older than 60 years of age (all P < 0.015). Occurrence of GA and neovascularization were important determinants of final visual acuity in eyes with the cuticular drusen phenotype (both P < 0.015). Small cuticular drusen typically demonstrated a homogenous ultrastructural appearance similar to hard drusen, whereas fragmentation of the central and basal contents was seen frequently in larger cuticular drusen.

**Conclusions:** Although the ultrastructural characteristics of cuticular drusen appear more similar to those of hard drusen, their lifecycle and macular complications are more comparable with those of soft drusen. Cuticular drusen phenotype may confer a unique risk for the development of GA and neovascularization. Ophthalmology 2018;125:100-118 © 2017 by the American Academy of Ophthalmology

Supplemental material available at www.aaojournal.org.

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may confer unique risks for the development of sight-threatening complications.

Major advances in imaging techniques have permitted study of retinal diseases at a submicrometer level in living people, building on histologic knowledge derived from postmortem human donor eyes. The resolution of in vivo imaging is comparable with histologic results in certain contexts and has the added advantage of allowing the assembly of temporal information regarding disease time course. Multimodal imaging studies have elucidated the phenotypic characteristics and natural course of hard drusen, soft drusen, and subretinal drusenoid deposits (SDDs); the latter are sometimes referred to as reticular pseudodrusen. However, similar studies on cuticular drusen phenotype have been limited by small patient cohorts and the nonsystematic acquisition of multimodal imaging data.

Increasing evidence suggests that the morphologic features, volume, and topographic features of drusen distribution are integrally linked to the risk of severe vision loss that results from geographic atrophy (GA) and chorioidal neovascularization. Furthermore, a recent single-center trial demonstrated reduction in large drusen in age-related macular degeneration (AMD) after lipid-targeted treatment. For these reasons, precise drusen phenotyping serves an important purpose for stratifying the risk of complications in AMD as...
well as defining patient subsets that will benefit from specific therapies. Our understanding of cuticular drusen phenotypes and life cycle is arguably less than it is for other drusen subtypes. Furthermore, our knowledge regarding cuticular drusen ultrastructure is limited to information gathered from 3 eyes of 3 patients. The purpose of this study was to expand our knowledge of cuticular drusen by providing a detailed phenotypic characterization using state-of-the-art multimodal imaging. A cohort of 240 eyes was evaluated, and the temporal course and age-dependent variations in cuticular drusen morphologic features were defined. The prevalence and clinical characteristics of macular complications such as neovascularization, GA, and acquired vitelliform lesions (AVLs) also were determined. Finally, we reviewed light and electron microscopy results of clinically identified cuticular drusen, soft drusen, and hard drusen to seek explanations for these imaging characteristics. This study provided new clinical and histologic information about cuticular drusen that has important relevance for AMD, the most common cause of legal blindness in the developed world.

**Methods**

This study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board at North Shore Long Island Jewish Health System and the human research ethics committee at the University of Sydney and The University of Western Australia. Institutional review boards approved the retrospective analysis of patient notes and multimodal imaging data as well as the histologic analysis of postmortem human tissue. Data were stored and managed in compliance with the Health Insurance Portability and Accountability Act.

**Participants**

Patients with cuticular drusen phenotype seen between March 2014 and September 2016 by 6 authors (L.A.Y., K.B.F., F.K.C., R.M., S.M., and C.B.) were included in this study. Patients were recruited from the offices of the Vitreous Retina Macula Consultants of New York (New York, New York), Lions Eye Institute (Perth, Australia), Canberra Retina Clinic (Canberra, Australia), and Ophthalmologic National Hospital (Paris, France). Included eyes demonstrated the characteristics of cuticular drusen phenotype in at least 3 of 4 imaging methods: color photography, OCT, FA, and fundus autofluorescence (FAF), using the following criteria (Fig 2): color photography—multiple yellow or pale, uniform, and round accumulations under the RPE; FA—discrete hyperfluorescence that corresponded to drusen during the early arteriovenous phase, conferring a starry-sky appearance; fundus autofluorescence (FAF)—drusen characterized by central hypoautofluorescence and a rim of hyperautofluorescence; and OCT—drusen localized beneath the RPE and characterized by RPE elevations.

For each patient, demographic information including age at first and last clinic visits, gender, and race was recorded. Information regarding best-corrected visual acuity (BCVA), refractive error, ocular and medical comorbidities, and previous ocular therapies also was obtained. Snellen fractions and letter scores from Bailey-Lovie style charts were converted to logMAR of the minimum angle of resolution (logMAR) units before statistical analysis. Clinical and multimodal imaging findings at each visit were reviewed.

**Multimodal Imaging**

All study patients were studied with 4 or more of the following imaging methods: color photography, red-free photography, FA, indocyanine green angiography (ICGA), FAF, and OCT. A detailed account of the instruments and techniques used is provided in the Supplemental Methods (available at www.aaojournal.org).

The peripheral retina was evaluated using Optos ultrawide-field imaging (Optos 200Tx with an angular range of approximately 200° horizontally and 170° vertically; Optos, Dunfermline, United Kingdom), or by montaging Topcon (Topcon Imagemet, Tokyo, Japan) or Zeiss (Carl Zeiss Meditec, Inc., Dublin, CA) images. In 14 eyes of 7 patients, we acquired high-density spectral-domain OCT scans of the macula (distance between B-scans, 11 μm), registering the OCT volume to confocal scanning laser ophthalmoscope—derived FA images (HRA2+OCT or Spectralis; Heidelberg Engineering, Heidelberg, Germany). Fundus autofluorescence images were acquired from these patients using Topcon and Heidelberg instruments (Topcon Imagemet, HRA2+OCT, or Spectralis).

**Image Analysis**

Cuticular drusen morphologic and topographic features were assessed by 2 observers (C.B. and R.D.-M.). We adapted the regional nomenclature of Lee et al. for SDD for use with cuticular drusen. We classified topographic features as either macular, defined as drusen distributed only within the major vascular arcades, or diffuse, defined as drusen involving the macula, but also extending beyond the vascular arcades. We also determined whether drusen and RPE changes were present anterior to a line connecting the vortex veins (approximately zone 3 of the OPERA study). The retinal area occupied by drusen was approximated in disc areas under the assumption that the average disc diameter was 1.5 mm.

The natural course of cuticular drusen phenotype was studied in patients with more than 5 years of follow-up. In these eyes, clinical and imaging data from all visits were evaluated and the frequency of drusen resorption or disappearance, drusen coalescence, and appearance of new pigmented RPE abnormalities were determined. For eyes in the cohort that were imaged with OCT, subfoveal choroidal thickness measurements from the first and final visits were used.

The prevalence of AVLs, neovascularization, and GA during the follow-up period was determined as follows: AVL—based on the presence of yellowish subretinal material on color photography corresponding to hyperreflective material bounded by the external limiting membrane anteriorly and the RPE—basal lamina—Bruch’s membrane band posteriorly on OCT and hyperautofluorescence on FAF; neovascularization—evaluated using OCT and dye angiography and classified into type 1, 2, and 3 neovascularization using the Gass-Freund classification and GA—clinically characterized by a sharply demarcated area of depigmentation with increased visibility of large choroidal vessels. Geographic atrophy corresponded to loss of outer retinal structures overlying loss or attenuation of the RPE—basal lamina—Bruch’s membrane band on OCT with choroidal hypertransmission (enhanced spectral-domain [SD] OCT signal penetration below Bruch’s membrane).

**Statistical Analysis**

Data were analyzed with descriptive statistics, provided as mean ± standard deviation. Because patients underwent bilateral imaging, the analysis of variance and generalized estimating
equations were used to handle clustered data, including intereye and intraeye associations. Statistical analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria) and SigmaPlot software version 12.0 (SPSS, Inc., Chicago, IL). A P value of 0.05 or less was considered statistically significant.

Histologic Analysis
Donor eyes with cuticular drusen (n = 2); small, hard drusen (n = 1); and soft drusen (n = 1) from a well-described clinicopathologic archive were studied using light and electron microscopy. Inclusion criteria included (1) clinical documentation during life, (2) histologic validation of clinical findings after death, and (3) availability of macular tissue embedded in epoxy resin. Exclusion criteria included (1) other coexisting retinal disease or eye disease and (2) poor tissue preservation. Color imaging and FA features of the cuticular drusen donor eyes, as well as areas chosen for histopathologic analysis, are provided in Figure S1 (available at www.aaojournal.org). The donor eyes with cuticular drusen have been described previously. New sections were prepared and analyzed in this study as described in the Supplemental Methods (available at www.aaojournal.org).

Results

General

Of 266 eyes from 133 patients that were reviewed, 240 eyes from 120 patients met the inclusion criteria. Eyes demonstrating the features of a cuticular drusen phenotype in only 1 or 2 imaging methods (Fig S2, available at www.aaojournal.org) were excluded from further analysis.

Demographic and clinical features of the cohort are summarized in Table 1. Mean age at first visit was 57.9±13.4 years (median, 58.2 years; range, 22.6—90.9 years; P = 0.060, Shapiro-Wilk test, normal distribution; Fig S3, available at www.aaojournal.org). The cohort comprised 72 women (60%). Mean duration of follow-up was 3.7±4.5 years (median, 1.8 years; range, 0—22.5 years). Twenty-five patients were evaluated only once. Of the 120 patients, 117 were white.

Best-corrected visual acuity at the initial visit was 0.2±0.3 logMAR (median, 0.1 logMAR; range, 0.2 to −2.0 logMAR). Mean Snellen acuity was 20/31. At the first visit, visual acuities were not normally distributed (P = 0.027, Shapiro-Wilk test; Fig S4, available at www.aaojournal.org), and 72% of eyes had......

Figure 2. Multimodal imaging characteristics of the cuticular drusen phenotype in the right eye of a 55-year-old woman with 20/25 visual acuity. On (A) color and (B) red-free photographs, cuticular drusen appear as a cluster of pale or yellow, sub-retinal pigment epithelium (RPE) lesions, with the diameter of an individual druse of approximately 30 μm. Cuticular drusen appear (C) hyperfluorescent in the early arteriovenous phase of fluorescein angiography and (D) demonstrate a hypofluorescent center with a surrounding rim of hyperfluorescence on fundus autofluorescence. Magnified images of cuticular drusen as seen by these 2 methods are provided in the insets. E, OCT confirms the sub-RPE location of cuticular drusen.
Multimodal Imaging Characteristics of the Cuticular Drusen Phenotype

The proportion of the cohort imaged with each method is summarized in Table 2, and a representative case is shown in Figure 2. On color photographs, cuticular drusen appeared as clusters of multiple yellow or pale spots. Size and spatial density of cuticular drusen as seen in color and red-free photographs were comparable. On FA, cuticular drusen exhibited discrete dotlike hyperfluorescence during arteriovenous transit with reduced fluorescence intensity in the recirculation phase. During the FA study, the area of hyperfluorescence colocalized to each druse did not appear to change. On FAF, cuticular drusen were characterized by a hypofluorescent center with a hyperautofluorescent margin. The number and spatial density of cuticular drusen on FA and FAF imaging were considerably greater than on color and red-free photography. However, individual drusen appeared larger on color photographs compared with FA and FAF.

A representative case demonstrating correlations between OCT, FA, and FAF is provided in Figure 3. The size of cuticular drusen as seen on FA and FAF was highly concordant. The area of central hyperfluorescence on FA closely resembled the area of central hypofluorescence on OCT. The height of lesions on SD OCT (i.e., elevation of the RPE—basal laminar band from Bruch’s membrane) did not correlate with the area of hyperfluorescence on FA or hypofluorescence on OCT. The morphologic features of cuticular drusen seen on SD OCT B-scans could be categorized broadly into 3 patterns (Fig 4): type 1 pattern (33% of eyes)—shallow elevations of the RPE—basal laminar band, with druse internal contents difficult to discern; type 2 pattern (49% of eyes)—drusen of triangular morphologic characteristics resulting in a saw-tooth appearance and hyporeflective internal contents; and type 3 pattern (18% of eyes)—broad, mound-shaped elevations of the RPE—basal laminar band with hyporeflective internal contents.

The reflectivity of cuticular drusen interiors on OCT was highly variable, with isoreflective, hyporeflective, and hyperreflective signatures evident within the same eye (Fig 3). Because it is possible that this variability reflects inconsistencies in the locations of B-scans with respect to each druse, we analyzed the near-infrared reflectance (NIR) image obtained simultaneously with each SD OCT study. These images showed variable reflectivity patterns of cuticular drusen (Fig S5, available at www.aaojournal.org). The NIR of cuticular drusen showed hyporeflective centers with a surrounding hyperreflective margin in 96 eyes (53.9%), diffuse hyperreflectivity in 27 eyes (15.2%), heterogeneous reflectivity in 7 eyes (3.9%), and a combination of these patterns in 48 eyes (27.0%). Relative to FA, fewer cuticular drusen were seen on NIR imaging.

Twenty-four eyes (10%) were imaged with ICGA. Of these, cuticular drusen appeared hyperfluorescent in 12 eyes (50%; Fig 5). When present, discrete hyperfluorescence typically occurred in the early arteriovenous frames and persisted throughout the late frames of the angiogram. Cuticular drusen appeared smaller and less numerous on ICGA compared with FA. In the remaining 50% of eyes, cuticular drusen were not evident on ICGA despite being evident on images obtained with other methods (Fig S6, available at www.aaojournal.org).
Figure 3. Cuticular drusen phenotype as seen on fluorescein angiography (FA), fundus autofluorescence (FAF), and spectral-domain OCT. In this figure, the OCT volume was registered to the FA image to permit precise spatial correlation between the 2 methods. The morphologic features of cuticular drusen visualized in 2 OCT line scans (I and II) are presented, as are magnified FA and FAF views of the area of the line scans. In line scan I, the area and intensity of fluorescence of 2 drusen (green and teal arrowheads) appear similar, but the degrees to which the retinal pigment epithelium—basal lamina band is elevated are markedly different. A similar finding is seen in OCT line scan II (red and blue arrowheads). Note that the internal reflectivity of individual druse also is highly variable, with some drusen appearing hyporeflective (green and yellow arrowheads), whereas others are isoreflective (blue arrowheads). The size of cuticular drusen as seen on (A) FA and (B) FAF are highly concordant. The area of hyperfluorescence correlating to each druse on FA is similar to the area of central hypoautofluorescence on FAF.
Figure 4. Morphologic patterns of cuticular drusen phenotype as seen on spectral-domain (SD) OCT. Three morphologic patterns of cuticular drusen were evident on SD OCT, despite consistent fluorescein angiography (FA) and fundus autofluorescence (FAF) features. Representative findings of each morphologic pattern as seen on FA, FAF, and SD OCT are presented. High-magnification images of OCT findings are provided in the insets. Type 1 pattern was characterized by shallow elevations of the retinal pigment epithelium (RPE). In the type 2 pattern, cuticular druse demonstrated triangular morphologic features, resulting in a saw-tooth appearance. In the type 3 pattern, cuticular druse demonstrated broad, mound-like elevations of the RPE band.
Figure 5. Hyperfluorescence of cuticular drusen on indocyanine green angiography (ICGA). Fluorescein angiography (FA) images appear in the left panel and ICGA images appear in the right panel. Fifty percent of cases of cuticular drusen demonstrated early hyperfluorescence on ICGA. Representative examples of this finding from 3 patients are provided. In comparison with FA, fewer cuticular drusen seem to appear on ICGA, and individual drusen also appear smaller. This feature is best illustrated in patient A. Patient B demonstrates a vitelliform lesion (red arrows) associated with cuticular drusen. In contrast to cuticular drusen, vitelliform lesions appear hypofluorescent in the early frames of FA and ICGA. Patient C demonstrates large drusen (blue arrows) interspersed with cuticular drusen. Note that large drusen appear hyperfluorescent on FA, but hypofluorescent on ICGA.
Topographic Features of Cuticular Drusen Distribution and Age-Related Variations in Morphologic Features

All but 3 study patients showed bilateral involvement and a similar pattern of cuticular drusen distribution in both eyes. The distribution pattern was macular in 79 eyes (32.9%) and diffuse in 161 eyes (67.1%; Fig 6). The cuticular drusen phenotype involved the peripapillary region in 63.3% of eyes. The total retinal area occupied by cuticular drusen at the first visit was judged to be fewer than 5 disc areas in 13.3% of eyes and more than 5 disc areas in 86.7% of eyes.

Ultrawide-field imaging was performed in 110 eyes (45.9%). In these images, drusen were seen anterior to the vortex veins in 24 eyes (21.8%; Fig 7). Areas with peripheral drusen also demonstrated hyperpigmentary and hypopigmentation alterations of the RPE. On FA, peripheral drusen demonstrated discrete hyperfluorescence during arteriovenous transit with decreased fluorescence during the recirculation phase of the angiogram.

In some eyes, large drusen (at least 3 times the greatest height or diameter of typical cuticular drusen) were seen interspersed among cuticular drusen (Fig S7, available at www.aaojournal.org). Large drusen frequently were associated with pigmentary RPE abnormalities. On FA, large drusen demonstrated hyperfluorescence similar to the surrounding cuticular drusen during the early arteriovenous phase. However, on ICGA, unlike typical cuticular drusen, large drusen appeared hypofluorescent (Fig 5).

In the entire cohort, new pigmentary RPE abnormalities were identified in 47.5% of eyes and large drusen were identified in 45.4% of eyes. Visual acuity in these eyes did not differ from eyes lacking these findings ($P ≥ 0.106$). By dividing the cohort into patients 60 years of age or younger ($n = 64$) and patients older than 60 years ($n = 56$; Table 3), we observed that RPE abnormalities (36.7% vs. 59.8%; $P = 0.003$) and large drusen (36.7% vs. 45.4%; $P < 0.010$) were significantly more frequent in eyes of patients older than 60 years.

The life cycle of the cuticular drusen phenotype was studied in 48 eyes (20%) of 24 patients with more than 5 years of follow-up (mean, 10.5±4.1 years; median, 9.5 years; range, 5.3–22.5 years). Of these eyes (Fig 8; Fig S8, available at www.aaojournal.org), drusen resorption was seen in 28 eyes (58.3%), drusen coalescence was seen in 34 eyes (70.8%), and new RPE changes were seen in 27 eyes (56.2%). All 3 changes were seen in 12 eyes (25%). In some eyes, extensive resorption of cuticular drusen involving a confluent area of more than 3 disc areas was seen (Fig 8; Fig S8, available at www.aaojournal.org).

Choroidal thickness measurements were available for 198 eyes (82.5%). Mean subfoveal choroidal thickness at the first visit was 272.1±109.8 μm (median, 265 μm; range, 17–629 μm; $P = 0.002$, Shapiro-Wilk test, not normally distributed; Fig S9, available at www.aaojournal.org). Mean subfoveal choroidal thickness at the final visit was 260.6±118.4 μm (median, 240 μm; range, 18–839 μm). Choroidal thickness did not differ between the first and final visits ($P = 0.467$).

Acquired Vitelliform Lesions, Choroidal Neovascularization, and Atrophy

The frequencies of AVLs, neovascularization, and GA are summarized in Table 3. Acquired vitelliform lesions involving the central macula were seen in 58 eyes (24.2%) of 40 patients. Bilateral AVLs occurred in 18 patients (Fig 9). The frequency of AVLs in patients older than 60 years was significantly greater than in those 60 years of age or younger (33.0% vs. 16.4%; $P = 0.015$). Visual acuity in eyes with AVLs was not significantly different from that in eyes without AVLs ($P = 0.069$).

Thirty eyes (12.5%) from 23 patients were complicated by neovascularization (Table 3), bilaterally in 7 patients. Neovascularization involved the central macula in all but 1 eye, in which only the peripapillary region was involved. Using the Gass-Freund classification, 23 of these cases (76.7%) were type 1 neovascularization and 9 cases were mixed type 1 and 2 lesions (Fig 10). There were no cases of type 3 neovascularization. The frequency of neovascularization in patients older than 60 years was significantly greater than in those 60 years of age or younger (19.6% vs. 6.2%; $P < 0.014$). Visual acuity in eyes with neovascularization was significantly worse than in those without neovascularization (0.4 vs. 0.16 logMAR; $P = 0.015$).

The mean Snellen equivalent was 20/50 versus 20/29.

Geographic atrophy was identified in the macula in 60 eyes (25%; Fig 11), 6 bilaterally. The frequency of atrophy in patients older than 60 years was significantly greater than in those 60 years of age or younger (42.9% vs. 9.4%; $P = 0.001$). Visual acuity in eyes with atrophy was significantly worse than in those without atrophy (0.32 vs. 0.14 logMAR; $P < 0.001$). The mean Snellen equivalent was 20/42 versus 20/28.

Histologic Analysis and Transmission Electron Microscopy

Cuticular, small, hard and soft drusen are compared morphologically in Figure 1. Cuticular drusen were located in the same anatomic plane as small, hard drusen and soft drusen. On light microscopy, cuticular drusen displayed similar staining characteristics as small hard drusen (Fig 1A, B). Individual cuticular drusen were indistinguishable morphologically from small, hard drusen because both were 30 μm in diameter. In some eyes, extensive resorption of cuticular drusen involving a confluent area of more than 3 disc areas was seen (Fig 8; Fig S8, available at www.aaojournal.org). The RPE immediately overlying both cuticular drusen and hard drusen were both 30 μm or less in diameter. However, cuticular drusen were far more numerous than small, hard drusen, occurring in continuous runs or coalescing clusters, such that they appeared confluent rather than discrete (Figs 1 and 12).

The internal contents of typical cuticular drusen frequently were homogeneous. Cuticular drusen 20 μm or more in height demonstrated a range of additional morphologic features, including (1) disintegration or dispersion of internal contents centrally and basally, leaving a rim of the original material (Fig 12E, F; Fig S10, available at www.aaojournal.org); and (2) a heterogeneous internal appearance with fragments of electron-dense material interspersed with vacuoles suggesting extracted lipid (Fig 12G, H).

The RPE immediately overlying both cuticular drusen and small, hard drusen was attenuated (Fig 1D, E). Retinal pigment epithelium cells immediately adjacent to drusen of both types appeared hypertrophied and hyperpigmented. Bruch’s membrane demonstrated small electron-dense excrences on its innermost aspect at sites of both cuticular drusen and small, hard drusen (Fig 1G, H).

In contrast to cuticular and hard drusen, soft drusen (Fig 1C) typically were larger (>30 μm in diameter) and were characterized by sloping sides. Soft drusen predominantly comprised lipid- and lipoprotein-derived debris (originally called...
membranous debris), as seen on electron microscopy (Fig 1I). Basal linear deposits and continuous basal laminar and basal linear deposits were associated preferentially with soft drusen (Fig 1F, I), although they can appear with hard drusen. Retinal pigment epithelium changes associated with soft drusen varied from mild hypertrophy and hyperpigmentation to attenuation, atrophy, and hypopigmentation.

**Discussion**

In his original publication, before the advent of OCT and wide-field imaging, Gass1 speculated that cuticular drusen represented focal, nodular thickenings of the RPE—basal lamina that differed from typical drusen, which he proposed were sites of RPE detachment without basal laminar thickening. Despite several detailed investigations, the clinical and histologic features that distinguish cuticular drusen from other drusen subtypes are somewhat controversial. These controversies are exemplified by varied nomenclature; the terms cuticular drusen, basal laminar drusen, and small, hard drusen have been used interchangeably to describe the same lesion. Other authors have referred to cuticular drusen as early adult-onset grouped drusen or a variant of AMD.18,33 Imaging features that currently are agreed on regarding the cuticular drusen phenotype include its sub-RPE location as seen on OCT and the starry-sky pattern on FA.32 Because long-term visual outcomes in macular diseases are associated inherently with specific drusen phenotypes, further refining the imaging characteristics of the cuticular drusen phenotype is of great clinical relevance.

This report is arguably the most extensive multimodal imaging cohort analysis of cuticular drusen. The wide-ranging morphologic manifestations seen with each method highlight the importance of multimodal imaging for precisely defining druse phenotypes. Previous reports using OCT have suggested that cuticular drusen demonstrate a pathognomonic saw-tooth appearance resulting from a geometric congruence between the basal diameter and the height of individual druse.3,20,35 However, in our cohort, the saw-tooth pattern was not seen in all eyes that demonstrated the characteristic starry-sky pattern on FA, with some cases resembling soft drusen and others barely discernible on OCT. The morphologic correlation between OCT and FA or FAF also appeared to be inconsistent. We found that a cuticular drusen phenotype characterized by shallow or marked RPE elevations can result in comparable FA and FAF patterns. Therefore, as was demonstrated for SDD,3,40 accurate detection of the cuticular drusen phenotype requires the integration of data from more than one imaging method.

Because photoreceptor topography is organized precisely, drusen topographic features convey vital information about whether and how signaling pathways from rod and cone physiologic characteristics drive pathologic features in the photoreceptor support system.41,42 Because SDD has a predilection for the superior macula and frequently spares the fovea, investigators have speculated that the pattern of SDD distribution may be related to that of rod photoreceptors.41 Some authors have suggested that cuticular drusen often are first visible in the peripheral or mid-peripheral retina,33,44 where the rod-to-cone ratio is highest. A major strength of the present report is that 110 eyes were evaluated with ultrawide-field techniques, permitting visualization of up to 200° of the retina. This analysis revealed peripheral drusen anterior to the vortex veins in only 21.8% of eyes with macular cuticular drusen. Our data can be compared with those from Tan et al,25 who found peripheral drusen in 58% of neovascular AMD eyes and 18.4% of control eyes, and the OPERA study, which found peripheral drusen in 64% to 78% of intermediate AMD eyes and in 9% to 21% of control eyes.23
together, the frequency of peripheral retinal involvement in eyes with a cuticular drusen phenotype seems more similar to that of control eyes than to that of AMD eyes.

Authors who described large drusen in eyes manifesting cuticular drusen speculated about how these large drusen might form.\textsuperscript{15,36,44} Gass et al\textsuperscript{15} proposed that the appearance of large drusen was an illusion resulting from the RPE fading between cuticular drusen clusters. Querques et al\textsuperscript{36} referred to large drusen as \textit{atypical cuticular drusen} that accumulated lipid such that they resembled age-related

![Figure 7. Ultrawide-field imaging of cuticular drusen phenotype in a 51-year-old woman: (A, B) color imaging and (C, D) fluorescein angiography findings of the right and left eyes. Peripheral drusen were associated with hyperpigmentary and hypopigmentary abnormalities of the retinal pigment epithelium. The fluorescein angiographic patterns of peripheral drusen (insets I and IV) and cuticular drusen in the posterior pole (insets II and III) were similar. Almost 25% of eyes with cuticular drusen in the posterior pole also demonstrated peripheral drusen anterior to the vortex veins.](image)

Table 3. Age-Related Variations in the Morphologic Features and Complications of Cuticular Drusen

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<th>Age Older than 60 Years (n = 112)</th>
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Data are number (%), unless otherwise indicated.

AVL = acquired vitelliform lesion; CNV = choroidal neovascularization; GA = geographic atrophy; RPE = retinal pigment epithelium.

*Comparison between eyes in patients 60 years of age or younger and those from patients older than 60 years.
soft drusen. However, neither longitudinal nor histologic data were included to support these hypotheses. By using image-registered SD OCT and multimodal imaging, we could study time-dependent changes precisely, thereby demonstrating that large drusen can result from coalescence or enlargement of typical cuticular drusen (Fig 8; Fig S8, available at www.aaojournal.org). Furthermore, differences in the ICGA fluorescence properties between cuticular and large drusen suggest differences in lipid and protein contents between these drusen subtypes. Large drusen

Figure 8. Time-dependent changes in a woman with cuticular drusen phenotype with visual acuity of 20/25 at the first and final visits. Baseline (left column) and follow-up images (12 years later; right column) illustrate important features of the cuticular drusen life cycle. A, B, At the final visit, color photography shows coalescence of cuticular drusen with new retinal pigment epithelial changes (black arrows). C, D, Red-free imaging shows resorption of cuticular drusen (area demarcated by yellow fenestrated line). E, F, Fundus autofluorescence imaging shows development of geographic atrophy (red arrows).
appeared hypofluorescent on ICGA, whereas cuticular drusen in many eyes appeared hyperfluorescent. In Table S1 (available at www.aaojournal.org), our data are combined with those of Sarks et al\textsuperscript{10} and Arnold et al,\textsuperscript{46} who previously evaluated ICGA characteristics of drusen in AMD. They showed that hard cluster—derived drusen were hyperfluorescent, whereas soft cluster—derived drusen, like our large drusen, were hypofluorescent. They postulated

Figure 9. Acquired vitelliform lesions (AVLs) in a cuticular drusen phenotype from the left and right eyes of a 60-year-old man. Acquired vitelliform lesions appear (A, B) yellow in color photographs, (C, D) predominantly hypofluorescent in the early phase of the fluorescein angiogram, and (E, F) intensely hyperautofluorescent on fundus autofluorescence imaging. G, H, OCT confirms the subretinal location of vitelliform material. Bilateral involvement occurred in 45% of patients with AVLs. The position of OCT line scans are illustrated on lines in the color photographs.
that breakdown and softening of hard drusen, with subsequent accumulation of globular material, may account for the different ICGA staining of hard and soft drusen. Recent data suggest that softening is the result of enrichment of hard druse contents with lipoproteins and lipoprotein-derived debris of RPE origin that backs up from Bruch’s membrane during decades of accumulation.47

Our report unequivocally demonstrates that, like soft drusen, cuticular drusen are dynamic and exhibit characteristics of coalescence, resorption, and RPE disturbances.50,51 Increasing evidence suggests that RPE disturbances associated with drusen and drusenoid pigment epithelial detachments (PEDs) are time locked to the life cycle of these deposits.5,16,52,53 Ouyang et al52 showed that the occurrence of intraretinal hyperreflective foci overlying druse was predictive of atrophy. We recently demonstrated that intraretinal hyperreflective foci and disruptions of the RPE–basal laminar band preceded collapse of drusenoid PEDs and subsequent atrophy.5 Previous investigators postulated that cuticular drusen may be an indicator of generalized RPE dysfunction.38 However, our recent data suggest that RPE atop large drusenoid PEDs are

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Figure 10. Choroidal neovascularization in a cuticular drusen phenotype. An illustrative case of the left eye of a 52-year-old woman demonstrates the imaging characteristics of a mixed neovascularization lesion (types 1 and 2) as seen on (A) color photography, (B) red-free photography, (C) fluorescein angiography, (D) fundus autofluorescence imaging, and (E) OCT. In this case, subretinal hemorrhage and subretinal fluid are associated with neovascularization. Approximately 12% of the cohort demonstrated neovascularization. I = inferior; N = nasal; S = superior; T = temporal.
functional for months to years, whereas the deposits grow because of continued secretion of druse components that are backed up by Bruch’s membrane and choriocapillary endothelium dysfunction in clearing them. Only further research will reveal whether similar mechanisms are also operative for cuticular drusen.

Although the natural history and sequelae of cuticular drusen may share similarities with those of soft drusen, from a histologic standpoint, cuticular drusen seem to be ultrastructurally and immunohistochemically similar to hard drusen. Patients with a cuticular drusen phenotype also share similar complement factor H polymorphisms with those with small, hard drusen. One explanation for this paradox is a mass effect; that is, eyes with a cuticular drusen phenotype typically have very high drusen loads, and this may be the most important risk factor for the development of RPE pigmentary changes, GA, and neovascularization. Arguably, eyes manifesting only hard drusen have much lower drusen loads, and this may be why we rarely see complications in these cases. According to epidemiologic and longitudinal clinical imaging studies, numerous hard drusen and cuticular drusen increase the risk for progression only in the aggregate and over the long term (10–20 years). Based on our clinical and histologic data, we hypothesize the following regarding the life cycle of cuticular drusen. First, cuticular drusen, like hard drusen, begin as small nodules of hyalinized, protein-rich material external to the RPE (entrapment sites). Second, with time, cuticular drusen can remodel, regress, or increase in size and number. Cuticular drusen that enlarge undergo biochemical alterations. The disintegrating appearance on electron microscopy is possibly the result of suboptimal preservation of extracellular lipid. Using soft drusen formation by retention of lipoproteins as a model, it is possible that hard and cuticular drusen are both retentive matrices that permit conversion to soft drusen over an extended period. Third, clusters of cuticular drusen eventually join, resulting in continuous deposits that constitute a substantial biophysical diffusion and transport barrier between the RPE and choriocapillaris and a nidus for inflammation, increasing the risk of complications, as postulated for soft drusen.

Macular complications of RPE-related changes, AVLs, neovascularization, and GA associated with cuticular drusen are significantly more frequent in patients older than 60 years of age. Patients with a cuticular drusen phenotype also experience a significant age-dependent decline in BCVA between the first and final visits. This study demonstrated that the occurrence of neovascularization and GA are the most important determinants of poor VA, supporting previous findings by Cohen et al. We did not compare visual outcomes between eyes with typical AMD and cuticular drusen; such an analysis was performed previously for 2 separate cohorts by Gass et al. These authors concluded that patients with cuticular drusen have a better visual prognosis than those with typical AMD, a conclusion possibly confounded by the presence of many patients treated with laser photocoagulation in their AMD group.

Age-related macular degeneration is an important cause of severe vision loss in the developed world. The projected number of people with this disease is estimated to rise to 288 million by the year 2040. Longitudinal studies of SDD and soft drusen have shown that the risk of developing macular complications is intrinsically linked to the AMD status. We suggest that a cuticular drusen phenotype constitutes a specific subtype of AMD that has
Figure 12. Variations in cuticular drusen size and morphologic features. Panoramic light microscopic images are shown in the left column; detailed electron microscopic images, in the right column. A, Cuticular drusen can be small and occur singly (arrows). The retinal pigment epithelium (RPE) overlying small cuticular drusen show minimal morphologic changes. These may correspond to OCT pattern 1 (shallow elevations of RPE with difficult-to-discrim contents). B, Ultrastructurally, cuticular drusen have homogenous contents (asterisk). The smallest cuticular drusen appear as nodular elevations of the inner aspect of Bruch’s membrane (arrow). C, As cuticular drusen enlarge and coalesce, RPE changes, including attenuation (arrow), hypopigmentation (X), hyperpigmentation, and enlargement become notable. Attenuated RPE overlying cuticular drusen likely produces the classical so-called window defect on angiography and central hypofluorescence of cuticular drusen, because RPE cells containing lipofuscin and melanolipofuscin are displaced peripherally. Coalesced cuticular drusen may correspond to OCT pattern 2 (saw-tooth pattern), with possible progression to OCT pattern 3 (broad mound-shaped elevations of the RPE band) when they enlarge further. D, Ultrastructurally, coalesced cuticular drusen can resemble those of small single cuticular drusen. However, some larger cuticular drusen (>20 μm height) show distinct changes, either (E, F) appearing to disperse or disintegrate at their center and base or (G) becoming heterogeneous, with (H, white arrow) electron dense fragments and (H, red arrowhead) vacuoles signifying processing-related extraction of lipid. Disintegration and heterogenization of cuticular drusen contents may give rise to variations in OCT reflectivities. They also may explain differences in fluorescein and indocyanine green uptake and hence angiographic staining characteristics. Images (A, B, E, F) represent macular sections of the left eye, and images (C, D, G, H) represent macular sections from the right eye (clinical imaging for both eyes are shown in Fig S1, available at www.aaojournal.org). BrM = Bruch’s membrane; Ch = choroid; ChC = choriocapillaris; IS = inner segment; ONL = outer nuclear layer; OS = outer segment; SDD = subretinal drusenoid deposit.
clinical relevance for prognosticating long-term visual outcomes. Strengths of this study include a large clinical cohort that was evaluated meticulously using state-of-the-art multimodal imaging techniques as well as comparative histologic analysis of drusen subtypes. This study reiterated the importance of multimodal imaging for precise drusen phenotyping. The diagnosis of cuticular drusen may be erroneous if made in the absence of multimodal imaging (Fig S2, available at www.aaojournal.org), and the authors recommend imaging of all patients manifesting drusen using a combination of OCT, FAF imaging, NIR imaging, and color photography at the baseline visit. These noninvasive imaging methods are likely to provide the information required to differentiate drusen subtypes. This study also provided evidence to suggest that drusen load and drusen composition are independent risk factors for the development of sight-threatening complications in AMD. With the application of newer techniques such as the development of sight-threatening complications in AMD. With the application of newer techniques such as polarization-sensitive OCT that allow automated calculation of drusen volume and also drusen composition, it may be possible to prognosticate clinical outcomes in AMD better using in vivo imaging data and to differentiate hard drusen from cuticular drusen clinically. We emphasize that this study was not designed to determine the sensitivity and specificity of different imaging methods for detecting cuticular drusen, and this important issue will need to be addressed in future studies. Furthermore, there is an urgent need for studies to determine whether and how baseline multimodal imaging impacts patient outcomes in AMD. Limitations of this study include the retrospective study design and the availability of only 2 histologic specimens (from 1 patient) with cuticular drusen. Tissue analysis of more specimens clearly is needed to validate the clinical observations in this study. Importantly, although morphologic characteristics are a necessary starting point in defining a phenotype, a full characterization of cuticular drusen composition and associated functional changes within retina and Bruch’s membrane—choriocaipillaris remains to be performed. Another limitation of this work is the non-standardized interval of patient follow-up visits; it is possible that patients with poorer vision had more frequent follow-up than those with relatively good vision. Finally, a significant number of patients in our cohort were within the age range for typical AMD. Prospective studies with age- and gender-matched control groups reviewed at fixed intervals will help to refine further whether, and how, eyes manifesting a cuticular drusen phenotype differ from those with typical AMD.

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References


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Abbreviations and Acronyms:
AMD = age-related macular degeneration; AVL = acquired vitelliform lesion; BCVA = best-corrected visual acuity; D = diopter; FA = fluorescein angiography; FAF = fundus autofluorescence; GA = geographic atrophy; ICGA = indocyanine green angiography; logMAR = logarithm of the minimum angle of resolution; NIR = near-infrared reflectance; PDE = pigment epithelial detachment; RPE = retinal pigment epithelium; SD = spectral-domain; SDD = subretinal drusenoid deposits.

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