Published in final edited form as:

Ophthalmology. 2010 March ; 117(3): 489–499. doi:10.1016/j.ophttha.2009.12.002.

Natural History of Drusenoid Pigment Epithelial Detachment in Age-Related Macular Degeneration: AREDS Report Number 28

Cathy Cukras, MD PhD¹, Elvira Agrón, MA¹, Michael L. Klein, MD³, Frederick L. Ferris III, MD¹, Emily Y. Chew, MD¹, Gary Gensler, MS⁴, Wai T. Wong, MD PhD², and the Age-Related Eye Disease Study Research Group⁵

¹Division of Epidemiology and Clinical Research National Eye Institute, National Institutes of Health, Bethesda, MD, USA

²Office of the Scientific Director, National Eye Institute, National Institutes of Health, Bethesda, MD, USA

³Devers Eye Institute, Legacy Good Samaritan Hospital and Medical Center, Portland, Oregon

⁴AREDS Coordinating Center, The EMMES Corporation, Rockville, Maryland, USA

⁵For complete listing, please see AREDS Report #8, Arch Ophthalmol 2001;119:1417-36

Abstract

Objective—To describe the natural history of eyes with drusenoid pigment epithelial detachments (DPED) associated with age-related macular degeneration (AMD).

Design—Multi-center clinic-based prospective cohort study.

Participants—Among 4757 participants enrolled in the Age-Related Eye Disease Study (AREDS), 255 were identified as having DPED in at least one eye and having 5 or more years of follow-up after the initial detection of the DPED.

Methods—Baseline and annual fundus photographs were evaluated for the evolution of the fundus features and the development of advanced AMD in the forms of central geographic atrophy (CGA) or neovascular (NV) AMD. Kaplan-Meier analyses of progression to advanced AMD and of moderate vision loss (≥ 15 letters compared with baseline) were performed.

Main Outcome Measures—Rate of progression to advanced AMD and change in visual acuity from baseline (in terms of mean letters lost and proportion losing ≥ 15 letters).

Results—A total of 311 eyes (from 255 participants) with DPED were followed for a median follow-up time of 8 years subsequent to the initial detection of a DPED. Of the 282 eyes that did not have advanced AMD at baseline, advanced AMD developed within 5 years in 119 eyes (42%) (19% progressing to CGA and 23% to NV-AMD). In the remaining eyes that did not develop advanced AMD ($n = 163$), progressive fundus changes, typified by the development of calcified drusen and pigmentary changes, were detected. Visual decline was prominent among study eyes, with

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Correspondence and Reprint requests to: Wai T. Wong, MD, PhD, Office of the Scientific Director, National Eye Institute, National Institute of Health, 7 Memorial Drive, Bldg 7, Room 217, Bethesda, Maryland 20892, Tel: (301) 496-1758. Fax: (301) 496-1759. wongw@nei.nih.gov .

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approximately 40% of all eyes decreasing in visual acuity by 15 or more letters at 5 years follow-up. Mean visual acuity decreased from 76 letters (~20/30) at baseline to 61 letters (~20/60) at 5 years. Five-year decreases in mean visual acuity averaged 26 letters for eyes progressing to advanced AMD and 8 letters for non-progressing eyes.

Conclusion—The natural history of eyes containing DPED is characterized by a high rate of progression to both CGA and NV-AMD. Among eyes not progressing advanced AMD, progressive development of pigmentary changes and calcified drusen were observed. Decline of visual acuity is a common outcome, with or without progression to advanced forms of AMD.

Introduction

Large drusen, a defining feature of intermediate age-related macular degeneration (AMD), together with pigmentary changes of the retina pigment epithelium, are lesions that have been previously associated with increased risk of progression to advanced AMD 1–3. A related macular lesion, termed drusenoid retinal pigment epithelial detachment (DPED), has also been identified in the spectrum of fundus lesions associated with AMD. In the Age-Related Eye Disease Study (AREDS), a DPED is defined as a fairly well-circumscribed, shallow elevation of the retinal pigment epithelium (RPE) formed by a confluence of soft drusen, often located in the central macula 4–5. Historically, this fundus lesion has been distinguished from other pigment epithelial detachments (PEDs), such as fibrovascular PEDs and hemorrhagic PEDs, by clinical appearance, fluorescein angiography⁵, histopathology⁶, and a better short-term visual prognosis⁵. In addition, DPEDs are associated with intermediate AMD, unlike other types of PED which are generally associated with advanced neovascular AMD 7.

While the risks of progression to advanced AMD and vision loss have been studied for eyes containing large drusen and pigmentary changes 8, similar risks for eyes containing DPEDs have not been as well established. Roquet et al.,⁹ had retrospectively examined 61 eyes with DPED (among which only 27 eyes had ≥ 3 years of follow-up), and reported an association with high risks of AMD progression and poor visual acuity. However, a long-term prospective natural history study of eyes with DPEDs has not been previously performed.

In the present study, we reviewed participants enrolled in the Age-Related Eye Disease Study (AREDS), a prospective, long-term, multicenter study of AMD. The prospective standardized evaluation of best-corrected visual acuity and the centralized grading of the annual stereoscopic fundus photographs performed in AREDS provides useful data for a comprehensive analysis of the natural history of DPED associated with AMD. A natural history study of eyes with DPED will allow a better assessment of visual prognosis associated with this AMD-associated lesion, and may provide additional insight into AMD progression and the etiologies of visual loss in AMD.

Materials and Methods

Study Population

Details of the design and methods of the AREDS have been presented elsewhere^{7, 10} and is briefly summarized here. Eleven retinal specialty clinics enrolled 4757 participants in the AREDS from 1992 through 1998. Participants were 55 to 80 years of age at enrollment and had best-corrected visual acuity of 20/32 or better in at least one eye. Media were sufficiently clear to obtain adequate quality stereoscopic fundus photographs of the macula in all study eyes. The Institutional Review Board for each clinical center approved the protocol, and informed consent was obtained from all participants.

Participants were recruited into AREDS based on the severity of AMD. Fundus photographs were obtained of both eyes of each study participant at the baseline visit and also at annual visits after year one, and then graded by a centralized Reading Center. The study eyes were categorized according to the size and extent of drusen, presence of central geographic atrophy, and neovascular changes in AMD, as previously described^{10, 11}. Progression to advanced forms of AMD (either central geographic atrophy (CGA), and/or neovascular AMD (NV-AMD)) was defined by the study protocol based on the grading of fundus photographs. Other fundus features, including the presence of a DPED, were also graded. DPED is defined in the AREDS study as a well-defined, pale yellow or white, large mound consisting of many large drusen or confluent drusen which is at least 350 microns in the narrowest diameter and appears elevated on stereoscopic fundus photographs. Participants with photographic grades of a DPED (graded as definitely or questionably present) within a 3000- μ m radius grading circle centered on the fovea were identified. Of these, we identified and admitted for analysis participants in whom DPED(s) have been identified in at least one eye, and for whom at least five years of follow-up, following the identification of the DPED, was available.

Procedures

Detailed questionnaires were administered to obtain medical history and demographic information including: history of smoking, specific prescription and nonprescription medication use and vitamin and mineral use. General physical and ophthalmic examinations included: measurement of height, weight, blood pressure (BP), manifest refraction, best-corrected visual acuity and intraocular pressure as well as dilated slit-lamp biomicroscopy and ophthalmoscopy. Slit-lamp photographs and Neitz photographs of the lens were taken along with red reflex lens photographs and stereoscopic fundus photographs of 3 stereoscopic fields: centered at the optic disk, the macula and an area temporal to the macula. Fundus photographs were obtained at baseline and also at annual visits, with the exception of the first annual visit following the baseline visit.

Natural History Outcomes

Natural history outcomes were evaluated based on data collected during the participants' annual visits. The first visit for which a study eye was graded as having a DPED was designated as the "DPED baseline". The timing of the evolution of fundus features and visual acuity outcomes were described relative to this baseline. We evaluated study eyes for: 1) the development of advanced forms of AMD, namely central geographic atrophy (CGA) and neovascular AMD (NV-AMD), 2) the initial presence, development, and evolution of other concomitant fundus features, such as the presence of large drusen, pigmentary changes, and calcified drusen, and 3) changes in mean visual acuity and the loss of visual acuity of ≥ 15 letters.

The development of advanced AMD (CGA or NV-AMD) was determined by the gradings of stereoscopic color fundus photographs. CGA was defined as geographic atrophy definitely present in the central subfield and definitely or questionably involving the center point of the macula. Geographic atrophy in the macula, either central or non-central, was defined as a somewhat circular patch (of area approximately equivalent to that of a circle of diameter 175 μ m) of sharply defined, partial or complete depigmentation of the retinal pigment epithelium, through which underlying choroidal blood vessels may be exposed. Neovascularization was defined as presence of a non-drusenoid pigment epithelial detachment or serous/hemorrhagic sensory retinal detachment within the central 3000- μ m circle, the presence of subretinal or sub-RPE hemorrhage or subretinal fibrosis in this same area, or the presence of photocoagulation scars consistent with the treatment of AMD. The presence of fundus features such as presence of large drusen, total drusen area, hyper- and hypopigmentary changes, and calcified drusen were determined from fundus photographic gradings as previously described⁷. Functional

outcome measures included mean best-corrected visual acuity (BCVA, as measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart) and the proportion of participants losing 15 letters or more from DPED baseline.

Statistical Analysis

As all eyes included in the study have at least 5 years of follow-up after DPED baseline, the five-year rates of development of examined outcomes may be directly calculated, although eyes recognized to have a DPED at the start of the study would have had the lesion for an undocumented period of time. Outcomes examined at time points beyond 5 years following DPED baseline were performed using Kaplan-Meier analyses. All analyses were performed with the SAS system (SAS Institute, Cary, NC).

Results

Of the 4757 participants in AREDS, 387 participants had a DPED in at least one eye at some point in the study with 68 of them having DPED in both eyes at some point during the study. Of these 387 participants, 255 participants had at least 5 years of follow up subsequent to the initial detection of the DPED. Fifty-six of these 255 participants (22%) have DPEDs in both eyes during the duration of the study. A total of 311 DPED-containing eyes with at least 5 years of follow up were available for this natural history analysis. Approximately half of these eyes ($n = 150$ eyes or 48%) had DPEDs that were present at the AREDS study baseline.

Baseline Characteristics of Eyes with Drusenoid Pigment Epithelial Detachments

The average age of the participants at the time of detection of the DPED was 69.5 years (range = 56–80 years). One hundred and fifty-eight (62%) participants were female, and all were white. One hundred and forty-five (57%) participants reported a current or previous smoking history, 85 (33%) reported a history of hypertension, and 7 (3%) reported taking medication for hypercholesterolemia at baseline. Further description of the baseline characteristics of these participants upon enrollment into the AREDS is summarized in Table 1.

Fundus characteristics of eyes with DPED ($n = 311$) at DPED baseline are summarized in Table 2. The majority (62%) of eyes had total drusen area exceeding 1 disc area. Pigmentary changes were also common, with hyperpigmentation being considerably more prevalent than hypopigmentation (87% versus 25% of all eyes respectively). A minority of eyes (9%, $n = 29$) had evidence of concurrent advanced AMD at time of DPED detection (1 CGA, 28 NV-AMD).

Mean visual acuity of all DPED-containing study eyes at DPED baseline was 75.6 ± 14.6 letters (approximately $20/32 \pm 3$ lines), with approximately 90% of this cohort having visual acuity better than 20/40.

Progression of Eyes with Drusenoid Pigment Epithelial Detachments to Advanced AMD

Table 3 and Fig. 1A summarize the prevalences of CGA or NV-AMD in all study eyes ($n = 311$ eyes) at DPED baseline and at 5 years. At baseline, only 29 eyes had advanced AMD (28 eyes had concurrent evidence of NV-AMD while only 1 eye had concurrent CGA) (Fig.1A). In eyes without evidence of advanced disease at baseline ($n = 282$), the annual incidence of either CGA or NV was based on both fundus photograph assessment and clinical exam. Incident advanced AMD was defined as the first clinical or photographic evidence of either form of advanced AMD. As such, analyses on progression to advanced AMD included only eyes without CGA or NV at baseline ($n = 282$), and excluded eyes with advanced disease that was present at baseline. Figure 1B displays the incidence of advanced AMD during the 5 years following DPED detection. The incidence of NV-AMD in the first 2 years was markedly higher than new progressions to CGA, but after year 3 the number of new progressions to CGA

increased relative to progressions to NV-AMD. Of the 282 eyes initially without advanced AMD, 119 (42%) progressed to advanced AMD by 5 years, with the incidence of CGA approaching that of NV-AMD (19% CGA and 23% NV-AMD).

The incidence of advanced disease beyond 5 years of follow-up was assessed with a Kaplan-Meier survival analysis (Fig. 1C). At 7 years following the detection of DPED, the number of eyes cumulatively progressing to CGA exceeded those progressing to NV-AMD. Similarly, results of an age-adjusted Cox proportional hazard model showed a lower interval hazard ratio for incident CGA compared to that for incident NV-AMD in the early years of follow-up, but this value exceeds that of NV-AMD after 8 years of follow-up (data not shown).

In order to compare the rates of progression to advanced AMD observed in these eyes with DPEDs to comparable eyes lacking DPEDs, we identified a comparison group of eyes from the AREDS study that 1) contained large drusen ($> 125 \mu\text{m}$ in diameter) and hyperpigmentary changes at study baseline, 2) were without any clinical signs of advanced AMD (CGA or NV-AMD) at study baseline, and 3) lacked a DPED throughout the duration of the study. We compared this comparison group (1122 eyes) to the group of eyes with DPEDs that did not have advanced AMD at baseline (282 eyes). By 5 years following baseline, the rate of progression to advanced AMD was significantly lower in the comparison group than in the DPED group (25% versus 42%; $p < 0.001$). At 5 years, the proportion of eyes with CGA only (no concurrent NV-AMD) was also significantly lower in the comparison group than in the DPED group (7% versus 18%, $p < 0.001$). The proportion of eyes containing NV only (no concurrent CGA) was slightly, but not significantly, lower in the comparison group (16% versus 19.5%, $p = 0.19$). The proportion of eyes containing both CGA and NV-AMD was however significantly lower in the comparison group than in the DPED group (2% versus 4%, $p < 0.01$).

Changes in Fundus Features in Eyes with Drusenoid Pigment Epithelial Detachments Not progressing to Advanced AMD

Of the 311 eyes DPED eyes studied, 163 did not demonstrate evidence of progression to either form of advanced AMD in 5 years. The prevalences of fundus characteristics, as assessed from the grading of annual stereoscopic fundus photographs, were analyzed. Fundus features scored included: 1) the presence of hyperpigmentary changes, 2) the presence of hypopigmentary changes, 3) the presence of calcified drusen, and 4) the total estimated drusen area within the central 3000- μm circle. Analyses revealed that common fundus features, such as hyperpigmentary changes (present in 82% of all non-progressing eyes at baseline), maintained their prevalence at similar levels throughout the 5 years following the baseline visit (Fig 2A). However, other fundus features that were less prevalent at baseline, such as hypopigmentary changes (14%) and calcified drusen (4%), increased in prevalence over the next 5 years (increasing to 71% for hypopigmentary changes, and to 36% for calcified drusen) (Fig. 2B,C). The number of eyes in this group with non-central geographic atrophy (i.e., GA not involving the center of the fovea) also increased from none at baseline to 11% by 5 years (Fig. 2D). In addition, analyses of total estimated drusen area showed that the proportion of eyes in the largest drusen area category (> 1 disk diameter) decreased progressively from 70% to 57% while the proportion of eyes in the smallest area category ($<$ grading circle O2 of diameter $660 \mu\text{m}$)⁷ increased from 4% to 11% over the first 5 years of follow-up (Fig. 2F). Taken together, these analyses indicate that DPED-containing eyes that do not progress to advanced AMD are not anatomically invariant in their fundus features but are instead undergoing progressive anatomical changes characterized by an increase of calcified drusen and hypopigmentary/atrophic changes, and a trend towards decreasing total drusen area. These fundus changes may be possibly related to the pathophysiological processes leading to advancement to both CGA and NV-AMD.

Natural History of Fundus Changes in Eyes with Drusenoid Pigment Epithelial Detachments: Case Examples

Case 1 features the left eye of a 73 year old white woman with a DPED that did not progress to either CGA or NV-AMD during 8 years of follow-up. As seen in this example (Fig. 3), eyes containing DPEDs, even in the absence of progression, can demonstrate marked changes in the size and distribution of large drusen and DPEDs. Although the overall prevalence of large drusen and hyperpigmentary changes are maintained throughout the period of observation (Fig. 2A, B), the exact location and configuration of these features in this example are seen to vary dynamically over time.

Case 2 is an example of an eye with DPED that progressed to CGA during follow-up (Fig. 4). Progressive fundus changes in this example include an initial decrease and disappearance of the DPED, changes in the distribution of hyperpigmentary changes, and the emergence of patchy areas of hypopigmentation that subsequently progress and enlarge to form well-circumscribed areas of atrophy involving the center of the fovea.

Case 3 illustrates the progression of an eye with DPED to neovascular AMD with the acute emergence of retinal edema, subretinal lipid, and recurrent subretinal hemorrhage (Fig. 5).

Natural History of Vision Loss in Eyes with Drusenoid Pigment Epithelial Detachments

Best-corrected visual acuity (BCVA) measurements, collected at annual visits, were analyzed for eyes with DPEDs. Overall, a broad trend towards a declining mean visual acuity and an increasing proportion of eyes with clinically important visual acuity loss was observed over the follow-up period. Considering all DPED-containing eyes in the study, the distributions of BCVA, assessed at DPED baseline and at 5 years follow-up (Fig. 6A), reflected a four-fold increase in the proportion of eyes with visual acuities between 20/40 and 20/200 (8.7% vs. 35.5%) and a three-fold increase in the proportion of eyes with visual acuities <20/200 (4.5% vs. 14.0%). Mean BCVA visual acuity for all eyes with DPED decreased by 15.0 letters during the five years of follow-up (Fig. 6B).

Decreases in visual acuity were found both in eyes progressing to advanced AMD as well as in eyes that did not progress to advanced AMD. As expected, these decreases are larger in eyes progressing to advanced AMD compared with eyes that did not progress. Eyes progressing to advanced AMD had a 5-year mean decrease in BCVA of 25.9 letters compared with a 5-year mean decrease of 8.2 letters in eyes that did not progress to advanced AMD. At 5 years, loss of three or more lines (≥ 15 letters) of visual acuity occurred in 49% of eyes progressing to advanced AMD compared with 21% of eyes that did not progress. Overall, 37% of all eyes with DPED lost 15 letters or more by 5 years (Fig. 6C). For DPED eyes progressing to advanced AMD, vision loss in eyes progressing to NV-AMD and CGA at 5 years are tallied separately in Table 4.

Kaplan-Meier analysis of the natural history of visual decline in eyes with DPED beyond 5 years demonstrated that the rate of vision loss was maintained over time for up to 12 years, with an estimated 69.4% of all eyes losing ≥ 15 letters of visual acuity at 10 years and 82.7% losing ≥ 15 letters at 12 years (Figure 6D). While survival analyses for vision loss can in some situations (e.g., where vision loss is transient, or when subsequent visual recovery occurs) result in over-estimations, this is unlikely for this study population; of all eyes losing ≥ 15 letters at 5 years follow-up ($n=194$), 90% maintained a ≥ 15 letter loss from baseline at their final available follow-up visit.

The rate of vision loss observed in eyes with DPED was also higher than that for eyes in our above-mentioned comparison group (eyes without DPEDs but containing large drusen and hyperpigmentary changes). Considering all eyes, significantly more eyes in the DPED group

lost 15 or more letters over 5 years than in the comparison group (39% versus 27%, $p < 0.001$). Among eyes progressing to advanced AMD (CGA or NV-AMD), the 5-year rates of vision loss (≥ 15 letters) were not statistically distinct between eyes in 2 groups. However, among eyes that did not progress to advanced AMD, significantly more eyes in the DPED group lost ≥ 15 letters compared to the eyes in the comparison group (22% versus 13%, $p < 0.01$).

Discussion

Previous reports have described a clinically important risk of progression to CGA and NV-AMD in eyes with DPEDs 4, 5, 9, 12. The calculated rates of progression to CGA and NV-AMD in these studies varied over a wide range, in part due to their retrospective nature and paucity of subjects with long follow-up periods. In the present study, we were able to identify a large, prospectively-identified population of patients with a DPED in at least one eye who were followed for at least 5 years (range 5 – 12 years) at regular intervals with clinical examinations, standardized visual acuity testing and standard fundus photography, with phenotypic evaluations derived from standardized stereoscopic grading of fundus photographs at a centralized reading center. The design of the study thus permitted a comprehensive and long-term evaluation of natural history of eyes containing DPEDs.

Our findings confirm that eyes with DPEDs possess a high risk of progressing to advanced forms of AMD in 5 years. A relatively small proportion (9%) of our study eyes had evidence of concurrent CGA or NV-AMD at baseline and progression rates to advanced AMD were determined from the remainder ($n = 282$). Of these 282 eyes, 17% of eyes progressed to NV-AMD by 3 years follow-up and 23% by 5 years. The cumulative rate of progression to CGA was lower in the initial phase of follow-up but was estimated to rise with time and exceed the cumulative rate of progression to NV-AMD at 7 years. Overall, approximately 42% of eyes with DPED progressed to either form of advanced AMD by 5 years, a rate of progression that was significantly higher than that found in a comparison group of eyes containing large drusen and hyperpigmentation but lacking a DPED (25%).

Although the factors predisposing an eye with DPED to progress to CGA versus NV-AMD are unclear, the trend for increasing risk of progression to CGA support previously described concepts concerning the “life-cycle” of drusen and DPEDs^{13–15}. In this study, many DPEDs were pre-existing at study baseline, and time of follow-up is likely to underestimate the average “age” that the DPEDs analyzed here have been in existence. Despite this limitation, the increasing incidence of CGA with follow-up supports the notion that CGA may represent the end-stage in a multi-stage evolution of a DPED, and eyes containing DPEDs, absent the development of NV-AMD, are likely, given sufficient time, of arriving at this fate. Consistent with this, we found that eyes with DPED progressed to CGA at a rate over twice that found in the comparison group lacking DPEDs. We did not find evidence that the natural history of study eyes were strongly influenced by the presence or absence of a DPED in its fellow eye. Separate analyses of eyes that either had (38%) or lacked (62%) a fellow eye with a DPED, did not reveal statistically different rates of progression to CGA or NV-AMD between these 2 groups (data not shown).

In eyes with DPEDs not progressing to either CGA or NV, our analyses indicate that dynamic and progressive changes occur in a number of co-existing fundus features. Features such as the presence of drusen and hyperpigmentary changes are seen in most eyes with DPEDs, suggesting that the evolution of these features are related and concurrent with the development of DPEDs. More significantly, the percentages of eyes accumulating hypopigmentary changes, central and non-central geographic atrophy and calcified drusen were found to increase during follow-up, suggesting gradual RPE cell death associated with the DPEDs and large drusen. Interestingly, the proportion of eyes having a total drusen area in the highest category (circle

of >1 disk area in diameter) also decreased with time, also suggesting an evolution of large drusen to hypopigmentation or geographic atrophy. Consistent with this, previous histopathological studies of eyes with AMD have suggested that the later stages of the DPED life-cycle may involve varying degrees of drusen collapse and regression that are associated with RPE degeneration and disorganization that are clinically observed as hypopigmentary change, while the emergence of calcified or refractile drusen may be related to remnant end products of regressed drusen and apoptotic RPE cells¹⁵.

These observations of progressive change are congruous with those found in a previous study examining precursor characteristics associated with the subsequent development of CGA¹⁴. In that study, at the location of future GA, most eyes demonstrated a succession of precursor lesions comprised of large drusen (including DPEDs), hyperpigmentation, hypopigmentation, and in some cases, refractile/calcified drusen. In the present study, this general pathway was again noted in the evolution of eyes with DPED, often resulting in overt GA as a terminal step. Taken together, these analyses indicate that there is a consistent pathway for the evolution of fundus features in intermediate AMD, common to eyes with large soft drusen and DPED. The presence of these features, accompanied by pigmentary changes, constitutes the first step in an evolution sequence, which progresses to the accumulation of hypopigmentary changes and refractile/calcified drusen as a second step, and then the development of overt geographic atrophy or hypopigmentation without geographic atrophy as a terminal step.

Consistent with the high risk of progression to advanced forms of AMD, eyes with DPED in this study demonstrated a natural history of overall decreasing mean visual acuity and increasing rates of moderate to severe vision loss (≥ 15 letters), which have also been noted also in previous studies^{4, 5, 9, 12}. Interestingly, our study found that even among eyes with DPED that did not progress to advanced AMD, the percentage of eyes losing ≥ 15 letters increased over time and was significantly higher at 5 years than in non-progressing eyes in the comparison group that lacked DPEDs (22% versus 13%). The anatomical cause for this visual decline may be related to incipient atrophic RPE changes represented by hypopigmentary changes or functional loss in photoreceptors located above a chronically elevated DPED. The observed visual acuity losses, with or without the development of advanced AMD, constitute a poor overall functional prognosis for eyes with DPED, with mean visual acuity declining from 76 letters (~20/30) to 61 letters (~20/60) over 5 years.

Limitations of the present study include the sole reliance on reading center-based grading of photographs to score fundus phenotypes, without analysis of additional imaging modalities such as fluorescein angiography, indocyanine green angiography, optical coherence tomography (OCT) or fundus autofluorescence (FAF) imaging. Additional modalities, some of which were not available at the time of the study, could be helpful both in the detection and characterization of DPEDs as well as the identification of concurrent fundus changes⁹, as have been described in previous case reports for OCT imaging⁹ and FAF imaging¹⁶. Future prospective studies of AMD using these modalities may provide further details on the natural history of anatomical change occurring in these eyes and further our understanding of the dynamic pathophysiological changes occurring in different stages of intermediate AMD.

In summary, this natural history study involves a large cohort of eyes with DPED that were followed systemically over a long follow-up period. Our study indicates that eyes with DPED are at high risk for progression to both CGA and NV-AMD and for clinically important decreases in visual acuity. DPEDs are associated with the presence of large soft drusen and hyperpigmentary changes, and appear to progress through a life-cycle involving the later development of hypopigmentation and calcified drusen, and, for eyes not progressing to NV-AMD, the final development of CGA or hypopigmentation. Future studies examining

anatomical and other associations with DPEDs, using additional imaging modalities such as OCT and FAF, may provide further insight into the pathogenesis of this macular lesion.

Acknowledgments

This work has been supported by funding from the National Eye Institute Intramural Research Program. Dr Ferris is an inventor on a U.S. patent owned by Bausch & Lomb. Dr. Ferris has assigned his interest in the patent to the U.S. Government and receives government compensation.

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Figure 1.

Progression of study eyes with drusenoid pigment epithelial detachments (DPED) to advanced forms of age-related macular degeneration (AMD). **A.** Proportions of eyes ($n = 311$) with DPED with concurrent central geographic atrophy (CGA), neovascular (NV) AMD, both NV AMD and CGA, and without any advanced forms of AMD at DPED baseline (left) and at 5 years following baseline (right). **B.** Cumulative percentage of eyes ($n = 282$ eyes; eyes with no evidence of advanced AMD at baseline) progressing to either CGA or NV AMD in the first 5 years of follow-up. **C.** Kaplan-Meier analysis of the cumulative percentage of eyes progressing to either CGA or NV AMD up to 10 years after baseline. The cumulative

percentage of eyes progressing to CGA was estimated to exceed that progressing to NV AMD at year 7.

Figure 2.

Natural history of fundus changes in eyes with drusenoid pigment epithelial detachments (DPEDs) not progressing to advanced forms of age-related macular degeneration (AMD) by 5 years ($n = 163$). Prevalences of the presence of each fundus finding at year 0, 1, 2, 3, 4, 5 following baseline are plotted. **A.** Percentage of eyes with hyperpigmentary changes. **B.** Percentage of eyes with hypopigmentary changes. **C.** Percentage of eyes with calcified drusen. **D.** Percentage of eyes with geographic atrophy (GA) not involving the center of the fovea (i.e. non-central GA). **E.** The total drusen area in each eye was estimated and classified in one of the following categories: smaller than area of grading circle O2 (circle diameter = 660 microns), from area of circle O2 to $\frac{1}{2}$ disk area (DA), from $\frac{1}{2}$ DA to 1 DA, and greater than 1 DA. The

proportions of eyes in each area category are shown for each year of follow-up. The total numbers of eyes for each time point are as follow: 163 eyes at year 0, 87 eyes at year 1, 156 eyes at year 2, 155 eyes at year 3, 149 eyes at year 4, 152 eyes at year 5).

Figure 3.

Case 1: Fundus changes occurring in the left eye of a 73 year-old woman with a drusenoid pigment epithelial detachment (DPED) at baseline. **A.** Fundus at year 0 (baseline): A centrally located DPED is seen with scattered large drusen in the inferior macula. **B.** At year 4, new calcified, refractile drusen emerge in the temporal macula (black arrow). Central DPED is decreased in height and area. **C.** At year 7, new hyperpigmentary changes appear at the fovea (black arrowhead). Large drusen in the inferior macula enlarge in size and coalesce to form a new DPED (white arrows). **D.** At year 8, DPEDs in both the central and inferior macula have disappeared. Calcified drusen are increased in number and an area of hypopigmentation has appeared in the nasal macula (white arrowhead). Central hyperpigmentary changes have also

decreased as areas of hypopigmentation have increased. This natural history illustrates the dynamic changes in fundus features over a 8-year period, involving the appearance and disappearance of DPEDs, hyper- and hypopigmentary changes and calcified drusen, without overt progression to advanced forms of age-related macular degeneration.

Figure 4.

Case 2: Fundus changes occurring in the left eye of a 73-year old man with a drusenoid pigment epithelial detachment (DPED) that progressed to central geographic atrophy (CGA) during the course of the study. **A.** Fundus at year 0: A centrally located DPED is present with hyperpigmentary changes. **B.** At year 2, most of the DPED has disappeared and a new area of hypopigmentation has emerged (black arrow). **C.** At year 4, an additional area of hypopigmentation has arisen (black arrows). In the meantime, the hyperpigmentary changes seen earlier have decreased. **D.** At year 7, areas of geographic atrophy have emerged from earlier patches of hypopigmentation that have enlarged and coalesced.

Figure 5.

Case 3: Fundus changes occurring in the left eye of a 72 year-old woman with a drusenoid pigment epithelial detachment (DPED) that progressed to neovascular age-related macular degeneration (NV AMD) during follow-up. **A.** Fundus at year 0: A DPED with associated hyperpigmentary changes is located in the temporal perifovea (black arrowhead). **B.** At year 4, additional hyperpigmentary changes have emerged (black arrow) overlying the DPED. **C.** At year 9, new onset retinal edema, subretinal lipid exudate emerged in the region of the DPED. **D.** Three months after the onset of retinal edema, subretinal hemorrhage, indicative of NV AMD is seen in the same location.

Figure 6.

Change in best corrected visual acuity over time in eyes with drusenoid pigment epithelial detachments (DPED). **A.** Proportions of eyes in each visual acuity range at baseline and at 5 years. All eyes with DPEDs ($n = 311$) were included. **B.** Change in mean best corrected visual acuity (BCVA) as measured in letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart over the first 5 years after DPED baseline for all eyes with DPED ($n = 311$), eyes progressing to advanced age-related macular degeneration (AMD) by year 5 (either central geographic atrophy (CGA) or neovascular (NV) AMD) ($n = 148$), and eyes not progressing to advanced AMD ($n = 163$) over this time period. **C.** Percentage of eyes losing ≥ 15 letters of best corrected visual acuity (BCVA) from DPED baseline for all eyes, and also separately for eyes progressing to advanced AMD, and eyes not progressing to advanced AMD. **D.** Kaplan-Meier analysis of the percentage of all eyes losing ≥ 15 letters of BCVA up to 12 years after DPED baseline.

Table 1

Participant information on demographics, social history, medical history and history of use of medications obtained by questionnaire at baseline study visit in the Age-related Eye Study

	N (%)
Total	255 (100)
Sex	
Female	158 (62)
Race	
White	255 (100)
Education	
High school or Less	92 (36)
Some College	85 (33)
College Graduate	78 (31)
Body Mass Index (BMI)	
Underweight Normal	89 (35)
Overweight	99 (29)
Obese	67 (26)
History of Smoking	
Never	110 (43)
Former	128 (50)
Current	17 (7)
Diagnosis of Hypertension	85 (33)
Diagnosis of Angina	22 (9)
Diagnosis of Arthritis	117 (46)
Use of Antacids	23 (9)
Use of Thyroid hormone	
Not obtained	2 (1)
Yes	17 (7)
Use of hydrochlorothiazide	24 (9)
Use of cholesterol-lowering drug	7 (3)
Use of Aspirin	29 (11)

Table 2

Fundus characteristics of eyes with drusenoid pigment epithelial detachments analyzed at time of detection.

	Number of eyes (Column %)	Number of eyes without advanced amd at baseline (Column %)	Number of eyes progressed to advanced disease at 5 years (Column %)
Total number of eyes	311	282	119
Large drusen (greater than 125 µm in size)			
Present	303 (97)	279 (99)	118 (99)
Hypopigmentation			
Present	77 (25)	57 (20)	35 (29)
Hyperpigmentation			
Present	272 (87)	245 (87)	112 (94)
Estimated total drusen area within			
Less than area of circle 660 µm (<O ₂) in diameter	6 (2)	6 (2)	0
Greater than area of circle 660 µm in diameter, but less than area of circle half disk in diameter (O ₂ – 1/2 DA)	27 (9)	27 (10)	11 (9)
Greater than area of circle half disk in diameter, but less than area of circle one disk in diameter (1/2 DA-1DA)	56 (18)	56 (20)	29 (24)
Greater than area of circle one disk in diameter (>1DA)	193 (62)	193 (68)	79 (66)
End stage disease, unable to grade	29 (9)	0	0
Calcified drusen			
Present	13 (4)	10 (4)	3 (3)
Maculopathy severity			
Presence of drusen without geographic atrophy or neovascular changes (3A, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B)*	279 (90)		
Presence of non-central geographic atrophy less than 2 disk diameters of center of macula (8A, 8B)*	3 (1)		
Presence of geographic atrophy definitely or questionably involving the center point of the macula (i.e. central geographic atrophy)(9A, 9B)*	1 (0.3)		
Presence of lesions/fundus findings indicative of neovascular disease (non-drusenoid pigment epithelial detachment, serous/hemorrhagic sensory retinal detachment, subretinal hemorrhage or fibrosis, photocoagulation scars consistent with treatment of neovascular disease)(10, 11A, 11B)*	28 (9)		

* Categories established in Age-related Macular Degeneration Severity Scale as used in the Age-related Eye Study (AREDS); DA = disk areas.

Table 3

Prevalence of Advanced Age-related Macular Degeneration (Central Geographic Atrophy and/or Neovascular disease) in eyes with drusenoid pigment epithelial detachments at Baseline and at 5 years.

	Number of eyes At baseline (Column %)	Number of eyes At 5 years (Column %)
Total Eyes	311	311
Eyes with evidence of neovascular disease (NV) only	28 (9)	79 (25)
Eyes with evidence of central geographic atrophy (CGA) only	1 (0.3)	53 (17)
Eyes with evidence of both central geographic atrophy and neovascular disease	0	16 (5)
Total Eyes with Advanced AMD	29 (9)	148 (48)

AMD = age-related macular degeneration

Table 4

Visual acuity outcomes in eyes with drusenoid pigment epithelial detachments

	Number of eyes at DPED baseline	Mean visual acuity (letters)			% of eyes losing ≥ 15 letters of visual acuity at 5 years
		At DPED baseline	At 5 years after DPED baseline	Change over 5 years	
Eyes not progressing to advanced AMD by 5 years	161	80	72	8	21
Eyes progressing to advanced AMD by 5 years	119	78	52	26	62
Eyes progressing to CGA by 5 years	52	77	54	23	62
Eyes progressing to NV-AMD by 5 years	55	79	51	28	59
Eyes progressing to both CGA and NV-AMD by 5 years	12	77	49	27	75
All eyes by 5 years	280	79	63	16	39

DPED = drusenoid pigment epithelial detachment; AMD = age-related macular degeneration; CGA = central geographic atrophy; NV-AMD = neovascular age-related macular degeneration.