Extensive Macular Atrophy with Pseudodrusen-like appearance (EMAP): progression kinetics and late-stage findings

ABSTRACT

Purpose

To describe the clinical outcome and late-stage findings of Extensive Macular Atrophy with Pseudodrusen-like appearance (EMAP).

Study design

Retrospective cohort study.

Participants

Seventy-eight patients (156 eyes) affected by EMAP.

Methods

We collected data on best-corrected visual acuity (BCVA), kinetic perimetry, optical coherence tomography (OCT), short-wavelength autofluorescence (SW-AF) and near-infrared autofluorescence (NIR-AF). Genetic testing for the *TIMP3* and

C1QTNF5 genes was performed via Sanger sequencing for 58 subjects, with no pathogenic variants identified.

Main outcome measures

BCVA, visual field, and imaging findings at the last examination. Incidence rates and time-to-event curves for blindness with the United States Social Security Administration (US-SSA) and World Health Organization (WHO) criteria, foveal involvement, and atrophy enlargement beyond the 30° and 55° field of view.

Results

At the most recent visit, the mean age was 70.9 ± 5.2 years. 58.1% of the patients were blind with the US criteria, and 25.8% according to the WHO. All eyes had large central scotomas, in 22.7% of the cases associated with visual field constriction. We detected focal openings or large dehiscences of the Bruch's membrane in 25.4% of the eyes. NIR-AF shows increased visibility of the choroidal vessels beyond the atrophy in 87.2% of the eyes. The incidence rates for blindness were 3.95/100-subjects-year with the US criteria and 1.54/100-subjects-year according to the WHO. The incidence rates were 22.8/100-eye-year for foveal involvement, 12.0/100-eye-year for atrophy enlargement beyond the 30° and 6.6/100-eye-year for atrophy enlargement beyond 55°. The estimates were not influenced by the age of onset.

Conclusion

We identified characteristic imaging findings, including Bruch's membrane ruptures, in elder EMAP patients and calculated

incidence rates for different functional and anatomical outcomes.

INTRODUCTION

In 2009, Hamel et al. described Extensive Macular Atrophy with Pseudodrusen-like appearance (EMAP) as an aggressive form of adult-onset macular atrophy characterized by the funduscopic triad of macular atrophy with major vertical axis, mid-peripheral pseudodrusen-like lesions, and peripheral pavingstone degeneration.[1,2] On short-wavelength autofluorescence (SW-AF), macular atrophy features a typical faint ("grayish") hypoautofluorescence with multilobular borders and vertical orientation, whereas a diffuse separation between the Bruch's membrane (BM) and the retinal pigment epithelium (RPE) is an optical coherence tomography (OCT) hallmark of EMAP.[1,3,4,5] Because of these characteristics, EMAP is frequently undistinguishable from the "diffuse-trickling" pattern of geographic atrophy (DTGA) secondary to age-related macular degeneration (AMD) based on multimodal imaging alone.[1,2] Some phenotypic overlap also exists with dominantly inherited forms of macular atrophy, namely the *C1QTNF5*-related Late-Onset Retinal Degeneration (L-ORD) and the *TIMP3*-related Sorsby fundus dystrophy (SFD).

In EMAP, macular atrophy begins superior to the fovea and rapidly grows on the vertical axis. Foveal involvement occurs within 4 years, leading to severe visual loss, although no survival analysis has been performed to date.[1] Subsequently, the atrophy spreads beyond the vascular arcades, eventually merging with peripheral pavingstone-like degeneration, suggesting that the burden of EMAP goes beyond mere visual acuity loss and the

development of central scotoma.
Despite the existence of cases with a later onset, a common 55-year-old cut-off is widely used for diagnosing EMAP.[11] As a result, most published data pertain subjects in their 60s,[1,2,4,5] and the prognostic implication of developing EMAP at an advanced age is unknown. Furthermore, while refined functional testing of the macula, such as microperimetry, is invaluable for detecting early alterations in EMAP, there is an unmet need for data on patients with a longer disease course.

We therefore designed this study to report the clinical outcome and imaging findings of a large, single-center, elder cohort of EMAP patients.

METHODS

This was a retrospective cohort study. All patients were enrolled at the Reference Center for rare diseases, REFERET, Quinze-Vingts Hospital, Paris. All individuals undergoing genetic analysis signed a written informed consent. All studies were carried out in accordance with the declaration of Helsinki and were approved by a national ethics committee (CPP Ile de France V, Project number 06693, N◦EUDRACT 2006-A00347-44, 11 December 2006).

EMAP was diagnosed based solely on its phenotypic features, without applying an age cut-off for symptom onset. This approach mitigated recall bias and included cases with later onset. The diagnosis required the presence of macular atrophy with multilobular borders and faint (“grayish”) hypoautofluorescent aspect on SW-AF associated with pseudodrusen-like lesions in the mid-periphery.[1] The diagnosis

was further supported by the presence of diffuse Bruch-RPE separation on OCT, macular atrophy reflecting the known natural history (debut superior to the fovea and rapid enlargement on the vertical axis), and peripheral pavingstone-like degeneration. Disease onset was estimated as the age when patients first noticed visual symptoms or when they were first referred to our center.

Clinical and imaging data were gathered from patients' past medical records, including best corrected visual acuity (BCVA) measured with a standard Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, OCT, SW-AF, near-infrared autofluorescence (NIR-AF) and kinetic perimetry. Visual impairment was defined according to the World Health Organization (WHO) as moderate-to-severe visual impairment (MSVI) with a vision <20/63 but ≥20/400 in the best-seeing eye, and blindness with a vision <20/400 (ICD-11 code: 9D90). Additionally, we noted the United States Social Security Administration's (US-SSA) definition of legal blindness (visual acuity of 20/200 or less).

Specifically for kinetic perimetry, we reported the major scotoma diameter detected by the most recent test, rounded to the nearest multiple of 5, covering both the binocular (III4e stimuli) and monocular (V4e and V1e stimuli) Goldmann visual field (GVF). Visual field constriction, defined as concentric constriction of the V4e isopter relative to the normal values provided by the company software, was recorded as well. Cross-sectional analyses utilized data from patients' most recent visit, while longitudinal analyses included data from all available examinations.

Image acquisition and analysis

OCT, SW-AF (488 nm excitation) and NIR-AF (787 nm excitation) images were acquired with a Spectralis HRA + OCT device (Heidelberg Engineering, Heidelberg, Germany). When available, OCT images acquired with a raster pattern of at least nineteen 20° angle OCT B-scans were reviewed for the presence of the following findings: subfoveal RPE atrophy; subfoveal fibrosis, visible as subretinal hyperreflective material; lipid globules, defined as non-reflective spherical to polyhedral structures with a posterior hypertransmission tail;[7] focal interruptions and large breaks (> 250 µm) of the BM; intraretinal pseudocysts; and hyperreflective pyramidal structures (HPS) within the atrophic lesion. Cases with a history of neovascular complications were identified, and OCT scans were utilized to localize them. Lastly, a single grader (AA) manually measured foveal thickness and subfoveal choroidal thickness (SCT).

On SW-AF images, we recorded the presence of macular atrophy beyond the posterior pole and the mid-periphery, defined as atrophic lesions expanding outside the 30° and 55° field of view acquisitions centered on the fovea (Figure 1). If entirely included in the 55° SW-AF, a single grader (AA) manually measured the atrophic lesion. NIR-AF images were classified based on increased choroidal vessel visibility beyond the atrophic area identified on SW-AF.

Figure 1**Short-wavelength autofluorescence (SW-AF) and near-infrared autofluorescence (NIR-AF) across different stages in EMAP.** Left patient (CIC n/a) shows macular atrophy entirely enclosed in the 30° scan and foveal sparing. CIC6973 is a younger patient with comparable atrophy size but without foveal sparing. CIC7859 displays extensive posterior pole atrophy exceeding the 30° but not the 55° image frame. Lastly, SW-AF of CIC5482 shows atrophy extending beyond the 55° acquisition. On NIR-AF (bottom row), all patients display increased visibility of the underlying choroidal vessels outside the area of RPE atrophy, eventually making a

precise distinction of the lesion boundaries challenging (CIC7859 and CIC5482).

Genetic Analyses

Total genomic DNA was extracted from whole blood as previously described. Direct Sanger sequencing was performed on DNA samples extracted from peripheral blood leukocytes from 58 patients for all exons and flanking exonic regions of the *C1QTNF5* (RefSeq NM_001278431.2) and *TIMP3* (RefSeq NM_000362.5) genes. Detailed protocols will be delivered on request. A de-identification number (i.e. CICXXXXX, CIC standing for Clinical Investigation Center) was assigned to all patients who underwent a blood draw.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range, while categorical variables were expressed as frequency and percentages. When only foveal scans were available, we recorded OCT findings if detected; otherwise, their absence was treated as missing value. The Shapiro-Wilk test was used for normality testing of continuous variables. Kaplan-Meier curves were generated with the survminer package (version 0.4.9) in R Studio and time-to-event data for blindness (≤ 20/200 for the US system and <20/400 for the WHO) and atrophy outcomes (loss of foveal sparing and atrophy extension beyond the 30° and 55° image frames) were reported. To account for inter-eye correlations, the effect of the age of onset on the outcome variables was investigated by calculating the hazard ratio (HR) using the shared frailty model provided by the R Studio survival package (version 3.5.5). Left censored data, i.e. instances where

the event of interest had already occurred before the observation period, were excluded from all the analyses. All tests were performed with R studio (version 2023.03.0+386).

RESULTS

Study cohort

The study involved 78 patients (156 eyes). The mean age at the most recent visit was 70.9 ± 5.2 years, with 28 patients (35.9%) being men. Except for one patient that referred the earliest visual symptoms roughly 26 years before the last examination, the average disease duration was 5.7 ± 4.4 years, with a mean age at diagnosis of 65 ± 5.6 (range: 52 – 86) years. Twenty-two (28.2%) patients had no follow-up visits, while 56 patients underwent a mean of 5 ± 3 visits with an average follow-up of 4.4 ± 2.5 years (range: 0.5 – 12 .7). One-third (33.9%) of them had been followed up for more than 5 years.

Out of 78 patients, 16 had no available BCVA at last examination. The remaining 62 had an average BCVA of 30.4 ± 23.1 ETDRS letters (approximately 20/250 Snellen), with 33 (53.2%) having MSVI and 16 (25.8%) being blind, according to WHO definitions. With the US criteria, the proportion of legally blind EMAP patients increased to 58.1% (Table 1).

Table 1Patients' characteristics at last visit

Due to available blood samples, 58 out of 78 subjects were eligible for genetic screening, with none carrying pathogenic variants in the exonic regions of both *C1QTNF5* and *TIMP3*. All identified variants and are listed in Supplemental Table 2.

Goldmann visual field

Kinetic perimetry data could be retrieved for 54 eyes from 27 (34.6%) patients. In 16 instances, GVFs were conducted within 6 months of the most recent visit, whereas the remaining 11 perimetries were performed a median of 2.1 (IQR: 1.5 – 4.2) years before the most recent examination. Central scotomas were mapped with V4e and V1e stimuli in 32 out of 54 instances. The remaining 22 monocular visual fields could only be assessed for peripheral visual field restriction.

In binocular testing, most scotomas (85.2%) had a major diameter of 30° or less. One of the remaining 4 patients displayed a 110-degrees central visual field loss, while 2 had unmeasurable scotomas because they merged with peripheral field defects. In monocular testing, larger scotomas became more prevalent; 68.8% exceeded 20° with V4e stimuli, increasing to 96.9% with V1e stimuli. Notably, 12 eyes (22.2%) showed a constriction of the visual field. Moreover, scotoma diameters could not be measured in 5 eyes with V4e and 7 eyes with V1e stimuli due to their confluence with peripheral visual field defects. The prevalences of different scotoma sizes are reported in Supplemental Figure 2.

Imaging data at last visit

SW-AF was available for all eyes. However, in 49 eyes (31.4%) the area of macular atrophy could not be measured because it exceeded the 55° field of view, in 6 (3.8%) due to unclear lesion boundaries, and in 16 (10.3%) due to poor image quality. The remaining 85 eyes showed a mean atrophy area of 33.4 ± 18.7 mm^2. NIR-AF was performed in 132/156 eyes. With this

technique, 116 eyes (87.2%) displayed an increased visibility of the choroidal vessels beyond the atrophy borders (Figure 1). Of note, 4 out of the 16 instances lacking this characteristic had an unusually thick choroid ranging from 350 to 480 µm on OCT, compared to the cohort's median of 68 (IQR: 44 – 115) µm. Foveal thickness was also reduced to a median of 104 (IQR: 67 – 156) µm.

Moving to imaging findings, HPS were found within the atrophy area in 30% of the eyes. They could either manifest as triangular hyperreflective mounds with a hyporeflective core, occurring alone or in clusters (Figure 3A, 3C), or as longer irregular lesions with a less reflective interface (Figure 3B).

Figure 3**Optical coherence tomography (OCT) scans of hyperreflective pyramidal structures (HPS) and Bruch's membrane ruptures.** (A-C) HPS could be identified in clusters (A) or isolated (C) as triangular lesions with hyporeflective core and hyperreflective interface. Alternatively, they could take the form of longer, irregular lesions with heterogeneous internal reflectivity and a less hyperreflective interface (B). (D-F) White arrowheads mark the boundaries of Bruch's membrane interruptions.

Lipid globules had a similar prevalence (30.4%), while intraretinal pseudocysts and outer retinal tubulations were less frequent (7.8% and 3.9% of eyes, respectively). Subfoveal hyperreflective material attributable to fibrosis was detected in 41 eyes (31.5%) of 28 patients. Conversely, 19 eyes (14.7%) had a history of NV, 5 of which were bilateral. Of them, 9 (47.4%) were subfoveal, 7 (36.8%) extrafoveal and 3 (15.8%) peripapillary, including one that was extramacular, nasally to the optic disc.

Regardless of NV presence, ruptures of the BM were noted in 25.4% of the eyes on OCT, ranging from focal openings to large interruptions (Figure 3D-F). OCT generally revealed two distinct

edges, even for lesion diameters <250 µm. On fundus examination, smaller ruptures were not evident, whereas large dehiscences appeared pale, likely due to exposure of the underlying sclera. These large dehiscences within the macular atrophy could manifest as irregular cracks or as regular, linear ruptures crossing the macula vertically or horizontally.
BM ruptures were hyperreflective on infrared reflectance images and were more clearly visualized as hypoautofluorescent lesions using SW-AF than NIR-AF. One patient also underwent angiographic exams, which revealed diffuse hypofluorescence on both fluorescein and indocyanine green angiography (Figure 4). Supplemental Figure 5 shows the progression of the BM dehiscence in the same patient.

Figure 4**Multimodal imaging of a large BM rupture.** CIC09061 at the age of 70 (A-C), 68 (D-I) and 74 (J, K) years. (A) On IR, the BM rupture appears as a horizontally oriented irregular crack with highly hyperreflective signal. (B) On SW-AF, the lesion appears more hypoautofluorescent than the surrounding atrophy. (C) In NIR-AF, the lesion is nearly undetectable, arguably corresponding to a thin, slightly hyperautofluorescent line that crosses the poorly contrasted macular atrophy. (D-F) Fluorescein angiography: due to underlying choroidal atrophy, the BM rupture appears as deeply hypoautofluorescent throughout the exam, while the macular atrophy becomes increasingly hyperautofluorescent due to window effect. (G-I) Indocyanine green angiography: in the early phase, the BM rupture is obscured by the diffuse hypoautofluorescence within the atrophic region. It becomes apparent minutes later, as the residual choriocapillaris within the atrophy stains. (J) Color fundus photograph taken six years after the angiographies shows extensive multilobular atrophy extending into the retinal mid-periphery. At this time, the BM rupture has increased in length and width and has a pale aspect, overlaid by dark pigment migration. Please note how the break remains confined within the atrophy area. (K) The corresponding OCT crosses the BM rupture horizontally. Pigment migration is visible as hyperreflective lesions with a posterior hypotransmission tail. White arrowheads mark the boundaries of the rupture. IR = Infrared reflectance; SW-AF = Short-wavelength autofluorescence; NIR-AF = Near-infrared autofluorescence; BM = Bruch's membrane.

Larger ruptures were associated with a thinner choroid ($p < 0.01$) and tended to occur after a longer disease course, although this association was not statistically significant ($p = 0.057$) (Supplemental Figure 6). Figure 7 illustrates multimodal imaging

of an advanced EMAP case. All imaging findings are summarized in Table 3.

Figure 7**Multimodal imaging of advanced EMAP.** CIC13482 exhibits a diffuse retinal involvement with “confluent” pavingstone-like degeneration merging with the extensive macular atrophy. Optical coherence tomography reveals large hyperreflective pyramidal structures within the atrophic fovea, that are not clearly visible on color fundus photograph.

Table 3Imaging characteristics of study eyes

Incidence of blindness and foveal, posterior pole and mid-periphery-involving atrophy

Fifty-six patients (112 eyes) were eligible for the longitudinal analyses since they had undergone at least 2 examination visits.

At the initial visit, 11 patients (19.6%) were identified as legally blind following US criteria, with an incidence rate of 3.95/100-subjects-year (95% confidence interval [CI]: 2.4 – 5.5). In contrast, according to the WHO definition, 7 patients (12.5%) were already blind, with a lower incidence rate of 1.54/100-subjects-year (95% CI: 0.63 – 2.4) (Table 4). Survival curves for visual outcomes are reported in Figure 8A.

Table 4Time-to-event data for visual and atrophy outcomes

Figure 8**Time-to-event curves for blindness, loss of foveal sparing and atrophy expansion beyond 30° and 55° field of view autofluorescence images.** (A) Median survival time for legal blindness (US) is 4 years, while less than half of the population experiences blindness in a 10-year frame when applying the WHO definition. (B) Median survival time is approximately 3.4 years for loss of foveal sparing, (C) 4.7 years for atrophy expansion beyond the posterior pole, and (D) 7.4 years for atrophy exceeding the mid-periphery.

Out of the 112 eyes that were assessed at first referral, 58 (51.8%) had foveal involvement, 44 (58.4%) exhibited posterior pole atrophy, and 15 (13.4%) presented with atrophic lesions

extending beyond the mid-periphery. Given that Kaplan-Meier curves for the left and right eyes were superposable (Figures 8B, 8C, 8D) time-to-event data were reported for the left eyes (Table 4). Incidence rates were calculated as 22.8/100-eye-year (95% CI:12.8 – 33.0) for foveal involvement, 12.0/100-eye-year (95% CI: 5.9 – 18.0) for posterior pole atrophy, and 6.6/100-eye-year (95% CI: 3.2 – 10.0) for atrophy involving the mid-periphery. Of note, no differences in the age of onset influenced any of the three outcomes (all $p > 0.05$; Table 5).

Table 5Influence of the age of onset on foveal involvement and atrophy extension over time

DISCUSSION

Despite the recent identification of new cohorts worldwide, EMAP remains an underrecognized condition, especially among the elderly, who are more likely to be misdiagnosed with AMD. This is particularly true for patients that seek the advice of a retina specialist in their 60s or later, after the established 55-year-old cut-off, and for those who cannot recall the earliest onset of their symptoms.

For this reason, it is crucial to shift our focus on the phenotypic characteristics of EMAP to ensure accurate and timely diagnoses. The identification of several, relatively young cohorts in Northern Italy allowed for a better characterization of the earliest stages of EMAP, even before atrophy development.[11] By contrast, little was known on the clinical outcome of aged EMAP patients, and on their imaging findings as well. As the largest single-center study on EMAP to date, this study encompassed a relatively elder cohort of patients, which allowed us to gain

insights on the advanced stage of the disease.
At the most recent examination, over half of EMAP patients were legally blind according to the US standards, whereas only a quarter met the WHO's <20/400 blindness criteria. Indeed, based on our survival analyses, BCVA in EMAP frequently remains above the WHO blindness threshold or takes several years to reach it (Figure 8). Conversely, a vision of 20/200 or worse is typically attained after about 4 years, aligning with the median time before foveal atrophy occurs (3.4 years). Subsequently, the atrophy extends beyond the central 30° within 4.7 years, and beyond the mid-periphery after 7 years or later. In EMAP, the atrophy initially grows vertically rather than enlarging in a strictly centrifugal pattern, before radiating towards the periphery. Thus, the visual acuity plateau experienced by our patients might be linked to the development of an eccentric preferred retinal locus in adjacent preserved areas, like in AMD or Stargardt disease. This hypothesis needs confirmation through future microperimetry studies.
Our estimates should be interpreted with caution since some patients may have a predominantly peripheral or confluent disorder, while others may never experience such a degree of retinal degeneration. This heterogeneity is reflected in the broad range of visual field defects detected with kinetic perimetry. In our cohort, binocular testing revealed central scotomas in all subjects, with the majority having a maximum diameter of 30° or less. However, when testing each eye separately, we found considerably larger scotomas, which were occasionally unmeasurable due to their confluence with peripheral defects. Indeed, 22% of all eyes displayed a constricted visual field. Given the older age of out cohort, we expected to observe wider scotoma diameters than those reported by Hamel et al. in 2009,

who found defects ranging from 10° o 20° in diameter using I4 stimuli. Nonetheless, for the first time, we documented an involvement of the peripheral visual field in a considerable proportion of EMAP cases. This aligns with the known the varying degree of peripheral pavingstone-like degeneration among these patients, though we could not assess the retinal periphery specifically.

Another aim of our study was to investigate the influence of age of onset on the disease's course. Our analyses revealed that the age at which a patient first experiences symptoms or receives a diagnosis does not significantly influence the risk of atrophy involving the fovea or expanding beyond the central 30° and 55°. In essence, a later onset does not necessarily correlate with milder progression, in contrast with the patterns observed in most IRDs.

Despite this, EMAP shares several similarities with certain pseudodrusen-associated monogenic disorders, such as SFD and L-ORD, that also manifest multilobular macular atrophy and diffuse BM-RPE separation.[1] Still, like in previous studies, none of the 58 patients whose blood samples could be screened carried pathogenic variants in the *TIMP3* and *C1QTNF5* genes. Moving to the imaging findings, we found that approximately one-third of the eyes displayed HPS on OCT. These have been found also in L-ORD and SFD by Khan et al., although without histological correlation. Conversely, HPS have been demonstrated to correspond to calcified drusen in AMD.[1] They result from the formation of calcific nodules within the core of drusen, concurrent with RPE loss, which leaves a thick cap of basal laminar deposits (BLamD). In EMAP, however, drusen are exceptional; instead, RPE loss is preceded by a diffuse BM-RPE

separation, which has been attributed to BLamD, and followed by leftover subretinal hyperreflective material.[7] Even though histological studies have yet to be conducted in EMAP, it is possible that HPS in this context represent the calcified form of this material, explaining both their formation in the absence of drusen and their variable aspect on OCT (Figure 3).
Another interesting finding was the occurrence of degenerative BM changes in a quarter of the eyes, ranging from focal openings to large ruptures. These had been previously reported both in association with MNV and independently,[7] though our study is the first to systematically record their presence and multimodal imaging characteristics. BM ruptures are the hallmark lesion of pseudoxanthoma elasticum (PXE), in this context called "angioid streaks", where they result from the progressive calcification of the BM. Although they look similar in infrared reflectance and SW-AF, fundus examination reveals angioid streaks as jagged reddish lines radiating from the optic disc. In contrast, EMAP's BM ruptures are notably different, often presenting a regular linear shape without specific orientation and frequently associated with profound choroidal atrophy, as confirmed by OCT and angiographic exams.
Lastly, using NIR-AF imaging, that employs longer wavelengths than SW-AF to enhance focus on RPE and melanin, we found an increased visibility of the choroidal texture beyond the atrophic area in over 80% of the cases. This phenomenon could reflect a diffuse RPE sufferance because of the toxic effect of the sub-RPE deposits or the longstanding separation from the BM. Alternatively, choroidal thinning could have influenced the visibility of the underlying sclera, like in reflectance imaging.

Our study has some limitations. Most importantly it is a

retrospective study, which is responsible for an inhomogeneous data acquisition and incomplete genetic screening. Moreover, age of onset was approximated as either symptom onset, which is prone to recall bias, or the date of the diagnosis, which is a better proxy for the onset of visual symptoms related to macular atrophy.

In summary, we calculated incidence rates for blindness and different atrophy checkpoints. These were unaffected by age of onset, emphasizing the need of proper phenotyping for correctly diagnosing EMAP even in patients outside the conventional age range. These patients experience severe visual impairment beyond visual acuity decline, with large central scotomas and, eventually, peripheral visual field constriction. Furthermore, our imaging findings suggest a primary role of the RPE-BM complex in the pathogenesis of the disease. In conclusion, our findings expand the knowledge on one of the most aggressive retinal diseases, and provide insights regarding its progression kinetics and visual outcomes.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT4 in order to improve readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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PRÉCIS

The late stage of Extensive Macular Atrophy with Pseudodrusen-like appearance (EMAP) is characterized by a severe impairment of the visual function and distinct imaging findings that include degenerative changes of the Bruch's membrane.

Identification

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Figures

Figure 1**Short-wavelength autofluorescence (SW-AF) and near-infrared autofluorescence (NIR-AF) across different stages in EMAP.** Left patient (CIC n/a) shows macular atrophy entirely enclosed in the 30° scan and foveal sparing. CIC6973 is a younger patient with comparable atrophy size but without foveal sparing. CIC7859 displays extensive posterior pole atrophy exceeding the 30° but not the 55° image frame. Lastly, SW-AF of CIC5482 shows atrophy extending beyond the 55°

acquisition. On NIR-AF (bottom row), all patients display increased visibility of the underlying choroidal vessels outside the area of RPE atrophy, eventually making a precise distinction of the lesion boundaries challenging (CIC7859 and CIC5482).

Figure 3**Optical coherence tomography (OCT) scans of hyperreflective pyramidal structures (HPS) and Bruch's membrane ruptures.** (A-C) HPS could be identified in clusters (A) or isolated (C) as triangular lesions with hyporeflective core and hyperreflective interface. Alternatively, they could take the form of longer, irregular lesions with heterogeneous internal reflectivity and a less hyperreflective interface (B). (D-F) White arrowheads mark the boundaries of Bruch's membrane interruptions.

Figure 4**Multimodal imaging of a large BM rupture.** CIC09061 at the age of 70 (A-C), 68 (D-I) and 74 (J, K) years. (A) On IR, the BM rupture appears as a horizontally oriented irregular crack with highly hyperreflective signal. (B) On SW-AF, the lesion appears more hypoautofluorescent than the surrounding atrophy. (C) In NIR-AF, the lesion is nearly undetectable, arguably corresponding to a thin, slightly hyperautofluorescent line that crosses the poorly contrasted macular atrophy. (D-F) Fluorescein angiography: due to underlying choroidal atrophy, the BM rupture appears as deeply hypoautofluorescent throughout the exam, while the macular atrophy becomes increasingly hyperautofluorescent due to window effect. (G-I) Indocyanine green angiography: in the early phase, the BM rupture is obscured by the diffuse hypoautofluorescence within the atrophic region. It becomes apparent minutes later, as the residual choriocapillaris within the atrophy stains. (J) Color fundus photograph taken six years after the angiographies

shows extensive multilobular atrophy extending into the retinal mid-periphery. At this time, the BM rupture has increased in length and width and has a pale aspect, overlaid by dark pigment migration. Please note how the break remains confined within the atrophy area. (K) The corresponding OCT crosses the BM rupture horizontally. Pigment migration is visible as hyperreflective lesions with a posterior hypotransmission tail. White arrowheads mark the boundaries of the rupture. IR = Infrared reflectance; SW-AF = Short-wavelength autofluorescence; NIR-AF = Near-infrared autofluorescence; BM = Bruch's membrane.

Figure 7**Multimodal imaging of advanced EMAP.** CIC13482 exhibits a diffuse retinal involvement with "confluent" pavingstone-like degeneration merging with the extensive macular atrophy. Optical coherence tomography reveals large hyperreflective pyramidal structures within the atrophic fovea, that are not clearly visible on color fundus photograph.

Figure 8**Time-to-event curves for blindness, loss of foveal sparing and atrophy expansion beyond 30° and 55° field of view autofluorescence images.** (A) Median survival time for legal blindness (US) is 4 years, while less than half of the population experiences blindness in a 10-year frame when applying the WHO definition. (B) Median survival time is approximately 3.4 years for loss of foveal sparing, (C) 4.7 years for atrophy expansion beyond the posterior pole, and (D) 7.4 years for atrophy exceeding the mid-periphery.

Tables

Table 1Patients' characteristics at last visit