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Incidence, Characteristics, and Outcomes of Macular Neovascularization in Extensive Macular Atrophy with Pseudodrusen-like Appearance.

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Summary Statement: We estimated a cumulative incidence of MNV in EMAP of 15.2% at 4 years (4.2% excluding left-censored data), most being type 2 lesions and located subfoveally. While BCVA changes were comparable, MNV eyes showed faster RPE atrophy progression, suggesting a more aggressive phenotype or increased fibro-atrophic changes.

ABSTRACT

Purpose: To report the incidence, features, and clinical outcomes of macular neovascularization (MNV) in a large Italian cohort of patients with extensive macular atrophy with pseudodrusen-like appearance (EMAP).

Methods: Retrospective, longitudinal study including 79 EMAP patients (158 eyes) with ≥6 months of follow-up at three retina clinics. Medical records and imaging were reviewed for demographic and clinical data, including age, best-corrected visual acuity (BCVA), MNV features, and retinal pigment epithelium (RPE) atrophy size, measured by short-wavelength autofluorescence and refined with near-infrared and OCT imaging. Main outcomes included cumulative MNV incidence, MNV risk factors, and BCVA and RPE atrophy changes in eyes with and without MNV.

Results: Over a mean follow-up of 40.4 months, MNV developed in 14 eyes (10 patients), with a 4-year cumulative incidence of 15.2%. Most MNVs were type 2 (86%) and subfoveal (64%). Cox regression identified younger age, fellow eye involvement, smaller RPE atrophy size, and greater central subfield thickness (all $p<0.01$) as significant risk factors for MNV. While eyes with MNV had lower baseline BCVA (58.4 vs. 71.4 letters, approximately 20/63 vs. 20/40 Snellen; $p=0.005$), BCVA decline over time was similar between the two groups (-3.9 vs. -4.1 letters/year, $p=0.69$). However, RPE atrophy progressed faster in MNV eyes (3.4 vs. 2.8 mm²/year, $p=0.02$).

Conclusions: In this EMAP cohort, MNV had a cumulative incidence of 15.2% at 4 years. Although BCVA outcomes were comparable, MNV was associated with faster atrophy progression, potentially due to a more aggressive disease phenotype or fibro-atrophic changes.

INTRODUCTION

Extensive macular atrophy with pseudodrusen-like appearance (EMAP) is a severe bilateral retinal degenerative disorder first described in France by Hamel *et al.*[1] EMAP predominantly affects middle-aged women, though onset can vary, and typically leads to legal blindness within five years.[1,2] While its precise etiology remains unclear, the EMAP Case-Control National Clinical Trial identified links with chronic low-dose organophosphates exposure and nonspecific complement system activation.[3,4]

EMAP diagnosis is primarily clinical, based on a triad of vertically-oriented macular atrophy, diffuse pseudodrusen-like deposits, and peripheral paving stones.[1,5,6] Advances in retinal imaging have identified additional key features, including the separation between the retinal pigment epithelium (RPE) and Bruch's membrane (BrM) preceding atrophy, BrM ruptures, and an oval area of relative photoreceptor-RPE sparing, located temporal to the macula.[5,7–10]

Romano *et al*. developed the first EMAP classification based on longitudinal observations over three years.[5,11] Stage 1 is characterized by RPE-BrM separation with few or no confluent areas of atrophy and preserved visual acuity. Stage 2 involves more extensive confluent areas of atrophy without foveal involvement, while stage 3 presents with significant visual loss due to foveal involvement – either from expansion of macular atrophy or development of subfoveal non-neovascular fibrosis.

Recently, macular neovascularization (MNV) has been reported as a complication of EMAP, contributing to additional visual loss.[5,10,12] Information on this rare complication is limited to few reports.[13–15] Romano *et al* included MNV as a '+' feature in their classification, indicating its possible occurrence at any stage. However, longitudinal data on MNV characteristics and their

outcomes remain scarce. This study aims to report the incidence, clinical characteristics, and long-term outcomes of MNV in a large cohort of EMAP patients from three Italian referral clinics.

METHODS

This retrospective, longitudinal study included data from three Italian referral centers for retinal disorders: Ospedale Luigi Sacco (Milan), Ospedale San Raffaele (Milan), and Ospedale Borgo Roma (Verona). The research adhered to the Declaration of Helsinki. Institutional review board (IRB) approval was obtained from each center, and all participants provided written informed consent.

We reviewed electronic medical records and imaging studies of EMAP patients followed at these clinics between January 2009 and February 2024. Inclusion criteria were: (1) diagnosis of EMAP based on the classic clinical triad,[1] (2) age <55 years at diagnosis or symptoms onset, (3) at least two clinical examinations with retinal imaging over a follow-up of ≥6 months, and (4) negative genetic test for inherited phenocopies of EMAP using next-generation sequencing (Illumina MiSeq; Illumina, San Diego, CA), including screening for late-onset retinal degeneration (L-ORD; C1QTNF5, OMIM #605670), Sorsby fundus dystrophy (SFD; TIMP3, OMIM #136900), and pseudoxanthoma elasticum (PXE; ABCC6, OMIM #264800).[2,16] Exclusion criteria included: (1) other ocular or systemic conditions affecting the analysis, (2) refractive errors exceeding |6| diopters, (3) media opacities impairing image quality, and (4) history of intraocular inflammation or ocular surgery other than cataract extraction and intravitreal anti-VEGF injections.

Retinal imaging required for eligibility included fundus photographs (Sacco: EIDON, CenterVue from 2016; previously FF 450plus, Carl Zeiss; San Raffaele & Borgo Roma: Optos California, Optos plc. from 2015; previously TRC-50DX, Topcon), 30°x30° short-wavelength autofluorescence (SW-AF) and macular spectral-domain optical coherence tomography (SD-OCT; at least 20°x20°, centered on the fovea) using the Spectralis HRA+OCT system (Heidelberg Engineering GmbH, Heidelberg, Germany). Given the retrospective design, follow-up and

treatment strategies were not standardized across centers. However, common protocols were: (a) follow-up every 6-12 months for patients without MNV, (b) anti-VEGF treatment for active MNV, and (c) monthly monitoring for active MNV cases, with extended intervals (up to 4 months) once inactivity was achieved.

Study Protocol and Data Collection

Baseline and follow-up data collected included demographic and clinical information: age, sex, smoking status, lens status, best-corrected visual acuity (BCVA, converted to early treatment for diabetic retinopathy study [ETDRS] letters), presence of MNV, anti-VEGF agent used (bevacizumab, ranibizumab, aflibercept), and lesion activity (percentage of visits with active MNV). The frequency of anti-VEGF injections and lesion activity were reported annually, as previously described.[17]

MNV diagnosis required identification of a neovascular network on indocyanine green angiography (ICGA) or, if contraindicated, OCT angiography, along with leakage on fluorescein angiography (FA).[18] Treatment was initiated with either a single intravitreal anti-VEGF injection or a loading dose of three monthly injections, as determined by the treating physician, followed by a *pro re nata* (PRN) regimen. Re-treatment criteria included: (1) persistent or recurrent intra-/sub-retinal exudation, (2) significant growth or undefined neovascular membrane margins on SD-OCT, (3) hemorrhages on fundus photography, or (4) leakage on FA.[19]

Imaging Analysis

Imaging studies from all available visits were independently graded by two masked retina specialists (F.R. and M.B.P.) using Heidelberg Eye Explorer software (HEYEX; version 1.10.4.0, Heidelberg Engineering GmbH, Germany). Any qualitative discrepancies and quantitative measurements differing by >10% were resolved by a third senior grader (G.S.).

30°x30° SW-AF images were analyzed to measure the size of RPE atrophy and assess the autofluorescence signal at the atrophic borders (iso- or hyper-autofluorescent).[2,20] Specifically, RPE atrophy areas, which appeared hypo-autofluorescent, were measured with the semi-automated Heidelberg RegionFinder tool (version 2.6.4) and manually adjusted using co-registered near-infrared (bright hyperreflectivity) and SD-OCT (outer retinal and RPE loss) scans to exclude other hypo-autofluorescent lesions (e.g., macular pigments, hemorrhages, and RPE tears).[21,22,2]

The following SD-OCT biomarkers were assessed: (1) presence of any vitreomacular interface disorder (VMID),[23] (2) central subfield thickness (CST),[24] defined as the distance from the internal limiting membrane to BrM within the central 1 mm circle, (3) outer retinal tubulations (ORTs),[25] and (4) subfoveal choroidal thickness (SCT), measured from the outer RPE line to the sclero-choroidal interface.[26] Non-neovascular fibrosis (stage 3b) was identified on fundus photographs as a well-demarcated mound of yellowish-white tissue, without exudative signs on SD-OCT or a neovascular network on OCT angiography.[5,27]

For eyes with MNV, baseline images were reviewed to determine the type and location of neovascularization, based on the CONAN (type 1, 2, 3, or polypoidal choroidal vasculopathy) and CATT study group criteria.[18,28] Specifically, MNV location was categorized as subfoveal (involving the foveal center), juxtafoveal (1-200 µm from the foveal center), or extrafoveal (>200 µm) using ICGA images, obtained 1-to-10 minutes post-injection, and overlaid on near-infrared and SD-OCT scans.[17]

Statistical analysis

All analyses were conducted using Stata/MP 18 (StataCorp; College Station, TX, USA) and R Studio Version 2023.12.0+369 (RStudio, PBC; Boston, MA). Significance was considered at $\alpha<0.05$ for two-sided tests. Descriptive statistics included mean (standard deviation, SD), median (interquartile range, IQR), or frequencies (%), with variable distributions assessed via Shapiro-Wilk

test. Inter-grader agreement was evaluated using Cohen's kappa for categorical measurements and two-way mixed-effects intraclass correlation coefficients (ICCs) for continuous data.

MNV incidence was calculated per 100 person-years, and cumulative incidence was presented using Kaplan-Meier estimates (expressed as %), both for the whole cohort and after excluding left-censored data (MNV at baseline). Mixed-effects Cox regression determined the risk factors for MNV development, reported as hazard ratios (HR). Time-varying variables included age, smoking status, fellow eye involvement, atrophy borders, RPE atrophy size, VMID, CST, SCT, and ORT. Only variables significant in univariable analysis were considered in multivariable models. Linear mixed-effects models assessed the effects of MNV, time, and their interaction term on BCVA and RPE atrophy size, adjusted for baseline values and age. Random intercepts accounted for data hierarchy (eyes nested within patients). Scaling was applied to age (per 0.1), CST (per 0.01), and square-rooted RPE atrophy size to enhance model stability and account for baseline lesion size. Results are reported as mean estimates with 95% confidence intervals (95% CI).

RESULTS

Our study included 158 eyes from 79 EMAP patients, predominantly female (52, 65.8%), with a median age of 57.3 years [IQR: 53.8-60.4] at baseline. Of the 176 eyes initially considered (88 patients), 18 eyes from 9 patients were excluded due to insufficient follow-up (8 eyes), glaucoma (4 eyes), high refractive errors (4 eyes), and prior subthreshold laser treatment (2 eyes).

The mean baseline BCVA was 70.7 [SD: 21.0] ETDRS letters (approximately 20/40 Snellen), with a median RPE atrophy size of 8.2 mm^2 [IQR: 2.2-18.0]. Table 1 summarizes the demographic and clinical characteristics. Inter-grader agreement was substantial-to-good for all variables (Supplemental Digital Content 1).

Characteristics of the MNV

MNV was identified in 14 eyes (8.9%) of 10 patients, with bilateral involvement in 4 patients (40%). MNV was present at baseline in 8 eyes (57.1%). MNV onset was associated with visual symptoms in 11 cases (78.6%). Most lesions were type 2 (12 eyes, 85.7%) and primarily subfoveal (9 eyes, 64.3%) (Figure 1). MNVs were active in 41.7% [SD: 23.9] of visits during the first year and responded well to anti-VEGF treatment, with a median of 2 [IQR: 1–3.8] injections needed in the first year and reactivations in 4 eyes (28.6%). Notably, 3 eyes (21.4%) experienced a significant BCVA decline attributable to fibrovascular scarring from MNV, while most cases had stable or improved vision following treatment. One eye (7.1%) developed an RPE tear following anti-VEGF treatment. Median RPE atrophy size at MNV onset was 9.1 mm^2 [IQR: 6.2-22.1], with a bimodal distribution (peaks at 3.1-6.0 mm^2 and 21.1-24.0 mm^2; Figure 2). Specifically, MNV cases were classified as stage 1 (5 eyes, 35.7%), stage 2 (6 eyes, 42.9%), and stage 3 (3 eyes, 21.4%) (Table 2).

Incidence and Factors Associated with MNV

Over a mean follow-up of 40.4 months, MNV developed in 14 eyes, yielding a cumulative incidence of 6.1% [4.1-8.0] at 1 year and 15.2% [11.6-18.7] at 4 years. Excluding left-censored data, the cumulative incidence was 0.9% [0.0-2.7] at 1 year and 4.2% [0.0-8.9] at 4 years. The median incidence rate was 2.3 [1.0-3.6] events per 100 person-years (1.2 [0.2-2.2] after excluding left-censored data). The Kaplan-Meier curve of MNV incidence is shown in Figure 3A.

Univariable Cox regression revealed that younger age (per 0.1; HR=0.001, p<0.001), fellow eye involvement (HR=2.1, p<0.001), smaller RPE atrophy size (HR=0.51, p<0.001), greater CST (HR=2.1, p=0.002), and greater SCT (per 0.01; HR=19.1, p<0.001) were associated with a higher MNV risk. Multivariable Cox regression confirmed associations with younger age (HR=0.03, p<0.001), fellow eye involvement (HR=18.4, p=0.01), smaller RPE atrophy size (HR=0.63, p=0.001), and greater CST (per 0.01; HR=2.2, p=0.002) (Figure 3B and Table 3).

Impact of MNV on BCVA and RPE Atrophy

Eyes with MNV had lower baseline BCVA compared to those without MNV (58.4 vs. 71.4 ETDRS letters, approximately 20/63 vs. 20/40 Snellen; β= -12.9, p=0.005). However, after adjusting for age and baseline BCVA, the rate of BCVA decline was similar between groups (-3.9 vs. -4.1 ETDRS letters/year; β=0.24, p=0.69).

At baseline, eyes with MNV had a moderately smaller, though not significant, RPE atrophy size (5.6 vs. 11.9 mm^2; β= -0.25, p=0.27). After adjusting for age and baseline RPE atrophy size, eyes with MNV showed a faster rate of RPE atrophy growth compared to those without MNV (3.4 vs. 2.8 mm^2/year; β=0.05, p=0.02). Changes in BCVA and RPE atrophy size over time are shown in Figure 4. Figure 5 illustrates RPE atrophy measurements over time in an eye with MNV.

No significant associations were found between MNV lesion activity and the rates of RPE atrophy growth (β=0.002, p=0.88) or BCVA loss (β=0.14, p=0.12).

DISCUSSION

This study retrospectively analyzed the incidence, clinical features, and risk factors for MNV in a large Italian cohort of 79 EMAP patients. Most MNV cases were type 2, predominantly subfoveal, and demonstrated a favorable anatomical response to anti-VEGF treatment. We also evaluated the impact of MNV on visual outcomes and RPE atrophy progression. While MNV had limited impact on BCVA after treatment, it was associated with a significantly faster rate of RPE atrophy growth in affected eyes.

EMAP is an increasingly recognized retinal degeneration leading to legal blindness within five years from onset.[1,2,10,12] Visual loss is generally due to foveal RPE atrophy or subfoveal non-neovascular fibrosis,[5] though MNV can occasionally worsen visual outcomes. Prior studies on MNV in EMAP are limited and mostly consist of isolated case reports.[12–15] Kamamy-Levy *et al*[15] reported choroidal neovascularization in approximately 10% of their cohort (4 eyes from 3 patients), with good anatomical but limited functional response to anti-VEGF or laser treatment. More recently, Antropoli *et al.*[12] identified choroidal neovascularization in 19 cases (14.7%) in a

large French cohort, though extra-macular cases were included and clinical outcomes were not assessed.

In our study, MNV developed in 14 eyes over a mean follow-up of ~40 months, with a cumulative incidence of 6.1% at 1 year and 15.2% at 4 years for this complication (0.9% and 4.2% after excluding baseline MNV). These rates align with those reported by Kamamy-Levy and Antropoli,[12,15] and with the prevalence of exudative MNV in geographic atrophy (GA) from AMD.[29,30] Although MNV incidence in L-ORD –a phenocopy of EMAP– remains uncertain,[31] the rates in our cohort are notably lower than in other phenocopies like PXE (42-86%) and SFD (60-80%).[32,33] The high incidence in PXE may reflect BrM degradation and disrupted RPE-choriocapillaris communication, leading to VEGF upregulation,[34,35] while differences with SFD suggest distinct angiogenic mechanisms in EMAP despite imaging similarities.

Most MNV cases in our study were type 2 (85.7%) and subfoveal (64.7%) lesions, consistent with patterns seen in GA and inherited EMAP phenocopies.[15,29] This may reflect the significant EMAP-associated RPE alterations, which compromise the barrier function and promote subretinal invasion. Interestingly, unlike AMD,[36] we found no type 3 MNV cases, despite the presence of pseudodrusen-like deposits. Table 4 summarizes the clinical and MNV characteristics of EMAP and its phenocopies. Although treatment protocols varied, all MNV cases responded well to anti-VEGF injections on a PRN basis. The median number of injections in the first year was two, with fewer reactivations over time – suggesting PRN may be an effective approach for MNV in EMAP.

Furthermore, Cox regression analysis identified several factors associated with MNV development in EMAP. The increased risk with fellow eye involvement may indicate strong inter-eye dependence, similar to AMD.[37] However, the associations with younger age, smaller RPE atrophy size, and greater CST suggest that neovascular complications are more likely in the earlier stages of EMAP. This may represent a para-physiological response to support hypoxic photoreceptors and locally inhibit RPE atrophy progression, as proposed in AMD.[38] We also observed a bimodal distribution of MNV occurrence by RPE atrophy size, with peaks around 3.1-

6.0 mm² (stage 1) and 21.1–24.0 mm² (transition to stage 3). The first peak may reflect increased VEGF production from viable RPE in response to the diffuse RPE-BrM separation acting as a barrier to photoreceptor nutrition.[7,9] The second peak could indicate a late attempt to protect the fovea or result from BrM ruptures, which have been reported in 25% of late-stage EMAP cases.[12] Based on these findings, and the asymptomatic nature of MNV in some cases, we recommend closer monitoring during stages 1 and 2, particularly for patients with fellow eye involvement.

Lastly, the recent FDA approval of anti-complement treatments for GA has sparked interest in their potential application to other forms of macular atrophy.[39] This is especially relevant given EMAP's resemblance to the diffuse-trickling phenotype of GA and the altered complement levels detected in the initial French cohort.[4,6] However, since anti-complement therapy in AMD has been associated with higher MNV rates,[40,41] understanding the clinical impact of MNV in EMAP—beyond its incidence—becomes essential. While MNV was associated with worse BCVA at presentation (59 vs. 71 ETDRS letters, approximately 20/63 vs. 20/40 Snellen), we found no significant difference in BCVA decline over time between EMAP eyes with and without MNV. In contrast, RPE atrophy progression was faster in MNV eyes (3.4 mm² vs. 2.8 mm²/year), even after adjusting for baseline size, diverging from previous clinical and histological findings in AMD.[21,30,42] Potential explanations for accelerated atrophy in MNV eyes include: (1) MNV-related fibro-atrophic changes, particularly due to the high prevalence of type 2 lesions; (2) possible side effects of physiological VEGF levels suppression, though patients received few injections and lesion activity was not correlated with atrophy growth; and (3) a more aggressive EMAP phenotype characterized by MNV and rapid atrophy progression. Studying untreated EMAP cohorts may help clarify this aspect. Yet, we cannot rule out that current models using square-root transformation and adjustment for baseline size may not fully capture the exponential growth of macular atrophy in EMAP, suggesting a need for alternative regression models for atrophy assessment.

It is important to acknowledge some limitations, particularly the retrospective design, which prevented standardized follow-up and treatment protocols across centers. While the number of

MNV cases was relatively small (14), MNV is a rare complication of EMAP, and our cohort remains one of the largest with longitudinal follow-up in the literature. Additionally, functional tests such as microperimetry may correlate more closely with EMAP stages than BCVA alone.[11] Future studies incorporating functional assessments beyond BCVA may offer a more nuanced understanding of MNV's impact on visual function. We also did not assess extra-macular neovascularization due to the lack of standardized widefield imaging, and non-exudative type 1 MNV may have been missed in the absence of routine longitudinal OCTA assessments. Moreover, while BrM ruptures have recently emerged as a relevant biomarker in advanced EMAP, its low prevalence in our relatively younger cohort precluded its inclusion in the statistical analysis. We look forward to exploring the relationship between BrM ruptures and MNV in future prospective studies. Lastly, measuring RPE atrophy using SW-AF can be challenging in eyes with MNV.[22,43] To minimize this, we employed a validated method incorporating near-infrared imaging and structural OCT,[22] which resulted in excellent intergrader agreement.

To conclude, we reported a 4-year cumulative incidence of 15.2% for MNV in a large Italian cohort of EMAP patients, identifying younger age and smaller RPE atrophy size as significant risk factors. The high prevalence of type 2 lesions and the bimodal distribution of RPE atrophy size at MNV onset suggest two possible pathways in MNV pathogenesis: (1) early-stage involvement of a dysfunctional yet viable RPE layer, and (2) BrM ruptures promoting neovascularization in more advanced stages. Clinically, while anti-VEGF treatment led to prompt BCVA improvement, RPE atrophy expanded more rapidly in MNV eyes, potentially due to fibrosis-related atrophic changes or a more aggressive disease phenotype. These findings provide critical insights into EMAP's natural history and may guide future targeted therapies aimed at slowing macular atrophy growth.

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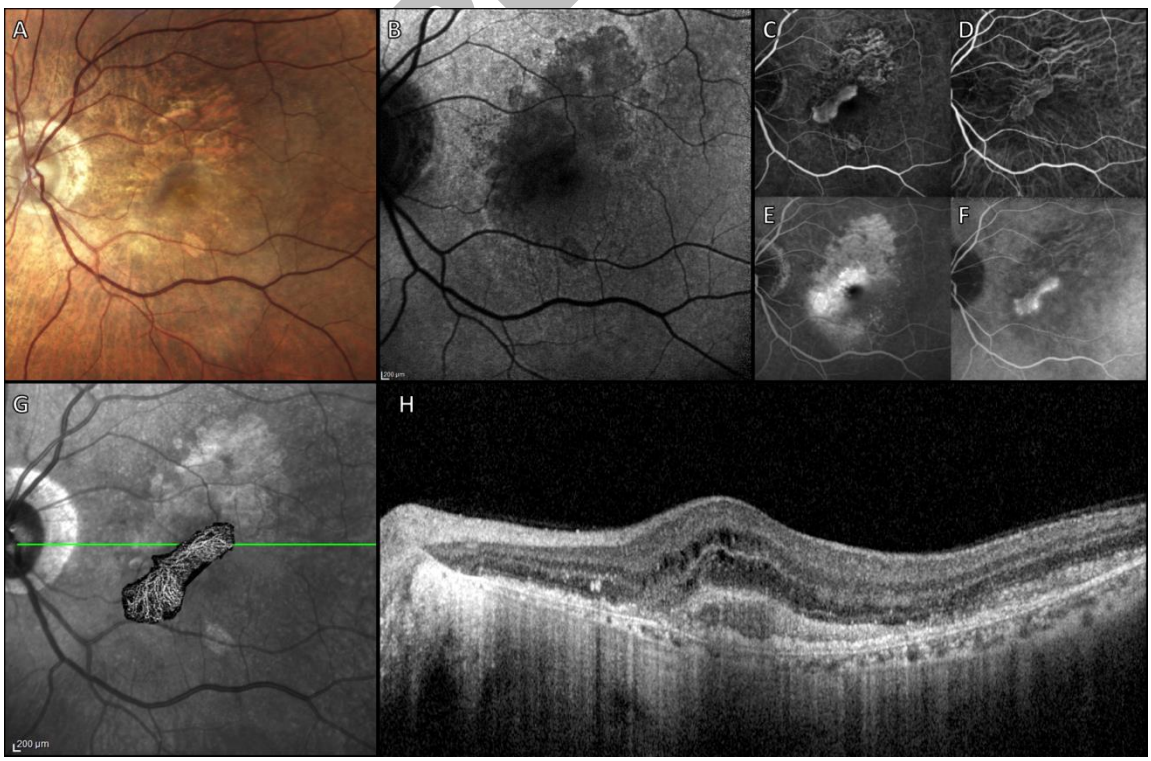
FIGURES LEGEND.

Figure 1. Multimodal imaging of type 2 macular neovascularization (MNV) in a patient with extensive macular atrophy with pseudodrusen-like appearance (EMAP).

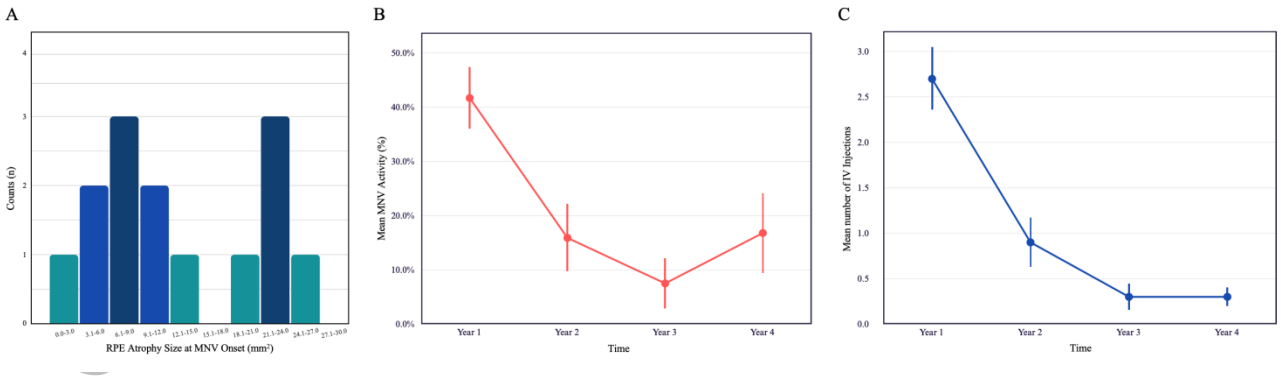


(**A**) A true-color fundus photograph shows large areas of retinal pigment epithelium (RPE) atrophy with a predominant vertical axis, surrounded by several pseudodrusen-like lesions. A loss of the foveal reflex is visible just inferior to the RPE atrophy. (**B**) Short-wavelength autofluorescence reveals moderately hypo-autofluorescent areas corresponding to RPE atrophy, with a pronounced hypo-autofluorescent signal superonasal to the fovea.

(**C**) Early-phase fluorescein angiography displays a hyperfluorescent neovascular membrane, with pronounced leakage in the late phase (**E**). Indocyanine green angiography highlights the neovascular network (**D**), with characteristic late-phase staining (**F**).

Swept-source optical coherence tomography angiography, superimposed on the near-infrared image, provides further visualization of the neovascular network (**G**). The optical coherence tomography scan through the fovea shows significant neuroretinal thickening due to intraretinal cysts, subretinal hyperreflective material, subretinal neovascularization (**H**).

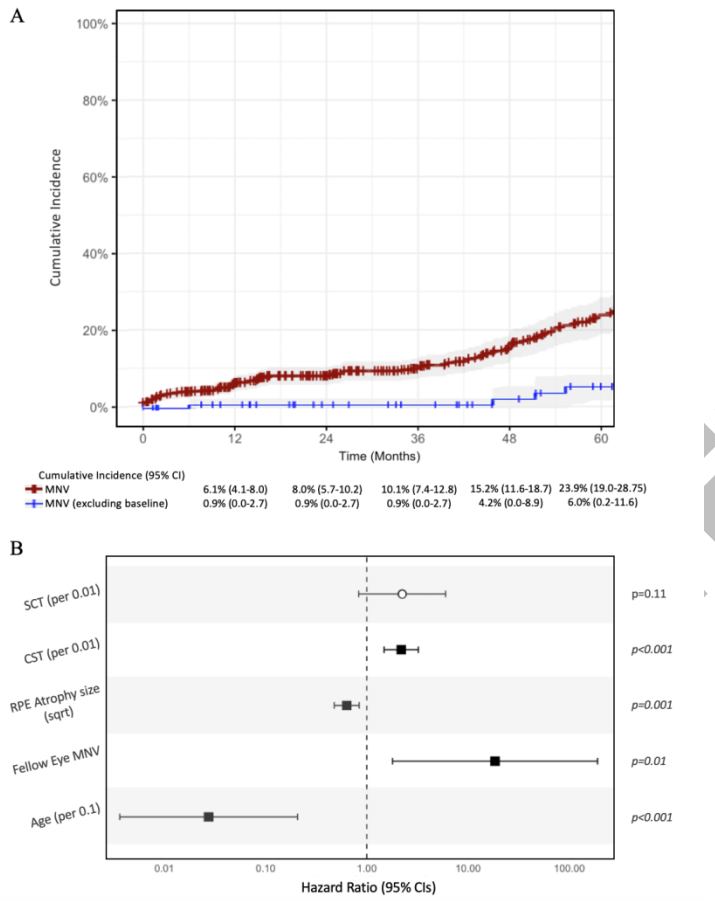
Figure 2. Retinal pigment epithelium (RPE) atrophy size, lesion activity, and intravitreal injection frequency in eyes with extensive macular atrophy with pseudodrusen-like appearance (EMAP) complicated by macular neovascularization (MNV).



(**A**) A bimodal distribution of MNV development can be observed in relation to RPE atrophy size, with the first peak occurring between 6.1 and 9.0 mm^2 and the second peak between 21.1 and 24.0 mm^2. (**B**) Mean lesion activity was highest in the first year (41.7%) and progressively declined over time, ranging from 7.5 to 16.8% in subsequent years. (**C**) Similarly, the average number of

intravitreal anti-VEGF injections decreased from 2.7 in the first year to 0.3-0.9 per year during years 2 to 4. Error bars in panels (**B**) and (**C**) represent the standard error of the mean.

Figure 3. Cumulative incidence and risk factors for macular neovascularization (MNV) development in extensive macular atrophy with pseudodrusen-like appearance (EMAP).

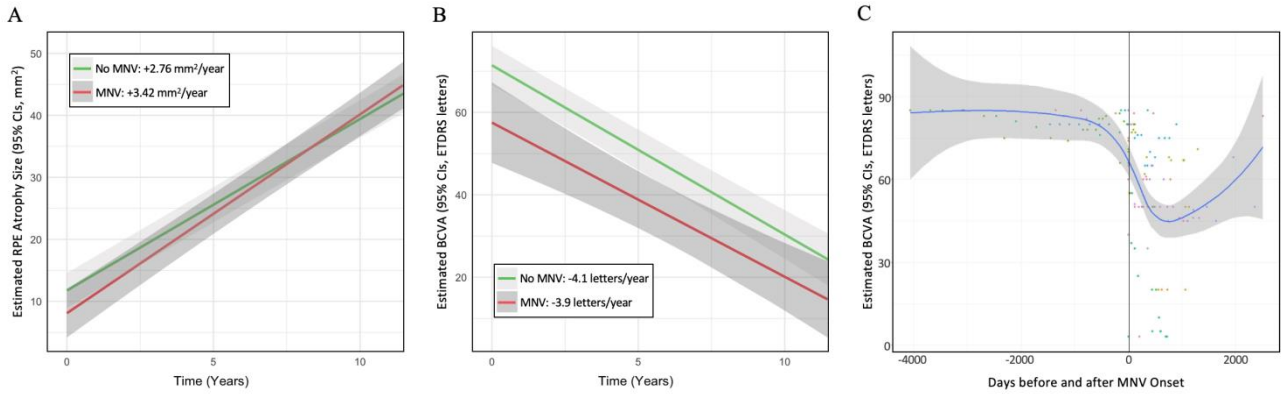


(**A**) The Kaplan-Meier curve demonstrates a steady increase in MNV cases over time, with a cumulative incidence of 6.1% [95% CI: 4.1-8.0%] at 1 year, rising to 15.2% [95% CI: 11.6-18.7%] by year 4 (red curve). Excluding left-censored data, cumulative incidence was estimated at 0.9 % [95% CI: 0.0-2.7] at 1 year and 4.2% [95% CI: 0.0-8.9] at 4 years (blue curve). The 95% confidence intervals are shaded in gray.

(**B**) Forest plots depict hazard ratios and 95% confidence intervals from a multivariable mixed-effects Cox regression analysis, identifying significant risk factors for MNV development. Notably, greater central subfield thickness (CST; p<0.001)), smaller retinal pigment epithelium (RPE)

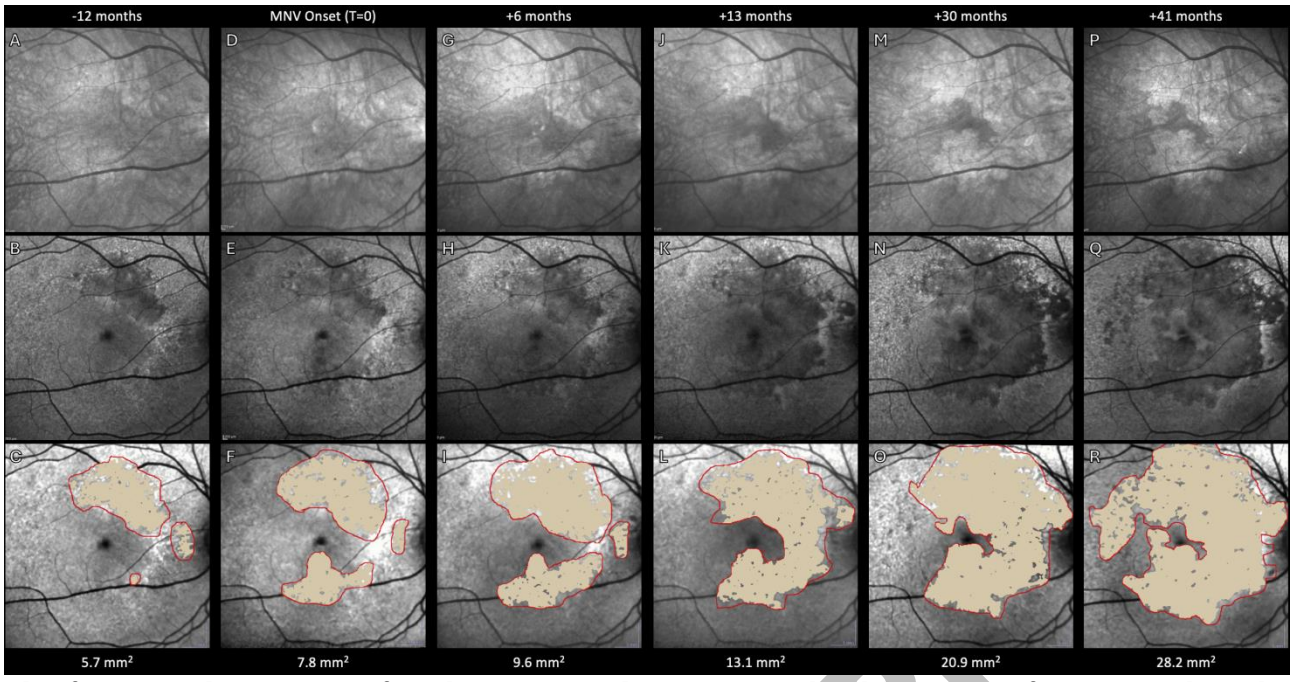
atrophy size (p=0.001), fellow eye involvement (p=0.01), and younger age (p<0.001) were all significantly associated with an increased risk of MNV.

Figure 4. Estimated changes in retinal pigment epithelium (RPE) atrophy size and best-corrected visual acuity (BCVA) between eyes with and without macular neovascularization (MNV) over time.



(**A**) After adjusting for age and baseline areas, eyes with MNV demonstrated a significantly higher rate of RPE atrophy progression compared to eyes without MNV (3.42 vs 2.76 mm^2/year, p=0.02). (**B**) After adjusting for age and baseline BCVA, no difference in the rate of BCVA decline was observed between eyes with and without MNV (-3.9 vs -4.1 ETDRS letters/year, p=0.69). (**C**) This panel illustrates the predicted trend of BCVA changes around the onset of MNV, showing a marked decline in BCVA followed by visual improvement after anti-VEGF treatment.

Figure 5. Longitudinal measurement of retinal pigment epithelium (RPE) atrophy in an eye with extensive macular atrophy with pseudodrusen-like appearance (EMAP), complicated by macular neovascularization (MNV), from 12 months before its onset (A-C) to the final follow-up (P-R).



The first row shows near-infrared images used to improve the delineation of RPE atrophy. The second row illustrates the progression of atrophy over time, as captured by short-wavelength autofluorescence (SW-AF). The third row depicts the measured RPE atrophy area using the expert modus of the RegionFinder software (version 2.6.4; Heidelberg Engineering GmbH), with atrophic areas highlighted in yellow and constraints marked in red.

Supplemental Digital Contents

Supplemental Digital Content 1.pdf

Table 1. Demographic and clinical characteristics of the analyzed extensive macular atrophy with pseudodrusen-like appearance (EMAP) cohort.

EMAP Group		
Patients (eyes)	79	(158)
Age years, *mean (SD) & median (IQR)*	57.2 (5.0)	57.2 (53.8 - 60.5)
Sex		
Males *n (%)*	27	(34.2%)
Females *n (%)*	52	(65.8%)
Lens Status		
Phakic eyes *n (%)*	148	(93.7%)
Pseudophakic eyes *n (%)*	10	(6.3%)
Smoking Status		
Never *n (%)*	51	(64.6%)
Former/Current *n (%)*	5	(6.3%)
Unknown *n (%)*	23	(29.1%)
Baseline BCVA ETDRS letters, *mean (SD) & median (IQR)*	70.7 (21.0)	80.0 (65.0 - 84.0)
(Snellen Equivalent)	(20/40)	(20/25)
Baseline RPE Atrophy Size mm^2, *mean (SD) & median (IQR)*	11.3 (9.0)	8.2 (2.2 - 18.0)
Follow-up months, *mean (SD) & median (IQR)*	40.4 (34.7)	34.4 (8.3 - 61.3)

Legend: EMAP, extensive macular atrophy with pseudodrusen-like appearance; IQR, interquartile range; BCVA, best-corrected visual acuity; ETDRS, early treatment for diabetic retinopathy study; RPE, retinal pigment epithelium; SD, standard deviation.

Table 2. Clinical and imaging features of extensive macular atrophy with pseudodrusen-like appearance (EMAP) eyes complicated by macular neovascularization (MNV).

EMAP Eyes with MNV		
Eyes (patients)	14 (10)	
MNV Types		
Type 1 *n (%)*	2 (14.3%)	
Type 2 *n (%)*	12 (85.7%)	
Type 3 *n (%)*	0 (0%)	
PCV *n (%)*	0 (0%)	
MNV Location		
Subfoveal *n (%)*	9 (64.3%)	
Juxtafoveal *n (%)*	2 (14.3%)	
Extrafoveal *n (%)*	3 (21.4%)	
RPE Atrophy Size mm^2, *mean (SD) & median (IQR)*	8.5 (9.3)	9.1 (6.2-22.1)
Anti-VEGF Agent used		

Bevacizumab *n (%)* Ranibizumab *n (%)* Aflibercept *n (%)*	7 (50.0%) 5 (35.7%) 2 (14.3%)	
Time to Fellow Eye Involvement months, *mean (SD) & median (IQR)*	13.6 (9.2)	11.5 (6.5-17.9)

Legend: EMAP, extensive macular atrophy with pseudodrusen-like appearance; MNV, macular neovascularization; PCV, polypoidal choroidal vasculopathy; RPE, retinal pigment epithelium; IQR, interquartile range; VEGF, vascular endothelial growth factor.

Table 3. Mixed-effects Cox proportional hazards regression analysis assessing the relationship between demographic features, imaging biomarkers, and time-dependent risk of developing macular neovascularization (MNV) in eyes affected by extensive macular atrophy with pseudodrusen-like appearance (EMAP).

Covariates	**Cox PH Regression**			
	Univariable Analysis		**Multivariable Analysis**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (0.1)	0.001 (0.0001-0.003)	*<0.001*	0.03 (0.004-0.21)	*<0.001*
Smoking Status	2.40 (0.49-11.81)	0.28	-	-
Fellow Eye Involvement	2.14 (1.48-3.07)	*<0.001*	18.45 (1.79-189.75)	*0.01*

SW-AF Atrophy Borders	1.39 (0.08-25.51)	0.82	-	-
RPE Atrophy Size (square-rooted)	0.49 (0.45-0.54)	*<0.001*	0.63 (0.48-0.84)	*0.001*
VMID	2.39 (0.00-5.79)	0.07	-	-
ORT	0.49 (0.23-1.04)	0.07	-	-
CST (0.01)	2.06 (1.30-3.26)	*0.002*	2.19 (1.48-3.22)	*<0.001*
SCT (0.01)	19.06 (7.11-51.08)	*<0.001*	2.23 (0.83-6.00)	0.11

Legend: PH, proportional hazards; HR, hazard ratio; CI, confidence intervals; SW-AF, short-wavelength autofluorescence; RPE, retinal pigment epithelium; VMID, vitreomacular interface disorder; ORT, outer retinal tubulations; CST, central subfield thickness; SCT, subfoveal choroidal thickness.

Table 4. Clinical and macular neovascularization characteristics in extensive macular atrophy with pseudodrusen-like appearance (EMAP) and key phenocopies.

	EMAP (our series)	GA	PXE	SFD	L-ORD

Large Drusen	Absent or rare	Present (sometimes regressed)	Absent	Present from 3rd decade, also nasal to the ONH and along vascular arcades (*Sivaprasad S et al. Am J Ophthalmol 2008*) (*Gliem M et al IOVS 2015*)	*Absent (Duncan HJ et al. BMJ Open Ophthalmol 2023)*
RPD / RPD-like lesions	100%, with pan-retinal distribution (*Hamel C et al. Am J Ophthalmol*)	>60% (*Schmitz-Valckenberg S et al. IOVS 2011*)	~50% (age-dependent) (*Gliem M et al. JAMA Ophthalmol 2015*)	>70% after 6th decade (*Gliem M et al Ophthalmology 2015*)	100%, from 5th decade (*Borooah S et al. Ophthalmol Retina 2021*)
BrM Ruptures	25% of late-stage cases (*Antropoli et al. Ophthamology 2024*)	16%, especially in the presence of RPD (*Sacconi R et al.*	85-95% (*Finger RP et al. Surv Ophthalmol 2009*)	Rare (*Capon MR et al. Ophthalmology 1989*)	Not documented

		Ophthalmol Ther 2023)			
Choroidal Thickness	Variable at baseline, rapidly thinning (including atrophy) (*Romano F et al. Ophthalmol Sci 2021*)	Thin (especially in diffuse-trickling SW-AF phenotype) (*Lindner M et al. IOVS 2015*)	Thinner in the presence of CNV or macular atrophy (*Hidalgo-Dìaz T et al. Int Ophthalmol 2020*)	Thinner with the onset of macular atrophy (*Gliem M et al IOVS 2015*)	Thin and rapidly thinning (*Borooah S et al. Retina 2021*)
MNV Frequency	~15% by 4 years	~11% by 4 years (*Sunness JS et al. Ophthalmology 1999*) (*Sacconi R et al. Br J Ophthalmol 2022*)	42-86% (*Risseeuw S et al. Retina 2019*)	60-80% (*Sivaprasad S et al. Am J Ophthalmol 2008*)	No definitive studies
MNV Types	Type 2 >> type 1; no reports of type 3, PCV, and non-exudative MNV	Type 2 >> type 1 > type 3. Absent/rare PCV. No definitive studies on non-	Type 1 > type 2; no reports of type 3; isolated reports of PCV; non-exudative	Type 2 > type 1 and PCV; no reports of type 3 and non-exudative MNV	No definitive studies: both type 1 and 2 MNV sporadically described (*Jeffery*

		exudative MNV frequency (*Sacconi R et al. Br J Ophthalmol 2022*)	MNV (33%) (*Cicinelli MV et al. Ophthalmol Retina 2024*) (*Marques JP et al. Graefes Arch Clin Exp Ophthalmol 2021*)	(*Sivaprasad S et al. Am J Ophthalmol 2008*) (*Gliem M et al. IOVS 2015*)	*RCH et al. Surv Ophthalmol 2024*)
MNV Location	Subfoveal >> extrafoveal ≥ juxtafoveal	Subfoveal >> juxta-/extrafoveal (*Sacconi R et al. Br J Ophthalmol 2022*)	Subfoveal > extrafoveal > juxtafoveal (*Rohart C et al. Retina 2023*)	Sub-/juxtafoveal > extrafoveal (*Sivaprasad S et al. Am J Ophthalmol 2008*)	No definitive studies: typically, temporal to the fovea (*Jeffery RCH et al. Surv Ophthalmol 2024*)
MNV-Atrophy Relationship	Faster progression of atrophy	Slower local progression of atrophy (*Pfau M et al. Ophthalmol Retina 2020*)	Atrophy associated with type 2 MNV onset and greater extent of AS (*Risseeuw S et al. Am J Ophthalmol*	Unknown; SFD cases without MNV may have faster progression of atrophy	Unknown.

			2020) (*Gliem M et al.* *IOVS* 2016)		

Legend: GA, geographic atrophy; PXE, pseudoxanthoma elasticum; SFD, Sorsby fundus dystrophy; L-ORD, late-onset retinal degeneration; RPD, reticular pseudodrusen; BrM, Bruch's membrane; MNV, macular neovascularization; PCV, polypoidal choroidal vasculopathy; SW-AF, short-wavelength autofluorescence; AS, angioid streaks.