

Type 4 Macular Neovascularization in a Consecutive Age-Related Macular Degeneration Cohort: Prevalence and Multimodal Imaging Findings

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Abstract

Background

To determine the prevalence of type 4 macular neovascularization (MNV) in an age-related macular degeneration (AMD) cohort, the applicability of the proposed multimodal imaging criteria in an independent center was assessed, and the clinical and imaging features were characterized.

Methods

This single-center retrospective cohort study included 4658 structural OCT examinations from 962 eyes of 500 patients with age-related macular degeneration (AMD). Eyes with structural OCT findings suggestive of type 4 MNV underwent multimodal evaluation via structural OCT and available OCT angiography (OCTA). Cases were classified as definite, probable, or non-Type 4 MNVs according to predefined multimodal imaging criteria. Prevalence was calculated at the patient and eye levels with exact 95% Clopper–Pearson confidence intervals (CIs).

Results

The prevalence of definite type 4 MNV was 2.00% (95% confidence interval [CI], 0.96–3.65%) at the patient level and 1.04% (95% CI, 0.50–1.90%) at the eye level. The hyperreflective oblique band (HOB), subretinal hyperreflective material (SHRM), and ellipsoid zone (EZ) loss were present in all the definite cases. Central posterior hyaloid fibrosis (CPHF) was observed in half of the definite cases, whereas the remaining eyes exhibited posterior hyaloid central hyperreflectivity (PHCH). OCTA demonstrated the characteristic flow pattern in all definite cases. During follow-up, HOB, CPHF, and PHCH remained stable, whereas exudative activity varied.

Conclusions

Type 4 MNV is a rare but distinct AMD phenotype. Structural OCT is suitable for screening, whereas OCTA is essential for definitive diagnosis. Our findings support the applicability of the proposed multimodal imaging criteria in an independent center and further characterize the clinical and imaging features of type 4 MNVs.

Introduction

Age-related macular degeneration (AMD) is one of the leading causes of irreversible vision loss among older adults worldwide (1). Approximately 85–90% of patients with AMD have the dry (atrophic) form, whereas 10–15% have the neovascular form (2). Accurate anatomical classification of neovascular AMD (nAMD) is essential for predicting the disease course and guiding appropriate treatment strategies (3, 4).

According to the current optical coherence tomography (OCT) consensus classification, macular neovascularization (MNV) is classified into Type 1 (sub-RPE), Type 2 (subretinal), and Type 3 (intraretinal) lesions (3, 4).

However, with the widespread clinical use of optical coherence tomography angiography (OCTA) and high-resolution structural OCT, vitreomacular interface–related morphological features and complex neovascular architectures have become increasingly well characterized (5, 6). Recently, described by Chan et al., the type 4 MNV phenotype is characterized by a hyperreflective oblique band (HOB) extending from the subretinal lesion into the inner retina, central posterior hyaloid fibrosis (CPHF), and a continuous flow signal extending from the choroid to the preretinal space (7). Furthermore, because of its preretinal neovascular extension, prominent fibroproliferative course, and overlapping features with Type 3 MNV, it has been proposed as a distinct phenotype that may be difficult to differentiate within the current classification system (7, 8).

However, the available evidence on type 4 MNV remains limited and is based on only a small number of case series (7). The prevalence of this phenotype in a large, consecutive AMD cohort representative of real-world clinical practice remains unknown. In addition, it is unclear whether type 4 MNV represents an end-stage change secondary to chronic, inadequately treated neovascularization or a distinct MNV phenotype that can arise de novo in treatment-naïve eyes. Likewise, whether the tractional or fibrotic bands observed on structural OCT truly harbor preretinal neovascular flow requiring confirmation by OCTA remains an important diagnostic uncertainty. Addressing these questions is essential for improving the recognition of type 4 MNV, identifying eyes that may still benefit from anti-VEGF therapy, and avoiding unnecessary anti-VEGF treatment in eyes with predominantly advanced fibroproliferative changes (9, 10).

The aim of this study was to determine the prevalence of the type 4 MNV phenotype recently described by Chan et al. in a consecutive AMD cohort, assess the applicability of the proposed multimodal imaging criteria in an independent tertiary retina center, and evaluate the diagnostic value of OCTA for differentiating type 4 MNV from other MNV subtypes.

Methods

Study design and patient selection

This single-center, observational, retrospective cohort study was conducted at the Retina Unit of the Department of Ophthalmology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye. The study protocol was approved by the Eskişehir Osmangazi University Noninterventional Clinical Research Ethics Committee (approval no. 65, May 2, 2024). The study adhered to the tenets of the Declaration of Helsinki.

To minimize selection bias, consecutive sampling was used. Consecutive patients followed at the retina unit with a diagnosis of AMD were screened retrospectively, beginning with the most recent follow-up

visit (July 3, 2026) and proceeding backward in time until a cohort of 500 consecutive patients was assembled (February 2, 2024). A total of 38 eyes were excluded (Fig. 1). The remaining 4658 structural OCT images from 962 eyes were systematically screened for type 4 MNV, and eyes with suspicious findings were further evaluated. The sample size was not determined by a formal power calculation but was pragmatically defined to establish a sufficiently large cohort to enable the systematic evaluation of the prevalence and imaging characteristics of this newly described and uncommon phenotype.

The cohort included all consecutive patients followed at the retina unit with a diagnosis of AMD and was not restricted to eyes with neovascular AMD (nAMD). As our institution is a tertiary referral retina center, a substantial proportion of patients are referred from other centers after a diagnosis of nAMD or initiation of anti-VEGF therapy, and previous diagnoses and treatment histories cannot always be reliably verified from institutional records alone. Consequently, some eyes with nAMD diagnosed at outside centers could be misclassified as having dry AMD if the classification relies solely on our institutional records. Therefore, the entire consecutive AMD cohort was used as the denominator for the prevalence calculations.

Although the cohort was assembled on the basis of the date of the most recent follow-up visit, all available clinical records, structural OCT imaging sessions, and OCTA images (when available) from each patient's initial presentation to the final follow-up visit were reviewed. Consequently, the evaluated imaging sessions included examinations performed before the cohort assembly period. The follow-up duration was defined as the interval between the initial retina visit and the most recent follow-up visit, whereas a visit was defined as a structural OCT imaging session performed on a single date.

Inclusion and exclusion criteria

Inclusion criteria

- Diagnosis of AMD.
- Availability of at least one evaluable structural macular OCT imaging session.

Exclusion criteria

Eyes meeting any of the following criteria were excluded:

- Type 2 macular telangiectasia (MacTel type 2), pathologic myopia, prosthetic eye, or pachychoroid spectrum disease.
- Structural OCT images that are unevaluable because of poor image quality (e.g., dense cataract, corneal opacity, dense vitreous opacity, vitreous hemorrhage, or imaging artifacts) or inadequate patient cooperation.

Data collection

Electronic medical records and available imaging data were reviewed retrospectively. For the entire study cohort, age, sex, date of the initial retina visit, date of the most recent follow-up visit, and follow-up duration were recorded. For all eyes classified as definite, probable, or non-Type 4 MNV, the affected eye, lens status, number of visits, AMD subtype in the fellow eye, history of anti-VEGF therapy, anti-VEGF agent, total number of intravitreal injections, best-corrected visual acuity, and history of vitreoretinal surgery (vitrectomy) were recorded. Age was calculated based on the date of the first suspicious structural OCT finding.

Best-corrected visual acuity data were obtained from the clinical records at the initial presentation, and the most recent follow-up visit via a Snellen chart. In eyes with low vision, visual acuity was recorded as counting fingers at 1–5 m. For statistical analysis and graphical presentation, all visual acuity measurements were converted to logMAR values via the standard logarithmic conversion for Snellen acuity and a commonly used clinical convention for counting fingers (counting fingers at X meters $\approx$ Snellen X/60; see Fig. 3).

Imaging protocol

All structural OCT images were acquired as part of routine clinical practice via a swept-source OCT device (DRI OCT Triton; Topcon Corporation, Tokyo, Japan). OCTA images were also obtained via the same device with a 6 × 6 mm scan protocol according to the routine clinical imaging protocol, with the built-in projection artifact removal (PAR) algorithm enabled. As part of the retrospective review, all available structural OCT imaging sessions for each patient were evaluated in chronological order. Volumetric OCT datasets and corresponding B-scan images from each session were systematically reviewed. Because of the retrospective study design, diagnostic confirmation was limited to available OCTA examinations, and no additional OCTA imaging could be performed for eyes without OCTA records.

Image evaluation

All structural OCT imaging sessions were systematically screened for features suggestive of type 4 MNV by two ophthalmology residents and two retina specialists. During this initial screening, only the imaging data were evaluated, and the clinical records were not reviewed. Images considered suspicious for type 4 MNV were subsequently reassessed independently by two retina specialists.

For each patient, structural OCT imaging sessions were reviewed in chronological order to identify the first visit showing structural findings suspicious for type 4 MNV. From this time point onward, the corresponding clinical records and available OCTA images were reviewed, and the eyes were classified according to the predefined diagnostic criteria described below (see Diagnostic Classification). Following the independent assessments, all suspicious cases were reviewed jointly by the two retina

specialists to establish a consensus-based final classification, after which the study database was finalized.

Assessment of type 4 MNVs

The diagnosis of type 4 MNV was based on the multimodal imaging criteria proposed by Chan et al. Structural OCT examinations were systematically evaluated for morphological features associated with type 4 MNV (7). Central posterior hyaloid fibrosis (CPHF) was assessed according to the structural OCT characteristics described by Khan et al. and Venkatesh et al. (5, 6).

Structural OCT examinations were systematically screened for the following morphological features suggestive of type 4 MNV:

- Type 1, Type 2, or mixed Type 1–Type 2 MNV morphology
- Subretinal hyperreflective material (SHRM)
- Hyperreflective oblique band (HOB)
- Structural changes suggestive of inner retinal or preretinal proliferation
- Central posterior hyaloid fibrosis (CPHF)

In eyes suspected of having type 4 MNV, additional descriptive structural OCT findings, including vitreomacular adhesion/traction (VMA/VMT), ellipsoid zone (EZ) loss, intraretinal fluid (IRF), subretinal fluid (SRF), prechoroidal cleft, and the presence of hemorrhagic MNV at the initial presentation, were also recorded.

Diagnostic Classification

Eyes were classified as having definite type 4 MNV when all of the following criteria were fulfilled:

- MNV secondary to age-related macular degeneration (AMD);
- Structural OCT findings consistent with Type 1, Type 2, or mixed Type 1–Type 2 MNV morphology together with structural changes suggestive of inner retinal or preretinal proliferation;
- On OCTA, a continuous flow signal extending from the inner choroid to the preretinal space was observed.

In addition to these OCTA findings, supportive OCTA features, including Type 1, Type 2, or mixed MNV flow patterns; flow signals within the HOB; and flow signals within the CPHF, were also evaluated.

Eyes with structural OCT findings suggestive of type 4 MNV but without corresponding OCTA imaging at the same visit were classified as probable type 4 MNV. Eyes with suspicious structural OCT findings in which a continuous flow signal extending from the inner choroid to the preretinal space could not be demonstrated on OCTA were classified as non–type 4 MNVs.

Statistical analysis

The prevalence of definite type 4 MNV and the expanded prevalence, including probable cases, were calculated separately at the patient and eye levels. Exact 95% confidence intervals (CIs) were calculated via the Clopper–Pearson method in Python with the SciPy statistical library (version 1.15.3). Because no patient had bilateral definite or probable type 4 MNV, the assumption of independence was preserved for eye-level analyses. The demographic, clinical, and imaging characteristics of definite, probable, and non-Type 4 MNV patients were summarized descriptively. Categorical variables are presented as numbers (percentages), and continuous variables are presented as medians (ranges). Owing to the limited number of Type 4 MNV cases, no inferential statistical analyses were performed.

Results

A total of 4658 structural OCT images from 962 eyes of 500 consecutive patients were systematically reviewed. Based on this screening, 16 eyes with morphological findings suggestive of type 4 MNV were selected for further evaluation (Fig. 1). Of these, 10 (62.5%) were classified as definite Type 4 MNVs, 3 (18.8%) as probable Type 4 MNVs, and 3 (18.8%) as non-Type 4 MNVs. Each eye belonged to a different patient, and no bilateral involvement was identified. Cases were assigned consecutive identifiers (C, case): C1–C10 for the definite group, C11–C13 for the probable group, and C14–C16 for the non-Type 4 MNV group. These identifiers are used throughout the manuscript.

Characteristics of the definite Type 4 MNV group

The prevalence of definite type 4 MNV was 2.00% at the patient level (10/500; 95% Clopper–Pearson CI, 0.96%–3.65%) and 1.04% at the eye level (10/962; 95% CI, 0.50%–1.90%). When probable Type 4 MNV cases ($n = 3$) were included, the expanded prevalence increased to 2.60% at the patient level (13/500; 95% CI, 1.39%–4.41%) and 1.35% at the eye level (13/962; 95% CI, 0.72%–2.30%) (Fig. 2).

The demographic and clinical characteristics of the 10 definite type 4 MNV patients are summarized in Table 1. No surgical intervention was performed in any patient during follow-up.

Table 1
Demographic and clinical characteristics of eyes with definite type 4 MNV (n = 10).

Variable	Value
Age at diagnosis, median (range), years	75.5 (55–89)
Sex, male/female, n	8/2
Affected eye, right/left, n	4/6
Lens status, phakic/pseudophakic, n	5/5
Number of visits, median (range)	3 (1–9)
Follow-up duration, median (range), months	14.1 (0–26.5)
Patients receiving anti-VEGF therapy, n (%)	5/10 (50%)
Anti-VEGF agent	Bevacizumab (5/5)
Number of injections, median (range)	3 (3–4)
Patients receiving anti-VEGF injections before the first suspicious OCT finding, n (%)	0/10 (0%)
Fellow-eye AMD subtype, dry/neovascular, n (%)	6/4 (60%/40%)

Visual acuity was evaluated in the eight patients with at least two visits by comparing the measurements obtained at the initial presentation and the final follow-up visit, irrespective of the date of the Type 4 MNV diagnosis. Patients C3 (counting fingers at 1 m) and C8 (counting fingers at 2 m), which had only a single visit, were excluded from this analysis. The results are presented in Fig. 3. Visual acuity remained stable in most cases, with the greatest change observed in Patient C9 (from counting fingers at 2 m to counting fingers at 5 m).

Among the 10 eyes with definite type 4 MNVs, central posterior hyaloid fibrosis (CPHF) was identified in five eyes, whereas the remaining five exhibited a similar hyperreflective pattern with separation of the posterior hyaloid from the fovea. This latter finding was defined as a distinct structural OCT feature and termed posterior hyaloid central hyperreflectivity (PHCH). The structural OCT and OCTA findings at diagnosis are summarized in Table 2, and representative structural OCT images of CPHF and PHCH patients are shown in Fig. 4.

On OCTA, a mixed type 1–type 2 MNV pattern, a flow signal within the hyperreflective oblique band (HOB), and preretinal neovascular extension were identified in all eyes (Table 2). Flow signals within central posterior hyaloid fibrosis (CPHF) were detected in all five eyes with CPHF (5/5, 100%). A continuous flow signal extending from the inner choroid to the preretinal space, the defining diagnostic feature of type 4 MNV, was observed in all eyes (10/10, 100%) (Fig. 5).

Table 2
OCT and OCTA findings at diagnosis (n = 10)

Optical coherence tomography (OCT) findings	n (%)
Hyperreflective oblique band	10/10 (100%)
Subretinal hyperreflective material	10/10 (100%)
Ellipsoid zone loss	10/10 (100%)
Central posterior hyaloid fibrosis	5/10 (50%)
Posterior hyaloid central hyperreflectivity	5/10 (50%)
Vitreomacular adhesion/traction	5/10 (50%)
Intraretinal fluid	9/10 (90%)
Subretinal fluid	6/10 (60%)
Hemorrhagic macular neovascularization at diagnosis	2/10 (20%)
Prechoroidal cleft	2/10 (20%)
Optical coherence tomography angiography (OCTA) findings	
Mixed Type 1–Type 2 MNV	10/10 (100%)
Flow signal within the hyperreflective oblique band	10/10 (100%)
Flow signal within the central posterior hyaloid fibrosis	5/5 (100%)
Preretinal neovascular extension	10/10 (100%)
Continuous flow signal extending from the inner choroid to the preretinal space	10/10 (100%)

The follow-up findings of the eight eyes with at least one postdiagnosis visit (C1, C2, C4, C5, C6, C7, C9, and C10) are summarized in Table 3. The hyperreflective oblique band (HOB), the overall type 4 MNV phenotype, and the findings of central posterior hyaloid fibrosis (CPHF) and posterior hyaloid central hyperreflectivity (PHCH) were preserved in all eyes in which they were initially identified, whereas subretinal fluid (SRF) and intraretinal fluid (IRF) showed variable changes over time.

Table 3
Follow-up findings in eyes with at least one postdiagnosis visit (n = 8).

Finding	Value
The hyperreflective oblique band was preserved	8/8
* The central posterior hyaloid fibrosis was preserved	4/4
* The posterior hyaloid central hyperreflectivity was preserved	4/4
Overall Type 4 phenotype preserved	8/8
Persistent SRF (eyes with SRF at baseline)	2/5
Resolution of SRF (eyes with SRF at baseline)	3/5
New-onset SRF (eyes without SRF at baseline)	1/3
Persistent IRF (eyes with IRF at baseline)	6/8
Resolution of IRF (eyes with IRF at baseline)	2/8

Comparison of Probable Type 4 MNV and non-Type 4 MNV cases

The demographic, clinical, and structural OCT characteristics of the probable Type 4 MNV (n = 3; C11–C13) and non-Type 4 MNV (n = 3; C14–C16) groups are compared in Table 4. Unlike in the definite type 4 MNV group, anti-VEGF therapy was initiated before the first suspicious OCT finding in all eyes with probable type 4 MNV. Patient C13 received both bevacizumab and ranibizumab, and all three patients had dry AMD in the fellow eye. In contrast, none of the eyes in the non-Type 4 MNV group, nor their fellow eyes, had a history of anti-VEGF treatment. The most notable structural OCT difference between the two groups was the absence of the hyperreflective oblique band (HOB) and central posterior hyaloid fibrosis (CPHF) in all non-Type 4 MNV group, whereas these findings were frequently observed in the probable Type 4 MNV group (Table 4). Representative structural OCT images demonstrating HOB, CPHF, and posterior hyaloid central hyperreflectivity (PHCH) in the probable Type 4 MNV group are shown in Figure 6.

The OCTA findings of the three eyes classified as non-type 4 MNVs were heterogeneous. Patients C14 and C15 presented flow signals consistent with Type 1 MNVs only, whereas Patient C16 presented Type 1, Type 2, and mixed Type 1–Type 2 MNV patterns. However, none of the three eyes demonstrated preretinal neovascular extension or a continuous flow signal extending from the inner choroid to the preretinal space. Therefore, regardless of the OCTA flow pattern, all three eyes failed to meet the diagnostic criteria for definite type 4 MNV and were classified as non-type 4 MNV.

Table 4
Demographic, clinical, and structural OCT characteristics of eyes classified as having probable type 4 MNV (n = 3) and non-type 4 MNV (n = 3).

Variable	Probable Type 4 MNV (n = 3)	Non-Type 4 MNV (n = 3)
Age at the first suspicious OCT finding, median (range)	64 (61–74)	74 (63–84)
Sex, male/female	3/0	1/2
Affected eye, right/left	3/0	1/2
Lens status, phakic/pseudophakic	2/1	3/0
Number of visits, median (range)	10 (9–12)	1 (1–3)
Follow-up duration, median (range), months	27.9 (21–31.2)	0 (0–3.3)
Visual acuity at initial presentation	CF 2 m (1.48), CF 2 m (1.48), CF 1 m (1.78)	0.3**(0.52), CF 1 m (1.78), CF 4 m (1.18)
Visual acuity at final visit	CF 2 m (1.48), 0.1* (1.00), CF 1 m (1.78)	0.3** (0.52), CF 1 m (1.78), CF 4 m (1.18)
Patients receiving anti-VEGF therapy, n (%)	3/3	0/3
Number of injections, median (range)	6 (5–8)	–
Hyperreflective oblique band	3/3	0/3
Subretinal hyperreflective material	3/3	2/3
Ellipsoid zone loss	3/3	3/3
Central posterior hyaloid fibrosis	2/3	0/3
Posterior hyaloid central hyperreflectivity	1/3	3/3
Intraretinal fluid	2/3	3/3
Subretinal fluid	0/3	3/3
Vitreomacular adhesion/traction	2/3	2/3
<i>*In Patient C12, visual acuity improved beyond the counting finger threshold at the final visit and was therefore measured via a Snellen chart (0.1).</i>		
<i>**In Patient C14, visual acuity was above the counting fingers threshold at baseline and was therefore measured via a Snellen chart (0.3).</i>		
CF: counting fingers		

* Only eyes with corresponding findings at baseline were included in the analysis.

Discussion

Systematic screening of 962 eyes from 500 consecutive patients with AMD revealed a definite Type 4 MNV prevalence of 2.00% at the patient level and 1.04% at the eye level. These findings indicate that Type 4 MNV is an uncommon phenotype within the AMD spectrum (Figures 1 and 2). To date, however, no previous study has specifically investigated the prevalence of type 4 MNV. In a cohort of 266 eyes with newly diagnosed neovascular AMD, Jung et al. classified lesions via fluorescein angiography and structural OCT as Type 1 (39.9%), Type 2 (9.0%), Type 3 (34.2%), or mixed Type 1–Type 2 (16.9%) MNVs (11). In our study, the prevalence of AMD was calculated across the entire AMD cohort without distinguishing between dry AMD and neovascular AMD. Therefore, the resulting prevalence estimates are not directly comparable with studies reporting the distribution of MNV subtypes exclusively in eyes with neovascular AMD. Nevertheless, the rarity of type 4 MNVs in the literature and their limited systematic characterization highlight the value of our findings in expanding the current epidemiological understanding of this phenotype.

The multimodal imaging characteristics of type 4 MNV, which was originally proposed by Chan et al. as a novel subtype within the OCT-based MNV classification, were evaluated in an independent patient cohort. These findings indicate that this phenotype can be recognized in another clinical population while exhibiting the same morphological and angiographic characteristics. However, the current definition of type 4 MNV is based on a limited number of descriptive case series and has not yet been adequately validated in independent cohorts (7). Therefore, to maximize diagnostic specificity, we adopted a conservative approach and classified only eyes fulfilling all predefined structural OCT and OCTA criteria as definite type 4 MNVs. To the best of our knowledge, this is the first study reporting the prevalence of type 4 MNV based on the systematic screening of a consecutive AMD cohort.

Structural OCT serves as the primary screening tool for identifying eyes suspicious for type 4 MNV, whereas the diagnosis of definite type 4 MNV requires OCTA of continuous neovascular extension from the inner choroid to the preretinal space. The importance of this diagnostic approach was illustrated by three eyes with suspicious structural OCT findings in which this continuous neovascular extension could not be demonstrated. Although these eyes exhibited Type 1 or mixed Type 1–Type 2 MNV patterns, they did not fulfill the diagnostic criteria for definite Type 4 MNV (Table 4).

In the original descriptive series, the hyperreflective oblique band (HOB) was present in all eyes, and its persistence even in eyes without central posterior hyaloid fibrosis (CPHF) suggested that it may represent one of the core morphological features of Type 4 MNVs (7). Consistent with the original report, HOB was identified in all eyes (10/10) in our series. Moreover, the equal distributions of central posterior hyaloid fibrosis (CPHF) and posterior hyaloid central hyperreflectivity (PHCH) further support HOB as one of the most consistent structural OCT features of type 4 MNV.

In a previous case series describing CPHF, this finding was associated primarily with chronic, highly fibrotic type 2 MNV and was interpreted as a manifestation of the profibrotic influence of the neovascular complex on the posterior hyaloid (5). Venkatesh et al. reported CPHF in 4% of eyes in an overall neovascular AMD cohort and in 6% of eyes within the predominantly scarred MNV subgroup (5). Given the advanced fibroproliferative nature of Type 4 MNV, the frequency of CPHF observed in our series is consistent with these previous observations. However, the absence of CPHF in the remaining half of our definite cases suggests that, although characteristic, this finding is not essential for the diagnosis of type 4 MNV. Notably, posterior hyaloid central hyperreflectivity (PHCH) was identified in all definite Type 4 MNV eyes without CPHF. According to the proposed mechanism, disruption of the retinal pigment epithelium barrier allows proinflammatory and profibrotic mediators to enter the subretinal space, thereby strengthening posterior hyaloid adhesion, whereas progressive subretinal fibrosis may further contribute to this process through mechanical traction (5, 6). Although vitreomacular adhesion has been implicated in the development of neovascular AMD (12), our findings suggest that CPHF and PHCH may not simply represent sequential stages of the same pathological process but may instead reflect different underlying clinical contexts.

The age distribution of the CPHF patients in our series was generally consistent with that reported by Venkatesh et al. (median age, 69 years [range, 54–89 years] vs. mean age, 72.76 ± 9.09 years, respectively) (5). In contrast, the PHCH cases were clustered within a narrower and older age range (median age, 76 years; range, 75–79 years). Because the prevalence of posterior vitreous detachment (PVD) increases with advancing age, this age distribution may partly explain the predominance of PHCH in older patients (13). These findings suggest that CPHF may develop in eyes in which the posterior hyaloid remains attached to the fovea, whereas PHCH may be observed during the more advanced stages of posterior vitreous detachment (PVD; Stages 3–4). In the PHCH group, Stage 3 PVD could be identified on structural OCT in two eyes. However, in complete PVD (stage 4), the detached posterior hyaloid may move away from the retina and beyond the imaging depth of structural OCT, limiting the reliable assessment of this stage via macula-centered structural OCT (13). This interpretation is further supported by the absence of reported posterior vitreous detachment in the CPHF cases described by Venkatesh et al. (5).

Clinically, visual acuity was already at the finger level in most eyes at the patients' initial presentation to the retina service, and ellipsoid zone loss was observed in all eyes (Table 2; Figure 3), indicating that advanced structural and functional macular damage had already been established by the time type 4 MNV was diagnosed. None of the definite patients in our series had received anti-VEGF therapy before the first suspicious OCT finding was identified (Table 1), suggesting that type 4 MNV is not exclusively a phenotype that develops following anti-VEGF treatment. However, because of the retrospective study design and the advanced disease stage at presentation, the possibility of an unrecognized chronic neovascular process before diagnosis cannot be excluded. Furthermore, the absence of appreciable regression of the HOB, CPHF/PHCH, or overall type 4 MNV phenotype during follow-up, even in treated eyes (Table 3), supports the concept that these structural findings represent relatively stable structural characteristics that are at least partly independent of exudative activity (7). The description of the Type 4

MNV complex by Chan et al. as a mature, low flow neovascular network (7) is consistent with the OCTA flow patterns observed in our series and suggests that this morphological maturity may be associated with reduced VEGF dependence, thereby partly explaining the structural stability observed during follow-up. Considering that all definite cases in our series were treatment-naïve at the time of the first suspicious OCT finding, this mature appearance is more likely to represent an intrinsic characteristic of the type 4 MNV phenotype than a consequence of prior anti-VEGF therapy. Visual acuity remained stable in most eyes throughout follow-up, with the only notable exception being Case C9, in which vision improved from counting fingers at 2 m to counting fingers at 5 m (Figure 3). Despite this functional improvement, the HOB, CPHF, and overall Type 4 MNV phenotypes remained structurally unchanged throughout the follow-up period (Table 3). This dissociation suggests that the observed visual improvement cannot be attributed to structural regression of the underlying neovascular complex and was more likely related to factors independent of the structural phenotype, such as changes in exudative activity. All 16 eyes identified during screening were from different patients, and no bilateral involvement was observed, indicating that the phenotype was unilateral in this cohort. However, given the limited sample size, no conclusion can be drawn regarding unilateral involvement as a characteristic feature of type 4 MNV.

Several methodological limitations should be considered when interpreting the findings of this study. First, the retrospective, single-center design may limit the generalizability of the results to other clinical populations. In addition, because the cohort was assembled retrospectively based on the date of the last follow-up visit and included variable follow-up durations, the incidence of type 4 MNV could not be assessed; therefore, only its prevalence within the defined study population could be estimated. Furthermore, because the cohort comprised all patients followed with a diagnosis of AMD rather than being restricted to neovascular AMD (nAMD), the true prevalence of type 4 MNV within the nAMD subgroup cannot be determined directly from the present study.

Because OCTA evaluates flow signals from volumetric scans via cross-sectional sampling, vascular segments with low-flow signals, particularly within densely fibrotic tissue, may not be visualized on every B-scan. Consequently, the absence of the characteristic OCTA flow pattern does not necessarily exclude the presence of a retinochoroidal anastomotic network. Therefore, the possibility of misclassification in some eyes because of the technical limitations of OCTA cannot be excluded (14). In addition, because visual acuity was at the counting fingers level in most eyes, conversion to logMAR values was based on a widely used clinical convention (counting fingers at X meters $\approx$ Snellen X/60) rather than an empirically validated conversion method. Consequently, quantitative comparisons with other studies should be interpreted with caution. During image evaluation, all suspicious cases were independently reviewed by two retina specialists, followed by a consensus meeting to establish the final classification. Because the aim of the study was not to assess interobserver agreement, a formal agreement analysis (e.g., Cohen's kappa coefficient) was not performed. Furthermore, as image evaluation was not masked, the possibility of observer bias cannot be completely excluded.

This study provides the first systematic prevalence estimates for type 4 MNV in a large consecutive AMD cohort and demonstrates that the multimodal diagnostic criteria proposed by Chan et al. can be applied in an independent cohort. Our findings further suggest that CPHF and PHCH may represent distinct morphological manifestations influenced by vitreous status.

Further multicenter, prospective studies incorporating standardized imaging protocols are needed to better define the location and clinical significance of type 4 MNVs within the spectrum of neovascular AMD. Such studies should confirm the prevalence of this phenotype across different populations, refine its diagnostic criteria, clarify its natural history, and further strengthen its ability to differentiate it from type 3 MNVs. In addition, it remains unclear which anatomical or exudative features are most likely to benefit from anti-VEGF therapy and at what stage of disease treatment should be initiated. Addressing these questions will help identify patients most likely to benefit from treatment and define the potential limitations of anti-VEGF therapy in eyes with advanced fibroproliferative changes.

Conclusions

In this large consecutive AMD cohort, the prevalence of type 4 MNV was 2.00% at the patient level and 1.04% at the eye level, increasing to 2.60% and 1.35%, respectively, when probable cases were included. Definite type 4 MNVs exhibit a recognizable morphological pattern characterized by the hyperreflective oblique band (HOB), subretinal hyperreflective material (SHRM), ellipsoid zone loss, and either central posterior hyaloid fibrosis (CPHF) or posterior hyaloid central hyperreflectivity (PHCH) on structural OCT. Confirmation of the diagnosis relies on demonstrating continuous neovascular extension from the choroid to the preretinal space on OCTA (7).

The evaluation of suspicious cases further highlights the complementary role of multimodal imaging in both confirming and excluding the diagnosis of type 4 MNV. During follow-up, the structural features remained largely unchanged, whereas exudative activity showed variable changes, and visual acuity remained stable in most eyes. Overall, our findings indicate that type 4 MNV is an uncommon but structurally and angiographically distinct phenotype within the spectrum of AMD. Further prospective studies incorporating serial multimodal imaging are warranted to clarify its natural history, pathogenesis, and clinical significance.

Abbreviations

Abbreviation	Definition
AMD	Age-Related Macular Degeneration
CF	Counting Fingers
CPHF	Central Posterior Hyaloid Fibrosis
EZ	Ellipsoid Zone
HOB	Hyperreflective Oblique Band
IRF	Intraretinal Fluid
MNV	Macular Neovascularization
nAMD	Neovascular Age-Related Macular Degeneration
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
PHCH	Posterior Hyaloid Central Hyperreflectivity
PVD	Posterior Vitreous Detachment
RPE	Retinal Pigment Epithelium
SHRM	Subretinal Hyperreflective Material
SRF	Subretinal Fluid
VEGF	Vascular Endothelial Growth Factor
VMA	Vitreomacular Adhesion
VMT	Vitreomacular Traction

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University (approval no. 65; May 2, 2024). Owing to the retrospective design of the study and the use of anonymized patient data, the requirement for informed consent was waived by the Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain potentially identifiable clinical information but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MDB designed the study. MDB, MKÖ, ET, and NE collected the data. MDB and NE analyzed the data. MKÖ and ET drafted the manuscript. MDB and NE revised the manuscript. All the authors read and approved the final manuscript.

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Not applicable.

Declaration of Generative AI in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) and Claude (Anthropic) to improve the language, readability, and overall clarity of the manuscript. After using these tools, the authors critically reviewed and edited the content as needed and took full responsibility for the content of the publication.

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Figures

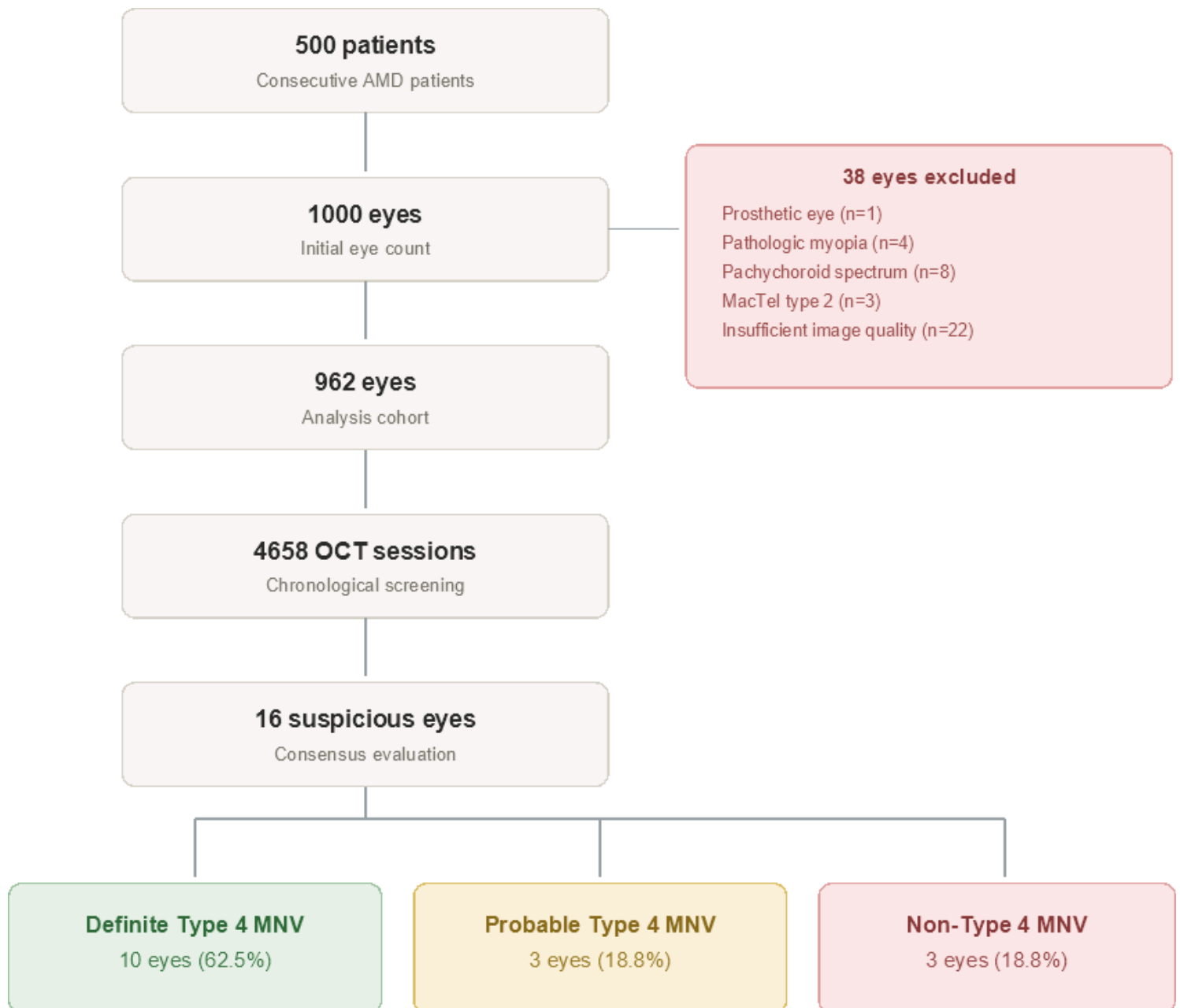


Figure 1

Study cohort selection and diagnostic classification workflow for type 4 MNV. AMD, age-related macular degeneration; OCT, optical coherence tomography; MNV, macular neovascularization.

Type 4 MNV Prevalence

Prevalence, % (95% CI)

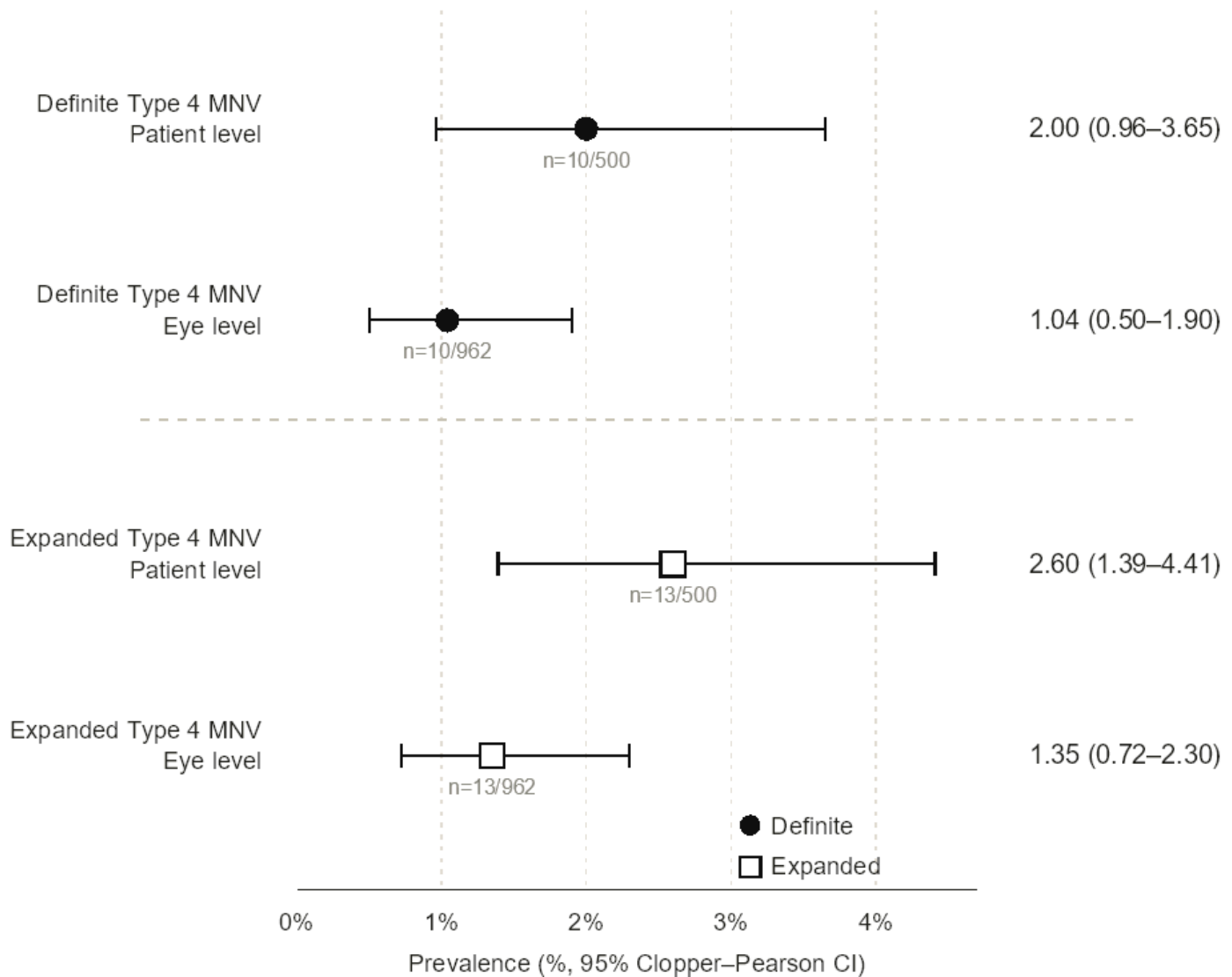


Figure 2

Forest plot showing the prevalence of type 4 MNV at the patient and eye levels. Point prevalence estimates and 95% Clopper–Pearson confidence intervals are presented for the definite and expanded (including probable cases) definitions. The filled circles represent definite prevalence estimates, whereas the open squares represent expanded prevalence estimates.

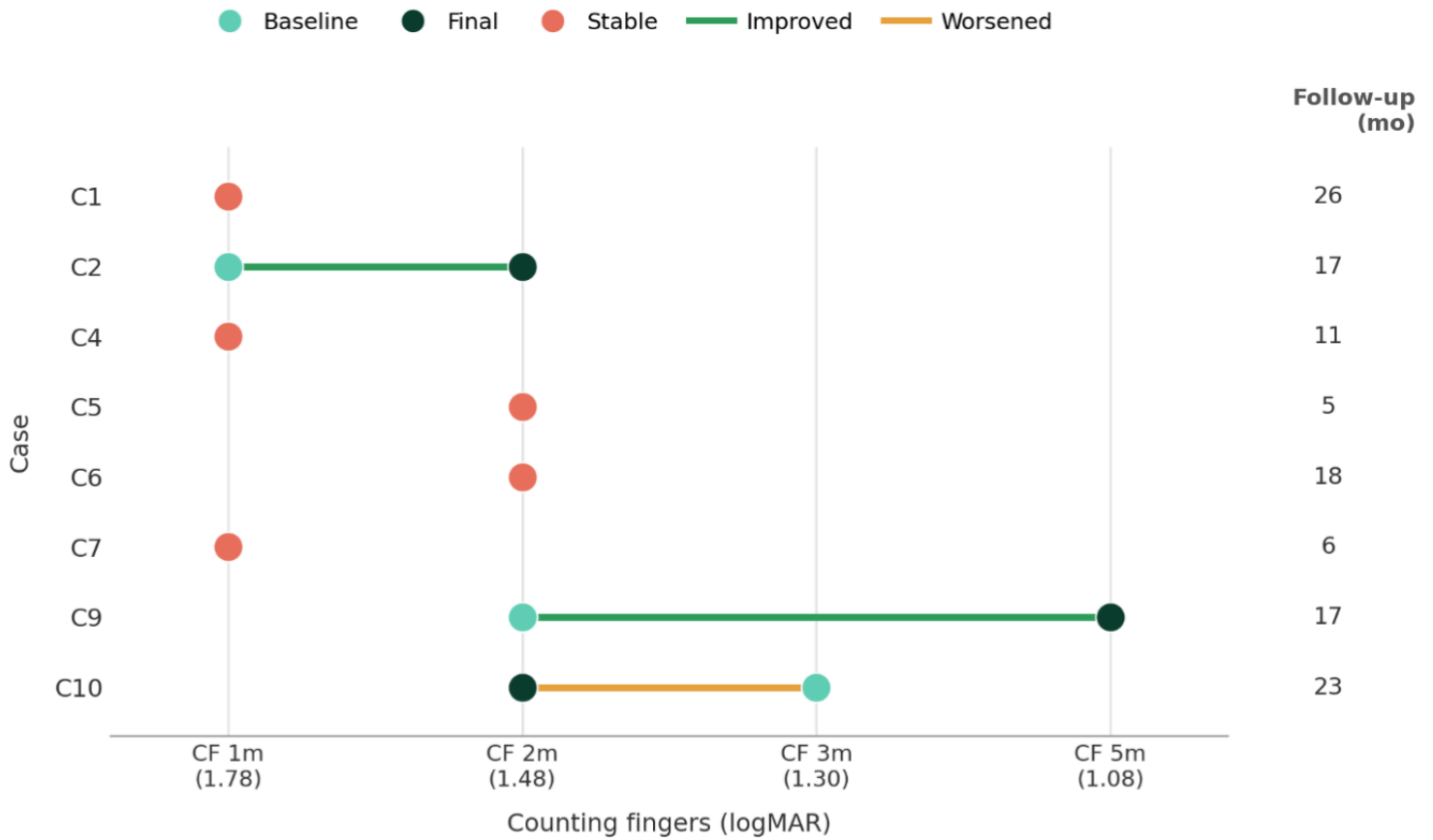


Figure 3

Change in visual acuity (counting fingers and logMAR) from the initial presentation to the final follow-up visit in eyes with definite type 4 MNV (C1–C10) that had at least one follow-up visit ($n = 8$). The baseline value represents visual acuity at the patient's initial presentation to the retina clinic rather than at the time of the Type 4 MNV diagnosis. The duration displayed next to each case indicates the follow-up interval (months) between the initial and final examinations. The counting fingers values were converted to logMAR values according to the convention of X-meter counting fingers $\approx$ Snellen X/60 (1 m = 1.78, 2 m = 1.48, 3 m = 1.30, 4 m = 1.18, and 5 m = 1.08 logMAR).

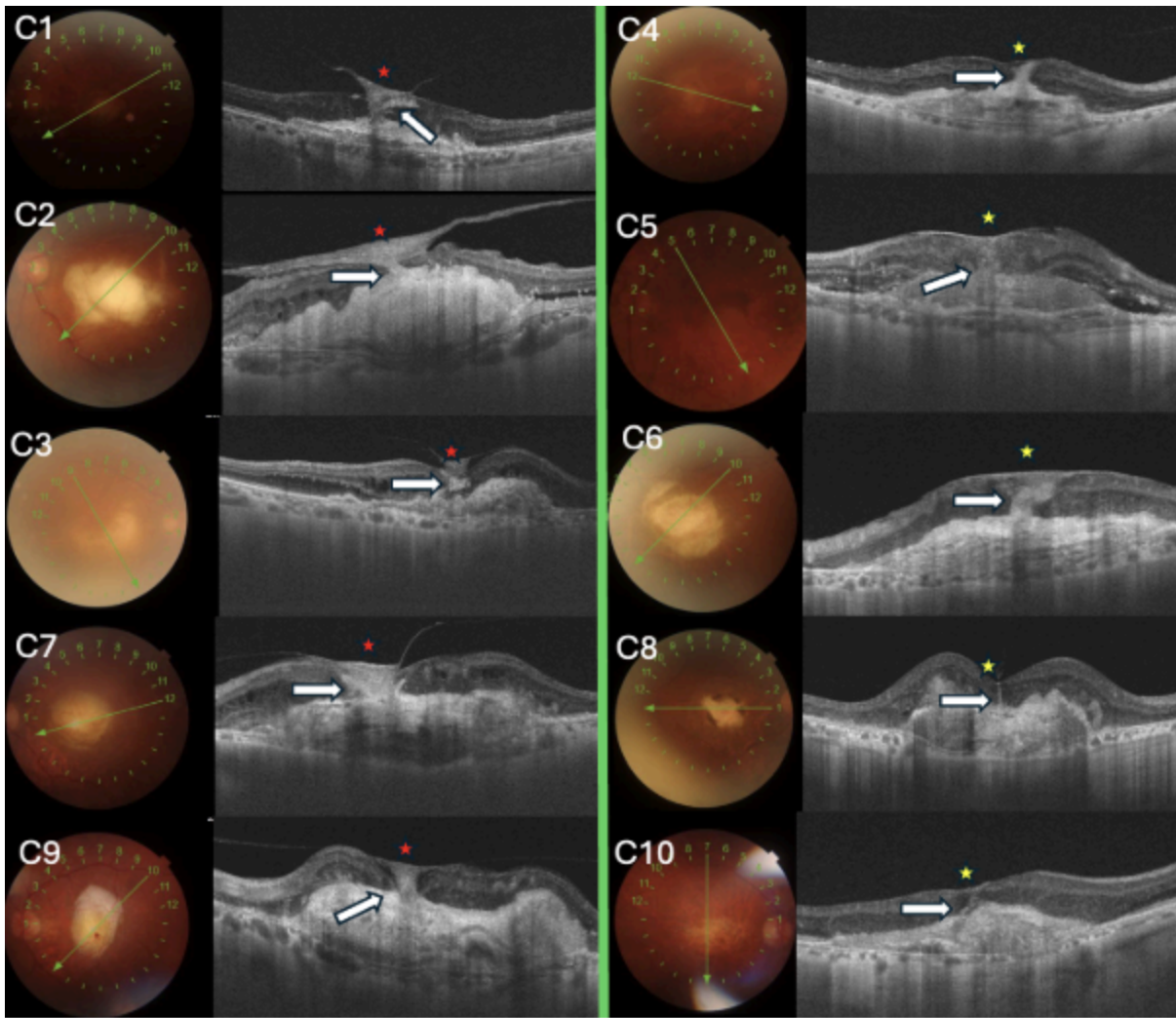


Figure 4

Fundus photographs and corresponding structural OCT images of all eyes with definite type 4 MNVs ($n = 10$). Left panel (red asterisks): eyes with central posterior hyaloid fibrosis (CPHF; C1, C2, C3, C7, and C9). Right panel (yellow asterisks): eyes with posterior hyaloid central hyperreflectivity (PHCH; C4, C5, C6, C8, and C10). The white arrows indicate the hyperreflective oblique band (HOB). A disciform scar was present in the fundus photographs of all the eyes.

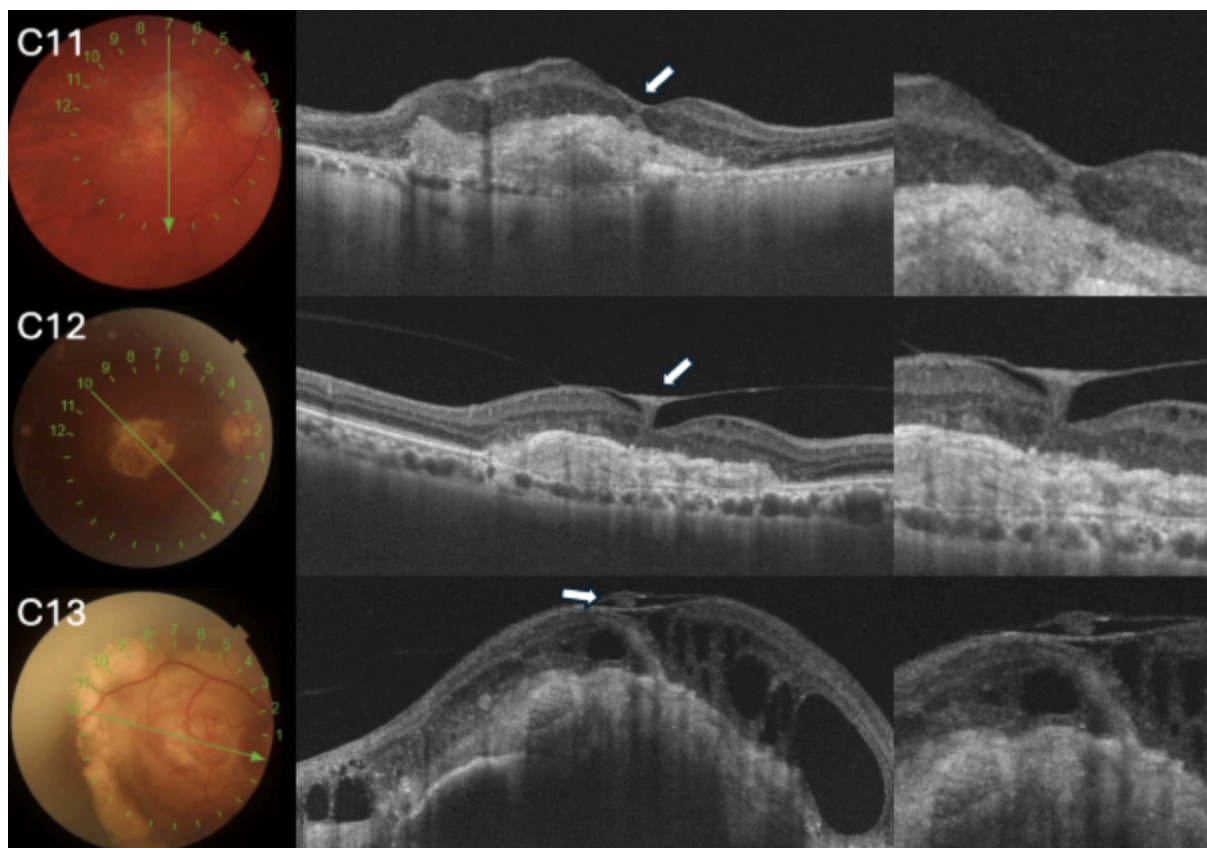


Figure 5

Color fundus photographs and corresponding structural OCT images of eyes with probable type 4 MNVs (C11–C13, $n = 3$). The white arrows indicate posterior hyaloid central hyperreflectivity (PHCH) in Patient C11 and central posterior hyaloid fibrosis (CPHF) in Cases C12 and C13. The magnified structural OCT images in the right panel demonstrate the hyperreflective oblique band (HOB) in all three eyes.

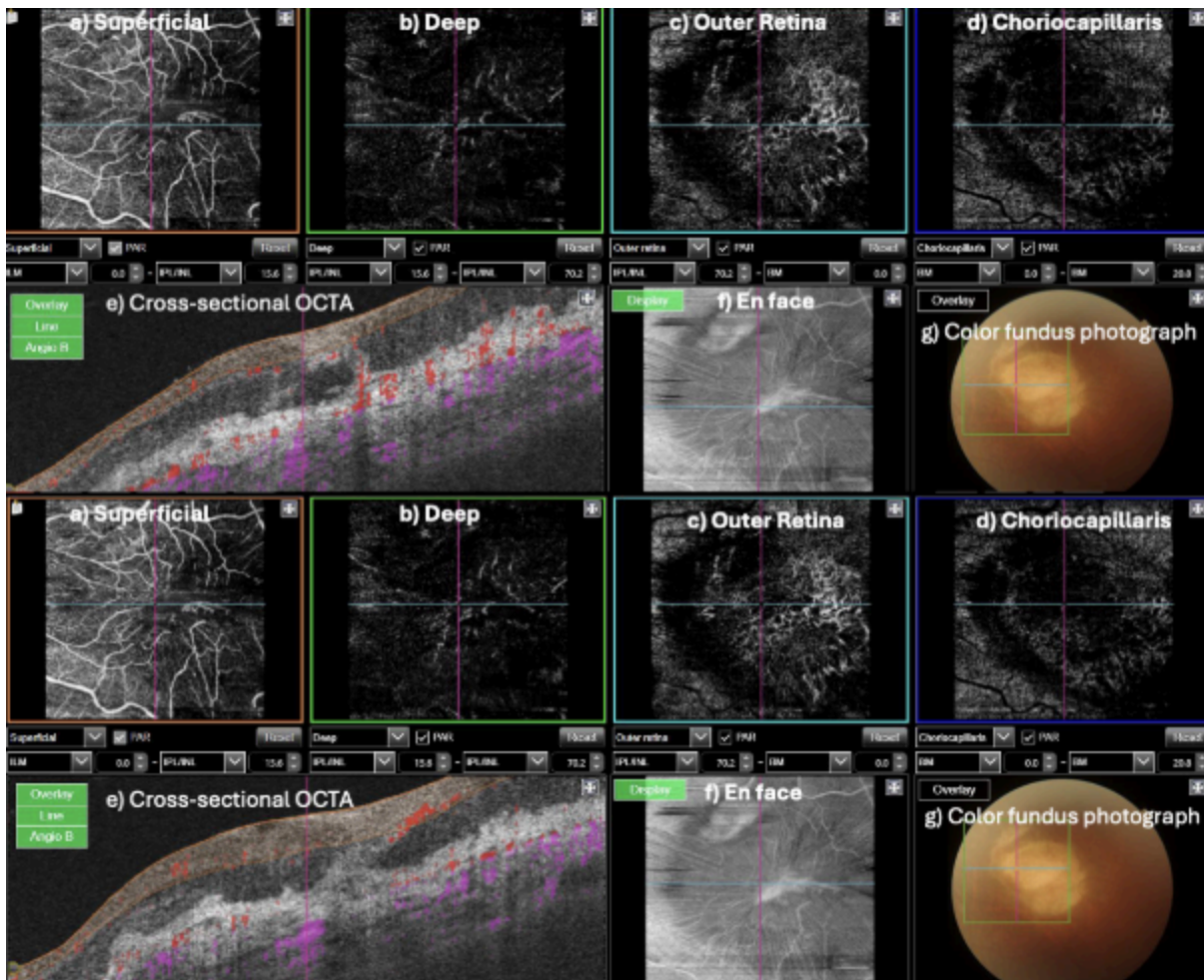


Figure 6

Multimodal OCTA images from Patient C6. The upper and lower panels show images acquired during the same visit from two different scan lines through the lesion. (a–d) En face OCTA images at different segmentation levels: (a) superficial capillary plexus, (b) deep capillary plexus, (c) outer retina, and (d) choriocapillaris. (e) Cross-sectional OCTA, (f) en face structural OCT, and (g) color fundus photograph. The cross-sectional OCTA images revealed a continuous flow signal extending from the choriocapillaris through the outer and inner retina to the preretinal space.