# Evolution of naive non exudative type 1 macular neovascularization detected by OCT angiography

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**Research Article**

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# Abstract

Background: The aim of the study was to explore the features of eyes with non exudative macular neovascularization (NE-MNV) . OCT angiography (OCTA) was used to evaluate the natural history of NE-MNV.

Methods: Retrospective case series. Patients with intermediate AMD (iAMD) were imaged using OCTA. Patients with NE-MNV were selected. The en face choriocapillaris slab was used to calculate the area and the flow of MNV.

Results: From October 2016 through October 2020, 211 patients with iAMD underwent OCTA. OCTA showed NE-MNV in 18 eyes. Nine eyes developed an exudative MNV during the follow-up. We considered the sensitivity and specificity of the area and flow measurements to predict exudation by the area under the receiver operating characteristic (AUROC). The AUROC of the basal area was 0,91 (0.78-0.99) and the the AUROC of the basal flow was 0,86 (0.68-0.99), showing discriminable ability for predicting exudation.

Conclusion: Based on our results, we found at high risk of exudation those eyes with larger areas of neovascularization. We recommend more frequent follow-up in those eyes and prompt treatment when exudation occurs.

retrospectively registered

Bari ethics committee approved the study protocol. Reference number is 7176


# Background

According to the most recent nomenclature on Age-Related Macular Degeneration (AMD) proposed by Spaide et al in 2019 we define macular neovascularization (MNV) as a neovascular pathology of the macula resulting from various causes [1]. In AMD Three types of neovascular growth patterns are considered: MNV type 1: growth of vessels starting from the choriocapillaris inside and below the retinal pigment epithelium. MNV type 2: neovascularization originating from the choroid and crossing the Bruch membrane and the retinal pigment epithelium (RPE) and proliferating in the subretinal space. MNV type 3: neovascularization originating from the retinal circulation, typically from the deep capillary plexus, which grows in the direction of the external retina [1, 2]. Non-exudative MNV (NE-MNV) is defined as type 1 MNV diagnosed by indocyanine green angiography (ICGA) and showing no hemorrhage or exudation. In fluorescein angiography (FA), NE-MNV appears as an early hyperfluorescent lesion defined in late times, without leakage or dye pooling (typical properties of active MNV). At ICGA, NE-MNV appears as a hyperfluorescent lesion in the early and intermediate times, and as a late phase hyperfluorescent fibrovascular plaque. NE-MNV presents an absence of detectable intraretinal or subretinal fluid in SD-OCT imaging [3–5]. Optical coherence tomography angiography (OCT-A) has emerged as a non-invasive technique for microvascular imaging of the retina and choroid [6, 7]. OCT-A technology uses the reflectance of laser light on the surface of moving red blood cells to accurately depict blood vessels

across different areas of the eye, thereby eliminating the need for intravascular dyes.The image produced is segmented into four areas: the superficial retinal plexus, the deep retinal plexus, the external retina and the choriocapillaris. OCT-A is a fast, non invasive, contrast free technique that can be particularly effective in identifying and monitoring non exudative MNV [8–10]. Currently, with the increased availability of OCTA, studies have begun to explore the incidence, prevalence and evolution of nonexudative MNV in asymptomatic eyes with AMD [11–13]. The purpose of this study was to explore the natural history of eyes with nonexudative MNV and to find characteristics that could serve as predictors of future exudation.

# Methods

The design of the study was a retrospective case series. 211 patients with macular drusen and/or pigmentary abnormalities classified as intermediate AMD (iAMD), underwent OCT-A imaging between October 2016 and October 2020, at the Ophthalmology Operating Unit of the “F. Miulli” General Hospital. 18 patients affected by treatment naive NE-MNV detected by OCT-A and more than one exam were selected. Time to symptomatic MNV was defined by the date the patient received intravitreal treatment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local review committee. Inclusion criteria were: the diagnosis of treatment naive type 1 NE-MNV, defined as an ipereflective neovascular complex on choriocapillaris slab OCT-A enface image,and confirmed flow signal in b-scan image; absence of hypo-reflective fluid in the intraretinal / subretinal space at SD-OCT; the presence of transparent dioptric means and stable fixation, to allow the acquisition of high quality OCT-A scans. Exclusion criteria included any disease except AMD (including retinal vascular disease,vitreoretinal interface disorders) and any other previous treatment for MNV, such as intravitreal injections of anti-vascular endothelial growth factor (VEGF), laser photocoagulation, photodynamic therapy or vitrectomy. Each enrolled patient underwent a complete ophthalmological examination, including best corrected visual acuity measurement, anterior segment examination, fundus biomicroscopy and OCT-A OCT-A was performed using the AngioVue RTVue XR Avanti model (Optovue, Fremont California). A 3x3 and a 6x6 mm surface scan, centered on the fovea, was performed in all patients. AngioVue is based on an A-scan rate of 70,000 scans per second, using a light source of 840 nm and a bandwidth of 50 nm. The automatic segmentation created by OCT-A was manually corrected for a correct visualization of the capillary plexus, the external retinal layers and the choriocapillaris, and to better identify the plane of the macular lesion. The OCT-A images and the corresponding B-Scans were examined to evaluate the localization of the lesion, calculate its surface (selected area) and the corresponding flow area. The area measurements were executed to determine if the size or the flow of the MNV correlated with exudation development. The slab used for visualization of the MNV was the choriocapillaris en face slab, with the upper limit situated 9 micron above the Bruch’s membrane and the lower boundary localized 31 micron beneath the Bruch’s membrane. Projection artifacts were removed for better visualization of the MNV. Area and flow measurements were based on choriocapillaris slab. Flow detection was evaluated by drawing a closed contour around the region of interest. The software automatically highlighted in yellow the areas of flow. The system reported the measurements of the selected area and the total flow area in

$mm^{-2}$. The scans obtained were also cataloged on the basis of the location and contour of the lesion. The outline was classified as "well defined" or "poorly defined". Localization was classified as "foveal" or "extrafoveal" according to the MPS terminology.

Data were reported as mean ± standard deviation or percentage for categorical variables. Wilcoxon matched-pairs signed-rank test was used to evaluate the equality of matched pairs of observations (baseline vs last follow-up). Mann-Whitney two-sample statistic was used to test the distribution of values between groups (group 1, NE-MNVs without evidence of exudation during the follow-up vs group 2, NE-MNVs that demonstrated exudation during the follow-up). Fisher exact test was used to evaluate associations between categorical data. A non-parametric Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the ability of AREA and FLOW in discriminating between patients with and without active disease. The area under the ROC curve was reported with 95% confidence interval. A p value of 0.05 or less was considered statistically significant. All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, Tex).

# Results

The demographic and clinical characteristics of patients with subclinical macular neovascularization are listed in Table 1 (placed at the end of the document file). They were enrolled in 18 eyes of 18 patients with NE- MNV. Nine patients didn’t show exudation during follow-up time (group 1), instead nine eyes developed active MNV with exudation (group 2). Mean follow-up was 20 ± 15 months. Mean age was 64 ± 18 years. All of the eyes in which a non exudative MNV was identified presented a type 1 MNV. In the eyes that have developed exudation 78% had an extrafoveal presentation of MNV, among the 9 eyes without exudation during the follow-up 44% had an extrafoveal NE MNV, usually with a well defined contour (89%). Figure 1 depicts an eye of an asymptomatic patient with a flat ped, OCTA en face slab image with removal of vessel projection artifacts demonstrates a small extrafoveal neovascular complex in choriocapillaris.

Table 1
Demographic and clinical characteristics

| | All | Group 1 | Group 2 | |
|---|---|---|---|---|
| | n = 18 | n = 9 | n = 9 | p |
| Age | 64 ± 18 | 61 ± 25 | 68 ± 5 | 0.508 |
| Ill defined contour | 28% | 11% | 44% | 0.294 |
| Extrafoveal | 61% | 44% | 78% | 0.335 |
| Area baseline (1) | 0.62 ± 0.52 | 0.28 ± 0.25 | 0.95 ± 0.50 | **0.003** |
| Area last follow-up (2) | 0.79 ± 0.66 | 0.46 ± 0.60 | 1.11 ± 0.57 | **0.024** |
| Area 2- Area 1 | 0.17 ± 0.51 | 0.18 ± 0.68 | 0.16 ± 0.32 | 0.480 |
| Area 2/Area 1 (%) | 174 ± 232 | 229 ± 326 | 119 ± 30 | 0.825 |
| Flow baseline (1) | 0.39 ± 0.29 | 0.22 ± 0.22 | 0.55 ± 0.25 | **0.009** |
| Flow last follow-up (2) | 0.45 ± 0.30 | 0.30 ± 0.28 | 0.60 ± 0.25 | **0.024** |
| Flow 2-Flow 1 | 0.06 ± 0.12 | 0.08 ± 0.08 | 0.04 ± 0.15 | 0.352 |
| Flow 2/Flow 1 (%) | 136 ± 67 | 160 ± 86 | 111 ± 29 | 0.058 |
| Follow-up (months) | 20 ± 15 | 15 ± 11 | 26 ± 16 | |
| Demographic and clinical characteristics of patients with subclinical macular neovascularization | | | | |

The eye shown in Fig. 2 demonstrated a small neovascular complex located adjacent to an area of atrophic retina, as seen by the enhanced choroidal signal owing to retinal pigment epithelium loss.

We evaluated if there were a correlation between the size of the lesion and the risk of exudation. We also explore whether there was a correlation with the flow within the area of the lesion and the risk of developing active disease. We considered the sensitivity and specificity of the area and flow measurements to predict exudation by the area under the receiver operating characteristic (AUROC). The AUROC of the basal area was 0,91 (0.78–0.99) and the the AUROC of the basal flow was 0,86 (0.68–0.99), showing discriminable ability for predicting exudation. We observed in both groups an increase in size and flow of the vascular network, but we found no grow rate dependent correlation between eyes that developed exudation and eyes that remained non exudative (P = 0.48, P = 0.52).

# Discussion

Neovascular AMD is the most common cause of vision loss in people over the age of 65 [14]. With the evolution of diagnostic imaging this portion of the population, at greatest risk of developing neovascular AMD, can be efficiently and effectively screened for MNV using OCT-A. Currently, dye angiography and SD

OCT remain the gold standard for the diagnosis and follow up of MNV, and these techniques have guided the approach to treating neovascular AMD for years. This approach was in fact based on "reactive" therapeutic regimens [15, 16]. However, dye angiography is an invasive method requiring a long time to perform, also providing only two-dimensional imaging and is not free from a series of risks (albeit with a low incidence) such as nausea, allergy and, rarely, anaphylaxis. In addition, FA has a low sensitivity for type 1 MNV, since these lesions present a poorly defined area of leakage both in the early and late times of angiography [2–5]. On the other hand, the SD OCT has a limited ability to discriminate the MNV themselves; this method is able to recognize the indirect pathological signs of neovascularization, such as serous exudation, elevation of the RPE and retinal thinning. Furthermore, SD OCT has limited specificity, since it is not always able to differentiate active MNVs from normal choroidal vascularity, fibrotic scars, and accumulation of lipids or fibrous material under the RPE. Finally, it can be difficult to distinguish NE-MNV from drusenoid retinal pigment epithelial detachments resulting from the confluence of soft drusen, as both appear as collections of moderately reflective material in the sub-RPE space at SD-OCT [17–20]. Recent studies have shown that OCT-A can accurately identify microvascular structures and that it can be used to classify the morphology of type 1, type 2 and type 3 MNV [20]. Using OCT-A the MNVs can be visualized with particular attention to the morphological details, thus allowing a qualitative and quantitative evaluation of the microvascular characteristics and a classification based on size, morphology, caliber of the vessels and the presence of retinal fluid [19]. The appearance of MNV does not depend on its activity and vascular loss, therefore both exudative and non-exudative forms are diagnosable with OCT-A [17–20]. Precise localization and measurement in MNV with OCT-A can be an effective tool for monitoring NE-MNVs and may contribute to therapy planning. In fact, repeated scans of the lesion allow an effective measurement of the growth rate in a faster and safer way than angiography. In our study OCTA imaging revealed 18 non exudative type 1 MNV in 211 eyes with intermediate AMD. In eyes where subclinical MNV was detected, exudation developed in 9 patients. The neovascular lesions were classified as type 1 MNV and all the lesions presented elevation of the RPE associated with the MNV. Usually MNV was associated with a flat ped in b-scan imaging (Fig. 1), sometimes the RPE elevation was at the margin of an area of geographical atrophy (Fig. 2). In all eyes that showed exudation, we found a larger basal and final area of the lesion and a larger flow area. Both groups exhibited a similar growth rate, so the MNVs that developed exudation were probably in a more advanced stage. It is our interest to follow in the next months the patients who did not show exudation to understand if a further increase in area and flow coincides with an activation; this could be useful to understand if there is an area of the lesion beyond which the exudation is very likely. It is common practice in clinical practice not to treat asymptomatic MNV as they are not associated with intra or sub retinal fluid, as they do not possess the criteria for eligibility for treatment with anti VEGF [18]. However, the widening of the surface of the lesion could represent a sign of progression to more aggressive forms of the disease. Laighinhas et al.[20] found in the reviewed studies about 25% of NE-MNV lesions became exudative. Some authors have shown that enlargement of NE-MNV may be predictive of exudation, whereas others have not. In our study the area and the flow of nonexudative lesions seems to be an important predictive factor for exudative disease. However, OCT-A imaging has several limitations, such

as poor fixation by the patient and projection artifacts. A limitation of this study is the number of patients, since non exudative MNV is an uncommon form of AMD.

## Conclusion

In conclusion, we have described the characteristics of non exudative naive OCT-A MNV and we recommend close follow-up of these eyes and prompt treatment when exudation occurs. It seems reasonable to consider at high risk of exudation those eyes with larger areas of neovascularization. The use of OCT-A allows the clinician to identify non exudative MNV and can be considered a useful tool to follow disease progression. Further prospective studies are needed to understand the evolution of these subclinical lesions so that we can better understand disease progression and design preventive strategies to prevent exudation.

## Abbreviations

- NE-MNV non exudative  macular neovascularization
- OCT : Optical coherence tomography
- OCTA: Optical coherence tomography angiography
- iAMD: intermediate Age-Related Macular Degeneration
- AUROC: area under the receiver operating characteristic
- MNV: macular neovascularization
- AMD: Age-Related Macular Degeneration
- RPE:  retinal pigment epithelium
- ICGA: indocyanine green angiography
- FA: fluorescein angiography
- SD-OCT: Spectral domain optical coherence tomography
- VEGF: Vascular endothelial growth factor
- MPS: Macular Photocoagulation Study
- ROC: Receiver Operating Characteristic

## Declarations

Ethics approval and consent to participate: all procedures were conducted in accordance with the ethical standards established by the tenets of Declaration of Helsinki. All experimental protocols were approved by Bari ethics committee

Bari ethics committee approved the study protocol: reference number is 7176.

Informed consent was obtained from all subjects.

Consent for publication: Informed consent was obtained from all patients.

Availability of data and materials: All data generated or analyzed during this study are included in the article and in the table. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions: ML analyzed the patient data and the OCT-A imaging and was one of the major contributor of the manuscript. LMF interpreted and analyzed the OCT-A images. DAG was one of the major contributor in writing the manuscript and prepared the figured. GM revised the manuscript and the bibliography. MVC carried out bibliographic research. EN performed all the OCT-A and selected the patients. TMF corrected and revised the manuscript. All authors read and approved the final manuscript.

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# Figures

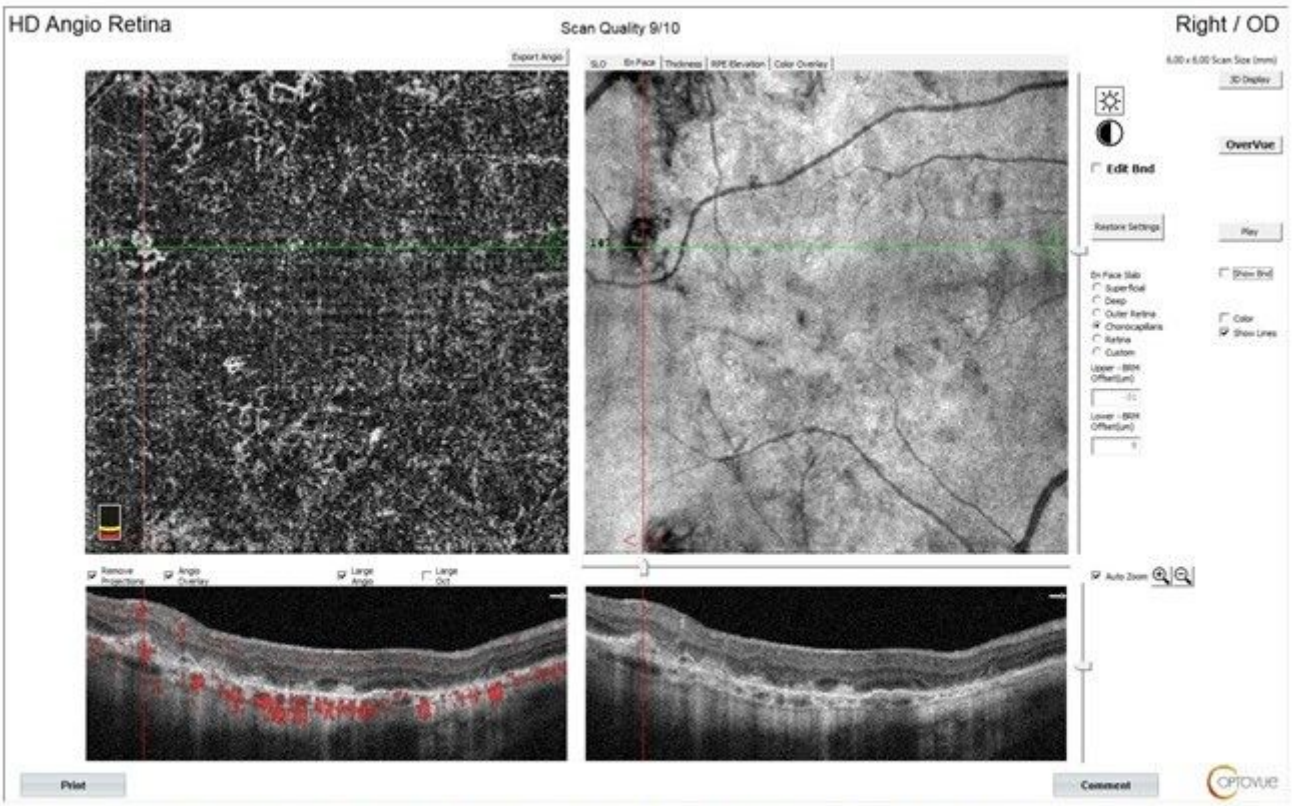
Figure 1: small extrafoveal neovascular complex in choriocapillaris


OCT angiography (OCTA; 3X3 mm) of an asymptomatic eye from a patient with nonexudative age-related macular degeneration. OCTA en face slab image with removal of vessel projection artifacts demonstrates a small extrafoveal neovascular complex in choriocapillaris.

## Figure 1

See image above for figure legend

Figure 2: small neovascular complex l adjacent to atrophic retina




OCT angiography (OCTA; 3X3 mm) of an asymptomatic eye from a patient with nonexudative age-related macular degeneration. A small neovascular complex is located adjacent to an area of atrophic retina, as seen by the enhanced choroidal signal.

## Figure 2

See image above for figure legend