Quiescent Macular Neovascularization: Clinical Characteristics, Multimodal Imaging Features and Current Recommendations

Omer Karti[1], *Ali Osman Saatci*[2]

ABSTRACT

The term quiescent macular neovascularization (MNV) was introduced to describe new vessel formation located beneath the retina pigment epithelium without any exudation and/or hemorrhage in association with age-related macular degeneration on repeated optical coherence tomography (OCT) examinations for at least six months apart. This entity was established with the help of newer diagnostic tools such as OCT and/or OCT-angiography prior to occurrence of any visual impairment. Though its diagnosis becomes relatively easier thanks to multimodal imaging techniques, management of quiescent MNV is still uncertain and under debate among retina specialists. We aimed to overview the clinical characteristics of quiescent MNV, its multimodal imaging features, and management in this mini-review.

Keywords: Age-related macular degeneration, Non-exudative macular neovascularization, Quiescent macular neovascularization, Subclinical macular neovascularization, Type 1 macular neovascularization.

INTRODUCTION

Age-related macular degeneration (AMD) is a progressive disease of the macula that causes irreversible central vision loss in advanced age worldwide.[1,2] The disease has a significant socioeconomic impact and is a very important public health problem as the disease is expected to affect approximately 300 million people by 2040.[3] The pathogenesis of AMD is multifactorial and quite complicated and is associated with a dysregulation in many pathways including the angiogenic, complement, extracellular matrix, and inflammatory pathways.[1] AMD is clinically classified into two main forms as non-exudative (dry AMD) and exudative (wet AMD). Non-exudative AMD is the most common form, affecting approximately 75-85% of the patients, and is sub-classified as early, intermediate, and advanced disease stages according to the number and size of drusen and degree of retina pigment epithelium (RPE) alterations and the presence of geographic atrophy.[4] The exudative form affects approximately the 10-15% of AMD patients but is responsible for 80% of the AMD-related central visual impairment and even legal blindness. In this advanced form of AMD, vision loss occurs due to abnormal growth of blood vessels, called neovascularization (NV), originating from the choroid and extending into the sub-RPE, sub-retinal space, and outer retinal layers.[4-6] The term choroidal NV (CNV) is somewhat inappropriate as the origin of neovascular tissue can also be from the deep capillary plexus in the outer retina, apart from the choriocapillaris. Therefore, CONAN (Consensus on Neovascular Age-Related Macular Degeneration Nomenclature) study group recommends the terminology of ‘’macular NV (MNV)’’ instead of ‘’CNV’’. The term MNV is generally used to describe NV in the macula due to any cause, independent of the origin of neovascular tissue.[7] Invasive and non-invasive fundus imaging techniques yield important clues to differentiate the various types of MNV.[7,8] Dye angiography with fluorescein (FA) and/or indocyanine green (ICGA) assists the clinicians to identify the type of MNV by demonstrating both the retinal and choroidal vasculature and provides important data on the possible pathophysiology of these lesions.[9] On the other hand, novel

1- MD., İzmir Democracy University, Department of Ophthalmology, İzmir, Türkiye.

2- MD., İzmir Dokuz Eylul University, Department of Ophthalmology, İzmir, Türkiye.

Received: 01.03.2023
Accepted: 02.03.2023

J Ret-Vit 2023; 32: 1-8

DOİ:10.37845/ret.vit.2023.32.1

Correspondence Adress:
Ali Osman Saatci
Mustafa Kemal Sahil Bulvarı. No: 73 A Blok, Daire: 9, Narlıdere, 35320, İzmir/Türkiye

Phone: +90 532 743 7071
E-mail: osman.saatci@yahoo.com

non-invasive imaging techniques such as optical coherence tomography (OCT) and OCT-angiography (OCTA) open the door of a new era in detecting the neovascular network even make it posssible to reveal the previously undetected neovascular lesions, and sub-classify its types. In addition, OCTA becomes a front-runner technique to detect the MNVs earlier and facilitate the management of exudative or non-exudative AMD, and help monitoring the progression of the disease process.[4,8] MNVs can be classified as type 1 (known as occult CNV), type 2 (known as classic CNV), type 3 (retinal angiomatous proliferation), mixed-type (type 1 and 2 variant), polypoidal choroidal vasculopathy (type 1 variant), sub-threshold exudative and quiescent MNV.[4] The term "treatment-naïve quiescent MNV" was first used by Querques et al.[10] However, the term has changed over the past years. Several studies examining its incidence, prevalence, and natural course have proposed various terms such as "quiescent", ''subclinical", and "non-exudative" MNV. This mini-review aims to briefly overview its definition, possible pathogenesis, distinctive clinical characteristics, and multimodal imaging features of quiescent MNV, and discuss its current management. Previous and recent studies were searched through PubMed with the general terms ''age-related macular degeneration," and ''macular neovascularization," and specific terms like ''type 1 macular neovascularization," ''subclinical MNV," ''treatment-naïve quiescent macular neovascularization," and ''quiescent macular neovascularization". Additionally, appropriate references given in those studies were also examined and included in our mini-review where appropriate.

Definition, Pathogenesis, and Multimodal Imaging Characteristics of Quiescent MNV

The entity of non-exudative MNV was identified by Hanutsaha et al.[9] for the first time in 1998 with the help of ICGA. In their ICGA study comprising of 432 non-exudative AMD eyes with exudative AMD in the fellow eye, the authors reported the presence of a plaque or focal spot unaccompanied by exudation in approximately 11% of the eyes. However, the term ''quiescent MNV'' was first used by Querques et al.[10] in 2013, approximately 15 years after its original description with the help of OCT features. The authors characterized quiescent MNV as type 1 MNV secondary to AMD without any exudation or hemorrhage (intraretinal or subretinal) on repeated OCT examinations during two consecutive visits for at least 6 months apart. Interestingly, presence of MNV was actually shown in postmortem histopathological studies in eyes without significant NV and exudation on dilated fundus exam about half a century ago.[11,12] Quiescent MNV is also observed in other macular disorders including angioid streaks, geographic atrophy, large colloid drusen, and pachychoroid neovasculopathy.[13-16] Though the prevalence of quiescent MNV is not exactly known, its estimated prevalence is ranged from 1.58% to 2.52% in AMD patients with OCT and OCTA.[10,17]

The pathogenesis of quiescent MNV has not been fully elucidated. In a histological study, Grossniklaus et al.[5] reported that type 1 MNV showed similar histological features with the native choriocapillaris. Quiescent MNVs have tangled networks or filament-like structures, and mature vasculature with tight junctions between the endothelial cells that prevent exudation. However, it may grow over time and cause exudation.[18,19] On the other hand, exudative MNV has much rigid, much straighter, and much thicker vessels without tiny capillaries. In an experimental study by Miller et al.[20], the correlation between the morphological properties of induced MNVs and the amount of leakage on FA was investigated and it was determined that the ultrastructural features of leaky and non-leaking subretinal vessels were identical. However, the researchers suggested that the presence or absence of fluid accumulation from MNV might be associated with extravascular components of the subretinal environment. Additionally, Miller et al.[20] proposed that MNV might represent a regressed form of new neovascular formation.

The diagnosis of quiescent MNV can be confirmed by traditional imaging techniques including FA, and ICGA as previous studies already established and it can be detected as late-phase-speckled hyperfluorescent lesions without well-demarked borders on FA. Unlike occult type 1 MNV, late-phase leakage of undetermined source or dye pooling in the subretinal area is not observed. ICGA findings consist of a hypercyanescent vascular network or plaque on mid-late phase frames similar to occult type 1 MNV. OCT is a very valuable diagnostic tool for visualizing the lesion as well as evaluating the findings of activation such as exudation during the follow-up visits. On OCT quiescent MNV is characterized by irregularly and slightly elevated RPE from the underlying intact Bruch membrane (double layer sign) without any hyporeflective looking fluid accumulation in the intraretinal/subretinal space. Other OCT findings include moderately reflective material collections beneath the RPE and marked visualization of the hyperreflective Bruch membrane. Additionally, there should be no signs of MNV activation such as poorly defined lesion boundaries, midreflective exudative material, and intraretinal hyperreflective flecks.[10,21,22] The importance of OCTA has been established in detecting the presence of MNV in association with various retinal diseases as OCTA

contributes reaching out the diagnosis of MNV by directly visualizing the neovascular network with good sensitivity (81.8%) and specificity (100%).[17] Moreover, the detection rate of quiescent MNV with OCTA is higher than with the conventional dye angiography. Carnevali et al.[17] reported in an OCTA study on 15 eyes with treatment-naïve quiescent MNV that the neovascular network was well-defined in 11 eyes, while 4 eyes had poor-defined neovascular network borders that could be distinguished from the normal choroid by a dark halo. The multimodal imaging features of the fellow eye of a 65-year-old woman with an asymptomatic quiescent MNV who received multiple anti-VEGF agent injections for her right eye with wet AMD are illustrated in Figure 1.

Natural Course of the Quiescent MNV

When a quiescent MNV is discovered exudation time and thus the need for treatment is a matter of interest. The risk of exudation was higher in eyes with quiescent MNV when compared to eyes without any NV during the course. Main studies investigating clinical features and natural course of quiescent MNV are summarized in Table 1. In a prospective, observational OCTA study, Carnevali et al.[17] investigated the natural course in 15 eyes of 14 patients with treatment-naïve quiescent MNV during a follow-up of one year. Only in one eye (6.6%) clinical activation was observed and MNV was noted in two of 14 patients at baseline, and in three patients at 6 and 12 months. Ten of 14 eyes had well-defined borders and there was foveal involvement in eight eyes. Interestingly, MNV area showed enlargement in all eyes (Three of 14 eyes at 6 months and ten of 14 eyes at 12 months) when compared to the baseline MNV area. However, vessel density of the MNVs remained stable. The authors demonstrated that the biological activity of the neovascular network was not accompanied with the clinical activity and suggested that the absence of exudation was probably due to lack of a change in vessel density despite the growth in MNV. In another study, Fukushima et al.[23] investigated the presence of fluid or type 1 MNV with OCT and OCTA in 38 eyes of 37 patients with treatment-naïve quiescent MNV. Twelve eyes (30%) developed exudation during a mean follow-up of two years. Though not statistically significant, MNV size enlarged in eyes that developed exudation during the visits. Bailey et al.[24] compared the risk of developing exudative

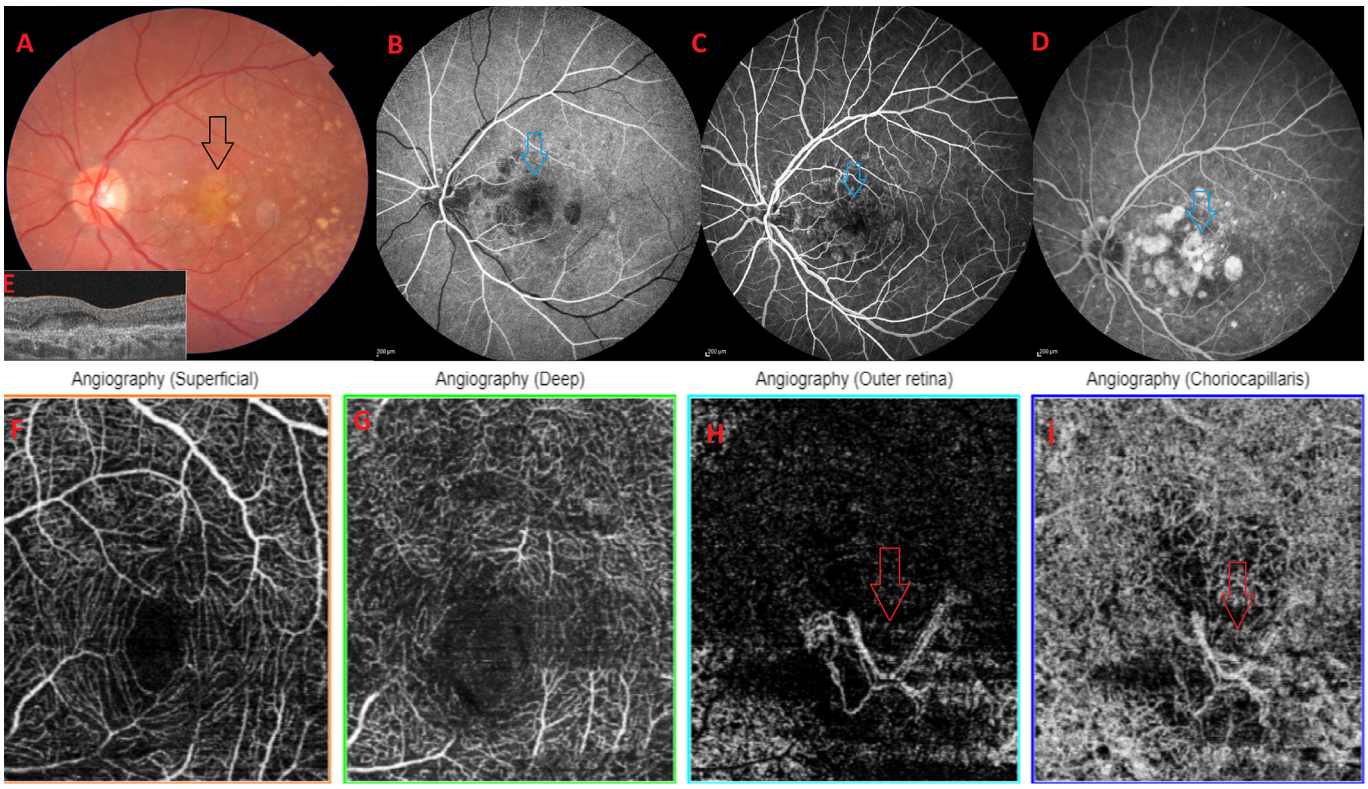

Figure 1: *Left quiescent MNV in a 65-year-old female patient with non-exudative AMD. Color fundus picture depicting the retina pigment epithelial changes with soft-confluent drusen (black arrow) (A). FA images (B-D) showing hypo-fluorescent lesion in early-mid phase angiogram (B, C), with late-phase staining (D) (blue arrows). OCT image (E) illustrating the irregular, slightly elevated RPE from the underlying intact Bruch membrane with some reflective material depositions beneath the RPE. OCTA images of the superficial (F) and deep (G) slabs revealing the normal retinal vasculature but outer retina (H) and choriocapillaris (I) slabs demonstrating the subfoveal neovascular network (red arrows).*

Table 1: Key findings of the Main Studies Investigating the Clinical Features and Natural Course of Quiescent MNV

Study, year, design, and mean follow-up	**Ancillary diagnostic tools used in the study**	**Main findings of the studies**
Hanutsaha et al.[9] 1998 Cohort study 21.7 months	FA and ICGA	- 432 eyes with non-exudative AMD - 386 eyes had drusen with normal IGCA (89%) - 46 eyes had abnormal ICGA (36 plaques and 10 focal spots) - The rate of non-exudative MNV: 11% (46 eyes) - Exudative changes: 6 of 58 eyes (10%) in normal ICGA eyes 9 of 38 eyes (24%) in abnormal ICGA eyes
Querques et al.[10] 2013 Case series 23.8 months	ICGA, OCT, microperimetry, and preferential hyperacuity perimeter	-11 eyes of 11 patients quiescent MNV due to AMD -Significantly larger MNV lesion area on mid-late phase ICGA at follow-up compared with earliest measurements nearly 23 months before (3.52 mm2 vs. 3.24 mm2, p= 0.01). -Significant correlation between functional impairment (metamorphopsia severity) and ICGA extension of quiescent MNV. -Significant correlation between microperimetry and preferential hyperacuity perimeter based on location of affected areas.
Carnevali et al.[17], 2018 Prospective, consecutive case series 12 months	FA, ICGA, OCT and OCTA	- 15 eyes of 14 patients with quiescent MNV (14 eyes at baseline, 2 eyes at 6 months and 3 eyes at 12 months) -The rate of clinical activation at 1 year → 6.6% (1 of 15 eyes) -Well defined MNV margin → 10 of 14 eyes (71%) -Foveal involved MNV → 8 of 14 eyes -Significantly increase in MNV area compared with baseline measurements → 13 of 14 eyes (3 eyes at 6 months and 10 eyes at 12 months) →1.511mm^2 at baseline, 1.769 mm^2 at month 6 and 1.930 mm^2 at month 12. -No change in vessel density in MNV during the follow-up period.
Bailey et al.[24] 2019 Prospective, observational study 24 months	OCT and OCTA	-63 patients with dry AMD in the study eye and exudative AMD in fellow eye -Non-exudative MNV → 10 of 63 eyes (5 eyes at baseline examination and 5 eyes during follow-up visit). - The rate of mean MNV growth → 20% per month -Development of exudation in eyes with quiescent MNV → 8 of 10 eyes with a mean time of 8 months. -Development of exudation in eyes without quiescent MNV → 6 of 53 eyes -The risk of subsequent exudation in presence of quiescent MNV in one eye → 18.1-fold Cox proportional hazard
Fukushima et al.[23] 2021 Retrospective study 25.1 months	OCT and OCTA	- 38 eyes of 37 patients with quiescent MNV - The rate of exudation in quiescent MNV eyes during a mean 2-year follow-up period → %31.6 (12 eyes) - Larger MNV size in eyes developing exudation
Querques et al.[26] 2021 Retrospective study 22 months	FA, ICGA, OCT and OCTA	-31 eyes of 28 patients with quiescent MNV due to AMD -The rate of stable quiescent MNV → 21 of 31 eyes (68%) -The rate of short-term activation (before 6 months) → 4 of 31 eyes (13%) -The rate of late activation (after 6 months) → 6 of 31 eyes (19%)

*Abbreviations: AMD, age-related macular degeneration; FA, fluorescein angiography; ICGA, indocyanin green angiography; MNV, macular neovascularization; OCT, optical coherence tomography; OCTA, OCT-angiography.

MNV between the eyes with or without quiescent MNV in a prospective observational OCTA study. Sixty-three patients comprised the study group and the patients were followed up for two years. Mean age of the patients was 78 years and 60.3% of them were female. The authors noted exudation in eight of 10 eyes with quiescent MNV over a mean period of eight months during the follow-up. On the other hand, exudation was observed in only six of the remaining 53 patients without quiescent MNV. The authors estimated that quiescent MNV presence in one eye increased the risk of subsequent exudation approximately 18-fold Cox proportional hazard analysis. Yang et al.[25] evaluated the presence or occurence of subclinical MNV in eyes with unilateral non-exudative AMD through 2 years in a prospective cohort study and furthermore analyzed the risk of developing exudation and relationship between the neovascular lesion size and occurrence of the exudation. The study included 227 patients (intermediate AMD: 154 eyes and late AMD: 73 eyes). Subclinical MNV was detected in a total of 42 eyes, including 30 eyes (13.2%) at the initial imaging and 12 eyes (%8.9) at the follow-up. Exudation was observed in 19 of 191 eyes during the follow-up and 14 of them had pre-existing subclinical MNV. Exudation incidence was 34.5% in subclinical MNV. Markedly, exudation risk was approximately 13-fold higher in eyes with subclinical MNV compared to eyes without it. Moreover, the association between the risk of developing exudation and the lesion size alone was not meaningful. Thus, the authors recommended closer follow-up in eyes with subclinical MNV due to the high risk of exudation. Querques et al.[26] retrospectively investigated the natural course, clinical and anatomical outcomes in 31 eyes of 28 AMD patients with a quiescent MNV (mean age 75 ± 9 years) during a follow-up of at least a year. Eyes were classified into two groups according to the activation time as the eyes with short-term activation (activation before six months) and eyes with no or late activation noted after 6 months. Twenty-one of 31 study eyes did not exhibit activation (68%) while four eyes (13%) developed short-term activation and six (19%) developed late activation. The authors noticed that eyes with short-term activation had significantly higher neovascular network growth rates and greater perfusion density. The features of a patient who has quiescent MNV in the right eye without any sign of exudation during the follow up of 15 months and exudative AMD in the fellow eye are seen in Figure 2 and 3.

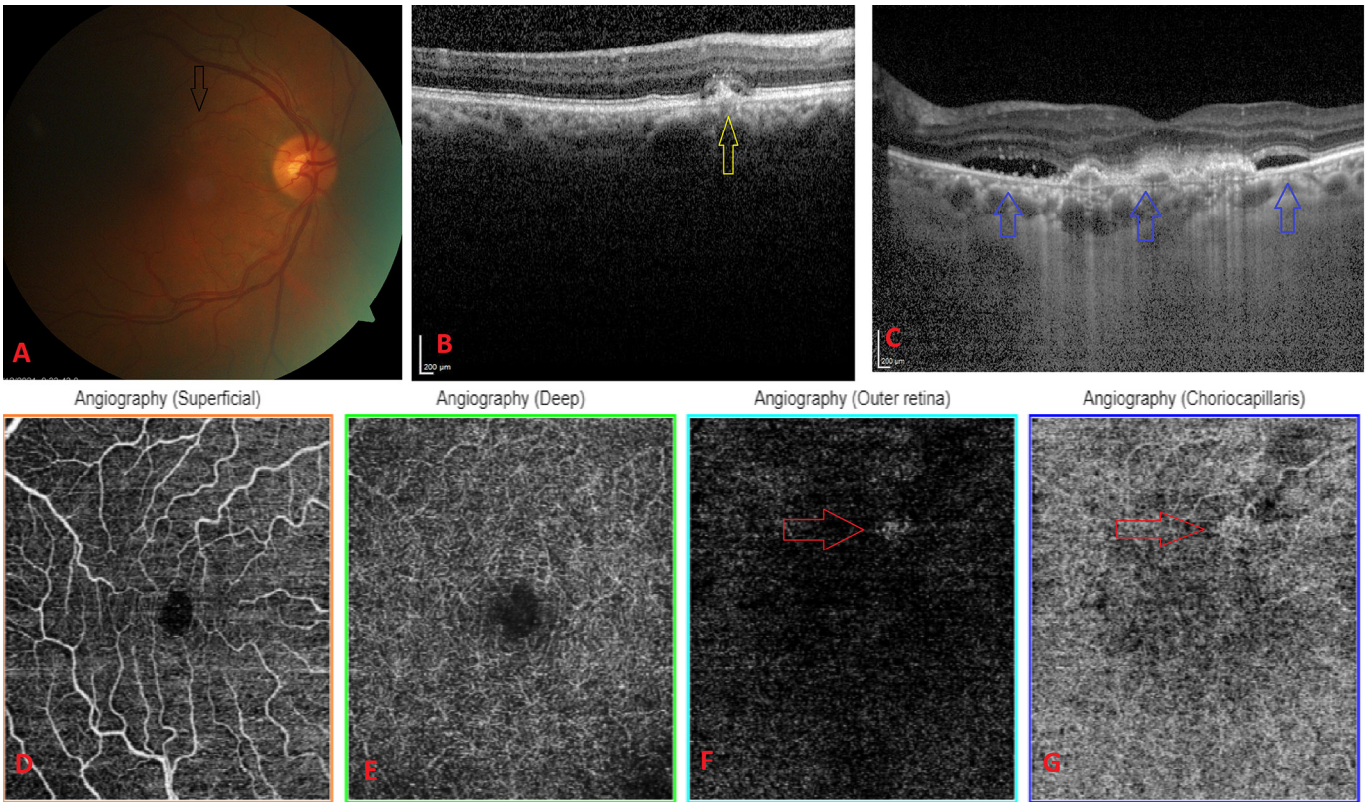

Figure 2: *Right quiescent MNV in the right eye and exudative MNV in the left eye. Color fundus picture (A) showing the RPE changes (black arrow). OCT image of the right eye (B) depicting the irregularly elevated RPE with moderately reflective material collections under the RPE (yellow arrow), and left eye (C) showing exudative MNV (blue arrows). OCTA images of superficial (D) and deep (E) slabs illustrating the normal appearance, but outer retina (F) and choriocapillaris (G) slabs showing the tiny extrafoveal neovascular network (red arrows).*

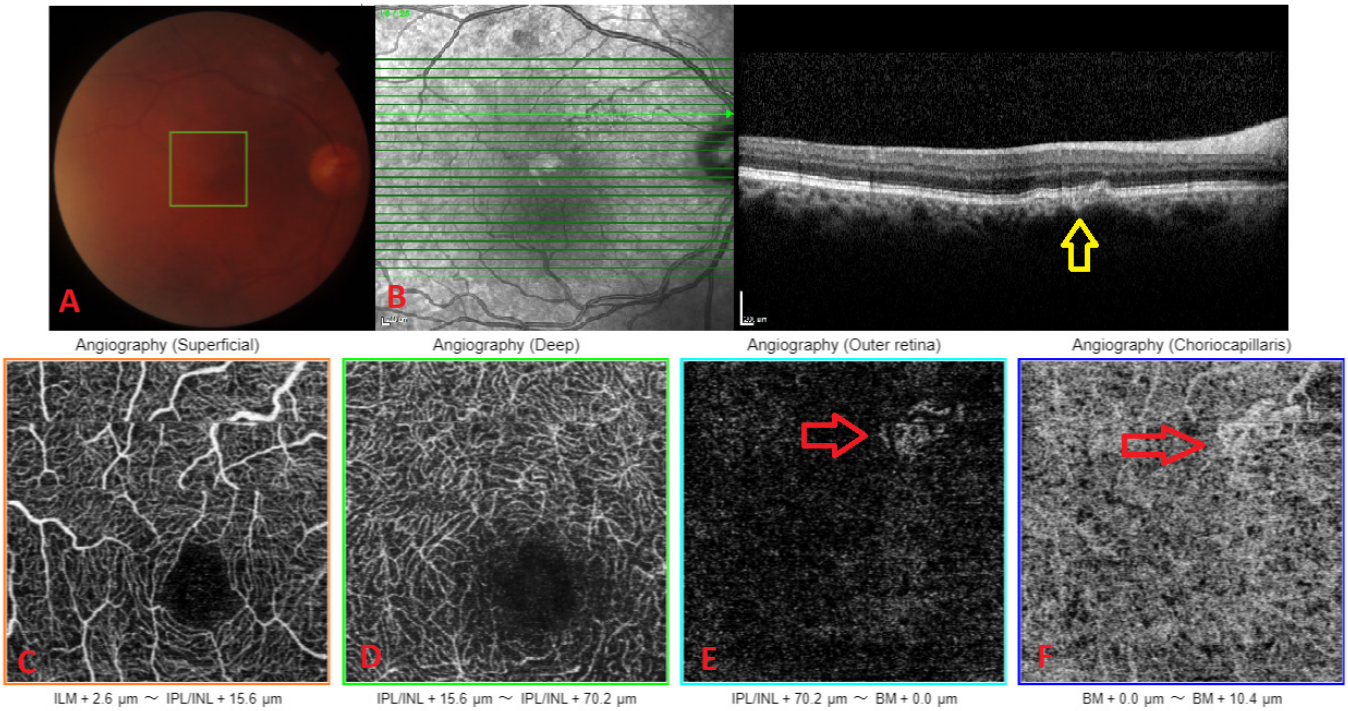

Figure 3: *15 months later with frequent control visits. Color fundus picture (A) featuring the RPE changes, OCT section (B) showing the irregularly elevated RPE with moderately reflective material collections under the RPE (yellow arrow), OCTA images of the superficial (D) and deep (E) slabs depicting the normal appearance whereas outer retina (F) and choriocapillaris (G) slabs revealing a slightly enlarged neovascular network without any activation.*

Management of the Quiescent MNV

There is no widely accepted treatment protocol for the management of patients with quiescent MNV and it is still uncertain whether these patients should be treated or observed. One suggestion is to treat early with anti-VEGFs to achieve more favorable outcomes by avoiding the possible exudation and its sequelae such as fibrosis and outer retinal disorganization. On the contrary, the presence of a quiescent MNV may have a protective role in eyes with intermediate AMD by reducing the RPE atrophy rate. This is because of its histological features resembling the native choriocapillaris which are beneficial to the overlying RPE and photoreceptor layer by providing metabolic and oxygen support and hormonal effects. Therefore, it can be argued that anti-VEGF treatment-induced vessel regression may result in RPE and outer retinal atrophy.[5,27] Heier et al.[28] investigated whether the intravitreal aflibercept treatment provides a protective effect on conversion of high-risk eyes with non-exudative AMD to exudative AMD (PRO-CON study). High-risk eyes were described as follows; intermediate AMD in one eye (>10 intermediate size drusen, > 1 large druse, and/or RPE changes) and neovascular AMD in the fellow eye. This prospective, single-blind study included 128 eyes with high-risk dry AMD, and participants were randomly divided into two treatment groups as intravitreal aflibercept and sham injection. All participants were treated quarterly and followed up for 24 months. PRO-CON study did not show a beneficial effect of prophylactic intravitreal aflibercept injection on avoiding the conversion to exudative AMD in high-risk eyes at the 24 month. In this study, six of 63 eyes (9.52%) receiving the intravitreal aflibercept and seven of 64 eyes (10.9%) in the sham group developed exudative AMD. Although the rate of exudative AMD was higher in eyes with quiescent MNV, there was no difference between the treatment (3 of 11 eyes; 27%) and sham groups (4 of 13 eyes; 31%) (p=0.79). Additionally, the authors emphasized that the development and progression of geographic atrophy were not affected by aflibercept treatment.

The alternative approach is the observation with strict monitoring for early detection of the exudation from MNV. With this approach, outer retina and RPE atrophy that may occur in association with anti-VEGF treatment may be presumably prevented. Although strict monitoring may have a great burden for the patients almost similar visit frequency (nearly 4-6 times a year) is required when the anti-VEGF therapy is administered. Moreover, since some of the patients with non-exudative MNV also receive anti-VEGF therapy for the exudative AMD in the fellow eyes, they will visit the clinic for their control visits.

CONCLUSION

Quiescent MNV is usually detected in asymptomatic patients with non-exudative AMD as an incidental finding in a routine examination and generally carries a better visual prognosis. Although this quasipathological entity mainly may accompany non-exudative AMD quiescent MNV may also be observed in other diseases affecting the macula much rarely. By utilizing powerful diagnostic tools such as OCT and OCTA it is realized that this entity is not uncommon. This impermeable neovascular network may remain stable, or become activated over time and evolve into an exudative form. However, the genetic and environmental conditions that cause the activation are still unclear. Moreover, no specific criteria have been established for the prediction of the activation so far. There is no consensus on the management of quiescent MNV. However, most of the previous studies recommend tight control rather than administering immediate treatment. OCT and /or OCTA biomarkers that may help predicting the exudation carry a paramount importance when monitoring the patients with quiescent MNV. There are several unanswered questions; Should these patients be treated with anti-VEGF agents to prevent exudation? If so which antiVEGF agent should be preferred? What should be the treatment interval and treatment protocol, and what is the correct time to stop the treatment? This questions can only find answers with future randomized studies involving sufficient number of patients. For the time being, individualized follow-up interval and subsequent treatment decision should be elected.

REFERENCES

1. Mitchell P, Liew G, Gopinath B, et al. Age-related macular degeneration. Lancet. 2018;392:1147-59.
2. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med. 2008;358:2606-17. Erratum in: N Engl J Med. 2008;359:1736.
3. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2:e106-16.
4. Douglas VP, Garg I, Douglas KAA, et al. Subthreshold Exudative Choroidal Neovascularization (CNV): Presentation of This Uncommon Subtype and Other CNVs in Age-Related Macular Degeneration (AMD). J Clin Med. 2022;11:2083.
5. Grossniklaus HE, Green WR. Choroidal neovascularization. Am J Ophthalmol. 2004;137:496-503.
6. Green WR, Enger C. Age-related macular degeneration histopathologic studies: the 1992 Lorenz E. Zimmerman Lecture. 1992. Retina. 2005;25:1519-35.
7. Spaide RF, Jaffe GJ, Sarraf D et al., Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. Ophthalmology. 2020;127:616-636. Erratum in: Ophthalmology. 2020;127:1434-5.
8. de Carlo TE, Romano A, Waheed NK, et al. A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous. 2015;1:5.
9. Hanutsaha P, Guyer DR, Yannuzzi LA, et al. Indocyanine-green videoangiography of drusen as a possible predictive indicator of exudative maculopathy. Ophthalmology. 1998;105:1632-6.
10. Querques G, Srour M, Massamba N, et al. Functional characterization and multimodal imaging of treatment-naive "quiescent" choroidal neovascularization. Invest Ophthalmol Vis Sci. 2013;54:6886-92.
11. Sarks SH. New vessel formation beneath the retinal pigment epithelium in senile eyes. Br J Ophthalmol. 1973;57:951-65.
12. Green WR, Key SN 3rd. Senile macular degeneration: a histopathologic study. Trans Am Ophthalmol Soc. 1977;75:180-254.
13. Mentes J, Karaca I, Sermet F. Multimodal imaging characteristics of quiescent type 1 neovascularization in an eye with angioid streaks. Am J Ophthalmol Case Rep. 2018;10:132-6.
14. Capuano V, Miere A, Querques L, et al. Treatment-Naïve Quiescent Choroidal Neovascularization in Geographic Atrophy Secondary to Nonexudative Age-Related Macular Degeneration. Am J Ophthalmol. 2017;182:45-55.
15. Carnevali A, Capuano V, Sacconi R, et al. OCT Angiography of Treatment-Naïve Quiescent Choroidal Neovascularization in Pachychoroid Neovasculopathy. Ophthalmol Retina. 2017;1:328-32.
16. Carnevali A, Sacconi R, Querques L, et al. Abnormal Quiescent Neovascularization in a Patient with Large Colloid Drusen Visualized by Optical Coherence Tomography Angiography. Retin Cases Brief Rep. 2018;12:S41-S45.
17. Carnevali A, Sacconi R, Querques L, et al. Natural History of Treatment-Naïve Quiescent Choroidal Neovascularization in Age-Related Macular Degeneration Using OCT Angiography. Ophthalmol Retina. 2018;2:922-30.
18. Matysik-Woźniak A, Loewenstein A, Bielecka E, et al. Activation of a Quiescent Choroidal Neovascularization in a Patient with Age-Related Macular Degeneration. Case Rep Ophthalmol. 2021;12:433-7.
19. Lumbroso B, Huang D, Souied E, et al. Understanding OCT angiography from patophysiology to clinical imaging. London; New Dehli: Jeypee Brothers Mrdical Publishers; 2020. 85–90.
20. Miller H, Miller B, Ryan SJ. Newly-formed subretinal vessels. Fine structure and fluorescein leakage. Invest Ophthalmol Vis Sci. 1986;27:204-13.
21. Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? Retina. 2010;30:1333-49. Erratum in: Retina. 2011;31:208.

22. Giani A, Luiselli C, Esmaili DD, et al. Spectral-domain optical coherence tomography as an indicator of fluorescein angiography leakage from choroidal neovascularization. Invest Ophthalmol Vis Sci. 2011;52:5579-86.

23. Fukushima A, Maruko I, Chujo K, et al. Characteristics of treatment-naïve quiescent choroidal neovascularization detected by optical coherence tomography angiography in patients with age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2021;259:2671-7.

24. Bailey ST, Thaware O, Wang J, et al. Detection of Nonexudative Choroidal Neovascularization and Progression to Exudative Choroidal Neovascularization Using OCT Angiography. Ophthalmol Retina. 2019;3:629-36.

25. Yang J, Zhang Q, Motulsky EH, et al. Two-Year Risk of Exudation in Eyes with Nonexudative Age-Related Macular Degeneration and Subclinical Neovascularization Detected with Swept Source Optical Coherence Tomography Angiography. Am J Ophthalmol. 2019;208:1-11.

26. Querques G, Sacconi R, Capuano V, et al. Treatment-naïve quiescent macular neovascularization secondary to AMD: The 2019 Young Investigator Lecture of Macula Society. Eur J Ophthalmol. 2021;31:3164-76.

27. Chen L, Messinger JD, Sloan KR, et al. Nonexudative Macular Neovascularization Supporting Outer Retina in Age-Related Macular Degeneration: A Clinicopathologic Correlation. Ophthalmology. 2020;127:931-47.

28. Heier JS. Prophylaxis Intravitreal Aflibercept Against Conversion to Neovascular Age-Related Macular Degeneration in High Risk Eyes (PRO-CON): 24-Month Results. Presented at: American Society of Retina Specialists annual meeting; July 27-30, 2019; Chicago.