THE RAP STUDY, REPORT 5: REDISCOVERING MACULAR NEOVASCULARIZATION TYPE 3
Multimodal Imaging of Fellow Eyes over 24 months

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Purpose: To explore the condition of fellow eyes of patients with macular neovascularization Type 3 (MNV3) and to verify whether the retinal–choroidal anastomosis (RCA) develops equally in all MNV types.

Methods: The contralateral eyes of 94 patients with MNV3, 96 patients with MNV1, and 96 patients with MNV2 were included. Multimodal imaging was performed. The MNV3 stage including the development of fibrosis and RCA over 24 months was determined.

Results: In the contralateral eyes of patients of the solitary (one lesion) MNV3 group, 32 eyes (42.1%) showed early/intermediate age-related macular degeneration, 25 eyes (33%) showed MNV3, and 11 eyes (14.5%) experienced fibrosis, of which 4 eyes (5.2%) had a RCA, 7 eyes (9.2%) had atrophy after resolved MNV3, and 1 eye (1.3%) developed MNV1. In the multifocal (more than one lesion) MNV3 group, 2 eyes (11.1%) showed early/intermediate age-related macular degeneration, 9 eyes (50%) showed 15 MNV3 lesions, and 4 eyes (22.2%) showed fibrosis, of which 2 eyes (11.1%) manifested with a RCA and 3 eyes (16.7%) showed atrophy after resolved MNV3. The number of eyes with a RCA accounted for 40% of all eyes with fibrosis. The count of simultaneous bilateral multifocal MNV3 was 5 (55.6%). In the MNV1 and MNV2 groups, no eye developed a RCA. The incidence of RCAs in the scarred eyes in MNV3 was significantly higher ($P < 0.0001$).

Conclusion: Retinal–choroidal anastomosis is an exclusive clinical feature of MNV3. The development of the multifocal MNV3 is usually bilateral and simultaneous. The occurrence of fibrosis in MNV3 has decreased dramatically after the introduction of the antiangiogenic therapy.

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Gass in 1971 who named it “retinal arterialization of a subretinal fibrous tissue plaque.” Consequently, it has become common knowledge that it is a specific vascular image of a scarred MNV indifferent of its type. Recently, we observed this phenotype in some scarred fellow eyes of patients recruited because of active MNV3 in their first eyes at the Vienna Reading Center. As MNV3 is a bilateral disease, this finding refers that this anastomosis is likely not equally common in all three types of MNV and could be a late funduscopic manifestation confined to MNV3. Therefore, we aimed to study the degenerative state of the fellow eyes of patients with newly diagnosed MNV3 over 24 months and to verify whether the RCA, first seen at the fibrosis stage, develops equally in all MNV types. In addition, we wanted to interpret the findings of Green and Gass based on the current established histological, topographical, and imaging facts.

Methods

Ninety-four consecutive fellow eyes of patients with newly diagnosed treatment-naive Stage 3 MNV3 (76 solitary and 18 multifocal) were included in this cross-sectional study to verify their degenerative condition. All patients were recruited from prospective international randomized double-blinded clinical trials to evaluate the efficacy of antiangiogenic therapy in nAMD from the Vienna Reading Center imaging database. Data were filtered by indication and treatment regimens, and no specific clinical trials were used. All patients came from trials recruiting patients with treatment-naive nAMD, including MNV3, for standard treatment with an anti-VEGF drug under investigation. Treatments received included as needed (pro re nata), treat and extend and fixed treatment in 4-weekly and 8-weekly intervals of a Food and Drug Administration–approved drug. The contralateral eyes of all patients were included in our study.

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Ethical approval for this post hoc analysis was obtained from the Ethics Committee of the Medical University of Vienna, and for the core trials, it was gained from the institution’s review board of each of the participating centers of the multicenter clinical trials.

Multimodal imaging was used for this post hoc analysis including OCT, color fundus photography (CFP), fluorescein angiography (FA), and optional indocyanine green angiography and autofluorescence imaging at least at three different visits including baseline, one visit in between, and the 24-month visit. We classified the status of the fellow eyes, which are the “study” eyes of our investigation, as follows:

Early or Intermediate Age-Related Macular Degeneration

The presence of drusen, hypopigmentation, and hyperpigmentation in the macular region without bleeding, scar, leakage, or atrophic areas of more than 175 μm diameter on CFP, FA, or OCT.

MNV1, 2, and 3

We used the definitions of MNV types mentioned in a recent consensus publication (CONAN). For staging of MNV3 lesions, we applied the classification proposed by Su et al using OCT (Figure 1). In particular, the diagnosis of MNV3 at the precursor stage was defined retrospectively because of its considerable false-positive rate. Thus, it was considered to be found when an active MNV3 lesion developed at the same location of the hyperreflective foci in the outer retina during the follow-up time. MNV3 was divided into solitary and multiple MNV3 subgroups according to the lesion count. We explored the possibility of development of other types of MNV in the same eye. All eyes were followed for 24 months to check the possibility of developing fibrosis with or without a RCA.

Fibrosis

A white or yellow scarred tissue in the macular region on CFP. It shows staining on FA and appears as a hyperreflective layered subretinal or subretinal pigment epithelial (sub-RPE) material on OCT. We assessed the occurrence of a RCA using CFP and FA (similar imaging modalities as used by Green and Gass). In addition, we studied the corresponding OCT to check the axial extension of the lesion (Figures 2, 3).
Atrophy

It is crucial to differentiate between typical geographic atrophy (GA), where there is no angiogenic activity in dry AMD and the type of atrophy associated with MNV3. Therefore, we divided this category into two subgroups according to its etiology and the subsequent morphologic and topographic characteristics:

1. Geographic atrophy, which represents the type of RPE atrophy seen in dry AMD. Typically, there is
more than one round or oval demarcated area of hypopigmentation with good visualization of the choroidal vessels of more than 175 μm diameter on CFP. Areas can increase in size and coalesce together forming larger areas. FA illustrates a well-defined window defect. A thinning or loss of the outer retina and RPE with hypertransmission in the underlying choroid without signs of MNV are usually seen on OCT.15,16

2. Focal circumscribed atrophic area which is usually seen after a resolved MNV3 lesion under anti-VEGF treatment.17 According to our second RAP
report, MNV3 lesions are mainly located in the temporal half of the macula between 500 and 1,500 μm from the center.5 Thus, the resulting atrophy develops in the same perifoveal temporal half. It is independent of the number of anti-VEGF injections.18 Occasionally, the coexistence of surrounding residual exudates confirms its origin as an emerging atrophy of treated MNV3 lesions19 (Figure 1).

To explore the incidence of fibrosis and a RCA in eyes with MNV1 and MNV2 as two control groups, we included 192 consecutive fellow eyes of patients with treatment-naive MNV1 or MNV2 (96 eyes of each type). Eyes of all three groups (MNV1–3) were treated with anti-VEGF.

All eyes with early/intermediate AMD, MNV, or scarring were followed over 24 months. The multimodal images of the fellow eyes were acquired prospectively according to each related core study protocols. All images were graded independently by two trained and certified experienced graders of the Vienna Reading Center, and a retina specialist acted as a judge in case of disagreement.

We used the chi-square test for this post hoc analysis. A 2-sided P value lower than 0.05 was considered to indicate statistically significant results.

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**Fig. 3.** Multimodal imaging presenting the development of fibrosis and a retinal–choroidal anastomosis (RCA) in the left eye of a patient with bilateral macular neovascularization Type 3 (MNV3): Color fundus photography (CFP) of the right eye illustrates the neovascular lesion as a small red lesion at the end of a retinal arteriole (arrow) (1a). A red-free image shows the turning of the arteriole at the location of the lesion (arrow) (1b). An early fluorescein angiography (FA) image depicts a focal hyperfluorescence at the lesion (arrow) (1c). Severe leakage on a late phase FA image (1c). A near-infrared image reveals the location of the OCT B-scan in f (1e). The corresponding OCT B-scan confirms the presence of stage 3 MNV3 as a hyporeflective mass overlying the interrupted retinal pigment epithelial (RPE) detachment (arrow) (1f). Panels 2 to 6 illustrate the progression of the fibrosis and RCA in the left eye using the same modalities at baseline and at months 4, 13, and 24: Abrupt turning of a retinal arteriole (red arrow) with massive exudation and two normal adjacent venules (2 blue arrows) (2a,b). A focal hyperfluorescence with a surrounding fibrovascular pigment epithelial detachment at the location of the fibrovascular lesion (2c,d). The corresponding OCT B-scan presents MNV3 changes similar to 1f (2f). The formation of fibrosis as a yellow lesion, and the vessels (one red and two blues arrows) are closer to each other with regression of the exudates (3a,b). Staining of the scarred tissue in addition to a big window defect due to development of an RPE tear (3c,d), which is manifested as subretinal hyperreflectivity and discontinuation of the RPE (arrow) on the corresponding OCT image, respectively (3e,f). The RCA (red arrow) with two venules (2 blue arrows) (one is a corkscrew-like venule) have larger diameter and are easily identified (4a-b). Staining because of the fibrosis close to the RPE tear area (4c,d). The fibrosis is thicker (4f). The RCA and two venules are prominent with peripheral hyperpigmentation and the fibrosis became thicker and wider (5a-e).
Results

Two hundred eighty-four contralateral eyes of 94 eyes with MNV3 (76 solitary and 18 multifocal), 96 eyes with MNV1, and 96 eyes with MNV2 have been included in this analysis.

The main findings are presented in Table 1.

Analysis of MNV3

Solitary MNV3. Of 76 eyes, 32 eyes (42.1%) presented with early or intermediate AMD. No eyes developed MNV2 lesions. Twenty-five eyes (33%) showed MNV3 in the following stages: 10 eyes (13.2%) had precursor MNV3, no eyes were found at stage 1, 5 eyes (6.6%) were diagnosed at stage 2, and 10 eyes (13.2%) were diagnosed at stage 3. Eleven (14.5%) eyes demonstrated macular fibrosis of which 4 (5.3%) had a RCA accounting for 36.4% of scarred eyes (Figures 2, 3). Seven eyes (9.2%) had atrophic changes after the resolution of an MNV3 lesion under treatment (Figure 1). Only one eye (1.3%) developed MNV1. None of the eyes presented with GA. No coexisting MNV1 or MNV2 has been found elsewhere in the macular region.

Multifocal MNV3. Of 18 eyes, only 2 eyes (11.1%) presented with early or intermediate AMD; significantly less than in the solitary group ($P = 0.04$). Nine eyes (50%) showed 15 MNV3 lesions of the following distribution: four precursor MNV3 lesions in three eyes, none at stage 1, three lesions at stage 2, and 8 lesions at stage 3 in six eyes. The distribution of established MNV3 lesions at stages 2 and 3 among the eyes was as follows: two eyes (11.1%) showed one lesion, 3 eyes (16.7%) had two lesions, and one eye had three lesions. Neither MNV1 nor MNV2 alone or combined with MNV3 was identified in the macular region. The count of simultaneous bilateral multifocal MNV3 was five eyes (55.6% of eyes with bilateral MNV3 lesions). Four (22.2%) eyes showed a fibrosis in the macular region, where 2 (11.1%) of them manifested with a RCA accounting for 50% of scarred eyes. Three eyes (16.7%) showed atrophic changes by resolved MNV3 lesions under anti-VEGF treatment; one of them was bifocal. Like solitary MNV3, none of these eyes presented with GA.

The incidence of fibrosis was 15 eyes (16%) for both (solitary and multifocal) MNV3 subgroups. The number of eyes with a RCA accounts for 40% of the total scarred eyes in both subgroups.

Fibrosis and Retinal–Choroidal Anastomosis in Other MNV Types

MNV1 and MNV2. The incidence of fibrosis was 11 (11.7%) and 12 (12.8%) eyes. The difference in occurrence of fibrosis compared with the MNV3 subgroup was not statistically significant ($P = 0.3261$ and $P = 0.4415$, respectively). No scarred eye developed a RCA in the macular region over 24 months. The difference in occurrence of RCAs in scarred tissue compared with MNV3 was statistically highly significant ($P < 0.0001$).

Discussion

In this study, we explored many characteristics of the fellow eyes of patients with newly diagnosed solitary and multifocal MNV3 and compared the incidence of fibrosis and RCAs over 24 months with those of the fellow eyes of patients with MNV1 and MNV2.

Table 1. Incidence of Fibrosis With and Without RCA, Early and Intermediate AMD, MNV Types 1–3 and Atrophy Over 24 Months in 94 Fellow Eyes of Patients With Solitary and Multifocal MNV3

|                | 94 MNV3, No (%) | 96 MNV1, No (%) | 96 MNV2, No (%) |
|----------------|-----------------|-----------------|-----------------|
| Fibrosis       |                 |                 |                 |
| With RCA       | 4 (5.2%)        | 2 (11.1%)       | 0 (0%)          |
| Without RCA    | 7 (9.2%)        | 2 (11.1%)       | 0 (0%)          |
| AMD early/intermediate | 32 (42.1%) | 2 (11.1%) | 0 (0%) | 0 (0%) |
| MNV1           |                 |                 |                 |
| Precursor      | 10 (13.2%)      | 9 eyes (50%)    | 15 MNV3 lesions |
| Stage 1        | 0 (0%)          | (4 precursors, 3 Stage 2, and 8 |
| Stage 2        | 5 (6.6%)        | Stage 3)        |
| Stage 3        | 10 (13.2%)      |                 |                 |
| MNV2           |                 |                 |                 |
| Resolved MNV3  | 7 (9.2%)        | 3 (16.7%)       |                 |
| Geometric      | 0 (0%)          | 0 (0%)          |                 |
| Total          | 76 (100%)       | 18 (100%)       |                 |

Fibrosis with and without RCA in 192 fellow eyes of patients with MNV1 and MNV2 were quantified for comparison with MNV3.
We found that most cases of MNV3 were either at asymptomatic precursor stage or at advanced stages (2/3). This outcome correlates with other studies reported on the fast progression of MNV3. Therefore, once MNV3 is diagnosed in one eye, a close follow-up for the fellow eye is mandatory to offer prompt therapy because the prognosis is stage dependent. Moreover, the precursor stage, diagnosed with OCT, accounted for more than one third of MNV3 cases. This emphasizes the importance of OCT to detect the disease at its earliest stage.

Interestingly, the appearance of fibrosis in eyes with MNV3 has decreased from 37% in 2001 to 15.95% in our study. This dramatic drop in less than two decades proves the efficacy of anti-VEGF in lowering the burden of fibrosis after its usage as the standard of care. In addition, we found that the highest incidence of fibrosis was in the MNV3 group affecting one of six eyes. It can be a result of the dual (retinal and choroidal) supply of the lesion and the higher load of VEGF. In addition, the incidence of fibrosis was higher in the multifocal than in the solitary MNV3 subgroup. An explanation can be the higher expression of VEGF and inflammatory products which result in more leakage, retinal thickening, and damage of the outer retina and RPE.

The incidence of fibrosis is usually higher in MNV2 than in MNV1. Nevertheless, in many cases, it was impossible to identify retrospectively which type (MNV1, MNV2, or mixed) caused the fibrosis in the control groups because there is no clear predilection of either type to be bilateral.

In the multifocal MNV3 subgroup, more than half of the patients experienced multifocal MNV3 in their fellow eyes, which means that the multifocal variant is frequently bilateral. Moreover, we noticed statistically significant decrease in early and intermediate AMD with concurrent increase in the frequency of stages 2/3 MNV3 lesions compared with the solitary MNV3 subgroup. This characteristic feature in the natural course of the multifocal variant suggests that the development of bilateral multifocal lesions tend to be simultaneous. Furthermore, we found that there were no multifocal MNV3 lesions in the fellow eyes of patients with solitary MNV3, whereas fellow eyes of patients with multifocal MNV3 developed solitary lesions in half of cases. This outcome can be interpreted in a way that in bilateral MNV3 cases, the multifocal variant in one eye tends to emerge before the development of a solitary MNV3 in the fellow eye.

In addition, we found that MNV3 was the only type developed in the fellow eyes except in one case. This outcome supports previous findings presenting MNV3 as a bilateral pathology not to be coexisted with the other types.

MNV3 usually affect older patients than MNV1 and MNV2. Nevertheless, we found that there was no MNV1 or MNV2 elsewhere in eyes with MNV3 lesions. This finding correlates with our findings on solitary, cilio-retinal, and multifocal MNV3 which indicate that the main predisposing factors of this type are different from those of MNV1 and MNV2, or the development of MNV1 or MNV2 prevents the progression of MNV3.

Interestingly, the identification of a RCA in the scarred eyes was exclusively seen in the MNV3 group in our study. We suppose that this outcome is related to its unique pathogenesis. A retinal–choroidal anastomosis is formed during the early stage, followed by the development of an aberrant RCA which cannot be identified using fundoscopy or CFP but with dye angiography or OCT (angiography) only. In long-standing MNV3, when fibrosis starts to appear, the RCA becomes well established and has a larger caliber due to the disturbed perfusion of the abnormal vascular communication. Subsequently, it would be possible to recognize it using fundoscopy or CFP as it was the case in the study of Green and Gass (Figures 2, 3).

Green and Gass described, for the first time, the RCA histologically and angiographically in scarred nAMD in 1971. Their observation has since been applied as a late vascular manifestation in MNV irrespective of its type. Otherwise, all their seven nAMD eyes (5 of them with RCA) demonstrated clinical and histological characteristics which strongly refer to MNV3. These changes were 1) retinal and choroidal neovascularization and anastomosis, 2) extrafoveal location of the neovascular membrane, 3) advanced age, 4) quick (several months) involvement of the second eye, 5) damage of the outer retina at the location of the lesion, 6) bilateral involvement in three of four patients, 7) all five RCAs in the five eyes were located in the temporal half of the macula (Figure 4), 8) severe visual loss at presentation (before the development of fibrosis), 9) extension of the fibrous tissue into the subretinal space and between the two layers of Bruch membrane, 10) apparent cholesterol deposition on both sides of the RPE (Figures 2, 3), and 11) occasionally, adjacent retinal venules were also found dipping into the subretinal plaque (Figures 2–4). Therefore, we could conclude, from our multimodal analysis and the study of Green and Gass, that the late clinical identification of the RCA is an exclusive marker of MNV3. Consequently, MNV3 was not first described by Hartnett in 1992 but by Green and Gass in 1971. Furthermore,
it was probably described and painted by Oeller in 1904 because there was bilateral fibrosis in an older (79 years) patient. In the left eye, there were enlarged temporal retinal vessels turning suddenly into the plaque (Figure 4B). A similar image was seen in the right eye two years later.

In addition, Green and Gass found a “diffuse sclerosis of the choriocapillaris” and in some areas the choriocapillaris was absent. These striking changes combined with decreased choroidal thickness and perfusion are also preferentially seen in MNV3. In particular, two special epidemic factors are important reasons for these changes in MNV3: hypertension and advanced aging. These data support the key role of the compromised chorioidal supply on the pathogenesis of MNV3 we suggested in the RAP Study, Report 2.

We did not find GA in early and intermediate AMD and MNV groups. This may refer that the manifestation of GA in patients with early or intermediate AMD may need a longer period of follow-up to appear or the fellow eyes of patients with MNV3 do not develop GA.

The lack of demographic characteristics of our cohort is a limitation of this study. Otherwise, patients enrolled in this report were participants in prospective international randomized clinical studies, where multimodal standardized imaging was performed prospectively on a regular basis and patients were deidentified according to the reading and study protocols. Another limitation was the possibility of including patients with atrophy after the resolution of MNV3 in the early and intermediate AMD group because of the absence of marked atrophy (less than 175 μm diameter). Nonetheless, this is very uncommon. A third limitation was the small sample size in some subgroups that led to the inability to perform valid statistics to test for the differences.

In conclusion, in this work we rediscovered MNV3, added a comprehensive clinical and historical update of solitary and multifocal MNV3, and determined that a RCA is confined to this type.

Key words: disciform scar, macular fibrosis, macular neovascularization, multimodal imaging, optical coherence tomography, retinal angiomatous proliferation, retinal–choroidal anastomosis.

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