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Towards a better understanding of non-exudative choroidal and macular neovascularization

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ABSTRACT

Non-exudative macular and choroidal neovascularization (MNV and CNV) usually refers to the entity of treatment-naïve type 1 neovascularization in the absence of associated signs of exudation. Histopathological studies, dating back in the early 70s, identified the presence of non-exudative MNV, but the first clinical report of this finding was in the late 90s using indocyanine green angiography in eyes with age-related macular degeneration (AMD). With more advanced retinal imaging, there has been an ever increasing appreciation of non-exudative MNV associated with AMD and CNV with other macular disorders. However, consensus regarding the exact definition and the clinical management of this entity is lacking. Furthermore, there may be variation in the imaging features and clinical course suggesting that a spectrum of disease may exist. Herein, we review the large body of published work that has provided a better understanding of non-exudative MNV and CNV in the last decade. The prevalence, multimodal imaging features, clinical course, and response to treatment are discussed to elucidate further key insights about this entity. Based on these observations, this review also proposes a new theory about the origin and course of different sub-types of non-exudative MNV/CNV which can have different etiologies and pathways according to the clinical context of disease.

1. Introduction

Choroidal and/or macular neovascularization (NV) refers to the process of generating abnormal new blood vessels from the choroid and/or retinal circulation. This phenomenon can complicate various retinal diseases including for example age-related macular degeneration (AMD) (Ferris et al., 1984; Green and Key, 1977; Sarks et al., 1994), myopic degeneration (Fang et al., 2018; Ohno-Matsui et al., 2021), pachychoroid spectrum disorders (Dansingani et al., 2015; Pang and Freund, 2015), angioid streaks (AS) (Parodi et al., 2018; Ramakrishnan et al., 2021; Risseeuw et al., 2020), and inherited chorioretinal dystrophies (Marano et al., 2000; Patel et al., 2016; Spaide, 1999).

AMD is the most common cause of blindness in developed countries, with an increasing prevalence of disease estimated to reach 288 million affected individuals worldwide in 2040 (Kawasaki et al., 2010; Klaver et al., 2001; Klein et al., 1999; Mitchell et al., 1995; Wong et al., 2008, 2014). The clinical hallmarks of AMD include drusen and abnormalities of the retinal pigment epithelium (RPE) which define the early and

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intermediate non-neovascular stages of the disease (Ferris et al., 2005). AMD could be complicated by neovascularization, evolving into the neovascular form of AMD. Progression rates to neovascular AMD vary from 3.2% to 15.2% per 100 person-years according to the fellow eye status, representing one of the most common disorders associated with neovascular disease (Chakravarthy et al., 2020). A clinical phenotype predisposing to high-risk conversion to neovascular AMD includes the presence of large drusen and pigmentary abnormalities (Ferris et al., 2013; Waldstein et al., 2020).

Neovascularization occurring in AMD most commonly originates from the choriocapillaris but may also originate from the deep retinal circulation. Neovascularization of choroidal origin penetrates Bruch's membrane (BrM) defects to proliferate in the sub retinal pigment epithelium (RPE) or the subretinal space (Rudolf et al., 2008; Sarks et al., 1994). For this reason, the term choroidal neovascularization (CNV) has long been used. Recently, the term macular neovascularization (MNV) has been proposed in AMD by a panel of experts, as it denotes the growth of new vessels in the macular region comprising all forms of neovascularization, including type 3 MNV originating from the retinal circulation. The term CNV is still used to describe neovascularization in diseases other than AMD (Spaide et al., 2020). In fact, the term MNV in other diseases could be confounding, because it should include for example retinal neovessels from diabetes. For this reason, in this paper, we will use the term MNV referring only to neovascularizations in nAMD (as suggested also by the CONAN group), the term CNV in other retinal diseases, and the term NV including both MNV and CNV in all the diseases.

NV is typically associated with exudation leading to visual decline. In clinical practice, there is widespread consent that the presence of "exudation" of a MNV is defined as the presence of subretinal and/or intraretinal hyporeflective fluid, and/or subretinal hyperreflective material (SHRM) using structural optical coherence tomography (OCT). It is still debated by the experts if the presence of sub-RPE fluid should be considered or not a sign of exudation; thus, this will not be included as a sign of exudation in this paper. However, it has been noted that NV may remain in a non-exudative state for variable periods of time. These lesions without active exudation occur in patients who are often asymptomatic, and their occurrence raises new pathogenic implications and clinical management considerations (Dansingani and Freund, 2015; Querques et al., 2013). Histopathological studies conducted post-mortem in eyes with clinically dry AMD demonstrated the presence of concomitant neovascularization (Green and Key, 1977; Sarks, 1973). This histopathological evidence was later confirmed in vivo with the introduction of indocyanine green angiography (ICGA), demonstrating non-exudative sub-RPE MNV in eyes diagnosed clinically as having dry AMD (Hanutsaha et al., 1998; Schneider et al., 1997). Presumably, the limited availability of ICGA among retinal specialists at the time and a need for intravenous dye injection, resulted in limited interest in these findings despite evidence that these eyes were at increased risk for conversion to exudative MNV. It was not until the advent of a more sophisticated and non-invasive multimodal imaging techniques, including OCT and OCT Angiography (OCTA), that interest in non-exudative NV was renewed.

In 2013, Querques et al. first performed a study focused on non-exudative MNVs in AMD, introducing the terminology "treatment-naïve quiescent" MNV (Querques et al., 2013). Since then, several studies have explored the incidence, prevalence, and natural history of these lesions and have proposed different nomenclatures, including 'quiescent,' 'subclinical,' and the more recently recommended terminology 'non-exudative' (Chen et al., 2020). The early detection of non-exudative MNV in asymptomatic patients is beneficial in identifying eyes at high risk for exudation (de Oliveira Dias et al., 2018; Yanagi et al., 2018a,b).

The present work aims to provide a comprehensive review of the non-exudative forms of neovascularization in various retinal disorders, analyzing the multimodal characterization, clinical, and prognostic implications. Indeed, non-exudative MNV (referring to neovascularizations in AMD) and CNV (referring to choroidal neovascularizations in other retinal diseases) could represent a spectrum of neovascularization with different pathogenesis, multimodal imaging characteristics, and clinical course.

2. Choroidal and macular neovascularization

2.1. Nomenclature and classification for CNV and MNV

Donald Gass first classified two distinct histological forms of CNV based on the location of the vascular network below or above the RPE (Braunstein and Gass, 1979).

Type 1 NV refers to new vessels originating from the choriocapillaris and extending into the sub-RPE space through defects in BrM. With fluorescein angiography (FA), these lesions typically show an indistinct pattern of staining and leakage in the mid and late phases of the study, described as "occult neovascularization". With ICGA, type 1 NV often appears as a faint neovascular network in the early phases of the angiogram, and a well-delineated area of hyperfluorescence in the late phases termed a 'plaque' (Yannuzzi et al., 1992).

OCT offers a depth-resolved structural representation of the lesion, characterized by an RPE detachment of variable reflectivity accompanied by various degrees of exudation. A peculiar OCT signature can be identified whereby the hyperreflective BrM is detected beneath the elevated RPE configuring a double layer sign (Sheth et al., 2018). Type 1 NV may remain undiagnosed for years until the lesion exhibits exudative complications. In these cases, the vessels grow slowly under the RPE with normal visual function. This pathoanatomy has been hypothesized to be protective against the development of RPE atrophy as the neovascularization may recapitulate the choriocapillaris and sustain and nourish the overlying RPE and outer retina (Freund et al., 2010; Grossniklaus and Green, 2004).

Polypoidal choroidal vasculopathy (PCV) is a variant of type 1 NV in which aneurysmal changes prone to exudation occur within the neovascular lesion and is commonly observed in Asian AMD populations (Cheung et al., 2018a). The first description was reported more than 30 years ago by Yannuzzi (Yannuzzi LA, Idiopathic PCV, Presented at Macula Society Meeting, 1982; Miami, FL). This aneurysmal lesion with a morphology resembling polyps were initially thought to originate directly from dilated choroidal vessels. However, recognizing that PCV is a variant of type 1 NV, the term 'aneurysmal type 1 NV′ has been proposed to describe this entity; however, consensus regarding the histologic basis, predisposing factors, and preferred terminology related to these complicated vascular structures is lacking (Fragiotta et al., 2018; Freund et al., 2010; Li et al., 2019; Spaide et al., 2020). This neovascular pattern seems to be more common in eyes with long-standing type 1 NV with saccular or fusiform dilatations forming as the neovascular tissue enlarges and matures (Freund et al., 2010). The pathophysiology of PCV seems to be related to ethnicity. Indeed, PCV development in the Asian population shows different multimodal imaging features in comparison to Caucasian patients. First, PCV in the Asian population seems to be more adverse in terms of BCVA loss, greater rate of hemorrhagic complications, and a greater area of hemorrhage. Secondly, the polypoidal neovascular network in Asian patients is typically located in the peripapillary area, and is often associated with the concomitant presence of pachyvessels and choroidal hyperpermeability. On the other hand, PCV in the Caucasian population is more associated with drusen and more typically located in the macular area (Corvi et al., 2022). All these features suggest that PCV in the Asian population is more related to the pachychoroid neovasculopathy, whereas PCV in the Caucasian population is more related to the neovascular AMD.

Although several studies have assessed the diagnostic accuracy of various non-invasive imaging modalities, ICGA is still considered the gold standard to detect polyps. ICGA demonstrates a branching vascular network associated with a variable number of aneurysmal dilations at

the margin of the lesion. These aneurysmal lesions appear as hyperfluorescent spots in the early phases of ICGA (Balaratnasingam et al., 2016; Cheung et al., 2018a). On OCT, a "thumb-shaped" or "U-shaped" pigment epithelial detachment (PED) containing well-defined ovoid lesions with a hyperreflective ring may be appreciated (Sato et al., 2007). OCTA has shown variable sensitivity and specificity in detecting aneurysmal type 1 MNV (Inoue et al., 2015; Srour et al., 2016; Peiretti et al., 2019). Of note, OCTA nicely discloses the branching neovascular network of aneurysmal type 1 NV, but often fails to disclose the aneurysmal lesion.

Type 2 NV is located in the subretinal space, often presenting as a well-defined hyperfluorescent lesion in the early phases of FA examination with leakage in the late phases, described as "classic neovascularization" (Macular Photocoagulation Study Group, 1991). Neovascular tissue is located in the subretinal space above the RPE. OCT examination reveals SRHM with separation of the neurosensory retina from the RPE (Dansingani et al., 2016a; Spaide et al., 2020). Type 2 NVs are associated with exudation or hemorrhage directly into the subretinal space, leading to early disorganization and destruction of the photoreceptors and poorer visual prognosis (Keane et al., 2008). OCTA shows a neovascular network above the level of the RPE (El Ameen et al., 2015). Type 2 NVs can occur in association with entities other than AMD, such as myopic degeneration and lacquer cracks, pseudoxanthoma elasticum and angioid streaks, and punctate inner choroidopathy, typically in younger patients (Spaide et al., 2020).

Alternatively, neovascularization can originate from the deep retinal capillary plexus, hence the proposal of the term MNV to replace CNV in nAMD (Spaide et al., 2020). Freund et al. coined type 3 MNV to describe this distinct clinical entity characterized by intraretinal neovascularization (Freund et al., 2008). Several clinical and anatomical correlations corresponding to type 3 MNV were previously described. Notably, in 1992 Hartnett et al. evaluated a series of 11 patients diagnosed with AMD presenting with "retinal vascular anomalous complexes (RVACs)," which cannot be categorized as type 1 or type 2 MNV (Hartnett et al., 1992). Using FA and ICGA, RVACs were associated with a clearly defined anastomosis connecting the retinal circulation to a vascular complex in the deep retina (Hartnett et al., 1996). A similar neovascular phenotype referred to as "occult chorioretinal anastomosis (OCRA)" was then described by Kuhn et al. (1995). The analysis conducted on 186 consecutive eyes with PED revealed that 54 eyes presented with a hot spot on ICGA and 50 of these eyes showed an evident anastomosis between one or more retinal vessels and the choroidal circulation within the hot spot. The descriptive term 'hot spot' indicated a focus of hyperfluorescence caused by vessels arranged in a perpendicular orientation relative to the retinal surface. Later, Yannuzzi et al. coined the term "retinal angiomatous proliferation (RAP)," proposing a three-stage model of clinical progression (Yannuzzi et al., 2001). In the first stage, intraretinal hemorrhage and edema may be found in association with vascular proliferation arising from the deep capillary plexus and confined within the neurosensory retina. In the second stage, neovascular tissue invades the subretinal space above RPE, while the third stage was characterized by sub-RPE and choroidal neovascularization with a documentable chorioretinal anastomosis. Corresponding FA shows a well-defined area of early hyperfluorescence, with intraretinal leakage and cystoid changes in the late phases of examination, while ICGA shows a small hyperfluorescent lesion in the late phases of examination, referred to as "hot spot". Structural OCT shows an outer retinal hyperreflective lesion often accompanied by a PED visible underneath the lesion.

An updated staging of type 3 MNV based on spectral-domain OCT has been proposed. The precursor stage is characterized by an intraretinal hyperreflective focus. Stage 1 is defined by an intraretinal hyperreflective focus associated with cystoid spaces without outer retinal disruption, which becomes evident in stage 2 with or without RPE involvement. Stage 3 consists of progressive downgrowth of the neovascularization through the RPE producing a PED. The outer retinal neovascular lesion is identified at the crest of the PED with associated subsidence or downward deflection of the outer plexiform layer ("steer sign"). Although sub-RPE extension was observed, evidence of choroidal neovascularization at this level was not confirmed (Su et al., 2016).

The CONAN group recommended the use of 'retinal-choroidal anastomosis' to specifically describe communication between vessels through neovascular networks connecting from the retina to the choroid or the opposite, visible with dye-based angiography or OCTA (Spaide et al., 2020) (Fig. 1).

Multicolor image (A) and short-wave fundus autofluorescence (B) showing the presence of an atrophic area, drusen, and retinal pigment epithelium (RPE) alterations. Combined infrared reflectance and horizontal structural optical coherence tomography (OCT) showing the presence of intraretinal cysts with increase in retinal thickness (upper structural OCT, passing through the green arrow), and the presence of hyperreflective lesion growing from the inner plexiform layer to the RPE (lower structural OCT, passing through the yellow arrow). En-face OCT-angiography of the avascular slab and b-scan with flow showing the presence of flow inside the hyperreflective lesion detected by structural OCT, confirming the diagnosis of type 3 MNV.

2.2. Nomenclature and classification for NE-NV

In 2012, Amissah-Arthur and coworkers examined the fellow eyes of nAMD patients receiving ranibizumab intravitreal therapy and identified the presence of retinal pigment elevation without sub-retinal fluid and discovered that these fellow eyes were high-risk for progression to exudative lesions (Amissah-Arthur et al., 2012). In 2013, Querques et al. described patients with subclinical, treatment-naïve, type 1 MNV lesions in the absence of frank exudation on OCT for at least 6 months, defining this entity as "quiescent" MNV (Querques et al., 2013). The term 'quiescent' is derived from Latin "quiescentia" meaning literally "inactivity, without symptoms" (Querques et al., 2013, 2021). The follow-up of 6 months was arbitrarily chosen because it represents the clinical follow-up of patients with large drusen (intermediate AMD). Due to the absence of exudation, at that time, patients with quiescent MNV were classified as intermediate AMD. The CONAN group did not reach a consensus on the term 'quiescent' and encouraged adoption of the term non-exudative MNV (Spaide et al., 2020).[25] Beyond the terminology, a non-exudative or "quiescent" MNV designates a type 1 MNV without intraretinal or subretinal exudation on repeated OCT b-scans for at least 6 months (Querques et al., 2013, 2021).[26,53] Non-exudative NV lesions are usually identified in the context of intermediate AMD, but they can also be associated with other macular abnormalities, including geographic atrophy, pachychoroid neovasculopathy, large colloid drusen, and angioid streaks (Capuano et al., 2017; Carnevali et al., 2017, 2018a; Mentes et al., 2018).

The most significant challenge when approaching the characterization of non-exudative lesions is understanding the distinction between a stable phenotype, which remains inactive over time, described originally as 'quiescent' lesions' versus a de novo neovascular lesion, which is non-exudative at a given time point. The latter has been referred to by some authors as subclinical MNV. These lesions may include both quiescent lesions and newly developed neovascularization in an active growth phase. New onset MNV may exhibit a shorter interval before exudative changes manifest. Therefore, these lesions are not truly quiescent or stable but represent MNV in a pre-exudative stage.

It has been well known for decades that exudative type 1 NV can initially exhibit a pre-exudative stage in its evolution (Agarwal, 2012; Grossniklaus and Gass, 1998). Neovascularization, driven by VEGF and other cytokines, extends from the choriocapillaris and grows into the sub-RPE space through breaks in Bruch's membrane. The sub-RPE space is characterized by low resistance to the lateral growth of the firmly adherent MNV to the RPE, resulting in a shallow irregular RPE elevation (referred to as SIRE) (Narita et al., 2020) or double layer sign (Shi et al., 2019). In these early stages of MNV development, the blood flow inside

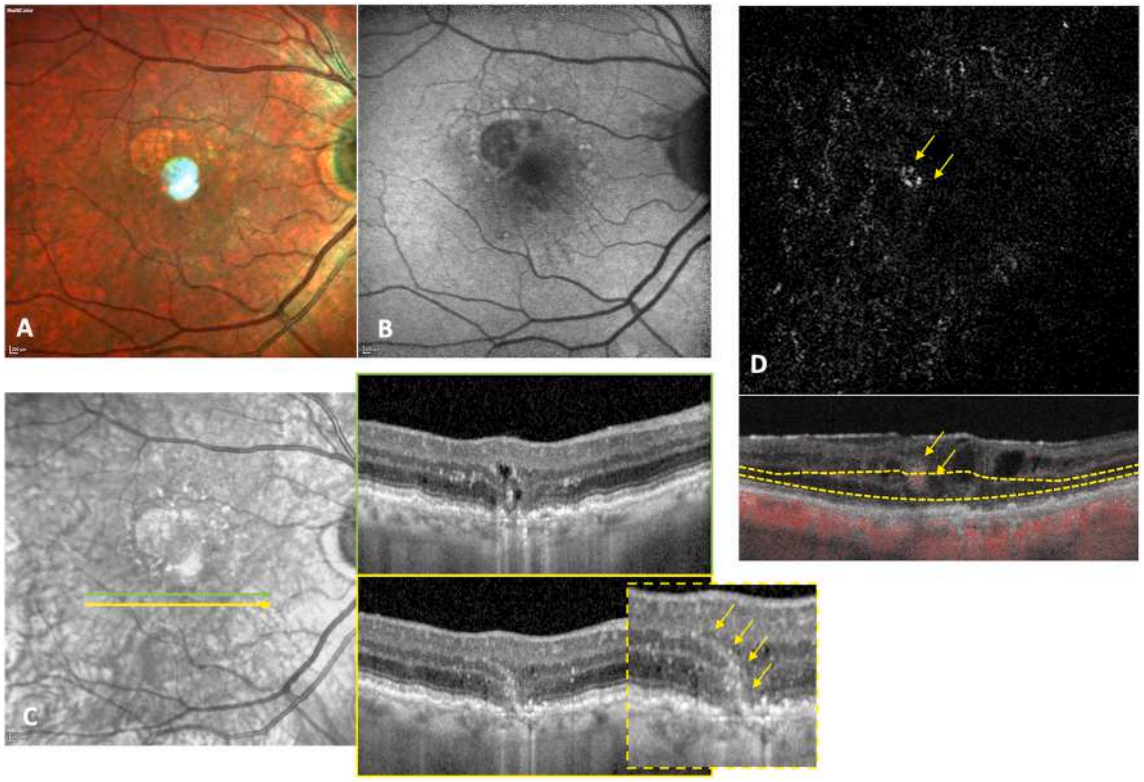

Fig. 1. Multimodal imaging evaluation of a 80-year-old patient affected by type 3 macular neovascularization (MNV) in the right eye.

the neovessels seems to be slow, and thus there is often no exudation (i.e. pre-exudative stages of type 1 MNV development). With progressive growth however, there is an increase of the blood flow inside the neovascularization, presumably resulting in decompensation of the endothelial cells, and thus exudation. Exudation manifest first in the sub-RPE space, and, later in the subretinal space (i.e. subretinal fluid). Supporting this theory, Invernizzi et al. detected thickening of the outer retinal layer (starting from the external limiting membrane to the BrM) using structural OCT that develops a mean of 8 months before the onset of exudation, but progresses significantly 2 months before exudation (Invernizzi et al., 2021). The thickening of the outer retinal layer before exudation could represent the pre-exudative stage of type 1 MNV development. Indeed, there is first the development of a small flat irregular pigment epithelium detachment with double-layer sign using structural OCT and no exudation, and, after that a more rapid increase in thickening of the outer retinal layer in the weeks before exudation (Fig. 2).

To date, there is a lack of a universal classification system that includes the clinical course, management, and prognostic value of non-exudative lesions (Capuano et al., 2017; Chen et al., 2020; Grossniklaus et al., 2004; Spaide et al., 2022). Non-exudative MNV can represent various phenotypes including new-onset type 1 MNV in the early pre-exudative stage of development versus a more mature type 1 MNV that has become "quiescent" without exudation for an extended period longer than 6 months (Figs. 3 and 4). Therefore, the absence of frank exudation for at least 6 months can help to differentiate these different lesion types, although frequent intervening follow-up may be required to definitely exclude the development of transient exudation during the 6 month interval. Regardless of the designated cut-off interval of 6 months, non-exudative MNVs may be considered as a spectrum of disease with different phenotypes. New high-resolution multimodal imaging techniques could be very useful to better understand and classify these different non-exudative MNV phenotypes.

Although "non-exudative" MNV usually refers to type 1 MNV, other subtypes of MNV can also be identified without exudation. It is worthwhile mentioning that more recently, thanks to the advances in OCTA technology, a preclinical stage of type 3 has been described. The original description from Sacconi et al. illustrated hyperreflective foci typically located in the outer nuclear layer, outer plexiform layer, and the inner nuclear layer on structural OCT with detectable flow on OCTA (Sacconi et al., 2018a). These hyperreflective foci with OCTA flow represent early intraretinal vascular proliferation originating from the deep vascular complex of the retina and they are characterized by the absence of exudation (i.e. non-exudative MNV). Non-exudative type 3 MNV progressively grows towards the RPE (i.e. nascent type 3 MNV), or, more rarely, can regress without other manifestations. Usually, non-exudative type 3 MNV develops exudation when neovessels grow from the deep vascular complex into the RPE and sub-RPE space, resulting in the exudative stage of type 3 MNV (Fig. 5). This downgrowth of the early non-exudative neovascular tuft into the RPE is the key feature characterizing nascent type 3 MNV.

However, the existing literature on either quiescent or non-exudative NV lesions refers mainly to type 1 NV (Bailey et al., 2019; Capuano et al., 2017; Querques et al., 2013; Spaide, 2018; Spaide et al., 2020). Due to the different origin of non-exudative type 3 MNV in comparison to type 1 MNV (from the retinal circulation instead of the choriocapillaris), type 3 MNV should be considered a distinct clinical entity.

Combined infrared reflectance and vertical structural OCT passing through the fovea, and en-face OCT-A of the retinal pigment epithelium (RPE)-RPEfit slab showing no signs of MNV two months before the baseline (A). At the baseline (B), there was the development of an irregular pigment epithelium detachment (PED) with a double-layer sign (white triangle), matching a non-exudative stage in the development of type 1 MNV. During the follow-up, there was a progressive enlargement of the PED and the appearance/enlargement of the neovascular network after 2 months (C), 4 months (D), and 6 months (E) (white triangles and white asterisks). After 8 months (F), type 1 MNV showing the appearance of exudative signs (sub-retinal fluid), matching an exudative stage of type 1 MNV.

Combined infrared reflectance and structural OCT passing through

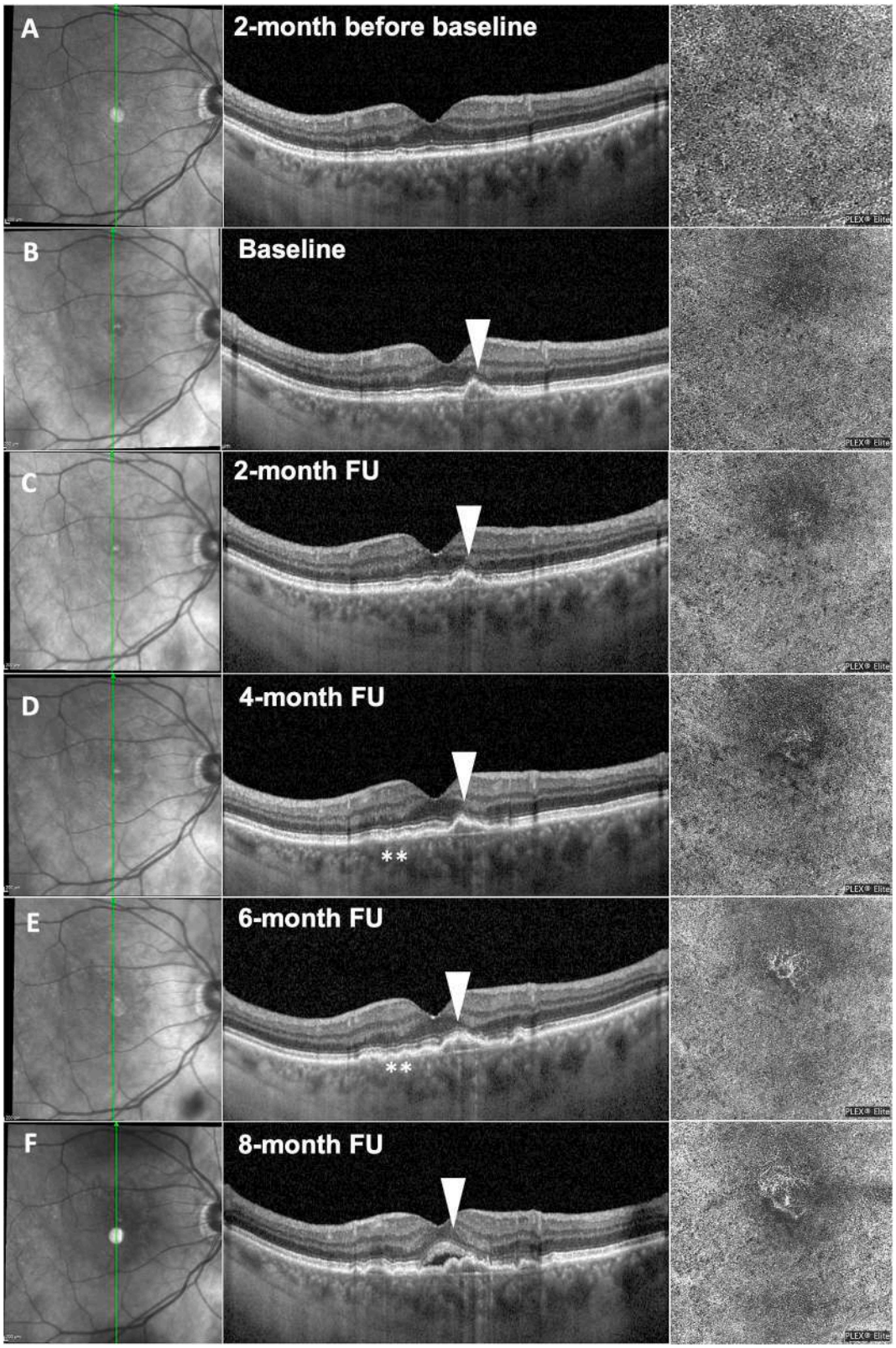

Fig. 2. Serial structural optical coherence tomography (OCT) and OCT-angiography (OCT-A) during the time of a 74-year-old patient affected by a non-exudative type 1 macular neovascularization (MNV), with exudation after 8 months.

the fovea (A) and OCT-A b-scan with flow (B) showing the presence of a small intraretinal hyperreflective dot with detectable flow, without contact with the retinal pigment epithelium and no signs of exudation. The diagnosis of non-executive type 3 MNV was performed. At 6-month follow-up, structural OCT (C) and OCT-A b-scan with flow (D) showing the development of an exudative form of type 3 MNV.

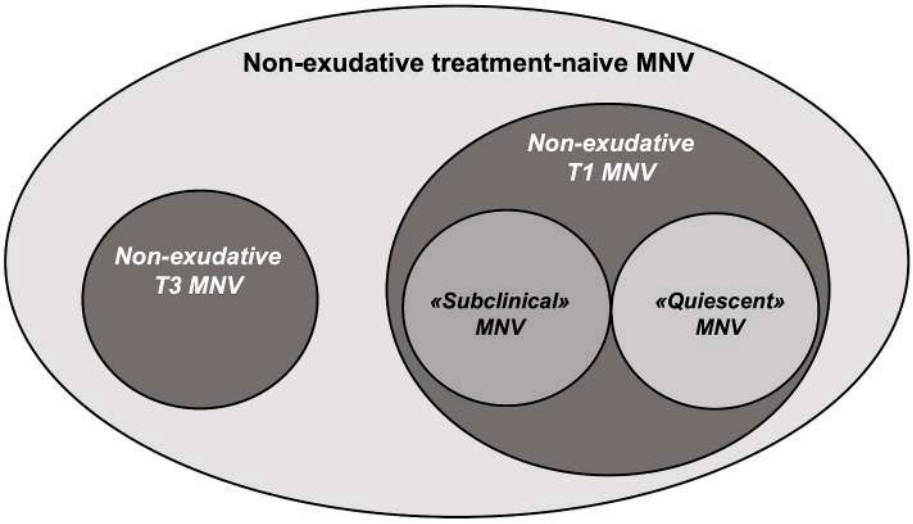

Fig. 3. Diagram showing different sub-types included in the spectrum of non-exudative treatment-naïve macular neovascularization.

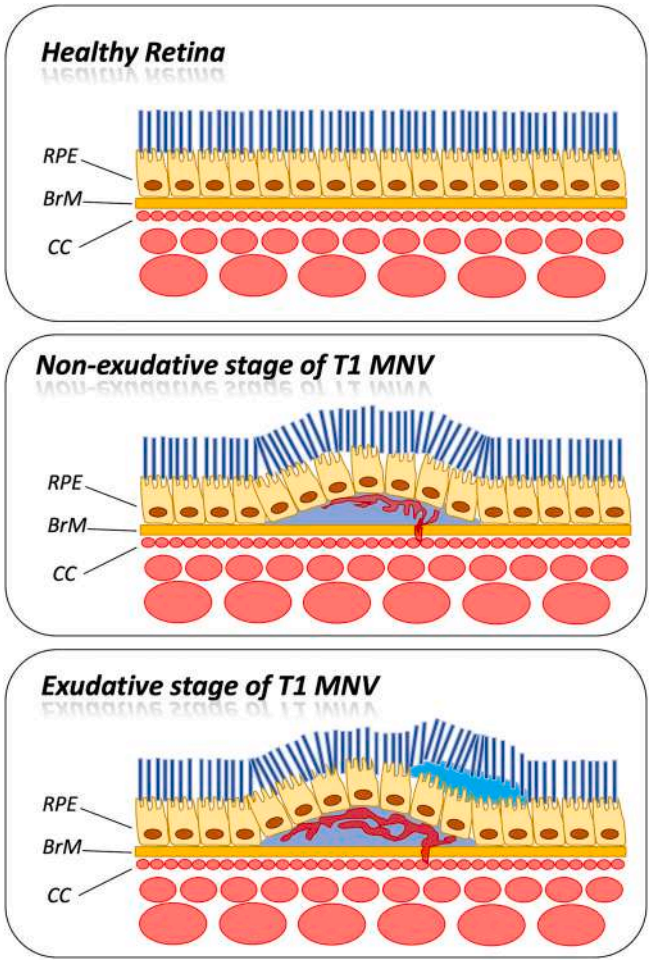

Fig. 4. Schematic representation of the different stages characterizing the development of type 1 macular neovascularization. BrM: Bruch's membrane; CC: choriocapillaris; RPE: retinal pigment epithelium.

2.3. Exudative features of NV

The recognition of active or exudative NV results in various recognizable signs on multimodal imaging. Leakage is a characteristic FA feature characterized by progressive or expanding hyperfluorescence from the neovascular complex. The dye may accumulate in the form of 'staining' within the tissue or 'pooling' into fluid-filled cavities. When leakage exceeds the resorptive capabilities, fluid accumulations can be detected in the intraretinal or subretinal space (Macular Photocoagulation Study Group, 1991). ICGA is very useful in the detection of type 1 NV as a hyperfluorescent plaque in the late phases of the study, due to the staining of the dye inside the fibrovascular tissue (Yannuzzi et al., 1992). As it was demonstrated that MNV size detected by ICGA is significantly greater in comparison to OCTA, we can speculate that ICGA could be also influenced by choroidal permeability and dye leakage in exudative type 1 MNV (Costanzo et al., 2016; Cicinelli et al., 2020). Furthermore, ICGA features of exudation are seen in type 3 MNV as a hot spot in the late stages of the examination, whereas this finding is not seen in pre-exudative stages of type 3 MNV (Sacconi et al., 2018a).

By means of structural OCT, subretinal fluid (SRF) accumulates between the outer border of the photoreceptor band and the RPE. SRF is often associated with a type 1 NV and type 2 NV in the exudative phase. Intraretinal fluid (IRF) is represented by cystoid spaces of fluid within the inner retina, mostly related to type 2 and type 3 MNV. The detection of IRF is considered the most significant negative prognostic factor associated with fibrosis and atrophy development (Guymer et al., 2019; Jaffe et al., 2013, 2016; Spaide et al., 2020), although this is not true considering type 3 MNV (Sacconi et al., 2022). Sub-retinal hyperreflective material is characterized by the evidence of hyperreflective material in the subretinal space detected through OCT, which has been correlated with a poor visual outcome in neovascular AMD (Balaskas et al., 2019; Jaffe et al., 2013; Keane et al., 2008; Willoughby et al., 2015).

Sub-RPE fluid develops in the context of RPE separation or detachment from the BrM and can also have prognostic significance like IRF and SRF (Chaudhary et al., 2021; Jaffe et al., 2013; Spaide et al., 2020). The CATT and HARBOR trials and other more recent studies have shown that sub-RPE fluid present at the final outcome visit correlates with a more favorable anatomic and visual outcome (Fang et al., 2021). The development of a multilayered PED morphology with a fusiform complex of sub-RPE hyperreflective lamella, with or without an outwardly bowed hyporeflective cavity referred to as pre-choroidal cleft, has been associated with very favorable long-term visual outcomes in eyes with AMD (Au et al., 2019; Rahimy et al., 2014). This signature OCT morphology is illustrative of the mature organization of the fibrovascular NV complex, the innermost layer of which may be recapitulating the choriocapillaris, acting as an anatomical surrogate of the inner choroid and protecting against RPE atrophy (Chen et al., 2020;

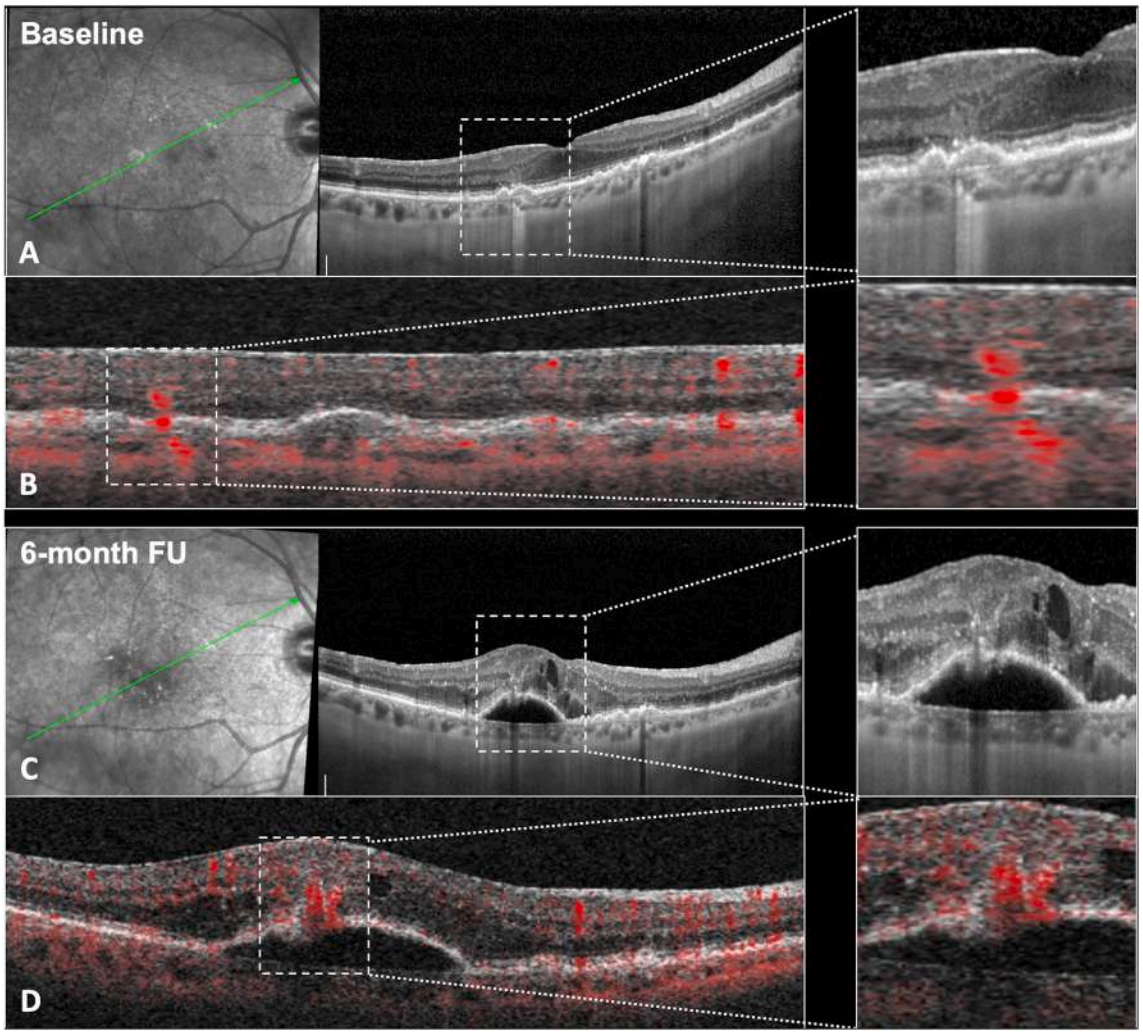

Fig. 5. Structural optical coherence tomography (OCT) and OCT-angiography (OCT-A) during the time of a 78-year-old patient affected by a non-exudative type 3 macular neovascularization (MNV), with exudation after 6 months.

Grossniklaus et al., 2004 Rahimy et al., 2014).

2.4. Histological characteristics of non-exudative NV

First histologic reports of non-exudative NV were published many decades ago. Green et al. and Sarks reported the presence of neovascularization below the RPE with no evidence of exudation in patients with AMD (Green and Key, 1977; Sarks, 1973, 1976). In a series of 150 eyes of patients between 62 and 96 years of age, 11% of cases showed new vessels passing through Bruch's membrane and growing under the basal laminar deposits. Interestingly, all patients were clinically asymptomatic with no evidence of exudation at clinical examinations.

Recently, Seddon et al. reported new relevant histological findings that are very useful in understanding the early stages of non-exudative MNV (Seddon et al., 2016). In this paper, the authors reported the presence of neovascular buds internal to the choriocapillaris (below the Bruch's membrane) in patients with early AMD (22% of patients) and intermediate AMD (40% of patients). The development of neovascular buds could be a compensatory process to choriocapillaris loss. Indeed, choroidal remodeling and choriocapillaris loss has been shown to develop in the early stages of AMD in histologic and clinical studies (Biesemeier et al., 2014; Borrelli et al., 2022; Friedman, 2008; Li et al., 2018; Sacconi et al., 2020, 2021a). Neovascular buds could represent the precursors of non-exudative and of exudative MNV. Indeed, with progressive choriocapillaris loss and subsequent hypoxia, the RPE might increase VEGF production, leading to a stimulation of neovascular development (Corvi et al., 2021).

Recently, Chen et al. reported the clinicopathological correlation of a case of a 90-year-old female with a 9-year history of non-exudative MNV (Chen et al., 2020). Histological examination of the post-mortem eye was correlated to previous in vivo structural OCT examinations. Bruch's membrane defects were detected and correlated with bridge vessels between the non-exudative MNV and the choroidal circulation. Interestingly, the histological morphology of the non-exudative MNV just below the RPE was very similar to the native choriocapillaris (CC) and this innermost layer of MNV harbored ultrastructural characteristics of the CC. For this reason, Chen et al. suggested 2 different phenotypes of non-exudative MNV in AMD: the first is characterized by lesions with a high risk of exudation and vision loss and the second by a low risk for exudation and preservation of visual acuity with a surrogate choriocapillaris (Chen et al., 2020). This theory was also proposed by Querques et al. using a clinical approach to non-exudative MNV (Section 3.2) (Querques et al., 2021). However, Chen et al. supported this theory with histopathological confirmation (Chen et al., 2020).

2.5. Dye angiographies characteristics of non-exudative NV

The first description of possible non-exudative MNV using ICGA was reported by Hanutsaha et al., in 1998 (Hanutsaha et al., in 1998). Analyzing the fellow drusen eyes of 432 patients with unilateral

exudative AMD, the Authors disclosed 36 eyes showing a plaque in the late phases of video-ICGA examination, despite the absence of exudative signs.

However, the confirmation and description of "quiescent" MNV were reported by Querques et al., in 2013 (Querques et al., 2013). In their paper, the Authors reported that quiescent MNVs appear as "late speckled hyperfluorescent lesions lacking well-demarcated borders (without late-phase leakage of undetermined source or pooling of dye in the subretinal space, which defines typical occult type 1 CNVs)". Furthermore, using ICGA, quiescent MNVs appear as a delineate plaque in the mid-late phase of ICGA, similarly to typical exudative type 1 MNV).

2.6. OCT and OCTA characteristics of non-exudative NV

A better understanding of the natural history of non-exudative NV became possible thanks to the widespread use of OCT. This instrumentation can precisely assess the presence of fluid and characterize the nature of activity of type 1 NVs.

2.6.1. OCT characteristics for non-exudative NV

The first characterization of non-exudative type 1 NV through both OCT and ICGA was made by Querques et al., in 2013 (Querques et al., 2013). The original description used the terminology "treatment-naïve quiescent MNV" to describe neovascularization detected with ICGA in the absence of intraretinal or subretinal exudation on structural OCT in nAMD patients. Eleven eyes of 11 patients followed for a mean of 23.8 $\pm$ 16 months were retrospectively analyzed. A minimum of $\geq$6 months follow-up was established to discriminate from pre-exudative stages of type 1 MNV. Structural OCT revealed an irregularly slightly elevated RPE detachment or shallow irregular RPE elevation (SIRE) i.e. the double layer sign, with a major axis in the horizontal plane. At this level, a collection of moderately hyperreflective material was identified within the sub-RPE space with a clear visualization of the BrM. The outer retinal architecture overlying the non-exudative lesion was preserved with no evidence of subretinal fluid. The OCT imaging findings could be correlated with histopathologic findings. Knowing that neovessels originate from the choriocapillaris, breaking through Bruch's membrane and growing under the RPE, we can correlate the hyperreflective material in sub-RPE space as identified with structural OCT with the neovessels detected using histological specimens. The visualization of two hyperreflective layers with OCT (RPE and the Bruch's membrane), i.e. a flat irregular RPE detachment and reflective material inside, corresponds to the "double-layer sign" (Fig. 6). This term was originally coined by Sato et al. to characterize the branching vascular networks in polypoidal choroidal vasculopathy (Sato et al., 2007). In 2019, Shi et al., studied 64 eyes with intermediate AMD and demonstrated that the double-layer sign-on structural OCT was associated with non-exudative MNV, with good sensitivity and specificity (Shi et al., 2019). Of note, this is a structural OCT sign that suggests the presence of a non-exudative MNV, but the term merely denotes a distinction between Bruch's membrane and RPE and not necessary the presence of a neovascular network. After the first description, the same group expanded the features of the double-layer sign characterizing non-exudative MNV and introduced the term shallow, irregular RPE elevation (SIRE) (Narita et al., 2020). SIRE is characterized by a double layer sign with nonhomogeneous internal reflectivity, RPE elevation greater than 1000 μm in horizontal length and less than 100 μm in height. The choice of 1000 μm is questionable as it is an arbitrary designation, and, using the SIRE definition, small, focal non-exudative MNV smaller than 1000 μm may remain undetected. However, eyes with non-exudative AMD showing SIRE on structural OCT are likely to harbor non-exudative MNV. For this reason, structural OCT alone could be considered a good tool in the screening and diagnosis of non-exudative NV in the context of non-exudative AMD.

More precise and accurate identification of non-exudative NV has been possible with the advent of OCTA that can illustrate the presence of neovascular networks without the need of a dye-based test.

Combined infrared reflectance and horizontal structural optical

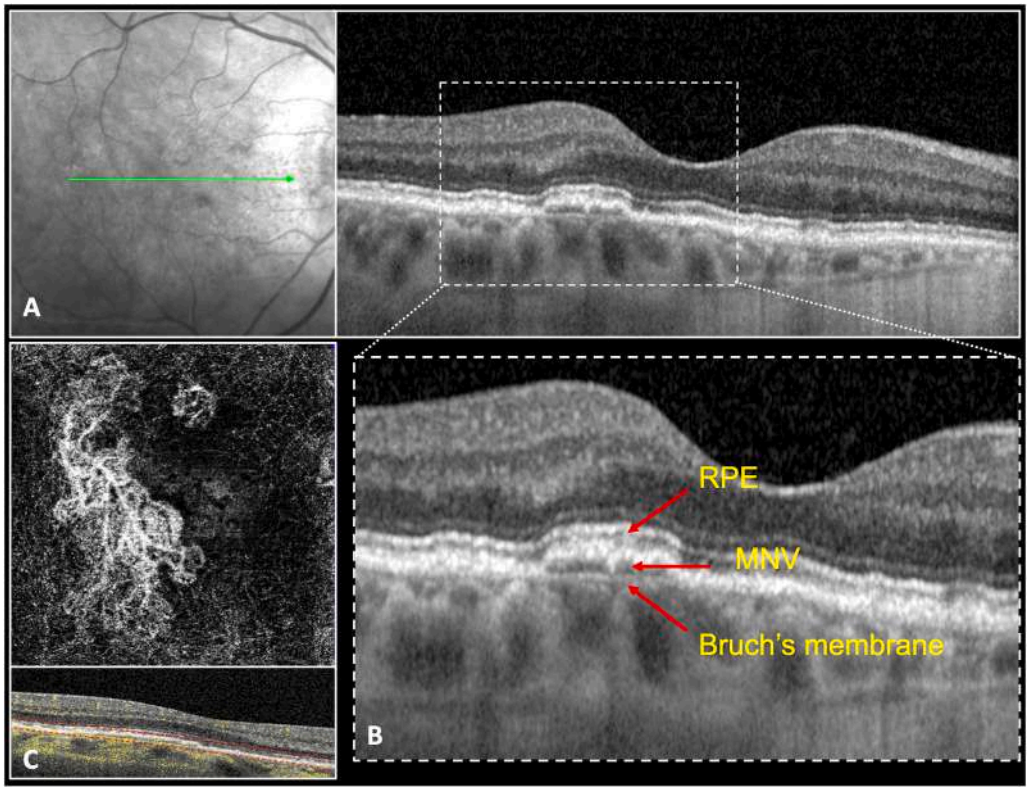

Fig. 6. The « double layer sign » characterizing a non-exudative type 1 neovascularization (NV).

coherence tomography (OCT) passing through the fovea (A) showing the presence of a flat irregular pigment epithelium detachment with no signs of exudation (i.e. intra- or sub-retinal fluid, or sub-retinal hyper-reflective material). Magnification of structural OCT (B) well disclosed the presence of two layers with high reflectivity (retinal pigment epithelium (RPE) and the Bruch's membrane), mixed reflective material inside and hyporeflective space below, corresponding to the "double-layer sign». Enface OCT-angiography and b-scan with flow (C) nicely showed the presence of a non-exudative type 1 NV.

2.6.2. OCTA characteristics of non-exudative NV

The introduction of OCTA into clinical practice has allowed us to improve our knowledge and our ability to diagnose non-exudative NV. OCTA allowed us to visualize the movement of the particles relative to the static surrounding tissue, thus creating an image of vascular flow. This technology has significant advantages over FA and ICGA in the detection of non-exudative NV. First, it is a non-invasive tool that does not require dye injection. OCTA can be performed much faster than FA and at every single examination. Finally, OCTA allows a customized visualization of the retinal capillary plexuses and choriocapillaris, thanks to the automated segmentation of the retinal vascular and choroidal networks. However, the current hurdles (e.g. artifacts) and inabilities of OCTA should be kept in mind. Regarding non-exudative NV detection, we need to consider the projection artifacts and the inability

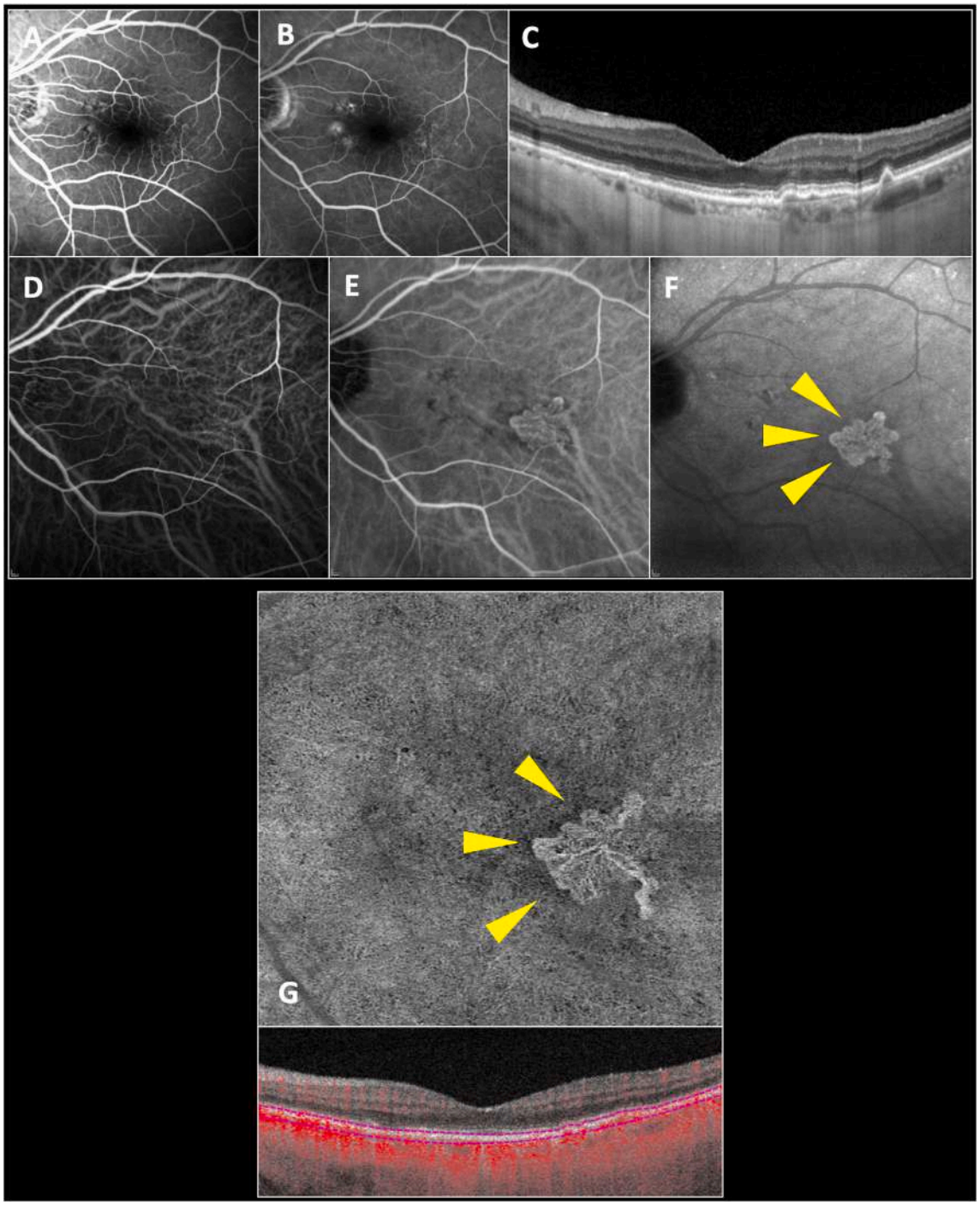

Fig. 7. Multimodal imaging evaluation of a 76-year-old patient affected by type 1 non-exudative macular neovascularization (MNV) in the left eye.

of OCTA to detect flow that is too slow and/or too fast, depending on the interscan time. Projection artifacts could cause the misdiagnosis of a neovascular network in an avascular PED. On the other hand, non-exudative NV with very slow flow may not be detected using OCTA.

OCTA can differentiate a fibrovascular from a drusenoid PED the latter of which develops due to confluence of soft drusen. Carnevali et al. first investigated the detection rate of non-exudative MNV in nAMD with OCTA, reporting a sensitivity and specificity of 81.8% and 100%, respectively (Carnevali et al., 2016). The neovascular lesion patterns were characterized in terms of size, morphology, vascular caliber, and location on the en-face OCTA slab (Fig. 7). The most frequent lesion types observed on OCTA included those with irregular shape, non-visible core, well-defined margins, and foveal-sparing. Non--exudative was defined as the absence of exudative features for a minimum follow-up period of 6 months as previously recommended (Querques et al., 2013). Many studies subsequently described what was defined as "non-exudative subclinical MNV", without a pre-determined exudation-free interval (Bailey et al., 2019; de Oliveira Dias et al., 2018; Roisman et al., 2016; Treister et al., 2018; Yanagi et al., 2018a,b). Although this difference seems only a matter of terminology, non-exudative subclinical MNV, as defined in many prospective and retrospective clinical studies, is a quite different clinical entity versus "quiescent MNV" initially described by Querques et al. (2013). In fact, many authors use the term "subclinical" to define non-exudative lesions with no obvious exudation or related symptoms at the time of diagnosis whereas "quiescent" non-exudative lesions fail to show evidence of exudation for at least 6 months.

The OCTA patterns and features of the size, shape, and density of non-exudative MNV can differ according to the clinical context and are described in the sections below.

Early (A) and late phases (B) of fluorescein angiography (time: 0:32 and 4:58 after dye injection, respectively) showing the presence of mixed hypo- and hyper-fluorescent area in the macular area, with pinpoints inferotemporal to the fovea. Horizontal structural optical coherence tomography (OCT) passing through the fovea (C) showing the presence of a flat irregular pigment epithelium detachment with no signs of exudation (i.e. intra- or sub-retinal fluid, or subretinal hyperreflective material). Early (D), intermediate (E), and late phases (F) of indocyanine green angiography (time: 0:30, 6:13, and 26:21 after injection, respectively) showing the neovascular network with a hyperfluorescent plaque in the late phases of the examination (yellow triangles). En-face OCT-angiography and b-scan with flow (G) showing the presence of a neovascular network, matching non-exudative type 1 MNV (yellow triangles).

3. Age-related macular degeneration (AMD)

3.1. Non-exudative MNV in early AMD

Most studies have reported non-exudative MNV in the context of intermediate AMD. There is evidence that neovascularization may be present earlier than expected within single or confluent drusen (Or et al., 2019; Querques and Souied, 2015). In 2015, Querques et al. coined the term "vascularized drusen" (Querques and Souied, 2015). The presence of drusen characterizes both early and intermediate stages of AMD, depending on the size of drusen (smaller or greater than 125 μm) and the concomitant presence of AMD pigmentary abnormalities (Ferris et al., 2013). Vascularized drusen could complicate drusen in the early or intermediate stages of AMD based on the drusen dimension. This clinical entity masquerades as normal drusen appearing as a dome-shaped RPE elevation rather than a flat RPE detachment with a major axis in the horizontal plane, as described for quiescent MNV (Fig. 8). Vascularized

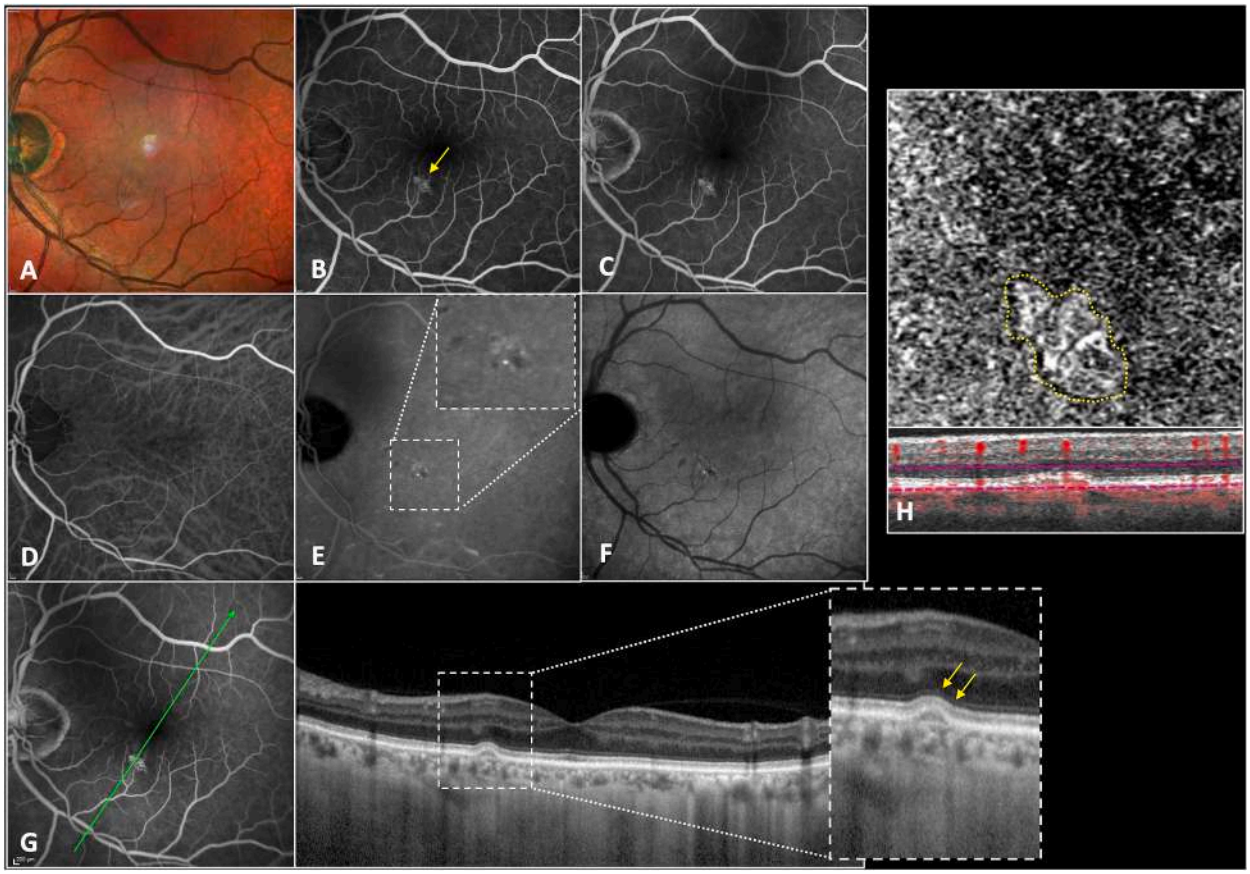

Fig. 8. Multimodal imaging evaluation of a 64-year-old patient affected by vascularized drusen in the left eye.

drusen can appear as calcific or regressed drusen with a hyperreflective signal beneath the RPE. Unlike classic drusen, OCTA and ICGA show evidence of MNV flow within the drusen itself. Structural OCT usually fails to detect vascularized drusen, because, in most cases, they are characterized by uniform sub-RPE hyperreflectivity, without the double-layer or SIRE sign. For this reason, OCTA is very useful in the detection of vascularized drusen. Using OCTA, vascularization within drusen was identified in 7 of 128 eyes with intermediate AMD, accounting for a prevalence of 5.5% (Or et al., 2019). The risk of conversion to exudative is not known, because the longitudinal studies on the evolution of vascularized drusen are lacking in the literature. However, we suggest performing OCTA at least once in patients affected by intermediate AMD. It is important not to confuse pseudoflow within drusen with vascularized drusen as hyperreflective lesions like large drusen (or even pseudo reticular drusen) can exhibit false positive flow signals due to projection and other artifacts of OCTA technology (Hou et al., 2019). Nevertheless, vascularized drusen should be considered as an entity of the non-exudative MNV spectrum.

Multicolor image (A) showing the presence of a drusen-like lesion inferonasal to the fovea. Early (B) and late (C) phases of fluorescein angiography (time: 1:20 and 5:49 after injection, respectively) showing an irregular hyperfluorescent lesion without leakage. Early (D), intermediate (E), and late phases (F) of indocyanine green angiography (time: 0:44, 15:54, and 40:12 after injection, respectively) showing a hyperfluorescent lesion in the intermediate and late phases of the examination (magnification), matching a type 1 neovascularization. Combined fluorescein angiography and structural optical coherence tomography (OCT) passing through the lesion and to the fovea (G) showing a dome-shaped retinal pigment epithelium (RPE) elevation, with uniform sub-RPE hyperreflectivity without the double-layer sing, and a hyperreflective signal beneath the RPE. En-face OCT-angiography and b-scan with flow (H) showing the presence of a neovascular network inside the RPE elevation, using the outer retina and choriocapillaris (ORCC) slab. The multimodal imaging appearance confirmed the diagnosis of vascularized drusen.

3.2. Non-exudative MNV in intermediate AMD

3.2.1. Prevalence

The exact prevalence of non-exudative MNVs among patients with intermediate AMD is still uncertain. Recent studies have found a prevalence ranging from 1.58 to 27% in AMD eyes using OCTA (Carnevali et al., 2018b; de Oliveira Dias et al., 2018; Palejwala et al., 2015; Roisman et al., 2016; Solecki et al., 2021) (Table 1).

The existing literature often investigated the prevalence of non-exudative MNV in a cohort of patients with late neovascular AMD in one eye and intermediate AMD in the fellow eye. These studies are heterogeneous in terms of sample size, study design, and imaging methods used to detect MNV. Palejwala et al. analyzed 32 fellow eyes of patients with exudative neovascular AMD and reported subclinical MNV in 2 eyes (6%)(Palejwala et al., 2015). Heiferman et al. followed 34 contralateral eyes of patients with exudative MNV, demonstrating the evidence of a subclinical MNV in 5 out of 34 eyes (14.7%) at baseline (Heiferman and Fawzi, 2019). Yanagi et al. identified 8 eyes (24%) with subclinical MNV in a sample of 33 patients with neovascular AMD in the fellow eye (Yanagi et al., 2017). In their retrospective study, Treister et al. identified 5 out of 34 cases (14.7%) of subclinical MNV in patients with unilateral neovascular AMD (Treister et al., 2018). Similar results were reported by De Oliveira Dias et al.: in 160 patients with exudative neovascular AMD in one eye, subclinical MNV was identified in 23 fellow eyes (14.4%) (de Oliveira Dias et al., 2018). In a large cross-sectional cohort of 1230 patients with AMD, the prevalence of non-exudative MNV (quiescent for at least 6 months) was 2.52% (95% CI: 1.64–3.40) (Querques et al., 2021).

Table 1
Prevalence and rate of exudative conversion of non-exudative CNV in different diseases.

Disease	Prevalence	Rate of exudative conversion
Age-related macular degeneration		
- Intermediate	1.58–27%	6.6–52% (12-month FU)
- Geographic *Atrophy*	11%	26% (20-month FU)
Pachychoroid neovasculopathy	10.9%	na
Angioid Streaks	33.3–86%	33.3% (24-month FU)

FU: follow-up; na: not available.

3.2.2. Incidence of exudative conversion of non-exudative MNV

The existing literature demonstrates that the presence of a newly diagnosed MNV in a non-exudative state represents a strong risk factor for the future development of exudation, indicating the need for close monitoring after detection. The mechanism of conversion from the non-exudative to the exudative stage of MNV is not completely understood. We can speculate that the exudation is the result of the increased vascular permeability of the MNV during its lifecycle. However, leakage may alternatively be explained by other factors related such as RPE impairment induced by chronic “stress” of the MNV or underlying choroidal ischemia (Hilely et al., 2021).

De Oliveira et al. demonstrated exudation during follow-up in 13 out of 160 eyes (de Oliveira Dias et al., 2018). Specifically, eyes with subclinical MNV at the time of the first OCTA presented an incidence of exudation of 21.1% at 12 months. In the remaining eyes without subclinical MNV at presentation, the incidence of exudation was 3.6% at 12 months. The cumulative incidence of exudation estimated from the first observation of subclinical MNV, either at baseline or during follow-up, was 24% at a 1-year follow-up. This study was extended to 2 years of follow-up with a cumulative incidence of exudation reaching 34.5%. Similar findings were reported by Yanagi et al., analyzing 95 patients with an exudative neovascular lesion in one eye (35 eyes with typical AMD and 60 with PCV) and non-exudative AMD in the fellow eye (Yanagi et al., 2018a). The majority of patients were of Asian ethnicity. Exudative changes occurred in 6 fellow eyes during the follow-up period: 4 of 18 eyes (22.2%) with subclinical MNV and 2 of 77 eyes (2.6%) without subclinical MNV at baseline. The authors concluded that subclinical MNV at presentation carries a significant risk of developing exudative conversion (estimated annual incidence, 18.1%) whereas eyes without previous subclinical MNV less frequently developed de novo exudative neovascularization (estimated annual incidence, 2.0%).

Bailey et al. studied 65 fellow eyes with neovascular AMD in the first eye and detected non-exudative MNV at baseline in 7.9% (n = 5 cases) of eyes (Bailey et al., 2019). Of these 5 eyes, 3 developed exudation after a mean of 10 months. During follow-up, 5 eyes developed a de novo non-exudative MNV that evolved into an exudative lesion in all the cases. Of the total 10 non-exudative MNV lesions identified through OCTA, 80% developed exudation, representing the highest conversion rate reported.

Solecki et al. estimated that subclinical MNV imparts a 23.1 relative risk of developing exudation (Solecki et al., 2021). The study included 144 fellow eyes of patients with neovascular AMD, of whom 23 eyes were diagnosed with subclinical MNV at baseline, with the development of exudative conversion in 52% during the 12-month follow-up. Of the remaining 121 eyes, only 3% developed subclinical MNV during follow-up, with exudation in all of the cases. It further confirms that a newly developed non-exudative neovascular lesion is more prone to early exudative conversion. In fact, these lesions more likely represent a pre-exudative stage of a type 1 lesion, reflecting the physiologic lifecycle of a neovascular lesion (Fig. 7).

These results reflect the taxonomic heterogeneity of non-exudative lesions that can have a high rate of exudative conversion when they are immature and newly detected, in contrast to more chronic mature lesions that can remain quiescent without exudation for 6 months or longer or possibly even indefinitely. Therefore, recognizing a de novo

non-exudative lesion only reflects the physiologic lifecycle of a neovascular lesion. Supporting this concept, it is interesting to note that Carnevali et al. investigated non-exudative MNV lesions inactive for at least 6 months selected from a pool of neovascular AMD patients without consideration of the fellow eye status (Carnevali et al., 2018b). These 2 factors may account for the lower rate of exudation (6.6%) diagnosed after 1 year of follow-up in this study which likely selected neovascular lesions in a pre-existing and prolonged non-exudative stage, a non-exudative neovascular phenotype where vessels may remain stable and quiescent or inactive for years (Chen et al., 2020).

3.2.3. *Predictive factors for exudative conversion*

The 2-year cumulative exudation risk is 13.6 times greater in eyes with non-exudative MNV compared with eyes without detectable lesions, thus highlighting the importance of frequent monitoring in this population. However, this study did not reveal significant risk factors predicting exudation at baseline (Yang et al., 2019). The role of biomarkers that could predict exudation is of paramount importance in order to personalize the follow-up of AMD patients, and in order to initiate treatment with the earliest signs of exudation. Indeed, it is well-established that intervention with anti-VEGF therapy as early as possible after the development of an active or exudative MNV lesion, the better the visual outcome due to reduced rate of development of fibrosis and atrophy (Shen et al., 2022).

Different groups have tried to identify predictors of exudation in non-exudative MNV, using different strategies. The most critical indicator for exudation seems to be represented by the dimensional growth of the neovascular lesion. Querques et al. affirmed that although MNV could be "clinically quiescent" such lesions retained a certain degree of biological activity, showing growth during the follow up period. Indeed, the lesions tended to increase in size according to ICGA evaluation after 6 months (Querques et al., 2013). Carnevali et al. also demonstrated growth of quiescent MNV detected with OCTA at 12-months, with a statistically significant enlargement in 71.4% of lesions (Carnevali et al., 2018b). Vessel density modifications did not accompany the dimensional growth of the MNV area. The authors suggested that the absence of vessel density changes may distinguish a 'quiescent' from an 'active' phenotype, potentially leading to exudation.

Yanagi et al. found that eyes with subclinical MNV that developed exudation showed a significant increase in the vascular network evident 6 months before the exudative changes on OCTA (Yanagi et al., 2017). Bailey et al. also described an increase of vessel area in 5 out of 6 non-exudative MNV lesions that subsequently developed exudation (Bailey et al., 2019). Moreover, Heiferman et al. confirmed an increase of MNV area in eyes that converted to the exudative form (Heier et al., 2012). The importance of enlargement of non-exudative MNV is still debated in the literature as it is clear that both clinically inactive and active forms of MNV clearly grow over time as determined by OCTA (Xu et al., 2018). Of note, we consider MNV as "clinically active" when they display signs of exudation (i.e. presence of subretinal or intraretinal fluid, SHRM, and/or hemorrhages). On the other hand, clinically inactive MNV can show biological activity as indicated by enlargement of the MNV size over time. However, different groups have demonstrated that a faster growth rate of non-exudative MNV may indicate a greater risk of exudation (Bailey et al., 2019; Heier et al., 2012; Yanagi et al., 2017). Carnevali et al. showed a more significant enlargement of the MNV area for lesions developing exudation compared to lesions that remained quiescent (Figs. 9 and 10) (Carnevali et al., 2018b). This outcome was also duplicated by Solecki et al., who found a significantly enlarged area for lesions that developed exudation compared to those remaining quiescent (+250% vs. +22.6%) (Solecki et al., 2021). A doubling in size was associated with a sixfold increase in the risk of exudation. Therefore, rapid significant growth may predict clinical activity and greater risk of exudation (Fig. 10). These data were also supported by Invernizzi et al. using a different approach (Invernizzi et al., 2021). By means of structural OCT, they demonstrated that thickening of the outer retinal layers (from the external limiting membrane to the Bruch's membrane) can be detected about 8 months before the onset of exudation in the area overlying the eventual development of exudative MNV. This increased outer retinal thickening accelerates in the 2 months before the onset of exudation. These data suggest, using structural OCT, that there is an increase in the enlargement rate of growth of non-exudative MNV before

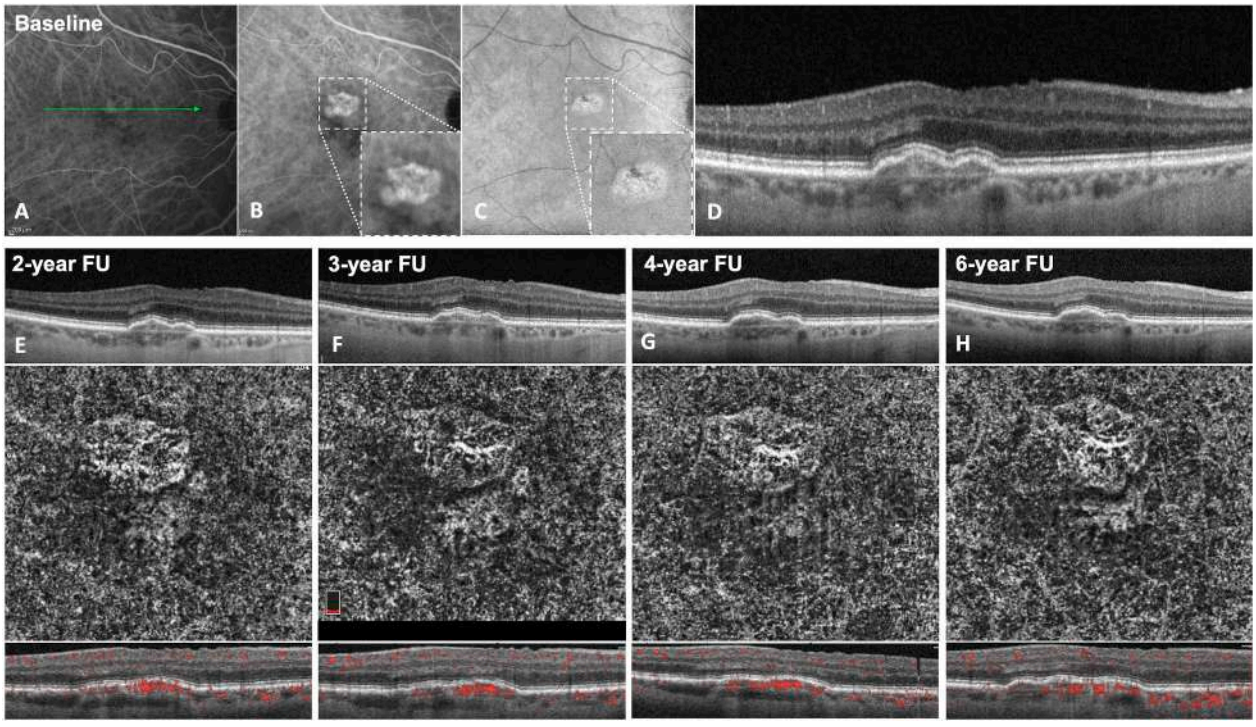

Fig. 9. Multimodal imaging evaluation of a 71-year-old patient affected by non-exudative type 1 macular neovascularization (MNV) in the right eye with long-term follow-up (FU).

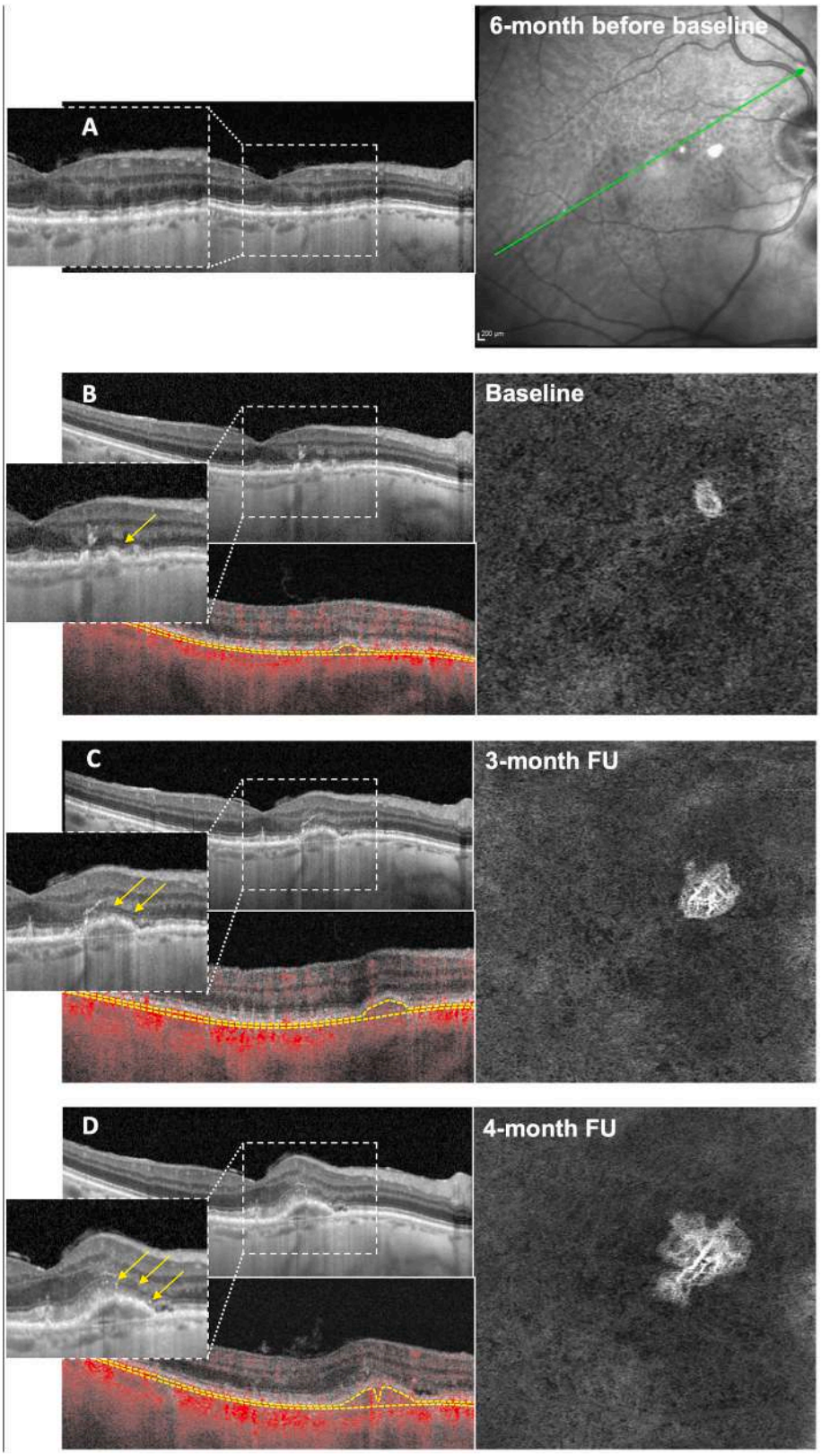

Fig. 10. Multimodal imaging evaluation of a 76-year-old patient affected by non-exudative type 1 macular neovascularization (MNV) in the right eye at the baseline, with short-term exudation.

the exudation (Fig. 2). However, we cannot exclude that the enlargement of the PED could be due, in part, to sub-RPE exudation, preceding the retinal/sub-retinal exudation. In this case, subretinal and/or intraretinal fluid occurs only when the RPE barrier is disrupted. In a recent paper, Querques et al. also demonstrated that non-exudative MNV eyes with early exudative conversion (less than 6 months) were characterized by a faster growth rate in comparison to non-exudative MNV without conversion (Figs. 9–11) (Querques et al., 2021). This supports again the importance of the growth rate in the prediction of short-term exudation (i.e. activation) of non-exudative MNV. In detail, the Authors analyzed 31 non-exudative MNV eyes for a mean of 22 ± 9months, identifying three different patterns of growth. Lesions were staged as 'persistently quiescent MNV' that did not develop signs of exudation during the entire follow-up duration (68%), 'long-term activated' that showed exudation after 6 months (19%), and 'short-term activated' (13%) that developed exudation before 6-month follow-up. Results from this analysis demonstrated that short-term activators (<6 months) were characterized by the greater growth rate of MNV area, but also by higher perfusion density at baseline (Querques et al., 2021). The persistently quiescent phenotype did not differ in anatomical characteristics with the long-term activated MNV group. Therefore, these results reinforced the importance of a clinical distinction between quiescent and subclinical MNVs. The quiescent phenotype presented a low activity grade with a slow growth rate and low perfusion density. This group lacks clinical predictors of activation. By contrast, the subclinical lesions are characterized by short-term activation within 6 months associated with a faster growth rate and higher perfusion density at baseline. This group can be considered a pre-exudative stage of a type 1 lesion, reflecting the physiologic process of neovascular maturation and development and progression (Fig. 10). The higher perfusion density reflects the higher number of capillaries comprising the non-exudative MNV with a high risk of short-term exudation. In this scenario, angiogenesis could represent the most relevant driver in the development of the MNV (Kuehlewein et al., 2015; Spaide, 2015). Angiogenesis is a VEGF-dependent process in which there is a framework of vascular endothelial cells to form neovessels (Adams and Alitalo, 2007; Weis and Cheresh, 2011). This process leads to the proliferation of several new capillaries, resulting in an expansion of the neovascular network and an increase of the perfusion density due to the high number of new capillaries (Fig. 12). Definitely, newly-formed capillaries are characterized by high risk of exudation. This process of angiogenesis is continued until the stimulus of vessel proliferation is interrupted. Since the main stimulus is represented by VEGF, it is easy to understand that by acting with anti-VEGF drugs we are able to reduce and stop the process of angiogenesis.

On the other hand, among the 'quiescent' features described by Querques et al., the low perfusion density may indicate the process of arteriogenesis in which the neovascular lesion is mainly comprised of trunks and large branches (not capillaries) supplying oxygen and nutrients to the RPE and outer retina (Figs. 9 and 11). Arteriogenesis is another process in the development of neovascularization. Arteriogenesis is not characterized by the sprouting of new capillaries as in angiogenesis, but it is characterized by dilation of preexisting channels due to the activation and remodeling and proliferation of the wall of the neovessels (Kuehlewein et al., 2015; Spaide, 2015). This process is driven by a shear stress of the blood flow to the endothelial cells of neovessels when there is high-stress and high-flow due to closure or insufficient flow of other vessels (Pipp et al., 2004; Tzima et al., 2005). The result is activation and remodeling of extracellular matrix and smooth muscle cells of the vascular wall, driven mainly by the PDGF and other cytokines (Schierling et al., 2009; Wu et al., 2010). Indeed, arteriogenesis is not driven by VEGF (as angiogenesis), but by PDGF. The process of arteriogenesis leads to the development of large vessels, with a lower number of capillaries and lower perfusion density of the neovascular network using OCTA (Fig. 12). This process is less responsive to anti-VEGF drugs in comparison to angiogenesis.

Based on these vascular pathophysiology concepts, we can speculate that non-exudative MNV with short-term exudation is driven mainly by angiogenesis. This process is characterized by sprouting of new capillaries, resulting in exudation (Figs. 10 and 12). Therefore it is likely that this process represents a pre-exudative stage of exudative type 1 MNV development (Fig. 7). As reported also by Invernizzi et al., this process usually starts several months before exudation, with an acceleration in the 2 months before exudation (Invernizzi et al., 2021). On the other hand, we can speculate that non-exudative MNV with a long-term history of non-exudation (i.e. quiescent MNV) is driven mainly by arteriogenesis. Arteriogenesis could be considered a chronic process in the progression of non-exudative MNV (Figs. 9 and 12). Indeed, in the beginning, MNV development is driven by VEGF (i.e. angiogenesis). However, for some reason (perhaps due to low VEGF levels), there is closure of small capillaries, resulting in higher pressure of remaining new vessels, an increase of blood flow, and, thus, a stimulus of arteriogenesis. In this way, arteriogenesis characterizes the "maturation" of the neovascularization with large vascular trunks (as explained above). The "maturation" and dynamic changes of type 1 MNV were previously reported from a histological point of view. In the beginning, new vessels are like capillaries, but, with time, they become arterial and venular (Grossniklaus et al., 2004). The Authors suggested that, after the first steps driven by angiogenesis, the balance shifts to antiangiogenic activity resulting in the involutional stage of MNV. In this stage, the closure of vessels and thrombus formation is possible (Gass, 1967; Grossniklaus et al., 2004). This process is very similar to what happens in exudative MNV treated by anti-VEGF injections (Kuehlewein et al., 2015; Querques et al., 2020; Spaide, 2015).

Various groups have tried to identify predictors of exudation by analyzing different morphological parameters. Shen et al. focused their attention on the choriocapillaris around the non-exudative MNV itself, on the analysis of choroidal vascularity index, and on the volume of the PED (Shen et al., 2021). Interestingly, they identified that the near-term onset of exudation was associated with lesions showing smaller PED volume and less vascularity. On the other hand, no correlations were observed with the choriocapillaris flow deficit, mean choroidal thickness, on choroidal vascularity index. On one hand, these data are in agreement with the previous theory. Indeed, smaller non-exudative MNV represents the early stages in the development of an exudative type 1 MNV, whereas larger non-exudative MNV represent "chronic" and long-standing non-exudative MNV (i.e. quiescent MNV) that by their history have already demonstrated a lower tendency to exudation. On the other hand, the association of exudation with less vascular MNV is surprising and in contrast with previously reported data. It is well known that clinically "active" MNV is characterized by a higher vascular density of MNV in comparison to inactive MNV, showing the presence of a high number of capillaries. This was demonstrated also in non-exudative MNV. Querques et al. and Teo et al. reported that a greater vascular density of non-exudative MNV at baseline is a predictor of exudation (Querques et al., 2021; Teo et al., 2021). On the other hand, Shen et al. reported the opposite (Shen et al., 2021). However, Shen et al. did not consider the baseline features of non-exudative MNV but the features of only the two visits preceding the exudation. For this reason, the data are not reliable, and they are of less interest. In fact, clinicians want to know the risk of exudation at the diagnosis of an MNV, in order to plan the correct management and follow-up of the patients. Finally, Solecki et al., confirmed the importance of growth of the RPE detachment and increase in the surface area of the neovascular complex on OCTA as predictors of exudation, and also identified qualitative features such as the branching pattern of the MNV and the hypointense halo surrounding the lesion as biomarkers of activity (Solecki et al., 2021). The emergence of a branching pattern was associated with a higher risk of exudation. Before exudation, there is a remodeling of the neovascularization itself, with an increase of the anastomosis and capillary growth that are known to be associated with exudation (Al-Sheikh et al., 2018; Coscas et al., 2015). Also, the dark halo is known

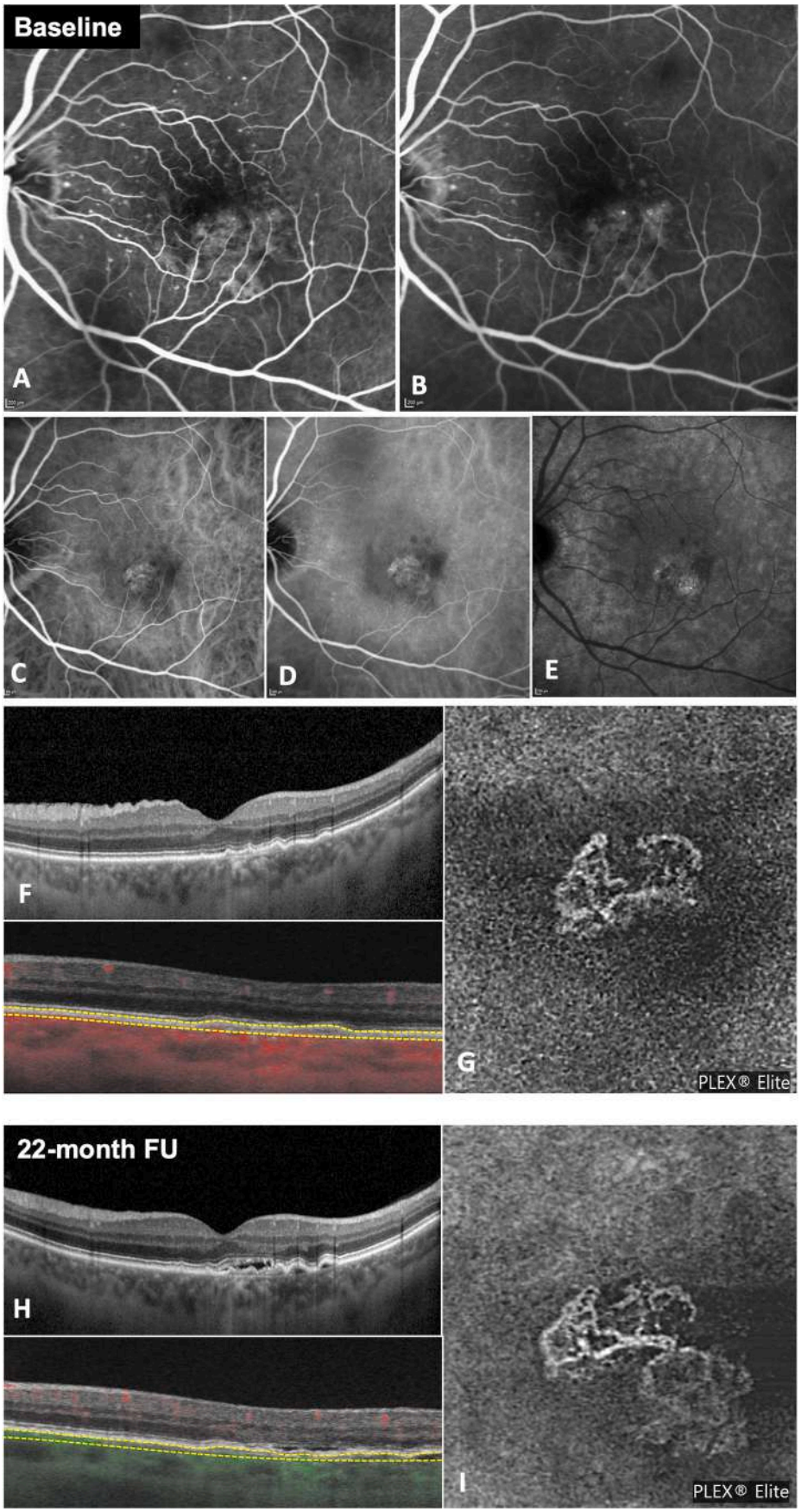

Fig. 11. Multimodal imaging evaluation of a patient affected by non-exudative type 1 macular neovascularization (MNV) in the left eye at the baseline, with long-term exudation.

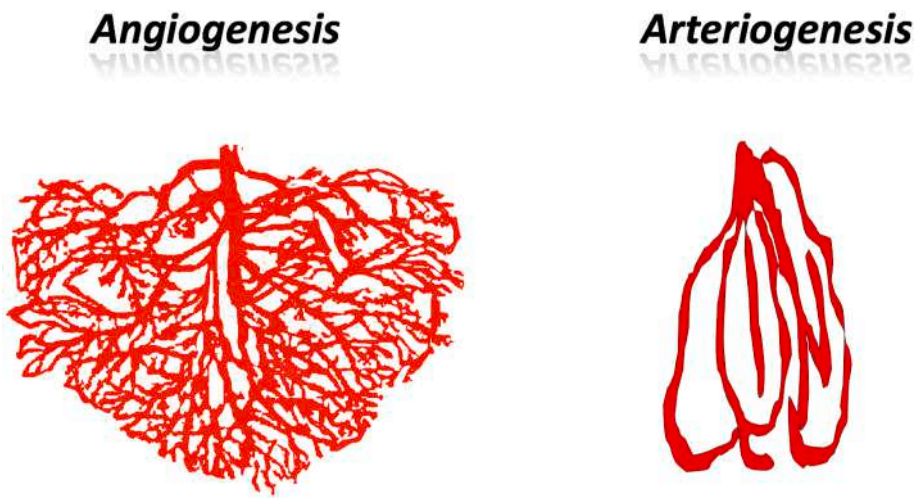

Fig. 12. Schematic representation of an MNV driven by angiogenesis (left one) and an MNV driven by arteriogenesis (right one).

to be associated with active MNV lesions. The presence of the dark halo was explained as a vascular steal of the neovascularization or as a decrease of choriocapillaris vessels around the neovascularization itself (Coscas et al., 2015, 2018; Rispoli et al., 2018). However, none of these OCTA biomarkers have been validated as true predictors of exudative activity.

Early (A) intermediate (B), and late phases (C) of indocyanine green angiography (time: 1:58, 7:21, and 40:00 after injection, respectively) showing a hyperfluorescent lesion with a plaque in the mid and late phases of the examination (magnification), matching a type 1 MNV. Horizontal structural optical coherence tomography (OCT) passing through the fovea (D) showing a flat irregular pigment epithelium detachment with a double-layer sign at the baseline, with no signs of exudation (i.e. intra- or sub-retinal fluid, or subretinal hyperreflective material). Structural OCT, en-face OCT-angiography, and B-scan with flow showing the type 1 neovascular network with no signs of exudation at 2 years (E), 3 years (F), 4 years (G), and 6 years FU.

Combined infrared reflectance and structural optical coherence tomography (OCT) passing through the fovea showing reticular pseudodrusen 6 months before the "baseline" (A). Six months later, structural OCT passing through the same line (B) showing the presence of a small elevation of the retinal pigment epithelium (RPE) (yellow arrow). Of note, enface OCT-angiography (OCT-A) and b-scan with flow showing a neovascular network inside the RPE elevation, matching a non-exudative type 1 MNV. Three months later (C), structural OCT and OCT-A showing the great enlargement of the RPE elevation and of the neovascular network. At a 4-month follow-up, there was another fast enlargement of the MNV at OCT-A, and type 1 MNV showed early signs of exudation (i.e. subretinal hyperreflective material).

At the baseline, early (A) and late (B) phases of fluorescein angiography (time: 0:32 and 5:24 after injection, respectively) and early (C), intermediate (D), and late (E) phases of indocyanine green angiography (ICGA) (time: 1:09, 6:59, and 36:44 after injection, respectively) showing the presence of a type 1 neovascular network with a hyperfluorescent plaque in the late phases of ICGA at the baseline. Structural optical coherence tomography (OCT) passing through the fovea showing a flat irregular pigment epithelium detachment with no signs of exudation at the baseline (F). En-face OCT-angiography (OCT-A) (G) and b-scan with flow showing a neovascular network with large vessels and a small number of capillaries. Based on multimodal imaging, the diagnosis of non-exudative type 1 MNV was performed. Interestingly, 22 months later, the MNV showed signs of exudation (i.e. subretinal fluid) at structural OCT (H) and OCT-A (I) showed the enlargement of the neovascularization.

3.2.4. *The role of the choriocapillaris*

The choriocapillaris plays a crucial role in supporting the RPE cells and photoreceptors with nutrients and oxygen. Previous evidence suggested that choriocapillaris impairment could be one of the first steps in the pathogenesis of MNV (Bhutto and Lutty, 2012; Hayashi and de Laey, 1985; Moult et al., 2020). In this scenario, neovascular AMD may be considered a vascular disease with choriocapillaris impairment and secondary degeneration of the RPE cells and photoreceptors. Furthermore, it was proven that also the choriocapillaris around the area of exudative MNV is impaired (Moult et al., 2020; Forte et al., 2020). Interestingly, this impairment was also disclosed in patients affected by non-exudative MNV. Scharf et al. enrolled 16 patients with treatment--naïve exudative MNV and 7 patients with treatment-naïve non-exudative MNV (Scharf et al., 2020). The authors noted that the choriocapillaris around the dark halo of the MNV was impaired in both groups in comparison to age-matched healthy controls. Moreover, although not statistically significant, the choriocapillaris impairment was greater in eyes with exudative versus non-exudative MNV in both rings of choriocapillaris outside the MNV and its dark halo. In another series, expanding the number of eyes, we have confirmed this observation. Due to the greater choriocapillaris impairment of the exudative MNV in comparison to non-exudative MNV, we wondered if the impairment of the choriocapillaris around the lesion could be considered as a predictor of exudation in non-exudative MNV. This was recently investigated by Shen et al., who found that the flow deficit percentage of the choriocapillaris did not correlate with short-term exudation (Shen et al., 2021). However, Shen et al. did not exclude the dark halo around the non-exudative MNV as performed by Scharf et al., and thus the results could be influenced by the presence of the dark halo itself. Furthermore, we cannot also exclude that the impairment of the choriocapillaris around the MNV at baseline could correlate with a higher risk of exudation during the long-term follow-up. Based on this evidence, we are unable to draw definitive conclusions on the role of the choriocapillaris around non-exudative MNV. Surely, the choriocapillaris impairment is a crucial driver in the development of neovascularization (also non-exudative). MNV is a compensatory response to the deficit of the underlying choriocapillaris itself (Biesemeier et al., 2014). The flow around the neovascular lesion may be altered due to the vascular steal phenomenon of diverted flow through the MNV (i.e. presence of dark halo) (Coscas et al., 2015, 2018; Forster et al., 2017; Moult et al., 2014; Rispoli et al., 2018). Furthermore, the flow deficit of the choriocapillaris is greater outside the dark halo in patients with exudative MNV in comparison to non-exudative MNV. The development of new advanced OCT-A devices with greater resolution and a faster scanning rate will allow us to better detect and understand small

differences in the choriocapillaris flow, elucidating the potential role of choriocapillaris perfusion as a predictor of exudation.

3.3. Non-exudative MNV in geographic atrophy

The beneficial effect of a non-exudative type 1 MNV on the outer retina and RPE has been purported based on histological analyses. Neovessels support the native choriocapillaris and overlying RPE and photoreceptors providing oxygen and metabolic supply (Grossniklaus et al., 2004). This is of paramount relevance in GA because the choriocapillaris and choroidal layers are more significantly impaired in comparison to other stages of AMD (Sacconi et al., 2021a). The crucial role of the choriocapillaris in the pathogenesis of GA has been elucidated in recent years thanks to the introduction in the clinical practice of OCTA (Corbelli et al., 2017). Sacconi et al. first reported that the choriocapillaris is more significantly impaired surrounding the RPE atrophic area in GA patients, suggesting a potential role in the development of GA (Sacconi et al., 2018b). Subsequently, different groups demonstrated that the impairment of the choriocapillaris could predict the rate of enlargement and the direction of enlargement of the GA areas (Alagorie et al., 2020; Nassisi et al., 2019; Sacconi et al., 2021b; Thulliez et al., 2019). In this scenario, the development of non-exudative MNV could play an essential role in the nutrition of RPE and photoreceptors, protecting this area from GA expansion (Fig. 13). On the other hand, we cannot exclude that the choriocapillaris damage is secondary to a RPE and photoreceptor degeneration; in this hypothesis, the RPE dysmorphia seems to play a crucial role in the pathogenesis of GA expansion, leading to a secondary choriocapillaris degeneration due to the loss of RPE-derived trophic factors such as secreted VEGF (Mullins et al., 2011; Bui et al., 2021).

The presence of non-exudative MNV in patients with GA was first reported by Capuano et al., in 2017 (Capuano et al., 2017) (Table 1). In their paper, the authors evaluated 19 patients diagnosed with GA associated with non-exudative neovascularization with at least 6 months without exudation (i.e. quiescent MNV). In the context of GA, the OCTA examination presented a sensitivity of 66.6% in detecting non-exudative MNV, which was significantly lower than the detection rate found in intermediate AMD (82%). This difference was explained as the result of a strong OCTA signal from the choroid due to a loss of the overlying RPE and choriocapillaris. Following the 19 patients for a mean of 45.7 months (range 27–65), 14 eyes remained stable without exhibiting exudation over time, whereas 5 out of 19 eyes (26%) developed exudation (i.e. activation of quiescent MNV). The exudative complications in GA seem to occur in a higher percentage of cases compared to intermediate AMD (26% vs. 6.6%, respectively), but needs to be also considered in light of a longer follow-up in the GA cohort (12 vs. 20 months). Despite this, the treatment of such lesions should be reserved only when exudation occurs in consideration of the protective effect of neovessels in preventing atrophy progression. In this way, Sacconi et al. have recently suggested that the treatment of exudation in MNV concomitant with GA should be reduced at the minimum (Sacconi et al., 2021c). Indeed, using a pro-re-nata regimen without a loading phase, many cases of MNV did not show signs of exudation after only one/two injections. Based on this evidence, we suggest treating exudative MNV concomitant with GA with a PRN regimen in order to reduce the number of anti-VEGF injections and thus preserve the presence of MNV itself, and also preserve the physiological role of VEGF in the maintenance of the choriocapillaris. The crucial role of VEGF in the preservation of choriocapillaris in dry AMD is supported by animal models. Indeed,

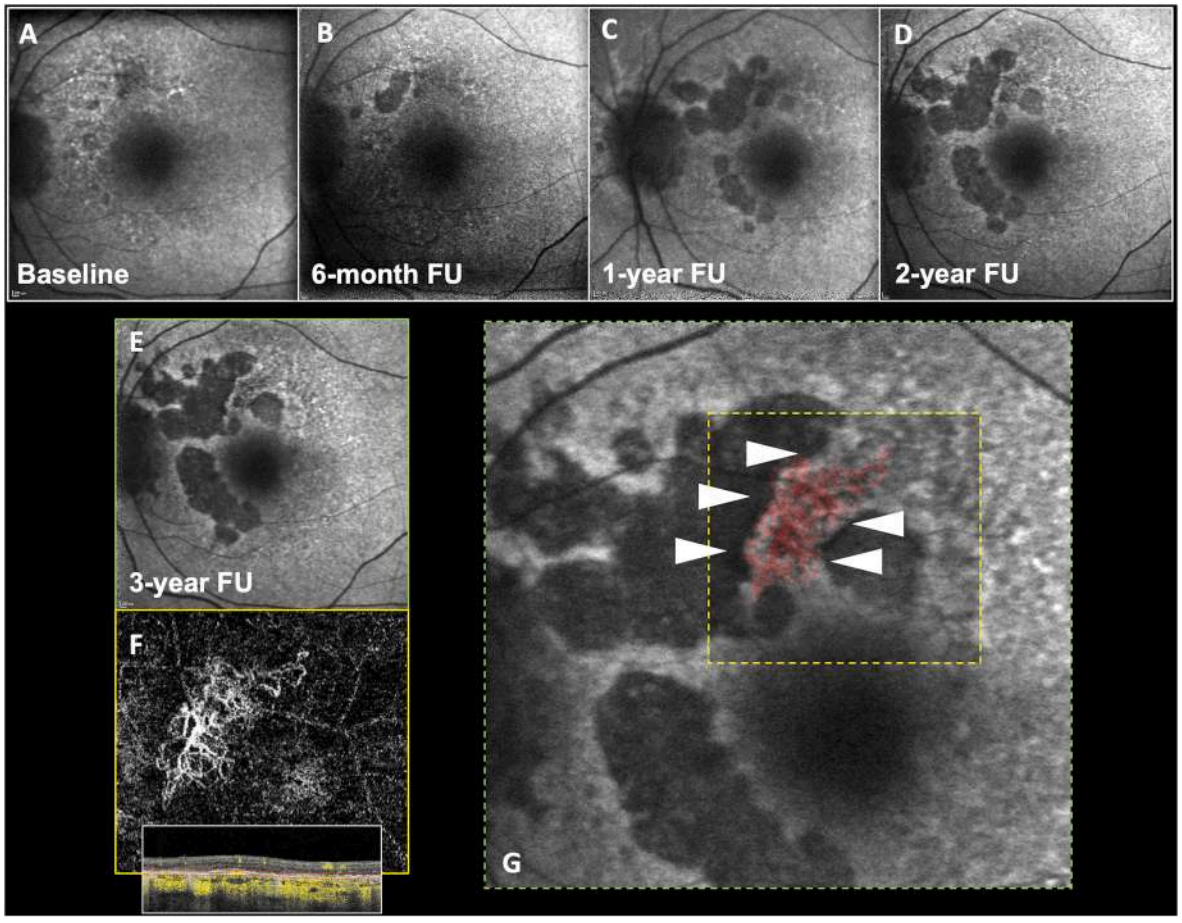

Fig. 13. Serial short-wave fundus autofluorescence (FAF) images during the time of a 79-year-old patient affected by geographic atrophy with concomitant non-exudative type 1 macular neovascularization (MNV).

Kurihara et al. demonstrated that the deletion of the VEGF-A gene in adult mouse RPE cells resulted in a dramatic loss of the endothelial cells of the choriocapillaris and, subsequently, vision loss due to photoreceptor death (Kurihara et al., 2012). The goal of the anti-VEGF treatment in the mixed phenotype (i.e. GA with neovascular AMD) may be not to close the neovessels, but to mature the neovascularization into a non-exudative stage. Indeed, maintaining MNV in a non-exudative stage could provide the beneficial effects of type 1 MNV, preventing the enlargement of atrophic lesions in the area of MNV (Fig. 13). However, other prospective studies are needed in order to confirm the previous data and to further support this strategy.

The OCTA evaluation of non-exudative MNV in GA revealed morphological features different in comparison to previously described non-exudative MNV lesions associated with intermediate AMD. In specific, Capuano et al. reported that non-exudative MNV in GA is characterized by large neovascular trunks, with less tortuosity of the neovascular network and a low number of capillaries (Fig. 14) (Capuano et al., 2017). These features denoted vessel arteriogenesis in the neovascular lesions associated with GA. In another series, we have currently collected patients with non-exudative MNV in the context of GA and in the context of intermediate AMD. Patients affected by MNV with intermediate AMD showed smaller vessels with a greater rate of capillaries, greater tortuosity, and anastomosis. This was noted also analyzing perfusion density of non-exudative MNV after binarization of OCTA images. Indeed, MNV with intermediate AMD showed greater perfusion density in comparison to non-exudative MNV with GA. Furthermore, non-exudative MNV in the setting of GA that developed exudation showed greater response to anti-VEGF injections in terms of fewer injections in comparison to activated non-exudative MNV in the setting of intermediate AMD. The current and previous data suggest the different drivers in the pathogenesis of non-exudative MNV in intermediate AMD and in GA. Features of MNV in some cases of intermediate AMD suggest the role of angiogenesis in the development of MNV. On the other hand, features of MNV in the setting of GA suggest the role of arteriogenesis in the development of MNV (Fig. 12). The different drivers at the basis of the non-exudative MNV development supported the beneficial nature of non-exudative MNVs in GA. Non-exudative MNV could represent a compensatory mechanism of microvascular remodeling in response to the severe ischemia of the choriocapillaris in GA. Thus, these long-standing MNVs play a fundamental role in the compensation of impaired choriocapillaris, supporting the RPE and photoreceptors. Recent histological evidence demonstrated the presence of a capillary circulation with fenestrations and caveolae at the anterior surface of the MNV in close proximity to the RPE which resembled the native choriocapillaris in a patient affected by non-exudative MNV with a long history of non-exudation (Chen et al., 2020). This "new" capillary circulation of the MNV lesion similar to the native choriocapillaris could be the explanation of the protective role of atrophy in this category of patients. Indeed, the new vascular tissue might support oxygen and nutrient delivery to the RPE cells, replacing the role of the impaired native choriocapillaris.

The protective role of quiescent MNV was also studied in the prevention of GA enlargement. Heiferman et al. observed that the rate of GA progression with an associated NE-MNV was slower than in patients with GA with no evidence of neovascularization (0.02 mm^2/year vs. 0.82 $\pm$ 1.20 mm^2/year, respectively) (Heiferman and Fawzi, 2019). Pfau et al. also reported a significant reduction of RPE atrophy progression in areas co-localizing with treatment-naïve quiescent type 1 MNV, further corroborating the protective effect of the non-exudative lesions (Pfau et al., 2020). Contrasting results were recently reported by a prospective study with only 9 participants diagnosed with a type 1 MNV adjacent to an area of GA $\geq$ 2.54 mm2 or multifocal GA lesions. The study provided a quantitative assessment of the changes in GA growth according to the distance-to-MNV. Among the study limitations, the authors emphasized that a nonlinear relationship between local GA growth rates and distance-to-MNV could have confounded Pearson's correlation analysis (Trivizki et al., 2022). However, the authors focused their attention only on the atrophic area growing near the non-exudative MNV, and not on the atrophic changes over the MNV itself. Indeed, in their images, it is apparent that RPE and outer retinal layers are still preserved in the area of the MNV, supporting the role of non-exudative MNV in the preservation of RPE and outer retinal layers (Trivizki et al., 2022).

Also, the topographical localization of non-exudative MNV was particularly interesting, considering that the lesions tended to co-localize at the GA border in subfoveal/perifoveal regions. A foveal sparing from atrophy was noted in all cases of the series of Capuano et al., with anatomical preservation of the outer retinal layers and a retained visual acuity until the last visit (Capuano et al., 2017). These findings supported the beneficial nature of non-exudative MNVs in GA.

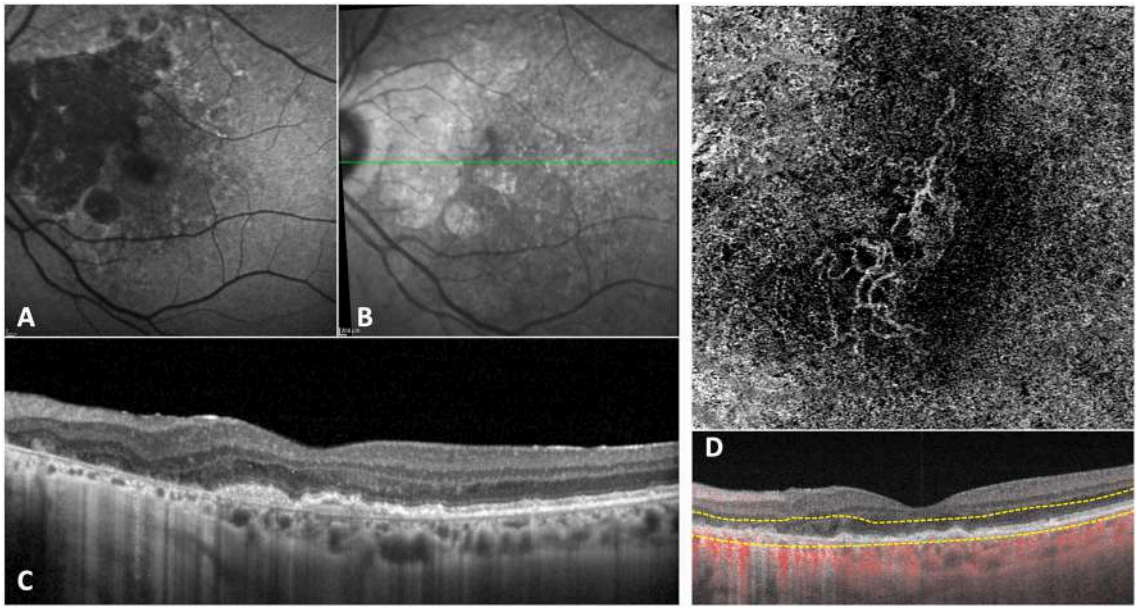

Fig. 14. Multimodal imaging evaluation of a83-year-old patient affected by geographic atrophy with concomitant non-exudative type 1 macular neovascularization (MNV) in the left eye.

Short-wave FAF image showing the presence of a small area of retinal pigment epithelium atrophy at the baseline (A). During the time, geographic atrophy showed great enlargement with the confluence of the atrophic lesions (B, C, D, and E). En-face optical coherence tomography angiography (OCT-A) and b-scan with flow showing the presence of a non-exudative type 1 MNV. Interestingly, overlapping FAF and OCT-A (G), the image demonstrated that the area affected by non-exudative MNV was spared from the confluence of geographic atrophy during the time (white triangles).

Short-wave fundus autofluorescence (A) and infrared reflectance (B) showing the presence of geographic atrophy partially sparing the fovea. Horizontal structural optical coherence tomography (OCT) (C) showing atrophy of the outer retina and retinal pigment epithelium with a backscattering effect nasally to the fovea, and the presence of a flat irregular pigment epithelium detachment in the subfoveal area, with no signs of exudation (i.e. intra- or sub-retinal fluid, or subretinal hyperreflective material). En-face OCT-angiography and b-scan with flow (D) showing the presence of a neovascular network matching a non-exudative type 1 MNV. Of note, the neovascular network is characterized by great neovascular trunks, with less tortuosity of the neovessels and a low number of capillaries.

3.4. Proposed clinical definition of non-exudative MNV

Establishing a standardized definition and consensus for the different entities characterizing the spectrum of non-exudative MNV is absolutely needed in order to enable more direct comparisons across different clinical research studies. Several retinal specialists agree that the terminology "non-exudative MNV" is the best way to characterize treatment-naïve type 1 macular neovascularization showing no exudation at the time of diagnosis. However, as can be seen from the previous sections, non-exudative MNV is a spectrum of the disease characterized by different entities, with different pathways driving the disease process, different imaging features, and, thus, different clinical courses (different risk of activation and different response to the treatment). In our clinical practice, we frequently see patients with non-exudative MNV stable for several years, without signs of exudation (Fig. 9). On the other hand, we also see patients with non-exudative MNV developing exudation in a few months (Fig. 10). Distinguishing between these entities is of paramount relevance (Fig. 3).

Due to the lack of sufficient knowledge and consensus to date about the imaging features characterizing different forms of non-exudative MNV, we suggest that the timing of the follow-up could be useful in differentiating non-exudative MNV with a low risk of exudation versus non-exudative MNV with a high risk of short-term activation. Therefore we suggest the classification of non-exudative MNV into quiescent versus subclinical forms where quiescent MNV represents non-exudative MNV (treatment naïve or otherwise) without any evidence of exudation for a period of at least 6 months. The recent paper of Invernizzi et al. suggested that this time period (in their series it was 8 months) represents the mean interval between the first detection of RPE elevation (i.e. early stages of type 1 MNV development) and the identification of exudation from the type 1 MNV (Invernizzi et al., 2021). So, using a threshold of 6 months with no exudation would allow better characterization of non-exudative MNV with a low risk of exudation and "quiescent" MNV would therefore represent a subgroup of non-exudative MNV.

"Quiescent" MNV could include not only non-exudative treatment-naïve MNV with low tendency to exudation, but also previously treated MNV that have become inactive or quiescent and no longer require injections and remain inactive or quiescent for several months/years. However, the focus of this review is about treatment-naïve MNV, and thus previously treated quiescent MNV are not covered in this paper.

4. Pachychoroid spectrum disorders

4.1. General information

4.1.1. Clinical classification

The term pachychoroid ("παχυ-" [Greek prefix] thick) was introduced to describe a phenotype characterized by focal or diffuse thickening of the choroid in which dilated choroidal veins in Haller's layer (*pachyvessels*) are often accompanied by thinning of the choriocapillaris and Sattler's layer with or without overlying RPE abnormalities (Balaratnasingam et al., 2016; Lee et al., 2016; Margolis et al., 2011; Pang and Freund, 2014; Warrow et al., 2013). Advances in imaging technology have informed a more precise characterization of pachychoroid disease features linked to a spectrum of macular manifestations in which choriocapillaris attenuation and RPE changes occur within regions of choroidal venous congestion (Bacci et al., 2022; Dansingani et al., 2019; Matsumoto et al., 2020; Pang et al., 2014; Spaide et al., 2022; Yanagi et al., 2018a,b). Dilated choroidal vessels and hyperpermeability are detected with ICGA in eyes with central serous chorioretinopathy (CSC) and polypoidal choroidal vasculopathy (PCV) (Guyer et al., 1994). With the advent of enhanced-depth imaging OCT (EDI-OCT) and subsequent swept-source OCT (SS-OCT), the quantification of choroidal thickness was greatly facilitated (Dansingani et al., 2016b; Ferrara et al., 2014). Although a thick choroid can be frequently observed, the choroidal thickness per se should not be considered a criterion for defining the pachychoroid disease phenotype. The diagnosis is based instead on the characteristic anatomical changes affecting the choroid and reflecting the key pathophysiological mechanisms (Balaratnasingam et al., 2016). Focal or diffuse increase in choroidal thickness, evidence of pachyvessels, attenuation of the inner choroid, and choroidal vascular hyperpermeability evident on ICGA are the main features defining pachychoroid disease. The pachychoroid disease spectrum incorporates a myriad of macular complications that include CSC (Sartini et al., 2020a,b; Van Rijssen et al., 2019), pachychoroid pigment epitheliopathy (Warrow et al., 2013), focal choroidal excavation (Chung et al., 2017), peripapillary pachychoroid syndrome (Phasukkijwatana et al., 2018; Xu et al., 2020), pachychoroid neovasculopathy (Phasukkijwatana et al., 2018; Sartini et al., 2020a,b), and aneurysmal type 1 macular neovascularization/PCV (Fung et al., 2012).

When evaluating pachychoroid disease related complications, an essential concept is that pachychoroid neovasculopathy may occur due to a focal choroidal abnormality in the macula and can even develop in myopic eyes, without the need of diffuse choroidal thickening (Pang and Freund, 2014).

Further, the differentiation between pachychoroid and AMD should consider the recently described extracellular deposits resembling macular drusen, referred to as pachydrusen (Lee et al., 2020). Pachydrusen are similar to soft drusen in size, but several features can help differentiate the lesions beyond the context of a thick choroid (Lee et al., 2020; Spaide, 2018). Pachydrusen have the following characteristics: (1) size >125 μm (large drusen), (2) irregular and more well-demarcated borders, (3) scattered distribution over the posterior pole, (4) isolated or grouped in a few clusters and (5) associated with a thick choroid (reduced fundus tessellation), especially when located at the macula (Spaide, 2018). The presence of pachydrusen was more frequent in the Asian population than Caucasians, in line with the higher prevalence of pachychoroid disease spectrum in this demographic (Cheung et al., 2018b; Lee et al., 2020).

Neovascularization development represents a well-known complication of pachychoroid disorders due to attenuation of the choriocapillaris (Fung et al., 2012). Type 1 CNV has been highlighted as the most frequent neovascularization subtype complicating chronic CSC (Fung et al., 2012). Pang and Freund defined "pachychoroid neovasculopathy" as a clinical entity characterized by type 1 neovascularization in eyes with pachychoroid features in the absence of age-related macular

degeneration or degenerative changes (Pang and Freund, 2015). Polypoidal structures can also arise within type 1 neovascularization progressing to larger polyps and to a more extensive branching vascular network with the growth of the lesions (Cheung et al., 2018a, 2019). Pachychoroid neovasculopathy is often associated with saccular dilatations arising from sub-RPE neovascular tissue, similar to aneurysmal/polypoidal lesions. To distinguish such lesions from the PCV described initially as peripapillary choroidal polyps in middle-aged females, mainly of African ancestry, and to more accurately reference the anatomy of the saccular dilations, the alternative term aneurysmal type 1 CNV was proposed without reaching universal consensus regarding this nomenclature (Fragiotta et al., 2018; Li et al., 2019; Spaide et al., 2020; Dansingani et al., 2018).

Pachychoroid neovasculopathy can be commonly misdiagnosed as CSC in middle-aged patients, while in elderly patients, it can often be confused with neovascular AMD, as recently described (Borrelli et al., 2020). The occurrence of pachychoroid neovascularization is more likely in older patients with a long history of CSC (Borrelli et al., 2020; Fung et al., 2012; Pang and Freund, 2015). In the pre-OCTA era, the detection of type 1 neovascularization within a shallow irregular PED showed a 19% prevalence on dye-based angiography and the remaining PED cases persisted without evidence of CNV on dye angiographies (Hage et al., 2015). On OCTA, the detection of a type 1 tangled neovascular network within a shallow irregular PED was evident in 95% of cases using OCTA technology (Dansingani et al., 2015). The authors concluded that dye-based angiogram underestimates the prevalence of neovascularization, possibly due to the quiescent state of this neovascular form. Therefore, detection of a shallow irregular PED on OCT in eyes with evidence of pachychoroid spectrum disease is highly suggestive of type 1 neovascularization, including non-exudative type 1 CNV.

4.1.2. *Imaging features*

Characteristic clinical features of pachychoroid neovasculopathy include the presence of type 1 CNV, which appears on OCT as a flat or shallow irregular elevation of the RPE detached from the underlying Bruch's membrane, i.e. a "double layer sign", and overlying pachyvessels. The evidence of heterogeneous hyperreflective material in the sub-RPE space further corroborates the presence of neovascularization (Cheung et al., 2019). Determining choroidal thickness may help differentiate among drusen subtypes and phenotypes of neovascularization. Eyes with pachydrusen exhibit a thick choroid, more prone to develop pachychoroid neovasculopahy or aneurysmal type 1 CNV/PCV (Cheung et al., 2018a).

Eyes with CSC develop serous PED due to excess leakage from choriocapillaris and thickened choroid leading to alteration of the RPE pump function. Serous PEDs appear as a sharp demarcated RPE elevation that can eventually convert to neovascularization in 28–34% of cases. Predictors of conversion include aging, history of CNV in the fellow eye, baseline turbidity of the serous PED, and baseline diameter greater than 1000–1500 mm (Meredith et al., 1979; Mrejen et al., 2013; Poliner et al., 1986). The identification of sharp-peaked PED (i.e. a thumb-shaped PED) and a sub-RPE ring like structure on OCT combined with an orange nodule evident on color fundus photography can distinguish PCV from typical neovascular AMD in treatment naïve cases (Cheung et al., 2021). In the absence of ICGA, the combination of the three major OCT criteria (sub-RPE ring-like structure, complex RPE elevation on en-face OCT, and sharp-peaked PED) achieved an AUC of 0.90 for the accurate diagnosis of PCV (Cheung et al., 2021). However, in recent years, the introduction into clinical practice of OCTA has significantly improved the accurate detection of CNV complicating chronic CSC. OCTA overcomes several limitations of traditional dye-based angiography techniques in patients affected by CSC. Traditionally, ICGA was considered the gold standard in the diagnosis of type 1 CNV, displaying a hyper-fluorescent plaque in the late phases of the angiogram. However, several studies reported that, in the context of pachychoroid, CNV can be characterized by the "classic" hyperfluorescent plaque in the late phases of ICGA, but also by a hypofluorescent aspect (Carnevali et al., 2017; Quaranta-El Maftouhi et al., 2015; Sacconi et al., 2019; Soomro et al., 2018). This no late hyperfluorescence of the neovascular network is a peculiar feature characterizing the type 1 CNV in pachychoroid. Furthermore, the images of late-phases ICGA are characterized by hyper- and hypo-fluorescent areas due to the RPE alterations of chronic CSC. For these reasons the detection of type 1 CNV complicating CSC can be facilitated with dye-based angiography. Recently, several studies confirmed that OCTA can detect CNV more frequently than any other imaging modality, including dye-based angiography systems, in the setting of pachychoroid disease (Bousquet et al., 2018; Dansingani et al., 2015; Demirel et al., 2017). Chronic CSC is frequently characterized by the presence of flat irregular PED. Type 1 CNV complicating chronic CSC is usually located inside the flat irregular PED. However, the prevalence of the neovascular network inside the flat irregular PED is variable depending on the reported series (Bousquet et al., 2018; Dansingani et al., 2015; Daruich et al., 2015; Song et al., 2012; Warrow et al., 2013). On the one hand, Dansingani et al. reported that type 1 CNV could be detected by OCTA within a shallow irregular PED on structural OCT in 95% of cases (21 out of 22 eyes) (Dansingani et al., 2015). On the other hand, Bousquet et al. reported that type 1 CNV was present in only 35.6% of cases with a flat irregular PED in a study of 88 chronic CSC patients (Bousquet et al., 2018). Despite the prevalence of the neovascular network inside the flat irregular PED, the presence of subretinal fluid might not always be a sign of CNV activity (Bousquet et al., 2018). Indeed, subretinal fluid could be due to the RPE pump dysfunction (i.e. activity of chronic CSC) with a concomitant presence of a non-exudative type 1 CNV. Therefore, discerning the origin of subretinal fluid in this scenario (CSC versus exudative or non-exudative CNV) is not always possible.

To summarize, pachychoroid-driven neovascular complications include flat irregular PED and type 1 CNV, which may develop polypoidal or aneurysmal dilatations (Pichi et al., 2018; Sheth et al., 2018). Type 1 neovascular membranes in shallow irregular RPE detachment can be more sensitively diagnosed with OCTA than dye-based angiography (Dansingani et al., 2015). More importantly, OCTA is able to detect eyes with pachychoroid neovasculopathy at a quiescent stage (Carnevali et al., 2017; Forte et al., 2020).

4.2. *Non-exudative CNV in pachychoroid spectrum disorders*

As introduced above, neovascular lesions described in the setting of pachychoroid spectrum disease can be identified more easily on OCTA compared to ICGA because most of the lesions are believed to be in a quiescent stage (Carnevali et al., 2017; Dansingani et al., 2015, 2018). The characterization of treatment-naïve "quiescent" pachychoroid neovasculopathy was evaluated by our group (Carnevali et al., 2017). In this study, the definition of pachychoroid was choroidal thickness above 270 mm with pachyvessels visible on ICGA. The estimated prevalence of treatment naïve quiescent (i.e. non-exudative) CNV was 10.9% in a cohort of patients with pachychoroid neovasculopathy/Table 1). The treatment-naïve "quiescent" CNV was diagnosed as a flat irregular elevation of the RPE with moderately reflective material in the sub-RPE space and absence of intraretinal or subretinal hypo-reflective fluid on structural OCT. On fluorescein angiography, the quiescent neovascularization appeared as an ill-defined hyperfluorescent lesion on late frames, without late leakage or pooling. On ICGA the neovascular network was easily detectable as a hyperfluorescent lesion during the early to mid-phases of the study, but was not represented in a unique way in the late phases of the angiogram (Figs. 15 and 16). Contrary to type 1 CNV secondary to AMD, the neovascular network secondary to pachychoroid was characterized by an hypofluorescent aspect and no late hyperfluorescence (Fig. 15). On the other hand, cases with the "classic" hyperfluorescent plaque in the late phases of ICGA were also identified (Fig. 16). In this context, the role of structural OCT to detect

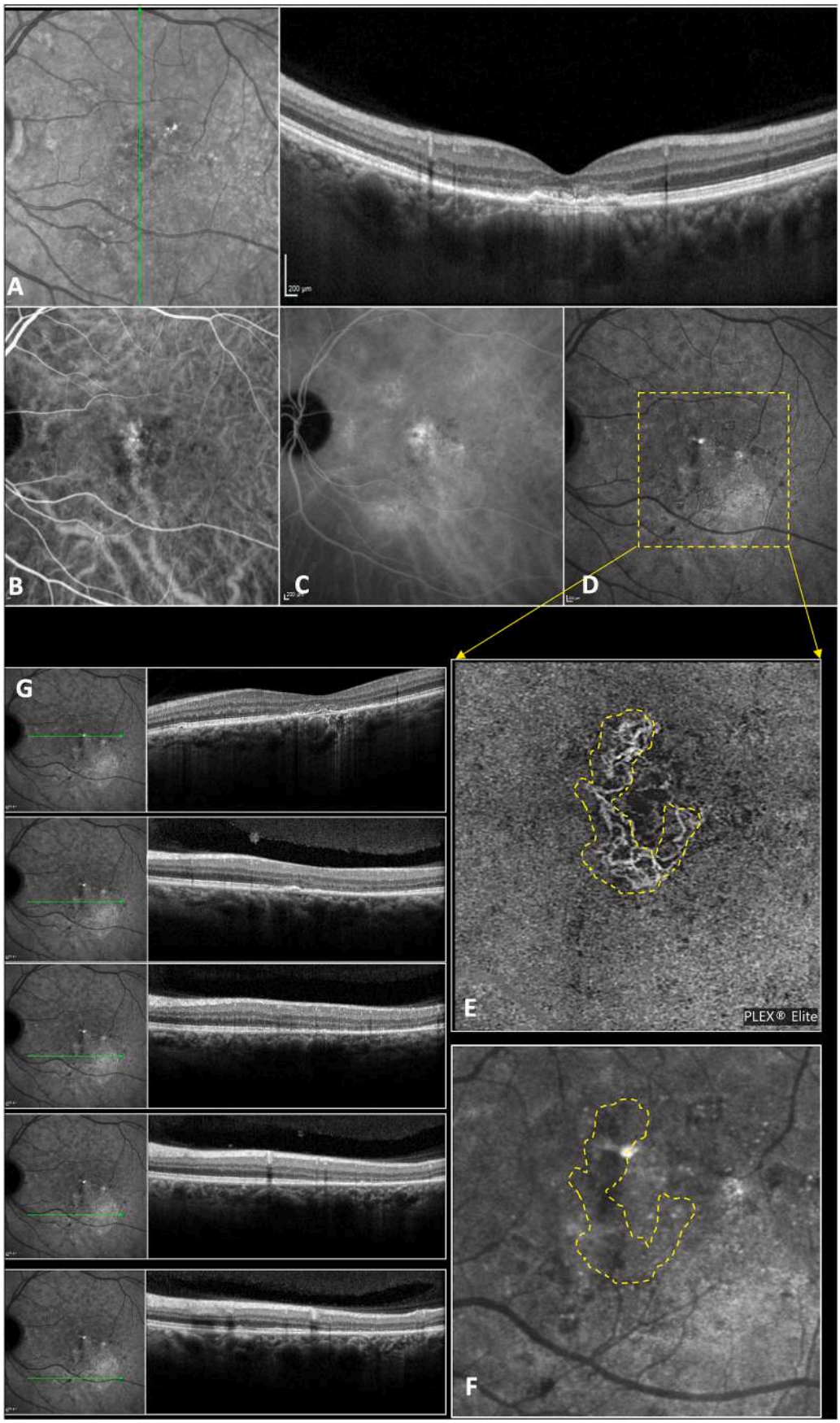

Fig. 15. Multimodal imaging evaluation of a 64-year-old patient with pachychoroid and a non-exudative type 1 choroidal neovascularization (CNV) in the left eye.

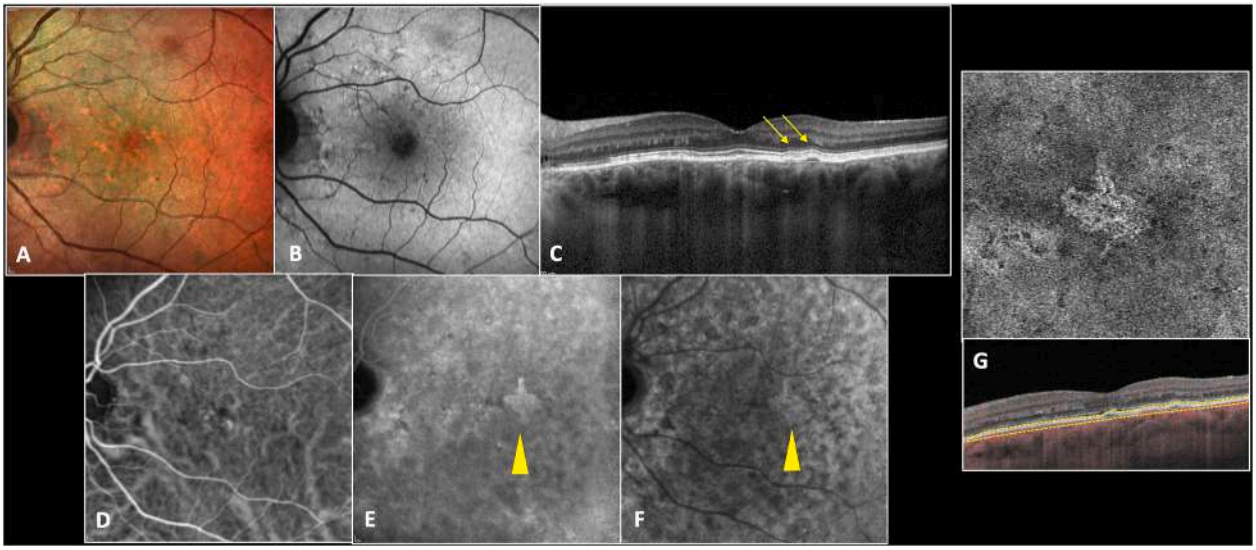

Fig. 16. Multimodal imaging evaluation of a 59-year-old patient with pachychoroid and a non-exudative type 1 choroidal neovascularization (CNV) in the left eye.

the presence of a double-layer sign and/or SIRE sign) and OCT-A is of paramount importance in order to make the accurate diagnosis of quiescent or non-exudative type 1 pachychoroid neovasculopathy.

Non-exudative CNV secondary to pachychoroid differs from non-exudative MNV secondary to AMD, in terms of pathogenesis, imaging features, and clinical response to the treatment.

The different OCTA features of non-exudative CNV secondary to pachychoroid in comparison to AMD implicate different triggers at the basis of the CNV development. CNV secondary to pachychoroid is usually characterized by large-caliber vessels with a paucity of capillaries within the lesions, suggesting that the genesis of the CNV may be more related to arteriogenesis rather than angiogenesis (Sacconi et al., 2019). As discussed before, arteriogenesis is characterized by dilation of pre-existing mature vessels as opposed to angiogenesis which is characterized by sprouting of new capillaries. Furthermore, arteriogenesis is not driven mainly by VEGF (as angiogenesis), but by PDGF. This theory might explain the presumed lower levels of VEGF in pachychoroid neovasculopaty and the imaging features of non-exudative CNV secondary to pachychoroid (Matsumoto et al., 2018). Supporting the different roles of VEGF in the genesis and activity of type 1 CNV, several studies showed different changes of CNV morphology after anti-VEGF treatment in eyes with CNV secondary to pachychoroid disease versus AMD. In the setting of neovascular AMD, Lumbroso et al. reported that the area of MNV and its vessel density decreased immediately after anti-VEGF treatment, due to the closure of smaller capillaries (Lumbroso et al., 2015). This was reported not only for type 2 MNV, but also for type 1 MNV in the setting of neovascular AMD (De Carlo et al., 2015; Muakkassa et al., 2015). On the other hand, Sacconi et al. reported that CNV area and vessel density did not significantly change 1 month after aflibercept injections, in eyes with both treatment-naïve and previously treated CNV secondary to chronic CSC (Sacconi et al., 2019). Furthermore, previous data has shown that pachychoroid neovasculopathy requires fewer anti-VEGF injections over 2 years of therapy compared with type 1 MNV secondary to AMD (Fung et al., 2012). Comparing 12 pachychoroid eyes and 16 AMD eyes with non-exudative MNV that developed exudation during the follow-up, Forte et al. showed that activated CNV secondary to pachychoroid disease showed greater response to anti-VEGF injections in terms of lower required number of injections, suggesting that reduced levels of VEGF may be driving CNV associated with pachychoroid disorders (Forte et al., 2020; Hata et al., 2017).

In this scenario, CNV secondary to pachychoroid could serve a "compensatory" role in chronic diseases. Patients with pachychoroid are usually affected by long-standing PED that could result in a disruption of Bruch's membrane and stimulation of the growth of the neovascular network (Fung et al., 2012). Progression of non-exudative CNV would be the "compensatory" result of this long-standing impairment of the RPE-Bruch's membrane complex characterizing eyes with pachychoroid.

Another complicating factor in diagnosing non-exudative CNV in the setting of pachychoroid spectrum disease is that there may be multiple mechanisms of fluid accumulation in these individuals. RPE pump failure may result in the transudative accumulation of fluid (CSC mechanism) and not from the associated CNV lesion which itself may not be contributing to the observed fluid. In that context one can envision a technically nonexudative CNV lesion with associated transudative fluid. A trial of anti-VEGF therapy with a follow-up assessment a week or two later to verify the absence of reduction in fluid may be of help in establishing the diagnosis.

Combined infrared reflectance and vertical structural optical coherence tomography (OCT) passing through the fovea (A) showing a flat irregular pigment epithelium detachment (PED) with double layer sing, no signs of exudation, and a pachychoroid with pachyvessels. Early (B), intermediate (C), and late phases (D) of indocyanine green angiography (ICGA) (time: 1:46, 11:39, and 34:50 after injection, respectively) showing the presence of type 1 neovascular network in the early phases of examination, with no hyperreflective plaque in the late phases. Enface OCT-angiography (E) nicely disclosed the presence of a neovascular network with large vessels and a low rate of capillaries. Of note, the area of the neovascular network corresponded to the hypofluorescent area in the late phases of ICGA (F). Combined late-phase ICGA and horizontal structural OCT scans (G) showing the presence of a flat irregular PED matching the hypofluorescent area of the neovascular network, and atrophic changes of the outer retinal layers and retinal pigment epithelium matching the hyperfluorescent area of ICGA.

Multicolor image (A) and short-wave fundus autofluorescence (B) showing retinal pigment epithelium changes due to the pachychoroid disease. Horizontal structural optical coherence tomography (OCT) passing through the fovea (C) showing a flat irregular pigment epithelium detachment with no signs of exudation (yellow arrows) and a pachychoroid with pachyvessels. Early (D), intermediate (E), and late phases (F) of indocyanine green angiography (time: 1:09, 14:52, and 41:52 after injection, respectively) showing the presence of a type 1 CNV with a hyperreflective plaque in the intermediate and late phases of the examination (yellow triangles). Enface OCT-angiography and b-scan with flow confirming the presence of a neovascular network.

5. Angioid streaks

5.1. General information

Doyne published the first characterization of angioid streaks (AS) in 1889 and described irregular radial lines extending from the optic nerve head to the peripheral retina in a patient with retinal hemorrhages after blunt trauma (Doyne, 1889). The term AS was then coined by Knapp (in 1892) who noted a similar appearance to an obliterated system of blood vessels (Knapp, 1892). Histologically, angioid streaks are crack-like breaks in a degenerated and calcified Bruch's membrane (Verhoeff, 1948). Angioid streaks can occur isolated but are associated with systemic diseases in approximately 50% of patients, especially pseudoxanthoma elasticum, but also Ehlers–Danlos syndrome (only type 6), Paget disease, and hemoglobinopathies including sickle cell trait disease and thalassemias (Gurwood and Mastrangelo, 1997). Pseudoxanthoma elasticum is an autosomal recessive disorder secondary to mutations in the ABCC6 gene with a prevalence between 1:25000 to 1:100000 (Bergen et al., 2000; Chassaing et al., 2005). A variety of chorioretinal findings may develop in eyes with PXE, including peau d'orange, angioid streaks, chorioretinal atrophy, comet lesions, and choroidal neovascularization. Although the diagnosis of AS is mainly clinical, multimodal imaging features can be useful to diagnose, evaluate, and monitor angioid streaks. Structural OCT has shown highly reliable correspondence with the histologic findings, including the identification of linear breaks in BrM (Charbel Issa et al., 2009). Patients with AS are usually asymptomatic unless they develop macular complications, in particular choroidal rupture and CNV (Georgalas et al., 2009). Marchese and coworkers have described the importance of ultra-widefield imaging in patients with angioid streaks since peripheral lesions are often present (Marchese et al., 2017).

Choroidal neovascularization is the primary cause of severe visual loss, occurring in 42%–86% of AS patients during follow-up, with most eyes progressing to legal blindness (Lim et al., 1993). Despite conventional imaging allowing prompt identification of CNV, this diagnosis may be missed or delayed in AS patients, limiting the final functional and anatomical macular recovery that can be achieved after anti-vascular endothelial growth factor therapy (Lafaut et al., 1998). Corbelli et al. described the OCTA characteristics of AS that can eventually predict CNV activity (Corbelli et al., 2018). In most cases, choriocapillaris rarefaction was noted and interpreted as atrophic changes associated with overlying breaks of the thickened BrM. However, in some cases, an irregular vascular network in correspondence of the BrM defects was noted on OCTA, without evident intra- or subretinal fluid accumulation (Corbelli et al., 2018). OCTA may be particularly valuable in detecting CNV and also the irregular vascular network between the RPE and BrM, possibly representing fibrovascular tissue in areas affected with AS. The interlacing CNV pattern was characterized by dense vascular hyperintensity with a cobweb shape, vascular tortuosity, and a perilesional halo which was more often associated with signs of neovascular activity on multimodal imaging (71.4%) (Corbelli et al., 2018).

5.2. Non-exudative CNV in angioid streaks

As previously mentioned, neovascularization is a frequent complication of angioid streaks, affecting up to 86% of PXE patients during the course of their disease (Table 1). It significantly impacts visual function due to subretinal hemorrhage, exudation, atrophy, and/or fibrovascular scarring (Risseeuw et al., 2019). Exudative CNV in patients with AS has shown an optimal long-term response to anti-VEGF therapy that remains the mainstay therapeutical option in such cases (Sekfali et al., 2020; Tilleul et al., 2016). However, the onset of exudation does not necessarily coincide with the formation of neovascular lesions. Andreanos et al. first reported a case of non-exudative type 1 CNV in a patient with PXE (Andreanos et al., 2017). The authors monitored the patient closely with OCTA examinations every 2 months and found no evidence of exudation, despite a slight increase in the CNV area. Recently, the prevalence of non-exudative CNV in PXE patients was estimated at 33.3%, with an incidence of exudative changes in 33.3% of cases during follow-up. All non-exudative CNV cases were classified as type 1 CNV, with an interlacing vascular network observed on OCTA. A double-layer sign was found in 4 of the 6 eyes, with foveal involvement in one case. The diagnosis of non-exudative lesions can be challenging in PXE patients that usually retain good visual acuity until exudation occurs. The frequency of non-exudative lesions in PXE seems to be higher compared to the AMD spectrum, although comparative studies have not been performed (Marques et al., 2021). The identification of non-exudative CNV in PXE requires close monitoring to allow prompt anti-VEGF treatment. On the other hand, there is also evidence suggesting that a stable non-exudative neovascular complex is not always detrimental as it may even prevent or reduce the progression of RPE atrophy (Laiginhas et al., 2020).

6. Hereditary retinal dystrophies

Hereditary retinal dystrophies are a group of rare diseases characterized by progressive degenerations of the neurosensory retina, RPE, and/or choroid. While a broader spectrum of hereditary retinal dystrophies could potentially be complicated by CNV, in this section we will address only those retinal dystrophies with published reports of non-exudative CNV.

6.1. Best vitelliform macular dystrophy

Best vitelliform macular dystrophy (BVMD) is one of the most common macular dystrophies, affecting 1 in 10.000 individuals. About 150 mutations involving the BEST1 gene have been described, with a broad range of phenotypes. The clinical presentation is heterogeneous and can be classified into five stages: stage 1 (previtelliform/subclinical, with no biomicroscopic alterations), stage 2 (vitelliform), stage 3 (pseudohypopyon), stage 4 (vitelliruptive/scrambled egg), and stage 5 (atrophic/cicatricial) (Boon et al., 2009; Gass, 1997). Macular neovascularization can complicate the course of BVMD and may contribute to a further decline in visual acuity (Khan et al., 2017).

6.2. Non-exudative CNV in best vitelliform macular dystrophy

Parodi et al. described the quantitative characteristics of macular neovascularization in BVMD (stages 2–5) by means of OCTA, with a total of 78 eyes recruited for the study (Parodi et al., 2020). CNV was identified in 50 eyes (64%) at baseline and in 51 eyes (65%) at the end of the follow-up (mean follow-up, 24.7 $\pm$ 9.7 months). The prevalence of CNV according to the disease stage was 13% in stages 2 and 3; these lesions all showed exudative manifestations treated successfully with intravitreal ranibizumab. The remaining cases were identified in stages 4 and 5. OCTA detected a neovascular network with the outer retinal and choriocapillaris slabs in 96% of cases. All these stage 4/5 cases of CNV showed no signs of exudation by clinical exam and no leakage on FA and were therefore classified as non-exudative CNV and observed over the follow-up without treatment. At the end of the follow-up, 47 out of 48 eyes displayed CNV (98%) and non-exudative CNV remained stable during this period. The authors hypothesized that two CNV phenotypes can characterize BVMD. The exudative CNV phenotype, a rare condition occurring in the early stages of the disease, is accompanied by bleeding and fluid formation. Non-exudative CNV is a prevalent finding characterizing the advanced stages of BVMD, without any exudative manifestation with clinical stability over time. On OCTA, exudative CNV was characterized by higher vessel tortuosity (VT), higher vessel dispersion (VDisp), and larger size, whereas the vessel density (VD) of the three vascular plexi (i.e. superficial and deep retinal vascular plexuses and choriocapillaris) was similar to the non-exudative subgroup in the 3 $\times$ 3 mm area. These observations raised the hypothesis that the exudative

form may be associated with a rapidly growing neovascular network, possibly related to a cytokine/trophic factor imbalance. While non-exudative CNV, characterized by lower perfusion and less vascular disorganization, may develop gradually, stimulated by the trophic demand of the outer retina due to the increasingly impaired metabolic exchanges between the RPE and photoreceptor outer segments (Parodi et al., 2020).

Neovascularization in BVMD co-localizes within hyperreflective material visualized at the level of RPE on OCT b-scans; OCTA is valuable in this high risk situation for the detection of a neovascular network (Miyagi et al., 2022).

6.3. Retinitis pigmentosa

Retinitis pigmentosa (RP) is characterized by the progressive degeneration of photoreceptors and RPE, leading to night blindness, tunnel vision, and a gradual reduction of central vision. However, the clinical findings in RP vary widely due to the large number of genes involved, each of which can have several allelic mutations (Verbakel et al., 2018). Choroidal neovascularization represents an uncommon complication, rarely observed in RP (Battaglia Parodi et al., 2010, 2012; Sayadi et al., 2017). The pre-existing visual impairment could limit the diagnosis and management of such complications. Multimodal imaging can be critical in the diagnosis and follow-up of RP, with a vital role of OCTA in detecting rare neovascular complications (Liu et al., 2016).

6.4. Non-exudative CNV in retinitis pigmentosa

Falfoul et al. first reported multimodal imaging findings, including OCTA, of a patient presenting with quiescent CNV complicating retinitis pigmentosa (RP) linked to a *PRPH2* pathogenic variant (Falfoul et al., 2021). The patient was a 40-year-old female with visual loss secondary to exudative type 2 CNV, and an incidental finding of asymptomatic non-exudative "quiescent" CNV in the fellow eye. The exudative lesion was managed with intravitreal bevacizumab injections, while the non-exudative lesion was regularly monitored. Mutation analysis of *PRPH2* exons identified a known heterozygous pathogenic missense variation c.646C > T, p.P216S in exon 2 (Falfoul et al., 2021). This variant has been previously reported in a case of pattern dystrophy associated with retinitis pigmentosa (Richards and Creel, 1995). Patients with this genetic variant seem to be more prone to develop macular complications, and thus careful monitoring should be advised in cases with PRPH2 mutations.

7. Treatment and management of non-exudative neovascularization

There is considerable debate about whether to treat non-exudative neovascularization with anti-VEGF injections. It is well known that, in the case of exudative neovascularization, the sooner we start anti-VEGF therapy, the better the visual outcome due to less fibrosis and atrophic changes. The role of biomarkers is therefore of paramount importance to predict the risk of exudation and the conversion from non-exudative to the exudative form of MNV/CNV. However, to date there is no consensus on the relevant biomarkers that we need to consider for the conversion risk of non-exudative neovascularization. It is difficult to advocate therapy for non-exudative MNV/CNV in the absence of a prospective trial validating this approach. As discussed before, patients may not develop exudation (i.e. activation) for years (Fig. 9), and thus, treating non-exudative neovascularization risks the possibility of administering unnecessary injections for extended periods. Furthermore, these neovascular lesions may actually provide nutritional support to the overlying RPE and photoreceptors, thus preserving foveal function, and can persist for many years without affecting vision (de Oliveira Dias et al., 2018). Anti-VEGF treatment of non-exudative MNV/CNV may reduce the perfusion of these lesions, limiting their protective role.

Recently two clinical trials were published giving us relevant insights into this topic: the PRO-CON and PREVENT clinical trials (Heier et al., 2021; Lalezary et al., 2017). In the PRO-CON study, 129 intermediate AMD eyes of patients affected by exudative AMD in the fellow eye were treated with quarterly aflibercept injections versus sham injections (Heier et al., 2021). The study demonstrated no difference in the rate of conversion to exudative AMD during the 2 year follow-up between patients treated with prophylactic anti-VEGF injections versus sham (rate of conversion of 9.5% and 10.9%, respectively). Interestingly, a cohort of patients with non-exudative MNV was identified at the baseline visit. No differences were observed regarding the conversion rate to exudative AMD during follow-up between patients treated with prophylactic anti-VEGF injections versus sham (27.3% and 30.8%, respectively). Similar results were achieved in the PREVENT trial using a different anti-VEGF agent (Lalezary et al., 2017). A total of 108 eyes of patients with intermediate AMD in the study eye and neovascular AMD in the fellow eye were injected quarterly with 0.5 mg ranibizumab. There were no differences in the treatment versus the sham injection arm in the conversion rate to exudative AMD. At 24-month, the cumulative incidence of neovascular AMD was 14% in the ranibizumab group and 15% in the sham group, with no differences in terms of visual acuity.

The lack of prophylactic benefit of anti-VEGF injections in the conversion from non-exudative to exudative AMD may be attributable to various factors. One element to consider is the low dosing frequency used in both trials. Anti-VEGF treatment was administrated every three months, not monthly or every 2 months as is recommended for neovascular exudative AMD (Brown et al., 2006; Heier et al., 2012; Rosenfeld et al., 2006). We can also speculate that while the development of neovascularization may be VEGF driven, the conversion to exudative AMD may be driven by other pathways (Ambati et al., 2013). For example, we cannot exclude that what is called "exudation" might not result from vascular permeability but could result from RPE pump impairment induced by chronic "stress" of the MNV or underlying choroidal ischemia (Hilely et al., 2021). For this reason, prophylactic treatment should not be recommended in clinical practice. Other strategies of prevention should be investigated. A deeper knowledge of the triggers involved in the conversion to exudative AMD is necessary.

Based on previous evidence, we recommend the close follow-up of patients with non-exudative neovascularization and immediate anti-VEGF treatment with evidence of the earliest signs of exudation (i.e. presence of subretinal fluid, intraretinal fluid, SHRM, or macular hemorrhages) (Invernizzi et al., 2021; Querques et al., 2021). Since there is no consensus on biomarkers that can predict the conversion to exudative AMD, we suggest following patients closely in the first months after the diagnosis. In the "normal" development of an exudative type 1 MNV from non-exudative MNV, previous studies suggest that the conversion occurs over a mean of 6–8 months (Agarwal, 2012; Grossniklaus and Gass 1998; Invernizzi et al., 2021; Querques et al., 2021). After this period, the non-exudative MNV may be at a lower risk of conversion to exudative AMD, and, for this reason, the follow-up timing can be extended. Although structural OCT remains the most sensitive strategy to detect the exudative conversion of NE-MNV, monthly follow up on an indefinite basis is not feasible (Banister et al., 2022). For this reason, we suggest extending the follow-up timing after the high-risk period, but adding a self-monitoring test between two consecutive OCTs. Patients should be instructed to perform close self-monitoring, using self-testing, e.g. Amsler grid, and prompt referral to their treating clinicians in case of new symptoms. Self-monitoring tests alone showed a lower level of sensitivity (about 78%) for the detection of nAMD conversion compared to structural OCT (Do et al., 2012). However, we suggest using self-monitoring tests in addition to the examinations including OCT monitoring.

8. Conclusions and future perspective

8.1. Conclusions

Treatment-naïve non-exudative neovascularization in eyes with different acquired or inherited maculopathies is a clinical scenario that is more common than previously reported when studies were performed using dye-based angiography systems. The adoption in clinical practice of a multimodal imaging approach, in particular OCT-angiography and high-definition structural OCT, has shown that the presence of non-exudative MNV and CNV is very common. Non-exudative MNV/CNV typically refers to a type 1 neovascular lesion with localization between Bruch's membrane and the RPE, although the first report of non-exudative type 3 MNV has been published. There is a need for international consensus on the definition of non-exudative neovascularization and for the characterization of different entities included in this group of diseases. This could facilitate research and improve the comparability of findings reported across different studies. As such, we have proposed a clinical definition based on the timing of the disease (Section 3.4). Briefly, based on previously reported evidence that 6–8 months represents the higher risk interval for exudation, we suggest that the timing of the follow-up could be useful in differentiating non-exudative neovascularization with a low risk of exudation versus non-exudative neovascularization with a high risk of short-term activation (Invernizzi et al., 2021). In this way, using a threshold of 6 months with no exudation would allow better characterization of non-exudative neovascularization with a low risk of exudation and "quiescent" neovascularization would therefore represent a subgroup of non-exudative neovascularization.

The prevalence of non-exudative MNV/CNV may vary according to the associated maculopathy, the different imaging techniques, and on the study referenced. For example, considering AMD, the prevalence is between 9 and 11% in reports using ICGA. On the other hand, recent studies using OCTA have found a prevalence ranging from 1.58 to 27% (Section 3.1 and 4.2.1). Less is known about the prevalence of non-exudative CNV in other maculopathies, due to the lack of published studies.

There is stronger evidence that the presence of non-exudative MNV/CNV is associated with a higher risk of development of exudation, especially in AMD patients. Depending on the different definitions used for non-exudative MNV, the rate of conversion from non-exudative to exudative MNV in intermediate AMD ranges between 6.6% and 80% at the 1-year follow-up, and 34.5% at the 2-year follow-up (Section 4.2.2). The relative risk of conversion is between 13 and 22 times greater in eyes with non-exudative MNV versus intermediate AMD eyes without detectable lesions. These findings underscore the prognostic significance of non-exudative MNV. Unfortunately, there is no consensus on the value of different MNV features that could predict exudation. The dimensional growth of the neovascular lesion is reported to be associated with the biological activity of non-exudative MNV. Although debated in the literature, the faster growth rate of non-exudative MNV seems to be associated with conversion to the exudative form and may be a marker of short-term or long-term activation (Section 4.2.3). Thanks to OCTA, we are able to better visualize the morphologic patterns and features of the non-exudative MNV. The morphology of MNV may provide a clue regarding the relevant pathophysiological pathway driving growth. As discussed in Section 4.2.3, MNV may be driven by angiogenesis (VEGF dependent process, with the endothelial proliferation of multiple new capillaries and a commensurate increase in perfusion density) or arteriogenesis (driven mainly by PDGF, less capillary proliferation and greater enlargement and perfusion of large vessels with low perfusion density). In the spectrum of non-exudative MNV, both these pathways may be relevant. Angiogenesis is the most important driver of exudative MNV characterized by fast growth, high perfusion density, endothelial sprouting of new capillaries, and high risk of short-term exudation. In contrast, arteriogenesis is the most important driver of non-exudative MNV characterized by slow growth, low perfusion density, low number of capillaries but the presence of large vessels, and low risk of short-term exudation. Based on these differences, we can sub-type non-exudative MNV. Non-exudative MNV driven by angiogenesis is comparable to exudative MNV and may represent the "pre-exudative" stage in the development of exudative MNV (Invernizzi et al., 2021). On the other hand, non-exudative MNV driven by arteriogenesis may be a chronic compensatory mechanism to mitigate choroidal ischemia secondary to AMD. Indeed, histological reports have documented the presence of neovascular buds internal to the choriocapillaris in 22%–40% of patients with AMD. Chronic choriocapillaris loss seems to be the driver for the development of these neovascular buds that may represent a precursor of neovascular disease (Section 3.2).

Clinical and imaging features suggest that a VEGF-dependent process may be less relevant in the development of non-exudative CNV as pertains to geographic atrophy and pachychoroid spectrum disorders. Indeed, the morphology of non-exudative CNV associated with these disorders is characterized by large neovascular trunks, with less tortuosity of the neovascular network and a low number of capillaries. Usually, these lesions are characterized by long-standing presence, reflecting again the possible compensatory role of non-exudative CNV in these long-standing and chronic diseases (i.e. geographic atrophy, pachychoroid spectrum disorders, and angioid streaks) (Section 4.3, 5.2, and 6.2).

The prevention and treatment of non-exudative MNV is a debated topic. Thanks to the PRO-CON and PREVENT clinical trial, there is evidence to indicate that prophylactic treatment using anti-VEGF agents is not useful in the prevention of conversion from non-exudative to exudative stages of MNV in nAMD (Section 8). Using fixed quarterly dosing of aflibercept injections for 24 months, no differences were disclosed about the conversion rate to exudative AMD between patients treated with anti-VEGF injections versus sham injections. Other strategies of prevention should be investigated. In this way, a deeper knowledge of the triggers involved in the conversion to exudative AMD may be elucidated. To date, the treatment of non-exudative NV should be initiated when exudative changes occur. Non-exudative NV should be closely monitored during the follow-up, especially in the first months after the diagnosis, and treated with intravitreal anti-VEGF only once/if exudative changes develop. Prophylactic treatment before conversion should be avoided in order to preserve the potential protective and nutritional role of NV in support of the outer retina and RPE.

8.2. Future perspective

The spectrum of non-exudative NV is characterized by different entities. To continue to improve our understanding of non-exudative NV, a consensus definition to define the features of all subtypes of non-exudative NV is mandatory. Using the same definitions, the results of different studies could be compared and replicated. Another relevant issue prohibiting the comparison of results of different clinical studies about non-exudative NV to date is the population of origin. Some studies include only high-risk patients (i.e. patients with exudative MNV in the fellow eye), while other studies include patients with intermediate AMD in both eyes. In this scenario, it is difficult to determine the independent impact of non-exudative AMD, and to compare results of prevalence and/or rate of exudative conversion between different cohorts.

Another important issue relates to the biomarkers that can predict the short-term or long-term activation of non-exudative NVs. We need to continue to improve our knowledge about possible predictors of exudation, in order to personalize the follow-up and the treatment of our patients. More robust studies with more rigorous inclusion criteria and a larger population cohort are needed. Furthermore, the development of new higher-resolution structural OCT and OCTA (e.g. 400 kHz swept-source OCT instrument) and the development of new techniques of imaging analysis (e.g. variable interval scan time analysis) may allow us to better identify new biomarkers or confirmed possible predictors

suggested by the current studies.

Finally, we need to consider the application of novel artificial intelligence (AI) systems in patients affected by non-exudative NV. AI could be very useful in the more rapid diagnosis and screening of non-exudative NV in patients affected by different maculopathies. Analyzing much larger cohorts of individuals, AI could be very useful in order to better understand the epidemiology and clinical features of non-exudative NV and to more powerfully elicit potential predictors or biomarkers of exudative conversion. As AI is an objective and automated method, it could be valuable in more precisely identifying and quantifying NV features, providing new knowledge and insight into this spectrum of diseases.

Finally, further investigation of animal models or post-mortem human eyes affected by non-exudative NV is needed to provide new insights into the pathogenesis of non-exudative NV. Understanding the pathophysiological and biochemical pathways at the basis of the non-exudative NV development is of paramount importance in order to develop new strategies in the prevention and treatment of this very common entity.

Author statement

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