# MYOPIC CHOROIDAL NEOVASCULARIZATION: A REVIEW

**Ayushi Sinha, DNB, FVRS; Manaswini Dodla, MS**

**ARTICLE INFORMATION**

| | |
|---|---|
| Article received | January 2023 |
| Article accepted | March 2023 |
| Article on line | March 2023 |
| Keywords | High Myopia, Pathologic Myopia, Choroidal Neovascularization, Anti-VEGF therapy |
| Presented at | Not Presented |

**AFFILIATION OF ALL AUTHORS:**

Department of Vitreo-Retina Services Aravind Eye Hospital, Puducherry, India-605007

**ABSTRACT**

Myopia is a common refractive error with a rapid increase in prevalence worldwide. Pathological myopia (PM) is a serious consequence of high myopia, associated with degenerative changes. Myopic choroidal neovascularization (CNV) is a dreaded complication of PM, often resulting in a sudden, progressive diminution in central vision, requiring prompt treatment. OCT and FFA are highly valuable in the diagnosis and monitoring of myopic CNV. Outcomes for patient with myopic CNV have significantly improved with the introduction of intravitreal anti-vascular endothelial growth factor (VEGF) as therapy.

## INTRODUCTION

Myopia is a common refractive error with a rapid increase in prevalence worldwide, particularly in East Asian countries in which prevalence rates of 40% are seen[1-4]. Known as a serious consequence of myopia, pathological myopia affects up to 3% of the global population[5]. Pathological myopia (PM) particularly presents in eyes with high myopia (>DS 6.0) characterized by progressive elongation of the globe, degenerative changes, and abnormal choroidal vasculature[6]. Pathological myopia or "degenerative myopia" can also be defined as eyes with chorioretinal atrophy (CRA) equal to or more severe than diffuse atrophy[7]. There are many factors for the occurrence of pathological myopia, commonly the lack of outdoor activity at a younger age and prolonged near work.

Myopic choroidal neovascularization (CNV) is a dreaded complication of PM, often resulting in a sudden, progressive diminution in central vision8 with poor prognosis, requiring prompt treatment. Nearly 5% to 11% of patients with PM will develop myopic CNV in one eye, with the fellow eye developing myopic CNV within 8 years in 35% of these patients[9]. Myopic CNV is more common in middle-aged patients[10,11], often having worse visual prognosis if the patient is more than 40 years old[12]. Thus, age of onset is an important factor to prognosticate the course of the disease.

Outcomes for patient with myopic CNV have significantly improved with the introduction of intravitreal anti-vascular endothelial growth factor (VEGF) as therapy, but the long-term results of these treatments are still unknown.

## RISK FACTORS FOR MYOPIC CNV

In-depth knowledge of the pathogenesis of myopic CNV is lacking but some studies have identified ocular, systemic, and genetic risk factors for the development of myopic CNV. Ocular risk factors are patchy retinal atrophy, myopic maculopathy, lacquer cracks, and choroidal thinning at the posterior pole[9,13,14]. Steidl and Pruett[15] reported that eyes with a shallow staphyloma had higher frequency of CNV. They hypothesised that eyes with a shallow staphyloma may be healthier and metabolically active with good capacity to respond to injury by neovascular ingrowth.

Systemic risk factors are less well defined with several references of inflammation in association with myopic CNV. Few studies have shown a link with inflammatory markers such as C-reactive protein (CRP), complement factors C3 and CH50, interleukin 6 and interleukin [816,17,18]. Genetic risk factors for myopic CNV include a single nucleotide polymorphism (SNP [rs10033900]) in the complement factor I gene[19]. In another study, a pigment epithelium-derived factor gene SNP (rs12603825) was associated with myopic CNV in highly myopic patients[20]. VEGF has a role in

*Corresponding author*
***Ayushi Sinha, DNB, FVRS***
*Consultant*
*Consultant Department Vitreo-Retina Services Aravind Eye Hospital, Puducherry, India-605007*
*Email- drsinha927@gmail.com*

the pathogenesis of this disease based on increased levels of VEGF found in the aqueous humor of eyes with myopic CNV[17,18,21].

## BRUCH'S MEMBRANE IN MYOPIC EYES

Bruch's membrane is located between the RPE and the choriocapillaris and it continues to undergo remodelling over time. However, in higher degrees of myopia, ocular expansion occurs in which the Bruch's membrane undergoes stress leading to dehiscences called lacquer cracks. The cracks disrupt the capillaries in the choriocapillaris since the outer lamella of Bruch membrane is the basement membrane of the choriocapillaris. This results in subretinal haemorrhages and these can be difficult to differentiate from those caused by choroidal neovascularization (CNV). Lacquer cracks are known precursors of myopic CNV. CNV tends to develop along the foveal margin of the chorioretinal atrophy, which is formed by increased width of the lacquer cracks.

## COURSE OF THE DISEASE

Studies are inconsistent in regards to the natural course of myopic CNV due to different inclusion criteria, methodology for CNV diagnosis, management, and follow-up. In terms of visual outcomes, the initial decrease in visual acuity (VA) often stabilizes but it is followed by a slower, progressive deterioration of visual acuity. In the long run, a study showed that more than 90% of patients had VA worse than 20/200 after 5 to 10 years of disease onset[22]. Progressive diminution of vision is due to the development of retinal atrophy surrounding the areas of regressed CNV.

Various factors affect the final visual outcome for myopic CNV patients, such as the age, lesion size and location, development of hemorrhages, VA at presentation, refractory error, and axial length[23]. Fundus fluorescein angiography (FA) may provide insight into the progression of myopic CNV. For instance, myopic CNV with extensive fluorescein leakage beyond the borders of the CNV lesion on FA may result in extensive fibrovascular scars, while those with fluorescein leakage restricted to the borders of the lesion may result in atrophic scars[24]. Patients in the atrophic stage of myopic CNV require periodic ophthalmic evaluation, particularly optical coherence tomography (OCT), to monitor for macular holes or retinoschisis.

There is a high chance of developing myopic CNV bilaterally. In a study of 325 highly myopic eyes, the incidence of myopic CNV was greater in patients with myopic CNV in the fellow eye (34.8%) than in those with no previous myopic CNV (6.1%)[9]. Retrospectively, of 73 patients with PM, 17 (23%) had myopic CNV in both eyes at presentation[25].

## CLASSIFICATIONS OF PATHOLOGICAL MYOPIA AND MYOPIC CNV

As previously mentioned, PM lacks a standardized classification, thus making analysis of study data cumbersome. Many studies are available on PM in regards to clinical findings, imaging such as FA and OCT, axial length and refractive errors, but disparities arise between each study due to lack of a definite classification[5]. Pathological myopia is also known as "myopic macular degeneration (MMD)," "myopic maculopathy," or "degenerative myopia."

PM has been given various definitions over the years. The current agreement for the definition of PM includes a decrease in the best corrected VA, an elongation of axial length, and associated fundus abnormalities[9]. Degenerative changes associated with PM are thinning of the RPE and choroid, lacquer cracks, subretinal hemorrhage, posterior staphyloma, and myopic CNV[26]. Other ocular complications of PM are cataracts, glaucoma, retinal detachment, myopic maculopathy, and myopic retinopathy[27]. In 2010, Hayashi et al28 defined various stages of MMD, with tessellated fundus being the first sign.

Following are the features of Proposed Classification Systems of Pathological Myopia (also Termed "Myopic Macular Degeneration," "Myopic Maculopathy," or "Degenerative Myopia")[29]:

| Author | Stage | Features |
|---|---|---|
| Avila et al | M0 | Normal-appearing posterior pole |
| | M1 | Choroidal pallor and tessellation (reduced RPE pigmentation means that the choroidal vessels can be seen through the retina) |
| | M2 | Choroidal pallor and tessellation with posterior staphyloma |
| | M3 | Choroidal pallor and tessellation with posterior staphyloma and lacquer cracks |
| | M4 | Choroidal pallor and tessellation with lacquer cracks, posterior staphyloma, and focal areas of deep choroidal atrophy |
| | M5 | Posterior pole with large geographic areas of deep CRA and "bare" sclera |
| Hayashi et al | 1 | Tessellated fundus |
| | 2 | Progression to diffuse atrophy, lacquer cracks, or directly to the formation of a CNV (rare) |
| | 3 | Diffuse atrophy can progress to patchy atrophy, lacquer cracks, or the formation of a CNV<br>Lacquer cracks can progress to patchy atrophy or the formation of a CNV |
| | 4 | Atrophic patches can fuse to form larger areas of atrophy and eventually macular atrophy<br>CNV can progress to macular atrophy |
| International classification; Ohno-Matsui et al | 0 | No macular lesions |
| | 1 | Tessellated fundus |
| | 2 | Diffuse CRA |
| | 3 | Patchy CRA |
| | 4 | Macular atrophy |

"Plus" lesions:

- Lacquer cracks
- CNV
- Fuchs' spot

CNV = choroidal neovascularization; CRA = chorioretinal atrophy; FAF = fundus autofluorescence; RPE = retinal pigment epithelium.

Tessellated fundus alone progressed the least, while the appearance of degenerative changes more likely developed functional defects. Ohno-Matsui et al30 have proposed the current International Classification of PM with a photographic classification and grading system for PM based on long term clinical observations and retinal photographic examination of myopic eyes. There are 5 categories in this system, 0 (no macular lesions), 1 (tessellated fundus), 2 (diffuse CRA), 3 (patchy CRA), and 4 (macular atrophy). The higher the category, the higher the chances of developing myopic CNV. Three "plus" lesions are described in this classification including lacquer cracks, CNV, and Fuchs' spots, which can appear in any category. Posterior staphyloma is not solely limited to the macular area and is thus described separately.

Coming to our current topic of interest, in 1998, Tokoro[31] classified myopic CNV into 3 stages: active, scar, and atrophic. In the active stage of myopic CNV, a fibrovascular membrane (with or without evident bleeding) forms around the lesion. In the scar stage, there is absorption of the bleeding and formation of a macular scar. Once the CNV regresses, CRA develops (atrophic stage). Sawa et al[32] proposed a fundus autofluorescence (FAF) based classification for the development of myopic CNV. This also helps detect CNV-related macular atrophy and predict visual and therapeutic outcomes of myopic CNV.

## CLINICAL FEATURES

In the active stage of myopic CNV, patients present with a rapid deterioration of central vision which can be associated with a central scotoma or metamorphopsia[33,34]. Clinically, the CNV appears as a localized, flat, greyish membrane most commonly subfoveal in location[24,33]. Juxtafoveal and extrafoveal CNV may also develop[33]. Rarely, a triangle or oval shaped peripapillary CNV can develop[35]. The location of the CNV affects the VA at presentation. In the scar stage, exudation decreases, resulting in an improvement in or maintenance of vision. At this stage, the lesion may become a hyperpigmented Fuchs' spot[34]. In the final atrophic stage, vision further deteriorates, leading to a decrease in the quality of life for the patient.

A high myope presenting with a sudden loss of central vision, with or without scotoma and metamorphopsia, should be evaluated with a high degree of suspicion.

## IMAGING OF MYOPIC CNV

Fundus Fluorescein Angiography (FFA) findings of myopic CNV show a classic well-defined lesion with hyperfluorescence in the early phases and dye leakage during the later phases[36]; but these findings are not consistent in all eyes with myopic CNV because hemorrhage can mask the FFA findings[34]. In such cases, indocyanine green angiography (ICGA) is superior in determining the presence and absence of CNV and its location[36]. Staging of myopic CNV is done with the use of spectral domain OCT. During the active stage, a highly reflective dome-shaped projection above the RPE is seen, with other associated biomarkers of CNV such as subretinal and intraretinal fluid. In the scar stage, the surface of the dome-shaped CNV shows high reflectivity, while in the atrophic stage, the CNV flattens with an increase in surrounding choroidal reflectivity due to CRA[37].

## DIFFERENTIALS

Myopic CNV must be differentiated from a number of other ocular disorders presenting with similar findings. Simple myopic hemorrhage or Myopic subretinal macular hemorrhage following a new lacquer crack formation can present with symptoms similar to myopic CNV. FFA helps differentiate the two, with the distinct hyper-fluorescence of myopic CNV being absent in hemorrhage alone[36]. CNV caused by inflammatory disorders, include multifocal choroiditis and punctate inner choroidopathy, present with multiple and recurrent lesions[38]. The RPE on FA appears hypofluorescent in these conditions[34]. Idiopathic CNV is more common in young people, with no obvious cause, and has a better clinical outcome than myopic CNV. Thus, it is important to differentiate the two entities[39].

## MANAGEMENT

Risk factors for the development of myopic CNV were already discussed. Lacquer cracks are known to be a predisposing factor, warranting the need for regular evaluation of these patients[9,14,28]. Macular choroidal thickness is a marker on SD-OCT to predict the development of lacquer cracks. This was superior to axial length and refractive error in an Asian population in predicting the risk of development of lacquer cracks[40].

The previously mentioned genetic markers, such as SNPs in the complement factor I gene (rs10033900)[19], pigment epithelium-derived factor gene (rs12603825)[20], and VEGF gene (rs2010963)[41], could be used for disease screening since they are associated with an increased risk for myopic CNV. However, larger multi-ethnic trials of these genetic candidates are needed before utilizing them as screening biomarkers. Fellow eye can develop myopic CNV in one third of the patients[9], requiring monitoring of the fellow eye for development of the disease.

The following imaging modalities are available for the diagnosis of myopic CNV: FA, ICGA, OCT, FAF.

### Fluorescein Angiography (FA)

Fluorescein angiography is an invasive procedure commonly used to examine retinal and choroidal circulation. As previously mentioned, myopic CNV appears as a hyperfluorescent lesion in the early phase, followed by dye leakage during the later phases. FA provides insight into the location of the lesion and helps to differentiate myopic CNV from myopic macular hemorrhage[24]. Following intravenous administration of fluorescein dye, the patient may develop dizziness, and rarely, allergic reactions. In spite of these risks, FA is considered an important tool in active myopic CNV evaluation and was shown to have a higher sensitivity than OCT in monitoring lesions post-injection and detecting lesions requiring re-treatment[42].

### Indocyanine Green Angiography

Indocyanine green angiography can be used as an adjuvant to FA since it provides details about the choroidal circulation, in addition to the location and extent of lacquer cracks. ICGA plays a pivotal role in differentiating myopic CNV from that of exudative age-related macular degeneration in myopic eyes[43].

### Optical Coherence Tomography

Optical coherence tomography is a rapid method that can help diagnose and stage the disease[37]. SD OCT has an advantage over FA, being noninvasive and providing higher image resolution. OCT has high sensitivity and specificity for identifying hyper-reflective lesions and assessing disease

activity[44]. Time domain OCT, on the other hand, has not proven to be effective in providing image resolution to assess CNV and its associated PM lesions. For examining the deeper structures such as the choroid and sclera, enhanced depth imaging OCT and swept-source OCT (SS-OCT) are advisable[45,46]. High penetration Doppler optical coherence angiography with high resolution, brings out images comparable to that of FA and ICGA[47].

### Fundus Autofluorescence

Fundus autofluorescence reveals abnormalities that aid in the diagnosis of myopic CNV. Fundus autofluorescence helps detect CNV-related macular atrophy and monitoring the extent of outer retinal atrophy[32].

Currently, FA alongside OCT are best equipped to help diagnose and differentiate myopic CNV.

## TREATMENT OF MYOPIC CHOROIDAL NEOVASCULARIZATION

Treatment modalities for myopic CNV have evolved over the years. Methods such as surgical CNV removal and macular translocation, laser photocoagulation of juxtafoveal and extra-foveal CNV, PDT, and corticosteroid treatment were employed in the past. Currently, anti-VEGF therapy is considered the first-line of treatment for subfoveal and juxtafoveal myopic CNV, backed by several studies[48-50].

### Anti-Vascular Endothelial Growth Factor Therapy

Intravitreal anti-VEGF therapy has emerged as a promising treatment option for myopic CNV. Typical response includes regression of the subretinal hyperreflective lesion visualized on SD-OCT. Of all the intravitreal anti-VEGF therapies available only two molecules i.e ranibizumab and aflibercept are currently approved for this indication. A systematic review and meta-analysis of anti-VEGF therapy for myopic CNV secondary to PM by Wand Et al[51] concluded that anti-VEGF therapy should be considered as a first-line therapy for this condition.

Dosing of Anti-VEGF therapy starts with 1 or 3 initial monthly loading injections, followed by additional injections as needed[49]. It is important to note that Anti-VEGF therapy may not be safe to administer to pregnant women during the first trimester[50].

### Intravitreal Ranibizumab

Ranibizumab was the first anti-VEGF drug approved for the treatment of myopic CNV[52]. It received approval for treating vision loss in myopic CNV by the European Medicines Agency (EMA) in 2013 and US FDA in 2017. These approvals were based on the results of the RADIANCE clinical trial11,[53].

Ranibizumab is a Fab fragment of a humanized murine monoclonal anti-VEGF antibody that specifically binds to the vascular endothelial growth factor A (VEGF-A) molecule at the VEGFR-1 and VEGFR-2 receptor binding sites to inhibit all biologically active VEGF-A isoforms54. As it is a Fab and does not contain the Fc-portion of the full-length antibody, it has shown better penetrance to retinal and choroidal tissues and less absorption to the systemic circulation55. Pharmacokinetic studies have shown that ranibizumab has a vitreous elimination half-life of around 9 days.

Multiple successful trials have established the efficacy of ranibizumab in myopic CNV. RADIANCE was a phase III, randomized, double-masked, multi-center clinical trial which evaluated the efficacy and safety of two dosing regimens of ranibizumab compared with verteporfin photodynamic therapy (vPDT) control group for myopic CNV11,53. At the 3-month primary endpoint and 12 months of study, the two ranibizumab dosing groups had significantly better mean BCVA improvement as compared to the vPDT control group.

The majority of intravitreal ranibizumab 0.5 mg studies have a follow-up of 12 months and all of them have shown significant BCVA gains irrespective of the dosing regimen[56,57,58,59]. The significant visual gains with intravitreal ranibizumab 0.5 mg were well maintained till 36 months follow up as established in long-term studies[60,61].

### Intravitreal Aflibercept

Aflibercept is a fusion recombinant protein (115 kDa) which contains the second binding domain of the human VEGFR-1 and third binding domain of human VEGFR-2 fused with the Fc portion of human

It binds to all isoforms of VEGF-A, VEGF- B, and placental growth factor (PlGF)62. The VEGF binding capacity of aflibercept is around 79 days as compared to 30 days.

The MYRROR study was a phase III, multi-center, double- masked, randomized sham-controlled study which evaluated the efficacy and safety of intravitreal aflibercept in patients with myopic CNV63. The primary end point was mean change in BCVA at 24 weeks. At week 48, the mean BCVA gain was significantly higher in the aflibercept group than in the sham + aflibercept group. The results pointed towards early initiation of treatment after diagnosis to achieve optimal results.

Chorioretinal atrophy progression rate after Anti-VEGF treatment for myopic CNV was assessed in a retrospective study by Sayanagi et al64 where 15 eyes received intravitreal aflibercept and 12 eyes received intravitreal ranibizumab with a follow up for 1 year. At the end of study, the progression of chorioretinal atrophy was at 40% in aflibercept group and 35% in ranibizumab group. Also, the subfoveal CNV was more likely to have chorioretinal atrophy progression as compared with non-subfoveal CNV.

Below is the summary of phase III clinical trials on intravitreal anti-VEGF agents for myopic choroidal neovascularization[65].

| Study | Total duration of study | Time of primary end-point | Treatment groups | No. of Eyes | Treatment schedule/protocol | Mean BCVA change at the primary end-point (ETDRS letters) | Mean BCVA changes at the end of study (ETDRS letters) | Mean no. of injections during the study |
|---|---|---|---|---|---|---|---|---|
| RADIANCE | | | Ranibizumab 0.5 mg (guided by visual stabilization) | 106 | Two loading doses of ranibizumab injections at baseline and Month 1, followed by monthly PRN ranibizumab injections guided by BCVA. | +10.5 | +13.8 | 4.6 |
| | 12 months | 3 months | Ranibizumab 0.5 mg (guided by disease activity) | 116 | One single ranibizumab injection at baseline, followed by monthly PRN ranibizumab injections guided by disease activity criteria. | +10.6 | +14.4 | 3.5 |
| | | | vPDT | 55 | One session of vPDT at baseline, followed by PRN ranibizumab or vPDT after Month 3 as per investigators. | +2.2 | +9.3 | 2.4 |
| BRILLANCE | | | Ranibizumab 0.5 mg (guided by visual stabilization) | 182 | Two loading doses of ranibizumab injections at baseline and Month 1, followed by monthly PRN ranibizumab injections guided by BCVA. | +9.5 | +12. | 4.6 |
| | 12 months | 3 months | Ranibizumab 0.5 mg (guided by disease activity) | 184 | One single ranibizumab injection at baseline, followed by monthly PRN ranibizumab injections guided by disease activity criteria. | +9.8 | +13.1 | 3.9 |
| | | | vPDT | 91 | One vPDT session at baseline, followed PRN ranibizumab or vPDT after Month 3 as per investigators. | +4.5 | +10.3 | 3.2 |
| MYRROR | 48 weeks | 24 weeks | Aflibercept 2 mg | 91 | One single aflibercept injection as baseline followed by PRN aflibercept injection every 4 weeks based on CNV activity. | +12.1 | +13.5 | 4.2 |
| | | | Sham | 31 | Sham injections until Week 24, followed by single mandatory aflibercept injection at Week 24 then PRN aflibercept injections every 4 weeks based on CNV activity. | −2.0 | +3.9 | 3.0 |
| SHINY | 9 months | 3 months | Conbercept 0.5 mg | 131 | Three loading doses of conbercept injections at baseline, 1 month and 2 months, followed by monthly PRN injections. | +12.0 | +13.28 | 4.9 |
| | | | Sham | 43 | Sham injections for 3 months, followed by single mandatory conbercept injection at Month 3 then monthly PRN conbercept injections. | +0.56 | +11.26 | 3.5 |

Abbreviations: PRN: pro re nata; vPDT: verteporfin photodynamic therapy; BCVA: best-corrected visual acuity; ETDRS: Early treatment diabetic retinopathy study

### Intravitreal Bevacizumab

Bevacizumab is a full length humanized monoclonal anti-VEGF antibody containing the Fc fragment of the humanized IgG that specifically neutralizes all active isoforms of VEGF. It is not licensed for intravitreal use but has been used off-label for many years now. Bevacizumab has shown significant improvement in mean BCVA compared to vPDT at 12 months post-treatment66,67. Long-term studies have also established the role of bevacizumab in myopic CNV upto 3 years post treatment[68].

There have been many clinical trials and real-world evidence studies that have consistently demonstrated the benefits of intravitreal anti-VEGF therapy for myopic CNV with no major adverse events. Most of the adverse events were mild such as conjunctival hemorrhage, corneal punctate keratitis, transient increase in eye pressure and lens changes. The progression of CRA, subretinal fibrosis is unrelated to the use of intravitreal anti VEGFs and rather related to the natural course of the disease. Therefore, the standard care for the treatment of myopic CNV is anti VEGF injections due to its favourable outcomes and safety profile.

An important point to note regarding systemic safety when using anti-VEGFs in patients who are pregnant or planning for pregnancy. There are few case reports where anti VEGFs were either planned or given accidentally in pregnant women with myopic CNV69-71. In all these cases, the infants were born full-term without any complications. However, the potential risk of miscarriage always poses a challenge in treating pregnant women and therefore women of reproductive age should be educated to avoid becoming pregnant during and for at least 3 months after the anti-VEGF therapy.

### Alternative Treatments prior to Anti VEGF era

Before anti-VEGF therapy became an established first-line treatment for myopic CNV, the main therapeutic approaches included thermal laser photocoagulation, vPDT, submacular surgeries, and corticosteroids.

## RECOMMENDED GUIDELINES FOR TREATMENT OF MYOPIC CHOROIDAL NEOVASCULARIZATION

- After confirmation of diagnosis, the treatment should begin immediately or at the earliest.
- The initial goal is to make the lesion inactive – assessed by consolidation of lesion on OCT, resolution of hemorrhage, and improvement in BCVA.
- The first 3 to 6 months are crucial in terms of monitoring of the CNV activity. Follow up visits should include VA testing, clinical examination, SD OCT/ SS-OCT or FFA if needed.
- Standard of care is a single injection of anti-VEGF therapy with additional injections as required depending on CNV disease activity.
- Treatment delays can lead to a poor visual outcome.
- If no evidence of CNV activity is found during the initial visits, the monitoring interval can be extended to every 2-3 months.
- Re-treatment is governed by a decrease in BCVA, the occurrence of new symptoms, OCT/FA signs of Myopic CNV.
- Alternative treatment options should be considered only if anti-VEGF therapy is contraindicated.

## TREATMENT OF MYOPIC CHOROIDAL NEOVASCULARIZATION

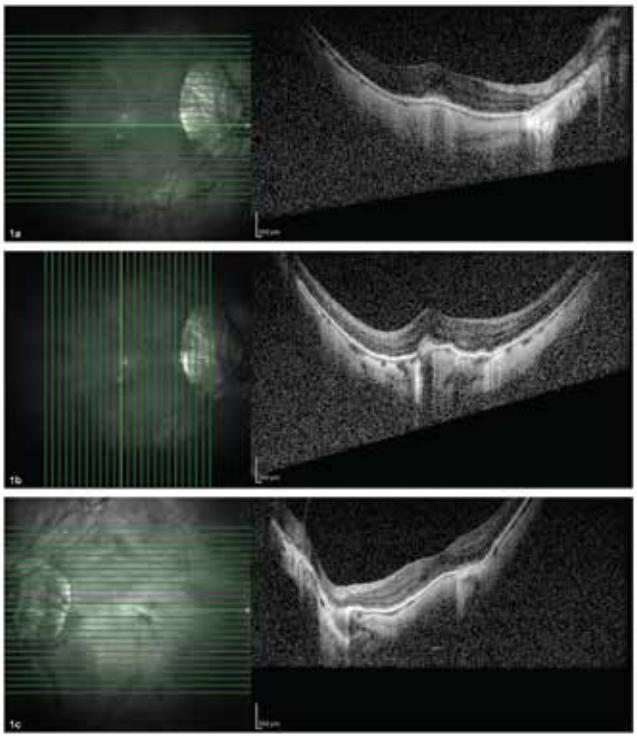

**Figure 1a, 1b:** Horizontal and vertical sections of EDI-OCT of the right eye of a 43-year-old female with pathological myopia, showing subretinal hyperreflective lesion suggestive of myopic CNV. Figure 1c shows intact macular layers with posterior staphyloma on OCT of the other eye.

**Figure 2a, 2b, 2c:** Early, mid, and late phases of FFA of the right eye showing classic CNV pattern, confirming the diagnosis of myopic CNV.

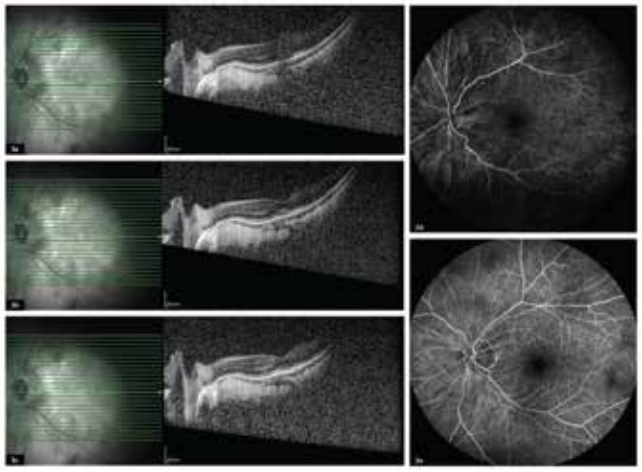

**Figure 3a:** Left eye EDI-OCT of a 33-year-old male with high myopia presenting with metamorphopsia and drop in vision. Clinically, subretinal hemorrhage was noted at the fovea. OCT showed disruption of the ellipsoid zone with subretinal hyperreflectivity. **Figure 3d** and **3e** show the early and late phases of FFA of the same eye without evidence of CNV. **Figure 3b** and **3c** show resolution of the subretinal hemorrhage (subretinal hyperreflectivity) secondary to lacquer crack at one and two month follow up visit, respectively.

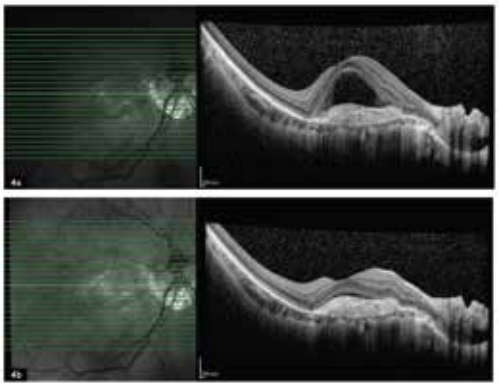

**Figure 4a:** EDI-OCT of myopic CNV lesion with subretinal fluid. Figure **4b** shows resolving subretinal fluid with consolidation of the CNV lesion after 1 dose of intravitreal anti-VEGF injection.

**FOOTNOTES AND DISCLOSURES**

Financial disclosure None
Conflict of Interest None
Acknowledgements Nil

## REFERENCES

1. Lin LL, Shih YF, Hsiao CK, et al. Epidemiologic study of the prevalence and severity of myopia among school-children in Taiwan in 2000. J Formos Med Assoc. 2001;100:684-691.
2. He M, Zeng J, Liu Y, et al. Refractive error and visual impairment in urban children in southern china. Invest Ophthalmol Vis Sci. 2004;45:793-799.
3. Pan CW, Zheng YF, Anuar AR, et al. Prevalence of refractive errors in a multiethnic Asian population: the Singapore epidemiology of eye disease study. Invest Ophthalmol Vis Sci. 2013;54:2590-2598.
4. Gao LQ, Liu W, Liang YB, et al. Prevalence and characteristics of myopic retinopathy in a rural Chinese adult population: the Handan Eye Study. Arch Ophthalmol. 2011;129:1199-1204.
5. Wong TY, Ferreira A, Hughes R, et al. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. Am J Ophthalmol. 2014;157:9-25.e12.
6. Moriyama M, Ohno-Matsui K, Futagami S, et al. Morphology and long-term changes of choroidal vascular structure in highly myopic eyes with and without posterior staphyloma. Ophthalmology. 2007;114:1755-1762.
7. Ohno-Matsui K, Lai TY, Lai CC, Cheung CM. Updates of pathologic myopia. Prog Retin Eye Res. 2016;52:156-187.
8. Hotchkiss ML, Fine SL. Pathologic myopia and choroidal neovascularization. Am J Ophthalmol. 1981;91:177-183.
9. Ohno-Matsui K, Yoshida T, Futagami S, et al. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. Br J Ophthalmol. 2003;87:570-573.
10. Yoshida T, Ohno-Matsui K, Ohtake Y, et al. Long-term visual prognosis of choroidal neovascularization in high myopia: a comparison between age groups. Ophthalmology. 2002;109:712-719.
11. Ikuno Y, Jo Y, Hamasaki T, Tano Y. Ocular risk factors for choroidal neovascularization in pathologic myopia. Invest Ophthalmol Vis Sci. 2010;51:3721-3725.
12. Ikuno Y, Sayanagi K, Soga K, et al. Lacquer crack formation and choroidal neovascularization in pathologic myopia. Retina. 2008;28:1124-1131.
13. Steidl SM, Pruett RC. Macular complications associated with posterior staphyloma. Am J Ophthalmol 1997;123:181–7.
14. Long Q, Ye J, Li Y, et al. C-reactive protein and complement components in patients with pathological myopia. Optom Vis Sci. 2013;90:501-506.
15. Tong JP, Chan WM, Liu DT, et al. Aqueous humor levels of vascular endothelial growth factor and pigment epitheliumderived factor in polypoidal choroidal vasculopathy and choroidal neovascularization. Am J Ophthalmol. 2006;141: 456-462.
16. Yamamoto Y, Miyazaki D, Sasaki S, et al. Associations of inflammatory cytokines with choroidal neovascularization in highly myopic eyes. Retina. 2015;35:344-350.

17. Leveziel N, Yu Y, Reynolds R, et al. Genetic factors for choroidal neovascularization associated with high myopia. Invest Ophthalmol Vis Sci. 2012;53:5004-5009.

18. Miyake M, Yamashiro K, Nakanishi H, et al. Evaluation of pigment epithelium-derived factor and complement factor I polymorphisms as a cause of choroidal neovascularization in highly myopic eyes. Invest Ophthalmol Vis Sci. 2013;54: 4208-4212.

19. Wakabayashi T, Ikuno Y, Oshima Y, et al. Aqueous concentrations of vascular endothelial growth factor in eyes with high myopia with and without choroidal neovascularization. J Ophthalmol. 2013;2013:257381.

20. Yoshida T, Ohno-Matsui K, Yasuzumi K, et al. Myopic choroidal neovascularization: a 10-year follow-up. Ophthalmology. 2003;110:1297-1305.

21. Hayashi K, Ohno-Matsui K, Yoshida T, et al. Characteristics of patients with a favorable natural course of myopic choroidal neovascularization. Graefes Arch Clin Exp Ophthalmol. 2005;243:13-19.

22. Avila MP, Weiter JJ, Jalkh AE, et al. Natural history of choroidal neovascularization in degenerative myopia. Ophthalmology. 1984;91:1573-1581.

23. Leveziel N, Caillaux V, Bastuji-Garin S, et al. Angiographic and optical coherence tomography characteristics of recent myopic choroidal neovascularization. Am J Ophthalmol. 2013;155:913-919.

24. Rashid A, Grossniklaus HE. Update on the pathology of pathological myopia. In: SpaideRF, Ohno-Matsui K, Yannuzzi LA, eds. Pathologic Myopia. New York: Springer-Verlag; 2014:83-95.

25. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. Ophthalmic Physiol Opt. 2005;25:381-391.

26. Hayashi K, Ohno-Matsui K, Shimada N, et al. Long-term pattern of progression of myopic maculopathy: a natural history study. Ophthalmology. 2010;117:1595-1611.e4.

27. Cheung CMG, Arnold JJ, Holz FG, Park KH, Lai TYY, Larsen M, Mitchell P, Ohno-Matsui K, Chen SJ, Wolf S, Wong TY. Myopic Choroidal Neovascularization: Review, Guidance, and Consensus Statement on Management. Ophthalmology. 2017 Nov;124(11):1690-1711.

28. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. Am J Ophthalmol. 2015;159:877-883.e7.

29. Tokoro T. Atlas of Posterior Fundus Changes in Pathologic Myopia. Tokyo, Japan: Springer; 1998.

30. Sawa M, Gomi F, Tsujikawa M, et al. Abnormal fundus autofluorescence patterns in myopic choroidal neovascularisation. Br J Ophthalmol. 2008;92:1236-1240.

31. Hampton GR, Kohen D, Bird AC. Visual prognosis of disciform degeneration in myopia. Ophthalmology. 1983;90:923-926.

32. Spaide RF. Choroidal neovascularization. In: Spaide RF, Ohno-Matsui K, Yannuzzi LA, eds. Pathologic Myopia. New York, NY: Springer; 2014:211-230.

33. Nagaoka N, Shimada N, Hayashi W, et al. Characteristics of periconus choroidal neovascularization in pathologic myopia. Am J Ophthalmol. 2011;152:420-427.e1.

34. Neelam K, Cheung CM, Ohno-Matsui K, et al. Choroidal neovascularization in pathological myopia. Prog Retin Eye Res. 2012;31:495-525.

35. Baba T, Ohno-Matsui K, Yoshida T, et al. Optical coherence tomography of choroidal neovascularization in high myopia. Acta Ophthalmol Scand. 2002;80:82-87.

36. Neri P, Lettieri M, Fortuna C, et al. Inflammatory choroidal neovascularization. Middle East Afr J Ophthalmol. 2009;16: 245-251.

37. Ho AC, Yannuzzi LA, Pisicano K, DeRosa J. The natural history of idiopathic subfoveal choroidal neovascularization. Ophthalmology. 1995;102:782-789.

38. Wang NK, Lai CC, Chou CL, et al. Choroidal thickness and biometric markers for the screening of lacquer cracks in patients with high myopia. PLoS One. 2013;8:e53660.

39. Miyake M, Yamashiro K, Akagi-Kurashige Y, et al. Vascular endothelial growth factor gene and the response to antivascular endothelial growth factor treatment for choroidal neovascularization in high myopia. Ophthalmology. 2014;121:225-233.

40. Ladaique M, Dirani A, Ambresin A. Long-term follow-up of choroidal neovascularization in pathological myopia treated with intravitreal ranibizumab. Klin Monbl Augenheilkd. 2015;232:542-547.

41. Adatia FA, Luong M, Munro M, Tufail A. The other CNVM: a review of myopic choroidal neovascularization treatment in the age of anti-vascular endothelial growth factor agents. Surv Ophthalmol. 2015;60:204-215.

42. El Matri L, Chebil A, Kort F. Current and emerging treatment options for myopic choroidal neovascularization. Clin Ophthalmol. 2015;9:733-744.

43. Wong TY, Ohno-Matsui K, Leveziel N, et al. Myopic choroidal neovascularisation: current concepts and update on clinical management. Br J Ophthalmol. 2015;99:289-296.

44. Wang E, Chen Y. Intravitreal anti-vascular endothelial growth factor for choroidal neovascularization secondary to pathologic myopia: systematic review and meta-analysis. Retina. 2013;33:1375-1392.

45. Ng DSC, Fung NSK, Yip FLT, et al. Ranibizumab for myopic choroidal neovascularization. Expert Opin Biol Ther. 2020;20:1385–1393.

46. Holz FG, Tufail A, Leveziel N, et al. Ranibizumab in myopic choroidal neovascularization: a subgroup analysis by ethnicity, age, and ocular characteristics in RADIANCE. Ophthalmologica 2016;236:19–28.

47. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina. 2006;26:859-870.

48. Mordenti J, Cuthbertson RA, Ferrara N, et al. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. Toxicol Pathol. 1999;27:536–544.

49. Lorenzo D, Arias L, Alcubierre R, et al. Intravitreal ranibizumab for choroidal neovascularization secondary to pathological myopia: 12-month follow-up. Ophthalmologica. 2011;226:103-109.

50. Monés JM, Amselem L, Serrano A, et al. Intravitreal ranibizumab for choroidal neovascularization secondary to pathologic myopia: 12-month results. Eye (Lond). 2009;23: 1275-1280.

51. Wu TT, Kung YH. The 12-month outcome of three consecutive monthly intravitreal injections of ranibizumab for myopic choroidal neovascularization. J Ocul Pharmacol Ther. 2012;28:129-133.

52. Pasyechnikova NV, Naumenko VO, Korol AR, et al. Intravitreal ranibizumab for the treatment of choroidal neovascularizations associated with pathologic myopia: a prospective study. Ophthalmologica. 2015;233:2-7.

53. Cohen SY, Nghiem-Buffet S, Grenet T, et al. Long-term variable outcome of myopic choroidal neovascuet al. Effect of intravitreal injection of aflibercept or ranibizumab on chorioretinal atrophy in myopic choroidal neovascularization. Graefes Arch Clin Exp Ophthalmol. 2019;257:749–757. 133-139.e1.

54. Hong YJ, Miura M, Makita S, et al. Noninvasive investigation of deep vascular pathologies of exudative macular diseases by high-penetration optical coherence angiography. Invest Ophthalmol Vis Sci. 2013;54:3621-3631.

55. Adatia FA, Luong M, Munro M, Tufail A. The other CNVM: a review of myopic choroidal neovascularization treatment in the age of anti-vascular endothelial growth factor agents. Surv Ophthalmol. 2015;60:204-215.

56. El Matri L, Chebil A, Kort F. Current and emerging treatment options for myopic choroidal neovascularization. Clin Ophthalmol. 2015;9:733-744.

57. Wong TY, Ohno-Matsui K, Leveziel N, et al. Myopic choroidal neovascularisation: current concepts and update on clinical management. Br J Ophthalmol. 2015;99:289-296.

58. Wang E, Chen Y. Intravitreal anti-vascular endothelial growth factor for choroidal neovascularization secondary to pathologic myopia: systematic review and meta-analysis. Retina. 2013;33:1375-1392.

59. Ng DSC, Fung NSK, Yip FLT, et al. Ranibizumab for myopic choroidal neovascularization. Expert Opin Biol Ther. 2020;20:1385–1393.

60. Holz FG, Tufail A, Leveziel N, et al. Ranibizumab in myopic choroidal neovascularization: a subgroup analysis by ethnicity, age, and ocular characteristics in RADIANCE. Ophthalmologica 2016;236:19–28.

61. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina. 2006;26:859-870.

62. Mordenti J, Cuthbertson RA, Ferrara N, et al. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. Toxicol Pathol. 1999;27:536–544.

63. Lorenzo D, Arias L, Alcubierre R, et al. Intravitreal ranibizumab for choroidal neovascularization secondary to pat hological myopia: 12-month follow-up. Ophthalmologica. 2011;226:103-109.

64. Monés JM, Amselem L, Serrano A, et al. Intravitreal ranibizumab for choroidal neovascularization secondary to pathologic myopia: 12-month results. Eye (Lond). 2009;23: 1275-1280.

65. Wu TT, Kung YH. The 12-month outcome of three consecutive monthly intravitreal injections of ranibizumab for myopic choroidal neovascularization. J Ocul Pharmacol Ther. 2012;28:129-133.

66. Pasyechnikova NV, Naumenko VO, Korol AR, et al. Intravitreal ranibizumab for the treatment of choroidal neovascularizations associated with pathologic myopia: a prospective study. Ophthalmologica. 2015;233:2-7.

67. Cohen SY, Nghiem-Buffet S, Grenet T, et al. Long-term variable outcome of myopic choroidal neovascularization treated with ranibizumab. Jpn J Ophthalmol. 2015;59:36-42.

68. Hefner L, Riese J, Gerding H. Three years follow-up results of ranibizumab treatment for choroidal neovascularization secondary to pathologic myopia. Klin Monbl Augenheilkd. 2013;230:401-404.

69. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012;15 (2):171–185.

70. Ikuno Y, Ohno-Matsui K, Wong TY, et al. Intravitreal aflibercept injection in patients with myopic choroidal neovascularization: the MYRROR study. Ophthalmology. 2015;122:1220-1227.

71. Sayanagi K, Uematsu S, Hara C, et al. Effect of intravitreal injection of aflibercept or ranibizumab on chorioretinal atrophy in myopic choroidal neovascularization. Graefes Arch Clin Exp Ophthalmol. 2019;257:749–757.

72. Ng DSC, Ho M, Iu LPL, Lai TYY. Safety review of anti-VEGF therapy in patients with myopic choroidal neovascularization. Expert Opin Drug Saf. 2022 Jan;21(1):43-54. doi: 10.1080/14740338.2021.1952979. Epub 2021 Jul 21. PMID: 34228553.

73. Ikuno Y, Nagai Y, Matsuda S, et al. Two-year visual results for older Asian women treated with photodynamic therapy or bevacizumab for myopic choroidal neovascularization. Am J Ophthalmol. 2010;149:140-146.

74. Baba T, Kubota-Taniai M, Kitahashi M, et al. Two-year comparison of photodynamic therapy and intravitreal bevacizumab for treatment of myopic choroidal neovascularisation. Br J Ophthalmol. 2010;94:864-870.

75. Peiretti E, Vinci M, Fossarello M. Intravitreal bevacizumab as a treatment for choroidal neovascularisation secondary to myopia: 4-year study results. Can J Ophthalmol. 2012;47:28- 33.

76. Wu Z, Huang J, Sadda S. Inadvertent use of bevacizumab to treat choroidal neovascularisation during pregnancy: a case report. Ann Acad Med Singapore. 2010;39:143-145.

77. Introini U, Casalino G, Cardani A, et al. Intravitreal bevacizumab for a subfoveal myopic choroidal neovascularization in the first trimester of pregnancy. J Ocul Pharmacol Ther. 2012;28:553-555.

78. Polizzi S, Mahajan VB. Intravitreal anti-VEGF injections in pregnancy: case series and review of literature. Journal of Ocular Pharmacology and Therapeutics. 2015;31(10):605–610.