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· Review Article ·

Macular hemorrhage in high myopia

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HIGHLIGHTS

- This review identifies the diverse etiologies of macular hemorrhage (MH) in high myopia (HM), distinguishing between CNV-related MH and non-CNV MH. CNV-associated MH is most frequently linked to pathological myopia and punctate inner choroidopathy (PIC), whereas non-CNV cases are often attributed to lacquer cracks, trauma, or surgery. Key discoveries include:
  - Anti-VEGF therapy is the first-line treatment for CNV-related MH, demonstrating significant efficacy in improving visual outcomes.
  - For non-CNV MH, conservative observation is generally recommended, highlighting the importance of tailored treatment strategies.
  - Secondary CNV from PIC may benefit from adjunctive anti-inflammatory therapies, although more evidence is needed.
- This study employs a comprehensive review methodology to synthesize knowledge on the pathogenesis, clinical characteristics, and treatment options for MH in HM. Specific innovations include:
  - Integration of findings on structural, hemodynamic, genetic, and systemic factors influencing CNV formation, providing a holistic understanding of MH pathogenesis.
  - Highlighting the need for a diagnostic approach that differentiates CNV-associated MH from non-CNV MH to inform targeted therapies effectively.
- The review underscores critical gaps and potential advancements, suggesting several avenues for future work:
  - **Mechanistic Research:** Investigating the molecular and genetic factors driving CNV and non-CNV MH development to inform preventative strategies.
  - **Diagnostic Improvements:** Development of advanced imaging tools to improve early detection and enable precise differential diagnosis of MH types.
  - **Therapeutic Optimization:** Refining anti-VEGF protocols, exploring combination therapies (e.g., anti-inflammatory treatments for PIC-related CNV), and evaluating long-term outcomes.
  - **Personalized Medicine:** Advancing individualized treatment strategies based on the underlying etiology and patient-specific factors, ultimately improving care for high-myopia patients.

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Full Text

Abstract: Macular hemorrhage (MH) is one of the most severe complications of high myopia, posing a significant threat to vision. MH can occur with or without choroidal neovascularization (CNV), with the CNV-associated form being the most prevalent. CNV-related MH may develop secondary to conditions such as pathological myopia, and punctate inner choroidopathy. Conversely, MH without CNV is often linked to factors like lacquer cracks, trauma, ocular surgery. While the exact mechanisms of CNV in high myopia are still not fully understood, anti-VEGF injections have been shown to be effective in improving visual function in patients with CNV. This review summarizes the clinical characteristics of various causes of MH and their respective treatments, providing valuable insights to help clinicians make informed diagnostic and therapeutic decisions.

Keywords: high myopia; macular hemorrhage; pathogenesis; treatment

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INTRODUCTION

High myopia (HM) is a significant vision-impairing disease, with a concerning increase in prevalence worldwide, particularly among younger generations.[1] Consequently, the complications associated with HM especially pathological myopia (PM) can have a profound impact on this population.[2] Among these complications, macular hemorrhage (MH) is one of the most severe, often resulting in a sudden and dramatic loss of vision. Although detailed prevalence data for MH in high myopia are currently lacking, it is estimated that the overall prevalence of MH in adults with HM in Asia is approximately 0.9%.[3] For myopic choroidal neovascularization (myopic CNV), the reported prevalence ranges from 0.9% to 2.7%.[4] MH refers to the accumulation of blood in the macular area due to the alternation of the retinal or choroidal circulation.Based on its position, MH can be classified into several categories which affect its natural course: preretinal (situated beneath the inner limiting membrane or hyaloid), intraretinal, subretinal, mixed (invading both the subretinal and subpigment epithelial layers), or encompassing multiple layers within the macular region.[5] In addition to the toxicity of blood to the retinal structure, the separation of photoreceptors from the pigment epithelium in cases of subretinal hemorrhage is also considered a mechanism of damage.

In high myopia, MH is typically subretinal or mixed, with two major types identified: one involves isolated bleeding from the rupture of Bruch's membrane (BM) without choroidal neovascularization (CNV), and the other involves bleeding associated with concurrent CNV. The latter can result from classical pathologic myopia or myopic CNV, punctate inner choroidopathy (PIC), choroiditis, and conditions concurrent with HM. While the presence of CNV may influence treatment choices, anti-VEGF therapy has been proven effective for CNV. However, for isolated MH without CNV, there are currently no effective treatment options available.

Since various primary diseases can induce MH in high myopia, and these underlying conditions determine the treatment strategy and prognosis, it is essential to summarize the different characters of MH in high myopia. This allows clinicians to make more accurate diagnoses and choose appropriate treatment methods based on the distinct clinical features of MH from different etiologies.Therefore, the purpose of this review is to explore the varied etiology, clinical features, natural history, and treatment options for MH secondary to different causes.

CNV SECONDARY TO PATHOLOGIC MYOPIA

The most common cause of MH in HM is myopic CNV. myopic CNV is considered the most frequent cause of CNV in young individuals in many countries, accounting for 62% of CNV cases in patients aged 50 years or younger. A recent systematic review summarized

the epidemiology of CNV based on 39 reports and found that the prevalence of CNV in individuals with pathologic myopia ranged between 5.2% and 11.3%, with approximately 15% of cases being bilateral.[2] Furthermore, in individuals with myopic CNV (with disease duration ranging from less than 3 months to 21.5 years), a deterioration in best-corrected visual acuity (BCVA) was observed over time.[2]

Myopic CNV is more likely to occur in patients who are older, have more severe chorioretinal atrophy, thinner choroid thickness, and the presence of lacquer cracks (LC).[6-8] Factors associated with worse visual outcomes include older age (>40 years), subfoveal CNV location, larger baseline lesion size (>400 μm), and lower baseline BCVA.[2, 9] Conversely, younger age, smaller CNV, and better initial visual acuity are associated with a more favorable prognosis.[10] Patients with myopic CNV typically develop the condition in their mid-fifties, with a mean AL approximately 29 mm.[11] The development of CNV can significantly alter the natural course of myopia, leading to retinal hemorrhage, edema, and eventually a fibrotic scar, resulting in permanent loss of visual function. Studies have shown that the development of CNV, CNV-related macular atrophy, and the enlargement of CNV-related macular atrophy are strongly associated with loss of BCVA. Approximately 92.7% of myopic CNV cases progress to macular atrophy, resulting in significant visual acuity loss.[11]

Typically, myopic CNV presents as a small, flat, grayish subretinal membrane, located between the neurosensory retina and the retinal pigment epithelium (RPE), often near the fovea, with or without associated hemorrhage.[12-13] On optical coherence tomography (OCT), these lesions appear as highly reflective signals with blurred upper boundaries of the RPE cells (Fig.1, typical of type 2 macular neovascularization) and are usually associated with minimal subretinal fluid.[14] The determination of activity on OCT mainly relies on four signs:[15] 1) intraretinal or subretinal fluid, 2) subretinal hyperreflective material, 3) disruption of the external limiting membrane, and 4) blurred lesion boundaries. Optical coherence tomography angiography (OCTA) is a valuable tool for detecting myopic CNV, showing a vascular network pattern in the outer retina and choriocapillaris slab, with high sensitivity (90.48%) and specificity (93.75%).[16] On OCTA, the assessment of activity is based on four indicators:[17] 1) a jellyfish-like or sea fan-shaped appearance of myopic macular neovascularization lesions, 2) numerous tiny capillary branches, 3) presence of vascular anastomoses or loops,

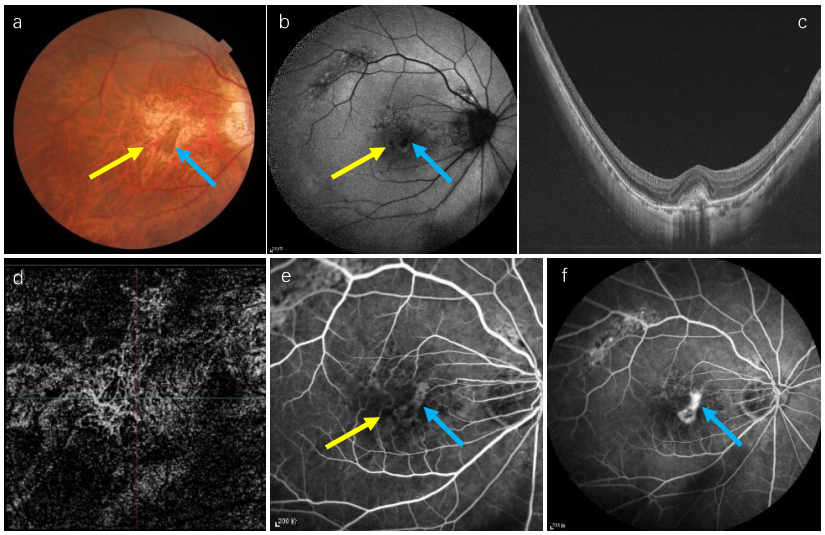

Figure 1 Multimodal imaging of macular hemorrhage in pathological myopia-associated choroidal neovascularization (myopic CNV)

(a) Funduscopy image showing a small, flat gray lesion with macular hemorrhage at the edge of the lesion. (b) Autofluorescence (AF) image showing hypofluorescence in both the hemorrhage and CNV lesion. (c) Optical coherence tomography (OCT) image showing the CNV lesion with highly reflective signals and blurred boundaries. (d) Optical coherence tomography angiography (OCTA) image displaying a clear vascular network in myopic CNV. (e, f) Fluorescein angiography (FA) images showing early-phase well-defined hyperfluorescence of the lesion with late-phase fluorescent leakage and blocked fluorescence due to the hemorrhage. Yellow arrow: hemorrhage; Blue arrow: CNV lesion.

and (4) a dark halo surrounding the lesion. The combined use of these methods can improve the sensitivity and specificity of activity assessment. However, fluorescein fundus angiography (FFA) remains the gold standard for diagnosis, showing early-phase well-defined hyperfluorescence of the lesion with late-phase fluorescent leakage. Indocyanine green angiography (ICGA) shows that ICG is minimally absorbed by the RPE and blood, allowing better differentiation of CNV from other pathologies, especially when hemorrhage is present.

Understanding the natural history of myopic CNV is crucial for guiding treatment approaches. If left untreated, myopic CNV can cause scarring with expanding macular atrophy, leading to irreversible vision loss within a period as short as five years. In a 10-year follow-up study of 27 eyes with myopic CNV, the visual acuity of almost all eyes (approximately 96.3%) dropped to 20/200 or worse within 5 to 10 years after the onset of CNV, due to the development of chorioretinal atrophy around the regressed CNV.[18] The average time for complete bleeding absorption from myopic CNV was about 7.6 months (range, 1-15 months) without any intervention, and rebleeding occurred in 22.2% of eyes during follow-up.[18] These findings suggest that long-term visual acuity decline may be due to macular atrophy rather than the presence of CNV itself; however, the onset of CNV can definitely induce and accelerate chorioretinal atrophy. In another long-term follow-up study, chorioretinal atrophy developed around the regressed CNV in 26 eyes (96.3%) at 5 and 10 years after CNV onset.[18] After the absorption of MH, most patients exhibited intraretinal hyperreflective (IRH) signs on OCT. In a 24-month follow-up of a small sample with IRH signs after MH absorption in eyes with pathologic myopia, most signs remained stable. IRH may predict future myopic traction maculopathies.[19]

Few studies have reported favorable outcomes with observation alone; most studies describe a poor prognosis. Therefore, timely treatment of myopic CNV can lead to quick resolve of the CNV lesion and get better visual acuity outcomes. Previously, Laser photocoagulation, Photodynamic therapy[20] with verteporfin was applied to the treatment of myopic CNV, however, due to the high rate of recurrence and relative low benefit of visual acuity, and given the superior efficacy and long-term effect displayed by anti-vascular endothelial growth factor(anti-VEGF) therapy, Currently, anti-VEGF therapy is the standard of care and the recommended first-line treatment option for myopic CNV.[12, 21] It contributes to the reduction in CNV lesion size and central macular thickness improvement in myopic population (Fig.2). Long-term studies have demonstrated that early treatment of confirmed myopic

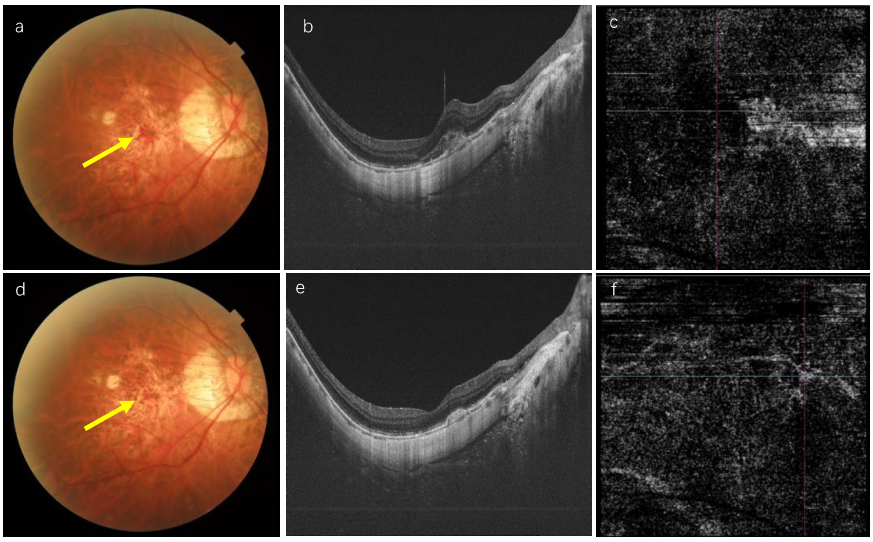

Figure 2 Anti-VEGF treatment for myopic CNV

(a-c) Baseline imaging of myopic CNV, showing macular hemorrhage on fundus photography (a), a CNV lesion with highly reflective signals on OCT (b), and a vascular network on OCTA (c). (d-f) Imaging one month after anti-VEGF injection, showing a reduction in macular hemorrhage (d), decreased CNV lesion size on OCT (e), and OCTA (f).

CNV cases with an intravitreal anti-VEGF agent is effective in preventing late-stage complications.[21- 22] However, the optimal treatment regimen for anti-VEGF in myopic CNV remains debated. .Initially, a 3-loading-dose followed by pro re nata (PRN) approach, similar to that used in age-related macular degeneration (AMD), was suggested. , It was found that more than 70% myopic CNV eyes only required only three initial intravitreal injection of bevacizumab or ranibizumab, and average of 3.8 injection in 2 years follow up, about 65% had three or more lines visual gain.[23] Subsequently, studies began to compare different anti-VEGF regimens for myopic CNV, primarily focusing on 1+PRN *versus* 3+PRN. Wang et al. conducted a systematic review including three non-randomized controlled studies with a 1-year follow-up, comparing 1+PRN to 3+PRN in terms of BCVA and central retinal thickness (CRT). The 3+PRN group demonstrated better BCVA at 3 and 6 months (LogMAR MD = 0.11, 95% CI [0.01, 0.21]), but this difference diminished over time, with no significant differences at 1 year. There were also no significant differences in CRT between the two groups at 3, 6, or 12 months. Importantly, the 1+PRN group required, on average, 1.37 fewer injections than the 3+PRN group ($P < 0.001$).[24] Li et al. conducted the SMILE study, a single-center randomized controlled trial comparing the efficacy of ranibizumab using 1+PRN versus 3+PRN in patients with active myopic CNV. After 12 months, there were no significant differences between the two groups in BCVA changes, anatomical parameters such as CRT, CNV thickness, CNV area, leakage area, or recurrence rates. The 1+PRN group required 1.54 fewer injections on average than the 3+PRN group over the 12-month period.[25] A retrospective study investigating the efficacy of conbercept for myopic CNV also compared the 1+PRN and 3+PRN regimens. At 12 months, there were no significant differences in BCVA or CRT between the two groups, but the 1+PRN group required fewer injections (2.14 ± 1.06 *vs.* 3.37 ± 0.76, $P < 0.001$).[26] Additionally, a network meta-analysis compared treatments for myopic CNV, including anti-VEGF, photodynamic therapy (PDT), intravitreal triamcinolone acetonide, and observation. The analysis found that anti-VEGF therapy resulted in the highest visual acuity gain, approximately 14.1 letters, and that the 1+PRN regimen was comparable to the 3+PRN regimen in terms of efficacy.[27] We also summarized all randomized controlled trials (RCTs) using anti-VEGF in myopic CNV,[25,28-34] which showed favorable results for improving visual acuity (Table 1).

CNV SECONDARY TO PUNCTATE INNER CHOROIDOPATHY

PIC is an uncommon idiopathic inflammatory chorioretinal disease that most commonly affects young, myopic females.[35] Myopia has been reported in 80% to 100% of PIC cases, with a mean refractive error ranging from –4.6 to –7.0 diopters, extending from –14 to +4 diopters, and a median age of 30 years (range, 15 to 55).[36-37] The etiology and pathogenesis of PIC remain unclear. Hypotheses suggest it is an autoimmune disease that manifests in individuals predisposed by polygenic susceptibility, triggered by environmental factors such as infection, immunization, or stress.[35]

Symptoms of PIC include photopsia, floaters, decreased night vision, blurred vision, and visual field loss. These symptoms are often acute and transient, without long-term visual consequences. Visual acuity at presentation varies and depends on the location of inflammatory lesions and their complications. Clinically, the fundus of PIC is characterized by multifocal, small (100-300 μm), yellow-gray lesions that are well-defined and confined to the posterior pole (Fig. 3), specifically at the inner choroid and outer retina.[38] Notably, the peripapillary and peripheral regions are spared from these lesions, and there is no sign of inflammation in the anterior chamber or vitreous. Over time, some lesions tend to resolve, while most result in permanent structural changes, especially the formation of atrophic chorioretinal scars at the previous sites of inflammation. These scars display a “punched-out” appearance and acquire pigmentation.[39] Although PIC typically presents unilaterally, more than 50% of cases eventually affect both eyes.[40]

MH in PIC is mainly due to secondary CNV. CNV is a common complication of PIC and tends to manifest as the disease progresses, presenting with MH similar to myopic CNV and resulting in vision loss. The risk of developing CNV in PIC is higher compared to other forms of posterior and panuveitis.[41] The rate of CNV

Table 1 prospective and randomized clinical trials of anti-VEGF for the treatment of PM-CNV

Study design	Sample size (eyes)	treatment	Anti-VEGF pattern	Mean Follow-up (y)	NO. of IV	Baseline VA	VA at last visit
RCT study [28]	182	Ranibizumab (VA stabilization)	(1+PRN)	1	4.6 (2.4)	53.6 (12.6) letters	66.7 letters
	184	Ranibizumab (disease activity)	(1+PRN)	1	3.9 (2.5)	54.2 (13.0) letters	66.2 letters
	91	vPDT	-	1	3.2 (2.3)	52.1 (12.7) letters	62.4 letters
prospective randomized study [29]	24	Aflibercept	(3+PRN)	0.25	3	0.53 (0.10)LogMAR	0.38(0.11)LogMAR
	24	Ranibizumab	(3+PRN)	0.25	3	0.55 (0.11)LogMAR	0.39(0.12)LogMAR
Prospective randomize study[30]	16	Ranibizumab	(1+PRN)	0.5	2.81(1.17)	26.44 (12.58) letters	43.75 (9.92) letters
	16	Bevacizumab	(1+PRN)	0.5	2.44(0.89)	29.50 (12.98)letters	45.37 (9.95) letters
RCT study [31]	23	Ranibizumab	(1+PRN)	1.5	2.56 (1.61)	0.60 (0.29)LogMAR	0.40 (0.38)LogMAR
	25	Bevacizumab	(1+PRN)	1.5	4.72(2.24)	0.60 (0.26)LogMAR	0.44 (0.32)LogMAR
RCT study [32]	50	Ranibizumab	(2+PRN)	2	2.5(0.9)	0.21 (0.14) LogMAR	0.43 (0.24)LogMAR
	47	Aflibercept	(2+PRN)	2	2.6(1.0)	0.2 (0.14) LogMAR	0.41(0.2)LogMAR
RCT study [25]	26	Ranibizumab	(1+PRN)	1	2.04(1.22)	54.1(15.5) letters	67.5(13.3) letters
	24	Ranibizumab	(3+PRN)	1	3.58(0.72)	48.7(13.1) letters	65.8(11.2) letters
RCT study [33]	90	Aflibercept	(1+PRN)	0.46	4.2	56.4(9.8) letters	68.5letters
		Sham	-	0.46	0	56.6 (9.8) letters	54.6 letters
RCT study [34]	40	Bevacizumab	(1+PRN)	1.53(0.40)	2.75(1.24)	0.52(0.34)LogMAR	0.53(0.33)LogMAR
	38	Ranibizumab	(1+PRN)	1.65(0.43)	2.29(1.16)	0.62(0.36)LogMAR	0.50(0.35)LogMAR

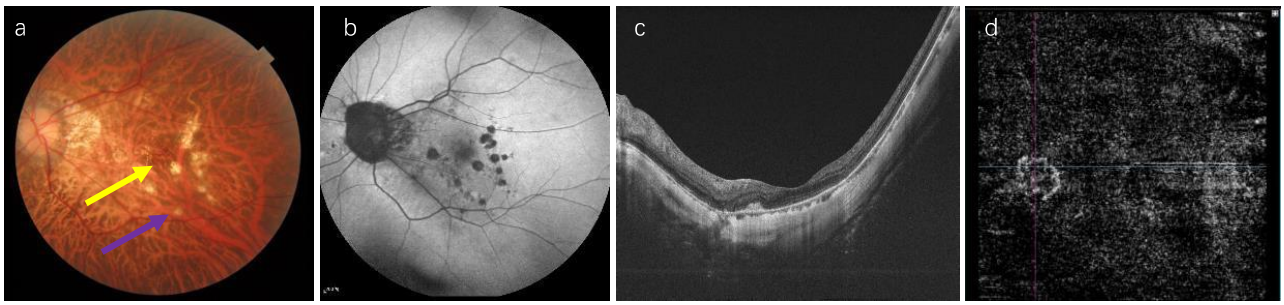

Figure 3 Multimodal imaging of macular hemorrhage in punctate inner choroidopathy (PIC)

(a) Image showing multifocal, small, yellow-gray lesions that are well-defined and located around the macula, along with macular hemorrhage. (b) AF image showing hypofluorescence for both the PIC lesion and macular hemorrhage. (c) OCT image showing a small CNV lesion. (d) OCTA image displaying a clear vascular network of secondary CNV in PIC. Yellow arrow: hemorrhage; Purple arrow: PIC lesion.

development in PIC varies across studies, ranging from 17% to 75%.[36, 42] The presence of CNV in the fellow eye increases the risk of developing CNV, while previous oral corticosteroid treatment is associated with a reduced risk of developing CNV.[42] CNV secondary to PIC shares some features with inflammatory lesions, such as symptoms of vision loss and scotomata, and pathological manifestations including infiltrating lesions and heterogeneous material in the outer retina and subretinal space.

In FA, punctate hyperfluorescent choroidal lesions persist throughout the early and late venous phases, and CNV lesions are characterized by a zone of hypofluorescence surrounding a hyperfluorescent area in the early venous phase, associated with leakage in the late phase. ICGA shows lesions as hypofluorescent regions in both the early and late phases. OCT is effective for differentiating and monitoring the progression of inflammatory lesions and secondary CNV. Zhang et al. used OCT to divide PIC into five stages depending on disease activity.[43] In some cases, it is challenging to distinguish between active inflammatory lesions and CNV, as both exhibit disruption of the blood-retina barrier and infiltrative lesions.[44] Chen et al. found that RPE disruption and hyper-transmission are early signs of secondary CNV in PIC.[45] OCTA is a non-invasive technique for imaging the microvasculature of the retina and choroid, making it a useful alternative tool for detecting CNV in PIC and differentiating it from inflammatory lesions.[46] Distinguishing PIC from multifocal choroiditis with panuveitis (MCP) is challenging, as they share a similar disease spectrum. However, the absence of peripheral chorioretinal lesions and intraocular inflammation are key characteristics that differentiate PIC from MCP.[47] Additionally, PIC shows a preference for affecting young, myopic women.

Due to the varying stages of PIC, limited evidence surrounding treatment strategies, and the scarcity of prospective clinical trials, the management of PIC remains a significant challenge. However, intervention is warranted when secondary CNV occurs, or when new or active inflammatory PIC lesions develop, especially those posing a threat to the fovea.[35] There is no standardized protocol for treating CNV resulting from PIC, and considerable debate persists regarding the appropriate management of CNV secondary to PIC. There are two major strategies for treating CNV secondary to PIC: corticosteroids and anti-VEGF therapy. Corticosteroids have both anti-inflammatory and anti-angiogenic effects. Several case reports and case series have demonstrated that oral corticosteroids not only stabilize or improve vision in PIC-associated CNV but also decrease the incidence and reduce the frequency of CNV recurrences.[48,49] The suggested protocol for oral steroids in PIC involves initiating therapy at a dose of 1 mg/kg, followed by a relatively fast tapering over 4-6 months.[50] However, due to the low level of evidence supporting the use of oral steroids for PIC and the potential adverse effects, careful consideration of treatment choices and patient characteristics is necessary. There is limited evidence regarding the use of immunomodulatory or immunosuppressive agents for treating PIC inflammatory lesions and secondary CNV. The effectiveness of anti-VEGF treatment for CNV secondary to AMD has been well-established in many randomized controlled trials. Although no RCTs have explored the effect of anti-VEGF therapy for CNV secondary to PIC, various retrospective studies have provided evidence that anti-VEGF agents, including bevacizumab,[51] ranibizumab,[52] and aflibercept,[53] can effectively stabilize or improve visual outcomes by reducing CNV activity or completely regressing CNV lesions in PIC. A retrospective study also indicated that combining anti-VEGF therapy with oral corticosteroids may be more effective than monotherapy in reducing CNV recurrence and preventing new PIC lesions.[54]

LACQUER CRACK

In addition to CNV, MH in HM is also associated with LC, which are considered another important sign of PM.[55] Lacquer cracks result from mechanical breaks in BM and the RPE, caused by the mechanical stretching and distortion of the posterior segment in highly myopic eyes.[56] The prevalence and incidence rates of LC vary substantially depending on different stages of HM.[8] The reported incidence of LC formation from a tessellated fundus ranges from 1% to 18.9%, and from diffuse chorioretinal atrophy (CRA) ranges from 2.2% to 23.1%, over follow-up periods ranging from 10 to 18.7 years, with a minimum of 5 years.[57-59]

The exact etiology of LC formation in PM remains

unclear, but several theories have been proposed. The "mechanical stretch theory," suggested by Klein and Curtin in 1975, is currently the most widely accepted.[56] According to this theory, LC are healed mechanical breaks caused by the stretching of the retina and choroid within the posterior staphyloma, rather than a consequence of a primary atrophic process in the choroid. These ruptures in BM may lead to small hemorrhages and predispose high myopic eyes to rapid visual loss. In some cases, larger subretinal or intraretinal hemorrhages can occur. While these typically have a better prognosis, in some patients, the bleeding reabsorbs spontaneously, and vision improves. However, visual impairment may persist, especially in cases with thick subretinal bleeding, even after the bleeding has completely resolved.[60] After several months, the repair process involves scar tissue formation and atrophy of the RPE above the damaged BM and choriocapillaris. Eventually, LC become visible as yellowish linear and stellate lesions when observed ophthalmoscopically.[61]

On the fundus, LC appears as irregular, yellowish-white or grayish, linear or stellate lesions, which can be single or multiple, mainly branching in the posterior pole (Fig.4). LCs are mostly seen in the macular region, with the temporal quadrant being most affected.[62] The detection rate of LC in good-quality color fundus photographs has been found to be 97.8%.[62] LCs can be detected on photographs once the healing process associated with BM rupture is complete, including secondary changes in the RPE layer. On fundus autofluorescence (FAF) images, LCs appear as linear hypo-autofluorescent lines due to RPE atrophy over the site of the BM rupture, with a reported detection rate of 85.1%.[62] In FFA, LCs appear as linear hyperfluorescent lesions from early to late phases of the angiogram. Early hyperfluorescence is caused by window defects due to RPE atrophy, while late hyperfluorescence results from staining of scar tissue within the BM rupture. Indocyanine green (ICG) angiography is considered the best imaging modality for identifying LCs. On ICG angiograms, LCs appear as well-delineated hypofluorescent streaks, first visible during the mid-phases (10–15 minutes) and becoming more pronounced in the later phases (over 20 minutes after dye injection). On OCT images, LCs appear as discontinuities of the RPE layer along with increased hypertransmission into deeper tissues.[63] OCT is the only imaging modality that can detect discontinuities of the RPE-BM complex at the site of a crack, which is

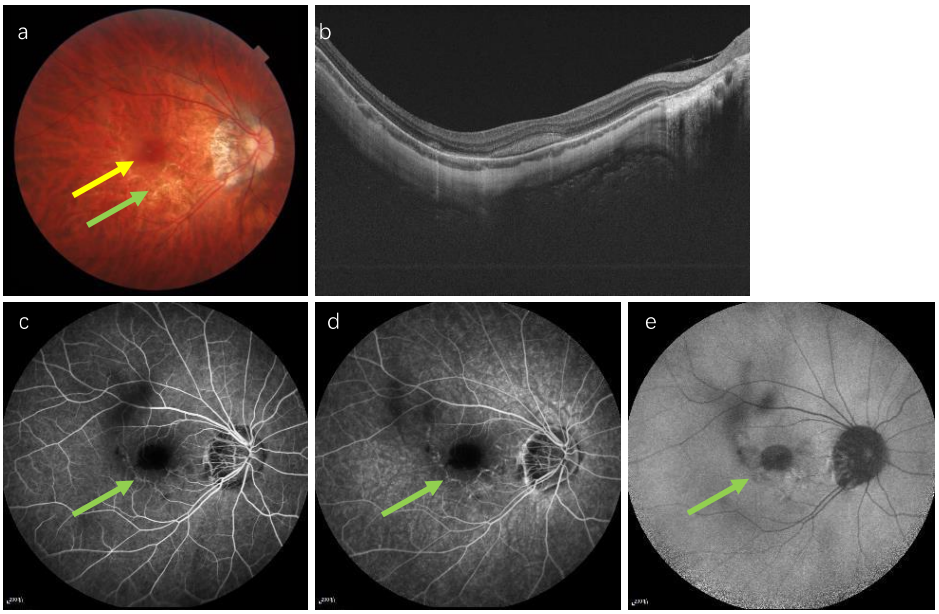

Figure 4 Multimodal imaging of macular hemorrhage in lacquer crack (LC)

(a) Fundus image showing an irregular, yellowish-white linear LC lesion along with macular hemorrhage. (b) OCT image showing flat, regular, subretinal high reflectance indicative of macular hemorrhage. (c-d) FA images showing LCs as linear hyperfluorescent lesions from early to late phases, with blocked fluorescence due to the hemorrhage. (e) AF image showing LCs as linear hypo-autofluorescent lines. *Yellow arrow: hemorrhage; Green arrow: LC lesion.*

an essential feature of LC. OCTA can differentiate, with high reliability, between the presence of CNV in patients with HM presenting with new MH and a single bleeding event without CNV.[64]

Macular hemorrhageis commonly associated with LC and may be the only sign of new LC formation in some eyes.[65] These hemorrhages are usually round, known as "coin lesions," .[19] In cases of larger hemorrhages, a dark spot may appear in the center, surrounded by a lighter edge, indicating a concentration gradient of red blood cells focused around a single rupture. Occasionally, multiple small hemorrhages may be observed along the path of an LC, suggesting a gradual progression of the crack lesion. These hemorrhages are found beneath the neurosensory retina, usually along the course of an LC, and are associated with choriocapillaris disruption at the crack site.[19] In cases where these hemorrhages are thick and extend into the inner retinal layers beyond the external limiting membrane, defects in the ellipsoid zone (EZ), especially in the foveal region, may persist, resulting in permanent visual impairment.[66] After the complete resolution of simple hemorrhages, an LC is typically visible at the site of the previous bleed. However, an LC may sometimes not be visible after hemorrhage absorption if the crack lesion is too small to detect or if diffuse CRA obscures the view of newly formed cracks.

While LCs do not usually directly affect visual acuity, except when they involve the fovea, they are strongly associated with an increased risk of developing other sight-threatening complications of HM, such as macular holes (MH), patchy chorioretinal atrophy, diffuse atrophy, and, most notably, myopic CNV.[67] Subretinal hemorrhages in the presence of an LC can also indicate myopic CNV, making it essential to rule out this vision-threatening condition in all patients. Myopic CNV associated with LC is typical of PM—generally small in size and with minimal exudation. However, the hypofluorescent rim, a characteristic feature of myopic CNV seen in 70% of cases, is typically absent in myopic CNV that arises from LC progression.[68] Approximately 13.3% of LCs develop into CNV over a 10-year follow-up period, and LCs are found in 82% of eyes with CNV.[69] Several risk factors may predispose eyes with LC to develop myopic CNV, including systemic factors (older age and female gender) and ocular factors (LC morphology, severity, progression pattern, and the presence of type II staphyloma).[6, 61]

LC should be differentiated from myopic stretch lines (MSL) and similar-looking lesions in BM, such as angioid streaks and choroidal rupture, which may also cause MH. Patients with MSL tend to be older and exhibit more severe atrophy compared to those with LC. Notably, both LCs and MSLs exhibit hyperfluorescent in NIA images and ICGA.However, these lesions can be distinguished by FAF, when MSL present as linear hypofluorescent stretches while LCs showed linear hyperauto fluorescence.[70] And MSLs rare have MH, unless they coexit with LC.[70] OCT images show irregularity or clumps of RPE on and around occasionally visible, protruding large choroidal vessels, along with an extremely thin choroid on MSL.[63] Another condition that needs differentiation from LCs is angioid streaks, which are usually reddish, have a spider-web-like configuration centered on the optic disc, and follow a relatively straighter course compared to LCs.[71] Choroidal ruptures involve breaks in the choroid, BM, and the RPE layer, typically with a reported history of ocular trauma.

Regarding the treatment of MH associated with LC, most cases resolve on their own, and additional treatment is not usually required. However, in cases of LC-associated CNV, timely intravitreal injection of anti-VEGF is recommended.

TRAUMA RELATED

Traumatic choroidal ruptures (TCR) are rare conditions that can cause MH. Every individual with TCR typically has a history of ocular trauma.[72] Given the abnormal elongation of axial length and thinning of the ocular wall in HM, it is reasonable to speculate that myopic eyes may be more susceptible to choroidal rupture and retinal hemorrhage following trauma.[73] Relatively few studies have specifically focused on MH in the context of TCR. There are two types of MH associated with TCR: one is a "single bleeding" that occurs immediately after trauma due to the sudden rupture of the choroid. Later on, at the site of rupture, secondary CNV may develop.

Choroidal ruptures typically manifest as curvilinear or crescent-shaped lines, predominantly yellow or white, widest at the center, and tapering toward the ends

during ophthalmoscopic examination. They may also appear as white streaks with pigmented margins due to RPE hyperplasia.[74] These ruptures are hyperreflective on infrared reflectance and hypofluorescent with hyperfluorescent edges on blue autofluorescence imaging. OCT reveals disruption of the RPE/BM complex and the EZ. A hyperreflective lesion, protruding from the RPE/BM rupture to the EZ and outer nuclear layer, is associated with backscattering, likely due to dehemoglobinized blood and other debris. FFA shows that choroidal ruptures are hypofluorescent in the early phases and become hyperfluorescent in the mid to late phases. OCTA provides a non-invasive approach to monitor choroidal neovascular complexes and detect CNV progression. In the early stages, the choriocapillaris vascular network appears disrupted in the area corresponding to the choroidal rupture.[74]

CNV is a well-known complication of choroidal rupture resulting from severe ocular injuries.[75] Neovascularization in this context often follows a relatively benign course, with spontaneous regression commonly observed as part of the natural healing process . Risk factors for the development of CNV secondary to choroidal rupture include older age, the presence of macular rupture, and the greater length of the rupture.[76] Approximately 5%-25% of eyes with choroidal ruptures will progress to develop persistent CNV, which can lead to late visual loss in these eyes.[77]

The intravitreal injection of anti-VEGF agents is recognized as the gold standard therapy in cases of CNV development. Typically, a small number of injections, usually ranging from one to three, are sufficient to induce quiescence of the choroidal neovascular complex, following CNV spontaneous regression and subsequent involution.[78]

OCULAR SURGERY RELATED

MHis a rare but serious complication of ocular surgery. It has been reported following various refractive surgeries, including laser in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), and the implantation of a posterior chamber collamer lens.[79-80] Highly myopic eyes are particularly prone to bleeding in areas with LC and the formation of myopic CNV.[81] The characteristic symptom of MH following ocular surgery is severe unilateral visual loss, which is often irreversible and occurs during the postoperative period.[79] Typically, these patients are young individuals with HM, and MH tend to occur within 1 to 5 months after the surgical procedure. Therefore, the relationship between the surgical technique and MH remains unclear, as MH can also spontaneously occur in the highly myopic population.

The use of multiple diagnostic tools is beneficial for identifying and assessing MH in these cases. Initially, MH is typically identified through fundoscopic examination, which may show varying patterns such as scattered MH or hemorrhage at the edge of a CNV. FA can reveal a distinct area of blocked choroidal and retinal fluorescence that corresponds precisely to the hemorrhage location. ICGA provides additional information about the presence or absence of CNV, both of which can be associated with ocular surgery-related MH.[81]

MECHANISMS OF MH IN MYOPIA

MH without CNV

MH without CNV, secondary to conditions such as LC, trauma, or ocular surgery, typically results from the rupture of BM. In HM, the progressive and excessive elongation of the eyeball induces mechanical strain on ocular tissues, causing thinning of the retina and choroid and weakening of the sclera. This condition can promote the development of posterior staphyloma, further exacerbating the stretching and thinning of the retina and choroid. These changes ultimately lead to characteristic lesions, including lacquer cracks.[71, 82] In cases of trauma, the anteroposterior compressive forces elongate the radius of curvature, especially along the temporal half of the globe. This can lead to an elastic recoil of the retinal and scleral layers, causing fractures along the RPE-BM-choriocapillaris complex, resulting in retinal hemorrhage.

MH with CNV

The mechanisms underlying CNV in PM remain unclear. However, various factors, including structural alterations, hemodynamic changes, genetic predispositions, and systemic influences, may contribute to CNV formation.[83] The rupture of BM and RPE in areas of LC can initiate a wound healing response, disrupting the balance between pro-angiogenic and

anti-angiogenic factors, such as VEGF and pigment epithelium-derived factor (PEDF). This imbalance promotes the ingrowth of neovascular tissue from the underlying choroid, leading to CNV development.[9, 84] Moreover, the breaks in the RPE-BM complex provide a pathway for inflammatory cells, fibroblasts, and new blood vessels to infiltrate from the choroid into the subretinal space, with many neovessels branching from a lacquer crack.[21] Recent studies using ICGA and OCTA have shown that perforating scleral vessels (PSV) originating from the short posterior ciliary arteries are implicated in the onset of myopic CNV.[85] Additionally, scleral dilation at the site of these perforating vessels may contribute to the formation of lacquer cracks, a known risk factor for CNV.[86]

VEGF is a major driver of retinal and CNV, and it is essential for VEGF-induced endothelial permeability.[87] The level of VEGF in the aqueous humor of eyes with myopic CNV is significantly higher compared to highly myopic eyes without CNV, similar to interleukin-8 (IL-8) levels.[83, 87] CNV, when developing anterior to the RPE, causes a physical disruption of the RPE barrier. Conversely, sub-RPE CNV exerts multifactorial stresses on the RPE, including inflammatory, mechanical, and proteolytic stress, all contributing to RPE barrier dysfunction. Fluid accumulation in the subretinal and intraretinal spaces in neovascular macular disorders results from both the abnormal neovascular structure and the associated outer blood-retinal barrier disruption.[88]

In addition to structural changes, hemodynamic alterations in choroidal circulation are also believed to play a role. These alterations include delayed choroidal filling beneath the macular area due to slow blood flow within the choroidal vessels. Thinning of the choroid, resulting from the loss of large vessels, choriocapillaris, and stromal tissue, further contributes to these changes. Such hemodynamic disturbances lead to choroidal ischemia, which triggers the upregulation of angiogenic factors, ultimately facilitating the development of CNV.[89-90] Genetic polymorphisms and systemic factors are also involved in the pathogenesis of myopic CNV. Studies have shown that single-nucleotide polymorphisms in genes such as VEGF, complement factor I, and collagen type VIII alpha 1 are associated with myopic CNV.[83, 91-93]

Physiological changes during pregnancy can impact the visual system and exacerbate pre-existing ocular conditions,[94] including diabetic retinopathy and central serous retinopathy, and can also increase the risk of CNV in myopic eyes, especially in those with PIC. VEGF levels tend to rise in the first trimester and then decrease, while placental growth factor (PIGF) steadily increases throughout pregnancy.[95-96] Both factors elevate the risk of CNV in pre-existing myopic or PIC-affected eyes.[97]

CONCLUSION

In this review, we have explored the complex etiology and pathogenesis of macular hemorrhage (MH) in high myopia (HM). The most common underlying causes include myopic CNV, CNV secondary to punctate inner choroidopathy (PIC), and lacquer cracks (LC). Additionally, trauma and ocular surgery can also induce MH in high myopia. Table 2.

Macular hemorrhage in high myopia can arise from various primary conditions, and multiple contributing factors—such as structural changes, hemodynamic disturbances, genetic predispositions, and systemic influences—play a role in CNV formation. Therefore, treatment should not only address the hemorrhage but also target the underlying disease.

The therapeutic approach depends on whether MH is associated with secondary CNV. Anti-VEGF therapy remains the first-line treatment for CNV, while cases of isolated macular hemorrhage without CNV may be managed conservatively with observation. For CNV secondary to PIC, anti-inflammatory therapy may offer additional benefit, though more clinical evidence is needed to support this approach.

Future research should aim to clarify the precise mechanisms driving different types of macular hemorrhage in high myopia, improve imaging techniques for accurate differential diagnosis, and identify the most effective treatment strategies.

METHOD OF LITERATURE SEARCH

A systematic literature search of the PubMed database(http://www.ncbi.nlm.nih.gov/pubmed) was

Table 2 Differential diagnosis of macular hemorrhage in high myopia

Disease	inducement	Hemorrhage at fundus	fundus	OCT	Treatment
Myopic CNV	Abnormal elongation of AL and posterior staphyloma	Irregular, thin, small, located at the edge of CNV	Myopic fundus, A small, flat gray lesion, usually with pigmentation, accompanied by peripheral bleeding	Type 2 CNV	Anti-VEGF
CNV secondary to PIC	Inflammation	Irregular, small, located at the edge of CNV	multifocal, small, yellow-gray lesions that are well-defined	Type 2 CNV	Anti-VEGF. or combined with steroid
lacquer crack	Break of BM	Small, thin, flat, regular	irregular, yellowish-white or grayish, linear or stellate lesions	Flat, regular, subretinal high reflectance	Self resolved
Trauma related	Ocular trauma	At the edge of choroidal rupture	curvilinear or crescent-shaped lines, predominantly yellow or white	disruption of the RPE/Bruch's membrane (BM) complex and the ellipsoid zone (EZ)	Self resolved or combined with anti-VEGF
Surgery related	Ocular surgery	Scattered small hemorrhage	Myopic fundus	Similar with LC	Self resolved or combined with anti-VEGF

performed from database inception to August 31, 2024, for randomized-controlled trials, cohort, case-control, Reviews, case-reports, and cross-sectional studies on macular hemorrhage in high myopia. using the following keywords: in various combination: “myopic choroidal neovascularization”, “neovascular myopic maculopathy”, “high myopia”, “pathogenesis”, “macular hemorrhage”,“Punctate inner choroidopathy”, “mechanical structure”, “lacquercracks”, “ocular trauma”, “ocular surgery”, “retina hemorrhage”, “risk factors”, “anti-VEGF”, “treatment”. All matching study abstracts were reviewed, and full texts of appropriate studies were obtained for complete review and inclusion. Additional information and related sources were obtained from the reference lists of the identified publications.

Correction notice

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Author Contributions

(I) Conception and design: Shida Chen, Lin Lu
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Patient consent for publication

None

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