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Clinical characteristics and visual outcome of macular hemorrhage in pathological myopia with or without choroidal neovascularization

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ABSTRACT

Background/Purpose: This study aims to evaluate the clinical characteristics and visual outcome of macular hemorrhage in pathological myopia with or without choroidal neovascularization.
Methods: We conducted a retrospective study of 55 patients with macular coin hemorrhage who were followed for at least 3 months from January 1997 to December 2013 at Shin Kong Wu Ho-Su Memorial Hospital (Taipei, Taiwan). All patients were evaluated using fluorescein angiography and optical coherence tomography for the detection of choroidal neovascularization (CNV). We also recorded clinical characteristics such as age, sex, refractory error, and myopic fundus, to determine the relationship between CNV and non-CNV associated macular hemorrhage.
Results: A total of 55 patients (30 females, 54.55%) were reviewed. The mean age was 39.7 years old. The CNV group was found to be significantly older than the non-CNV group ($p < 0.05$), and there was no significant difference between sex, visual acuity myopic severity, and the prevalence of fundus findings between CNV and non-CNV groups. Twenty one patients (38.18%) were found to have CNV and were all treated with intravitreal antivascular endothelial growth factor (VEGF). The other 34 patients without CNV were not treated. In both groups, the visual acuity significantly improved (anti-VEGF treated, CNV associated group, 0.7 to 0.39, $p = 0.002$, and untreated, non-CNV associated group, 0.56 to 0.34, $p = 0.0018$, respectively).
Conclusion: Age significantly correlated to the CNV formation in high myopia with macular hemorrhage. Favorable visual outcomes were found in pathological myopic macular hemorrhage either in the anti-VEGF treated, CNV associated group or in the untreated, non-CNV associated group.

1. Introduction

Pathologic myopia (PM) is a major vision-threatening morbidity throughout the world and has been found to be increasing in frequency in many countries, especially in Asia. It is estimated to affect 1.4–2.5% of the general population in Western countries,[1–3] and 6.8–26% in East Asia,[4–7] including Korea, China, and Taiwan. A higher prevalence was found in younger generations, or people living in urban areas in these countries.[4–7] Consequently, complications of pathological myopia may pose great socioeconomic impacts in East Asian countries because it can lead to vision loss in people of working age.[5] One of the major complications of PM is macular hemorrhage, which often presents with sudden impairment of visual acuity (VA) in the affected patients. The pathogenesis of macular hemorrhage in PM may be related to either simple rupture of Bruch's membrane, or a bleeding from concurrent choroidal neovascularization (CNV). The presence of CNV is particularly detrimental to long-term visual function when involved in the foveal area, because it would usually lead to scar formation,[8] as in age-related macular degeneration (AMD) or other choroidal pathologies. Recently, inhibitors of vascular endothelial growth factor (VEGF) have been used for the treatment of CNV in PM with good results.[8] As a result, prompt detection of the concurrence of CNV in PM patients presenting with macular hemorrhage is of great importance in regard to treatment choices and prognosis. The purpose of this study is to identify the clinical

Conflicts of interest: All contributing authors declare no conflicts of interest.

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characteristics and visual prognosis of macular hemorrhage in PM patients with or without choroidal neovascularization.

2. Methods

We conducted a retrospective chart review of 55 patients with PM and subretinal coin hemorrhage at Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, between 1997 and 2013. The study passed the institutional review board of our hospital and was conducted according to the principles of the Declaration of Helsinki for human participants. The inclusion criteria comprised:

1. Patients with at least one of the following conditions: (a) refractive error < −6 D when the macular hemorrhage was found; (b) previous documented refractive data < −6 D before receiving refractive surgery or cataract surgery; (c) axial length > 26.5 mm of the involved eye.
2. The fundus of patients in which characteristic findings suggested pathological myopia, such as tessellated fundus, geographic atrophy, posterior staphyloma, lacquer cracks and Fuchs' spot formation.

The subretinal hemorrhage was defined as one or more reddish spots found in the subfoveal and juxtafoveal (<200 μm from the fovea center) area in the ophthalmoscopic examination and recorded in the color fundus photographs. Our study excluded patients suspected to have AMD, any retinal vasculopathies (including diabetic retinopathy, retinal vein occlusions, retinal vasculitis, etc.), advanced glaucoma, or intraocular pressure in the study eye >22 mmHg despite adequate treatment, and acute ocular or periocular infection. Recurrence of macular hemorrhage was defined as the reappearance of any macular hemorrhage after a complete absorption of the previous macular hemorrhage in any follow-up visit.

Differentiation of macular hemorrhage associated with or without myopic CNV was made by a combination of fluorescein angiography (FA) (Heidelberg Retina Angiograph2; Heidelberg engineering, Heidelberg, Germany) and optical coherence tomography (OCT) (Stratus, Zeiss, Model 3000; Carl Zeiss Meditec, Inc., Dublin, CA, USA) modified from previous published literature.[9,10] The diagnostic criteria for CNV in FA included a patch of lacy or irregular hyperfluorescence in the early arteriovenous phase, leakage of dye from the lesion in the late arteriovenous phase, and staining of the lesion with fluorescein in the late phase. In most cases, a hyperpigmented ring was found around the hyperfluorescent CNV. The OCT criteria for CNV included an elevated submacular hyperreflective lesion with evidence of exudative characteristics, including subretinal fluid, macular thickening, or retinal cysts (Figure 1). Macular hemorrhage without myopic CNV was defined as flat or elevated submacular hyperreflective lesions without evidence of exudative characteristics on OCT, and hypofluorescence of lesion without accompanying dye staining, leakage, and hyperfluorescence on FA (Figure 2).

If myopic CNV was detected, further intravitreal injection of anti-VEGF was arranged. Otherwise, the non-CNV patients were only observed.

In this study, we aimed to identify the visual outcomes and accompanying findings in patients with and without myopic CNV. We evaluated the patients' best corrected visual acuity (BCVA) during every visit using a Snellen chart in a standard condition. BCVA was then converted to logarithm of minimal angle of resolution (logMAR) for statistical analysis. The Mann–Whitney *U* test was used to assess the numerical clinical characteristics, such as age and refraction, between CNV and non-CNV groups. A paired *t*-test was used to compare changes in VA from baseline to the 3-month follow up in all patients within both myopic CNV and non-CNV groups. The categorical clinical characteristics, including sex, lacquer cracks, Fuchs' spot, and geographic atrophy were compared using a Chi-squared test. Values of $p < 0.05$ were considered statistically significant.

3. Results

A total of 55 eyes in 55 patients (30 females, 54.55%) who had PM with macular hemorrhage were included in this study. The

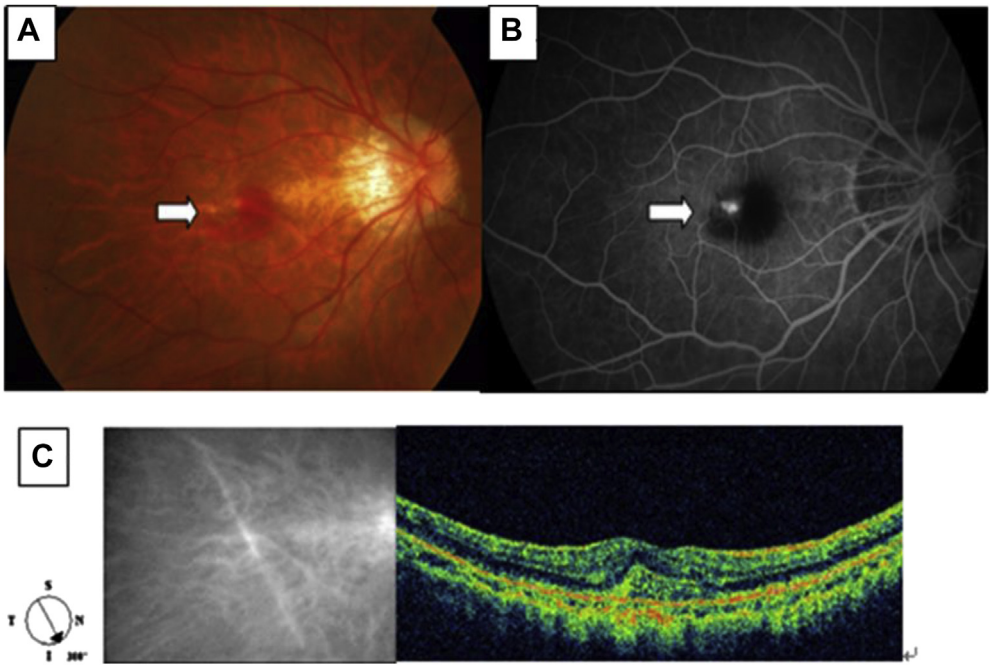

Figure 1. A 46-year-old woman with macular hemorrhage due to myopic choroidal neovascularization (arrows in A and B). (A) Color fundus; (B) fluorescein angiography; and (C) time-domain optical coherence tomography.

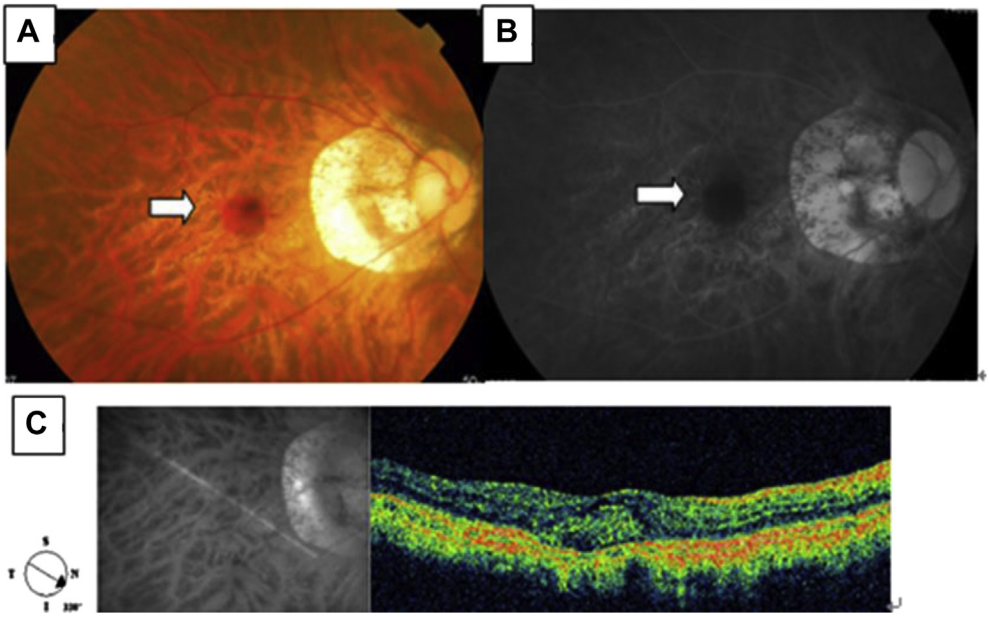

Figure 2. A 39-year-old woman with macular hemorrhage without myopic choroidal neovascularization (arrows in A and B). (A) Color fundus; (B) fluorescein angiography; and (C) time-domain optical coherence tomography.

mean age was 39.7 ± 12.8 (range 17–72) years old, and the mean refractory error was −14.31 ± 4.06 D. The prevalence of lacquer crack, Fuchs' spot, and geographic atrophy were found to be 20.0%, 14.5%, and 7.3%, respectively in our patients. Twenty one patients (38.18%) were found to have CNV and were treated with intravitreal anti-VEGF (bevacizumab: 19 patients; ranibizumab: 2 patients). The CNV group had a mean of 1.5 ± 0.7 (range 1–3) injections during a mean period of 6.1 ± 4.8 (range 1–20) months of their clinical follow up. The other 34 patients without CNV were not treated [mean follow-up time of 1.7 ± 1.3 (range 1–5) months].

3.1. Clinical characteristics

The CNV group was found to be significantly older than the non-CNV group (44.0 ± 22.9 years vs. 37.0 ± 19.8 years, respectively, $p = 0.024$). There was also a more frequent occurrence of the Fuchs' spot in the CNV group ($p = 0.021$). Otherwise there was no significant difference in sex, refractory error, presenting VA, and other fundus findings such as lacquer crack and geographic atrophy between the CNV and non-CNV groups (Table 1).

3.2. Visual outcome

Baseline and 3-month VA outcomes are shown in Figure 3. Thirteen (three in the CNV group, 10 in the non-CNV group) of the patients who lost follow up at 3 months were excluded from the statistical analysis of the visual outcomes. The range of BCVA when patients enrolled in the CNV group was from 1.30 to 0.22, mean BCVA was 0.7 ± 0.35; and in the non-CNV group was from 2.00 to 0.00, mean BCVA was 0.56 ± 0.56. Patients with or without CNV both showed significant improvement in BCVA. The BCVA in the anti-VEGF treated, CNV associated group improved from 0.7 to 0.39 (Snellen equivalent 6/30 to 6/15), $p = 0.002$. The BCVA in the untreated, non-CNV associated group improved from 0.56 to 0.34 (Snellen equivalent 6/22 to 6/13), $p = 0.0018$. There was no significant difference in improvement of BCVA between the non-CNV group and the CNV group ($p = 0.168$).

Table 1
The clinical features, except age and Fuchs' spot, had no relationship in CNV and non-CNV groups.

	CNV	Non-CNV	*P*
Sex (male)	11 (52.4%)	14 (41.2%)	0.417[a]
Age (y)	44 ± 22.9	37 ± 19.8	0.024[b]
Refraction (diopter)	−13.6 ± 4.1	−14.8 ± 3.9	0.114[b]
Lacquer crack	4 (19.0%)	7 (20.6%)	0.692[a]
Fuchs' spot	6 (28.6%)	2 (5.9%)	0.021[a]
Geographic atrophy	2 (9.5%)	2 (5.8%)	0.617[a]

CNV = choroidal neovascularization.
[a] Chi-square test.
[b] Mann–Whitney *U* test.

4. Discussion

High myopia is often regarded as the most important risk factor for the development of CNV in young patients (≤50 years of age), regardless of ethnic group.[11] While the presence of CNV is the most important pathology for macular hemorrhage in aged patients with

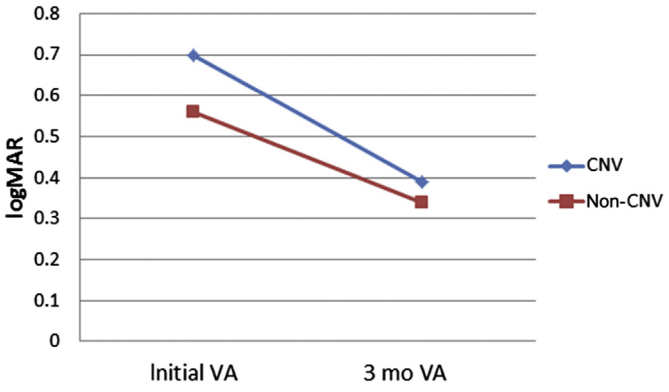

Figure 3. The visual outcome of patients with and without CNV. The BCVA of the CNV associated group improved from 0.7 to 0.39, $p = 0.002$. The non-CNV associated group improved from 0.56 to 0.34, $p = 0.0018$. BCVA = best corrected visual acuity; CNV = choroidal neovascularization; VA = visual acuity.

AMD, it is not always true in patients with PM. In this study, we found that a concurrent presence of CNV was found in only 21 (38.18%) of 55 PM patients who presented with fresh symptomatic macular hemorrhage. We also revealed that patients with macular hemorrhage and concurrent CNV were significantly older (44.0 ± 22.9 years vs. 37.0 ± 19.8 years respectively, $p = 0.024$) and had a greater prevalence of Fuchs' spot ($p = 0.021$) than those without concurrent CNV. Other clinical features including sex, refractive error, lacquer cracks, and geographic atrophy were not statistically different between the two groups.

The pathogenesis of macular hemorrhage is not fully understood in patients with PM but without CNV.[12] It is postulated that the elongation of the eyeball in PM may induce the rupture of Bruch's membrane and choriocapillaris, resulting in a spreading-out of the hemorrhage into the subretinal space or even the retinal tissue. However, macular hemorrhage associated with CNV may more likely be a result of bleeding of fragile new vessels in the CNV tissue. The pathogenesis of the development of CNV in AMD has been postulated to be a consequence of focal secretion of angiogenic factors, such as VEGF from the ischemic tissues in the older macular area, which result from the accumulation of water insulating metabolic waste known as drusen. However, the pathogenesis of the development of CNV in PM may be different since there is usually not much drusen material in the macula of PM eyes. Nevertheless, recent evidence suggests that CNV in both PM and AMD could be treated successfully with anti-VEGF agents. It is therefore possible that a common pathway in the pathogenesis involving VEGF, and thus ischemic conditions may occur in both PM and AMD.

One possible mechanism of ischemic change in the macula of PM may be related to a decrease in choroidal thickness.[13–15] Flores-Moreno et al[14] reported a decrease in choroidal thickness by 25.9 ± 2.1 μm for each additional millimeter in high myopia. Ikuno et al[15] found that thinner choroid is a risk factor for the development of CNV in PM. There is also evidence suggesting that older patients with PM may suffer from more ischemic conditions than younger patients.[16] Many studies have reported that choroidal thickness decreases with increased age in the normal population, with a 14–15.6-μm decrease each decade.[17–19] Ho et al[16] further demonstrated that in myopia patients, choroidal thickness decreases not only with the severity of myopia, but also significantly with age. This may be a mechanism that supports our finding that patients with concurrent CNV are significantly older than patients without concurrent CNV. In 1990, Hayasaka et al[20] also reported that the subretinal hemorrhages without CNV were more frequent in younger patients (mean 36.8 years old), while CNV was more common in older patients (mean 61 years old).

The appearance of the Fuchs' spot in the fundus also correlated with concurrent CNV in PM patients with macular hemorrhage. A Fuchs' spot represents an old scar of previous CNV.[21] This result suggests that eyes with previous CNV were more prone to have recurrent CNV in PM patients. Interestingly, in our study we found that the occurrence of macular hemorrhage in the CNV group was most likely due to a new CNV formation instead of recurrence from previous Fuchs' spots. During FA examination, we found new CNV in five out of seven eyes with macular hemorrhage in the CNV group (Table 2).

However, in this study we found that there was no statistically significant correlation between concurrent CNV and other fundus findings such as lacquer cracks or patchy chorioretinal atrophy. Lacquer cracks are caused by stretching and rupture of the Bruch's membrane-pigment epithelium-choriocapillaris complex.[12,22,23] The formation of lacquer cracks may be associated with subretinal hemorrhage but are usually not found to be associated with concurrent CNV.[12,22,23] The prevalence of lacquer cracks in PM was very variable in previous studies. Some studies reported a prevalence of 0.6–4.2%,[24,25] while another study reported that lacquer cracks were noted in 82% of 149 eyes with CNV and in 96% of 58 eyes with isolated subretinal hemorrhages.[26] In this study, we did not find such a high occurrence in our PM cases. We only found lacquer cracks in 19% of the isolated macular hemorrhage group and 20.6% of the concurrent CNV group during the fundus examination. Patchy chorioretinal atrophy is another characteristic finding in myopic maculopathy, and was reported to be present in 11.4% of fundus findings in PM eyes.[24] In our patients, it presented in only four cases (7.3%). Both lacquer cracks and patchy chorioretinal atrophy did not significantly differ in prevalence between the CNV and non-CNV groups in our study (Table 1). Also the refractive error was not found to be associated with the concurrent CNV in our study, which was similar to the conclusion of an earlier study conducted by Hayasaka et al.[20]

Table 2
Number of patients with recurrent macula coin hemorrhage.

	Recurrent with CNV	Recurrent without CNV
CNV group	5	2
Non-CNV group	3	6

CNV = choroidal neovascularization.

In our study, we found that BCVA in PM eyes with solitary macular hemorrhage improved spontaneously from 0.56 to 0.34 logMAR (SE 6/22 to 6/13) in 3 months without treatment. Several studies have revealed similar results. The VA in patients with subretinal hemorrhage but no neovascular membrane detected had a fair visual improvement rate.[27] Hayasaka et al[20] reported that the macular hemorrhages in PM reabsorbed almost completely within 3 months. Li et al[28] reported that the VAs of macular hemorrhage in pathological myopia without choroidal neovasculopathy improved spontaneously in 81.6% of eyes during the following 3–21 months. However, PM with subfoveal CNV usually would not get better without treatment.[29] The Verteporfin in Photodynamic Therapy (VIP) Study reports that untreated eyes with PM and CNV deteriorate a median of 1 line in 3 months and 1.8 lines in 12 months.[30] Recently, anti-VEGF has been shown to be effective in improving visual outcome in PM with CNV, and has been shown to be more effective than photodynamic therapy.[31–34] Several studies have reported that anti-VEGF is effective not only for short-term but also for long-term visual outcomes.[35–37] However, most studies did not focus on PM patients with current CNV and macular hemorrhage. Our study specifically revealed that in PM eyes with CNV and concurrent macular hemorrhage, anti-VEGF treatment could significantly improve BCVA from a mean of 0.7 to 0.39 logMAR (SE 6/30 to 6/15) in 3 months, which is similar to the spontaneous improvement of solitary macular hemorrhage without treatment.

In conclusion, our study revealed that approximately 38% of Taiwanese patients with myopic macular hemorrhage were associated with concurrent CNV. These patients tend to be older and have more occurrences of Fuchs' spots. We also revealed that in patients with concurrent CNV and macular hemorrhage, anti-VEGF is very effective in improving their visual outcomes. However, in eyes with solitary macular hemorrhage, observations could lead to similar favorable visual outcomes. However, there were several limitations in our study such as the retrospective design, limited case numbers and very short-term results. Up to 23.6% (13 in 55) of patients failed to visit for longer than 3 months, which further compromised the accuracy of our outcome measures. Nevertheless, our results suggest that in PM patients with newly occurred macular hemorrhage, a detailed investigation for the concurrence of CNV using FA and OCT is necessary to determine a more appropriate strategy of treatment.

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