

Visual outcome of retinal angiomatous proliferation in Chinese patients following photodynamic therapy or direct laser photocoagulation

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Abstract

Aims: To report the prevalence of retinal angiomatous proliferation in Chinese patients presenting with neovascular age-related macular degeneration and to evaluate the outcomes following photodynamic therapy or laser photocoagulation.

Methods: This was a retrospective review of patients who presented with neovascular age-related macular degeneration to a tertiary eye hospital from January 2005 to December 2005. Patients with retinal angiomatous proliferation were identified based on fluorescein angiography, indocyanine green angiography, and their medical records. Clinical outcomes of patients with retinal angiomatous proliferation during the follow-up period were analyzed.

Results: Of the 104 patients reviewed, 7 eyes of 7 patients (6.7%) were found to have retinal angiomatous proliferation. Five eyes (71.4%) had stage 2 retinal angiomatous proliferation and 2 (28.6%) had stage 3 retinal angiomatous proliferation. Three eyes were treated by photodynamic therapy with or without intravitreal triamcinolone acetonide, 1 eye was treated with laser photocoagulation, and 3 eyes were managed by observation alone. After a mean follow-up of 17

months, the median best-corrected visual acuity decreased from 20/160 to 20/400 ($p = 0.043$). Five patients (71.4%) developed visual loss and 2 (28.6%) had stable vision at the last follow-up.

Conclusions: Retinal angiomatous proliferation appeared to be less frequent in Chinese patients with neovascular age-related macular degeneration than in Caucasians. The visual outcomes for retinal angiomatous proliferation following photodynamic therapy and laser photocoagulation are generally poor and other therapeutic options should be considered.

Key words: Asian continental ancestry group, Hong Kong, Laser coagulation, Macular degeneration, Photochemotherapy

Introduction

Retinal angiomatous proliferation (RAP) is a distinctive subgroup of neovascular age-related macular degeneration (AMD) characterized by neovascularizations originating from the middle and inner retina instead of the choroidal circulation as in choroidal neovascularization (CNV).^{1,2} These neovascularizations may eventually grow into the choroidal layer forming a retinal-choroidal anastomosis.¹ RAP has been found to occur in around 10% to 15% of Caucasian patients with neovascular AMD and was thought to be rare in Asian and black patients.¹⁻³ In 2 recent studies conducted in

Chinese⁴ and Japanese⁵ populations presenting with neovascular AMD, 4.5% of patients were found to have RAP. It is important to differentiate patients with RAP from those with other forms of neovascular AMD since treatment outcomes of eyes with RAP for PDT are generally less favorable than of eyes without RAP.⁶ This study evaluated the prevalence of RAP in Hong Kong Chinese patients presenting with neovascular AMD and the treatment outcomes.

Methods

This was a retrospective review of consecutive patients aged 50 years or older who presented to the Hong Kong Eye Hospital, Hong Kong, with neovascular AMD from January 2005 to December 2005. Patients with RAP were identified by review of the fluorescein angiography (FA), indocyanine green angiography (ICGA), and medical records by 2 ophthalmologists independently. RAP was diagnosed based on the clinical and angiographic features of RAP, including preretinal, intraretinal, or subretinal hemorrhages, retinal edema, retinal-retinal anastomosis, lipid exudates, pigment epithelial detachment, and retinal-choroidal anastomosis.^{1,2} RAP was classified into 3 stages according to Yannuzzi

et al.¹ Data collected included the initial and final best-corrected visual acuity (BCVA), clinical and angiographic features, duration of follow-up, fellow eye status, treatment modality used, and complications such as severe visual loss and retinal pigment epithelium (RPE) tear. Patients were classified according to diagnoses of occult CNV, minimally classic CNV, predominantly classic CNV, polypoidal choroidal vasculopathy (PCV), and RAP. The study was performed prior to availability of anti-vascular endothelial growth factor (anti-VEGF) agents, and the treatments included direct laser photocoagulation, and PDT with or without intravitreal triamcinolone acetonide (IVTA). PDT was performed using the standard dose of 6 mg/m² with a normal laser fluence of 600 mW/cm² for 83 seconds. For patients who had combined PDT with IVTA, 0.1 mL of triamcinolone acetonide 4 mg was given on the same day 10 to 20 minutes after PDT. Patients who received anti-VEGF treatment during follow-up were excluded.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc, Chicago, USA). The patients' demographics between the clinical

Table 1. Demographics of 104 Chinese patients who presented with neovascular age-related macular degeneration by diagnosis.

Diagnosis at presentation	Number of patients (%)	Age at presentation (years) Mean $\pm$ SD	Median baseline visual acuity (range)	Median final visual acuity (range)
Occult choroidal neovascularization	55 (52.9)	74.6 $\pm$ 7.5	20/200 (HM to 20/25)	20/400 (HM to 20/30)
Minimally classic choroidal neovascularization	13 (12.5)	71.8 $\pm$ 10.6	20/200 (CF to 20/30)	20/500 (CF to 20/20)
Predominantly classic choroidal neovascularization	9 (8.7)	74.4 $\pm$ 8.6	20/200 (CF to 20/40)	20/320 (20/800 to 20/50)
Polypoidal choroidal vasculopathy	20 (19.2)	63.9 $\pm$ 8.5	20/200 (HM to 20/30)	20/200 (CF to 20/40)
Retinal angiomatous proliferation	7 (6.7)	77.9 $\pm$ 4.6	20/160 (CF to 20/70)	20/400 (CF to 20/100)
Total	104 (100)	72.4 $\pm$ 9.1	20/200 (HM to 20/25)	20/320 (HM to 20/20)

Abbreviations: CF = counting fingers; HM = hand movements.

Table 2. Demographics and visual outcomes of 7 Chinese patients with retinal angiomatous proliferation.

Patient number	Age (years)/sex	RAP stage*	Clinical features at presentation	Follow-up (months)	Treatment	Initial BCVA	Final BCVA
1	74/M	2	Drusens, intraretinal hemorrhage, intra- and sub-retinal fluid, subretinal neovascularization	24	Combined PDT + IVTA x 1 cycle	20/100	20/400
2	78/M	2	Drusens, intraretinal hemorrhage, intra- and sub-retinal fluid, subretinal neovascularization	24	Combined PDT + IVTA x 3 cycles	20/160	20/400
3	81/M	3	Drusens, intra- and sub-retinal hemorrhage, subretinal fluid, hard exudate, choroidal neovascularization	21	PDT x 1 session	20/70	20/200
4	70/M	2	Drusens, intraretinal hemorrhage, subretinal neovascularization	15	Observation	20/80	20/100
5	76/F	3	Drusens, marked hard exudate, intraretinal hemorrhage, subretinal fluid, choroidal neovascularization	12	Direct thermal laser photocoagulation	CF	CF
6	83/M	2	Drusens, intraretinal hemorrhage, subretinal neovascularization	12	Observation	20/400	CF
7	76/M	2	RPE atrophy, intraretinal hemorrhage, subretinal neovascularization	12	Observation	20/200	20/200

*Stage 2 = subretinal neovascularisation; stage 3 = choroidal neovascularization.

Abbreviations: BCVA = best-corrected visual acuity; CF = counting fingers; IVTA = intravitreal triamcinolone acetonide; PDT = photodynamic therapy with verteporfin; RAP = retinal angiomatous proliferation; RPE = retinal pigment epithelium.

subgroups were compared using 1-way analysis of variance (ANOVA) using Tukey's post-hoc test or Fisher's exact test. The serial changes in the visual acuity findings were compared using non-parametric Mann-Whitney U-test. A p value of <0.05 was considered to be statistically significant.

Results

Of the 104 consecutive patients reviewed, 7 eyes of 7 patients (6.7%) were found to have RAP (**Table 1**). The most common diagnoses were occult CNV and PCV, which were found in 55 patients (52.9%) and 20 patients (19.2%), respectively. The mean age of the patients with RAP at presentation was 77.9 years. There were statistically significant differences in the mean age of presentation between patients with different diagnoses ($p < 0.001$, 1-way ANOVA). The mean age of patients presenting with RAP was significantly higher than that of patients with PCV ($p = 0.001$, 1-way ANOVA Tukey HSD test), but was similar to that of patients with other forms of CNV ($p > 0.50$, 1-way ANOVA Tukey HSD test). Six (85.7%) of the 7 patients with RAP were men compared with 69 (71.1%) of the patients without RAP ($p = 0.67$, Fisher's exact test).

The demographic details of the patients with RAP are listed in (**Table 2**). Five eyes (71.4%) had stage 2 RAP and 2 eyes (28.6%) had stage 3 RAP. The baseline median BCVA was 20/160 (range, 20/70 to counting fingers). Two (28.6%) of the patients with RAP had subretinal fibrosis in the fellow eye consistent with advanced AMD. All 7 eyes with RAP had leakage on FA and hot spots on ICGA. An example of

the fundus photograph, FA, and ICGA of a patient with RAP is shown in **Figure 1**.

Three patients received verteporfin PDT for treatment of RAP, of whom 2 had combined IVTA injections and 1 had PDT monotherapy. One patient underwent thermal laser photocoagulation of extrafoveal RAP and 3 had observation alone due to treatment refusal. The patients were followed up for a mean of 17 months (range, 12 to 24 months). At the last follow-up, the median BCVA was reduced significantly to 20/400 ($p = 0.043$, Wilcoxon-signed rank test). Five patients (71.4%) had visual loss and 2 (28.6%) had stable vision. All 3 patients who received PDT developed moderate visual loss of 3 or more lines. None of the patients developed RPE tear after treatment.

Discussion

RAP was originally described in Caucasian populations, and was estimated to occur in 10% to 15% of patients with neovascular AMD.¹⁻³ More recently, RAP has also been described in Chinese⁴ and Japanese⁵ patients and was found to account for approximately 5% of patients with neovascular AMD. In this study, RAP was found in 6.7% of Chinese patients with neovascular AMD, thus confirming the suggestion that RAP appears to be less frequent in Chinese people than in Caucasians. This study and the study by Liu et al⁴ also demonstrated a male predominance among the patients, in contrast to the female predominance in Caucasian populations.^{1,2} These findings suggest that Chinese men are more likely than Chinese woman to develop RAP.

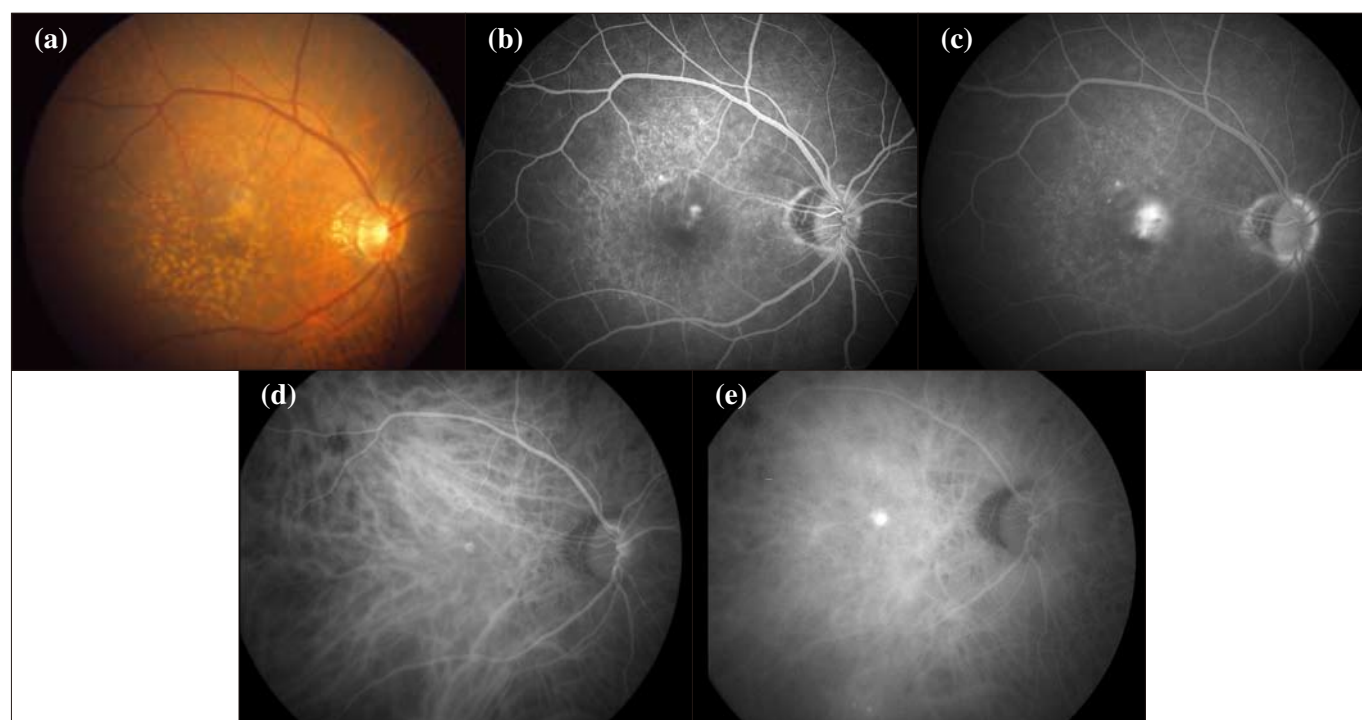


Figure 1. Right eye of patient 2 with stage 2 retinal angiomatous proliferation. (a) Fundus photograph showing intraretinal hemorrhage associated with retinal-retinal anastomosis, multiple drusen, and retinal edema; (b) early-phase fluorescein angiography demonstrating active leakage from the lesion; (c) late-phase fluorescein angiography demonstrating active leakage from the lesion; (d) early-phase indocyanine green angiography showing a hot spot with subretinal neovascularization; and (e) late-phase indocyanine green angiography showing a hot spot with subretinal neovascularization and progressive leakage.

The optimal treatment for RAP remains uncertain. Various treatment modalities, including surgical ablation, PDT, and laser photocoagulation have been performed for the treatment of RAP.⁶⁻⁹ This study showed that similar to RAP in Caucasians, a high proportion of patients developed visual loss despite receiving laser photocoagulation or PDT. One of the reasons for the poor visual outcome is related to the high recurrence rate of RAP following treatment. Moreover, PDT with verteporfin, which is commonly performed for CNV in AMD, might not be effective for RAP, as intraretinal activation of the drug during PDT might cause retinal damage.¹ Patients are also more prone to develop RPE tear after PDT.^{6,9} A recent study by Hikichi et al has also demonstrated that PDT was only effective in 1 of 9 eyes with RAP, and combination therapy with IVTA might be needed to stabilize the visual acuity.¹⁰ This was clearly demonstrated in this study, as none of the patients who underwent PDT or laser photocoagulation had visual gain following therapy. Another reason for the poor visual outcome following treatment might be the poor natural history of RAP, as patients who opted for observation alone also did not develop any visual gain.

The main limitations of this study were the retrospective nature and that patients who did not have ICGA were not evaluated in the study. Moreover, optical coherence tomography measurements were not available for many patients and ICGA was not

performed using a confocal laser scanning system, so some patients with PCV and RAP might have been missed. In addition, the small number of eyes with RAP reduced the statistical significance of the analysis. Finally, patients with advanced presentation of AMD, such as disciform scar, could not be evaluated and were not classified based on the clinical features. Nonetheless, this study provided additional information to the clinical spectrum of RAP in a local Hong Kong setting. The poor visual outcome following PDT and laser photocoagulation observed in this study also illustrated that these treatment modalities are ineffective for treating RAP.

Recently, an animal model of RAP has demonstrated increased expressions of proangiogenesis factors such as VEGF and basic fibroblast growth factor within the lesion; therefore anti-angiogenesis therapy with anti-VEGF agents might be useful in the treatment of RAP.¹¹ Several studies have reported the use of intravitreal anti-VEGF agents, including bevacizumab and ranibizumab, to be effective for treating RAP, resulting in significant visual improvement.¹²⁻¹⁵ Moreover, combination therapy using intravitreal bevacizumab and PDT has also been shown to be effective for improving or maintaining the vision of Japanese patients with RAP in the short term.¹⁶ Increased use of anti-VEGF agents will hopefully improve the visual outcome for patients with RAP, and further studies to evaluate the role of combination therapy for RAP are warranted.

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