Six Month Visual Prognosis in Eyes with Submacular Hemorrhage secondary to Age-Related Macular Degeneration or Polypoidal Choroidal Vasculopathy

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ABSTRACT

Background: To determine clinical or imaging prognostic features for visual outcome in eyes with submacular hemorrhage secondary to age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy (PCV).

Methods: A prospective case series of 11 eyes from 11 patients with submacular hemorrhage secondary to AMD or PCV. All participants had measurement of clinical characteristics, fundus angiogram and indocyanine green angiography, spectral domain optical coherence tomography (OCT, Cirrus, Zeiss) at baseline and 6 months.

Results: Median visual acuity improved from 20/132 to 20/63 at month 6. The median improvement in vision was 0.20 logMAR units. Proportion of eyes with best corrected visual acuity (BCVA) ≥1.0 increased from 6/11 (54.5%) at baseline to 8/11 (72.7%) at month 6. Eyes with BCVA>1.0 were more likely to have larger area of hemorrhage, and thinner subfoveal neurosensory retinal thickness at baseline and at month 6.

Conclusion: Thinner neurosensory retina demonstrated on OCT at baseline may be a useful prognostic sign for limited visual recovery.

INTRODUCTION

Large submacular hemorrhage is an uncommon but known complication of neovascular age-related macular degeneration (AMD).[1-4] It is generally associated with poorer visual prognosis and its optimal management remains a challenge.[1-3] Such hemorrhagic presentation, including hemorrhagic pigment epithelial detachment, has been described to occur more frequently in the context of polypoidal choroidal vasculopathy (PCV), a condition more common in Asians.[5-8] The prognosis in such cases has been variable.

There is no consensus regarding the best management for submacular hemorrhage. Current management options either target the underlying choroidal neovascularization (CNV) (such as intravitreal anti-vascular endothelial growth factor (VEGF)[9,10] and photodynamic therapy (PDT),[11,12]), or aim to displace or clear the submacular hemorrhage (such as intravitreal tissue plasminogen activator (tPA),[13-17] pneumatic displacement[14-17] and vitrectomy[17-20] or various combinations). However, there is limited evidence to support each of these treatment options. In the case of anti-VEGF treatment, large submacular bleeds comprising more than 50% of the lesion were not enrolled into major clinical trials such as the MARINA [21] and ANCHOR.[22] Several recent small case series have shown favorable visual outcome with anti-VEGF monotherapy. The evidence for surgical interventions is also limited to case series, which show highly variable visual outcome and occasionally significant surgical complications.[14-20] The difficulty to predict the outcome results from many factors, such as the duration and size of hemorrhage, timing of intervention and status of the macula (e.g., presence of atrophy, fibrosis). Studies simultaneously correlating size, extent and location of the submacular hemorrhage, underlying lesion (CNV vs. PCV) and anatomical and visual outcomes are limited.[23]

In the current study, we prospectively described the visual outcome of submacular hemorrhage secondary to AMD or PCV and evaluated a range of clinical and imaging features that may be possible prognostic markers of poor visual outcome.

METHODS

Patient Population

The Asian AMD Phenotyping Study is a prospective, observational clinical study of Asian patients with exudative maculopathy secondary to CNV from AMD or PCV in Singapore. The study followed the principles of the Declaration of Helsinki, and approval was obtained from the Institutional Review Board. Informed consent form was signed by all participants. The study aims to recruit consecutive patients with new onset AMD or PCV who will provide a comprehensive set of data to phenotype the clinical condition. For the purpose of the current study, patients presenting with submacular hemorrhage involving the fovea were identified from retinal photographs and OCT images.

All patients underwent a complete ophthalmic examination including best-corrected visual acuity (BCVA, measured in Snellen and converted to LogMAR for analysis), dilated fundus examination, fluorescein and indocyanine green angiography, fundus autofluorescence (FAF) imaging, colour fundus photography and optical coherence tomography (OCT) at baseline according to a standardized protocol.

Fundus photography was performed using a digital mydriatic retinal camera (TRC-50X/ IMAGEnet 2000, Topcon, Tokyo, Japan). Autofluorescence images were acquired using the same fundus camera with the Spaide filter which has a 580nm exciter wavelength and 695nm barrier wavelength (Topcon, tokyo, Japan). Optical Coherence Tomography (OCT) was performed with the Cirrus OCT (Carl Zeiss Meditec, Dublin, CA) using the 512x128-volume cube setting.

Participants received treatment according to standard of care, and treatment was not altered by entering into the study. Patients were followed up at month 1, month 3 and month 6. Visual acuity testing and repeat fundus photography and FAF imaging were performed at each visit. OCT performed at baseline and month 6 were compared.

Participants were excluded if alternative causes for the submacular haemorrhage (such as macroaneurysm) could not be excluded.

Definition of Submacular hemorrhage and Image Analysis

All measurements were performed independently in a masked manner by two observers (GC and MB). Each observer records the average of three measurements. The average of the two observers' readings was then used for statistical analysis.

The area of hemorrhage was measured using the measuring tool on imageNET. Patients were included if thick blood of at least 1 disc area (DA) was masking the centre of the fovea either on FA or ICG. The level of blood was further confirmed on OCT. In the presence of subfoveal hemorrhage, the neurosensory retina is separated from the RPE complex. Therefore central neurosensory retinal thickness was measured manually from the posterior boundary of the outer nuclear layer (ONL) to the internal limiting membrane (ILM) subfoveally.

Statistical Analyses

Due to the small sample size, traditional exact test may not give adequate inference. Therefore Bayesian model using Deviance Information Criterion (DIC) analysis was chosen with the aim to give more rational inference of the data. DIC was calculated using WinBUGS and R software, by the means of Gibbs sampling. In the model used for analyzing the current data, a positive difference of 10 and above between DIC implies overwhelming evidence that the means

of the two groups are different. A positive difference of 5 to 10 implies substantial evidence that the means of the two groups are different.

RESULTS

During the study period (March 2010 to March 2011), 96 patients were recruited to the Asian AMD Phenotyping study. Of these, 11 eyes from 11 patients presented with submacular hemorrhage. The median age at presentation was 65 years (SD 7.9 years). Seven (53.8%) were male. Duration of symptom of blurred vision was highly variable, ranging from several days to months. The median presenting visual acuity was 20/132 (range 6/6 to counting fingers at 2 metres).

The fovea was involved by hemorrhage in all cases. The mean area covered by hemorrhage was 27.7 sq mm (3.6 – 109.0, SD 29.3). Breakthrough vitreous hemorrhage occurred in 4 (36.4%) eyes. CNV was confirmed on FA in all cases, and polypoidal lesions were identified in 8 eyes (72.7%). Patient demographics and baseline findings of the submacular hemorrhage are summarized in **Table 1**.

Patients in whom no PCV was demonstrable (n=3) received intravitreal Bevacizumab monotherapy. Of the remaining eight patients with demonstrable PCV, five received focal laser for extrafoveal polyps, whereas three received photodynamic therapy (PDT). Adjunctive anti-VEGF injection was given in 4 patients with PCV (3 Bevacizumab, 1 Ranibizumab).

At Month 6, median visual acuity was 20/63 (range 6/6 to 20/400). Visual acuity was improved in 8 eyes, unchanged in 2 eyes and reduced in 1 eye. Mean improvement in vision was 0.36 logMAR unit (Median 0.20, range +0.06 to -1.3, SD0.45). Subfoveal hemorrhage was resolved by 1 month in 6 eyes (54.5%), by 2 months in 4 eyes (36.4%) and by 3 months in 1 eye (9.1%). There were no retinal pigment epithelial tears in our series.

Predictors for Best-Corrected Visual Acuity at Month 6

We divided the patients into 2 groups according to their BCVA at month 6: Group 1 consisted of 8 eyes with VA≤1.0 and Group 2 consisted of 3 eyes with VA>1.0 (**Table 2**). Among the factors studied, only central retinal thickness at month 6 and central retinal thickness at baseline were associated with VA≤1.0 at month 6.

DISCUSSION

The optimal management of submacular hemorrhage secondary to AMD or PCV remains a challenge for several reasons, despite recent advances in the management of neovascular AMD. First, the presence of dense submacular hemorrhage may mask the underlying lesion and limit the information that can be obtained from angiography. Second, significant hemorrhage may be associated with more aggressive neovascular lesions, although this has not been systematically studied. Third, the blood within the subretinal space may cause retinal damage by direct toxicity and also through the physical separation of the neurosensory retina from the retinal pigment epithelium.[24-26] There have been some small case series describing favorable visual outcome with anti-VEGF monotherapy in cases with submacular hemorrhage. However lack of standardized definitions and quantification of the extent of the hemorrhage may limit the ability to compare different treatment modalities. Further, anatomical outcome such as scarring or atrophy are likely to directly impact the visual outcome despite resolution of the hemorrhage. It has been suggested that studies correlating the extent of hemorrhage with both anatomical and visual outcomes are needed.[23] In our series, we have reported the size and location of the hemorrhage and anatomical details in terms of neurosensory retina thickness at baseline and at month 6. We analyzed these factors for their value in predicting visual outcome at month 6.

In this prospective case series, we followed-up 11 eyes of 11 patients presenting with submacular hemorrhage secondary to AMD or PCV. At month 6, visual acuity was improved in 8 eyes, unchanged in 2 eyes and reduced in 1 eye. Mean improvement in vision was 0.36 logMAR unit. Importantly we found that baseline visual acuity was not predictive of visual outcome. Indeed one patient improved from 1.30 to 0.00 after receiving PDT and anti-VEGF therapy. Of the range of factors analyzed, we found thinner neurosensory retina at baseline and at month 6 correlated strongly with worse visual outcome at month 6. Neurosensory retinal thickness is therefore a useful prognostic marker. A reduction of neurosensory retinal thickness at baseline should alert clinicians to the presence of established retina damage and atrophic changes which are likely to be related to poor visual outcome.

There are few other studies for direct comparison. Scupola followed up 60 eyes with subfoveal hemorrhage of at least 1 disc diameter secondary to AMD and found vision worsened in 80%, with significant fibrosis (38%), atrophy (25%) and retinal pigment epithelial tear (22%). [2] Avery followed-up 41 eyes with subfoveal hemorrhage secondary to AMD and reported mean vision decreased by 3.5 lines at 36 months. However, 33% did have improved or stable vision.[3] Both studies found that the initial size and thickness of the hemorrhage correlated to visual outcome.[2,3] Neither study included Asian eyes or eyes with PCV. Our series comprises a significant proportion of eyes with underlying PCV. Presentation with submacular hemorrhage has been described to be more common in PCV than in neovascular AMD.[5-8] Dramatic improvement in vision has been described in some PCV cases, especially where the polyp is extrafoveal. In our series, we did not find a significant difference in visual outcome between eyes with PCV and CNV. However, the small sample size in each group is likely to limit our findings.

Since these early studies, various modes of management have been proposed for treating submacular hemorrhage, [9-19] although results have been variable. From the early 90s, attempts

to surgically remove the subretinal blood, with aspiration or mechanical clot extraction were reported.[18, 19] However these approaches did not deliver significant visual gain and were also occasionally associated with significant side effects, such as retinal detachment. With the advent of tPA, attempts to dissolve the subretinal blood with tPA alone or in combination with pneumatic displacement or surgery were described.[12-17] While these reports suggested tPA may be a useful adjunct; the final visual outcome remained limited by the presence of underlying advanced AMD lesion. The optimal timing of tPA was also unclear.[12,14] Better visual outcome was described with the advent of PDT, which targets the underlying CNV rather than the blood itself.[10,11] Impressive visual gain was reported particularly in selected cases of PCV.[11] The advent of anti-VEGF therapy has revolutionized the treatment of exudative AMD.[20,21] In cases of submacular hemorrhage secondary to AMD, significant improvement in vision and macular anatomy have also been reported resulting from intravitreal anti-VEGF therapy.[9] In our series, visual outcome was favorable in the majority of cases without resorting to surgical intervention despite poor presenting vision. This could be attributable to the availability of newer treatment modalities such as PDT and anti-VEGF, which were used in combination in some cases. Similarly, the relatively shorter period before the clearance of blood compared to previous series may also be attributable to newer treatment modalities.[2,3] However our analysis did not show any particular treatment to be superior. This may be due to the heterogeneity between eyes and also the small sample size. Interestingly, 4 patients with extrafoveal PCV were treated with focal laser alone and all were stabilized or improved. These results may support that focal laser remains to be valuable in selected cases, despite the availability of newer, often more expensive therapeutic options.

It is important to highlight that in the presence of subfoveal hemorrhage, the RPE is often distorted by sub-RPE blood. In addition, the neurosensory retina is often separated from the RPE

complex by subretinal blood. In such circumstances, the central retinal thickness measurement is a poor reflection of the status of the retina. An increase in central retinal thickness often results from measuring the distance between the RPE complex and the ILM, incorporating the thick subretinal blood. In addition, segmentation error may occur due to difficulty in selecting the RPE layer. Therefore measurement of the neurosensory retina thickness, as used in our study, offers a better insight into the health of the retina in the presence of submacular hemorrhage. Presence of significant thinning of the neurosensory retina at presentation suggests there may be photoreceptor loss and retinal atrophy, which likely accounts for the negative prognostic value of this OCT sign.

There are limitations in our small case series. In particular there were only three subjects in the group with poor visual outcome. Also the choice of 1.0LogMAR as cut-off between the two groups was arbitrary. However this level was chosen as it is often regarded as important for one's navigational vision, and often requirement for blind registration.[27,28] A variety of treatments were prescribed to our study patients. Due to the rarity of this condition, an interventional trial to compare specific treatment was not feasible in the study timeframe. Our analysis did not identify any treatment mode as superior. However the small sample size and small number in each treatment group could have masked any difference. In our experience, the outer retina is often distorted in the presence of submacular hemorrhage. For this reason, we did not analyze IS/OS line integrity, as this was often not reliably identifiable in the presence of subretinal hemorrhage. We also did not analyze thickness of blood as the posterior extent of sub-RPE blood could not be reliably identified. The area of hemorrhage measured from photographs may be affected by magnification factors due to refractive error and axial length as data on these two variables were not collected. This new information about the potential prognostic value of OCT thickness may be helpful for clinicians treating future cases in terms of case selection and patient counseling.

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Legends

Fig. 1 Patient 1 presented with Left submacular hemorrhage, visual acuity 1.30 (a). Fluorescein angiogram showed occult leakage and masking by subretinal blood (b). Indocyanine green angiogram showed masking by blood under retinal pigment epithelium and possible polyp (arrow) (c). At month 6, the submacular hemorrhage had cleared, visual acuity 0.00 (d). OCT at baseline (e) showed retinal pigment epithelial detachment and subretinal blood. Red line denotes the posterior boundary of the neurosensory retina (thickness=160um). OCT at month 6 (f) showed resolution of foveal contour (thickness=116um) and residual pigment epithelial detachment.

Fig. 2 Patient 9 presented with right submacular hemorrhage, visual acuity 1.80 (a). Fluorescein angiogram showed occult leakage and masking by subretinal blood (b). Indocyanine green angiogram showed polypoidal lesions (c). At month 6, the submacular hemorrhage had cleared, visual acuity 1.30 (d). OCT at baseline (e) showed subretinal blood. Red line denotes the posterior boundary of the neurosensory retina (thickness = 66um). OCT at month 6 (f) showed significant foveal atrophy (thickness=31um).

Table 1. Baseline characteristics of 11 eyes presenting with submacular hemorrhage secondary to age-related macular degeneration or polypoidal choroidal vasculopathy

	Age/ Sex	Symptom Duration (weeks)	Baseline Vision LogMAR	Area of Blood (mm sq)	Vitreous Hemorrhage	FA/ICG	Baseline Neurosensory retina thickness (μm)	Level of blood	Treatment	Duration of Bleed after presentation	Month 6 Neurosensory retina thickness (μm)	Month 6 vision LogMAR
1	72 F	<1	1.30	16.3	N	Occult CNV PCV	167	Sub retina N Sub RPE Y	PDT Anti-VEGF	≤1 month	119	0.00
2	61 F	>2	0.02	47.8	N	Occult CNV PCV	140.5	Sub retina N Sub RPE Y	Focal Laser	≤1 month	114.5	0.00
3	74 M	Unknown	0.64	3.9	N	Occult CNV PCV	104.5	Sub retina Y Sub RPE Y	Focal Laser	≤2 month	100	0.30
4	71 F	1-2	0.44	99.5	Y	Occult CNV PCV	148.5	Sub retina Y Sub RPE Y	PDT Anti-VEGF	≤1 month	139.5	0.30
5	59 M	1-2	0.60	35.3	N	Occult CNV PCV	112.5	Sub retina Y Sub RPE Y	Focal Laser	≤2 month	101.5	0.40
6	82 M	>2	1.00	6.0	Y	Occult CNV	123.5	Sub retina N Sub RPE Y	Anti-VEGF	≤1 month	106	0.50
7	64 F	>2	0.64	39.0	N	Occult CNV PCV	226	Sub retina Y Sub RPE Y	Focal Laser	≤2 month	140.5	0.70
8	78 F	<1	1.80	10.8	N	Occult CNV	261	Sub retina N Sub RPE Y	Anti-VEGF	≤1 month	108	0.78
9	59 F	Unknown	1.80	47.5	N	Occult CNV PCV	73.5	Sub retina Y Sub RPE Y	PDT Anti-VEGF	≤2 month	34	1.30
10	66 M	1-2	1.30	28.0	Y	Occult CNV PCV	103.5	Sub retina Y Sub RPE Y	Focal Laser Anti-VEGF	≤1 month	74.5	1.30
11	62 M	>2	1.30	42.2	Y	Occult CNV	59.5	Sub retina Y Sub RPE Y	Anti-VEGF	≤3 month	58	1.30

Table 2. Comparison of Prognostic factors based on Month 6 vision.

		VA≤1.0 (n=8)	VA>1.0 (n=3)	Difference in DIC (>10 implies overwhelming evidence of difference;** >5 implies substantial evidence of difference)*
Age, years		70.1 (8.0)	62.3 (3.2)	1.4
Duration of symptom				
Presenting vision		0.8 (0.5)	1.5 (0.5)	1.7
Area of hemorrhage, sq mm		27.7 (10.3)	42.1 (1.3)	2.4
Baseline CRT, µm		146.0 (23.9)	60.3 (3.7)	16.4 *
Blood in subretinal space		4/8	3/3	-1.3
Vitreous Hemorrhage		2/8	2/3	-2.3
Presence of PCV		6/8	2/3	-2.5
Treatment mode	Anti-VEGF only Laser only PDT + anti-VEGF Laser + anti-VEGF Any Anti-VEGF	2/8 4/8 2/8 0/8 4/8	1/3 0/3 1/3 1/3 3/3	-3.8
Time to resolution of blood	< 1 week 1-2 weeks >2 weeks	5/8 3/8 0/8	1/3 1/3 1/3	-3.2
Month 6 CRT		112.9 (11.8)	59.4 (15.7)	>20.0
Macular Hypoautofluorescence at month 6		2/7	2/3	-2.1
Presence of Transient hyperautofluorescent material		0/7	3/3	0.9

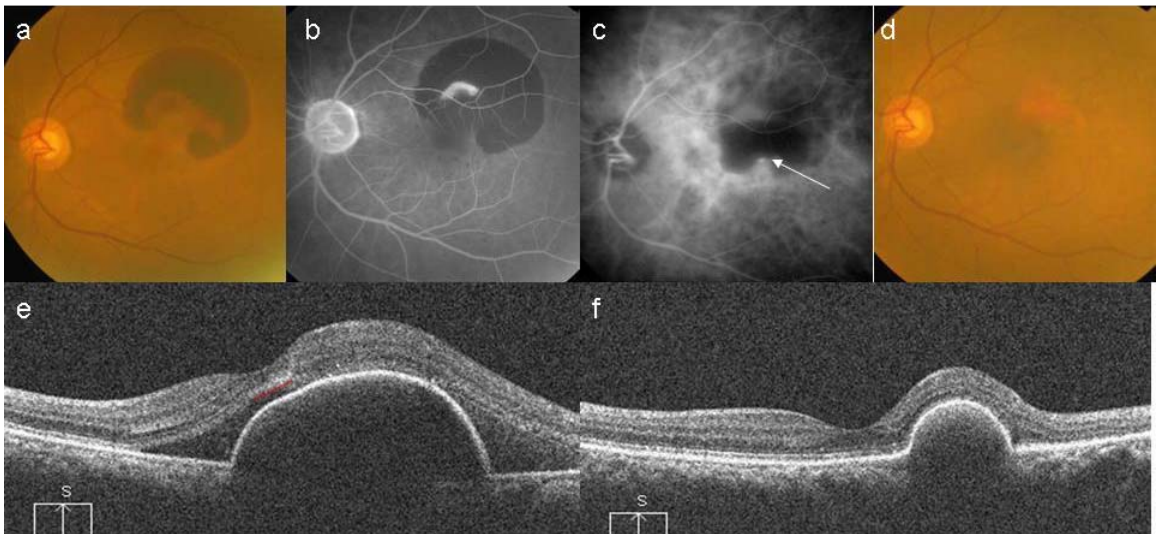

Figure. 1

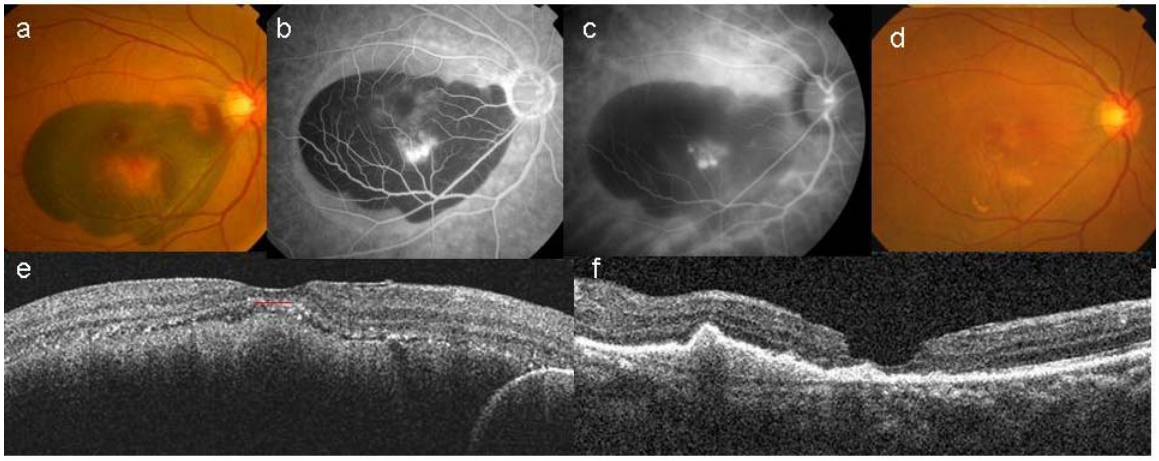

Figure. 2

	Age/ Sex	Symptom Duration (weeks)	Baseline Vision	Area of Blood (mm sq)	Vitreous Hemorrhage	FA/ICG	Baseline Neurosensory retina thickness (μm)	Level of blood	Treatment	Duration of Bleed after presentation	Month 6 Neurosensory retina thickness (μm)	Month 6 vision
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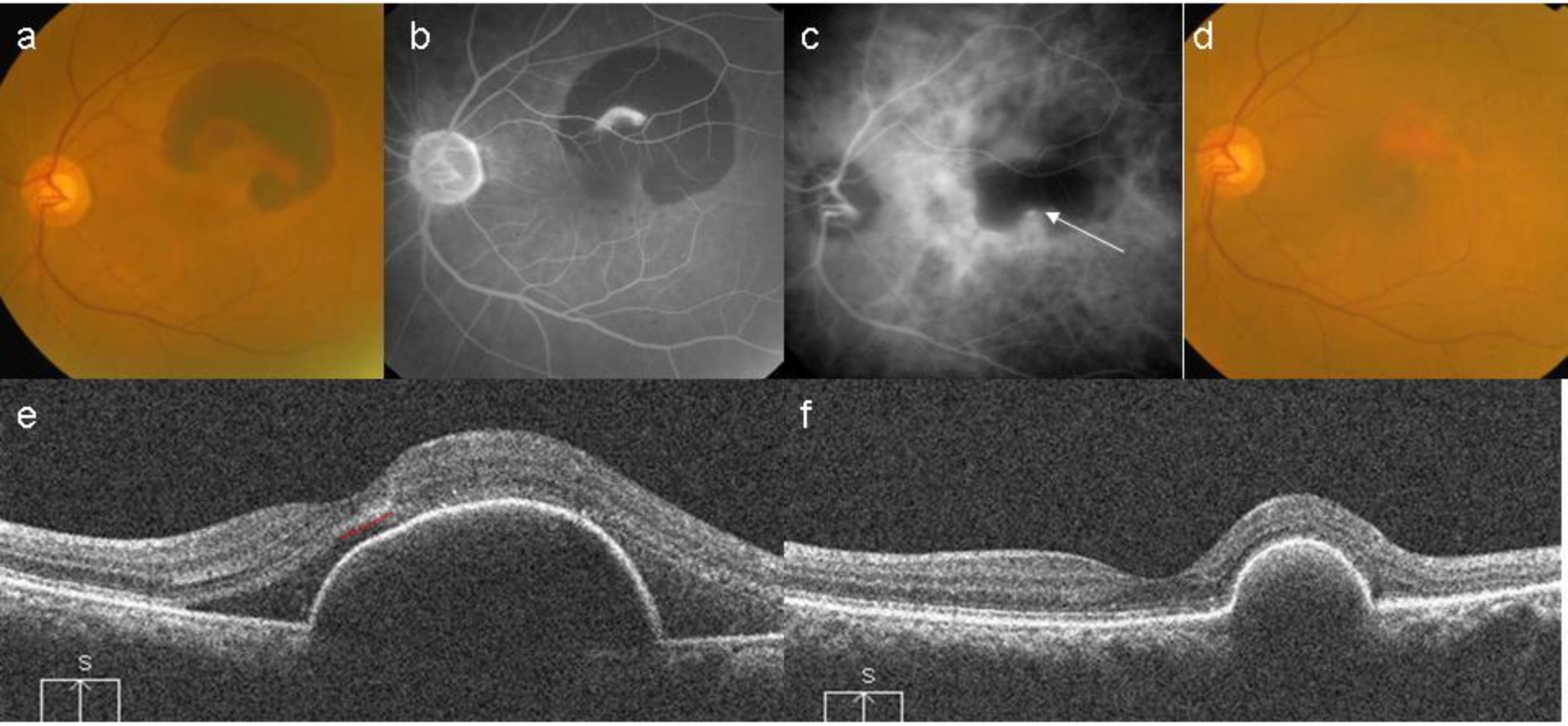
Vitreous Hemorrhage		2/8	2/3	-2.3
Presence of PCV		6/8	2/3	-2.5
Treatment mode	Anti-VEGF only Laser only PDT + anti-VEGF Laser + anti-VEGF Any Anti-VEGF	2/8 4/8 2/8 0/8 4/8	1/3 0/3 1/3 1/3 3/3	-3.8
Time to resolution of blood	< 1 week 1-2 weeks >2 weeks	5/8 3/8 0/8	1/3 1/3 1/3	-3.2
Month 6 CRT		112.9 (11.8)	59.4 (15.7)	>20.0**
Macular Hypoautofluorescence at month 6		2/7	2/3	-2.1
Presence of Transient hyperautofluorescent material		0/7	3/3	0.9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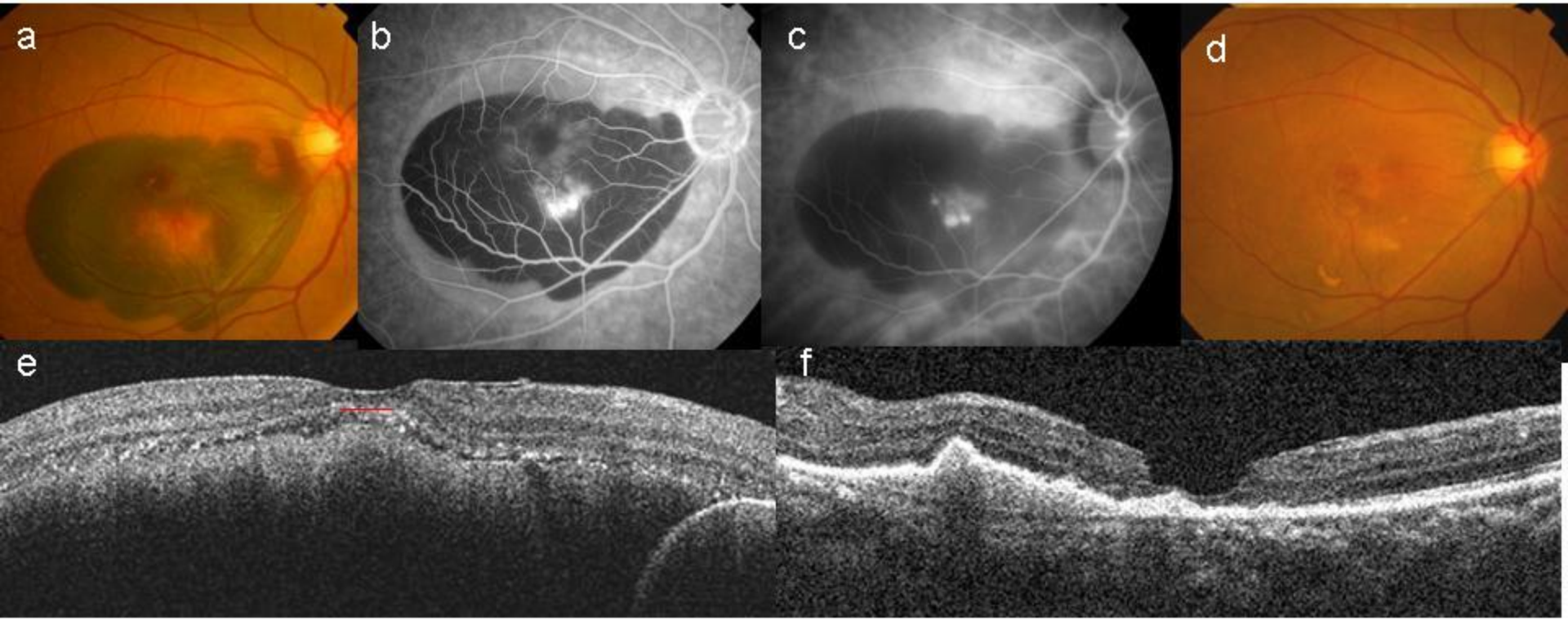
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