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Case Report

Long-Term Management of Complications of Retinal Artery Macroaneurysms with Intravitreal Aflibercept Injection

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Keywords
Retinal artery macroaneurysms · Macular edema · Aflibercept

Abstract
Purpose: To report the 1-year follow-up results of intravitreal aflibercept injection (IAI) for the management of complications of retinal artery macroaneurysms (RAM). ***Methods:*** A retrospective, noncomparative, interventional case series of 4 eyes of 4 patients (all female, aged 68–91 years, 3 treatment naive) treated with IAI 2 mg for complications of RAM [macular edema (ME) 2, submacular hemorrhage (SMH) 1, and vitreous hemorrhage (VH) 1] was conducted. Baseline parameters consisted of complete ocular examination, medical history, best-corrected Snellen VA, fundus photography, IVFA and SD OCT, unless precluded by VH (1). All patients completed ≥1 year follow-up. ***Results:*** Baseline VA was hand motions in the eye with SMH (31 mm^2 area and 1,478 µm thickness); 20/40 and 20/100 with ME (CST 390 and 337 µm, respectively), and 20/200 in the eye with VH. At 1 month, both patients with ME showed resolution of ME with CST <300 µm with improvement in VA which was maintained through 1 year. VH resolved in one eye at 1 month with no recurrence after 1 year. The eye with SMH developed macular scar and had counting fingers vision at 1 year. Thrombosis of RAM was noted in all eyes and hairpin-like remodeling of artery in one. No eye required repeat injection or laser. ***Conclusion:*** ME and VH from RAM were effectively treated with IAI. However, the eye with thick SMH had poor visual outcome despite thrombosis of RAM. Sin-

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gle IAI provided effective therapy for complications of RAM with excellent anatomical and visual results in each eye, except one with thick SMH, and merits further study.

Introduction

Retinal arterial macroaneurysms (RAM) are outpouchings of the arterial wall and usually occur within the first three bifurcations of the central retinal artery [1]. Their incidence has been estimated to be 1 in 4,500 individuals over age 40 [2], with female preponderance and strong association with systemic hypertension, diabetes and hyperlipidemia. RAM can be symptomatic due to exudation, bleeding or both. Although RAM have a tendency for spontaneous involution [1], the natural history is worse for eyes with macular edema (ME) and those with submacular hemorrhage (SMH) compared to those with vitreous hemorrhage (VH) or preretinal hemorrhage (PRH) [3, 4]. Laser treatment with argon or yellow dye laser applied directly to RAM in an attempt to induce fibrosis and seal the aneurysm, first reported by Lewis et al. [5], is not always successful, can occasionally result in serious complications such as arterial occlusion [6], choroidal rupture, capillary closure, and subfoveal scarring [7], and was associated with worse visual outcome compared to observation in a retrospective study [8].

Since the initial case report by Chanana and Azad in 2009 [9] demonstrating resolution of RAM-induced ME after two intravitreal injections of 1.25 mg bevacizumab (IVB) administered 1 month apart, intravitreal anti-VEGF agents, both bevacizumab and ranibizumab (RZB) have been used for the management of complications of RAM [10–13]. Anti-VEGF therapy may improve outcome in symptomatic RAM eyes by anti-permeability effects of VEGF inhibition [10, 13], resolution of hemorrhages by an unknown mechanism similar to anti-VEGF treated eyes with retinal vein occlusion, encouragement of gliosis within the RAM by 'profibrosis switch' [14], or a combination of these factors. Pharmacologic therapy may be superior to the conventional laser treatment due to its predictable dose delivery, relative safety and ease of administration as needed, and elimination of laser-related complications. Most publications regarding intravitreal anti-VEGF injections for RAM are either case reports or small case series with mostly short-term follow-up. Publications with fewer injections [11] seem to show worse anatomical and visual outcomes compared to those with mandated monthly injections [10].

Aflibercept (IAI, Eylea®, Regeneron Pharmaceuticals, Inc. Tarrytown, N.Y., USA) may exhibit a longer duration of the therapeutic effect primarily due to its stronger affinity for VEGF [15] and is currently approved by the FDA for neovascular age-related macular degeneration (N-AMD), diabetic ME and ME from retinal vein occlusions. In the management of N-AMD, IAI administered every 2 months after the first 3 monthly loading doses was equivalent to monthly RBZ injections regarding visual outcomes, although a slight increase in central subfield thickness (CST) was noted 1 month after IAI injection [16].

Herein, I would like to report my experience in the management of complications of RAM with IAI.

Methods

A retrospective, noncomparative, interventional case series of 4 eyes of 4 patients with complications of RAM was performed. The study was conducted according the tenets of Declaration of Helsinki and in compliance with the Health Insurance Portability and Accountability Act (HIPPA) of 1996. An approval from Institutional Review Board was obtained. All patients were female and pseudophakic. The age ranged from 68–91 years. Two eyes presented with ME, one with recurrent VH and one with SMH. Baseline evaluation consisted of complete medical history, ocular examination, best-corrected Snellen visual acuity (BCVA), and color fundus photography. Intravenous fluorescein angiography and spectral domain OCT were performed at baseline in all eyes except one with VH (table 1).

After a thorough discussion with the patients regarding available treatment options and obtaining informed consent, off-label intravitreal aflibercept injection (IAI) 2.0 mg/0.05 ml was administered 3.5 mm behind the limbus in the inferotemporal quadrant under sterile precautions according to instructions provided in the Package Insert. Patients were followed every month for 6 months and less frequently thereafter. BCVA, CST on SD OCT and appearance of RAM were recorded at every visit. Findings at month 1, 3, 6 and 12 are reported in table 2 and are summarized below.

Case 1

A 75-year-old pseudophakic female presented with 20/100 vision OD secondary to ME (CST 337 μm) due to exudation from a RAM (fig. 1a–c). She was treated with IAI 2 mg/0.05 ml at baseline. CST and VA improved to 296 μm and 20/50 respectively at 1 month. Her VA continued to improve to 20/25 at 6 and 12 months without any further interventions. Color photos and IVFA at 1 year showed thrombosis of RAM (fig. 1d) with normal blood flow through the affected artery (fig. 1e) and resolution of ME on SD OCT (fig. 1f).

Case 2

A 68-year-old female presented with 20/40 vision and 390 μm CST OS due to ME from a RAM in the superotemporal artery (fig. 2a–c) and was treated with IAI 2 mg/0.05 ml. At 1 month, her VA improved to 20/20 with a dry macula (CST 250 μm), and was maintained throughout 2 years of follow-up without any further treatment. At 1 year, Color photos and FA showed fibrosis at the site of RAM along with hairpin-like remodeling of the affected artery with a dry macula on OCT (fig. 2d–f).

Case 3

A 91-year-old female presented with hand motions vision OS due to a large SMH, 31 mm^2 size measured on color photos using OIS Winstation™, version 11.2.1 (p) for Windows software (Merge Healthcare, Chicago, Ill., USA), and 1,478-μm thickness measured manually on transverse scan through the fovea on SD OCT from a ruptured RAM (fig. 3a–c). As she was a poor surgical candidate due to her multiple medical problems including chronic congestive heart failure, she was treated with IAI 2 mg. At 1 year, color photos showed a fibrosed RAM but macular scar (fig. 3d). Her VA was counting fingers.

Case 4

A 78-year-old female presented with recurrent VH from a RAM causing her vision to decrease to 20/200 OS (fig. 3e). She was previously treated with 4 intravitreal 1.25 mg/0.05 ml bevacizumab injections and one laser treatment over the past 3 years, the last treatment

being IVB 10 months prior to current episode, for VH from the same RAM. A single IAI led to resolution of VH within 1 month with no recurrence. Color fundus photos at 1 year showed fibrosis of RAM with uninterrupted blood column in the artery (fig. 3f).

Discussion

Robertson [1] in 1973 introduced the term macroaneurysm to describe an aneurysm arising from a retinal artery within the first three orders of bifurcation. He described 13 patients with macroaneurysms that were frequently associated with hemorrhage and exudation producing impairment of central vision. Although the natural history of RAM is involution due to fibrosis [1], particularly after bleeding and less commonly in those with ME [3], the eyes presenting with ME and SMH have worse visual outcomes compared to those presenting with VH or PRH. All six eyes with ME in the natural history of Cleary et al. [3] had 6/24 or worse vision (range 6/24 to 6/60) at final the follow-up. In another study, patients with ME had median final VA of 20/40 with 22% eyes being <20/200, whereas those with SMH had median VA of 20/200 (range 0.03–1.0 decimal VA) despite laser in 67% eyes in each group [4].

Laser therapy applied directly to RAM in an attempt to seal the RAM by inducing fibrosis was first reported by Lewis et al. [5] in 1976. However, its role in the management of complications of RAM remains unproven and controversial due to the well-known tendency for RAM to undergo spontaneous involution, and the risks of laser-induced complications, which may include rupture of RAM, branch retinal artery occlusion [6], choroidal rupture [7] and subfoveal scarring. One retrospective study showed worse visual outcomes in laser treated eyes compared to those observed [8]. As the study was retrospective and nonrandomized, it is difficult to determine whether worse final VA in laser treated eyes was due to laser or to selection bias. A recent publication showed equivalent visual outcomes in laser treated eyes and those that were observed [17].

Numerous case reports and small case series seem to suggest beneficial role of anti-VEGF therapy for complications of RAM. Although 11 IVB treated eyes recovered vision faster than 12 eyes that were observed in a study by Cho et al. [11], final anatomical and visual results were equivalent in bevacizumab treated and untreated eyes after a mean follow-up of 10 months. Interestingly, eyes received only a mean of 1.4 injections throughout the study period. By contrast, another study of 37 eyes treated with monthly injections of IVB for 3 months showed excellent visual and anatomical outcomes at 3 months with anatomical closure of RAM in 95% [10]. However, the duration of follow-up of patients having been limited to only 3 months was rather short and the study was noncomparative. Seemingly, worse outcomes in Cho et al. [11] compared to Pichi et al. [10] may have been due to fewer number of injections and longer duration of follow-up in Cho or to different patient characteristics. All published reports of RZB in the management of RAM so far were either case reports or small case series, consisted of less than 10 eyes with a short follow-up. However, multiple injections were needed with RZB as with IVB. As microvascular alternations including capillary closure have previously been shown in eyes with RAM [5], it is conceivable that VEGF might be upregulated in these eyes secondary to hypoxia and might be responsible for increased capillary permeability leading to ME. VEGF blockade might reverse capillary permeability. Other possible mechanisms for the beneficial role of anti-VEGF therapy might be resolution of hemorrhages and profibrotic switch encouraging fibrosis and closure of RAM [14]. Pharmacotherapy eliminates complications associated with laser and is relatively easy

to administer with a very low incidence of side effects as shown in numerous randomized clinical trials involving anti-VEGF therapy for a variety of retinal disorders.

Aflibercept is a fusion protein containing portions of human VEGF receptors 1 and 2 fused to the Fc fragment of human IgG1. It acts as soluble 'decoy' receptor for VEGF showing 140 times stronger binding affinity for VEGF compared to ranibizumab. The anti-VEGF activity of IAI at 28 days following a 2mg injection has been calculated to be 84 times that achieved RZB 0.5 mg administered every 2 weeks [15]. All eyes in this study showed favorable anatomical response for more than 1 year following a single injection of IAI, including in an eye that had previously failed laser treatment and 4 intravitreal bevacizumab injections. In View 1 and View 2 studies, IAI administered every 2 months after the first three monthly loading doses was equivalent to monthly RZB injections regarding visual outcomes although slight increase in CST was noted o1 month after IAI injection [16]. Other publications have demonstrated superior therapeutic efficacy of IAI in more severely affected eyes with diabetic ME, at least during the initial first year of therapy [18] and ME in a vitrectomized eye secondary to BRVO that had previously failed both RZB and IVB [19]. Although the strength of the current study is relatively long follow-up on all eyes treated with IAI, the limitations include small sample size, and retrospective and noncomparative nature.

To conclude, IAI appears to provide safe and effective therapy for exudative complications of RAM and also those with VH. Therapeutic benefit was observed early at 1 month and was maintained through 1 year and beyond with a single injection. However, eyes with thick SMH have poor visual outcome either naturally, or with anti-VEGF injections as shown previously [20], and should be considered for surgical evacuation of SMH. As direct comparison with other anti-VEGF agents was not performed in this study, it is neither possible nor appropriate to comment on the relative efficacy of different anti VEGF agents in the management of complications of RAM. However, resolution of retinal pathology with a single IAI in each of the 4 eyes, including in case 4 that had previously failed multiple IVB injections, is very encouraging. Further studies are needed to confirm the observations in this preliminary report and to determine whether stronger affinity of IAI for VEGF compared to other anti-VEGF agents offers therapeutic advantage in this clinical situation.

Statement of Ethics

The patients presented in this report have given informed consent for this publication.

Disclosure Statement

The author has no conflicts of interest to disclose.

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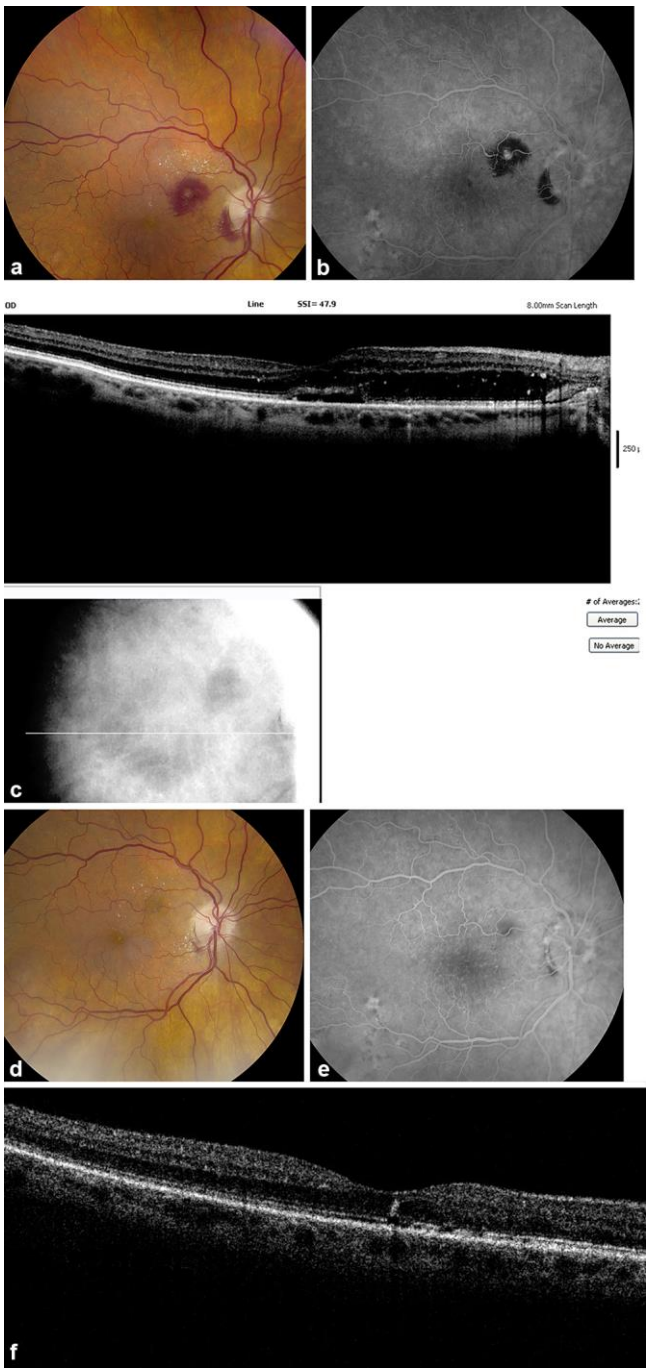

Fig. 1. **a** Case 1. Color fundus photo OD at baseline showing RAM associated with thin retinal hemorrhage superonasal to fovea and lipid exudation. **b** Case 1: intravenous fluorescein angiogram in arteriovenous phase at baseline showing hyperfluorescence from RAM superonasal to fovea and blocked fluorescence due to retinal hemorrhage. **c** Case 1: transverse SD OCT scan through the fovea at baseline showing subfoveal fluid. VA 20/100. **d** Case 1 at 1 year. Color photo showing fibrosis at the site of RAM. **e** Case 1 at 1 year. IVFA showing uninterrupted flow through the artery at the site of RAM. Blocked fluorescence at the RAM site corresponds to the fibrosis seen on color photographs. **f** Case 1: transverse SD OCT scan through the fovea at 1 year. Subfoveal fluid has resolved. However, mild disruption of the ellipsoid zone, and cystic changes in middle retinal layers can be seen nasal to fovea. VA improved to 20/25.

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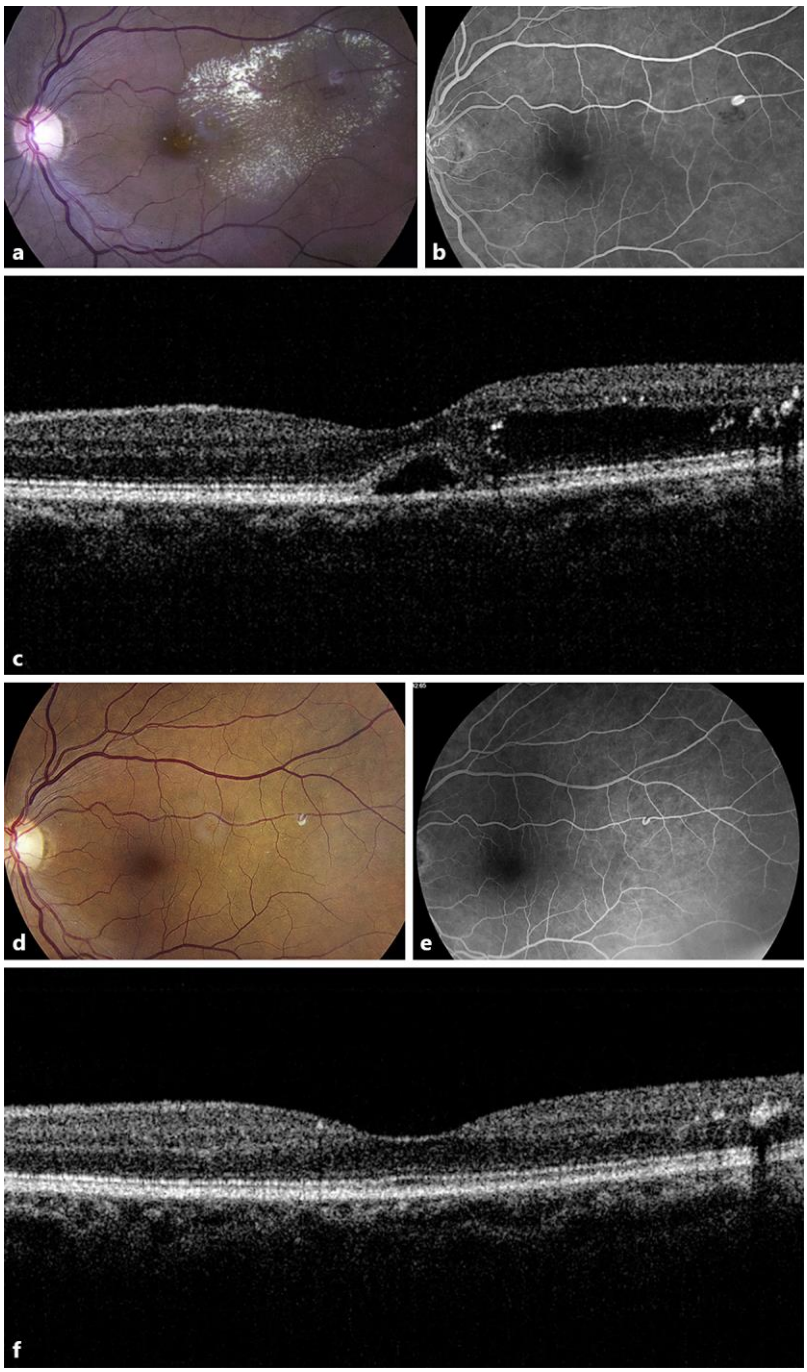

Fig. 2. **a** Case 2. Color fundus photo left eye at baseline showing a RAM along the superotemporal artery associated with small intraretinal hemorrhage and a prominent lipid ring. **b** Case 2. IVFA at baseline showing hyperfluorescence from RAM. Mild diffuse intraretinal capillary leakage is also visible around the RAM along with hypofluorescence from retinal hemorrhages. **c** Case 2. Transverse SD OCT scan through the fovea at baseline showing neurosensory detachment under the fovea and intraretinal cystic changes temporal to fovea. **d** Case 2 at 1 year after IAI. Color fundus photo shows normal fovea. Fibrosis at the site of RAM is clearly visible along with hairpin-like remodeling of the artery. **e** Case 2 at 1 year. IVFA in arteriovenous phase shows hairpin-like remodeling of the affected artery at the site of RAM without any evidence of leakage or staining. **f** Case 2 at 1 year. SD OCT shows a dry fovea with intact ellipsoid zone. VA 20/20.

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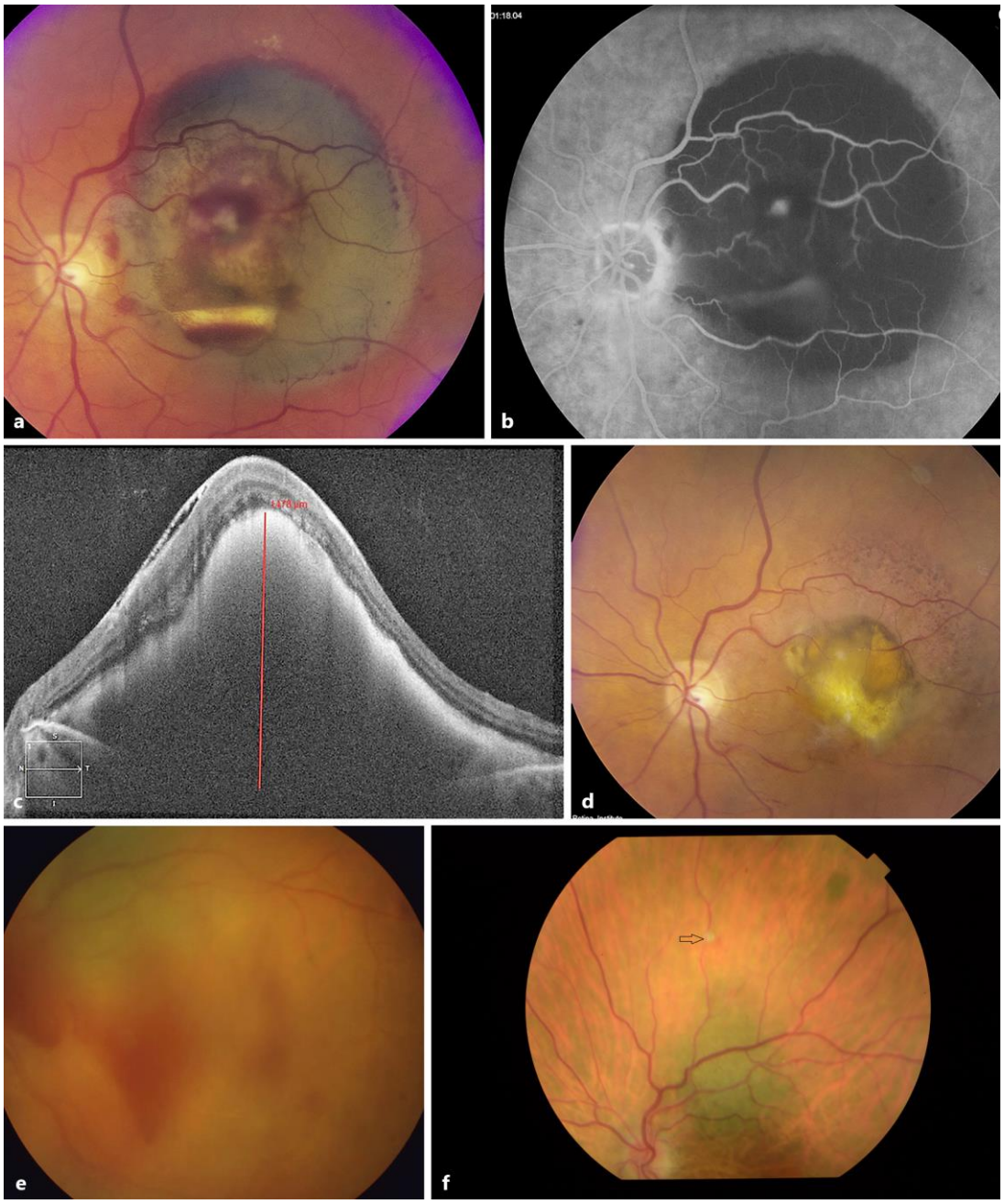

Fig. 3. **a** Case 3: color fundus photos of the left eye at baseline showing a large and thick SMH from a RAM along superotemporal artery. A small subhyaloid hemorrhage can also be seen inferior to fovea. **b** Case 3: IVFA at baseline in arteriovenous phase showing RAM along superotemporal artery surrounded by a small intraretinal blood and a large submacular blood. **c** Case 3: transverse SD OCT scan through the fovea at baseline showing a thick SMH (1,478 μm). **d** Case 3 at 1 year. Color photo shows a fibrosed RAM but submacular scar. **e** Case 4: color photo at baseline shows VH from a ruptured RAM. **f** Case 4. Color photo at 1 year showing fibrosed RAM (arrow) along with normal appearing artery.

Table 1. Baseline characteristics of patients

Patient	Age/sex, years	Systemic conditions	Eye/location of RAM	Type of complication	Duration of symptoms, months	Best-corrected Snellen visual acuity	Central subfield thickness on SD OCT, μm	Prior treatment
1	75/F	HTN, DM, high cholesterol	OD/ST	Exudative	2	20/100	337	None
2	68/F	High cholesterol	OS/ST	Exudative	1	20/40	390	None
3	91/F	HTN, high cholesterol	OS/ST	Large thick submacular hemorrhage (31 mm^2)	0.5	Hand motions	1,478 (height of submacular hemorrhage)	None
4	78/F	HTN, high cholesterol	OS/ST	Vitreous hemorrhage	1 (recurrent hemorrhage over past 3 years)	20/200	Unable	Bevacizumab X4, laser X 1. Last treatment 10 months ago

HTN = Hypertension; DM = diabetes mellitus; OD = right eye; OS = left eye; ST = superotemporal quadrant. All eyes were pseudophakic.

Table 2. Visual and anatomical results after a single IAI (2.0 mg/0.05 ml)

Case	1 month Snellen VA (CST in microns)	3 month Snellen VA (CST)	6 month Snellen VA (CST)	12 month Snellen VA (CST)	Appearance of RAM at 1 year
1	20/50 (296)	20/30 (262)	20/25 (243)	20/25 (257)	Normal flow at RAM site; fibrosis noted, RAM no longer visible
2	20/20 (250)	20/25 (261)	20/20 (259)	20/20 (240)	Fibrosis of RAM and hairpin-like remodeling of arterial wall at RAM site
3	CF (not done)	CF (1,478)	CF (963)	CF (820)	Fibrosed RAM
4	20/40 (225)	20/50 (229)	20/50 (not done)	20/50 (not done)	Fibrosed RAM, uninterrupted blood flow at RAM site

CST = Central subfield thickness; CF = counting fingers; SMH = submacular hemorrhage. CST numbers for case 3 represent height of submacular hemorrhage. Vitreous hemorrhage resolved in case 4 at 1 month. Reduced vision due to atrophic macular degeneration