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Retinal Arterial Macroaneurysms: Updating your Memory on RAM Management

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Abstract

Purpose of review: This is a comprehensive review of management options for retinal arterial macroaneurysms (RAMs). Although close observation is typically recommended for RAMs not involving or threatening the macula, other treatment modalities can be considered for exudative or hemorrhagic complications that are vision-threatening.

Recent findings: New imaging technologies like optical coherence tomography angiography (OCT-A) have been able to detect RAMs without the need of dye injection, further elucidating our understanding of blood flow within and around them. Observation alone is usually adequate treatment when lesion not threatening the fovea. Laser photocoagulation and intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors have effectively been used for management of exudative RAMs, whereas options including injection of VEGF inhibitors, tissue plasminogen activator (tPA), vitrectomy, gas, and yttrium aluminum garnet (YAG) laser have been used for hemorrhagic RAMs.

Summary: To date, there is no consensus regarding management of symptomatic exudative or hemorrhagic complications of RAM. Additionally, a case report is presented within this paper to illustrate the successful treatment of a hemorrhagic RAM in a symptomatic 65-year-old man using intravitreal bevacizumab.

Keywords

retinal artery macroaneurysm; macroaneurysms; bevacizumab; VEGF; vascular endothelial growth factor; laser; photocoagulation

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Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Clinical Description and Diagnosis

Acquired retinal arterial macroaneurysms (RAMs) are round or fusiform dilatations that occur within the first three branches of the retinal artery.[1] Although RAMs are classically a unilateral finding observed in women in their sixties with systemic hypertension, they can also manifest bilaterally or with multiple aneurysms occurring within the same eye.[2, 3] Funduscopically, these macroaneurysms can evolve into an exudative retinopathy consisting of retinal edema and lipid deposition, often forming a circinate ring pattern around the macroaneurysm. Approximately half of the patients with RAMs also have surrounding intraretinal retinal hemorrhage and associated subretinal, preretinal, and vitreous hemorrhage.[4] Although a RAM may be an incidental exam finding in an asymptomatic patient, when associated hemorrhage or exudation occurs within the macula, it can result in either sudden or gradual vision loss.[4, 5] RAMs are also associated with both venous and arterial occlusions as well as macular holes.[2, 3, 5–7]

To assist in the diagnosis of RAM, various imaging modalities may be utilized (Figure 1). One should be careful to differentiate the observed retinal aneurysmal changes from other causes of this finding including Coats' disease, von Hippel-Lindau disease, diabetic retinopathy, and radiation retinopathy.[4, 5] The differential diagnosis of RAM also includes causes of macular subretinal hemorrhage including choroidal melanoma, age-related macular degeneration, polypoidal choroidal vasculopathy, and valsalva retinopathy.[8, 9] When associated hemorrhage or exudate is present, fluorescein angiography (FA) may be unable to demonstrate the macroaneurysm due to blockage. In these cases, indocyanine green angiography (ICG) may prove to be a useful tool due to the greater penetration of its near-infrared light. ICG is also 98% protein bound and thus can produce better defined images due to less leakage.[9]

Optical Coherence Tomography (OCT) may also be utilized to assist in the diagnosis of RAM. The specific retinal layer in which the hemorrhagic component is located can be identified by its high reflectivity that also causes shadowing of deeper tissue. Additionally, OCT may demonstrate hyporeflective intraretinal or subretinal fluid and the focal intraretinal hyperreflectivity of retinal exudates.[10] OCT Angiography (OCT-A) may also be used to demonstrate the focal vascular outpouching seen in a RAM, providing a noninvasive alternative to FA or ICG.[11, 12] OCT-A may also demonstrate circular regions of increased signal in areas where fluid is present called “suspended scattering particles in motion.”[13] Furthermore, OCT-A can delineate changes in RAM size over time and demonstrates a lack of flow within the lesion once involution occurs. As such, in addition to assisting with the diagnosis of RAM, both OCT and OCT-A can be used in its management and can show interval changes in fluid and vasculature over time.[10–12]

Management

Once a diagnosis of RAM is made, medical management of vascular risk factors, including elevated blood pressure and cholesterol levels, should be optimized with the assistance of the patient's primary care provider. RAMs often remain stable over time, with a natural history of eventual thrombosis with spontaneous involution.[4] Thus, if the RAM is not involving or

threatening the macula, one can consider close observation without treatment. Otherwise, treatment options may be explored for either the exudative or hemorrhagic complications of RAM, as described below.

Treatment of RAM associated with hemorrhage

Pharmacologic and Laser

The use of VEGF inhibitors may also be used in the treatment of RAM associated with hemorrhage.[14, 15] In addition to mechanisms that may lead to reduction of exudation, VEGF has also been demonstrated to be a regulator of the coagulation cascade, with its inhibition leading to reduction of both bleeding time and clotting time in an animal model. [16] Pichi *et al* found that in their prospective study of 18 eyes with symptomatic hemorrhagic RAMs (defined with size of 1–4 disc diameters and excluding dense vitreous hemorrhage), a series of three monthly bevacizumab injections led to closure of the aneurysm in nearly all cases and significant visual improvement.[17] Within Cho *et al*'s retrospective study, there were 7 eyes with symptomatic hemorrhagic RAMs (excluding cases with dense vitreous hemorrhage) that were treated with bevacizumab and 10 hemorrhagic eyes that were left untreated.[18] In contrast to the aforementioned study, *pro re nata* treatment was utilized, with each eye requiring an average of 1.6 injections (with a range of 1 to 3). While 43% of these eyes required more than 1 injection, there was complete resolution of hemorrhage in all treated eyes within a maximum of 3 monthly injections. While the authors made comparisons between treated and untreated RAMs in this study, it was likely difficult to compare the subgroup of RAMs that were hemorrhagic in regards to improvement of visual acuity due to the wide range of baseline visual acuities within each group (ranging from 20/30 to count fingers). Figure 2 illustrates the potential successful treatment of a patient with hemorrhagic RAM using intravitreal bevacizumab, with vision improving from count fingers to 20/30 (baseline of 20/25) one month after two monthly bevacizumab injections. Hemorrhage may also be present under the internal limiting membrane (ILM), which if large, can be slow to resorb as well as make it difficult to determine the presence of a submacular hemorrhage. Yttrium aluminum garnet (YAG) laser has been effectively used to release the trapped sub-ILM hemorrhage into the vitreous to improve its resolution, but recurrent hemorrhage has been reported to occur in some cases after treatment.[19, 20]

Surgical

It is worth noting that the majority of cases of vision loss due to vitreous hemorrhage secondary to RAM tend to do well without the need for surgical intervention, with the natural history of resorption typically lasting up to about 6 to 10 weeks.[4, 21] Vitrectomy, however, should be considered if, after 3 months, hemorrhage is either still of unclear etiology or anti-VEGF is not available. This may not only possibly expedite improvement of vision, but may also facilitate assessing the extent of maculopathy.[22]

Submacular hemorrhage can damage photoreceptors with the result that eyes affected by such hemorrhage generally have poor visual outcomes if left untreated.[23] The thrombolytic properties of tissue plasminogen activator (tPA) can be used to assist in overall

treatment.[21] Indeed, visual improvement has been accomplished with gas tamponade in conjunction with either intravitreal or subretinal tPA when performed with or without surgical drainage as well as with or without vitrectomy.[24–29] Vitrectomy, however, is not without risk, with possible resulting complications that may include cataract formation, retinal break or detachment, active bleeding, macular hole, and endophthalmitis.[22] During pneumatic displacement, perfluorocarbon gas is injected into the eye to physically displace the macular hemorrhage. Patients are then instructed to lie prone for at least a week to assist such displacement. During the procedure, tPA may be utilized to assist in hemorrhage clearance along with surgical drainage of submacular blood. Unfortunately, sudden and severe vitreous hemorrhage may be an immediate complication of intravitreal injection of tPA and gas for treatment of submacular hemorrhage associated with retinal macroaneurysm.[30] While authors including Kishor advocate that early physical displacement of subfoveal hemorrhage provides the best chance for visual improvement, Cho *et al* argue that use of tPA is not without risk and that eyes with submacular hemorrhage treated by intravitreal bevacizumab injection can also achieve good visual outcomes.[31] As such, removal of dense subretinal hemorrhage remains controversial and has the potential to cause many serious complications.

Treatment of RAM associated with exudation:

Vascular leakage may either occur directly from the aneurysm or from the surrounding incompetent vessels.[2] If this fluid and intraretinal lipid exudates extend into the macula, chronic changes resulting in structural damage to the retina can lead to permanent vision loss.[2, 4, 32] There are two types of treatment that have been utilized to reduce leakage: laser and pharmacologic.

Laser

Thermal laser has been utilized over the past several decades for the treatment of RAMs and can be performed by direct laser photocoagulation, indirect laser photocoagulation, or a combination of both. Direct photocoagulation, which attempts to seal the aneurysm, is performed by applying large (200–500 micron) laser spots of medium-long duration (200–500 milliseconds) with the lowest power necessary to create a light burn.[4] It is important to use care when performing this laser as the aneurysm's walls are already thin and distended. Direct laser treatment may cause additional weakness to the aneurysm's walls, potentially leading to aneurysm rupture, hemorrhage, and arterial occlusion.[33, 34] Although laser treatment can be effective in resolving the RAM and associated fluid, there are mixed reports in regards to visual outcomes, with some authors noting improved visual outcomes,[4, 35] while others finding no difference as compared to its natural history.[5, 29, 33] It has been suggested that case selection is at least somewhat responsible for this discrepancy in results, as eyes with more chronic changes were less likely to improve and less severe cases were more likely to be observed.[5, 29]

Indirect thermal photocoagulation is performed by applying confluent burns of shorter duration (100–200 milliseconds) and medium darkness around the lesion, specifically, to the incompetent retinal capillaries surrounding the RAM.[4, 29, 36, 37] Indirect laser may also

have a beneficial effect on RAM resolution by reducing the blood flow and pressure in the artery as a result of decreased oxygen demand to nearby retinal tissue.[4, 34] Indirect thermal laser theoretically has a lower risk of rupture and hemorrhage in comparison to direct laser.[4] Both direct and indirect methods of laser treatment may result in a transient increase in accumulation of exudates, which has also been noted to occur with treatment of chronic fluid in other macular conditions. Additionally, laser treatment may need to be repeated.[29]

More recently, the use of subthreshold laser has been evaluated in the management of foveal-involving exudative RAMs. In contrast to the thermal laser photocoagulation described in the previous paragraph, subthreshold laser does not result in a visible burn mark. The effects of subthreshold laser are thought to be related to an increased expression of heat shock protein.[38] In a pilot study, Parodi *et al* applied subthreshold laser to the entire RAM and surrounding area in nine symptomatic patients (settings: 125nm spot size, 0.3 seconds exposure time, power 1400mW, 15% duty cycle).[39] Four months after treatment, all patients experienced improvement of fluid (average OCT central thickness of 340µm decreased to 274µm) as well as visual acuity (approximately 20/125 to 20/80). As a follow-up study, 12 patients with symptomatic exudative RAMs were randomized to subthreshold laser (using the same settings as in the prior study) while 13 received indirect thermal laser.[40] In this study, there was a statistically significant improvement in both visual acuity and OCT central thickness in both groups at month 3 (visual acuity improved from approximately 20/100 to 20/40 in both groups while OCT central thickness improved from 341µm to 289µm in the subthreshold group and from 332µm to 282µm in the indirect thermal group). Improvements in both visual acuity and OCT continued to take place over a 12-month period; however, no difference was found between the two groups at any measured time point.

Pharmacologic

Pharmacologic therapy for the treatment of exudative RAMs using vascular endothelial growth factor (VEGF) inhibitors was first reported in 2009.[41] The mechanism by which these anti-VEGF agents act on leakage in RAM has yet to be fully elucidated. One proposed mechanism is that VEGF inhibitors lead to a reduction of nitric oxide levels which subsequently cause vasoconstriction and decreased vascular permeability and, thus, less leakage and edema.[18, 42] It is also proposed that anti-VEGF agents may lead to a tighter alignment of endothelial cells.[43]

There have been various reports on the use of anti-VEGF agents in the treatment of exudative RAMs, as summarized in Table 1. In many cases, it appears that only a limited number of injections are required for resolution of fluid. Pichi *et al* demonstrated that after a series of 3 monthly bevacizumab injections in exudative RAMs, there was closure of the aneurysm in almost all cases. This study also demonstrated that both resolution of macular fluid resolution and improvement of vision were sustained over a 12 month period.[17] Although Chatziralli *et al* found that only one injection was needed for resolution of macular edema,[44] other authors reported requiring more injections until fluid resolved completely.[43, 45, 46] The use of anti-VEGF agents does not preclude the use of laser, which Chen *et*

a/ suggest may better reduce macular edema.[20] In one report, once 6 injections were performed, indirect thermal laser was applied with subsequent complete resolution of fluid. [46]

Conclusion

In summary, RAMs are acquired dilatations of the retinal arteries that most commonly occur in women in their sixties with a history of hypertension. Although the diagnosis of RAM can be primarily based on the fundusoscopic appearance of the lesion, imaging including FA, ICG, as well as OCT and OCT-A can be invaluable as far as assisting in its diagnosis, determining the proper treatment, and following the lesion over time. While many RAMs are asymptomatic, others can lead to vision loss due to either their exudative or hemorrhagic complications.

There is no consensus regarding the management of symptomatic exudative or hemorrhagic complications of RAM. That being said, observation of asymptomatic patients where there is no immediate threat of vision loss is recommended. Exudative lesions typically respond well to relatively few intravitreal anti-VEGF injections, which may be advantageous over laser for those lesions close to the fovea. Laser treatment is also effective for resolution and can be used in conjunction with anti-VEGF treatment, particularly if there is persistent exudation after several injections. Although the technique of laser treatment employed appears to be practitioner-dependent, it seems most reasonable to us to use indirect laser over direct laser due to the theoretically lower risk of rupture and hemorrhage. Additionally, although reports are limited, subthreshold laser thus far appears to be effective and to achieve similar results to indirect thermal laser. As for hemorrhagic complications of RAM affecting vision, there is once again no consensus as to preferred treatment modality. That being said, anti-VEGF agents seem like a reasonable choice for submacular hemorrhages that are not too large or dense. For more extensive hemorrhages, options that physically displace the hemorrhage including vitrectomy, tPA, and tamponade should be considered. Last but not least, it is recommended that communication take place with a patient's primary care provider so that vascular risk factors, particularly those for hypertension and atherosclerotic disease, can be best managed.

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Figure 1.

Sixty-five-year-old gentleman presents with a hemorrhagic RAM with count fingers vision. A. Fundus photo demonstrates a large macular hemorrhage with associated nasal exudates and inferior sub-internal limiting membrane (ILM) hemorrhage. B. Fluorescein angiography (right) exhibits blockage from hemorrhage and leakage inferiorly originating from the macroaneurysm, which is better visualized with indocyanine green angiography (left; macroaneurysm at red arrow). C. Optical coherence tomography shows a large area of sub-ILM hyperreflectivity from hemorrhage that blocks penetration of signal to the underlying tissue. Prehyaloid hyperreflectivity from hemorrhage is also visible inferiorly. *Photo Credit: Luis Bernhard, CRA*

Figure 2.

Treatment course of the 65-year-old gentleman illustrated in the previous figure with a hemorrhagic RAM. Each panel demonstrates an *en face* optical coherence tomography (OCT) fundus image (top), horizontal central b-scan (middle), and vertical central b-scan (bottom). A. At the initial visit, vision was count fingers (CF) and he was treated with intravitreal bevacizumab. B. The patient returned one month later and vision improved to 20/400 with interval improvement of hemorrhage seen on both *en face* OCT and the central b-scans. He was then treated a second time with intravitreal bevacizumab. C. One month after the second bevacizumab injection, his vision improved to 20/30, almost back to his baseline vision of 20/25. The area of hemorrhage is seen to be significantly smaller on *en face* OCT and the fovea is now discernable on both central b-scans. No additional injections were given.

Table 1.

Pharmacologic Treatment of Exudative RAM

Study Authors	Study Type	Agent +/-adjuvant (N)	VA	OCT	# of Treatments (range)	Follow-up (range)
Chanana <i>et al</i> (2009) [41]	Retrospective	IVB (N=1)	20/400 → 20/50	607 µm → 173 µm	2	6 weeks
Jonas <i>et al</i> (2010) [47]	Retrospective	IVB (N=2)	20/50->20/25; 20/400->20/200	Resolution of fluid	1	8 months
Wenkstem <i>et al</i> (2010) [48]	Retrospective	IVR + iFocal (N=2)	20/50 →20/20	510 µm → 148 µm	2	5 months
Golan <i>et al</i> (2011) [49]	Retrospective	IVB (N=1)	20/160->20/20	364 µm → 248 µm	2	13 months
Pichi <i>et al</i> (2013) [17]	Prospective (nonrandomized)	IVB (N=19)	20/70->20/25	496 µm → 216 µm	3	12 months
Cho <i>et al</i> (2013) [18]	Retrospective	IVB (N=4)	20/80 →20/30	406 µm → 217 µm	1 (1-2)	12 months (8-17)
Zweifel <i>et al</i> (2013) [43]	Retrospective	IRB (N=5) IVR (N=5)	20/100->20/50	366 µm → 266 µm	3 (1-7)	6 months (2-12)
Menezes <i>et al</i> (2015) [45]	Retrospective	IVR (N=1)	20/200->20/50	310 µm → 233 µm	6	11 months
Leung <i>et al</i> (2015) [46]	Retrospective	IVB+ iFocal (n=1)	20/60->20/30	312µm → 241 µm	6	20 months
Erol <i>et al</i> (2015) [50]	Retrospective	IVR (n=7)	20/250-> 20/30	428 µm → 209 µm	2	11 months (6-19)
Chen <i>et al</i> (2017) [20]	Retrospective	vFocal only (n=3) vFocal +IVI (n=8)	20/80 →20/30	330 µm → 236 µm	1	10 months (3-30)
Bormann <i>et al</i> (2017) [51]	Retrospective	IVR +iFocal (n=1) IVA (n=1).	20/70 →20/25; 20/100 →20/50	Resolution of fluid	2 (IVR) 1 (IVA)	12 months

Note: Only eyes with exudative RAMs are reported above. Additionally, to most accurately represent visual outcomes, studies with 2 or fewer eyes have vision listed individually instead of pooled. VA = visual acuity (converted to Snellen equivalent if not provided). N (number of eyes with exudative RAM); OCT = central macular thickness on optical coherence tomography; IVA = intravitreal aflibercept; IVB = intravitreal bevacizumab; IVR = intravitreal ranibizumab; IVI = unspecified or various intravitreal agents; iFocal = indirect thermal laser utilized; vFocal = various laser techniques utilized (i.e. subthreshold, direct thermal, indirect thermal).