Case Report of a Retinal Arterial Macroaneurysm Using Diagnostic Optical Coherence Tomography and Optical Coherence Tomography Angiography

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Abstract
Retinal arterial macroaneurysm (RAM) is a focal dilation of a retinal arteriole. The rupture of a macroaneurysm may occur spontaneously with varying degrees of retinal hemorrhage, exudation and edema. A case of retinal arterial macroaneurysm is presented with use of optical coherence tomography (OCT) and optical coherence angiography (OCTA) imaging to provide diagnostic information in a fundus obscured by a dense multilayer hemorrhage.

Introduction
Retinal arterial macroaneurysm (RAM) can be either an idiopathic or an acquired dilation of a retinal arteriole that is often located within the first three orders of bifurcations at branch points or areas of arteriovenous crossing. This condition affects older persons with a greater predilection for women, and an association with systemic hypertension and arteriosclerotic disease is well documented. Locating a saccular or fusiform dilation point of an arteriole wall is a pathognomonic sign that confirms the RAM diagnosis. The spectral domain optical coherence tomography (OCT) and optical coherence angiography (OCTA) are non-invasive modalities that provide depth-resolved structural and functional imaging information respectively from all layers of the retina and the choroid and can aid in the diagnosis and management of these lesions. Although retinal arterial macroaneurysm may involute spontaneously, the high metabolic demand of retinal tissue relies on adequate circulation and prolonged compromise from hemorrhagic complications can cause irreversible structural damage. Therefore, treatment is beneficial in the presence of associated macular edema, intraretinal exudate or hemorrhagic neurosensory detachment.

Case Report
A 93-year-old white male presented to the clinic for an urgent evaluation of a same day, sudden onset vision loss in his right eye. The vision loss began shortly after waking and was described as a red spot in his vision that progressively became darker. He denied prior head trauma or an eye injury. He had no history of systemic hypertension, diabetes, or hyperlipidemia. The patient had a history of anemia, cobalamin deficiency, and atrial fibrillation, and was previously prescribed oral vitamin B12 and Eliquis® (apixaban).

The best-corrected visual acuity was hand motion in the right eye with no pinhole improvement and 20/20 in the left eye. There was no afferent pupillary defect. Extraocular muscle movements were full in all positions of gaze without pain on eye movement. Confrontation fields were full to finger counting in each eye. Biomicroscopy revealed well-centered intraocular lenses with open posterior capsules in each eye. All other anterior segment structures showed no diseased variations. Intraocular pressure measured by Goldmann applanation tonometry was 12mmHg in the right eye and 10mmHg in the left eye.

The dilated ophthalmoscopic examination revealed a large multilayer hemorrhage affecting the subhyaloid space, intraretinal layers, and submacular region in the right eye (Figure 1A). The optic nerve was well-perfused with superior superficial hemorrhages, and the retinal vasculature showed an attenuated artery with moderate sclerosis exiting the temporal optic nerve aspect before it disappeared into the macular hemorrhage. The left eye showed minimal retinal vascular changes and was otherwise without pathology (Figure 1B). Neither a right nor a left bruit was detected on carotid auscultation.

Spectral domain optical coherence tomography (SD-OCT) directed through the dense macular hemorrhage localized the morphological structure of the aneurysm. The presence of a round inner retinal lesion with a broad hyperreflective wall and a dark lumen consistent with a retinal macroaneurysm was detected (Figure 2A). Early hyperreflectivity within the lumen of the RAM indicated early thrombus formation. The deep retinal plexus scan on the optical coherence tomography angiography study also showed the location of the retinal macroaneurysm (Figure 2B). Additionally, multiple hemorrhagic neurosensory detachments were detected with OCT (Figure 3). Due to the
resultant dense macular hemorrhage, the retinal arterial macroaneurysm was treated with the intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy, Avastin® (bevacizumab), to improve the visual prognosis (Figure 4).

At the time of diagnosis, the patient’s blood pressure was elevated to 147/92mmHg and he was referred to his internist for medical evaluation. The patient had a history of intermittent elevated blood pressure readings, but not a documented hypertension diagnosis prior to this vascular event. The anticoagulant Eliquis®, an antagonist for venous thromboembolism (VTE) prevention6, may have exacerbated the amount of hemorrhage that dispersed after the aneurysmal rupture. This medication selectively and reversibly blocks the activity of coagulation factor Xa in the coagulation cascade of blood, and within a pre-existing clot7. It is a novel anticoagulant agent (NOAC) and we hypothesize that in light of the healthy appearance of the unaffected retinal vasculature, it may have a role in arteriole macroaneurysm decompensation and rupture, and that this theory warrants future investigation.

Since hypertension is classified as a blood pressure reading of 130/80mmHg, our patient had been at high risk for a spectrum of retinal vascular disease changes for several years. His stat laboratory evaluation showed an elevated INR, denoting slow coagulation. His lipid profile measured an elevated LDL cholesterol, normal HDL, and normal triglycerides. A normal ESR, normal C reactive protein level, and normal glucose were found. He had normal platelets, normal hemoglobin, and a normal hematocrit, which eliminated polycythemia as the hemorrhage etiology.
vision loss has been shown to increase when hemorrhages in the submacular space produced secondary morphologic changes and permanent architectural damage to the retinal pigment epithelium and photoreceptors. Subretinal blood toxicity has also been documented as a cause for severe, irreversible damage to the retina, and the factors presumed to cause retinal toxicity are the prevention of metabolic exchange between the retinal pigment epithelium and outer retina, iron related toxicity, and fibrin-mediated retinal damage.

Retinal arterial macroaneurysms present in two morphological forms. One is the fusiform or widening of the artery that is associated with atherosclerosis and the other is a saccular outpouching dilation that occur from hemodynamic stress at arterial bifurcations. Both are most often located within the first three orders of arteriolar bifurcation or at an arterio-venous crossing. In a clinical study that described the fluorescein angiographic features in 34 patients over eight years, the macroaneurysms were differentiated by saccular and fusiform lesions and a hemorrhage was the predominant feature in 72% of the saccular lesions and in 90% of the fusiform lesions.

Fibroglial proliferation surrounding the distention of the retinal arteriole is a common characteristic. OCT in a retinal arterial macroaneurysm rupture, the optical coherence tomography technology produces unrivaled images of retinal structure and can detect the extent of the vertical penetration of the hemorrhage. OCT also shows the grossly dilated arteriole signaling a fusiform or saccular aneurysmal lesion. Retinal arterial macroaneurysms present with a round inner retinal lesion that has a thick hyperreflective wall and a dark lumen, the signal intensity of which is lower than the central retinal arteries, suggesting slow blood flow within the lumen. Detecting this morphology with OCT is the hallmark for a retinal arterial macroaneurysm and hyperreflectivity within the retinal pigment epithelium and photoreceptors.

According to data from the Beijing eye study a retinal arterial macroaneurysm may occur in about one in 9000 eyes. The condition has a preponderance for women and occurs in the sixth and seventh decades of life. Most cases of retinal arterial macroaneurysm are unilateral although bilaterality occurs in 10% of cases. The retinal arterial macroaneurysm was defined by Robertson in 1973, and the contributory vascular pathophysiology was described as a characteristic increase in intimal collagen and a replacement of the vessel medial muscle fibers with collagen. As the arterial wall becomes less elastic and more susceptible to dilation from an elevated hydrostatic pressure in hypertension, macroaneurysm predisposition increases. Moreover, the raised arteriole transmural pressure is directly proportional to released wall tension and furthers the susceptibility to macroaneurysm formation. It was shown that patients with hemorrhagic retinal arterial macroaneurysm had higher systolic blood pressures and there was an associated transmural tension and greater amplitude of pulsations that contributed to mechanical vascular damage. The association with uncontrolled hypertension has been well established and after medical interventions to preclude further vascular damage, macroaneurysms thrombose and spontaneously involute. In some cases, the exudative process can progress and causes structural damage and vision loss.

The supratemporal artery is the most reported site of involvement when visual impairment is documented, as was with this case. Additionally, in this patient, a rapid onset of visual impairment occurred after the aneurysm rupture caused an immediate multilayer retinal hemmorhage that obscured the macula and caused the development of a sub-foveal neurosensory detachment. The risk for permanent central vision loss has been shown to increase when hemorrhages in the submacular space produced secondary morphologic changes and permanent architectural damage to the retinal pigment epithelium and photoreceptors. Subretinal blood toxicity has also been documented as a cause for severe, irreversible damage to the retina, and the factors presumed to cause retinal toxicity are the prevention of metabolic exchange between the retinal pigment epithelium and outer retina, iron related toxicity, and fibrin-mediated retinal damage.

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Fluorescence from dye leakage, which allows OCT angiography to produce high-resolution images of the retinal arterial macroaneurysm including the depth location of vascular abnormalities. OCT angiography can also be utilized to calculate lesion vessel density and flow indices. An active retinal arterial macroaneurysm presents as a focal distension of the vessel with a hyperreflective lumen on OCT angiography. In this case, a reduced flow signal and early hyperreflectivity within the lumen of the retinal arterial macroaneurysm indicated early thrombus formation. OCT angiography image degradation due to the multilayer hemorrhage caused the best observation of the retinal arterial macroaneurysm to appear in the deep plexus image.

**Differential Diagnoses**

Retinal arterial macroaneurysms can present in a variety of clinical manifestations, therefore, they are frequently misdiagnosed. Differential diagnoses for retinal arterial macroaneurysms depend on the clinical presentation of each case and vary by the retinal location of the aneurysm, the presence of exudates, retinal hemorrhages, and atypical vascular structure. Subretinal hemorrhage, intraretinal hemorrhage, preretinal hemorrhage, vitreous hemorrhage, macular exudation and macular edema are possible manifestations in a retinal arterial macroaneurysm rupture. Exudative age-related macular degeneration resembles retinal arterial macroaneurysm rupture when submacular hemorrhage and exudation are present. The bilateral nature of macular degeneration can aid in the diagnosis although, RAM can occur as bilateral disease in up to 10% of cases. Valsalva retinopathy, proliferative diabetic retinopathy and complicated posterior vitreous detachment are differentials for preretinal hemorrhages. Differentials for the presence of a vitreous hemorrhage are proliferative diabetic retinopathy, retinal vein occlusion, retinal tear and exudative age-related macular degeneration. In cases of significant exudate, Coats' disease, Leber's miliary aneurysm and angiomatosis retinae are primary causes. Other differentials for retinal arterial macroaneurysms include radiation retinopathy, cavernous hemangioma, retinal capillary hemangiomias, von Hippel-Lindau disease, and polypoidal choroidal vasculopathy. Also, a retinal...

**OCT Angiography**

Optical coherence tomography angiography illustrates blood flow signals within exudative retinal arterial macroaneurysms. To assist with RAM diagnosis and management, OCT angiography enables visualization of the lesion within the superficial, middle and deep capillary plexus, and the choroidal vascular plexus. It can be used in place of or as a supplement to fluorescein angiography, which only allows for visualization of the superficial capillary plexus.

In contrast to fluorescein angiography, OCT angiography is unable to depict abnormalities in vascular permeability and therefore does not display pooling, staining or leakage. However, OCTA images are not concealed by hyper-fluorescence from dye leakage, which allows OCT angiography to produce high-resolution images of the retinal arterial macroaneurysm including the depth location of vascular abnormalities. OCT angiography can also be utilized to calculate lesion vessel density and flow indices. An active retinal arterial macroaneurysm presents as a focal distension of the vessel with a hyperreflective lumen on OCT angiography. In this case, a reduced flow signal and early hyperreflectivity within the lumen of the retinal arterial macroaneurysm indicated early thrombus formation. OCT angiography image degradation due to the multilayer hemorrhage caused the best observation of the retinal arterial macroaneurysm to appear in the deep plexus image.

**Figure 5.** Left eye optical coherence tomography (OCT) showing the hyperreflective microvasculature dots within the retinal layers and vitreomacular adhesion.

**Figure 6A.** Right eye ocular coherence tomography angiography (OCTA) of the retinal arterial macroaneurysm.

**Figure 6B.** Right eye OCT angiography montage angio analysis showing the superior temporal location of the retinal arterial macroaneurysm lesion.
arterial macroaneurysm hemorrhage in the space beneath the retinal pigment epithelium may produce a dark lesion simulating an ocular tumor such as malignant melanoma21. The case history and the dilated fundus examination of the fellow eye are of value when confirming the RAM diagnosis.

In this case, there was a question about the natural history of the retinal arterial macroaneurysm rupture in relation to Eliquis®. Novel antithrombotic agents are considered safe treatments for atrial fibrillation, thromboembolic disease, and acute coronary syndrome when compared to conventional medications25 and require less coagulation monitoring25,26. Systemic hemorrhagic adverse events have been reported although intraocular hemorrhaging resulting from novel antithrombotic medications is uncommon, yet, there are documented adverse visual outcomes3. Novel oral anticoagulants inhibit factor Xa25,26 and when clot formation is inhibited, the risk for intraocular hemorrhagic complications increases26. Collaborative efforts between eye care providers and primary care providers are necessary to modify oral anticoagulant treatment when a NOAC related intraocular hemorrhage etiology is suspected27.

In addition to OCT and OCT angiography, fluorescein angiography (FA) and indocyanine green (ICG) can aid in differentiating macroaneurysms from other retinal diseases4,21,22,23. Fluorescein angiography is used routinely to diagnose retinal vascular disease and is the standard when the diagnosis of a retinal arterial macroaneurysm is uncertain21. However, if a dense hemorrhage is present and views of the aneurysm are obstructed, ICG is more useful due to its penetration abilities21,22. OCT remains the best modality for monitoring retinal edema after retinal arterial macroaneurysm rupture21,22. In short, the differentiation and rapid diagnosis of retinal arterial macroaneurysms is vital to the management of systemic etiologies and risk factors21.

Treatment and Management

There are numerous treatment and management options for retinal arterial macroaneurysms although there is no consensus on which is most effective21. Spontaneous resolution of RAM can occur and therefore, observation is recommended for asymptomatic patients with non-vision threatening aneurysms21,22,23,28,29. When persistent macular exudation and hemorrhages threaten photoreceptor function and cause visual loss, treatment is initiated21,22,23,28,29. Focal laser photocoagulation, combined focal laser and intravitreal anti-vascular endothelial growth factor agents, yttrium aluminum garnet (YAG) laser membranectomy, pars plana vitrectomy (PPV), submacular surgery, and submacular pneumatic displacement are effective in cases of retinal arterial macroaneurysms with exudative and hemorrhagic lesions21,22,23,28,30,31.

Focal laser photocoagulation is applied directly to the macroaneurysm to accelerate its involution21,22,32. Indirect laser is administered to the adjacent retina to reduce macroaneurysm leakage proximal to the macula21,22,32 and subthreshold laser treatment is performed to decrease laser exposure and reduce the adverse effects of conventional laser21,23,32. Rapid reduction of macular exudation from retinal arterial macroaneurysm rupture is accomplished with combined focal laser and anti-VEGF injections30. Anti-VEGF agents including Avastin®, Lucentis®, and Eylea® are effective therapies for the resolution of macular edema, hemorrhage and exudation in vision-threatening retinal arterial macroaneurysms21,22,23,28,31.

YAG laser membranectomy and pars plana vitrectomy are indicated in cases with pre-retinal hemorrhage21,30. A pars plana vitrectomy is performed for unresolved vitreous hemorrhages, and the PPV procedure follows submacular surgery27. Submacular surgery or pneumatic displacement is a treatment option for submacular hemorrhage21,22. Hence, the most effective treatment for retinal arterial macroaneurysms is dependent on the clinical presentation. Medical management of comorbidities including hypertension, arteriosclerosis, cardiovascular disease, hyperlipidemia and polycythemia is initiated by the internist21,22,23,31.

Conclusion

The case-study patient had the retinal arterial macroaneurysm risk factors of age and hypertension. The ocular coherence tomography technology was employed to make an early diagnosis, therefore, investigations into other etiologies such as polycythemia, hyperlipidemia, and cerebrovascular disease were considered non-contributory to this event. The severe macular hemorrhage caused significant vision loss, which may have been exacerbated by his anticoagulant medication, Eliquis®. Although the patient was being treated with Eliquis® for cardiovascular accident (CVA) prevention, there were no findings to support a CVA history before or after his diagnosis of atrial fibrillation. Our patient remained on the medication and anti-hypertensive treatment was not initiated. The patient was ordered to keep a diary of his daily blood pressure readings, which ranged from 93/64mmHg to 120/87mmHg prior to his three-week follow-up visit.

The anti-vascular endothelial growth factor intravitreal injection, Avastin®, was initiated four days after the initial RAM presentation. Mild changes in the hemorrhage appearance signaled an appreciable therapeutic effect at the three-week follow-up examination. The patient continued with a series of Avastin® injections and the clinical appearance continued to improve.

References


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