

## American Academy of Optometry: Case Report 5

### Age Related Macular Degeneration: Retinal Angiomatous Proliferation

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#### **Abstract**

Retinal Angiomatous Proliferation (RAP) represents the development and formation of a distinctive shunt vasculature originating from outer retina potentially communicating with deeper choroidal neovascularization. RAP is relatively uncommon and may be observed in end-stage age related macular degeneration (ARMD) as a result of ischemic tissue pathology. It has been well established that with the release of vascular endothelial growth factor (VEGF) under these conditions, classic or occult choroidal neovascular membranes (CNVM) can occur with characteristic clinical and angiographic findings. Likewise, RAP can be considered a unique entity having its own clinical features with respect to fundus findings, angiography, and progression. The presence or development of RAP can indicate an impending or severe visual consequence; therefore, proper recognition of the disorder is imperative so that aggressive therapy can be initiated. Management is considered challenging, with combined anti-inflammatory and photodynamic therapy (PDT) or anti-VEGF treatment alone showing the greatest potential to date.

**Keywords:** *Age Related Macular Degeneration, ARMD, Choroidal Neovascular Membrane, CNVM, Laser Photocoagulation, Photodynamic Therapy, PDT, Retinal Angiomatous Proliferation, RAP, Vascular Endothelial Growth Factor, VEGF*

## Introduction

Retinal Angiomatous Proliferation (RAP) is a somewhat rare finding, which can lead to a form of end-stage age related macular degeneration (ARMD) in response to chronic surrounding tissue ischemia. A formation of intra-retinal neovascular shunt vessels occur, which can extend posteriorly through Bruch's membrane, into deeper choroid, with the creation of and possible anastomoses to choroidal neovascular membranes (CNVM). The development of an RAP complex or lesion can have a potentially devastating effect on central visual acuity, possibly leading to an irreversible relative or absolute central scotoma.

The clinical presentation of RAP can be quite dramatic with respect to ophthalmoscopic findings. As evident in the case study, advanced progression can reveal a deep central clustering of retinal neovascular shunt vessels and/or choroidal neovascularization, pigmentary epithelial detachment (PED), serous macular detachment, macular and paramacular fibrosis, as well as adjacent intra-retinal hemorrhages.

In addition to ischemia, the clinicopathological findings of progressive RAP have implicated an inflammatory mechanism producing this distinctive neovascular pathology. Drusen, macrophage migration, vascular endothelial growth factor (VEGF)-positive retinal tissue, as well as hypoxia inducible factors have been histologically isolated supporting a dual etiologic origin.<sup>1</sup> Posterior retinal and choroidal anastomoses have been confirmed utilizing indocyanine green angiography (ICG-A), moreover, ICG-A has been noted as a superior method for detecting retinal angiomatous proliferation compared to traditional fluorescein angiography (FA).<sup>2</sup>

A model describing three stages of RAP advancement has been adopted as initially proposed by Yannuzzi et al in 2001. Stage I involves proliferation of intraretinal capillaries. Stage II is determined by a growth of retinal vessels beyond the photoreceptor layer and into the subretinal space. Stage III occurs when choroidal neovascularization develops. The formation of deep retinal and choroidal anastomoses, however, is not always present and is therefore not pathognomonic of RAP.<sup>3</sup>

Current treatment considerations in RAP include combined intravitreal Kenalog (Triamcinolone) and photodynamic therapy (PDT) with Visudyne (Verteporfin) which has been found effective in reducing or eliminating retinal edema, regression of neovascularization, and stabilizing or improving visual acuity.<sup>4</sup> Most recently, studies involving anti-angiogenesis (anti-VEGF) therapy of intravitreal Avastin (Bevacizumab) have shown to be promising. Pedersen et al (2007) produced stable visual acuity with reduced CNVM activity being demonstrated in eyes 2 – 4 weeks post treatment.<sup>5</sup> Joeres et al (2007) have found intravitreal Bevacizumab resulted in a reduction of leakage in intra- and subretinal fluid and have reported an increase in visual acuity observed only 4 weeks after the first injection.<sup>6</sup> Conventional focal argon laser photocoagulation has also been employed alone and in conjunction with other modalities producing encouraging results for this complex entity.<sup>7,8,9</sup>

## Case Report

An 87-year-old caucasian gentleman presented as a new patient in January 2007 with a chief complaint of “worsening hazy vision” in the left eye first noted approximately 2 months prior to his visit. He reported having uneventful cataract surgery for both eyes in 2002; otherwise, he had an unremarkable ocular history. He had recently been prescribed Antivert (Meclizine) for symptoms of vertigo without relief; therefore, he thought his blurred vision might be the cause. He had no other systemic history and was unaware of an ocular or systemic family history.

Best-corrected visual acuity (VA) with refraction was 20/30 OD and 20/HMO OS, NIPH. Stereopsis was not present with Randot testing. Ishihara color testing was normal OD but unreliable OS due to HMO VA. Pupils were equal, round, and responsive to light and accommodation. An afferent pupillary defect was not elicited OS. Extra-ocular muscles were smooth, with good alignment, and without subjective diplopia. There was mild dermatochalasis present with slight associated ptosis in each eye; however, levator function was intact OU. Confrontation visual field was full without defect OD, however, a distinct central scotomatous defect was evident OS with the remaining peripheral field full.

Biomicroscopic examination revealed a well-placed posterior chamber intra-ocular lens (PC IOL) in each eye with a deep and quiet anterior chamber; grade IV by Von Herrick method OU. There was no indication of concurrent or previous ocular inflammatory disease in either eye. The cornea appeared clear without evidence of dystrophic or degenerative changes OU. Applanation intra-ocular pressure (IOP) was 19mm Hg and 18mm Hg for the right and left eye respectively.

Dilated 20D and 90D ophthalmoscopic evaluation of the right eye demonstrated a posterior vitreous detachment (PVD) present with an unremarkable periphery, posterior pole, vessels, and optic disc. A c/d of 0.45/0.45 was estimated with healthy rim tissue. The macula showed only minimal dry degenerative changes in the form of trace retinal pigment epithelial (RPE) hyperplasia and early drusen formation.

Dilated 20D and 90D ophthalmoscopic evaluation of the left eye also demonstrated the presence of a PVD along with an unremarkable periphery. A c/d of 0.45/0.45 with healthy rim tissue was observed in the left eye as well. Incidentally, an underlying choroidal nevus measuring approximately  $\frac{1}{2}$  x 1 disc diameters (DD) was found at the inferior disc margin and was of no consequence. With 90D biomicroscopy, the macula displayed a large raised central fibrotic lesion with 360° fibrous proliferation extending anteriorly into the



Figure 1

vitreous. Intra-retinal hemorrhages were also present just infero-temporal to the edge of proliferation. Within the center of the lesion appeared both small and large diameter vessels, representing retinal – retinal and retinal – choroidal neovascular shunting protruding directly through the fovea (Figure 1).

Based on the above findings, a diagnosis of atypical end-stage neovascular ARMD was concluded. Specifically, Retinal Angiomatous Proliferation was suspected. Considering the extent of involvement through the fovea as well as the degree of vision loss, the possibility for therapeutic intervention was unlikely. The poor prognosis was explained and merely observation recommended. A second opinion was subsequently obtained with a retinal specialist confirming the diagnosis. Unfortunately, it was also agreed that treatment would be unsuccessful through current therapeutic alternatives available.

In view of the early dry ARMD changes present in the fellow eye, along with the associated slight reduction in acuity, careful monitoring was emphasized for that eye with 4 – 6 month return visits recommended. Macular Heidelberg retinal tomography (HRT), stereo digital photography, ophthalmoscopy, central visual field testing, visual acuity, color vision, as well as home Amsler grid testing are important elements in the prospective management plan. Eventually, ICG angiography may also be necessary if progression ensues. An antioxidant vitamin therapy and polycarbonate spectacle lenses with UV protection was also advised.

## **Discussion**

Retinal Angiomatous Proliferation can be distinguished as a unique neovascular manifestation occasionally found in progressive age related macular degeneration with its own defining characteristics. In contrast to the posterior - anterior choroidal neovascular membrane formation typifying the common wet ARMD presentation, RAP first begins in the deep or outer retinal vasculature. Neovascular shunt vessels may advance into the sub-retinal space, breaking through retinal pigment epithelium and Bruch's membrane, eventually finding their way into the choroid with the possibility of creating occasional anastomoses to choroidal neovascularization. Understandably, as exemplified in the case report, central acuity loss with relative or central scotoma can often be the end result.

Studies utilizing multiple diagnostic techniques have reported varying degrees of RAP prevalence ranging from 8% to 13%<sup>12-14</sup> Understanding that ARMD is normally a bilateral condition, the possibility of RAP development and progression in both eyes is naturally a concern. Unfortunately, in patients diagnosed with unilateral RAP lesions, the form of neovascularization that develops in the fellow eye is virtually always RAP. In addition, the risk of neovascularization in the fellow eye is higher in patients with RAP than in those with other forms of neovascular ARMD.<sup>18</sup> With the continued advancement in imaging technology and methods, perhaps an even greater incidence and prevalence will be found as more clinicians develop awareness and learn to recognize the diagnostic features of RAP.

With respect to CNVM often observed in clinical practice, the pathophysiology is not completely understood. Pathologic conditions that involve RPE or damage to Bruch's membrane have been known to induce neovascular membrane formation by stimulating the release of vascular endothelial growth factor from the RPE. VEGF targets vascular endothelial receptor cells activating signal transduction pathways that conclude with the formation of neovascular vessels. An additional protein also derived from the RPE was recently discovered which is now known as pigment epithelium derived factor (PEDF). PEDF was found to have an inhibitory effect on ocular neovascularization whereas VEGF is a known ocular angiogenic stimulator. It is theorized that a balance between PEDF and VEGF needs to be maintained for proper retinal vasculature to exist. Therefore, an imbalance in these factors may determine the development of retinal or choroidal neovascularization.<sup>10</sup>

Considering traumatic, mechanical, or ARMD effects on the RPE and Bruch's membrane have been primarily implicated in the formation of ocular neovascularization, specifically classic or occult CNVM, the pathophysiologic mechanism behind *intra*-retinal neovascularization and RAP may be even more difficult to isolate. Interestingly, other neovascular biochemical mediators from the vitreous, retina, and even the choroid have been associated with new vessel proliferation in the retina and are perhaps contributors to the etiology of RAP. These mediators may also alter capillary permeability to produce leakage, hemorrhages, exudates, and the retinal vascular changes characterizing RAP. In that regard, emerging over time, there is predominantly a vertical extension of the deep intra-retinal neovascularization representing proliferating capillaries extending to the retina's anterior and posterior boundaries.<sup>3</sup>

In 2001, stages of progression were classified according to Yannuzzi et al, which described the extent of retinal and choroidal involvement.

**Stage I:**

Intraretinal neovascularization can be recognized on slit lamp examination as a small nodular mass of angiomatous tissue in the middle and inner retina, accompanied by intraretinal hemorrhages and intraretinal edema. A small cluster of intraretinal dilated capillaries is the earliest clinically recognized manifestation in RAP (Figure 2). Retinal-retinal anastomoses (RRA) were seen in 30% of the cases.



Figure 2

**Stage II:**

A localized neurosensory retinal detachment and an increase in intraretinal edema are seen. Pre, intra, and subretinal hemorrhages are present. An associated serous PED was seen in 94% of eyes as the sub-retinal



Figure 3

neovascularization (SRN) reached or fused with the RPE (Figure 3). Nearly 50% of patients were diagnosed in this stage, as the SRN progresses more rapidly, becomes associated with an increase in the exudative changes, and induces alterations in vision. RRA was seen in 39% of patients.

**Stage III:**

Clinical and angiographic examinations can clearly demonstrate the presence of CNVM but is found in only 7% of the cases (Figure 4). CNVM in the subretinal space, or the presence of a vascularized PED is best determined with ICG-A. Indocyanine green angiography has been found to be the most effective in resolving findings in all stages.



Figure 4

The advent of ICG-A and its diagnostic capabilities in the evaluation of RAP progression is considered superior to traditional fluorescein angiography (FA). Due to the molecular properties of indocyanine green dye, there is not profuse leakage into subretinal or sub-RPE spaces; therefore, neovascular intra-retinal tissue can be observed as a “hot spot” with more posterior exudative RPE or sensory retinal detachments staying hypofluorescent (Figure 5). In contrast, FA utilizing fluorescein sodium dye will create hyperfluorescence within multiple regions of retinal and choroidal tissue making the intra-retinal localization of RAP more difficult (Figure 5).<sup>2</sup>

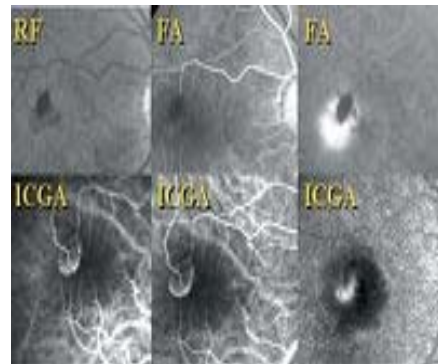


Figure 5

Ocular Coherence Tomography (OCT) has also been found to be useful in evaluating and documenting RAP. OCT can reveal the typical pattern of structural change in RAP demonstrating increased foveal thickness, cystoid macular edema (CME), serous retinal detachment, reflective intraretinal neovascular vessels, as well as RPE elevation and detachment (Figure 6). These findings correlate well with ICG angiography suggesting the utilization of both methods in conjunction will provide a more complete diagnostic picture.<sup>11</sup>

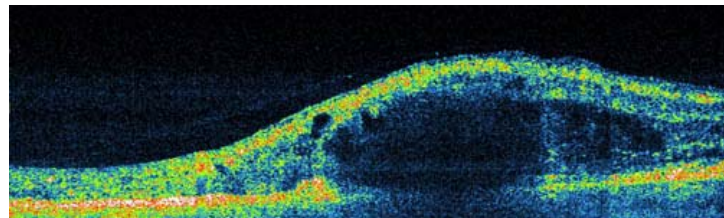


Figure 6

Existing management considerations include periocular sub-tenon Kenalog (Triamcinolone Acetonide) injections, anti-VEGF therapy, conventional focal argon laser photocoagulation, as well as intra-vitreous Kenalog often in conjunction with PDT and

Verteporfin. These modalities have been used separately as primary mono-therapies as well as in combination or succession exhibiting various degrees of success.

In patients with evidence of stage III RAP with CNVM, one recent study demonstrated a sub-tenon injection of Kenalog delayed moderate to severe visual loss after a period of 10 – 11 months.<sup>15</sup>

Two short-term 3-month trials of the intravitreal anti-VEGF drug Avastin (Bevacizumab) have also produced encouraging outcomes. Reduction of leakage, diminished intra and subretinal fluid, along with an increase in visual acuity was apparent in just 4 weeks after only one injection.<sup>6</sup> After 3 months, a significant decrease in macular thickness and improvement or stabilization of visual acuity was demonstrated as well.<sup>16</sup>

Therapy incorporating direct focal laser argon photocoagulation of RAP lesions seems to be a practical and safe method of managing neovascular leakage; however, results are shown to be better for patients with early stage disease. Focal laser treatment alone applied purely to the intraretinal component of the lesion may be adequate to reduce leakage and may impede the angiomatous process resulting in stabilization of the pathology and visual acuity.<sup>8</sup> In cases of considerable macular edema in stage I disease, direct laser photocoagulation combined with prior intravitreal Triamcinolone injection is also considered a viable treatment option producing improved visual acuity.<sup>9</sup> Not surprisingly, a multiple approach strategy of focal laser photocoagulation, PDT with Verteporfin, and intravitreal Kenalog was found to be most efficacious compared to other combined treatments in stage I disease.<sup>7</sup> Of course, long-term stabilization or advancement may require additional laser treatments or adjunctive measures.

A review of literature from 12 – 18 months prior to June 2007 will reveal a majority interest in the simultaneous or successive combined therapy of intra-vitreous Triamcinolone with PDT and Verteporfin for the treatment of RAP. Results have shown real potential with respect to creating a proper therapeutic protocol.

Van de Moere et al have evidence of complete resolution of angiographic leakage achieved in 83% of patients after 12 months who initially presented with stage I – II RAP progression and underwent simultaneous combined treatment. OCT also confirmed this effective reduction or elimination of retinal edema in addition to a regression of neovascularization (Figure 7). Visual acuity was improved in 35% and was stable in 47% of patients. A small percentage of patients developed recurrent leakage after 6 – 12 months but resolved completely after repeat simultaneous combined treatment.<sup>4</sup>

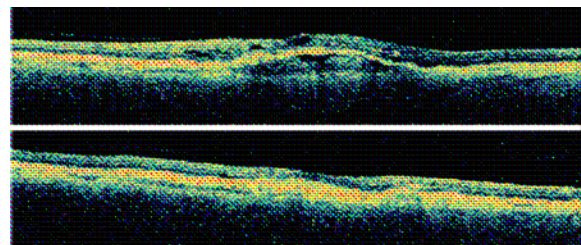


Figure 7

A complete remodeling of intra-retinal vascular structure has also been exhibited in stage II RAP after successive Triamcinolone and PDT with Verteporfin treatment. A feeding

retinal artery found shunting significant blood flow from an original arteriole toward an intraretinal neovascular complex before treatment, regained a normal appearance after treatment. Blood flow was restored through the original retinal arteriole with the feeder RAP vessel eventually no longer visible.<sup>20</sup>

Additionally, Mantel et al examined the use of intravitreal Triamcinolone followed by PDT with Verteporfin in eyes with stage II RAP and found a potential benefit in terms of stabilization or even improvement of vision. After follow-up visits at 3, 6, 9, and 15 months, the greatest improvement in visual acuity was found initially with a slight decline over time; however, there was overall improvement from baseline. Additionally, only 18% of patients lost visual acuity  $\geq 3$  lines with retreatment being required in 45% of eyes.<sup>21</sup>

Of course, the final outcome of therapy may be undermined depending on the RAP stage when treatment is initiated. Smaller stage I lesions will naturally have a greater chance of being successfully treated. Deeper stage II and III involvement containing a more complex vasculopathy and/or associated serous retinal detachment, RPE detachment, or retinal and choroidal anastomoses will certainly be most resistant.

Additional management strategies have been attempted but have proven ineffective. Posterior juxtascleral injection of Anecortave Acetate, a synthetic anti-angiogenic derived from Cortisol, has been found to reduce capillary permeability and thus exudative material in patients with RAP. Interestingly however, a progression of neovascularization and a significant loss of vision has been the outcome in all patients.<sup>17</sup> Finally, surgical ablation combined with PDT has also been attempted but was found inadequate due to a high incidence of reperfusion from retinal inflow vessels.<sup>19</sup>

## **Conclusion**

Retinal Angiomatous Proliferation is indeed a unique variation of neovascular ARMD. Considered a rather newly described entity, the presence of RAP has undoubtedly always been a potential part of the ARMD process. Advancing technology in diagnostic imaging will allow for a better understanding of the pathomorphologic stages, and provides an opportunity to develop greater knowledge in the pathophysiology of angiogenesis. Unfortunately, with current therapeutic modalities available today, progressive ARMD leading to RAP has a poor visual prognosis. As discussed, the complexity of the pathological process potentially creates a multitude of clinical scenarios providing for challenging management decisions. Fortunately, anti-angiogenesis research continues to be widely studied which will unquestionably lead to more definitive and effective therapeutic protocols on the horizon.

## Bibliography

1. Shimada, Hiroyuki; Kawamura, Akiyuki; Mori, Ryuzaburo; Yuzawa, Mitsuko  
Clinicopathological findings of retinal angiomatous proliferation.  
Graefe's Archive for Clinical and Experimental Ophthalmology, Volume  
245, Number 2, February 2007 , pp. 295-300(6)
2. Iranmanesh R, Eandi CM, Peiretti E, Klais CM, Garuti S, Goldberg DE, Slakter  
JS, Yannuzzi LA.  
The nature and frequency of neovascular age-related macular degeneration.  
Eur J Ophthalmol. 2007 Jan-Feb;17(1):75-83.
3. Van de Moere A, Sandhu S, Talks J.  
Retinal Angiomatous Proliferation: Diagnosis and Treatment Options.  
Ophthalmology 2003;110:1517-25. 15.
4. Van de Moere A, Kak R, Sandhu SS, Talks SJ.  
Anatomical and visual outcome of retinal angiomatous proliferation treated with  
photodynamic therapy and intravitreal triamcinolone.  
Am J Ophthalmol. 2007 Apr;143(4):701-4.
5. Pedersen R, Soliman W, Lund-Andersen H, Larsen M.  
Treatment of choroidal neovascularization using intravitreal bevacizumab.  
Acta Ophthalmol Scand. 2007 May 18; [Epub ahead of print]
6. Joeres S, Heussen FM, Treziak T, Bopp S, Jousen AM.  
Bevacizumab (Avastin) treatment in patients with retinal angiomatous  
proliferation.  
Graefes Arch Clin Exp Ophthalmol. 2007 Apr 17; [Epub ahead of print]
7. Olea JL, Sastre M, Aragon JA, Cardona A, Mateos JM.  
Treatment of retinal angiomatous proliferation (RAP). A retrospective study.  
Arch Soc Esp Oftalmol. 2007 Jan;82(1):27-35.
8. Johnson TM, Glaser BM.  
Focal laser ablation of retinal angiomatous proliferation.  
Retina. 2006 Sep;26(7):765-72. Erratum in: Retina. 2007 Feb;27(2):263.
9. Kriegelstein TR, Kampik A, Ulbig M.  
Intravitreal triamcinolone and laser photocoagulation for retinal angiomatous  
proliferation.  
Br J Ophthalmol. 2006 Nov;90(11):1357-60. Epub 2006 Aug 2.

- 10.** Wu L.  
Neovascularization, Choroidal, eMedicine. Retrieved June 25, 2007 (Updated March 11, 2005) from <http://www.emedicine.com/oph/topic534.htm>
- 11.** Polito A, Napolitano MC, Bandello F, Chiodini RG.  
The role of optical coherence tomography (OCT) in the diagnosis and management of retinal angiomatous proliferation (RAP) in patients with age-related macular degeneration.  
Ann Acad Med Singapore. 2006 Jun;35(6):420-4. Review.
- 12.** Kuerzinger GR, Lang GK, Lang GE.  
Retinal angiomatous proliferation in age-related macular degeneration.  
Klin Monatsbl Augenheilkd. 2006 Aug;223(8):691-5. German.
- 13.** Salazar-Diez JL, Iturralde-Errea D, Diaz-de-Durana-Santacoloma E, Fernandez-Ares ML, Vazquez-Cruchaga E, Lopez-Garrido JA.  
Results of treatment of retinal angiomatous proliferation with photodynamic therapy.  
Arch Soc Esp Oftalmol. 2006 Jul;81(7):401-4. Spanish.
- 14.** Cohen SY, Dubois L, Tadayoni R, Delahaye-Mazza C, Debibie C, Quentel G.  
Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularisation.  
Br J Ophthalmol. 2007 Mar;91(3):354-9. Epub 2006 Sep 14.
- 15.** Rutishauser-Arnold Y, Tholen AM.  
Periocular sub-tenon triamcinolone acetonide injections for the treatment of retinal angiomatous proliferation (RAP) and occult choroidal neovascularization.  
Klin Monatsbl Augenheilkd. 2007 Apr;224(4):269-73. German.
- 16.** Meyerle CB, Freund KB, Iturralde D, Spaide RF, Sorenson JA, Slakter JS, Klancnik JM Jr, Fisher YL, Cooney MJ, Yannuzzi LA.  
Intravitreal bevacizumab (Avastin) for retinal angiomatous proliferation.  
Retina. 2007 Apr-May;27(4):451-7.
- 17.** Klais CM, Eandi CM, Ober MD, Sorenson JA, Sadeghi SN, Freund KB, Spaide RF, Slakter JS, Yannuzzi LA.  
Anecortave acetate treatment for retinal angiomatous proliferation: a pilot study.  
Retina. 2006 Sep;26(7):773-9.
- 18.** Gross NE, Aizman A, Brucker A, Klancnik JM Jr, Yannuzzi LA.  
Nature and risk of neovascularization in the fellow eye of patients with unilateral retinal angiomatous proliferation.  
Retina. 2005 Sep;25(6):713-8.

19. Nakata M, Yuzawa M, Kawamura A, Shimada H.  
Combining surgical ablation of retinal inflow and outflow vessels with photodynamic therapy for retinal angiomatous proliferation.  
*Am J Ophthalmol.* 2006 May;141(5):968-70.
20. Bottoni F, Romano M, Massacesi A, Bergamini F.  
Remodeling of the vascular channels in retinal angiomatous proliferations treated with intravitreal triamcinolone acetonide and photodynamic therapy.  
*Graefes Arch Clin Exp Ophthalmol.* 2006 Nov;244(11):1528-33. Epub 2006 Apr 12.
21. Mantel I, Ambresin A, Zografos L.  
Retinal angiomatous proliferation treated with a combination of intravitreal triamcinolone acetonide and photodynamic therapy with verteporfin.  
*Eur J Ophthalmol.* 2006 Sep-Oct;16(5):705-10.

## Figures

1. Martinelli, JR.  
Age Related Macular Degeneration: Retinal Angiomatous Proliferation  
*American Academy of Optometry.* 2007 Jun;Case Report #5
- 2 – 4. Yannuzzi, LA.  
Retinal Angiomatous Proliferation in AMD, Review of Ophthalmology  
Online. Retrieved on June 25, 2007 from  
[http://www.revophth.com/index.asp?page=1\\_372.htm](http://www.revophth.com/index.asp?page=1_372.htm)
5. R. Brancato, et al.  
Optical coherence tomography (OCT) in retinal angiomatous proliferation (RAP), *European Journal of Ophthalmology*  
Online. Retrieved on June 25, 2007 from  
<http://www.eur-j-ophthalmol.com/ejo/index.asp?a=fulltext&id=FF88248D-2242-4354-BAE5-13B9E2E>
6. Copernicus Online.  
Retrieved on June 25, 2007 from  
<http://www.optopol.com/index.php?op=gallery&lang=en>
7. Van de Moere A, Sandhu S, Talks J.  
Retinal Angiomatous Proliferation: Diagnosis and Treatment Options.  
*Ophthalmology* 2003;110:1517-25. 15.