

Multimodal Approach for Management of Retinal Angioma: A Case Series

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Abstract

Purpose: To evaluate outcomes of multi modal approach in management of Retinal Angioma.

Material and Methods: Medical reports of 15 eyes of 12 patients having retinal angioma presented over a period of 12 years were retrospectively analyzed. Age, gender, presenting complaint, general physical examination and neurological examination findings, initial Visual Acuity, eye involved, tumor location, growth pattern, ocular complications were noted. Fundus photographs and FFA, OCT at initial visit as well as those taken during follow-up and final visual acuity were noted. CT/MRI brain and abdominal ultrasound reports were reviewed. Any pedigree association with von-Hippel-Lindau disease was recorded.

Results: Records of 15 eyes of 12 patients with retinal angioma were reviewed including 7 males and 5 females. Mean age of presentation was 27.7 yrs. Initial vision was 6/6 –6/18 in 27%, 6/24 –6/60 in 20%, 5/60 –3/60 in 27%, <2/60 in 26%. Laser was given as initial treatment in 8 eyes in which 4 eyes received intravitreal anti VEGF along with laser. Cryotherapy was done in 2 eyes and VR surgery was done in 5 patients. At final follow-up all patients had stable tumor and resolution of exudates and macular edema and vision was better than 6/18 in 73% 6/18 - 6/60 in 7% and less than 3/60 in 7%.

Conclusion: Early diagnosis and treatment of retinal angiomas with multimodal approach yields good visual outcome. If untreated the tumors may eventually have exudative RD and have a poor visual prognosis even with vitreoretinal surgery.

Keywords: Retinal Angioma; Multi modal approach; VHL disease; Cryotherapy; Laser; VR surgery; Macular edema; Anti VEGF

Introduction

Capillary hemangioma of the retina may occur as an isolated lesion within the retina or as a part of phakomatosis with central nervous system and systemic tumors when it is called von Hippel-Lindau (VHL) syndrome [1].

In a patient with solitary hemangioma, the risk of developing VHL is 45% if the patient is <10 years of age and decreases to 1% if the age at diagnosis is >60 years [2]. Multiple or bilateral angiomas indicate the presence of VHL tumor and screening for central nervous system or systemic disease should be done. Periodic ocular, neurological, and systemic evaluation with MRI of the brain and spine once in 2–3 years (every 3–5 years in patients >51 years), urinary catecholamines and abdominal ultrasound/computerized tomography every year of patients and screening of family members at risk is very important [3].

The ocular lesions are usually diagnosed between 10 and 30 years of age. The early angioma appears as a yellow spot between a dilated tortuous feeding arteriole and a draining venule. The choice of treatment is determined by the size, location, and associated findings of sub retinal fluid, retinal traction, and the visual potential of the eye [4]. It is also been proven that early treatment of retinal capillary angioma leads to better visual results [5]. Early angiomas not at the juxtapapillary areas without RD (Retinal Detachment) are treated with

laser photocoagulation. Lesions <2 mm are treated with a direct photocoagulation. For lesions 3–5 mm, it is preferable to try occlusion of the feeder vessels – the arteriole in the first session and the venule later. The angioma as such can be treated in subsequent sessions. For tumors larger than 5 mm, it is preferable to use triple freeze-thaw cryotherapy. Advanced vitreoretinal form of the disease may need vitrectomy to relieve tractional or rhegmatogenous RD (TRD or RRD) [6]. Most recently systemic and intravitreal administration of inhibitors of vascular endothelial growth factor (VEGF) have demonstrated mixed treatment outcomes suggesting that the general efficacy of anti-angiogenic agents in VHL is uncertain [7].

Vision loss occurs due to exudation at the macular region, or secondary TRD or RRD (due to development of gliotic tissue) involving the macula. Without treatment, most eyes progress to total RD, neovascular glaucoma, and a painful blind eye [3]. Timely diagnosis and aggressive treatment using multimodal approach is necessary to combat this notorious tumor of eye. Hence, the aim of the study is to describe various clinical presentations, and to evaluate the outcomes of multimodal approach in management of retinal angioma.

Material and Methods

Fifteen eyes of 12 patients with retinal angioma were reviewed retrospectively from 7, 51,324 hospital records from 2006 to 2018. Age at presentation, gender, presenting complaint, and general physical and neurological examination findings was reviewed. In all patients visual acuity was noted with Snellen's visual acuity chart. Ocular examination

was done with slitlamp biomicroscopy and indirect ophthalmoscopy. Anterior segment and posterior segment findings were noted. Eye involved, location of tumor, size of tumor, growth pattern, associated ocular complications were noted. OCT and Fluorescein angiography findings were evaluated. Investigations like urinary catecholamine levels, CT/MRI brain to rule out CNS tumors, ultrasound abdomen reports were reviewed.

Depending on the size of tumor and associated complications patients were treated with available modalities. Small size tumors located at posterior pole and not in juxtapapillary area were treated with Argon green LASER (514 nm). Large, peripheral tumors and tumors not amenable to LASER were treated with cryopexy (triple

freez-thaw technique). Tumors associated with macular edema received intravitreal Avastin monthly injections until regression of macular edema. Tumors with TRD or RRD and non-resolving vitreous hemorrhage underwent PPV along with Endo LASER (EL), membrane peeling (MP) and intraocular tamponade. In patients with exudative RD (ERD) if the tumor is seen or in peripheral location cryotherapy was done, if tumor is not amenable for treatment by cryotherapy or laser, PPV, EL, MP, FAX, Tamponade was done. Belt buckle is given if there is combined RRD and ERD. Treatment outcomes, visual acuity, any complications associated with treatment at different follow-ups were noted. Findings of family members of patients were noted to rule out VHL disease.

Serial number	Age	Laterality	Gender	Initial VA	Location of tumor	Type of presentation	Mode of treatment	Final VA
1 (Figure 1)	19	U/L	M	5/60	Superotemporal	<5 mm with macular edema	Laser 4 sittings+Anti VEGF	6/6
2	18	U/L	F	6/6	Inferotemporal	<5 mm, peripheral and with clear media	3 sittings of Laser	6/6
3	24	B/L	M	6/36	temporal	>5 mm+macular edema+VH	Cryo+Anti VEGF	6/9
4	24	B/L	M	1/60	Superotemporal	>5 mm+VH	PPV+EL+MP+Tamponade followed by Anti VEGF	6/9
5	11	B/L	F	6/6	Superotemporal	<5 mm	2 sittings of Laser	6/6
6 (Figure 2)	11	B/L	F	HM	Superotemporal	VH	PPV+EL+MP+ Tamponade	6/12
7	50	U/L	M	1/60	Inferotemporal	>5 mm + TRD	PPV+ EL+ MP+ Tamponade followed by 2 sitting Laser + Anti VEGF	6/12
8	30	B/L	M	HM	Superotemporal	>5 mm + ERD+ TRD	PPV+ EL+ MP+ Tamponade	1/60
9	30	B/L	M	4/60	Inferotemporal	<5 mm + Macular edema	Anti VEGF+ 1 sitting of Laser	6/9
10	36	U/L	F	6/6	Temporal	<5 mm	2 sittings of Laser	6/6
11	25	U/L	M	6/36	Inferotemporal	<5 mm with macular edema	Laser followed by cryo and Anti VEGF	Lost to follow-up
12 (Figure 3)	30	U/L	F	6/9	Superotemporal	>5 mm + macular edema	Cryotherapy followed by Anti VEGF	6/6
13	22	U/L	M	5/60	Inferotemporal	<5 mm with macular edema, later developed TRD	Anti VEGF+ Laser Followed by PPV+ EL+ MP+ Tamponade	6/60
14	27	U/L	F	3/60	Temporal	>5 mm+ TRD	PPV+ EL+ MP+ Tamponade	lost to follow-up
15	40	U/L	M	6/24	Superotemporal	<5 mm with macular edema	Anti VEGF+ 1 sitting of Laser	6/6

Note: VH- Vitreous Hemorrhage; TRD- Tractional Retinal Detachment; ERD- Exudative Retinal Detachment; Cryo- Cryotherapy; PPV- Pars Plana Vitrectomy; EL- Endo Laser; MP- Membrane Peeling

Table 1: Clinical features and intervention in patients with retinal hemangioma.

Results

Fifteen eyes (12 patients) out of 7,51,324 clinical records had retinal angioma. Of these 7 were males and 5 were females; with 3 eyes having bilateral disease. In bilateral disease group 2 were males and one was female. Mean age of presentation was 27.7 years. Mean follow-up time was 1.6 years. All these information along with specific modalities for management of each case is compiled in Table 1. Each modality of management along with outcome and visual acuity according to different presentations are described in the following paragraphs (Figures 1-3).

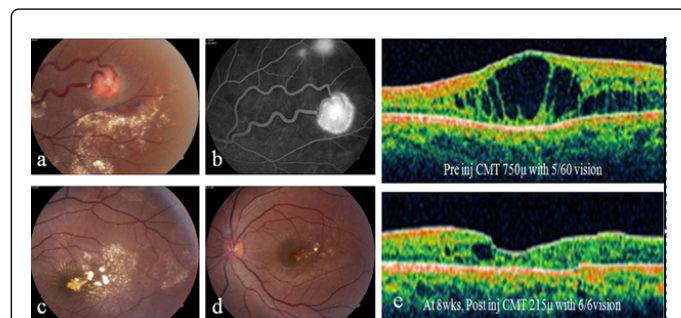


Figure 1: (a) Clinical picture (b) fluorescein angiographic finding of superotemporal retinal angioma (c) Fundus picture showing resolution of macular edema after treatment with laser (e) OCT pre and post injection of anti VEGF showing resolution of macular edema.

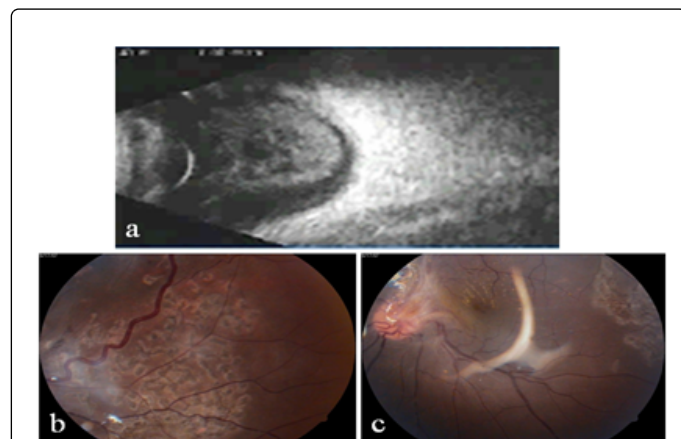


Figure 2: (a) B scan ultrasonography of 11 yr male with vitreous hemorrhage and retinal angioma (b) (c) Post VR surgery fundus photographs.

Visual acuity at presentation ranged from hand movement (HM) to 6/6 by Snellen's visual acuity chart. Presenting vision was 6/6 to 6/18 in 4 eyes (27%), 6/24 - 6/60 in 3 eyes (20%), 5/60 - 3/60 in 4 eyes (27%), two eyes (13%) had visual acuity between 2/60 - 1/60 and <1/60 each. The growth pattern of tumor was endophytic in all cases. Tumor was located in superotemporal retina in 7 (47%) cases, inferotemporal retina in 5 (33%) cases and in temporal retina in 3 (20%) cases.

Laser photocoagulation was given as initial treatment in 8 patients with mean sitting of 1.8 times. Out of these 3 patients had received only laser and all these patients had final visual acuity 6/6 and tumor

size was reduced. Four patients (50%) had associated macular edema and started on intravitreal anti-VEGF along with laser. Out of these 3 patients had VA better than 6/12 and in one patient VR surgery was done due to development of complication (TRD) and that patient had stable vision of 6/60 at last follow-up. Cryotherapy was needed in one patient following laser treatment due to non-resolution of tumor, and anti VEGF was given due to associated macular edema.

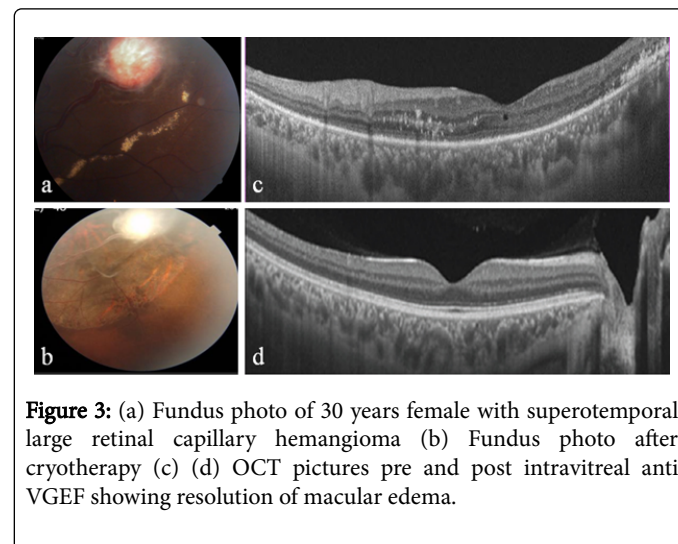


Figure 3: (a) Fundus photo of 30 years female with superotemporal large retinal capillary hemangioma (b) Fundus photo after cryotherapy (c) (d) OCT pictures pre and post intravitreal anti VEGF showing resolution of macular edema.

Cryotherapy was done as initial treatment in 2 patients, the first one had larger tumor located peripherally along with VH and macular edema who improved to 6/9 from 6/36 at 2 wks and maintained the same till final follow-up at 6 months along with good regression of tumor as well as VH who received anti VEGF to take care of macular edema. The second patient had a large tumor located in mid periphery along with extrafoveal exudation and responded well to cryotherapy alone. As patient developed macular edema 2 wks following cryotherapy anti VEGF was added to treatment following which vision improved to 6/6 with reduction in size of tumor.

Five patients presented with complications associated with tumor like non resolving VH (2 patients), TRD (2 patients), Combined TRD and ERD (1 patient). These patients underwent VR surgery. Following surgery 1 patient had improvement in vision to 6/9. Two patients received anti VEGF due to persistent macular edema following VR surgery in which 1 patient lost to follow-up and other had final VA of 6/12. Fifth patient with combined RD was able to maintain vision of 1/60 till final follow-up.

With multimodal approach for treatment of retinal angioma, 73% patients had final visual outcome better than 6/18 and 7% (1 eye) had visual acuity less than 3/60 and 100% achieved stable tumor size at final follow-up.

In all the cases no systemic lesion identified. Urinary catecholamine levels, CT/MRI brain and ultrasound abdomen reports were normal in all patients including patients with bilateral presentation. No patients met the diagnostic criteria for VHL disease.

Discussion

The prevalence of VHL disease was estimated to be about 19 per million, [8] and the prevalence of solitary retinal capillary hemangioma is reported to be 9 per million [9]. The probability of VHL disease in patients with solitary retinal capillary hemangioma

was estimated to be 45% [2]. In our study we had 12 patients with in time span of 12 years. The mean age of diagnosis was about 17 to 27 (range, 1-67) years for retinal capillary hemangioma patients with VHL disease. The mean age of diagnosis was about 30 to 40 (range, 3-74) years for retinal capillary hemangioma patients without VHL disease [10-12]. In our study, none of the patients with retinal capillary hemangioma met the diagnostic criteria of VHL disease by systemic survey and pedigree investigation. The average age of diagnosis in our study was 27.7 years. In a study by Kuo et al. [13] of 13 eyes the mean age was 37.4 yrs.

Clinical features of retinal capillary hemangioma are a red vascular mass with a dilated feeder artery and drainage vein. They are usually located at the retinal periphery, but also occur on the posterior pole [9,14,15]. In our study, clinical picture was similar and hemangioma of all the eyes was located at far or near periphery of retina without any juxtapapillary lesion. Retinal capillary hemangiomas can grow with an endophytic or an exophytic pattern. The endophytic type is more common than the exophytic type. Exophytic growth is more difficult to detect. This may be one of the reasons why there are few cases, and all patients in our study had an endophytic growth pattern. Our study results are comparable to study done by Kuo et al. [13] who reported all endophytic tumors with most common location being superotemporal retina.

The goal of treatment of RCH is preserve vision, without destruction of the retina around the tumor. Treatment depends on location and size of hemangioma and the clinical manifestations. Treatment options include observation, laser photocoagulation, cryotherapy, PDT; Anti VEGF's and pars plana vitrectomy [16].

In a study by Krivosic Valerie et al. [17] on laser photocoagulation in peripheral hemangioma in VHL disease, photocoagulation alone has inactivated 100% of tumors upto 1 DD in size and 73% tumors of larger size in which additional cryotherapy was done, and increased inactivation of tumor to 94%. In our study following multiple sittings of photocoagulation out of 3 patients with good visual acuity without macular edema and exudates and tumor size < 5 mm 3 patients (100%) attained good visual acuity and tumor reduction without any complications. In 4 patients with associated macular edema, laser along with intravitreal anti VEGF has improved VA to 6/60 or better in 100% of patients and 6/12 or better in 75% patients at last follow-up with reduction in tumor size in 100% of cases at last follow-up.

Wong WT et al. [18] in a study on intravitreal Ranibizumab monotherapy for retinal hemangioma found that ranibizumab had minimal beneficial effect on most VHL related RCHs; possible treatment efficacy was noted in small lesions with less exudation. Saitta A et al. [19] found promising results with the combined therapy (PDT plus anti VEGF) (VR surgery plus PDT plus antiVEGF). In our study we had given combination therapy with laser photocoagulation or cryotherapy with anti VEGF as initial treatment in 5 eyes, out of which 4 eyes had final VA of better than 6/18 or better, one eye developed tractional RD in further followup and underwent PPV and attained visual acuity of 6/60 at last follow-up. All these patients achieved a stable tumor size with reduction of macular exudates at final follow-up.

Although cryotherapy and laser photocoagulation can effectively induce tumor regression and occasional release of vitreomacular traction, this therapy can occasionally cause worsening vision [20]. Complications of the cryotherapy such as posterior subcapsular cataract and exudative detachment of the retina progression after treatment are also reported [21] Anti-VEGF therapy has been reported

to reduce vascular permeability by altering the balance of vasoactive cytokines like nitric oxide and endothelin-1 or by directly altering endothelial tight junction proteins [22]. It is postulated that excessive accumulation of hypoxia-induced factor in the neoplastic stromal cells of RCH leads to the production of other angiogenic factors that are able to maintain and promote the growth of primary hemangiomas [23]. In our study Anti VEGF along with laser photocoagulation or cryotherapy reduced macular edema.

Tumors associated with non-resolving vitreous hemorrhage and tractional RD had shown good results with PPV along with laser photocoagulation. Out of 5 eyes treated with PPV, membrane peeling, endo laser and intraocular tamponade, anti VEGF was needed in 2 eyes due non resolution of macular edema. We found that VR surgery alone had good outcomes in 1 patient (25%). VR surgery along with anti VEGF had good outcomes in 3 patients (75%) in which one patient was lost for follow-up. In our study patient with combined TRD and ERD had poor gain in vision but tumor size was reduced.

Visual prognosis in patients with retinal capillary hemangioma is dependent upon the number of tumors, size, location and degree of exudative or tractional retinal detachment. In general, prognosis is guarded, even in cases that have been adequately treated. More than 25% of eyes develop permanent visual loss and 20% have a visual acuity worse than 20/100 in at least one eye. Hence, early diagnosis with multimodal approach to these notorious tumors is essential to arrest tumor progression and complications and to attain good final visual acuity.

Conclusion

Management of retinal angioma is tricky. Timely management of tumor long term follow-up to detect any recurrence, complications is necessary. Many times these notorious tumors do not respond to a single treatment. Hence multiple treatment options should be given to these tumors simultaneously to obtain good final visual outcome and multimodal approach is the key to the success of these cases.

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