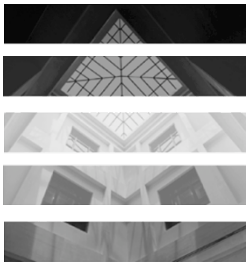
Jules Stein Eye Institute



Advances in treatments for hemangiomas of the retina

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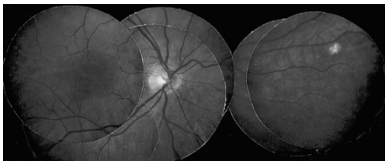
What is a retinal angioma or hemangioma or hemangioblastoma?

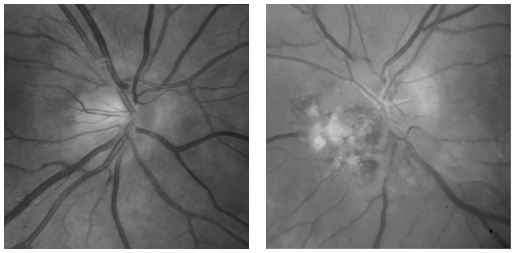
- All of these terms refer to the same lesion
- There is a local proliferation of a vascular growth or tumor either in the retina or under the retina
- Larger lesions tend to have feeder veins and arteries that are dilated from the increased blood flow
- Small lesions appear reddish and are flat
- Over time, angiomas are associated with proliferation of cells on the surface of the retina.

- Age of onset: as early as 3-4 years old reported
- 70% of VHL patients will have retinal HBs
- 20% of lesions are less than 200 microns in diameter
- 20% of lesions are anterior to equator
- 14% of our patients with VHL had only retinal angiomas as their clinical finding



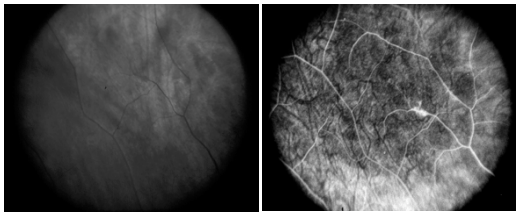
Peripapillary hemangioblastomas

- Often have an atypical appearance
- May appear as a "segmental" blush to the disc
- Almost always leak on fluorescein angiogram



Small hemangioblastomas:

- Often do not have feeder vessels
- Initially appear as flat, telangectatic lesions
- Can be mistaken for a hemorrhage or "large" microaneurysm
- Usually leak on fluorescein angiogram, but not always



Biology of Retinal Angiomas

- The VHLprotein is expressed in all cells and acts to degrade certain proteins, hypoxia inducible factors (HIFs), that control the expression of other genes
- HIFs are made by cells when they are exposed to low oxygen levels and serve to increase the production of proteins that can help reverse low oxygen, such as erythropoietin, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).

Biology of Retinal Angiomas

- Loss of VHL function by mutation of the VHL gene results in increased levels of HIF, and these proteins then activate the production of these other genes that would normally be seen only with low oxygen levels.
- The abnormally elevated and continuous levels of proteins such as VEGF and PDGF stimulate blood vessel growth, and cell division, either contributing to tumor formation and/or growth.

TREATMENT OF RETINAL HBs

What are the indications for treatment?

- Any lesion that is jeopardizing the retina due to hemorrhage or exudation
- Any lesion that could in the future jeopardize the retina that is readily treatable

Is a lesion ever too small to treat?

- The smallest lesions are the easiest and most successful to treat.
- Very small lesions rarely have exudation or bleeding associated with direct treatment
- Easier to treat before there is blood or exudation from the lesion

TREATMENT OF RETINAL HBs

When can one observe a lesion without treatment?

- Convenience for the patient and physician for a limited time.
- Lesions can double in size within 6 months

If one is going to observe an HB, what should be the criteria to stop watching and start treating?

- If the goal is to minimize retinal damage, why wait until the lesion leaks or bleeds?
- There are no good criteria for deciding if a lesion can be watched - unless the patient and/or physician feel that the potential complications of treatment are comparable to the potential effects of the lesion

TREATMENT OF RETINAL HBs

When do you not treat a retinal hemangioblastoma?

- Peripapillary hemangioblastomas have a different natural history than lesions in the retinal vasculature.
- They tend to be indolent and if there is no significant exudation or hemorrhage in the macula, they can be observed indefinitely.
- Exudation and hemorrhage are frequent side effects of treatment, thus macular damage is a consideration.
- Previous laser treatment trials of peripapillary hemangioblastomas indicated that laser was less successful than observation alone.

TREATMENT OF RETINAL HBs

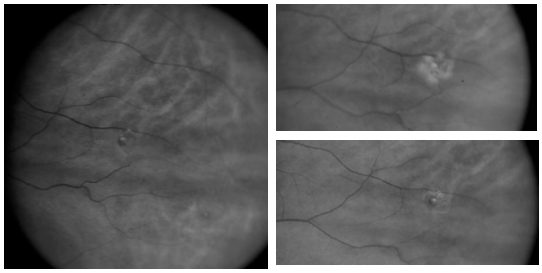
When do you not treat a retinal hemangioblastoma?

Concerns regarding exudative retinal detachments (RD) from the treatment of a hemangioblastoma are valid. However a lesion capable of causing an exudative RD during treatment is one which can spontaneously cause an RD on its own. Successful closure is easier if one starts prior to a spontaneous hemorrhage and/or RD. Treatment is generally advised.

TREATMENT OF RETINAL HBs

Small lesions: **Traditional argon laser**

Safe and effective for lesions <500 microns



TREATMENT OF RETINAL HBs

Large lesions: **Cryotherapy**

- Significant damage to surrounding tissue
- Works poorly if there is an exudative RD
- Can be painful and precipitate choroidals and exudative RDs
- Generally a single session

Radiation

- Used effectively in a number of cases
- Different methods are available
- Key issue is selective targeting and shielding eye structures to limit collateral damage
- Requires careful calculation and titration of dose

TREATMENT OF RETINAL HBs

Large lesions: **Traditional argon laser**

- Relatively ineffective, poor uptake into lesions

Photodynamic therapy

- Excellent potential, but no clinical experience
- Very expensive dyes and specialized lasers
- Patients must avoid sunlight for several days after treatment.
- Multiple sessions are likely (based on experience with other retinal vascular lesions)
- Because dyes are activated by infared lasers, tissue penetration is excellent compared to FPAL which relies on visible wavelengths.

TREATMENT OF RETINAL HBs

Large lesions: **Anti-angiogenic therapy**

- Easy to perform
- Can be done repeatedly
- Several potential agents have been tried, primary one is Avastin or Lucentis
- Works well on lesions with exudative detachment and may have a direct effect to reduce edema (retinal swelling)
- Efficacy is unaffected if there is substantial blood in the vitreous or media opacities
- No photosensitization of the patient

TREATMENT OF RETINAL HBs

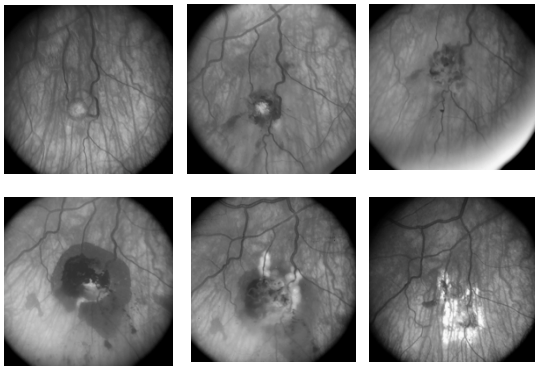
Large lesions: **Anti-angiogenic therapy**

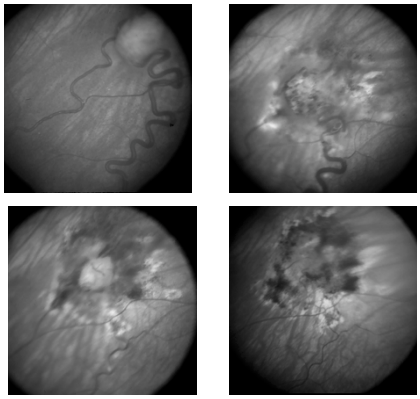
- Current small trials and case reports have been relatively discouraging.
- Some reduction of tumor size and/or leakage have been reported but not consistently. Total elimination of retinal angiomas has not been observed.
- A prospective, pilot study of systemic sunitinib, targeting multiple receptor tyrosine kinase receptors, including PDGF receptor and VEGF receptor is underway at the National Eye Institute and MD Anderson Cancer Center.

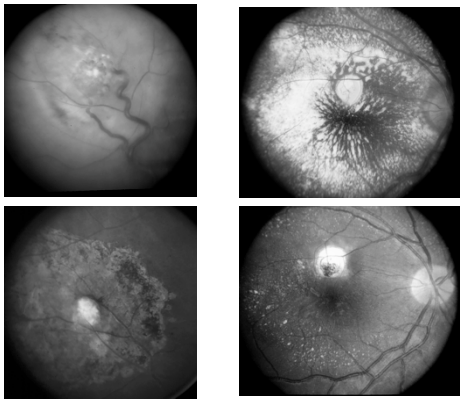
TREATMENT OF RETINAL HBs

Large lesions: **Fluorescein-potentiated argon laser (FPAL)**

- Easy to perform
- Can titrate the amount of treatment and distribute over multiple sessions.
- Uses a safe, inexpensive, readily available dye
- Primarily enhanced thermal effect by using the dye to absorb the blue/green laser light
- Works well on lesions with exudative detachment
- Limited efficacy if there is substantial blood in the vitreous or media opacities
- No photosensitization of the patient







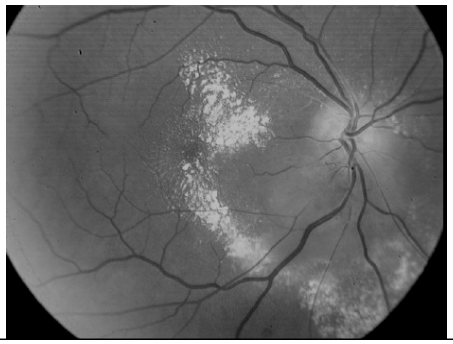
Managing Peripapillary Lesions With FPAL

Patient #1

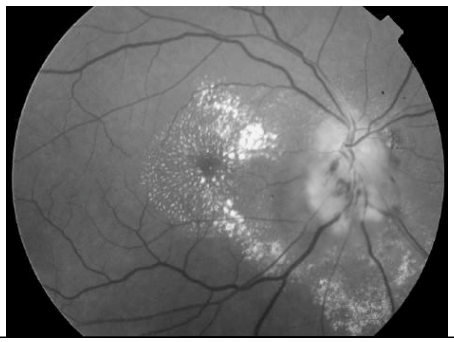
- **60 yo WM**
  - **Peripapillary hemangioma, OD**
  - **Initial visual acuity 20/100-**
  - **Normal vision and exam - OS**
  - **Workup for VHL (CNS and systemic) - negative**

April 4, 2000

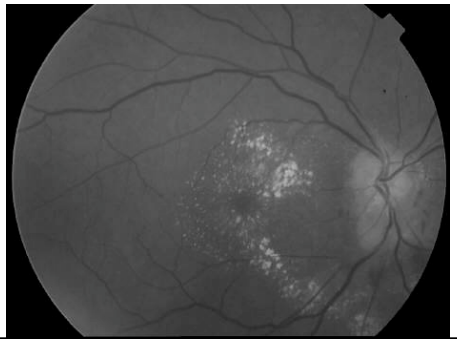
June 8, 2000



July 20, 2000



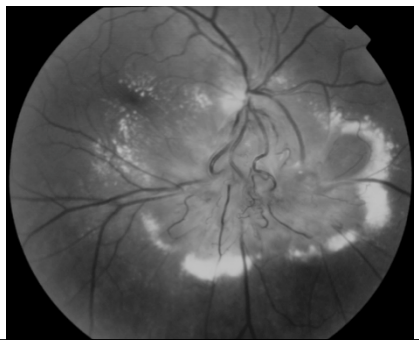
August 31, 2000



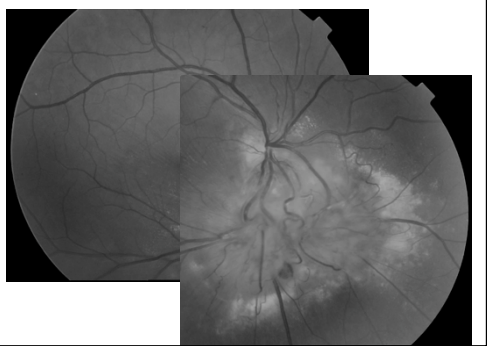
Patient #2

- 25 yo WF
  - Peripapillary hemangioma OD
  - Visual acuity 20/25 with difficulty
  - No lesions - OS
  - Documented VHL lesions in brain and spine
  - Treated with 5 sessions of FPAL from 5-17-01 through 9-13-01 Vision remained at 20/20-2.
  - Visual acuity decreased to CF at 10 ft on 11-18-01. Recovered spontaneously to 20/40 by 1-10-02.
  - Pt lost to follow up.

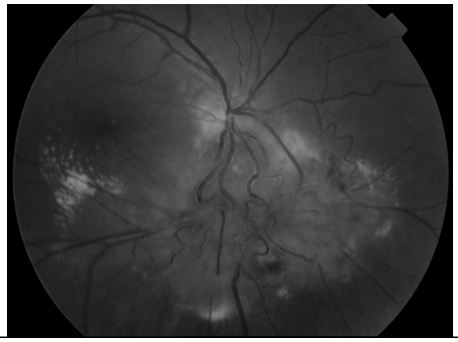
April 4, 2001

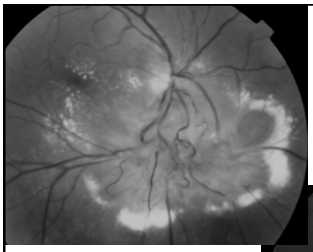


October 4, 2001



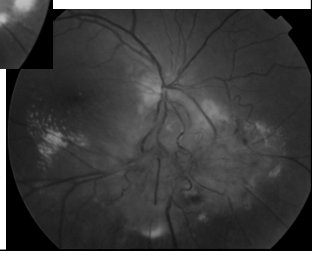
May 30, 2002





Before treatment

After treatment



- Surgical Intervention
  - Lesion closure or removal
  - Treatment of retinal detachment
    - Vitrectomy,
    - Scleral Buckle
    - Silicone Oil

Ongoing Challenges

- Better recognition and treatment of lesions when they are small
- Treatments that limit the leakage of fluid and/or blood from the tumors that can damage the retina
- Therapies that will destroy the lesions to a point at which they pose no recurrent threat and yet preserve retinal function and integrity
- Maintain good surveillance to manage recurrences or new new lesions.