Proliferative Sickle Cell Retinopathy

Primary author: Laura Ashley Lossing, OD
Secondary Author: Andrea Murphy, OD

Abstract

Sickle cell disease is a commonly encountered genetic disorder worldwide and in the United States [1]. Characterized by abnormal erythrocyte function, sickle cell is a multi-organ disorder with variable systemic and ocular symptoms [3]. Sickle cell retinopathy results from peripheral retinal microvasculature occlusion [4].

Case History

- **Patient demographics:**
  - 32 year old black male
  - Chief complaint:
    - No visual complaints reported to clinic for annual eye exam

- **Ocular/medical history:**
  - Accommodative insufficiency
  - Low risk glaucoma suspect
  - Sickle cell anemia diagnosed in 2007 (HbSS)

- **Medications**
  - Amlodipine besylate
  - Hydrochlorothiazide
  - Recorded allergies to lisinopril and losartan

- **Family History**
  - Brother with sickle cell trait (HbSA)

Pertinent Findings

Clinical:

Exam #1 May 18, 2009 White River Junction, VA Eye clinic

- Symptoms: No ocular symptoms
- VA: 20/20 OD and OS
- Refraction
  - OD Pl -0.50 x 090
  - OS Pl -0.50 x 090
- Pupils: Equal, round, reactive to light - APD
- EOM's: no pain or diplopia
- Confrontation fields: Full to finger counting OD and OS
- Cover Test: 2pd XP at distance/4pd XP near

- Slit Lamp Examination:
  - Lids/Lashes: Clear OU
  - Sclera/Conjunctiva: White and quiet OU
  - Cornea: Clear and intact OU
  - Iris: Flat and brown OU
  - Anterior Chamber: Deep and quiet OU; Angles 4/4 by Van Herrick

- IOP @ 10:20am Goldmann tonometry
  - OD: 13mmHg
  - OS: 14mmHg
- Dilation: 1gt Tropicamide 1% and 1gt Phenylephrine 2.5% OU

- Dilated fundus exam
  - Lens: Clear OU
  - Vitreous
    - Clear OD
    - Resolving vitreal hemorrhage peripherally OS
  - Optic Nerve
    - OD: C/D 0.65V/0.70H, healthy rim tissue, large disk
    - OS: C/D 0.65 round, healthy rim tissue, large disk
  - Macula: flat with clear foveal reflex and no macular edema OU
  - Vessels: healthy OU with arterial-venous ratio of 2/3 OU
  - Periphery
    - OD: Black sunbursts (chorioretinal scars) were present at 11, 12, 2, and 6 o’clock.
    - Seafan neovascularization superior temporal with vitreoretinal traction and a tractional retinal detachment temporally
    - OS: Black sunbursts at 11, 12 and 5 o’clock
    - Seafan neovascularization at 2 o’clock (2DD in size) with vitreoretinal traction, an adjacent resolving vitreous hemorrhage and bridging tractional retinal detachment

**Differential diagnosis**
- Primary: Sickle cell retinopathy
- Other differential diagnosis
  - Sarcoïdosis
  - Diabetic retinopathy
  - Talc retinopathy
  - Eales disease

**Follow – Up # 1 May 19, 2009 Jamacia Plain VA retina clinic**
- Dilated fundus exam was again performed and results were stable from the previous day at WRJ.
- Diagnosis remained proliferative sickle cell retinopathy and fundus photos were taken.
- He was scheduled to return in two days for focal laser treatment.

**Follow – Up # 2 May 21, 2009 Jamacia Plain VA retina clinic**
- Focal laser treatment
- OD 199 focal laser spots anterior to the area of peripheral retinal neovascularization and covering the entire area of retinal ischemia
- OS 196 focal laser treatment spots were applied anterior to the areas of neovascularization OS.
- The patient was scheduled to return the following day for a fluorescein angiography.

**Follow – Up # 3 May 22, 2009 Jamacia Plain VA retina clinic**
- Fluorescein angiography
  - Results were consistent with the diagnosis of proliferative sickle cell retinopathy
  - Fibrovascular tissue was visible on the color photos taken at both JVPA and WRJ
  - Transit phase showed arteriovenous anastomoses and multiple fronds of new vessel growth from the edge of the retinal circulation pointing towards the avascular retina.
  - Late phase of the angiogram showed extensive leakage of dye from these new vessels.
  - He was scheduled to follow up with the Richmond, Virginia VA in one month to monitor for regression of the neovascular vessels.
Follow – Up #4 September 8, 2009 Richmond, Virginia VA
- Dilated fundus exam
- Flat retina in all four quadrants OD, OS
- Partial panretinal photocoagulation (PRP) OD, OS
- Scattered black sunburst lesions OU with apparent resolution of the previously treated neovascularization
- The patient was diagnosed with proliferative sickle cell retinopathy, s/p laser treatment OU and was scheduled to return to the next available retina clinic.

Exam #2 December 10, 2010 White River Junction, VA
- Anterior segment findings the same as Exam #1
- IOP @ 8:15am Goldmann tonometry
  - OD: 10mmHg
  - OS: 11mmHg
- Dilation: 1gtt Tropicamide 1% and 1gtt Phenylephrine 2.5% OU
- Dilated fundus exam
  - Lens: Clear OU
  - Vitreous: Clear OU
  - Optic Nerve
    - OD: C/D 0.65V/0.70H, healthy rim tissue, large disk
    - OS: C/D 0.65 round, healthy rim tissue, large disk
  - Macula
    - Flat with clear foveal reflex and no macular edema OU
    - Diffuse epiretinal membrane was observed in the superior arcade without any associated traction
  - Vessels: Healthy OU with arterial-venous ratio of 2/3 OU
  - Periphery
    - OD
      - Vitreo-retinal scarring around an inactive area of neovascularization superiotemporally
      - Black sunbursts were noted at 9, 11, 12, 2 and 7 o’clock
      - PRP scars from 8 to 11 o’clock
    - OS
      - Vitreo-proliferative tissue with elevation and apparent traction at 3 o’clock

Diagnosis
- Proliferative retinopathy from sickle cell anemia with possible areas of new neovascularization OU and vitreo-retinal traction, possibly at risk for retinal detachment OS.
- A retina consult was scheduled with JPVA within one week.

Follow Up #1 February 3, 2011 Jamacia Plain VA retina clinic
- Dilated fundus exam
- Findings similar results as recorded at the December 10, 2010
- Specific note was made that although there was a new area of neovascular vessels nasally OD and a questionable area of neovascularization OS, there was no proliferation into the vitreous or intraretinal exudation.
- A discussion of the risks and benefits of treatment versus careful monitoring was conducted. Due to the fact that there was no new vitreal proliferation, the decision was made to monitor these findings for now
- Follow up was directed for 6 months back at the WRJ VA eye clinic.

Diagnosis and discussion
- Sickle cell disease is an inherited autosomal recessive red blood cell disorder, characterized by abnormal erythrocyte function.
- RBC abnormality is the result of a single base pair substitution in the gene responsible for coding the hemoglobin molecule. [1, 2]
- A single point mutation on chromosome eleven makes erythrocytes capable of undergoing a conformational sickle change in shape under deoxygenated conditions. [1, 2]

- Worldwide 250,000 children are born each year with sickle cell disease [2]
  - 60,000 of these children are located in the United States and 10,000 in the United Kingdom.
  - Sickle cell is most prevalent in countries where malaria is endemic, in some areas of Africa as much as 45% of the population has been identified as carriers of the sickle cell trait.
  - 8.5% of black Americans carry the sickle cell trait, 2.5% of black Americans have the heterozygous sickle cell disease (AC) genotype and 0.15% of black Americans have the homozygous (SS) sickle cell anemia genotype.

- There are five hemoglobin variations that play a role in sickle cell disease. [2]
  - HbA normal adult hemoglobin
  - HbF normal fetal hemoglobin
  - HbS results when valine is substituted for glutamic acid
  - HbC has lysine substituted glutamic acid
  - Hb Thalassemia has an abnormal Hb chain synthesis.

- The various inherited sickle cell genotypes and the expected symptom severity are outlined in the following chart.

<table>
<thead>
<tr>
<th>Inherited genotypes</th>
<th>Disease terminology</th>
<th>Ocular disease course</th>
<th>Systemic disease course</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS + HbS</td>
<td>Sickle cell anemia</td>
<td>Variable/ More severe with increasing age</td>
<td>Severe systemic disease</td>
</tr>
<tr>
<td>HbS + HbC</td>
<td>Sickle cell C disease</td>
<td>Severe retinopathy</td>
<td>Moderate systemic disease</td>
</tr>
<tr>
<td>HbA + HbS</td>
<td>Sickle cell trait (carriers)</td>
<td>None</td>
<td>None / Immune to malaria</td>
</tr>
</tbody>
</table>

- The pathophysiology of sickle cell retinopathy involves abnormalities in erythrocytes and the blood vessel endothelium. [11]
  - Erythrocyte abnormalities
    - Defective potassium chloride co-transport channels leading to cellular dehydration, decrease cell volume and increased concentration of Hbs. [11]
    - Increased lamin protein expression causing the RBCs to be more adherent to blood vessel endotheliums. [4]
  - Blood vessel abnormalities
    - Increased endothelial expression of adhesion molecules. [6]

- Systemic manifestations of sickle cell disease [2]
  - Renal failure, stroke and organ damage due to vaso-occlusion of macrovasculature. [2]
  - Skin ulcers, increased number of infection, gallstones and abnormal growth and development have also been documented. [2]
  - Sickle cell crisis is defined as extreme claudication (hypoxic pain) in the back chest and extremities resulting from microvasculature vaso-occlusion. [2]

- The ocular manifestations of sickle cell disease are separated into two categories: non-proliferative and proliferative retinopathy. [3]

- Classic non-proliferative signs include
  - Salmon patches, intraretinal hemorrhages of deoxygenated blood
  - Black sunbursts, areas of RPE hyperplasia in response to blood being trapped between the RPE and neurosensory retina
  - Tortuous retinal vasculature due to sluggish blood flow. [3,7]
- Proliferative sickle cell retinopathy
  - Sea-fan neovascular vessels
  - The major vision threatening complication of sickle cell eye disease
  - Results from altered retinal circulation due to sickled hemoglobin, coupled with hypoxia in the peripheral retina. [3]
  - Proliferative retinopathy has been reported as high at 70% in sickle cell C disease (HbSC) and is increasing in frequency in sickle cell anemia patients as life expectancies increase with new drug therapies. [4]
  - Many patients are asymptomatic and can maintain 20/20 visual acuity because ocular changes are typically located peripherally. [8]
  - Early detection and treatment are essential to avoid the potential need for scleral buckle or vitrectomy procedures, which have increased risk of complication in patients with sickle cell. [8]

Treatment

Previous treatment protocols for proliferative retinopathy relied on feeder vessel photocoagulation. [12] Panretinal photocoagulation (PRP) has gained favor in recent years due to similar effectiveness and lower risk of choroidal neovascularization and retinal detachment. [8] Early trials with Avastin and Lucentis have shown promising results, but there are not currently any large clinical-based studies examining this treatment option.

The decision to treat or monitor retinal neovascularization associated with sickle cell retinopathy remains a point of controversy. Lesions are generally peripheral and most patients retain good visual acuity, even in the presence of seafan neovascularization, in the absence of vitreal hemorrhage or retinal detachment. [8] Autoinfarction of the neovascular areas has been observed in anywhere from 32 -60% of eyes. [8] [12] However, early PRP treatment can be beneficial by preventing the need for vitrectomy and scleral buckle- both procedures which have increased risks of erythrocyte-induced glaucoma and anterior segment ischemia in sickle cell patients. [12]

Conclusion

This case demonstrates the role of clinical observation, retinal photography and angiographic studies in the management of proliferative sickle cell retinopathy. It demonstrates the role of both interventional and observational treatment protocols. It is important for clinicians to educate sickle cell patients in depth on the changes that are taking place in their retina and why there is the potential for vision loss. Many patients will maintain normal vision until a vitreal hemorrhage or retinal detachment occurs, if proliferative changes occur peripherally. Careful monitoring and annual dilated exams for all sickle cell patients is essential for early detection of potentially visually-devastating retinal changes.

Images

Image 2: Fluorescein angiography images
Bibliography