This is Your Membrane on Drugs

History
A 91 year-old male with a history of glaucoma, bilateral trabeculectomies and bilateral cataract surgeries presented with a complaint of left eye foreign body sensation, irritation and blurriness for the last two months. He was previously managed elsewhere, taking preservative free tafluprost 0.0015% QHS OU, timolol maleate 0.5% BID OU, and serum drops TID OS; but prior to arrival had used multiple glaucoma medications for many years. He reported that the outside specialist had attempted two amniotic membrane grafts in addition to the above, but still continues to have symptoms. When the patient presented to the UC Irvine ophthalmology clinic, he noted that he was having worsening symptoms.

Examination
His visual acuity was 20/400 and count fingers of the right and left eye respectively. Initial slit lamp examination revealed a filtering bleb under the conjunctiva and 1+ punctate epithelial erosions on the surface of the right eye cornea. Exam of the left eye conjunctiva showed two prior trabeculectomies in the superior quadrants and its corneal epithelium was loose and adopted a whorled pattern. There was evidence of a recently healed epithelial defect and fine neovascularization in the periphery of the left eye cornea as well. There were no notable infiltrates or corneal thinning OU.

Diagnosis
Given his extensive history of using multiple preservative-containing antihypertensive medications over many years and corneal epithelial pattern, the patient was diagnosed with limbal stem cell deficiency in the left eye.

Treatment
Our patient was recommended to undergo a 270 degree keratolimbal stem cell transplantation (KLAL) and had significant improvement just one week after surgery.

Discussion
Limbal stem cell deficiency (LSCD) is a disorder that develops after the disruption of stem cell function within the corneal limbus secondary to a multitude of inflammatory, infectious, genetic, mechanical, or chemical disorders. Common etiologies include alkali or acid injury, thermal injury, Stevens Johnson Syndrome (SJS), mitomycin C, Ocular Cicatricial Pemphigoid, contact lenses, aniridia, and chronic exposure to preservative-containing medications. Typical symptoms of patients with LSCD include mild to severe decreased visual acuity, photophobia, pain, redness, foreign body sensation, and tearing.

On examination the corneal epithelial membrane can demonstrate an irregular and blunted reflex with possible underlying corneal opacity. Depending on etiology there may be corneal thinning. A whorl-like, streaming epithelial pattern may be observed. Late fluorescein staining of the corneal surface is known to be a classic sign due to the glandular composition found on encroaching conjunctiva not normally present on corneal epithelium.1

The most commonly used preservative in ophthalmic solutions is benzalkonium chloride (BAC). Accumulated evidence suggests that its long-term application may be a potent risk factor for many ocular surface disorders including LSCD.2 Dosing studies with BAC have shown that it is able to penetrate through the corneal epithelium to corneal endothelium as well as peripheral
somatosensory nerves and deep conjunctiva. Combining evidence described by Pauly et al., in which they systematically demonstrated predictable development of deep limbal architectural changes in Lewis rats after extended BAC exposure, it is theorized that BAC’s ability to dissolve into deeper tissue may directly injure the Palisades of Vogt wherefrom the limbal stem cells differentiate and proliferate.

In addition to the known direct toxicities attributed to BAC, the results from injury have been shown to recapitulate surface inflammatory disorders similar to those commonly associated with LSCD, including SJS. CD4-positive T cells have been identified in the limbal regions of mouse models after sustained delivery. This second, compensatory inflammation may result in further signaling which may lead to encroachment of the proximal conjunctiva, a process known as conjunctivalization. In some cases, squamous metaplasia (including loss of conjunctival Goblet cells, normal stratification) has been identified and theorized to lead to possible surface neoplasm.

The first treatment of choice in BAC-induced LSCD is cessation of the offending agent. Treating the ocular surface with frequent preservative free artificial tears, preservative free lubricating ointments, autologous serum drops, punctual plugs, and possibly cyclosporine or lifitegrast may be effective. Cessation and surface treatment have been suggested to lead to some degree of disease reversal. Nevertheless, there are many patients who must continue medications containing BAC for chronic conditions and many times corneal epithelial changes from LCSD are permanent. For this reason, limbal transplantation is indicated in refractory cases. Transplantation is usually in the form of conjunctival limbal autograft (CLAU), using tissue from the contralateral eye, conjunctival limbal allograft (lr-CLAL), using tissue from a living relative, or keratolimbal allograft (KLAL), utilizing tissue from a cadaveric donor.

Conclusions
Limbal stem cell deficiency (LSCD) is a disease entity with many antecedent events including those that lead to inflammation, direct toxicity, mechanical injury, or genetic predisposition. Medications that contain the preservative benzalkonium chloride (BAC) have been shown to injure limbal stem cells which in turn leads to an secondary inflammatory reaction resulting in a deficiency of corneal epithelial growth and conjunctival proliferation and covering of the clear cornea. This disease can be treated conservatively but may ultimately require replacement of stem cells in the form of a limbal stem cell transplantation. Here we describe one case in which BAC was implicated in the development of LSCD, however the patient had a good result after transplantation.


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Case Presentation

CC: left eye foreign body sensation, irritation and blurriness x 2 months

• 91 year old male with a history of glaucoma for many years

• Status post cataract extraction and trabeculectomy of both eyes

• No recent exposures, no upper respiratory infection symptoms

• Currently uses preservative free tafluprost 0.0015% QHS OU and timolol maleate 0.5% BID OU; however has a history of using multiple glaucoma medications over many years

• Outside ophthalmologist attempted two amniotic membranes and serum drops TID OS

• His symptoms worsened, and he presented to the UC Irvine Ophthalmology clinic
Past Medical Hx
major depression
hypertension
hyperlipidemia

Past Surg Hx
appendectomy

Past Ocular Hx
CE/IOL OU
Primary Open Angle Glaucoma
trabeculectomy OU

Fam Hx
unknown glaucoma Hx

Meds
atorvastatin
finasteride
tafluprost 0.005% QHS OU
timolol mal 0.15% BID OU
serum drops TID OS

Social
lives at home with family
no recent travel
vaccination is current
Exam

VA sc distance
OD: 20/400 PH 20/200
OS: CF

Pupils
OD: 3 -> 2 mm round and reactive, no APD
OS: 3 -> 2 mm round and reactive, no APD

IOP (tonopen)
OD: 11 mm Hg
OS: 10 mm Hg
<table>
<thead>
<tr>
<th></th>
<th><strong>OD</strong></th>
<th><strong>OS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>facial</strong></td>
<td>WNL, no proptosis</td>
<td>WNL, no proptosis</td>
</tr>
<tr>
<td><strong>L/L</strong></td>
<td>WNL</td>
<td>WNL</td>
</tr>
<tr>
<td><strong>C/S</strong></td>
<td>White and quiet, superior bleb</td>
<td>tr injection, superior bleb</td>
</tr>
<tr>
<td><strong>K</strong></td>
<td>1+ punctate epithelial erosions</td>
<td>Loose epithelium, recently healed defect, fine KNV, loss of limbal architecture, whorled streams of epithelium</td>
</tr>
<tr>
<td><strong>A/C</strong></td>
<td>Deep and quiet</td>
<td>Deep and quiet</td>
</tr>
<tr>
<td><strong>Iris</strong></td>
<td>Round, no rubeosis</td>
<td>Round, no rubeosis</td>
</tr>
<tr>
<td><strong>Lens</strong></td>
<td>Posterior chamber IOL</td>
<td>Anterior chamber IOL</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Vitreous</td>
<td>clear</td>
<td>clear</td>
</tr>
<tr>
<td>Cup to disc</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>Cupping without swelling or hyperemia</td>
<td>Cupping without swelling or hyperemia</td>
</tr>
<tr>
<td>Macula</td>
<td>Normal contour and reflex</td>
<td>Normal contour and reflex</td>
</tr>
<tr>
<td>Vessels</td>
<td>Mild tortuosity</td>
<td>Mild tortuosity</td>
</tr>
<tr>
<td>Periphery</td>
<td>Flat and attached 360 degrees</td>
<td>Flat and attached 360 degrees</td>
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Fluorescein Staining
Limbal Stem Cell Deficiency (LSCD)
Differential Diagnosis

**Acute**
- Chemical injury
- Stevens Johnson Syndrome (SJS)
- Ocular Cicatricial Pemphigoid
- Thermal injury

**Chronic**
- Contact Lenses
- Aniridia
- Medication preservatives
- Atopic disease
- Mitomycin C
Limbal Stem Cell Deficiency (LSCD)

- A disorder in which inflammation, infection, trauma, medications or genetics predispose to injury of the corneal limbal stem cells at the Palisade of Vogt leading to poor corneal surface architecture.

- Patients describe foreign body sensation, blurry vision, photophobia, redness, and tearing.

- The result is changed corneal epithelial growth, poor vision, and possible need for aggressive therapies and vision rehabilitation, including surgery.
Medication Induced LCSD

- Stem cell injury can be caused by a variety of medications, including the most commonly used ophthalmic solution preservative: benzalkonium chloride (BAC).

- Animal studies have shown deep limbal architectural changes at the Palisade of Vogt and predictable penetration of BAC to these deeper tissues in the ocular surface.

- A secondary, inflammatory reaction occurs after BAC exposure which can recapitulate inflammatory conditions known to lead to LCSD such as SJS and OCP.
Examination

- Corneal epithelial reflex is blunted and irregular.
- Possible underlying or deep corneal opacities or thinning depending on the etiology.
- A whorl-like, streaming corneal epithelial pattern.
- So called “conjunctivalization” of the cornea.
- Possible evidence of a recently healed epithelial defect.
- Late staining of the corneal epithelium due to the glandular changes that accompany the over-growth of conjunctiva.
Treatment

- Discontinue the causative medication if able.

- Aggressive surface lubrication with preservative free artificial tears, lubricating ointments, autologous serum drops, cyclosporine, lifitegrast, and/or punctal plugs.

- Stem cell transplantation.
Conclusion

- LSCD is a disorder in which inflammation, infection, trauma, medications or genetics predispose to injury of the corneal limbal stem cells at the Palisade of Vogt leading to poor surface architecture.

- A case is presented in which benzalkonium chloride is implicated in the etiology of the stem cell deficiency.

- Treatment includes cessation of the offending agent, surface lubrication, and corneal limbal stem cell transplantation.
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Thank You
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