Glaucoma Gauntlet: Managing the Challenging Cases

Pseudoexfoliative (PXE) Glaucoma/ Exfoliative Glaucoma

- True Exfoliation: peeling of anterior lens capsule due to heat/radiation (glass blowers/ welder's disease). This is truly rare.
- Pseudoexfoliation: age-related generalized disorder of the extracellular matrix characterized by the deposition of abnormal basement membrane (fibrillar extracellular material) on anterior lens capsule, iris, and in trabecular meshwork. Abnormal basement membrane comes from lens, iris, ciliary body, and uvea. In that true "exfoliation" is clinically very rare, pseudoexfoliation syndrome and pseudoexfoliative glaucoma are often termed "exfoliation"
  - Exfoliation is probably the best term because issues arise when this material is rubbed off.
- This is the most common identifiable cause of open angle glaucoma worldwide
- Sixth to eighth decade
  - Rare under age 40
- Bilateral, but may be asymmetric
  - Unaffected "normal" eye will have subtle histopathologic changes
- Mechanism of glaucoma is nearly always open angle, however in some uncommon cases, the PXE material may lead to lens dislocation with pupil block angle closure
- High prevalence in northern Europeans
  - Scandinavia, Ireland, USA
  - Also common in Middle East, Southeast Asia, India, South Africa, South America
  - Less common in patients of African descent though it does happen.
  - Has only occurred rarely (some have said never) in Eskimos
- High altitude, northern climate, exposure to UV radiation are risk factors
  - In the United States, people who live in the northern tier (above 42° latitude) have the highest incidence of exfoliative syndrome. Those in the southern tier (below 37°) have the lowest incidence.
- Peripupillary transillumination (may be seen in absence of clinically detectable pseudo-exfoliative material)
  - The presence or development of peripupillary TID is a very important indicator of PXE
    - PXE suspects

Exfoliative Glaucoma: Pathophysiology

- Exfoliative material produced
  - Abnormal basement membrane
    - Disturbed basement membrane metabolism
    - Lens epithelium, trabecular meshwork, iris stroma and vessels, and corneal endothelium as sources
- Deposited on anterior lens capsule, not from lens
- Pigment released from pupil border
  - Peripupillary transillumination defects – very important finding
    - Patients with peripupillary TIDs can be considered "pseudoexfoliation suspects"
  - Posterior synechia can form as this material is very sticky – like Velcro

- Dilation may reveal a large amount of pigment on the lens surface. While true exfoliative material isn't present, this pigment in a similar radial pattern represents posterior synechia and the iris sticking to the material. This also makes a patient a pseudoexfoliative/ exfoliative suspect.

- Heavy pigment (and exfoliative material) found in trabecular meshwork and may block trabecular meshwork, but the mechanism is not well understood
  - Liberated pigment may cause blockage
  - Material likely causes trabecular cell dysfunction
    - Essentially functions the same as pigmentary glaucoma
- Phacodonesis may be present if material has led to significant zonular dehiscence
  - PXE is a significant complicating factor in cataract extraction- loss of lens
- Lensectomy is not curative-material will deposit on IOL as well as remaining anterior capsule
- Now recognized as a generalized disorder of the extracellular matrix
  - Exfoliation material is present in the walls of posterior ciliary arteries, vortex veins, and central retinal vessels as well as in the heart, lung, liver, kidney, gall bladder, and cerebral meninges
    - Associated with central retinal vein occlusion (CRVO)
  - Systemic associations include TIA's, stroke, Alzheimer's disease, hearing loss, hyperhomocysteinemia, and heart disease
- Polymorphisms in the coding region of the lysyl oxidase-like 1 (LOXL 1) gene on chromosome 15 are specifically associated with syndrome and glaucoma
  - LOXYL 1 is a member of the lysyl oxidase family of enzymes, which are essential for the formation, stabilization, maintenance, and remodeling of elastic fibers and prevent age-related loss of elasticity of tissues
  - LOXYL 1 protein is a major component of the exfoliation deposits

Exfoliative Glaucoma

- Elevated IOP develops in 22-81% of pseudoexfoliative cases
  - Overall, about 40% likelihood of developing glaucoma throughout life
- When glaucoma develops, IOP is usually higher than in POAG
  - More rapid progression than POAG
  - IOP very labile
  - Difficult to control
  - More likely to need surgery
  - More complications with cataract surgery
    - Zonular dialysis, capsular rupture, and vitreous loss
  - Loss of zonular support
    - Can allow for angle closure as lens rocks forward and causes pupil block
    - Rare but can happen. Thus, a second mechanism is secondary angle closure with pupil block.
- Highest IOP is often occurring outside normal office hours.
- IOP may transiently rise after dilation due to pigment liberation

Exfoliative Glaucoma: Management

- Treat as POAG
  - Beta blockers
  - Prostaglandins
  - Adrenergic agonists
  - CAI's
- ALT/ SLT - good modality
- Trabeculectomy/tube, maybe MIGS but disease is usually too severe
- Pseudoexfoliative/ Exfoliative glaucoma is more severe than primary open angle glaucoma. More medications and surgery are needed to control exfoliative glaucoma than POAG. Pseudoexfoliative glaucoma is one of the worst chronic open angle glaucoma types to be encountered regularly in clinical practice.
- Exfoliative material is easily missed without a dilated lens evaluation.
- The transillumination defects in pigmentary glaucoma are mid-peripheral and are peri-pupillary in pseudoexfoliation syndrome.
- Pseudoexfoliation syndrome is now generally considered to be a widespread systemic condition of abnormal extracellular matrix that manifests most clearly in the eye.
- Occasionally, patients with diagnosed "POAG" develop peripupillary TIDs and eventually clinically visible exfoliative material. Thus, the patients likely always had exfoliative glaucoma. Always look for the development of pseudoexfoliative material in older, "at risk" patients.
- Patients with radial oriented pigment on the anterior lens surface, pigment liberation with dilation (with or without IOP rise), and peripupillary TIDs can be considered to be 'exfoliation suspects'. Very significant.

Steroid Induced Glaucoma

- Outflow difficulty- steroids are thought to change the TM ability to process aqueous.
- Glycoaminoglycan (GAG) accumulation is thought to be the underlying difficulty
- TM endothelium decreases phagocytotic ability
  - Steroids may prevent release of enzymes that normally depolymerize gags and prevents TM endothelial cells from keeping TM properly cleaned up and healthy.
- Increased difficulty of outflow
- Topical or oral corticosteroids can cause IOP rise
  - Ointment or creams periorbital and inhaled steroids can cause IOP increase
- May be seen in patients endogenously producing excess steroids (e.g., Cushing's syndrome)
- 2 week onset (often longer)
- About 2/3 of population are steroid responders
- Steroids commonly affecting IOP are prednisolone, dexamethasone, betamethasone, and difluprednate
  - Difluprednate often affects IOP faster and more significantly, but not to a greater prevalence than prednisolone
  - *Any* steroid can elevate IOP
    - Loteprednol is considered a soft steroid with less propensity to elevate IOP, but it can cause glaucoma like any steroid
- Response is dependent upon:
  - Frequency of application

    - Dose
    - Duration
- Genetic predisposition
    - Genetic relationship - TIGR/Myocillin gene
        - The incidence points to an autosomal recessive inheritance pattern
- Those at risk include:
    - Myopes
    - Pts. with POAG
    - Children
- Treatment:
    - D/C steroids
        - After prolonged use, IOP may not lower with medication cessation
    - Aqueous suppressants, Prostaglandins (depending upon the amount of inflammation and route of steroid)
    - Anything designed to enhance trabecular outflow (Trabeculoplasty, miotics) will have a poor effect; trabeculectomy works better

- Steroid induced pressure elevations only occur in approximately 2/3rds of the population and it typically takes 2 weeks (minimum) to 5 weeks (typically) in order for IOP elevations to become apparent. Less than 10% of the population ever becomes a significant problem. Be aware that difluprednate tends to cause IOP elevations faster and higher than most other steroids

Phacomorphic Glaucoma

- Unilateral or asymmetric cataract associated with asymmetric shallowing of the anterior chamber not explained by other factors
- Difficult to differentiate from primary angle closure
- Acute to intermittent red, painful eye, typically at night
- May present asymptomatically with chronic angle closure
- Blurred vision from corneal edema
- Often have rapidly developing cataract from trauma or inflammation
- Mild anterior segment inflammation
- Typically, vision is greatly reduced (<20/400) from the cataract
- Due to increasing lens thickness: irido-lenticular apposition from growth of the lens cortex and intumescence of the lens.
    - May be associated with short globe axial length
    - Occasionally, phacomorphic glaucoma will occur not due to mature cataract formation, but due to microspherophakia (often associated with Weill-Marchesani syndrome)
        - Presents as acute or chronic angle closure in eyes with high myopia.
- Pupil block and posterior chamber pressure increase
- Secondary iris bombé
- Angle closure with possible PAS formation
- Alternately, the swelling of the lens may press upon the iris and ciliary body, forcing them anteriorly and shallowing the anterior chamber without true pupil block. Thus, an angle

closure may be created that does not respond to laser peripheral iridotomy (LPI).

Phacomorphic Glaucoma: Management

- As with acute primary angle closure glaucoma, medical therapy is initially used to lower the IOP in acute, symptomatic cases. Beta-blockers, alpha-2 adrenergic agonists, topical corticosteroids, topical or oral carbonic anhydrase inhibitors may be all systematically employed. An exceptional effect of prostaglandin analogs in managing the IOP of patients with chronic angle closure glaucoma both before and following LPI has been reported. Pilocarpine 2% and corticosteroids can also be used. Superior IOP control and shortening the duration of the attack preoperatively is essential in improving the final visual outcome.
- In cases where pupil block precipitates the angle closure, LPI is indicated following medical treatment to attempt to relieve the resultant aqueous congestion and IOP rise. This is especially true where a relative pupil block, secondary to the unusual lens anatomy is the main pathogenesis. In cases where pupil block only partially contributes to the angle closure, argon laser peripheral iridoplasty (ALPI) can reverse the apposition and alleviate the condition. It has recently been shown that ALPI offers greater safety, consistency, and efficacy than systemic IOP-lowering medications as initial treatment for acute phacomorphic angle closure.
- Should LPI and/or argon laser iridoplasty, combined with topical anti-glaucoma medications, relieve pupil block and successfully lower and stabilize IOP, then patients with phacomorphic glaucoma could be potentially continued on medical therapy, especially if poor visual potential following lens removal is suspected. Cataract extraction in these patients has a high rate of exudative detachment of the choroid and ciliary body with rhegmatogenous retinal detachment. It is safer to do LPI and iridoplasty with medical therapy, especially if visual potential is poor. Lens extraction ultimately relieves the condition. The decision in these cases is contingent upon the potential visual improvement with lens removal. Extracapsular cataract extraction, either with or without secondary lens implantation, has historically been the most common procedure to correct phacomorphic glaucoma. Manual small incision cataract surgery is safe and effective in controlling IOP and restoring visual function. Phacoemulsification combined with anterior vitrectomy is also an option in these cases. Anecdotally, femtosecond laser-assisted cataract surgery may be a viable option.
- Phacomorphic glaucoma is the most common lens-induced glaucoma.

Neovascular Glaucoma

- Neovascularization of the iris and angle (NVI/NVA)
- Mechanism is secondary angle closure without pupil block
    - Many possible causes: Central Retinal Vein Occlusion (CRVO), diabetes/ diabetic retinopathy, Carotid artery disease (ocular ischemic syndrome) are most common causes
    - Branch and hemi-retinal vein occlusion (BRVO, HRVO)
    - Central retinal artery occlusion (CRAO)
    - Giant cell arteritis
    - Coat’s disease
    - Eale’s disease
    - Sickle cell retinopathy
    - Uveitis

- Retinal detachment
- Ocular neoplasia

Neovascular Glaucoma Pathophysiology

- Hypoxia from above conditions
- Vascular Endothelial Growth Factor – VEGF: Vasoproliferative angiogenic substance diffuses to viable tissue
- Neovascularization develops
- Rubeosis
- Angle neovascularization
  - Vessels bridge scleral spur and arborize on trabecular meshwork
- Fibrovascular membranes
- Synechial closure of angle
  - Tent-like PAS initially, later broad areas of angle closure
- Inflammation and high IOP
- Poor prognosis
  - Poorly responsive to medical treatment
- Called the 90 day glaucoma- usually occurs within 90 days of antecedent vascular occlusion
  - Don't be fooled. It can and does happen a lot sooner in many cases.
- This is unique in that the mechanism is secondary angle closure without pupil block

Neovascular Glaucoma Management

- Initial medical tx: cycloplegia (atropine) and Pred forte used for inflammatory component. May also temporarily use aqueous suppressants until more definitive treatment can be done.
  - Generally, you do not chronically medically treat this type of glaucoma.
- Trabeculectomy if not too much of the angle is compromised- high likelihood of failure
  - Not clear if trabeculectomy with anti-metabolites is preferable to a tube implant procedure
- Pan-retinal photocoagulation (PRP) to destroy the ischemic retina and reduce the vasoproliferative substance and induce regression of neovascular vessels. Generally successful (90% success) in diabetic retinopathy if <270 degrees of closure. Much less successful in ocular ischemic syndrome. Cryotherapy may be used in place of PRP.
- A newer modality to manage refractory NVG involves trans-scleral diode laser cyclophoto-coagulation. This reduces aqueous production through the laser-induced ablation of the ciliary processes.
- A still newer modality (used in conjunction with methods mentioned above) involves ocular injection of Avastin or Lucentis, which are anti-VEGF drugs
  - Not definitive treatment though temporarily very effective.
  - Must be accompanied by PRP- otherwise vessels will return.
- Overall poor prognosis
- Medically treating neovascular glaucoma is like arranging deck chairs on the Titanic.
- Neovascular glaucoma is typically the worst glaucoma that a patient can have.
- Always obtain an ESR and C-reactive protein on patients over the age of 60 years who have anterior segment neovascularization.
- Definitive treatment of NVG typically will begin immediately with atropine, steroids, and

aqueous suppressants. Following that, the patient will likely be treated with intravitreal anti-VEGF injection followed by PRP. Often, the patient will then undergo either trabeculectomy with mitomycin C or a tube implant procedure.

Glaucomatocyclitic Crisis

- AKA Posner-Schlossman Syndrome
- Idiopathic and idiosyncratic
  - May be related to herpes virus- unproven
    - Cytomegalovirus also implicated
  - Similarities to herpetic keratouveitis
  - There has been evidence of the herpes virus in the anterior chambers of patients with glaucomatocyclitic crisis
  - Idiosyncratic in that despite the very high IOP, damage doesn't commonly occur and patients are minimally symptomatic
- Ocular hypertensive syndrome associated with mild AC reaction
- Occurs mostly between ages of 20 and 60 years, and is rare over age 60
- Unilateral
- Recurrent
  - Intervals of months to years
- Mild symptoms, or may be asymptomatic
- Blurred vision secondary to corneal edema common
- Mild anterior chamber reaction
- Keratic precipitates are often the only sign of inflammation, and may not even be present
  - Flat, round, and non-pigmented
  - Concentrated over inferior endothelium usually
- The conjunctiva may be white and quiet, or mildly injected
- Anterior chamber angle is open and normally pigmented
- Pupil may be mid-dilated
- Iris hypochromia may occur, but is uncommon
- High IOP (30mm hg-60mm hg is typical, but 90 mm Hg has been reported. Personally, I have seen 70s).
  - IOP elevation can precede inflammation signs
  - IOP level is disproportional to amount of inflammation
- Self-limiting
- Duration: hours to weeks- typically will last for several days, but can persist for months
- Normal fields and discs in many cases, but damage will occur over time with repeated outbreaks
  - There is a strong association with POAG in these patients
- All findings normal between attacks

Glaucomatocyclitic Crisis: Pathophysiology

- An obscure etiology.
- Decreased outflow suggests a trabeculitis as the causative mechanism.
- Prostaglandin E (causing a breakdown of the blood-aqueous barrier) found in high

concentrations, which may increase the blood-aqueous barrier permeability and lead to increased aqueous production.
    - Also, prostaglandins will lead to an increase in cells and proteins in the AC due to the barrier breakdown.
    - Prostaglandin E has been found in high levels during acute attacks and normal levels have been found in the same patients during normal times.
- There is something unique about the Herpes virus that causes trabeculitis.

Glaucomatocyclitic Crisis: Treatment

- This is self-limiting and will spontaneously resolve. If you decide to treat (especially if IOP is very elevated), direct treatment at the inflammation first and the ocular hypertension secondarily. Avoid miotics and prostaglandin analogs. Cease treatment between attacks, but monitor closely between attacks as there is a high incidence of concomitant POAG in these patients. These patients may develop POAG or they may spend more time in attacks than normal and this will lead to permanent damage.
- Corticosteroids are treatment of choice- most significant medication to use.
- Cycloplegics/mydriatics are generally unnecessary
- Beta blockers, alpha adrenergic agonists, CAI's; PGAs as last alternative and generally not needed as other meds and steroids rapidly do the job.
- GCC is not always a benign condition. Patients *can* lose vision.
- Glaucomatocyclitic crisis behaves much like a virus and both herpes and CMV have been found in association. Likely, a virus is the cause.
- Patients with GCC and proven CMV in their aqueous respond to ganciclovir.