Grand Rounds Presentation

SUNY Downstate Medical Center

10.23.14

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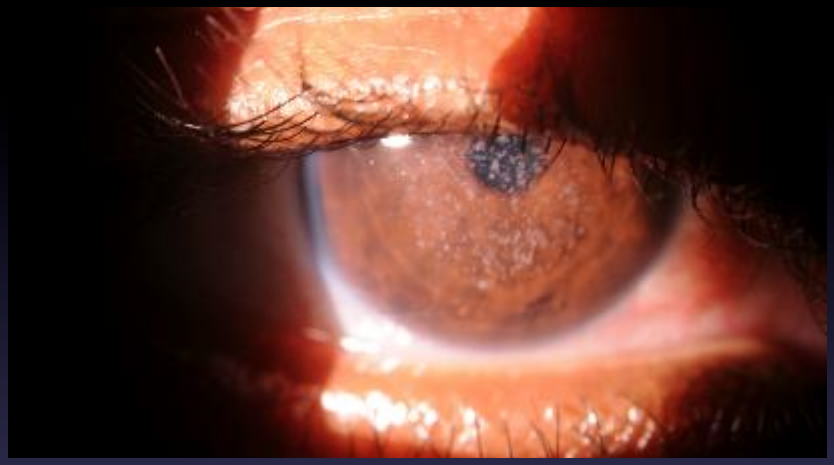
Patient Presentation

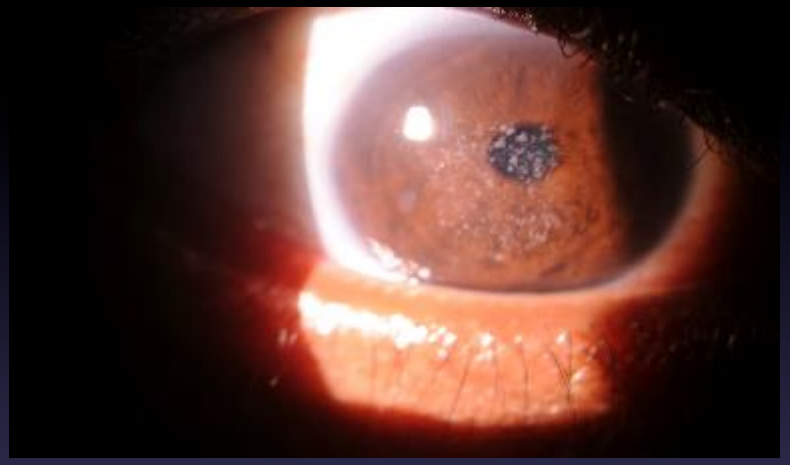
- HPI: 51 BF with POH 'poor vision' in both eyes since childhood. Patient recently diagnosed Glc (s) and presents for review of OCT ON. No acute changes in vision and no new ocular complaints . ROS (-)
- PMH: none
- Meds: none
- Gtts: none
- PSH: none
- FH: (-) for glc or blindness
- SH: (-) x 3

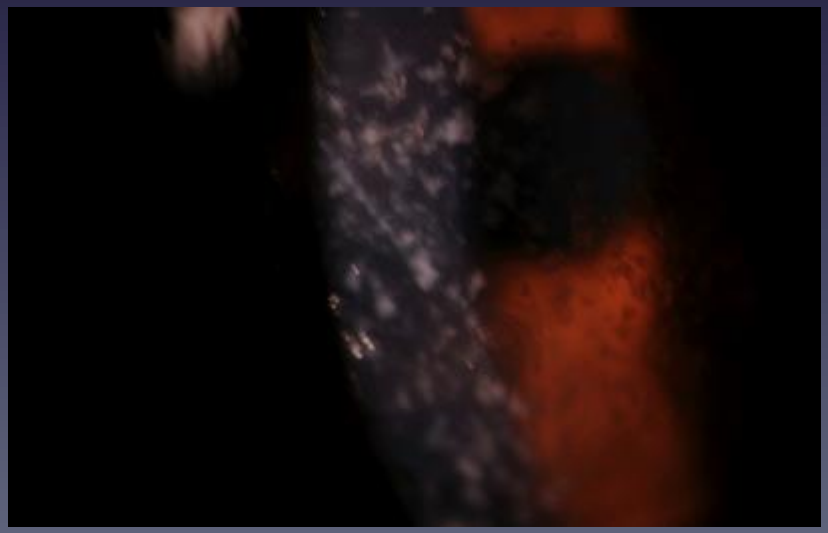
Exam

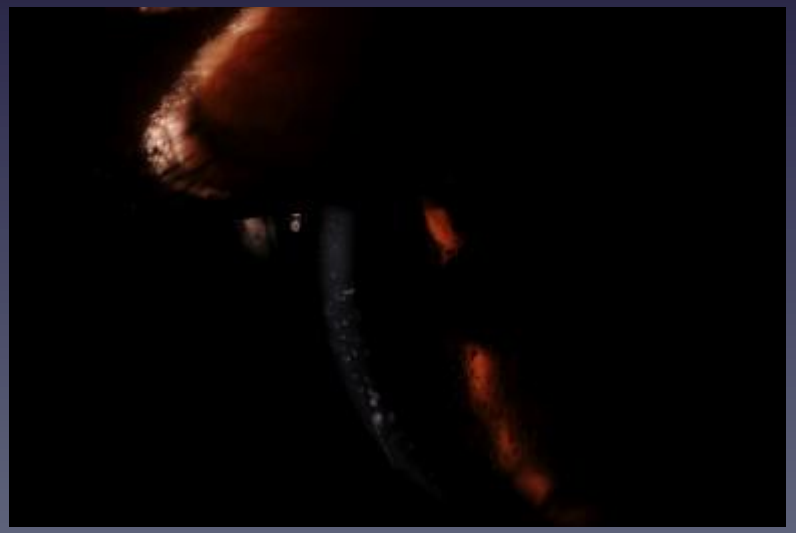
- dVAsc: 20/40 PH to 20/30 OD; 20/50-2 PH to 20/25-2
- Mrx: + 2.0 -2.5 x 150 to 20/30 OD; +2.0, -1.75 x 20 to 20/20 OS
- Pupils: 4-2 no APD
- EOMS full
- CVF full
- Tapp: 10/10 at 5:30 pm

SLE









Exam, cont'd

- SLE:
  - LLA: MGD OU
  - C/S: White and Quiet OU
  - **K: Centrally-located** bilateral infiltrates within the stroma **Present since childhood
  - **AC: Deep and Quiet OU**
  - Iris/Pupil: Flat, Round and Reactive OU
  - Lens: trace-1+ ns OU
- DFE:
  - Vitreous: clear OU
  - C/D: 0.75 s/p with thinning inferiorly OU
  - Mac: flat OU
  - V/P: Vessels WNL, no heme, holes or tears

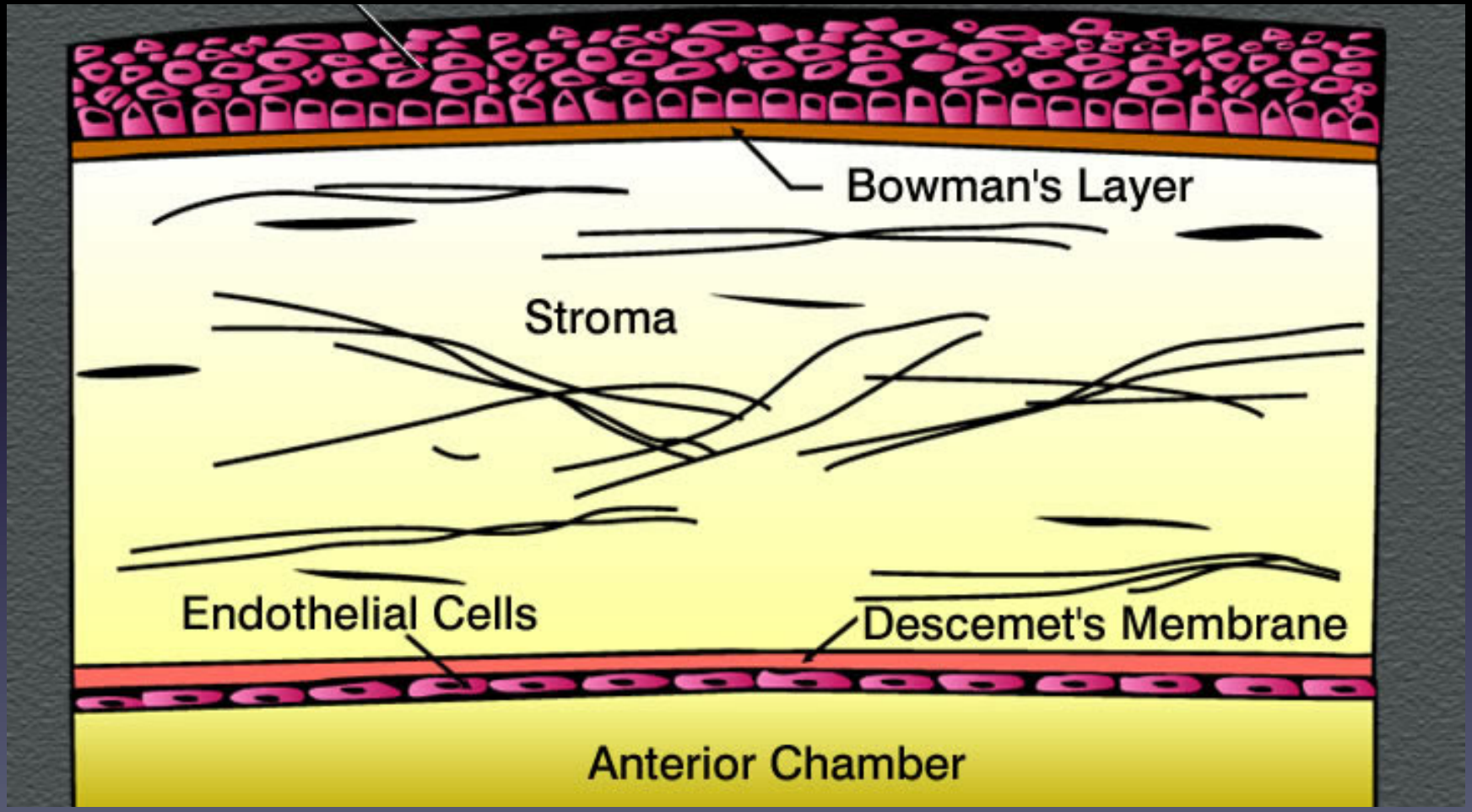
Differential Diagnosis

- Granular Dystrophy
- Macular Dystrophy
- Lattice Dystrophy
- Schnyder Corneal Dystrophy
- Salzman's Nodular Corneal Degeneration
- Infections- Strep viridans, Haemophilus, Enterococcus
- Staph Hypersensitivity
- DIAGNOSIS: Granular Dystrophy

Dystrophy vs Degeneration

- Corneal Dystrophy vs Corneal Degeneration
  - Dystrophies:
    - Genetic (usually Aut Dom) with onset in childhood/early adulthood
    - Not associated with systemic disease
    - Bilateral
    - Centrally located within the cornea
    - Typically involve only one layer of the cornea
  - Degenerations:
    - Progressive (onset typically after age 40)
    - Usually unrelated to family history or genetic predisposition
    - Commonly associated with systemic disease (rheumatologic, infectious)
    - Usually unilateral, asymmetric if bilateral, and peripherally located on the cornea
    - Can involve one or multiple layers of the cornea
    - Often associated with neovascularization

Layers of the Cornea



Corneal Dystrophies

Anterior Corneal Dystrophies	Stromal Corneal Dystrophies	Posterior Corneal Dystrophies
Epithelial Basement Membrane Dystrophy	Granular Corneal Dystrophy Type 1	Congenital Hereditary Endothelial Corneal Dystrophy 1
Lisch Corneal Dystrophy	Granular Corneal Dystrophy Type 2 (Avellino)	Congenital Hereditary Endothelial Corneal Dystrophy 2
Meesmann Corneal Dystrophy	Lattice Corneal Dystrophy Type 1	Posterior Polymorphous Corneal Dystrophy
Reis-Buckler Corneal Dystrophy	Lattice Corneal Dystrophy Type 2	Fuchs Endothelial Corneal Dystrophy
Thiel-Behnke Corneal Dystrophy	Macular Corneal Dystrophy	X-linked Endothelial Corneal Dystrophy
	Schnyder Corneal Dystophy	

Stromal Dystrophies

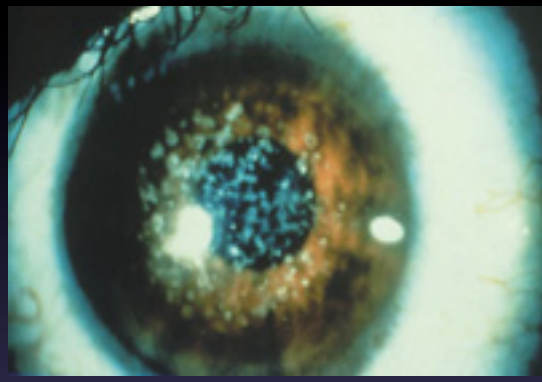
- Schnyder Corneal Dystrophy
- Granular Corneal Dystrophy Type 1
- Granular Corneal Dystrophy Type 2
- Lattice Corneal Dystrophy Type 1
- Lattice Corneal Dystrophy Type 2
- Macular Corneal Dystrophy

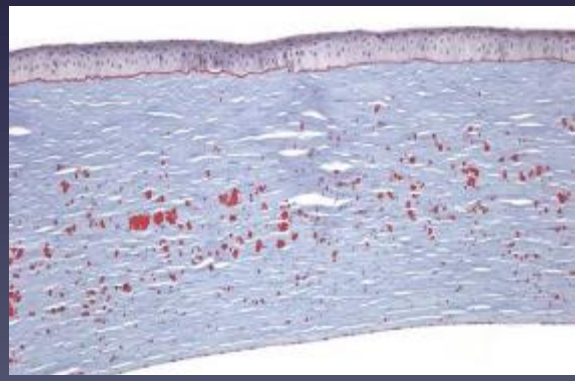
TGFβ1 and Corneal Dystrophies

- Transforming Growth Factor Beta Induced Protein (gene product of TGFβ1) is very abundant in cornea
  - >30 mutations in TGFβ1 gene that result in corneal dystrophies
  - 68 kDa protein known as keratoepithelin
    - It is secreted by corneal epithelial cells and is found in normal stroma bound to type VI collagen
  - Mutations in the TGFβ1 gene → protein aggregation in the cornea 2/2 protein misfolding
    - TGFβ1 induced protein accumulates as insoluble products in various forms. The severity, clinicopathologic variations , age of onset, and location of deposits all depend in the type of amino acid alterations in the protein

Granular Dystrophy Type 1 (Groenouw Type 1)

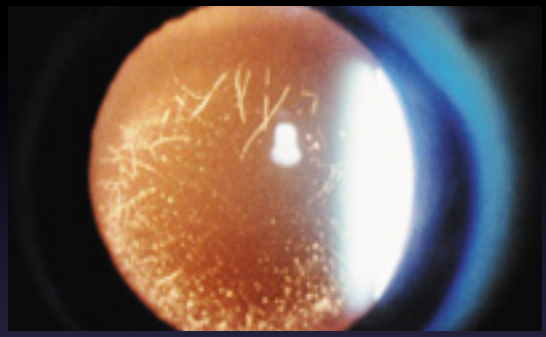
- Gen: Autosomal Dom defect in TGFB1 gene 5q31
- SLE: Stromal deposits with a breadcrumb appearance (discreet spots in central cornea with intervening clear zones). As patients age, spots tend to coalesce and extend into post. stroma
- Sx: Onset in childhood. Photophobia and glare. VA affected in 4th decade
- Pathology: Multiple stromal deposits from deep epithelium to Descemet's membrane + stain with Masson Trichrome, weakly PAS positive

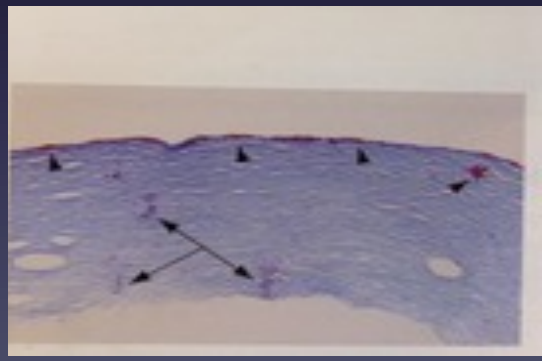




Granular Dystrophy Type 2 (Avellino/Granular-Lattice Dystrophy)

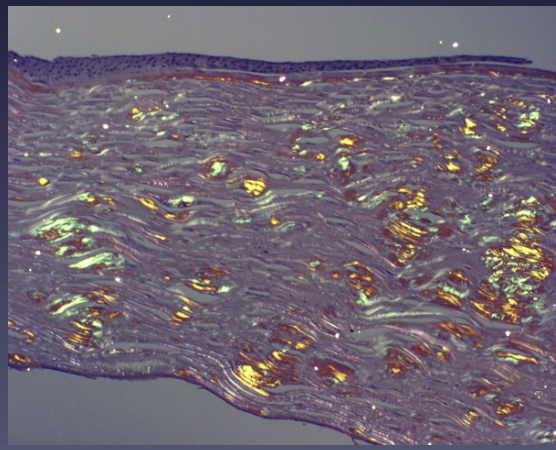
- Gen: Autosomal Dom TGFBI gene 5q31
- SLE: both granular and reticular infiltrates in central cornea
  - Recurrent erosions and photophobia are more common than in Type 1
- Sx: Onset earlier in homozygotes (early childhood) than heterozygotes (late childhood). VA loss typically occurs in adolescence but stabilizes at ~20/70
- Pathology: mixed deposits of hyaline and amyloid; hyaline stains with Masson Trichrome and amyloid stains Congo Red





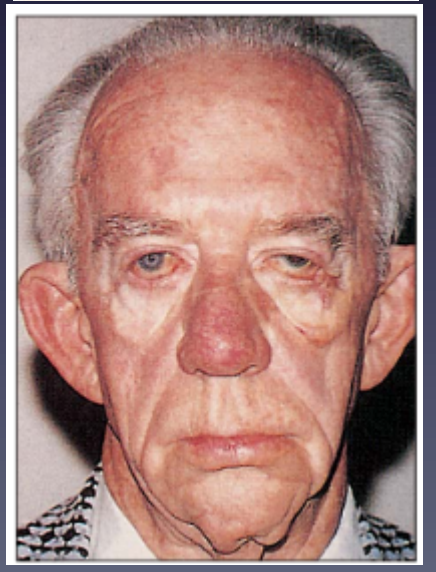
Lattice Dystrophy Type 1 (Biber-Haab-Dimmer)

- Gen: Aut dom TGFBI gene 5q31
- SLE: glass-like filamentous lesions that extend deep into stroma
  - Appearance changes over time with opacification of lesions and progressive haziness of cornea
- Sx: onset in 1st decade. Irregular astigmatism, surface erosions and VA loss
- Pathology: atrophy/degeneration of basal epithelial cells, thinning of Bowman's layer. Amyloid deposits in stroma stain with Congo Red (shows apple-green birefringence when exposed to polarized light)
  - On EM, deposits are electron dense randomly oriented fibers



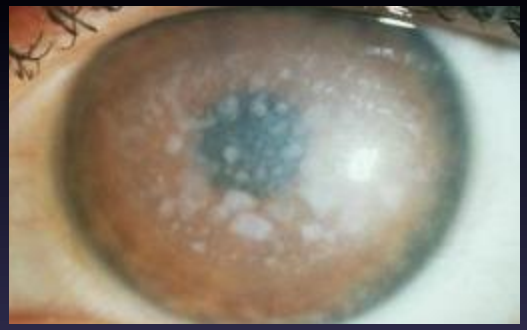
Lattice Dystrophy Type 2 (Finnish Familial Amyloidosis/Meretoja Syndrome/Amyloidosis V, Familial Amyloidotic Polyneuropathy)

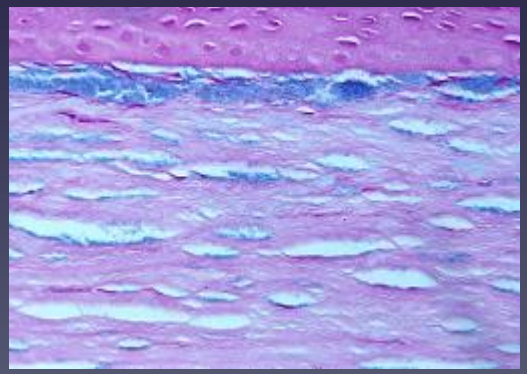
- Gen: Aut dom defect in Gelsolin gene
- SLE: glass-like filamentous lesions located mostly in the periphery of the cornea (start at limbus and progress inward) within anterior stroma
  - Corneal hypoesthesia, dermatochalasis and lagophthalmus, +/- POAG
  - Associated with systemic findings dry skin, skin laxity, nephrotic syndrome, cardiac conduction abnormalities, mask-like facies with facial droop)
- Sx: Onset in 3rd decade. Severe dry eye and corneal erosions (typically in middle age) and decreased corneal sensation
- Pathology: Amyloid deposits in stroma most prominent in the limbus that stain with Congo Red (apple-green birefringence when exposed to polarized light).



Macular Dystophy (Groenouw Corneal Dystrophy Type 2/Fehr Spotted Dystrophy)

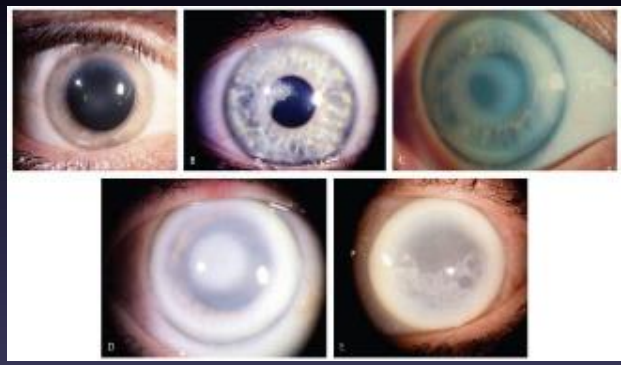
- Gen: Aut rec CHST gene 16q22
- SLE: stromal opacities which accumulate in central and superficial layers of the stroma and then spread aggressively to limbus.
  - There are no clear areas between stromal opacities.
- Sx: Onset in childhood. Severe VA loss, painful erosions and photophobia
- Pathology: Glycosaminoglycans stain + with colloidal iron or Alcian Blue (3 subtypes)





Schnyder [Crystalline] Corneal Dystrophy

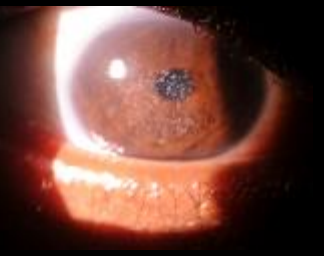
- Gen: Aut Dom UBIA1 gene 1p36
- SLE: Patients <23 years old have central corneal haze or subepithelial crystals. Ages 23-38: arcus lipoides. Ages >38 mid peripheral pan-stromal haze. Only 50% have crystals
- Sx: Onset in childhood but diagnosis typically made in 2nd/3rd decade. VA decreases with age. Glare is common
- Pathology: deposits of intra and extra-cellular esterified and unesterified phospholipids and cholesterol in basal epithelial cells, stroma and Bowman's layer. Lipid stains require Oil Red O or Sudan Black.



Epidemiology

- Men and women affected equally (except Fuchs, which affects women: men 4:1)
- Depending on subtype, presentation ranges from early childhood to mid-adulthood

Our Patient



- SLE: Centrally located, discreet lesions with inter-lesional clearing
- Onset most likely in childhood/adolescence
- Impaired VA but denied photophobia, glare or pain
- No systemic symptoms
- Granular Dystrophy Type 1

Management of Corneal Dystrophies

- **Depends on the patient's symptoms
- Initial tx: non-surgical
  - Lubricating drops, Restasis, or autologous serum therapy
  - Punctal plugs
  - Bandage Contact Lenses +/- antibiotics for recurrent erosions
  - Muro 128

Surgical Management

- PTK: Phototherapeutic Keratectomy
  - Excimer laser removes superficial opacities (recurrent epithelial erosion syndrome), smoothes the corneal surface and allows epithelium to re-adhere more tightly
  - Smoother stromal surface improves post-operative corneal clarity and decreases scarring
- Deep opacities that cause significant visual disturbances may require corneal transplantation
  - Lamellar or full thickness

Corneal Transplant

- Partial Thickness CT: ALK, DALK
  - ALK (Automated Lamellar Keratoplasty): endothelium is retained: risk of rejection may be decreased, and healing may be faster
    - Best for keratoconus and partial thickness corneal scars
  - DALK (Deep Anterior Lamellar Keratoplasty): epithelium and stroma are removed leaving the endothelium and Descemet's membrane left intact
- Full Thickness Corneal Transplantation (Penetrating Keratoplasty) – PKP
  - Most frequently performed corneal transplant – entire cornea removed and replaced with a donor cornea
- Intralase Enabled Keratoplasty (IEK) **new
  - Both full thickness (PK) and Anterior Lamellar Transplants (ALK and DALK) can be assisted with intralase femtosecond laser
    - Rather than preparing the corneal transplant graft with traditional trephine, both the patient and recipient corneas are fashioned with the laser
      - Benefit: personalized edge shapes which may induce stronger healing of the transplant and thus faster recovery of vision

Tailored Surgical Options

- *Granular Corneal Dystrophies*: because visual impairment is typically not severe, corneal grafting does not need to be done until the disease is advanced
  - PKP +/- phototherapeutic keratectomy is successful usually for 30 months. Recurrence is common in the superficial portions of the graft
  - LASIK is contraindicated in GD type 2
- *Lattice Corneal Dystrophies*: PKP has high success rate
- *Macular Corneal Dystrophy*: because entire stroma is affected, lamellar kp is insufficient, and PKP is more successful
- *Schnyder Corneal Dystrophy*: phototherapeutic keratectomy for sub-epithelial crystals and PKP for pan-stromal involvement.

Data on Recurrence of CDs

- Recurrence of Granular Dystrophy tends to be superficial (usually centrally located and epithelial)
  - Time of recurrence is 13-73 months following surgical intervention and there has not been a consistently apparent sig diff between PK and LK
- Patanelli et al (2014): case study
  - 28 M Granular Corneal Dystrophy Type 1 who underwent DALK
  - Recurrence 3 yrs post-op : full-thickness PKP was performed and cornea was sent for pathology
  - Recurrence of granular deposits was entirely within the stroma (as opposed to anterior/epithelial)
  - ** host keratocytes are a source of recurrence

Recurrence cont'd

- Rama et al (2013) presented a case study of 43 F GCD who underwent DALK
  - 6 month f/u she was found to have early recurrence of corneal opacities
  - 2 years later she was found to have deep stromal deposits, which were identified with H and E staining using Masson Trichrome
  - Genetic analysis: TGFB1 heterozygous variants (missense mutation)
  - Conclusion: host keratocytes play a role in the formation of these deposits

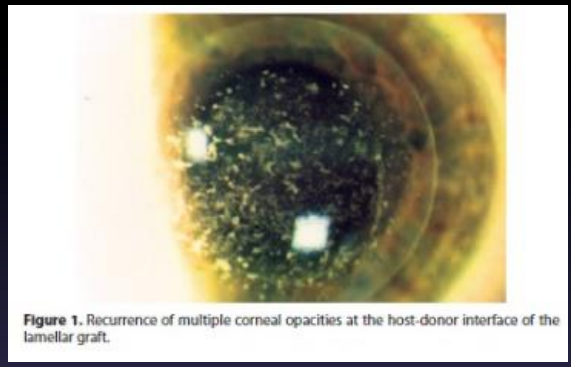


Figure 1. Recurrence of multiple corneal opacities at the host-donor interface of the lamellar graft.

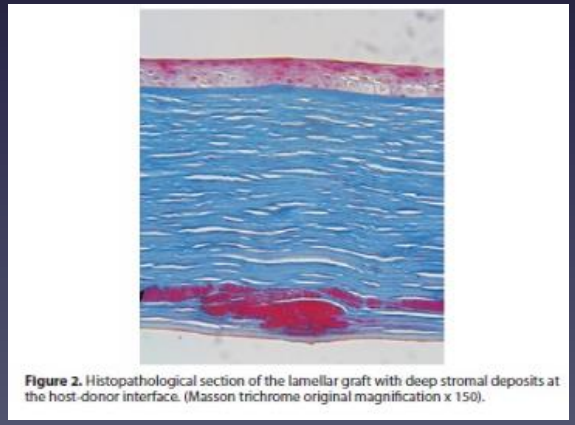


Figure 2. Histopathological section of the lamellar graft with deep stromal deposits at the host-donor interface. (Masson trichrome original magnification x 150).

Recurrence cont'd

- Cheng et al (2013) compared the therapeutic effects of PKP and DALK on patients with Macular Corneal Dystrophy (retrospective, comparative study of 78 eyes)
- Results: best corrected VA was much better in PKP group compared to DALK group at 1,2,3 and5 years
- Incidence of complications at 1 yr: 21% PKP and 4.8% DALK
- Rate of recurrence in PK group was 17.5%and 42.9% in DALK group (5x higher than PK)
- Selection of PK vs DALK should be patient-tailored

Are Preservatives *Precipitants* in some Corneal Dystrophies?

- Formation of amyloid fibrils is accelerated by surfactants such as SDS (sodium dodecyl sulfate)
- Most eye drops contain BAC, which is a cationic surfactant
- Kato et al (2013) used 3 types of synthetic peptides containing different amino acid varieties of the keratoepithelin sequence
- The time course of spontaneous amyloid fibrillation and seed dependent fibril elongation were monitored in the presence of various concentrations of BAC or SDS
- Results indicates that both BAC and SDS accelerated fibrillation of all synthetic peptides
- Eye drops containing BAC may deteriorate corneal dystrophies

What happened to Our Patient?

- Best corrected dVAcc 20/30 and 20/20. The patient was started on AT for symptomatic relief
- Surgical options were discussed as a potential treatment in the future if VA becomes significantly impaired

Reflective Practice

- This case demonstrated the importance of a thorough ophthalmic exam and diagnostic workup and allowed me to learn more about a rare disease entity and its complications.
- This case also allowed me to evaluate the literature for the differential diagnoses of this disease entity while keeping in my mind my patient's expectations

Core Competencies

- Patient Care: The case involved thorough patient care and careful attention to the patient's past medical history. Once diagnosed the patient received proper management and follow up care.
- Medical Knowledge: This presentation allowed me to review the presentation, differential diagnosis, proper evaluation/workup and different treatment options for corneal dystrophies
- Practice-Based Learning and Improvement: This presentation included a current literature search of current studies in the roles of TGFbeta genes and corneal dystrophies
- Interpersonal and Communication Skills: The patient was treated with respect and every effort was made to communicate with the patient in a timely manner.
- Professionalism: The patient was diagnosed in a timely manner. She was informed of her diagnosis and explained current treatment options.
- Systems Based Practice: The patient was discussed with several cornea specialists in order to facilitate proper management

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Thank You

- Patient
- Dr Allison Rizzuti
- Dr Kichiemon Asoma