GRAND ROUNDS

SUNY DOWNSTATE OPHTHALMOLOGY

SHAILY SHAH, PL-1

APRIL 28, 2016

HISTORY

33 y/o black male with no PMHx, ocular hx of keratoconus s/p PKP OU, presents with pain, redness, foreign body sensation and tearing from left eye x 2 days.

(+) Decreased vision OS

(+) "cloudiness" of left K graft when looking in mirror, not present previously

(-) recent trauma

(-) recent steroid taper

(-) headache, deep ocular pain

(-) flashes/halos/floaters/curtains/veils

HISTORY, CONT'D

- PMHx:
  (+) Asthma
- Meds:
  - None
- Ocular Hx:
  (+) keratoconus
  (+) s/p PKP OD 2012 (NYEE)
  (+) s/p PKP OS 2015 (NY Presb)
- Gtts:
  - None
- Family Hx:
  - None
- Social Hx:
  - None
- Allergies:
  - NKDA

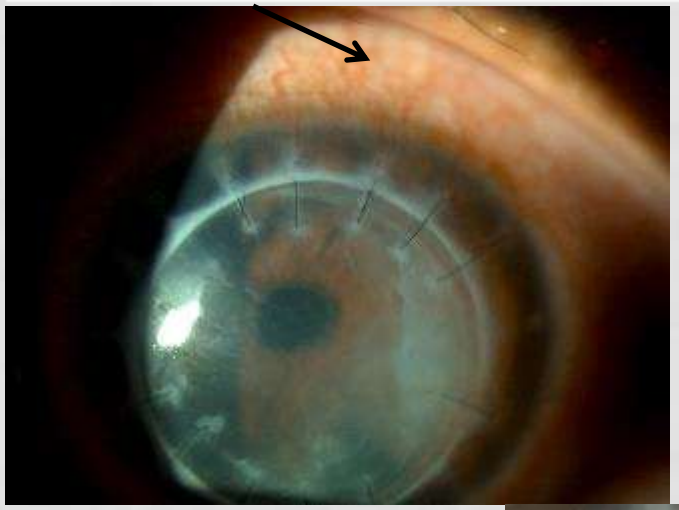
EXAM

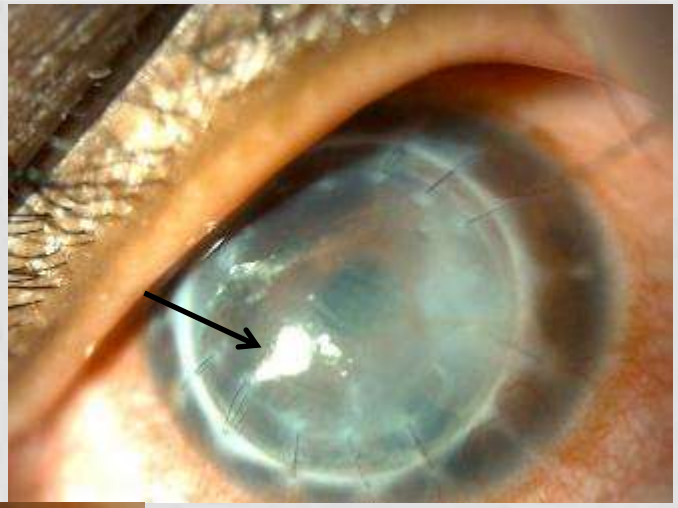
- dVAsc: OD 20/50-2, PH NI; OS 20/150, PH NI
- Pupils: ERRL, no rAPD
- EOMs: full OU
- CVF: fffc OU
- Tapp: 16/16 @ 7:15pm

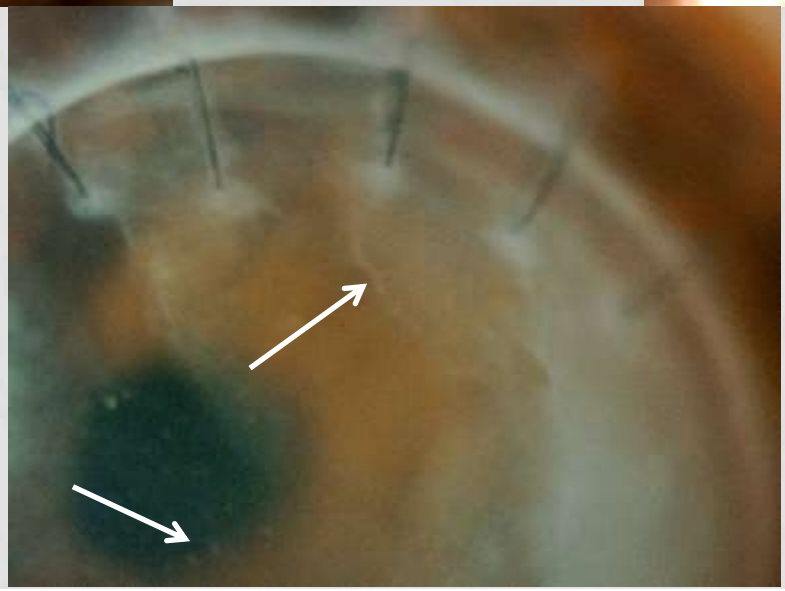
SLIT LAMP EXAM

	OD	OS
LLL	floppy eyelids	See photos
C/S	1+ injection	See photos
K	PKP graft in place, clear with good K light reflex. Sutures intact. Slight inferonasal opacity	See photos
A/C	Deep/quiet	See photos
I/P	flat, RR, no NVI	See photos
L	clear	See photos

SLIT LAMP EXAM OS







SLIT LAMP EXAM OS

	OD	OS
LLL	floppy eyelids	Floppy eyelids
C/S	1+ injection	2+ injection
K	PKP graft in place, clear with good K light reflex. Sutures intact. Slight inferonasal opacity	PKP graft in place, 2+ stromal edema with DM folds diffusely and small area clear K superiorly. Diffuse endothelial pigment deposition and scattered blood vessels at periphery of graft. (+) 2 loose sutures with fluorescein uptake and (+) khodadoust line superotemporally
A/C	Deep/quiet	Hazy view
I/P	flat, RR, no NVI	Flat, RR, no NVI
L	clear	clear

FUNDOSCOPIC EXAM

	OD	OS
Vitreous	Clear	Appears clear OS
C/D	0.35, sharp/distinct	0.35, sharp/distinct
Macula	Flat	flat
Vessels/Periphery	WNL, no heme/holes/tears 360deg	WNL, no heme/holes/tears 360deg

** limited view OS due to corneal haze**

DIFFERENTIAL DIAGNOSIS?

- Acute Corneal Graft Rejection
- Late graft failure
- Sterile/infectious endophthalmitis
- Epithelial downgrowth
- endotheliitis
- herpetic keratitis
- Other infectious keratitis
- Posner-Schlossman Syndrome

CORNEAL TRANSPLANTS

- Cornea = first successfully transplanted tissue
- Less commonly rejected compared to other transplanted tissues
  - Cornea as an "immune privileged site"
  - Absence of blood and lymphatic channels
  - Absence of MHC class II APCs in graft
  - Expression of T-cell deleting CD95 ligand (Fas ligand)
  - Immunosuppressive microenvironment of aqueous humor

ACUTE CORNEAL GRAFT REJECTION

- Initially described by Paufique et al in 1948 and later elaborated on by Khodadoust and Silverstein in 1969
- Sudden graft edema with anterior segment inflammatory signs in a graft that has previously been clear for at least 2 weeks
- Immunologically mediated process
- May lead to reversible or irreversible corneal graft damage

REJECTION VS. FAILURE?

- Acute graft rejection:
  - Sudden graft edema with anterior segment inflammatory signs in a graft that has **previously been clear for at least 2 weeks**
    - Immunologically mediated!

- Graft Failure:
  - Any irreversible change in graft preventing recovery of useful vision

ACUTE CORNEAL GRAFT REJECTION

- Complex immune mediated process resulting in the decompensation of the graft
- Characterized by 1 of the following:
  - Epithelial or endothelial rejection line and stromal rejection band
  - Recent unilateral anterior chamber reaction with keratic precipitate (KP)
  - Edema in a previously clear graft with visible aqueous cells
- Other Features:
  - Can start as early as 3 weeks or as late as 10 years out in a
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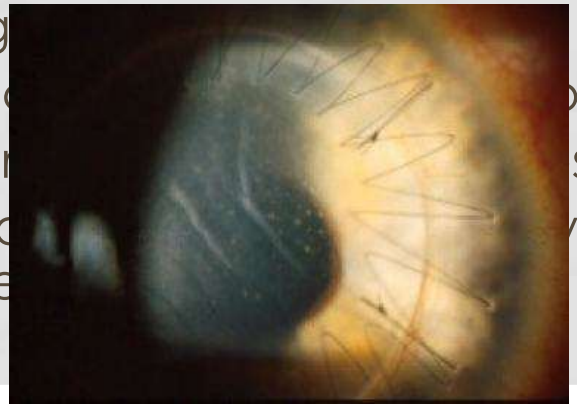
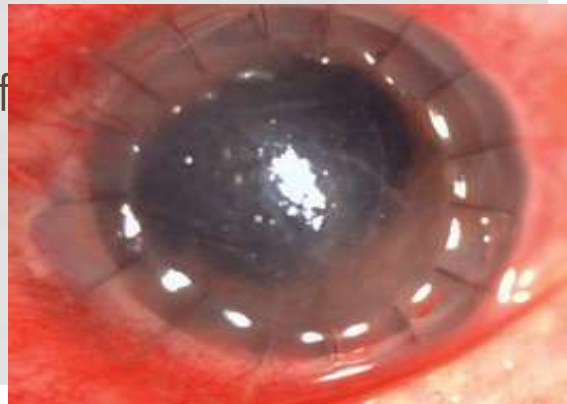




INCIDENCE

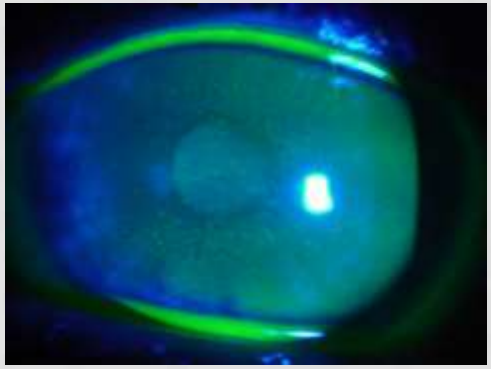
- 60,000 K grafts performed annually world-wide
- 30% of eyes with PKP experience at least 1 episode of rejection
  - 5-7% of rejection episodes lead to eventual graft failure
- Reported incidence varies from 2.3% to 68%
  - Australian Corneal Graft Registry:
    - 3,608 total K graft rejections
    - incidence of graft rejection 33%
  - Alldrege and Krachmer (1981):
    - Rejection occurs up to 50% of recipients
    - Rejection = single most important cause of graft failure
- Varies depending on vascular bed in which graft is placed, ABO compatibility of donor and host, etc.

RISK FACTORS FOR CORNEAL GRAFT REJECTION

- Donor Factors:
  - Antigenic load of donor (HLA and ABO compatibility between donor and host)
  - Method and duration of storage of donor cornea
    - Death to preservation time
    - Per Collaborative Corneal Transplantation Studies (CCTS), donor cornea preservation characteristics had minimal influence on outcome of graft
  - Age of donor
    - Cornea Donor Study showed that age of donor is NOT a prognostic indicator of graft survival
  - Endothelial cell count
  - Nature of donor button cutting

RISK FACTORS FOR CORNEAL GRAFT REJECTION

- Host Factors
  - Most important risk factor = vascularization of host cornea
    - Low Risk, Medium Risk, High Risk
  - Previously rejected corneal graft
    - Pre-sensitization of host
  - Ocular surface disease
  - Active Keratitis (and associated inflammation)
  - Young patients, bilateral grafts
  - Atopic dermatitis
  - Tear film insufficiency



RISK FACTORS FOR CORNEAL GRAFT REJECTION

- Other risk factors:
  - Jonas et al:
    - Suture loosening
    - Post-op corneal vascularization
  - Massry and Assil:
    - Post-operative pilocarpine use
  - Herpetic eye disease
  - Prolonged surgical time
  - Younger donor age

JAMA Ophthalmol. 2015 Mar;133(3):246-54. doi: 10.1001/jamaophthalmol.2014.3923.

Factors associated with corneal graft survival in the cornea donor study.

Writing Committee for the Cornea Donor Study Research Group, Sugar A, Gal RL, Kollman C, Raghinaru D, Dontchev M, Croasdale CR, Feder RS, Holland EJ, Lass JH, Macy JI, Mannis MJ, Smith PW, Soukiasian SH, Beck RW.

- Multicenter, prospective, double blind, RCT
- 1090 patients undergoing PKP for moderate risk condition (Fuchs Dystrophy or pseudophakic/aphakic corneal edema [PACE])
- Corneas from donors younger or older than 66 years were blindly assigned and transplant + post-op care were done as per surgeon's routine. 12 year follow up
- Outcome: graft failure
- 10 year cumulative probability of graft failure was higher in patients with PACE compared to Fuchs
  - Also higher in patients with hx of glaucoma prior to PKP or glaucoma surgery prior to PKP
- Increased graft failure in recipients > 70 y.o. versus <60 y.o.
- Increased graft failure in smokers vs. non-smokers
- Lower endothelial cell counts or higher CCT at 6 months and 1 year associated with subsequent graft failure

*** OVERALL MOST OF THESE GRAFTS STILL STAY CLEAR AT 10 YEARS ***

CLASSIFICATION OF GRAFT REJECTION

- Epithelial rejection:
  - Elevated, undulating line with fluorescein staining
  - Starts at periphery and moves toward center of graft
  - Kaye's Dots: superficial epithelial infiltrates which progress centrally from suture lines
  - Average onset is 3 months
  - Lymphocyte mediated
  - Often asymptomatic
    - Incidence under-reported

Often can cause or be associated with other forms of rejection (ie endothelial)

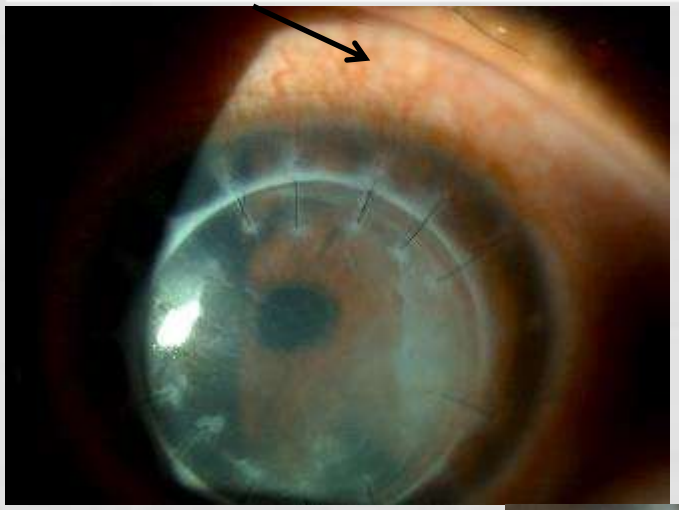
CLASSIFICATION OF GRAFT REJECTION

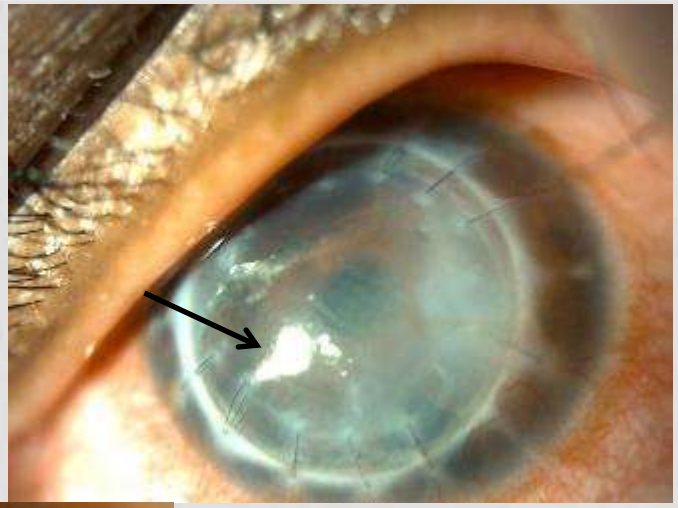
- Stromal Rejection:
  - Chronic:
    - Small white opacities at or below Bowman's Layer, strictly present only in donor tissue
    - Sub-epithelial infiltrates
    - Often respond well to steroids
    - Isolated stromal rejection will not cause graft failure but DO indicate that host is sensitized → impending endothelial rejection
  - Acute:
    - Simultaneously occurs with endothelial rejection
    - Sudden onset full thickness haze

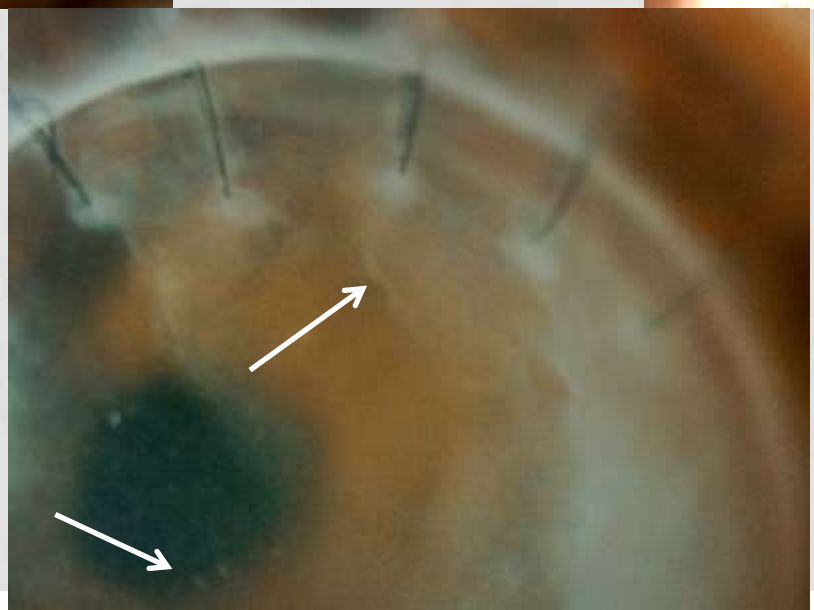
CLASSIFICATION OF GRAFT REJECTION

- Endothelial Rejection:
  - Most symptomatic and devastating
    - Pain, redness, decreased vision
  - Avg. time of onset = 8 months post-op
    - Can occur up to 35 years later!
  - Direct correlation with degree of vascularization (Khodadoust)
  - Large sized grafts more prone to endothelial rejection
  - Clinically:
    - Conjunctival hyperemia
    - A/C reaction
    - KPs (Khodadoust Line)
    - Graft edema with DM folds

DIAGNOSIS??







PREVENTION

- Pre-operatively:
  - Matching donor and host tissues to minimize antigenic difference
- Intra-operatively:
  - Reduce antigenic load of donor tissue:
    - Use CENTER of graft
    - Remove donor epithelium was previously considered helpful
    - Exposure of donor graft to UV light (possible depletion of Langerhans cells)
    - Pre-treating graft with hyperbaric O2
    - Endothelial transplant instead of PKP
- Post-operatively:
  - Corticosteroids (topical)

TREATMENT OF ACUTE GRAFT REJECTION

- Epithelial or sub-epithelial rejection
  - Corticosteroids:
    - Topically 6x/day, usually without systemic steroids
- Endothelial Rejection
  - Corticosteroids:
    - Topically q1h until acute rejection is arrested or reversed
    - Supplement with systemic corticosteroids
      - Initially high dose, then continue maintenance dosing depending on severity of episode and responsiveness to treatment
  - Cytotoxic Agents:
    - Azathioprine: inhibits cell proliferation in specific phase of cell cycle
      - Only useful in early rejection
    - Cyclosporine A: works on T cells, inhibits antigen presentation
      - High incidence of several side effects with no proven efficacy in resolving acute graft rejection – not used frequently

Cornea. 2015 Jun;34(6):609-14. doi: 10.1097/ICO.0000000000000403.

Prevention and treatment of corneal graft rejection: current practice patterns of the Cornea Society (2011).

Kharod-Dholakia B[1], Randleman JB, Bromley JG, Stulting RD.

- Electronic Survey sent in 2011 to 670 members of Cornea Society worldwide
  - Management of K transplants at different time points
  - Treatment of various manifestations of graft rejection
  - Preferred surgical techniques
- Results:
  - 204 total completed surveys (30% response rate)
  - All respondents used topical steroids for routine post-op rx and for endothelial graft rejection
  - Steroid of choice = prednisolone
    - Decreased 10% from prior surveys and difluprednate was used in 13% of high-risk eyes during first 6 months
  - 75% respondents felt graft rejection happens more frequently after PK compared to EK
- Conclusions:
  - Prednisolone remains treatment of choice for management of graft rejection but has decreased since introduction of difluprednate
  - No difference in prophylactic steroid treatment for PK and EK despite perceived differences in rejection rates for the two procedures

Cochrane Database of Systematic Reviews

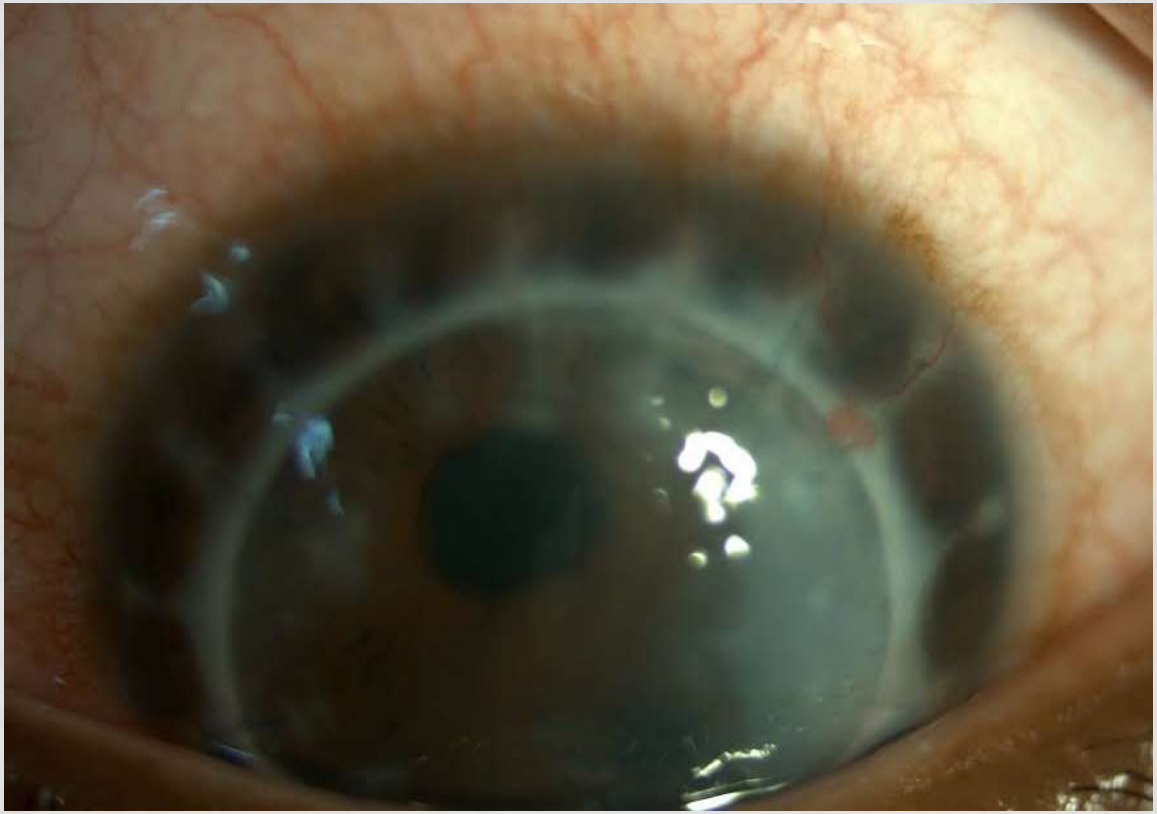
Immunosuppressants for the prophylaxis of corneal graft rejection after penetrating keratoplasty

- Included 6 studies from Germany, Iran, India, China
- 3 studies with patients undergoing high-risk PKP
  - Systemic MMF vs. no MMF
  - Systemic MMF vs. Cyclosporine A
  - Topical cyclosporine A vs. placebo
- 1 study compared topical tacrolimus to topical steroids in patients undergoing normal-risk PKP
- 2 studies compared topical cyclosporine A to placebo in patients experiencing graft rejection after normal risk PKP
- Results:
  - MMF may not improve clear graft survival but may decrease risk of graft rejection compared to no MMA
  - 3 year follow up suggests no difference between systemic MMF vs. systemic CsA on clear graft survival
  - Topical CsA likely makes no difference on clear graft survival or graft rejection at 1 year compared to placebo
- Most studies either did not report visual acuity or did not show a clear difference in visual acuity
- Conclusions:
  - Current evidence is low quality
    - Number of trials is limited
    - Trials that do exist are quite small and biased

BACK TO OUR PATIENT

- Initial Treatment:
  - Removal of 2 loose sutures
  - Topical prednisolone acetate q1h OS
  - prednisone 70mg PO daily
  - Ofloxacin QID OS

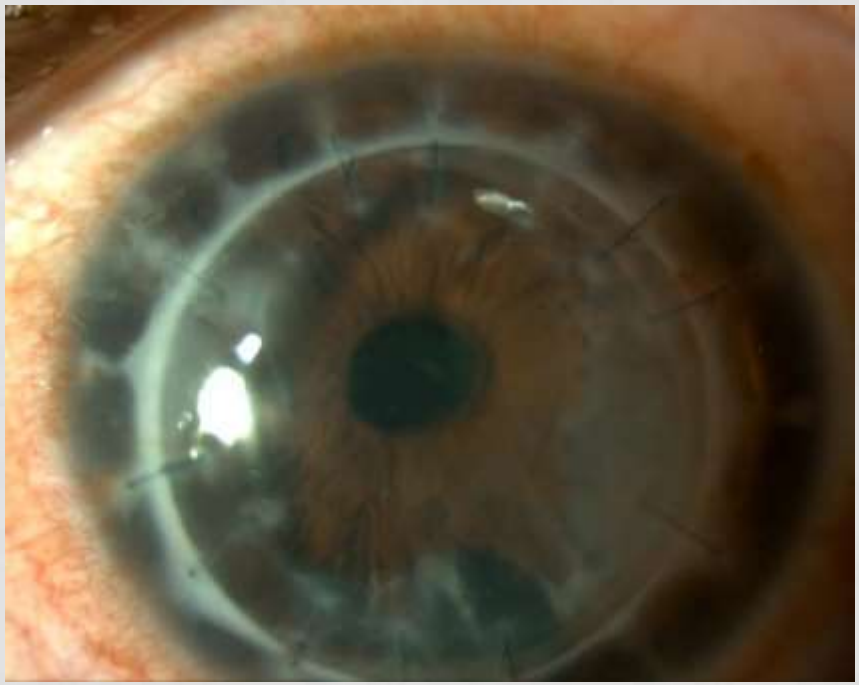
POST-TREATMENT DAY 1

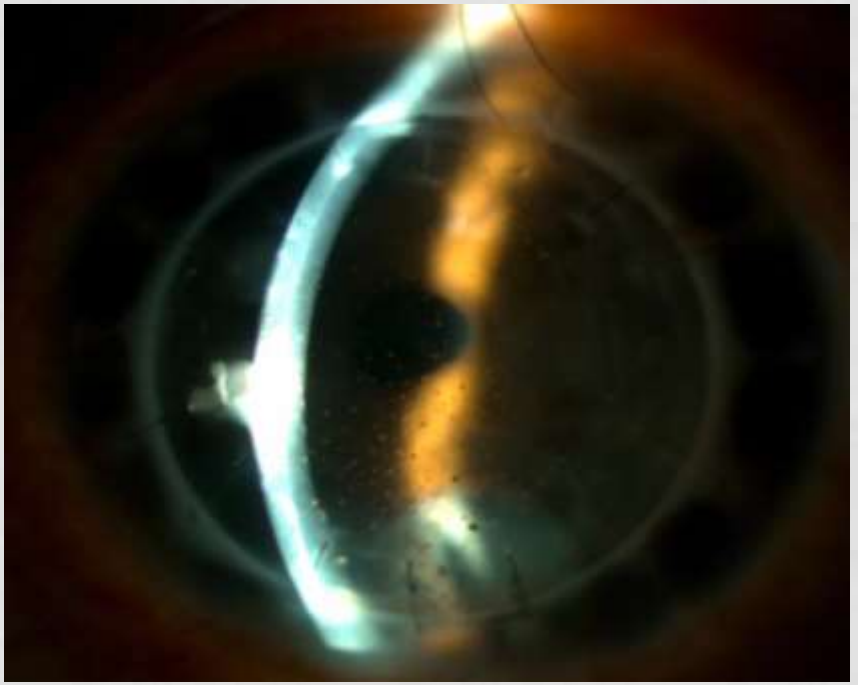


dVAsc OS: 20/150 (stable)

Pain improved

POST-TREATMENT DAY 6





dVAsc OS: 20/70+, PHI 20/25- (from 20/150, PH NI)

Pain significantly improved, graft appears more clear

REFLECTIVE PRACTICE

- This case demonstrated the importance of patient education and explanation of post-operative risks
- This case showed me the importance of thorough slit lamp examination in differentiating and classifying types of corneal graft rejections
- This case allowed me to learn more about an important and devastating disease entity and its presentation, treatment modalities, and complications
- This case allowed me to review the literature for management of this disease entity, while keeping in mind the prognosis and expectations of my patient

CORE COMPETENCIES

- Patient care: The case involved thorough patient care and careful attention to the patient's presenting 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 treatment options for acute corneal graft rejection
- Practice-based Learning and Improvement: this presentation included a literature search of current studies in the clinical presentation of acute corneal graft rejection
- 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.

REFERENCES

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THANK YOU!

- Patient
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