

Ophthalmology Grand Rounds

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SEPTEMBER 22, 2011

Case Presentation

- 81 year old female presents from an outside ophthalmologist for oculoplastic evaluation.
- POHx: 5 months prior to referral, “involutional” LLL entropion noted by ophthalmologist and patient had entropion repair.
- Symblepharon was noted LLL at that time.
- 1 month prior to referral patient had routine CE OS by the same ophthalmologist.
- After CE, noted to have a “corneal ulcer” & referred to corneal specialist for “ulcer and symblepharon”.
- Started on Azasite, Vigamox, bacitracin ointment, artificial tears, lacrilube and PO doxycycline.
- “Ulcer” progressed.
- Dosages of medications were increased.
- “Ulcer” progressed.

History

- PMH: HTN
- POHx: as above
- Meds: amlodipine, “water-pill”
- Gtts: as above
- SH: denies
- FH: denies

Physical Exam

- dVAsc: OD 20/25 OS 20/200 ph ni
- P: RR, no APD
- EOMS: restricted OS (almost frozen globe)
- CVF: full OU
- Tapp: 12,9 @ 2:30pm



Ptosis LUL > RUL

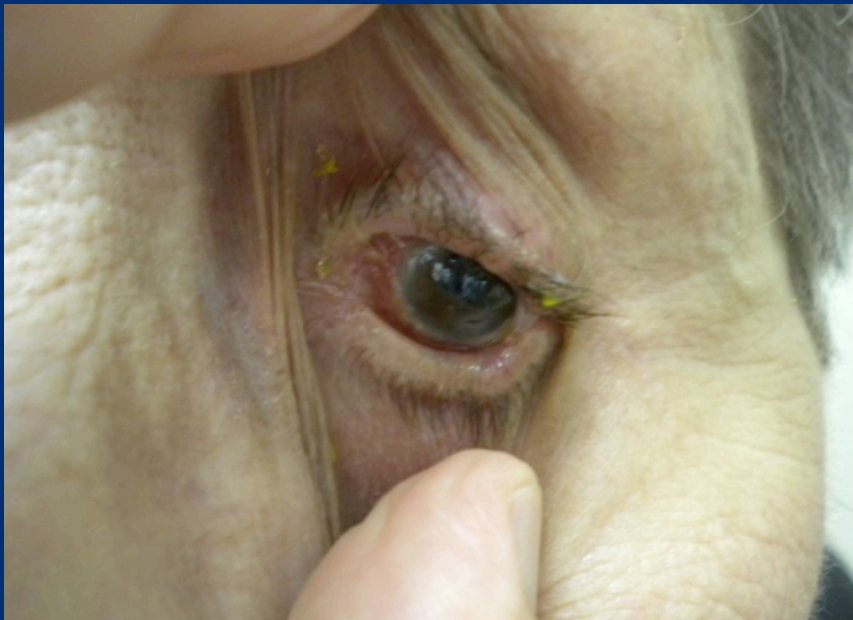
Dermatochalasis x4 lids

Tear trough deformity OU

Deep superior sulcus OU



- Symblepharon at lateral canthus OD



- Significant LUL trichiasis & distichiasis
- Foreshortened fornices inferior > superior OS
- Symblepharon 360 deg (largest at lateral canthus and lower lid temporally)

Physical Exam

■ SLE

- LLA: as described
- C/S: white and quiet OD, trace injection OS
- K: PEE OD > OS. Epithelial defect 3 x 4mm with 50% thinning, 6 o'clock midperiph OS, no infiltrate. Surrounding haze and pannus. Corneal sensation intact OS.
- AC: deep and quiet OD, trace cell OS
- IP: RR OU
- L: 1+NS OD, PCIOL OS

■ DFE

- V: clear OU
- M: flat OU
- C/D: 0.2 sharp and pink OU
- V/P: wnl OU

Differential Diagnosis?



Differential Diagnosis

Causes of cicatricial conjunctivitis

- **Autoimmune**
 - Ocular Cicatricial Pemphigoid
 - Epidermolysis bullosa acquisita
 - Linear IgA disease
 - Dermatitis Herpetiformis
 - Bullous Pemphigoid
 - Paraneoplastic Pemphigus
 - Lichen Planus
- **Infectious**
 - Trachoma
 - Corynebacterium Diphtheriae
 - Streptococcal Conjunctivitis
 - Adenoviral Keratoconjunctivitis
- **Systemic**
 - Sarcoidosis
 - Scleroderma
 - Sjogrens Syndrome
- **Allergic/Atopic**
 - Atopic keratoconjunctivitis
 - Stevens-Johnson Syndrome
 - Toxic Epidermal Necrolysis
- **Miscellaneous**
 - Ocular Rosacea
 - Trauma/Chemical burns/irradiation/surgery/ligneous conjunctivitis
 - Porphyrea Cutanea Tarda

Ocular Cicatricial Pemphigoid (OCP)

- Chronic, slowly progressive and relentless autoimmune disease.
- Chronic conjunctivitis, fibrosis and distortion of eyelid anatomy
- Chronic dry eye, entropion, trichiasis and corneal complications (infection, vascularization, scarring, perforation).
- Bilaterally blinding if left untreated.



End stage disease. Photo courtesy of Foster, S. Ocular Cicatricial Pemphigoid, A Patient Education Monograph. American Uveitis Society. January 2003.

Mucous Membrane Pemphigoid (MMP)

- A group of autoimmune diseases characterized by blistering of mucous membranes and skin.
- Can involve any mucous membrane: oral cavity and eye are the most common. Other locations include pharynx, larynx, trachea, esophagus, genitalia, anus and skin.
- Autoantibodies directed against the mucous membrane basement membrane zone (BMZ) at the epithelial-subepithelial junction.
- Inflammation follows, and the result is blister formation which eventually leads to scarring.
- Benign if it affects the oral mucosa. Blinding if it affects the eyes. Life threatening if it affects the trachea or esophagus.

OCP Epidemiology

- 80% of patients with MMP have ocular involvement → OCP
- Isolated or associated with extraocular lesions.
- Annual incidence of 1/20,000 to 1/46,000.
- Most often diagnosed in late stage of the disease.
- More common in the elderly. Average age of 64 years. Range from 20 to 84 years.
- Affects women more than men (1.6:1)
- No racial or geographic predilection.
- Genetic predisposition: associated with DQw7 gene, HLA DR4.

Pathophysiology

- Genetic susceptibility + environmental factor → Immune dysregulation → Production of autoantibodies.
- Several auto-antigens have been identified, all located in the basement membrane zone (BMZ): laminin 5, $\alpha 6$ -integrin, B4 integrin.
- Spectrum of related diseases depending on the antigen.
- Linear deposition of immunoglobulins (IgG, IgA) and complement at the basement membrane zone.
- Antibodies interfere with adhesion properties of the BMZ → blister formation.
- Conjunctival stromal infiltration of inflammatory cells: macrophages, plasma cells, lymphocytes, eosinophils, mast cells.
- High levels of TNF- α , TNF- β , IL-1 and IL-6
- Fibroblast stimulation → scarring.

Signs & Symptoms

- Begins with a chronic conjunctivitis: redness, tearing, burning, foreign body sensation.
- May be unilateral at onset.
- Symblepharon formation from the palpebral to the bulbar conjunctiva. Inferior fornix involved first.
- Distorted anatomy: entropion, trichiasis, dystichiasis, lagophthalmos
- Ankyloblepharon- obliterates the conjunctival sac.
- Severe dry eyes.
 - Destruction of lacrimal ducts
 - Destruction of goblet cells → depletion of mucin → rapid tear break up time.
- Corneal Damage.
 - Dry eyes + mechanical factors + inflammatory agents
 - Infectious keratitis, vascularization, perforation, decreased vision.
- Extraocular involvement.

Extraocular Involvement

- In one study, 16% of patients with OCP had skin lesions and 42% had oral mucosal lesions.
- Mouth involvement: painful recurrent erosions
- Progressive scarring can lead to esophageal stenosis requiring dilatation procedures. Supraglottic involvement can lead to airway compromise.
- Skin lesions develop in approximately one third of patients, manifesting as tense vesicles or bullae that may be hemorrhagic.

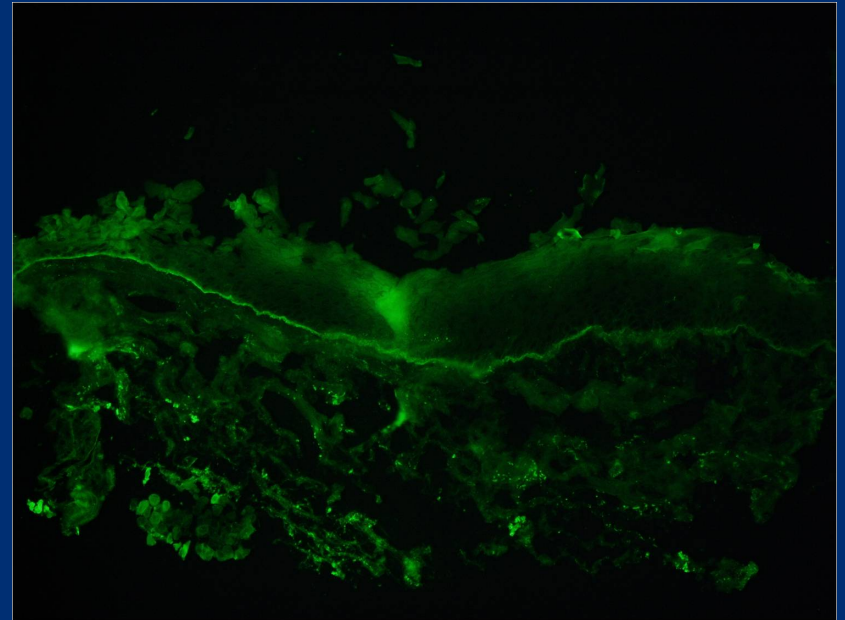


Pseudo-Pemphigoid

- Some topical and systemic medications have been shown to cause symblepharon which can mimic OCP.
 - Pilocarpine
 - Topical beta blockers
 - Topical epinephrine
 - Systemic beta blocker (practolol)
- Unilateral, affecting the eye receiving the medication.
- Cessation of disease progression on discontinuation of medication.
- Biopsy negative for MMP.

Diagnosis

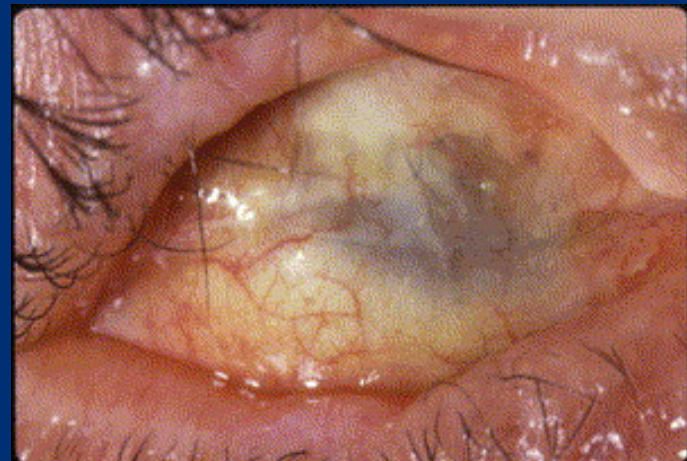
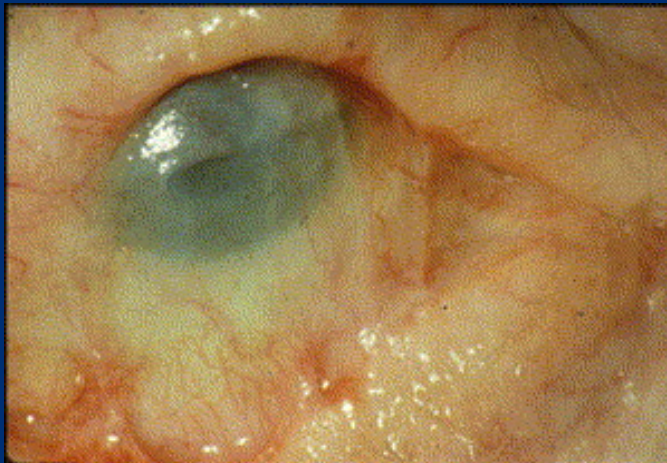
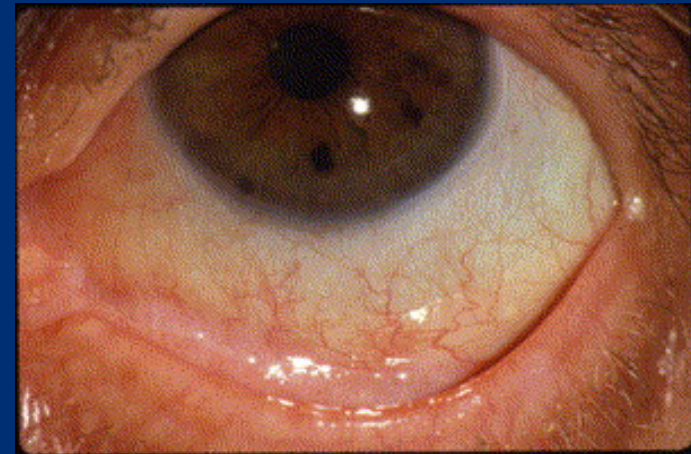
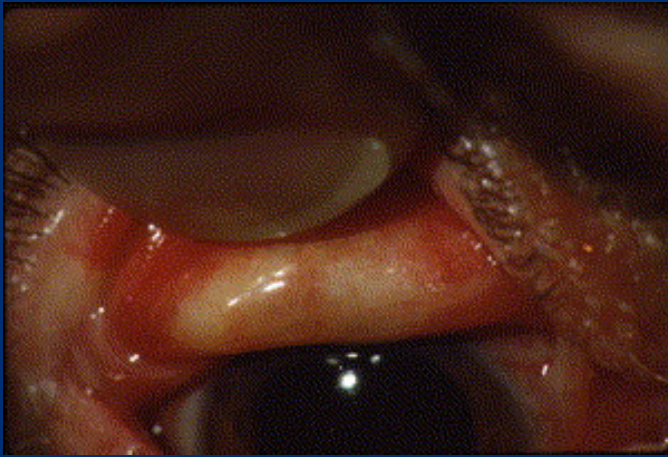
- High clinical suspicion for early diagnosis.
- Conjunctival biopsy + direct immunofluorescence is the gold standard.
- Immunoreactants (IgG, IgA, C3) are deposited in a linear fashion along the BMZ.
- Not specific! Also seen in epidermolysis bullosa acquisita, bullous pemphigoid, linear IgA disease.
- Sensitivity of 50-70%. Increases to 80% with immunoperoxidase technique.
- Serum antibody tests in a minority of patients.



Foster Staging System

- Stage I
 - Conjunctival inflammation
 - Mucous discharge
 - Small patches of rose bengal staining conjunctival epithelium
 - Subepithelial fibrosis
- Stage II
 - Foreshortening of inferior conjunctival cul-de-sac
 - Blunting of angle of reflection from the eyelid and fornix onto the globe.
- Stage III
 - Progressive sub-epithelial bands of connective tissue
 - Symblepharon formation
 - Corneal neovascularization
 - Keratopathy
 - Trichiasis + dystichiasis
 - Decreased tear production
- Stage IV
 - Severe sicca syndrome
 - Ocular surface keratinization
 - Ankyloblepharon

OCP Staging



Images courtesy of: Ahmed, M, Zein, G, et al Ocular cicatricial pemphigoid: pathogenesis, diagnosis and treatment. Progress in Retinal and Eye Research.

Treatment

- Patients usually present in late stage disease requiring aggressive immunosuppressant therapy.
- No topical medications have shown to be effective. topical steroids, cyclosporin, mitomycin C and retinoids have all failed.
- High dose systemic steroids can reduce scarring and inflammation, but do not adequately control OCP when used alone.
- More than one agent is often needed to adequately control OCP.
- Therapy for > 1 year with weekly or biweekly visits.
- Slow taper and lifelong follow up.
- High rate of recurrence after discontinuation of agents.
- Therapy can arrest scarring, but does not reverse it.

Systemic Conventional Immunosuppressive therapy (CIST)

- Diaminodiphenylsulfone (Dapsone): First line for mild to moderate disease.
 - Test for glucose-6-phosphate dehydrogenase, because it is contraindicated in G6PD deficiency.
 - Side effects include leukopenia and hemolytic anemia.
- Azathioprine, methotrexate or mycophenolate mofetil: may be substituted or added.
- Cyclophosphamide +/- systemic steroids: First line for severe disease.
 - 2mg/kg/day + prednisone 1mg/kg/day
 - Prednisone taper over 3-4 months
 - Continue cyclophosphamide for 12-14 mo.
 - Shown to induce long-term remission in several studies.
 - Side effects: bone marrow suppression, hemorrhagic cystitis, bladder ca, AML.
- IVIG: For patients resistant to chemotherapy, intolerant to its side-effects or unresponsive to long-term use of immunomodulators.

Treatment of Ocular Mucous Membrane Pemphigoid with Immunosuppressive Drug Therapy

Thorne, JE, Woreta FA, Jabs, DA, Anhalt GJ, Ophthalmology 2008

- Retrospective study of 94 patients from Wilmer's pemphigoid clinic treated from 1984-2006.
- At the time of presentation 74% had stage III disease.
- Authors looked at control of inflammation, remission and relapse rates.
- 82.9% of patients had complete control of inflammation after 1 year of treatment regardless of initial treatment regimen
- 80% achieved remission (no disease after 3 months of discontinuation of therapy) regardless of regimen.
- Of those receiving cyclophosphamide + prednisone, 91% achieved remission after 2 years.
- 18.2% of patients had an ocular relapse.
- Cyclophosphamide associated with a 8.5-fold increase in the likelihood of achieving ocular remission, independent of disease severity.

Side Effects Associated with Cyclophosphamide Therapy

- Anemia: 38.8%
- Thrombocytopenia: 22.7%
- Severe Leukopenia: 16.2%
- Neutropenia: 14.5%
- Cancer: 11.6%
 - 9 cases: 4 skin, 2 leukemia, 1 breast Ca, 1 laryngeal squamous cell ca, 1 bladder Ca
- Bladder Cancer: 1.4%
- Pneumonia: 5.8%
- Any infection: 48.6%

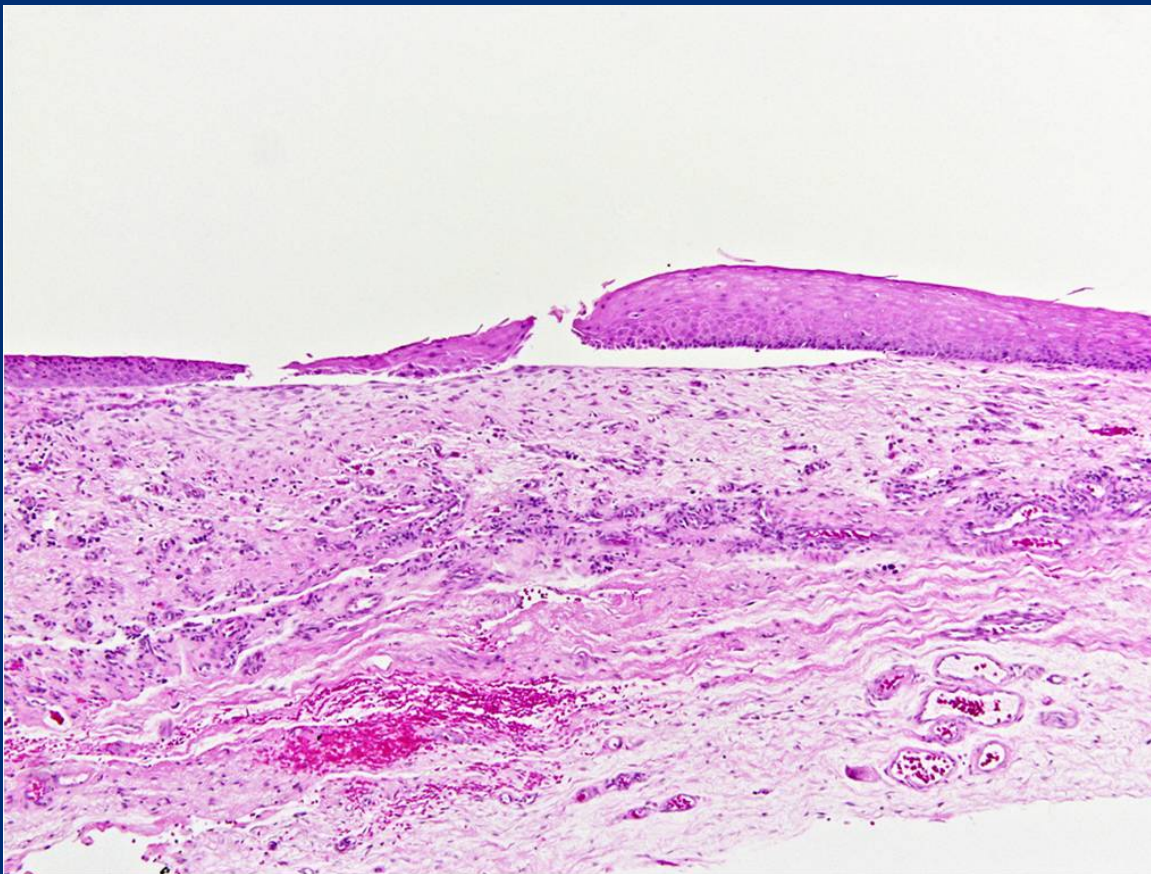
Surgical Management

- All surgery should wait until active inflammation has subsided & patient shows stability!!
- Trichiasis & dystichiasis:
 - Mechanical epilation, electrolysis, cryotherapy.
- Dry Eye & Exposure:
 - Punctal occlusion + lubricants, lid hygiene.
 - Tarsorrhaphy
- Entropion
 - Mucous membrane graft, full thickness lid resection, modified Weis.
 - Retractor plication technique-shortening of inferior retractor fascia, does not involve conjunctival operation.
- Fornix Reconstruction
 - With amniotic membrane transplant
 - Oral mucosa graft: places a smooth lining between the diseased lid margin and cornea.
- Penetrating Keratoplasty
 - Poor outcomes in OCP.
- Keratoprosthesis



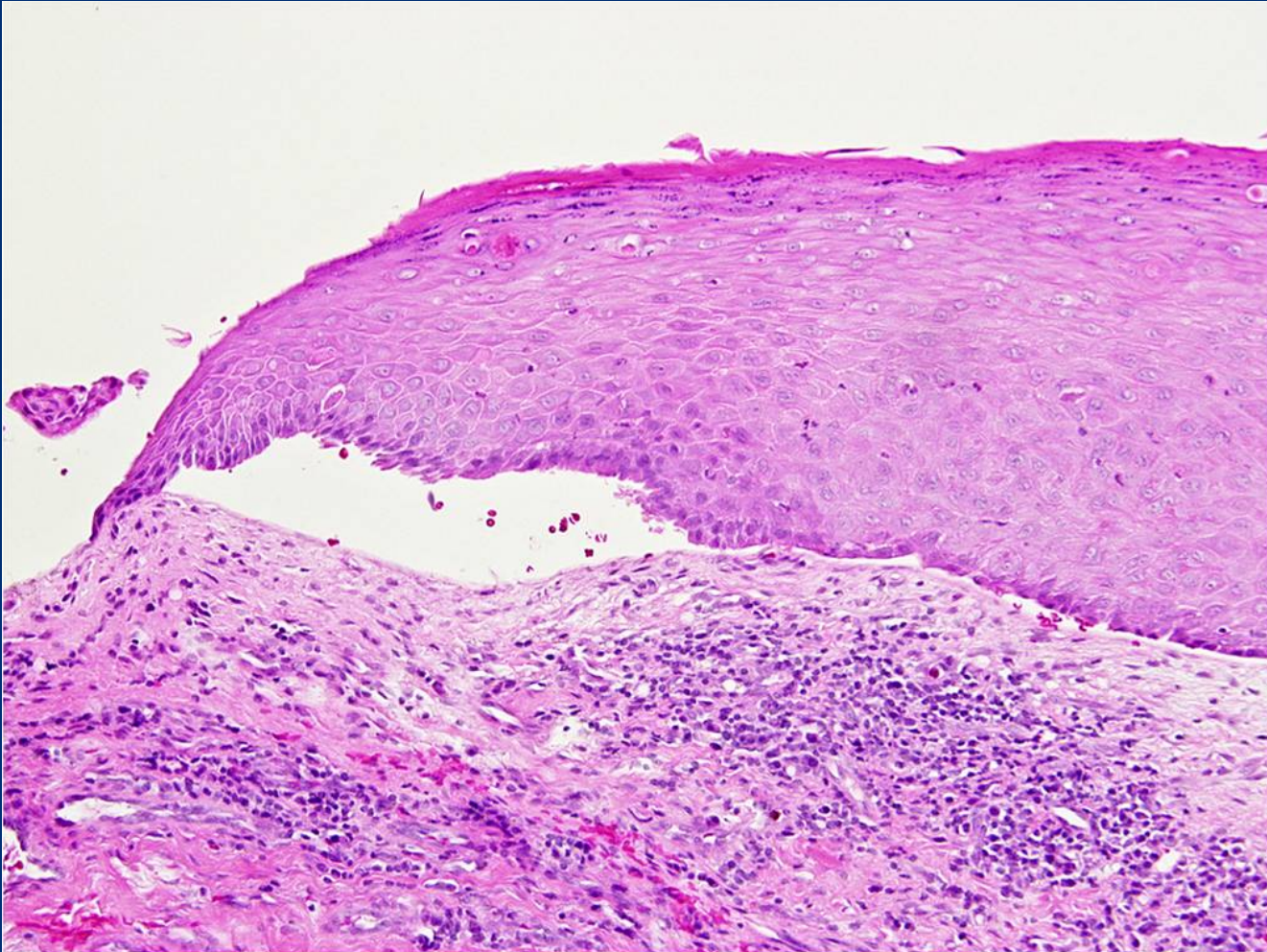
OUR PATIENT...

- 2 large samples of diseased conjunctiva and symblepharon were obtained, one sent for H&E and one sent for immunofluorescence...

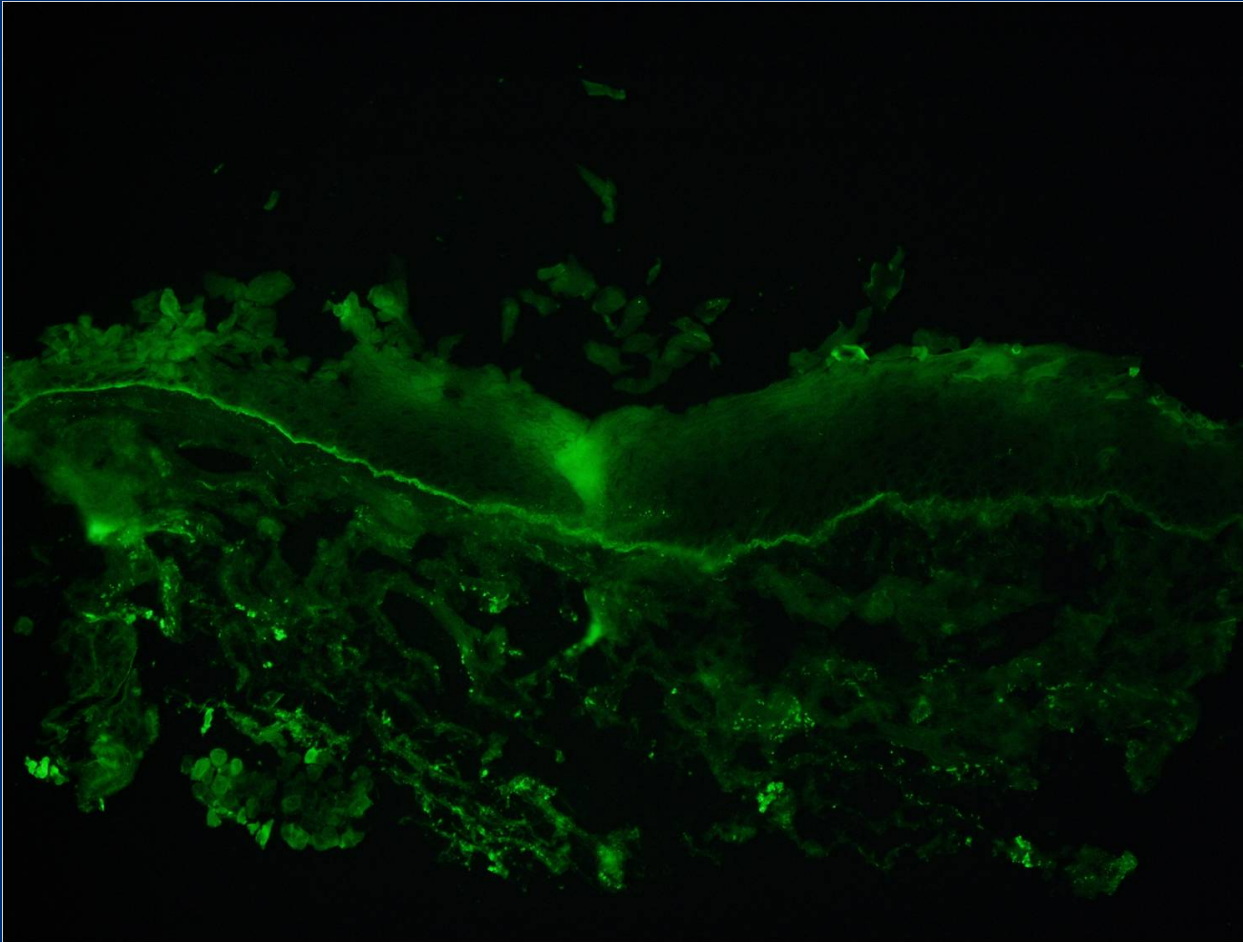


- Surface keratinization
- Loss of goblet cells
- Subepithelial bulla
- Fibrosis & chronic inflammation in substantia propria

H&E

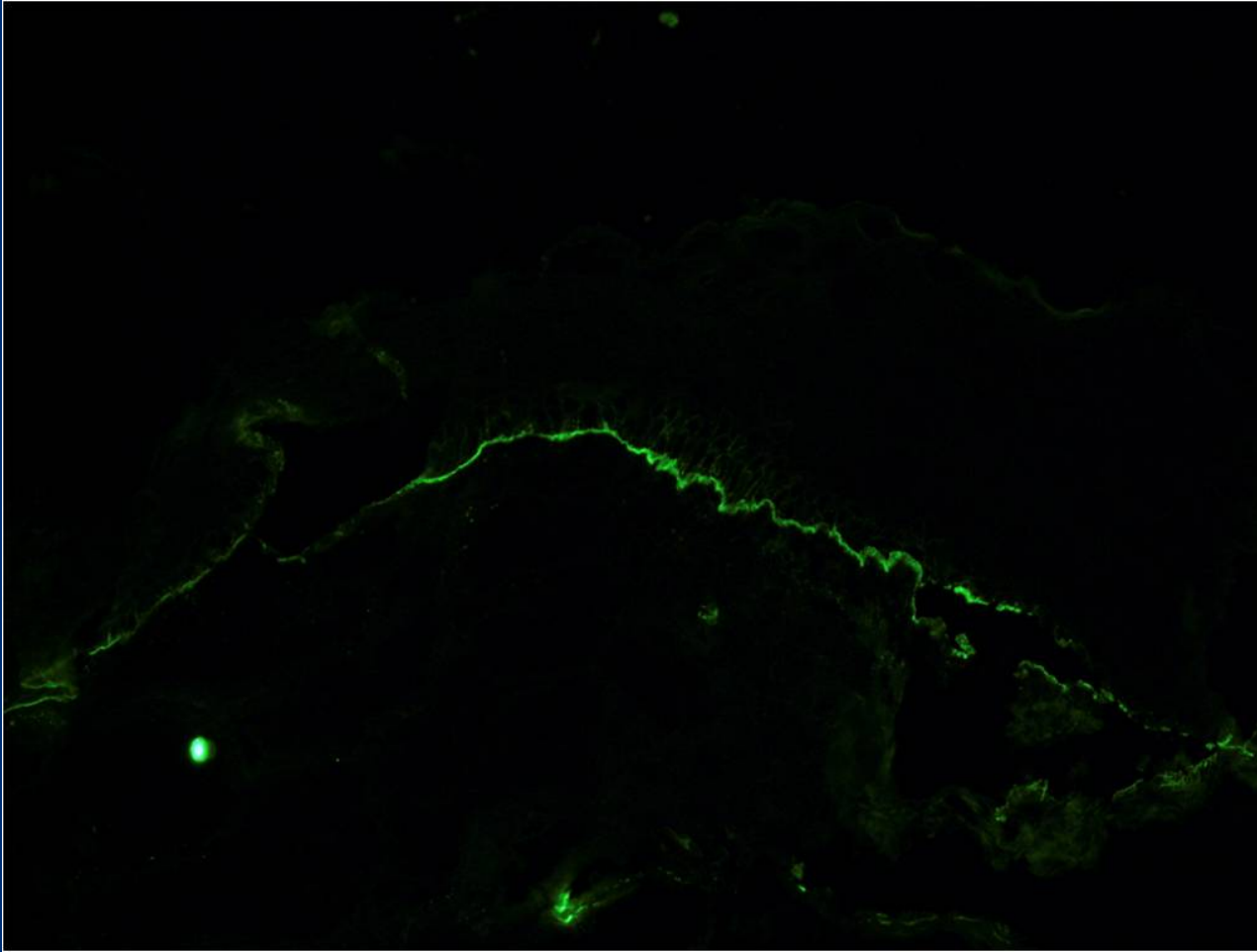


Immunofluorescence



- IgG direct immunofluorescence of BMZ

Immunofluorescence



- IgA direct immunofluorescence of BMZ

Management

- Biopsy confirms OCP.
- Started patient on PredForte q1hour OS + Tobradex ointment qid.
- Patient was checked for oral and skin lesions. History negative for any extraocular involvement.
- Rheumatology consulted for immunosuppressive expertise.
- Started on cyclophosphamide and prednisone 40mg with plan for switch to mycophenolate mofetil.
- Rheum increased prednisone to 60mg after mild progression.
- BCVa OS 20/70 last visit, no surgery planned yet.
- Follow up in 3 weeks...

Reflective Practice

- This case is an example of a rare pathology that if not treated urgently and appropriately with systemic immunomodulators, will ultimately progress to bilateral blindness. The diagnosis is easily missed, particularly in its early stages, and ophthalmologists must have a high clinical suspicion.
- An interdisciplinary team approach is appropriate for the OCP patient- calling on rheumatologists, pathologists, and dermatologists, as well as ophthalmologists.
- Risks and benefits of therapy need to be weighed, with consideration of adverse effects in an elderly population. While a majority of patients do respond to the treatments we have available, there are patients who progress or relapse despite aggressive immunosuppressive therapy.

Core Competencies

- **Patient Care:** Care was provided that was compassionate, and appropriate and effective for the management of OCP.
- **Medical Knowledge:** This case allowed us to review the presentation, differential diagnosis, and management of OCP.
- **Practice Based Learning & Improvement:** Evidence based medicine was a driving force in our management decisions. The presentation of this case may help us maintain a high clinical suspicion for future patients with OCP.
- **Interpersonal & Communication Skills:** The patient and family were provided with explanations and treatment options in non-medical terminology. Frequent communication with the patient, family and other medical services was and is still maintained.
- **Professionalism:** The patient was treated with respect
- **Systems-Based Practice:** We were aware of the many facets of the healthcare system and made an effort to call on all available resources.

Thank You!



- Dr. Shinder
- Dr. Calderon
- Dr. Gutman
- Dr. Narang
- And the rest of the KCH Residents

References

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