Ocular Manifestations of MMP

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No Conflicts of Interest
Mucous Membrane Pemphigoid (MMP)

• Chronic autoimmune diseases characterized by blistering lesions of various mucous membranes.

• Presentation:
  – Oral Involvement (90%)
  – Ocular involvement (61%)
  – Skin (15%)
  – Oropharynx
  – Nasopharynx
  – Esophagus
  – Larynx
  – Genitalia
  – Anus
Ocular MMP

- Previously called ocular cicatricial pemphigoid (OCP)
- Autoimmune vesicobullous disease primarily affecting the ocular conjunctiva
- Leads to a chronic, cicatricizing conjunctivitis
Epidemiology

• Incidence rate: 1 in 12,000 to 1 in 60,000
  – RDU has about 2 million people = about 165 people with ocular MMP in this area
• Woman > Men, 2:1
• Age of onset: 60-70 years

Mechanism of Ocular Damage

• Type II hypersensitivity (cell injury due to autoantibodies against a cell surface antigen in the basement membrane zone)

• Possible autoantigens
  – Bullous pemphigoid antigen II (BP180)
  – Laminin 332

• Antibody activates complement $\rightarrow$ breakdown of the conjunctival membrane $\rightarrow$ blister $\rightarrow$ scar

• Pro-inflammatory cytokines (IL-1, TNF alpha) are overexpressed
Mechanism of Ocular Damage in Ocular MMP

- Cellular immunity may also play a role
- Specific HLA types (a special genetic locus in the MHC complex) are associated with this condition, but not all individuals have this
Physiology of Damage in Ocular MMP

• Recurrent conjunctival inflammation → destruction of goblet cells and obstruction of lacrimal gland ductules → mucous and aqueous tear deficiency state → keratinization of the ocular surface
Physiology of Damage in Ocular MMP

- Inflammation also → scarring → trichiasis and entropion, which → mechanical irritation → abrasions, corneal vascularization, scarring, ulceration, and keratinization
- Corneal abrasions should be treated immediately to minimize scarring, perforation, and ankyloblepharon (fusion of palpebral and bulbar conjunctiva)
Historical Clues

• Other body system symptoms
  – Difficulty swallowing
  – Voice changes
  – Oral mucosal lesions
  – Genital ulcerations
  – Possibly GI bleeding or nosebleeds
Early Symptoms of Ocular Involvement

• Any dry eye symptom
  – Pain
  – Burning
  – Light sensitivity
  – Blurry vision
  – Red eye
  – Itching
Early Signs of Ocular Involvement

- Linear subepithelial conjunctival scars
- Inflammation of the conjunctiva (initially recurrent attacks of mild and non-specific conjunctival inflammation with occasional mucopurulent discharge)
- Conjunctival edema or erosions
- Tear dysfunction/dry eye
- Unexplained persistent epithelial defects
- Entropion
- Trichiasis
- Usually one eye is involved first, followed by the second eye within 1-2 years
Common manifestations

• Progressive scarring
  – Symblepharon
  – Corneal scarring
Foster Staging System

- **Stage I**
  - **Subepithelial fibrosis** (fine grey/white linear opacities, best seen with thin slit beam in the deep conjunctiva, caused by rupture of transient conjunctival bullae)

- **Stage II**
  - Loss of goblet cells
  - **Shortening of inferior fornices** (< 8 mm is abnormal)

- **Stage III**
  - **Symblepharon formation** (subtle symblepharon can be seen when lower eyelid is pulled down and patient looks up)

- **Stage IV**
  - **Restricted motility with extensive adhesions** between the eyelid and globe
Possible Triggers for Disease Activity

• Trauma (eye surgery)
Usual Course in Ocular MMP

• Progressive deterioration (with times of remission and exacerbation) if untreated
• Surgical intervention can incite inflammation, but may be necessary to prevent further mechanical damage
Differential Diagnosis

- **Infectious**
  - Adenovirus
  - Corynebacterium diphtheriae
  - Trachoma

- **Allergic**
  - Atopic keratoconjunctivitis
  - Steven-Johnson syndrome

- **Autoimmune**
  - Lichen planus
  - Lupus
  - Sarcoidosis
  - Scleroderma
  - Linear IgA dermatosis

- **Neoplastic**
  - Paraneoplastic MMP
  - Sebaceous cell carcinoma
  - Squamous cell carcinoma

- **Miscellaneous**
  - Chemical burns
  - Medicamentosa (pseudopemphigoid)
  - Ocular rosacea
  - Radiation
  - Trauma
  - Porphyria cutanea tarda
  - Congenital Icthyosiform erythroderma

Unilateral ocular MMP is very rare – make this diagnosis with caution!
Pseudopemphigoid

- Associated with long term use of certain topical ocular drops (or systemic practolol)
  - Pilocarpine, timolol, epinephrine, demecarium bromide, ecothiophate iodide, idoxuridine
- Disease progression usually stops once the drops are stopped
- Biopsy may or may not be positive for immunoreactants
Lab Evaluation of Ocular MMP

- Immunohistochemical staining demonstrates complement 3, IgG, IgM, and/or IgA in the conjunctival epithelial basement membrane zone (BMZ)
- Specimens should be obtained from an active area of inflammation, or, if activity is diffuse, from the inferior conjunctival fornix
- False negative results are common (estimated at 3-80%)
Serum testing in Ocular MMP

- Circulating anti-BM antibody has been identified in the serum of some patients with MMP
  - May have false positives or false negatives also
- End stage disease can create negative results because of the complete destruction of the conjunctival basement membrane
Mondino Staging System

• Stage I
  – 0-25% loss of inferior fornix depth
• Stage II
  – 25-50% loss of inferior fornix depth
• Stage III
  – 50-75% loss of inferior fornix depth
• Stage IV
  – 75-100% loss of inferior fornix depth
Tauber Staging System: Incorporates Mondino and Foster

- Foster stage I
- Foster stage II
  - A, 0-25% loss of fornix depth
  - B, 25-50% loss of fornix depth
  - C, 50-75% loss of fornix depth
  - D, 75-100% loss of fornix depth
- Foster stage III
  - A, 0-25% horizontal involvement (X number of symphblephara)
  - B, 25-50% horizontal involvement (X number of symphblephara)
  - C, 50-75% horizontal involvement (X number of symphblephara)
  - D, 75-100% horizontal involvement (X number of symphblephara)
- Foster stage IV
Management Strategies for Controlling Disease

• Multidisciplinary approach
• Important to carefully monitor and stage patients
• Requires systemic treatment
• Any eyelid or eye surgery can cause a flare, so adequate immunosuppression is necessary prior to surgery
• Surgical correction of eyelid deformities or trichiasis is important (hard palate or buccal mucosal grafting might be necessary, punctal occlusion, corneal transplant is rarely successful, keratoprosthesis as a last resort)
• It is frequently difficult to tell if progression is due to active disease, or is a consequence of mechanical damage already done
Treatment: Systemic Immunomodulators

• Mild
  – Dapsone (50 to 200 mg/day for 12 weeks)
    • Complications: Hemolysis and methemoglobinemia.
    • Contraindication: G6PD deficiency
  – No improvement within 3 months: Methotrexate or azathoprine.

• Moderate to Severe:
  – Methotrexate, azathoprine, mycophenolate mofetil, tetracyclines

• Severe to refractory:
  – Cyclophosphamide plus prednisone for ≤ 12 months

• Refractory
  – IVIG
  – Rituximab
Treatment Continued

• **Treating Ocular Symptoms**
  • Ocular lubricants, punctal plugs or cautery, moisture chambers, scleral contact lenses, cyclosporine, topical steroids, autologous serum, tacrolimus
  • Prevention and treatment of infection

• **Surgical Options**
  • Eyelash removal
  • Removal of symblephara
  • Repair of entropion
  • Limbal stem cell transplant
  • Corneal transplant
  • Keratoprosthesis

Less Risk

More Risk
Dry eyes: Commercial advice

Dry eyes? Use artificial tears!
Ocular Lubricants

- Preservative free variety are best
- Do not recommend use of any “gets the red out” drops
- Gel tears or ointments are more moisturizing but because they are thicker they can blur the vision, many patients like to use these at night before bed
Creating Increase Ocular Moisture

• There are many types of moisture chamber goggles to choose from
  – MEGS
  – 7 eyes
  – “Onion goggles” available from cooking stores
  – Swim goggles
  – “moisture chamber goggles” online
Punctal plugs

• Either made of silicone or copolymer (dissolve, typically within 3 months)
• Block the drainage system of the eye, keeping more of the patient’s own tears on the surface of their eye
• Can be placed in the office
Punctal Cautery

- Use a thermal cautery to permanently close the tear ducts (although these can open up on their own sometimes)
- Same function as plugs, but no foreign body within the tear ducts
- Is a procedure that is typically performed in the office, with local anesthesia
Autologous Serum Tears

- Eyedrops made from a patient’s own blood
- Typically a lab will draw the blood, and then send it to a compounding pharmacy where the blood is spun down to separate out the serum, which is placed into vials
- Typically the patient receives several months worth of vials at once, and they store these in their freezer and use one vial per day
Cyclosporine 0.05%

- Affects T cell function
- Has been shown to increase tear volume in some patients
- Can also be compounded to give higher percentages
- Takes about 6 weeks to work
Lifitigrast

- Also affects T cell function, through a different mechanism
- Has been shown to improve dry eye symptoms and signs
- Should take about 2 weeks to work
“True Tear” device

- Sends an electrical stimulus to the nose, which produces tearing
- Newer product
Electrocautery of Eyelash Follicle

- Procedure typically performed with local anesthesia in a minor procedure room or operating room
- Goal is to eliminate eyelash regrowth
- May need to repeat several times to permanently inhibit growth
Treatment for Entropion/Ectropion

- Surgical Repair
- Scleral lenses
- Moisture chamber goggles
- Plastic wrap (especially press and seal variety) can be helpful to place over eye at bedtime
Enhancement of MG Function

- Omega 3 supplementation (fish oil, walnuts, flax oil)
- Warm compresses
- Lipiflow
- Topical steroid eyedrops (long term use can have side effects)
- Intense pulsed light (mechanism unknown)
- Oral minocycline, doxycycline, or azithromycin
- Topical azithromycin
Treatment for Ocular Exposure

- Ointment
- Contact lens (scleral or bandage lens)
- Taping eyes shut
- Tarsorrhaphy (suturing eyelids partially closed, either permanent or temporary)
Repair of Symblepharon

- Use amniotic membrane frequently, with symblepharon ring
Limbal Stem Cell Transplant

• Easier if only one eye is involved
• If both eyes involved, would need a donor and the patient would need to immunosuppressed afterwards to prevent rejection
Corneal Transplant

• High risk for ocular MMP
Keratoprosthesis

• Very high risk for complications (glaucoma, infection, melting of surrounding ocular tissue)

• Can give patients vision who are otherwise blind from corneal scarring
MOOKP

- Rarely performed in the United States
- A patient’s tooth is extracted and shaped so that it can be implanted in the front of their eye and an artificial cornea is then implanted in the tooth
Prognosis

• In most patients, ocular MMP progresses slowly
  – Initial conjunctival inflammation -> end stage disease (10-30 or more years)

• Without treatment, disease progression occurs in up to 75% of patients

• Physicians will often discontinue systemic therapy if disease remains dormant for several years
  – Up to 22% relapse rate
Thank you

• Jamie Prince, UNC medical student
• IPPF
References

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- rarediseases.org
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- Medscape Ocular Cicatricial Pemphigoid (OCP) Treatment & Management
- Up to Date