Photodynamic therapy for IMMK in horses

Overview

- Immune mediated keratitis in horses
- Traditional treatment options
  - Sustained release implant
- Photodynamic therapy
  - Use in veterinary medicine
  - Treatment for IMMK

Immune mediated keratitis

- Progressive, chronic or recurring
  - Mild to moderate cellular infiltrate
  - Vascularization
  - Corneal edema
  - Absence of overt uveitis
- Varying mild to no signs of discomfort
- Average age: 12 years
- Unilateral to bilateral

Pathogenesis

- Candidate pathogenesis
  - Auto antigen in the cornea
- Contributions of environmental and genetic factors

Histopathology

10 client owned horses with IMMK

- IHC staining: CD3 (T cell), CD79a (B cell), CD4 (T Helper), CD8 (T cell cytotoxic)
- CD3, CD4, CD8

Pathogenesis appears to be governed by both cytotoxic and helper T cells

IMMK in horses

- Classifications
  - Epithelial
  - Stromal
    - Superficial stroma
    - Mid-stroma
    - Endothelial
  - Eosinophilic keratitis
Epithelial
- Multifocal punctate areas
  - Non-ulcerative, cellular infiltrate
  - Usually no vascularization
- DDx: Fungal keratitis
  - EHV-2 or 5

Superficial stromal
- Sub-epithelial, white to yellow stromal cellular infiltrate
- Surrounded by superficial vascularization

Mid-stromal
- Cellular infiltrates, deep vascularization
- Less responsive to medical management

Endothelial
- Chronic, slowly progressive, non-painful
  - Diffuse ventrolateral or ventral
  - Dark cellular infiltrate on endothelium
  - +/- Bullous keratopathy
- DDx: Glaucoma, uveitis, Stromal abscess (painful)

Eosinophilic
- White plaques
  - surrounding corneal edema
  - superficial stromal, perilimbal yellow infiltrate
  - Can be self-limiting
    - Tx: Can speed recovery
      - Systemic cetirizine, dexamethazone
  - Moderate discomfort

Traditional therapy
Traditional medical therapy

- Careful consideration of DDx
  - Infectious keratitis
  - Stromal abscess
  - Diagnostic sample
- Immunomodulatory or Anti-inflammatory drugs
  - Steroids: Contraindicated of ulcerative
  - Cyclosporine A
  - NsAIDs: (Bromfenac)

Topical steroids

- Dexamethasone
- Prednisolone acetate 1%
- Concern for secondary infections from longterm use

Topical NSAIDs

- Bromfenac 0.09% $$
- Potentially good response with endothelial IMMK (Giger and Brooks 2009 at IEOC symposium)

Cyclosporine

- **Selective effect in lymphoid or T-cells

Topical drug release implants

- Sustained drug release implants
  - Multiple dosing of conventional dosage form
  - Single dose of a conventional tablet/implant
  - Plasma Drug Concentration
  - Toxic level
  - Therapeutic level
  - Zero-order controlled release
  - Initial level

Traditional medical therapy: keratectomy

- Keratectomy with or without conjunctival graft
- Eliminates or minimizes corneal antigen load?

Pate et. al. abstract at ACVO 2009

13 eyes did not have recurrence of disease (superficial IMMK) after keratectomy

No recurrence 6-12 months
Cases selected (20 eyes, 19 horses)

- 2-4 implants per eye
- “Controlled” if the disease inactive when medications were tapered (≤1)

Outcome

- Superficial stromal: 9/9 controlled
- Mid-stromal: 3/3 not controlled
- Endothelial: 5/5 controlled, 3/5 on bromfenac q24 or q48hr

Traditional therapy

- Poorly understood pathogenesis
- Can be difficult to control long-term, with recurrences or continual disease progression commonly noted
- As a result, alternative treatment options should be investigated

Photodynamic therapy

- Uses photochemical reactions with use of
  - Photosensitizing agent
  - Light-appropriate wavelength
  - Oxygen
- Achieves highly selective treatment of a target area, while minimizing damage to adjacent, healthy structures

Indocyanine green

- FDA approved photosensitizer
- 750-810 nm peak spectral absorption
- Elicits cytotoxic effects both in vitro and in vivo when used in light for PDT
- Exact underlying cytotoxic mechanism unknown
- Singlet oxygen production?
PDT in human medicine

- Used for the following:
  - Acne vulgaris
  - Dermal basal cell carcinoma
  - Resistant bacterial strains
  - Periodontitis
  - Choroidal neovascularization

Current uses of PDT in veterinary medicine

- Squamous cell carcinoma
- Sarcoids
- Eyelid melanoma
- Injection site sarcomas in cats

So would it work on immune mediated diseases?

PDT for IMMK

- Had been used for corneoconjunctival SCC
- Would it work for IMMK?
  - Curiosity + Frustrated owner
    - First horse treated

Preparation

- Under standing sedation
  - Detomidine (0.01-0.02 mg/kg) IV
  - Butorphanol (0.01-0.02 mg/kg) IV
  - Butorphanol (0.02-0.04 mg/kg) IM

Blocks

- Auriculopalpebral and frontal blocks
- 2% mepivacaine
- Topical 0.5% proparacaine HCL
Retrobulbar block

- 10-12 mLs 2% mepivacaine
- Potential complications
  - Chemosis
  - Laceration of extraocular muscles, optic nerve, sclera - uncommon

PDT-ICG

- Intrastromal injections of indocyanine green (EmunDo®)
- Using loupe magnification - superficial to midstromal
- Using slit lamp biomicroscopy - deep

Intrastromal injection of ICG

Diode laser application

Safety goggles

Probe
Post-operative therapy and follow-up
- Tapering topical or subconjunctival NSAIDs
- Topical or subconjunctival antibiotic therapy
  - 10-14 days or until concurrent ulceration epithelialized
- Systemic flunixin meglumine

Cases treated up to February 2018
- 43 horses treated
- Eye: 23 OD, 20 OS, 1 not listed

Cases treated so far
- IMMK classification
  - Epithelial (anterior): 19
  - Midstromal: 13
  - Deep stromal: 2
  - Endothelial: 2
  - Not listed: 8

Cases treated so far
- Medications used at the time of PDT
  - Topical: Cyclosporine, Steroid, NSAID (q8-q12 hrs)
  - Systemic NSAID, Steroid
  - Uncontrolled at the time of PDT

Laser use
- QUADRANT
- ENTIRE CORNEA

Complications
- Stromal fracture (2/44)
- From inadvertent injection of air
- Intracameral injection (2/44)
  - No adverse reactions noted
Complications

- Superficial ulcer (5/44)
  - *more common with deep PDT
  - *They can take longer than typical to epithelialize

Complications

- Secondary infections
  - 2/44 (*Required surgical intervention)

Complications

- Dye retention (Temporary vision loss)
  - 1-behavior problems while blind
  - ICG dye will remain present for up to 6 weeks

Outcome: preliminary

- Comfortable post procedure
- ~75-80% Off of medications at time of last follow-up
  - Time to taper off of meds ~4-6 weeks
- Recurrence or required additional treatment
  - 3 have required additional PDT
    - Quadrant
    - Previous poor control

Summary

- IMMK is a commonly diagnosed ocular disease in horses
- Can be challenging to treat
- Often requires long-term topical medications
- Wax and wanes

As a result, alternative treatment options should be investigated

- Positive clinical response for IMMK has been shown with photodynamic therapy
Questions

What do you call a deer with no eyes?

NO EYE-DEER.