Melting Corneal Ulcer

Gordon B. Bijvoet

College of Veterinary Medicine

Class of 2018

Clinicopathologic Conference

Advisor: Caroline Betbeze, DVM, MS Diplomate ACVO

August 11, 2017

Introduction

A melting corneal ulcer, or keratomalacia, is used to describe the cornea when there is collagenolysis of the cornea stroma. This condition is also termed collagenolytic keratitis.[3] With the lysis of the corneal collagen, there is liquefaction of the corneal stroma resulting in a sagging and oozing appearance, giving the melting corneal ulcer its name. This can be seen in other species such as dogs, especially brachycephalic breeds, and lagomorphs, but is more commonly presented in horses.[3] The collagenases present in the disease process are usually from an inciting cause such as microbial keratitis, chemical burns, or trauma. There is often increased proteolytic activity in any of these events, leading to rapid degradation of the cornea. This disease has a high progression rate since the normal healing mechanism of the cornea is overwhelmed. The progression is usually rapid and can lead to vision loss within 12-18 hours.[12] It is imperative to make a quick diagnosis and recognize the severity of this subset of corneal ulcers in order for treatments to be initiated quickly and reduce the chances of further complications, such as corneal perforation, iris prolapse, descemetocele, or synechia. Corneal perforation, especially with keratomalacia, carries a poor prognosis for a return of vision in the horse. Aggressive medical therapy can be attempted but surgical intervention is often implemented due to the quick progression rate of the disease. Even with appropriate treatment, keratomalacia carries a guarded prognosis and can result in loss of the eye.[11] The melting corneal ulcer is considered an ophthalmic emergency.

History

Copper is a 5-year-old buckskin paint gelding who presented to MSU-CVM Ophthalmology Service on March 31, 2017 with a history of a corneal ulcer in his left eye.

Excessive tearing was noted in Copper's left eye the day prior to presentation, which caused the owner to schedule an appointment with the referring veterinarian. When examined, the ulcer had progressed to a melting corneal ulcer and he was referred to MSU-CVM immediately for further evaluation. Upon presentation, his temperature, pulse, and respiratory rate were within normal limits. No significant findings were appreciated on physical examination, except for his left eye. Copper presented with excessive tearing, blepharospasm, and conjunctival hyperemia. A one centimeter diameter malacic corneal ulcer was present on the ventromedial aspect of the left eye. Aqueous flare was noted on evaluation with a slit lamp biomicroscope. A corneal culture was collected after administration of one drop of topical anesthetic (Proparacaine). Fluorescein staining was positive. The intraocular pressures were measured with applanation tonometry and were 14mmHg and 13mmHg in the left and right eye respectively. Corneal cytology was collected from the left corneal ulcer with a microbrush and revealed 4+ rods. *Staphylococcus epidermidis* was grown on aerobic culture and fungal culture was negative for any growth. On sensitivity, *Staphylococcus epidermidis* was resistant to Penicillin and Polymyxin B.

Clinical Presentation

Horses that present with a melting corneal ulcer will have severe ocular pain and discomfort. As with most corneal diseases, the horse will present with epiphora, blepharospasm, increased amount of mucoid to mucopurulent discharge, and an influx on inflammatory cells into the infected cornea leading to corneal opacification.[9] Horses with ulcerative keratitis tend to have a concurrent anterior uveitis. This is referred to as an axon reflex uveitis and occurs from an increase in stimulation of the ophthalmic branch of the trigeminal nerve.[4,11] Anterior uveitis is usually accompanied with miotic pupils, photophobia, corneal edema, and hypopyon.[12] With chronicity of an ulcer, the normal avascular cornea may undergo neovascularization and corneal

vessels can be present. However, keratomalacia can occur rapidly, so corneal vascularization is not always present. The preceding clinical signs can be seen with many disease associated with the equine eye. The melting and oozing appearance of the corneal stroma caused by the liquefaction of the stroma by proteases is characteristic of a melting corneal ulcer.

Pathophysiology

Horses with melting corneal ulcers have a history of compromise of the corneal epithelial barrier, such as an ulcer, chemical burn, or trauma, resulting in colonization of opportunistic bacteria or fungus, leading to keratitis.[3, 11] The underlying cause to the disruption is often unknown and usually cannot be determined. Mycotic keratitis occurs more commonly in the Southeast in the spring in summer, when it is warm and humid, but it can be seen in numerous geographical areas throughout the year.[3] It is believed that horses are more prone to develop a melting corneal ulcer because their environment exposes them to micro-organisms involved in the process, and due to an increased amount of proteolytic enzymes in their tear film.

The cornea is avascular and consists of the tear film, epithelium, stroma, descement's membrane, and endothelium and is approximately 0.8 to 1mm thick in the horse.[4] The three components of the tear film are the mucous layer, aqueous layer, and lipid layer which provide protection and nourishment to the cornea. The corneal epithelium is lipophilic, contains 8 to 10 cell layers, and acts as a physical barrier to pathogenic organisms. The stroma maintains its transparency by being in a relative dehydrated state, keeping the collagen lamellae parallel to each other, and being avascular.[9] These conditions can be altered when the cornea is diseased, reducing corneal transparency. Descement's membrane is a single basal cell layer of the corneal endothelium.

Horses that present with a melting corneal ulcer usually have an underlying condition

affecting the integrity of the corneal epithelium. The epithelium is always undergoing regeneration to replace the cells that are lost under normal conditions. The tear film, upper, lower, and third eyelid offer corneal protection. When there is an increase in loss of corneal epithelium, or a decrease in the protection of the cornea, a corneal ulcer can result. Conditions affecting corneal protection, or excessive abrasion predispose the horse to corneal ulcers. Abnormalities in the eyelids or eyelashes, trauma, foreign bodies, and infectious agents can also affect the integrity of the cornea.[4] Once the corneal epithelium is disrupted, micro-organisms can infect the cornea, including commensal micro-organisms, resulting in a bacterial or a mycotic keratitis.

With bacterial keratitis, the most common organisms involved are Staphylococcus spp., Streptococcus spp., and *Pseudomonas aeruginosa*.[9] The most common fungi present in mycotic keratitis are *Aspergillus* sp. and *Fusarium* sp.. The cornea becomes infected with these micro-organisms and inflammatory cells start to influx. The inflammatory cells, stromal fibroblasts, corneal epithelial cells, and the infectious organisms release proteolytic enzymes that overwhelm the normal anti-proteases and prevent normal corneal wound healing.[5] Neutrophil elastase, which is a serine protease, and matrix metalloproteases (MMPs) are the two most common types of proteases in corneal inflammation.[5] These work by breaking down the collagen in the stroma, contributing to the depth of the corneal ulcer. The stroma becomes liquefied, causing a melting appearance, and rearrangement of lamella and collagen results in the loss of transparency.

Diagnostic Approach/Considerations

Upon presentation of any suspected ophthalmic disease, a physical exam should occur before the ophthalmic exam. A full physical exam will ensure that other concurrent diseases are

diagnosed and treated. Once the physical exam is completed, one should proceed with a basic ophthalmic exam.

Prior to examination of the cornea, the menace response and dazzle reflex should be assessed in order to determine the potential for vision in the eye. These tests are best performed prior to sedation. The eye is often painful, so sedation and eyelid nerve blocks are necessary to provide comfort to the horse and continue the exam. The two main nerve blocks used for examination are the auriculopalpebral nerve block and supraorbital nerve block. An auriculopalpebral neve block is performed by administering 2-3 milliliters (mls) of mepivacaine or lidocaine subcutaneously over the auriculopalpebral nerve as it courses over the zygomatic process.[10] This will result in akinesia, blocking the motor function of the palpebral branch of the facial nerve, so the eyelids can be opened for evaluation. A supraorbital nerve block can be performed, which will block sensation to the central upper eyelid.[5] This is achieved by administering mepivacaine subcutaneously over the frontal branch of the trigeminal nerve, over the supraorbital foramen.[10] Once the blocks have been performed, the rest of the ophthalmic exam can be performed.

Vision can be assessed via the menace response, maze test, tracking, and dazzle reflex. The eye should be evaluated by starting with the superficial structures (cornea, sclera, conjunctiva, and palpebrae), and then working toward the posterior segment examination.[2] Keratomalacia is often evident to the naked eye, and a presumptive diagnosis can be made based on corneal examination. A slit lamp biomicroscope provides a more magnified view of the cornea, allows for evaluation of ulcer depth, and is used to evaluate the anterior chamber. With ulcerative keratitis, aqueous flare, protein in the anterior chamber, is often appreciated due to the

presence of reflex anterior uveitis.[9] The protein in the anterior chamber will reflect the light and one solid beam will appear instead of two distinct light beams hitting the cornea and lens.

Tropicamide, a short acting mydriatic, is placed topically on the eye to dilate the pupil and perform a fundic exam during a full ophthalmic examination. The fundic exam should be normal in a horse with a melting corneal ulcer and is often difficult to visualize due to corneal edema and cellular infiltrate. The pupil may also be difficult to dilate due to reflex uveitis, so occasionally a fundic examination is not possible in these cases. Schirmer tear test is typically not evaluated in horses due to the low prevalence of keratoconjunctivitis sicca in the species, however, if one was performed, the affected eye could have an elevated schirmer tear test due to increased tear production. Fluorescein staining is imperative in cases of corneal melting. Fluorescein stain is hydrophilic and if any corneal stroma is exposed, as expected in these cases, there will be uptake of fluorescein stain.[2]

If corneal perforation is suspected, a seidel test should be performed. This is a test used to determine if all the layers of the cornea have been compromised allowing leakage of aqueous humor. A seidel test can be achieved by placing fluorescein stain on the eye without irrigation with eyewash afterwards.[5] This results in a high concentration of the fluorescein stain on the cornea that will appear yellow to orange. A corneal perforation can be detected when leakage of aqueous humor dilutes the yellow to orange fluorescein stain and causes it to fluoresce green.[5]

Tonometry is used to evaluate the intraocular pressure, which is found to be decreased in these cases. Hypotony, a decreased intraocular pressure, is from the concurrent anterior uveitis. Anterior uveitis causes the production of aqueous humor from the ciliary body to be decreased, and the outflow to be increased due to the release of prostaglandins.[2]

To determine the etiology of the melting corneal ulcer, corneal cytology, culture, and possibly biopsy (if corneal surgery is being performed) should be performed. A corneal scraping can aid in determining if the ulcer is bacterial or fungal in origin and can help aid in treatment choices. To prevent alteration of results, the affected area should be cultured before any topical solutions or ointments are administered.[11] These tests are imperative in order for immediate and appropriate treatment to be initiated. When a keratectomy is performed, histopathology should be performed. Histopathology can provide additional information on the disease and help determine a cause.[11]

Treatment and Management

With the rapid manifestation and progression of keratomalacia, aggressive medical therapy is warranted. Bacteria and fungi can be present concurrently, so both antibiotics and antifungals should be initiated. Since culture and sensitivity will take a few days to weeks for growth, treatment choices should be based on the most common organisms isolated in these cases and cytology results. Fortified amikacin, fortified cefazolin, and ofloxacin are all good choices for antibiotics since the common bacteria, *Staphylococcus, Streptrococcus*, and *Pseudomonas,* tend to be sensitive to these medications.[11] Voriconazole, miconazole, amphotericin B, and natamycin are some common choices for topical anti-fungals.[11] Although natamycin is the only commercially available antifungal, fungi are commonly resistant and it is cost prohibitive. In recent year, voriconazole 1% solution has become the drug of choice to treat fungal keratitis. The antibiotics and the antifungals require a frequent dosing interval of every one to four hours depending on the severity of disease.

Anti-collagenase therapy should also be initiated to help mitigate the proteolytic enzymes liberated from the microorganisms, inflammatory cells, epithelial cells, and keratocytes.

Tetracyclines, serum, and EDTA are anti-collagenases used in the horse. Tetracyclines can be used as an antibiotic, but they offer additional therapy by inhibiting matrix metalloprotease activity.[4, 11] The serum can be harvested directly from the horse, and is able to be stored in the refrigerator for up to eight weeks.[5] Serum is administered directly onto the cornea every 4 to 24 hours.

Treatment for concurrent uveitis should also be initiated. Atropine, an anti-cholinergic, is administered topically into the affected eye to dilate the pupil. This will help treat the anterior uveitis, increase the horse's comfort level by reducing ciliary body spasm, reduce aqueous flare, and aid in preventing synechia.[8,12] It is important to remember that atropine can alter normal digestion and predispose the horse to colic. Systemic NSAIDs, such as flunixin meglumine, or phenylbutazone, are administered for analgesia and to reduce inflammation.

The topical medications require a frequent dosing interval and would be nearly impossible without the placement of a subpalpebral lavage system. A subpalpebral lavage consists of a footplate that is placed in the fornix of the upper or lower eyelid, and a catheter is run through the eyelid to a port placed in the horse's mane.[9] The topical eye medications can then be administered by injecting them into the port instead of placing them directly onto the eye. This will ease the process, increase safety, and help keep the horse from becoming head shy.[11]

Due to the complex nature of keratomalacia, surgical intervention is necessary in addition to medical treatment to resolve the ulcer. Surgery will involve a keratectomy to remove inflammatory cells, pathogens, and necrotic tissue.[5] A keratectomy can remove a large portion of the cornea decreasing its protective mechanisms and increasing the risk of perforation. To add

structural support and a blood supply to the corneal wound, a corneal or conjunctival graft is placed over the debrided cornea.

A conjunctival pedicle graft is typically the treatment of choice among ophthalmologists.[5] The conjunctival pedicle graft maintains communications with the bulbar conjunctiva and offers support and direct blood supply to the corneal ulcer.[5,11] The vascularization delivers fibroblasts and growth factors that enhance healing, along with anti-proteases, and anti-collagenases to prevent further destruction of the cornea.[5] All of the medications, except for the anti-proteases, that were originally initiated, should be continued. The graft will remain permanently on the cornea. If appropriate healing has occurred and the flap interferes with the visual axis, the pedicle portion of the graft can be trimmed 4-6 weeks post-operatively to decrease the size of the corneal scar.[5]

Enucleation is an option for a melting corneal ulcer or perforated cornea and is often warranted in severe cases that do not have a chance to regain vision. Sometimes the ulcer has progressed too far and there is a grave prognosis for vision and comfort even with aggressive medical and surgical therapy. Enucleation is a relatively safe procedure that can be performed standing or under general anesthesia and can offer rapid comfort and a good quality of life to the animal.

Case Outcome

The outcome of a melting corneal ulcer greatly depends on the treatments, duration of disease, and the nature of the ulcer. In cases that are non-responsive to treatment, the disease can progress to globe perforation, iris prolapse, glaucoma, or phthisis bulbi.[11] In these events, a grave prognosis is given to the eye and enucleation is often elected. When the ulcers have healed, the horse's vision can be impaired because of corneal scarring or anterior synechia. Small ulcers

that respond well to treatment can have a visual outcome of 90% and a globe survival of 95% while cases that prolapsed the iris have a visual outcome of 40% and globe survival of 67%.[11] Several factors play into the prognosis for the eye, but even with aggressive medical and surgical treatment the eye is given a guarded prognosis.

In Copper's situation, a subpalpebral lavage was placed on March 31, 2017 to initiate aggressive medical treatment. Atropine and flunixin meglumine were used to treat the anterior uveitis, while voriconazole, EDTA, serum, ofloxacin, and cefazolin were used to treat the keratomalacia. Between March 31st and April 3th, Copper was hospitalized so he could receive flunixin meglumine every twelve hours, atropine as needed, ofloxacin every one hour, voriconazole every one hour, serum every four hours, 0.2% EDTA every two hours, and cefazolin every four hours. The flunixin meglumine was given orally, while the rest of the medications were administered through the subpalpebral lavage with a five-minute interval between each medication. The ulcer did not respond to treatment and became more malacic. He was taken to surgery on April 4th for a keratectomy and conjunctival pedicle flap. Surgery and recovery were uneventful. He was kept in the hospital for the next five days for further monitoring and medicating. Following surgery, the frequency of 0.2% EDTA was reduced to every four hours, ofloxacin to every four, and voriconazole to every four hours. The rest of his medications were continued on the same dosing schedule. Copper was discharged on April 9th and the owners were instructed to continue his medications at a decreased frequency. On Copper's two week recheck, the conjunctival flap was still in place and adequate healing was evident. There was no evidence of corneal malacia and the ulceration surrounding the flap had healed. Histopathology results confirmed the suspicion of suppurative and necrotizing keratitis, but no organisms were found. Copper's eye carries a good prognosis and he is expected to have

very minimal vision abnormalities with the flap in place because the location is not within the central visual axis and the diameter of the ulcer was small.

References

1. Barnett, K. C. *Equine Ophthalmology*. 2nd ed. London: Equine Vet. Assoc., 1990. Print

2. Betbeze, Caroline. "The Ophthalmology Examination." MSU-CVM, Starkville. 2015. Lecture.

3. Dubielzig, Richard R., Kerry L. Ketring, Gillian J. McLellan, and Daniel M. Alberts. *Veterinary Ocular Pathology: A Comparative Review*. Edinburgh: Elsevier, 2010. Print.

4. Gelatt, Kirk N. *Veterinary Ophthalmology*. Fourth ed. Vol. 2. Ames, Iowa: Blackwell, 2013. Print.

5. Gilger, Brian C. Equine Ophthalmology, 2nd ed. Ames, IA: John Wiley & Sons, 2017. Print

6. Grahn, Bruce H., and Cheryl L. Cullen. “Diagnostic Ophthalmology. Melting Corneal Ulcer.” *The Canadian Veterinary Journal* (2001): n. page. Print.

7. Maggs, David, and Paul Miller. *Slatter's Fundamentals of Veterinary Ophthalmology (Fourth Edition)*. 4th ed. N.p.: W.B. Saunders, 2008. Print.

8. Mochal-King, Cathleen. "Equine Ophthalmology: Recurrent Uveitis (ERU).” Equine I. MSU-CVM, Starkville. 2015. Lecture.

9. Mochal-King, Cathleen. "Ophthalmology Diseases of the Cornea." Equine I. MSU-CVM, Starkville. 2015. Lecture.

10. Mochal-King, Cathleen. "Ophthalmology: The Basics." Equine I. MSU-CVM, Starkville. 2015. Lecture.

11. Ollivier, Franck J. “Medical and Surgical Management of Melting Corneal Ulcers Exhibiting Hyperproteinase Activity in the Horse.” *Clinical Techniques in Equine Practice* 4.1 (2005): 50-71.Web

12. Sandmeyer, Lynne S., Bianca S. Bauer, and Bruce H. Grahn. "Diagnostic Ophthalmology." *The Canadian Veterinary Journal*. Canadian Veterinary Medical Association, Jan. 2014. Web. 26 July 2017. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3866863/>.