Moe's Misshapen Mishap

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Class of 2020

Clinicopathological Conference

August 16th, 2019

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Introduction

Equine Recurrent Uveitis, otherwise known as “Moon Blindness” or Periodic Ophthalmia is the leading cause of blindness in horses worldwide. It is estimated that its prevalence in the United States is somewhere between 2-25%. Equine Recurrent Uveitis is an overreaction of a horse’s immune system, which causes inflammation in the eye first impacting the uveal tract. This overreaction can be triggered by some form of ocular injury, an autoimmune reaction, or exposure to pathologic agents; with Leptospira being the most implicated. Prognosis for horses diagnosed with ERU is guarded. Early initiation of treatment and recognition of the inciting insult to the blood ocular barrier is important in maximizing a horse’s ability to retain vision and reduce pain in affected eyes.

History and Presentation

Moe is an approximately 6-year-old crossbred draft gelding that presented to MSU-CVM Equine and Ophthalmology Departments on September 6th, 2018 for an approximately three year history of inflammation in his right eye and had been diagnosed with Equine Recurrent Uveitis by his primary veterinarian. Moe had been preventatively vaccinated against Leptospirosis for the last few years. Moe presented to his primary veterinary on September 5th, 2018 after a two week history of his right eye looking more cloudy. During that appointment, he was started on flunixin meglumine and topical atropine to the right eye for a corneal ulcer. Referral was recommended. Historically, Moe has been on low dose Aspirin daily for treatment of ERU, however, he had not received this medication since June 2018. Prior to Moe’s presentation at MSU-CVM he was noted to be otherwise healthy with no signs of systemic disease.

On presentation, Moe was anxious, alert and responsive. His vitals were within normal limits with a rectal temperature of 101.2^{o}F, a heart rate of 48 beats per minute, and 16 breaths per minute. His mucous membranes were pink and moist and had a capillary refill time of less than two seconds. He had normal gastrointestinal sounds in all four quadrants and none to slight digital pulses in all four limbs. He also had loose, wet feces at the time of presentation.

Moe's ophthalmic exam at presentation was abnormal for both eyes. Intraocular pressure of his right eye was 20 mmHg and 15 mmHg in the left eye, with normal range being 17-28 mmHg. He did not have a dazzle reflex or positive menace response in the right eye which indicated that he was blind in that eye. The right eye had diffuse corneal edema with a large area of deep stromal corneal ulceration that was malacic and contained cellular infiltrate. The ulcer was fluorescein positive. Haab's striae could also be appreciated in the right eye which suggested previous glaucoma in that eye. The posterior segment of the right eye could not be evaluated due to anterior segment disease. The left eye had vision, however, there were significant changes appreciated on ophthalmic examination. These changes included keratic precipitates, trace aqueous flare, incipient cortical cataracts, lens coloboma, and persistent pupillary membranes. Fundic examination of the left eye revealed an area of depigmentation lateral to optic nerve head. All of these changes could be attributed to ERU, except the lens coloboma and persistent pupillary membranes which are hereditary.

Diagnostic Approach/Considerations

Due to the severity of disease present in Moe's right eye and his medical history, the need for extensive diagnostic testing was not necessary. Moe's right eye was non-visual,

painful, and the prognosis that vision would return was grave. Therefore, it was decided to remove the right eye as it was a nidus for pain and inflammation.

The day of presentation Moe was started on a 1.1 mg/kg dose of intravenous flunixin meglumine, ¼ inch strip of Neo-Poly-Dex in his left eye, and atropine in the left eye as needed.

On September 11th, 2018, Moe was prepped for surgery. A standing enucleation was performed on Moe's right eye and it was submitted for histopathological evaluation. A 47mm silicone implant was placed within the orbit. The surgical site was closed and a figure of 8 bandage was placed over the surgical site.

Results of Moe's biopsy confirmed the severity of disease in that eye. He was diagnosed with marked suppurative panophthalmitis with anterior synechia, corneal ulceration and retinal degeneration and detachment. Intralesional bacteria were also noted but mycotic agents were not seen after specimens were stained with GMS. Possible etiologies of the initial blood ocular barrier compromise included ocular trauma with secondary bacterial infection. If signs of uveitis were present prior to any historical trauma, Leptospirosis as the initial insult could not be ruled out.

After surgery Moe's left eye was thoroughly evaluated. At that time there was trace aqueous flare and an immature cortical cataract. His recovery was uneventful. He was continued on 1.1 mg/kg intravenous flunixin meglumine every 12 hours, 30 mg/kg Uniprim (Trimethoprim and Sulfadiazine) orally every 12 hours for two weeks, a ¼ inch strip of Neo-Poly-Dex in the left eye every 6 hours and atropine in the left eye as needed.

Three days after surgery, flunixin meglumine was decreased to once a day and Neo-Poly-Dex was decreased to twice daily administration. This was due to the inflammation in his left eye appearing to be well controlled. The following day, September 14th, Moe seemed blind in the left eye. Examination of his left eye revealed hypopyon, 1+ aqueous flare, and weak menace response. His eye was negative for fluorescein stain uptake and his IOP was 15 mmHg. Moe did have a positive dazzle reflex at this time. During this exam, his surgical incision was healing well, swelling was present but discharge was not present. The frequency of Moe's anti-inflammatory medications were increased. Furthermore, it was noted on this day that Moe began to show some gastrointestinal abnormalities and for this he was monitored very intensely for adequate fecal output, water input, and normal gut sounds.

Three days later, on September 17th, Moe's fecal output was determined to be inadequate. A rectal examination was performed which revealed no structural abnormalities. However, precautionary measures, such as mineral oil, steamed hay, and alfalfa were added to his treatments for their lubricating and laxative effects. The following day, Moe's eye possessed less hypopyon, a normalized menace response, and overall more visual acuity than the previous three days.

On September 21st, Moe was sedated to undergo an intravitreal injection of low-dose preservative free gentamicin. 4mg of gentamicin was injected 10mm dorsal to the limbus at the 12 o'clock position. The injection was rotated gently, but deliberately toward the optic nerve as to avoid the lens. The procedure resulted in a very mild amount of subconjunctival hemorrhage and conjunctival hyperemia. A treatment of ¼ inch Neo-Poly-Bac every 8 hours was instituted after this injection was performed.

On September 23rd, his flunixin meglumine was again reduced to once a day and his topical anti-inflammatory was started on a tapering frequency. On September 25th, his bandage was removed and flunixin meglumine was discontinued.

On October 6th, 2018, 31 days after presentation, Moe was discharged from the hospital with instructions to a continue applying Neo-Poly-Dex to the eye every 12 hours for one more week.

Pathophysiology

In order to understand the pathophysiology of this disease it is important to review the fundamental anatomical structures of the eye. The eye can be easily divided into three main layers. The outer fibrous layer includes the cornea and sclera. The middle vascular component, called the uvea, contains the choroid and iris. Finally, the inner neurological layer is solely made up of the retina. Many tissues of the eye are immunoprivileged due to the presence of the blood ocular barrier. This barrier restricts antigenic material from entering the eye. This holds true until the blood ocular barrier becomes overloaded with the volume of antigen present in the blood stream. The result of this antigen load leads to the breakdown of the blood ocular barrier. When this occurs, blood vessels of the iris, ciliary body, and choroid become fenestrated allowing cells and inflammatory cytokines to enter the eye. This leads to inflammation known as uveitis. A loss of ocular immunoprivilege is thought to be the inciting factor for Equine Recurrent Uveitis. (4) The initial breakdown of the blood ocular barrier results in its permanent compromise leading to continued exposure of the eye to foreign antigens,

immune cells and inflammatory cytokines. The infiltration of white blood cells forms follicles within the eye resulting in a chronic state of inflammation.

Uveitis is considered recurrent when more than two episodes have been noted. After the initial insult, the risk of recurrence is decreased after two years of quiescence. After determining that a case is truly recurrent further classification can be pursued. There are three subclasses of disease: classic, posterior, and insidious. Classic uveitis is characterized by intense intraocular inflammation followed by periods of an eye that is clinically quiet. The posterior form is almost exclusively seen in warmblood breeds. It is described as chronic low-grade inflammation involving the posterior segment of the eye. The anterior segment is only minimally involved. This form commonly results in retinal detachment. Lastly, the insidious form seems to occur more in Appaloosas and draft breeds. Horses affected with the insidious form experience chronic low-grade intraocular disease. These cases usually go unnoticed by owners as they are not typically painful. Usually, by the time the disease is noticed there is extensive damage to the eye.

Currently, there are two classes of thought for the cause of the initial insult of the blood-ocular barrier. The first is exposure to bacterial agents, specifically *Leptospira spp.*. Leptospirosis has been implicated for two possible pathways. The first thought is that presence of the pathogen leads to persistent intraocular infection. The second thought is that through antigenic mimicry of *Leptospira* microbial peptides and intraocular autoantigens of the cornea, lens, ciliary body, and retina. Therefore, it is possible that exposure to leptospiral organisms stimulates autoimmunity. The most commonly implicated serovars in ERU in the Unites States and Europe include *L. grippotyphosa, L. pomona,* and *L. bratislava.* (6)

The second class of thought regarding the initial insult to the blood-ocular barrier, is an autoimmune response or inappropriate immune response to the horse's normal ocular structures. Much is still unknown about this autoimmune response, but one study suggests a genetic predisposing marker found in Appaloosa horses. In this study, three genetic markers from the ECA1 region associated with the Appaloosa color were significantly correlated with a horse's likelihood to develop Equine Recurrent Uveitis without the presence of any other inciting cause. Description of the three implicated markers are: a SNP within intron 11 of the TRPM1 gene on ECA1, an ELA class I microsatellite located near the boundary of the ELA class III and class II regions and an ELA class II microsatellite located in intron 1 of the DRA gene. (5) Research has shown that Appaloosas are 8.3 times more likely to develop uveitis than other breeds. (8) Appaloosa horses that are seropositive to *Leptospira interrogans* serovar *pomona* have been shown to have more severe clinical signs and near 100% occurrence of blindness. Draft breeds and European Warmblood breeds are also overrepresented for this disease. However, a genetic link has not yet been determined. (8)

Following the initial insult to the blood ocular barrier the introduction of inflammatory mediators, prostaglandins, leukotrienes, and histamines result in inflammation of the eyelids, conjunctiva, cornea, lens, retina, and optic nerve. The inflammation of these structures is characterized by vascular congestion. Dilation of scleral and conjunctival blood vessels give the eye a reddened, hyperemic appearance.

The same inflammatory mediators cause ciliary body and iris sphincter muscles to spasm eliciting pain and miosis. The iris can develop a dull appearance and may develop a

mottled pigmentation with hyperemia. In chronic cases, corpora nigra atrophy and hyperpigmentation of the iris can be appreciated.

Additionally, these same mediators lead to vascular permeability and breakdown of the blood aqueous barrier. As this barrier becomes compromised, introduction of protein, fibrin, and cells spill into the aqueous humor. These changes are considered the hallmark of equine recurrent uveitis and can lead to dysfunction of the ciliary body and thus decreased production of aqueous humor. This can be objectively appreciated by decreased intraocular pressure. However, in chronic cases aqueous outflow channels may become occluded leading to glaucoma. Aqueous humor inflammation can secondarily lead to corneal endothelial cell malfunction through the disruption of metabolic pump mechanisms ultimately causing corneal edema. Several days after the onset of inflammation, neovascularization of the corneal stromal tissue can be seen. (8)

The lens is also affected by this disease process. Similar to the pathologic process seen with the corneal endothelial cells, the lens's metabolic function is affected by changes seen in the aqueous humor. This results in a loss of lens transparency thus resulting in a cataract formation. In chronic cases, degeneration or detachment of the lens zonules can result in anterior or posterior luxation of the lens. Early lens opacities also occur as inflammatory exudates adhere to the lens capsule. Pigment can also develop on the lens surface from pigment migration from the iris or from posterior synechia. (8)

Cellular infiltrate of the acellular vitreous body can give rise to the distinct yellow color seen with ERU. Chronic inflammation can lead to fibrous strands of inflammatory debris known

as vitreal traction bands. Vitreal liquefactive degeneration along with vitreal traction bands can physically pull on the retina thus leading to retinal detachment in severe ERU cases. (8)

Inflammatory episodes can cause changes in chorodial blood flow causing retinal cellular hypoxia. Severe chorodial inflammatory insults can lead to disruption in blood flow to the optic nerve and eventually optic nerve damage. (8)

Treatment and Management

In horses with suspected ERU, Appaloosas, or other horses that may be predisposed vaccinating with multivalent vaccines or administering more than one vaccine at a time has been clinically associated with recurrence of ocular inflammation. Giving one vaccine per week and limiting the use of unnecessary vaccines is advised. Vaccinating against Leptospirosis remains highly controversial. A study by Rohrbach et.al., looked at the effect of Leptospirosis vaccination on 41 horses with prior diagnosis of equine recurrent uveitis. The study indicated that vaccinated horses had an increase in the number of days to recurrence compared to a control group of unvaccinated horses. Conversely, the same study showed that vaccination failed to slow the progression of the disease when compared to an unvaccinated control group. This was demonstrated by an increase in synechiae or progression of pre-existing or development of cataracts in both vaccinated and unvaccinated groups. (9)

The goals of Equine Recurrent Uveitis management are to maintain vision and reduce pain. Topical and systemic anti-inflammatory medications are crucial in the treatment of ERU. Flunixin meglumine is favored over phenylbutazone due to its more effective intraocular anti-inflammatory effects. Topical steroids combined with antibiotics are also recommended in

acute cases with negative fluorescein uptake. In the event that a corneal ulcer were to develop while a patient in receiving steroidal therapy, the immunosuppressive effects may allow for the ulcer to become infected. Therefore, their long-term use is not advised. The same is true of subconjunctival steroidal injections. Topical non-steroidal anti-inflammatory medications can be used on a more long-term basis if necessary.

Topical atropine is effective at stabilizing the blood-aqueous barrier, reducing vascular permeability, and reducing pain from ciliary muscle spasm. Atropine also dilates the pupil which decreases the risk for synechia. Potential drawback to the use of atropine include the possibility of horses to develop signs of colic secondary to atropine's effect on the gastrointestinal tract. Controversy over this potential deleterious side effects exists. A difference in patient sensitivity to topical atropine is also considered. (10)

As an approach to long term immunomodulation, Cyclosporine implants have been developed. Studies have shown promising results and indicate that their use in controlling inflammation in the eyes of ERU patients was significant. This implant is surgically inserted under the sclera and in the suprachoroidal space. The advantage of this site compare to episcleral implantation, is that medications can bypass the fibrous scleral layer and be directly delivered to the choroid and potentially the retina. A study by, Gilger et.al., showed that deep scleral implantation of cyclosporine significantly decreased the number of uveitis flare-ups per month in horses when compare to their flare ups prior to surgery. (11) One disadvantage to this therapy is the need for an eye to be clinically quiet at the time of implantation.

Pars plana vitrectomy is another invasive approach to treating equine recurrent uveitis. This procedure is performed by surgically skilled ophthalmologists. This procedure has been shown to reduce the recurrence of inflammation in horses with vitreal opacities and those with detectable *Leptospira spp.* titers within the vitreous. The surgery involves removal of the inflamed vitreous through a small scleral incision while irrigating the vitreous through a similar scleral incision. Simultaneous aspiration of diseased vitreous and addition of lavage fluid is important as to maintain the appropriate pressure within the eye. This procedure can be performed on an affected eye during a period of quiescence. (3)

Intravitreal low-dose, preservative free gentamicin injections has been utilized anecdotally in horses with ERU since the early 1990's. Gentamicin is frequently used in the pars plana vitrectomy lavage solution. A study published earlier this year indicated that intravitreal gentamicin injections (IVGI) showed fewer complications than the pars plana vitrectomy procedure. Additionally, this study indicated that IVGI could control inflammation within the eye despite the *Leptospira* status of that eye. (2)

Unfortunately, in the most severe Equine Recurrent Uveitis cases or those that are refractory to medical or surgical treatment, enucleation of the eye is needed. Severely affected and blind eyes are exceptionally painful and removal of the eye aids in patient comfort long term.

Case Outcome

After discharge, Moe did well for a while. Over the last few months the cataract in his left eye has progressed. Moe's owners report that he is now mostly blind. They note, however,

that Moe is adapting well. He currently shares a thirty acre pasture with another draft cross named Leo whom is also mostly blind. They are happy to know that Moe is comfortable and that he has another horse to learn with.

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