Tucker's Tip of the Eyesburg

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Introduction

Ulcerative keratitis, commonly referred to as corneal ulceration, is one of the most common ophthalmic conditions in veterinary medicine. It is defined as a break in the corneal epithelium and may result clinically as blepharospasm, photophobia, lacrimation, conjunctival hyperemia, corneal edema, and aqueous flare.[2] It can be classified into superficial keratitis, deep corneal ulcer keratitis, descemetocele keratitis, and perforation keratitis with reference to the loss of corneal layers. There are a variety of etiologies including, but not limited to, congenital, infection, allergy, trichiasis, distichiasis, ectopic cilia, entropion, trauma, a foreign body, or lack of tears. Ulcerative keratitis can be treated medically or by various surgical procedures which depend on corneal stromal lesion severity.[4] Brachycephalic dog breeds have a higher risk of developing ulcerative keratitis; Cavalier King Charles Spaniels and Shih Tzus males affected by keratoconjunctivitis sicca (KCS) have a significantly higher incidence of ulcerative keratitis.[2]

History and Presentation

Tucker is an approximately 5-year-old, male-neutered Shih Tzu that presented to MSU-CVM Ophthalmology department on July 1, 2020 for an evaluation of a corneal ulcer in the left eye (OS). Tucker was seen by his referring veterinarian (rDVM) on June 29, 2020 after his owner noticed acute blepharospasm OS. The rDVM prescribed topical Ofloxacin three times daily, topical Atropine twice daily, and systemic Previcox (57mg q24h) for pain control. Tucker was referred to MSU-CVM by his rDVM with concerns about the depth of the ulcer.

On presentation, Tucker was bright, alert, and responsive. He had an ideal body condition score of 5/9 and weighed 5.7 kg. His heart rate was 84 beats per minute, a respiration rate of 20 breaths per minute, and a temperature of 101.1 degrees Fahrenheit. On auscultation, no

arrhythmias, murmurs, crackles, or wheezes were appreciated. All other physical exam parameters were within normal limits.

On gross ophthalmic examination, there was mild, mucoid ocular discharge in both eyes (OU). There was profound blepharospasm and epiphora of the left eye (OS). There was also a noticeable central corneal ulceration OS. Upon further examination of the left eye, aqueous flare, corneal edema, and conjunctival hyperemia were noted. The right eye (OD) had a spot of mild corneal fibrosis but was otherwise within normal limits.

Diagnostic Approach

Initial ophthalmic diagnostic approach starts grossly with a complete history and physical examination. The eyes should be evaluated for symmetry, size, position, and motility. A thorough cranial nerve examination should also be performed. Of particular interest are vision tests which include menace response, tracking, and maze test. Light perception is tested with pupillary light reflex (PLR) and dazzle reflex. The eyelids and eyelid margins, nictitating membrane, and conjunctiva should be subsequently evaluated. After a complete physical examination, an in-depth ophthalmologic examination can be performed. The external eye and adnexa, anterior and posterior segments of the eye should be evaluated under magnification. Then, the cornea should be evaluated for the loss of transparency, opacity, vascularization, pigmentation, dryness, growths, foreign bodies, lacerations, changes of contour, and ulceration.[9] Diagnostic tests performed OU include a Schirmer tear test (STT), fluorescein stain, and measuring intra-ocular pressure via tonometry.

If any mucoid or mucopurulent discharge is present, a Schirmer tear test should be performed bilaterally prior to instillation of any diagnostic or irrigating solutions.[3] Dogs with a

STT less than 15mm/min have a decrease in the aqueous component of the tear film.[9] Fluorescein dye is commonly used for the diagnosis of corneal ulcers. It is a water-soluble dye which is taken up by the hydrophilic corneal stroma. The corneal epithelium and endothelium are hydrophobic so a defect in these regions would not result in stain uptake.[9] The cornea is best seen using a direct ophthalmoscope or slit-lamp with a cobalt blue filter which enhances the fluorescence dye.[9] Tonometry should be performed to measure intraocular pressure in both eyes. Indirect (noninvasive) measured estimation of IOP is called tonometry.[9] The two most commonly used types of tonometers are the Tono-Pen applanation tonometer and TonoVet rebound tonometer. While the Tono-Pen measures the force required to applanate a given area of the cornea, the Tono-Vet assesses IOP by quantifying the deceleration of a probe after its impact on the corneal surface.[9] The normal range of IOP for dogs is 10 to 25 mm Hg. However, the normal IOP range will vary according to the instrument and technique used, the examiner, the degree of restraint, and any surface disease.

In our case, Tucker's Schirmer tear test was decreased OD (9 mm/min) and within reference OS (24 mm/min). Although his left eye's production was technically within normal limits, he likely had increased tear production secondary to irritation from his corneal ulcer. Tucker's tear film quality was deemed poor in both eyes. Fluorescein stain was applied OU. The left eye was fluorescein stain positive and revealed that Tucker's corneal ulcer had progressed to a descemetocele, as the stain adhered to the stromal walls but did not adhere to the center of the lesion, indicating it had progressed to Descemet's membrane. Intraocular pressures (IOP) were 13mmHg OD and 7mmHg OS. The decreased IOP OS is likely associated with a reflex uveitis. Tucker's pupil OS was mydriatic from atropine administration. He also had an absent direct PLR OS and absent consensual PLR from OD to OS due to atropine administration. He had a positive

direct PLR OD and positive consensual PLR from OS to OD. The left anterior chamber was noted to have 2+ cells along with 2+ flare. Then the lens, vitreous, and fundus were examined OU and were unremarkable.

Since Tucker's corneal ulcer had progressed into a descemetocele, surgical intervention was warranted. Also, Tucker was being given twice the suggested dose of Previcox so a pre-operative minimum database, consisting of a complete blood count, small animal anesthesia profile, and creatinine were performed in order to assess organ function and check for NSAID toxicity. The only bloodwork abnormality was a mildly elevated blood urea nitrogen (BUN) (32 mg/dl) so precaution was taken moving forward. An aerobic culture and sensitivity of the corneal lesion were also performed prior to surgery. Indications for corneal cytology and culture include: the presence of a rapidly deepening ulcer of any size, a superficial or deep ulcer with indistinct borders, or a minor erosion or ulcer in an eye with a disproportionately severe inflammatory response.[3]

Anatomy & Pathophysiology

Ulcerative Keratitis is largely classified with reference to depth: superficial, deep, descemetocele, perforation, and ease of healing: uncomplicated, complicated, refractory, progressive.[9] The cornea is an avascular, transparent structure on the outermost portion of the fibrous tunic.[9] It is normally moist, and unpigmented, with a smooth even contour.[9] Its function is to transmit and refract light and protect intraocular structures. Since the cornea is avascular, it is dependent on precorneal tear film and aqueous humor for nutrition and waste removal. The cornea is composed of four layers, from superficial to deep: stratified epithelium, collagenous stroma, Descemet's membrane, and the endothelium.[9] Corneal erosion or abrasion is defined as loss of one or more corneal epithelial layers. Corneal ulceration is described as full-thickness

loss of epithelium with at least some stromal loss. Complicated corneal ulceration involves delayed healing commonly associated with infection or other pathological processes, while progressive ulceration involves an enlarged or deepening area.[3]

The corneal epithelium is covered by nonkeratinized, stratified squamous epithelium that is 5 to 7 cell layers thick and is completely replaced every 7 to 14 days. The corneal stroma composes majority of the corneal thickness and is relatively dehydrated compared to other tissues. This is important because hydration of the corneal stroma will appear clinically as a bluish opacity and is termed corneal edema. The corneal stroma is also hydrophilic, unlike the epithelium and endothelium, which is important for the diagnosis of ulcerative keratitis when using water-soluble fluorescein dye.[9] Interior to the stoma is Descemet's membrane and is the basement membrane of the corneal endothelium; it is also hydrophobic and will not retain fluorescein stain.. It serves clinically as the final barrier to perforation of a progressive corneal ulcer. Deep corneal ulcers that fail to retain fluorescein stain in the central portion are termed descemetoceles and are considered a surgical emergency. The inner most layer of the cornea is the endothelium which is composed of a single layer of cells that functions to keep the corneal stroma dehydrated.[9]

Healing of corneal wounds is a complex process which involves the integrated actions of proteinases, growth factors, and cytokines produced by epithelial cells, stromal keratocytes, inflammatory cells, and the lacrimal glands.[5] Small, uncomplicated corneal ulcers heal within 24 to 72 hours by migration and mitosis of adjacent epithelial cells. Therefore, if a corneal ulcer endures beyond 5 to 7 days, the defect should be considered refractory and reevaluated with respect to etiology, exacerbating factors, and treatment.[9] Healing of a full-thickness corneal laceration, or corneal perforation, can be divided into approximately 6 phases. The first phase

begins immediately with mechanical factors, the fibrin plug, and corneal stromal edema. The stromal fibers and Descemet's membrane are elastic and recoil when severed; when the fibrinogen of the inflamed aqueous humor encounters the cut edge of the wound, it leads to fibrin and forms a plug which seals the wound and acts as a scaffold. The second, or leukocytic, phase beings when polymorphonuclear (PMN) leukocytes migrate into the corneal wound from conjunctival blood vessels and lacrimal gland via the tear film. The third or epithelial phase begins by sliding and mitosis where the epithelium grows into the anterior part of the wound and is an important moderator for healing of the underlying stroma. If the defect is too large and the epithelium does not cover the wound, healing is significantly delayed. The epithelium also secretes enzymes, such as collagenase, when the cells are damaged. Proteolytic enzymes, such as collagenase and protease that are released by epithelial cells, neutrophils, and keratocytes may be major factors in the continued progression of corneal ulcerations. The fourth stage begins after 12 hours and converts keratocytes to fibroblasts. The fifth stage is the endothelial phase which begins 24 hours after injury and heals by endothelial sliding. The endothelial cells produce a new Descemet's membrane after a few weeks. The sixth and final phase of corneal healing begins 7 days after injury where a thin scar is formed from the fibroblastic tissue. Maintenance and repair of the corneal stromal extracellular matrix (ECM) require a tightly coordinated balance of ECM synthesis, degradation, and remodeling. Proteolytic enzymes (proteinases) perform physiological functions in the slow turnover and remodeling of the corneal stroma. Excessive degradation of normal healthy tissue is prevented by natural proteinase inhibitors in the cornea. Pathological degradation of corneal stromal collagen occurs when the balance between proteinases is greater than proteinase inhibitors. Bacteria, inflammatory cells, corneal epithelial cells, and fibroblasts produce and release proteolytic enzymes which tip the scale further proteinase imbalance.

Imbalance with high levels of proteinases (metalloproteinases (MMPs) or plasmin) might also contribute to the pathogenesis of certain types of superficial nonhealing ulcers in dogs. In dogs with chronic superficial keratitis, MMP was present in both the corneal epithelium and anterior stroma.[5]

Ulcerative keratitis etiologies are vast and may be congenital, result from infection, allergies, trichiasis, distichiasis, ectopic cilia, entropion, trauma, foreign bodies, or lack of tears (keratoconjunctivitis sicca or KCS). One study determined the frequency of ulcerative keratitis in Shih tzu and Pekingese breeds were higher than other breeds because both suffer from lagophthalmos. Lagophthalmos and KCS are the most frequent causes of ulcerative keratitis in brachycephalic breeds. Regardless of breed, it is important to determine the etiology and eliminate the cause, followed by attempts to create an ideal environment for lesion repair, prevention of progression, and surgical treatment to prevent corneal rupture.[4]

Tucker was diagnosed with KCS and lagophthalmos, the inability to completely close the eyelids, on initial ophthalmic exam which is likely the cause for the corneal ulcer. The corneal ulcer progressed into a descemetocele because the KCS and lagophthalmos remained untreated. Tear volume deficiency and eyelid dysfunction cause inadequate corneal protection which leads to excessive epithelial damage. Eyelid, eyelash and tear film dysfunctions tend to occur more frequently in dogs, although brachycephalic dogs seem more likely to be affected.[2] It is suspected that physiologic exophthalmos in brachycephalic dogs associated with incomplete blinking can result in tear film abnormalities, such as a considerably thinner lipid layer and a decrease in the aqueous layer in the central cornea. These abnormalities may lead to drying of the ocular surface and decrease in the barrier function. For these reasons, brachycephalic dogs may be more prone to bacterial contamination leading to complicated ulcerative keratitis.[4] One

study published that Shih Tzus, Pugs and Pekingese are more frequently affected by severe ulcerative keratitis. The risk of a corneal ulcer in brachycephalic dogs has been previously reported that reduced corneal sensation and fewer numbers of corneal nerves associated with brachycephalic skull conformation may lead to increase the development of ulcerative keratitis.[9]

Treatment & Management

No single therapeutic plan is appropriate for all situations because of the vastness of ulcerative keratitis. In general, these objectives should be fulfilled when applicable: prevention or elimination of contamination or infection, control of anterior uveitis, analgesia, arrest of tissue destruction, preservation of corneal clarity and function, and tissue support.[3] Prophylactic topical antibiotic therapy is indicated for noninfected superficial epithelial ulcers with a broad-spectrum antibiotic to prevent secondary bacterial infections.[9] The choice of antibiotic formulation, solution or ointment, is largely dictated by the urgency of therapy and owner compliance. Ointments may last a few hours in the conjunctival sac while solutions may penetrate the damaged cornea more rapidly but may have a duration of only minutes. Ointments may be best avoided for eyes that threaten perforation because the manipulation required for administration may promote perforation. It is also more irritating to intraocular structures than a drop if applied in an already perforated eye. In addition, topical parasympatholytic drugs, like atropine, are indicated for analgesia which decrease ciliary muscle and iris sphincter spams that cause discomfort. Atropine also causes pupil dilation, which helps decrease the chances of anterior or posterior synechiae in the presence of corneal perforation and uveitis, respectively. Atropine also can close off the iridocorneal angle and result in increased intraocular pressure and is thus contraindicated in cases of glaucoma.[3]

Stromal ulcers can be divided into progressive and nonprogressive types. Nonprogressive stromal ulcers can be managed medically in the same manner as superficial ulcers. However, progressive, deep stromal ulcers are potentially vision and globe threatening and therapy should be aggressive. Aggressive topical antibiotic therapy is required, and selection should be based on cytology and culture and sensitivity results. Topical atropine should again be administered to reduce pain and prevent synechiae formation. Surgical treatment of progressive deep ulcers is often indicated and includes conjunctival grafts or flaps and corneal grafts.[9] Again, a descemetocele and corneal perforation are considered surgical emergencies and require specialized equipment for globe sparing-repair. The surgical treatment of choice varies according to the size and depth of the corneal defect.[9] Systemic antibiotic therapy is not routinely indicated for ulcerative keratitis unless perforation threatens or occurs. Follow-up examination of all corneal ulcerations, even minor abrasions, is required every 2-3 days until fluorescein staining is absent.[3]

Case Outcome

As Tucker was being prepped for surgery, the descemetocele perforated. A conjunctival flap surgery with porcine small intestinal submucosa (SIS) graft was then performed OS. SIS is a biomaterial derived from porcine jejunum that is synthesized to leave an acellular extracellular matrix that acts as a three-dimensional scaffold for tissue repair and remodeling.[1] In Tucker's case, SIS was used only because his eye perforated. If the eye had not perforated, a conjunctival flap would have likely been sufficient to provide support to the descemetocele. The ulcer was measured and was noted to be 3 mm in circumference. A rotating conjunctival flap was harvested from the dorsolateral bulbar conjunctiva. Once harvested, calibri forceps were used to remove any unhealthy epithelium overlying the area of ulceration. A cotton tip applicator was

also used to debride the unhealthy epithelium from the area of the defect so that the flap would adhere. Removal of the epithelium is also essential for the graft to adhere and incorporate into the cornea over time; otherwise, the graft will fall off. A 4 mm piece of SIS was cut and placed over the defect. The 4 mm section of SIS was then sutured into place over the area of ulceration using 8-0 vicryl using a simple interrupted pattern. The flap was then positioned over the corneal defect and sutured to the cornea in a simple interrupted pattern using 8-0 Vicryl. A temporary lateral tarsorrhaphy was performed with 4-0 Prolene. Tucker recovered from surgery uneventfully in the ICU. Post-surgical medications in hospital included Ofloxacin (1 drop OS Q2h), Cefazolin (1 drop OS Q2h), Optimmune (1/8 inch strip OD Q12h), Atropine (1 drop OS Q12h), Refresh tears (1 drop OU Q4h), sucralfate (0.5 tablet PO Q12h), omeprazole (1 tablet PO Q8h), Clavamox (1 tablet PO Q12).

Tucker was discharged the next day, July 2, 2020. The owners were instructed to keep a hard E-collar on at all times, watch for increased ocular pain, loss of vision, and ocular discharge. The owners were also advised to watch for complications post-surgery which include graft necrosis, dehiscence, infections, and corneal perforation under the graft. He was diagnosed with a descemetocele OS that ruptured prior to surgery and Keratoconjunctivitis sicca OU. He was discharged with the following ophthalmic medications waiting 5 minutes between each ophthalmic medication: Ofloxacin (1 drop OS QID), Cefazolin (1 drop OS QID), Optimmune (1/8 inch strip OD Q12h), Atropine (1 drop OS Q24h), Refresh tears (1 drop OU QID). He was also sent home with the following oral medications: Clavamox 62.5mg (1 tab PO Q12h), Sucralfate (1/2 tab PO Q8-12h), Omeprazole (1/4 tab PO Q12h), and Trazodone (1/4 to ½ tab PO Q12h PRN). His culture & sensitivity came back as light growth of Staphylococcus sp. with susceptibility to his current ophthalmic antibiotics.

During his recheck on July 10, 2020, 10 days post-operative, the lateral tarsorrhaphy was removed. Tucker's eye was healing well following the conjunctival flap surgery with SIS. His vision remained intact OU and the only ophthalmic abnormality was a decreased STT of 11 mm/min OD (left was not performed). The rest of his ophthalmic exam was unremarkable. The owners were instructed to discontinue the Atropine solution, continue with the cefazolin and ofloxacin as previously prescribed, and give Optimmune OU. Tucker was then seen 3 weeks after his initial recheck and his cornea had fully healed following surgery. His KCS had improved from his previous visits but his owners were instructed that this could be lifetime treatment. They were also instructed to monitor Tucker for any changes to the eye. As of now, Tucker is still doing well at home.

Conclusion

In conclusion, ulcerative keratitis is an ophthalmic condition that will be seen commonly in general practice. It is classified into superficial keratitis, deep corneal ulcer keratitis, descemetocele keratitis, and perforation keratitis with reference to the loss of corneal layers. Common clinical signs include blepharospasm, photophobia, lacrimation, conjunctival hyperemia, corneal edema, and aqueous flare. There are many etiologies for ulcerative keratitis and the causative agent should be identified for proper treatment. The standard ocular work up includes gross examination, direct and indirect ophthalmoscopy, Schirmer tear test, fluorescein dye staining, and tonometry. Brachycephalic breeds are more commonly predisposed to ulcerative keratitis, largely due to lagophthalmos and higher frequency of KCS. Superficial ulcers and nonprogressive stromal ulcers can be treated medically with topical antibiotics and atropine. Deep stromal ulcers and progressive stromal ulcers should be treated aggressively medically and may require surgery. Descemetocele and corneal perforations are surgical

emergencies and should be referred to an ophthalmologist for globe sparing procedures. The surgical treatment of choice varies according to the size and depth of the corneal defect. Follow-up examination of all corneal ulcerations, even minor abrasions, is required every 2-3 days until fluorescein staining is absent.

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