“Big Pugs Don’t Cry”

Keratoconjunctivitis Sicca in the Canine

Haleigh B. Schreckengost

Mississippi State University

College of Veterinary Medicine

Class of 2020

Clinicopathologic Conference

March 13, 2020

Advisor:

Caroline Betbeze, DVM, MS, Associate Clinical Professor

Introduction:

Keratoconjunctivitis sicca (KCS), commonly referred to as dry eye, is an inflammatory ocular surface condition in dogs with reported incidences ranging from 11-14.7%.[9] KCS develops from a pathologic reduction in the aqueous component of the pre-ocular tear film.[1] KCS is most often immune-mediated, but may also be drug or surgically-induced, or induced by infectious, traumatic, neurogenic, congenital, metabolic and idiopathic causes.[2,3] Immune mediated KCS is the most common underlying cause and occurs in certain breeds. Predisposed breeds for immune mediated KCS include, but are not limited to, Cavalier King Charles spaniel, cocker spaniel, English bulldog, pug, shih tzu, and West Highland white terrier.[5] Clinical signs consistent with KCS include blepharospasm, conjunctival hyperemia, dull corneal appearance, corneal neovascularization, corneal pigmentation, and blindness in severe cases.[1] It is important to rule out other causes of a red eye in cases where KCS is suspected. A schirmer tear test confirms the diagnosis of KCS, where <15 mm/min is abnormal, with <5 mm/min being severe. However, corneal ulcers, glaucoma, and uveitis can present to the practitioner with similar clinical signs to KCS. Other tests such as a fluorescein stain and tonometry are imperative to help rule out other causes of a red eye. Treatment consists of life-long medical management, and in refractory cases may require surgical treatment in addition to medical treatment.[5] If left untreated, KCS can lead to ocular pain, discomfort, and ultimately blindness.

History and Presentation:

Jack is an 11-year-old, intact male Pug who presented to the MSU-CVM Ophthalmology service on June 4, 2019. Jack was referred from his primary veterinarian for further evaluation after being diagnosed with severe KCS. Jack has a long history of ocular problems starting with a puncture wound to his left eye at 3 months of age. At age 6, Jack began to exhibit clinical signs

consistent with KCS that progressively worsened, especially within the last year. In November 2016, Jack presented to a veterinarian to check his eyes. At this time, tear production was 6 mm/min OS and 12 mm/min OD, there was pigmentary keratitis OU and he had a positive menace OU. He was treated with Tacrolimus OU BID and Neomycin-Polymyxin B-Dexamethasone OU BID. In August 2017, Jack presented to the same veterinarian to recheck the eyes and at this time, both eyes contained mucous and there was noted irritation under the left eye. He was continued on the same medications as above. In December 2018, Jack presented to a different veterinarian to check both eyes. At this time, he was prescribed cyclosporine 0.1% solution in oil OU BID. In February 2019, Jack was given another prescription of cyclosporine 0.1% solution in oil OU BID. On June 3, 2019 Jack presented to the referring veterinarian to check both eyes and at this time, no pupillary light response or menace was present OU. Tear production was 0 mm/min OS and 5 mm/min OD. Jack was referred to MSU-CVM to discuss further options for maintaining the best quality of life. Upon questioning at MSU-CVM, it was noted that Jack was treated topically with tacrolimus ophthalmic solution, Neomycin-Polymyxin B-Dexamethasone ophthalmic solution, cyclosporine 0.1% ophthalmic solution, cyclosporine 0.2% ophthalmic ointment, and a variety of artificial tear supplements within the last 2-3 years with little to no improvement in tear production or clinical signs of KCS. Jack rubs his face against objects multiple times per day and the owners recently noted that he was no longer able to see in dark light. He is otherwise healthy.

On presentation to MSU-CVM, Jack was bright and alert. He had an ideal body condition score of 5/9 and weighed 9.4 kilograms. His vital parameters were within normal limits with a heart rate of 88 beats per minute and a rectal temperature of 100.3 degrees Fahrenheit. His respiratory rate was obscured by sniffing at 60 breaths per minute. On thoracic auscultation,

there were no murmurs or arrhythmias noted. On auscultation of the lungs, there was an inspiratory stertor present with no other abnormal lung sounds noted. There was mild brown debris present in both ears, consistent with diagnosis of a yeast infection the day before. There was normal wetness of both nostrils. Cranial nerve examination was within normal limits. The abdomen was soft and non-painful on palpation.

On ophthalmic exam, several abnormalities were present. There was absent menace response and tracking in both eyes, a negative dazzle reflex of the left eye and a positive dazzle reflex of the right eye. Mucopurulent ocular discharge, conjunctival thickening, severe pigmentary keratitis, conjunctival hyperemia, and corneal fibrosis were present in both eyes. The corneal pathology obscured visualization of the rest of the anterior segment and the posterior segment of both eyes.

Diagnostic Approach & Considerations:

A schirmer tear test was performed which revealed 0 mm/min aqueous tear production bilaterally. Fluorescein stain was negative for both eyes and tonometry via Tono-Pen was within normal limits with a value of 16mmHg OU. Conjunctival cytology was obtained from the right eye with a microbrush^{tm} and evaluated with a commercial Romanowsky type stain (Diff-Quick^{tm}). The sample contained epithelial cells, multiple clusters of Malassezia, lymphocytes and neutrophils. Conjunctival cytology was obtained from the left eye and contained epithelial cells, lymphocytes, and neutrophils. Both cytology of the right and left eyes was submitted for pathology review. The predominate cell types observed were non-degenerate neutrophils and conjunctival epithelial cells. The epithelial cells exhibited mild amounts of atypia, likely representing epithelial hyperplasia/dysplasia. Focal aggregates of Malassezia were seen. No bacteria were observed and there was no evidence of neoplasia. Based on history, ophthalmic

exam findings, schirmer tear test, and conjunctival cytology, Jack was diagnosed with severe KCS in both eyes. Because of the severity and chronicity of KCS, pigmentary keratitis developed in both eyes, leading to irreversible blindness. Fungal conjunctivitis of the right eye was suspected based on cytology.

Pathophysiology:

The etiopathogenesis of KCS is poorly understood.[8] The precorneal tear film consists of three layers, covering the cornea and conjunctiva. The outer layer is produced from the meibomian/tarsal glands and is composed of oily materials and phospholipids to limit evaporation of the aqueous layer and to bind the precorneal tear film to the corneal lid margins.[1,2] The middle aqueous layer consists of water from the lacrimal gland and gland of the third eyelid. This layer is the thickest layer and functions to flush foreign material and bacteria from the conjunctival sac, to lubricate the eyelids and nictitating membrane as they move over the cornea, to supply the cornea with nutrients such as oxygen, amino acids, vitamin A, growth factors, white blood cells and antibodies, to remove metabolic waste products, to give a smooth surface to the cornea for optical efficiency, and to act as a source of antibacterial substances, such as immunoglobulins, lactoferrin, and lysoenzyme. Tears also contain protease inhibitors that protect the cornea from degradative enzymes released by bacteria, inflammatory cells, and keratocytes.[2] The inner mucoid layer, produced by conjunctival goblet cells and stratified epithelial cells of the ocular surface, consists of hydrated glycoproteins.[1,2] This layer is important in binding the lipophobic aqueous layer to the lipophilic corneal surface.[2] The aqueous layer of the tear film is pathologically reduced leading to the development of KCS.[1,8]

Two types of KCS have been identified: deficiency of tear production and deficiency of tears due to premature evaporation. Dry eye disease attributed to tear evaporation is observed in

brachycephalic breeds in which lagophthalmos leads to a central area of tear film deficiency. This can cause ulcerative and nonulcerative keratitis. Reduction in aqueous tear production leads to corneal inflammation, and in severe cases, can result in blindness due to complete corneal pigmentation and fibrosis.[5,14] There are several known causes of KCS in dogs: congenital, infectious, drug induced, metabolic, radiation, neurogenic, iatrogenic, idiopathic, and immune-mediated.[5,10,11] Congenital KCS has been shown to occur in Yorkshire terriers, Bedlington Terriers, and pugs.[2,3] It is thought to occur due to lacrimal gland agenesis or hypoplasia. Clinical signs are usually severe and are noted at birth in the Yorkshire Terrier, Bedlington Terrier, English Cocker Spaniel, Shih Tzu, Pug and Cavalier King Charles Spaniel.[2,3,5] Infectious causes include canine distemper virus and leishmania. Temporary dry eye disease has been observed with local or systemic anesthetics, sedatives, atropine and etodolac.[5,9] Permanent KCS has been associated with potentiated sulfonamide drugs in dogs. Diabetes mellitus and hypothyroidism are metabolic causes of KCS. The use of radiation therapy can damage the lacrimal glands leading to KCS. Neurogenic KCS ensues when there is damage to the efferent portion of the facial nerve and an ipsilateral dry nose is often seen.[5,10] Iatrogenic KCS occurs from the surgical removal of the gland of the third eyelid.[5,11] Immune-mediated KCS is argued to be the most common cause of KCS, and therefore will be the main focus of this paper.

Immune-mediated KCS is often bilateral and is confirmed with evidence of inflammation and destruction of the lacrimal glands on histopathology. Breed predispositions for immune-mediated KCS include: American Cocker Spaniel, Bloodhound, Boston Terrier, Cavalier King Charles Spaniel, English Bulldog, English Cocker Spaniel, English Springer Spaniel, Lhasa Apso, Miniature Schnauzer, Pekingese, Pug, Samoyed, Shih Tzu, West Highland White Terrier, and Yorkshire Terrier. For brachycephalic breeds, such as the Pug, lagophthalmos increases

evaporation of tears and contributes to the development of KCS.[5] There is proposed female prevalence that is thought to occur due to male lacrimal glands being larger than female.[9]

Lacrimal gland secretion is under neural and hormonal control, with parasympathetic and sympathetic innervation from sensory nerves in the cornea that activate efferent parasympathetic and sympathetic nerves of the facial nerve. The neurotransmitters acetylcholine, vasoactive intestinal peptide, substance P, noradrenaline, and calcitonin gene-related peptide are all important in lacrimal secretion. Hormonal control by the hypothalamopituitary-gonadal axis has a profound effect on tear secretion and influence on lacrimal gland function.[8]

Corneal-conjunctival inflammation in dogs with dry eye is mainly characterized by T-cell infiltration.[9] Inflammatory changes in KCS lead to profound reduction in tear production; however, it is unclear how this occurs. One suggestion is that lymphocyte-associated cytotoxicity of lacrimal tissue is central in the pathologic effects on lacrimation. A second is that apoptosis of glandular epithelial cells is critical in tear hyposecretion. A third is that cytokine release from inflammatory cells alters tear production. A fourth is inflammatory cells or their associated cytokines or autoantibodies may influence neurotransmitter function in the lacrimal gland, inhibiting neurologic stimulation of tear secretion. One or more of these pathologic factors may be contributing to tear deficiency.[8]

Initial presentation of KCS appears as a common mucopurulent conjunctivitis. The ocular surface becomes dull and the conjunctiva become extremely reddened with very thick yellow-gray discharge. This is a progressive disease, with chronic KCS manifesting as corneal vascularization, fibrosis, pigmentation, and recurrent corneal ulceration. Blindness or loss of the eye may result from dense corneal opacification or deep corneal ulceration, although only a small group of animals are affected by blindness.[5]

Treatment and Management:

Medical management of KCS via topical drugs is considered the first line of therapy and may require life-long treatment.[5,9] The goals of medical therapy are to reactivate the tear film, stimulate tear production, and reduce inflammation.[5] Two types of medications are used: lacrimomimetics, with moisturizing substances for replacing deficient components of the tear film, and lacrimostimulants, which stimulate tear production and are immunosuppressive/anti-inflammatory.[9] Gel artificial tear drops are ideally applied q1h for STT values between 0-7 mm/min, and at least six times a day for values >7 mm/min .[5] Immunomodulating agents, such as Cyclosporine (CsA) and Tacrolimus/Pimecrolimus, reduce glandular inflammation and improve tear secretion, and therefore are most commonly used to treat KCS.[4] A key feature suggesting that immunologic changes play a role in the pathogenesis of KCS is the effectiveness of Cyclosporine as an immunomodulator in dogs.[8] Cyclosporine prevents lymphokine production as a calcineurin inhibitor, inhibits helper T cell proliferation and infiltration of lacrimal gland acini, and binds to the cyclophilin receptor inhibiting prolactin, resulting in regeneration of the gland and stimulating tear production.[2,4,6,7,8] It also has lacrimomimetic effects. Commercially available cyclosporine is available in a 0.2% ointment to be applied q8-12h for 30-45 days, and then decreased to q12-24h long-term if improvement is noted.[4,8] Compounded formulations are available as 1% or 2% solutions.[2,9] Tacrolimus has been suggested to have a 10-fold increased potency effect over cyclosporine and therefore is available as 0.02% solution.[7,8] Its mechanism of action is believed to be similar to cyclosporine. Studies have shown that dogs who did not respond to cyclosporine did respond to tacrolimus, and suggests that tacrolimus may have enhanced lacrimogenic properties over cyclosporine; however, tacrolimus may have more

potential toxic effects.[2,7] Pilocarpine is a parasympathomimetic used for the treatment of neurogenic KCS and will likely not benefit animals with immune-mediated.[5]

A sustained release episcleral silicone matrix cyclosporine (ESMC) implant in dogs with KCS has been studied. In the study, 27 eyes received the ESMC implant with 15 eyes being responsive to topical CsA and 12 eyes not responsive. Both groups showed significant improvement in STT values and clinical signs, and the implants were well tolerated by all dogs. This sustained release technology helps to eliminate or minimize the effects on the patient and owner noncompliance in drug administration. Sustained release allows for higher concentrations of CsA than topical therapy without systemic side effects. The estimated duration of release in vitro is 18-24 months. Implantation does require surgery under general anesthesia.[12]

Uncontrolled KCS can result in blinding and chronic ocular pain.[13] Refractory cases of KCS may require surgical therapy. Once the lacrimal gland has reached the fibrotic stage, no immunomodulatory lacrimogen acts to increase tear production.[8] In cases of severe KCS where medical management has proven unsuccessful, parotid duct transposition (PDT) is often the surgical option of choice to improve comfort and avoid potential blindness.[13,14] The parotid duct supplies saliva from the parotid gland to an oral papilla near the carnassial tooth. In the transposition surgery the duct and papilla are mobilized and transferred to the conjunctival sac to provide lubrication.[2] Facial (open) and oral (closed) approaches have been studied.[2,13] Both surgical and post-operative complications are common. Surgical complications include trauma to the duct and temporary/permanent partial or complete parotid duct failure.[13,14] Post-operative complications include facial swelling and facial wound dehiscence. Long-term complications include corneal and eyelid calcium deposition, continuous salivary epiphora with ocular discomfort, parotid duct dilation, and salivary intolerance from quality/quantity of saliva.[2,13] Due

to increased mineral content in saliva, it is a suboptimal substitute for the corneal tear film; however, for refractory cases of KCS this is still a viable option.[13] A retrospective study of PDT surgery in 92 eyes with acquired immune-mediated KCS showed a success rate of 92% with complications occurring in 50% of eyes, and 33% of eyes still required long-term topical treatment. Overall, the study showed that PDT improves ocular comfort, improved vision, and reduces the frequency of topical medication; however, it does not fully replace medical treatment and has a high complication rate.[13]

A minimum of 3-6 months of medical management is recommended before surgical therapy is considered.[2] Other medical treatment options to recognize with KCS are: mucolytic agents, such as acetylcysteine, antibiotics as necessary for corneal ulceration and secondary bacterial infections, corticosteroids used cautiously to improve symptoms, and interferons used to increase tear production.[2,5,9]

Case Outcome:

Due to the severe nature of Jack's KCS he was started on aggressive topical therapy with goals aimed at stimulating tear production and providing comfort for his eyes. Jack's owners were also counseled about the severity of his KCS and the poor prognosis for response to medical therapy. They were also counseled about his blindness which was irreversible. Jack was prescribed a combination of medications including a 0.25% hyaluronic acid artificial tear drop to be given in both eyes every 2 hours as a topical lubricant, a carbomer hyaluronic acid eye lubricant plus antioxidants given in both eyes 5-6 times per day, tacrolimus 1% ophthalmic ointment 1/8 inch strip in both eyes every 8 hours as a topical immunomodulatory agent and cyclosporine 0.2% ointment 1/8 inch strip in both eyes every 8 hours as a topical immunomodulatory agent. Itraconazole/DMSO ointment 1/8 inch strip given into the right eye

four times per day as an antifungal agent. It was instructed to wait 5 minutes between eye medications to allow for proper absorption and to give the 0.2% cyclosporine as the last medication. Jack's surgical options were the subconjunctival cyclosporine implant, parotid duct transposition, or enucleation. Following discharge, Jack was instructed to return to MSU-CVM in 10-14 days for a follow-up appointment to observe any progress with the topical medications. Unfortunately, Jack never returned to MSU-CVM. He was also lost to follow-up with his primary veterinarian.

Conclusion:

Keratoconjunctivitis sicca (KCS) is a common ocular disorder in dogs that has a multifactorial etiopathogenesis. Immune-mediated is thought to be the most common cause of KCS in dogs. Diagnosis is achieved using the schirmer tear test and clinical signs. Most cases of KCS can be managed life-long with topical medications that aim to stimulate tear production, increase comfort, and decrease inflammation. Topical cyclosporine has been efficacious and successful in the management of most cases with KCS. Tacrolimus can be used instead of or in conjunction with cyclosporine for more severe cases or for some cases that do not improve with cyclosporine alone. For refractory cases that do not respond to medical therapy, surgical options, such as cyclosporine implant or parotid duct transposition, have been successful in managing this condition. Ultimately, if KCS goes untreated, blindness or loss of the eye may ensue.

References:

1. Cooper, Sarah. "Keratoconjunctivitis Sicca in the dog." *UK Vet Companion Animal* 17.8 (2012): 37-42.
2. Maggs, David J., et al. *Slatter's fundamentals of veterinary ophthalmology*. Elsevier Health Sciences, 2013.Williams, David L. "Immunopathogenesis of keratoconjunctivitis sicca in the dog." *Veterinary Clinics of North America: Small Animal Practice* 38.2 (2008): 137, 157-171.
3. Westermeyer, Hans D., Daniel A. Ward, and Kenneth Abrams. "Breed predisposition to congenital alacrima in dogs." *Veterinary ophthalmology* 12.1 (2009): 1-5.
4. Reinstein, Shelby. "Dry eye in dogs: When good glands go bad." *Veterinary Team Brief* (2017): 33-37.
5. Dodi, Pier Luigi. "Immune-mediated keratoconjunctivitis sicca in dogs: current perspectives on management." *Veterinary Medicine: Research and Reports* 6 (2015): 341.
6. Izci, Celal, et al. "Histologic characteristics and local cellular immunity of the gland of the third eyelid after topical ophthalmic administration of 2% cyclosporine for treatment of dogs with keratoconjunctivitis sicca." *American journal of veterinary research* 63.5 (2002): 688-694.
7. Berdoulay, Andrew, Robert V. English, and Brad Nadelstein. "Effect of topical 0.02% tacrolimus aqueous suspension on tear production in dogs with keratoconjunctivitis sicca." Veterinary ophthalmology 8.4 (2005): 225-232.
8. Williams, David L. "Immunopathogenesis of keratoconjunctivitis sicca in the dog." *Veterinary Clinics of North America: Small Animal Practice* 38.2 (2008): 251-268.

9. Ribeiro, Alexandre Pinto, et al. "Qualitative and quantitative tear film abnormalities in dogs." Ciência Rural 38.2 (2008): 568-575.
10. Matheis, Franziska L., Ladina Walser-Reinhardt, and Bernhard M. Spiess. "Canine neurogenic keratoconjunctivitis sicca: 11 cases (2006–2010)." *Veterinary ophthalmology* 15.4 (2012): 288-290.
11. Almeida, Denise Eliza de, et al. "Iatrogenic keratoconjunctivitis sicca in a dog." *Ciência Rural* 34.3 (2004): 921-924.
12. Barachetti, Laura, et al. "Use of episcleral cyclosporine implants in dogs with keratoconjunctivitis sicca: pilot study." *Veterinary ophthalmology* 18.3 (2015): 234-241.
13. Rhodes, Mike, et al. "Parotid duct transposition in dogs: a retrospective review of 92 eyes from 1999 to 2009." *Veterinary ophthalmology* 15.4 (2012): 213-222.
14. Young, Whitney M., et al. "Enucleation or exenteration in two dogs with previous parotid duct transposition: parotid duct ligation versus reverse parotid duct transposition." *Veterinary ophthalmology* 21.4 (2018): 413-418.