Dry Eye, No Cry

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Introduction

Keratoconjunctivitis sicca (KCS) is a common ophthalmic disease that is reported to affect 1% of dogs[1]. Although relatively common in our canine population, it is often under recognized or misdiagnosed due to its various etiologies and clinical presentation. KCS can be divided into two different types, caused by either a qualitative or quantitative alteration to the tear film[2]. Quantitative KCS is characterized by deficient production of the aqueous portion of the tear film, whereas qualitative disease is characterized by inadequate production of the lipid or mucoid portions of the tear film that can increase tear evaporation[3]. This results in desiccation and subsequent redness, irritation and inflammation of the corneal and conjunctival surfaces of the eye. In veterinary medicine, this disease is primarily diagnosed via a Schirmer tear test and may be better understood in each patient by determining an underlying etiology. KCS can be associated with immune and metabolic diseases, drug toxicities, trauma, ocular surgery, viral diseases, neurological deficits, and radiation therapy among others[5]. The most common causes are immune-mediated and breed-related[6]. The following case report will review the history and presentation, pathophysiology, diagnostic consideration, treatment and management, and case outcome of keratoconjunctivitis sicca in a canine patient.

History and Presentation

Gunny is an 8-year-old, neutered male bulldog that presented to MSU-CVM Ophthalmology Department on 9/28/2021. His presenting complaint was excessive mucoid discharge, particularly in the left eye. The owner expressed frustration that despite frequent wiping and cleaning of the eye's multiple times a day, the discharge promptly returned and matted the fur surrounding the eyes. Gunny was initially evaluated by his primary care veterinarian 3-months prior, where he was given NeoPolyDex applied to the left eye twice daily,

and Refresh eye drops applied to both eyes three times a day. Gunny's owner reported no significant response to these therapies.

On physical exam, Gunny was bright, alert, and responsive. He was overweight, weighing 25.0 kilograms with a body condition score of 7/9. His vitals included a temperature of 101.9F, a heart rate of 130 beats per minute, and he was panting. He appeared adequately hydrated and no heart murmurs, arrythmias, crackles or wheezes were auscultated. On initial ocular examination, his left cornea appeared lackluster with severe ropey mucoid discharge observed around his left eye. This was accompanied with conjunctival hyperemia and squinting of the left eye. He had an intact PLR and menace response in both eyes, indicating he was still visual. He also had marked hyperkeratosis of the nasal planum. On continued ophthalmic exam, Gunny's eyes were free of ulcers and fluorescein stain negative; and his intraocular pressures measured normal at 15 mmHg in the left eye and 14 mmHg in the right eye using applanation tonometry. His slit lamp biomicroscopy and indirect ophthalmoscopy were limited in the left eye due to diffuse corneal pigment causing limited visibility and demonstrated an incipient anterior cortical cataract in the right eye with normal vitreous and fundus.

Etiology and Pathophysiology

Tears are a unique substance, comprised of different components involved in lubrication, defense, and nourishment of the ocular surface. Keratoconjunctivitis sicca in dogs occurs when there is quantitative or qualitative deficiency of one or more components of the tear film[9]. The primary glands that produce tears are the lacrimal gland, the gland of the third eyelid and accessory glands that surround the eyelid margins. Secretions from these glands drain via multiple microscopic duct openings and are distributed over the surface of the eye via blinking and gravity[6]. The different components from the glands come together and form precorneal tear

film, containing three different functional layers. The most superficial layer is a thin lipid layer, composed of oily material and phospholipids produced by Meibomian glands and the glands of Zeiss. This layer acts as a lubricant for smooth movement of the eyelid over the globe, as well as preventing evaporation of the underlying aqueous layer[8]. The aqueous layer is the intermediate layer and is the major component of tear film. This layer is composed of water, electrolytes, and proteins with 70% produced by the lacrimal gland, and 30% produced by the gland of the third eyelid[3]. This fluid not only nourishes and moistens the cornea, but also plays an important role in flushing foreign material and pathogens. It contains antimicrobial substances such as immunoglobulins, lysozyme, lactoferrin and protease inhibitors that protect the eye from viruses and bacteria[3 6]. The inner layer is a mucus layer composed of hydrated glycoprotein produced by Goblet cells of the conjunctival epithelium. This layer primarily corrects corneal surface irregularities and promotes adhesion of the lipophobic aqueous layer to the lipophilic corneal surface [3 6 8].

Deficiency in the aqueous portion of the tear film is direct result from decreased production or secretion from the lacrimal glands resulting in quantitative KCS. Quantitative dry eye disease is what is most commonly seen in our canine patients due to its various etiologies. Immune mediated disorder is widely accepted as the primary cause of dry eye in dogs. The eye is considered one of the few immune privileged sites within the body, and under normal conditions limits local inflammatory immune responses. This acts to preserve vision that may be obscured by swelling and tissue changes associated with inflammation[3]. As a primary defense mechanism, a blood-tear barrier protects the immune-privileged tissues of the eye including the lacrimal acinar epithelial cells[6]. Although the inciting cause that leads to such immune events is still unknown, compromise to this barrier allows infiltration of inflammatory cells, predominantly T-

lymphocytes. This further results in immune-mediated destruction of the lacrimal gland tissues and conjunctival goblet cells[1112]. Additionally, studies have shown up to 40% of animals with KCS may concurrently be affected with other autoimmune and metabolic disorders as well, including systemic lupus erythematosus, pemphigus foliaceus, rheumatoid arthritis, polyarthritis, atopy, hypothyroidism, Cushing's disease, and diabetes mellitus [10 11 16]. Keratoconjunctivitis sicca in dogs has also been associated with use of certain drugs that may result in permanent damage to the lacrimal glands. Association has been reported with oral administration of the nonsteroidal anti-inflammatory etodolac; as well as potentiated sulfonamides including sulfasalazine, sulfadiazine, and trimethoprim-sulfonamides; and phenazopyridine, a medication used as a urinary analgesic[6 9 13]. The pathogenesis to how this occurs is still unclear, however it is proposed pyrimidine and pyridine metabolites of the drugs have direct toxic effects on lacrimal gland tissue[6 13 14]. Associations between breeds have been made in various studies; indicating English bulldogs, West Highland Terrier, Cavalier King Charles Spaniel, Cocker Spaniels, and Shih Tzu's are of the most predisposed breeds[15 18]. Yorkshire terriers and Bedlington Terriers are overrepresented with congenital alacrima; a developmental absence of lacrimal tissue resulting in permanent KCS present since birth. Neurogenic KCS results from loss of parasympathetic innervation from cranial nerve VII to the lacrimal glands. This form of the disease is typically unilateral with an ipsilateral dry nostril due to the sharing of innervation[6]. Other notable causes of KCS in dogs include iatrogenic KCS from surgical removal of the third eyelid, often performed due to gland proptosis or "cherry eye." Trauma directly to the eye resulting in decreased tear distribution from impaired blinking and increased evaporation, or trauma to the lacrimal glands or nerves themselves. Radiation therapy can cause damage to the glands if in the

direct field; and finally, infectious KCS that may occur due to Canine Distemper virus or leishmaniosis infections resulting in lacrimal adenitis obstructing precorneal tear secretions[6 17 18].

Qualitative KCS results from deficiencies of the lipid or mucin portions of the precorneal tear film, decreasing overall quality and stability of the tear film. Deficiency of the lipid portion results in increased tear evaporation. It is typically due to inflammation of the eyelid margin and meibomian glands, known as blepharitis and meibomianitis. This most commonly occurs secondary to infections with *Staphylococcus, Malassezia, Candida* and demodex species, however certain autoimmune conditions that affect the eyelids such as atopy, lupus erythematosus and bullous pemphigoid may also decrease meibomian gland lipid secretions[6 20]. Deficiency in the mucin layer is most common with chronic conjunctivitis. As the inflammatory process progresses, inflammatory cell infiltrates may reduce or eliminate conjunctival goblet cells. This results in an unstable tear film, that can no longer bind the aqueous portion of the tear film to the ocular surface. Tears no longer uniformly moisten the surface of the eye, resulting in a lackluster appearance and corneal desiccation[6 21].

Regardless of the etiology, the pathophysiology of dry eye disease is a direct effect from a tear film deficiency. Decrease in the aqueous portion of the tear film results in hypertonicity of the remaining tear film, which further dehydrates the corneal and conjunctival epithelial cells. The lack of lubrication over the ocular surface combined with the roughened epithelium results in increased frictional damage by the eyelids with every blink. This causes chronic inflammation secondary to the increased surface friction on the corneal and conjunctival surfaces. In early stages of the disease, the conjunctiva typically becomes hyperemic and chemotic. Red, irritated, and painful eyes may be the only clinical signs, and this stage may easily be misdiagnosed as bacterial or allergic conjunctivitis. As gradual progression occurs, compensatory conjunctival

cell hyperplasia results in increased mucin production. Furthermore, with a reduction in the rinsing function of the aqueous portion, the mucin and lipid portions blend forming a thick and ropy ocular discharge which is often characteristic of the disease. Corneal epithelial cells are more readily exfoliated and lost by the increased friction, making central corneal ulceration not an uncommon clinical sign. Further progression of the disease is often very painful, causing animals squint, blink excessively or hold the eye shut. The conjunctival and corneal epithelium continue to thicken and undergo squamous metaplasia and keratinization. This further exacerbates the condition by contributing even more irregularities on the ocular surface. Eventually, blood vessels and inflammatory cells infiltrate the anterior chamber resulting in corneal vascularization and pigmentation. These signs demonstrate chronicity of the disease and unfortunately can result in vision loss. Another complication associated with KCS is secondary infection. With a significant decrease of the antimicrobial substances usually found in the aqueous portion of the tear film and overall decrease of the natural defense mechanisms of the eye, this increases susceptibility to secondary bacterial infections. Increased protease and inflammatory debris from these bacteria may lead to corneal malacia, melting and even eventual perforation[6 21].

Diagnostic Approach

With Gunny displaying the typical presenting signs of keratoconjunctivitis sicca including copious sticky mucoid discharge and with apparent conjunctival hyperemia, further ophthalmic exam was warranted to confirm diagnosis. Diagnosis of quantitative KCS is suggested by clinical signs and confirmed with a Schirmer Tear Test I (STT) which is the standard-test used in veterinary ophthalmology to evaluate aqueous tear production[22]. Schirmer tear test readings should be taken prior to performing other tests or cleaning the eyes. An absorbent paper test strip

with millimeter markings is folded at the notch and placed over the lower eyelid for 60 seconds. The reference range for normal tear production is >15mm/minute. Gunny's Schirmer Tear Test of the right eye was within normal range at 23 mm/min, and his left eye as expected was decreased at 8mm/min. To evaluate a qualitative tear film deficiency, a Tear Film Breakup Time (TFBT) test may be performed. A drop of fluorescein stain can be placed in the eye and observed for how long it takes to clear the stain over the cornea. On Gunny, it was observed to have taken 20 seconds to clear the stain in his left eye. A tear film breakup time of <10 seconds is considered abnormal, indicating Gunny's KCS is more quantitative rather than qualitative. With the supporting clinical signs of mucoid discharge and conjunctivitis, and a decreased Schirmer tear test of the left eye, this was enough evidence to confirm suspicions and diagnose Gunny with Keratoconjunctivitis sicca.

Treatment

The main goals of medical therapy for both quantitative and qualitative KCS include replacement of the precorneal tear film, control of secondary infection, removal of excess mucus and stimulation of normal tear secretion [6]. For most patients diagnosed with KCS, management will be lifelong, and clients should be educated on long-term topical therapy. Gunny was already prescribed Refresh eyedrops by the referring veterinarian, which his owner was instructed to continue for tear replacement 2-3 times a day. Tear replacement therapy provides lubrication until tear stimulants are effective. A severe mucopurulent discharge is suggestive of a secondary bacterial infection, which if present should be sampled for culture. Due to previous long-term use of NeoPolyDex with no apparent infection the day of his evaluation, this medication was discontinued. Gunny's owner was instructed to continue to clean his eyes and carefully remove

excess mucus daily with a moist cotton ball, and he was prescribed Cyclosporine 1% ophthalmic drops to stimulate tear production.

Cyclosporine is an immunomodulant drug that blocks interleukin-2 production, which inhibits T-lymphocytes in the lacrimal gland. It also acts as an anti-inflammatory agent, can reduce corneal pigment, normalize goblet cell mucin secretions, and directly stimulate lacrimation [23]. Cyclosporine, labeled as Optimmune, is the preferred tear stimulant in veterinary medicine as it is FDA labeled for KCS in dogs. Other tear stimulants include off label Tacrolimus which could be used in cases unresponsive to Cyclosporine, and Pilocarpine which is no longer commonly used due its narrow therapeutic window[20]. Up to 80% of patients are reported to respond to Cyclosporine therapy, to the extent that other medications can eventually be adjusted or discontinued[6]. This emphasizes the importance of frequent rechecks and reassessment of medications after starting therapy.

In severe cases that do not respond to medical management, surgical treatment can be considered. The main surgical option is a parotid duct transposition, in which the parotid duct is carefully transferred to the conjunctival sac, providing saliva for lubrication of the eye. This is a technically demanding surgery and owners should be aware it is considered a salvage procedure for the eyes[24].

Case Outcome

On November 5th, 2021, Gunny received a follow-up exam from the MS State Ophthalmology Service, two months after starting Cyclosporine therapy. The pigment in his left cornea persisted as this is usually a permanent change, however the neovascularization and overall appearance of his cornea was improved. His Schirmer tear test value greatly improved with 20mm/min in the right eye and 16mm/min in the left eye.

Conclusion

In summary, disruption of any one of the three layers of the precorneal tear film leads to dry eye disease, although deficiency in the aqueous portion is the most common in dogs. The disease can be broken down into qualitative or quantitative categories depending on the precorneal tear film layer affected. There are numerous etiologies, with idiopathic immune mediated being the most common. Diagnosis can be made with observation of consistent clinical signs including mucoid ocular discharge and conjunctival hyperemia, along with a decreased Schirmer Tear Test and/or decreased Tear film breakup time. This disease is uncomfortable and painful, and frequent blepharospasm is a common clinical sign. As the disease progresses, corneal vascularization and pigmentation can lead to vision loss. Stimulating tear production with the use of immunomodulating ocular drugs is the mainstay of medical therapy, with improvement in about 80% of patients. Treatment is life long, and frequent rechecks are recommended to monitor improvement and adjust other medications as needed. In some instances, a parotid duct transposition surgery may be warranted.

References

1) Kaswan, Renee L. et al. "A new perspective on canine keratoconjunctivitis sicca: treatment with ophthalmic cyclosporine." *Veterinary clinics of North America: Small animal practice* 20.3 (1990): 583-613.

2) Williams, David L. "Immunopathogenesis of keratoconjunctivitis sicca in the dog." *Veterinary Clinics of North America: Small Animal Practice* 38.2 (2008): 251-268.

3) Ribeiro, Alexandre Pinto, et al. "Qualitative and quantitative tear film abnormalities in dogs." *Ciência Rural* 38 (2008): 568-575.

4) Dutu, Georgiana, et al. "Comparative Therapies in Keratoconjunctivitis Sicca in Dogs." *Scientific Works. Series C. Veterinary Medicine* 63.2 (2017) Online.

5) Sanchez, R. F., et al. "Canine keratoconjunctivitis sicca: disease trends in a review of 229 cases." *Journal of Small Animal Practice* 48.4 (2007): 211-217.

6) Maggs, David J. et al. *Slatter's Fundamentals of Veterinary Opthamology.* 5th ed. St. Louis: Saunders (2013)

7) Stern, M. E., Gao, J., Siemasko, K. F., Beuerman, R. W., & Pflugfelder, S. C. "The role of the lacrimal functional unit in the pathophysiology of dry eye." *Experimental eye research*, *78*.3 (2004): 409-416.

8) Menaka, R., & Puri, G. "Role of Lacrimal Gland in Tear Production in Different Animal Species. A Review" *Livestock Research International, 3* (2015): 40-42.

9) Dodi, P. L. (2015). Immune-mediated keratoconjunctivitis sicca in dogs: current perspectives on management. *Veterinary Medicine: Research and Reports*, *6*, 341.

10) Kaswan, R. L., Martin, C. L., & Dawe, D. L. (1985). Keratoconjunctivitis sicca: immunological evaluation of 62 canine cases. *American Journal of Veterinary Research*, *46*(2), 376-383.

11) Watté, Christine. "Ocular Immunology." (2018). *North Carolina State University College of Veterinary Medicine.* Document. January 2022. Microsoft Word - Watte_BSC-Immunology_and_ACAID-CW_FINAL (ncsu.edu)

12) Hermida-Prieto, M., García-Castro, J., & Mariñas-Pardo, L. (2021). Systemic Treatment of Immune-Mediated Keratoconjunctivitis Sicca with Allogeneic Stem Cells Improves the Schirmer Tear Test Score in a Canine Spontaneous Model of Disease. *Journal of Clinical Medicine*, *10*(24), 5981.

13) Klauss, G., Giuliano, E. A., Moore, C. P., Stuhr, C. M., Martin, S. L., Tyler, J. W., ... & Crawford, D. A. (2007). Keratoconjunctivitis sicca associated with administration of etodolac in dogs: 211 cases (1992–2002). *Journal of the American Veterinary Medical Association*, *230*(4), 541-547.

14) Trepanier, L. A. (2004). Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. *Journal of veterinary pharmacology and therapeutics*, *27*(3), 129-138.

15) O'Neill, D. G., Brodbelt, D. C., Keddy, A., Church, D. B., & Sanchez, R. F. (2021). Keratoconjunctivitis sicca in dogs under primary veterinary care in the UK: an epidemiological study. *Journal of Small Animal Practice*, *62*(8), 636-645.

16) Williams, D. L., Pierce, V., Mellor, P., & Heath, M. F. (2007). Reduced tear production in three canine endocrinopathies. *Journal of Small Animal Practice*, *48*(5), 252-256.

17) De Almeida, D. E., Roveratti, C., Brito, F. L., Godoy, G. S., Duque, J. C., Bechara, G. H., & Laus, J. L. (2009). Conjunctival effects of canine distemper virus-induced keratoconjunctivitis sicca. *Veterinary ophthalmology*, *12*(4), 211-215.

18) Rhodes, M. (2014). Canine keratoconjunctivitis sicca: an overview. *UK-Vet Companion Animal, 19(7), 336-340.*

19) Herring, I. P., Pickett, J. P., Champagne, E. S., & Marini, M. (2000). Evaluation of aqueous tear production in dogs following general anesthesia. *Journal of the American Animal Hospital Association*, *36*(5), 427-430.

20) Best, L. J., Hendrix, D. V., & Ward, D. A. (2014). Diagnosis & treatment of keratoconjunctivitis sicca in dogs. *Today's Vet. Pract*, *4*, 16-22.

21) Gelatt, K.N, Caryn, E. *Essentials of Veterinary Ophthalmology*. 2nd ed. Ames: Wiley-Blackwell (2008)

22) Williams, D. L. (2005). Analysis of tear uptake by the Schirmer tear test strip in the canine eye. *Veterinary Ophthalmology*, *8*(5), 325-330.

23) Moore CP, McHugh JB, Thorne JG, Phillips TE. Effect of cyclosporine on conjunctival mucin in a canine keratoconjunctivitis sicca model. Invest Ophthalmol Vis Sci 2001; 42(3):653-659

24) Rhodes, M., Heinrich, C., Featherstone, H., Braus, B., Manning, S., Cripps, P. J., & Renwick, P. (2012). Parotid duct transposition in dogs: a retrospective review of 92 eyes from 1999 to 2009. *Veterinary Ophthalmology*, *15*(4), 213-222