Changes in tear production in a dog with keratoconjunctivitis sicca for a year after inevitable nictitating membrane gland resection due to suspicion of a malignant tumour

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Abstract
Since the removal of the NM causes KCS in dogs, it was contraindicated to remove the NM unless unavoidable such as in a malignant tumour. However, to the best of author’s knowledge, there are no reports of conjunctivitis and keratitis owing to decreased tear production following removal of the NM gland. This case study demonstrates the tear production changes in a dog for a year after removal of the nictitating membrane (NM) due to suspicion of a malignant tumour. A 13-year-old spayed female English Cocker Spaniel who had suffered from severe ocular discharge, discomfort, keratoconjunctivitis sicca (KCS), and NM enlargement in the right eye was brought to our hospital. The dog could not tolerate treatment with topical 0.2% cyclosporine or corticosteroids. The dog’s right eye had NM gland prolapse, severe follicular conjunctivitis and a very low Schirmer tear test-1 (STT-1) value of 3 mm/min. Furthermore, the result of fine needle aspiration of the enlarged NM gland suggested a risk of malignancy. Despite the risk of KCS, complete NM resection was performed to diagnose the tumour. Fortunately, the final histopathological evaluation revealed chronic inflammation without any evidence of malignancy. Contrary to concerns that the STT-1 value would further decrease after the removal of the NM gland, the STT-1 value remained elevated compared to that before surgery, and the clinical symptoms improved for a year. It is generally known that NM gland resection is not recommended due to the risk of developing iatrogenic KCS unless a malignant tumour is suspected. In this case, surgical removal of the inflammatory NM gland that was not responsive to medications had a positive effect on KCS. Since the inflammatory and structural disease of the NM was strengthening KCS, the outcome was thought to be different from that when the normal third eyelid was removed.

KEYWORDS
complete excision of the nictitating membrane, follicular conjunctivitis, keratoconjunctivitis sicca, nictitating membrane gland protrusion
**INTRODUCTION**

The nictitating membrane (NM) in dogs is important for two major reasons: tear production and immune response (Peruccio, 2018). First, the NM protects the eyeball and aids in the production and distribution of the precorneal tear film (Peruccio, 2018). Thus, excision of the canine NM has been associated with an increased risk of developing keratoconjunctivitis sicca (KCS) (Peruccio, 2018; Sanchez, 2014). Some reports confirming a decrease in tear production after experimental removal of the normal NM or removal of NM due to a tumour support this (Giuliano, 2021; Perlman et al., 2009). Therefore, resection of the NM is contraindicated, except in cases of malignant tumours. Second, the conjunctiva, including the NM, has its own immune system known as conjunctiva-associated lymphoid tissue (CALT), which is similar to the mucosa-associated lymphoid tissue (MALT) in various sites of the body (Giuliano, 2021). CALT is believed to provide defence against infection in conjunction with physical barriers such as blinking and lacrimation (English & Gilger, 2021). However, when there is chronic antigenic stimulation, excessive immune response of CALT can lead to inflammatory disease such as follicular conjunctivitis (Hartley & Hendrix, 2021). Overactivation of this inflammatory response can lead to immune-mediated lacrimal gland damage, which in turn increases the risk of KCS (Leiva & Gimenez, 2018). Therefore, the excessive immune response of the conjunctiva needs to be suppressed.

Herein, we report a case in which the NM was excised due to suspicion of a malignancy in a dog with chronic follicular conjunctivitis that did not respond to medications. We monitored the change in the tear production in STT-1 before and after surgery. Since the NM was completely removed, there was some concern regarding the decrease in the tear production; however, this was not the case. We therefore reported the STT-1 changes in the eyes with severe KCS following NM removal.

### 1.1 Case description

A 13-year-old spayed female English Cocker Spaniel suffering from severe ocular discharge, discomfort, KCS, and NM gland enlargement in the right eye for the past 2 years was brought to our hospital. Cyclosporine ointment 0.2% (Optimmune®, Schering-Plough, France) had been applied to the eye at a local animal hospital for 2 years, but there had been no significant improvement despite continuous administration.

Complete ophthalmic examination was performed. All ophthalmic reflexes and responses were normal. The right eye showed a low Schirmer tear test-1 (STT-1) value of 9 mm/min, low tear breakup time (TBUT) of 0 s and low intraocular pressure (IOP) of 10 mmHg. Severe ocular discharge and eyelid oedema and erythema were also detected and the NM gland showed severe hyperplasia and prolapse. The conjunctiva of the NM showed a diffuse follicular lesion (Figure 1a); severe conjunctival hyperaemia and pigmentary keratitis were also detected (Figure 1b). The left eye also showed a relatively low STT-1 value of 13 mm/min, low TBUT of 0 s, and low IOP of 11 mmHg. Except for NM gland hyperplasia and prolapse, all ophthalmic abnormalities of the left eye were the same as those of the right eye; however, the clinical signs were milder in the left eye.

The patient was temporarily diagnosed with severe follicular conjunctivitis, KCS and pigmentary keratitis in both eyes and NM gland prolapse in the right eye. A tissue biopsy was recommended to diagnose and rule out the possibility of neoplasia, but the owner refused any further examinations. Thus, both eyes were prescribed dexamethasone, polymyxin B and neomycin eye drops thrice a day (Maxitrol®, Alcon, Belgium); sodium hyaluronate 0.1% eye drops thrice a day (Cualone®, Unimed, South Korea); and Optimmune® (twice a day). We then scheduled a follow-up appointment in a week. However, the owner did not visit the hospital with the patient. Three months later, the owner brought the patient to the hospital with more severe symptoms. During this period, the owner had only applied Maxitrol® to the patient, not Optimmune® at will by the owner. At this time, the STT-1 value in the right eye had decreased to 3 mm/min, and the symptoms had deteriorated (Figure 2). The follicles and mass were excessively bulged (Figure 2). We conducted fine needle aspiration (FNA) of the enlarged gland. A clinical pathologist suspected the possibility of...
**FIGURE 3** Changes in STT-1 value after nictitating membrane gland resection. The blue line represents the STT-1 value of the present case, and the red line represents the previous experimental data (Saito et al., 2001). In this case, the pre-operative STT-1 value was measured at 6 days pre-operatively. It was measured twice in Phase I (post-operative days 19 and 33), thrice in Phase II (post-operative days 64, 69 and 85) and once in the remaining phases (179 days in Phase III, 199 days in Phase IV, 250 days in Phase V and 310 days in Phase VI). STT-1: Schirmer tear test-1; PRE: pre-operative phase; PHASE 1: 14–60 days; PHASE 2: 61–120 days; PHASE 3: 121–180 days; PHASE 4: 181–240 days; PHASE 5: 241–300 days; PHASE 6: 301–360 days

malignant plasmacytoma of this gland. Based on the FNA results, surgical resection of the entire NM was performed. However, histopathological results of the resected NM gland showed chronic and nonspecific inflammatory reaction affecting the NM conjunctiva and gland without any evidence of malignancy. The resected tissue was diagnosed as severe plasma cell-rich lymphoplasmacytic, follicular and proliferative conjunctivitis and idiopathic NM gland adenitis. Cyclosporine 2% eye drops (Sandimmun Neoral®, Delpharm Huningue, France) diluted in corn oil was applied twice a day for 64 days after the operation. It was then switched to 0.05% cyclosporine eye drops twice a day (Cyporin N®, Taejoon, Korea) because the STT-1 value and clinical symptoms had improved. Maxitrol® was applied twice a day for 19 days, then once a day until post-operative day 69.

Regarding the possibility of tear production decreasing, the STT-1 value was monitored and classified into phases in the same way as in a previously reported study (Figure 3) (Saito et al., 2001). According to Saito et al.’s study, the follow-up period after the operation was divided into six periods: Phase I (14–60 days), Phase II (61–120 days), Phase III (121–180 days), Phase IV (181–240 days), Phase V (241–300 days) and Phase VI (301–360 days). The STT-1 value was measured at each visit, and if it was measured several times within a phase, the average was calculated. The STT-1 value was 3 mm/min in the pre-operative phase (6 days pre-operatively). And the mean STT-1 value was 11 mm/min in Phase I (19 and 33 days post-operatively), 11.3 mm/min in Phase II (64, 69 and 85 days post-operatively), 10 mm/min in Phase III (179 days), 10 mm/min in Phase IV (199 days), 12 mm/min in Phase V (250 days) and 13 mm/min in Phase VI (310 days). After the operation, clinical signs such as itching, lid discharge, conjunctival hyperaemia and chemosis obviously decreased. Although the client was satisfied with that, there was no quantitative evaluation of these symptoms. Moreover, the TBUT was same as that in the pre-operative examination (0 s) owing to severely degenerated and irregular corneal surface.

**2 DISCUSSION**

Since the removal of the NM causes KCS in dogs, it was contraindicated to remove the NM unless unavoidable such as in a malignant tumour. However, to the best of author’s knowledge, there are no reports of conjunctivitis and keratitis owing to decreased tear production following removal of the NM gland. Instead, there is a study on the amount of change in the tear volume following the removal of the NM gland using experimental animals (Saito et al., 2001). Our present report aimed on asking the question of whether the tear production really decreases significantly in the clinical cases following the inevitable removal of the NM, and whether this could be the primary cause of KCS in dogs. In this report, after the NM gland was removed owing to severe inflammation and suspected cancer, the amount of tear production was rather limited but significantly increased. Moreover, it was confirmed that the change in the amount of tear production demonstrated a similar pattern as that of Saito’s study (Saito et al., 2001). Thus, the removal of the NM gland can reduce the amount of tear production; however, it is questionable whether the removal of the NM gland is sufficient to cause keratitis and conjunctivitis with decreasing tear production.

In the present study, the STT-1 in the right eye changed with surgery and medication. Before surgery, the STT-1 value significantly decreased from 9 to 3 mm/min with Maxitrol® alone for 3 months. This was not fully understood because the inflammation was controlled with Maxitrol®. After surgery, 2% cyclosporine was used in Phase I, and the mean STT-1 value increased (11 mm/min). When
0.05% cyclosporine was used in Phase II, the mean STT-1 value once again increased slightly (11.3 mm/min). Further, despite the use of low-concentration cyclosporine in Phase II, the STT-1 value steadily increased when compared to Phase I (11 mm/min). With cessation of 2% cyclosporine, we were concerned about a decrease in STT-1 or worsening of clinical signs. According to previous study, upon improvement of KCS with 2% CsA, a decrease in the STT-1 was confirmed following the discontinuation of the drug suggesting a long-term (> 30 days) possibility of KCS recurrence (Izci et al., 2002). However, the STT-1 value continued to increase until 1 year. Although there are limitations to certainty of this occurrence because our case report was not a designed experiment; however, it seems to be related to the surgery rather than drugs.

We compared the change in the STT-1 value in this case with previous research data (Saito et al., 2001) (Figure 3). In a previous study, the STT-1 value significantly decreased from Phase II, reached the lowest point in Phase IV and then increased again from Phase V (Saito et al., 2001). This case differs from the previous data in that the post-operative STT-1 value remains significantly higher than the pre-operative exam, but it is similar to the previous data in that the lowest point among the measured post-operative STT-1 value is confirmed in Phase IV. Initially, we only expected the possibility that the STT-1 values might not decrease. However, it is noteworthy that 10 mm/min, the lowest measured STT-1 value after surgery, is also higher than the pre-operative values. There are no other clinical data that can be clearly obtained in this case. We were able to demonstrate the improvement in the clinical symptoms of keratitis and in other examinations; however, it was virtually impossible to properly examine the eye owing to the already severely degenerated keratoconjunctival surface. In addition, the owner did not maintain the treated condition well; hence, further examination was not possible.

Eye-associated lymphoid tissue (EALT) comprises lacrimal drainage-associated lymphoid tissue, CALT and lacrimal sac, all of which interact with one another (Gilger, 2008). When the immune system in CALT is upregulated, autoimmune disease can occur (Gilger, 2008). In this case, we discussed the possibility of immune-mediated lacrimal gland injury and KCS preceding chronic conjunctivitis and severe lymphoid hyperplasia. The increase in STT-1 value after the removal of upregulated lymphoid tissue supports this possibility.

This case report is the first to monitor the STT-1 after NM resection in a dog with both NM gland disease and KCS. NM gland resection is generally contraindicated due to the possibility of iatrogenic KCS after surgery. The result of this case is different from prevailing knowledge that tear production in the STT-1 potentially decreases following NM gland resection.

To summarise, the patient had NM gland prolapse, lymphoid hyperplasia, and KCS, all of which may induce chronic irritation and trigger immune responses around the eyes (Figure 4). Excessive immune responses due to chronic irritation result in further deterioration. The removal of an NM that has lost its primary function may play a role in breaking this vicious circle and may help stabilise the abnormal immune response of EALT. Although this is an unusual case, it warrants further research. However, there are some questions regarding whether the amount of tear production actually decreases subsequently causing KCS following NM gland removal. In this study, following the severe inflammatory NM gland removal, the tear production was increased from 3 to 13 mm/min in STT-1 examination. Moreover, the clinical symptoms of the eye were rather improved. Hence, we intend to share our concerns with other researchers. Therefore, further clinical research is warranted to clarify whether the complete removal of the NM gland may indeed cause clinically inflammatory KCS of the canine eye. Through this case report, we suggest that clinicians should consider not only the tear production of the NM gland but also the integrity of the overall immune system when removing the NM gland.

**FIGURE 4** A diagram of immune response and tear production. Nictitating membrane (NM) gland prolapse is caused by lymphoid hyperplasia and anatomical laxity. NM gland prolapse, lymphoid hyperplasia (follicular conjunctivitis) and keratoconjunctivitis sicca (KCS) may lead to chronic irritation of the cornea and conjunctiva. Chronic irritation induces immune responses in the eyes. Abnormal immune responses deteriorate KCS and lymphoid hyperplasia. All these result in signs of inflammation.

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**DATA AVAILABILITY STATEMENT**
The data that support the findings of this study are available upon request from the corresponding author.

**ETHICS STATEMENT**
The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page, have been adhered to. No ethical approval was required for this particular case report.
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