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Characterization of progressive keratitis in Otariids

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Abstract

Objective To characterize a form of progressive keratitis that occurs commonly in otariids.

Materials and methods One hundred and thirteen captive otariids were evaluated by ophthalmologic examination and digital photography.

Results Forty-six females and 67 males were in the reference population, average age of 14 years. California sea lions predominated (n = 100); there were also six Steller sea lions, five brown fur seals, one Guadalupe fur seal and one northern fur seal. Three stages of progressive keratitis are described. Overall, 64.6% animals and 142 eyes from 113 animals (62.8%) were affected with one of three stages. The mildest form, Stage 1 keratitis, occurred in 78 of 226 eyes (34.5%); the intermediate Stage 2 keratitis occurred in 30 of 226 eyes (13.3%); and the most severe, Stage 3 keratitis, occurred in 34 of 226 eyes (15%). All but six animals had bilateral disease. Animals with Stage 1 keratitis were significantly younger than those in more advanced stages.

Discussion 'Otariid Keratitis' occurs in all populations of eared seals evaluated. A large-scale epidemiological study is ongoing to identify the risk factors that contribute to this disease. Exposure to chronic sunlight appears to be an important risk factor as shade diminishes clinical signs; animals kept out of sunlight the majority of the time have less severe clinical signs. Age may be important since exposure accumulates with aging. Progression of the disease is also associated with secondary opportunistic bacterial and fungal infections. The surface immune system may be imbalanced contributing to these infections and progression.

Key Words: cornea, corneal ulcer, keratitis, otariid, pinniped, stromal abscess

INTRODUCTION

Corneal disease in captive pinnipeds can impair vision and cause pain. It can affect both true seals (phocids) and eared-seals (otariids). The cause of corneal disease is being investigated in both wild and captive populations, as the etiology in each likely differs. In captivity, many otariids become visually impaired by their late teenage years due to cataracts and lens luxations. However, prior to this, subadult and adult pinnipeds can be affected by mild to moderate ulcerative corneal disease. Keratitis can cause uveitis to varying degrees, and uveitis can contribute to cataractogenesis. Conversely, cataracts at all stages cause lens induced uveitis,[1] and uveitis can exacerbate keratitis.

There are numerous anecdotal theories implicating environmental factors for inducing keratitis in pinnipeds. These include changes in water quality, excessive sunlight, viral infections, underlying uveitis, trauma, and others. Published studies in stranded pinnipeds found keratitis to be a common problem. An abstract that evaluated captive pinnipeds found that California sea lions were commonly affected by corneal disease.[2]

The purpose of this study was to characterize a form of progressive keratitis that occurs commonly in California sea lions and other eared seals (otariids).

MATERIALS AND METHODS

Complete ophthalmic examination of 113 captive otariids (100 California sea lions [*Zalophus californianus*], one Guadalupe fur seal [*Arctocepharlus townsendi*], one Northern fur seal [*Callorhinus ursinus*], six Steller sea lions [*Eumetopias jubatus*] and five brown fur seals [*Arctocephalus pusillus*]) were performed over a 6-year period at 12 facilities in North America, the Bahamas and northern Germany. Eyes were photographed at each examination and animals were evaluated between 1 and 6 times. Affected animals were grouped by age and stage of disease, with more severely affected eye determining what stage animal was assigned. Then, average ages for each stage were compared using an analysis of variance (ANOVA) and Tukey's test for comparison of multiple means. Graph was generated using PRISM 4.0 software program (GraphPad Software Inc, San Diego, CA). A value of $P < 0.05$ was deemed statistically significant.

RESULTS

There were 46 females and 67 males in the reference population. Age range was 6 months through 34 years with an average age of 14 years. There were 39 female and 61 male California sea lions with an average age of 14 years. There was one Guadalupe fur seal aged 16 years and one northern fur seal aged 13 years. There were four female and two male Steller sea lions with an average age of 12.8 years. There were three female and two male brown fur seals with an average age of 15 years.

Overall, 142 eyes from 113 animals (226 eyes; 62.8%) were affected with keratitis. Seventy-three of 113 animals (64.6%) were affected. Seventeen eyes had asymmetric disease. Of these, six animals had one affected eye (five had Stage 1 disease and one had Stage 2 disease) and the other eye was unaffected. One eye had phthisis bulbi due to a severe corneal ulcer, though the diagnosis of keratitis could not be made based on the history; the contralateral eye was normal. One eye had a previous perforation with extensive corneal fibrosis that also precluded diagnosis, the contralateral eye did not have keratitis. When evaluated by age groups, all groups over 5 years of age had a greater than 50% incidence of keratitis (Fig. 1). The animals over 26 years of age, though few in numbers, had a 100% incidence. Table 1 summarizes the details of the three stages of Otariid Keratitis.

Stage 1

The earliest and most common manifestation was defined as Stage 1 keratitis (78 of 226 (34.5%) eyes at initial evaluation. Sixty-three eyes were from California sea lions, six were from brown fur seals, and nine were from Steller sea lions. Twenty-three eyes (10.2% of 226 eyes) from 14 females were affected and 10 showed this early stage affecting both eyes (OU). Fifty eyes (22.1% of 226 eyes) from 30 males were affected and 20 were affected OU with Stage 1 lesions. Average age of affected animals was 14.17 years, these animals were significantly younger than animals with Stages 2 and 3 Otariid Keratitis ($P = 0.0077$, Fig. 2).

Stage 1 was typically a focal gray to white superficial corneal opacity located dorsotemporal to the axial cornea. The lesion was nonulcerative (Fig. 3a) or had a small superficial ulcer (Fig. 3b). A common finding was perilimbal edema (Fig. 3a) and occasionally there as pigmentation streaming in from the lateral and dorsotemporal conjunctiva evident in finger like projections and extending approximately 2–4 mm

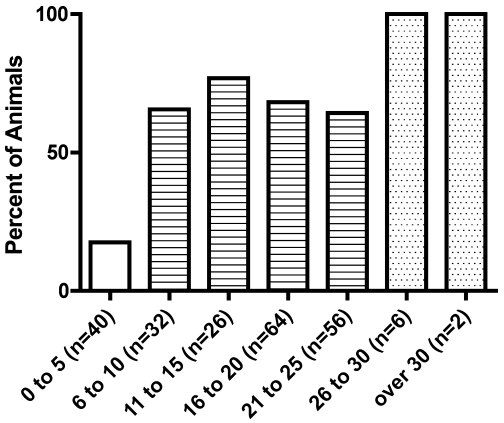

Figure 1. Graph showing incidence of keratitis in otariids in 5-year increments.

Table 1. Summary of details of Otariid Keratitis

	Stage 1	Stage 2	Stage 3
Average age	14.17	19.43	19.22
Corneal changes	Superficial gray-white opacity located dorsotemporal to axial cornea. Can have superficial ulceration	Affects 10–20% of cornea in same location. Indolent-like ulceration. Secondary infections. Diffuse edema when active.	Affects 20–80% of cornea in same location. Recurrent ulcerations, secondary infections and/or abscesses. Epithelium easily sloughs. Stroma attenuated. Diffuse edema when active.
Limbal changes	Perilimbal edema. Pigmentation may cross limbus.	Perilimbal edema. Pigmentation crosses limbus. Vascularization rare but seen crossing limbus.	Perilimbal edema. Pigmentation less than Stage 2.
Other	Epiphora, periocular debris, blepharospasm.	Epiphora, periocular debris, blepharospasm. Conjunctival hyperemia.	Epiphora, periocular debris, blepharospasm. Conjunctival hyperemia.

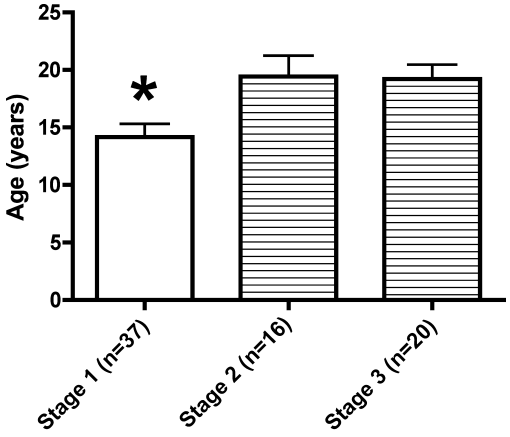

Figure 2. Graph showing average age of animals affected with the three stages of Otariid Keratitis. Average age of animals with Stage 1 Otariid Keratitis were 14.17 years of age, those with Stage 2 Otariid Keratitis were 19.43 years of age, and those with Stage 3 Otariid Keratitis were 19.22 years of age. Average age of animals with Stage 1 disease was significantly younger than those with Stages 2 or 3 disease ($P = 0.0077$).

into the adjacent cornea (Fig. 3a,b). There were clinical signs of pain especially when the lesion was ulcerated. This manifested clinically as epiphora, variable amounts of periocular brown debris caked on the eyelid fur, diffuse corneal edema in the area of the ulcer, and blepharospasm.

Stage 2

Cases with Stage 2 keratitis occurred in 30 of 226 (13.3%) eyes at initial evaluation. Twenty-four eyes were from California sea lions, four eyes were from brown fur seals, two eyes were from one Steller sea lion, and no other otariids were affected with this stage. Twenty eyes (8.8% of 226 eyes) from 11 females were affected and eight showed this intermediate stage OU. Eleven eyes (4.9% of 226 eyes) from 10 males were affected and one manifested with OU Stage 2 lesions. Average age of affected animals was 19.43 years (Fig. 2).

The intermediate stage manifested as a lesion that encompassed approximately 10–20% of the cornea in the same location as Stage 1. This progressed when the superficial corneal epithelium showed a break seen as a linear (regular or irregularly jagged, straight or curved) breech (Fig. 4), that passively sloughed within a few days leaving a geographic superficial ulcer often with a movable flap of epithelium still attached. If debrided with a dry cotton swab, following topical anesthesia, the epithelium easily sloughed beyond the edges of the obvious lesion similar to a canine indolent ulcer.[3] This stage was clinically painful until the ulcer healed and the inflammation subsided. Clinical signs of pain as described for Stage 1 were the same or worse and the eye remained closed the majority of the time. Other clinical signs included perilimbal edema that was clinically worse than the diffuse corneal edema affecting the rest of the cornea. Severe aqueous flare was uncommon, though difficult to assess in some cases. Conjunctival hyperemia was mild to moderate and perilimbal corneal vascularization was rare and mild. The lateral and dorsotemporal pigmentation extended further into the cornea and was extensive in the adjacent conjunctiva (Fig. 5). Periocular tear staining and debris were common (Fig. 6). This stage became opportunistically infected with bacteria or yeast/fungi (e.g. *Klebsiella pneumoniae*, *Vibrio alginolyticus*, *Acinetobacter baumannii*, *Aspergillus* spp, and nonspecific yeasts) that were present in the environment, water or the periocular region. The infection often caused the Stage 2 lesions to appear larger when active. When quiescent, the gray corneal opacity remained and involved approximately 10–20% of the dorsotemporal cornea (Fig. 7a,b).

Stage 3

The most severe stage, Stage 3 keratitis, was seen in 34 of 226 (15%) eyes at initial presentation; all were from California sea lions. Eleven eyes (4.9% of 226 eyes) from seven females were affected and four had OU Stage 3 lesions. Twenty-three eyes (10.2% of 226 eyes) from 13 males were affected and nine had OU Stage 3 lesions. Average age of affected animals was 19.22 years (Fig. 2).

Twenty to eighty percent of the cornea was involved with Stage 3 keratitis. This stage commonly had recurrent ulcers or abscesses with opportunistic secondary bacterial or yeast/fungal infections. The superficial epithelium sloughed easily (Fig. 8), the stroma became attenuated, especially in the area

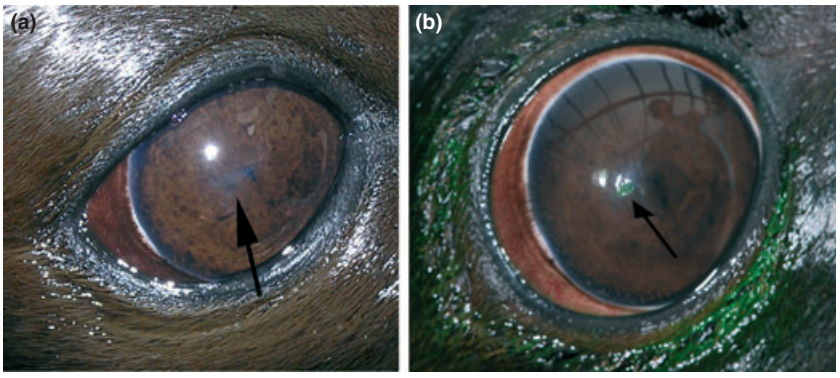

Figure 3. Stage 1 Otariid Keratitis. (a) OD shows a small gray superficial corneal opacity located dorsotemporal to the axial cornea that is fluorescein negative (black arrow). There is also mild perilimbal edema evident and a small amount of conjunctival pigment branching onto the temporal limbus. (b) OS shows a small fluorescein positive superficial ulcer that is located dorsotemporal to the axial cornea (black arrow). Temporally, there are numerous areas of conjunctival pigment migrating onto the limbus.

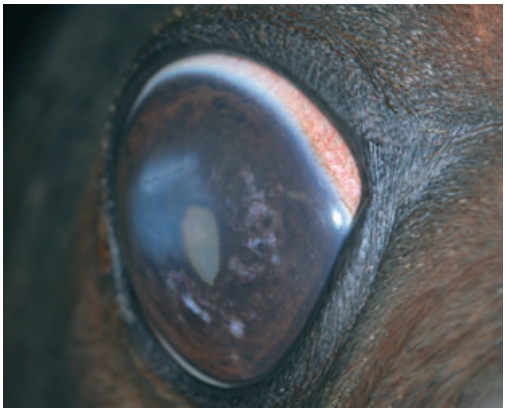

Figure 4. Active Stage 2 Otariid Keratitis. OD has a moderate sized gray-white opacity located dorsotemporal to the axial cornea. The lesion has a horizontal linear lesion that is ulcerating, it is an early active stage of the disease. There is also perilimbal corneal edema, iris hypoplasia and an incipient anterior subcapsular cataract.

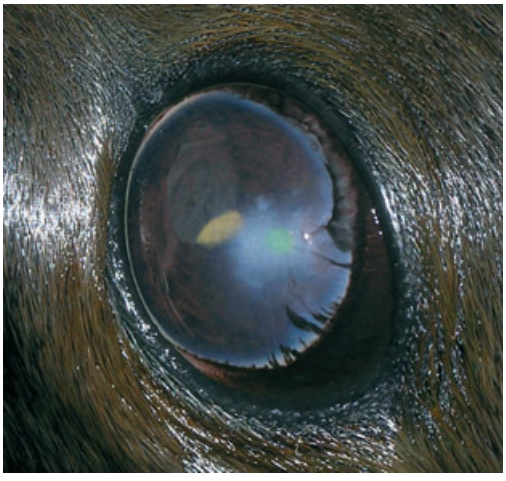

Figure 5. Active Stage 2 Otariid Keratitis. There is a small fluorescein positive superficial ulcer with surrounding edema and fibrosis dorsotemporal to the axial cornea. Dorsally and temporally, from approximately 11 o'clock to approximately 5 o'clock, there is a moderate amount of pigmentation migrating onto the cornea towards the ulcerated lesion.

of the initial lesion dorsotemporal to the axial cornea (Fig. 9a). Corneal vascularization was slightly active in terms of presence of vessels, but they still never reached the initial lesion (Figs. 9a,10). When quiescent, the lesion still encompassed a significant portion of the cornea (Fig. 9b). The corneal pigmentation became sparse compared with Stage 2. Perilimbal edema was consistent as were the clinical signs of pain and inflammation. Some cases of Stage 3 keratitis also presented with stromal abscess formation, often in the fall and winter months (Fig. 11). Commonly cultured organisms have included *Aspergillus* spp, and unidentified yeast species.

Anecdotally, most animals had approximately 2–4 flare-ups per year initially based on observation by trainers and curators, then confirmed by photography and examinations

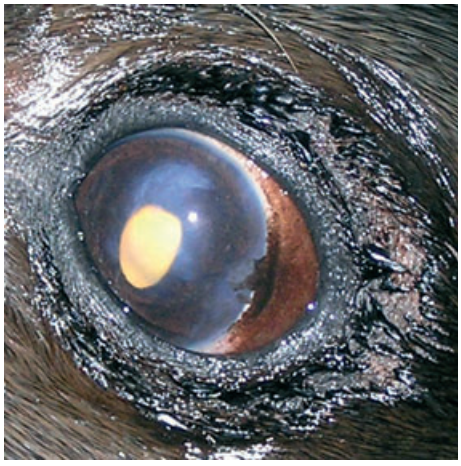

Figure 6. Quiescent Stage 2 Otariid Keratitis. There is a moderate sized gray superficial area of fibrosis located dorsal and dorsotemporal to the axial cornea. There is perilimbal corneal edema and temporally there is pigmentation migrating over the limbus and onto the cornea. There is periocular debris due to chronic epiphora.

by veterinarians, though definitive counts are under investigation. They initially developed blepharospasm, epiphora, and increased corneal opacity including diffuse edema and suspected WBC and microorganism infiltration into the affected stroma. Fluorescein uptake was variable in these lesions depending on whether they had the indolent-type ulceration or stromal abscessation. These flare-ups occurred primarily when daylight duration increased and the UV or sunlight exposure became more intense in the tropical climates. In colder climates, there were flare-ups when there was consistent snow on the ground and the days were very sunny. The ongoing epidemiological survey will also determine whether there is a seasonal impact on types of secondary infections.

DISCUSSION

Keratitis was seen in 62.8% of eyes evaluated and 73 animals (64.6%) of animals evaluated. This condition was initially thought to only affect California sea lions due to the overwhelming numbers of this species in most aquatic animal facilities; however, access to other otariids allowed the diagnosis of this disease in, Guadalupe fur seals, northern fur seals, brown fur seals, and Steller sea lions. Fur seals are not true seals, but are otariids or eared seals like sea lions. Lesions in affected animals were exacerbated during seasons when the sun was most intense and daylight hours were maximal. Winter months where the snow is long-standing and the days are sunny can also trigger a clinical episode. We have not yet shown that sun exposure is truly a risk factor but a large-scale epidemiologic survey is ongoing and will determine the risk factors for this painful and devastating disease. Age may be a risk factor as well; animals affected with the earliest stage of keratitis were significantly younger than those in Stages 2 and 3. Approximately twenty

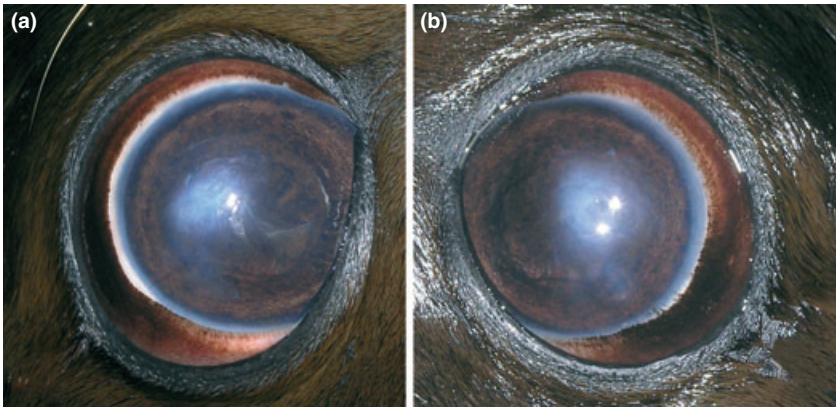

Figure 7. Quiescent Stage 2 Otariid Keratitis. (a and b) There are dorsotemporal superficial gray corneal opacities consistent with fibrosis and there is perilimbal corneal edema. Conjunctival pigment is migrating onto the limbus OS, more than in OD.

Figure 8. Active Stage 3 Otariid Keratitis. The small arrows outline the edges of an anterior stromal corneal ulcer with diffuse corneal edema and moderate fibrosis. There is perilimbal edema that is slightly worse than the diffuse generalized edema.

facilities are participating in the epidemiological study across the world.

Pinnipeds have variably keratinized corneal epithelia; i.e. keratinization increases towards the periphery.[4] They also have a thin Bowman's layer and an extremely thin Descemet's membrane. The corneal epithelium has 1–2 layers of polyhedral cells and 6–8 layers of squamous cells. The cornea is relatively thick compared with terrestrial mammals but is thinnest axially and thickens towards the periphery. The cornea is relatively flat, compared with the dog, and it has a very flattened area just inferomedial to the axial cornea.[5]

Ultraviolet radiation is a constant factor in most aquatic animal facilities. Shade structures, even when present, are often incomplete and the animals are drawn to the sunny areas. The cornea absorbs most of the ultraviolet B (UVB) and all of the ultraviolet C (UVC) radiation that reaches the eye; the majority of the energy is absorbed in the epithelium and Bowman's layer.[6] The human cornea absorbs 92% of UVB at 300 nm; this data is unknown for pinnipeds.[7] Sunlight is capable of damaging all layers of the cornea.[8] UV exposure also causes stromal attenuation.[9] Maximum UVB exposure occurs in tropical latitudes at midday during summer.[6] In addition, local surface reflection can increase surface UVB levels immensely. For example, local surface reflection increases 15–18% from sand, 3–13% from water, 4–9% from asphalt, and up to 90% from snow.[10,11] Paint color of the pool and the area around the pool also play a role with brighter colors reflecting more light. Facilities where the colors have been changed to tan or similar hues report fewer corneal problems and less blepharospasm (L. Gage, personal communication). Three facilities included here have animals that primarily live indoors with minimal exposure to outdoor sunlight. These animals have less severe disease for their age (average age was 22 years) and have fewer flare-ups of this disease throughout the year. When allowed access to the outdoors due to maintenance or other issues in their usual enclosures, the corneas become inflamed, they develop characteristic ulcers and severe signs of pain. Chronically, the corneal stroma thins, there is mini-

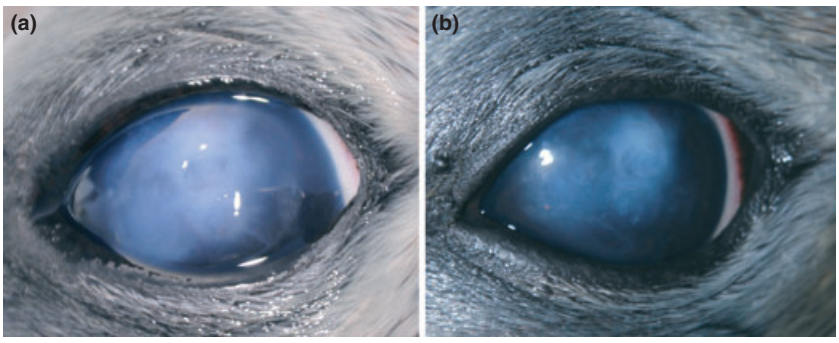

Figure 9. Stage 3 Otariid Keratitis. (a) OD active Stage 3 Otariid Keratitis with irregular thinning of the stroma, diffuse corneal edema with fibrosis and cellular infiltrate. (b) OD of the same eye 6 weeks later with diffuse fibrosis, less edema and resolved peripheral edema.

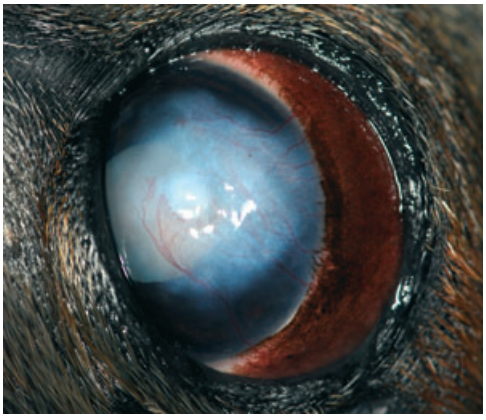

Figure 10. Quiescent Stage 3 Otariid Keratitis. The OS with multiple areas of superficial corneal vascularization surrounding a dense area of fibrosis without infiltrating the denser lesion. There is corneal edema associated with the vascularization. Dorsotemporally and temporally, the corneal pigmentation has grown over the limbus and into the peripheral cornea. The pupil is mydriatic showing a mature cataract.

Figure 11. Active Stage 3 Otariid Keratitis. The OD with a corneal stromal abscess that has thinned stroma in the center and has suspected cellular infiltrate along with diffuse corneal edema. There is a mild amount of corneal vascularization temporally and dorsotemporally as well.

mal vascularization and the clinical episodes occur more frequently.

Water quality and salinity issues are important etiologic factors that differ between facilities. The majority of facilities house pinnipeds in salt water. In one study, there was a strong association ($P < 0.00001$) between California sea lions and corneal edema when they were kept in fresh water.[2] Other factors that will be evaluated in the epidemiological analysis include water temperature, coliform counts, chlorine and other halide oxidant levels, salinity, method sea water is produced (ocean vs. synthetic mixed sea salt), filtration method, levels of ammonia, and others.

The local corneal and conjunctival immune system is also important for the response to disease. There are two arms to the ocular surface immunological system, the innate and the adaptive immune systems. These two systems may have distinct functions but they work synergistically to balance the limited blood and lymphatic supply to the cornea, balance the exposure to environmental oxidative stressors, and balance tolerance to normal bacterial and fungal flora.[12] The local immune system has many mechanisms that prevent microbial invasion, infection and tissue destruction. These include the barrier functions of the surface mucins and epithelium, proteins in the tear film, Toll-like receptors, antigen presenting cells, and a lacrimal gland that provides IgA and white blood cells.[12] Most species have entirely non-keratinized epithelia; pinnipeds have keratinization peripherally. Their tear film is very mucin-rich and does not have a lipid component as pinnipeds do not have meibomian glands. There are ongoing studies investigating the specific components of the pinniped tear film.[13] Mucins serve to anchor the ocular tear film to the epithelium and they prevent bacterial colonization. Otariid eyes with keratitis commonly develop secondary bacterial and fungal infections. The cause of this is unknown, but it is possible that an imbalanced response to insult with inappropriate or insufficient white blood cells, an innate inability to grow corneal blood vessels to a significant degree, insufficient tear film components, or other inappropriate responses, including loss of tolerance, are responsible for their common and chronic keratitis problems. Use of topical cyclosporine or tacrolimus may help to re-establish the tolerance of ocular surface antigens and self-antigens.

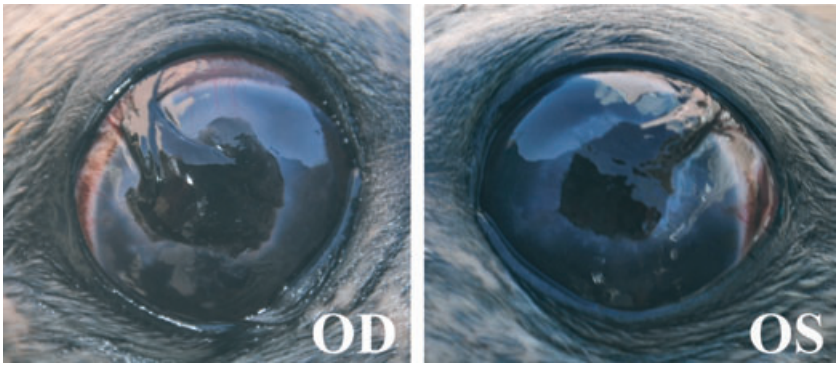

Figure 12. Bilateral conjunctival pedicle flaps. Both eyes underwent debridement of the superficial epithelia, followed by conjunctival flap procedures. These flaps were pink in color when initially sutured into place and became gradually more pigmented within 3–4 months. The adjacent corneas did not vascularize extensively as occurs in other species e.g. dogs and cats.

When keratitis is active with superficial ulcers, it must be treated aggressively because loss of the superficial epithelium predisposes them to secondary infections. Once a secondary infection is identified, it is imperative that aggressive antibiotic and anti-inflammatory therapy be initiated to avoid progression. Initially, topical antibiotics should address the possible pathogens in the water. The pathogens in their water habitats includes *Pseudomonas* spp, coliforms, and others as well as *Aspergillus* spp. These microorganisms and others have been cultured from active cases of this disease. It is imperative, when possible, that cultures with sensitivities are submitted from the ulcers to amend treatments that may not be addressing the infections. Oral medications typically used include oral doxycycline to stabilize the corneal stroma, speed epithelialization, and anti-inflammatory effects, and oral nonsteroidal anti-inflammatory medications for pain and secondary uveitis.[14–17] In addition, access to shade is important in accelerating the resolution of the keratitis. The author uses topical cyclosporine (2%) or tacrolimus (0.03%) in otariids to try to diminish recurrence of active disease. Anecdotally, this appears to diminish the occurrences but does not completely prevent them. One California sea lion had conjunctival pedicle flap surgery and the recurrences of the disease have diminished in number and severity (Fig. 12).

This study's intent was to describe a progressive keratitis in otariids that we have named Otariid Keratitis. The reason for naming this disease is to allow it to be easily described based on stage and progression. The name may change once we understand the etiology and pathogenesis. Identification of its risk factors was beyond the scope of this study and is under investigation.

CONCLUSION

Otariid Keratitis is a clinically prevalent, painful, and progressive disease with no known etiology. Indoor exhibition and shade appear to slow its progression and keep active recurrences from occurring as frequently. There is no known therapeutic or management regimen that will resolve or prevent this disease permanently. We are attempting to minimize the flare-ups by feeding antioxidants, such as lutein and grape seed extract, known to protect against UV damage, improving shade structures, and the prophylactic use of cyclosporine or tacrolimus topical medications. Shade structures should be implemented in housing and show areas, but most importantly where the pinnipeds are working or exhibiting trained behaviors since they have their eyes open at these times more than when they are at rest.

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