P-ISSN: 2304-3075; E-ISSN: 2305-4360
International Journal of Veterinary Science
www.ijvets.com; editor@ijvets.com

Case Report https://doi.org/10.47278/journal.ijvs/2023.084

Novel Treatment of Chronic Superficial Keratitis in Dog – Case Report

Amila Šunje-Rizvan[1]✉, Amina Rizvanović[2], Ismar Lutvikadić[1], Amela Livnjak[2], Nermina Spahija[1] and Alan Maksimović[1]

[1]Department of Clinical Science, Veterinary Surgery, Anesthesia and CPR, Veterinary Faculty, University of Sarajevo, 71000 Sarajevo, Bosnia and Herzegovina
[2]PhD Student
***Corresponding author:** amila.sunje@vfs.unsa.ba

Article History: 23-239 Received: 02-Jul-23 Revised: 18-Jul-23 Accepted: 30-Jul-23

ABSTRACT

This case report describes the remission of the fibrovascular corneal lesions in both eyes after bilateral superficial keratectomy combined with medical treatment in a German Shepherd dog. A completely blind German Shepherd dog diagnosed with chronic superficial keratitis (CSK, pannus) underwent bilateral superficial keratectomy along with subconjunctival administration of 0.1 mL of bevacizumab and mitomycin C, which where topically applied over the degenerated area of the cornea. Following the surgical procedure, cyclosporine topical ointment was given daily as life-long therapy. Notable improvements in behavior and physical activity were evident in the patient three to four weeks after the treatment. During a follow-up period over 24 months, complete remission of the fibrovascular corneal lesions was observed in both eyes, with minor seasonal conjunctival hyperemia successfully managed by administering dexamethasone and mitomycin C eye drops. This is the first report of using this specific combination of drugs during and after keratectomy in the dog, resulting in remission of CSK with no reported side effects. Superficial keratectomy, along with the administration of bevacizumab via subconjunctival injection, may present a novel approach for addressing superficial corneal neovascularization in dogs.

Key words: Chronic Superficial Keratitis, Pannus, Mitomycin C, Bevacizumab, Keratectomy, German Shepherd

INTRODUCTION

Chronic keratitis accompanied by corneal neovascularization is a common pathological condition in veterinary ophthalmology. Chronic superficial keratitis (CSK), also known as Uberreiter's Disease, degenerative pannus, or German Shepherd pannus, is a persistent and progressive condition that affects the cornea of dogs, it is primarily observed in middle-aged German Shepherds but can occur in other breeds as well. CSK is an inflammatory and bilateral disease characterized by the presence of fibrovascular tissue with a distinct border, covering the cornea and surrounded by a clear ring composed of the first invading cells along with corneal edema and seromucous secretion. In some dogs, the disease is self-restricting, but in other cases, it advances and leads to complete corneal involvement, ultimately causing blindness (Williams 1999; Ergin et al. 2021). The disease can be divided into four identifiable phases, delineated by the visual characteristics of the cornea. To distinguish these stages, the authors have embraced terminologies commonly used in human literature. These terms are as follows: *pannus tenuis* (infiltration of corneal tissue by cells), *pannus vasculosus* (vascularization of corneal tissue), *pannus en epaulet* (arrangement of connective tissue elements within the corneal tissue), and *pannus siccus* (formation of scars) (Bedford and Longstaffe 1979).

Currently, there is no cure for CSK, and no standard treatment is yet determined (Bedford and Longstaffe 1979). Therapeutic success is considered as delay of progression which can be achieved by topical application of corticosteroids alone or in combination with cyclosporine but only in mild cases (Williams et al. 1995; Maggs et al. 2007; Beteg et al. 2021; Zubrický and Trbolová 2022). In cases where immunosuppressive treatments are not effective, more invasive therapeutic approaches such as superficial keratectomy, radiotherapy (Allgoewer and Hoecht 2010), or cryosurgery (Holmberg et al. 1986). Therefore, there is a significant need for targeted therapies in the treatment of CSK.

Cite This Article as: Šunje-Rizvan A, Rizvanović A, Lutvikadić I, Livnjak A, Spahija N and Maksimović A, 2023. Novel treatment of chronic superficial keratitis in dog – case report. International Journal of Veterinary Science x(x): xxxx. https://doi.org/10.47278/journal.ijvs/2023.084

The healthy cornea does not contain any blood vessels and is fully transparent, providing accurate vision. Corneal neovascularization (CNV) is a part of many chronic pathological processes both in humans and animals including CSK (Gilger et al. 2007; Hosseini and Khalili 2007). Vascular endothelial growth factor (VEGF) plays a crucial role in the development of new blood vessels (angiogenesis) in the cornea of dogs affected by CSK. (Balicki and Trbolova 2010; Balicki and Sobczyńska-rak, 2014).

Anti-human vascular endothelial growth factor (anti-human VEGF) administration has shown promising outcomes in the treatment of CSK and corneal neovascularization in both animal and human patients (Hosseini and Nejabat 2007; Muellerleile et al. 2019a,b). Bevacizumab, recognized as one of the most potent inhibitors of VEGF, has demonstrated its effectiveness in human (Gunther and Altaweel 2009) and animal (Muellerleile et al. 2021) ophthalmology for treating these and other pathological conditions. Therefore, inhibition of neovascularization is an important treatment strategy for various ophthalmologic conditions in both human and veterinary medicine.

Corneal fibrosis is a natural reparative reaction that occurs in response to corneal injuries caused by trauma, disease, or surgery. However, it can lead to the clouding or opacity of the typically clear and transparent cornea. There is limited targeted treatment available for this condition in veterinary ophthalmology (Hu et al. 2009). Over the past two decades, mitomycin C (MMC), an antibiotic with anti-fibrotic and genotoxic properties, has been used as a supplementary topical treatment in ophthalmology to manage corneal diseases and surgical procedures. (Song et al. 2007). MMC has been used intra-operatively after surface ablation to prevent corneal haze formation (Hu et al. 2009) and to restore clarity after surgical management of corneal injuries (Thajunnisa et al. 2020).

Our report aims to document the successful treatment of CSK in a dog using anti-human VEGF, bevacizumab, and chemotherapeutic drug MMC, which are widely used in human ophthalmology. We hypothesized that intraoperative subconjunctival administration of bevacizumab and MMC immersed sponge is safe and effective both systemically and topically, showing good healing properties on CSK with minimal or no side effects.

CASE PRESENTATION

An 8-year-old intact male German Shepherd dog was referred to the clinic of the Veterinary Faculty University of Sarajevo with a history of bilateral eye problems. According to the owner, the dog had been experiencing eye issues for at least one year, and the condition had been progressively deteriorating. Over the last month, the patient started to show signs of significant visual impairment and mental depression. A standard ophthalmologic examination revealed generalized bilateral corneal pigmentation, keratinized epithelium with prominent corneal epithelial vascularization, conjunctival hyperemia, and depigmentation accompanied by seromucous secretion, and a diagnosis of CSK was made. Previous treatment included the use of dexamethasone topical ointment (Dexagel, PharmaSwiss, Czech Republic). Physical examination showed no abnormalities. Complete blood count and serum biochemistry profile were within reference values. The eye swab was found sterile (Fig. 1).

Written informed consent was obtained from the owner of the dog described in this case report. The patient was premedicated with xylazine (1 mg/kg, IM). Anesthesia was induced with the 70% mixture of diazepam (0.2mg/kg, IV) and ketamine (4 mg/kg, IV) combined in the same syringe. A local peribulbar block was performed using 0.3mL/kg of 2% lidocaine (Lidocaine hydrochloride 2%, Galenika, Serbia). The Surgical plane of anesthesia was maintained subsequently with 20% of the same drugs. A balanced electrolyte solution (5mL/kg/h NaCl) was used intraoperatively.

After stabilizing the eye with a lid speculum, the patient underwent bilateral superficial keratectomy combined with 0.1mL bevacizumab (Avastin®) injected subconjunctival bilaterally (2.5mg/mL) at the limbus, in close proximity to the origin of the actively proliferating pathological blood vessels entering the cornea. Superficial keratectomy was performed by scraping the abnormal corneal epithelial tissue and superficial blood vessels using the ophthalmic surgical blade. No samples were submitted for histopathology. After superficial keratectomy and epithelial removal, an ophthalmic sponge immersed with MMC (10mg/mL) was applied over the area of degenerated area for 3min on each eye and subsequently removed. The cornea was flushed or rinsed with a balanced salt solution (Fig. 2a). Finally, contact lenses were applied as bandages on both eyes to protect them for two days. Postoperatively, the patient received cyclosporine ophthalmic emulsion 0.05% (Restasis®) twice daily in both eyes as a lifelong therapy. One month after the surgery, corneal neovascularization regressed, and significant improvement in vision was observed. The dog also showed remarkable improvement in behavior and physical activity (Fig. 2b).

During the 24-month follow-up period, seasonal conjunctival hyperemia was observed during the summer months and successfully managed with topical dexamethasone eyedrops (Maxitrol®) given 7-10 days, 3 times per day, along with topical MMC solution applied to the hyperemic eye for 3-5 days, twice per day.

DISCUSSION

We would like to report the effect of bevacizumab and MMC as a possible treatment for CSK in dogs. In our case, the described protocol resulted in complete remission of the fibrovascular corneal lesions and significant improvement in vision. As reported in human studies (Song et al. 2007; Dastjerdi et al. 2009), these drugs demonstrate significant potential in treating various pathological conditions. In human studies, no systemic side effects have been documented with the topical application of bevacizumab, even at higher concentrations or when applied bilaterally (Dastjerdi et al. 2009). Therefore, bevacizumab is widely used in managing various eye conditions in humans, particularly those with abnormal blood vessel growth. Limited information is available regarding the effectiveness, safety, and medical suitability of bevacizumab in veterinary medicine. Our case report supports the findings of a study conducted by Muellerleile et al. (2019), which concluded that topical administration

Fig. 1: Presurgical – Corneal appearance before treatment. Corneal superficial keratitis is present ant it covers ¾ of the cornea. Seromucous discharge is visible, as well as neovascularization.

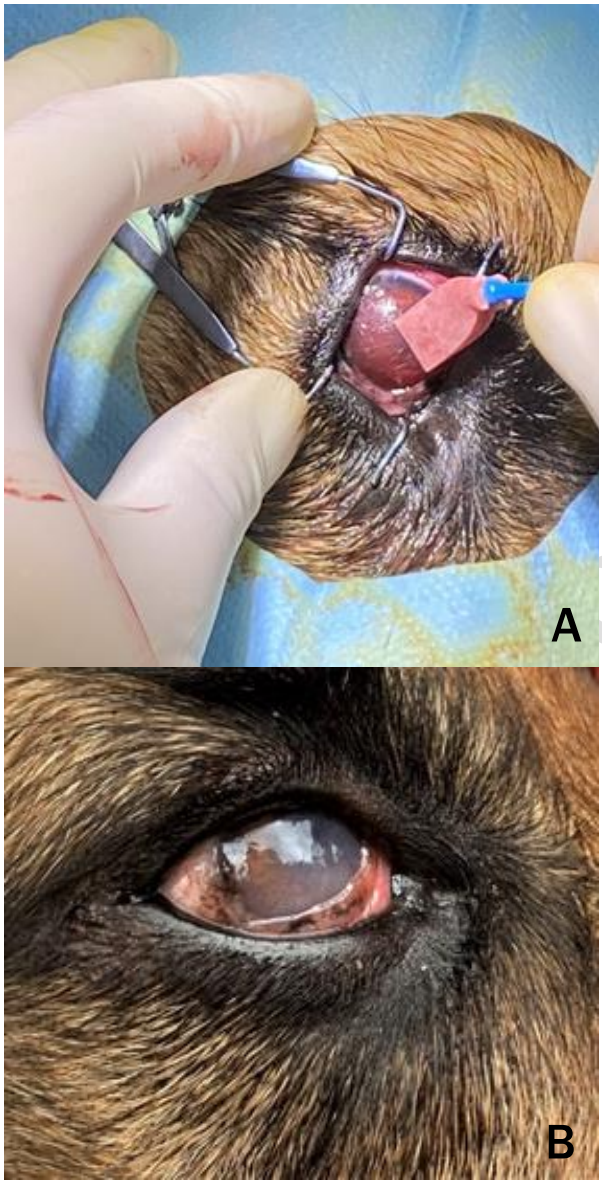

Fig. 2: A: Intraoperatively, ophthalmic sponge immersed with MMC (10mg/mL) was applied over the degenerated area for three minutes on each eye; B: Postsurgical: clinical examination showed very good results and revealed significant regression of superficial chronical keratitis and neovascularization.

of bevacizumab at 2.5mg/mL is considered safe both topically and systemically in healthy dogs. While mitomycin C has demonstrated effectiveness in treating corneal fibrosis in various animal species (Gupta et al. 2011), there are contradictory studies in humans regarding its safety. To mitigate the potential side effects associated with mitomycin C, different protocols with different exposure times and doses have been reported (Song et al. 2007). Physician ophthalmologists widely use clinically tested doses of MMC (0.02% for 2 min) to prevent corneal haze formation (Thornton et al. 2008). To the best of our knowledge, (Gupta et al. 2011) are the only researchers who specifically investigated the safety of mitomycin C on canine corneal keratocytes, evaluated its efficacy in managing corneal scarring in dogs, and examined its potential to reduce corneal fibrosis using an in vivo model. We used MMC in 1% concentration with an exposure time of 3min with no side effects observed.

Our case yielded promising outcomes, which could serve as a foundation for future advancements in the development of anti-vascular endothelial growth factor treatments in veterinary medicine, especially in ophthalmology practice. Moreover, the specific combination and dosages of the drugs we used showed remarkable efficacy in relieving symptoms of CSK, which is very important for animal well-being and quality of life. Additional studies are needed to investigate and validate the most appropriate dosage of MMC and/or bevacizumab for treating corneal fibrovascular lesions in dogs.

Authors' Contribution

Amila Šunje-Rizvan was the veterinarian on patient admission and was included in the treatment plan and manuscript preparation. Amina Rizvanović and Amela Livnjak are PhD students involved in research and manuscript preparation, Ismar Lutvikadić was the anesthesiologist and involved in manuscript preparation, Alan Maksimović and Nermina Spahija was included in the treatment plan and manuscript preparation.

Conflict of interests

The authors have not declared any conflict of interest.

Acknowledgment

Thank you for your cooperation in the preparation of your work for a publishable version.

REFERENCES

Allgoewer I and Hoecht S, 2010. Radiotherapy for canine chronic superficial keratitis using soft x-rays (15 kv). Veterinary Ophthalmology 13: 20-25. https://doi.org/10.1111/j.1463-5224.2009.00750.x

Balicki I and Trbolova A, 2010. Clinical evaluation of tacrolimus eye drops for chronic superficial keratitis treatment in dogs. Bulletin of the Veterinary Institute in Pulawy 54: 251-258. https://doi.org/10.2147/OPTH.S229405

Balicki I and Sobczyńska-rak A, 2014. Serum vascular endothelial growth factor concentration in dogs diagnosed with chronic superficial keratitis. Acta Veterinaria Hungarica 62: 22-32. https://doi.org/10.1556/avet.2013.040

Bedford PG and longstaffe JA, 1979. Corneal pannus (chronic superficial keratitis) in the German Shepherd dog. Journal of Small Animal Practice 20: 41-56. https://doi.org/10.1111/j.1748-5827.1979.tb07019.x

Beteg F, Lelescu CA, Urdă-cîmpean AE, Taulescu MA and Mureșan C, 2021. Long-term prospective assessment of subconjunctival triamcinolone acetonide in addition to topical therapy in the management of chronic superficial

keratitis. *Ankara Üniversitesi* Veteriner *Fakültesi* Dergisi 61: 61-68. https://doi.org/10.33988/auvfd.724846

Dastjerdi MH, Al-arfaj KM and Nallasamy N, 2009. Topical bevacizumab in the treatment of corneal neovascularization: results of a prospective, open-label, noncomparative study: results of a prospective, open-label, noncomparative study. Archives of Ophthalmology 127: 381-389. https://doi.org/10.1001/archophthalmol.2009.18

Ergin I, Sainkaplan S and Senel OO, 2021. Clinical assessment of chronic superficial keratitis (Uberreiter's Syndrome) in dogs: a retrospective study (2012-2019). Veterinaria 70: 185-195. https://doi.org/10.51607/22331360.2021.70.2.185

Gilger BC, Bentley E and Ollivier FJV, 2007. Diseases and surgery of the canine cornea and sclera. In: KN Gelatt (Editor), Veterinary Ophthalmology. 4th Ed. Blackwell Publishing, Ames, USA, pp: 722–723.

Gunther JB and Altaweel MM, 2009. Bevacizumab (avastin) for the treatment of ocular disease. Survey of Ophthalmology 54: 372–400. https://doi.org/10.1016/j.survophthal.2009.02.004

Gupta R, Yarnall BW, Giuliano EA, Kanwar JR, Buss DG and Mohan RR, 2011. Mitomycin C: a promising agent for the treatment of canine corneal scarring: Mitomycin C for treating canine corneal scarring. Veterinary Ophthalmology 14: 304-312. https://doi.org/10.1111/j.1463-5224.2011.00877.x

Holmberg DL, Scheifer HB and Parent J, 1986. The cryosurgical treatment of pigmentary keratitis in dogs an experimental and clinical study. Veterinary Surgery 15: 1-4. https://doi.org/10.1111/j.1532-950x.1986.tb00164.x

Hosseini H and Khalili MR, 2007. Therapeutic potential of bevacizumab (avastin) in herpetic stromal keratitis (hsk). Medical Hypotheses 69: 568-570. https://doi.org/10.1016/j.mehy.2007.01.032

Hosseini H and Nejabat M, 2007. A potential therapeutic strategy for inhibition of corneal neovascularization with new anti-vegf agents. Medical Hypotheses 68: 799-801. https://doi.org/10.1016/j.mehy.2006.06.063

Hu C, Ding Y, Chen J, Liu D, Zhang Y, Ding M and Wang G, 2009. Basic fibroblast growth factor stimulates epithelial cell growth and epithelial wound healing in canine corneas. Veterinary Ophthalmology 12: 170-175. https://doi.org/10.1111/j.1463-5224.2009.00696.x

Maggs D, Miller P and Ofri R, 2007. Slatter's fundamentals of veterinary ophthalmology. 4th Ed. W B Saunders.

Muellerleile LM, Bernkopf M, Wambacher M and Nell B, 2021. Topical bevacizumab for the treatment of corneal vascularization in dogs: a case series. Veterinary Ophthalmology 24: 554–568. https://doi.org/10.1111/vop.12931

Muellerleile LM, Tichy A and Nell B, 2019a. Serum vascular endothelial growth factor changes and safety after topical anti-human vegf antibody bevacizumab in healthy dogs. Veterinary Ophthalmology 22: 600-606. https://doi.org/10.1111/vop.12628

Muellerleile LM, Buxbaum B, Nell B and Fux DA, 2019b. In-vitro binding analysis of anti-human vascular endothelial growth factor antibodies bevacizumab and aflibercept with canine, feline, and equine vascular endothelial growth factor. Research in Veterinary Science 124: 233-238. https://doi.org/10.1016/j.rvsc.2019.03.018

Song J-S, Kim J-H, Yang M, Sul D and Kim H-M, 2007. Mitomycin-c concentration in cornea and aqueous humor and apoptosis in the stroma after topical mitomycin-c application: effects of mitomycin-c application time and concentration: effects of mitomycin-c application time and concentration. Cornea 26: 461-467. https://doi.org/10.1097/ico.0b013e318030d217

Thajunnisa AS, Sainulabdeen A, Dileepkumar KM, Laiju MP, Vasudevan VN and Devanand CB, 2020. Comparative evaluation of decellularized bovine omentum alone and in combination with mitomycin-C in the management of corneal injuries in dogs. Veterinary World 13: 2401-2410. https://doi.org/10.14202/vetworld.2020.2401-2410

Thornton I, Xu M and Krueger RR, 2008. Comparison of standard (0.02%) and low dose (0.002%) mitomycin c in the prevention of corneal haze following surface ablation for myopia. Journal of Refractive Surgery 24: 68-76. https://doi.org/10.3928/1081597X-20080101-13

Williams DL, 1999. Histological and immunohistochemical evaluation of canine chronic superficial keratitis. Research in Veterinary Science 67: 191-195. https://doi.org/10.1053/rvsc.1999.0329

Williams DL, Oey AJ and Smitherman P, 1995. Comparison of topical cyclosporin and dexamethasone for the treatment of chronic superficial keratitis in dogs. Veterinary Record 137: 635-639.

Zubrický P and Trbolová A, 2022. Hereditary eye diseases in German shepherd dog. Folia Veterinaria 3: 48-53. https://doi.org/10.2478/fv-2022-0026