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Canine endotheliitis: Clinical characteristics, advanced imaging features and treatment

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Abstract

Objective: To describe the clinical findings, multimodal corneal imaging features and treatment in canine patients diagnosed with endotheliitis.

Animals studied: Four canine patients met inclusion criteria for bilateral corneal disease with endothelial inflammation and secondary corneal edema that responded to topical anti-inflammatory treatment.

Methods: The patients selected underwent a complete ophthalmic examination with emphasis on the cornea including ultrasound pachymetry (USP), Fourier-domain optical coherence tomography (FD-OCT), *in vivo* confocal microscopy (IVCM), and digital slit lamp photography.

Results: All patients in this study demonstrated thickened corneas due to edema with USP and FD-OCT. With IVCM, mild to severe polymegathism and pleomorphism of corneal endothelial cells, reduced endothelial cell density (ECD), hyperreflective keratic precipitates (KPs) and

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CONFLICT OF INTEREST

While the netarsudil (Rhopressa®) was donated by Aerie Pharmaceuticals and could be viewed as a possible conflict of interest, we highlight that they had no input in the design, analysis or interpretation of the data presented in the manuscript or the manuscript itself.

extracellular debris as well as hyporeflective pseudoguttata were observed. With FD-OCT, hyperreflective KPs were commonly observed on the inferior cornea. Clinical examination and advanced imaging results were consistent with a diagnosis of endotheliitis. All patients initially responded to topical anti-inflammatory treatment and required continued therapy. All patients received topical anti-inflammatory treatment and two patients received topical netarsudil, a rho-associated coiled-coil kinase (ROCK) inhibitor.

Conclusion: Endotheliitis should be considered for canine patients with bilateral edema that is most severe in the inferior cornea. Careful inspection of Descemet's membrane-endothelial complex should be performed for KPs or inflammatory debris. Chronic administration of topical anti-inflammatories may be necessary to prevent flare-ups of endotheliitis.

Keywords

endotheliitis; ROCK inhibitor; *in vivo* confocal microscopy; optical coherence tomography; corneal edema

1. INTRODUCTION:

The corneal endothelium maintains corneal deturgescence and transparency. In dogs, causes of corneal endothelial degeneration include endothelial dystrophy, anterior uveitis, glaucoma, intraocular surgery, lens luxation, diabetes mellitus, canine adenovirus-1 infection (CAV-1), senility, and endotheliitis.[1–5] Corneal endotheliitis is the result of primary inflammatory damage to the corneal endothelium that typically manifests with corneal edema, keratic precipitates, and inflammatory changes in the anterior chamber, such as aqueous flare. With chronicity, endotheliitis can result in permanent endothelial degeneration.[6] In this case series, we describe the clinical findings, advanced imaging characteristics, and treatment of four canine endotheliitis cases.

2. MATERIALS AND METHODS:

Four canine patients were presented to the Comparative Ophthalmology Service at the University of California, Davis William R. Pritchard Veterinary Medical Teaching Hospital (UCD-VMTH). Two cases were suspected to have corneal endothelial dystrophy while the other two were suspected to have anterior uveitis with endotheliitis. All presented cases had bilateral corneal edema that responded to anti-inflammatory medication. Cases in which a primary cause of anterior uveitis were identified were excluded from this study. Patients underwent an ophthalmic examination with multimodal corneal imaging including anterior segment photography (Canon ROS 5D; Tokyo, Japan), intraocular pressure (IOP) measurement by rebound tonometry (Tonovet, Icare, Vantaa, Finland), digital slit lamp imaging (Topcon SL-D7, Tokyo, Japan), ultrasound pachymetry (USP, Pachette 4; DGH Technology, Inc., Exton, PA), Fourier-domain optical coherence tomography (FD-OCT, RTVue 100; Optovue, Inc., Fremont, CA) and *in vivo* confocal microscopy (IVCM, ConfoScan 4; Nidek Technologies, Gamagori, Japan). Corneal endothelial cell density (ECD) was calculated as previously described.[1]

3. CASE DESCRIPTIONS:

3.1 Case 1:

A 6-year-old male castrated Chihuahua mix was referred to the UCD-VMTH with blepharospasm, serous discharge, moderate conjunctival and episcleral hyperemia and mild chemosis in both eyes (oculus uterque, OU). Corneal edema OU was present and was most severe inferiorly (Figure 1), with pinpoint keratic precipitates (KPs). Mild and trace aqueous flare was present in the right (oculus dexter, OD) and left eye (oculus sinister, OS), respectively; IOPs were normal (OD 11; OS 14) (reference range 7–22 mm Hg).[7] Non-ulcerative keratoconjunctivitis and anterior uveitis OU were diagnosed, and prednisolone acetate 1% ophthalmic suspension (PA) was prescribed OU six times daily for one week and tapered and replaced by diclofenac 0.1% ophthalmic solution twice a day (BID). Four weeks after initial presentation, and one week later after discontinuing PA, the patient developed corneal edema; dexamethasone 1% ophthalmic solution three times daily (TID) was prescribed. At the 5-week recheck, no anterior uveitis was present, and the corneal edema was improved but still present OU. On FD-OCT and IVCM few, small, hyperreflective deposits consistent with KPs were identified (Figure 1). The dexamethasone was slowly tapered and replaced by diclofenac TID. Four months after initial presentation, the patient was comfortable, and corneal edema was resolved OD. Subtle edema with mild increased inferior corneal thickness (729 μm, reference range 575–623 μm) was still present in OS.[8] On IVCM, hyporeflective pseudoguttata and hyperreflective KPs were identified OU (Figure 1); ECD was markedly lower than normal at 870 (OD) and 878 (OS) cells/mm^2; (reference range: 2300 to 2500 cells/mm^2).[5] Discontinuation of diclofenac resulted in a relapse of corneal edema one week later. Dexamethasone 1% ophthalmic suspension was resumed and one month later, the patient was receiving 1 drop OU BID and was comfortable with clear corneas. Eight months after the initial presentation, the patient was comfortable and with no grossly visible corneal edema. The ECD were low at 610 (OD) and 544 cells/mm^2 (OS). Topical netarsudil 0.02% ophthalmic solution (Rhopressa©) BID was prescribed in addition to topical dexamethasone. Eight months later, the ECD was slightly increased OS (791 cells/mm^2) and increased OD (1235 cells/mm^2), but there were marked regional differences in ECD and cell morphology OD (Figure 1). Few hyperreflective KPs were still visible on the corneal endothelium (Figure 1).

3.2 Case 2:

A 2-year-old male castrated Chihuahua mix was presented after receiving a diagnosis of anterior uveitis and corneal edema two months prior. The patient was receiving topical 5% sodium chloride ointment (NaCl) four times daily (QID) and neomycin-polymyxin B-dexamethasone (NPD) ophthalmic ointment BID OU. The corneas were clear (Figure 2) and corneal thicknesses were normal, including inferiorly (OD 571 μm, OS 558 μm); IOPs were 23 (OD) and 22 (OS) mm Hg. Mildly enlarged and irregularly shaped endothelial cells with enlarged, hyperreflective nuclei OU were observed with IVCM (Figure 2); ECD was low at 1371 (OD) and 1018 (OS) cells/mm^2. The patient was tapered off the NPD ointment. Two weeks later, intermittent blepharospasm, severe conjunctival hyperemia, mild chemosis and diffuse corneal edema with the inferior cornea more severely affected were observed OU; superficial blood vessels were visible in the inferior and nasal cornea. The IOPs were

15 (OD) and 14 (OS) mmHg. Punctate KPs were most dense in the inferior cornea and visible with slit lamp biomicroscopy, FD-OCT and IVCM (Figure 2); the inferior cornea thickness had increased >50% from the previous visit (901 μm OD; 861 μm OS). Topical NPD ophthalmic suspension QID OU was prescribed then tapered to once a day over a 5-week period.

Seven months later, the corneas were clear and inferior corneal thickness was normal (OD: 529 μm; OS: 536 μm). Subtle punctate crystalline opacities in the temporal paraxial cornea were observed OU consistent with steroid keratopathy.[2] The NPD ophthalmic suspension was tapered over 4 weeks and replaced with topical diclofenac BID. Six weeks later, the patient was comfortable; however, trace flare OU, subtle corneal edema and increased inferior corneal thickness (OD 636 μm, OS 714 μm) were observed. With FD-OCT, small hyperreflective KPs and few cells in anterior chamber were observed and small hyporeflective pseudo-gutatta and hyperreflective deposits compatible with KPs were found with IVCM (Figure 2). Oral carprofen (2 mg/kg BID) was prescribed for five days, along with NPD ophthalmic suspension, diclofenac 0.1% ophthalmic solution and tacrolimus 0.03% ophthalmic suspension OU BID.

3.3 Cases 3 and 4:

Two 1.3-year-old littermate Australian cattle dogs were vaccinated at 6 weeks of age with a modified live vaccine (Canine Spectra 5, Durvet Inc., Blue Springs, MO) that protects against canine distemper virus, CAV-1 and −2, parainfluenza, and parvovirus type 2b. The dogs were then adopted by different households. Case 3 was a spayed female while case 4 was an intact female.

Case 3 developed corneal opacity OU at 3 months of age. A veterinary ophthalmologist diagnosed corneal endothelial degeneration secondary to anterior uveitis OU and prescribed NPD ophthalmic suspension TID. After three months, the corneal edema had resolved, and the NPD was tapered to once a day. Ten months later, the patient was presented to the UCD-VMTH. Subtle stromal and endothelial corneal opacities were present OU (Figure 3); IOPs were mildly elevated (OD 29, OS 26 mm Hg) but the patient was excitable and easily stressed. With USP, corneal thicknesses were normal including inferiorly at 533 μm (OD) and 532 μm (OS). Descemet's membrane (DM)-endothelial complex was hyperreflective OU with FD-OCT and slit lamp biomicroscopy (Figure 3). With IVCM, KPs were observed (Figure 3). While most endothelial cells were hexagonal in shape (Figure 3), ECD was decreased at 1480 (OD) and 1893 (OS) cells/mm^2.

Case 4 presented to a veterinary ophthalmologist at 4 months of age and diagnosed with endotheliitis OU; IOPs were low at 3 (OD) and 8 (OS) mmHg. Topical PA and NaCl OU were prescribed TID. After improvement, the PA was slowly tapered over 5 months then discontinued. Six weeks after discontinuing topical PA, a relapse of clinical signs was observed with corneal edema and hypopyon OU, and PA was restarted QID. A month later, the hypopyon had resolved but corneal edema remained static, and the PA was tapered to BID.

One year after initial diagnosis the patient was referred to the UCD-VMTH. Severe inferior corneal edema was observed OD with multifocal to coalescing KPs present on the endothelium (Figure 4); IOPs were 19 (OD) and 14 (OS) mm Hg. Severe, diffuse corneal edema was observed OS with sparing of only the superior perilimbal cornea (Figure 4); inferior corneal thickness was 1300 μm (OD) and 1703 μm (OS) as measured with FD-OCT. Thick hyperreflective deposits on the DM-endothelial complex were observed OU with FD-OCT consistent with KPs (Figure 4). With IVCM, the corneal endothelium was visible only OD and ECD was low (974 cells/mm^2, OD) with occasional elongated, hyperreflective nuclei present. Multifocal web-like hyperreflective deposits were present over the endothelial cells and were interpreted as KPs.[9] The patient was prescribed topical PA QID, NaCl QID, netarsudil BID, and tacrolimus 0.03% ophthalmic suspension BID OU. Four months later, the previously identified areas of corneal edema were markedly reduced OD but unchanged OS (Figure 4). The FD-OCT and IVCM findings were static from the previous visit other than a thin, hyperreflective band in the anterior stroma of the nasal cornea consistent with steroid keratopathy.[2] After ophthalmic exams, serum was submitted for ancillary testing and the patient had a positive titer against CAV-1.

4. DISCUSSION:

This case series demonstrates multimodal corneal imaging features of canine endotheliitis. Clinically, the patients presented bilateral diffuse corneal edema that improved after anti-inflammatory treatment. In contrast to acute anterior uveitis whereby edema is typically diffuse and mild to moderate in severity, these cases demonstrate more severe edema that persists beyond resolution of uveitis and is typically worse inferiorly. The IVCM findings included endothelial pleomorphism and polymegathism, pseudoguttata, and hyperreflective deposits consistent with what is observed in humans and horses with endotheliitis and endothelial immune-mediated keratitis, respectively.[10,11] Pseudoguttata are dark, acellular regions that result from endothelial cell edema and occur during bouts of inflammation.[12] The hyperreflective deposits overlying the DM-endothelial complex in the inferior cornea were interpreted as KPs that can persist for months after anti-inflammatory treatment.[9] While the composition of this material is unknown and histopathological investigation is warranted, we presume these aggregates represent inflammatory debris. Our findings suggest that inspection of the DM-endothelial complex at high magnification with slit-lamp biomicroscopy should be performed in patients suspected to have endotheliitis, and that IVCM and FD-OCT are useful in cases where endotheliitis cannot be confirmed solely on ophthalmic examination. Exclusion of primary anterior uveitis through complete ophthalmic examination and additional imaging, if necessary, is also recommended in these cases.

In all four cases, ECD was markedly reduced suggesting that corneal edema not only results from endothelial dysfunction due to inflammation, but also from endothelial decompensation as a critical low number of cells is reached. In addition, two patients had elongated, hyperreflective nuclei which is associated with corneal endothelial trauma or disease in humans.[13] Dogs have a moderate endothelial regenerative capacity, particularly at a young age.[14] Since our patients were young to middle aged, it is possible that some endothelial regeneration could occur. We prescribed netarsudil to two patients and observed improvement in ECD in one patient and reduction in percentage of the cornea affected

by edema in the less severe eye of a second patient. Topical ROCK inhibitors accelerate endothelial proliferation, migration and reduce apoptosis *in vitro* and *in vivo* in animal models as well as human patients.[15–17] While acknowledging regional variation in ECD and cell morphology in some of these patients, these data suggest that ROCK inhibitors may have a role in the treatment of endotheliitis in combination with anti-inflammatory treatment, and further studies are warranted.

In humans, cytomegalovirus and human herpesviruses cause endotheliitis.[9] A positive titer against CAV-1 was detected in patient 4. However, since both CAV-1 and CAV-2 are antigenically very close and cross-reaction is possible, it was not possible to determine whether the titer in this particular case was associated with natural infection or vaccination. It is possible that the endotheliitis in cases 3 and 4, who are littermates, could be attributable to natural infection with CAV-1 or vaccination with the attenuated CAV-2.

During natural infection, CAV-1 enters the eye during the viremic phase and replicates in corneal endothelial cells, causing endotheliitis. In a posterior phase or after vaccination, the production of neutralizing antibodies can lead to further damage through type III hypersensitivity reaction. During this process, immunocomplexes deposit in the anterior chamber, resulting in complement fixation and leukocyte recruitment which causes severe uveitis and endotheliitis with corneal edema; no antiviral treatment is currently available.[18,19] The potential role of viruses other than CAV-1 in canine endotheliitis has yet to be determined and necessitates further study.

In 3 patients, discontinuation of anti-inflammatory treatment led to relapse of clinical signs requiring re-institution of therapy. Furthermore, case 4 has had continuous anti-inflammatory treatment since the initial diagnosis and displayed the mildest changes in endothelial morphology and density of the presented cases. Thus, canine endotheliitis patients should be closely monitored if anti-inflammatories are discontinued; continuous treatment with a topical steroid at a low frequency may be preferable. Topical tacrolimus, a calcineurin inhibitor, may be beneficial in the long-term management of canine endotheliitis given that it can achieve adequate intraocular concentrations in human patients;[20] it was used in two patients in the present study in combination with other medications. This case series suggests that some canine patients with endothelial disease may require lifelong topical anti-inflammatory therapy.

CONCLUSIONS

The presentation of canine endotheliitis can vary but should be considered in patients with corneal edema that is more severe inferiorly and persists beyond resolution of anterior uveitis. Careful inspection of DM-endothelial complex for KPs should be performed with slit-lamp biomicroscopy, FD-OCT and/or IVCM. Long-term administration of topical anti-inflammatories may be necessary to manage canine endotheliitis.

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REFERENCES

1. Thomasy SM, Cortes DE, Hoehn AL, Calderon AC, Li JY, Murphy CJ. In Vivo Imaging of Corneal Endothelial Dystrophy in Boston Terriers: A Spontaneous, Canine Model for Fuchs' Endothelial Corneal Dystrophy. Investigative ophthalmology & visual science. 2016;57(9):OCT495–503. doi:10.1167/iovs.15-18885 [PubMed: 27454658]
2. Dubielzig RR, Ketring K, McLellan GJ, Albert DM. Chapter 8: Diseases of the cornea and sclera. In: Dubielzig RR, Ketring K, McLellan GJ, Albert DM, eds. Veterinary Ocular Pathology. W.B. Saunders; 2010:201–243. doi:10.1016/B978-0-7020-2797-0.00008-4
3. Yee RW, Matsuda M, Kern TS, Engerman RL, Edelhauser HF. Corneal endothelial changes in diabetic dogs. 1985;4(7):759–766. doi:10.3109/02713688509020031
4. Andrew SE. Immune-mediated canine and feline keratitis. Vet Clin North Am Small Anim Pract. 2008;38(2):269–290, vi. doi:10.1016/j.cvsm.2007.11.007 [PubMed: 18299007]
5. Gwin RM, Lerner I, Warren JK, Gum G. Decrease in canine corneal endothelial cell density and increase in corneal thickness as functions of age. Invest Ophthalmol Vis Sci. 1982;22(2):267–271. [PubMed: 7056641]
6. Suzuki T, Ohashi Y. Corneal Endotheliitis. Seminars in Ophthalmology. 2008;23(4):235–240. doi:10.1080/08820530802111010 [PubMed: 18584561]
7. Ben-Shlomo G, Muirhead SF. Estimation of intraocular pressure in normal canine eyes utilizing the newly introduced TonoVet Plus and TonoPen Avia, and their comparison to the established TonoVet. Vet Ophthalmol. 2021;24 Suppl 1:171–174. doi:10.1111/vop.12747 [PubMed: 32154987]
8. Samuel M, Thomasy SM, Calderon AS, Kass PH, Collins K, Murphy CJ. Effects of 5% sodium chloride ophthalmic ointment on thickness and morphology of the normal canine cornea. Veterinary Ophthalmology. 2014;22(3):229–237. doi:10.1111/vop.12582
9. Mocan MC, Kadayifcilar S, Irkec M. Keratic precipitate morphology in uveitic syndromes including Behçet's disease as evaluated with in vivo confocal microscopy. Eye. 2009;23(5):1221–1227. doi:10.1038/eye.2008.239 [PubMed: 18654603]
10. Porzukowiak TR, Ly K. In Vivo Confocal Microscopy Use in Endotheliitis. Optom Vis Sci. 2015;92(12):e431–436. doi:10.1097/OPX.0000000000000729 [PubMed: 26540476]
11. Ledbetter EC, Irby NL. Laser scanning in vivo confocal microscopic characterization of equine immune-mediated keratitis. Vet Ophthalmol. 2020;23(1):4–15. doi:10.1111/vop.12677 [PubMed: 31050168]
12. Krachmer JH, Schnitzer JI, Fratkin J. Cornea pseudoguttata: a clinical and histopathologic description of endothelial cell edema. Arch Ophthalmol. 1981;99(8):1377–1381. doi:10.1001/archopht.1981.03930020251007 [PubMed: 7259610]
13. Patel DV, Phua YS, McGhee CNJ. Clinical and microstructural analysis of patients with hyper-reflective corneal endothelial nuclei imaged by in vivo confocal microscopy. Experimental Eye Research. 2006;82(4):682–687. doi:10.1016/j.exer.2005.09.006 [PubMed: 16359661]
14. Park S, Leonard BC, Raghunathan VK, et al. Animal models of corneal endothelial dysfunction to facilitate development of novel therapies. Annals of Translational Medicine. Published online 2020.
15. Meekins LC, Rosado-Adames N, Maddala R, Zhao JJ, Rao PV, Afshari NA. Corneal Endothelial Cell Migration and Proliferation Enhanced by Rho Kinase (ROCK) Inhibitors in In Vitro and In Vivo Models. Investigative ophthalmology & visual science. 2016;57(15):6731–6738. doi:10.1167/iovs.16-20414 [PubMed: 27951595]
16. Okumura N, Kinoshita S, Koizumi N. Application of Rho Kinase Inhibitors for the Treatment of Corneal Endothelial Diseases. Journal of Ophthalmology. 2017;2017:2646904. doi:10.1155/2017/2646904 [PubMed: 28751979]

17. Miyagi H, Kim S, Li J, Murphy CJ, Thomasy SM. Topical Rho-Associated Kinase Inhibitor, Y27632, Accelerates Corneal Endothelial Regeneration in a Canine Cryoinjury Model. Cornea. 2019;38(3):352–359. doi:10.1097/ICO.0000000000001823 [PubMed: 30516555]

18. Carmichael LE, Medic BL, Bistner SI, Aguirre GD. Viral-antibody complexes in canine adenovirus type 1 (CAV-1) ocular lesions: leukocyte chemotaxis and enzyme release. Cornell Vet. 1975;65(3):331–351. [PubMed: 1095299]

19. Greene, Craig E Chapter 4, Infectious canine hepatitis and canine acidophil cell hepatitis. In: Infectious Diseases of the Dog and Cat. 4th ed. Elsevier/Saunders; 2012:42–47.

20. Shoughy SS, Aljassar FM, Tabbara KF. Aqueous penetration of topical tacrolimus. Am J Ophthalmol Case Rep. 2020;17. doi:10.1016/j.ajoc.2019.100582

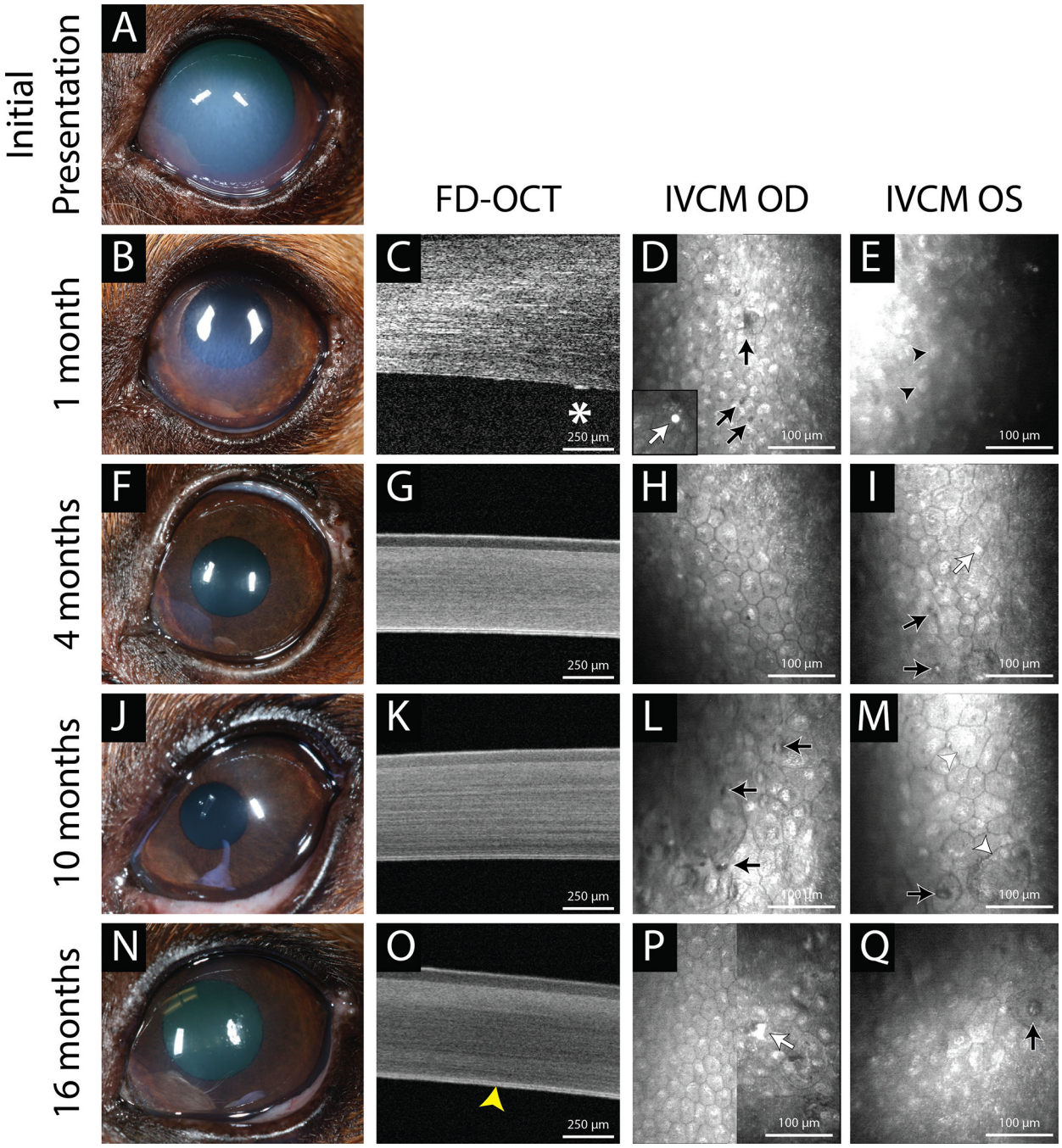

Figure 1.

Clinical course of canine endotheliitis in a 6-year-old male castrated Chihuahua mix with 16 months of follow up. At initial presentation, the patient had bilateral corneal edema (A). One month after the patient was receiving dexamethasone 1% ophthalmic solution TID, the corneal edema was improved OS (B) and resolved OD (not shown) and was completely resolved OU four months later (F). At one month after initial presentation, FD-OCT demonstrated hyperreflective deposits on the endothelium consistent with KPs (C, asterisk). With IVCM, mild to moderate pleomorphism (D, E), endothelial cells with

hyperreflective, elongated nuclei (E, black arrowhead), pseudogutatta (D, black arrows) and hyperreflective deposits consistent with KPs (D inset, white arrow) were observed 1 month after initial presentation. Four and ten months later, the corneas were clear (F, J). With FD-OCT, DM-endothelial complex was thickened (G, K) and hyperreflective on FD-OCT. With IVCM, progressive endothelial pleomorphism and polymegathism (M, white arrowhead), hyperreflective KPs (I, white arrow) and pseudogutatta (I, L, M, black arrows) were observed. Sixteen months after initial presentation and after 8 months of topical netarsudil, the endothelial complex was still thickened with FD-OCT (O, yellow arrowhead). Endothelial morphology was improved OS but variable with IVCM (P). Hyperreflective KPs (P inset, white arrow) and pseudogutatta (Q, black arrow) persisted in this patient.

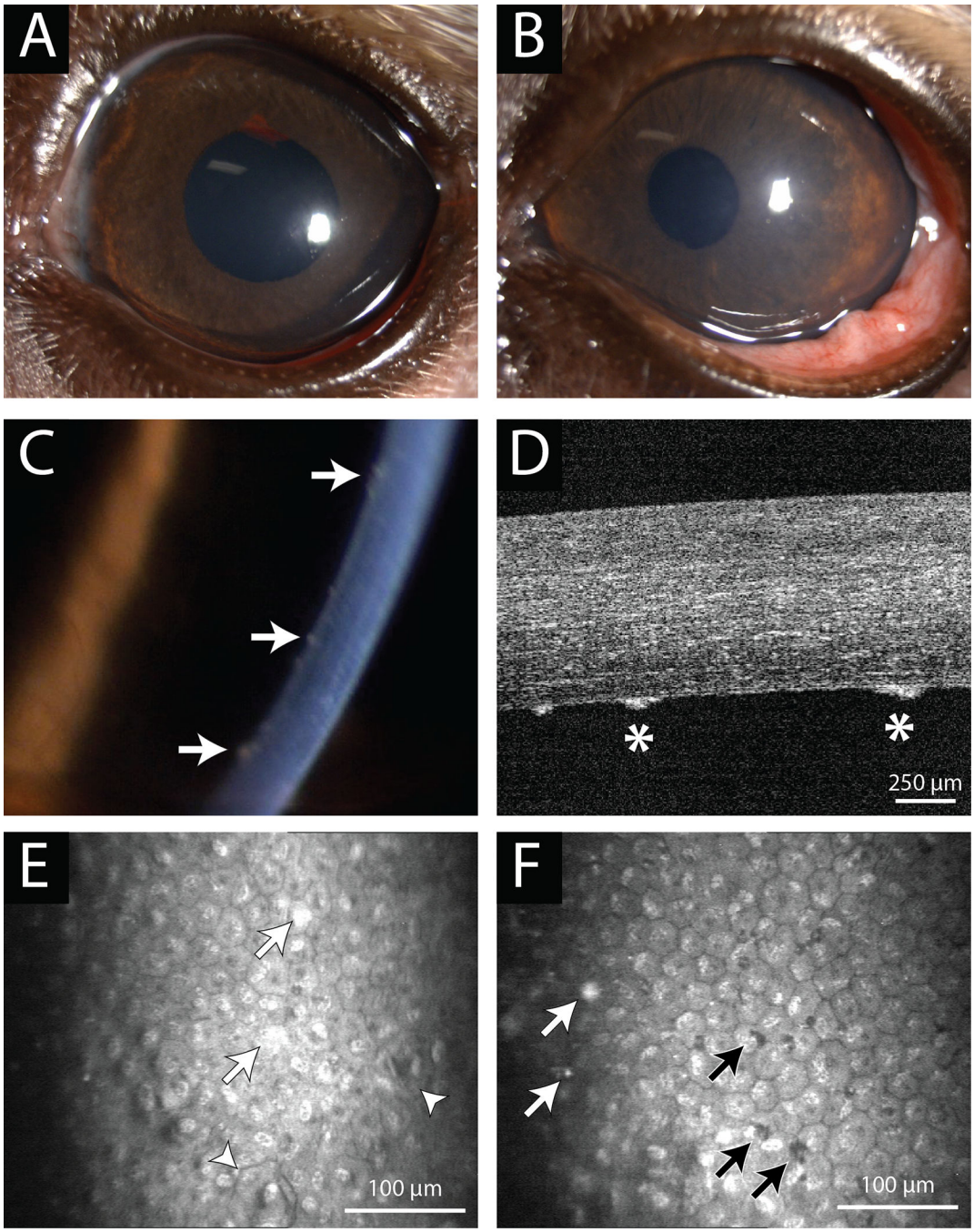

Figure 2.

Active endotheliitis was present in a 2-year-old castrated male Chihuahua receiving topical diclofenac 1% ophthalmic solution twice daily. At initial presentation, the patient was receiving topical NPD ophthalmic ointment with no apparent clinical signs (A, OS). Two weeks after replacement of the NPD ophthalmic ointment by diclofenac twice daily, the patient was presented for ocular discomfort, mild corneal edema, and conjunctival hyperemia (B, OS). KPs were observed with slit lamp biomicroscopy (C, white arrows OS), FD-OCT (D, asterisk, OS) and IVCM (E, white arrows, OD). After replacing topical NPD

with diclofenac BID, pseudogutatta (black arrows) and hyperreflective deposits compatible with KPs were observed with IVCM (F, white arrows, OD).

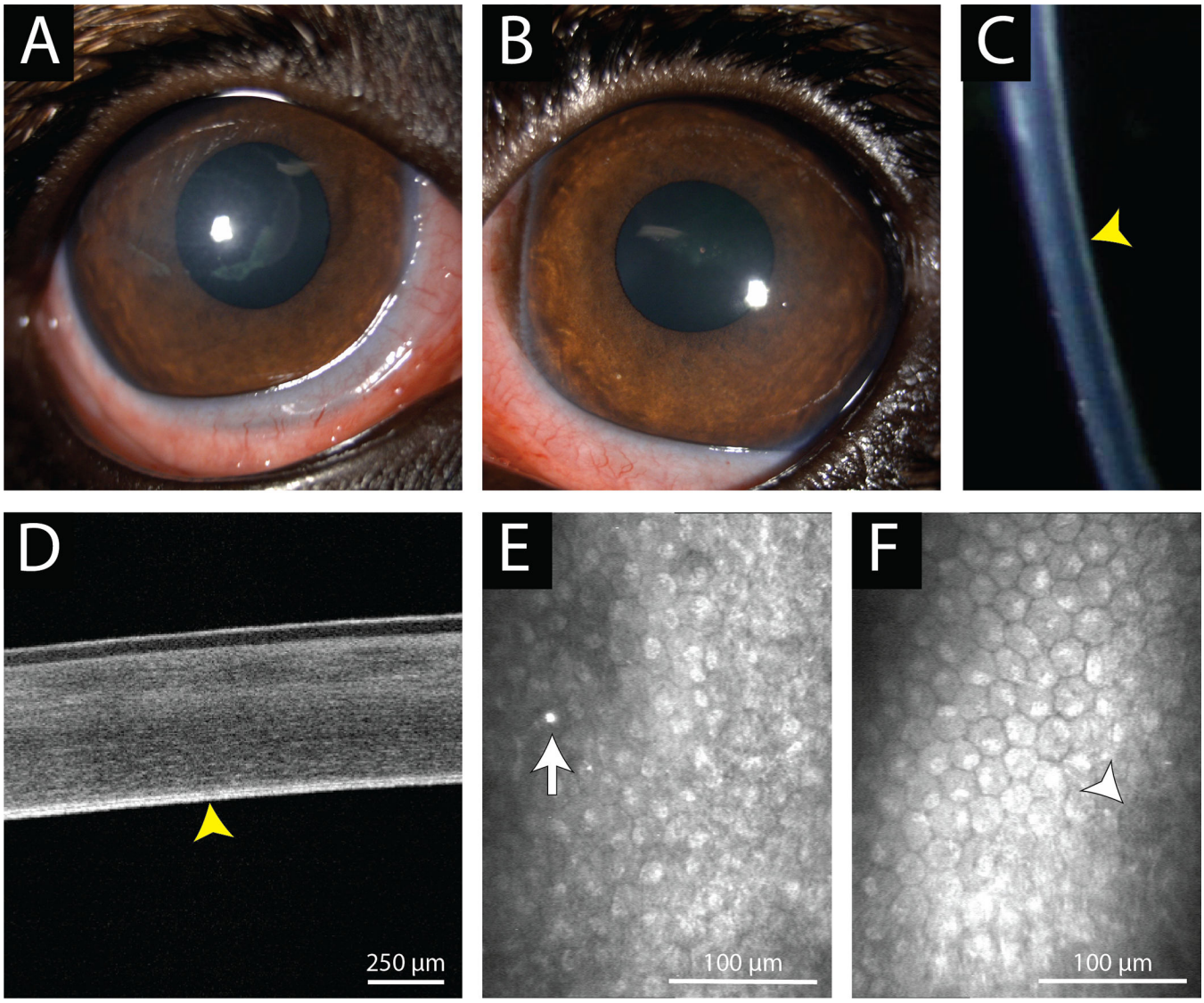

Figure 3.

Changes to the endothelium and Descemet's membrane were visible in a 1-year-old female Australian cattle dog diagnosed with endotheliitis at 3 months of age. This patient was receiving NPD ophthalmic ointment once daily OU. Subtle opacity was present in the axial cornea OU (A, B) due to increased hyperreflectivity of the DM-endothelial complex observed with slit lamp biomicroscopy at 10X magnification and FD-OCT (C and D, yellow arrowheads). With IVCM, few, mildly pleomorphic endothelial cells (F, white arrowhead) and scant hyperreflective KPs were observed (E, white arrow).

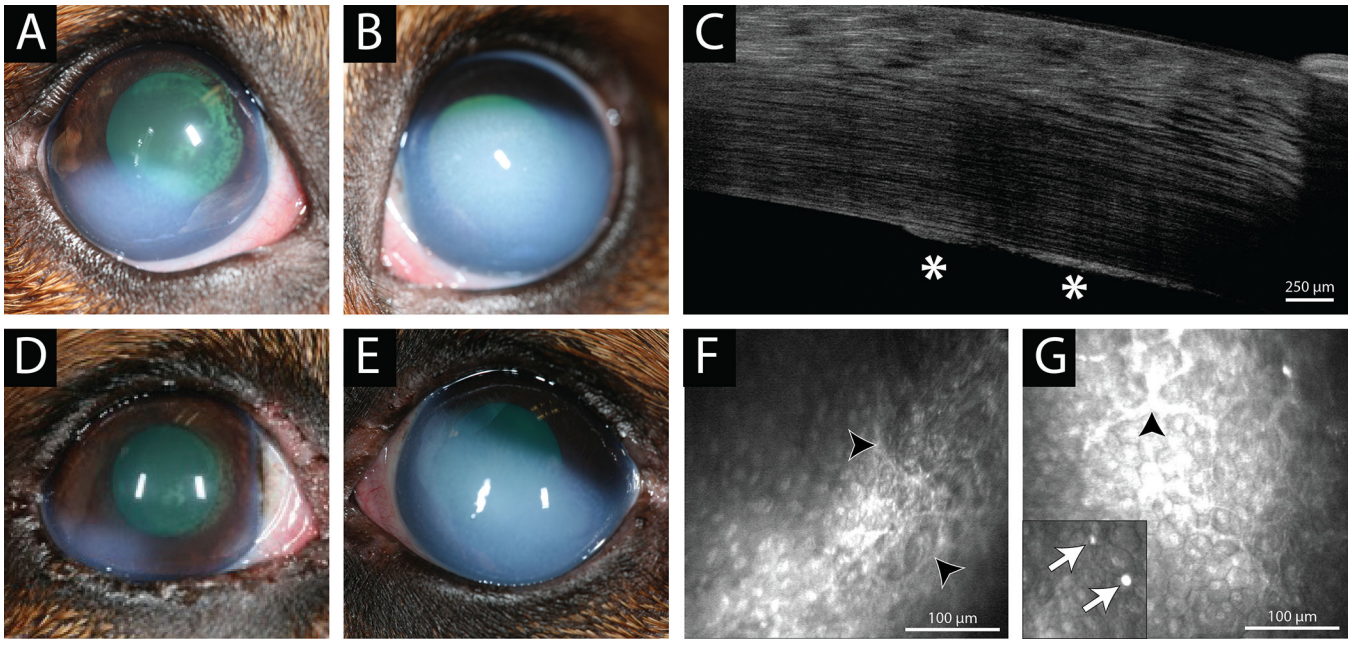

Figure 4.

A 1-year-old female Australian cattle dog with repeated bouts of severe canine endotheliitis demonstrates marked changes to the corneal endothelium OU; corneal edema improved in the less affected OD four months later with topical netarsudil, anti-inflammatory and immunosuppressive therapy. One year after initial diagnosis of endotheliitis, marked inferior edema OD (A) and severe diffuse edema with only sparing of the superior perilimbal OS (B) was observed. With FD-OCT, hyperreflective deposits interpreted as KPs in the inferior cornea attached at the corneal endothelium were observed OD (C, asterisks) and OS (not shown). With IVCM, multifocal hyperreflective deposits partially cover a mildly pleomorphic endothelium (F, black arrowheads). After 4 months of topical netarsudil BID in combination with increased frequency of PA and NaCl to QID and the addition of tacrolimus BID, the corneal edema is improved OD (D) and static OS (E); With IVCM, persistence of hyperreflective deposits consistent with KPs (G, black arrows) were observed.