TWO OCULAR SURFACE ENIGMAS: ENDOTHELIAL DYSTROPHY AND EPISCLERITIS

Ron Ofri, DVM, PhD, DECVO
Koret School of Veterinary Medicine, Hebrew University of Jerusalem
PO Box 12, Rehovot 76100, Israel (ron.ofri@mail.huji.ac.il)

Keywords: Endothelial dystrophy, Scleritis, Episcleritis.

1. CORNEAL ENDOTHELIAL DYSTROPY

Endothelial cell dystrophy is a disease of spontaneous, progressive corneal edema resulting from abnormal dystrophic endothelial cells.[1, 2] In the dog, this condition is most prevalent in the Boston Terrier, Chihuahua, and Dachshund, and occurs more frequently in middle-aged females.[3] Canine endothelial cell dystrophy resembles Fuchs' dystrophy in humans, a disease inherited as an autosomal dominant inherited disease with incomplete penetrance trait that is likewise three times more common in women[4]. In human patients, specular, confocal, light, scanning electron, and transmission electron microscopy demonstrate a decreased number of endothelial cells and endothelial fibrous metaplasia. Descemet's membrane is thickened because of fibrillar deposits and exhibits some guttata (droplet-like accumulations of non-banded collagen on the posterior surface of Descemet's membrane). Similarly, Boston Terriers with endothelial dystrophy have significantly decreased corneal endothelial density, significantly increased central corneal thickness, and significantly increased endothelium Descemet's complex thickness compared with age-matched controls.[4]

Clinically, dogs with endothelial dystrophy present with an opaque, blue/white cornea without corneal vascularization or conjunctival hyperemia. The initial lesion, corneal edema, is located temporally and progresses slowly, over several months to a few years, to involve the entire cornea. Involvement of the two eyes is often initially asymmetric but progresses to bilateral, complete corneal opacity. On biomicroscopy, the main observations are increased corneal thickness, corneal opacity, epithelial bullae, and subepithelial scarring. In some dogs, the posterior corneal surface has fine, bright, compacted striae and occasionally, with specular reflection, black spots or holes in the endothelial mosaic pattern. Specular microscopy may assist in early diagnosis and therapy.[1-3]

Palliative therapy is most commonly used for canine endothelial dystrophy. Most dogs maintain limited vision with this disease and only develop morbidity when corneal ulcers develop after rupture of epithelial bullae. These ulcers are managed using topical broad-spectrum antibiotics and topical hyperosmotic medications (e.g., 5%sodium chloride). Hyperosmotic agents may decrease the extent of epithelial bullae formation, but significant corneal clearing does not occur, and there are no controlled studies proving their efficacy. Ocular irritation and lacrimation from use of hyperosmotic preparations, which may cause drug dilution and reduce corneal contact time, also limits their usefulness. Topical corticosteroids have been advocated on an empiric basis for stromal edema in humans with Fuchs' dystrophy and in affected dogs; however, topical corticosteroids (e.g., dexamethasone) or nonsteroidal medications appear to have no beneficial effect in dogs.[1-3]

Dogs with persistent bullous keratopathy and non-healing corneal ulcers as a result of endothelial dystrophy or degeneration may benefit from thermokeratoplasty (TKP).[5] In TKP, the use of multifocal points of superficial thermal cautery applied in a circular fashion to the exposed corneal stroma results in contraction of the anterior stromal collagen fibers. The goal is to develop mild superficial stromal contracture and opacity, and not a focal burn, with the use of minimal probe temperatures. The resulting subepithelial scar tissue acts as a

partial barrier to the flow of fluid through the cornea and helps to reduce the buildup of fluid that results in epithelial bullae. The procedure is performed in sedated or anesthetized dogs. A lid speculum is placed, and the cornea and conjunctiva flushed with 1% povidine-iodine and rinsed with sterile eyewash. Loose corneal epithelium is debrided with sterile cellulose sponges or cotton-tipped applicators. TKP is performed only in the areas of exposed stroma, after debridement of nonadherent epithelium. Post-TKP medications include the topical administration of antibiotics, a topical mydriatic/cycloplegic, and oral nonsteroidal anti-inflammatory medications for pain management. In a study reviewing the results of TKP in 13 dogs with corneal ulcers from endothelial disease (for a mean duration of 16.1 weeks), the mean time to corneal ulcer healing after TKP was 2.2 ± SD 1.1 weeks.[5] Recently, it has been suggested that corneal crosslinking with riboflavin and ultraviolet light radiation can achieve similar results without sedation or corneal scarring). Presumed therapeutic mechanisms are an increase in collagen packing density and a reduction in the swelling tendency of the glycosaminoglycan-rich hydrophilic ground substance of the cornea.[6]

Superficial keratectomy with conjunctival advancement hood flap has been used with considerable success to slow the progression of edema and help with ulcerations. It is suggested that partial coverage of the corneal surface with a thin conjunctival flap can function as a drainage sink for the edematous fluid in the stroma, and increase corneal transparency.[1, 2] However, the only definitive treatment for endothelial dystrophy is replacement of the endothelial cells via a homologous corneal transplant. Surgical transplantation techniques include Descemet's stripping endothelial keratoplasty (DSEK) and Descemet's membrane endothelial keratoplasty (DMEK). In DMEK, selective transplantation of Descemet's membrane and endothelium is performed while DSEK involves the selective transplantation of Descemet's membrane, endothelium, and posterior stromal lamellae.[7] Nonpenetrating and penetrating keratoprosthesis implantation is also described in a limited number of dogs with vision loss attributed to endothelial dystrophy.[8]

Ripasudil (Glanatec ophthalmic solution 0.4%; Natural Pharmacy, Osaka, Japan) is a new ophthalmic solution that has recently been shown to be efficacious in 2/3 of dogs treated 4 times daily. It is a ROCK inhibitor, which promotes corneal endothelial cell proliferation and adhesion, and inhibits apoptosis of corneal endothelial cells.[9] It is hoped that this drug can replace the more invasive, and less effective, surgical techniques.

2. SCLERITIS AND EPISCLERITIS

There are several inflammatory disorders that affect the episclera and sclera in dogs. These are a group of idiopathic, non-neoplastic, non-infectious diseases, which appear to represent a spectrum of disease pathology of variable but similar clinical presentation. They are considered to be immune mediated on the basis of histological findings and the response to immunomodulatory medication.[1, 2. 10, 11]

2.1 Episcleritis

Episcleritis in the dog may be divided into primary and secondary types. Breeds most commonly affected by primary episcleritis include the collie breeds, American Cocker Spaniel and Shetland sheepdog, but any breed can be affected.

The primary form can be further subdivided into simple episcleritis and NGE. Simple episcleritis is found infrequently, and it is not associated with systemic disease. Simple diffuse episcleritis is recognized by signs of generalized or regional episcleral vascular injection with thickening of the surrounding episclera. Usually, there is mild corneal edema

and peripheral neovascularization adjacent to the inflamed area. These clinical signs can be confused with glaucoma and, therefore, careful ocular examination and tonometry are indicated. It is usually responsive to topical or corticosteroid therapy and, in most cases, is self-limiting. [11, 12]

Secondary episcleritis may occur as a result of deep fungal or bacterial ocular infection, infection with *Ehrlichia canis*, *Toxoplasma gondii*, *Leishmania* spp. or *Onchocerca* spp., systemic histiocytosis, chronic glaucoma or ocular trauma.

2.2 Nodular granulomatous episcleritis (NGE)

NGE is the term most commonly used to describe several similar disease processes, including nodular fasciitis, fibrous histiocytoma, proliferative conjunctivitis, pseudotumour, limbal granuloma and collie granuloma. The condition presents as a unilateral or bilateral inflammatory disease, characterized by one or more discrete, pink fleshy nodular masses or thickened areas, most often located at the temporal limbus, in conjunction with hyperemia of the episcleral. It is common for adjacent tissues to be inflamed, and additional presenting clinical signs may include any combination of conjunctivitis, keratitis, scleritis, blepharitis and chorioretinitis. The inflammation may result in lipid infiltration of the cornea (lipid kerato pathy). The main differential diagnoses are the neoplastic diseases lymphoma, squamous cell carcinoma and amelanotic limbal melanoma. Therefore, in some cases, biopsy is indicated. [11, 12]

Histopathologic features of NGE are consistent with those of chronic granulomatous inflammation. The predominant cell types are histiocytes, lymphocytes, and plasma cells. Epithelioid cell accumulations, fibroblastic cells, abundant reticulin fiber formation, and neovascularization with perivascular polymorphonuclear inflammatory cell infiltration also occur. Production of lymphokines by the T lymphocytes and the resulting chemotaxis of histiocytes is a proposed pathogenesis of NGE. This was supported by a study of granulomatous scleritis in dogs where inflammatory aggregates contained T lymphocytes, IgG plasma cells, macrophages, and immune-complex deposition, suggesting types III and IV immunopathogenesis[13].

Because azathioprine and cyclosporine are T-cell suppressors, it is logical they would be effective therapy for NGE. Generally, NGE tends to be benign, with good response totopical administration of corticosteroids with or without the use of oral azathioprine treatment or topical or systemic cyclosporine.

Treatment:[1, 2, 10, 11, 14, 15]

• Topical corticosteroids, such as 1% prednisolone acetate or 0.1% dexamethasone, are the preferred first-line treatment. Initially, the recommended frequency of application is three to four times daily. This can be gradually reduced and, in some cases, withdrawn; although, a less frequent maintenance dose may be required to limit recurrence of the disease.

• Oral corticosteroids are indicated for cases that do not respond to topical corticosteroids alone.

• Subconjunctival or intralesional corticosteroids are administered in some situations.

• Azathioprine may be used alone or in combination with oral corticosteroids. It is administered orally at 1.5–2.0 mg/kg once daily for 3–10 days, and then at

0.75–1.00 mg/kg once daily for 10–18 days. Baseline complete blood count (CBC) and serum biochemical panels are obtained before starting azathioprine treatment. Toxic effects

of azathioprine include gastrointestinal toxicosis (i.e., vomiting and bloody diarrhea), hepatotoxicosis, and myelosuppression. Elevated serum alkaline phosphatase and alanine transaminase activities are present in acute hepatic necrosis. Many dogs can be kept in remission with 1–2 mg/kg once every 3–7 days for 1–8 months (then discontinued).

• An alternative systemic immunosuppressant is Cyclosporine A (CsA). It can be used topically in conjunction with steroids initially, but then a sole treatment is necessary to help prevent recurrence once the mass has resolved. CsA can also be given orally if the NGE is resistant to therapy. Pretreatment CBC and serum chemistry profile should be performed, and CsA therapy should be avoided if renal or hepatic insufficiency is present in the dog. The starting dose is 5 mg/kg/day for approximately 30 days (once the dog clinically responds well to treatment), then reduce to either 5 mg/kg po every other day or 2.5 mg/kg every 24 hours. Typical total treatment time is approximately 75–90 days (or longer if needed). Monitor CBC and serum chemistry profile at 2, 6, and 10 weeks into treatment

• Tetracycline together with niacinamide (NOT niacine) may be administered orally three times a day at the recommended dose of 250 mg of each drug for animals <10 kg in bodyweight, and 500 mg of each drug for animals >10 kg in bodyweight.

• Surgical excision with lamellar keratectomy, debulking and cryosurgery, and beta radiation therapy have been used.

• If an infectious agent is identified or suspected as the causative agent (see above), specific etiological diagnosis should be pursued and appropriate medical therapy prescribed.

2.3 Scleritis

Scleritis is an uncommon, primary, idiopathic, immune-mediated disorder in dogs. It may present as a unilateral or bilateral condition. It may be classified as necrotizing or non-necrotizing based on the presence or absence of collagen necrosis on scleral biopsy.

Dogs with scleritis usually present with pink "tan" colored sector lesions arising near, but posterior to, the limbus. There may also be some adjacent corneal edema. Clinical signs include ocular pain, photophobia, and excessive lacrimation. In some cases, keratitis, anterior uveitis, or both may be present because the scleral inflammation extends into these adjacent tissues. Anterior uveitis, when present, is nongranulomatous. Gonioscopic evaluation of the iridocorneal angle may reveal congestion of the peripheral iris in the area of affected sclera. In advanced scleritis, there may be diffuse corneal stromal infiltration as well as posterior scleral and choroidal progression, with secondary retinal involvement. The scleral lesions may or may not be associated with systemic collagen diseases. Ophthalmoscopically, fundus lesions may be seen if there is posterior scleral involvement. Fundus observations are facilitated when the cornea, lens, and ocular media are clear. Active posterior segment involvement is characterized by focal or regional areas of retinochoroidal degeneration, with preretinal and vitreal exudates.

REFERENCES

1. Whitley RD, Hamor RE. Diseases and surgery of the canine cornea and sclera. In Veterinary Ophthalmology, 6th edition. Edited by Gelatt KN. Wiley-Blackwell, Hoboken, NJ, 2021, pp 1082-1172.

2. Maggs DJ. Diseases of the cornea and sclera. In Maggs DJ, Miller PE, Ofri R. Slatter's Fundamentals of Veterinary Ophthalmology, 6th edition. Elsevier, St. Louis, 2018, pp 213-253
3. Leonard BC, et al. A Retrospective Study of Corneal Endothelial Dystrophy in Dogs (1991-2014). Cornea. 2021;40(5):578-583.
4. Thomasy SM. In Vivo Imaging of Corneal Endothelial Dystrophy in Boston Terriers: A Spontaneous, Canine Model for Fuchs' Endothelial Corneal Dystrophy. Invest Ophthalmol Vis Sci. 2016;57(9):495-503
5. Michau TM et al. Use of thermokeratoplasty for treatment of ulcerative keratitis and bullous keratopathy secondary to corneal endothelial disease in dogs: 13 cases (1994–2001). JAVMA 2003;222:607–612.
6. Pot, SA et al. Treatment of bullous keratopathy with corneal collagen cross-linking in two dogs. Vet Ophthalmol 2015;18:168–173.
7. Boo G, et al. Early postoperative results of Descemet's stripping endothelial keratoplasty in six dogs with corneal endothelial dystrophy. Vet Ophthalmol 2019;22(6):879-890.
8. Allgoewer IA et al. A keratoprosthesis prototype for the dog. Vet Ophthalmol 2010;13: 47–52.
9. Michalak SR et al. Topical Ripasudil for the Treatment of Primary Corneal Endothelial Degeneration in Dogs. Transl Vis Sci Technol. 2022;11(9):2
10. Mitchell N. The sclera, episcleral and limbus. In BSAVA manual of canine and feline ophthalmology, 3rd edition. Edited by Gould D and McLellan GJ. BSAVA, Gloucester 2018, pp 32-240,
11. Grahn BH, Sandmeyer LS.Canine episcleritis, nodular episclerokeratitis, scleritis, and necrotic scleritis. *Veterinary Clinics of North America*. *Small Animal Practice*, 2008;**38:**291–308.
12. Paulsen ME et al. Nodular granulomatous episclerokeratitis in dogs: 19 cases (1973-1985). JAVMA 1987;190(12):1581-7.
13. Breaux CB, et al. Immunohistochemical investigation of canine episcleritis. Vet Ophthalmol 2007;10:168–172.
14. Barnes LD et al. Surgical management of orbital nodular granulomatous episcleritis in a dog. Vet Ophthalmol 2010;13:251–258.
15. Wheeler C et al. Cryosurgery for treatment of recurrent proliferative keratoconjunctivitis in five dogs. JAVMA 1989;195:354–357.