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Ophthalmic Emergencies Mini Series

Session Two: The Red and Cloudy Eye

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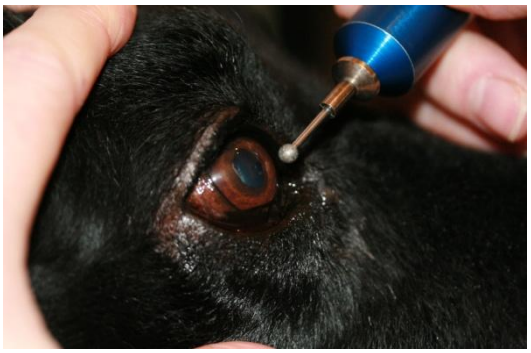

The red and cloudy eye ('Blue eye')

'Blue eye' usually used to describe episcleral reddening in association with corneal oedema, which gives a cloudy appearance to the ocular surface (owners often describe the eye as 'glazed').

The normal cornea is optically transparent. One of the mechanisms for maintaining transparency of the normal cornea is its relative dehydration. This is achieved by a combination of a hydrophobic epithelium that repels ocular surface water, and a sodium/potassium ATPase pump system within the corneal endothelium, which actively removes water from the corneal stroma. A failure in one or other of these systems (either breakdown of the corneal epithelium, such as corneal ulceration, or reduction of the endothelial pump mechanism) leads to corneal oedema.

Because oedema gives the cornea a cloudy appearance, this condition is too often mistaken for keratitis; a misdiagnosis that can actually be sight threatening. But whilst corneal oedema and keratitis can look similar at first glance, they are actually quite different in appearance. Corneal oedema gives a characteristic 'stippled' appearance (like the stippling on the surface of an orange). This stippling is due to hydration of the stromal collagen fibrils, which then swell and separate, scattering light to cause this characteristic appearance.

On the other hand, non-ulcerative keratitis also causes corneal clouding, but without the stippled appearance, and often with additional signs such as vascularisation or pigmentation. So if you see the tell-tale stippled appearance of corneal oedema, first perform fluorescein-staining to rule out corneal ulceration, and then look for an intraocular cause, with particular emphasis of identifying potentially serious and blinding intraocular causes such as anterior uveitis, glaucoma, or lens luxation.

Recognising intraocular disease

Thankfully, it is actually a rather simple task to identify intraocular causes of an acutely painful red and cloudy eye using just a penlight. If you think intraocular disease is present, or if in doubt about your diagnosis, then seek urgent specialist advice. Failure to recognise and correctly treat glaucoma at first presentation will cause irreversible blindness in many cases.

Signs of intraocular disease include the following:

- Abnormal pupil size (large in glaucoma, constricted in anterior uveitis)
- Abnormal iris (especially in anterior uveitis, in which it may appear reddened or swollen)
- Abnormal pupillary light response
    - Reduced in anterior uveitis
    - Reduced or absent in glaucoma
- Corneal oedema (do not mistake this for keratitis)
- Visual deficits (especially in glaucoma)

ANTERIOR UVEITIS

SIGNS OF ANTERIOR UVEITIS

Acute anterior uveitis	Chronic anterior uveitis
Ocular discomfort Episcleral hyperaemia Miosis (pupil constriction) Iris swelling/hyperaemia Reduced intraocular pressure Corneal oedema Aqueous flare	Iris hyperpigmentation (darkening) Anterior cataract Synechiae formation (iris adhesions) Keratic precipitates (deposits on corneal endothelium)

Causes of uveitis

- Infectious causes
    - Viral (CAV-1, uncommon in dogs; in cats consider FIP, FIV, FeLV)
    - Bacterial (penetrating or haematogenous spread. Less commonly tick-borne)
    - Protozoal (Toxoplasma, Neospora. Consider Leishmania in imported animals)
    - Mycotic/ algal (rare in UK)
    - Parasitic (uncommon in UK, except perhaps Wales and SW England (Angiostrongylus vasorum)

- Non-infectious causes are probably more common than infectious causes
    - Traumatic (especially if unilateral)
    - Reflex (secondary to corneal ulceration)
    - Lens-induced (common in dogs). Two forms:
        - Leakage of lens protein in rapidly growing cataracts (phacolytic uveitis)
        - Traumatic lens rupture (phacoclastic uveitis) (see Lens section)
    - Systemic disease (e.g. Toxaemia, bleeding disorders, diabetes mellitus, hyperlipidaemia, systemic hypertension, granulomatous meningoencephalomyelitis (GME), systemic histiocytosis)
    - Neoplasia (esp. lymphoma)
    - Autoimmune disease/ immune-mediated
    - Idiopathic
        - In many cases the cause is obscure

Diagnostic approach to uveitis

1. History Signalment, vaccination status, worming/ flea treatment, history of travel abroad, environment, hunter/ scavenger, history of trauma, previous or concurrent disease, other clinical signs.
2. Ophthalmic examination Perform an external and internal eye examination, comparing both eyes. Look for signs of blunt or penetrating injury (remember the fluorescein!). Check pupil size and pupillary light responses, appearance of iris, menace response. Perform a fundus examination.
3. General physical examination For signs of systemic disease, traumatic injury.
4. Serology/virology If infectious agent is suspected: • Dogs: *T.gondii*, *N. caninum*, (± others e.g. PCR screen for tick-borne disease) • Cats: FIV, FeLV, FIP, *T. gondii,* (± others e.g. PCR for *Bartonella henselae*)
5. Haematology/serum biochemistry If an infectious agent or systemic disease is suspected, perform routine haematology (including smear) and serum biochemistry. Serum protein electrophoresis (SPE) may be useful if serum proteins are elevated. E.g. gamma globulinaemias may be seen in chronic infections or chronic immune stimulation (especially ehrlichiosis, leishmaniasis, neoplasia in dogs; FIP, FIV, toxoplasmosis, neoplasia in cats).
6. Diagnostic imaging Ocular ultrasonography may be indicated if there is suspicion of intraocular neoplasia, intraocular haemorrhage, or retinal detachment. Chest and abdominal radiography and ultrasonography to look for effusions if FIP is suspected, or to look for metastatic disease.
7. Further tests may be indicated, depending on earlier findings. Seek specialist advice if in doubt.

Treatment of uveitis

The mainstay of treatment for all causes of uveitis is anti-inflammatory treatment. For anterior uveitis:

- Topical corticosteroids (unless corneal ulceration is present)
    - Prednisolone acetate
- Topical non-steroidal anti-inflammatories (NSAID's)
    - Ketorolac trometamol

- Topical mydriatic
    - Atropine drops or ointment. This is best avoided in cats (or at least, use the ointment formulation)
- Topical antibacterials if bacterial infection is suspected (eg in cases of penetrating injury)
    - Chloramphenicol has excellent ocular penetration and has broad-spectrum activity
    - Gentamicin, ciprofloxacin, ofloxacin, for selected cases
- Systemic NSAID's (carprofen or meloxicam)
- For certain types of aggressive uveitis, such as golden retriever uveitis and UVD, systemic immunosuppressants such as corticosteroids, azathioprine or cyclosporine may be indicated.
- For posterior uveitis, systemic medication is needed, which will vary depending on the underlying cause.

In addition to the above, any underlying cause should be identified and treated.

GLAUCOMA

This is basically defined, at least in the veterinary species, as raised intra-ocular pressure (IOP) above the normal range of 10-25mmHg. Although tonometry is required for definitive diagnosis, there are a number of characteristic signs of acute glaucoma (especially in dogs) that are easy to recognize:

SIGNS OF ACUTE CANINE GLAUCOMA:

- Ocular pain (often severe)
- Blindness in affected eye
- Episcleral congestion
- Corneal oedema ('steamy' cornea)
- Dilated pupil (mydriasis)

Acute canine glaucoma is an ophthalmic emergency, and it is important to seek specialist advice if in doubt as to diagnosis or treatment or if you are unable to ascertain the initiating cause (it is vital to distinguish primary from secondary glaucoma and specialist examination is often required for this).

In cats, glaucoma tends to be less acute in presentation, and affected cats may show minimal signs of ocular pain, minimal corneal oedema and retain vision until later stages of the disease.

Tonometry

Tonometry is required for definitive diagnosis of glaucoma and to monitor efficacy of treatment. There are a number of tonometers available, the 3 most common in veterinary practice being:

- Schiotz (indentation tonometer)
    - Cheap
    - Relatively tricky to use in painful eyes
    - Not as accurate as applanation or rebound tonometers
- Tonopen (applanation tonometer)
    - Relatively expensive
    - Simple to use although risk of causing corneal ulceration if used incorrectly or very frequently on the same eye
- Tonovet (rebound tonometer)
    - Relatively expensive
    - Simple to use

Causes of glaucoma

Anything that blocks outflow of aqueous humour from the eye can cause glaucoma. Common causes include:

- Inherited (primary) closed-angle glaucoma
    - Abnormal formation of the iridocorneal drainage angle (goniodysgenesis, or pectinate ligament dysplasia)
    - Certain pure-bred dog breeds are affected (common breeds include American cocker spaniel, Basset, Cocker spaniel, Flat-coated retriever, Golden retriever, Siberian husky, Welsh springer).
    - Usually bilateral, although one eye is usually affected before the other. Always try to arrange referral to a veterinary ophthalmologist for evaluation of the contra-lateral eye.
    - Diagnosed by gonioscopy (a specialist procedure).
    - Onset of glaucoma usually occurs in early middle age.
- Inherited (primary) open-angle glaucoma
    - Rare but is seen in some breeds such as the Petit Basset Griffon Vendeen.
- Secondary glaucoma
    - Lens luxation, chronic uveitis, intraocular neoplasia, may cause secondary glaucoma

Treatment of glaucoma

- Emergency treatment:
    - Mannitol solution i/v @ 1g/kg (=10mls/kg of 10% mannitol solution)
- Dorzolamide (Trusopt) or brinzolamide (Azopt)

Used 3x to 4x daily. A topical carbonic anhydrase inhibitor that reduces formation of aqueous humour in the ciliary body. Minimal systemic side-effects

- Latanaprost (Xalatan) or travaprost (Travatan)
    - Used once or twice daily. A prostaglandin analogue that increases aqueous humour outflow via an alternative drainage route to the iridocorneal drainage angle. Also causes intense miosis. NB Latanoprost/travoprost are contra-indicated in some types of glaucoma (eg secondary to lens luxation, glaucoma associated with uveitis) so should only be used when the cause of the glaucoma has been established. In general, I would recommend referral of all glaucoma cases to an ophthalmologist to determine the initiating cause
- Analgesia (eg systemic carprofen 2mg/kg BID)
- Treat underlying cause if secondary glaucoma
- Surgical management
    - Laser ablation of ciliary body will control glaucoma and retain vision in some cases. Cryosurgical ablation will control glaucoma but usually does not retain vision. Drainage implants can also be used. Seek specialist advice regarding these
    - Endolaser photocoagulation is a new technique that shows promise but is expensive and can cause severe complications
- If the eye remains blind and painful, enucleate it

Other anti-glaucoma medical treatments available:

Systemic carbonic anhydrase inhibitors (CAI's) (acetazolamide, dichlorphenamide) can have severe side-effects. They have now superseded by topical CAI's. Pilocarpine constricts the pupil to increase the size of the iridocorneal drainage angle. Now largely superseded by newer medications such as latanaprost. Timolol is a topical beta-antagonist which reduces aqueous humour formation. Useful in feline glaucoma, less effective in dogs.

LENS LUXATION

Lens luxation is an inherited condition most commonly affecting terrier breeds, although it is recognised in a wide number of other breeds. A genetic test is available and should be encouraged in breeding animals. Anterior lens luxation is a surgical emergency and urgent referral for lensectomy is indicated.

Although usually presenting unilaterally, it is a bilateral condition and the contralateral eye usually shows signs such as iridodonesis ('iris wobble'), aphakic crescent, or vitreal presentation (wisps of vitreous emerging between the lens and the iris).

In some cases, posterior lens luxation can be managed medically with long term miotics (eg travaprost BID).

CORNEAL ENDOTHELIAL DEGENERATION

This is an age-related degeneration of the corneal endothelial pump mechanism, leading to slowly progressive corneal oedema (it is also recognised as a breed-related condition in the Boston terrier). It can mimic glaucoma or anterior uveitis because of the corneal oedema, but intraocular examination is normal in this condition. It can be managed by topical hyperosmotic agents such as 5% NaCl, although some dogs may not tolerate this.

Corneal Ulceration

Corneal ulceration develops when there is a breach in the epithelial layer, exposing the underlying stroma and sensory nerve endings. Causes include:

- Traumatic injury
- Foreign body
- Infectious (feline herpesvirus-1)
- Topical irritants (acid, alkali, dust, smoke, heat)
- Secondary to existing ocular or periocular disease
    - Eyelid defects
    - Blink disorders
    - Tear film defects
    - Anatomical eg brachycephalics
    - Intraocular disease
- Spontaneous Chronic Corneal Epithelial Defects (‘indolent’ epithelial erosion)

Management of corneal ulcers consists of assessing the depth (the key question being ‘is the ulcer deep enough to warrant surgical intervention?’), identifying and correcting any underlying cause, and managing the ulcer depending on the above. Assessing corneal thickness is most accurately achieved by use of a slit lamp. However, as a rule of thumb, if there appears to be any depth to an ulcer then it should be considered potentially deep and specialist advice should be sought.

Shallow corneal ulcers can be treated medically (appropriate topical antibiotic, systemic analgesia, lubricants if indicated) but regular monitoring is required and any underlying cause should be identified and treated.

- Contact bandage lenses are helpful for pain relief but are contra-indicated if infection is present and in keratoconjunctivitis sicca. They should be avoided in deeper ulcers where surgical treatment is more appropriate
- Third eyelid flaps, whilst somewhat out of fashion for many ophthalmologists, do have their place in the treatment of shallow, non-infected corneal ulcers but should be avoided in deep, infected or progressive ulcers
- Despite recent intense marketing drives, there is no evidence of the benefit of topical cross-linked hyaluronic acid (Remend) in the treatment of canine or feline corneal ulcers
- Topical serum is useful for 'melting' corneal ulcers, but there is little evidence of its benefit in other types of corneal ulceration.
- Topical ketorolac trometamol 0.5% (Acular eye drops) is an effective analgesic in human patients. In veterinary patients it is a good topical anti-inflammatory agent but its analgesic effects appear minimal, and it should be borne in mind that all multi-dose vials contain preservatives and stabilizers that can damage the corneal epithelium. Owner compliance need also be considered.
- Topical local anaesthetics (eg proxymetacaine drops) are excellent analgesics but should only used for examination or for short procedures (eg corneal scrapes, swabs, debridement). They are epitheliotoxic so should not be used as part of a treatment regime.
- **Debridement and grid or punctate keratotomy is not a general treatment for corneal ulcers and should only be used for one type of corneal ulcer; a Spontaneous Chronic Corneal Epithelial Defect (SCCED)- see below**

Deeper ulcers (> half-depth) may warrant surgical intervention. Options include conjunctival grafting, corneo-conjunctival transposition (CCT) grafting, or the use of material such as A-Cell or amniotic membrane.

SCCED (Indolent corneal erosion)

One of the most common and stubborn fallacies in veterinary practice is the belief that if a corneal ulcer is failing to heal satisfactorily it should be debrided or gridded in order to stimulate healing. Most ophthalmologists are mystified as to who is perpetuating this myth (if you know, please let on) but it is one that should be dispelled. **Debridement and grid keratotomy are procedures that should be reserved for one particular type of corneal ulcer in dogs, and one type only: the spontaneous chronic corneal epithelial defect (SCCED).** Alternative terms for this condition include non-healing ulcer, under-run ulcer, refractory ulcer, persistent corneal erosion, recurrent epithelial erosion, basement membrane epithelial dystrophy, Boxer ulcer.

A typical SCCED is:

- Seen in middle-aged to older dogs (hardly ever in young dogs)
- Seen in any breed of dog, including mixed breeds, although some breeds may be over-represented (eg Boxer)
- Superficial, involving the epithelium only (no stromal involvement)
- Surrounded by non-adherent epithelium
- Usually, but not exclusively, located in the axial or paraxial cornea
- Non-infected
- Associated with varying signs of discomfort
- Non-vascularized early in its course, becoming vascularized in time (NB the blood vessel response that aids healing of stromal ulcers is ineffective for SCCEDs and often complicates treatment, especially surgical intervention)
- Non-responsive to medical management
- Responsive to surgical management

Pathology of SCCEDs

In the normal cornea, epithelial basal cells are firmly attached to the underlying basement membrane (BM) by hemidesmosomes that attach to BM anchoring fibrils. The anchoring fibrils (composed of type VII collagen) aggregate to form strap-like molecules that penetrate deep (up to 2um) into the anterior stroma, where they branch and attach to anchoring plaques (composed of laminin and type 1 collagen). The entire complex (hemidesmosomes, anchoring fibrils, BM, anchoring plaques) is termed an adhesion complex. An adhesion complex is so strong that when epithelial erosion occurs the BM is usually left intact on the stromal surface. This allows rapid epithelial regeneration and hemidesmosome re-attachment.

In SCCED, pathological abnormalities that have been described include:

- An abnormal epithelial basal cell layer, with reduction in hemidesmosome numbers
- Reduced levels of epithelial-expressed factors involved in epithelial migration (E-cadherin, beta-cadherin, beta-actin, desmoplakin)
- A poorly-defined or absent BM and adhesion complexes
- Abnormal maturation and thickness of surrounding epithelium
- Stromal abnormalities including fibroplasia, vascularization and leukocyte infiltration
- Formation of a thick (4.4um) acellular layer of hyalinized collagen on the surface of the anterior stroma
- Abnormal corneal innervation, with altered levels of substance P

The last two abnormalities do not develop in experimental dogs subjected to chronic epithelial debridement, implying that they may play a primary role in the pathophysiology of the condition, rather than be a consequence of chronic erosion.

WORK-UP OF SCCEDS

Don't forget a detailed ophthalmic examination of both eyes to check for any underlying conditions such as KCS, distichiasis, ectopic cilia, entropion etc

TREATMENT

SCCEDs rarely heal spontaneously or with topical antibiotic therapy alone. Surgical options include:

- Debridement alone (approximately 50% healing rate)
- Debridement followed by grid or punctate keratotomy (approximately 70% healing rate)
- Debridement followed by phenol cautery and saline flushing (no studies of healing rate, but anecdotal reports suggest around 70%)
- Diamond burr debridement (90% success rate according to one study, in combination with bandage contact lens placement)
- Superficial keratectomy (approximately 100% healing rate)
    1. In contrast to the first three procedures, superficial keratectomy requires general anaesthesia and the use of an operating microscope, and should be performed by an ophthalmologist. It has an excellent success rate, but can create moderate corneal scarring. This is especially so in chronic cases where corneal neovascularisation is present. To reduce this, early surgical intervention is advised if possible.

NB Keratotomy, diamond burring or superficial keratectomy performed on a cornea that already has a marked neovascularisation response can lead to a dramatic and severe excess granulation tissue response that may take weeks to resolve (although it will resolve with topical ciclosporin ointment).

In summary:

- **DEBRIDEMENT AND GRID (OR PUNCTATE) KERATOTOMY SHOULD BE USED** ONLY **FOR SCCEDs**
- **THEY ARE NOT A GENERAL TREATMENT FOR ULCERS AND SHOULD NEVER BE USED ON DEEPER (STROMAL) ULCERS**
- **IN CATS, DEBRIDEMENT IS INDICATED FOR UNDERRUN SHALLOW CORNEAL ULCERS, BUT GRID KERATOTOMY SHOULD BE AVOIDED AS IT CAN PREDISPOSE TO CORNEAL SEQUESTRUM FORMATION**

'MELTING' CORNEAL ULCERS

Acute stromal collagenolysis (liquefactive stromal necrosis) describes a rapid and progressive corneal melt that should be treated as a medical and/or surgical emergency. It can occur when an existing epithelial erosion or ulcer:

- Becomes infected with a bacterium that releases proteases
- Is treated with topical corticosteroids

Corneal melts may also be associated with chemical injuries (especially alkali burns) and, rarely, insect bites.

The bacterial species most commonly isolated from corneal melts are *Pseudomonas aeruginosa* and beta-haemolytic streptococcus. They release a variety of proteolytic enzymes that dissolve the corneal stroma and lead to progressive deepening of the ulcer. Topical corticosteroids induce corneal melts by activating release of endogenous proteases (matrix metallo-proteases, MMP's) from keratocytes and neutrophils.

Signs of an early corneal melt include:

- A corneal ulcer with an ill-defined gelatinous rim, which may be grey, white or yellow
- Increasing ocular discomfort
- Progression from serous to mucopurulent ocular discharge
- Progressive deepening of the ulcer
- Secondary uveitis (miosis and iris hyperaemia)

Work-up and treatment

Melting ulcers should be classed as an emergency. Immediate referral should be considered. If not, animals should be hospitalised and carefully monitored. If this is not possible, then it is vital that the owner returns for regular (*at least* daily) check-ups, and is made aware of the risk of sudden globe rupture.

A typical work-up would consist of:

- History-taking (including prior ophthalmic disease, use of topical corticosteroids, exposure to chemicals)
- Thorough eye examination. Proceed carefully if the ulcer is deep. If there is a risk of imminent globe rupture it may be necessary to omit certain procedures such as STT or tonometry
- PH testing of conjunctival fornices if there is a history of acid or alkali exposure
- Fluorescein staining
- Conjunctival or corneal swab under topical anaesthesia (care!). In-house cytology can be used to identify bacterial rods or cocci, which may help in selection of antibacterials. The swab can also be sent for bacterial culture and sensitivity, which may be of retrospective use

Medical treatment consists of:

- Autologous serum q30-60mins. This has broad-spectrum anti-protease activity to help to stop the melt
- Topical antibacterials. Because the antibiotic sensitivity of the two main bacterial causes of melts are so different, it is important to identify which bacteria, if either, is present. DiffQuik stains can be used to look for the presence or rods (Pseudomonas) or cocci (beta-haemolytic strep). Fluoroquinolones such as ciprofloxacin and ofloxacin have good activity against Pseudomonas, but streptococci are often resistant. Beta-haemolytic streptococcus may be sensitive to chloramphenicol. As well as performing an in-house DiffQuik, send a swab for bacterial culture/ sensitivity ('eye panel') and be prepared to switch antibiotics depending on the sensitivity results
- Systemic antibacterials - beta-haemolytic streptococcus is usually sensitive to cephalosporins, and cephalexin is secreted in the tear film, making this a good choice for such infections
- Systemic NSAID's
- Other drugs that may have anti-protease activity and might be considered include topical acetylcysteine, topical EDTA, systemic tetracycline and vitamin C
- If the melt is due to an alkali burn, then copious irrigation of the corneal surface should be performed until the normal pH (around pH7.5) has been restored. Specialist advice should be sought.

Surgical intervention is often required, most commonly conjunctival grafting. Conjunctival pedicle, bridge, hood and 360^{o} grafts may be used. Conjunctival grafts not only give physical support to the weakened cornea, but also provide a blood supply, thus allowing direct access by serum anti-collagenases and systemically administered antibacterials.

A note on brachycephalics

These breeds are at high risk of corneal ulceration and are predisposed due to a combination of reasons:

- Reduced corneal sensation
- Reduced blink rate
- Shallow orbit / exophthalmos
- Medial trichiasis

When treating a corneal ulcer in such a breed, it is important to monitor it carefully since it may progress rapidly

- Topical antibiotics (chloramphenicol) plus frequent lubrication
- Frequent rechecks
- Seek advice or refer if the ulcer:
    - Is deep
    - Progresses/ deepens
    - Fails to heal
    - Is recurrent
    - Is associated with exposure keratitis, entropion or poor blink

In many cases, surgical intervention is necessary. In addition to surgical treatment of the ulcer, we will often attempt to reduce future risk by performing medial canthoplasty surgery to reduce the length of the palpebral fissure, improve tear coverage and reduce trichiasis,

When to refer a corneal ulcer

Consider referral to an ophthalmologist (or seek telephone advice) when a corneal ulcer is:

- Not responding to appropriate treatment
- Getting deeper
- Melting
- Down to Descemet's membrane
- Accompanied by significant corneal oedema
- Ruptured
- Likely to require microsurgery
- Attached to a pug!