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Ophthalmology Case Challenges Mini Series

Session 3: Uveal Tract: Case Presentations

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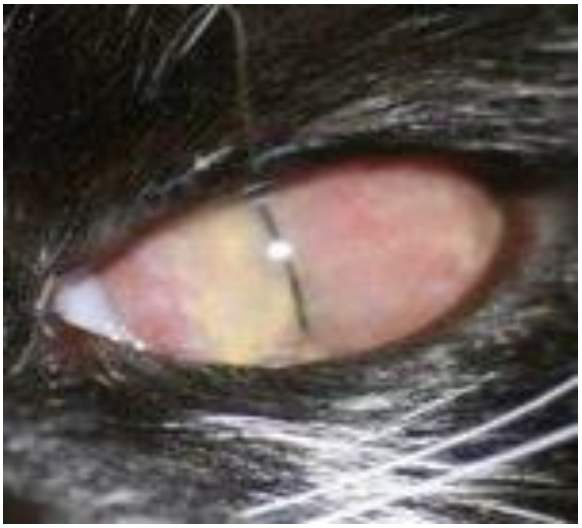

The Uveal Tract

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Anatomy and physiology

Iris

The iris divides the anterior segment of the eye into anterior and posterior chambers, which communicate via the pupil. Grossly, it consists of a central pupillary zone and a peripheral ciliary zone, separated by the iris collarette.

Histologically, the iris consists of three layers: an anterior border layer, a stromal and sphincter muscle layer, and a posterior pigmented epithelial layer.

- The *anterior border layer* consists of a sheet of fibroblasts above one or two layers of melanocytes.

- The *stromal layer* is composed of collagen, fibroblasts, blood vessels, nerves and melanocytes. Iris colour varies depending on the amount and type of pigmentation and degree of vascularisation. The iris constrictor muscle (sphincter muscle) is concentrated around the pupil and consists of smooth muscle innervated by parasympathetic nerve fibres
    - The anatomy of this parasympathetic nerve supply varies between the dog and cat. In the cat, the short ciliary nerve divides into lateral (malar) and medial (nasal) branches to innervate the sphincter muscle. In the dog, however, there are multiple branches around the pupil. This anatomical variation helps to explain the phenomenon of hemi-dilated pupil ‘(D-shaped’ or ‘reverse D-shaped’ pupil) which is seen in some feline conditions but is not recognised in dogs.

- The *posterior pigmented epithelial layer* consists of two layers of pigmented epithelium. The outer layer is really myoepithelium, forming the iris dilator muscle that extends from the iris sphincter to the peripheral iris, innervated by sympathetic nerve fibres. The posterior layer is densely pigmented.

Ciliary body

The ciliary body is divided into the pars plicata (ciliary processes) and the pars plana.

- The ciliary processes produce aqueous humour and play a role in visual accommodation. They consist of a double layer of epithelium overlying a central core of stroma, blood vessels and muscle. The ciliary epithelium produces aqueous humour and contributes to the blood aqueous barrier. Beneath the ciliary processes, the main mass of the ciliary body consists of smooth muscle in mammals. The ciliary body musculature mediates the process of accommodation.

- The pars plana extends from the posterior edge of the ciliary processes to the anterior termination of the retina (ora ciliaris retinae).

Choroid

The choroid can be divided into four layers:

- The suprachoroidea is the transition layer between the choroid and the sclera, and consists of loose layers of heavily pigmented connective tissue. It serves as a posterior drainage for the uveoscleral aqueous outflow.

- The large vessel layer consists of large veins and arteries.

- The medium sized vessel and tapetal layer lies internally to the large vessel layer. The tapetum is a reflective layer located in the dorsal portion of the choroid in dogs, cats and many other species. It is absent in diurnal species such as humans and pigs.

- The choriocapillaris is the innermost layer of the choroid, and forms a thin capillary layer adjacent to the retinal pigment epithelium, from which it is separated by Bruch's membrane. Its function is to supply blood to the outer retina, primarily the rod and cone photoreceptors

Selected conditions of the uveal tract

Glaucoma

This is 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:

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

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.

<u>Tonometry</u>

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) glaucoma
    - Abnormal formation of the iridocorneal drainage angle (goniodysgenesis)
    - 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

- 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 (although effects are cumulative). 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.

- Timolol (a topical beta blocker) is not particularly effective as a solo agent but may be in combination with a topical carbonic anhydrase inhibitor (eg timolol/ brinzolamide 'Azarga' or dorzolamide/ timolol 'Cosopt' TID). Timolol is a reasonable choice for treatment of glaucoma in cats, but be careful with possible cardiac side effects.

- Analgesia (eg systemic NSAIDs, systemic opioids)

- 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, but has now been largely superseded by newer medications such as latanaprost.

Anterior uveitis

Inflammation of the anterior uvea (iris and ciliary body) must be recognised early since, as well as being a painful condition, it may lead to blindness if treatment is not instigated rapidly.

Signs of anterior uveitis are summarised in the table below:

Acute anterior uveitis	Subacute /chronic anterior uveitis
Ocular pain Episcleral hyperaemia Corneal oedema Iris swelling Iris hyperaemia (rubeosis iridis) Miosis (pupil constriction) Aqueous flare	Keratic precipitates (deposits on corneal endothelium) Iris hyperpigmentation (darkening) Synechiae formation (iris adhesions) Ectropion uveae (eversion of pupil margin) Dyscoria (abnormal pupil shape)

Signs such as hypopyon (pus in anterior chamber) or hyphaema may also develop. Sequelae of chronic anterior uveitis include cataract, glaucoma, lens luxation and retinal detachment.

Since the ciliary body is contiguous with the choroid, anterior uveitis may also be associated with posterior uveitis (chorioretinitis) and therefore fundus examination should always be performed when examining a patient with suspected anterior uveitis.

Infectious and non-infectious causes of uveitis in dogs and cats are listed below:

Non-infectious causes of uveitis	
Cause	Examples
Traumatic	Blunt or penetrating injury
Reflex uveitis	Secondary to corneal ulceration/ corneal insult
Lens-induced	Phacolytic (rapidly growing or hypermature cataracts) Phacoclastic (lens capsule rupture)
Vaccine reaction	Eg adenovirus vaccination in dogs (CAV-2 vaccine)
Autoimmune disease	Uveodermatological syndrome (UVD), others
Systemic disease	Toxaemia, bleeding disorders, diabetes mellitus, hyperlipidaemia, systemic hypertension, granulomatous meningoencephalomyelitis (GME), systemic histiocytosis
Neoplasia, or secondary to intraocular disease	Lymphoma Intra-ocular tumour Local invasion from extra-ocular tissues Metastatic disease Secondary to glaucoma, lens luxation, other intraocular disease

Infectious causes of uveitis		
Agent	Dogs	Cats
Viral	Canine distemper Canine adenovirus (CAV-1) Canine herpes virus-1 Rabies	Feline coronavirus (feline infectious peritonitis, FIP) Feline Immunodeficiency Virus (FIV) Feline Leukaemia Virus (FeLV) Feline Herpes Virus (FHV-1)
Bacterial	Penetrating inoculation Bacterial septicaemia *Leptospira* spp. *Ehrlichia canis* *Ehrlichia platys* *Borrelia burgdorferi* *Brucella canis*	Penetrating inoculation Bacterial septicaemia *Bartonella henselae* *Mycobacterium* spp
Protozoal	*Toxoplasma gondii* *Neospora caninum* *Leishmania donovani*	*Toxoplasma gondii* *Leishmania donovani*
Mycotic/algal	*Blastomyces dermatiditis* *Histoplasma capsulatum* *Cryptococcus neoformans* *Coccidiodes immitis* *Prototheca* spp.	*Cryptococcus neoformans* *Histoplasma capsulatum* *Blastomyces dermatiditis* *Coccidiodes immitis* *Prototheca* spp.
Parasitic	*Angiostrongylus vasorum* *Toxacara canis* *Diptera* spp. *Dirofilaria immitis*	*Diptera* spp.

Investigation of anterior uveitis

Needless to say, it is imperative to identify and treat any underlying cause of uveitis. A detailed history should be obtained (including history of travel, exposure to possible infectious causes, previous and concurrent illnesses). Detailed ophthalmic examination of both eyes is needed to identify intraocular causes of uveitis or bilaterality of signs. A thorough general physical examination and neurological examination should be performed.

If a systemic cause is suspected then diagnostic work-up may include routine haematology and biochemistry, targeted serology/ PCR/ infectious disease testing and diagnostic imaging. Note that for Toxoplasma serology, IgM titres (indicating recent exposure) are indicated in addition to IgG.

Aqueocentesis (sampling of the aqueous humour) may be useful, and may be diagnostic in cases of ocular lymphoma (see later), but this technique carries some risk (exacerbation of uveitis, iatrogenic injury to the iris and lens) and specialist advice/referral may be advisable. PCR testing of aqueous humour samples for infectious diseases may be indicated depending on history and clinical signs (eg for feline coronavirus in suspected FIP uveitis). Faecal analysis may be indicated if *A. vasorum* is suspected in dogs.

Treatment of anterior uveitis

Since a large component of anterior uveitis (regardless of aetiology) is immune-mediated damage to intraocular structures, **anti-inflammatory medication is always indicated**:

- Topical corticosteroids (e.g. prednisolone acetate)
    - Check no corneal ulceration first. Initially apply e.g. 4x-6x daily until uveitis settles, then a gradually tapering dose (e.g. 3x daily for 1 week, twice daily for 1 week etc). Caution in diabetic dogs as it may affect diabetic control

- Topical NSAIDS (e.g. ketorolac trometamol)
    - Useful if corneal ulceration is present or in diabetic animals. Dose as for topical corticosteroids

- Systemic anti-inflammatories
    - NSAIDs (e.g. carprofen or meloxicam)
    - Systemic corticosteroids are indicated in some cases (e.g. in uveitis due to autoimmune disease)

- Topical atropine
    - Use to effect (but never more than 4x daily and never for more than a few days) to dilate pupil and relieve painful ciliary body muscle spasm. N.B. can have severe systemic side-effects in small dogs, so may be best avoided in such cases. Topical atropine drops cause excess salivation/frothing in cats due to its bitter taste, so may be inadvisable in this species

- Topical antibacterials (eg chloramphenicol) if infectious bacterial cause is suspected

- Identify and treat any underlying cause

Posterior uveitis (chorioretinitis)

Active chorioretinitis causes reduced tapetal reflectivity, whilst inactive chorioretinitis causes increased tapetal reflectivity, sometimes with pigment disturbances.

Chorioretinitis has similar aetiologies to anterior uveitis (see previously). Detailed history taking, detailed physical and neurological examination, serum biochemistry and routine haematology is usually indicated. Depending on the differential diagnosis further investigations may be required, such as targeted serology (i.e. depending on the differential diagnoses), serum protein analysis, CSF analysis, diagnostic imaging. Specialist advice or referral may be indicated. Treatment depends on the cause.

Chorioretinitis may be seen in combination with optic neuritis. Optic neuritis causes acute blindness, and causes include:

- Meningitis
- Granulomatous Meningo-encephalomyelitis (GME)
- Toxoplasma/ Neospora
- Cryptococcus
- Canine distemper
- Lymphoma

Neoplasia of the uveal tract

Anterior uveal melanoma

Melanoma is the most common primary intraocular tumour of dogs and cats. It usually arises from the anterior uveal tract (iris or ciliary body); choroidal melanoma is rare. In both species, older animals are most commonly affected.

- In dogs, the majority of anterior uveal melanomas are benign, although 25% are malignant (Giuliano et al, 1999). It is worth noting, however, that both benign and malignant types are locally invasive, with fewer than 10% remaining inside the sclera.

Dogs with malignant anterior uveal melanomas have reduced survival time compared to those with benign melanomas

- Treatment options for localised iris masses in dogs include iridectomy and diode laser photocoagulation. Alternatively, regular monitoring is advised, with enucleation recommended if secondary signs develop, such as glaucoma or significant local invasion

- Feline anterior uveal melanoma is very aggressive, with local invasion and metastasis the norm. It has a reported metastatic rate of up to 63% (Patnaik and Mooney 1988). Feline anterior uveal melanoma carries a guarded prognosis, with a high risk of metastatic disease to lungs and liver
    - Differentiating feline anterior uveal melanoma from benign pigmentation (iris naevi or 'freckles', pigmentation secondary to chronic uveitis) can be difficult, since definitive diagnosis can only be made histologically. Clinical markers that increase the suspicion of malignancy include: Change in pupil shape or mobility, thickening of the iris stroma (assessed with slit-lamp biomicroscopy), pigment shedding, invasion of the iridocorneal drainage angle, increased IOP, enlargement of submandibular lymph nodes, systemic signs). Specialist assessment is advisable
    - If there is a high index of suspicion for malignancy, enucleation is indicated (with prior chest/ abdominal radiography and abdominal ultrasonography) and the globe must be sent for histopathological examination. Mitotic index rate is the most accurate marker for malignancy in anterior uveal melanoma.

<u>Ciliary body adenoma/ adenocarcinima</u>

Epithelial tumours of the ciliary body and iris (primarily ciliary body adenoma and adenocarcinoma) are the next most common primary intraocular tumours of dogs. The incidence ratio of adenoma to adenocarcinoma is 5:1 (Dubielzig et al, 1998). Middle-aged to older animals are predisposed.

- In dogs the metastatic potential of both adenoma and adenocarcinoma is extremely low, although metastasis to the lungs has been documented.

- Ciliary body tumours are rare in cats but are also usually benign.

- Regular monitoring is advised, with enucleation recommended if secondary signs develop, such as glaucoma or significant local invasion.

Intraocular sarcoma

This is a primary intraocular tumour of cats, in which previous ocular trauma is a major predisposing factor. Middle-aged to older cats are most at risk, and the time from traumatic injury to diagnosis of sarcoma averages 5 years. Secondary uveitis or glaucoma is common. The tumour is highly malignant, and both local invasion and metastatic disease are common.

Secondary anterior uveal tumours

With the exception of lymphoma, secondary intraocular tumours are uncommon. They may invade the eye by haematogenous spread or by local extension. Local extension is rare because the tough fibrous coat of the globe offers a formidable physical barrier, although intracranial tumours such as meningioma may invade the posterior segment via the optic nerve sheath.

Haematogenous spread accounts for most secondary tumours and these include, in order of decreasing frequency, lymphoma, haemangiosarcoma, mammary carcinoma or adenocarcinoma, osteosarcoma, and oral malignant melanoma, amongst others. Of these, lymphoma is by far the most common. In one study, 37% of dogs with lymphoma had ocular involvement, making ocular disease the second most common presenting sign of lymphoma after lymphadenopathy (Krohne et al, 1994). Anterior uveitis and intraocular haemorrhage were the most common findings.

- In dogs, lymphoma with ocular involvement carries a poor prognosis and indicates stage V disease. Dogs presenting with ocular involvement have a life expectancy 60-70% that of dogs presenting without ocular signs (Krohne et al, 1994).
- Ocular involvement is also common in feline lymphoma, characterised by infiltration of tumour cells into the uveal tract and cornea. Anterior uveitis and secondary glaucoma is common.

- We will routinely perform aqueocentesis on cases of uveitis and have recently reported that around 9% of dogs and 20% of cats presenting with ‘idiopathic’ uveitis have neoplasia (most commonly lymphoma). It is important the topical corticosteroids are not given prior to aqueocentesis sampling as this can affect diagnosis (Linn-Pearl et al 2014).

References and further reading

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