

Uveitis in dogs

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This article, the first in a two-part series on uveitis in small animals, reviews the general pathogenesis of this condition and discusses its common causes as well as diagnosis and treatment in dogs.

INTRODUCTION

The uveal tract is the middle vascular region of the eye and comprises the iris, ciliary body and choroid. The iris is composed of an anterior border, connective tissue stroma, muscle fibres (sphincter and dilator), nerves and a posterior pigmented epithelium. The ciliary body is located behind the iris and produces aqueous fluid. The choroid is the vascular layer behind the retina (essential in providing nutrients to, and in removing waste products from, the retina).

Uveitis is a heterogenous group of diseases characterised by acute, recurrent, or chronic inflammation of the uveal tract, and is one of the most common causes of blindness in small animals. It is classified according to the affected anatomical segment of the tract, and can be **anterior** (involving the iris), **intermediate** (involving the ciliary body) and **posterior** (involving the choroid). **Panuveitis** refers to inflammation in all parts of the tract. Since the different regions of the uveal tract are continuous, inflammation commonly involves more than one segment of the tract, although clinically only one region may be visibly inflamed.

PATHOGENESIS

The consequences of ocular inflammation, whether appropriate (immune response to infectious agents) or inappropriate (immune-mediated or allergic responses), may be vision threatening. The normal eye is anatomically structured to provide an immunoprivileged environment to avoid this. Regulation of immunity within this privileged microenvironment involves a dynamic interaction of **anatomical**: blood-ocular barriers (BOB), including the blood-aqueous barrier (BAB) and blood-retinal barrier (BRB), **cellular** (B and T lymphocytes), and **soluble** factors (immunosuppressive neuropeptides in aqueous humour) that together act to suppress inflammation.

Infectious and immune mechanisms can trigger breakdown of this immunity, however, resulting in sight impairing inflammatory eye diseases such as uveitis. These mechanisms involve a complex array of

cells and inflammatory mediators, with activation of resident cells in the eye and recruitment of inflammatory cells. Chemical mediators from the arachidonic acid cascade (including prostaglandins and leucotrienes) are formed and contribute to enhanced vascular permeability and pathophysiological responses. The concomitant accumulation of inflammatory mediators (such as platelet-activating factor, interleukin-1, and tumour necrosis factor) in the uveal tract leads to extension of the intraocular inflammatory response and cellular damage. Free radicals generated by white blood cells and resident cells also contribute to the damage.

CAUSES OF UVEITIS

Since intraocular inflammation is largely mediated by vascular damage, the rich blood supply of the uvea makes it a natural target for diseases, infectious or neoplastic for example, originating elsewhere in the body. Specific immune-mediated conditions can also result in ocular involvement (Table 1) due to the vascular nature of the uveal tract, with inflammation and necrosis resulting from vascular deposition of immune complexes and subsequent activation of complement. Regardless of the aetiology, however, it should be remembered that all cases of uveitis are driven by the host's immune response and that this aggressive response produces much of the intraocular pathology. In many cases of uveitis, however, an underlying cause is not definitively identified and such cases are diagnosed as idiopathic.

Uveitis can therefore arise secondary to many diseases, and can be classified by pathogenesis (Table 1):

Exogenous causes (external to the eye) include **ocular trauma** and **corneal ulceration** (corneal injury may produce neurogenic reflex uveitis due to stimulation of inflammatory mediators from the ophthalmic branch of the trigeminal nerve from the cornea).

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Endogenous causes (from within the eye, or associated with systemic disease or haematogenous dissemination) include lens-induced uveitis, infectious

agents (numerous organisms are implicated, depending on geographical location), **systemic/metabolic disease, specific immune-mediated**

TABLE 1: Causes of canine uveitis

EXOGENOUS CAUSES	
Ocular trauma:	Penetrating injury Blunt injury
Corneal ulceration:	May cause neurogenic reflex anterior uveitis
ENDOGENOUS CAUSES	
Infectious causes (vary according to geographical location):	
Viruses	Canine adenovirus-1 Canine distemper virus Canine herpesvirus Rabies virus
Bacteria	<i>Leptospira</i> spp. <i>Borrelia burgdorferi</i> <i>Brucella</i> spp <i>Mycobacterium</i> spp <i>Bartonella</i> spp.
Protozoa	<i>Toxoplasma gondii</i> <i>Leishmania donovani</i> <i>Neospora caninum</i>
Rickettsia	<i>Ehrlichia</i> spp. <i>Rickettsia rickettsii</i>
Fungi	<i>Cryptococcus neoformans</i> <i>Blastomyces dermatitidis</i> <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i> <i>Aspergillus</i> spp <i>Candida</i> spp <i>Acremonium</i>
Algae	<i>Prototheca</i> spp.
Parasites	<i>Angiostrongylus vasorum</i> <i>Toxocara canis</i> <i>Dirofilaria immitis</i> spp <i>Diptera</i> spp
Systemic/Metabolic disease	Septicaemia/toxaemia (e.g. pyometra) Hypertension Diabetes mellitus (Hyperlipidaemia is not causative but can be responsible for the lipid laden aqueous seen with uveitis)
Immune-mediated	
Immune-mediated vasculitis	
Immune-mediated thrombocytopaenia	
Uveodermatological syndrome	A specific immune-mediated reaction against pigmented cells in the uvea and skin that produces panuveitis and dermal depigmentation in the Siberian Husky and Akita breeds especially.
Neoplasia	Primary ocular tumours (melanoma, ciliary body tumours) Local invasion of extraocular tumours Lymphoma Metastatic disease
Lens-induced	Phacolytic Phacoclastic
Toxic/drug-induced	Potentiated sulphonamides (possible immunogenetic predisposition in Doberman Pinschers) Intraocular miotic agents (e.g. pilocarpine)
Circulatory	Polycythaemia Hypergammaglobulinaemia
Genetic	Golden Retriever pigmentary uveitis (associated with iridociliary cysts)
Idiopathic	Diagnosis by exclusion of above causes Likely immune-mediated

conditions (such as uveodermatological syndrome, Fig. 1), **neoplasia** (Figs. 2 and 3), **vascular diseases** and **toxins**.

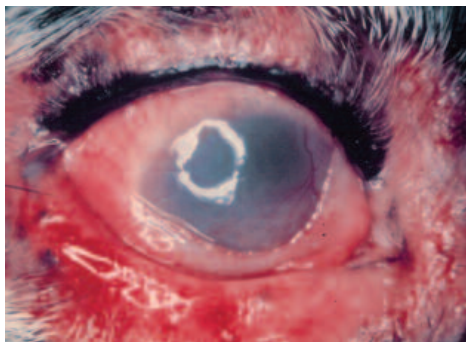


Fig. 1: Uveodermatological syndrome in a dog. Severe blepharitis and depigmentation, conjunctival hyperaemia, corneal oedema and vascularisation are all typical signs of this severe immune-mediated form of uveitis.

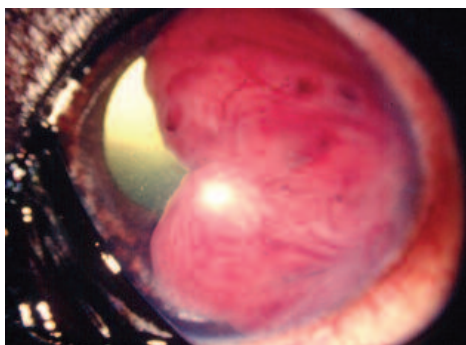


Fig. 2: Medulloepithelioma of the ciliary body in a dog. This congenital type of tumour affects young animals and steadily increases in size over time. It is locally invasive, but does not metastasise.

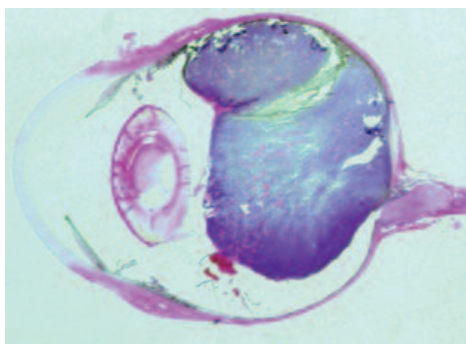


Fig. 3: Choroidal melanoma. A histopathological section of a canine globe showing a large tumour arising from the posterior uveal tract and expanding the posterior segment of the eye.

LENS-INDUCED UVEITIS

Lens-induced uveitis (LIU) is a well-recognised condition in veterinary ophthalmology. This naturally occurring disease results from an immune-mediated reaction and represents an inflammatory response of the uvea to lens proteins that leak into the anterior chamber. Although the lens proteins are the animal's own tissue, they are enveloped by the lens capsule and therefore have never been exposed to the host's immune system. When released into the anterior chamber, the body therefore detects these as foreign and antigenic and incites an inflammatory

reaction. LIU predominantly affects the anterior uvea and is divided into two forms:

Phacoclastic uveitis

Phacoclastic uveitis involves a response to lens proteins released after lens capsule rupture (spontaneous or traumatic). This can arise secondary to any penetrating eye injury that perforates the lens capsule, but is commonly associated with cat-scratch corneal injury. Blunt trauma may also cause capsular disruption. Subsequent to trauma or any other cause of uveitis, BOB breakdown results in production of a plasmoid (protein-rich) aqueous humour. Glaucoma is a common sequel to phacoclastic uveitis as inflammatory mediators liberated into the eye ultimately lead to a cascade of events culminating in changes in the iridocorneal angle: resultant inflammatory cell infiltrates and pre-iridal fibrovascular membranes cause obstruction of the angle, impeding aqueous fluid outflow and peripheral anterior synechiae (adhesions between the peripheral iris and corneoscleral region) may also further contribute to blockage of the angle.

Phacolytic uveitis

Phacolytic uveitis involves a response to gradual leakage of solubilised lens protein through an intact lens capsule of a hypermature cataract. Miniature Poodles and Toy Poodles are commonly affected breeds.

CLINICAL FINDINGS

Like any other inflammatory event in the body, intraocular inflammation is characterised by severe pain. Prostaglandins act directly on the ciliary body muscle and the iris sphincter, causing miosis and constriction, with subsequent severe ocular discomfort. Blepharospasm, increase in blinking rate, photophobia, third eyelid protrusion and ocular discharge are common pain-related signs in the uveitic dog (Table 2). Ocular redness, namely

TABLE 2: Clinical signs of uveitis

Anterior uveitis	Blepharospasm/photophobia Third eyelid protrusion Tearing/discharge Conjunctival hyperaemia Ciliary flush Miosis/anisocoria Iris hyperaemia/neovascularisation Iris swelling Iris thickening Changes in iris colour/shape Aqueous flare Keratic precipitates Hypopyon Hyphaema Decreased IOP
Posterior uveitis	Vitreous opacities/haemorrhages Chorio-retinal exudates Granulomas Retinal haemorrhages Retinal detachment Optic neuritis

conjunctival hyperaemia and ciliary flush, are caused by vasodilation (Fig. 4). The latter refers to the dilation and engorgement of the deep anterior ciliary vessels, located in close proximity to the limbus.

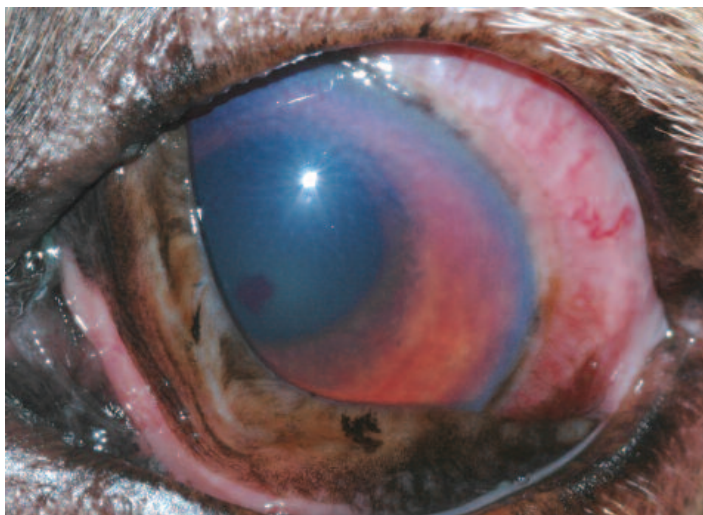


Fig. 4: Diffuse conjunctival hyperaemia, corneal oedema, miosis, iris congestion and a minor blood clot on the corneal endothelium in a dog with anterior uveitis.

In cases of unilateral uveitis, anisocoria with miosis of the affected pupil will ensue. Examination in a darkened room with the aid of a penlight is usually helpful in identifying pupillary constriction. The iris may also be affected by infiltration of inflammatory or neoplastic cells with iris swelling, change in iris colour (generally darker) and shape. Vascular congestion from dilation of the iris major arterial circle is usually present, but rarely visible clinically, unless present in dogs with blue irides.

As a result of the breakdown of the BAB, the inflow of plasma proteins and inflammatory cells into the anterior chamber gives rise to aqueous flare, or turbidity of the aqueous humour. A light source, usually from the smallest spot of a direct ophthalmoscope and directed through the anterior chamber, will be scattered by material present there (Tyndall phenomenon, also visible using the slit biomicroscope). The effect is similar to that of car headlights flashing through a foggy night. Various degrees of aqueous turbidity may be present, and

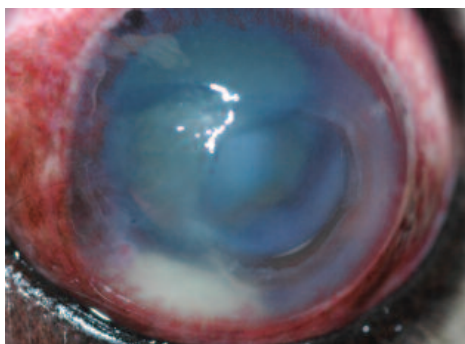


Fig. 5: A collection of inflammatory cells (hypopyon) is visible through the cornea in the ventral anterior chamber, due to uveitis secondary to a large melting ulcer on the central cornea. Conjunctival hyperaemia, corneal oedema and vascularisation are also present.

accumulations of inflammatory cells and fibrin can also be visible as small pigmented spots on the corneal endothelium. These accumulations, also known as keratic precipitates, are usually located ventrally due to the presence of convection currents in the anterior chamber and thus may be overlooked. Hypopyon and hyphaema are accumulations of inflammatory cells or blood respectively, typically in the ventral anterior chamber, and represent the most severe signs of BAB breakdown (Fig. 5). Hyphaema is not a feature of uveitis only, but could also result from ocular trauma, neoplasia, systemic hypertension and clotting or platelet disorders. Corneal oedema is also a typical sign of anterior uveitis, and is caused by damage to the corneal endothelial cells.

In uveitis, aqueous humour production by the ciliary body is usually impaired, while the uveoscleral outflow may be increased by the action of prostaglandins, with resultant ocular hypotony, or low intraocular pressure (IOP). In cases of chronic uveitis, drainage of the aqueous humour may be impaired by the presence of inflammatory cells and debris, leading to increased intraocular pressure and secondary glaucoma. In more severe and long-standing uveitis cases, often with secondary glaucoma or from traumatic causes, phthisis bulbi, or irreversible shrinking of the globe, may follow. Possible sequelae of chronic uveitis are listed in Table 3 (Fig. 6).

TABLE 3: Sequelae of chronic uveitis

Anterior and/or posterior synechiae
Iris atrophy
Cataract
Lens luxation
Pre-iridal fibrovascular membranes
Iris bombe
Secondary glaucoma
Focal/diffuse chorio-retinal degeneration



Fig. 6: Sequelae of chronic uveitis in the dog: dyscoria (irregular pupil shape), a large lateral posterior synechia, pigment dispersion on the anterior lens capsule and mature complete cataract.

Intermediate (cyclitis) posterior uveitis (choroiditis or chorioretinitis) present with other clinical findings. Vitreous cloudiness/flare may occur in a similar

fashion to aqueous flare, and its presence usually impairs the ability to clinically evaluate the posterior segment and the retina. Since retina and choroid are intimately associated, choroidal inflammation usually involves the retina and vice versa. Again, as a result of BRB breakdown, inflammatory or neoplastic cells, exudates or infectious agents are allowed into the retina and the sub-retinal space, resulting in chorioretinal effusions, granulomas, retinal and vitreal haemorrhages, retinal detachment and optic nerve oedema. Obviously, impaired vision or blindness follows. Almost all of these signs are usually characterised by the presence of darker and thicker areas of retinal hyporeflectivity (Fig. 7), due to the fact that the areas of increased retinal thickness absorb more light and will look duller at ophthalmoscopy. With time and in chronic cases, retinal degeneration may be present as diffuse or localised hyperreflective lesions, which in this case is explained by the fact that more light is now allowed through a thinner retina and reflected back to the observer by the tapetum.

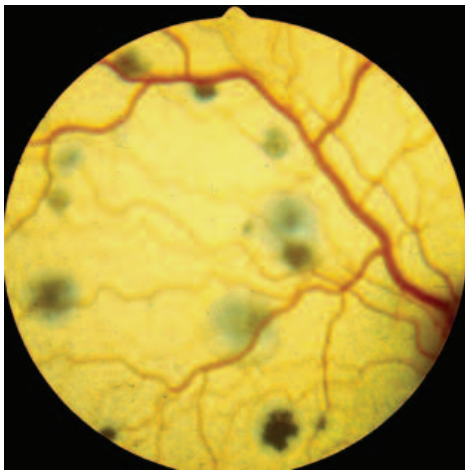


Fig. 7: Canine fundus. The dorsal tapetum shows several hyporeflective areas of different size, indicative of active chorioretinopathy. The dog was diagnosed with cryptococcal infection.

DIAGNOSIS

Uveitis is diagnosed on the basis of clinical ocular signs. A thorough ocular examination is therefore of paramount importance: careful examination and measurement of IOP are essential in diagnosing early uveitis. The use of the biomicroscope for diagnostic purposes is strongly recommended and allows easier and earlier clinical signs recognition. Fluorescein staining should also be performed to rule out the presence of corneal ulcerative lesions. Uveitis should be differentiated from other causes of ocular pain, redness or decreased vision, such as keratitis, conjunctivitis and glaucoma.

Collection of a thorough history and a general physical examination are mandatory, and further ancillary diagnostic tests are often performed to identify any possible primary systemic disease. CBC, serum chemistry panels, urinalysis, serology profiles, chest radiographs, abdominal ultrasound, blood pressure

measurement, lymph nodes or bone marrow aspirates/biopsy and faecal smears may often be required.

Sometimes, the severe cloudiness of ocular media may interfere with an accurate evaluation, in which case an ocular ultrasound examination can help identify the presence of posterior segment problems, such as retinal detachments or thickening, choroidal thickening, lens luxation, as a consequence or sometimes a cause of uveitis, or intraocular masses.

While aqueous paracentesis rarely succeeds in gaining helpful information, vitreal paracentesis may be considered when the eye is severely compromised. Culture and cytology of the material obtained are usually highly diagnostic for most systemic mycoses. Often, despite extensive diagnostic efforts, the primary cause remains unknown and the uveitis is classified as idiopathic.

TREATMENT

The mainstay of uveitis treatment is to control intraocular inflammation and pain, to address the specific cause and to remove or ameliorate any complicating agents or factors contributing to the disease.

Corticosteroids are considered the drug of choice. They inhibit vasodilation and vascular permeability, cellular chemotaxis, neovascularisation, collagen deposition and fibroblastic activity. At the ocular level, this translates into stabilisation of the BAB, with decreased exudation, scarring and cloudiness of the ocular media.

Corticosteroids should be applied topically in every case of uveitis, provided that the corneal surface is intact. Frequency of administration initially should be 4–6 times daily and then gradually tapered over the following weeks in line with improving clinical signs. Prednisolone acetate 1% and dexamethasone alcohol 0.1% are the most potent drugs for topical use, since their composition allows a better intraocular penetration than the water soluble preparations, such as phosphates and succinates. Systemic administration is often necessary in cases of severe inflammation, but contraindicated if mycotic or bacterial systemic diseases are present.

Nonsteroidal anti-inflammatories may be applied topically alone or synergistically with corticosteroids, two to four times daily or may be administered systemically. They inhibit the cyclooxygenase pathway, and their effects are similar to those of corticosteroids, although in their systemic application they may cause severe side effects, such as gastrointestinal haemorrhages and platelet inhibition, and are therefore more commonly used topically. As single agents they are useful when topical or systemic steroids are contraindicated, such as in cases of corneal ulceration or in diabetic patients, even though recent studies have discouraged their topical

use in cases of infectious keratitis. Also, caution is warranted in cases of pre-existent ocular or intraocular haemorrhages of unknown origin and in glaucoma patients.

Mydriatic-cycloplegic drugs, like atropine and tropicamide, act to relax the iris sphincter and ciliary body muscles, providing relief from pain and stabilising the BAB. They are usually applied one to three times daily, according to the severity of the inflammation and again tapered off in line with the clinical response.

Besides being treated with topical conventional anti-inflammatories, infectious uveitides need to be specifically addressed through systemic administration of the relevant anti-microbial agent, which may involve anti-fungal, anti-rickettsial, anti-viral or anti-protozoal treatment, according to the precise aetiology of the disease.

SUMMARY

Despite the many causes of uveitis in dogs, in practice only some are recognised. Many cases are considered idiopathic as a definitive aetiology is not always identified, and although infectious causes are documented, they are uncommon.

The second article in this series, to be published in the next issue, will review uveitis in cats.

ACKNOWLEDGEMENT

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These multiple choice questions are based on the above text. Answers appear on page 99.

- The origin of most cases of uveitis in dogs is:**
 - Bacterial infection
 - Viral infection
 - Neoplasia
 - Idiopathic
 - Trauma
- The most prominent feature of phacolytic uveitis is:**
 - Intact lens capsule
 - Corneal ulceration
 - Uveal inflammation
 - Lens protein leakage
 - Intralenticular inflammation
- Common ocular finding(s) in anterior uveitis is (are):**
 - Aqueous flare
 - Blepharospasm
 - Corneal oedema
 - Conjunctival hyperaemia
 - All of the above
- The pathophysiological basis of aqueous flare is:**
 - Lens luxation
 - Vitreous herniation
 - Vascular constriction
 - Decreased intraocular pressure
 - Breakdown of the blood-aqueous barrier
- The drug(s) used for treatment of uveitis is/are:**
 - Corticosteroids/cycloplegics
 - Timolol/dorzolamide
 - Proparacaine
 - Latanoprost
 - Pilocarpine

