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Canine and Feline Uveitis

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MORPHOLOGY

The uvea is composed of the highly vascular and often pigmented iris, ciliary body, and choroid. The iris and ciliary body comprise the anterior uvea. The choroid comprises the posterior uvea. The uveal tract regulates the quantity of light allowed into the eye by varying the pupillary aperture; produces aqueous humor, which provides nourishment and removes waste from the cornea and lens; and provides nutrients to the outer layers of the retina [1].

TERMINOLOGY

Uveitis is simply inflammation within the uveal tract. More precise terminology to describe the portion of the uveal tract involved includes iritis (inflammation of the iris), iridocyclitis or anterior uveitis (inflammation of the iris and ciliary body), choroiditis or posterior uveitis (inflammation of the choroid), and pan-uveitis (inflammation of the entire uveal tract) [2]. Differentiating whether inflammation arises from the iris or the ciliary body can be difficult because of their close anatomic proximity and the similar clinical signs [3]. Posterior uveitis can occur independent of anterior uveitis [3]. Endophthalmitis occurs when ocular inflammation is confined to three or more tissues inside the eye [2]. Panophthalmitis indicates that ocular inflammation involves all layers of the eye, including the sclera [2]. Determining the extent of involvement is clinically important, because involvement of the posterior segment may decrease the likelihood of maintaining a visual globe. Therapeutic agents must also be administered systemically to achieve effects within the posterior segment.

PATHOPHYSIOLOGY

Uveitis is a significant cause of ocular disease in dogs and cats [4,5]. Uveitis occurs after damage to uveal tissue or vasculature disrupts the ocular blood-aqueous barrier (BAB) or the blood-retinal barrier [6]. The BAB is composed of an epithelial barrier at the level of the nonpigmented ciliary epithelium and an endothelial barrier at the level of the iridal blood vessels [7,8]. The blood-retinal barrier is created by tight junctions within retinal capillaries and

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the cells of the retinal pigment epithelium [9,10]. The BAB prevents the movement of molecules across the vascular endothelial surface [6], which results in aqueous humor protein concentrations 200 times less than that of plasma [11]. Disruption of the BAB causes the aqueous humor protein concentration to increase to greater than normal levels, and the resultant light scattering (Tyndall effect) makes the beam from the slit-lamp visible as it traverses the anterior chamber [12]. This phenomenon is known as flare and is a hallmark of uveitis. Disruption of the blood-retinal barrier results in retinal edema, retinal hemorrhage, and detachment of the neurosensory retina [13].

The acute inflammatory phase of uveitis begins with brief arteriolar vasoconstriction, followed by prolonged vascular dilation [3]. Prostaglandins and leukotrienes mediate the vasodilation and cause increased vascular permeability, which results in the breakdown of the BAB. During episodes of anterior uveitis, the intraocular prostaglandin concentrations may increase 200-fold [14]. Prostaglandins also induce hyperemia and reduction in intraocular pressure (IOP) [3]. $\text{PGF}_{2\alpha}$ constricts the iris sphincter muscle, causing miosis and pain. In a recently reported study measuring inflammatory mediators in aqueous humor after anterior chamber paracentesis, an increase in PGE_2 levels was noted along with elevations in inducible cyclooxygenase (COX)-2 and nitrites and nitrates [15].

Breakdown of the BAB allows proteins, cells, and additional inflammatory mediators entry into the iridal stroma and aqueous humor. Cytokines and chemokines are important chemotactic factors that recruit inflammatory cells. One particularly important cytokine seems to be leukotriene B₄, a classic chemoattractant that triggers adherence of leukocytes to the endothelium and recruits granulocytes and macrophages to the site of inflammation [16]. In an experimental model of uveitis in mice, blockade of the leukotriene B₄ receptor greatly reduced the intensity of the ongoing disease [16].

CLINICAL SIGNS

Nonspecific Signs

Blepharospasm, photophobia, excessive lacrimation, and enophthalmos are nonspecific signs of ocular discomfort noted with uveitis but also with ulcerative keratitis, scleritis, and glaucoma [17]. The globe often appears red because of hyperemia of the deep perilimbal anterior ciliary vessels [3,17]. The engorgement of these radially oriented vessels is called ciliary flush. The vascular dilation occurs secondary to the elevation in prostaglandin levels. Deep vessels may be distinguished from superficial conjunctival vessels by manipulation of the conjunctiva and application of 1:1000 epinephrine or 2.5% phenylephrine solution [17]. Deep vessels do not move with the conjunctiva and do not readily blanch after the application of topical epinephrine. Uveitis may result in corneal edema. Corneal edema may occur in association with uveitis as a result of reduction of the endothelial sodium potassium (NaK)-ATPase or epithelial Na-chlorine (Cl) pump activities or may be related to a rupture of the endothelial cell-cell junction barrier [18]. Either mechanism allows hydration of the corneal stroma noted clinically as corneal edema.

Anterior Segment Clinical Signs

The presence of aqueous flare confirms a diagnosis of anterior uveitis. Aqueous flare denotes breakdown of the BAB and increased permeability of the ocular vasculature. Because of this increase in vascular permeability, inflammatory cells may be visualized within the aqueous humor or vitreous body. An accumulation of purulent material within the anterior chamber is termed *hypopyon* (Fig. 1). Blood within the anterior chamber is termed *hyphema* (Fig. 2). Both may be noted during episodes of anterior uveitis. Aggregates of inflammatory cells may adhere to the corneal endothelium and are then called keratic precipitates (Fig. 3). Typically, the keratic precipitates are visualized on the ventral one half to one third of the cornea, where they are deposited by the aqueous humor thermal convection currents. Blepharospasm or an elevated third eyelid may prevent visualization of the keratic precipitates by obscuring the ventral portion of the cornea. Larger fatty-looking clusters of keratic precipitates have been termed *mutton fat* keratic precipitates (Fig. 4) and often indicate granulomatous inflammation [19].

Miosis, sometimes quite marked, occurs in response to prostaglandins, particularly PGF_2 [20,21], and other inflammatory mediators that act directly on the iris sphincter muscle [3]. The miosis and associated ciliary muscle spasm contribute greatly to the pain associated with anterior uveitis. Failure to dilate completely in response to the topical application of tropicamide 1% ophthalmic solution can be a subtle sign of anterior uveitis [3]. Iridal swelling may cause the iris to appear engorged or darker in color, possibly even yellow in animals with normally blue irides.

The IOP typically decreases during uveitis, because the inflammatory process leads to a reduction in active secretion of aqueous humor, possibly by

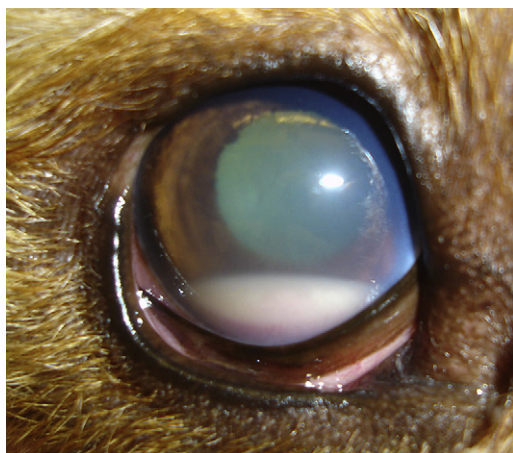


Fig. 1. Hypopyon fills the ventral quarter of this canine globe. Mild diffuse corneal edema is present.



Fig. 2. Moderate corneal edema obscures visualization of the hyphema present in the eye of a dog with uveitis secondary to immune-mediated thrombocytopenia.

means of interference with active transport mechanisms [22]. Prostaglandin release may also contribute to the ocular hypotony by increasing aqueous humor outflow through the uveoscleral route [23]. Subtle ocular hypotony, for example, an IOP within the normal range but 5 mm Hg less than the fellow eye is a significant finding that may be an early indication of inflammation [3,24,25].

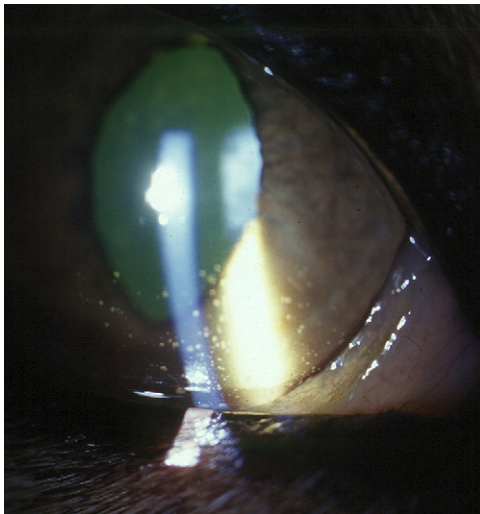


Fig. 3. Fine keratic precipitates in a cat with idiopathic uveitis as seen with a slit-beam. (Courtesy of David L. Williams, MA, VetMB, PhD, CertVOphthal, FRCVS, Cambridge, England.)

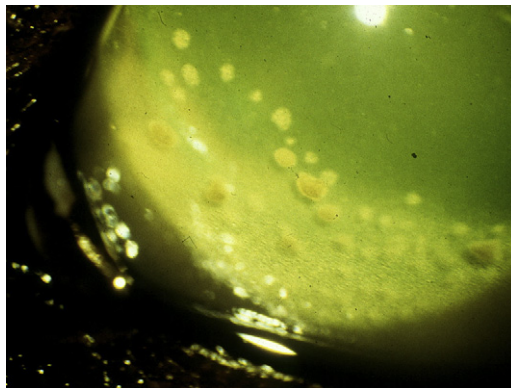


Fig. 4. Larger mutton-fat keratic precipitates in a cat with feline infectious peritonitis. (Courtesy of David L. Williams, MA, VetMB, PhD, CertVOphthal, FRCVS, Cambridge, England.)

Posterior Segment Clinical Signs

Examination of the posterior segment may reveal a cellular infiltrate within the vitreous body as inflammatory cells diffuse into the vitreous from the pars plana and pars plicata of the ciliary body. A complete fundic examination is necessary to evaluate alteration within the retina and choroid. Because of the close anatomic proximity of the retina and choroid, the choroid is infrequently inflamed as a sole process. The retina is typically involved primarily or secondarily. Areas of grayish discoloration over the tapetal fundus and grayish to white areas within the nontapetal fundus may occur as a result of retinal edema or cellular infiltration [13]. More extensive inflammation may result in areas of retinal detachment (Fig. 5). The detachments may be bullous with a fluid exudate in the subretinal space, which allows visualization of the underlying tapetum (Fig. 6). Retinal detachments may also be characterized by a cellular infiltrate in the subretinal space, which appears as grayish to pink-white accumulations of material beneath the retinal detachment. Hemorrhage may be present within the vitreous, retina, or subretinal space. Close inspection of the retinal vasculature may reveal changes in vascular caliber and tortuosity. Sheathing of the retinal vessels by inflammatory cells, called perivascular cuffing, occurs with some forms of uveitis.

Sequelae to Uveitis

Chronic inflammation of previous bouts of inflammation may incite multiple changes within the globe. Chronic inflammation stimulates ingrowth of peripheral corneal vascularization. The vessels bud from the limbal vasculature [26]. Matrix metalloproteinase 2 within the anterior chamber may be one of the stimuli that incite corneal angiogenesis [27].

The combination of inflammatory cells, fibrin, fibroblasts, iridal swelling, and miosis may create adhesions of the iris to the lens capsule or cornea [3]. Posterior synechiae occur if the iris is adherent to the anterior lens capsule.

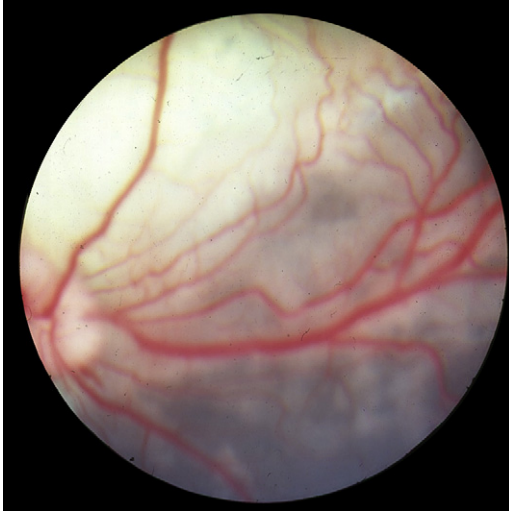


Fig. 5. Retinal detachment with perivascular infiltrates in a dog with idiopathic posterior uveitis. (Courtesy of David L. Williams, MA, VetMB, PhD, CertVOphthal, FRCVS, Cambridge, England.)

Anterior synechiae occur if the iris is adherent to the corneal endothelium. If extensive, posterior synechiae may occlude the flow of aqueous from the posterior chamber through the pupil into the anterior chamber, causing iris bombé, which is an anterior ballooning of the iris, and secondary glaucoma [19]. Pre-iridal fibrovascular membranes may form on the anterior surface of the iris. Angiogenic factors released by ischemic retina, neoplasms, or leukocytes involved in ocular inflammation can incite endothelial budding from vessels

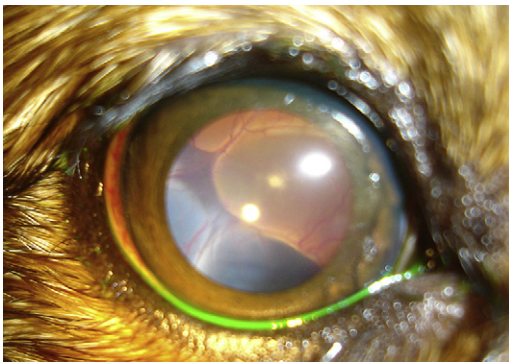


Fig. 6. Complete bullous retinal detachment is present in the right eye of a dog diagnosed with canine ehrlichiosis.

in the anterior iridal stroma [28]. The membranes may extend onto the anterior lens capsule or into the iridocorneal angle. Clinically, the term *rubeosis iridis* is applied, because the neovascular membrane on the anterior iridal surface causes a reddish cast to the iris (Fig. 7) [19].

Chronic inflammation often induces the formation of cataracts, presumably by the diffusion of inflammatory mediators across the lens capsule causing lens epithelial metaplasia, necrosis, or posterior migration and lens fiber degeneration, liquefaction, and necrosis [29,30]. Chronic uveitis may also result in lens luxation. The inflammatory products within the aqueous humor cause degradation of the zonular fibers, which then allows the lens to move from its normal position within the patellar fossa [31]. Although this process seems to be relatively rare in dogs [32], chronic uveitis seems to be a frequent cause of lens luxation in the cat [33]. Secondary glaucoma may occur from pupillary block as a result of iris bombé or lens luxation or may be attributable to occlusion of the iridocorneal angle by peripheral anterior synechiae [5].

Resolution of chorioretinitis may leave areas of retinal degeneration demarcated as areas of tapetal hyperreflectivity in the tapetal fundus as the overlying retina has thinned and mottled pigmentation in the nontapetal fundus. Hypertrophy of the retinal pigment epithelium may be noted as areas of dense pigmentation in areas of previous retinal detachment. If marked choroidal inflammation was present, there may be changes in tapetal coloration, pigment clumping, or loss of choroidal pigment, which exposes the choroidal vessels or sclera. Retinal vascular attenuation may be generalized or occur overlying the areas of retinal degeneration. Finally, phthisis bulbi may occur as chronic cyclitis, and the resultant tissue atrophy and fibrosis destroy the ability of the ciliary body to produce aqueous humor. Because the normal IOP can no longer be maintained, the globe begins to shrink [3]. The histologic hallmarks are an atrophic and disorganized globe typically characterized by a cyclitic membrane and variable degrees of chronic inflammation [34]. Fibrous or osseous metaplasia may occur as well.



Fig. 7. The fine branching vasculature noted on the iridal surface is termed *rubeosis iridis* and has developed secondary to chronic idiopathic uveitis in this cat.

Diagnostic Tests

Fluorescein staining should be performed routinely to rule out the presence of ulcerative keratitis and the possibility of a reflex uveitis [17]. The presence of ulcerative keratitis precludes the use of topical corticosteroids.

Because many significant systemic diseases can induce uveitis, a thorough physical examination, complete blood cell count, serum biochemistry profile, and urinalysis should be performed. During the physical examination, particular attention should be paid to the integument, lymphatic system, thoracic auscultation, and abdominal palpation. Thoracic radiographs, abdominal ultrasonographic examination, and select serologic titers are often valuable tools in the diagnostic investigation.

If a marked cellular infiltrate is present, cytologic evaluation of aqueous humor may be beneficial in identifying etiologic agents or neoplastic cells, particularly in cases of lymphoma [35]. The risks of aqueous centesis are low in the hands of an experienced ophthalmologist but do include cataract formation if one contacts the anterior lens capsule, hyphema [36], and exacerbation of the uveitis. If marked vitreal infiltrates or cellular retinal detachments are present, cytologic examination of those infiltrates is often more rewarding [37]. In a report by Brightman and colleagues [37], an etiologic agent was identified in 13 (65%) of 20 of cases using vitreous centesis and cytologic examination.

Aqueocentesis can also be used to determine the level of intraocular antibody production. The ratio of aqueous antibody titer to serum titer is known as the Goldman-Witmer coefficient, or C value. If greater than 1, this shows that an intraocular infectious agent is causing iridal plasma cells to produce antibody, thus demonstrating that an infectious agent is causing the uveitis rather than merely being a bystander [38,39].

Therapy

Primary treatment goals for uveitis are halting inflammation, stabilizing the BAB, minimizing sequelae, decreasing pain, and preserving vision. The agents used to attain those goals include topical mydriatics, topical (and, in select cases, systemic) corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs). If an underlying etiology can be detected, therapy should be directed toward removal of the inciting agent or alleviating the associated systemic disease.

Mydriatics

The mydriatic agent most often selected is 1% atropine ointment or solution. Atropine is a selective, reversible, direct-acting anticholinergic agent [40]. Topical administration results in pharmacologic blockage of the sphincter muscles of the iris and ciliary body, leading to pupillary dilation and cycloplegia [40]. The resultant pupillary dilation decreases the possibility of posterior synechia formation. The pupillary dilation may exacerbate congestion of the iridocorneal angle, however, and thereby decrease aqueous outflow. Therefore, atropine must be used with caution in patients that have or are at risk for secondary glaucoma. The cycloplegia greatly lessens the pain associated with

ciliary spasm. Administration of atropine also decreases the permeability of ocular blood vessels to proteins and intravenously administered fluorescein, thereby stabilizing the BAB [41,42].

In a normal canine or feline globe, the onset of action is within 30 to 60 minutes [43,44] and mydriasis may persist for up to 10 days after administration of the last dose [45]. In uveitic globes, atropine is initially applied up to four times daily to achieve mydriasis and is then administered once to twice daily to maintain mydriasis. Because the agent is bitter tasting, hypersalivation or, infrequently, vomiting may be noted after the instilled topical solution travels through the lacrimal puncta and nasolacrimal ducts and is tasted [46]. Cats may have particularly marked reactions [44]. Therefore, use of the ointment preparation is indicated in feline or potentially sensitive patients.

Corticosteroids

Anti-inflammatory therapy is a key element of therapy for uveitis. Corticosteroids are frequently used to suppress inflammation because they reduce production of metabolites of the arachidonic acid (inflammatory) cascade [47]. Glucocorticoids upregulate lipocortin expression [48]. Lipocortin is a key inhibitor of proinflammatory substances, such as phospholipase A₂, the enzyme responsible for initiating the arachidonic acid cascade [48]. Glucocorticoids can also directly reduce PGE synthesis and increase vascular stability [49].

To control anterior uveitis, topical application of the corticosteroid is often the preferred route because it allows for high local drug concentrations and minimal systemic side effects [47]. Prednisolone acetate 1% ophthalmic suspension and dexamethasone 0.1% are able to penetrate an intact corneal epithelium [50]. Therefore, they are the only topical corticosteroids that can achieve therapeutic concentrations in the aqueous humor [50]. Each of these agents may inhibit 40% to 50% of protein exudation from the iris and ciliary body [51]. The initial frequency of application may be every 2 to 4 hours depending on the severity of the inflammation. Once clinical improvement is noted, the frequency may be decreased but the therapy should be gradually tapered to diminish the likelihood of recurrence [47]. Topical corticosteroids are contraindicated in the presence of corneal ulceration because they delay normal wound healing.

Use of glucocorticoids, such as prednisone, prednisolone, or dexamethasone, to suppress inflammation within the posterior segment, for example, chorioretinitis, requires systemic administration of anti-inflammatory or, occasionally, immunosuppressive doses [47]. The dose is then incrementally decreased based on the response to therapy [50]. When using corticosteroids, one risks exacerbation of clinical signs if an infectious cause is present but has not yet been identified [47]. Systemic side effects, including endocrinopathies, may result with long-term use.

Nonsteroidal Anti-Inflammatory Drugs

The NSAIDs can be particularly useful in cases of mild anterior uveitis, as adjunctive therapy when combined with topical corticosteroids, and to control posterior segment inflammation when an infectious etiology has not been completely ruled out. The NSAIDs block the conversion of arachidonic acid to

prostaglandins by COX [52]. Prostaglandins are key mediators of ocular inflammation, causing breakdown of the BAB, exacerbating photophobia, and lowering the ocular pain threshold [53]. The NSAIDs are also beneficial because they have been shown to suppress polymorphonuclear cell locomotion and chemotaxis [54], decrease expression of inflammatory cytokines [55], and function as free radical scavengers [56]. Although many systemic NSAIDs are currently available, only a few have been evaluated to assess their efficacy in controlling ocular inflammation. Flunixin meglumine and aspirin have been shown to stabilize the BAB in experimental models of uveitis [57,58]. Flunixin meglumine had good effects, whereas the effects of aspirin were moderate when compared with the placebo. Both drugs induced some gastrointestinal bleeding, however. In a pilocarpine-induced model of uveitis in dogs, carprofen resulted in a 68% inhibition of aqueous flare [59]. In a clinical study, tolfenamic acid was shown to control postoperative intraocular inflammation [60]. When selecting a systemic NSAID, one must be cognizant of the potential systemic side effects, particularly the adverse gastrointestinal effects in all species [61], and the potential for bone marrow suppression and hemorrhage in cats [62].

Topical NSAIDs may be used to control mild inflammation or may be combined with topical corticosteroids to improve control of more severe ocular inflammation [52]. The application frequency typically varies from two to four times per day [62,63]. The relative efficacies have been studied in an anterior chamber paracentesis model and the order of BAB stabilizing efficacy was as follows: diclofenac greater than flurbiprofen, flurbiprofen greater than suprofen, and suprofen greater than tolmetin, which was equal to the control solution [64]. One must use caution in canine eyes with the potential for secondary glaucoma because the topical NSAIDs have been found to elevate the IOP [65]. One must also exercise caution when using topical NSAIDs in the presence of corneal ulceration. In people, topical NSAIDs have been associated with marked corneal collagenolysis [3].

Cases of immune-mediated uveitis that require long-term maintenance with systemic glucocorticoids or that fail to respond to conventional therapy may require use of immunosuppressive drugs, such as azathioprine. Azathioprine is a purine analogue with relatively select cytotoxicity for T helper lymphocytes [66]. Conditions like uveodermatologic syndrome and pigmentary uveitis are the conditions in which azathioprine is most frequently used [67,68]. The initial dose in dogs is 2 mg/kg every 24 hours [69]. The dose for long-term therapy is typically decreased to 0.5 to 1 mg/kg every other day. The lag period before successful treatment is recognized ranges from 3 to 5 weeks [69]. Complete blood cell counts should be monitored, because bone marrow suppression is a concern. Gastrointestinal side effects and hepatotoxicity may be noted as well [69].

Causes of Anterior Uveitis

A plethora of etiologies may incite uveitis. Infectious diseases, neoplasia, and immune-mediated conditions may all present with clinical signs of uveitis.

For the purposes of this discussion, the etiologies are grouped into noninfectious and infectious causes of uveitis.

NONINFECTIOUS CAUSES OF UVEITIS

Idiopathic Uveitis

Unfortunately, most cases of uveitis remain idiopathic despite intensive systemic evaluations. In a study by Massa and colleagues [4], 60% of cases of dogs that had uveitis were classified as idiopathic or immune mediated, because an underlying systemic cause could not be identified. The dogs with idiopathic uveitis were typically middle aged, did not exhibit any signs of systemic illness, and more often were presented with unilateral uveitis. In the study by Massa and colleagues [4], the degree of inflammation and ocular lesions did not vary between those dogs with infectious, neoplastic, or idiopathic uveitis. In studies of feline uveitis, approximately 30% to 62% of affected cats had no identifiable concurrent systemic disease [70,71]. Although the underlying etiology may often remain obscure, a complete diagnostic investigation remains essential because of the severity of the systemic diseases associated with uveitis.

Lens-Induced Uveitis

An excellent review article on this topic has been written by van der Woerd [72], and the reader is referred to that text for additional information. Two different forms of uveitis may be initiated by lenticular pathologic findings. A lymphoplasmacytic inflammatory process, termed *phacolytic uveitis*, occurs in association with hypermature or rapidly forming cataracts [31]. Phacolytic uveitis is typically mild. The prevalence has been reported to be as high as 71% in dogs screened for cataract surgery [73]. The high prevalence is not surprising, because fluorophotometric studies have demonstrated breakdown of the BAB in association with all stages of cataracts [74]. The lens-associated inflammation is proposed to occur after deviation of the normal low level of T-cell-mediated tolerance to lens proteins [72,75].

A more dramatic form of uveitis, termed *phacoclastic uveitis*, occurs in association with rupture of the lens capsule and release of lens proteins and membrane-associated antigens [31]. Histologic examination of affected globes revealed intralenticular neutrophils and a surrounding inflammatory response that ranges from suppurative to lymphocytic in nature [76]. In a study by Davidson and colleagues [77], prompt surgical removal of the lens material resulted in a visual eye in most cases. In contrast, attempts at medical management resulted in the loss of vision. In cats, because of the risk for traumatic ocular sarcoma, surgical removal of the lens material or globe is recommended if the eye cannot be salvaged. Rupture of the lens capsule is believed to induce traumatic ocular sarcoma, although the time from trauma to detection of the tumor averages 5 years [5,78].

Trauma

Blunt trauma and penetrating trauma can incite uveitis and are common causes of uveitis in domestic animals [17]. Hyphema and varying amounts of fibrin are

often present in cases of traumatic uveitis [5]. In cases of penetrating trauma, one must assess the extent of damage within the globe, including whether the lens capsule has been ruptured. Ultrasonographic examination may be required to evaluate the extent of the damage fully. The administration of broad-spectrum systemic antibiotics is strongly suggested, because bacterial or fungal contamination may occur at the time of globe penetration [5]. Endophthalmitis can progress rapidly and cause loss of the globe. If marked hyphema is present, administration of tropicamide can mobilize the pupil and assist in preventing the development of synechia [5]. Administration of tropicamide is preferable to atropine, because tropicamide produces greater iridoplegia than cycloplegia, and thus less often produces increases in IOP [40].

Golden Retriever Pigmentary Uveitis

Primarily reported in the golden retriever, pigmentary uveitis is characterized by anterior segment inflammation and the deposition of pigment on the anterior lens capsule, often in a radial fashion [67]. No systemic signs are associated with this condition. The mean age at presentation is 8.6 years [67]. In a report by Sapienza and colleagues [67], common sequelae were cataract formation (37%) and secondary glaucoma (46%). In a report by Deehr and Dubielzig [79], uveal cysts were noted in 15 of 18 eyes and were thought to be an important factor in the development of glaucoma. In the report by Sapienza and colleagues [67], uveal cysts were a common finding on histologic examination of the enucleated glaucomatous blind eyes, whereas they were only noted clinically in 13% of cases. Interestingly in those globes, microscopically, little inflammation was noted. Therapy often consists of combinations of topical and systemic corticosteroids, topical NSAIDs, medications to control secondary glaucoma, and azathioprine [67]. Administration of topical NSAIDs seems to exacerbate ocular hypertension frequently [65,67].

Uveodermatologic Syndrome

Uveodermatologic syndrome, or Vogt-Koyanagi-Harada-like syndrome, is an autoimmune condition of dogs in which melanocytes become the target of the cellular response [80]. An immunohistochemical examination of affected tissues from two dogs revealed that the skin lesions were mediated by T cells and macrophages (T helper [Th] 1 immunity), whereas the ocular lesions were more consistent with a B-cell and macrophage response (Th2 immunity). The breeds primarily affected are the akita, samoyed, Siberian husky, and Shetland sheepdog [3]. The condition does occur sporadically in other breeds, however. Affected patients are usually presented with anterior uveitis or panuveitis characterized by iridal or choroidal depigmentation, bullous retinal detachment, or blindness [3]. The ocular lesions may precede the cutaneous lesions, which include poliosis and vitiligo of the facial mucocutaneous junctions, nasal planum, scrotum, and footpads [81,82]. Generalized vitiligo may also occur [81]. Because of the chronic nature of the disease, affected patients typically develop extensive posterior synechia, iris bombé, cataract, and secondary glaucoma. Immunosuppressive drugs are the mainstay of therapy [3]. Azathioprine

is often combined with or substituted for corticosteroids to avoid the side effects associated with chronic systemic corticosteroid administration.

Neoplasia-Associated Uveitis

The presence of any neoplastic process, whether primary or metastatic, within the globe may induce clinical signs of uveitis, such as iris hyperpigmentation, intraocular fibrin exudation, and hemorrhage [83]. Therefore, the possibility of associated neoplasia must always be considered in patients that have uveitis, particularly if the inflammatory response or secondary glaucoma precludes complete visualization of the intraocular compartments [83]. The more common primary intraocular tumors include melanomas (dogs and cats) [5,84] and iridociliary epithelial tumors (dogs) [85]. Lymphosarcoma is the most frequent metastatic intraocular tumor in cats and dogs [5,86,87]. Ocular involvement in canine lymphoma may include anterior uveitis, posterior uveitis, panuveitis, retinal hemorrhage, and superficial disease [87]. Metastasis of angioinvasive pulmonary carcinoma has been described in four cats [88]. Ophthalmic examination revealed wedge-shaped tan discoloration of the tapetal fundus, variable but mild serous exudation under the retina, and profoundly attenuated retinal vasculature [88].

Infectious Causes of Uveitis in Cats

The more common infectious causes of uveitis in cats are feline infectious peritonitis (FIP), feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), toxoplasmosis, and the systemic mycoses. *Bartonella henselae* has also been proposed as a frequent cause of feline uveitis [89]. According to previously published reports, between 38% and 70% of cats with uveitis have an associated systemic disease [70,71].

Feline Infectious Peritonitis

FIP is caused when the immune response to feline coronavirus induces granulomatous necrotizing phlebitis and periphlebitis, protein-rich effusions into body cavities, and granulomatous inflammatory lesions in multiple organs [90,91]. The associated clinical signs include febrile episodes, weight loss, anorexia, depression, debility, and variable thoracic and abdominal involvement [5]. The uveitis associated with FIP is typically a panuveitis or panophthalmitis with diffuse and severe corneal edema, marked anterior uveitis, marked cellular infiltration of the vitreous (ie, vitritis), chorioretinitis, inflammatory retinal detachments, or optic neuritis [5]. Mutton fat keratic precipitates with occasional admixed hemorrhage occur most often with FIP because of the granulomatous nature of the infection. The granulomatous periphlebitis may be noted as perivascular cuffing surrounding the retinal vasculature.

The diagnosis of FIP can be challenging, because enteric coronaviruses cross-react and cause positive results on serologic tests and reverse transcriptase (RT)-polymerase chain reaction (PCR) assays. According to recommendations from the FIP workshop symposium [92], the first step in establishing a diagnosis of FIP is to compare the signalment, history, and clinical findings with those of

the typical individual infected with FIP. Most cats with FIP are from 6 months to 3 years of age, come from shelters or catteries, and show signs of cyclic antibiotic-resistant fevers and specific physical manifestations depending on the form of the disease and location of lesions [92]. Diagnostic test findings supportive of a diagnosis of FIP include characteristic analysis of peritoneal or pleural effusions, leukocytosis with neutrophilia and lymphopenia, hyperglobulinemia, hypoalbuminemia, increased fibrinogen, and nonregenerative anemia of chronic disease [92]. Finally, in a cat with suspect FIP, one may also submit effusions or surgical biopsies for immunohistochemistry or RT-PCR [92]. Serology or RT-PCR performed on serum samples can confirm exposure to feline coronavirus but must be paired with appropriate clinical signs to ensure an accurate diagnosis [92]. No therapy has been proved effective in the management of FIP [92]. Therapy remains symptomatic.

Bartonella spp

B. henselae was first suggested as a cause of feline anterior uveitis by Lappin and Black [89] in 1999 after a feline patient had a C value for IgG antibodies to *Bartonella* spp of 4.42, which indicated antibody production by ocular tissues [38,39], and no clinical response to therapy was noted until doxycycline was administered [89]. Since the initial report, Ketring and colleagues [93] have demonstrated elevated serum antibody production against *Bartonella* in cats with uveitis. In a more recent study by Fontanelle and colleagues [94], however, healthy cats were more likely to have elevated *Bartonella* titers than cats with uveitis. Therefore, serum antibody tests alone do not seem to be sufficient to confirm a diagnosis of *Bartonella*-induced uveitis. A definitive therapeutic protocol to resolve *Bartonella* infection does not currently exist [95,96]. The authors of one article [93] suggest azithromycin, doxycycline, or rifampin.

Feline Leukemia Virus

Illness in FeLV-infected cats results from the direct effects of the virus on bone marrow or lymphoid tissue [97]. The uveitis in association with FeLV infection is primarily a manifestation of lymphosarcoma. In the study by Peiffer and Wilcock [98], FeLV-associated lymphosarcoma was the third most frequent cause of uveitis in cats after idiopathic lymphoplasmacytic uveitis and FIP-associated uveitis. FeLV-induced lesions range from inflammatory cells and fibrin within the anterior chamber to small iris nodules or extensive neoplastic infiltration [99]. Funduscopically, one may note the characteristic lesions of retinopathy of anemia, which may occur secondary to FeLV-related anemia [100].

Cytologic examination of aqueous humor usually reveals variable amounts of lymphocytes and occasional plasmacytes and neutrophils [5]. The presence of lymphosarcoma may be confirmed based on bone marrow aspiration, lymph node biopsy, and direct biopsy of intraocular masses [101]. An ELISA antigen test of peripheral blood can demonstrate the presence of the FeLV antigen [99]. The diagnosis of a persistent infection should be confirmed by performing an immunofluorescent antibody (IFA) test or repeating the ELISA antigen test in 3 to 4 months [99].

Feline Immunodeficiency Virus

Direct viral damage of ocular tissues, initiation of secondary immune phenomena, or opportunistic infection secondary to immunosuppression may all contribute to the uveitis associated with FIV infection [102]. Clinically, pars planitis is often a significant feature of the disease, creating a “snow banking” phenomenon as cells are deposited throughout the anterior vitreous with a greater density toward the periphery [102]. Keratic precipitates are uncommon findings [102]. Coinfection with *Toxoplasma gondii* seems to increase the severity of clinical signs in cats that are infected with FIV [71,103], perhaps because the defense mechanisms for *T gondii* depend on CD4+ cells [103]. ELISA tests may be used to detect antibodies to FIV [104]. According to a recent study [105], the Snap Combo Plus (IDEXX Laboratories, Atlanta, GA) is the best performing in-hospital test kit, and the MAPIC FIV test (Sinovus Biotech, Inc., Lund, Sweden) should not be used because of the large number of invalid results or results that are difficult to interpret. Unfortunately, vaccination of cats for FIV produces antibodies that are indistinguishable from those used to diagnose FIV infection [104]. Currently, there is no method by which to differentiate vaccinal antibodies from those produced by natural infection. Therefore, attaining a definitive diagnosis in a cat whose vaccination status is unknown becomes nearly impossible. Symptomatic therapy is used to control the uveitis.

Toxoplasmosis

T gondii is a well-recognized cause of retinitis, choroiditis, and anterior uveitis [106]. Tachyzoites target the eye and multiply intracellularly within ocular tissues [107]. The classic fundoscopic appearance is multifocal dark gray lesions in the tapetal fundus and fluffy white infiltrates in the nontapetal fundus [106]. *T gondii* has frequently been implicated as a main cause of acute and chronic idiopathic feline anterior uveitis [106]. Supportive evidence for this hypothesis includes the higher seroprevalence rate to *T gondii* in cats with uveitis [71].

The only definitive diagnosis is histologic identification of the organism [108]. Because a histologic diagnosis is frequently not available, however, serologic testing is the primary diagnostic modality. Exposure to the organism is widespread within the feline population. Therefore, paired serologic titers are recommended, and most cases remain suspect rather than confirmed [106]. An ELISA test for IgM antibodies with a single titer greater than 1:256 or rising IgG titers is considered consistent with an active infection [108,109]. More recently, PCR (B1 gene) tests for *T gondii*-specific IgM and IgG have been evaluated in serum and aqueous humor samples [110,111]. *T gondii*-specific IgM or IgG was detected in the serum but not in the aqueous humor in 34.8% of healthy cats. In cats that had uveitis, *T gondii*-specific IgM or IgG was detected in the serum of 72% and in the aqueous humor of 39.5%, suggesting that the combination of serum and aqueous humor *T gondii* titers may be the most informative and useful method of testing. Anti-inflammatory therapy should be used to control the uveitis in conjunction with clindamycin hydrochloride at a dose of 12.5 mg/kg administered orally twice daily for 14 to 21 days [112].

Systemic Mycoses

A granulomatous anterior uveitis, often with concurrent chorioretinitis, may be associated with cryptococcosis [113], histoplasmosis [114], blastomycosis [115], or coccidioidomycosis [116]. From the literature, the incidence of blastomycosis in cats seems to be rare, except for sporadic clusters [117,118]. In most cases, hematogenous spread is the likely route of ocular involvement. Ocular cryptococcosis seems to be an exception, however, because extension from the central nervous system occurs more frequently. The diagnostic protocol for mycotic uveitides includes a complete physical examination, hematology, and clinical chemistries [5]. Diagnosis is often achieved by identification of the organism during cytologic examination of aspirates or impression smears from lymph nodes, bone marrow aspirates, cerebrospinal fluid, or cutaneous lesions [5]. Aqueous or vitreous paracentesis may be useful depending on the degree of ocular involvement (ie, anterior or posterior segment) [5]. Histoplasmosis may be effectively treated using itraconazole [119]. Blastomycosis may be treated with itraconazole or fluconazole, although the response is often poor [117,118].

INFECTIOUS CAUSES OF UVEITIS IN DOGS

Brucella canis

An excellent review article on this disease has been published by Wanke [120]. Endophthalmitis, chorioretinitis, and hyphema have all been reported in association with *Brucella canis* infection [121]. Vinayak and colleagues [121] reported that 14.2% of patients that had *B canis* infection demonstrated ocular signs. Other clinical signs include reproductive tract lesions (eg, abortions, epididymitis, failure to conceive) [120], diskospondylitis, osteomyelitis, splenomegaly, glomerulopathy, and meningoencephalitis [122,123]. Isolation of the organism is considered the “gold standard” diagnostic test [120]. This can be difficult, however. The rapid slide agglutination test is sensitive and can be performed early in the stage of infection [120]. Positive results are confirmed with other tests, including the tube agglutination test, agar-gel immunodiffusion, indirect fluorescent antibody test, and ELISA [122]. Achieving complete eradication of the organism is difficult [120]. Various suggested therapeutic regimens include minocycline and streptomycin, tetracycline and streptomycin, long-acting oxytetracycline [120], enrofloxacin [124], and gentamicin [121]. Complete resolution of ocular clinical signs and clearance of the organism have only been reported in one case in the literature [121].

Tick-Borne Diseases

Borrelia burgdorferi (Lyme disease), *Ehrlichia* spp, including *canis*, *platys*, and *risticii*, and *Rickettsia rickettsii* (Rocky Mountain spotted fever [RMSF]) have all been implicated as causative agents in cases of uveitis [122,125]. The ocular lesions are similar and include anterior uveitis, hyphema, retinal hemorrhage, and retinal detachment (see Fig. 7). The diagnosis is typically based on the combination

of clinical signs and serologic testing. Serum ELISA and IFA serologic tests can be used to document exposure to Lyme disease [126]. In patients previously vaccinated for Lyme disease, Western blot immunoassays may be used to differentiate natural exposure from vaccinal response [126]. The serum fluorescent antibody test is most reliable for the diagnosis of ehrlichial agents [125]. IFA and ELISA serum antibody titers are available for the diagnosis of RMSF [125]. The current therapeutic recommendations are also similar. Doxycycline is administered at a dosage of 10 mg/kg every 24 hours for 1 month as the primary therapy for Lyme disease in patients with positive serology and clinical signs of disease [126]. Two case reports document favorable responses to administration of doxycycline, sometimes paired with anti-inflammatory doses of corticosteroids in cases of canine ehrlichiosis [127,128]. Doxycycline is also used in the therapy of RMSF, and combination with systemic prednisolone has not been shown to decrease efficacy [129].

Leptospirosis

Uveitis is a relatively infrequent presentation of this re-emerging disease [122,130–132]. Reported cases have had anterior uveitis [122] and, in one case, bilateral serous retinal detachment [132]. The diagnosis is most commonly achieved using a serum microscopic agglutination test. A single high titer or rising titers are considered indicative of infection [133–137]. Therapy is directed toward elimination of the organism. High doses of penicillin, ampicillin, and amoxicillin can clear the leptospiremia phase, usually within hours of administration [138]. These drugs do not eliminate the carrier state, however [133,134]. Current recommendations are to use a 2-week course of doxycycline to clear the carrier state in dogs [138].

Systemic Mycoses

Blastomycosis, cryptococcosis, coccidiomycosis, and histoplasmosis are the systemic mycoses most commonly involved with uveitis [139,140]. Patients may be presented with anterior uveitis, chorioretinitis, panuveitis, endophthalmitis, or optic neuritis. A complete physical examination with particular attention to the cutaneous examination, thoracic auscultation, and abdominal palpation can aid in establishing a diagnosis. As discussed previously, cytologic identification of the organism within aspirates or impression smears is the gold standard for establishing a diagnosis. Serologic tests are available. The latex cryptococcal agglutination test detects cryptococcal antigen and can be a useful test for establishing a diagnosis and monitoring the response to therapy. The serologic tests for histoplasmosis, blastomycosis, and coccidiomycosis detect antibody production. False-negative responses, at least for blastomycosis, are not uncommon [141]. The preferred systemic therapy for each type of mycosis varies [3]. The current preferred therapy for blastomycosis is the administration of itraconazole [142]. Although many clinicians do not advocate systemic corticosteroid treatment in dogs with systemic mycoses [143], a recent retrospective study of dogs infected with blastomycosis by Finn and colleagues [144] did not note any

change in survival times and suggested that combination therapy of systemic prednisone and itraconazole may have assisted in the maintenance of vision.

SUMMARY

The clinical signs of uveitis occur as a result of inflammation within the vascular coat of the eye, which causes breakdown of the BAB and blood-retinal barrier. Clinical signs include blepharospasm, photophobia, conjunctival hyperemia, circumlimbal corneal vascularization, corneal edema, aqueous flare, inflammatory cells within the anterior chamber, keratic precipitates, iridal congestion, ocular hypotony, retinal hemorrhage, and retinal detachment. Sequelae to uveitis include cataracts, posterior synechiae, secondary glaucoma, and retinal degeneration. Many infectious and noninfectious causes can incite episodes of uveitis. Therefore, complete ocular and physical examinations are recommended for all patients that have uveitis. A complete blood cell count, serum biochemistry profile, urinalysis, thoracic radiographs, and select serologic tests may be performed in an effort to identify any underlying etiologic agents. Despite exhaustive workups, however, the underlying cause is not determined in many cases. The goals of therapy are preserving vision if possible, minimizing pain, and halting inflammation. Additional therapeutic agents may be used if the underlying etiologic agent can be identified.

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