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Feline infectious uveitis

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The uveal tract is composed of the iris, ciliary body and choroid. Uveitis in cats can be induced by either exogenous or endogenous causes. The most common causes of exogenous uveitis include trauma, corneal ulceration, and penetrating wounds which can usually be diagnosed on clinical examination. Endogenous uveitis can be classified as parasitic, infectious, lens-induced, neoplastic or idiopathic. Excluding lens-induced and neoplastic causes, there are no pathognomonic clinical ophthalmic changes associated with uveitis in the cat. Independent of etiology, aqueous flare, iritis, keratic precipitates, hyphema and hypopyon commonly develop in the anterior chamber. The choroid can be inflamed with or without concurrent anterior segment involvement. Appropriate management of uveitis in the cat is important to avoid lens luxations, cataract formation and glaucoma, three common sequelae to intraocular inflammation.

The most common infectious agents proposed to cause uveitis in naturally-exposed cats of the United States include *Toxoplasma gondii*, feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), feline infectious peritonitis virus (FIP), and mycoses including cryptococcosis, histoplasmosis, blastomycosis, coccidioidomycosis and candidiasis. Uveitis has been induced in cats following inoculation with FIV, FIP and *T gondii*. Recently, some information suggests that *Bartonella henselae* and herpesvirus 1 can induce intraocular inflammation in some cats. Clinically, these agents induce intraocular changes that are indistinguishable on ophthalmoscopic examination, particularly if only the anterior uvea is inflamed.

Diagnostic evaluation

Serological testing

Diagnosing the cause of endogenous uveitis in individual cats is extremely difficult. Serological tests for evidence of exposure to infectious causes of uveitis have been used in some epidemiologic studies. In one study, serum samples from cats (n=93) with uveitis without an obvious exogenous cause were assayed for FIV antibodies, feline coronavirus antibodies, FeLV p27 antigen, *T gondii*-specific immunoglobulin M (IgM), *T gondii*-specific immunoglobulin G (IgG), and *T gondii*-specific antigens. Serologic evidence of infection by *T gondii* (78.5%), FeLV (5.9%), FIV (22.9%) and feline coronavirus (antibody titre ≥1:1600; 4.1%) was present in some cats. The seroprevalence of *T gondii* in these cats was significantly higher than the seroprevalence in a group of healthy cats from a similar geographical area ($P<0.001$) suggesting that at least some of the cats had intraocular inflammation induced by *T gondii* infection. However, since positive results from serological tests for infectious agents occur in healthy cats as well as diseased cats they do not correlate to clinical disease of the eye in individual cats.

Additionally, depending on assay methodology, serological tests can also have false-positive and false-negative results. For example, many cats with uveitis have *T gondii*-specific IgM without *T gondii*-specific IgG in serum. It was shown that commercial latex agglutination and indirect haemagglutination kits for the detection of antibodies against *T gondii* fail to detect *T gondii*-specific IgM the majority of the time. These

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false-negative results have probably led to an underestimation of *T gondii* seroprevalence in cats with uveitis in the past. False-positive FIV antibody results as determined by ELISA may be common. Since enteric coronaviruses induce serum antibodies that cannot be distinguished from those induced by FIP-inducing strains of coronavirus, coronavirus antibody titres are extremely difficult to interpret. However, the combination of a coronavirus antibody titre >1:160, lymphopaenia and hypergammaglobulinaemia had a positive predictive value of 88.9% in cases with suspected systemic FIP. Serological evidence of exposure to more than one infectious agent is common in cats with uveitis and makes interpretation of test results even more difficult. For example, all FIV-seropositive cats with uveitis were also seropositive for *T gondii* in one study.

Aqueous humour testing

Several techniques using aqueous humour have been assessed in the diagnosis of uveitis in the cat. Cytology of aqueous humour is usually non-diagnostic. Fungal organisms are more commonly detected on cytological evaluation of vitreous humour.

Calculation of antibody production indices to determine ocular antibody production has been used to evaluate a number of ocular infectious diseases in humans and cats. The technique has been used frequently in studies of human ocular toxoplasmosis and was adapted for use in the cat. In the first study, serum and aqueous humour from 14 clinically normal cats and 96 cats with idiopathic endogenous uveitis were assayed for *T gondii*-specific IgM, *T gondii*-specific IgG, *T gondii*-specific antigens, total IgM, and total IgG (Lappin et al 1992). The Goldmann–Witmer coefficient (C-value) was then calculated as follows:

$$\frac{\textit{T gondii}\ \text{antibody (aqueous)} \times \text{Total antibody (serum)}}{\textit{T gondii}\ \text{antibody (serum)} \times \text{Total antibody (aqueous)}}$$

This formula corrects for antibody leaking into aqueous humour from serum secondary to inflammation. A C-value >1 is suggestive of local production of *T gondii*-specific antibody in aqueous humour. Clinically normal cats with serologic evidence of *T gondii* infection did not have *T gondii*-specific antibodies in aqueous humour. Of the cats with endogenous uveitis, 59 (61.4%) had *T gondii*-specific antibodies in serum; 51/59 had *T gondii*-specific antibodies in aqueous humour. Of these 59 cats, aqueous C-values were: C-value <1 (8/59, 13.6%); C-value 1–8 (20/59, 33.9%); and C-value >8 (23/59, 39.0%). These results suggest that *T gondii* may be a common cause of endogenous uveitis in the cat.

Similar techniques for detection of ocular production of feline herpesvirus 1 (FHV-1) and *Bartonella* spp antibodies have been developed. In a study of naturally exposed cats, FHV-1 ocular antibody production was not detected in FHV-1 seropositive normal cats (Maggs et al 1999). In cats for which the cause of uveitis was unknown, 22 of 44 (50%) had FHV-1 C-values >1 documenting ocular antibody production. Ocular production of *Bartonella* spp IgG (C-value >1) was detected in seven of 49 cats with uveitis, 0 of 49 healthy shelter cats, and four of nine experimentally inoculated cats (Lappin et al 2000).

Unfortunately, detection of ocular antibody production does not definitively prove that the organism in question is causing uveitis. For example, *T gondii*-specific IgG C-values >1 and *T gondii*-specific IgA C-values >1 can be detected in the aqueous humour of experimentally-inoculated, healthy cats, transiently. Additionally, *T gondii*-specific IgG antibody production in aqueous humour can be induced in chronically infected cats by non-specific immune stimulation. Thus, *T gondii*-specific IgG or IgA production in the aqueous humour of cats with uveitis does not correlate to disease induced by the organism in all cats. It is likely that multiple systemic infectious diseases induce ocular immune responses during the acute phase of infection whether or not ocular disease is occurring.

The class of antibody detected in aqueous humour may effect predictive value for disease. For example, *T gondii*-specific IgM has never been detected in the aqueous humour of experimentally-inoculated cats but IgM C-values >1 are common in cats with uveitis. *Bartonella* spp IgM C value >1 were only detected in cats with uveitis and *Bartonella* spp IgM antibodies were detected in serum of a greater number of cats with uveitis than healthy shelter cats. Based on these findings, we consider ocular production of the IgM class to be a better predictor of clinical illness than the IgG class.

We are using western blot immunoassay to compare antigen recognition patterns by antibodies in serum and aqueous humour as a diagnostic procedure for uveitis associated with FIV

(unpublished data, Gomez N, PhD dissertation, University of Buenos Aires) and *T gondii* (Powell et al 1998). While *T gondii*-specific antibodies in serum and aqueous humour occasionally have different antigen recognition patterns, results correlating with clinical ocular disease have not been identified to date.

Detection of the organism in aqueous humour could potentially aid the diagnosis of the cause of uveitis. In an early study, *T gondii* antigens were detected in the aqueous humour of some cats with uveitis documenting organism presence. The *Cryptococcus* antigen test can be used with aqueous or vitreous humour.

Recently, we have detected *T gondii* (Lappin et al 1996), FHV-1 (Maggs et al 1999) and *Bartonella* spp DNA (Lappin et al 2000) by PCR in the aqueous humour of eight of 43 (18.6%), 11 of 44 (25%) and three of 24 (12.5%) cats with uveitis, respectively. These results suggest that these three infectious agents enter the eye during infection. However, *T gondii* (two of 23; 8.7%), FHV-1 (one of 13; 7.8%), or *Bartonella* spp (one of 49; 2.0%) DNA can be detected by polymerase chain reaction in the aqueous humour of some healthy cats. Additionally, it has been shown that *T gondii* DNA can be detected transiently in the aqueous humour of experimentally inoculated cats without uveitis. Thus, detection of organismal DNA in aqueous humour does not always correlated to clinical disease.

Pathogenesis

Uveitis can result from organism replication in ocular tissues. For example, in acute, overwhelming toxoplasmosis, the organism is commonly detected in ocular tissues histologically. However, the organism is rarely detected histologically in *T gondii* infected cats with uveitis alone. Most cats with uveitis have lymphocytic–plasmacytic infiltrates in the iris and ciliary body. It is likely that the cellular infiltrates are secondary to immune-mediated phenomenon. Interleukin 6 (range=28.9 U/ml–15702 U/ml) was detected in 22/27 aqueous humour samples from cats with uveitis but 0/6 aqueous humour samples from normal cats, suggesting that this cytokine may be an inflammatory mediator in uveitis (Lappin et al 1997). It is likely that many ocular or systemic diseases can induce these changes. For *T gondii*, we have proposed that cats, like people, will be more likely to develop ocular disease if infected transplacentally or in the neonatal period. This hypothesis appears to be true, clinical ocular toxoplasmosis developed in five of nine surviving kittens from three infected queens (Powell & Lappin 1999).

Treatment

Since uveitis is an inflammatory disease, affected cats without keratic ulcers should be treated with topical glucocorticoids which do not appear to activate infectious causes of uveitis. In resistant cases, systemic or subconjunctival glucocorticoids are required.

Cases with fungal uveitis should always be treated with antifungal drugs. Fluconazole apparently penetrates ocular tissues the best of the orally administered drugs. Administration of 50 mg, PO, every 12–24 h for weeks may be effective.

Whether to treat *T gondii* seropositive cats with uveitis with anti-toxoplasma drugs has been controversial. A number of treatment protocols were evaluated in *T gondii*-seropositive and *T gondii*-seronegative cats. A greater number of *T gondii*-seropositive cats with uveitis responded to: (1) clindamycin HCl alone than to topical glucocorticoids alone; (2) clindamycin HCl alone than to any combination of glucocorticoids; (3) a combination of clindamycin HCl and any combination of glucocorticoids than to topical glucocorticoids alone; and (4) a combination of clindamycin and any combination of glucocorticoids than to any combination of glucocorticoids alone. *Toxoplasma gondii*-seropositive cats treated with clindamycin HCl with or without glucocorticoids were more likely to show a positive response to treatment than cats treated with glucocorticoids without clindamycin HCl. Overall, the percentage positive positive response to treatment in *T gondii*-seropositive cats (60.6%) was similar to that for *T gondii*-seronegative cats (75%). With topical glucocorticoids used alone, *T gondii*-seronegative cats were more likely to have a positive response than were *T gondii*-seropositive cats. Clindamycin was used in the treatment of 15 cats with *T gondii*-specific C-values >1; 13 cats showed clinical improvement independent of response to glucocorticoids. These treatment results have led to our recommendation to administer anti-Toxoplasma drugs to all *T gondii*-seropositive cats with uveitis, particularly if there is a poor response to topical glucocorticoids. Clindamycin hydrochloride at 12 mg/kg, PO, BID for 4 weeks or trimethoprim-sulfa at 15 mg/kg, PO, BID for 4 weeks have been recommended most frequently. Neither of these antibiotics clear the body of the

organism and so recurrence can occur. The clinician should also recognise that no serological or aqueous humour test result definitively documents clinical toxoplasmosis and so not all individual cats will respond to anti-toxoplasmic drugs.

The combination of doxycycline at 5 mg/kg, PO, BID, for 21 days with topic glucocorticoids successfully resolved uveitis due to bartonellosis in one cat (Lappin & Black 1999). Doxycycline may also be effective for treatment of ocular toxoplasmosis.

It is currently unknown whether cats with uveitis and herpesvirus 1 infections should receive primary therapy.

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