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Chapter 3

INFECTIOUS UVEITIS

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COMPLICATIONS OF UVEITIS

Uveal inflammation can result from a variety of causes, such as trauma, infections, neoplasia, and immune-mediated diseases.[1,2] In some cases of uveitis, the inflammatory reaction has no known primary cause and therefore is suspected to be an autoimmune disease. Uveitis is one of the most important groups of ocular disease in cats. It may be the first indication of a serious or life-threatening systemic disease, and the small size and close proximity of all intraocular structures make early recognition and treatment of uveitis imperative to avoid sight-threatening consequences.

ANATOMICAL CLASSIFICATION

Anterior uveitis or iridocyclitis involves inflammation of the iris and ciliary body. Although iritis implies inflammation of the iris only, it often is used synonymously with anterior uveitis. Intermediate uveitis, also referred to as pars planitis, involves predominantly the posterior portion of the ciliary body, the pars plana**.** Strictly speaking, posterior uveitis is inflammation of the choroid (choroiditis), but because the retina usually is affected concurrently, chorioretinitis is a more accurate term. Because the anterior and posterior uveal tissues are parts of a continuum, inflammation commonly occurs in both simultaneously. Panuveitis is the term used when the entire uveal tract is inflamed.

CAUSES

Many exogenous and endogenous causes of uveitis exist in cats. Most exogenous causes are from trauma to the eye, including blunt, penetrating, and surgical trauma that may or may not include infection or corneal ulceration. Endogenous uveitis may be parasitic, infectious, neoplastic, immune-mediated, or idiopathic. Infectious agents that have been associated with development of uveitis in cats can be found in Table 3-1. Between 25[3] and 90 per cent[4] of cases of uveitis in cats have been reported to be associated with clinical or serological evidence of infectious disease. The most common infectious diseases associated with uveitis are toxoplasmosis, feline infectious peritonitis (FIP), feline immunodeficiency virus (FIV), and feline leukemia virus (FeLV).

PATHOGENESIS

As with other tissues, intraocular inflammation is initiated by local tissue injury (e.g., trauma, infectious agent, antigen challenge). Tissue factors and chemoattractants are released from damaged tissue and microorganisms; vasodilation and changes in vascular permeability follow. These changes indicate disruption of the blood-ocular barrier. Inflammatory mediators, released by damaged tissue cells, cause leukocyte activation and migration. Because the globe has no lymphatic drainage, antigens from degraded organisms are transported to the spleen or other lymphoid tissue via the venous system to activate antigen-specific T and B lymphocytes. Immunocompetent T and B lymphocytes then migrate back to the eye and reside in the uvea.[5] Factors believed to help stop the immune response include elimination of the inciting antigen and production of inhibitory cytokines by T and B lymphocytes.[6] If the inciting antigen cannot be removed completely, as in autoimmune disease, chronic inflammation results. Some proposed mechanisms that contribute to development of autoimmune uveitis include (1) abnormal induction of tolerance to autoantigens, (2) release of normally sequestered autoantigens resulting from trauma or infection, (3) molecular mimicry (homology between pathogens and host tissue antigens), and (4) alteration of autoantigen structure resulting from tissue injury or inflammation.[5,7,8] Because uvea contains immunocompetent lymphocytes, chronic or recurrent inflammation also could result from specific or nonspecific activation of lymphocytes by non-self antigens.[9] The clinician must impress upon the client that even with an exhaustive diagnostic evaluation, a specific cause for uveitis may not be found. The client should understand that, regardless of the inciting cause, uveitis may become chronic, treatment may be palliative, and adverse sequelae are common.

Table 3-1 | **Infectious Causes of Uveitis in Cats**

BACTERIAL	VIRAL	MYCOTIC	PARASITIC
Mycobacterium spp.	FeLV	*Cryptococcus neoformans*	*Toxoplasma gondii*
Ehrlichia spp.	FIP	*Blastomyces dermatitidis*	Ophthalmomyiasis
Bartonella spp.	FIV	*Histoplasma capsulatum*	*Cuterebra* spp.
		Coccidioides immitis	Metastrongylus
		Candida albicans	

From Powell CC, Lappin MR: Causes of feline uveitis. Compend Contin Educ Pract Vet 23(2):128-141, 2001.

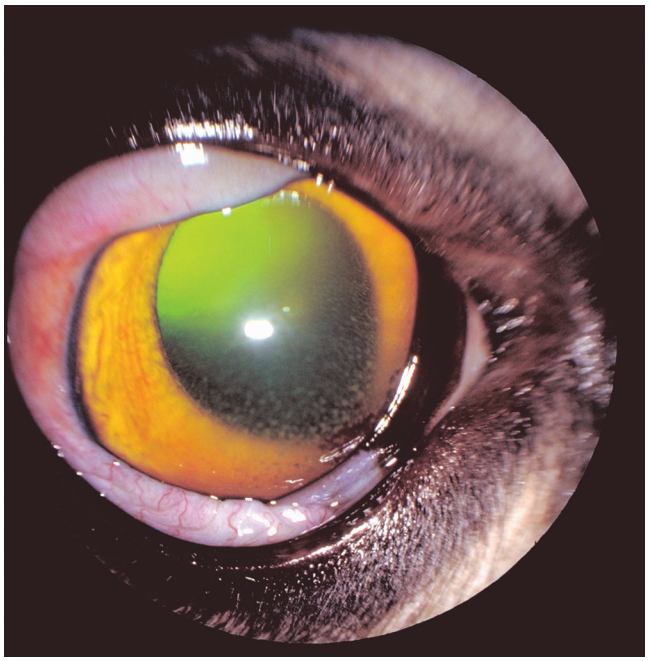

Figure 3-1. Keratic precipitates (KPs), which consist primarily of mononuclear cells, can be seen adhering to the corneal endothelium. Thermal convection currents within the eye cause KPs to be deposited primarily on the ventral half of the cornea. The presence of KPs indicates recent or active anterior uveitis.

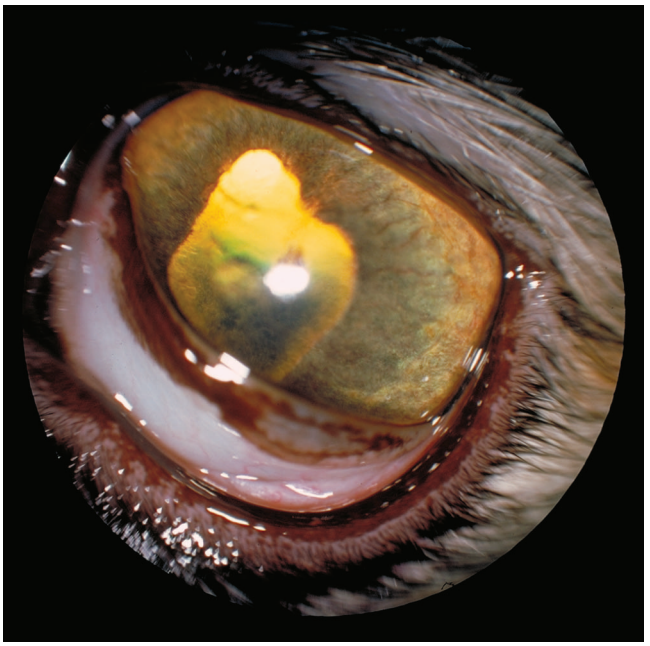

Figure 3-2. Posterior synechiae (adhesions of the iris to the lens capsule) have caused an abnormal shape to the pupil. Posterior synechiae are an indication of previous or active anterior uveitis.

CLINICAL FEATURES

Variations in clinical appearance of uveitis depend on location, duration, and severity. Ocular pain, manifested by photophobia, blepharospasm, enophthalmos, elevation of the third eyelid, and/or epiphora, is common with acute anterior uveitis but may be absent when chronic. Reddened sclera, caused by injection of conjunctival and episcleral vessels, and aqueous flare are the hallmarks of anterior uveitis. Aqueous flare is caused by increased protein concentration in the aqueous humor and is secondary to disruption of the blood-ocular barrier. Light passing through the anterior chamber is scattered in aqueous flare, and if severe, the aqueous humor appears cloudy. Corneal edema can result from the effects of inflammation on the corneal endothelium. As edema increases, the cornea becomes increasingly opaque and blue. Inflammatory cells in the aqueous humor may be deposited on the internal surface of the corneal endothelium as keratic precipitates (KPs). Normal convection currents in the aqueous humor cause KPs to be located primarily on the ventral half of the cornea. Keratic precipitates vary in size. Larger KPs are seen more often with granulomatous inflammatory processes associated with diseases such as FIP and toxoplasmosis (Figure 3-1).

The iris undergoes many changes with anterior uveitis. Inflammatory mediators, in particular prostaglandins, cause *miosis* by a direct effect on the iris sphincter. Very mild miosis is difficult to detect, so its absence should not be used to rule out uveitis. Iritis, manifested by iris vasodilation and increased iris vessel permeability, often causes a subtle to pronounced iris color change. On close examination, dilated iris vessels may be obvious, and the iris may appear swollen and have a thin coat of fibrin and cells giving it a velvet-like texture. As anterior uveitis becomes more chronic, the pupil margin may begin to form posterior synechiae (adhesions to the anterior lens capsule), which give the pupil an irregular shape and impair its ability to respond to light or dilating agents (Figure 3-2). If extensive posterior synechiae develop, aqueous humor cannot move from the posterior chamber to the anterior chamber. Aqueous humor then accumulates behind the iris and causes it to billow forward, a condition known as iris bombé. Because access to the anterior chamber is required for aqueous humor to reach the filtration angle, iris bombé is associated with increasing intraocular pressure and glaucoma. Peripheral anterior synechiae (adhesions of the peripheral iris to the cornea) can form with anterior uveitis as a result of iris bombé or secondary to iris swelling and inflammation. Inflammatory cells, iris swelling, and anterior synechiae also can impair aqueous outflow and contribute to the development of secondary glaucoma.

Aqueous humor formation is impaired when the ciliary body is inflamed. Thus anterior uveitis causes low intraocular pressure unless complicated by secondary glaucoma. Inflammation also causes ciliary muscle spasm, a major contributor to ocular pain. Accumulation of inflammatory cells in the peripheral anterior vitreous is referred to as pars planitis or intermediate uveitis. Because of its peripheral location, pars planitis often is not apparent without dilating the pupil.

Posterior uveitis is inflammation of the posterior uvea or choroid. Because of their close apposition, retinal inflammation often accompanies inflammation of the choroid, which creates chorioretinitis. Changes in the ocular fundus secondary to chorioretinitis are related to the breakdown of the blood-ocular barrier, located at the retinal blood vessels and the retinal pigment epithelium. Increased permeability of these barriers allows components of the blood to accumulate within and between the choroid and retina. Migration of inflammatory cells to the area of inflammation also occurs. Clinically, retinal and subretinal fluid exudes, and hemorrhage can be detected. Because the retina and subretinal space overlie the tapetum, tapetal reflectivity is diminished or obscured by areas of active chorioretinitis (Figure 3-3). Severe chorioretinitis can lead to partial or complete retinal detachment and decreased vision or blindness. Inflammation of both the anterior and posterior uvea is termed endophthalmitis.

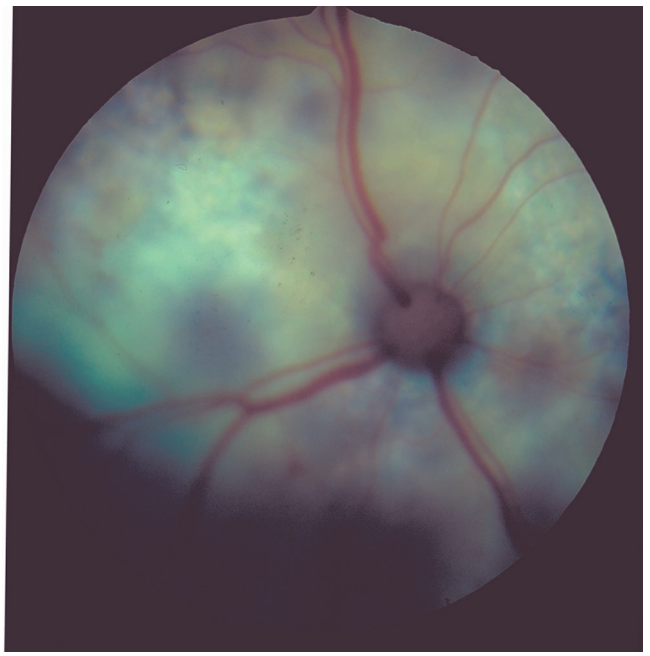

Figure 3-3. Active chorioretinitis in a cat with disseminated toxoplasmosis. Note the mottled, dull appearance of the tapetum. Retinal detachment also is present.

DIAGNOSIS OF INFECTIOUS CAUSES OF UVEITIS

The connection between uveitis and infectious disease can be difficult to make. The causes of uveitis generally cannot be differentiated by the clinical appearance. In addition to a complete physical examination, a complete blood count, urinalysis, and a serum biochemical panel in addition to ancillary diagnostic tests such as serology, aqueous or vitreous humor analysis, and histopathology often are needed to arrive at a specific diagnosis. Ocular fluids can be used for cytology, culture and sensitivity, polymerase chain reaction, and determination of antibody content.

Anterior Chamber Paracentesis

General anesthesia is recommended for anterior chamber paracentesis. To perform paracentesis, a 25-, 27-, or 30-gauge needle on a 1- or 3-ml syringe; small rat-toothed forceps; adequate lighting; and magnification are needed. The bulbar conjunctiva and cornea are flushed gently with a 1:20 povidone-iodine and sterile saline solution. Povidone-iodine soap should not be used because it irritates the cornea and conjunctiva. The globe should be grasped with forceps at the dorsolateral limbus. The needle should enter the eye at the limbus and parallel to the iris plane. The globe will be most stable if the needle enters the eye immediately adjacent to the hold of the forceps. Care should be taken to keep the needle bevel up and the tip away from the iris and lens (Figure 3-4). Up to 0.3 ml of aqueous humor usually can be removed slowly without collapsing the anterior chamber. After withdrawing the needle, gentle pressure is applied to the centesis site using a moistened cotton swab. Samples of aqueous humor can be dropped directly onto a swab for culture and sensitivity, or stored in a sterile container (such as a red top tube) for antigen, DNA, or antibody measurement techniques. Cytological examination is best performed on samples stored in a 1.5-ml blood collection tube that contains ethylenediaminetetraacetic acid (EDTA), concentrated by centrifugation, and stained with DifQuick or Wright's stain. Substrate requirements for PCR and real time-PCR (RT-PCR) assays vary by the assay; many can be performed on frozen samples. Clinicians should contact the appropriate laboratory for transport instructions. Indications for aqueous humor paracentesis are found in Table 3-2. Mild hyphema is the most common complication of aqueous humor paracentesis. Serious complications are rare if care is taken to avoid inadvertent contact with the iris or lens, if no more than

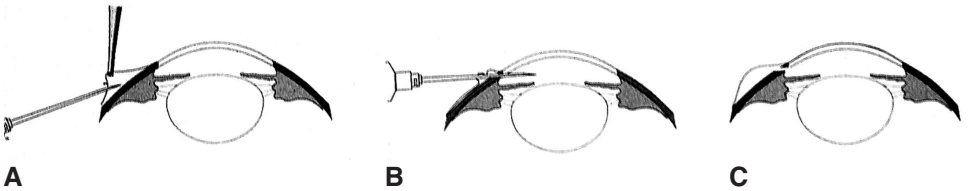

Figure 3-4. Anterior chamber paracentesis. **A,** The needle is tunneled beneath conjunctiva to the limbus. **B,** The needle enters the eye at the limbus with the bevel up and positioned parallel to the iris. **C,** After the needle is withdrawn, leakage of aqueous humor from the entrance site is common but can be controlled with gentle pressure from a cotton-tipped applicator.

Table 3-2 | **Diagnostic Tests for Ocular Fluids**

DIAGNOSIS	AQUEOUS HUMOR	VITREOUS HUMOR
Toxoplasma gondii	IgM, IgG (ELISA) PCR	
FIP, FIV	PCR	PCR
FeLV/Lymphoma	Cytology PCR	Cytology PCR
Bartonella henselae	Culture PCR	
Cryptococcus neoformans	Cytology, culture antigen (latex agglutination or ELISA)	Cytology, culture antigen (latex agglutination or ELISA)

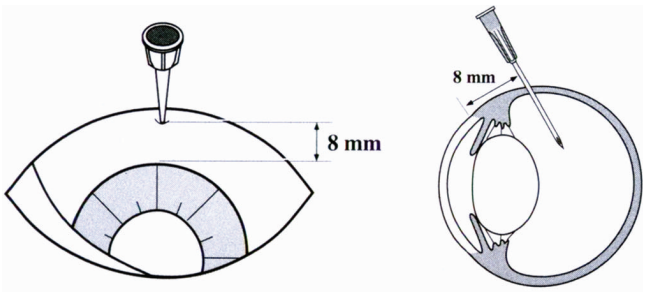

Figure 3-5. Posterior segment (vitreous) paracentesis. **A,** The needle enters the eye at the pars plana, approximately 7 to 8 mm behind the dorsolateral limbus. **B,** The needle is directed towards the middle of the vitreous so that the lens is avoided, or the needle is directed towards a targeted lesion such as a mass or exudate using direct visualization or ultrasound guidance.

0.3 ml of fluid is removed, and if aqueous humor is aspirated slowly.

Vitreous Paracentesis

Vitreous paracentesis should be considered when other methods of diagnosis have been unrewarding and a large vitreous mass or subretinal exudate can be found on ophthalmoscopy or ultrasonography. However, vitreous paracentesis generally is reserved for blind or nearly blind eyes because of the potential for causing severe ocular hemorrhage, retinal tear, and retinal detachment. General anesthesia is recommended. Before aspiration, the bulbar conjunctiva is cleaned gently with 1:20 povidone-iodine and sterile saline solution to remove all mucus and debris. The dorsolateral globe is grasped 6 to 7 mm behind the limbus with small, toothed forceps. Vitreous is viscous and can be difficult to aspirate, so a 3-ml syringe is needed for adequate suction. Aspiration through a 25-gauge needle can be attempted first, but a 22-gauge needle often is needed to obtain a sufficient sample for analysis. The needle should be aimed toward the center of the globe and should be introduced into the eye 7 to 9 mm posterior to the limbus, adjacent to the forceps for maximal stabilization (Figure 3-5). If a mass is present, the needle can be guided by ultrasound into the mass for aspiration. If the ocular media are clear, the needle can be guided visually with use of indirect ophthalmoscopy. Care should be taken not to advance the needle into the opposite retina and choroid. Slightly altering the needle position may help if aspirating fluid is difficult. If bacterial endophthalmitis is suspected and a vitreous injection of antibiotic is planned, the syringe should be removed and the needle left in place for injection. Vitreous samples should be handled the same as aqueous humor samples for culture, cytology, PCR assays, or RT-PCR assays (see Table 3-2).

GENERAL PRINCIPLES OF TREATMENT FOR UVEITIS

The primary treatment goals for uveitis are to stop inflammation, prevent or control the complications caused by inflammation, and relieve pain. Specific and nonspecific therapies are involved in treatment of uveitis. Specific therapies are used for infectious agents (e.g., bacteria, protozoans, fungi) or other contributors to inflammation (e.g., foreign body, corneal ulcer, luxated lens) identified through the examination and diagnostic evaluation. Nonspecific therapy includes decreasing the ocular inflammatory response with antiinflammatory drugs, mydriasis to prevent synechia formation, and cycloplegia to decrease pain. Glaucoma therapy also is instituted when evidence exists of decreased aqueous humor outflow. Therapy for specific agents causing uveitis is discussed under their individual headings.

Nonspecific Therapy for Uveitis

Antiinflammatory therapy is critical in the treatment of uveitis regardless of the cause. Failure to control inflammation can lead to posterior synechiae, glaucoma, cataracts, retinal detachment, vitreous degeneration, optic nerve atrophy, and retinal degeneration. Glucocorticoids and nonsteroidal antiinflammatory drugs (NSAIDs) are used commonly to control inflammation. Glucocorticoids (GC) can be administered topically, subconjunctivally, or systemically. Anterior uveitis usually is treated topically[10] a minimum of every 4 to 6 hours and as frequently as every 2 hours, depending on the severity of inflammation. Aggressive treatment is continued until the inflammation is controlled, and then the frequency of administration should be tapered slowly. If inflammation is not controlled, or if frequent treatments are not possible, supplementation with oral GC should be considered. Topical preparations with the best potency and corneal penetration are prednisolone acetate suspension (1 per cent), and dexamethasone solution (0.1 per cent) or ointment (0.05 per cent).[11] Topical GC are contraindicated in the presence of corneal ulceration because they inhibit wound healing and augment collagenase activity in the cornea.[12] Systemic administration of GC has minimal corneal effects unless the cornea is heavily vascularized; therefore they can be administered if concurrent corneal ulceration and anterior uveitis exist.[13]

Ocular release of prostaglandins can cause disruption of the blood-ocular barrier and uveitis. NSAIDs decrease inflammation by inhibiting cyclo-oxygenase, which results in decreased production of prostaglandins. NSAIDs, unlike GC, do not inhibit the lipoxygenase inflammatory pathway, and little information exists regarding their use for treatment of uveits in cats. Therefore use of NSAIDs should be considered primarily when GC are contraindicated. Frequently used topical ophthalmic NSAIDs include diclofenac 0.1 per cent, flurbiprofen 0.03 per cent, suprofen 1 per cent, and ketorolac 0.5 per cent. Ocular hemorrhage caused by platelet aggregation inhibition[12,14] can be

Table 3-3 | **Drugs Commonly Used to Treat Uveitis in Cats**

TOPICAL	DOSAGE
CORTICOSTEROID	
Prednisolone acetate 1% (suspension)	q1-12h
Dexamethasone sodium phosphate 0.1% (solution), 0.05% (ointment)	q1-12h
NSAID	
Diclofenac 0.1% (solution)	q6-12h
Flurbiprofen 0.03% (solution)	q6-12h
Suprofen 1% (solution)	q6-12h
Ketorolac 0.5% (solution)	q6-12h
MYDRIATIC/CYCLOPLEGIC (PARASYMPATHOLYTIC)	
Atropine sulfate 0.5%, 1% (solution and ointment)	q8-24h
Tropicamide 0.5%, 1% (solution)	q6-12h
MYDRIATIC (SYMPATHOMIMETIC) IN CONJUNCTION WITH PARASYMPATHOLYTIC	
Phenylephrine hydrochloride 2.5%, 10% (solution)	
ORAL	**DOSAGE**
CORTICOSTEROID	
Prednisolone, 5-mg tablet or prednisone 5-mg, 20-mg tablet	0.5 to 2.2 mg/kg q12-24h (higher dosages for initial therapy of severe inflammation)
NSAID	
Acetylsalicylic acid, 80-mg tablet	80 mg q48-72h
Ketoprofen, 12.5-mg tablet	2 mg/kg initially, 1 mg/kg daily maintenance
Phenylbutazone, 100-mg tablet	5 to 7 mg/kg q12-24h (recommended not to exceed 5 days)
Meloxicam, 1.5 mg/ml	0.025 mg/kg two to three times per week (not to exceed 0.1 mg maximal dose/cat)
SUBCONJUNCTIVAL	**DOSAGE**
LONG-ACTING CORTICOSTEROID	
Methylprednisolone acetate	4 mg/eye
Betamethasone	0.75 mg/eye
Triamcinolone	4 mg/eye

a potential complication of their use. Topical NSAIDs may complicate bacterial corneal infections and are not recommended when corneal infection is present.[12,15]

Systemic drug therapy is necessary to treat posterior uveitis, because therapeutic concentrations cannot be attained in the retina and choroid with topical drugs. Because GC suppress the immune response, they should be used with caution (if at all) when infection is suspected, especially if given systemically. If they are used during infection, concurrent treatment with an effective antimicrobial is essential. Drugs, dosages, and routes of GC administration can be found in Table 3-3. Use of systemic NSAIDs in cats has been associated with potentially serious side effects, including bone marrow suppression, gastrointestinal ulceration, hemorrhage, vomiting, and diarrhea.[16] Aspirin, phenylbutazone, ketoprofen, and meloxicam can be used systemically in cats with careful attention to dose, frequency of administration, and possible side effects.[17,18] The course of phenylbutazone therapy should be kept as short as possible, preferably not exceeding 5 days at higher dosages, and the drug should be withheld if inappetence or depression develops.[16] Duodenal perforation in a cat following treatment with oral carprofen has been reported.[19] Other reports indicate that carprofen can be administered safely to cats as a postoperative analgesic.[20]

Subconjunctival GC have been used to supplement topical or systemic GC therapy in cases of severe ocular inflammation or in patients in which frequent topical treatment is not possible.[10] Most subconjunctival preparations used are long-acting, and give a constant source of drug release for a 2- to 4-week period. A disadvantage to their use is the inability to withdraw the medication if complications arise. Drugs injected subconjunctivally enter the eye through the cornea, by leakage through the injection site, and through the sclera.[15] Subconjunctival GC are contraindicated with active corneal ulceration. Topical and subconjunctival GC use also may result in reactivation of feline herpesvirus-1 in carrier cats with previous episodes of viral keratitis or conjunctivitis.[21] Administration of subconjunctival GC to cats suspected to have recurrent feline herpesvirus ocular disease is not recommended.

Cycloplegics relieve pain associated with anterior uveitis by relaxing the ciliary body and iris muscle spasm. Mydriatics can prevent or break down posterior synechiae by dilation of the pupil and reduction of iris-lens contact. Cycloplegia and mydriasis can be accomplished by using a parasympatholytic agent. Topical 1 per cent atropine sulfate ointment is used most commonly, because the ocular solution is more likely to reach the mouth via the nasolacrimal duct and cause profuse salivation as a result of its bitter taste. The duration and frequency of application depend on the severity of ocular inflammation. Very mild inflammation usually is treated only once daily; severe inflammation may require treatment up to three to four times daily to maintain iris dilatation. Because parasympatholytics can cause decreased tear production, they are generally applied until the pupil dilates and then are discontinued until the pupil begins to constrict. The addition of a sympathomimetic agent may help to achieve mydriasis when synechiae have formed already (see Table 3-3).[22]

INFECTIOUS CAUSES OF UVEITIS

Toxoplasma gondii

Diagnosis

Serological evidence of infection by *Toxoplasma gondii* has been reported in as many as 78.5 per cent of cats with anterior and/or posterior uveitis,[4] and ocular lesions of toxoplasmosis have been well-documented.[23,24] No unique ophthalmological findings are associated with *T. gondii* infection. Because cats often become infected by carnivorism, a history of ingesting undercooked meat or hunting activity is common. Acute, polysystemic illness associated with toxoplasmosis is uncommon; fever and hyperesthesia possibly related to muscle inflammation are the most common systemic signs.[23] The actual prevalence of ocular toxoplasmosis is unknown. Many cats with uveitis and positive *T. gondii* serology have no other clinical evidence of disease. When available, ocular histopathology on these cases rarely identifies the organism,[3,25] which makes it difficult to correlate positive serology with ocular infection. This is especially true because many commercial laboratory tests for

T. gondii detect only serum IgG levels. IgG antibodies develop approximately 2 weeks post infection and may remain elevated for years, even in healthy animals.[26] A rising IgG titer (fourfold increase over 2 to 3 weeks) indicates recent or active infection and correlates better with disease. Alternatively, the presence of serum IgM against *T. gondii* can be used as an indication of recent infection, because IgM usually is not detectable 9 weeks post infection.[27]

Detection of *T. gondii* antibody production in the aqueous humor also is used to support the diagnosis of ocular toxoplasmosis in cats.[28,29] This test uses an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to *T. gondii* in both serum and aqueous humor. The Goldman-Witmer coefficient (C-value) is calculated to adjust for antibody leakage from the serum. A C-value greater than 1 indicates that *T. gondii*–specific antibody is being produced in the eye. Because IgM production has only been detected in the aqueous humor of cats with uveitis,[28,29] detection of IgM might indicate disease resulting from the organism. *Toxoplasma gondii* DNA has been amplified from blood and aqueous humor using a PCR assay.[30-32] However, because positive results are found in some apparently healthy research cats, the positive predictive value is not 100 per cent. Although a definitive diagnosis of ocular toxoplasmosis is difficult to make and confirm, treatment with an anti-*Toxoplasma* drug is justified when other causes of uveitis have been ruled out and serological evidence exists of recent or active infection, ocular *T. gondii* antibody production (particularly IgM) is identified, or organismal DNA is found in aqueous humor.

Treatment

Many cats with uveitis are seropositive for *T. gondii* but are otherwise clinically healthy. Most of these cats have anterior uveitis, and topical treatment with 1 per cent atropine (q12h to q24h to effect) and 1 per cent prednisolone acetate or 0.1 per cent dexamethasone is indicated. The frequency of GC treatment varies, depending on the severity of clinical signs, but generally q6h is minimal. If the response is poor, uveitis is severe, or more frequent administration of topical GC is needed but not possible, oral administration of prednisolone usually can be given safely in antiinflammatory dosages without a significant risk of potentiating systemic toxoplasmosis. Once inflammation subsides, the treatment is tapered slowly. If GC are tapered too quickly or discontinued too soon, inflammation will recur. The authors recommend aggressive treatment until uveitis has resolved. Oral GC usually are tapered first, followed by topical.

Systemically ill, *T. gondii*–seropositive cats always should be treated with an anti-*Toxoplasma* drug. In cats with uveitis alone, treatment with an anti-*Toxoplasma* drug can be justified in *T. gondii*–seropositive cats with uveitis, when other causes of uveitis have been ruled out, particularly if GC therapy has not elicited a response. Clindamycin is the drug of choice for treating clinical toxoplasmosis in cats.[27] Although several dose ranges have been reported, the authors currently recommend 10 to 12.5 mg/kg PO q12h for 4 weeks. Liquid clindamycin, administered at 4° C, is tolerated by most cats. Trimethoprim-sulfonamide combination therapy (15 mg/kg PO q12h for 2 to 4 weeks) also can be used for treatment of toxoplasmosis, although it is less suitable because of the potential side effects caused by folic acid deficiency in cats. Frequent monitoring for mental depression, anemia, leukopenia, and thrombocytopenia is required, especially if treatment is longer than 2 weeks.[27] Azithromycin is a potential alternate choice for cats intolerant of clindamycin or sulfa drugs; however, the most appropriate dose for the treatment of toxoplasmosis has not been determined. Nonspecific treatment for uveitis should be used concurrently. To date, no evidence suggests that the use of topical corticosteroids exacerbates systemic toxoplasmosis.

Feline Infectious Peritonitis

Diagnosis

Many cats with FIP are younger than 3 years old[33-35] and most have or will develop other clinical signs of systemic coronavirus disease. Ocular disease accompanied by ascites, thoracic or pericardial effusion, depression, icterus, renal failure, diarrhea, or neurological signs is suggestive of FIP. Ocular lesions are seen most often with the noneffusive or dry form of FIP. Anterior and/or posterior uveitis may be present. Iritis, large keratic precipitates, and clots of fibrin and blood in the anterior chamber are found commonly, along with cuffing of the retinal vasculature and chorioretinitis. Similar to toxoplasmosis, confirming a diagnosis of FIP can be challenging. Studies have shown 25 per cent of household pets and 80 per cent or more of cattery-reared cats carry serum antibodies against feline coronavirus.[31] Current serodiagnostic tests cannot distinguish between antibodies against pathogenic or nonpathogenic coronaviruses.[34-36] Therefore diagnosis usually is based on the combination of clinical signs, physical examination findings, and laboratory evaluation. High serum globulin (>5.1 g/dl), low albumin:globulin ratio, and effusion total protein content greater than 3.5 g/dl also are supportive. Although a high coronavirus antibody titer also is supportive, it does not correlate with disease as well as hyperglobulinemia or low albumin:globulin ratio.[34,37,38] RT-PCR tests on blood are not useful in the diagnosis of FIP because nonpathogenic coronaviruses can be found in the serum or plasma of normal cats.[38,39] Detection of coronavirus RNA in tissues, effusions, or aqueous humor by RT-PCR assay may correlate with the presence of FIP; however, nonpathogenic coronavirus also can be found in the tissues of normal cats.[38]

Treatment

The long-term prognosis for FIP is poor, even with treatment. However, some patients with ocular disease may be managed reasonably for several months to up to a year with medical therapy before the disease generalizes.[40,41] Because the pathogenesis of disease in FIP is immune mediated, the primary goal of treatment is to suppress the immune response. Several protocols have been described, but no current consensus exists regarding optimal treatment for systemic disease.[40,41] For ocular FIP, control of inflammation and prevention of sequelae are the goals of treatment for uveitis caused by FIP; both systemic and topical GC may be required (see Nonspecific Therapy for Uveitis).

Feline Leukemia Virus and Lymphoma

Diagnosis

FeLV-associated diseases are detected most often in young cats. Ocular disease can occur alone or in combination with systemic

signs of illness. Ocular disease does not occur with FeLV infection except by its association with the development of lymphosarcoma (LSA) or by immune suppression and increased susceptibility to other infectious diseases such as *T. gondii* and systemic mycoses. The incidence of ocular disease among clinically affected FeLV-positive cats is reported to be low (2 per cent or less)[42]; however, LSA has been shown to be a common cause of uveitis in enucleated eyes.[25] The ocular lesions of LSA result from neoplastic infiltration of the uveal tract and the clinical signs depend on tumor distribution. Nodular or diffuse infiltration of the anterior and/or posterior uveal tract is possible, and when diffuse, has an appearance similar to uveitis resulting from other causes.[43]

Although isolated ocular LSA probably does not occur, ocular disease may be the primary clinical sign, and many cats with ocular LSA appear to be clinically healthy otherwise.[43] Confirming the diagnosis of ocular LSA requires identification of neoplastic lymphocytes. Sometimes these can be found in aqueous humor cytology, but usually bone marrow cytology or biopsy of tumor located elsewhere in the body is necessary. Testing for infection by FeLV always is indicated because treatment and prognosis may be altered by the FeLV status.[44] However, the usefulness of FeLV testing for diagnostic purposes is limited because most FeLV-positive cats do not have LSA. Conversely, a negative FeLV test does not rule out LSA, because 20 to 70 per cent of cats with confirmed LSA are FeLV-negative.[45] The ELISA for detection of the p27 antigen in the blood is the most widely used, commercially available screening test for FeLV. A PCR assay that can be used to confirm lymphoma has been evaluated for use in dogs; further data are being collected concerning its use in cats.[46]

Treatment

Cats with LSA should be staged and their FeLV status should be determined, because both are related to treatment response and prognosis. Many chemotherapeutic drugs have been used to treat LSA in cats. An excellent review of these drugs and administration protocols can be found in the literature.[47] Ancillary therapy with topical GC and atropine helps control ocular inflammation and prevent sequelae (see Nonspecific Therapy for Uveitis). Systemic GC should be used with caution because their effect on viral replication is not known. Blind, painful eyes may require enucleation. If immunosuppression induced by the virus is considered part of the clinical syndrome, use of immunomodulator therapy or antiviral therapy can be considered. Administration of interferon alpha at 30 U/cat, PO q24h seems to improve quality of life in some cats but does not affect viremia. This protocol has not been assessed in controlled studies of ocular disease associated with FeLV. If antiviral therapy is considered, azidothymidine (AZT) administered as described for FIV may lessen the risk of secondary infections but has not been assessed in controlled studies for treating the ocular manifestations of FeLV.

Feline Immunodeficiency Virus

Diagnosis

Clinical disease in FIV-infected cats usually is detected in older, male cats with a history of exposure to other cats or a history of fighting. Clinical illness often is associated with immunodeficiency and resultant secondary infections, but several primary disease syndromes are attributed to the virus that include uveitis, enteritis, and renal disease. Histopathological evidence of anterior uveitis is found commonly in cats with advanced FIV infection,[48] which confirms the virus as a primary cause of uveitis. Local production of FIV antibodies and antigens in aqueous humor was documented recently in FIV-infected cats with uveitis but not in healthy FIV-seropositive cats.[49] These results support the hypothesis that FIV actively infects the eyes of some cats and can produce uveitis. *Toxoplasma gondii*, *Bartonella henselae*, and *Cryptococcus neoformans* infections all have been detected concurrently in FIV-seropositive cats, which suggests they may be the most common opportunistic infections.[50] Clinically, anterior uveitis, pars planitis, and glaucoma with or without concurrent uveitis have been identified in cats infected with FIV.[51] Pars planitis appears as white, punctate infiltrates concentrated in the peripheral, anterior vitreous.

Presently available commercial PCR tests for FIV are not sufficiently reliable to recommend their use for confirming or ruling out FIV infection. Serum antibodies against FIV can be detected by ELISA, Western blot immunoassay, or immunofluorescent antibody testing. The organism can be detected in blood by PCR or virus isolation. ELISA testing is used most frequently because it is available for in-clinic use.[52] FIV is not cleared by the immune response, and positive antibody tests generally indicate current infection. Because ELISA testing occasionally produces false-positive results, all positive tests should be confirmed with Western blot immunoassay. As an additional confounding factor, antibodies induced by a commercially available FIV vaccine (Fel-O-Vax, Fort Dodge Laboratories) cannot be distinguished from those induced by natural infection on any presently available FIV antibody test, so the vaccination status of all cats with uveitis must be determined. Detection of FIV antibodies does not prove that uveitis is due to FIV. Many FIV-seropositive cats with uveitis have serological evidence of exposure to other pathogens that can cause uveitis.[4,53] Other opportunistic infections should be excluded from the list of differential diagnoses before uveitis is attributed solely to FIV.

Treatment

Treatment of FIV is aimed primarily at management of secondary infections when they are identified. However, ocular inflammation (anterior uveitis and pars planitis) also can be a direct result of the virus. AZT may improve the quality of life and prolong life expectancy in cats with FIV infection.[54,55] When given at 5 mg/kg PO q8-12h, AZT is tolerated by most cats and has minimal toxicity. However, the efficacy of AZT for the treatment of ocular disease induced by FIV currently is unknown. Topical GC and atropine therapy are used to control pain and inflammation as discussed previously. As with FeLV-infected cats, systemic GC should be used with caution because their effect on viral replication is not known.

Systemic Mycosis

Diagnosis

Ocular disease has been reported in cats as the result of disseminated histoplasmosis, blastomycosis, coccidioidomycosis, cryptococcosis, and, rarely, candidiasis.[56,57] Cryptococcosis is the most common of the systemic mycoses seen in cats and

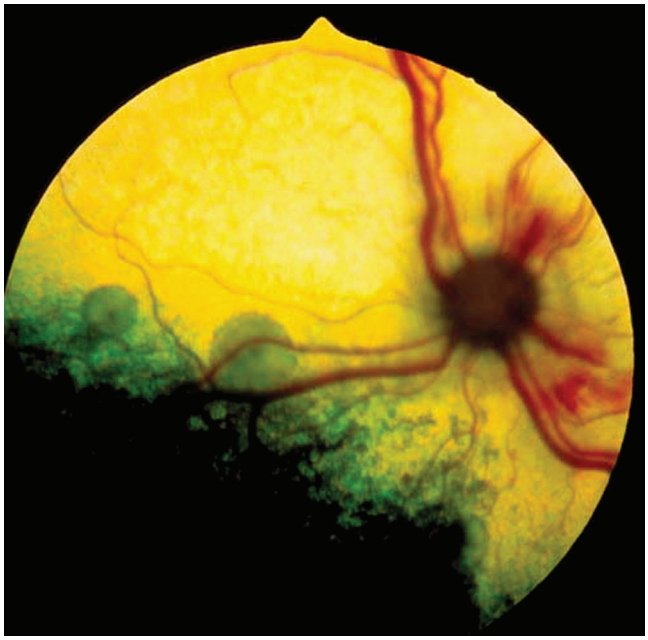

Figure 3-6. Two circular lesions of active inflammation can be seen near the tapetal-nontapetal junction of this eye infected with *Cryptococcus neoformans*. Optic neuritis also is present, indicated by peripapillary edema and hemorrhage.

usually is associated with nasal cavity disease. Cutaneous involvement, especially of the nasal region, and neurological signs also are common.[57,58] Intraocular manifestations of systemic mycoses include chorioretinitis, anterior uveitis, or both, although chorioretinitis alone is most common (Figure 3-6). Definitive diagnosis is made by demonstration of organisms in CSF, vitreous or aqueous humor, or from cytology of nasal exudates, aspirates of lymph nodes, or other tissues. Culture or tissue biopsy and histopathology may be necessary to confirm a diagnosis is some cases. *C. neoformans* antigen testing by latex agglutination and ELISA are available for use with serum, aqueous humor, and vitreous humor, and is superior to antibody testing because positive test results confirm the presence of the organism in the body. Even if the organism is identified by cytology, histology, or culture, serum antigen testing should be performed to serve as a baseline for therapeutic monitoring. Detection of antibodies against *Coccidioides immitis* and *Blastomyces dermatitidis* may be used to aid in the diagnosis if the organisms cannot be found, but false-positive and false-negative results may occur. Serological tests for *Histoplasma capsulatum* are unreliable in cats.

Treatment

Ketoconazole (KTZ), itraconazole (ITZ), and fluconazole (FTZ) are the drugs used most often for treatment of cryptococcal infections in cats. FTZ has the fewest side effects[59,60] and penetrates the CNS better than KTZ or ITZ. FTZ or ITZ are tolerated by most cats at the empirical dose of 50 to 100 mg/cat PO q24h. Treatment with antifungal agents should be continued for at least 1 month after resolution of clinical signs and after the cryptococcal antigen titer has dropped by at least two orders of magnitude.[60,61] When present, anterior uveitis should be treated with a topical GC, such as 1 per cent prednisolone acetate, and atropine. Treatment of chorioretinitis or optic neuritis requires systemic drug therapy. Extremely judicious use of oral GC along with antifungal therapy may be necessary to control the inflammation associated with posterior segment infection.[62] Some eyes with severe posterior segment infection that do not respond to antifungal medication may require enucleation.

Bartonella Species

Diagnosis

B. henselae and *Bartonella clarridgeiae* are two of the causes of cat-scratch disease in human beings.[63] Uveal tract inflammation from *B. henselae* infection in people has been reported.[64] Cats are the apparent reservoir host for *B. henselae* and 55 to 81 per cent of cats are *B. henselae*–seropositive. Fleas transmit the organism, so the incidence of infection is highest in areas with a warm, humid climate that are highly endemic for *Ctenocephalides felis*. The majority of naturally infected or experimentally infected cats show no clinical evidence of disease, but transient fever, lymphadenopathy, stomatitis, and neurological signs have been reported[65] (see Chapter 4). *Bartonella* spp. was suggested as a likely cause of anterior uveitis in one cat based on presence of *Bartonella* spp. antibody production in aqueous humor and a clinical response to doxycycline.[66] *Bartonella* spp. aqueous antibody production was evident in seven of 49 cats with uveitis, but in zero of 49 healthy cats in another study.[67] In that study, three of 24 cats with uveitis and one of 49 healthy cats had *Bartonella* spp. DNA in aqueous humor detected by PCR. These results suggest the organism can invade the eyes of cats and may be associated with uveitis in some cats.

Culture and PCR assay results can be used to confirm *Bartonella* spp. infections in cats.[68] However, because so many healthy cats are seropositive, PCR assay positive, or culture-positive in whole blood, these tests cannot be used to prove ocular bartonellosis. Because *Bartonella* spp. reside within red blood cells and hyphema often accompanies uveitis, detection of the organism in aqueous humor may indicate only bleeding into the eye. Further information concerning the diagnostic utility of aqueous humor testing is needed.

Treatment

Bartonella spp. should be considered on the list of differential diagnoses for cats with uveitis without other known causes, particularly if GC therapy is ineffective and a history of flea infestation exists. If patients fit these criteria, it may be prudent to administer a drug with anti-*Bartonella* activity. Doxycycline was effective given at 5 mg/kg q12h in one cat.[65] However, a dosage of 10 to 22 mg/kg PO q12h for 2 to 4 weeks has been recommended recently, because lower dosages have been shown to be ineffective for eliminating bacteremia.[65] Enrofloxacin at 22.7 mg/cat PO q12h is an alternate protocol for unresponsive cats or cats intolerant of tetracyclines. Lastly, azithromycin at 10 mg/kg PO q24h may be effective but has not been studied for the treatment of *Bartonella*-associated ocular disease in cats. Topical, nonspecific therapy should be used concurrently to treat uveitis.

Feline Tuberculosis

Diagnosis

Feline tuberculosis (TB) is caused most commonly by ingestion of uncooked meat or unpasteurized milk from cattle infected with *Mycobacterium bovis*. Because of eradication measures, the prevalence of bovine TB, and thus feline TB, is rare in the United States.[69] Chronic anterior uveitis, granulomatous chorioretinitis, ocular hemorrhage, and retinal detachment may be found in cases of feline tuberculosis.[69] Other clinical signs reflect the site of primary infection, and often are gastrointestinal. Diagnosis is made by identification of acid-fast bacilli from tissue aspirates or biopsy specimens. Intradermal skin testing and serological testing are unreliable in cats. Commercially available PCR tests likely will be available in the near future.[70]

Treatment

Although cats with *M. bovis* infection have been treated successfully with oral rifampin (4 mg/kg/day for 2 to 5 months) after excision of skin lesions, whether to treat is a serious concern because of the human health hazards and the potential for development of drug resistance.[70]

Intraocular Parasite Migration

Intraocular parasite migration (ophthalmomyiasis) is an uncommon cause of ocular disease in cats. Most cases are caused by larval stages of the rabbit and rodent bot fly, *Cuterebra* spp.,[71,72] although intraocular migration of an adult nematode also has been reported.[71] Anterior chamber involvement can cause acute, severe anterior segment inflammation, which often is poorly responsive to medical therapy. Retinal degeneration (by an unknown mechanism) may be a sequela to anterior segment *Cuterebra* spp. migration.[73,74] Posterior segment parasite migration causes minimal inflammation when confined to the subretinal space. Diagnosis is made by observing the parasite itself, or by observing the typical, curvilinear subretinal migration tracts.[74]

Treatment

When possible, the parasite should be removed surgically, followed by aggressive medical management of uveitis.

Feline Herpesvirus 1

Herpesvirus infections of people have been associated commonly with uveitis.[75] Until recently, feline herpesvirus-1 was believed to cause only conjunctivitis and keratitis. Serum and aqueous humor were collected from healthy cats, cats with idiopathic uveitis, and cats with suspected *Toxoplasma* spp. uveitis.[76] FHV-1 antibodies were measured in serum and aqueous humor, and FHV-1 DNA was measured in aqueous humor by PCR assay. Local production of FHV-1 antibodies was detected frequently in cats with uveitis; C values greater than 8 were detected only in cats with idiopathic uveitis. Additionally, herpesvirus DNA was detected in aqueous humor in 11 of 73 cats with uveitis but in only one of 22 healthy cats. These results show that FHV-1 enters the eyes of cats and may be associated with uveitis. Because the majority of client-owned cats are vaccinated or preexposed to FHV-1, antibodies are detected in most of their sera.[77] Thus serum antibody detection has no benefit in the diagnosis of FHV-1-associated uveitis. Further data are needed before treatment recommendations can be made.

Ehrlichia Species

Ehrlichia spp. are gram-negative rickettsia that infect a wide variety of hosts and usually are tick-borne. *Ehrlichia* spp. infections have been detected in some dogs with uveal tract inflammation.[78] The world's literature contains reports of a small number of cats with ehrlichiosis. The clinical syndromes reported have not included uveitis, but otherwise are very similar to those in dogs.[78,79] In an epidemiological study that compares incidence of clinical signs in cats with and without *Ehrlichia* spp. serum antibodies, a statistical association was made with ocular discharge and uveitis.[79] Further work is required to elucidate the involvement that *Ehrlichia* spp. infection has in cats with uveitis.

COMPLICATIONS OF UVEITIS

Aggressive treatment of uveitis is necessary to avoid secondary sight-threatening complications. Formation of synechiae can lead to glaucoma by obstructing the flow of aqueous humor through the pupil and/or out the iridocorneal angle. The intraocular pressure (IOP) of an eye with glaucoma secondary to anterior uveitis may be in the normal range because of the simultaneous decrease in aqueous humor production and outflow. Measurement of IOP should be performed on all patients with anterior uveitis. The development of secondary glaucoma should be suspected when IOP is greater than 10 mm Hg in an eye with anterior uveitis, and the eye should be monitored closely for increasing IOP. Glaucoma is treated best with carbonic anhydrase inhibitors and beta-blockers to decrease aqueous humor production. Carbonic anhydrase inhibitors can be administered orally (dichlorphenamide 0.5 to 1.5 mg/kg q12h to q8h or methazolamide 3 to 4 mg/kg q12h) or topically (dorzolamide or brinzolamide q8h). Systemic side effects (vomiting, diarrhea, panting, depression, potassium depletion) are less likely with topical treatment. Timolol, betaxolol, carteolol, levobunolol, and metipranolol are topical beta-adrenergic blocking agents and are administered q12h. Beta-blockers should be used with caution in animals showing signs of heart failure or bronchial asthma because of potential systemic absorption.

A cataract may result from uveitis, especially when chronic. The extent of cataract formation is dependent on the severity and duration of inflammation and may involve only the lens capsule or may affect the entire lens. Lens subluxation or complete luxation also can occur as a result of chronic uveitis and is especially common when the eye has become buphthalmic as the result of glaucoma. Removal of a cataract or a luxated lens caused by chronic or recurrent anterior uveitis usually is not rewarding, because uveitis remains a problem and may be exacerbated by surgery.

Chorioretinitis can lead to partial or complete retinal detachment. The end result of chorioretinitis is degeneration of the affected retina. Irregularly shaped areas of tapetal hyperreflectivity most often are indicative of retinal degeneration secondary to previous inflammation. Extensive chorioretinitis

results in visual impairment or, if the entire retina is involved, complete blindness resulting from retinal degeneration.

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