Pearls of Veterinary Practice

Bartonella: A New Etiological Agent of Feline Ocular Disease

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Introduction

During the past 13 years, numerous studies have demonstrated the medical and veterinary importance of a new group of bacteria, *Bartonella spp.*[1-6] The prototype *Bartonella* disease was recognized in humans in 1889 as cat scratch disease (CSD);[7] however, it was only in 1990 that the etiological agent for CSD, *Bartonella spp.*, was discovered.[1,3] As early as the 1960s, there were reports of associated ocular diseases in humans who had CSD,[8-10] and since then there have been numerous additional reports of ocular complications in humans infected with *Bartonella spp*.[11-21]

Most of the emerging *Bartonella* diseases were described first in humans and later in cats and dogs.[22-33] Recent studies have shown that pet cats serve as a major persistent reservoir host, with prolonged asymptomatic bacteremia, for five *Bartonella* species: *Bartonella henselae, Bartonella clarridgeiae, Bartonella koehlerae, Bartonella weissii,* and *Bartonella elizabethae*.[2,6,30,31] In one study, 41% of the cats were persistently bacteremic but showed no clinical signs.[6] Untreated infected cats may remain bacteremic for years and possibly even for life.[5,6] Cat and dog fleas and, less often, deer and dog ticks carry the bacteria and serve as the main vectors for transmission from cat to cat, and they also have the potential to act as vectors in transmitting *Bartonella* from cats to humans. There are approximately 60 million pet cats in nearly one-third of all households in the United States (US), of which 20% are infected with *Bartonella* and serve as potential reservoirs for human infection.[6,7,33,34]

In humans, ocular involvement occurs in 5% to 10% of patients with CSD.[17] In one study, the involvement appeared within 1 to 4 weeks after systemic signs of CSD.[18] Ocular *Bartonella* diseases in humans and cats are listed in Table 1. Neuroretinitis in humans can include optic disk edema, peripapillar subretinal fluid, multifocal retinitis and choroiditis, and a macular star. Of the ocular diseases, Parinaud's oculoglandular syndrome is the most common finding in humans where there is a regional lymphadenopathy usually associated with unilateral ocular involvement. Mild lid swelling occurs with serous to purulent discharge, and all conjunctival surfaces may be severely hyperemic with granulomatous nodules. Areas of necrosis of the conjunctival epithelium may also be present. Ocular involvement of *Bartonella* in humans has been proven by means of serological testing and finding *Bartonella* antibodies and deoxyribonucleic acid (DNA) in the eye.[35]

Table 1

Feline and Human Ocular Diseases Associated With *Bartonella*

Feline	Human
Uveitis	Uveitis
Chorioretinitis	Neuroretinitis
Conjunctivitis	Conjunctivitis
Karatitis	Disciform keratitis
Blepharitis	Blepharitis
	Parinaud's oculoglandular syndrome

Reports of human ocular *Bartonella* diseases prompted the authors and others to look for similar diseases in cats.[8-21] Two previous reports have shown *Bartonella spp.* to be the cause of several cases of uveitis in cats.[35,36] The incidence of anterior uveitis in the cat is second only to keratitis, conjunctivitis, or both, in its frequency in both general and specialty ophthalmology practices. Determining the etiology of anterior uveitis is often the most frustrating part of the entire clinical syndrome. It is generally accepted that both unilateral and bilateral involvement is most often associated with one or more systemic infections or neoplastic conditions [Table 2].[37-40]

It is important to establish a primary etiology for feline uveitis, since this may indicate specific therapy, may affect long-term prognosis, may identify a contagious disease among other cats in the household, and may establish the occurrence of a disease with public health significance. The diagnostic workup is often expensive and frustrating for both the client and veterinarian, and the results may prove to be very subjective or difficult to evaluate, with a definitive etiology determined antemortem in <50% of the cases. In severe cases where the animal's life is in jeopardy or where the eye does not respond to therapy and is blind and/or painful, enucleation and histopathology may be valuable aids in determining a definitive etiology. The type of inflammatory response, appearance of neoplastic cells, or in some cases (e.g., mycotic infections) the identification of organisms may lead to a specific etiology. One commonly held assumption is that many cases of lymphoplasmacytic anterior uveitis are caused by prior infections with toxoplasmosis. This hypothesis has been based on the known incidence of toxoplasmosis in cats, the frequent presence of low titers to this organism, the difficulty in identifying microorganisms in the ocular tissue, and the documented lymphoplasmacytic cellular response to *Toxoplasma spp.* infection. It is well documented that *Bartonella spp.* can also be associated with a lymphoplasmacytic inflammatory reaction in various tissues.[33-36]

Clinical Aspects

Detection of Bartonella Infection

For detection of *Bartonella* infection, a commercially available western immunoblot (WB) test[a] that detects antibodies against all species of *Bartonella spp.* that are known to infect cats and dogs is recommended.[33,34,41] The WB test correlates more closely with the ability to isolate *Bartonella spp.* from cats than does the immunofluorescent assay (IFA) test or the enzyme-linked immunosorbent assay (ELISA) *Bartonella* antibody test.[33,34,b] There is a high degree of serological cross-reactivity between all *Bartonella spp.*, and the WB will detect all *Bartonella* infections in cats and dogs.[33,34] Western immunoblot test results of +3 and +4 are considered positive, and these cats are considered to be actively infected with *Bartonella spp.* and, in the authors' opinion, should be treated.

Table 3 shows the *Bartonella* WB antibody test[a] results from serum submitted from cats throughout the US with ocular disease. The infection rate in cats with uveitis should be compared to the results of serum samples from healthy cats throughout the US evaluated with the same WB antibody test[a] that provided an overall *Bartonella* infection prevalence of 20%. Although the number of cases of chorioretinitis, keratitis, and corneal ulcers was small, 16 of the combined 23 cases tested were considered infected based on WB test results. In addition, 704 (51%) of the 1,375 cases of conjunctivitis were considered infected. None of the cats with uveitis, chorioretinitis, keratitis, and corneal

Table 2

Etiologies of Feline Anterior Uveitis

Bacteria
- *Bartonella* species

Viruses
- Feline leukemia virus (FeLV)
- Feline infectious peritonitis virus (FIPV)
- Feline herpes virus (FHV-1)
- Feline immunodeficiency virus (FIV)

Fungi
- Systemic fungal infections

Protozoa
- *Toxoplasma gondii*
- *Cuterebra* larva
- *Dirofilaria immitis*

Neoplasia
- Feline lymphosarcoma complex (FeLV)
- Metastatic neoplasia from a variety of primary sites

Table 3

Prevalence of *Bartonella* and Ocular Diseases Within the United States*

Ocular Disease	Number Tested	Number Positive	Percent Infected
Uveitis	251	145	58
Conjunctivitis	1375	704	51
Chorioretinitis	7	6	86
Keratitis	4	3	75
Corneal ulcer	12	7	58
Total	1649	872	53

* Samples evaluated by Western Blot analysis at the National Veterinary Laboratory[a]

ulcers were concurrently infected with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV), although the authors cannot rule out the possible coinfection with other microorganisms such as Herpesvirus and *Chlamydia*. In one author's (Ketring) ophthalmology practice, 27 (67.5%) of 40 cats with anterior uveitis were positive for *Bartonella* infection based on the WB test.[a]

Therapy

Previous *Bartonella* therapeutic trials were unsuccessful in humans and cats;[42-44] however, recent studies have shown that long-term antibiotic therapy with azithromycin, doxycycline, and rifampin have eradicated infections in both species.[45-48] Anti*Bartonella* therapy of infected cats consists of azithromycin (10 mg/kg body weight, per os [PO] given once daily for 21 days).[46-48] Alternatively, doxycycline (10 mg/kg body weight, PO every 12 hours for 6 weeks) or rifampin (10 mg/kg body weight, PO once daily for 21 days) can be used. Possible adverse reactions include azithromycin-intractable vomiting or diarrhea and doxycycline-induced esophageal strictures if the capsule lodges in the esophagus; this can be avoided with the administration of water following administration of the doxycycline capsules.

Generally, *Bartonella*-infected cats with uveitis are concurrently treated with routine topical anterior uveitis therapy (e.g., topical corticosteroids), nonsteroidal antiinflammatory drugs (NSAIDS), and, if required, topical atropine in conjunction with systemic antibiotics for eradication of the *Bartonella* infection.

In cats with blepharoconjunctivitis, the authors recommend that all *Bartonella* WB-positive cases be treated with azithromycin (as per previous dosing recommendations). If tear production is decreased (<10 mm per minute on Schirmer tear test), topical tear replacements should be applied as well. In cases of presumed herpetic keratitis, all cats should also be treated with oral L-Lysine and, depending on the case, topical antiviral drugs.

Evaluation of Bartonella Therapy

Six months following antibiotic therapy, a *Bartonella* WB antibody titration test can be performed to determine if there is a decrease in antibody titer, indicating successful elimination of *Bartonella*.[46-48] The antibody titers are determined by serial dilutions performed on both the prior and posttherapy serum samples; a two- to fourfold decrease in antibody titer between the pre- and posttherapy samples indicates successful *Bartonella* therapy.[46-50] It is necessary to wait 6 months from the end of therapy in order to allow the antibody levels to drop (catabolism) after removal of the *Bartonella* infection (antigenic).[46-50]

Discussion

Association of Bartonella With Feline Ocular Diseases

In general, *Bartonella spp.* involvement in the pathogenesis of feline ocular diseases is established on elimination of other causes (based on serology and clinical signs), positive *Bartonella* serology, response to therapy, decrease in *Bartonella* antibody titers after therapy, and, in select cases, histopathological diagnosis of lymphoplasmacytic anterior uveitis with no other apparent etiology. Positive identification of *Bartonella* infection by serology and detection of *Bartonella* antibodies and DNA in ocular fluid have recently been reported in several cases of uveitis in cats.[35,36] Many of the cats with ocular diseases seen at the author's (Ketring) ophthalmology practice also had concomitant inflammatory diseases in other tissues (e.g., gingivitis, stomatitis, upper respiratory diseases, gastrointestinal disease, and skin involvement) that may or may not be associated with *Bartonella* infection [Figures 1-6]. In this regard, one young cat with uveitis that was seen at the author's specialty practice also had bilateral skin eruptions on the ears, which was compatible with skin involvement in humans [Figure 1]. These lesions regressed with systemic *Bartonella* antibiotic medication.

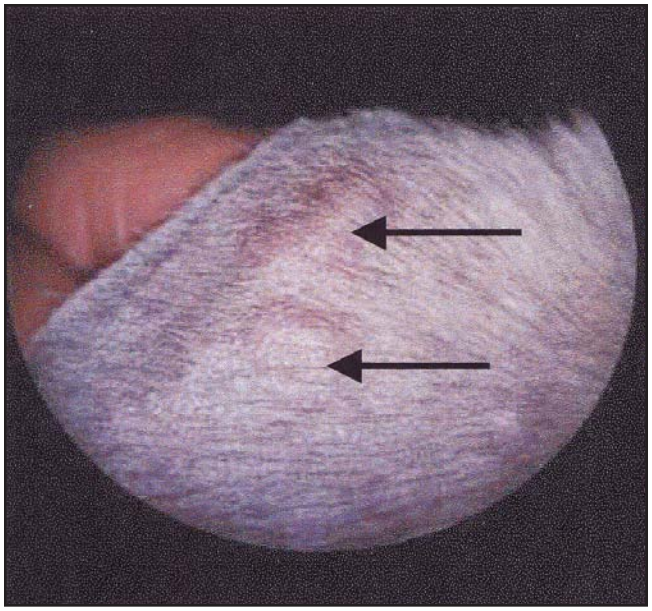

Figure 1—The ear of a 5-month-old Siamese cat that was *Bartonella*-infected on Western Blot testing. The multiple, nonpainful, raised skin nodules were present in both ears. These lesions are similar to cutaneous bacillary angiomatosis caused by feline *Bartonella spp.* infection in humans. At the time of this photograph, only the right eye was affected with anterior uveitis.

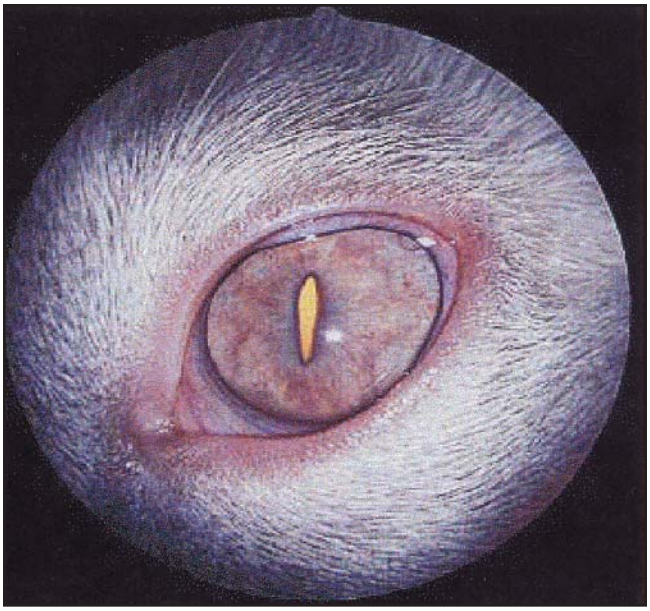

Figure 2—The left eye of the cat from Figure 1. At the time of this photograph, only the left eye was affected with anterior uveitis. The iris is swollen and darker than the opposite normal eye.

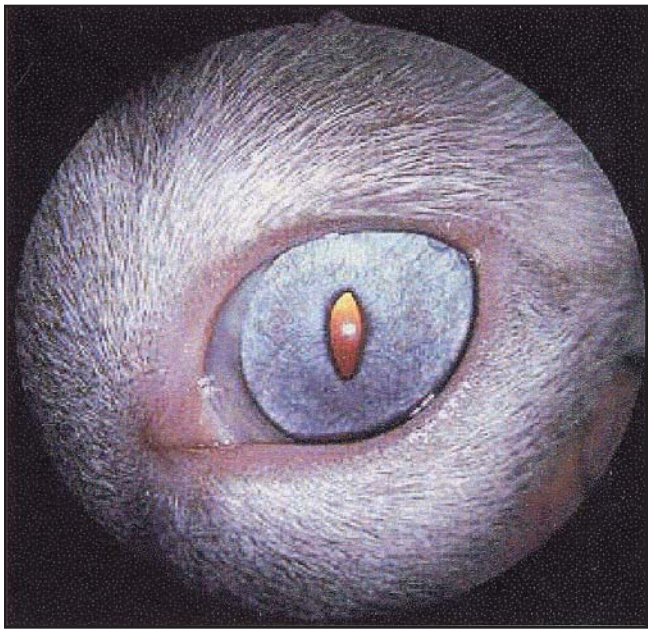

Figure 3—The left eye of the cat from Figure 2, 5 days after the start of a second course of azithromycin therapy, demonstrating marked improvement in the uveitis.

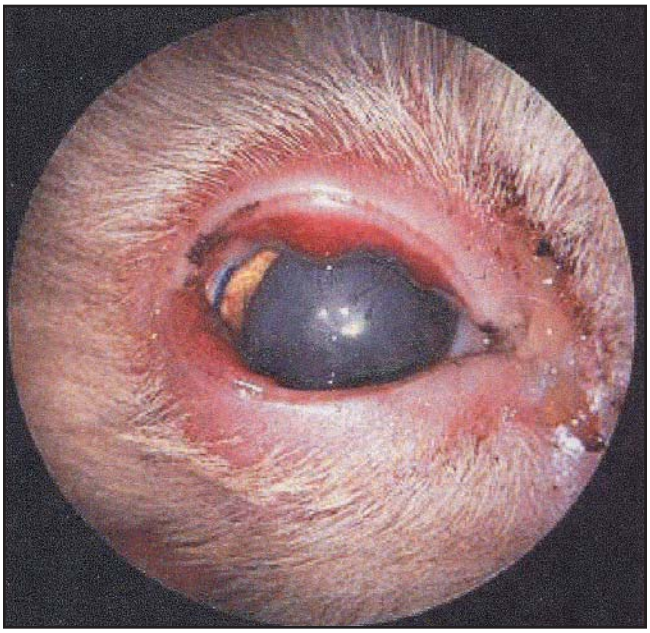

Figure 4—The right eye of a 15-year-old domestic shorthair cat with a history of bilateral corneal ulcers, blepharitis, conjunctivitis, and eosinophilic keratitis that was *Bartonella spp.*-positive on Western Blot testing. The lids of this eye were swollen; there was blepharospasm in both eyes; and the palpebral conjunctiva was severely hyperemic with multiple granulomas present.

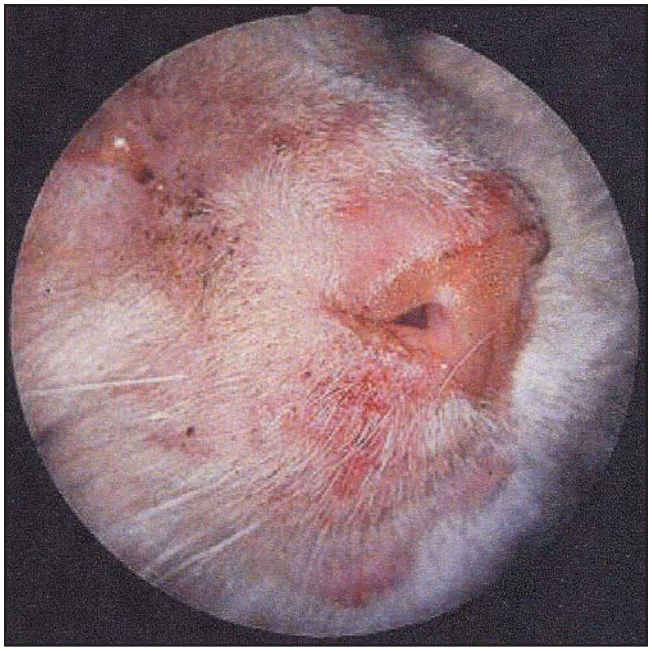

Figure 5—The muzzle of the cat from Figure 4 prior to azithromycin therapy. Self-inflicted excoriations of the skin of the muzzle and chin were seen, and a mild nasal discharge was present concomitantly with the eye lesions. The skin and nasal lesions resolved completely following azithromycin therapy.

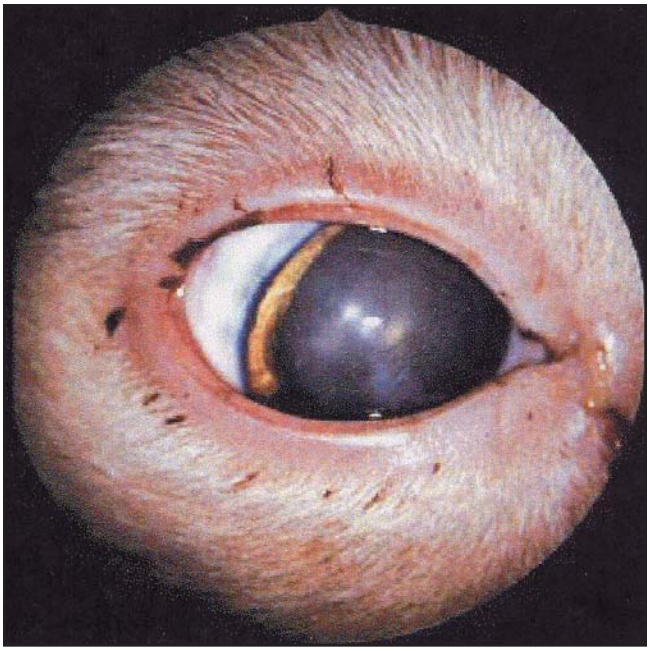

Figure 6—The right eye of the cat from Figure 4, after 21 days of azithromycin therapy, demonstrating marked improvement.

Bartonella: A New Etiological Consideration for Feline Ocular Diseases

Now a new group of bacteria has been recently incriminated as the cause of many previous feline cases of "lymphoplasmacytic anterior uveitis with no apparent etiology." Feline *Bartonella spp.* were first discovered in 1990, and a single case of the *Bartonella*-associated anterior uveitis was reported in 1999.[35] Even though there is a reported high incidence of *Bartonella spp.* in clinically normal cats (20% average prevalence for all areas in the US), it still can be the cause of disease in any cat.[6,33,34] There are examples of other common chronic infectious agents, such as FeLV, FIV, and *Toxoplasma spp.* in cats that do not result in clinical disease in every infected individual. Similarly, not all humans with *Bartonella* infection develop clinically apparent disease.

Ideally, confirmation of *Bartonella spp.* as the etiology of some ocular diseases can be made by culturing the organism or by using specific staining techniques on tissue samples. Unfortunately, *Bartonella spp.* are slow growing and extremely difficult to culture. Special staining with Warthin-Starry silver stain is difficult to evaluate in the eye, because the dark stain can be easily obscured by ocular pigmentation. Polymerase chain reaction-based techniques have been used in both human and veterinary medicine. However, serology appears to currently be the most reliable and readily available test to indicate the association of *Bartonella* infection with uveitis and other ocular diseases.

Some veterinarians question the necessity of determining a specific etiology for ocular diseases. In this regard, *Bartonella*-induced ocular disease can be treated with a readily available drug (e.g., azithromycin) that has few side effects and is effective against the agents that cause other ocular disease (notably *Chlamydia*, which causes conjunctivitis). Why not just treat? This philosophy ignores the veterinarian's responsibility to not over-use antibiotics, which can lead to formation of antibiotic-resistant bacteria, and to identify and inform the owner of a potentially dangerous zoonotic infection.

It is apparent that feline *Bartonella spp.* are etiologically involved in numerous chronic and acute inflammatory diseases of cats. *Bartonella spp.* may be the only etiological agent in some cats, but most likely *Bartonella spp.* are one of several microorganisms causing the inflammation. Concurrent infections with multiple microorganisms (e.g., viruses, fungi, bacteria) are thought to cause numerous chronic diseases in animals and in humans, and these diseases are called polymicrobial diseases.[51]

This report highlights the need for additional studies to determine the significance of *Bartonella spp.* as the etiology of a subset of ocular diseases in cats. If not the primary cause, the concomitant infection of *Bartonella spp.* with other microorganisms may explain the poor clinical response of some feline cases of anterior uveitis and blepharoconjunctivitis. Veterinary ophthalmologists and their clients have been frustrated for years with the lack of a definitive diagnosis for cases of feline anterior uveitis and blepharoconjunctivitis. The discovery of *Bartonella spp.* as a contributory factor in some ocular diseases allows the veterinarian to better diagnose, treat, and prevent ocular diseases in cats as well as to prevent potentially significant public health diseases.

[a] Fe*Bart* test; National Veterinary Laboratory, Franklin Lakes, NJ
[b] Hardy WD, Zuckerman EE. Unpublished observation. National Veterinary Laboratory, Inc., Franklin Lakes, NJ

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