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Ocular and periocular manifestations of leishmaniasis in dogs: 105 cases (1993–1998)

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Abstract

The purpose of this retrospective study was to determine the prevalence, type, and prognosis of ocular lesions associated with leishmaniasis in dogs. One hundred and five dogs (24.4% of all cases of leishmaniasis diagnosed during the study period) had ocular or periocular leishmaniasis, and 16 dogs (15.2% of ocular cases) had only ocular lesions and systemic signs were not apparent. Anterior uveitis was the most common manifestation and other prevalent findings included blepharitis and keratoconjunctivitis. Several distinct variations of eyelid lesions were seen including a dry dermatitis with alopecia, diffuse blepharedema, cutaneous ulceration, and discrete nodular granuloma formation. In some cases with keratoconjunctivitis, corneal lesions clinically resembled nodular granulomatous episclerokeratitis. Twenty-seven of the 34 cases with ocular lesions had improvement in signs following systemic antiprotozoal and topical anti-inflammatory therapy, although many cases with anterior uveitis required long-term topical therapy. Response of ocular signs correlated highly with overall, systemic response to therapy. Ophthalmic manifestations of systemic leishmaniasis are common in the dog, and this disease should be considered in the differential diagnosis of most adnexal and anterior segment ocular inflammatory lesions in dogs in endemic areas.

Key Words: anterior uveitis, blepharitis, canine, keratoconjunctivitis, leishmaniasis

INTRODUCTION

Canine leishmaniasis is a chronic and sometimes fatal disease which is endemic along the Mediterranean shore, parts of east Africa, India, and Central and South America. In the Mediterranean region, *Leishmania infantum* is the subspecies responsible for leishmaniasis, and the infection vectors are sand flies (*Phlebotomus* spp.). Following the vector bite, the leishmania amastigotes infect the dermal macrophages and, with a nonprotective immune response in some dogs, disseminate throughout the body and cause disease. Two clinical manifestations of the disease, which often coexist in the same dog, are commonly recognized including a visceral form, in which multiorgan involvement stems from infection of the reticuloendothelial system, and a cutaneous form with a wide variety of skin lesions.[1,2] Clinical signs associated with leishmaniasis are highly variable and, because of the diversity of clinical presentation, the disease may be difficult to diagnose.[1–3]

Ocular manifestations have often been described with canine leishmaniasis, generally concurrent with other systemic signs, but rarely independent of systemic findings.[4–12] Blepharitis and keratoconjunctivitis have been described as the most frequent lesions in some reports,[4,10,11] although a granulomatous or lymphocytic/plasmacytic anterior uveitis predominate in other studies.[10,13] Other ocular manifestations that are uncommon or rare that have been reported include cyclitis, chorioretinitis, retinal detachment, keratoconjunctivitis sicca, cataracts, and glaucoma.[4,6,9,11] The relative prevalence of ocular lesions in dogs with systemic leishmaniasis has been reported in three studies to vary between 16% and 80%.[4,10,12] However, details of ophthalmic examinations, or whether they were routinely performed on all dogs with leishmaniasis in these studies, was not reported, and as a result the ocular manifestations with canine leishmaniasis have not been well defined. The purpose of this study was to determine the prevalence and type of ocular and periocular lesions present, and prognosis of ocular lesions following antiprotozoal and topical anti-inflammatory therapy in a large series of sequential cases of canine

leishmaniasis that were referred to The Veterinary Teaching Hospital in Barcelona, Spain, which is in an endemic area.

MATERIALS AND METHODS

Medical records of all cases of confirmed leishmaniasis in dogs at The Autonomous University of Barcelona, College of Veterinary Medicine between 1993 and 1998 were reviewed. Dogs were included in the study only if the diagnosis was confirmed by at least two of three means: cytologic or histopathologic identification of the organism, serologic results, and/or polymerase chain reaction testing. The cytological identification was performed by direct observation of the parasite in bone marrow or lymph node aspirates, or by skin biopsies with or without a immunoperoxidase test as described previously.[14] Serologic studies were conducted with ELISA[15], using diagnostic criteria previously cited.[15–17] The polymerase chain reaction test was performed with bone marrow smears or by paraffin-embedded skin biopsies using a previously validated method.[18]

A preliminary ophthalmic examination which included inspection of the eyelids and globe with a focal light source was performed on all cases, generally by the attending (internal medicine) clinician. If abnormalities were noted, a complete ophthalmic examination, including slit-lamp biomicroscopy and indirect ophthalmoscopy was performed by an ophthalmologist and ocular signs were recorded.

Following a review of medical records of all 105 cases of ocular leishmaniasis and calculation of lesion prevalence rates, 34 of the cases in which follow-up ophthalmic examinations were available were studied in more detail to ascertain the response of ocular lesions to therapy. The cases were treated with subcutaneous *N*-methylglucamine antimoniate (Glucantime®, Rhone-Merieux, Lyon, France) daily at 80 mg/kg for a minimum of 30 days, and allopurinol (Zyloric®, Glaxo-Wellcome, UK) orally at 10 mg/kg every 12 h for 6 months to 1 year. Ocular inflammatory lesions were treated with topical 0.1% dexamethasone ointment or solution, or 1% prednisolone acetate suspension. Some dogs with anterior uveitis and all those with posterior uveitis concurrently received a short course of an anti-inflammatory dose of oral prednisolone (1.0 mg/kg BID for 5 days, 1.0 mg/kg/day for 5 days, and 1.0 mg/kg every other day for 5 days). Cycloplegia/mydriatic therapy was used for uveitis cases where appropriate. When a secondary bacterial infection of the adnexa or ocular surface was suspected, topical antibiotic was also prescribed. A variety of antihypertensive agents was prescribed when secondary glaucoma was present.

RESULTS

Four hundred and thirty cases of canine leishmaniasis were diagnosed during the study period and, of these, 105 (24.4%) were diagnosed with ocular or periocular lesions referable to the disease. Sixty-eight were males and 37 were females, and the mean age was 5.2 years (range 5 months to 13 years). Eighty-four dogs (80%) were large breeds (> 20 kg), and the most common breeds were German Shepherd ($n = 18$), and mixed breed ($n = 27$).

The dogs with ocular leishmaniasis most commonly presented for a variety of systemic signs including malaise, weight loss, diarrhea, renal or liver failure, anemia, lameness, dermatitis, or epistaxis. However, in 15 dogs, abnormalities involving the eyes were the presenting complaint by the owner. Cutaneous signs of leishmaniasis were present in 69 cases, signs of visceral leishmaniasis were present in 43 cases, and 31 dogs had both of these clinical findings of the disease. Sixteen of the 105 cases (15.2%) had only ocular lesions, and no identifiable systemic signs. In three of these 16 cases, the diagnosis was initially established by identification of the organism in cytological specimens from conjunctival scrapings.

Ocular lesions were bilateral in 103 cases and 78 of these had more than one ocular sign. In order of frequency, these included uveitis (45 dogs), periocular alopecia (28 dogs), blepharitis (33 dogs), conjunctivitis (33 dogs), keratoconjunctivitis (33 dogs), keratoconjunctivitis sicca (KCS, three dogs), and orbital cellulitis (two dogs) (Table 1).

The uveitis was confined to the anterior uveal tract in 41 cases, and in 26 of these, it appeared to be relatively acute in onset, and manifested with iris and corneal edema, miosis, and fibrin formation in the anterior chamber (Fig. 1). In 15 of these 41 cases, there was formation of discrete, multifocal nodules in the iris stroma (Fig. 2). Many of the latter type of uveitis cases developed at varying time intervals following antiprotozoal therapy, and were not apparent on initial examination. Secondary glaucoma developed in 15 eyes (7.1%) (nine dogs) with anterior uveitis. Bilateral posterior uveitis was diagnosed in eight eyes (four dogs), all of which had concurrent anterior uveitis. In all four of these cases (7/8 eyes), a multifocal chorioretinitis with small focal areas of hyporeflectivity and hemorrhage in the tapetal fundus were present. One of these dogs had a complete unilateral exudative retinal detachment (Fig. 3) with a multifocal chorioretinitis in the fellow eye.

Periocular alopecia was present in 28 dogs, and 21/28 of these cases also had alopecic areas in other cutaneous areas

Table 1 Distribution of ocular lesions in 105 dogs (210 eyes) with leishmaniasis

Ocular sign	Affected eyes (%)	Prevalence
Anterior uveitis	90	42.8%
Periocular alopecia	56	26.7%
Diffuse blepharitis	54	25.7%
Ulcerative blepharitis	8	3.8%
Solitary eyelid nodule	2	0.09%
Conjunctivitis	66	31.4%
Keratoconjunctivitis	66	31.4%
Keratoconjunctivitis sicca	6	2.8%
Posterior uveitis	8	3.8%
Orbital cellulitis	4	1.9%

of the body. The alopecic areas typically affected an area 4–5 mm wide adjacent to the lid margin and often had a dry, seborrheic lesion with desquamation. Several distinct variations of blepharitis were seen, including diffuse blepharal thickening, edema and hyperemia (54 eyes, 27 dogs; three of these cases also exhibited meibomitis, Fig. 4); superficial ulceration of the lid margin and adjacent skin with a moist dermatitis (eight eyes, four dogs, Fig. 5); and the presence of 1–3 cutaneous nodules 2–5 mm in diameter (two eyes, two dogs, Fig. 6).

Diffuse chemosis and an induration of the conjunctiva, hyperemia, and a purulent exudate typically characterized conjunctivitis (Fig. 7). Multifocal, discrete white nodules in the conjunctiva were occasionally noted. Keratoconjunctivitis was seen in association with these similar conjunctival lesions in addition to focal or geographic areas of corneal edema, vascularization, and interstitial cellular infiltrate, generally near the corneoscleral junction. In four of these cases, a focal pink, raised nodule 3–5 mm in diameter was present at the lateral corneoscleral junction (Fig. 8). Three dogs with keratoconjunctivitis had keratoconjunctivitis sicca (two bilateral, one unilateral). Bilateral orbital cellulitis was seen in two cases and was characterized by profound exophthalmos, chemosis, and periocular swelling.

In the 34 cases that were evaluated to ascertain prognosis and response to antiprotozoal therapy, the mean follow-up interval was 19.7 months (range 5 days to 6 years). In 16 of 34 cases, ocular signs developed after systemic manifestations (mean interval 10 months, range 17 days to 3 years); in 13 of 34 cases, ocular signs were seen either preceding or concurrent with systemic signs. In five of 34 cases only ocular, and no systemic signs, developed. Among these cases, 17 dogs had marked to complete resolution of ocular signs with a mean interval to resolution of 2.2 months (range 15 days to 8 months). In this group of 17 dogs, lesions included blepharitis (five cases), conjunctivitis (five cases), keratoconjunctivitis (two cases), orbital cellulitis (one case), and uveitis (four cases, one with secondary glaucoma). Ten additional cases had improvement of the ocular lesions but required a long period of topical therapy (months to years) to control ocular signs, including three cases with KCS, and seven cases with anterior uveitis (including three eyes with secondary glaucoma). Five cases failed to improve following treatment with lesions including conjunctivitis (one case), granulomatous keratitis (one case), and anterior uveitis (three cases). Two cases were lost to long-term follow-up and the status of response to therapy could not be definitively determined. The response of ocular signs correlated with the status of systemic signs in 29 cases, and was not correlated to systemic signs in three cases.

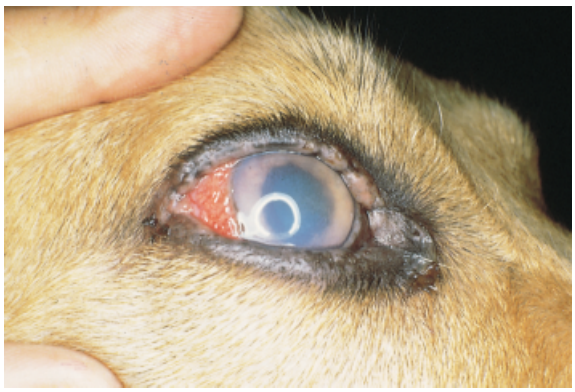
Redevelopment of ocular disease were seen in 11 cases from 2 months and 3 years after treatment; four of these cases have recurrence of anterior uveitis; and four additional cases subsequently developed an anterior uveitis following treatment, which was not present at the time of initial diagnosis.

DISCUSSION

Results of this study suggest that ocular and periocular tissues are commonly affected in dogs with systemic leishmaniasis, occurring in approximately 25% of confirmed cases of canine leishmaniasis diagnosed at the primary author's institution over a 5-year period. This percentage is somewhat higher than a previous study of canine leishmaniasis, in which 16% of 150 dogs had clinically evident ocular lesions, including keratoconjunctivitis and, less commonly, anterior uveitis and panophthalmitis.[4] The divergence of results between these two studies may be partially explained by the fact that we considered the periocular, seborrheic dermatitis with alopecia in the prevalence determinations, while this was categorized as dermatological involvement in the previous study. Additionally, details of ophthalmic examinations, or whether they were routinely performed, were not cited in the previous study. Another prior study of canine leishmaniasis found 80.5% of 41 dogs with systemic leishmaniasis had clinically evident ocular signs, and an even higher percentage of these same dogs (96.7%) had microscopic ocular lesions attributable to leishmania.[10] However, these authors appeared to study only selected cases with ocular lesions, and it is unclear whether a representative and sequential sample of dogs with other signs of leishmaniasis, as were evaluated in the current study, were included. The approximate 25% prevalence of ocular manifestations noted in the current study may be an underestimation as, for most of the 430 cases of leishmaniasis diagnosed, examination by an ophthalmologist was only performed if requested by the attending clinician, generally after they had noted a problem with the eye on a routine physical examination. As a result, mild, subclinical intraocular lesions, especially multifocal chorioretinitis, may have gone undetected.

Importantly, 15 cases in the current study had ocular lesions as the presenting complaint, and 16 dogs had no identifiable systemic signs as assessed by physical and clinicopathologic examination. In two of these cases, a solitary or multiple, focal, unilateral cutaneous nodule was present in the eyelid skin and was the only lesion evident. It has been proposed that focal cutaneous nodules such as these represented a granulomatous reaction at the original site of vector transmission of the organism, and they can be seen as the only clinical sign in dogs with leishmaniasis.[19] Whether the remaining 14 dogs with only ocular lesions were suffering from visceral signs of leishmaniasis that had either resolved or not yet developed, or subclinical infection which was not detected with our examination methods, could not be determined with certainty. The high seroprevalence rates of dogs to leishmania in endemic areas suggest that subclinical infection is common.[20,21]

In contrast to several other studies where uveitis was uncommon,[4,10,12] it was the most prevalent ocular finding in dogs in this study. The reasons for this difference were unclear but may have resulted from a more critical



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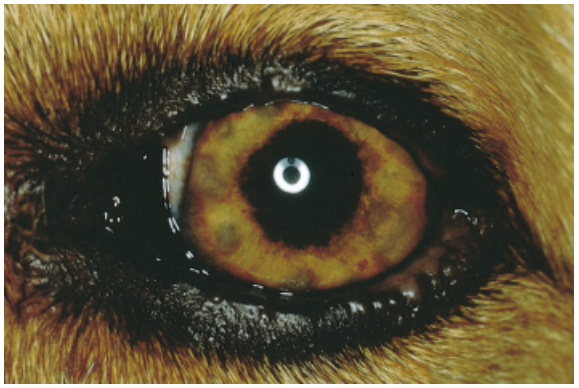

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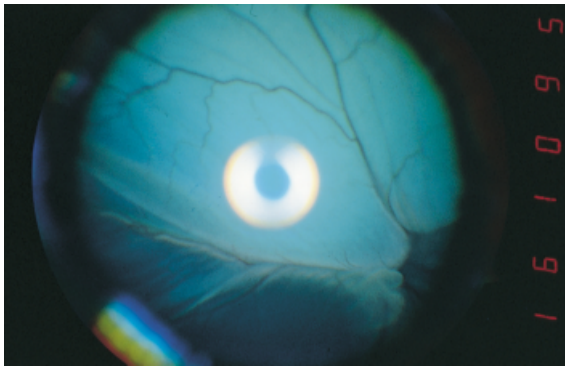

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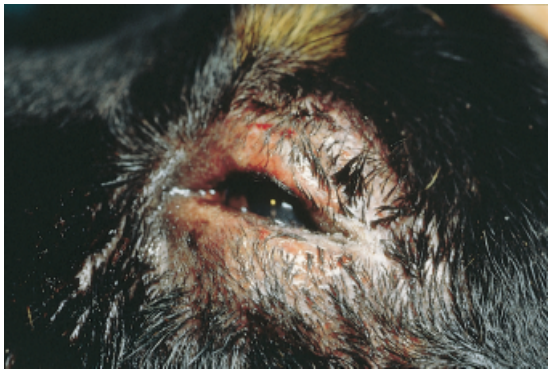

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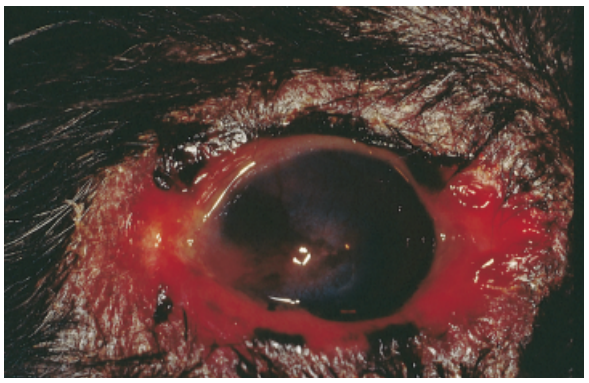

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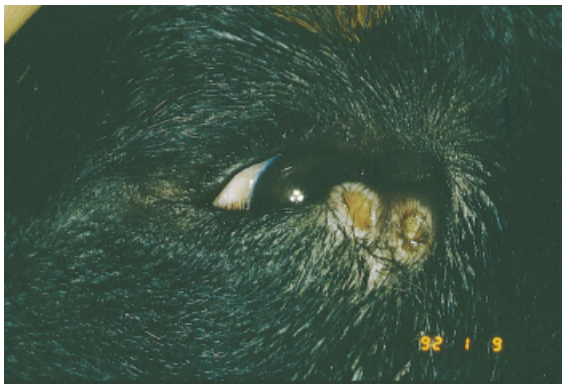

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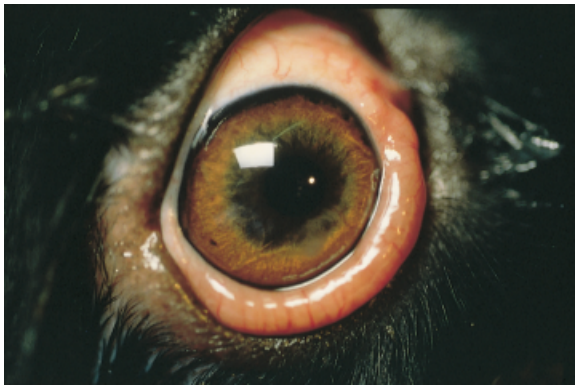

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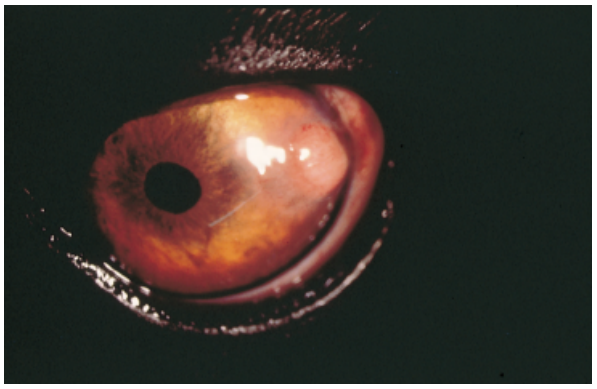

Figure 8.

Figure 1. Acute, anterior uveitis with secondary corneal edema in a dog with leishmaniasis. Blepharitis with a meibomitis and keratoconjunctivitis are also present.

Figure 2. Anterior uveitis characterized by the formation of multifocal, gray nodules in the iris stroma. In this case, the uveitis developed following initiation of systemic antiprotozoal therapy. Note also the blepharitis with meibomitis.

Figure 3. Complete, exudative retinal detachment from choroiditis in the left eye from a dog with leishmaniasis. The right eye of this patient exhibited a multifocal chorioretinitis.

Figure 4. Diffuse blepharedema with mild, superficial ulceration in a Rottweiler. Keratitis with corneal edema and neovascularization were also present in this dog.

Figure 5. Severe, ulcerative blepharitis with purulent exudate. A keratoconjunctivitis is also present with corneal edema, neovascularization and corneal pigmentation.

Figure 6. Multifocal cutaneous nodules in the medial canthal region in a dog with leishmaniasis. Such nodules are proposed to represent the original site of vector transmission of *Leishmania infantum*.

Figure 7. Conjunctivitis in a dog with leishmaniasis. Note the prominent thickening of the ventral bulbar conjunctiva. Cytologic evaluation of the conjunctiva revealed mononuclear inflammatory cells and numerous amastigotes of *Leishmania infantum*.

Figure 8. Keratoconjunctivitis with the formation of a focal, raised, pink nodule at the lateral limbus in a dog with leishmaniasis. Note the similar appearance to nodular granulomatous episclerokeratitis. Cytologic evaluation of scrapings from this nodule revealed numerous organisms.

intraocular examination in the current study, which was performed in all dogs with obvious anterior segment lesions and by an experienced clinician. Interestingly, the intraocular inflammation was almost exclusively diagnosed in the anterior segment. This anterior uveal predilection has been previously noted for ocular involvement in canine leishmaniasis and is in contrast to many other systemic infections, notably most systemic mycosis and toxoplasmosis, in which posterior segment lesions predominate. Posterior uveitis was diagnosed in only four cases, although this may be an underestimation because, in some cases, the fundus was not ophthalmoscopically visible due to the severity of anterior segment inflammation. The anterior uveitis manifested with either an acute, fibrinous form, or one characterized by the formation of multifocal nodules in the iris stroma, without excessive anterior chamber exudation.

Because leishmaniasis is characteristically associated with widespread immune complex formation and deposition, hyperglobulinemia from immune activation, and antinuclear antibody formation,[1,22] it has been suggested that the leishmania-induced uveitis, especially the nodular form, may have an immunopathogenic basis.[2,10,11] Additionally, one study suggested that anterior uveitis often develops following antiprotozoal therapy[12] and may have an allergic basis similar to the postkala-azar leishmaniasis of humans.[23] Other findings supporting an immune-mediated basis for the uveitis include evidence of local, specific immunoglobulin production, and diffuse deposition of immunoglobulin in anterior uveal tissues.[10,24] Analysis of a limited number of canine globes with leishmania and anterior uveitis have demonstrated two general types of anterior segment inflammation, namely a granulomatous iridocylitis with numerous amastigotes, and a lymphocytic/plasmacytic iridocyclitis with variable but often sparse presence of the organism.[2,6,10,11] Similarly, these two distinct types of uveitis were seen clinically in dogs in this study and the nodular form often developed following initiation of antiprotozoal therapy. As such, it may have an allergic basis resulting from death of the organism in ocular or systemic tissues. However, the immunology of canine leishmaniasis is complex and poorly understood,[2] and the hypothesis of an immune-mediated basis for leishmania-induced uveitis requires further investigation.

Cutaneous lesions in the eyelids were seen in a large proportion of dogs in this study and had varying clinical appearances. Cutaneous signs of leishmaniasis in dogs are often characterized by a dry, seborrheic dermatitis, desquamation, and associated alopecia. The prevalence of characteristic periocular alopecia (also known as 'lunettes') in dogs in this study was 45/430 (10.5%), similar to a previous report in which 27/150 (18%) demonstrated such lesions. In this study, we found several distinct varieties of blepharitis in addition to the alopecic type, including a diffuse nodular form with generalized edema, induration, and hyperemia of the eyelids; an ulcerative form; and in a small number of dogs, a solitary nodule. It has been suggested that the varying cutaneous manifestations of leishmania may be dictated by the immunologic response of the host to the organism, with the alopecic dermatitis containing appropriate numbers of antigen-presenting cells and low numbers of parasites; the nodular form containing large numbers of macrophages and parasites; and the ulcerative lesions showing a histologic appearance intermediate between these two.[25] As a result, cytologic confirmation of the parasite in eyelid lesions would be expected to be of greater diagnostic value with nonalopecic forms of blepharitis. The focal periocular nodule(s) seen in two dogs may represent the original site of vector transmission of the organism, with effective local immunologic control of infection.[19]

Conjunctival lesions, either alone or in conjunction with a peripheral keratitis, were also a common finding in dogs in this study. Similar to previous reports,[3,10,11] granulomatous nodules at the lateral limbus were present in some of these cases, resembling nodular granulomatous episclerokeratitis seen in Collies and a number of other breeds of dogs. In a limited number of cases in which cytology was performed, large numbers of organisms were found both in conjunctival scrapings and from peripheral corneal nodules. These findings suggest not only that cytology is of diagnostic utility with these lesions, but that the corneal and conjunctival inflammation may result from the presence of the parasite, rather than the altered immune response that follows infection.

The current treatment regimen for canine leishmaniasis at our institution includes a combination of *N*-methylglucamine

antimoniate for a minimum of 30 days and allopurinol for 6 months to 1 year. The mechanisms of action of these drugs on the organism are not defined, although antimony appears to block metabolism of leishmania through inhibition of adenosine triphosphate synthesis.[2] In this study, approximately 50% of the 34 cases studied for response to therapy had marked improvement or resolution of ocular signs following therapy. Additionally, another 10/34 of these cases improved but required long-term topical therapy; the majority of these cases, as well as those that failed to respond to therapy, had recalcitrant anterior uveitis. This suggests that most adnexal lesions and many cases of intraocular inflammation attributable to leishmaniasis carry a favorable prognosis with therapy, although anterior uveitis may be more difficult to resolve. Recurrence or development of new ocular signs was seen in approximately 1/3 of cases (11/34). Recurrence of systemic signs has been estimated to occur in as many as 75% of cases of canine leishmaniasis within 2 years of the time of diagnosis.[2,26] Elimination of clinical signs and the organism from affected animals is probably dependent on the development of an appropriate, TH1 immunologic response of the host more than specific therapy.[27,28] In immunocompetent humans with ocular manifestations of leishmaniasis, there is generally a good prognosis for improvement following antiprotozoal therapy.[23,29,30]

In summary, ocular manifestations are a common manifestation of canine leishmaniasis, occurring in approximately 25% of cases. Anterior uveitis is the most common finding and may have an immunologic basis. Adnexal lesions are also common, and appear to respond well, at least temporarily, to therapy. Leishmania should be considered in the differential diagnoses with eyelid alopecia or other forms of blepharitis, conjunctival or corneal inflammation, and anterior uveitis in dogs from southern Europe, other endemic areas, or dogs traveling from these geographic regions.

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