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Leishmaniasis, An Emerging Disease Found in Companion Animals in the United States

Christine A. Petersen, DVM, PhD

Abstract

This review discusses leishmaniasis in cats and dogs in the United States. Leishmaniasis is endemic in Foxhound populations in the United States and is still being characterized in this group. Pathophysiology, clinical signs, transmission, immunology, and treatment are examined in this review. Leishmaniasis is an emergent zoonosis of great public health significance.

Keywords

Canine diseases; feline diseases; *Leishmania*; protozoa; emerging infectious diseases

Introduction

Leishmania spp. are the causative agents of a spectrum of clinical diseases, all termed “leishmaniasis”. These forms vary in clinical presentation from focal cutaneous disease to disseminated visceralizing disease and in severity from non-symptomatic to fatal. Cutaneous leishmaniasis, as caused by *Leishmania mexicana*, is considered endemic in south-central Texas. Cutaneous leishmaniasis in this area of Texas is maintained within the ecosystem by small rodents, particularly including the burrowing wood rat (*Neotoma micropus*), but also opossums, armadillos and cotton rats [1–3]. Although an exact means of transmission has not been proven in this area, transmission by sand fly vector species [4,5] is thought to be a primary means. Several cats, people and dogs have been diagnosed with cutaneous leishmaniasis in this region of the United States [6–9]

Leishmania infantum is the causative agent of canine visceral leishmaniasis (VL) in the Mediterranean Basin and more recently in North America. Natural hosts include dogs and humans [10], although there are many recent studies indicating that cats can be infected in endemic areas [11–17], and may serve as a domestic reservoir for human infection [18]. Transmission in endemic areas is usually via sand fly vector. Infected dogs are the primary reservoir for zoonotic visceral leishmaniasis in endemic regions, and are the most significant risk factor predisposing humans to infection [19]. Dogs have a wide range of clinical presentation due to infection with *Le. infantum*, ranging from asymptomatic to fatal visceralizing disease. Host factors which determine clinical outcome with any *Leishmania* infection are poorly understood. When clinical signs of visceral disease in dogs occur, they include enlarged lymph nodes and hepato- and splenomegaly due to parasitic invasion of the

Address reprint requests to: Christine A. Petersen, DVM, PhD, Assistant Professor, Department of Veterinary Pathology, 2714 Vet. Med., Iowa State University, Ames, IA 50014, Phone: (515) 294 9013, Fax: (515) 294 5423, kalicat@iastate.edu.

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reticulo-endothelial system [20]. Due to its more exotic nature, cutaneous and visceral leishmaniasis symptoms often can persist in feline or canine patients for several weeks to months before they are brought to a veterinarian and in the United States it may be even longer before correct diagnoses are made. These patients are at risk of death from bacterial co-infections. Massive bleeding, severe anemia [20] and/or renal failure are complications with visceralizing cases.

Epidemiology of cutaneous leishmaniasis in companion animals in the United States

To date there have not been any published comprehensive serologic studies of *Leishmania* infection which cause cutaneous forms of disease in either dogs or cats in Texas or any other regions of the United States. There have been multiple case reports of disease in these animals in Texas [7–9]. Human cases (n=30) of non-travel-related (or autochthonous) disease have been reported since 1903 in the epidemic focus in south-central Texas. In 2008, 9 cases of non-travel-related cutaneous leishmaniasis in northern Texas, specifically in suburbs and smaller towns near the Dallas-Ft. Worth metro area, have been additionally reported, indicating an emerging, northward-spreading element to this disease [6]. As cats and dogs usually have a higher disease incidence than humans within endemic areas, it should be expected that animals living in the eastern half of Texas are at risk of cutaneous leishmaniasis. Further, more detailed, study using serologic and molecular methods to determine exposure and infection with *Leishmania* spp. in these areas is necessary to determine risks factors for infection, route(s) of transmission and the true burden of *Leishmania* infection in both dogs and cats in Texas and neighboring states.

Common clinical signs, diagnosis and treatment of cutaneous leishmaniasis

Cutaneous disease, in both dogs and cats, usually manifests initially as a single papule which then enlarges into a nodule or lesion with raised edges and may become ulcerative and plaque-like. Definitive diagnosis can often be made by impression smear or biopsy of the organism-dense periphery of the lesion. Lesions caused by *Le. mexicana* often spontaneously resolve within 6–12 months leading to a scar and persistent protective immune response. Despite this, due to the ulcerative nature of these lesions, treatment is often implemented to speed healing and prevent secondary bacterial infections. Infection with other species of *Leishmania* (including *Le. Brasiliensis*) should be suspected if a non-healing lesion occurs, requiring more aggressive treatment. Culture and quantitative polymerase chain reaction of biopsy specimens performed by the Centers of Disease Control and Prevention can definitively diagnose causative species. Treatment options are similar to those available for visceral leishmaniasis (summarized in Table 1).

Vector transmission of *Leishmania infantum*

In endemic areas, the primary means of *Le. infantum* transmission is vector-borne via the sand fly. Vector-borne transmission of *Le. infantum* has not been proven in the U.S. to date [21, 22]. Instead, vertical transmission appears to be a primary means of transmission in U.S. dogs without a travel history to an endemic region [21]. The frequency of vertical transmission in endemic areas is unknown due to the overwhelming likelihood of vector contact [23].

Lutzomyia shannoni is a possible sand fly vector of *Le. Infantum*, and is present within the Southern, Midwestern and Southeastern United States [21]. *Lu. shannoni* is known to bite dogs and other mammals and has been incriminated in the transmission of *Le. brasiliensis* in South America [24]. Anecdotal data indicate that U.S. species of *Lu. shannoni* can become infected with *Le. infantum*, but it is not known whether these flies permit *Le. infantum* development

into infectious metacyclic parasites. Vector feeding preferences can importantly influence disease transmission. *Lu. shannoni* has been shown to feed on dogs in the U.S. (Rowton, personal communication).

In many settings dogs may serve as a link between sylvatic and domestic cycles of visceral leishmaniasis. Dogs often cross forest-edge boundaries, thereby potentially bringing parasites to or from sylvatic systems and to and from other potential mammalian hosts (such as foxes and opossums). In the U.S., due to frequent exchange of Foxhounds between kennels and the dogs' penchant for spending time in the woods, these dogs may be a primary focal point for transmission of *Le. infantum* to continue transmission to sand flies. Thus, if *Lu. shannoni* indeed prefers to feed on dogs in comparison to other mammals, infected dogs may be likely to serve as a source of *Le. infantum* to an uninfected fly.

Epidemiology of Canine Visceral Leishmaniasis in the U.S

Although endemic in many parts of the world, this disease has only recently been described in the U.S. [25]. Previously, sporadic cases have been reported in the United States, in canine travelers returning to the U.S. from endemic areas [22]. However, in 2000, a kennel in New York State reported four Foxhounds to be clinically infected with *Le. infantum* [25]. By 2005, 60 kennels in 22 states and 2 Canadian provinces had reported seropositive Foxhounds [26]. A retrospective study performed by the Centers for Disease Control and Prevention, Division of Parasitic Diseases, employed sera samples that were collected between April 2000 and December 2003. Samples were taken from greater than 12,000 Foxhounds and other canids in the U.S., and an 8.9% seroprevalence was observed in Foxhounds but not other randomly selected domestic dogs or wild canids [21]. Samples detected at 1:16 and 1:32 were considered suspect [21]. This study initially had participation from almost all registered Foxhound kennels in the U.S., but after the first year participation greatly decreased, perhaps leading to a selection bias in further years of kennels with known clinical infection with *Le. infantum*.

Between years 2000 and 2001, even though the number of participating kennels decreased, the number of *Leishmania* seropositive samples increased, most likely indicating that there was increased infection/incidence of disease in these participating kennels. In current studies of Foxhound kennels, a similar 9.8% overall seropositivity/seroprevalence was observed, but among high risk kennels the seropositivity and presence of polysymptomatic disease is 13.5%. Infection in this cohort was greater than percentage observed by serology as indicated by a 22.8% quantitative Polymerase Chain Reaction Assay (qPCR) positivity in the overall cohort. The percentage of qPCR positive dogs in high-risk kennels was 44.8%. Roughly 50% of the qPCR positive (infected) population was clinically asymptomatic (Petersen, unpublished data). In dog breeds from endemic countries, a higher sero- or PCR-prevalence is also seen as compared to the overall canine population. This includes dog breeds from Southern Europe, such as Corsicas, Italian Spinones and Neapolitan Mastiffs (Petersen, qPCR and CDC serological unpublished data.)

Transmission of Visceral Leishmaniasis in the U.S

Visceral leishmaniasis is classically transmitted by the bite of an infected sand fly. Non-vector-based mechanisms postulated for transmission of canine visceral leishmaniasis in the U.S. include vertical transmission (transplacental or transmammary) and horizontal transmission by direct contact with infected cells in blood [21,22,27]. Transmission has been documented via packed red blood cell transfusion from infected Foxhounds [28]. It is not known how frequently vertical transmission occurs naturally in endemic areas, although studies which used collars or topical insecticides to prevent transmission do not note transmission reduction below 4% in dogs [19,29], indicating that non-vector-based transmission may maintain infection under these circumstances. There are reports of congenital transmission of visceral

leishmaniasis after experimental *Le. infantum* infection of beagles [26]. In spite of a possible change in primary suspected route of transmission, clinical signs and microscopic lesions of visceral leishmaniasis of U.S. Foxhounds is equivalent to that seen in dogs infected in endemic areas through sand fly transmission [27]. Whether vertical transmission itself is solely responsible for the focus of disease particularly in Foxhounds, Corsicas, Spinones and Neapolitan Mastiffs in the U.S. or whether there are genetic factors predisposing particular breeds to disease has not been well investigated. In endemic areas all breeds of dogs are affected.

The *Le. Infantum* genotype isolated from Foxhounds in the U.S. is MON-1. The MON-1 genotype is isolated most frequently from dogs living in the Mediterranean basin suggesting that infected dogs may have originally been brought to the U.S. from this area. A Centers of Disease Control and Prevention investigation indicated that it was most likely that these infected hounds first originated from Southern France, were imported into Great Britain, and subsequently brought to the U.S. (Schantz et al, unpublished data.)

Common clinical and pathologic findings with Visceral Leishmaniasis

Physical exam findings of dogs infected with VL may include depression, loss of condition particularly decreased muscle mass over shoulders, hips, and spine, with a mildly distended abdomen, serosanguineous nasal discharge, dull hair coat, splenomegaly and generalized lymphadenopathy. About one third of cases have fever. Other clinical signs may include diarrhea, vomiting, melena, dry brittle hair coat and long brittle nails. Although officially categorized as a form of visceral leishmaniasis, cutaneous lesions including bilaterally symmetrical non-pruritic alopecia, hyperkeratosis, excessive epidermal scale with thickening, depigmentation, and chapping of the muzzle and footpads, occur with some regularity. Abnormal clinicopathologic values observed with VL often include decreased hematocrit, thrombocytopenia, and signs of renal failure including azotemia, increased blood urea nitrogen and creatinine, hyperphosphatemia, hypermagnesemia, and proteinuria. Signs of hepatic compromise are also common including elevated alkaline phosphatase (ALP), elevated alanine transferase (ALT), and hypercholesterolemia. Other common clinical chemistry abnormalities include hyperproteinemia observed with hypergammaglobulinemia and hypoalbuminemia, often associated with protein-losing nephropathy.

Gross pathological examination may reveal emaciation with minimal adipose tissue in body cavities and subcutaneous tissues. Peripheral, mesenteric, and mediastinal lymph nodes demonstrate moderate to marked enlargement. The liver and spleen can also be diffusely enlarged. Kidneys may be moderately enlarged and diffusely pale. Impression smears obtained at necropsy from the spleen, popliteal lymph node and liver stained with Diff-Quick, often will reveal widely scattered macrophages with intracellular amastigotes consistent with *Leishmania* spp. Cytologically within the liver, spleen, bone marrow and lymph nodes there will often also be amastigotes consistent with *Leishmania* spp. These organisms are 1–3 μ m in diameter, and have a round, deeply basophilic nucleus and a rod shaped kinetoplast when stained with hematoxylin and eosin. These can be specifically identified as *Leishmania* by immunohistochemistry.

Diagnosis of Visceral Leishmaniasis

Canine *Le. infantum* infection frequently does not equate with clinical illness. The ratio of incident asymptomatic infection to clinical cases varies with location, vector, and parasite. Ratios of 18:1 in Brazil and 50:1 in Spain have been observed in human populations [20] and is estimated at 2:1 in high-risk U.S. Foxhounds. We suggest that a different means of transmission, as observed in U.S. Foxhounds, will also alter this ratio. At present, diagnosis

and control of visceral leishmaniasis is difficult as dogs can be infected but seronegative for years [30]. Various means of serology are the primary diagnostic tests used for surveillance of visceral leishmaniasis (Figure 1, light and dark blue bars). Public health surveillance in the U.S. (where this disease is not endemic in humans) constitutes testing performed via an indirect fluorescent antibody assay (IFA) by the Centers for Disease Control and Prevention (CDC). IFA is sufficient for screening purposes, but is found to cross react with antibodies to the kinetoplastid *Trypanosoma cruzi*. *T. cruzi* is endemic in wildlife in the Southeastern U.S., thus further testing is required to determine parasite specificity unless clinical signs are much more consistent with one infection over the other; e.g. cardiomyopathy in the case of Chagas' disease. Other serologic tests are available in the U.S. for detection of canine leishmaniasis including a highly sensitive and specific kELISA (Figure 1, dark blue bar) available through the Cornell University diagnostic laboratory and a K39-antigen based assay available through Heska. Positive CDC serology in Foxhounds appears to closely correlate with the appearance of clinical disease than the incidence of infection (Figure 1). Reports have shown that qPCR (Figure 1, orange bar) performed by a well-regulated and stringently tested laboratory can be a more sensitive test for *Le. infantum* infection in dogs and can detect asymptomatic dogs and/or dogs that have yet to seroconvert [27]. qPCR is available through Iowa State University and the CDC.

Pathogenesis of VL and genetic factors related to susceptibility

Mammalian host responses which prevent progression to clinical VL has been shown to be dependent on promoting T cell IFN- γ production-based immunity and parasiticidal activity within infected macrophages [20]. A key immunological feature of T cells from dogs with late stage clinical VL is an inability to proliferate or to produce IFN- γ in response to *Leishmania* antigen, [14, and Petersen preliminary data]. High levels of inflammatory cytokines, including TNF- α have been proposed to stimulate production of regulatory cytokines, specifically IL-10, as a homeostatic response to prevent further inflammation-mediated pathology. High lesional IL-10 mRNA production is frequently found in human patients with VL [31,32], and produced by polysymptomatic Foxhounds (Petersen preliminary data). One of the proposed mechanisms of IL-10 promotion of VL is by conditioning macrophages for parasite growth and survival versus killing of intracellular parasites.

In our surveillance studies, we have observed repeated cases where Foxhounds do not show clinical signs of visceral leishmaniasis until there is secondary immunosuppression due to pregnancy, concomitant Lyme disease or other tick-borne illness [27]. This clinical shift towards disease consistently appears upon a shift from seronegativity to seropositivity in these dogs. Further studies are required to determine the effects of immune alterations that lead to clinical disease in these dogs. In advanced disease it is not unusual to see immunosuppression including T-cell changes, in terms of both reduced CD4+ T cell proliferation in response to whole *Le. infantum* antigen and/or routine canine vaccines and decreased ability of these cells to produce IFN- γ in response to *Le. infantum* antigen.

Several genetic polymorphisms, including alterations in TNF- α and solute carrier family 11A1 (SLC11A1, formerly NRAMPI) allelic expression may predispose to clinical disease [33, 34]. However, heritable causative factors of disease susceptibility in dogs remain elusive. Breed type has been shown to alter the response to therapy, suggesting that canine breed-related genetic factors modulate disease progression and are therefore prognostically significant [35].

Numerous Foxhounds have tested positive for visceral leishmaniasis in the U.S. and infection appears to be endemic only within this breed here. If vertical transmission is indeed the primary route of transmission in these dogs, a particular genetic susceptibility is not absolutely

necessary for widespread infection to occur in the Foxhound population. Both the observance of visceral leishmaniasis within specific families of Foxhounds and finding dogs that are *Leishmania* disease-resistant suggests that it is highly likely that particular genetic traits of dogs at least in part determine which dogs develop visceral leishmaniasis vs. remain clinically disease-free.

Treatment/Prognosis

Treatment of canine visceral leishmaniasis (CVL) is rarely curative. Prognosis for emaciated chronically infected animals is very poor and in these cases euthanasia should be considered. It is critical to advise the owner of potential zoonotic transmission of organisms from lesions to humans prior to maintaining a *Leishmania*-infected dog in their household, particularly if there are immunosuppressed people sharing the household. The owner should be informed that the organism will never be completely eliminated (i.e. no “sterile cure”) and relapse occurs very frequently requiring retreatment. Treatment should be undertaken on an outpatient basis. Due to the chronic wasting that can occur with leishmaniasis, it is important to provide a good high-quality protein diet or a diet appropriate for renal insufficiency if this manifestation of leishmaniasis is present.

Due to difficulty obtaining certain drugs in the United States, treatment is recommended to begin with allopurinol (Zyloric®). This drug is efficacious and relatively non-toxic when used as a maintenance drug. Clinical remission is often achieved when used alone. Relapses are common when treatment ceases. Complete cures are rare but survival occurs in 80% of cases over 4 years if renal insufficiency is not present when treatment is initiated. This drug is sometimes used in combination with pentavalent antimony (Glucantime), as drug resistance is seen for pentavalent antimony alone in endemic areas (France, Spain and Italy). Pentavalent antimonials are not licensed for use in the United States and can only be obtained via an investigational drug use protocol from the CDC [36,37]. The two main drugs in this class are 1) sodium stibogluconate (Pentostam®, Wellcome Foundation Ltd, U.K.), which requires daily injection and has severe side effects, and 2) meglutamine antimoniate (Glucantime®, Pfizer/Merial, France), which has less side effects. Dosages have been listed (Table 1). Amphotericin B in the lipid emulsion or liposomal form is relatively non-nephrotoxic and is effective against the organism, although it is not thought to be superior to allopurinol as it is still both more costly and more toxic. Renal insufficiency must be treated prior to administration of antimonial drugs or amphotericin B as prognosis is dependent on renal function at the onset of treatment. Treatment efficacy is best monitored by clinical improvement and presence of organisms in biopsy or as measured by rigorously controlled qPCR. Relapses occur a few months to a year after therapy, so dogs should be re-checked at least every 2 months after the end of treatment. Prognosis for a cure is very guarded, but therapy does provide infected dogs improved quality of life.

Second-line drugs, which require further clinical studies to understand their efficacy in dogs, include miltefosine (Impavido® or Miltex®) and paromomycin (Humantin®). Paromomycin has fewer side effects than other drugs in humans, and paromomycin use has been primarily targeted to the cutaneous versions of *Leishmania*. Less is known about its ability to remove organ-based infection. There is no effective vaccine against CVL available in the United States. A secreted parasite antigen-based vaccine has recently been licensed for use in dogs in Brazil. Sand fly vector control measures, including deltamethrin or permethrin-impregnated collars are useful to date to prevent disease [38]. In many countries, culling of dogs is still used as a means to prevent human disease due to the association of canine infection to human disease [39,40].

Summary

Cutaneous leishmaniasis is endemic within south-central Texas and appears to be spreading northward into the Dallas-Ft. Worth metro area, affecting humans, cats, and dogs. Multiple vectors and rodent reservoir hosts exist within Texas, leading to consideration of vector-borne sand fly based transmission as the primary means of disease spread in this area. Canine VL is endemic in the U.S. Foxhound population. Current evidence indicates that vertical transmission may be a primary route of transmission of the parasite in this population, although *Lutzomyia* species in the U.S. may be involved in transmission. Further study is necessary to determine the likelihood of vector-borne transmission of both cutaneous and visceral leishmaniasis in the U.S. There are two main diagnostic tools to characterize ongoing disease in the U.S.; quantitative PCR to detect infection and serology to indicate the onset or presence of an antibody-based immune response to *Leishmania* spp. Treatment options include allopurinol, glucantime, and newer less-toxic formulations of amphotericin B, but none of these drugs lead to life-long sterile cure and recrudescence of both visceral and cutaneous disease is possible, although more common after infection with *Le. infantum* (visceral) or *brasiliensis* (cutaneous). Due to lack of surveillance and imperfect diagnosis in the United States, leishmaniasis may have been present within at-risk canine and feline populations prior to the more recently recognized “outbreaks” in Foxhounds or people and evidence indicates that this disease may be further emerging due to changes in the environment and closer contact between pets and sylvatic ecosystems.

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Figure 1.

Different *Leishmania* diagnostics are more or less effective due to alterations in parasite load and immune response. Due to cost and materials required, serology is the most common means of diagnosing *Leishmania* infection, both in the United States and elsewhere. The antibody response measured by serology can be against the whole parasite, for example the CDC IFA assay (CDC, light blue bar) or to a specific antigen, for example the Cornell-developed kELISA (kELISA, dark blue bar). This difference; whole parasite response vs. specific antigen in this case, may lead to different sensitivity and specificity to detecting infection. Whole parasite-based serology can also cross-react with antibodies to *Trypanosoma cruzi*, for instance. kELISA has been shown to identify infection earlier, as portrayed by the x-axis, and may detect a different subset of antibodies (non-productive and productive antibodies are portrayed by the bottom two sets of dashed lines). T cell based responses, for instance T cell proliferation to parasite antigen (TCP, tan bar) detects infection very early after infection and is able to consistently indicate infection throughout the course of infection until very late in disease when the T cell response wanes (small dashed line). Unfortunately this assay is currently only performed on an experimental basis due to the time and materials required for successful analysis of this cellular response. Measurement of actual parasites in the blood stream (solid

line) via detection of parasite kinetoplast DNA via quantitative polymerase chain reaction (PCR, orange bar) is another highly sensitive means of diagnosing parasite infection. This assay requires very rigid quality control to assure accurate results and due to the nature of the test can lead to occasional false positive results.

Table 1

Treatment options for visceral leishmaniasis.

DRUG	DOSE (mg/kg)	ROUTE	INTERVAL (HOURS)	DURATION (MONTHS)
Allopurinol	7 – 20	PO	8–12	3 – 24 ^a
Amphotericin B – Fungizone®	0.25 – 0.5 ^b	IV	48 ^c	^d
Meglumine antimoniate ^e – Glucantime®	100	IV, SC	24	1
Sodium stibogluconate – Pentostam®	30 – 50	IV, SC	24	1

^a Or for rest of dog's life.^b Reconstituted in 5% dextrose (not in electrolyte solutions which precipitate drug) and dilute to administer; if normal renal function, dilute in 60 – 120 ml 5% dextrose given over 15 minutes; if renal compromise, dilute in 0.5 to 1 liter 5% dextrose given over 3 to 4 hrs to reduce further renal toxicity.^c Or 3 times a week.^d Administer until a total cumulative dose of 5 – 10 mg/kg is reached.^e Not available in the U.S.