Review of Equine Cutaneous Leishmaniasis: Not Just a Foreign Animal Disease

Sarah M. Reuss, VMD, Diplomate ACVIM

Although long considered to be a foreign animal disease, cutaneous leishmaniasis has recently been identified in two horses in Florida with no history of international travel. Both horses were diagnosed with *Leishmania siamensis*, an organism with zoonotic potential. Practitioners in the United States should have this disease on their differential list for horses with ulcers and nodules on the ears, head, and neck. Author’s address: University of Florida, Department of Large Animal Clinical Sciences, PO Box 100136, Gainesville, FL 32610; e-mail: sreuss@ufl.edu. © 2013 AAEP.

1. Introduction

Leishmaniasis is a zoonotic disease most well described in people and dogs; however, cutaneous leishmaniasis has been documented in horses around the world. Although cases have been seen in the United States, most of these horses had a history of recent importation from endemic areas. In 2012, the first autochthonous (non–travel-related) case of equine cutaneous leishmaniasis in the United States was published with the discovery of *Leishmania siamensis* in a Morgan mare in Florida.¹ Since that time, a second horse in Florida (also with no history of international travel) has been diagnosed with *L. siamensis*.² Therefore, leishmaniasis should be included in the differential list for horses in the United States with cutaneous lesions regardless of their travel history or country of origin. The goal of this article is to raise the awareness of this disease amongst equine practitioners by reviewing the etiology, pathogenesis, clinical syndromes, diagnosis, and treatment of leishmaniasis.

2. Etiology/Method of Transmission

Leishmaniasis is caused by the obligate intracellular protozoa of the genus *Leishmania*. In mammals, the parasites reside as intracellular amastigotes within macrophages, where they replicate by binary fission. When infected macrophages rupture, surrounding macrophages phagocytize the amastigotes and become infected. The disease is endemic in tropical and subtropical regions but is spreading with global climate change. There are more than 30 species of *Leishmania* with a complex classification scheme. The species of *Leishmania* vary with region, and different species are often incriminated to cause different disease manifestations. In the Eastern Hemisphere, the “Old World” species *Leishmania donovani*, *Leishmania infantum*, *Leishmania tropica*, and *Leishmania aethiopica* are commonly found. In the Western Hemisphere, the “New World” species *Leishmania braziliensis* and *Leishmania mexicana* are frequently found, most commonly in South and Central America. However, *L. mexicana* has been reported as the causative organism of some vector-transmitted outbreaks of cutaneous leishmaniasis in people and dogs in Texas.² *L. siamensis* is a recently described species that had not been previously reported in North America until it was determined to be the etiologic organism in both Florida horse cases.¹ *L. siamensis*
was first described as the cause of autochthonous visceral leishmaniasis in two men in Southern Thailand\textsuperscript{3,4} but has also been identified as the cause of equine cutaneous lesions in central Europe\textsuperscript{5} and a cow in Switzerland.\textsuperscript{6}

In all mammalian species affected with leishmaniasis, the primary mode of transmission is believed to be by various species of sand flies. The promastigote stages of the protozoa are transmitted in the saliva of the female sand fly at the moment of blood feeding.\textsuperscript{7} Each species of \textit{Leishmania} is adapted to transmission in certain species of sandflies: \textit{Phlebotomus spp} in the Old World and \textit{Lutzomyia spp} in the New World. The vector in equine transmission in the United States remains unidentified; however, the phlebotomine sand flies \textit{Lutzomyia shannoni} and \textit{Lutzomyia vexator} are found in Florida, where the two autochthonous equine cases were diagnosed.\textsuperscript{8} \textit{Lutzomyia shannoni} is known to use both humans and other mammals as hosts, and it has been incriminated as a vector of \textit{L. braziliensis} in Central and South America. It has also been shown experimentally to be capable of becoming infected with \textit{L. infantum} when feeding on ill \textit{L. infantum}-infected dogs.\textsuperscript{9} However, it is not known whether \textit{L. shannoni} will permit \textit{Leishmania} development into infectious metacyclic parasites. \textit{Leishmania mexicana} is considered endemic in south-central Texas, where the organism is maintained within the ecosystem by small rodents and is presumably spread by a \textit{Lutzomyia spp} (possibly \textit{Lutzomyia diabolica}).\textsuperscript{10} Although vector-borne transmission is the primary means of spread between dogs in endemic areas, it is thought that vertical transmission (transplacental and transmammary) is probably the major means of spread in dogs in non-endemic areas of the United States.\textsuperscript{10}

The frequency of vertical transmission in endemic regions is difficult to determine because of the high likelihood of vector contact. Ticks have been shown experimentally to be capable of transmission in dogs, and horizontal transmission by direct contact with blood has also been shown.\textsuperscript{10}

3. Clinical Manifestations

Equine

Cutaneous leishmaniasis has been documented in horses around the world. Lesions are most commonly observed as nodules on the head, pinnae, scrotum, legs, and neck. They may be solitary or multiple, and are often ulcerated (Fig. 1). No other signs are seen, and visceral lesions have not been reported. Equine leishmaniasis was first reported in Argentina in 1927. In South America, \textit{L. braziliensis} has been identified as the causative organism in horses.\textsuperscript{11,12} In one endemic region of Brazil, 26 horses, donkeys, and mules were examined. Cutaneous lesions were found in 10 animals, and eight animals (30.8% of the examined population) had parasites seen on histopathology of ulcer margins.\textsuperscript{13}

In Europe, \textit{L. infantum} has been reported as the causative agent of cutaneous leishmaniasis in horses in Germany,\textsuperscript{14} Spain,\textsuperscript{15} and Portugal.\textsuperscript{16} Recently, a report from central Europe identified an organism with 98% identity to \textit{L. siamensis} as the cause of cutaneous lesions in four horses.\textsuperscript{4} Whereas equine leishmaniasis is documented in Puerto Rico,\textsuperscript{17} it is rarely seen in the continental United States. Historically, cutaneous leishmaniasis in the United States was seen in horses with a history of international travel or recent importation. Although autochthonous cases may have been observed,\textsuperscript{2} the first documented case occurred in 2011.\textsuperscript{1} To date, only cutaneous lesions have been documented in horses.

Human

Leishmaniasis is the second leading parasitic cause of death in people, after malaria. There are approximately 1.8 million new cases per year, making this a top priority for the World Health Organization. Three basic syndromes are seen in people: cutaneous, mucocutaneous, and visceral. Cutaneous disease presents as painless nodules, plaques, or ulcers. In general, lesions heal spontaneously in immunocompetent individuals. Mucocutaneous lesions involve the nares, nasal septum, pharynx, lar-
ynx, and genitalia; and they can occur concurrently or 1 to 5 years after resolution of cutaneous lesions. These lesions will not heal spontaneously. Visceral leishmaniasis, otherwise known as “kala azar,” is a chronic, insidious disease that may be preceded by cutaneous lesions. Visceral leishmaniasis is usually associated with species of the *Leishmania donovani* complex (*L* *donovani*, *L* *infantum*, *Leishmania chagasi*) and *L* *tropica*. Clinical signs include fever, weight loss, anemia, anorexia, cough, diarrhea, and darkening of the skin. Splenomegaly, hepatomegaly, lymphadenopathy, thrombocytopenia, and leukopenia may all be present as the parasite invades the reticuloendothelial system. Visceral disease is fatal unless treated, and treated patients will remain carriers and can recrudesce if immunosuppressed.

**Canine**

Dogs are the most commonly affected domestic species, with 63% to 80% seropositivity in endemic areas in which they are thought to be the primary reservoir for *L* *infantum* and maintain the disease in domestic cycles. In endemic areas, all breeds of dogs are affected. Dogs, like humans, can develop cutaneous or visceral disease. Cutaneous lesions can present as nonpruritic exfoliative dermatitis, nodules, ulcers, and long, brittle nails. Visceral disease results in lethargy, weight loss, anorexia, anemia, splenomegaly, epistaxis, hematuria, melanoma, chronic renal failure, and death. Ocular lesions have also been reported and include conjunctivitis, keratitis, and uveitis. The majority of cases of canine leishmaniasis in the United States have historically involved international travel. However, there have been reports of isolated cases and outbreaks, primarily in foxhounds. In 2000, a New York kennel reported four foxhounds with *L* *infantum* visceral leishmaniasis without a history of travel. This led to widespread testing, and by 2005, 60 kennels in 22 states and two Canadian provinces were found to have seropositive Foxhounds. Current studies of Foxhound kennels show a 9.8% seroprevalence; however, in high-risk kennels, the percentage of quantitative polymerase chain reaction (qPCR)-positive dogs is 44.8%.

**4. Diagnosis**

Microscopic evaluation of an impression smear or biopsy of the border surrounding the cutaneous lesion is often the preliminary means of diagnosis. There will be a marked inflammatory response, and numerous intracellular protozoa will be seen within macrophages and occasionally extracellularly. These 1- to 4-μm intracellular organisms have an eccentrically placed, basophilic, round nucleus and a rod-shaped kinetoplast oriented perpendicular to the long axis of the oval nucleus (Fig. 2). This morphology is indicative of the amastigote form of *Leishmania*. Electron microscopy will allow more detailed examination of the intracellular amastigotes. Immunohistochemistry can be used to confirm the diagnosis of leishmaniasis and has been performed successfully in the horse.

Culture and qPCR can be performed by the Centers for Disease Control and Prevention or by various university research labs. Isoenzyme analysis of cultured parasites has been the conventional approach for species identification. However, PCR and sequence analysis can identify the organism to the species level more rapidly and with greater sensitivity, depending on the targeted region. It is worth noting in the context of equine leishmaniasis that PCR methods used to detect Old World leishmaniasis have been reported to fail to detect *L* *siamensis*. Amplification of a 350-base pair internal transcriber spacer 1 (ITS1) fragment has been successful in identifying this organism. Sequence analysis of the ITS1 amplification products classifies *L* *siamensis* as neither Old World nor New World.

Serologic testing in humans and canines is the primary diagnostic test used for surveillance of visceral infections but is less reliable for cutaneous disease. Indirect fluorescent antibody (IFA) testing can be performed by the Centers for Disease Control. Unfortunately, it may cross-react with antibodies to *Trypanosoma cruzi*. One horse with *L* *braziliensis* was positive for anti-*Leishmania* antibodies on IFAT; however, IFAT in one horse in Germany with confirmed *L* *infantum* cutaneous lesions on PCR failed to yield a positive result. Cutaneous lesions in people may also result in no detectable level of serum antibodies; however, skin testing for delayed type hypersensitivity may be positive in human cutaneous disease. Delayed type hypersensitivity reaction skin testing has been performed in the horse but is not standardized. Anti-*L* *infantum* antibodies have been...
found in clinically normal horses in endemic areas through the use of a protein-A enzyme-linked immunosorbent assay (ELISA) and a specific lymphocyte proliferation assay to L infantum. Other serologic tests used in people and canines with visceral lesions include a kinetic-based ELISA and a K39-antigen-based assay. Quantitative PCR may be a more sensitive test, and can detect animals that are asymptomatic or have not yet seroconverted.

5. Treatment

Different species of Leishmania have varying responses to treatments. Systemic treatment is often indicated in humans to reduce the risk of dissemination to the mucosa or visera. Currently, the standard treatment for people is intravenous administration of the pentavalent antimony compounds sodium stibogluconate or meglumine antimonite. Unfortunately, these drugs have potentially severe side effects including arthralgia, myalgia, pancreatitis, and abnormal liver function tests, and results in treatment failure in 23.5% of cases. Intralesional pentavalent antimony can be an effective alternative, resulting in higher drug concentrations at the site of infection while reducing the risk of systemic toxicity. In some endemic areas, drug resistance to pentavalent antimony is seen. In the United States, pentavalent antimony can only be obtained for military or investigational use from the Centers for Disease Control and Prevention, thus limiting clinical access.

Other drugs that have been used for human and canine leishmaniasis include allopurinol, miltefosine, amphotericin B in the lipid emulsion or liposomal form, ketoconazole, paromomycin, itraconazole, and cryotherapy. A randomized, double-blind, placebo-controlled trial of oral fluconazole was found to be safe and shortened time to resolution in people with cutaneous lesions. However, a recent Cochrane database review of 38 clinical trials for cutaneous lesions through the use of different interventions found an absence of randomized, controlled, trial-based evidence for alternative treatments including surgery, oral itraconazole and fluconazole, rifampicin, metronidazole and cotrimoxazole, intravenous or topical amphotericin B, oral dapsone, photodynamic therapy, and laser and cryotherapy.

Many of the reports of cutaneous leishmaniasis in horses describe spontaneous regression of lesions. Surgical resection, pentavalent antimony, and amphotericin and fluconazole have all been used “successfully” in horses, but it is unclear how many would have resolved with no treatment.

6. Summary

Equine cutaneous leishmaniasis can no longer be considered just a foreign animal disease. With climate change and the spread of vector habitats, emerging diseases will continue to infiltrate the United States equine population. Leishmaniasis should be considered in the differential list for cutaneous lesions in horses; and cytology, histopathology, and/or molecular diagnostics should be performed on suspect lesions. Although this is not a fatal disease in horses, we can and should consider our equine patients as sentinels for this potentially fatal zoonotic disease.

References and Footnotes


