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Research paper

Feline leishmaniosis: Is the cat a small dog?

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ABSTRACT

Leishmania infantum is a vector-borne zoonotic disease transmitted by phlebotomine sand flies and dogs are considered the main reservoir of the parasite. Feline leishmaniosis (FeL) caused by *L. infantum* is an emergent feline disease more and more frequently reported in endemic areas. This review summarizes current knowledge focusing similarities and differences with canine leishmaniosis (CanL). Cats are infected by the same *Leishmania* species than dogs but prevalence of the infection is lower and cases of disease are less frequently reported. Scarce information is available on adaptive immune response of cats naturally exposed to *L. infantum* infection and mechanisms responsible for susceptibility or resistance of feline hosts. However, about half of clinical cases of FeL are reported in cats with possible impaired immunocompetence. Coinfections or comorbidities are frequently detected in sick cats and they can contribute to a misrepresentation of clinical FeL albeit lesions associated with the presence of the parasite have been detected in skin, lymph nodes, spleen, bone marrow, liver, oral mucosa, stomach, large bowel, kidney, nasal exudate, lung, eye. As for dogs, skin or mucocutaneous lesions are the most common reason for veterinary consultation and finding on physical examination in cats with leishmaniosis.

Molecular investigations of *Leishmania* DNA and anti- *Leishmania* antibody detection are largely used with the same methodologies for both CanL and FeL, however few information is available about their diagnostic performance in feline hosts. Treatment of cats with clinical FeL is still empirically based and off label by using the most common drugs prescribed to dogs. Life expectancy of cats with clinical FeL is usually good unless concurrent conditions or complications occur and prognosis does not seem significantly influenced by therapy or retroviral coinfection.

According to current knowledge, cats can play a role as additional reservoir host of *L. infantum* and, in a « One Health » perspective, preventative measures should be taken.

In conclusion, albeit feline infection and the associated cat disease caused by *L. infantum* is increasingly reported in endemic areas and have many similarities with CanL, consolidated evidence-based knowledge is not available and we cannot exclude that important differences between dogs and cats exist about transmission, immunopathogenesis and best practice for management and prevention.

1. Introduction

Leishmania infantum (Li),[1] is a vector-borne zoonotic disease transmitted by phlebotomine sand flies and dogs are considered the main reservoir host of the parasite (Solano-Gallego et al., 2009). In fact, the majority of infected dogs do not show clinical signs or develop a mild disease and sustain the survival of the parasite during cold seasons when vectors are not active (Bates, 2007; Pennisi, 2015). A huge amount of investigations have been − and still are − performed to better understand pathomechanisms of canine leishmaniosis (CanL)[2] make early and accurate diagnosis, manage the disease and prevent spreading of the infection.

Feline leishmaniosis (FeL)[3] caused by *Li* appears as an emerging feline disease, in fact in the past two decades it was more and more frequently reported in endemic areas and sporadically seen also in non-endemic areas in rehomed cats (Rüfenacht et al., 2005; Richter et al., 2014; Pennisi et al., 2015a; Maia et al., 2015; Basso et al., 2016; Pimenta et al., 2015). However, the increased level of medical care

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[1] *Li: Leishmania infantum.*
[2] CanL: Canine Leishmaniosis.
[3] FeL: Feline Leishmaniosis.

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given to cats contributed to the «emergence» of FeL as well as availability of more sensitive diagnostic tools and progress in understanding parasite-host-vector interactions (Cantacessi et al., 2015).

In recent years, more detailed information on FeL has been published and it increased evidence that there are more similarities with CanL than it was speculated in the past and the aim of this review is to summarize current knowledge about FeL focusing on similarities and differences with CanL.

2. Etiology, diffusion and transmission

Cats were found infected by the same *Leishmania* spp. detected in dogs and *L. infantum* is the species most frequently reported in both dogs and cats in the Old World and in Central and South America. *Leishmania infantum* has been detected in cats in Mediterranean countries (Italy, Spain, Portugal, France, Greece, Turkey, Cyprus), Iran and Brazil (Pennisi et al., 2015a; Can et al., 2016; Attipa et al., 2017; Metzdorf et al., 2017). Zymodeme MON1 is the most frequently characterized zymodeme in dogs, cats and humans in the Mediterranean area (Maia et al., 2015; Pennisi et al., 2015a; Pratlong et al., 2013). However, *L. infantum* antibody and molecular prevalence is usually considered lower in cats compared to dogs as well as cases of FeL are more rare (Otranto et al., 2017; Pennisi et al., 2015a). Sporadic or rare occurrence of both CanL and FeL in non-endemic areas can be the consequence of rehoming or travelling of companion animals (Solano-Gallego et al., 2009; Pennisi, 2015; Cleare et al., 2014; Svobodova et al., 2017; Richter et al., 2014; Rüfenacht et al., 2005; Best et al., 2014). Other *Leishmania* species are found in both dogs and cats in the New World (*Leishmania amazonensis, Leishmania braziliensis, Leishmania mexicana, Leishmania venezuelensis*) (Solano-Gallego et al., 2009; Pennisi et al., 2015a). *Leishmania tropica* and *Leishmania major* were rarely reported in dogs and found mainly associated with skin or mucocutaneous lesions (Baneth et al., 2017). Recently, these latter species were confirmed in cats in Turkey (Can et al., 2016; Paşa et al., 2015).

Sand fly-transmission is considered the most important way of transmission of *Leishmania* to humans and animals and, according to several studies about the feeding habit of sand flies, this is likely also in feline infection but it has never been investigated (González et al., 2017; Pennisi et al., 2015a).

Non-vectorial transmission ways of CanL are now well known and responsible for autochtonous cases in non-endemic areas (Solano-Gallego et al., 2009; Karkamo et al., 2014; Naucke et al., 2016; Svobodova et al., 2017) but similar information about FeL is lacking. However, blood transfusion could be a source of infection in cats as it is proven in dogs and humans. In endemic areas healthy cats − similarly to healthy dogs and humans − can be found positive at blood PCR (Pennisi et al., 2015b; Can et al., 2016; Persichetti et al., 2016; Attipa et al., 2017; Akhtardanesh et al., 2017; Brianti et al., 2017; Diakou et al., 2017; Metzdorf et al., 2017; Otranto et al., 2017).

3. Pathogenesis and clinical features

It is currently known that susceptibility to progressive infection and development of lesions and clinical signs in dogs is mostly linked to adaptive immune response evolving to immune exhaustion and associated with a predominant T helper 2 (Th2) and an impaired T helper 1 (Th1) response (Solano-Gallego et al., 2009; Esch et al., 2013). A similar pattern of humoral and cell mediated adaptive immune response is elicited by *L. infantum* in cats from endemic areas (Priolo et al., 2017). In fact, it was recently observed in a study involving cats from Italy and Spain that about one fourth of them produce *L. infantum* specific IFNγ by *ex vivo* stimulated blood and they have a significantly lower antibody level compared to non-producer cats (Priolo et al., 2017). Sick dogs with severe clinical disease, high blood parasitemia and antibody level, lack in specific IFN-γ production by *ex vivo* stimulated whole blood (Solano-Gallego et al., 2016b). Cats with *L. infantum*-associated clinical disease have high blood parasitemia and low to very high antibody levels but relationship between antibody titer and severity of disease and also their specific IFN-γ production were not investigated (Bardagi et al., 2016; Basso et al., 2016, p. 20; Brianti et al., 2015; Dedola et al., 2015; Maia et al., 2015; Pennisi et al., 2015a, 2016; Pimenta et al., 2015). However, longitudinal studies confirmed that progression to disease is associated in cats with increasing antibody titers as it occurs in CanL (Foglia Manzillo et al., 2013; Maroli et al., 2007). Moreover, in followed up cases of FeL clinical improvement obtained by anti- *L. infantum* therapy is associated with significant reduction of antibody level as it is reported in canine mild or moderate disease cases (Pennisi et al., 2004; Solano-Gallego et al., 2016a).

Duration of incubation is extremely variable in CanL but diagnoses obtained in animals imported to non-endemic areas years before demonstrate that it can be very long lasting in both dogs and cats (Richter et al., 2014; Rüfenacht et al., 2005; Solano-Gallego et al., 2011).

A complex genetic background modulates susceptibility or resistance of dogs and it contributes to the wide and dynamic clinical spectrum of CanL including subclinical infection, self-limiting mild disease or severe progressive illness (de Vasconcelos et al., 2017; Solano-Gallego et al., 2009). In the Balearic Islands the immunological pattern of resistant dogs is more frequently found in the autochthonous Ibizan Hounds than in other breeds and these dogs rarely develop clinical leishmaniosis (Martínez-Orellana et al., 2017; Solano-Gallego et al., 2000). Sanchez-Robert et al. (2005) studied polymorphism and mutations of the solute carrier family 11, member 1 gene (Slc11a1), also known as natural resistance-associated macrophage protein 1 gene (Nramp1), and they found a breed-specific haplotype distribution (six haplotypes exclusively found in Ibizan Hounds) and one haplotype significantly associated with the disease (Sanchez-Robert et al., 2008, 2005). Moreover, in Boxer dogs from endemic area specific alleles were respectively associated with susceptibility to severe disease or were found in healthy old individuals supposed to be resistant to clinical leishmaniosis, and analysis of single nucleotide polymorphisms confirmed as well the genetic component of the disease in this breed (Quilez et al., 2012; Sanchez-Robert et al., 2005). Genetic susceptibility may explain a peak of higher disease prevalence reported in dogs younger than three years (Abranches et al., 1991). Conversely, immunosenescence and the progressive chronic course of disease may explain another peak of disease seen in dogs older that eight years (Abranches et al., 1991; Day, 2010). Age range of cats reported with FeL is wide (2–21 years), however they are mostly mature cats (7–10 years old) at diagnosis and very few have 2–3 years of age (Bardagi et al., 2016; Basso et al., 2016; Britti et al., 2005; Hervás et al., 1999; Navarro et al., 2010; Pennisi et al., 2015a, 2016). Moreover, FeL was never reported in pedegree cats so that at present there are no data supporting a genetic susceptibility to the disease in some cats. However, studies comparing the genetic background of infected cats according to their clinical status can elucidate mechanisms of susceptibility of feline hosts going beyond the somatic phenotype of domestic shorthair cats (*Felis silvestris domesticus*) that have undergone thousands of years of natural selection in endemic areas. As concerning the age of cats affected by FeL, this is a further datum to support a chronic course of the disease as in dogs.

Other vector-borne co-infections (e.g. *Dirofilaria immitis*, *Ehrlichia canis*, *Hepatozoon canis*) can influence parasite burden and progression of CanL (De Tommasi et al., 2013; Morgado et al., 2016; Tabar et al., 2013). In cats the association between retroviral, coronavirus, *Toxoplasma* or some vector-borne co-infections in cats antibody and/or PCR positive to *L. infantum* has been explored (Attipa et al., 2017; Ayllón et al., 2012; Pennisi et al., 2012, 2000, 1998; Persichetti et al., 2016; Sherry et al., 2011; Sobrinho et al., 2012; Solano-Gallego et al., 2007; Spada et al., 2016, 2013; Vita et al., 2005). A significant association between Feline Immunodeficiency Virus (FIV) and *L. infantum* positivity was found only in few cases (Pennisi et al., 1998; Sobrinho et al., 2012; Spada et al., 2013). However, the review of 89 reported cases of FeL

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