

# Lyme borreliosis *simile*: an emergent and relevant disease to dermatology in Brazil\*

## *Borreliose de Lyme simile: uma doença emergente e relevante para a dermatologia no Brasil\**

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**Abstract:** This review article presents diseases related to spirochetes of the genus *Borrelia*, which are the etiological agents of many human and animal diseases. Focus was given to the *Borrelia burgdorferi sensu lato* complex, including nine different species that cause diseases often with multisystemic involvement and raising interest to many medical specialties, such as Dermatology, Rheumatology, Cardiology and Neurology. Due to differences concerning the etiologic agent, clinical and laboratorial presentations, when comparing with *B. burgdorferi*, *B. garinii* and *B. afzelli*, the infection must be referred as Lyme disease-like illness in Brazil. The recurrent erythema migrans is the main clinical manifestation of borreliosis observed in Brazil and in other countries. The classical reddish macular or papular skin lesion shows expanding features and is tick bite related; additionally, multiple secondary similar lesions may appear far from the original site. The clinical presentation of the disease, mainly skin manifestation, is the main diagnostic parameter, while serologic exams only confirm the clinical suspicion.

**Keywords:** *Borrelia*; Lyme disease; Erythema migrans.

**Resumo:** Neste trabalho de revisão são apresentadas doenças relacionadas com espiroquetas do gênero *Borrelia*, agentes etiológicos de diferentes enfermidades comuns ao homem e a animais. Enfatizou-se a *Borrelia burgdorferi lato sensu*, que inclui diferentes espécies causadoras de doenças e com envolvimento sistêmico, com interesse em várias especialidades médicas, como dermatologia, reumatologia, cardiologia e neurologia. Considerando que existem diferenças quanto ao agente etiológico, além dos aspectos clínicos e laboratoriais, quando comparada com a borreliose de Lyme causada pelas *Borrelia burgdorferi*, *B. garinii* e *B. afzelli*, a infecção no Brasil deve ser referida como borreliose de Lyme simile. O eritema migratório recidivante é a principal manifestação clínica da borreliose existente tanto no Brasil como nos demais países. Essa lesão clássica está relacionada com a picada do carrapato vetor e inicia-se como uma mácula ou pápula cutânea avermelhada, de caráter expansivo, eventualmente surgem lesões semelhantes múltiplas a distância. A manifestação clínica da enfermidade, em especial o envolvimento cutâneo, é o parâmetro diagnóstico mais relevante, e os exames complementares sorológicos confirmam a suspeita clínica.  
**Palavras-chave:** *Borrelia*; Doença de Lyme; Eritema migratório.

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## INTRODUCTION

Several diseases transmitted by ticks, such as Lyme borreliosis and Lyme disease-like illness, may affect both wild and domestic animals as well as human beings. The intense agricultural and stock raising activities in Brazil, the interaction of human beings with domestic animals and the growing interest in outdoor activities favor the spread of infectious agents transmitted by ticks and contribute to the emergence and recurrence of different etiological agents.<sup>1</sup>

*Borrelia burgdorferi lato sensu* complex comprises a group with a large number of infectious agents causing diseases that can affect several organs. Therefore, it has risen much interest in many medical specialties, such as Dermatology, Rheumatology, Cardiology, Neurology and Infectious diseases.<sup>2-4</sup> The spectrum of clinical presentation of this disease differs according to the geographical areas, and it is associated with the local antigenic characteristics of *Borrelia* spp as well as with its interaction with the ecosystem and the vector found in that area.<sup>2</sup> In North America, there is a predominance of skin and joint manifestations; in Europe, skin and neurological manifestations prevail, whereas in Asia the symptoms are basically skin-related.<sup>4,7</sup> Em qualquer situação o eritema migratório recidivante (EMR) é o mais relevante achado, permitindo a suspeita clínica.<sup>5</sup>

In any of these cases, the recurrent erythema migrans (EM) is the most relevant finding that raises the clinical suspicion. The pathogenic species of genus *Borrelia* may infect wild and domestic mammals, humans and birds.<sup>8,9</sup> As members of the order *Spirochaetales*, family *Spirochaetaceae*, they are morphologically different from *Leptospira* and *Treponema*, for being larger, having more periplasmic flagella and fewer spirilla.<sup>10</sup> Members of genus *Borrelia* multiply by transverse binary fission, are microaerophilic and can be observed under optical microscopy with the silver nitrate impregnation technique and by visualization in dark-field or phase-contrast microscopy.<sup>11,12</sup>

The currently known pathogenic *Borrelia* species account for five groups of distinct diseases:

(a) Epidemic relapsing fever, caused by *B. recurrentis*, and endemic relapsing fever, with more than 20 species of genus *Borrelia*, until recently named according to the tick responsible for its transmission;

(b) Avian borreliosis, which is caused by only one species, *B. anserina*, and produces anemia, fever, apathy and high morbidity rates in birds;

(c) Bovine borreliosis, caused by *B. theileri*. This is a cosmopolitan species that can cause mild anemia in ruminants and equines, and it has little

pathogenic effect;

(d) Epizootic bovine abortion, a disease that affects cattle and deer caused by *B. coriaceae*;

(e) Lyme borreliosis (Lyme disease) and Lyme disease-like illness, that are caused by *B. burgdorferi lato sensu*<sup>7</sup> (Chart).

Compared with the North American or European Lyme borreliosis and considering the etiological differences and the clinical and laboratorial aspects, the infection in Brazil must be referred as Lyme disease-like illness,<sup>13</sup> and the first cases were published in the beginning of the 1990's.<sup>14,15</sup> To this day, the etiological agent in Brazil has not been isolated yet,<sup>13,16</sup> and the ticks likely to be involved in the wild cycle belong to the genus *Ixodes*. The genus *Amblyomma* would be implicated in the transmission to domestic animals and humans.<sup>7,13,16</sup>

## Skin manifestations of Lyme borreliosis and Lyme disease-like illness

EM is the main manifestation of Lyme borreliosis.<sup>13,17,18</sup> Although pathognomonic, the skin lesion is not present in all patients and occurs in 60-80% of patients infected with *B. burgdorferi stricto sensu* in the US. It is less frequently associated with *B. garinii* or *B. afzelii*, which are species found in Europe.<sup>5,19</sup>

The classic lesion usually starts 8 to 9 days after the bite, at the inoculation site of *Borrelia* spp. A reddish, centrifugally expanding macule or papula is observed, and it classically reaches a diameter greater than 5cm (Figure 1). In Brazil, the available data suggest that EM appears, on average, 30 days after the tick bite and lasts for a period varying from few days to months.<sup>20</sup> The erythema is generally uniform in its initial phase, resulting in an reddish expanding plaque with different shades of this color; a papula can appear in the middle, corresponding to the site of the tick bite.<sup>21</sup> Edematous urticaria-like lesions can occur in some cases.<sup>18</sup>

The newly formed EM consists of a reddish lesion that is very often ring-shaped, initially measuring 0.5-2.0cm corresponding to the tick bites. This erythema tends to progress via peripheral expansion of its borders with central clearing (Figure 2).<sup>22</sup> The erythema is often circular, and it may show morphological variations such as triangular, oval or elongated shapes.<sup>5,19</sup> The size and shape of EM are variable, demonstrating a centrifugal and slow growth; however it can have a rapid expansion and become a plaque in a short period of time. Between 8 and 14 days after the tick bite, the lesion can reach a diameter greater than 15 cm.<sup>18</sup>

Although EM is normally found as a solitary lesion, multiple lesions can also occur, representing

CHART: Borreliosis Groups: species involved, vectors, hosts and distribution

Diseases	Etiological Agent	Vectors	Hosts	Geographical Distribution
Epidemic relapsing fever	<i>B. recurrentis</i>	<i>Pediculus humanus</i>	Humans	Cosmopolitan
Epidemic relapsing fever	<i>Borrelia spp*</i>	<i>Ornithodoros spp</i>	Rodents and humans	Cosmopolitan
Avian borreliosis	<i>B. anserina</i>	<i>Argas spp</i>	Birds	Cosmopolitan
Bovine borreliosis	<i>B. theileri</i>	<i>Boophilus spp</i>	Cattle, sheep and horses	Cosmopolitan
Epizootic bovine abortion	<i>B. coriaceae</i>	<i>O. coriaceus</i>	Cattle and deer	North America
Lyme borreliosis	<i>B. burgdorferi</i>	<i>Ixodes sp</i>	Wild and domestic animals, and humans	North America and Europe
	<i>B. garinii</i>	<i>Ixodes sp</i>	the same	Europe and Asia
	<i>B. afzelii</i>	<i>Ixodes sp</i>	the same	Europe and Asia
Lyme disease-like illness in the US	<i>B. andersoni</i>	<i>Ixodes sp</i>	the same	North America
	<i>B. lonestari</i>	<i>Amblyomma americanum</i>	the same	North America
	<i>B. barbouri</i>	<i>A. americanum</i>	the same	North America
	<i>B. bissettii</i>	<i>Ixodes sp</i>	the same	North America
Lyme disease-like illness in Europe and Asia	<i>B. valaisiana</i>	<i>Ixodes sp</i>	the same	Europe
	<i>B. lusitaniae</i>	<i>Ixodes sp</i>	the same	Europe
	<i>B. turdii</i>	<i>Ixodes sp</i>	the same	Asia
	<i>B. tanukii</i>	<i>Ixodes sp</i>	the same	Asia
	<i>B. miyamotoi</i>	<i>Ixodes sp</i>	the same	Asia
	<i>B. japonica</i>	<i>Ixodes sp</i>	the same	Asia
Lyme disease-like illness in Brazil	<i>Borrelia sp</i>	<i>Amblyomma cajennense</i>	Idem	Brazil

\* Approximately 25 species of the genus *Borrelia* are recognized, which are still named according to the transmitting tick species of the genus *Ornithodoros*.

the dissemination of the microorganisms through the blood vessels and lymphatic system. They are called secondary annular lesions and are less expanding than the EM.<sup>18,22,23</sup>

### Skin changes in EM

At the site of the tick bite, a dermal inflammatory process occurs, with a central infiltrate composed of macrophages, mastocytes, neutrophils, plasmocytes, lymphocytes, and usually few eosinophils.<sup>17,21,24</sup>

The main histopathological findings include proliferation and dilation of blood vessels, and vasculitis shows a primary lymphocyte infiltrate associated with plasma cells. As the lesion progresses, there is a reduction of the inflammatory process and marked atrophy of the epidermis and dermis.<sup>25,26</sup>

In the histopathological study of biopsies of the core of the EM lesions, Steere et al.<sup>19</sup> demonstrated a cuff-shaped dermal infiltrate composed of lymphocytes, histiocytes, plasma cells and mastocytes.

Berger<sup>22</sup> observed in the upper and deeper dermis the presence of perivascular and interstitial infiltrate mainly comprised of lymphocytes, plasmocytes and/or eosinophils. In biopsies of the edges on the lesion, the author found a predominance of plasmocytes, whereas in the center of the lesion, eosinophils prevail. There were lympho-histiocytic infiltrates in 38.23% of all biopsies in the superficial and deep dermis.

In skin biopsies of 31 patients from Manaus, Melo et al.<sup>27</sup> detected spongiosis in 15 (44.12%). When examining the dermis, 8 patients (15.69%) had an infiltrate composed of lymphocytes, histiocytes and eosinophils. In 9 patients (29.04%) they observed cuff-shaped infiltrate around the vessels. *Borrelia* spp was detected in one case (3.22%).<sup>27</sup> These biopsies were relevant to confirm the diagnosis of EM.

When EMR occurs isolate or accompanied by discreet symptoms it is considered as localized form, and when it presents multiple erythemas accompa-



FIGURE 1: Chronic migratory erythema in patient with primary Lyme disease-like illness, acquired in Campinas region, State of São Paulo, Brazil.

nied by more intense symptoms, it is deemed as disseminated EMR<sup>22</sup> (Figure 3). The distinction between the two situations is important because, in individuals with localized lesion, the response to antibiotics is usually favorable, while in patients with disseminated disease, the treatment takes longer and has to be frequently repeated, with a poorer prognosis in terms of definitive cure.<sup>22,23</sup>

The acrodermatitis chronica atrophicans<sup>2,6,18</sup> is the typical form that occurs in the chronic phase of the classic European Lyme borreliosis. Initially there is a red-bluish edematous lesion, usually in the feet or lower legs of elderly patients.<sup>2</sup> Erythema and edema



FIGURE 2: Recurrent annular erythema in patient with secondary Lyme disease-like illness, often with multiple lesions on trunk and limbs.

significantly vary in intensity. With time, the skin in that site becomes atrophic with a wrinkled appearance, and the subcutaneous vessels are more evident.<sup>17</sup>

### Extracutaneous manifestations in Lyme borreliosis and Lyme disease-like illness

According to Berger,<sup>18</sup> the most frequent general extracutaneous symptoms in Lyme borreliosis were fever (55%), fatigue (48%), musculoskeletal discomfort (47%) and headache (38%). Joint pain and neurological symptoms were also observed. General manifestations such as malaise, neck rigidity, and photosensitivity, conjunctivitis, lymphadenopathies are described and may last several weeks or longer if not treated.<sup>28</sup>

Secondary manifestations of Lyme borreliosis include neurological, joint and cardiac manifestations. Weeks or months after the onset of EMR, early neurological manifestations may be observed, such as aseptic meningitis, neuritis of cranial nerves, cerebellar ataxia, motor or sensory radiculoneuritis, myelitis and encephalitis.<sup>29,30</sup> Such manifestations may recur and last for months or become chronic.<sup>29,30</sup> Other publications mention the possibility of subluxations of small joints in the hands and feet associated with peripheral sensory neuropathy.<sup>28,31,32</sup> Cardiac disorders may also appear few weeks after EM, such as atrioventricular block, acute myocarditis or enlarged heart area.<sup>33</sup> Large-joint arthritis, especially in the knee, occur weeks or months after the initial stage and last few days or weeks, but they can relapse and evolve to a polyarticular involvement similar to that of rheumatoid arthritis.<sup>13,15</sup>

Approximately 60% of untreated patients in the US develop arthritis within two years, which often presents with sudden onset, oligoarticular or monoarticular involvement, affecting large joints, and with periods of remission or activities.<sup>3</sup> Mild fatigue and fever may accompany this stage. If left untreated, the joint condition may resolve spontaneously, but 10% of patients evolve to chronic erosive arthritis with synovial proliferation and no longer respond to antibiotics.<sup>31</sup> Spirochete antigens and structures similar to *B. burgdorferi*, may be demonstrated in perivascular sites and synovia by means of the silver impregnation technique or monoclonal antibodies. The presence of bacterial components in the joints was demonstrated in the chronic forms using the polymerase chain reaction (PCR) technique.<sup>29,34</sup>

The neurological involvement of Lyme borreliosis presents with clinical variations according to the stage of the disease. Fifteen percent of patients not treated in the primary stage evolved with central or peripheral neurological abnormalities, which had the





**FIGURE 3:** Chronic migratory erythema in cicatrization stage, localized in thigh of a boy, who acquired Lyme disease like illness after visiting a beach at State of São Paulo with vegetation, Mata Atlantica Forest, the boy saw ticks over your clothes.

potential to lead to irreversible damage.<sup>9</sup> Therefore, in the initial stages patients complain of headache, irritability and sleep disorders. These symptoms generally disappear with remission of the disease.<sup>9,28</sup> In its latent stage, various abnormalities can be found, the most frequent including cranial neuropathy, especially facial paralysis, peripheral sensory or motor neuropathy and meningitis. The latter presents with severe headache, pain and neck rigidity, photophobia, nausea, vomiting and irritability.<sup>9,28</sup>

Approximately 8% of untreated patients, within weeks or months after the primary infection, evolved into a cardiac condition consisting of variable degrees of atrioventricular block.<sup>19</sup> The cardiac damage is reversible and it usually does not require a pacemaker. There are some rare reports of death as a consequence of myocarditis, with *Borrelia* present in the heart tissue.<sup>35</sup>

There are reports of transplacental transmission of *B. burgdorferi lato sensu* leading to neonatal complications related to maternal infection during the first three months of pregnancy.<sup>36,37</sup>

#### Lyme disease-like illness in humans in Brazil

In 1989, the first review article on borreliosis was published in the Brazilian medical literature warning physicians about the possible existence of this disease in Brazil.<sup>38</sup> In that year, a multidisciplinary team assembled at the Universidade de Sao Paulo in order to further investigate this disease. A laboratory was set up specifically for its diagnosis, aiming to perform serologic tests and culture of *B. burgdorferi* in a Barbour-Stoenner-Kelly (BSK) medium. In the begin-

ning of the 1990's, some clinical cases of Lyme disease-like illness were reported in Rio de Janeiro,<sup>14,39</sup> Manaus,<sup>40,41</sup> São Paulo<sup>42</sup> and Mato Grosso,<sup>15,43</sup> with a predominance of skin manifestations. The same situation was observed in Argentina.<sup>44</sup>

The profile of Lyme disease-like illness was characterized with the report of 30 cases in humans, and the clinical manifestations, serum diagnosis, treatment and epidemiology with involvement of dogs, cattle, wild animals and ticks were discussed.<sup>28</sup>

Patients with skin involvement and positive serology who were in suburban or rural areas in contact with small and/or big animals in the State of Rio de Janeiro presented positive serum reaction to *B. burgdorferi*, with a predominance of skin manifestations and a few cases of joint and cardiovascular abnormalities.<sup>45</sup>

Studies conducted by Yoshinari<sup>13</sup> concluded that in Brazil there is a form of Lyme borreliosis with clinical and epidemiological characteristics that are different from those found in Europe and North America. Skin manifestations were the most frequent ones and were present in different forms of the disease. Joint, neurological and cardiac involvement were also reported at comparable frequency as that found in other continents. The recurrent nature of the disease in Brazil stood out.<sup>20</sup>

#### Lyme borreliosis in animals

Following the identification of the disease in humans, Lyme borreliosis was acknowledged as capable of infecting both wild and domestic animals. In the Northeastern region in the US, the agent is widely spread among rodents and deer,<sup>46</sup> constituting natural reservoirs.<sup>47</sup> Domestic animals such as dogs, horses and cattle act as carriers of the vectors to the domestic setting.<sup>47-50</sup> In contrast to the unnoticed infection of wild animals, this agent may cause clinical disease in domestic animals.<sup>48,51,52</sup>

Salles et al.<sup>53</sup> observed that horses highly infected by ticks also had a higher prevalence of seropositivity in the indirect ELISA and Western blotting assays for *B. burgdorferi*, in contrast to the animals that underwent a stringent tick control program. According to these authors, the humoral response of the horses studied presented good antigen recognition for *B. burgdorferi* strain G39/40 in both tests used, and the frequency of serum positive animals corroborated the hypothesis that there is a type of borreliosis similar to the Lyme borreliosis affecting horses in Brazil.

The finding of *Borrelia* sp was reported in the peripheral blood and urine of marsupials.<sup>54,55</sup> Barboza et al.<sup>54</sup> detected skunks that were naturally infected, after immunosuppression with cyclophosphamide. Domestic and wild animals have a higher risk of

becoming infected with the etiological agent because they are infested with a large number of ticks. In endemic areas, *B. burgdorferi lato sensu* was found in asymptomatic animals that can serve as a reservoir to humans.<sup>33</sup> Taking into account the potential transmission of the etiological agent through the urine of the host, Lyme borreliosis should be deemed as a serious public health problem.<sup>7</sup>

### Diagnostic methods

The diagnosis of *Borrelia* spp can be made by peripheral blood smear, especially when spirochetemia is increased.<sup>8,10</sup> Smears can be performed with fragments of tick tissues, such as intestine, salivary gland and hemolymph, stained with Giemsa, as *B. burgdorferi* was originally discovered.<sup>56,57</sup> This technique has been very much used in the study of *B. anserina* and *B. theileri* in ticks and vertebrate hosts.<sup>10,58</sup>

The finding of EM is relevant as a clinical and cutaneous marker of borreliosis. The histopathological exam of the skin biopsy or the culture in BSK medium as part of the search for the etiological agent are important tools for both specific and differential diagnosis.<sup>27</sup>

Serological methods have been widely used in studies on anti-IgG and anti-IgM antibodies in humans and animals in risk or enzootic areas for borreliosis, serving as a support both to confirm clinical cases and to prepare an epidemiological profile of this disease.<sup>13</sup>

In Brazil, the indirect ELISA test to detect anti-*B. burgdorferi* gG has already been standardized for bovine,<sup>59</sup> canines<sup>60</sup> and equines,<sup>53</sup> populations, with the use of total sonicated antigen of *B. burgdorferi stricto sensu* strain G39/40. Serological studies were performed using this assay; the frequency of anti-*B. burgdorferi* IgG antibodies was estimated at 72.51% in asymptomatic bovines in the Southeast region,<sup>61</sup> 20% in canines in the Baixada Fluminense region<sup>60</sup> and 9.80% in equines in the State of Rio de Janeiro.<sup>53</sup>

The finding and the culture of the etiological agent provide a definitive diagnosis.<sup>12</sup> To this day it has still not been possible to cultivate the microorganism of the genus *Borrelia* responsible for the Lyme disease-like illness in mammals or ticks in Brazil.<sup>13,16,34</sup> Nevertheless, the results of the researches carried out

showed the existence of a pathogenic agent related to ticks, which is able to boost the immune system of the host to produce antibodies against the North-American strain G39/40 of *B. burgdorferi stricto sensu*.<sup>16,59,62,63</sup>

To establish the epidemiological pattern, the Center for Disease Control (CDC, Atlanta, US) determined the following diagnostic criteria:

1) In endemic areas, Lyme borreliosis is considered if, after exposure to ticks, the patient presents EM or, in its absence, there is a report of cardiovascular, nervous system or musculoskeletal disease;

2) In areas considered at risk for having reservoirs and vectors, the individuals are considered infected with Lyme borreliosis if they develop EM with positive serology by Western blotting (presence of two IgM bands or four IgG bands or the concomitance of one IgM band with two IgG bands).

The clinical diagnosis of EM must be confirmed by serologic and histopathological exams, as well as by culture in a specific medium. The patients are usually positive to antibody tests using ELISA and Western Blotting techniques; however, they must be carefully interpreted in view of false-positive serology with other infectious or autoimmune diseases.<sup>44</sup> The interpretation of serologic tests must be a cautious procedure because of the risks of false-negative and false-positive results; for example, patients who receive early treatment may present a negative serology.<sup>7,62,64</sup> The sensitivity of these tests is low in the acute phase, increases after some weeks of disease progression and tends to recur during flare or re-infections. It was reported that a portion of patients with chronic disease may remain serologically negative.<sup>13,62</sup> The specificity of the serologic test is low because it presents cross reactivity with syphilis, visceral leishmaniasis, rheumatoid disease, infectious mononucleosis, subacute bacterial endocarditis, scleroderma and systemic lupus erythematosus.<sup>62</sup> □

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