



Lyme borreliosis

Borreliose de Lyme

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Abstract: Borreliosis is an infectious disease caused by spirochetes of the genus *Borrelia*. Lyme borreliosis, also known as Lyme disease, is a non-contagious infectious disease caused by spirochetes belonging to the complex *Borrelia burgdorferi sensu lato* and more often transmitted by the bite of infected ticks of the genus *Ixodes*. The disease is characterized by a varied clinical profile, which can trigger cutaneous, articular, neurological and cardiac manifestations.

Key words: Keywords: *Borrelia burgdorferi*, Lyme disease, chronic Erythema migrans; *Ixodes*

Resumo: As borrelioses constituem um grupo de doenças infecciosas causadas por espiroquetas do gênero *Borrelia*. A borreliose de Lyme, também denominada doença de Lyme, é uma doença infecciosa, não contagiosa, causada por espiroquetas pertencentes ao complexo *Borrelia burgdorferi Sensu Lato* e transmitida, mais frequentemente, por picada de carrapatos do gênero *Ixodes*. A doença apresenta quadro clínico variado, podendo desencadear manifestações cutâneas, articulares, neurológicas e cardíacas.

Palavras-chave: *Borrelia burgdorferi*; Doença de Lyme; Eritema migrans crônico; *Ixodes*

INTRODUCTION

Borreliosis is an infectious disease caused by spirochetes of the genus *Borrelia*. Infections caused by pathogenic species of *Borrelia* are grouped into five categories: a) relapsing fever, caused by *B. recurrentis* b) avian borreliosis, caused by *B. anserina* c) bovine borreliosis, associated with *B. theileri* d) bovine enzootic abortion, related to *B. Coriaceae*; e) Lyme borreliosis or Lyme disease, caused by different species of the *B. burgdorferi Sensu Lato* complex.¹

Lyme borreliosis (LB), also known as Lyme disease (LD), is a non-contagious infectious disease caused by spirochetes belonging to the *Borrelia burgdorferi Sensu Lato* complex and more often transmitted by the bite of infected ticks of the genus *Ixodes*. The disease is characterized by a varied clinical profile, which can trigger cutaneous, articular, neurologic and cardiac manifestations.²

HISTORY

The first reported cases of Lyme borreliosis are of Afzelius in 1910 in Sweden, and Lipschutz, in Austria, in 1914. These authors described the first cases of patients with single or multiple erythematous plaques of centrifugal growth, which they denominated Erythema Chronicum Migrans (ECM).^{3,4}

From the first reports, new cases of ECM were identified in several European countries, mainly in Central Europe. In 1958, Hollstrom achieved cure of patients with ECM using procaine penicillin, which led him to postulate bacterial etiology for the disease.⁵

In 1977, in the city of Lyme, Connecticut, USA, several cases of arthritis were described in young patients with skin lesions identical to ECM. The association of ECM and arthritis was called Lyme disease, Lyme arthritis or Lyme borreliosis (LB).⁶

Despite knowledge of the clinical

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manifestations and therapeutic results of the disease, its etiologic agent remained unknown until 1982, when Burgdorfer *et al.* noticed the presence of spirochetes in the gut of ticks of the *Ixodes dammini* species, which were called *Borrelia burgdorferi* Sensu Lato.⁷ The association between *B. burgdorferi* and ECM was consolidated with the identification of spirochetes in biopsies of skin lesions. Later, through polymerase chain reaction (PCR), DNA sequences of *B. Burgdorferi* were detected in skin, spinal fluid and synovial fluid samples from patients with Lyme disease, proving that the etiologic agent of the disease was indeed the spirochete found in the gut of *Ixodes*.⁸ Almost simultaneously, in Europe, new species belonging to the *B burgdorferi* Sensu Lato complex were identified, associated with clinical manifestations of LB.⁹

Considering the not always chronic evolution of the disease, Detmar *et al.* proposed in 1989 that the best designation for this disease was erythema migrans (EM) and not ECM.¹⁰ Currently, in addition to skin and rheumatic manifestations, it is well established that untreated infections by *Borrelia burgdorferi* may evolve to cardiac, neurologic and ophthalmic complications.¹¹

EPIDEMIOLOGY

LB has a worldwide distribution and has been diagnosed on all continents. In Europe, the disease is endemic in Germany, Austria, Sweden, Denmark, Norway, Slovenia, Poland, and often observed in the UK, Spain, Portugal, Switzerland, Croatia, Italy, Czech Republic and other countries.^{12,13,14}

On the American continent, it is endemic in the United States; there are cases reported in Brazil, Mexico, Canada, Chile, Costa Rica, Colombia and Venezuela.^{15,16,17} It is considered a public health issue in the United States, with on average 20,000 cases per year.¹⁸

In Brazil, the first three cases of EM were reported in 1987 by Talhari *et al.*, in patients of the metropolitan region of Manaus, the Amazon state. Later, another 12 new cases of EM were diagnosed, also in Manaus.¹⁹ After these reports, other cases of EM, with suggestive histological findings and positive serology for *Borrelia* sp were identified in other regions of Brazil.^{20,21,22} In 1992, the first cases of Brazilian patients with articular manifestations associated with infection by *B. burgdorferi* were described.²³ In Brazil, given the impossibility of identifying the etiologic agent, such cases have come to be known as “*Borrelia*-like.”²⁴

In 2010, Santos *et al.* assessed the seroprevalence of infection by *Borrelia* sp in patients with different dermatoses, not associated with

borreliosis, in Manaus. Of the 270 sera examined by ELISA, 19 (7%) were positive for the presence of antibodies specific for *B. Burgdorferi*. Of these 19 cases, samples of 13 patients underwent confirmatory testing by Western Blot. Six patients (46.2%) were positive by Western Blot. These results led to confirmation of infection by *B. burgdorferi* in the Amazon region.²⁵

In 2010, Talhari *et al.* demonstrated, for the first time, the presence of *Borrelia* in patients with EM using immunohistochemistry with polyclonal anti-*Borrelia* antibody and a visualization technique denominated “focus-floating microscopy.”²⁶

Etiologic agent, reservoirs and vectors

The causative agent of LB is *Borrelia burgdorferi* Sensu Lato. The *Borrelia burgdorferi* Sensu Lato complex comprises fourteen species: *Borrelia burgdorferi* Sensu Stricto, *B. garinii*, *B. afzelii*, *B. andersonii*, *B. bissetii*, *B. valaisiana*, *B. lusitaniae*, *B. japonica*, *B. tanukii*, *B. turdae*, *B. sinica*, *B. spielmanii*, *B. californiensis* and *B. carolinensis*.²⁷

Of these fourteen species, four are associated with LB: a) *Borrelia burgdorferi* Sensu Stricto, b) *B. garinii*, c) *B. afzelii*, and d) *Borrelia spielmanii*. In the United States, *B. burgdorferi* sensu stricto is the only species found. On the other hand, in Europe, apart from *B. burgdorferi* Sensu Stricto, *B. garinii*, *B. afzelii* and *Borrelia spielmanii* are also found. The latter has recently been associated with EM cases in Hungary.^{28,29}

The main vectors of *B. burgdorferi* Sensu Stricto are ticks of the genus *Ixodes* (*I. dammini*, *I. scapularis* and *I. pacifus*). *I. ricinus* and *I. persulcatus* are among the vectors of *B. garinii*. *I. ricinus*, *I. uria* and *I. persulcatus* are important in the transmission of *B. afzelii*. Although the main vectors of *B. burgdorferi* Sensu Stricto are ticks of the genus *Ixodes*, the species *Amblyomma americanum*, *A. cajennense*, and *Dermacentor variabilis* have also been associated with the transmission of *B. burgdorferi*.³⁰ In Brazil, the presence of *Borrelia* sp in ticks of the genera *Amblyomma* and *Rhipicephalus* has been shown, but without proof of involvement of these vectors in the transmission of LB.³¹

Ticks become infected during blood feeding on animals carriers of *B. burgdorferi*. In the U.S., the main reservoirs are white-tailed deer and mice. Elevated serum titers of specific antibodies to *B. burgdorferi* have already been found in cattle, goats and dogs, suggesting that these animals may also act as reservoirs. In Brazil, reservoirs have not yet been identified, although anti-*B.burgdorferi* antibodies have already been detected in dogs, marsupials,

horses and buffaloes. However, the participation of these animals in disease transmission has not been elucidated.^{32,33} The average life cycle of ticks varies from one to three years and their development includes four evolutionary stages: egg, larva, nymph and adult. Ticks can be infected in all evolutionary stages, although nymphs and adult ticks are the main transmitters of *B. burgdorferi*.³⁴

MODE OF TRANSMISSION

Spirochetes settle on microvilli and intercellular spaces of the midgut epithelium of ticks and transmission occurs during blood feeding, by the inoculation of infected saliva. In most cases human beings acquire *B. burgdorferi* through the bite of nymphs, which are painless and explain why many patients do not recall having had contact with ticks. For the occurrence of infection by *B. burgdorferi*, it is estimated that the tick needs to be attached to the skin, on average, for more than 12 hours.³⁵

Infection by *B. burgdorferi* may progress to spontaneous cure or to manifestations of early-stage borreliosis and / or late stage, with neurologic, cardiac, ophthalmic, articular and cutaneous disorders.³⁶

CLINICAL MANIFESTATIONS

In 1989 Steere *et al.* classified the disease into three stages:³⁷

1st stage or acute phase, with predominantly cutaneous lesions;

2nd stage, in which there may be articular, neurologic, cardiac and ophthalmic manifestations;

3rd stage, with chronic rheumatologic, neurologic, ophthalmic, and cutaneous manifestations.

Despite this clinical division, it is possible to observe clinical manifestations of the different clinical stages of the disease concomitantly.

The main manifestation of the early stage of the disease is EM, reported in 60-83% of patients. Clinically, this manifestation is initially characterized by erythematous macules or papules, which increase in size, forming isolated or multiple plaques with discontinuous edges and central clearing, cyanotic and / or scaly, which expands centrifugally and can reach large diameters (Figure 1).³⁸ Although EM can occur in any part of the skin, it predominates in the lower and upper limbs and face. Generally, EM is asymptomatic, but pruritus or burning can be referred in some cases.³⁹ In a study conducted in 2009 in Manaus, 22 cases of EM were analyzed, being 14 (63.6%) male patients and eight (36.4%) female, with a mean age of 34.5 years. Of the 22 patients studied,

only two (9%) reported pruritus in the lesions and only one (4.5%) reported fever and myalgia. These clinical findings indicate a behavior similar to that of LB diagnosed in Europe, with prevalence of skin lesions and few local or systemic manifestations in early disease.²⁶

Days or weeks after the onset of cutaneous manifestations, new EM lesions may develop, resulting from hematogenous or lymphatic dissemination of spirochetes. These lesions may appear with the primary lesion or after its disappearance.⁴⁰

In addition to EM, another important cutaneous manifestation of the initial phase of LB is lymphocytoma cutis, also called lymphadenosis benigna cutis. It is clinically characterized by a single erythematous nodule or plaque, 1 to 5 centimeters in diameter, usually located on the face, pinna, scrotal bag or mammary areola. Lymphocytoma is often associated with infection by *B. afzelli* and *garinii*.⁴¹

In the acute phase systemic manifestations such as asthenia, arthralgia, myalgia, skin rash, adenopathy, splenomegaly and signs of meningeal irritation may occur.⁴²

Early lesions of LB may disappear without treatment and manifestations of the second and third stage can appear months or years after initial infection. Among major alterations there is articular, cardiac, neurologic, ophthalmic, and cutaneous involvement. In some cases, these late manifestations may occur in conjunction with EM lesions.⁴³

Different species of *Borrelia* can lead to distinct clinical manifestations (Table 1). Erythema migrans lesions from infection by *B. burgdorferi* *Sensu Stricto* last longer and are more exuberant with systemic manifestations. On the other hand, when caused by *B.*



FIGURE 1: Erythema migrans: erythematous plaque with centrifugal growth

afzelii and *B. garinii*, manifestations are often shorter with fewer frequent local symptoms and are rarely accompanied by systemic involvement.⁴⁴

Articular involvement is more frequent in infection by *B. burgdorferi* *Sensu Stricto*, predominating in the United States. Early manifestations are characterized by seronegative oligoarthritis, with edema and pain, especially in large joints such as the knees. Chronic and erosive arthritis can be belatedly observed, which, if untreated, lead to the progressive destruction of cartilage and bone. In European patients, articular manifestations are less frequent and the symptoms are more subtle.⁴⁵

Cardiac involvement is found in 6-10% of the cases, mainly in patients infected with *B. garinii* and *B. afzelii*. Atrioventricular blocks, ventricular repolarization disturbances, myopericarditis and left ventricular dysfunction are the most common manifestations.⁴⁶

Neurologic involvement occurs in 15-25% of the cases, especially in patients infected with *B. garinii*. The most common disorders are encephalitis, cranial nerve palsies, meningitis and myelitis. Bell's palsy, caused by VII cranial nerve involvement, is the most frequent manifestation of neuroborreliosis in children and adolescents and may occur in up to 50% of the cases. Other pairs of cranial nerves may also be affected, among the: II, III, V, VI, and IX.⁴⁷ In chronic cases, after several years of evolution, multifocal encephalitis, demyelinating disease similar to multiple sclerosis and chronic encephalomyelitis with paraparesis, polyneuropathy, radicular pain, and paresthesia can be observed. In the U.S., neurologic alterations are rare, resulting mainly in cognitive disorders.⁴⁸

Several ophthalmic manifestations associated with infection by *B. burgdorferi* have been described, more frequently in European patients. The most common are conjunctivitis, optic nerve neuropathy, and iridocyclitis-panophthalmitis.⁴⁹ Diplopia with paralysis of the V and VI cranial nerves and ocular mobility impairment may also occur. Cases of pupillary abnormalities, such as Argyll-Robertson pupil and Claude Bernard-Horner syndrome have also been linked to infection by *B. burgdorferi*. Chronic intraocular inflammation and intraorbital

myositis can also be observed. It is common for chronic ophthalmic alterations to be associated with neurologic involvement.⁵⁰

In late-stage borreliosis, characteristic skin changes may occur, called acrodermatitis chronica atrophicans (ACA) or Pick-Herxheimer disease. Acrodermatitis chronica atrophicans is generally associated with infection by *B. afzelii* and is most often diagnosed in Europe. Clinically, it begins with an erythematous plaque, progressing to cutaneous atrophy and prominent blood vessels, located mainly in the lower limbs. Face and trunk may also be affected.⁵¹

CHRONIC LYME BORRELIOSIS or POST-LYME SYNDROME

This term is used to designate a series of symptoms that appear even after adequate treatment regimens with antibiotics. The main symptoms are chronic fatigue, chronic musculoskeletal pain, headache, drowsiness, irritability and cognitive impairment (memory loss, difficulty concentrating and thinking, reduced judgement ability, among others).⁵² Among all the symptoms, chronic fatigue is the most closely related to chronic LB and is referred to as deep and extremely debilitating fatigue. The cause of chronic LB is not yet fully understood, although several studies indicate as the main factor persistent infection by *B. burgdorferi*, despite proper treatment of this condition. Some authors argue that these manifestations are due to inflammatory and autoimmune phenomena, triggered by persistent infection and not by the presence of the infectious agent itself, similar to what occurs in syphilis. This explains why many patients with chronic LB do not respond to prolonged antibiotic regimens.⁵³

OTHER SKIN DISEASES ASSOCIATED WITH INFECTION BY BORRELIA

In addition to the lesions of erythema migrans, acrodermatitis chronica atrophicans and lymphocitoma, infection by *B. burgdorferi* may be associated with other skin diseases such as scleroderma plaque, lichen sclerosus (LS), anetoderma, atrophoderma of Pasini-Pierini (APP), and granuloma annulare.⁵⁴

Scleroderma plaque is an inflammatory

CHART 1: Different Borrelia species and major clinical manifestations

Borrelia species	Major Clinical Manifestations
<i>Borrelia burgdorferi</i> <i>Sensu Stricto</i>	<i>Erythema migrans</i> and <i>articular involvement</i>
<i>Borrelia afzelii</i>	<i>Erythema migrans</i> , <i>lymphocitoma</i> , <i>ACA</i> , <i>cardiac</i> and <i>ophthalmologic alterations</i>
<i>Borrelia garinii</i>	<i>Erythema migrans</i> , <i>lymphocitoma</i> , <i>neurologic</i> , <i>cardiac</i> and <i>ophthalmologic alterations</i>
<i>Borrelia spielmanii</i>	<i>Erythema migrans</i>

disease of connective tissue, belonging to the group of collagenoses and clinically characterized by plaques with atrophy and sclerosis. It can be triggered by physical trauma, infections or immunological changes.⁵⁵ In 1987 Aberer *et al.* published the first study suggesting the association of scleroderma plaque and *B. burgdorferi*.⁵⁶ Subsequently, other authors also correlated scleroderma and infection by *B. burgdorferi*. The presence of *B. burgdorferi* in lesions of scleroderma has been frequently described in European and Asian patients, but it is rare in Americans.⁵⁷

Lichen sclerosus is a rare skin disease characterized by whitish, papular, scaly and atrophic lesions. It is more common in females and lesions are most commonly found in the perianal and genital regions. The association of lichen sclerosus and *B. burgdorferi* has been found mainly in Europe. In South America cases of LS and infection by *B. burgdorferi* have been reported in Colombia.^{58, 59}

Atrophoderma of Pasini-Pierini is a rare dermatosis of unknown etiology, considered by some authors as a variant of scleroderma plaque and characterized by atrophic plaques without sclerosis. Cases of APP with anti-*B. burgdorferi* have been described in Europe.⁶⁰

Anetoderma is characterized by oval, atrophic, and wrinkled lesions, located mainly in the trunk. It is characterized by alterations of elastic fibers by an unknown mechanism, with likely genetic, autoimmune and infectious causes; among them infection by *B. Burgdorferi*. Patients with anetoderma associated with infection by *Borrelia sp* are found mainly in Europe.⁶¹

In a study conducted in Manaus in 2009, 15 patients with scleroderma and atrophoderma of Pasini-Pierini were analyzed using immunohistochemistry with polyclonal anti- *B. burgdorferi* antibody. Of these, ten (66.6%) were female and five (33.4%) male, with a mean age of 33 years. Presence of *B. burgdorfeiri* was confirmed in four (26.6%) of the 15 patients examined.⁶²

DIAGNOSIS

The diagnosis of LB is based on epidemiological, clinical and laboratory findings. Laboratory diagnosis is based on serology (detection of specific antibodies) and / or presence of the etiologic agent. Besides serology, histology, immunohistochemistry, PCR and culture are also important.⁶³

The detection of anti-*B. burgdorferi* IgM or IgG antibodies is commonly used for serologic diagnosis and epidemiological investigation. The main serologic tests are the ELISA (Enzyme-linked

immunosorbent assay) and indirect immunofluorescence (IIF).⁶⁴ However, these tests may show false positive results, given the cross-reaction with other diseases such as collagenoses, leishmaniasis, and syphilis. Hence, in non-endemic areas, conclusive diagnosis requires confirmatory testing that indicates the presence of the agent.⁶⁵

Hematoxylin-eosin (HE) staining of histological sections is considered suggestive when superficial and deep perivascular inflammatory infiltrate, with predominance of lymphocytes, histiocytes and eosinophils, is observed (Figure 2). Presence of *B. burgdorferi* can be demonstrated using silver staining (Warthin-Starry technique), but the sensitivity of this technique is low - ranging from 10 to 40%.⁶⁶

In 2007 Eisendle *et al.*, through immunohistochemistry for the detection of *Borrelia sp.* associated with focus floating microscopy (FFM), obtained better results than nested-PCR in the identification of *Borrelia* (96.0% vs 45.2%), with similar specificity (99.4% vs 100%). Focus floating microscopy consists in tissue sections being scanned through two planes: horizontally in serpentine and vertically by focusing through the thickness of the section with magnification up to 400x, under strong illumination. According to the author, these simultaneous movements facilitate visualization of *B. burgdorferi*.⁶⁷ In Manaus, 22 EM patients were analyzed through the technique described above and the presence of *Borrelia burgdorferi* was detected in five (22.7%) cases (Figure 3).²⁶

Although the PCR technique detects nucleic acid sequences of *Borrelia*, with high specificity, the sensitivity of this method is variable (20-81%). In 2008 Cerar *et al.*⁶⁸ showed, using the flagellin gene, that nested-PCR had higher sensitivity than PCR (64.6% vs 24%). Positivity of PCR is higher when fragments of skin lesions or of synovial membrane are used. It is less sensitive when performed with paraffin blocks, blood, synovial fluid and spinal fluid.⁶⁹

Culture, using BSK medium (Barbour, Stroenery, Kelly) or variations of this medium, shows 100% specificity. However, its sensitivity is relatively low. Given the difficulties of this technique and material contamination, the results are positive in approximately 45% of the cases.⁷⁰

TREATMENT

Treatment of LB varies according to the stage of the disease:

a) Erythema migrans, lymphocitoma cutis and other initial manifestations: the drug of choice is doxycycline, 100 mg, every 12 hours, orally (PO), 14 days. In children under 12 years old, the use of amoxicillin, 500 mg, PO, every 8 hours or

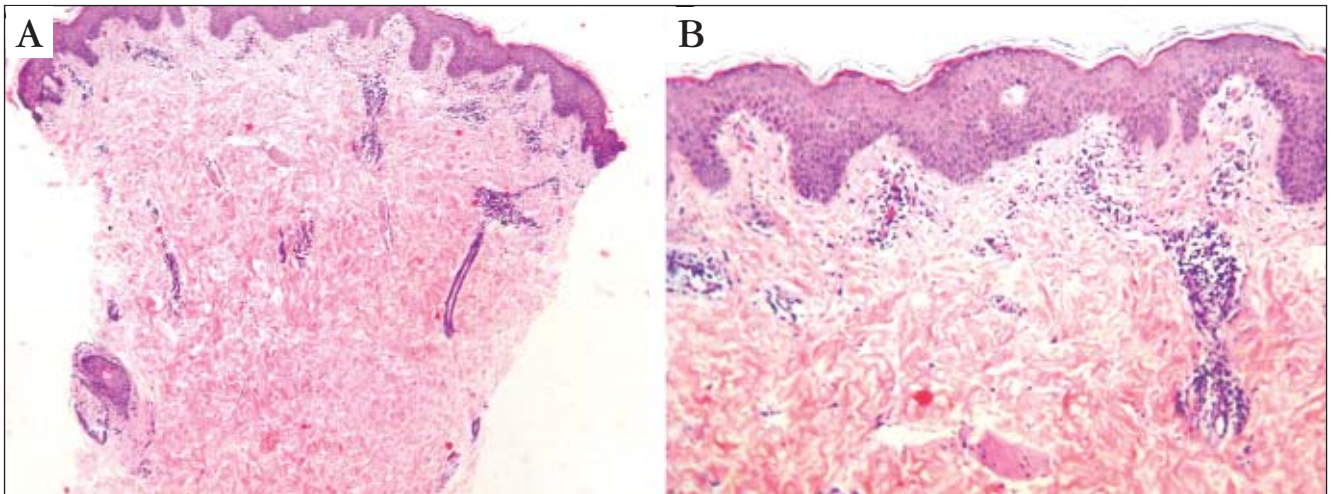


FIGURE 2: A and B: HE 100X (A) and 200X (B): superficial perivascular inflammatory infiltrate, constituted by lymphocytes and histiocytes

azithromycin, 20 mg / kg, PO, once daily, for 14 days is recommended. In pregnant women, erythromycin is recommended at a dose of 500mg, PO, every 6 hours, for 14 days.⁷¹

b) Neurologic, cardiac and ophthalmic manifestations: ceftriaxone, 2g/day intravenously (IV), for 21 to 28 days. Other treatment options are cefotaxime 2 g/day, IV, or crystalline penicillin, 18 to 24 million units / day, IV, divided into six daily doses for 21 to 28 days.⁷²

c) articular manifestations: patients are treated with doxycycline 100mg, PO, every 12 hours, for at least 28 days. If doxycycline cannot be administered, amoxicillin or erythromycin are used.⁷³

d) Acrodermatitis chronica atrophicans (ACA): doxycycline, 100mg, PO, every 12 hours, or amoxicillin 500mg, PO, every 8 hours for 21 days.⁷⁴

CONCLUSION

Brazilian cases of EM indicate the presence of infection by *B. burgdorferi* in our environment. In the Amazon region, particularly in the city of Manaus, the clinical cases of EM, the healing of skin lesions with antibiotic (Figure 4), the results of seroepidemiological investigations and immunohistochemistry of skin biopsies point to the need for further research about this disease.^{25,26} The investigation and diagnostic confirmation of LB are critical, because EM lesions are the initial phase of major health problems that, without proper diagnosis and treatment, can progress to neurologic, cardiac and ophthalmic alterations. So far, species of *Borrelia* that cause EM have not been identified in any of the patients. Reservoirs and vectors have also been insufficiently studied, indicating the need for further research. □

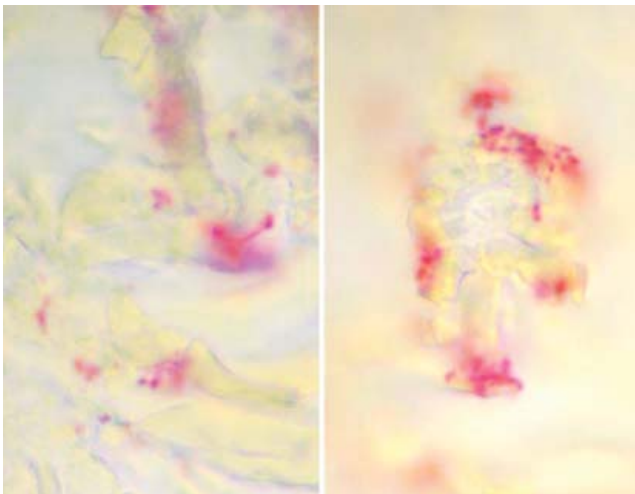


FIGURE 3: Immunohistochemistry of EM, viewed in different focus planes, showing the presence of *Borrelia* sp

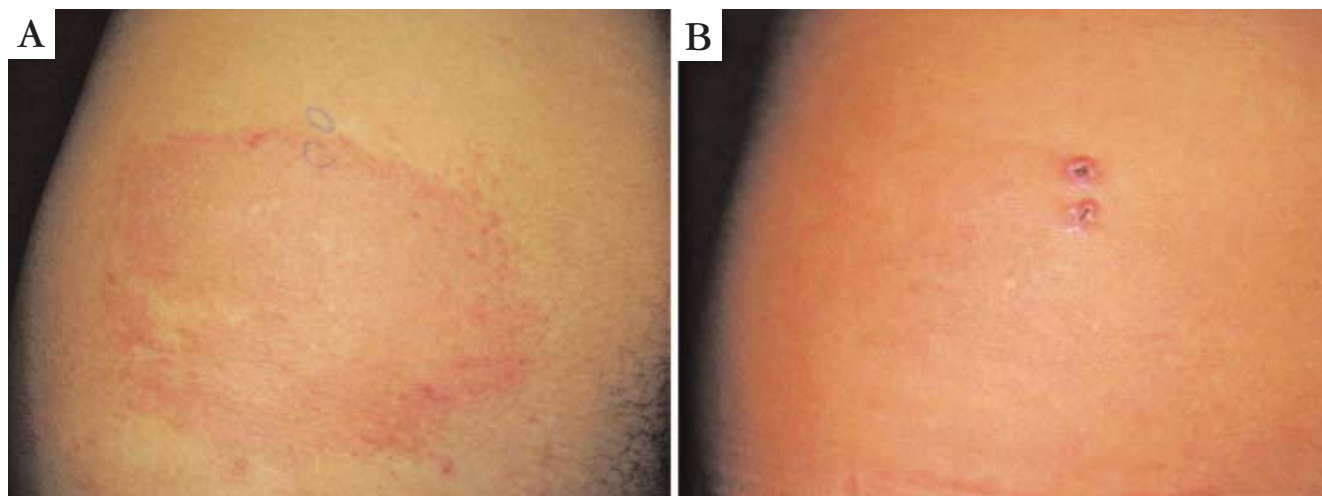


FIGURE 4: Erythema migrans before and after 14 days of treatment with doxycycline

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