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Case report

Lyme disease in the state of Tocantins, Brazil: report of the first cases

César Omar Carranza-Tamayo, José Nilton Gomes da Costa, Whisllay Maciel Bastos*

Superintendence of Surveillance and Health Protection, Department of Health of the State of Tocantins, Palmas, TO, Brazil

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ABSTRACT

Lyme disease is an underdiagnosed zoonosis in Brazil. There are no cases registered in the state of Tocantins, the newest Brazilian state. The cases of three patients in contact with rural areas in three Tocantins' districts are herein described, and the Brazilian literature is reviewed.

Introduction

Lyme disease (LD) is an emerging zoonosis in Brazil.[1] The first Brazilian cases of borreliosis were reported in Rio de Janeiro in 1988, and later in São Paulo in 1992.[2,3] Clinical picture in the prime infection involves skin (rash and erythema migrans) and systemic symptoms (fever, malaise, fatigue, headache, myoarthralgia),[4] followed by joint pain, and later it can cause cardiovascular and neurological complications. In Brazil, the diagnosis of LD is confirmed by clinical picture and epidemiological history of tick bites, in association with positive serology. Because the clinical picture of Brazilian patients and the vectors are different from those described in the Northern Hemisphere, this infection has been called Lyme-like disease or Baggio-Yoshinari syndrome.[5] The etiological agent of the disease observed in Brazil has not yet been well studied due to difficulties to isolate the putative microorganism. The etiologic agent of this zoonotic disease is *Borrelia burgdorferi sensu lato*, which comprises several different locations' genoespecies as described: *B. burgdorferi sensu strictu* (North America and Europe), *B. andersonii* (North America), *B. garinii* and *B. afzelli* (Europe), and *B. japonica* (Japan).[6] Several animals have been described as carriers of this agent, such as dogs, horses and cattle. The first patients diagnosed in São Paulo were reported in the region of Cotia city, where a seroprevalence of antibodies against *B. burgdorferi* of 7.5% in humans,[7] and 9.7% in dogs was also described.[8] Borreliosis is transmitted by tick bites. In Brazil, these ticks belong to the genera *Ixodes* and *Amblyomma*.[9] The former spreads the etiological agent among wild animals and the latter, in humans. The aim of this article is to describe the first three cases of LD diagnosed in the state of Tocantins (TO), Brazil's newest state. As the disease had never been described in the state, these patients had many different diagnostic hypotheses, and one progressed to death caused by complications.

* *Corresponding author at:* Secretaria da Saúde – Anexo 1. Superintendência de Vigilância e Proteção à Saúde. Edifício Lauro Knop. 104 Norte. Av. LO2 lote 30. Centro. Palmas, TO, 77006-022, Brazil.
E-mail address: rhasec3@yahoo.com (C.O. Carranza-Tamayo).
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Case presentation 1

A 27-year-old male, rural worker from Londrina, PR, Brazil and resident of the rural area of Goiatins, TO, Brazil was admitted in May 2007, complaining of fever for 30 days, accompanied by mild pain in the small joints. The patient was treated in various clinics, without a final diagnosis after a month of clinical investigations. After consultation with an infectious disease specialist in Londrina, PR, Brazil, he was suspected of LD, and he had blood collected for serologic analysis. The patient reported that he had been in contact with ticks since July 2005 in the rural area of the city. Subsequently, he remembered being bitten by ticks on his legs, and having developed erythematous macules accompanied by marked pruritus in the lesion. Patient's blood tests turned out positive for LD and he was treated with tetracycline. Control serum after several weeks of treatment was negative. A serological investigation conducted in 16 people in the farm house of the index case and a neighboring farm showed positive Western blot tests for *Borrelia* (IgG and IgM) in three of them, and was undetermined in one case (Western blot with two IgG bands and a band for IgM).

Case presentation 2

A 48-year-old female, physician, resident of the urban area of municipality of Porto Nacional, Tocantins was admitted in February 2011 complaining of pain throughout the body, malaise, polydipsia, headache, paresthesia in hands, fatigue, fever with chills, cramps, flushing, and facial swelling two days before admission. On admission, she had a fever (38 °C) and arterial pressure was 130/80 mmHg. The initial diagnosis was classic dengue. On the following day she complained of severe asthenia, and the blood count showed leukopenia (WBC = 2,200/mm^3) and thrombocytopenia (platelets 108,000/uL). She was discharged to her home. A day later the patient was hospitalized again for worsening of the symptoms, besides pyrosis, abdominal and chest pain, severe headache, and pallor. Blood count showed hemoglobin 12.4 g/dL, leukocytes 1,200/mm^3, and platelets 86,000/uL. Biochemical and electrolytes tests were performed daily with normal results (glucose, transaminases, alkaline phosphatase, gamma glutamyl transpeptidase, amylase, lipase, urea, creatinine, potassium, sodium, calcium, magnesium, and chloride). In the next days she got worse with intense pain and prostration, with defervescence of fever on the fifth day of the second hospitalization. Several serologic tests performed turned out negative (dengue, malaria, toxoplasmosis, cytomegalovirus, rubella, visceral leishmaniasis). From the eighth day on she began to improve slowly, but remained with joint pain. Blood count showed hemoglobin 10.6 g/dL, WBC 3,200/mm^3, and platelets 163,000/uL. On the fifth day of hospitalization, LD, Rocky Mountain spotted fever, and collagen diseases were suspected. The results for collagen diseases (antinuclear antibodies, rheumatoid factor, autoantibodies) were all negative, as was *Rickettsia* serology, but IgM antibodies against *Borrelia* (enzyme-linked immunosorbent assay – ELISA) were positive whereas and IgG was negative. The patient received specific treatment, progressing to clinical resolution of the infection. She reported often going to a farm in the rural area of the city, where there is presence of bats, and reported having been bitten by ticks in the weeks prior to the onset of clinical symptoms, without injuries caused by the bites.

Case presentation 3

A 19-year-old male, rural worker and resident of the rural area of Marianópolis, TO, Brazil was admitted in May 2011, with complains of fever, asthenia, abdominal pain, loss of appetite, vomiting, and intermittent diarrhea for 15 days. In a previous consultation a week before, he was prescribed antibiotics, without resolution of symptoms. On physical examination he was depressed, dehydrated ++/4+, BP 70/40 mmHg, temperature 36.8 °C, and had a bruise on the right eyelid. He was suspected as having dengue fever or visceral leishmaniasis, and he was initiated on hydration therapy with saline and symptomatic drugs. A complete blood count showed a hypochromic and microcytic anemia (hemoglobin = 9.3 g/dL), severe thrombocytopenia (30,000/uL), pronounced leukocytosis (WBC = 30,600/mm^3), and capillary glucose 238 mg/dL. Four hours later the patient remained hypotensive (BP = 90/50 mmHg). It was decided to transfer the patient to a reference hospital. At the time of admission, the patient was febrile and dipyrone was administered. He then developed dyspnea and auscultation presented gross crackles. Rapid tests for HIV and visceral leishmaniasis were ordered, with negative results. On the following day, the patient was transferred to the intensive care unit due to persistent dyspnea and decrease in hemoglobin saturation (up to 71%). Blood examination showed maintenance of moderate anemia, leukocytosis with a shift to the left, thrombocytopenia, uremia (urea 120 and 126 mg/dL and creatinine 1.6 and 1.0 mg/dL) and increased transaminases (1.5-2 times upper limit of normal). Ultrasound showed mild bilateral pleural effusion and fluid in abdominal fornix. Blood for serological evaluation of dengue, borreliosis, Rocky Mountain spotted fever, leptospirosis, and brucellosis was collected. All results were negative, except for borreliosis, with Western blot tests positive for IgM and IgG (three of four bands). The family reported that the patient had always lived and worked in the rural area of several Tocantins' municipalities, with potential exposure to ticks, wild animals, and farm animals. They noted that the patient had reported being bitten by ticks, but did not know of any bites in the weeks prior to the onset of illness. *Post mortem* studies confirmed septic shock complicating LD.

Discussion

LD is an important diagnosis of fever of unknown origin in Brazil.[1] After first reports of LD cases in Southeastern Brazil, the infection has also been seen in other areas. Cases of this disease have been identified in Northern Brazil, mainly in the city of Manaus.[10] Tocantins is the newest state of the Brazil, and consists of transitional forests between the Cerrado (Brazilian savanna) and the Amazon Rainforest, which creates a rich source of reservoirs and vectors for many zoonoses. As

part of entomological investigation of the first patient reported with LD in the state, ticks were collected in the municipality of Goiatins, demonstrating the presence of species of the genus *Amblyomma* and *Riphicephalus*, both able to transmit the zoonosis to humans and animals.[11] *Amblyomma cajennense*, implicated as a vector of LD in Brazil, was described in this study.[12] The description of this first case increased the level of suspicion of LD in both cases of skin lesions caused by tick bites and cases of fever of unknown origin, which led to the finding of more cases in the Tocantins state.

The clinical suspicion of LD is initially based on the finding of erythema migrans, which consists of a skin lesion or expansive macular erythematous papules, single or multiple, located around the bite by infected ticks. Tick bite lesions take an annular shape, and gradually increase to several centimeters, associated with an increase in local temperature. A few patients report pain in the lesion. In Manaus, none of the five patients with clinical and immunohistochemical confirmation of LD reported a history of tick bite.[13] In São Paulo, only six of 19 patients (31.6%) had skin lesions, whereas only one patient showed erythema migrans.[14] A study of children with LD in São Paulo did not find cases of erythema migrans, showing that this lesion is a rare manifestation of LD in Brazil.[15] In this report, only one of three patients reported skin lesions. All three patients presented with fever, while two of them had arthralgia as the chief complaint. Only the first case described injuries after tick bites, although these characteristics do not correspond to the most frequent clinical manifestations of the disease. Typically, half of the patients with LD report tick bites.[12,16] Due to its multisystemic characteristics, patients with LD may have different clinical pictures. Most of them present complaints such as arthralgias, arthritis, myalgias, and different degrees of cardiac or neurological disease during evolution.[17] A series of 19 patients reported in the state of São Paulo showed that the most frequent manifestations were fever (78.9%), neurological symptoms (42%), lymphadenomegaly (36.8%), skin lesions (31.5%), and arthralgia or arthritis (31.5%).[14] In North America, the predominant symptoms involve the skin and joints, while in Europe neurological manifestations are more frequent.[18] The framework of LD observed in Brazil has a higher relapse rate when compared to North American or European LD, especially if the disease is not recognized at an early stage and is not effectively treated.[19] A series of cases in Brazilian children demonstrated the seasonality of LD in autumn and summer, without a characteristic clinical presentation.[15]

In Brazil, it has not been possible to isolate the etiological agent of LD cases. It is believed that this difficulty is due to the difference of etiologic agent, vectors, and the lack of standardization of laboratory methods. Bacterias of the genus *Borrelia* do not grow on common culture media, and the use of specific medium, such as Barbour-Stoenner-Kelly (BSK) does not always solve this problem. In Brazil, *Borrelia burgdorferi* has not been isolated in samples of any kind, including human, animal reservoirs, or ticks. In São Paulo, *Borrelia*-like spirochetes have grown using BSK II culture media in samples of blood and tissue from marsupials, rodents, and ticks, with growth periods between 30 and 120 days at 33 °C.[20] Species identification is even more difficult, requiring immunohistochemical techniques,[13] molecular biology, and DNA sequencing for identification, as described in the first species of *B. lonestari/B. theileri* in Brazil, obtained from ticks captured in the state of Minas Gerais.[21] Laboratory confirmation in the Northern Hemisphere is based on serology, because culture is slow and unproductive. Polymerase chain reaction (PCR) is rarely used because it identifies only cases in which *Borrelia* spp. are circulating or deposited in tissues.[19] PCR tests can also give negative results in later stages of the disease, due to the small amount of microorganisms.[13] In Brazil, diagnosis is based on clinical suspicion associated with positive ELISA or Western blot serology, despite their poor sensitivity and specificity.[22] Two of the described patients were diagnosed by Western blot test and one by ELISA. In the patient who eventually died tests to investigate other etiologies or cross-reactions with other infections such as syphilis, mononucleosis, and rheumatic diseases could not be performed. The existence of distinct species of *Borrelia* causing LD in Brazil could explain the different clinical picture and lack of accuracy of serology,[23] which uses antigens of *Borrelia burgdorferi sensu strictu*.

Due to the lack of reports of LD in the state of Tocantins, the diagnosis was delayed in two of three cases. The patient who described a lesion suggestive of erythema migrans was not further investigated with skin biopsy, which could have helped confirming the serology results. All three patients reported contact with rural areas, and one lived in the urban area. Although there have been reports of borreliosis in the states of Amazonas,[10] Espírito Santo,[19] Mato Grosso do Sul,[24] Rio de Janeiro,[2,25] and São Paulo,[1,3,5] there is no consensus on the presence of LD in Brazil, postulating the existence of a disease similar to LD caused by a mutant spirochete descendant from *B. burgdorferi*, which vector species other than the genus *Ixodes*, and causes a disease known as Lyme-like disease or Baggio-Yoshinari syndrome.[12,16]

Conclusion

This report demonstrates the existence of LD diagnosed by serological methods in the state of Tocantins, Brazil. LD had not been previously identified in this state, although it would have been suspected by physicians in patients with prolonged fever presenting skin lesions without a definite diagnosis. More studies are necessary to strengthen the diagnosis and the extension of LD in state of Tocantins.

Conflict of interest

All authors declare to have no conflict of interest.

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