

## Primary Lyme Disease with Jarisch-Herxheimer Reaction Causing ARDS

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### Abstract

This is a case report of a patient having Lyme Disease without its classic Erythema Migrans, which was complicated with Jarisch-Herxheimer reaction after ceftriaxone, causing acute respiratory failure with pulmonary infiltrates consistent with ARDS. *Streptococcus pyogenes* septicemia was caused by multiple skin lesions caused by tick bites. He required three different antibiotics to control the disease suggestive of a persister *Borrelia burgdorferi* infection. .

**Keywords:** Lyme Disease; Jarisch-Herxheimer Reaction; Acute Respiratory Distress Syndrome; *Borrelia burgdorferi*

### Abbreviations

ARDS: Acute Respiratory Distress Syndrome; CPK: Creatine Phosphokinase; CRP: C-Reactive Protein; CT: Computed Tomography; EPAP: Expiratory Positive Airway Pressure; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IL: Interleukin; IPAP: Inspiratory Positive Airway Pressure; JHR: Jarisch-Herxheimer Reaction; PCR: Polymerase Chain Reaction

### Introduction

Lyme Disease affects approximately 300 000 persons primarily in endemic areas of the United States of America, primarily, at the Northeast coast. However, the Northern Midwest and Northern California areas are newly recognized due to reports indicating an increasing number of cases of Lyme Disease. Lyme Disease etiologic agent is the spirochete *Borrelia burgdorferi*, transmitted through the tick *Ixodes* sp. as a vector. Lyme disease can manifest acutely, following the tick bite, but there are descriptions of subacute and chronic presentations.

In the acute phase of Lyme Disease, the symptoms include arthralgias, fever, sore throat, headaches, and a unique rash called Erythema Migrans. The chronic phase is notorious for monoarthritis, peripheral neuropathy, chronic lymphocytic meningitis, seventh nerve palsy, and reversible second-degree heart block. The Jarisch-Herxheimer reaction is a vigorous inflammatory response believed to be caused by the release of the intracellular elements of the spirochete to the circulation. *Treponema* sp., and other spirochetal infections and can be associated with JHR causing significant acute hemodynamic instability.

### Case Presentation

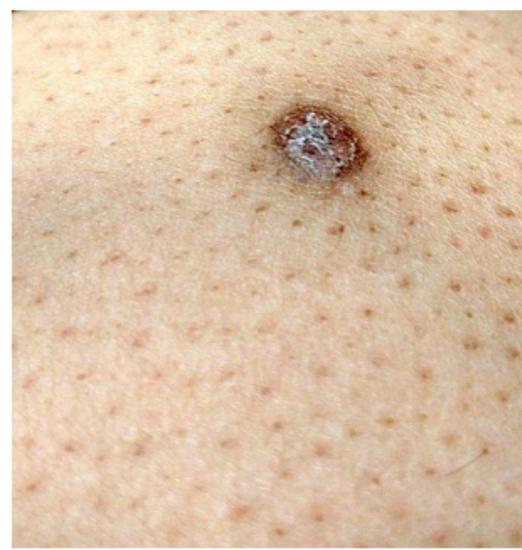
Here we present a 54 years old Hispanic male with arterial hypertension, hypercholesterolemia, and obesity using lisinopril 10 mg daily and simvastatin 10 mg daily. He was hospitalized with severe arthralgias at upper and lower extremities, spiking fever, general malaise and anorexia one day previous to admission. He had outdoor activities related to his occupation in the South Texas area. The patient received methylprednisolone and levofloxacin intravenously at the emergency department. He denied dyspnea, hemoptysis, tuberculosis

exposure, pruritus, nausea, vomiting, throat pain, peripheral swelling, cough, sputum production, oliguria, or recent travel outside the state of Texas. A chest x-ray and a computed tomography (CT) scan were negative on admission.

The physical exam showed a middle-aged male who appeared acutely ill with dry mucous membranes and dark violaceous plaques with scaling at the arms (Figure 1) and legs (Figure 2).



**Figure 1:** Tick-induced skin lesion of the right forearm of a patient with lyme disease.



**Figure 2:** Tick-induced skin lesion of the left leg of a patient with lyme disease.

The heart and lung sounds were normal. The patient had no lymphadenopathy, hepatosplenomegaly, nuchal rigidity, or swollen joints.

Laboratory results showed a mild elevation of blood urea nitrogen and creatinine due to dehydration (corrected within 24 hours after administration of fluids), but it was otherwise normal; including normal electrolytes, liver enzymes, cell blood count and CPK (creatinine phosphokinase) levels. The C reactive protein (CRP) was 256 mg/mL (very high). Vancomycin and ceftriaxone were initiated after a gram-positive bacterium was discovered in the blood cultures identified as *Streptococcus pyogenes*. This last bacterium is universally sensitive to penicillin.

After 48 hours of treatment with vancomycin and ceftriaxone, he had skin flushing, fever 39.4°C (103°F), worsening of arthralgias, and rigors. He required meperidine 25 mg administration intravenously every four hours for severe rigors associated with a lack of response to acetaminophen for fever. In six hours, he complicated with severe dyspnea and tachypnea associated with peripheral oxygen saturation dipping to 80% saturation of oxygen. The chest x-ray showed bilateral pulmonary infiltrates without cardiomegaly suggestive of acute noncardiogenic pulmonary edema predominantly at upper pulmonary lobes confirmed by a chest CT scan (Figure 3).



**Figure 3:** CT scan of the chest of a patient with Lyme disease with predominantly upper lobe infiltrates.

Due to a lack of response to a non-rebreather mask with 100% oxygen, he was initiated on noninvasive mechanical ventilation with 100% oxygen, expiratory airway pressure (EPAP) = 5 cm H<sub>2</sub>O, inspiratory airway pressure (IPAP) = 10 cm H<sub>2</sub>O. The EPAP was increased to 10 cm H<sub>2</sub>O and IPAP to 15 cm H<sub>2</sub>O to increase the oxygen saturation.

An echocardiogram was performed and was found to be normal with preserved left ventricular ejection fraction. He was given furosemide with mild improvement of hypoxemia on the following day. Nonetheless, he remained on noninvasive mechanical ventilation for 72 hours with a gradual decrease in hypoxemia.

The laboratory data revealed a positive IgM with a negative IgG-antibodies against *Borrelia burgdorferi* confirmed by immunoblot analysis on the fifth hospital day. Doxycycline was added to the therapy; within 24 hours, there was an improvement of fever and arthralgias. However, the pulmonary infiltrates resolved slowly, taking up to a week for full resolution. The chest x-rays were normal on the day of discharge after ten days of hospitalization.

During a follow-up visit, the patient informed that his wife had Lyme disease one-year ago, after having a tick bite on her back with the classic Erythema Migrans skin rash. The infection resolved after treatment with oral doxycycline. On the other part, the patient had two small ticks removed from his body last year after visiting his ranch. The last visit to his ranch was four months before this hospitalization. He found ticks at his garage in his home months afterward.

**Discussion**

Lyme disease infects 300,000 individuals yearly in the United States of America, mostly in the northeastern states of the country, with increasing reports in the North midwestern and Northern California areas. *Borrelia burgdorferi* and its tick-vector *Ixodes* spp. has been found in South Texas recently, a non-endemic area making this diagnosis challenging. Despite the acute infection with *B. burgdorferi*, there was no Erythema Migrans. The exposure to ticks outdoors, spiking fever, and severe arthralgias without response to antibiotics make the case suspicious for a tick-borne infection.

The paradoxical clinical worsening of high-grade fever, flushing of the skin, tachycardia and tachypnea after antibiotic administration was a frustrating development in the course of treatment. *Streptococcus pyogenes* was detected within 24 hours using polymerase chain reaction (PCR) and characterization of Gram-positive blood cultures. Even though aggressive antibiotics led us on an extensive search for a source that would explain his septicemia with *Streptococcus pyogenes*, we could not find one. The only reasonable explanation was the portal of entry is the skin at tick bite location area.

The case of refractory hypoxemia of sudden onset with pulmonary infiltrates and a normal heart function was suspicious of non-cardiogenic acute pulmonary edema specifically ARDS (acute respiratory distress syndrome) due to severe hypoxemia requiring the use of noninvasive mechanical ventilation at 100% oxygen concentration. Lyme disease, by itself, is not a known pathogen causing pneumonia.

The most likely explanation of this phenomenon was the Jarisch-Herxheimer reaction (JHR) after effective treatment of spirochetal infection. This reaction also occurs in trypanosomal infection, syphilis, leptospirosis, tick-borne fever. There is no diagnostic test for the JHR. The symptoms occur early from 24 to 36 hours after the administration of antibiotics and may last for 48 hours. The treatment is supportive. Medications described, in the medical field, to treat the reaction include the following list: opiates, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, fluid administration and diphenhydramine. The reaction is self-limited.

Cases JHR	Symptoms	Antibiotic
1. Lyme Disease	Tachycardia, fever, hypotension [1]	Ceftriaxone
2. Lyme Disease	Rigors, fever, hypertension [2]	Amoxicillin
3. Lyme Disease	Arthralgias, fever, exacerbation of cutaneous lesions [3]	Josamycin
4. Leptospirosis	ARDS [5]	Penicillin

**Table 1:** Cases of JHR associated with Lyme Disease and one case of JHR causing ARDS with leptospirosis.

Other reported symptoms of the JHR include nuchal rigidity, tachypnea, respiratory distress, severe headaches, abdominal pain, vomiting, uterine contraction in pregnancy, aseptic lymphocytic meningitis, seizures, worsening of the liver function, pulmonary alveolar hemorrhage, acute renal failure, acute systolic heart failure and acute respiratory failure with ARDS [4]. The case reported of ARDS as a complication of JHR developed three days after administration of antibiotics probably due to steroid use before hospitalization, similar to this case [5].

There were two cases of JHR with leptospirosis with pulmonary complications of respiratory distress and deterioration [6]. Penicillin, ceftriaxone (like in this case), doxycycline, cephalosporins, quinolones, meropenem and macrolides caused the JHR in multiple reports.

JHR mechanism of action involves a massive release of cytokines, tumor necrosis factor (TNF), interleukin 8 (IL-8), interleukin 6 (IL-6) after the fragmentation of spirochetes and its components into the bloodstream.

The patient persisted with the symptoms even five days after initiation of ceftriaxone with significant improvement when doxycycline. This last event may indicate a drug-tolerant persister variant of *B. burgdorferi*. Daptomycin has been active in persisters [7,8]. Vancomycin has been found more potent than ceftriaxone against *B. burgdorferi* *in vitro* [9,10].

There are very few cases reported in the non-endemic state of Texas, detected by enzyme-linked immunosorbent assay (ELISA) and reflexive immunoblotting [11]. The ELISA sensitivity is low (30 - 40%) during the early stages but is high in disseminated disease (70 - 100%). The specificity is high in all stages. The geographical distribution of reported cases in the state of Texas has been described [12]. Underreporting and surveillance variations in practice may affect the statistics [13]. The risk of developing the disseminated disease is higher in Hispanics, like in this case [14].

The cutaneous lesions found were not previously described as a specific manifestation of cutaneous Lyme Disease [15]. The serrated mouthparts of ticks may remain in the skin, leaving permanence of fragments causing foreign body type granulomas like the lesions described in this case [16].

*Streptococcus pyogenes* bacteremia is a surprising finding not described before as a coinfection in Lyme Disease. The familiar sources of bacteremia by *S. pyogenes* are erysipelas, necrotizing fasciitis, septic arthritis, pharyngitis, and pneumonia complicated with empyema [17].

Prolonged antibiotic therapy with *Clostridium difficile* and catheter-related infections caused coinfections in Lyme Disease [18]. We could not find cases of acute Lyme borreliosis with bacterial coinfection of non-tick-borne pathogens after reviewing the medical literature.

There are interventions to prevent Lyme Disease in humans like permethrin-coated uniforms, citriodiol (p-Menthane-3,8-diol) tick repellent, and preventive education [19].

## Conclusion

Lyme disease can present without the Erythema Migrans skin rash in the acute phase. However, discrete violaceous scaly plaques can indicate the presence of a previous tick bite. Multiple infected skin bites may cause bacteremia with *Streptococcus pyogenes*. Delayed onset of the JHR could be explained by previous corticosteroids use as described in another case. JHR may cause acute lung injury with ARDS, requiring mechanical ventilator support. A combination of antibiotics may be necessary to eradicate a possible persister *Borrelia burgdorferi* infection.

## Bibliography

1. Kadam P, *et al.* "Jarisch – Herxheimer Reaction in a Patient with Disseminated Lyme Disease". *Journal of Case Reports* (2013): 362-365.
2. Maloy AL, *et al.* "Lyme Disease Complicated by the Jarisch-Herxheimer Reaction". *The Journal of Emergency Medicine* 16 (1998): 437-438.
3. Trevisan G and Stinco G. "Jarisch-Herxheimer reaction in Lyme borreliosis treated with Josamycin". *Journal of the European Academy of Dermatology and Venereology* 3 (1994): 433-434.

4. Butler T. "The Jarisch-Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis". *The American Journal of Tropical Medicine and Hygiene* 96.1 (2017): 46-52.
5. Emmanouilides CE., et al. "Leptospirosis complicated by a Jarisch-Herxheimer reaction and adult respiratory distress syndrome: case report". *Clinical Infectious Diseases* 18.6 (1994): 1004-1006.
6. Guerrier G and D'Ortenzio E. "The Jarisch-Herxheimer Reaction in Leptospirosis: A Systematic Review". *PLoS ONE* 8 (2013): e59266.
7. Sharma B., et al. "Borrelia burgdorferi, the Causative Agent of Lyme Disease, Forms Drug-Tolerant Persister Cells". *Antimicrob Agents Chemother* 59.8 (2015): 4616-4624.
8. Feng J., et al. "Drug combinations against Borrelia burgdorferi persists in vitro: eradication achieved by using daptomycin, cefoperazone and doxycycline". *PLoS One* 10.3 (2015): e0117207.
9. Wu X., et al. "Identifying Vancomycin as an Effective Antibiotic for Killing Borrelia burgdorferi". *Antimicrob Agents Chemother* 62.11 (2018).
10. Harman MW., et al. "Vancomycin Reduces Cell Wall Stiffness and Slows Swim Speed of the Lyme Disease Bacterium". *Biophysical Journal* 112.4 (2017): 746-754.
11. Moore A., et al. "Current Guidelines, Common Clinical Pitfalls, and Future Directions for Laboratory Diagnosis of Lyme Disease, United States". *Emerging Infectious Diseases* 22.7 (2016).
12. Szonyi B., et al. "Exploratory spatial analysis of Lyme disease in Texas –what can we learn from the reported cases?" *BMC Public Health* 15 (2015).
13. Nelson CA., et al. "Incidence of Clinician-Diagnosed Lyme Disease, United States, 2005-2010". *Emerging Infectious Diseases* 21.9 (2015): 1625-1631.
14. Nelson CA., et al. "Lyme Disease in Hispanics, United States, 2000-2013". *Emerging Infectious Diseases* 22.3 (2016): 522-525.
15. Hofmann H., et al. "Cutaneous Lyme borreliosis: Guideline of the German Dermatology Society". *GMS German Medical Science* 15 (2017): Doc14.
16. Haddad V Jr., et al. "Skin manifestations of tick bites in humans". *Anais Brasileiros de Dermatologia* 93.2 (2018): 251-255.
17. Edwards RJ., et al. "Proteomic analysis at the sites of clinical infection with invasive Streptococcus pyogenes". *Scientific Reports* 8.1 (2018): 5950.
18. Marzec NS., et al. "Serious Bacterial Infections Acquired During Treatment of Patients Given a Diagnosis of Chronic Lyme Disease - United States". *MMWR. Morbidity and Mortality Weekly Report* 66 (2017): 607-609.
19. Richardson M., et al. "Interventions to prevent Lyme disease in humans: A systematic review". *Preventive Medicine Reports* 13 (2019): 16-22.

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