

Case report

Human *Borrelia miyamotoi* infection: A cause of persistent fever and severe hyperthermia in New England

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ABSTRACT

An adult male presented to a hospital in southwestern Connecticut with tachypnea, generalized weakness, altered mental status, and relapsing fever with maximum recorded temperature of 106 °F. He required active cooling, antipyretic therapy, broad spectrum antibiotics, and intubation for airway protection after an episode of emesis. Initial laboratory and imaging workup were remarkable for elevated inflammatory markers, acute kidney injury, and bilateral lower lobe infiltrates. Further workup with lumbar puncture and electroencephalography were unrevealing. Extensive testing for causes of relapsing fever including tickborne diseases revealed that the patient was seropositive for *Borrelia miyamotoi*. Notably, he had no rash, and workup found no evidence of coinfection by other *Borrelia*, *Ehrlichia* or *Anaplasma* species. This case illustrates the need for clinicians to test for tick-borne diseases when evaluating for cases of relapsing fever in New England and is among the first case reports to demonstrate *Borrelia miyamotoi* as a cause of severe pyrexia.

Case report

Lyme disease is a tick-borne illness that has been well described since the 1970's because of a cluster of cases in Lyme, Connecticut, but by contrast, *Borrelia miyamotoi* was first isolated from the *Ixodes persulcatus* tick in Japan in 1994 and the first documented case in the US was identified in 2013 [1,2]. Most cases of the illness have been identified in the northern hemisphere (Japan, Russia, Netherlands, and US), with notable plurality of cases in northeastern US states such as Massachusetts, Connecticut, New York and New Jersey. Due to its similarities to Lyme disease both in terms of presentation and geographic predominance as well as its relative novelty as a cause of human disease, cases of *Borrelia miyamotoi* can be difficult to diagnose. We present the case of an adult male who presented to a hospital in southwestern Connecticut with tachypnea, generalized weakness, altered mental status, and relapsing fever with maximum recorded temperature of 106 °F. Extensive testing for causes of relapsing fever including tickborne diseases revealed that the patient was seropositive for *Borrelia miyamotoi*. In addition to highlighting the similarities between *Borrelia miyamotoi* and Lyme disease, our case illustrates the need for clinicians to test for tick-borne diseases when evaluating for cases of relapsing fever in New England and is among the first case reports to demonstrate *Borrelia miyamotoi* as a cause of severe pyrexia.

A 75-year-old male presented to the emergency department (ED) in southwestern Connecticut with a 3-day history of generalized weakness and 1 day of altered mental status. According to collateral report, he was last known well on the evening prior to the day of admission, but he had reported becoming increasingly weak and drowsy. On the day of admission, he was found unresponsive in his home before being brought to the ED by ambulance.

His past medical history was significant for coronary artery disease, hypothyroidism (on levothyroxine), benign prostatic hypertrophy, and gastroesophageal reflux. At baseline, the patient was very active, independent in performing activities of daily living, and continued to work at his business. He spent time outdoors but on boats and not in high brush or heavily wooded areas. Family denied hearing the patient report any recent tick or mosquito bites. The patient had recently attended a party and encountered other attendees who had recently traveled to Tokyo, Japan, as well as another attendee who had recently recovered from a viral gastrointestinal illness. His most recent hospitalization was seven months prior when he was admitted to a different hospital for management of pneumonia with sepsis. The patient was not taking any psychoactive or antidepressant medications nor did he have any recent surgeries or other procedures that may have exposed him to anesthesia. He rarely drank alcohol according to his family, never in excess. He quit smoking tobacco 38 years prior with an estimated 20 pack-year smoking

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history.

In the ED, vital signs were temperature 103.0 °F (39.4 °C), heart rate 81 beats per minute, blood pressure 143/65 mmHg, respiratory rate of 32 breaths per minute, oxygen saturation of 94 % on room air. Laboratory testing revealed elevated lactic acid 3.2 mmol/L (normal range 0.4–2.0 mmol/L), C-reactive protein (CRP) 10.3 mg/dL (normal range 0.0–1.0 mg/dL), procalcitonin 3.72 ng/mL (bacterial infection is considered less likely when less than or equal to 0.25 ng/mL), d-dimer 4.95 mg/L FEU (normal range is less than 0.49 mg/L FEU), prothrombin time 13.1 s (normal range 9.4–12.0 s), international normalized ratio 1.21 (normal range 0.88–1.14), and creatinine 1.72 mg/dL (normal range 0.50–1.30 mg/dL) in a patient with normal creatinine at baseline. Normal labs included serum electrolytes, serum creatinine kinase (CK), liver enzymes, alkaline phosphatase, total bilirubin, pro-B-type natriuretic peptide, troponin I, sedimentation rate, random serum cortisol, fibrinogen, urinalysis, hemoglobin, hematocrit, platelet count, and white blood cell count, though absolute neutrophil count was elevated $8.1 \times 1000/\mu\text{L}$ (normal range $1.8\text{--}7.3 \times 1000/\mu\text{L}$), representing 85.8 % of white blood cells. Arterial blood gas drawn while patient was breathing room air found pH arterial 7.48 (normal range 7.35–7.45), pCO_2 29 (normal range 35–45 mmHg), pO_2 70 (normal range 75–100 mmHg), oxygen saturation 94 %, and calculated HCO_3 21.0 (normal range 20.0–26.0 mmol/L). Electrocardiogram demonstrated normal sinus rhythm with possible left atrial enlargement. Chest x-ray demonstrated a possible pneumonia at the left lung base (see Fig. 1); non-contrast computed tomography (CT) of the head demonstrated no acute intracranial abnormalities; bilateral lower extremity doppler ultrasound showed no evidence of deep vein thrombosis. CT chest with intravenous contrast revealed bilateral lower lobe infiltrates, left greater than right (see Fig. 2).

Active cooling with ice packs was initiated, and he was admitted to ICU due to monitor for impending intubation due to altered mental status. Over the next few hours, his temperature began to normalize, and he became more awake. However, his fever relapsed to a new high of 106 °F accompanied by acute decompensation with somnolence, tachypnea, tachycardia, hypotension, hypoxia, and rigors. Following an episode of emesis, he was intubated for airway protection, and Arctic sun was started for cooling.

Repeat laboratory studies were conducted, and the patient had developed leukocytosis along with further elevation in levels of procalcitonin and CRP with continued normality of total CK. Serum ethanol, acetaminophen, and salicylate levels were within normal limits. Urine toxicology screening for alcohol, amphetamine, barbiturate,

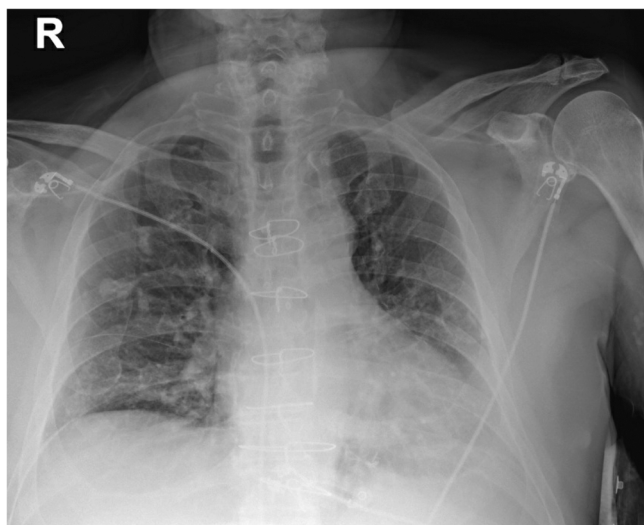


Fig. 1. Chest X-ray on hospital day 1 showing possible left lower lobe pneumonia.



Fig. 2. CT chest showing bilateral lower lobe infiltrates, left greater than right.

benzodiazepine, cannabinoids, cocaine, methadone, opiates, and phencyclidine was negative. Remainder of extensive laboratory workup including infectious, autoimmune, and endocrinologic causes of this presentation is summarized in Table 1. Given the lab results and persistent fever that was difficult to treat, blood and urine cultures were drawn. Lumbar puncture was performed but was nondiagnostic, as the patient's cerebrospinal fluid (CSF) tested negative for herpes viruses, enterovirus, West Nile virus or cryptococcal antigen, despite the mildly elevated protein and glucose levels in the CSF. Furthermore, electroencephalogram (EEG) did not show any evidence of epileptiform activity. Given patient's history of spending time outdoors, testing for tick borne diseases including Lyme, babesia, anaplasma and ehrlichia were initiated, all of which returned negative for acute infection. Infectious disease physician later recommended that the patient be tested for additional rare tick borne diseases including *Borrelia miyamotoi*. Please see Table 1 below for summary of results.

Given the background of a relative summer heat wave along with the patient's presenting symptom of altered mental status, he was initially suspected to suffer from heat stroke. Iatrogenic causes of his presentation including neuroleptic malignant syndrome and serotonin syndrome were ruled out by history as he had no record of psychiatric medication use. Illicit substance use was deemed unlikely given negative serum and urine toxicology testing, lack of a prior history of substance use, and family's denial of depressed mood or unusual behavior. Hyperthyroid state was a possibility as the patient was on levothyroxine and could have overdosed intentionally or accidentally, but TSH and Free T4 were within normal limits. Rhabdomyolysis could result from high fever or cause fever, but total CK was within normal limits on two separate checks, urinalysis was unremarkable, liver function was normal, and his kidney function rapidly normalized with initial fluid resuscitation. Differential also included infections such as viral, bacterial, and tickborne (Lyme disease, Human Monocytic Ehrlichiosis (HME), and Anaplasmosis). After initial infectious workup including serum, urine, and CSF testing was unrevealing, autoimmune diseases were considered but aside from a weakly positive ANA, the remainder of rheumatologic workup was negative. Clots can cause fever, but the patient was at low risk for deep vein thrombosis (DVT) or pulmonary embolism, and lower extremity dopplers were negative for DVT. Unremarkable EEG, CT head, and LP results decreased the likelihood of a primary neurologic cause for patient's presentation. Differential eventually broadened to include *Borrelia miyamotoi* due to the patient's history of spending time outdoors.

After initial cultures were drawn, he was started empirically on

Table 1

Serum and urine workup.

Laboratory data	Value	Reference range
Autoimmune (Serum)		
Anti-nuclear antibody (ANA)	1:80	< 1:80
ANA Pattern	Speckled	
Myeloperoxidase antibody	< 0.2	0.0–0.9 AI
Proteinase 3 IgG Antibodies	< 0.2	0.0–0.9 AI
Glomerular Basement Membrane Antibodies	< 0.2	0.0–0.9 AI
Endocrinologic (Serum)		
Thyroid Stimulating Hormone (TSH)	0.535 μ U/mL	0.320–3.850 μ U/mL
Free T4	1.34 ng/dL	0.76–1.46 ng/dL
Infectious (Serum/Urine/Nasal swab)		
Blood cultures	No growth	No growth
Urine culture	No growth	No growth
Urine, Legionella and S. pneumoniae antigen	Negative	Negative
Respiratory culture (after intubation)	No growth	No growth
Influenza type A/B PCR	Negative	Negative
SARS-CoV-2 PCR	Negative	Negative
Lyme Ab	0.40 LI	\leq 0.90 LI
Anaplasma and Ehrlichia Smear	Negative	Negative
Ehrlichia chaffeensis Ab IgG	< 1:64	< 1:64
Ehrlichia chaffeensis Ab IgM	< 1:20	< 1:20
Borrelia miyamotoi DNA, RT-PCR	Detected	Not detected
CSF		
Opening pressure	20.2 cmH ₂ O	6–25 cmH ₂ O
Appearance	Clear	
Color	No Xanthochromia	
Red Cell count, tube #4	210 cells	None
Nucleated Cell Count, tube #4	5 cells	< 6 Cells/ μ L
Granulocytes	20 %	0–6 %
Lymphocytes	57 %	40–80 %
Monocytes	23 %	15–45 %
Glucose, CSF	122 mg/dL	40–70 mg/dL
Protein, Total CSF	52.0 mg/dL	15.0–45.0 mg/dL
Bacterial culture	No growth	No growth
Gram stain	No white blood cells, no organisms seen	
Cryptococcal Antigen	Negative	Negative
West Nile IgG	< 1.30	< 1.30
West Nile IgM	< 0.90	< 0.90
Herpes Simplex Virus by PCR	Not Detected	Not Detected
Varicella-Zoster PCR	Not Detected	Not Detected
Enterovirus by RT-PCR	Not Detected	Not Detected
Fungal Culture	No growth after 4 weeks	No growth after 4 weeks
Acid Fast Bacteria Culture	No growth after 6 weeks	No growth after 6 weeks

intravenous ceftriaxone, doxycycline, ampicillin, and acyclovir for presumed meningitis or encephalitis. After LP, antibiotic coverage was narrowed to ceftriaxone and doxycycline. With continuous antibiotic therapy and cooling, he became normothermic, and mental status progressively improved to the point he was able to be extubated.

Two days later, patient was found positive for *Borrelia miyamotoi* on PCR testing. The patient was discharged home on hospital day 5 with plan for continued antibiotic therapy with doxycycline for total of 14 days, and outpatient follow up with the infectious disease physician.

Discussion

Overall, there are relatively few reported cases of *Borrelia miyamotoi*, which limits our knowledge and understanding of the natural history of the disease. Several published cases and case series include patients with a history of immunocompromise, but there are several reported cases in patients who are immunocompetent such as ours [3–13]. The age of cases ranges from as young as 5 years old to as old as 74 years old. Cases

have been reported in countries including the United States, Sweden, Germany, the Netherlands, Russia, Austria, and Japan. Presenting signs and symptoms typically include high fever, marked headache, fatigue, neck stiffness, and coma. One case featured significant monocytosis on complete blood cell count with differential testing [14]. Antibiotics reported as effective include ampicillin and doxycycline, though there is one reported case of a patient recovering with no antimicrobial treatment at all [15].

Important in understanding the pathogenesis of *Borrelia miyamotoi* is the points of contrast when compared to pathogenesis of *Borrelia burgdorferi* [16]. Despite the spirochete pathogens sharing similar vectors (ticks) and reservoirs (mice/rodents), transmission of *Borrelia miyamotoi* can occur within minutes of tick bites whereas transmission of *Borrelia burgdorferi* requires the tick to have bitten and remained attached to the human host for at least 36 h. Additionally, pathognomonic for a *Borrelia burgdorferi* infection is subacute development of the erythema migrans rash, while *Borrelia miyamotoi* has no associated skin exanthem, as was seen with our case. The clinical manifestations of *Borrelia miyamotoi* are varied and non-specific, with most patient exhibiting headache, generalized body aches and joint pains, fever, chills and fatigue. However, relapsing fever was present in nearly all cases of *Borrelia miyamotoi* infection, while relapsing fever was an atypical symptom of *Borrelia burgdorferi* infection. *Borrelia miyamotoi* has been characterized by a febrile illness most commonly occurring in the summer months of July and August, while *Borrelia burgdorferi* tends to cause Lyme infection most frequently in late summer through early fall. Despite this contrasts that allow for differentiation, there is a reported case of a patient co-infected with both *Borrelia miyamotoi* and *Borrelia burgdorferi* at the same time [17]. A study from the Netherlands conducted on patients who presented to their primary care physician with tick bite or erythema migrans found that the chances of a non-Lyme disease tick-borne disease such as *Borrelia miyamotoi* being diagnosed was as high as 2.4 % and among patients with Lyme disease, there was a 2.7 % risk of co-infection with a second tick-borne disease [18].

Borrelia miyamotoi can be diagnosed either through serological studies identifying presence of antibodies or through PCR detecting the bacterial antigens. A unifying factor that stands true for nearly all tick-borne diseases is that they are successfully treated with antibiotics, usually doxycycline. Of note, two patients have been reported in the literature as diagnosed initially with human granulocytic anaplasmosis but later being tested for *Borrelia miyamotoi* due to delayed response to treatment with doxycycline, which led to eventual diagnosis of *Borrelia miyamotoi* [19]. Both of those patients recovered with continued doxycycline use. As discussed previously, most reported cases appear to fully recover from *B. miyamotoi* infection, but long-term sequelae of the disease have not been clearly identified. From a practical perspective, while testing for *B. miyamotoi* infection along with Lyme disease makes sense from the perspective of determining the most accurate diagnosis to explain any given clinical picture, once a Lyme disease diagnosis is made, there's not much value added in testing for *B. miyamotoi* infection because *B. miyamotoi* appears to respond to the same therapy as Lyme disease. However, when approaching the diagnostic workup of high fever related to infection, particularly in the setting of headache and altered mental status, we recommend that *B. miyamotoi* testing should be considered in areas where the disease is endemic as this will help expedite diagnosis and treatment.

CRedit authorship contribution statement

Sotonye Bobojama: Conceptualization, Data curation, Writing – original draft. **Ju Young Bae:** Investigation, Writing – review & editing. **Gavin Xavier McLeod:** Investigation, Writing – review & editing. **Khalil Ian Hussein:** Writing – review & editing, Investigation, Supervision.

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Ethical approval

Our Institutional Review Board (IRB) does not require formal IRB review or approval for case reports.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Data Availability Statement

Data not available due to privacy/ethical restrictions.

References

- [1] Steere AC. Lyme disease. *N Engl J Med* 1989;321(9):586–96. <https://doi.org/10.1056/NEJM198908313210906> [PMID: 2668764].
- [2] Krause PJ, Fish D, Narasimhan S, et al. Borrelia miyamotoi infection in nature and in humans. *Clin Microbiol Infect* 2015;21(7):631–9. <https://doi.org/10.1016/j.cmi.2015.02.006> [Epub 2015 Feb 18. PMID: 25700888; PMCID: PMC4470780].
- [3] Mukerji SS, Ard KL, Schaefer PW, et al. Case 32-2020: a 63-year-old man with confusion, fatigue, and garbled speech. *N Engl J Med* 2020;383(16):1578–86. <https://doi.org/10.1056/NEJMcpc2004996> [PMID: 33053289].
- [4] Henningsson AJ, Asgeirsson H, Hammam B, et al. Two cases of Borrelia miyamotoi Meningitis, Sweden, 2018. *Emerg Infect Dis* 2019;25(10):1965–8. <https://doi.org/10.3201/eid2510.190416> [PMID: 31538916; PMCID: PMC6759261].
- [5] Yamano K, Ito T, Kiyonagi K, et al. Case report: clinical features of a case of suspected Borrelia miyamotoi disease in Hokkaido, Japan. *Am J Trop Med Hyg* 2017;97(1):84–7. <https://doi.org/10.4269/ajtmh.16-0699> [PMID: 28719293; PMCID: PMC5508891].
- [6] Krause PJ, Schwab J, Narasimhan S, et al. Hard tick relapsing fever caused by Borrelia miyamotoi in a child. *Pediatr Infect Dis J* 2016;35(12):1352–4. <https://doi.org/10.1097/INF.0000000000001330> [PMID: 27626914; PMCID: PMC5106309].
- [7] Boden K, Lobenstein S, Hermann B, et al. Borrelia miyamotoi-associated neuroborreliosis in immunocompromised person. *Emerg Infect Dis* 2016;22(9):1617–20. <https://doi.org/10.3201/eid2209.152034> [PMID: 27533748; PMCID: PMC4994329].
- [8] Sato K, Takano A, Konnai S, et al. Human infections with Borrelia miyamotoi, Japan. *Emerg Infect Dis* 2014;20(8):1391–3. <https://doi.org/10.3201/eid2008.131761> [PMID: 25061761; PMCID: PMC4111186].
- [9] Hovius JW, de Wever B, Sohne M, et al. A case of meningoencephalitis by the relapsing fever spirochaete Borrelia miyamotoi in Europe. *Lancet* 2013;382(9892):658. [https://doi.org/10.1016/S0140-6736\(13\)61644-X](https://doi.org/10.1016/S0140-6736(13)61644-X) [PMID: 23953389; PMCID: PMC3987849].
- [10] Gugliotta JL, Goethert HK, Berardi VP, et al. Meningoencephalitis from Borrelia miyamotoi in an immunocompromised patient. *N Engl J Med* 2013;368(3):240–5. <https://doi.org/10.1056/NEJMoa1209039> [PMID: 23323900; PMCID: PMC4018741].
- [11] Molloy PJ, Telford 3rd SR, Chowdri HR, et al. Borrelia miyamotoi disease in the Northeastern United States: a case series. *Ann Intern Med* 2015;163(2):91–8. <https://doi.org/10.7326/M15-0333> [PMID: 26053877].
- [12] Platonov AE, Karan LS, Kolyasnikova NM, et al. Humans infected with relapsing fever spirochete Borrelia miyamotoi, Russia. *Emerg Infect Dis* 2011;17(10):1816–23. <https://doi.org/10.3201/eid1710.101474> [PMID: 22000350; PMCID: PMC3310649].
- [13] Tobudic S, Burgmann H, Stanek G, et al. Human Borrelia miyamotoi infection, Austria. *Emerg Infect Dis* 2020;26(9):2201–4. <https://doi.org/10.3201/eid2609.191501> [PMID: 32818401; PMCID: PMC7454072].
- [14] Boden K, Lobenstein S, Hermann B, et al. Borrelia miyamotoi-associated neuroborreliosis in immunocompromised person. *Emerg Infect Dis* 2016;22(9):1617–20. <https://doi.org/10.3201/eid2209.152034> [PMID: 27533748; PMCID: PMC4994329].
- [15] Hoonstra D, Koetsveld J, Sprong H, et al. Borrelia miyamotoi disease in an immunocompetent patient, Western Europe. *Emerg Infect Dis* 2018;24(9):1770–2. <https://doi.org/10.3201/eid2409.180806> [PMID: 30124426; PMCID: PMC6106421].
- [16] Telford 3rd SR, Goethert HK, Molloy PJ, et al. Borrelia miyamotoi disease: neither lyme disease nor relapsing fever. *Clin Lab Med* 2015;35(4):867–82. <https://doi.org/10.1016/j.cll.2015.08.002> [Epub 2015 Sep 18. PMID: 26593262; PMCID: PMC4662080].
- [17] Oda R, Kutsuna S, Sekikawa Y, et al. The first case of imported Borrelia miyamotoi disease concurrent with Lyme disease. *J Infect Chemother* 2017;23(5):333–5. <https://doi.org/10.1016/j.jiac.2016.12.015> [Epub 2017 Feb 2. PMID: 28162921].
- [18] Jahfari S, Hofhuis A, Fonville M, et al. Molecular detection of Tick-borne pathogens in humans with Tick bites and erythema migrans, in the Netherlands. *PLoS Negl Trop Dis* 2016;10(10):e0005042. <https://doi.org/10.1371/journal.pntd.0005042> [PMID: 27706159; PMCID: PMC5051699].
- [19] Chowdri HR, Gugliotta JL, Berardi VP, et al. Borrelia miyamotoi infection presenting as human granulocytic anaplasmosis: a case report. *Ann Intern Med* 2013;159(1):21–7. <https://doi.org/10.7326/0003-4819-159-1-201307020-00005> [PMID: 23817701].