A Case of Travel-Associated Tick-Borne Relapsing Fever in Wisconsin

Michael E. Rockman, MD, PhD; Zaynab Almothafer, MD; Rylee Doucette, MD, MPH; Daniel J. Robbins, MD; Michael Scolarici, MD; Manlu Liu, BA; Caitlin S. Pepperell, MD; Eduard Matkovic, MD; Jordan Kenik, MD, MPH

ABSTRACT

Introduction: Tick-borne relapsing fever is a zoonotic infection caused by members of the *Borrelia* genus of spirochetes found predominantly in the southwestern United States.

Case Presentation: A 65-year-old woman presented to a Wisconsin emergency department with a 2-day history of fevers and altered mental status after returning from a 5-week stay in Colorado. Initial labs were notable for elevated transaminases, thrombocytopenia, mild hyponatremia, mild hypokalemia, and elevated procalcitonin.

Discussion: Rapid identification of patients with tick-borne relapsing fever is essential to minimize morbidity and mortality. Peripheral blood smear – especially during a febrile episode – can serve as a quick and accurate way to diagnose the illness with direct visualization of spirochetes.

Conclusions: Early analysis of a peripheral blood smear can lead to a swift diagnosis of tick-borne relapsing fever, particularly in nonendemic states such as Wisconsin.

INTRODUCTION

Tick-borne relapsing fever (TBRF) is a zoonotic infection caused by members of the *Borrelia* genus of spirochetes.[1] While cases have been reported throughout the continental United States, from 1990 to 2011, approximately 70% of cases were localized to California, Washington, and Colorado. TBRF is classically transmitted by soft ticks, such as *Ornithodoros spp,* which live in close proximity to mammal hosts and feed rapidly compared to the "wait and feed" approach of hard tick species. In contrast to Lyme disease, where tick attachment for 24 to 48 hours is necessary for transmission, TBRF transmission can occur in as little as 15 to 90 minutes.[2,3] Given the quick feeding time and susceptibility to be caused by nymph bites, patients often do not associate symptoms with a tick bite. The most commonly associated exposure with the illness is cabin-based lodging.[4-7]

Clinically, presentation of TBRF is characterized by fever presenting 4 to 18 days after exposure, most commonly with headache, myalgias, chills, and vomiting.[1] The fever pattern is recurrent, with the initial febrile episode typically lasting for 4 to 7 days. Subsequent febrile episodes are classically interspaced by up to 7 febrile-free days.[8] Neurologic involvement can manifest as meningismus, radiculopathy, facial palsy, and encephalitis. Neuropsychiatric disturbances such as apathy or delirium also have been reported. Ocular manifestations are rare and can manifest as iritis, choroiditis, and optic neuritis with rapid deterioration of vision.[9] Gastrointestinal manifestations of TBRF commonly involve nausea and vomiting but also can include abdominal pain, diarrhea, jaundice, and hepatosplenomegaly. On physical examination, localized neurologic findings, hepatomegaly, or splenomegaly can be suggestive of TBRF.[10] Laboratory findings can be nonspecific and include leukocytosis, thrombocytopenia, elevated liver enzymes, elevated erythrocyte sedimentation rate (ESR), and prolonged prothrombin time (PT) and partial thromboplastin time (PTT).

Fourteen *Borrelia* species have been found to cause tick-borne relapsing fever, with *B hermsii*, *B turicatae,* and *B parkeri* being the dominant forms in North America. *B miyamotoi* is transmitted by hard-bodied ticks and is the species identified to locally transmit

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Author Affiliations: Department of Medicine, University of Wisconsin School of Medicine and Public Health (UW SMPH), Madison, Wisconsin (Rockman, Almothafer, Doucette, Liu, Kenik); Department of Pathology, UW SMPH, Madison, Wisconsin (Robbins, Matkovic); Department of Medicine, Division of Infectious Disease, UW SMPH, Madison, Wisconsin (Scolarici, Pepperell); Department of Medical Microbiology and Immunology, UW SMPH, Madison, Wisconsin (Pepperell).

Corresponding Author: Michael E. Rockman, MD, PhD, Department of Medicine, University of Wisconsin School of Medicine and Public Health, 600 Highland Ave, Madison, WI 53792; email mrockman@wisc.edu; ORCID ID 0000-0002-8762-8604

TBRF in Wisconsin.[8] The first confirmed case of *B miyamotoi* in Wisconsin was in 2016, and there were a total of 23 cases reported from 2016 through 2022.[11] Here, we report a case of TBRF identified at an academic medical center in Wisconsin, with polymerase chain reaction indicating a *Borrelia* infection.

CASE PRESENTATION

In August 2023, a 65-year-old woman presented to an emergency department (ED) in Madison, Wisconsin, after a 2-day history of fevers and altered mental status. She had returned to Wisconsin the day prior from a 5-week solitary meditation retreat in Colorado, where she was staying in a cabin at an elevation of 8900 feet. During the initial 2 weeks of her trip, she had experienced headaches, polyuria, and skin dryness that she attributed to the elevation and which self-resolved. After returning to her usual state of health for the majority of the trip, she first experienced a subjective fever on the day prior to leaving Colorado. While driving to Wisconsin the following day, she reported continued subjective fevers and new urinary incontinence, in addition to neurological concerns such as confusion, forgetfulness, and difficulty completing tasks. She even described herself as having an uncharacteristically flat affect, which was concerning for her.

The following day, symptoms had progressed to include intermittent headaches, nausea, and bleeding gums while brushing teeth, which prompted her to self-present to the ED. While enroute, she experienced a low-impact motor vehicle collision after veering off the road. She could not recall the details surrounding the crash, though noted having no emotional reaction to crashing her car. She had no focal neurologic changes. An extensive history was collected related to her recent time in Colorado, which was notable only for multiple insect bites of unclear source and proximity to deer. She denied any tick exposures. Past medical history was notable only for asthma and migraines with aura.

During her initial presentation, the patient was found to be febrile to 38.8 °C. Physical exam revealed a small, well-circumscribed, erythematous lesion with central clearing on the lateral aspect of her right thigh. No bleeding gums were noted. The neurological exam was unremarkable. Her presenting labs were notable for elevated transaminases, thrombocytopenia, mild hyponatremia and hypokalemia, and elevated procalcitonin (Table 1). A workup of altered mental status included computed tomography (CT) head to rule out structural causes, chest x-ray, and CT abdomen/pelvis to evaluate for sources of infection – all of which were without acute abnormalities. She was started on cefepime and vancomycin initially and admitted to a general medicine service.

Upon admission, ESR was 44 and C-reactive protein (CRP) was 22.3. A peripheral blood smear was sent for review, and the patient was started empirically on doxycycline given high concern for tick-associated pathology. She continued to worsen clinically overnight, becoming mildly tachycardic and hypotensive with systolic blood pressure in the 70s to 80s refractory to multiple liters of fluid. Evaluation for intensive care unit (ICU) admission for vasopressor support was performed, though she did not meet ICU admission criteria. Shortly thereafter, blood smear demonstrated the presence of spirochetes (Figure 1), and a presumptive diagnosis of TBRF was made. Lumbar puncture demonstrated <10/LPF mononuclear cells and no neutrophils or organisms. She was continued on ceftriaxone and doxycycline.

Further negative infectious workup included murine typhus Ab titer (<1:64), Rocky Mountain Spotted fever Ab titer (<1:64), cerebrospinal fluid (CSF) bacterial culture (no growth at 5 days), CSF fungal culture (no growth at 7 days), blood culture (2/2 no growth at 5 days), urine culture (negative), *Borrelia burgdorferi* Ab (negative), Lyme PCR (not detected), *Babesia* IgG (<1:16), *Babesia* IgM (<1:20), *Anaplasma phagocytophilum* IgG (<1:80), *A phagocytophilum* IgM (<1:16), *E Chaffeensis* IgG (1:64), *E Chaffeensis* IgM (<1:16), and CSF meningitis/encephalitis panel. Relapsing fever

Table. Pertinent Lab Values at Time of Admission

Lab	Result	Normal Range	Units
Complete Blood Cell Count			
White blood cell count	6.3	(3.8–10.5)	K/µL
Red blood cell count	3.8	(3.8–5.2)	M/µL
Hemoglobin	12	(11.6–15.6)	g/dl
Hematocrit	35	(34–46)	%
Mean corpuscular volume	92	(80–97)	fL
MCHC	34	(32–36)	g/dL
RDW-CV	12.3	(11.7–14.7)	%
RDW-SD	41.7	(36–46)	fL
Platelet count	103	(160–370)	K/µL
Comprehensive Metabolic Panel			
Sodium	132	(136–145)	mM/L
Potassium	3.1	(3.5–5.1)	mM/L
Chloride	103	(98–107)	mM/L
Carbon dioxide	20	(22–29)	mM/L
Anion gap	9	(7–14)	mM/L
Blood urea nitrogen	12	(7–19)	mg/dL
Creatinine	0.84	(0.55–1.02)	mg/dL
Glucose	235	(70–99)	mg/dL
Calcium	8.7	(8.4–10.2)	mg/dL
Magnesium	1.8	(1.6–2.6)	mg/dL
Bilirubin (total)	2.1	(0.0–1.4)	mg/dL
Alkaline phosphatase	91	(40–150)	U/L
Aspartate aminotransferase	106	(5–34)	U/L
Alanine aminotransferase	116	(0–55)	U/L
Albumin	3.0	(3.5–5.0)	g/dL
Protein, total	6.0	(6.4–8.3)	g/dL
Other			
Thyroid-stimulating hormone	0.82	(0.35–4.94)	µIU/mL
Ammonia	24	(0–71)	µIU/mL
Procalcitonin	2.26	(< 0.25)	ng/Ml

Abbreviations: MCHC, mean corpuscular hemoglobin concentration; RDW-CV, red blood cell distribution width coefficient of variation; RDW-SD, red blood cell distribution width standard deviation.

Borrelia species PCR was positive, with results obtained 5 days after presentation.

The patient's neurological status quickly improved with doxycycline, and there was low concern for central nervous system involvement. She was discharged on hospital day 1 with a 10-day course of oral doxycycline. Liver function tests (alanine aminotransferase [ALT] 59, aspartate aminotransferase [AST] 55, total bilirubin 0.5, and thrombocytopenia (platelets 334 000) improved at time of discharge. She was seen in the primary care clinic a few days later with near complete resolution of symptoms and normalization of labs. She was seen for follow-up by Infectious Disease 1 month postdischarge, where she reported improved brain fogginess and word recall but continued balance issues treated with physical therapy.

DISCUSSION

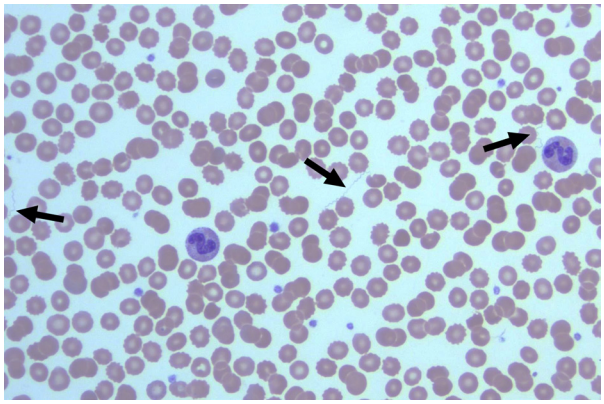
We describe a case of tick-borne relapsing fever identified in Madison, Wisconsin. Although transmission in this case most likely occurred secondary to travel to the endemic area of Colorado, current trends predict increasing prevalence of tick-borne infections to previously nonendemic parts of the country due to climate change.[12] This is attributed to more temperate winters and increasing overall precipitation, which promotes increased survival and activity of ticks, as well as their animal hosts. Since 2016, multiple cases of "nontraveler" TBRF have been identified in Wisconsin alone, suggesting that endemic expansion to the Midwest already may be occurring.[11]

Tick-borne illnesses such as TBRF can present with many nonspecific symptoms. As the name implies, the most prevalent symptom of TBRF is relapsing fever, which is estimated to occur in nearly 100% of cases.[1] The oscillating nature of fever is attributed to antigenic variation of the organism to evade the initial IgM immune response.[1] Other commonly identified symptoms include flu-like symptoms, such as headache (94%), myalgias (92%), nausea/vomiting (>70%), and chills (88%).[13] As observed in this present case, the presenting concern may be primarily neurologic. The exact mechanism of neurologic involvement is unclear but thought to be indirectly related to fevers and spirochetemia, rather than direct CNS involvement, as brain imaging and lumbar punctures often do not indicate pathology.[1] The described neurologic symptoms, including confusion, lethargy, or apathy, often occur in the absence of any localized neurologic findings.[1] Interestingly, our patient's presentation included amnesia and a self-described uncharacteristic flat affect and apathy to her recent motor vehicle collision while enroute to the hospital.

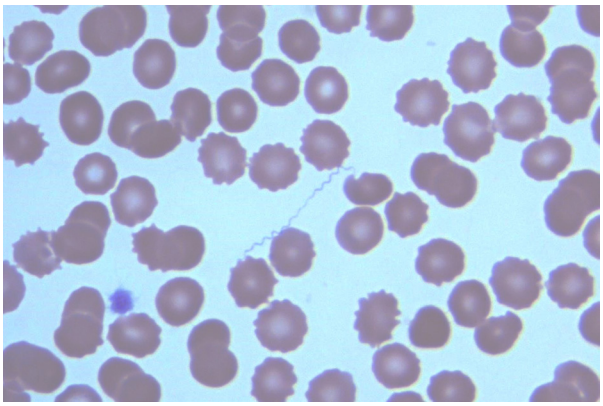
Transmission of TBRF occurs through tick bite, although only 25% of patients can identify a tick given the quick latch and unlatch time exhibited by soft shell ticks. Cabin-related exposures are highly associated with the infection, with 34% of patients identifying this risk factor in systematic review.[14] Our patient had taken a picture of one of the bites she had received in the days prior to her symptoms, which was somewhat targetoid in appearance, albeit small and unchanging. TBRF has been associated with erythema migrans in only about 10% of cases, all of which have occurred in regions with hard shell *Ixodes* ticks. Regardless of the identified tick exposure, she did note staying in a remote cabin during her trip. In terms of laboratory studies, the presence of thrombocytopenia is the only finding that has been reported relatively frequently (approximately 55% of cases), although elevation of ESR and CRP can occur approximately 25% of the time.[1] In this case, elevated procalcitonin without clinical features of pneumonia was a key lab value that suggested acute inflammation.[15]

Overall, if there is concern for TBRF, prompt blood smear can aid rapid diagnosis. Peripheral blood smear—especially during a febrile episode—is, on average, 80% sensitive for identifying spirochetes in cases of TBRF.[1] Peripheral blood smear is most useful in the diagnosis of TBRF, anaplasmosis, ehrlichiosis, and babesia. It is less useful in the diagnosis of Lyme disease and may not be a first-line diagnostic test for all cases of suspected tick-borne disease. PCR is the most sensitive test; however, it is time-intensive

Figure. Peripheral Blood Smear



50X magnification showing multiple extracellular spirochetes denoted with arrows.



100X magnification showing an extracellular spirochete with characteristic spiral, "corkscrew" morphology.

and more expensive. Due to the high molecular similarity between different *Borrelia* species, with reported 16S rRNA gene sequence variability ≤1%, it is challenging to provide exact species identification even with current PCR methods.[1]

When concern for tick-borne pathology is high, empiric treatment with doxycycline is warranted. Within hours of presenting to our institution, the patient in our case began to develop refractory hypotension, concerning for potential septic shock. Hours after administration of doxycycline, she had improved back to near baseline. Doxycycline is the most common agent used to treat TBRF and is administered as an oral regimen of 100 mg twice daily for 10 days.[13] Additional options may include macrolides and fluoroquinolones. It is important to note, however, that initiation of antibiotics in spirochete-based infections can result in Jarisch-Herxheimer reaction due to systemic release of cytokines. This reaction is demonstrated also by high fevers and hypotension and, therefore, can be difficult to separate from the infection itself.

CONCLUSIONS

Clinicians should consider tick-borne pathogens in patients with nonspecific symptoms, especially if fever, neurologic changes, and/or thrombocytopenia are present, regardless of travel history. Recent travel to the southwestern United States, presence of tick, and/or cabin exposure are notable risk factors for TBRF. Peripheral blood smear is an easy and inexpensive test that can help lead to a quick diagnosis of TBRF. Empiric treatment with doxycycline may be warranted if clinical suspicion for TBRF is high. Jarisch-Herxheimer reactions can occur with treatment of any spirochete infection, so it is important to monitor patients for worsening fever and hypotension after the initial dose of antibiotics.

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