

Relapsing fever in a traveller returning from Senegal

Eric J. Eckbo MD, Marthe Charles MD MSc, Robert Wolber MD, Gannon Yu MD

■ Cite as: *CMAJ* 2021 February 22;193:E285-8. doi: 10.1503/cmaj.201644

A 24-year-old man presented to his family physician with a 1-day history of subjective fever, chills, headache, myalgia, arthralgia and mild diarrhea; he was advised to proceed to the emergency department for further assessment. On arrival at our Vancouver-area emergency department, his temperature was 38.3°C (maximal documented temperature 38.4°C), blood pressure 117/67 mm Hg, heart rate 88 beats/min and respiratory rate 16 breaths/min. He was diaphoretic but appeared otherwise well.

The patient had been travelling extensively and had returned home 9 days earlier. Eight months previously, he had embarked on a solo trip that began in Europe before he continued on to Morocco and finally spent several weeks in Senegal. He had not received any pretravel medical counselling or vaccinations and did not take malaria chemoprophylaxis. While in Senegal, he had stayed in a small village and was housed by locals. He ate local food and drank from the local water supply. Most of his time was spent participating in cycling tours of the area. He had no sexual contacts and was not in close proximity to anyone who was sick. The patient noted that there were many dogs in the village, and many were visibly infested with ticks. Midway through his stay, he experienced an “insect bite” to the leg, which became pruritic and red. He then had 4 days of subjective fever, chills and headache. He sought medical attention at a local health care facility, where a moist gauze that smelled of gasoline was applied to the area of the lesion. A thick, white “worm” 2 cm in length was extracted and the patient’s systemic symptoms subsequently resolved without further treatment. A week later, he departed Senegal on a repatriation flight to Canada amid the coronavirus disease 2019 pandemic.

The patient was noted to be febrile at the time of blood collection. Complete blood count showed a normal leukocyte count ($9.7 \times 10^9/L$), but low lymphocytes of 0.8 (normal $1.2\text{--}3.5$) $\times 10^9/L$; his thrombocyte count and hemoglobin were normal. The results of his electrolyte, liver function and transaminase tests were all within normal range. His C-reactive protein level was elevated at 116 (normal range < 3.1) mg/L. Given the patient’s travel history and recurrent fever, malaria was high on our differential diagnosis, as was infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We obtained a nasopharyngeal swab for SARS-CoV-2 testing and ordered urgent

KEY POINTS

- A broad differential should be maintained in the returning traveller with fever, and a detailed travel, social and exposure history elicited to help guide appropriate diagnostics.
- Spirochetes seen in routine peripheral blood or malaria smears are pathognomonic for tick-borne or louse-borne relapsing fever caused by *Borrelia* species.
- In North America, tick-borne relapsing fever is endemic to British Columbia and the western United States, and is transmitted by *Ornithodoros* soft ticks.
- Patients should be closely monitored for the Jarisch–Herxheimer reaction after initiation of effective therapy for all forms of relapsing fever.

malaria testing. At our regional facilities, malaria testing is performed using a rapid antigen test and preliminary screening of Giemsa-stained thin smears. If these initial tests are negative, samples are forwarded to a centralized centre for polymerase chain reaction (PCR) testing and comprehensive review of thick and thin blood smears. In the case of our patient, the rapid antigen test was negative and no malaria parasites were seen on the thin smears; however, the emergency department physician later received a call from the laboratory, identifying spirochetes (Figure 1).

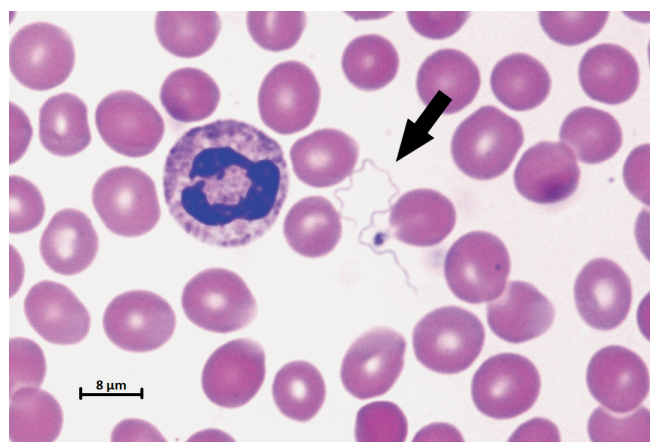


Figure 1: Peripheral blood smear showing single spirochete.

Box 1: Medically important spirochetes

Genus	Syndrome(s)
<i>Borrelia</i>	<ul style="list-style-type: none"> • Lyme borreliosis • Tick-borne relapsing fever • Louse-borne relapsing fever • Hard tick-borne relapsing fever (<i>Borrelia miyamotoi</i> disease)
<i>Treponema</i>	<ul style="list-style-type: none"> • Syphilis (sexually transmitted) • Bejel (endemic syphilis) • Yaws • Pinta
<i>Leptospira</i>	<ul style="list-style-type: none"> • Leptospirosis
<i>Brachyspira</i>	<ul style="list-style-type: none"> • Intestinal spirochetosis

The patient was referred to the infectious diseases rapid access clinic for further management. Spirochetes on microscopy with this clinical picture and exposure history was adequately specific to begin directed treatment for relapsing fever. We administered a dose of ceftriaxone and monitored for 6 hours; we noted no Jarisch–Herxheimer reaction. He was switched to doxycycline the following day, to complete 10 days of therapy. At the time of initial follow-up, 3 days into treatment, the patient was feeling greatly improved; repeat peripheral blood smear at that time was negative for spirochetes.

The bacterial phylum Spirochaetes, so named for their unique coiling structure, contains multiple genera that are pathogenic to humans (Box 1). Serology, PCR and sequencing were performed after consultation with the clinical microbiologist to confirm the diagnosis, by the British Columbia Centre for Disease Control. *Borrelia burgdorferi* enzyme immunoassay was positive, but confirmatory testing using Western blot was negative. *B. hermsii* immunofluorescence assay was reactive for immunoglobulin G (1:256), and nonreactive for immunoglobulin M. *Borrelia* PCR confirmed the presence of *Borrelia* species in the blood. Sequencing of 16S rRNA showed that the *Borrelia* was most closely related to *B. crocidurae* (endemic in West Africa) or *B. hispanica* (endemic to North Africa and the Mediterranean). Once *Borrelia* infection was confirmed by the laboratory, we concluded that the “worm” removed from the patient’s leg had probably been a fly larva (myiasis), and was not likely associated with his systemic symptoms.

Discussion

Relapsing fever

Relapsing fever is a distinct disease characterized by recurrent episodes of fever and nonspecific illness, which may include headache, myalgia, arthralgia, rigours and abdominal discomfort.^{1,2} It is caused by infection with 1 of several species of the spirochete *Borrelia*, which is transmitted by lice or ticks. Complications arise from involvement of the heart, lung, central nervous system, liver, spleen, lung, gastrointestinal tract and eyes.¹ Relapsing fever should not be confused with other causes of

recurrent febrile episodes; Box 2 provides a summary of infectious diseases that may present with recurrent fever as a prominent symptom. After establishing infection in the host, *Borrelia* species are capable of altering their surface antigens, which leads to the repeated cycles of spirochetemia and immune system stimulation.¹ The initial incubation period is 7 days (range 2–14 d), followed by the first episode of fever and associated symptoms, lasting about 3–5 days.⁴ The average time between resolution of the first episode and relapse of fever is 7–9 days.¹ Patients may feel completely well between febrile episodes, or may have lingering symptoms, such as malaise.¹

There are 3 forms of relapsing fever, each defined by its vector (Box 3). Louse-borne relapsing fever results from infection with a single species, *Borrelia recurrentis*, and transmission is mediated by the human body louse.⁵ It is characterized by 1 or more relapses, and tends to have a more aggressive course than other forms of relapsing fever. The fatality rate for louse-borne relapsing fever ranges from 10%–40% when left untreated, and 2%–4% with treatment. It remains a public health concern in regions of northern and eastern Africa, and among populations living in conditions conducive to body louse infestations.⁵ Unlike louse-borne relapsing fever, tick-borne relapsing fever is caused by more than 15 species of *Borrelia* and refers to the disease when it is transmitted by soft ticks. It may result in upward of 30 recurrent febrile episodes without treatment.^{3,4} Mortality from tick-borne relapsing fever remains less than 1% with effective treatment.^{1,6} British Columbia is the only region of Canada with endemic tick-borne relapsing fever; 19 patients showed evidence of infection with *B. hermsii* between 2006 and 2015.⁶ In the United States, this fever is found in the western states, concentrated mostly in California, Washington and Colorado. Between 1990 and 2011, 483 cases of tick-borne relapsing fever were reported in the western US, and most cases occurred in summer months.⁷ It can also be transmitted by hard ticks; the causative agent of hard-tick relapsing fever, *B. miyamotoi*, has been found in *Ixodes scapularis* ticks, identified with passive surveillance throughout Canada.⁸ In Manitoba, serologic evidence of *B. miyamotoi* infection has been documented in patients with suspected or confirmed Lyme disease.⁹

Diagnosis

Identification of spirochetes in a peripheral blood smear is highly suggestive of relapsing fever, although there are rare instances of other spirochetes being detected in Giemsa smears. A density of at least 10⁴ to 10⁵ spirochetes per millilitre of blood is required, which limits the sensitivity of the test. The highest yield occurs when a sample is obtained during a febrile episode.¹ Thick blood smears, such as those ordered for malaria diagnosis, may increase the sensitivity of the test.⁴ Although several other spirochetal infections can cause acute illness, such as Lyme borreliosis and syphilis, these organisms would not be readily visible on a Wright- or Giemsa-stained blood smear examined by standard light microscopy; visualization of these spirochetes requires immunofluorescent staining or dark-field microscopy.¹

It is important to recognize that the sensitivity of blood smears in diagnosing relapsing fever is limited compared with *Borrelia* molecular testing and, as a result, clinicians should not

Box 2: Differential diagnosis of relapsing fevers¹⁻³

Disease	Pathogen	Areas of endemicity
Viruses		
Colorado tick fever	Colorado tick fever virus	North America
Yellow fever	Yellow fever virus	South America, Africa
Dengue fever	Dengue virus	South or southeast Asia, South or Central America, Caribbean, Africa
African hemorrhagic fevers	Lassa virus, Marburg virus, Ebola virus, etc.	Africa
Lymphocytic choriomeningitis	<i>Lymphocytic choriomeningitis mammarenavirus</i>	Widespread
Viral hepatitis	Hepatitis A – E viruses	Widespread
Bacteria		
Brucellosis	<i>Brucella</i> species	Widespread
Leptospirosis	<i>Leptospira</i> species	Widespread, especially in tropical or subtropical areas
Rat-bite fever	<i>Streptobacillus moniliformis</i> , <i>Spirillum minus</i>	Predominantly North America, Asia
Bartonellosis	<i>Bartonella</i> species	Widespread
Typhoid fever	<i>Salmonella enterica</i> serovar Typhi or Paratyphi	Predominantly south or southeast Asia, southern Africa
Ehrlichiosis	<i>Ehrlichia</i> species	North America
Rickettsiosis	<i>Rickettsia</i> species	Widespread
Tularemia	<i>Francisella tularensis</i>	North America, Europe, Asia
Meningococemia	<i>Neisseria meningitidis</i>	Widespread, but predominantly in sub-Saharan Africa (“meningitis belt”)
Protozoa		
Malaria	<i>Plasmodium</i> species	Africa, Asia, South America
Babesiosis	<i>Babesia</i> species	North America, Europe, Asia
Visceral leishmaniasis (kala-azar)	<i>Leishmania</i> species	Africa, Asia, south or central America, Europe (Mediterranean)

Box 3: Comparison of relapsing fever syndromes

Syndrome	Pathogen	Vector	Reservoir hosts	Geographic distribution
Tick-borne relapsing fever	> 15 <i>Borrelia</i> species	Soft tick (<i>Ornithodoros</i> spp.)	Rodents	Worldwide
Louse-borne relapsing fever	<i>Borrelia recurrentis</i>	Human body louse (<i>Pediculus humanus humanus</i>)	Humans	Worldwide (primarily eastern Africa)
Hard tick-borne relapsing fever	<i>Borrelia miyamotoi</i>	Hard tick (<i>Ixodes</i> spp.)	Rodents	Northern hemisphere

rely on laboratories to routinely identify *Borrelia* in the absence of a request for serologic testing, as was the case here. Serologic testing can be performed with an immunofluorescence assay, with a titre of 1:256 or higher considered positive.^{1,6} Polymerase chain reaction testing is currently offered by the British Columbia Centre for Disease Control. Genomic sequencing allows for species-level identification; this service is offered by the National Microbiology Laboratory (Winnipeg) or any laboratory providing 16S rRNA sequencing of clinical samples.

Treatment

Single-dose therapy with 100 mg of doxycycline or 500 mg of tetracycline is recommended for the treatment of louse-borne relapsing fever in nonpregnant adults. Alternatively, a single dose of erythromycin (500 mg) or intramuscular procaine penicillin G (600000 U) is effective.^{1,2} Tick-borne relapsing fever requires a 7- to 10-day course of doxycycline (100 mg twice a day) or erythromycin (500 mg 4 times a day).^{1,2} In patients unable to tolerate oral medication or who have central nervous system involvement,

parenteral therapy with ceftriaxone (2 g daily) or penicillin G (3 million U intravenously every 4 hours) may be warranted.² After the first dose of any effective antibiotic, the patient should be closely monitored for the Jarisch–Herxheimer reaction, which typically occurs within the first 1–4 hours.^{1,2} This life-threatening reaction is caused by the release of endotoxins from rapidly dying spirochetes, which activates a cytokine storm; symptoms may include fever, rigours, tachycardia, diaphoresis, hypotension and respiratory distress.^{1,6}

Conclusion

Borrelia, the cause of our patient's relapsing fever, was identified incidentally by a laboratory technologist, after a diagnostic protocol for malaria. As per the Canadian guidelines,¹⁰ malaria should always be ruled out in febrile patients who have travelled to endemic areas; however, physicians should also keep an index of suspicion for relapsing fever, and order specific serologic and molecular testing when relevant.

References

1. Dworkin MS, Schwan TG, Anderson DE, et al. Tick-borne relapsing fever. *Infect Dis Clin North Am* 2008;22:449-68.
2. Cutler SJ. Relapsing fever *Borreliae*: a global review. *Clin Lab Med* 2015;35:847-65.
3. Thwaites GE, Day NPJ. Approach to fever in the returning traveler. *N Engl J Med* 2017;376:1798.
4. Southern PMJ, Sanford JP. Relapsing fever: a clinical and microbiological review. *Medicine (Baltimore)* 1969;48:129-50.
5. Badiaga S, Brouqui P. Human louse-transmitted infectious diseases. *Clin Microbiol Infect* 2012;18:332-7.
6. Morshed MG, Drews SJ, Lee M-K, et al. Tick-borne relapsing fever in British Columbia: a 10-year review (2006–2015). *BC Med J* 2017;59:412-7.
7. Tick-borne relapsing fever — distribution. Atlanta: Centers for Disease Control and Prevention; 2015. Available: www.cdc.gov/relapsing-fever/distribution/index.html (accessed 2020 Dec. 8)
8. Dibernardo A, Cote T, Ogden NH, et al. The prevalence of *Borrelia miyamotoi* infection, and co-infections with other *Borrelia* spp. in Ixodes scapularis ticks collected in Canada. *Parasit Vectors* 2014;7:183.
9. Kadkhoda K, Dumouchel C, Brancato J, et al. Human seroprevalence of *Borrelia miyamotoi* in Manitoba, Canada, in 2011–2014: a cross-sectional study. *CMAJ Open* 2017;5:E690-3.
10. Chapter 6 - Malaria diagnosis: Canadian recommendations for the prevention and treatment of malaria. Ottawa: Public Health Agency of Canada; [updated 2020 Jan. 16]. Available: www.canada.ca/en/public-health/services/catmat/canadian-recommendations-prevention-treatment-malaria/chapter-6-malaria-diagnosis.html (accessed 2020 Dec. 8).

Competing interests: None declared.

This article has been peer reviewed.

The authors have obtained patient consent.

Affiliations: Division of Medical Microbiology & Infection Control (Eckbo, Charles), Vancouver General Hospital; Department of Pathology & Laboratory Medicine (Eckbo, Charles, Wolber) and of Medicine (Yu), University of British Columbia; Department of Pathology & Laboratory Medicine (Wolber) and Division of Infectious Diseases (Yu), Lions Gate Hospital, Vancouver, BC

Contributors: All of the authors contributed to the conception and design of the work. Eric Eckbo and Robert Wolber acquired the data. Eric Eckbo drafted the manuscript. All of the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Content licence: This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) licence, which permits use, distribution and reproduction in any medium, provided that the original publication is properly cited, the use is noncommercial (i.e., research or educational use), and no modifications or adaptations are made. See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Acknowledgements: The authors thank Dr. Muhammad Morshed and Min-Kuang Lee at the British Columbia Centre for Disease Control for their assistance with acquiring and interpreting data, performing extensive diagnostics for this case, offering their expertise with spirochete infections and reviewing the manuscript.

Correspondence to: Eric Eckbo, eric.eckbo@vch.ca

The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.