

Case Report: The First Case of Imported Relapsing Fever in Japan

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Abstract. Tick-borne relapsing fever (TBRF) is endemic in discrete areas throughout the world; however, a domestic or imported case of relapsing fever has not been reported in Japan. Here, we report the first imported case. A previously healthy 20-year-old woman presented to our hospital on October 8, 2010, because of recurrent fever and lower leg pain. Before consultation, she had experienced four febrile episodes at 10–12-day intervals after returning from her stay in Uzbekistan from 1 to 8 September. Giemsa stain of peripheral blood showed *Borrelia* spirochetes. The spirochete was identified as *Borrelia persica* by sequencing of the amplicons of *flaB* using polymerase chain reaction and phylogenetic analysis. The patient was diagnosed with TBRF, and she completed a 10-day course of minocycline 100 mg twice daily. After treatment, her periodic fever subsided. Physicians should be aware of TBRF in patients with recurrent fever who have returned from TBRF-endemic countries, including areas of the former USSR.

Relapsing fever caused by spirochetes of the genus *Borrelia* is an acute febrile illness characterized by recurrent episodes of fever. These *Borrelia* spirochetes are transmitted to humans via the bite of an infected *Ornithodoros* tick (tick-borne relapsing fever; TBRF) or by contact with the body fluid of an infected human body louse (louse-borne relapsing fever). The TBRF is endemic in discrete areas throughout the world. Each *Borrelia* species that causes relapsing fever is different according to areas. The TBRF is caused by *Borrelia crocidurae* or *Borrelia duttonii* in Africa, whereas *Borrelia hermsii* or *Borrelia turicatae* in the North American continent. In central Asia, *Borrelia persica* or *Borrelia latyschewii* is the causative pathogen¹; a domestic or imported case of relapsing fever has not been reported in Japan. Here, we report the first imported case.

A previously healthy 20-year-old woman presented to our hospital on October 8, 2010, because of recurrent fever and lower leg pain. Before consultation, she had experienced four febrile episodes at 10–12-day intervals. She had visited Rishton, a town in Fergana Province, Uzbekistan, from 1 to 8 September while working as a Japanese language volunteer. She stayed in a house with a thatched roof with a local family in Rishton and meals were mainly taken at home. She recalled being bitten by a tick on her right thigh. Four days after returning from Uzbekistan, she visited her primary care doctor because of high fever and lower leg pain. She was diagnosed with common cold, and was prescribed cefcapene pivoxil (CFPN-PI). After taking CFPN-PI, her fever promptly resolved, and she discontinued treatment with CFPN-PI. However, she experienced two further episodes of recurrent high fever and lower leg pain, at 12 and 22 days, respectively, after the first febrile episode. She took CFPN-PI during each episode, and her fever rapidly abated. During the fourth febrile episode, occurring 11 days after the third episode, she presented to our hospital for further evaluation.

On examination, her temperature was 39.8°C, her blood pressure was 112/70 mm of Hg, and her pulse rate was 90/min. Her physical examination revealed normal findings except for eschar on her right inner thigh. Laboratory tests revealed

lymphopenia (1,110 μ g/mL), elevated levels of C-reactive protein (195 mg/L) and alanine aminotransferase (69 IU/mL). Leukocytes were 7,290 μ g/mL (73% of neutrophil and 15.2% of lymphocyte). Count of red blood cells and platelets were normal. Abdominal ultrasonography revealed mild splenomegaly. Blood culture was negative (BACTEC plus aerobic medium and anaerobic medium, Becton, Dickinson and Company, Franklin Lakes, NJ), and Giemsa stain of peripheral blood collected during the febrile phase showed helical bacteria suggestive of *Borrelia* spirochetes (Figure 1). Borrelial DNA was also detected in blood cultures and serum specimens obtained during the fourth febrile phase using *Borrelia*-specific flagellin gene (*flaB*)-based polymerase chain reaction (PCR).² The sequence was deposited in GenBank as accession no. AB781030. The spirochete was identified as *B. persica* by sequencing of the amplicons of *flaB* using PCR and phylogenetic analysis (sequence similarity was 99.6% to *B. persica* strain T [accession no. JF708953], whereas 86% to *Borrelia hispanica*, 84–85% to *B. duttonii* and *B. crocidurae*, 84% to *Borrelia recurrentis* strains). The post-treatment serum sample was negative in this PCR assay. The *Borrelia* was inoculated into culture bottles containing Barbour-Stoenner-Kelly medium with 10% rabbit serum (homemade); however, they did not propagate. The patient was diagnosed with relapsing fever, and she completed a 10-day course of minocycline (100 mg twice daily). Jarisch-Herxheimer syndrome did not occur. After treatment, her periodic fever subsided.

The TBRF is characterized by periodic fever with non-specific symptoms such as headache, myalgia, arthralgia, and nausea. These symptoms last several days, followed by an interval without fever, followed by another episode of fever. If left untreated, patients usually experience 1 to 4 episodes of fever before the illness spontaneously resolves. The definitive diagnosis of TBRF is primarily based on the detection of *Borrelia* spirochetes in smears of peripheral blood collected during the febrile period. The PCR techniques (e.g., *glpQ*-based PCR) along with sequence analysis can often identify the infectious *Borrelia* species³; although the preferred treatment is doxycycline 100 mg twice daily for 10 days, we prescribed minocycline as an alternative treatment in this case. De Pierpont and others all reported that minocycline was as effective as doxycycline in areas with limited resources.⁴

Borrelia persica is frequently detected in Israel, Iran, and Jordan. However, the tick *Ornithodoros tholozani*, the

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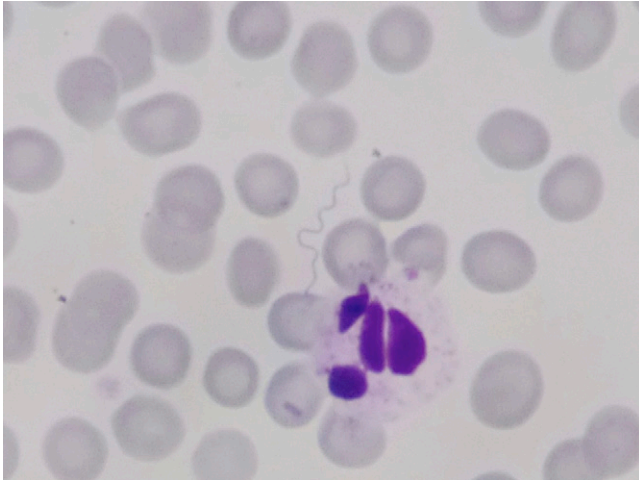


FIGURE 1. *Borrelia spirochaeta* in the Giemsa stain of the peripheral blood corrected at the febrile phase.

transmission vector of *B. persica*, is widely distributed throughout India, the southern countries of the former Union of Soviet Socialist Republics (USSR, including Kazakhstan, Kyrgyzia, Tajikistan, Turkmenistan, and Uzbekistan), Middle East and Near East countries, Turkey, Egypt, and Cyprus.^{1,5} To our knowledge, although the epidemiological evidence regarding TBRF is inadequate in the countries of the former USSR,⁶ Colin de Verdiere and others⁷ reported a case of TBRF caused by *B. persica* imported from Uzbekistan in 2011.

Several cases of imported TBRF have been reported throughout the world. Most are cases of disease imported to Europe from African countries^{8–10}; our case is the first TBRF case in Japan imported from Uzbekistan. Tick-borne relapsing fever is usually benign and self-limiting, but there are severe complications such as meningoencephalitis caused by *B. crocidurae*.¹¹ Preferred treatment of TBRF in adults is tetracycline or doxycycline, and erythromycin, penicillin, or ceftriaxone can be used as alternatives. There may have been previously overlooked cases in Japan that resolved spontaneously or during treatment with prolonged courses of antibiotics.

Physicians should be aware of relapsing fever in patients with recurrent fever who have returned from TBRF-endemic countries, including areas of the former USSR. Diagnosis is primarily based on examination of peripheral blood smears. Where available, PCR is useful because of its sensitivity and ability to identify the causative species.

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