Borrelia miyamotoi Disease

Neither Lyme Disease Nor Relapsing Fever

Sam R. Telford III, ScD[a,*], Heidi K. Goethert, ScD[a], Philip J. Molloy, MD[b], Victor P. Berardi[b], Hanumara Ram Chowdri, MD[c], Joseph L. Gugliotta, MD[d], Timothy J. Lepore, MD[e]

KEYWORDS

• *Borrelia miyamotoi* • Lyme disease • Deer ticks • Borreliosis • Zoonotic infection

KEY POINTS

- *Borrelia miyamotoi* was first described from Japanese *Ixodes persulcatus* ticks. Subsequently, it was detected as an inherited infection of *Ixodes dammini* ticks in the northeastern United States.
- The index case of *B miyamotoi* disease (BMD) in the United States comprised meningoencephalitis in an elderly immunocompromised patient. BMD is likely a common, underdiagnosed zoonosis wherever Lyme disease is reported.
- Cases typically present with headache, fever, chills, fatigue, and myalgia. BMD should not be considered a relapsing fever; there is no crisis with rigors or hyperpyrexia followed by diaphoresis and hypotension.
- BMD may be confirmed by PCR of acute blood samples or by seroconversion to a recombinant GlpQ antigen.
- Treatment is identical to that for Lyme disease.

Potential Conflicts of Interest: V.P. Berardi is an associate director of laboratory science and CEO of Imugen, Inc. P.J. Molloy and H.K. Goethert are employees of Imugen, Inc. H.R. Chowdri is a clinical consultant and S.R. Telford is a consultant and scientific advisor to Imugen, Inc.

S.R. Telford and H.K. Goethert are supported, in part, by grants from the National Institutes of Health (U01AI109656, R41AI078631); the Tufts Innovation Institute; the Evelyn Lilly Lutz Foundation; the Dorothy Harrison Egan Foundation; and the Bill and Melinda Gates Foundation.

[a] Department of Infectious Disease and Global Health, Tufts University, Cummings School of Veterinary Medicine, 200 Westboro Road, North Grafton, MA 01536, USA; [b] Imugen, Inc., 315 Norwood Park South, Norwood, MA 02062, USA; [c] Hawthorn Medical Associates, 275 Allen Street, Unit 3, New Bedford, MA 02740, USA; [d] Hunterdon Medical Center Infectious Diseases, 1100 Wescott Drive, Suite 306, Flemington, NJ 08822, USA; [e] Nantucket Cottage Hospital, 57 Prospect Street, Nantucket, MA 02554, USA

* Corresponding author.

E-mail address: sam.telford@tufts.edu

Clin Lab Med 35 (2015) 867–882

http://dx.doi.org/10.1016/j.cll.2015.08.002 **labmed.theclinics.com**

0272-2712/15/$ – see front matter

INTRODUCTION

Tick borne *Borrelia* spp are now usually divided into two taxonomic groups, which correspond to the typical human disease manifestations, Lyme disease and relapsing fever, and to their tick vectors, prostriate ixodid ticks and argasid ticks, respectively (**Table 1**). Theiler[1] demonstrated spirochetes in metastriate ixodid ticks infesting African cattle with a mild disease that was called "tick spirochetosis" or bovine borreliosis. *Borrelia theileri* subsequently has been globally reported, usually associated with cattle and their cosmopolitan tick *Rhipicephalus (Boophilus) microplus* and *Rhipicephalus annulatus*. Professor Kenji Miyamoto of Asahikawa Medical College, during 1990 to 1992, isolated spirochetes from *Ixodes persulcatus* ticks collected in Hokkaido, Japan. These isolates were subsequently demonstrated by analysis of the 23S-5S rDNA and other genes to be a new species related to the relapsing fever spirochetes.[2] The name *Borrelia miyamotoi* was applied to this new species, and subsequently, this spirochete has been detected wherever *I persulcatus* species complex ticks (*Ixodes dammini*, *Ixodes scapularis*, *Ixodes pacificus*, *Ixodes ricinus*, herein referred to as *Ixodes* spp) occur. In 1995, borreliae from American Lone Star ticks (*Amblyomma americanum*) were identified independently by two research groups[3,4] and provided the names *Borrelia lonestari* and *Borrelia barbouri*; the former name has prevailed in the literature.[1] Molecular phylogenetic analyses demonstrate that *B theileri*, *B lonestari*, and *B miyamotoi* comprise a group together, deep within the relapsing fever spirochete clade[5] and not within the other ixodid ("hard") tick maintained borreliae, namely those in *Ixodes* spp that are recognized as *Borrelia burgdorferi* sensu lato. Although phylogenetically considered to be relapsing fever spirochetes, the metastriate-transmitted *Borrelia* spp should not be assumed to be biologically similar to the true relapsing fever spirochetes maintained by argasid ("soft") ticks, or to cause typical relapsing fever.

As with *B burgdorferi* (discussed elsewhere in this issue), evidence is emerging that *B miyamotoi* comprises a species complex or group of genospecies[5] and should be referred to as *B miyamotoi* sensu lato. Asian, European, and American clades are apparent with phylogenetic analyses of typical gene targets, such as flagellin (**Fig. 1**). Unlike *B burgdorferi* s.l., for which less than half of the recognized genospecies have been associated with human infection, all three *B miyamotoi* clades recognized thus far have been associated with human clinical cases.

The biology of *B theileri* has been well studied, particularly clinical aspects of bovine borreliosis[6] and vector-pathogen interactions.[7] *B lonestari* has been circumstantially associated with a disease manifesting mainly as erythema migrans (southern tick–associated rash illness, or Masters disease), but its formal incrimination as the etiologic agent remains lacking.[8] Further discussion of southern tick–associated rash illness/Masters disease as a borreliosis is beyond the scope of this article. *B miyamotoi*, despite its global distribution in Lyme disease vectors, remained as an incidental finding in field surveys and was thought to be an endosymbiont of *Ixodes* spp ticks. In 2011, a case series comprising febrile Russian patients, some with a recurrent fever, was presented with polymerase chain reaction (PCR) evidence that implicated *B miyamotoi* as the etiologic agent.[9] This was the first suggestion that *B miyamotoi* was capable of causing human disease, and was followed in 2013 by the index case for

[1] The name *B lonestari* technically should be presented in quotation marks or referred to as Candidatus *Borrelia lonestari*, in as much as the requirements for naming a new bacterial taxon have not been fulfilled, in particular, formal publication in the *International Journal of Systematic and Evolutionary Microbiology* and its propagation in vitro that would enable deposition of cultures into an accepted biologic repository.