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Insights into *Borrelia Miyamotoi* Infection from an Untreated Case Demonstrating Relapsing Fever, Monocytosis and a Positive C6 Lyme Serology

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Abstract

We describe a patient from the United States with PCR- and serology-confirmed *Borrelia miyamotoi* infection who recovered without antibiotics. Our findings suggest that *B. miyamotoi* infection may cause relapsing fever, blood monocytosis and antibody reactivity to the C6 peptide. Further studies are required to better define the spectrum of clinical and laboratory findings for this emerging tick-transmitted infection.

Keywords

Borrelia; *Borrelia Miyamotoi*; Lyme disease; C6 serology; Monocytosis; Relapsing fever

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Borrelia miyamotoi is a relapsing fever spirochete that may be found in all *Ixodes* spp. ticks that potentially transmit *Borrelia burgdorferi* sensu lato [1–3]. However, in total less than 100 patients with this hard-tick transmitted infection have been reported on in the United States and for fewer than 10 of these patients were any of the specific clinical and laboratory data presented [4–7]. Cases have also been reported from Russia, the Netherlands and Japan [8–10]. In this report, we describe an adult patient from suburban New York City, in the Lower Hudson Valley region of New York State, with *B. miyamotoi* infection. This patient was not treated with antibiotics and experienced a relapsing febrile illness, providing insights into the natural history of this infection.

Case Summary

A 44-year old previously well Caucasian man from Westchester County, NY, who had no recent travel except to Connecticut and no history of Lyme disease or an immunocompromising condition, was evaluated on August 24, 2015 because of a 4 week history of fatigue and generalized weakness (Table 1). He had had 2 bouts of fevers with rigors and myalgias; the first at the end of July lasting 4–5 days, and the second occurred 3 weeks later. The patient was febrile on August 22 and August 23, 2015, but had no fever on August 24, 2015 and thereafter. He recalled at least 6 tick bites within the month preceding the onset of his illness. He had not seen a physician regarding his complaints. Physical examination revealed a temperature of 36.3 degrees centigrade, a blood pressure of 120/80 millimeters of mercury, and a pulse rate of 77 beats per minute. The rest of the examination was within normal limits.

Laboratory testing revealed normal values for the hemoglobin level (15.6 grams/dL), the white blood cell count (6,200 cells/mm³), the absolute neutrophil count (2,288 cells/mm³), and the lymphocyte count (2,492 cells/mm³). However, the patient had an elevated monocyte count of 1,073 cells/mm³ (normal range <500 cells/mm³ [11]) and mild thrombocytopenia of 140,000 cells/mm³ (normal range 150,000 – 450,000 cells/mm³); creatinine, liver enzymes and bilirubin were within normal limits. Testing for *Anaplasma phagocytophilum* and for *Babesia microti* by blood smear and polymerase chain reaction were negative. Serologic testing for antibodies to *Borrelia burgdorferi* was positive by an enzyme-linked immunosorbent assay (ELISA) using a whole cell sonicate (WCS) of *B. burgdorferi* as antigen, but supplemental IgM and IgG immunoblot testing was negative [12] (Table 1). PCR on blood for *B. burgdorferi* DNA was negative.

PCR on blood for *B. miyamotoi* DNA was positive, but because the test was in development when the patient presented, the original blood sample from August 24, 2015 was not able to be tested until approximately 1 month later. The patient was fully recovered without antibiotic therapy by August 26, 2015 and has remained well as of May 3, 2016. At about 14 weeks after the onset of illness his platelet count had risen to normal levels at 228,000 cells/mm³. The absolute monocyte count had fallen to 673 cells/mm³. At this time serologic testing for antibodies against the glycerophosphodiester phosphodiesterase (GlpQ) protein of *B. miyamotoi* was performed using both an ELISA and IgG and IgM immunoblots that was positive for IgM and IgG antibodies (Table 2). Repeat serologic testing for Lyme disease on

this date revealed both a positive WCS ELISA and a positive C6 ELISA, however, both IgG and IgM immunoblot testing remained negative. PCR for *B. miyamotoi* was also negative.

Methods

***Borrelia burgdorferi* serologic testing**

Testing for antibody to *B. burgdorferi* was done by an enzyme immunoassay using either a WCS of *B. burgdorferi* as the antigen by the Captia™ *Borrelia burgdorferi* IgG/IgM assay (Trinity Biotech, Jamestown, NY), or by the C6 Lyme ELISA kit (Immunetics, Inc., Boston, Mass.). Separate IgM and IgG immunoblots were performed using the *B. burgdorferi* IgG and IgM MARBLot strip test systems (Trinity Biotech, Jamestown, NY). All serologic testing was performed in accordance with the manufacturers' recommendations. Immunoblots were interpreted using the Centers for Disease Control and Prevention (CDC) guidelines [12].

***Borrelia burgdorferi* polymerase chain reaction testing**

DNA from blood samples was extracted using the Qiagen Blood Mini Kit as per the instructions of the manufacturer. A real-time PCR assay, with a specific probe targeting the 16S rRNA gene of *B. burgdorferi*, was performed as previously described by Barbour et al [13].

***Anaplasma phagocytophilum* polymerase reaction testing**

A real-time PCR assay targeting *A. phagocytophilum groE* [forward primer HS14 (5'-CATAGTCTTATGCTACGGTTG-3'), reverse primer HS197 (5'-AAGGCTTACTAATCGCTACAG-3) and probe Apw1 (5'-6FAM-TGCAGTTGGTTGTACTGCTGGTCCT-TAMRA 3')] was performed on an ABI 7500 instrument (Life Technologies, Foster City, CA) using the same protocol as previously described for a *B. microti* PCR assay [14].

***Borrelia miyamotoi* polymerase chain reaction and serologic testing**

The presence of *B. miyamotoi* DNA in blood samples was initially analyzed using a real-time PCR assay with a relapsing fever-specific probe targeting the 16S rRNA gene as described by Barbour et al. [13]. A second real-time PCR assay targeting the *glpQ* gene of *B. miyamotoi* [6] was subsequently performed for any positive samples. Sanger sequencing was used to verify that the amplicons were *B. miyamotoi*.

***Borrelia miyamotoi* and *Borrelia hermsii* serologic testing at CDC**

B. miyamotoi and *B. hermsii* culture (CDC reference collection) sonicate protein was bound to 96 well plates (Immulon) at 1 ug/well for WCS EIAs. Blocked and washed wells were incubated with patient or control sera diluted 1:100. Alkaline phosphatase conjugated goat anti-human IgA+IgG+IgM (H&L) and pNPP substrate buffer (both reagents KPL) were used to detect bound antibody. EIA positive cutoffs were set at 3 standard deviations above the mean absorbance (405 nm) of 6 negative control sera from healthy subjects with no history of *Borrelia* spp. infection. For immunoblotting similar culture preparations were used

to resolve proteins by polyacrylamide gel electrophoresis. Protein was transferred to nitrocellulose blots. The calculated culture protein per final blocked and washed 3×110 mm blot strip was 5ug. 20 ul of patient or control sera was incubated with Western blot strips and bound antibody was incubated with alkaline phosphatase conjugated goat anti-human IgM or IgG and detected with BCIP/NBT phosphatase substrate (KPL).

The *glpQ* gene of *B. miyamotoi* was amplified from an *I. scapularis* tick collected in Connecticut 2012. The full length *glpQ* gene was amplified and cloned into plasmid pCR-Blunt (Invitrogen). Primers were designed to amplify the sequence of the mature peptide, removing the leading 20 codons and the stop codon and ligated with plasmid pQE-60 (Qiagen) using the BamHI site. Sequencing was done to verify gene identity and reading frame. The mature peptide with a C-terminal 6xHis tag was expressed in *Escherichia coli* and purified per the manufacturer's instructions. Purified protein, 1 ug/well, was coated on 96-well plates as above. Serum samples, antibody detection and EIA parameters were as above for WCS EIA.

***Borrelia miyamotoi* serologic testing at Yale**

The IgG ELISA and IgM and IgG Western blot two-tier assays were carried out in a similar manner to that previously described [15].

Discussion

Borrelia miyamotoi infection is an emerging tick-borne infectious disease [4–10]. The largest case series published to date in the United States described the clinical profiles of 51 patients from Rhode Island, Massachusetts, New Jersey and New York diagnosed with *B. miyamotoi* infection, but the exact geographic locations of the infected patients within these States was not provided [6]. To our knowledge, the patient in this report is the first PCR-confirmed case from New York State to be described in detail.

Our case did not receive antibiotics, and, as might have been anticipated with an infection caused by a relapsing fever borrelia, had a fever recurrence. Recurrent fevers in *B. miyamotoi* infection were described in 2 of the 51 cases in the United States series and 5 of the 46 cases in a Russian series that was published in English [6,8]. However, few details on the timing of the fevers or on how long the recurrent fever lasted were provided [6–8]. The low percentage of cases with a relapse of fever may be due to the frequent use of empiric antibiotic therapy early in the course of febrile illnesses in patients with tick exposures. Although evidence of antigenic variation, which drives the relapsing course of other relapsing fevers due to borrelia, has not been demonstrated clinically or in an animal system thus far for *B. miyamotoi* [7], it has been shown that this species does have the genetic apparatus for this variation [16]. The typical duration of the initial fever episode in the soft tick transmitted relapsing fevers (TBRF) is 3 days, while that of louse-borne relapsing fever (LBRF) is 5.5 days [17]. The average interval between the initial bout of fever and fever recurrence is 7 days for TBRF and 9 days for LBRF [17]. Up to 6 relapses of fever have been described in a patient with TBRF [18]; the highest reported number of relapses in infections due to *B. miyamotoi* thus far is 2 [8]. In our patient the duration of the two febrile episodes was consistent with that of other TBRFs, however, the interval between relapses

was relatively long at ~3 weeks. Although we did not categorically establish the cause of the initial febrile episode in our patient, we believe it is extremely unlikely that the 2 episodes of fever had distinct etiologies. Our patient recovered without antibiotic therapy in about 4 weeks. Untreated TBRFs typically last for 3 weeks up to 7 months [19].

Our patient had mild thrombocytopenia on initial evaluation but hepatic enzyme levels were normal. In the United States case series of 51 patients, 22 (43%) had leukopenia, 26 (51%) had thrombocytopenia and 27 (53%) had elevated liver enzymes [6], whereas cytopenias were not observed in any of the patients described in a Russian case series [8]. This may be due to genetic differences in the strains of *B. miyamotoi* causing infection in these two widely separated geographic regions [20] or referral bias in terms of which patients had PCR testing performed [5,6]. In favor of the former possibility is that the cited Russian case series was from the Asian part of Russia, whereas patients with *B. miyamotoi* infection from European Russia have had cytopenia [21].

Of note, our patient had an elevated number of monocytes in peripheral blood. Data on the number of monocytes has been provided for only 2 of the other PCR-confirmed cases of *B. miyamotoi* infections from the United States [5]. Both patients also had a modestly elevated level of monocytes in the blood, varying from 693 to 855/mm³ during the acute illness, although no comment was made about this finding [5]. In neither of these 2 cases, however, did the initial complete blood count show an elevated value for the monocyte count, and in the one case for whom there was follow-up data at about 1 month after presentation, the monocyte count was still elevated at 994/mm³. Monocytosis is a well-established finding in patients with relapsing fever borrelia infections [19], as it is with both early syphilis and congenital syphilis [22,23]. It should be noted, however, that there is variability in the literature as to how blood monocytosis is defined, and certain authorities suggest using values higher than 500/mm³ and specifically using normative values that reflect the person's age, gender and race [24]. However, even if the cut-off were raised to 800/mm³, our patient and one of the 2 cases reported by Chowdri et al. [5] would still have been regarded as having monocytosis.

Another interesting feature of our patient was seroreactivity by WCS ELISA to *B. burgdorferi* antigens with negative immunoblot testing. Approximately 90% of the 30 patients in the United States cases series with convalescent sera available were also seropositive by WCS ELISA to *B. burgdorferi* antigens on at least the convalescent phase serum sample, but only 10% of these patients had a positive IgM or IgG immunoblot [6]. Of note, our case was also found to be strongly positive by the C6 ELISA when first tested at approximately 3 months after onset of the *B. miyamotoi* infection, although the Lyme disease immunoblots remained negative. The same phenomenon of C6 seropositivity despite negative immunoblot testing for *B. burgdorferi* antibody was also described in a patient with *B. miyamotoi* infection from the Netherlands, but no explanation was provided [9]. Based on similarities discovered by a Basic Local Alignment Search Tool protein (BLASTp) search (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>), using the amino acid sequence of the C6 peptide from the B31 strain of *B. burgdorferi* sensu stricto (which is identical to that used in the licensed C6 ELISA test) [25], we suspect that C6 seropositivity may be directly attributable to *B. miyamotoi* infection, as well as to other relapsing fever borrelia infections. The B31 C6

peptide was significantly similar to relapsing fever borrelia variable large protein (vlp) sequences, including vlp 15/16 of *B. miyamotoi*. Supporting this contention are the results of a study which found that of 35 healthy individuals with GlpQ serologic evidence of a possible prior *B. miyamotoi* infection, and without a history of Lyme disease within the preceding 2 years, 6 (17%) were C6 ELISA positive [15]. However, in another study, only 1 (7%) of 14 sera from patients with TBRF was C6 positive [26]. Limitations of this study included that no information was provided as to whether the sera tested were acute phase or convalescent phase samples, and the C6 test method differed from the United States Food and Drug Administration (FDA)-approved test kit, including using the C6 peptide derived from *B. garinii* IP90, which has much poorer matching to vlp sequences of relapsing fever borrelia, when compared with the *B. burgdorferi* sensu stricto B31 C6 peptide. In a more recent analysis, the FDA-approved C6 test was performed on sera from 10 patients who were confirmed to have TBRF by culture isolation and/or microscopic observation of spirochetes in blood samples collected during an early febrile period. TBRF was caused by *B. hermsii* in 9 of these patients and by *B. turicatae* in 1 patient. Sera or plasma collected 0–10 days post-onset of illness were considered acute and samples collected 10 or more days post-onset of illness were considered convalescent. Among the 6 acute phase samples, 4 were negative, 1 was equivocal and 1 was positive by C6. All 6 convalescent phase samples, however, were positive by C6, and both of the patients with acute-convalescent paired samples demonstrated seroconversion. Of the 2 patients who seroconverted, 1 was infected with *B. hermsii* and the other with *B. turicatae*. (M. Schriefer 2016, Unpublished data). These findings convincingly demonstrate that antibody to the C6 peptide may occur as a result of infections due to relapsing fever borrelia.

In conclusion, we have described the first report of an untreated patient with PCR- and serology-confirmed *B. miyamotoi* infection. Our findings suggest that *B. miyamotoi* infection may cause relapsing fever, blood monocytosis and positive serologic testing for antibody reactivity to the C6 peptide, similar to what has been observed with infections due to other relapsing fever borrelia species. Further studies are required to better define the spectrum of clinical and laboratory findings for this emerging tick-transmitted infection.

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Highlights

1. *Borrelia miyamotoi* is a relapsing fever borrelia transmitted by *Ixodes* spp. ticks.
2. We describe a patient with *B. miyamotoi* infection who recovered without antibiotics.
3. The patient had 2 episodes of fever 3 weeks apart, each episode <5 days in duration.
4. The patient demonstrated blood monocytosis and reactivity to the C6 peptide of *B. burgdorferi*.
5. Seroreactivity to the C6 peptide was also demonstrated in *B. hermsii* and *B. turicatae* infections.

Table 1

Chronology of Illness and of Selected Laboratory Test Results.

<u>Case</u>	
Chronology	Year 2015, except where indicated
Date of tick bite	July 4 to July 20, 6 tick bites
Date of onset of fever	July 28
Duration of fever	4–5 days
Date of onset of recurrent fever	August 22
Duration of fever	2 days
Date of initial clinical evaluation	August 24
Date of follow-up evaluation	September 9
Date of final evaluations	November 4 (in person) and May 3, 2016 (by telephone)
Total duration of symptoms	4 weeks
Lab testing	
<i>Borrelia miyamotoi</i> test results	August 24: Positive PCR on blood November 4: Positive GlpQ antibody (see Table 2); Negative PCR on blood
<i>Borrelia burgdorferi</i> serology *	August 24: Positive WCS ELISA (value 1.72); Negative immunoblots (IgM 41 kDa band, IgG 41 kDa band); C6 ELISA not done; November 4: Positive WCS ELISA (value 1.79); Negative immunoblots (IgM 41 kDa band, IgG no bands); Positive C6 ELISA (value 7.48)

* Only bands that are used to judge seropositivity by the Centers for Disease Control and Prevention criteria are listed [12]

Table 2Serologic Testing for *Borrelia miyamotoi* (Bm) and *Borrelia hermsii* (Bh)

	Bm GlpQ IgG EIA	Bm WCS IgG EIA	Bm IgM immunoblot	Bm IgG immunoblot	Bh GlpQ IgG EIA	Bh WCS IgG EIA
CDC test site	+	+	+	+	-	+
Yale test site	+	ND	+	+	ND	ND

WCS = whole cell sonicate

EIA = enzyme immunoassay

CDC = Centers for Disease Control and Prevention; ND = Not done