Annals of Internal Medicine | ORIGINAL RESEARCH

Borrelia miyamotoi Infection Presenting as Human Granulocytic Anaplasmosis

A Case Report

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Background: The diverse tickborne infections of the northeastern United States can present as undifferentiated flu-like illnesses. In areas endemic for Lyme and other tickborne diseases, patients presenting with acute febrile illness with myalgia, headache, neutropenia, thrombocytopenia, and elevated hepatic aminotransferase levels are presumptively diagnosed as having human granulocytic anaplasmosis (HGA).

Objective: To assign a cause for illness experienced by 2 case patients who were initially diagnosed with HGA but did not rapidly defervesce with doxycycline treatment and had no laboratory evidence of *Anaplasma phagocytophilum* infection.

Design: Case report.

Setting: 2 primary care medical centers in Massachusetts and New Jersey.

Patients: 2 case patients acutely presenting with fever.

Measurements: Identification of the causative agent by polymerase chain reaction and DNA sequencing.

Results: Molecular diagnostic assays detected *Borrelia miyamotoi* in the peripheral blood of both patients. There was no evidence of infection with other tickborne pathogens commonly diagnosed in the referral areas.

Limitation: One of the case patients may have had concurrent Lyme disease.

Conclusion: The presence of *B. miyamotoi* DNA in the peripheral blood and the patients' eventual therapeutic response to doxycycline are consistent with the hypothesis that their illness was due to this newly recognized spirochete. Samples from tick-exposed patients acutely presenting with signs of HGA but who have a delayed response to doxycycline therapy or negative confirmatory test results for HGA should be analyzed carefully for evidence of *B. miyamotoi* infection.

Primary Funding Source: National Institutes of Health and the Evelyn Lilly Lutz Foundation.

Ann Intern Med. 2013;159:21-27. www.annals.org

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Eleven tick-transmitted infections of the northeastern United States have been recognized (1). Deer ticks (*Ixodes dammini* [2], also known as *I. scapularis*) are vectors for 5 of these: Lyme disease due to *Borrelia burgdorferi* sensu stricto, babesiosis due to *Babesia microti*, human granulocytic anaplasmosis (HGA) (also known as human granulocytic ehrlichiosis, due to *Anaplasma phagocytophilum*), deer tick virus encephalitis, and *Borrelia miyamotoi* meningoencephalitis. All of the tick-transmitted infections may present solely as an undifferentiated flu-like illness.

Deer tick virus (3, 4) and *B. miyamotoi* (5, 6) have been the basis for recent case reports of human illness. As physician awareness and the availability of laboratory confirmation increase, the spectrum of known presentations caused by these agents will probably expand.

Human granulocytic anaplasmosis due to *A. phagocytophilum*, a rickettsia-like bacterium, was first identified as a zoonotic infection in 1994 (7) with a case series of 12 persons, 2 of whom died. The case patients experienced an acute febrile illness comprising severe myalgia and headache, shaking chills, and malaise. Intragranulocytic bacterial clusters were noted on Wright–Giemsa-stained buffy coat smears, and the identity of the agent was confirmed by polymerase chain reaction (PCR) amplification and sequencing of eubacterial 16S ribosomal DNA as well as by seroconversion to European ruminant-derived *Ehrlichia phagocytophila*.

Nearly all of the case patients had leukopenia with left shift, thrombocytopenia, and elevated serum aspartate aminotransferase and lactate dehydrogenase levels. Of note, among the 10 who recovered, all defervesced within 24 hours of receiving the first doses of oral doxycycline. This rapid response to treatment is so well-recognized that its absence in patients suspected of having HGA suggests a different cause (8).

A recent analysis (9) reported the presence of headache in 82% of 44 case patients with culture- or PCR-confirmed *A. phagocytophilum* infection; 89% with fever, sweats, and rigors; 84% with fatigue; and 73% with leukopenia and thrombocytopenia. These signs and symptoms are cardinal features of tickborne rickettsial diseases in general (10), and "[a]ny reported fever and one or more of the following: headache, myalgia, anemia, leukopenia, thrombocytopenia, or any hepatic transaminase elevation" constitute formal clinical evidence for the case definition from the National Notifiable Diseases Surveillance System (wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=667&DatePub=1/1/2008). Clinicians in the northeastern United States,

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Editorial comment. 61

Context

In the northeastern United States, an acute febrile illness with marked elevation of aminotransferase levels and thrombocytopenia is often caused by human granulocytic anaplasmosis (HGA).

Contribution

In 2 patients with presumed HGA, diagnostic studies were negative for *Anaplasma phagocytophilum* and all tickborne infections common in the northeastern United States. Molecular diagnostic assays detected *Borrelia miyamotoi*.

Caution

Co-infection with *B. burgdorferi* could not be excluded in 1 patient.

Implication

In patients with presumed HGA, especially those not rapidly responding to doxycycline, possible infection with *B. miyamotoi*, an emerging pathogen, should be considered.

—The Editors

where Lyme disease is endemic and Rocky Mountain spotted fever and other tickborne rickettsioses are rare, will frequently presumptively diagnose HGA in a patient experiencing fever, myalgia, leukopenia, and elevated aminotransferase levels.

We recently identified 2 febrile patients from sites in the northeastern United States (New Jersey and Massachusetts) where deer ticks are common and Lyme disease, babesiosis, and HGA are prevalent. These case patients were presumptively diagnosed with HGA because of their clinical presentation, with signs and symptoms severe enough for hospitalization, and were treated with doxycycline. Delayed (>24 hours) response to doxycycline therapy, as well as an absence of molecular evidence for *A. phagocytophilum* infection or for seroconversion to its antigens, led to a more thorough analysis.

Borrelia miyamotoi (11) was identified in acute whole blood samples by PCR, prompted by an intensified general approach to the diagnosis of tickborne infections due to our recent identification of the North American index case of this spirochetosis (6). We concluded that these case patients, who previously would have been reported to the Department of Public Health as possible HGA cases, were actually infected with *B. miyamotoi*, and that this spirochete, like *A. phagocytophilum*, may cause an undifferentiated febrile illness marked by elevated aminotransferase levels, leukopenia, and thrombocytopenia.

CASE REPORTS

Patient 1

A 61-year-old man presented in August 2012 with acute-onset fever and shaking chills for 48 hours before admission, worsening severe frontal headaches, photophobia, myalgia, and arthralgia. He had anorexia and was unable to consume adequate fluids. He had no nausea, vomiting, change in bowel habits or frequency of urination, abdominal pain, dysuria, or hematuria. He reported pain across the chest as though muscles were tightening; this pain was not associated with cough, dizziness, or syncope.

He was admitted to the hospital. The chest pain resolved the next day, but the patient continued to feel poorly, with drenching sweats and episodes of fever with shaking chills. Physical examination revealed an ill-looking man who was flushed, diaphoretic, and dehydrated. Vital signs included a temperature of 38.5 °C, pulse 90 beats/min, respiratory rate 18 breaths/min, and blood pressure 140/80 mm Hg.

The conjunctivae were clear and nonicteric, the throat was normal, and the neck was supple with no palpable adenopathy. The thyroid was normal. The lungs were clear, and the abdomen was soft and nontender. No organomegaly was noted. Cardiac examination revealed tachycardia; he had no murmurs. He was alert and oriented and had no focal deficits. Skin survey revealed no rashes other than psoriatic lesions.

He lived with his family, none of whom had a current illness. Before his illness, he had been active, playing golf daily in south coastal Massachusetts. He has a dog but did not state that he had removed ticks from the dog nor was he aware of having recently been bitten by a tick.

Laboratory studies on admission showed thrombocytopenia (**Table 1**), with the platelet count decreasing by 25% overnight, and relative leukopenia with left shift. A blood smear did not show leukocytic inclusions or *Babesia*. Aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase levels were elevated. Findings from urinalysis, urine and blood cultures, and chest radiography were normal.

The presumptive diagnosis was HGA, and intravenous doxycycline, 100 mg twice daily, with intravenous fluid replacement was administered. He remained febrile, with temperatures to 39.4 °C for 3 days after starting therapy with doxycycline, but his headache slowly decreased over this time. He became afebrile on the fourth day after admission and was discharged on a regimen of oral doxycycline, 100 mg twice daily, for 2 weeks.

He was seen for follow-up 1 week later. His signs and symptoms were completely resolved, and his blood laboratory work-up had returned to normal values.

Patient 2

An 87-year-old white man in previously good health presented in June 2011 with fever and malaise. Two days before admission, he developed severe fatigue, malaise, and a temperature greater than 38.9 °C associated with profound prostration. He became unsteady on his feet as well as short of breath with activities. He developed frank chills and rigors with the fever and became anorexic with very

Table 1. Laboratory Values for Case Patient 1

Test	19 August 2012	20 August 2012	21 August 2012	22 August 2012	23 August 2012	24 August 2012	18 September 2012
Leukocyte count, × 10^9 cells/L	6.5	5.8	4.9	3.6*	4.5*	4.7*	11.3
Hematocrit, %	43.0	39.1*	41.0	36.7*	37.1*	39.6*	42.5
Platelet count, × 10^9 cells/L	115*	86*	58*	60*	76*	87*	166
Neutrophil count, %	76	77	75	60	76	87	66
Bands, %	–	–	6	8	–	–	–
Monocytes, %	–	–	9	23*	19*	16*	8.8
Bilirubin level							
μmol/L	22.2*	22.2*	41.0*	22.2*	15.4	17.1	10.3
mg/dL	1.3*	1.3*	2.4*	1.3*	0.9	1.0	0.6
AST level, U/L	71*	73*	177*	126*	101*	105*	33
ALT level, U/L	73*	72*	127*	105*	92*	97*	55*
Alkaline phosphatase level, μkat/L	0.8*	0.7	0.7	0.7	0.8*	1.0*	0.7*
Creatinine level							
μmol/L	106	97	106	88	88	79	88
mg/dL	1.2	1.1	1.2	1.0	1.0	0.9	1.0
Creatine kinase level, μkat/L	5.2*	4.5*	–	–	–	–	–

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* Considered out of reference value range.

poor oral intake. He did not have headache, loss of consciousness, cough, chest or abdominal pain, nausea, or vomiting. He had no arthralgia or arthritic symptoms, although he did "feel stiff." The patient staggered as he was examined and was promptly admitted.

His medical history was significant for babesiosis in the summer of 2010, which was successfully treated with atovaquone and azithromycin. He lived with his wife, who did not have a current illness, in northern New Jersey. During winters, he resided in Florida. Before his illness, his outdoor exposure mainly consisted of domestic gardening and landscaping at his residence. He had no known recent tick bites or unusual skin lesions.

Blood pressure was 130/60 mm Hg, pulse was 88 beats/min, respiratory rate was 18 breaths/min, and temperature was 37.4 °C. Physical examination showed no skin rashes, such as erythema migrans, but scattered ecchymoses were present. Head examination was unremarkable; the neck was supple, and there was no neck vein distention. His lungs were clear. A soft systolic murmur was noted. His abdomen was soft and nontender with no organomegaly. Extremities were unremarkable. Neurologic examination showed no focal deficits.

A chest radiograph was normal. A complete blood count (**Table 2**) showed leukopenia, thrombocytopenia, and mild anemia; aminotransferase levels were greatly elevated. He was believed to have a tickborne illness with a presumptive diagnosis of HGA and responded within 48 hours to intravenous fluids, bed rest, and doxycycline loading with 200 mg intravenously every 12 hours.

Acute blood samples (EDTA disodium anticoagulated and serum) were taken on admission and sent to IMUGEN (Norwood, Massachusetts) for confirmation of the HGA diagnosis. Results of a monospot test, cytomegalovirus IgG and IgM tests, and an Epstein-Barr virus viral capsid antigen IgM test were negative; results of an IgG test were positive; and results of IgG and IgM tests for *Rickettsia rickettsii* were negative. Results of routine blood cultures were normal.

Two days after admission, his complete blood count showed left shift and thrombocytopenia, with blood chemistry indicating persisting elevated aminotransferase levels. He was discharged from the hospital on a regimen of oral doxycycline, 100 mg twice daily, for 2 weeks and had a full recovery, although prostration continued for several weeks after his febrile episode.

Table 2. Laboratory Values for Case Patient 2

Test	21 June 2011 (Admission)	22 June 2011	23 June 2011
Leukocyte count, × 10^9 cells/L	3.9*	2.8*	3.3*
Hemoglobin level, g/L	125	121	107*
Platelet count, × 10^9 cells/L	117*	88*	99*
Polymorphonuclear leukocytes, %	79.5	–	27.0*
Bands, %	–	–	8.0
Lymphocyte count, %	12.1*	–	36.0
Monocytes, %	7.1	–	21.0*
Eosinophils, %	0.7	–	6.0*
Bilirubin level			
μmol/L	10.3	–	–
mg/dL	0.6	–	–
AST level, U/L	126*	234*	141*
ALT level, U/L	103*	181*	159*
Alkaline phosphatase level, μkat/L	1.2	–	–
Creatinine level			
μmol/L	112	110	71
mg/dL	1.27	1.24	0.8
BUN level, nmol/L	8.6*	7.1	6.8

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen.
* Considered out of reference value range.

METHODS

Antibody Studies

Acute and posttreatment sera were tested at IMUGEN by antibody capture enzyme immunoassay (EIA) for IgA, IgM, and IgG isotypes to *B. burgdorferi* sensu stricto strain 49736 and by immunoblot assays for IgM and IgG to *B. burgdorferi* sensu stricto strains G39/40 and 49736 (12–14). Serum samples were also tested for IgG reactivity against *B. microti* (indirect fluorescent antibody test [IFAT]) (15) and to *E. chaffeensis* by IFAT and by indirect EIA for IgM and IgG antibodies to *A. phagocytophilum* (16, 17).

PCR and Phylogenetic Analysis

Specimen receipt and handling, DNA extraction, and PCR setup were performed with enhanced contamination control practices and precautions in the IMUGEN and Tufts laboratories. The receiving laboratory has environmentally discrete specimen processing, storage, and molecular setup areas not accessible to laboratory personnel performing serologic testing, PCR amplification, or other laboratory functions.

We analyzed blood that had been sampled before the initiation of antibiotic therapy. Extracted DNA from EDTA-anticoagulated whole blood was tested for *Borrelia* by real-time PCR by using primers targeting the 23S ribosomal RNA (rRNA) gene (*Bb23Sf*/*Bb23Sr* with probe *Bb23Sp-FAM*) as described previously (18). Additional primers were subsequently used for identification, including *OspA2*/*OspA4* (19), which targets the *OspA* gene of *B. burgdorferi* sensu lato. Two additional gene targets were amplified using primers specific for the flagellin gene of *Borrelia* species and will discriminate between *B. burgdorferi* and *B. miyamotoi* on the basis of amplicon size (*Fla349f*: GCA AAA ATT AAC ACA CCA GCA and *Fla591r*: AAY WGG AGA ATT AAC TCC RCC TT; amplicon size 231 base pairs for *B. miyamotoi* and 243 base pairs for *B. burgdorferi*) and primers specific for the *GlpQ* gene (*MglpQ flr*; amplicon size 143 base pairs). The *GlpQ* PCR will yield an amplicon only from *B. miyamotoi* and not from *B. burgdorferi*, which lacks this gene (6, 20, 21).

Amplicons for the flagellin gene and *GlpQ* gene assays were excised from agarose gels and commercially sequenced (GENEWIZ, Cambridge, Massachusetts). Sequences were aligned with representative *Borrelia* sequences from GenBank for phylogenetic analysis, which was performed with the maximum likelihood algorithm in Molecular Evolutionary Genetics Analysis 5 (22), selecting models of evolution a priori by using the Modeltest routine. The Kimura 2 parameter model plus G was used for flagellin analysis, and the Tamura 3 parameter model with uniform rates was used for *GlpQ* analysis. Real-time PCR targeting the *msp2* gene of *A. phagocytophilum*, the 18S rRNA gene of *B. microti*, and the 16S rRNA gene of *E. chaffeensis* were performed from EDTA whole blood DNA extractions as previously described (17).

Role of the Funding Source

This study was supported in part by grants from the National Institutes of Health and the Evelyn Lilly Lutz Foundation. These funding sources had no influence or input in the design, analysis, or interpretation of the research reported here.

RESULTS

Case Patient 1, Serologic Findings

Enzyme immunoassays with *B. burgdorferi* antigen were negative (<1 optical density unit) for IgM, IgA, and IgG isotypes in the acute serum specimen, as were immunoblots. Serologic testing for antibodies to *A. phagocytophilum* and *E. chaffeensis* was negative, and there was no IgG reactivity to *B. microti*. Convalescent whole blood specimens were collected from case patient 1 at 4 weeks and at 13 weeks after the acute presentation. Capture EIAs for IgG, IgM, and IgA and IgM and IgG immunoblots for evidence of seroconversion to antigens of *B. burgdorferi* were negative. Serology for IgM and IgG to *A. phagocytophilum* and IgG to *E. chaffeensis* and *B. microti* was negative as well.

Case Patient 2, Serologic Findings

Enzyme immunoassays with *B. burgdorferi* antigen were negative (<1 optical density unit) for IgM, IgA, and IgG isotypes in the acute serum specimen. However, IgG reactivity against a 31-kDa protein (*OspA*) was shown in an immunoblot assay by using strain G39/40 antigen but not with an immunoblot assay by using strain 49736. The use of 2 strains is designed to identify prior Lymerix (SmithKline Beecham Pharmaceuticals, Philadelphia, Pennsylvania) vaccination (14) inasmuch as strain 49736 is an *OspA* expression mutant. For case patient 2, the only reactivity against probable co-infections was against *B. microti* (IgG IFAT titer of 64; *B. microti* PCR was also positive at that time), which was consistent with his history of babesiosis from the summer of 2010 (IFAT titer ≥512 at that time). Serologic reactivity was not shown against *A. phagocytophilum* or *E. chaffeensis*.

One convalescent whole blood specimen was available for case patient 2, collected at 4 months after acute presentation. Real-time PCR assays for *E. chaffeensis*, *A. phagocytophilum*, *B. microti*, and *Borrelia* species (23S rRNA gene broad-range primers) were negative, as was serology for evidence of exposure to *E. chaffeensis* and *A. phagocytophilum*. As with the acute serum sample, evidence of exposure to *B. microti* was detected (IgG IFAT titer of 64). The *B. burgdorferi* capture EIA was positive for IgM (4.1 [normal range, <1]) and negative for IgG and IgA. An immunoblot assay for IgM was considered positive by the Centers for Disease Control and Prevention criteria (2 of 3 required bands: 41 and 24 kDa). The IgG immunoblot results again suggested vaccination against Lyme disease.

Assays to Directly Detect Causative Agents in Peripheral Blood

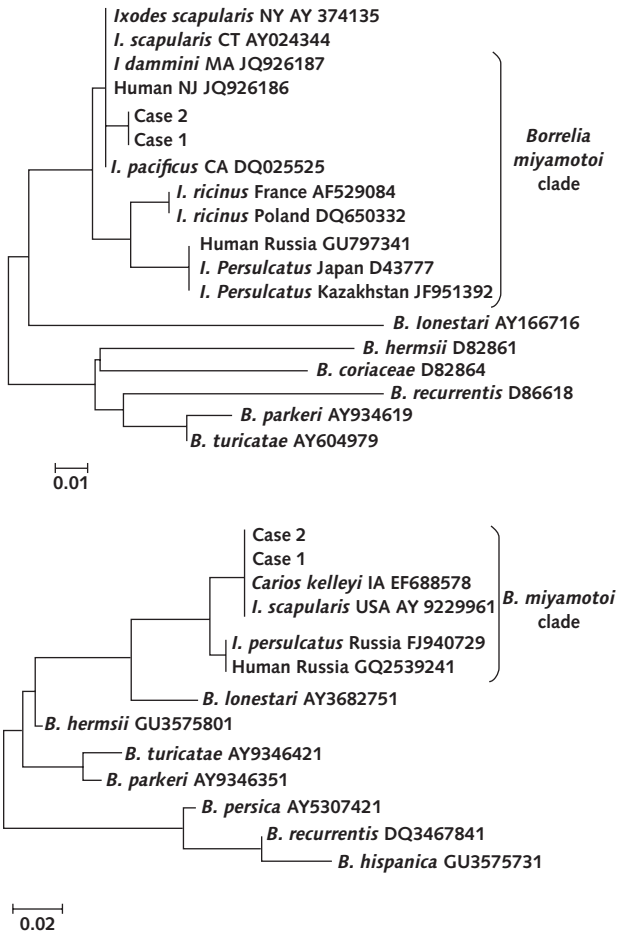
Blood smears from both patients were negative at presentation for *B. microti* or *A. phagocytophilum*; these blood smears were not available for retrospective analysis to determine the presence of *B. miyamotoi*. We detected no molecular evidence for concurrent infection in either patient. Polymerase chain reactions for *B. microti*, *B. burgdorferi*, *A. phagocytophilum,* and *E. chaffeensis* DNA were negative for blood samples taken at presentation.

Borrelia species DNA was detected in the blood of both patients by a real-time PCR by using a 23S rRNA gene primer set designed to detect all *Borrelia* species; however, the *B. burgdorferi*–specific *OspA* gene target failed to amplify, suggesting a different *Borrelia* species. The *Borrelia* species was identified by amplification and sequencing of the flagellin and *GlpQ* genes (GenBank accession numbers for flagellin sequences: KC544000, KC544001. Our *GlpQ* sequences are <200 base pairs; GenBank no longer allows deposition of shorter sequences. The *GlpQ* sequences are available by request.).

Phylogenetic analysis of the amplicons derived from the 2 patients (**Figure**) confirmed that the infecting agent for both belonged to the North American clade of the *B. miyamotoi*–like spirochetes. The sequences for both patients differed by 1 base pair from a laboratory strain of *B. miyamotoi* propagated in mice at Tufts University, showing that our results do not derive from PCR contamination. Our case patients had an illness associated with *B. miyamotoi.*

Babesia microti, *A. phagocytophilum*, and *Borrelia* species DNA (broad-range 23S rRNA gene real-time assay) were not detected in convalescent whole blood samples from either case patient. We concluded that both case patients had illness associated with the presence of *B. miyamotoi* DNA in their peripheral blood, with no evidence of the other common deer tick–transmitted infections.

Figure. **Phylogenetic analysis of portions of the flagellin (*top*) and *GlpQ* (*bottom*) genes amplified from case patients 1 and 2, showing placement of the presumptive causative agent within the North American clade of *Borrelia miyamotoi*.**



DISCUSSION

This report posits that *B. miyamotoi* infected 2 hospitalized patients, causing an illness that was diagnosed presumptively as HGA. Similar cases of fever, myalgia, and elevated aminotransferase levels have probably occurred elsewhere in the United States where deer ticks are common and are attributed to HGA even with a delayed response to doxycycline treatment but never confirmed by specific laboratory assays.

Serologic confirmation of rickettsial diagnoses requires a 4-fold change in antibody titer (10), but the HGA antibody response is delayed, with specific antibodies (IgM or IgG) first detected 11.5 days after the onset of symptoms (23). If patients are lost to follow-up, serologic confirmation of the presumptive diagnosis is not possible. Even when serologic analysis is performed, the sensitivity and specificity of the common indirect immunofluorescence procedure vary because of strain differences of HL60-cultivated *A. phagocytophilum* (24). As such, in the absence of DNA amplification or detection of morulae within leukocytes in blood smears, many cases of HGA remain unconfirmed and unreported. Unrecognized *B. miyamotoi* disease further confounds the measurement of HGA incidence.

The prominent laboratory finding of elevated hepatic aminotransferase levels in our cases, also noted in Russian febrile patients (5, 25), suggests that, unlike the agent of Lyme disease, *B. miyamotoi* may have a predilection for the liver. Cases of louseborne relapsing fever due to *Borrelia recurrentis* will also frequently present with hepatic findings (26); histopathologic examination of cases of relapsing fever on autopsy revealed acute congestion of the liver with central and midzonal infiltration of lymphocytes and neutrophils (27). Indeed, we have seen miliary microabscesses in the livers of mice with severe combined immunodefi-

ciency and chronic *B. miyamotoi* infection (Telford SR, Goethert HK, Alroy J. Severe hepatosplenomegaly due to *Borrelia miyamotoi* in SCID mice. In preparation.).

The implications of hepatic involvement in human *B. miyamotoi* disease remain to be described. *Borrelia miyamotoi* is more closely related to the agents of relapsing fever, such as *B. recurrentis*, than to those of Lyme disease. However, evidence is limited (5) that the disease caused by *B. miyamotoi* is a true relapsing fever, which is characterized by prominent febrile attacks ending with a shocklike crisis, followed by several fever-free days and then another cycle, and sometimes multiple cycles, of fever and crisis (26).

Prospective clinical studies are needed to determine the spectrum and typical course of illness of North American *B. miyamotoi* disease. We cannot ethically withhold treatment to determine whether patients would sustain a relapsing course of fevers. The Russian case series is probably confounded by an important difference in presumptive diagnoses: There, tickborne encephalitis is common and antibiotic treatment would not be indicated. Hence, some of the Russian case patients may have served as natural experiments providing evidence for a relapsing course of illness without treatment.

The frequency with which the standard 2-tiered Lyme serology protocol (28) may confirm exposure to *B. miyamotoi* is unknown. Unlike the North American index case of human *B. miyamotoi* infection (6), our 2 case patients were not immunocompromised and thus were capable of typical antibody responses. Case patient 2 showed a preexisting *B. burgdorferi* immunoblot reactivity that suggested prior Lymerix vaccination; indeed, serum from his summer 2010 presentation for babesiosis also showed that reactivity. When asked, the case patient subsequently confirmed a history of Lymerix vaccination, with the last dose received in May 2000.

The convalescent serum from case patient 2 showed an IgM response to *B. burgdorferi* antigens but not an IgG response that was detectable by EIAs as well as immunoblot assays. Such a pattern of reactivity is often observed in cases of early Lyme disease that are promptly treated (29). With the current evidence, we cannot exclude that case patient 2 may have had concurrent acute Lyme disease that manifested without erythema migrans.

Why such reactivity was not demonstrable for serum from case patient 1 is not clear. Sera were frequently reactive to *B. burgdorferi* sensu lato antigens by EIA (EUROIMMUN, Lubeck, Germany) for a case series from Russia (5) in which *B. miyamotoi* was implicated as the cause for fever. On the other hand, early serologic analyses of infected mice showed little to no crossreactivity of *B. burgdorferi* and *B. miyamotoi* (21), which renders the serologic findings of the Russian case series enigmatic. A letter describing a serosurvey for evidence of *B. miyamotoi* exposure (30) did not specifically comment on whether crossreactivity in the 2-tiered assay was observed.

Specific assays for exposure to *B. miyamotoi*, such as a recombinant *GlpQ* antigen enzyme-linked immunosorbent assay and immunoblot (referred to with no detail by Krause and colleagues [30]), need to be validated and tested in parallel with the 2-tiered serologic assay to determine the extent of crossreactivity. This serologic issue is epidemiologically interesting: Given the global distribution and 1% to 5% prevalence of *B. miyamotoi* in host-seeking vectors of Lyme disease (31–34) and probable frequent human exposure, confounding of case reporting of Lyme disease for cases not presenting with the pathognomonic erythema migrans is possible.

In conclusion, we have presented 2 cases of *B. miyamotoi* infection in hospitalized patients whose illness was consistent with a clinical diagnosis of acute HGA. In North American sites, and indeed globally across the Holarctic where Lyme disease and HGA are commonly zoonotic, clinicians need to be aware of this newly recognized pathogen and include *B. miyamotoi* infection in the differential diagnosis of tick-exposed patients presenting with fever, myalgia, and elevated aminotransferase levels.

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Grant Support: By National Institutes of Health (R41 AI 078631 and R21 AI 082436) and the Evelyn Lilly Lutz Foundation.

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-0290.

Reproducible Research Statement: *Study protocol and statistical code:* Not applicable. *Data set:* Available from Dr. Telford (e-mail, sam.telford@tufts.edu).

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