Borrelia miyamotoi Infection Presenting as Human Granulocytic Anaplasmosis
A Case Report

Hanumara Ram Chowdri, MD; Joseph L. Gugliotta, MD; Victor P. Berardi; Heidi K. Goethert, ScD; Philip J. Molloy, MD; Sherri L. Sterling, MBA, MLS; and Sam R. Telford III, ScD

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.

For author affiliations, see end of text.

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. Intracellular bacterial clusters were noted on Wright-Giemsa-staineduffy 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 PCRConfirmed A. phagocytophilum infection; 89% with fever, sweats, and chills; 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 (www.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=667&DatePub=1/1/2008). Clinicians in the northeastern United States,

See also:
Print
Editorial comment

© 2013 American College of Physicians
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 tick-borne 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

An 87-year-old 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 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

A 61-year-old man presented in August 2012 with acute-onset fever and shaking chills for 48 hours before
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 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 1. Laboratory Values for Case Patient 1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count, × 10^9 cells/L</td>
<td>6.5</td>
<td>5.8</td>
<td>4.9</td>
<td>3.6*</td>
<td>4.5*</td>
<td>4.7*</td>
<td>11.3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>43.0</td>
<td>39.1*</td>
<td>41.0</td>
<td>36.2*</td>
<td>37.1*</td>
<td>39.6*</td>
<td>42.5</td>
</tr>
<tr>
<td>Platelet count, × 10^9 cells/L</td>
<td>115*</td>
<td>86*</td>
<td>58*</td>
<td>60*</td>
<td>76*</td>
<td>87*</td>
<td>166</td>
</tr>
<tr>
<td>Neutrophil count, %</td>
<td>76</td>
<td>77</td>
<td>75</td>
<td>60</td>
<td>76</td>
<td>87</td>
<td>66</td>
</tr>
<tr>
<td>Bands, %</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>23*</td>
<td>19*</td>
<td>16*</td>
<td>8.8</td>
</tr>
<tr>
<td>Bilirubin level, µmol/L</td>
<td>22.2*</td>
<td>22.2*</td>
<td>41.0*</td>
<td>22.2*</td>
<td>15.4</td>
<td>17.1</td>
<td>10.3</td>
</tr>
<tr>
<td>AST level, U/L</td>
<td>71*</td>
<td>73*</td>
<td>177*</td>
<td>126*</td>
<td>101*</td>
<td>105*</td>
<td>33</td>
</tr>
<tr>
<td>ALT level, U/L</td>
<td>73*</td>
<td>72*</td>
<td>127*</td>
<td>105*</td>
<td>92*</td>
<td>97*</td>
<td>55*</td>
</tr>
<tr>
<td>Alkaline phosphatase level, µkat/L</td>
<td>0.8*</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8*</td>
<td>1.0*</td>
<td>0.7*</td>
</tr>
<tr>
<td>Creatinine level, µmol/L</td>
<td>106*</td>
<td>97</td>
<td>106</td>
<td>88</td>
<td>88</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>Creatine kinase level, µkat/L</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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

Table 2. Laboratory Values for Case Patient 2

<table>
<thead>
<tr>
<th>Test</th>
<th>21 June 2011 (Admission)</th>
<th>22 June 2011</th>
<th>23 June 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count, × 10^9 cells/L</td>
<td>3.9*</td>
<td>2.8*</td>
<td>3.3*</td>
</tr>
<tr>
<td>Hemoglobin level, g/L</td>
<td>125</td>
<td>121</td>
<td>102*</td>
</tr>
<tr>
<td>Platelet count, × 10^9 cells/L</td>
<td>117*</td>
<td>88*</td>
<td>99*</td>
</tr>
<tr>
<td>Lymphomononuclear leukocytes, %</td>
<td>79.5</td>
<td>-</td>
<td>27.0*</td>
</tr>
<tr>
<td>Bands, %</td>
<td>-</td>
<td>-</td>
<td>8.0</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>12.1*</td>
<td>-</td>
<td>36.0</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>0.7</td>
<td>-</td>
<td>6.0*</td>
</tr>
<tr>
<td>Bilirubin level, µmol/L</td>
<td>10.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AST level, U/L</td>
<td>126*</td>
<td>234*</td>
<td>141*</td>
</tr>
<tr>
<td>ALD level, U/L</td>
<td>103*</td>
<td>181*</td>
<td>199*</td>
</tr>
<tr>
<td>Alkaline phosphatase level, µkat/L</td>
<td>1.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine level, µmol/L</td>
<td>112</td>
<td>110</td>
<td>71</td>
</tr>
<tr>
<td>BUN level, mmol/L</td>
<td>8.6*</td>
<td>7.1</td>
<td>6.8</td>
</tr>
</tbody>
</table>

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 (Bb235F/Bb235r with probe Bb235p-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 (MgIpaQ-Fr; 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 ELAs 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 ELA 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 235 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.

**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 immunodeficiency disease (SCID) infected with *B. miyamotoi*.
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 zoo-notic, 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.

From Hawthorn Medical Associates and St. Luke's Hospital, New Bedford, Massachusetts; Hunterdon Medical Center, Flemington, New Jersey; Robert Wood Johnson Medical School, New Brunswick, New Jersey; IMUGEN, Norwood, Massachusetts; and Cummings School of Veterinary Medicine, Tufts University, North Grafton, Massachusetts.

Grant Support: By National Institutes of Health (R41 Al 07863) and R21 Al 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).

Requests for Single Reprints: Sam R. Telford III, ScD, Department of Infectious Disease and Global Health, Tufts University, Cummings School of Veterinary Medicine, 200 Westboro Road, North Grafton, MA 01536; e-mail, sam.telford@tufts.edu.

Current author addresses and author contributions are available at www.annals.org.

References
B. miyamotoi Infection Presenting as Human Granulocytic Anaplasmosis | ORIGINAL RESEARCH


