

Human granulocytic anaplasmosis acquired from a blacklegged tick in Ontario

Stefan Edginton MD, T. Hugh Guan MD, Gerald Evans MD, Siddhartha Srivastava MD

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A 79-year-old man was admitted to hospital in July after five days of fever (38°C as measured at home), headache, sensitivity to light, nausea and vomiting. Two weeks earlier, the patient had noticed a tick attached to his skin after hiking in the forest near his home. Subsequently, a red area developed around the bite that lasted one day.

The patient had a history of prostate cancer in 2001 that had been treated with prostatectomy, postoperative radiation and leuprorelin for three years; more recently, he had no medical issues and did not take any medications regularly. The patient lived in southeastern Ontario and had not left the region in the previous year.

On admission, the patient's heart rate was 114 beats/min and regular, with a blood pressure of 125/76 mm/Hg, respiratory rate of 16 breaths/min, oxygen saturation of 97% on room air and a temperature of 36.8°C. He had no neck stiffness and jolt accentuation was negative. Auscultation of the heart and lungs was normal, and there was no abdominal tenderness or hepatosplenomegaly. The patient had no rashes, arthralgia, or palpable lymphadenopathy.

Laboratory investigations (Box 1) showed that the patient had thrombocytopenia with leukopenia, lymphopenia, mild anemia, mildly elevated total bilirubin and aspartate aminotransferase, and elevated lactate dehydrogenase and C-reactive protein. Blood cultures showed no growth, and computed tomographic (CT) imaging of the patient's head was normal. A rapid slide test for mononucleosis was negative. Serologic tests for HIV, hepatitis B virus and hepatitis C virus were nonreactive. A test for Epstein-Barr virus immunoglobulin G (IgG) showed reactivity, but the mononucleosis slide test was negative, suggesting a previous infection.

The patient's presentation was atypical of Lyme disease, but suggested other tick-borne infections were possible. Serologic tests for Lyme disease (*Borrelia burgdorferi*), *Anaplasma phagocytophilum*, Rocky Mountain Spotted Fever (*Rickettsia rickettsii*) and murine typhus were performed, and a peripheral blood film was obtained to test for *Babesia microti*.

Because the patient had been bitten by a tick, he was given doxycycline (100 mg orally, twice daily). Within three days of admission, most of the symptoms had resolved, and the

KEY POINTS

- Human granulocytic anaplasmosis should be considered in patients with a history of tick bite who present with fever, headache, elevated transaminases, thrombocytopenia and leukopenia.
- Diagnosis involves detecting a fourfold increase in immunoglobulin G-specific antibodies on immunofluorescence antibody assay.
- Prevalence of this disease is likely to increase as *Anaplasma phagocytophilum* establishes itself in blacklegged tick populations in Canada.
- Public health officials could consider making human granulocytic anaplasmosis a reportable disease to better quantify its prevalence and incidence.

patient's platelet count had risen to $93\,000 \times 10^6$ cells/L. He was discharged home to complete a two-week course of antibiotics with follow-up at an internal medicine clinic. Before follow-up, the acute-phase serologic testing returned a negative result for Lyme disease, and blood smears did not show babesiosis. However, IgG antibodies to *A. phagocytophilum*, murine typhus and *R. rickettsii* all showed a titer of 1:64.

The *A. phagocytophilum* serologic test involved an indirect immunofluorescence assay for IgG and was done at the National Microbiology Laboratory in Winnipeg. Given the clinical and laboratory findings, and in consultation with Public Health Ontario, we felt that our patient likely had human granulocytic anaplasmosis, and the positive tests for murine typhus and Rocky Mountain Spotted Fever were false-positives caused by cross-reactivity between the tests. Alternatively, the patient may have been exposed to these organisms in the past, but was not acutely infected.

At the follow-up visit, the patient was well; his only symptom was minor fatigue, which was resolving. His platelet count was $153\,000 \times 10^6$ cells/L. Convalescent serologic testing showed no change in the IgG titres for *R. rickettsii* and murine typhus. However, the IgG titre for *A. phagocytophilum* had increased fourfold to 1:256, consistent with a diagnosis of human granulocytic anaplasmosis.

Discussion

Here, we document a case of domestically acquired human granulocytic anaplasmosis in Ontario. This disease is a tick-borne infection of neutrophils caused by *A. phagocytophilum*. The bacterium is

most commonly transmitted by bites from the blacklegged tick, *Ixodes scapularis*. The first cases of human granulocytic anaplasmosis were reported in Minnesota and Wisconsin in 1994. From 2008 to 2012, the mean reported annual incidence in the United States was 6.3 cases per million.¹ The first case of human granulocytic anaplas-

Box 1: Results of laboratory investigations on presentation and at follow-up, with normal ranges for reference, from a 79-year-old man with human granulocytic anaplasmosis

Variable	Reference range adult*	On presentation	At follow-up visit
White blood cells, $\times 10^6$ cells/L	4000–10 500	2400	4800
Neutrophils, $\times 10^6$ cells/L	2000–7500	1830	3130
Lymphocytes, $\times 10^6$ cells/L	1300–4000	260	1280
Platelets, $\times 10^6$ cells/L	150 000–400 000	32 000	153 000
Hemoglobin, g/L	138–170	124	138
Sodium, mmol/L	133–145	138	
Potassium, mmol/L	3.7–5.3	4.3	
Chloride, mmol/L	97–110	101	
Carbon dioxide, mmol/L	19–27	30	
Creatinine, μ mol/L	0–110	83	
Estimated glomerular filtration rate, mL/min	60–150	77	
Total bilirubin, μ mol/L	0–17	20	
Lactate dehydrogenase, U/L	120–315	368	
C-reactive protein, mg/L	0–1	21.5	
Erythrocyte sedimentation rate, mm/hr	< 20	7	
Aspart aminotransferase, U/L	10–46	47	
Alanine aminotransferase, mg/L	8–45	32	
Alkaline phosphatase, U/L	64–133	48	

*Reference values are affected by many variables, including patient population and the laboratory methods used. The ranges provided here are those used at the Kingston General Hospital for adults.

Box 2: Clinical presentation, testing and treatment for human granulocytic anaplasmosis, Lyme disease and babesiosis⁶

Variable	Human granulocytic anaplasmosis	Lyme disease	Babesiosis
Clinical presentation	Flu-like symptoms, headache, gastrointestinal symptoms	Localized: flu-like symptoms, lymphadenopathy Disseminated: rheumatologic, cardiac, neurologic complications	Flu-like symptoms, anorexia, nausea, hepatosplenomegaly, psychiatric symptoms
Rash	Uncommon	Erythema migrans at site of tick bite	Uncommon
Laboratory	Thrombocytopenia, leukopenia, mild anemia, moderate transaminitis	Normal hematologic panel, mild transaminitis	Thrombocytopenia, hemolytic anemia, acute kidney injury, mild transaminitis
Treatment*	Doxycycline, 100 mg orally, twice per day		Atovaquone, 750 mg orally, twice per day, or azithromycin, 250–1000 mg orally, daily
Duration of treatment, d	10–14	14–21	7–10

*Treatment of disseminated Lyme involves parenteral therapy.

mosis that originated in Canada was reported in 2009.² Since then, further cases have been documented in Manitoba, the only province for which it is a reportable disease. Since cases began to be tracked in January 2015, 21 have been reported, 17 of which were in 2016. A US case series of 42 cases of human granulocytic anaplasmosis found a mortality of 4.9%.³

A recent Canadian report postulated that the risk of tick-borne infections will continue to rise as populations of *I. scapularis* spread north at an estimated rate of 33–55 km per year.⁴ Many areas of Canada have become endemic for *I. scapularis* in recent years, including southeastern Ontario and the Thousand Islands region.⁵ Prevalence of *A. phagocytophilum* in ticks is increasing; in 2009 and 2010, ticks in the Thousand Islands region collected by drag sampling had a prevalence of infection with *A. phagocytophilum* of 3% ($n = 465$) and 3.2% ($n = 867$).⁵ When patients present with nonspecific symptoms in tick-endemic areas, serologic testing for Lyme disease (*B. burgdorferi*) is often done. However, *I. scapularis* is known to be a carrier of other pathogens, including *A. phagocytophilum* and *Babesia microti* (which causes babesiosis).

Clinical presentation

The initial clinical presentations of human granulocytic anaplasmosis, Lyme and babesiosis are often nonspecific (Box 2).⁶ Human granulocytic anaplasmosis typically presents one to two weeks after exposure, with fever, chills, myalgias, malaise, severe headache and gastrointestinal symptoms. Rash is uncommon, whereas it is often reported in Lyme disease.

Laboratory testing can help distinguish these infections. Patients with human granulocytic anaplasmosis typically have thrombocytopenia, and about half will have leukopenia.⁷ In addition, a mild-to-moderate increase in hepatic transaminases is common.⁶

Patients with Lyme disease generally have normal white blood cell and platelet counts, and may have a mild increase in hepatic transaminases. Babesiosis presents with thrombocytopenia and, in most cases, the presence of parasites on a peripheral blood film, often with pathognomonic “Maltese cross” formations. Hemolytic anemia may be present in addition to increased creatinine and urea, and mildly elevated hepatic transaminases.

Diagnosis

Human granulocytic anaplasmosis can be diagnosed by two methods. The first is detection of *A. phagocytophilum* DNA by polymerase chain reaction. This method is most sensitive within the first week of illness, and sensitivity typically decreases after antibiotics have been started. The second method is to show a fourfold increase in IgG-specific antibody by immunofluorescence antibody assay in serial samples. The first sample is typically sent within the first week of symptom onset, and the second should be sent two to four weeks later.⁶ Cross-reactivity between *Anaplasma* and *Rickettsia* is rare; we were unable to find previous reports in the literature.

Treatment

Human granulocytic anaplasmosis and Lyme disease are both effectively treated with doxycycline (100 mg orally, twice per day). Most patients given doxycycline for human granulocytic anaplasmosis will show rapid recovery and cure, but a delayed diagnosis

in older adults or immunocompromised patients can lead to adverse outcomes. In one study, 1 in 7 patients who did not receive antibiotics died.³ No clinical trials have been done to guide the duration of treatment, but a current guideline suggests 10–14 days to provide appropriate therapy for possible coinfection with *B. burgdorferi*.⁶ Lyme disease is typically treated for 14–21 days.

Public health implications

Our patient’s case confirms the establishment of *Anaplasma phagocytophilum* infection among resident blacklegged ticks and resident host populations in Ontario. Discovery of human illness from *A. phagocytophilum* beyond its previously described range provides evidence of the risk of emerging vector-borne diseases in the changing environment. Evidence from research on Lyme disease has catalogued the expanding range and establishment of *B. burgdorferi*-infected blacklegged ticks in Canada and the contributory role of climate change.⁸

Enhanced surveillance of emerging pathogens in previously unknown areas is needed. Through better surveillance, the evolving infection can be characterized and preventive measures developed. In the US, anaplasmosis is a reportable disease, which contributes to the understanding of its epidemiology, as well as to the detection of its emergence in unexpected areas and the identification of associated human health risks.⁹ This need for enhanced surveillance is highlighted in a Canadian review on emerging vector-borne diseases.¹⁰

Conclusion

Tick-borne infections are becoming more prevalent as ticks capable of carrying human pathogens such as *A. phagocytophilum* migrate further north. Consideration of tick-borne illnesses other than Lyme disease is needed when encountering patients with atypical clinical findings in tick-endemic areas. Testing for infections such as human granulocytic anaplasmosis should be considered when patients with a history of a tick bite present with fever, low white blood cell and platelet counts, and elevated hepatic transaminases. Provincial public health agencies could consider making human granulocytic anaplasmosis a reportable disease, which would enhance surveillance and subsequent knowledge of this emerging infectious pathogen.

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The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.

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Affiliations: Division of General Internal Medicine, Department of Medicine (Edginton, Srivastava); Public Health and Preventive Medicine Residency, Department of Family Medicine (Guan), Queen's University; Kingston, Frontenac, and Lennox & Addington Public Health (Guan); Division of Infectious Diseases,

Department of Medicine (Evans), Queen's University; Kingston Health Sciences Center (Edginton, Evans, Srivastava), Kingston, Ont.

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Correspondence to: Siddhartha Srivastava, srivastava.s@queensu.ca