

Borreliosis And Human Granulocytic Anaplasmosis Coinfection With Positive Rheumatoid Factor And Monospot Test: Case-Report

M Sami Walid, M Ajjan, N Patel

Citation

M Sami Walid, M Ajjan, N Patel. *Borreliosis And Human Granulocytic Anaplasmosis Coinfection With Positive Rheumatoid Factor And Monospot Test: Case-Report*. The Internet Journal of Infectious Diseases. 2006 Volume 6 Number 1.

Abstract

We are reporting a case of co-infection with *B.burgdorferi* and *A.phagocytophila* with unusual clinical and lab results.

A 36-year-old Caucasian man from Warner Robins, GA, an engineer, presented with a two-week history of febrile illness up to 103 F, severe headaches, fear of light, body aches, irritability, weakness and night sweats. This started two weeks after a 5-days trip to Panama City, Florida, where he had to work outdoors. Physical exam yielded no specific signs. Ultrasound showed hepatomegaly. Laboratory studies revealed elevated liver enzymes, *B.burgdorferi* IgM 3.7 index, *A.phagocytophila* IgM $\geq 1:1280$, rheumatoid factor, atypical lymphocytes and positive monospot test.

Patients who have been diagnosed with one tick-borne infection are at an increased risk and should be tested for other related infections. Rheumatoid factor and monospot test may be falsely positive in such cases.

INTRODUCTION

Anaplasmosis (ehrlichiosis) is the general name used to describe noncontagious infectious diseases of animals and humans transmitted by ticks caused by the organisms in the family Ehrlichiaaceae. Worldwide, there are currently four ehrlichial species that are known to cause disease in humans, three species of Ehrlichia in the United States and Europe (*Ehrlichia chaffeensis*, *E. ewingii*, and *E. phagocytophila*) and one in Japan (*Ehrlichia sennetsu*).

The family Anaplasmataceae (Ehrlichiaaceae) consist of gram-negative minute cocci that are obligate intracellular parasites classified in the order Rickettsiales. Recent studies on 16S-rRNA sequence analysis and energy metabolism showed that the family Ehrlichiaaceae is closely related to the family Rickettsiaceae. There is, however, no antigenic cross-reactivity between these genera. In contrast to the family Rickettsiaceae, members of the family Ehrlichiaaceae reside primarily in the cytoplasmic vacuoles of monocytes or granulocytes and cause hematologic abnormalities, lymphadenopathy, and other pathologic changes in the host.

The identification of *Anaplasma* (*Ehrlichia*) species is difficult because conventional bacteriological methods for cultivation and characterization cannot be used. Morphological and serological methods are also unreliable

to differentiate between them due to morphological similarities and antigen cross-reactivity between species [1].

Recently, Dumler et al. [2] unified *Ehrlichia phagocytophila*, *Ehrlichia equi*, and the human granulocytic ehrlichiosis (HGE) agent into the new species combination *Anaplasma phagocytophila*. *A. phagocytophila* is the bacterium that causes HGE, now called human granulocytic anaplasmosis (HGA). It infects the neutrophils of host organisms and multiples within the cytoplasm of the host cell. Like *Rickettsia*, and in contrast to *Coxiella*, it does not form a vacuole within the cytoplasm.

Cases of coinfection with tick-born microorganisms are being increasingly reported in the last decade [3,4], perhaps explaining the variable manifestations and clinical responses noted in some patients with tick-transmitted diseases. In such clinical settings, laboratory testing for coinfection is indicated to ensure that appropriate antimicrobial treatment is given.

We are reporting a case of Lyme Disease-human granulocytic anaplasmosis combination with unusual lab results.

CASE

A 36-year-old Caucasian man from Warner Robins, GA, an

engineer, presented with a two-week history of febrile illness up to 103 F, severe headaches, fear of light, body aches, irritability, weakness and night sweats. This started two weeks after a 5-days trip to Panama City, Florida, where he had to work outdoors and recollected being bitten by some insects. No other family members got ill.

The patient, non-smoker and a social drinker, had no significant past medical or surgical history. Family history was significant for multiple myeloma (mother) and aneurysm (father).

On physical examination, the patient was in no acute distress, intoxication or sepsis. On palpation, there was no marked lymphadenopathy or organomegaly.

Laboratory studies revealed white blood count with normal limits (from 7.7 to 9.8×10^9 per liter over six days since admission) developing anemia (hemoglobin fell from 14.3 g/dl to 12.9 g/dl), decreasing neutrophils (from 46.2% to 24.0%), increasing lymphocytes (from 41.0% to 60.4%) and monocytes (from 10.3% to 12.8%), atypical lymphocytes (from 18% to 10%), normal platelets count, elevated sedimentation rate (from 40 mm/hr to 30 mm/hr) and C-reactive protein (from 2.75 mg/dl to 1.59 mg/dl), elevated liver enzymes (GOT/AST from 61 iu/l to 139 iu/l, GPT/ALT from 95 iu/l to 177 iu/l, alkaline phosphatase from 107 to 173 iu/l), worsening hypoalbuminemia (from 3.3 g/dl to 2.9 g/dl), hyponatremia (131 mmol/l, corrected later), hypokalemia (3 mmol/l, corrected later), low osmolality (265 mos/kg), hypocalcemia (8.3 mg/dl), decreased BUN (4 mg/dl) and BUN/creatinine ratio (3.6), normal creatinine, normal glomerular filtration rate, hyperglycemia (161 mg/dl), elevated glucose point-of-care testing, positive rheumatoid factor, hepatitis A, B and C serum tests nonreactive or negative, *Borrelia burgdorferi* IgM 3.7 index (high), IgG negative, rickettsia IgM and IgG negative, cerebrospinal fluid negative for streptococcus B, streptococcus pneumoniae, haemophilus influenza B, neisseria meningitides, Escherichia Coli (BACTSFS), encapsulated yeast-forms (India ink) and herpes simplex virus (enzyme linked virus inducible system ELVIS), no malaria was seen on blood smear, blood and CSF cultures showed no growth after five days, no acid-fast bacilli, CSF VDRL negative, mononucleosis spot test positive, Anaplasma phagocytophila IgM ? $1:1280$ (high), IgG negative, Ehrlichia chaffeensis IgM and IgG negative. Ultrasound showed hepatomegaly $16.1 \times 16.7 \times 10.0$ cm. Brain MRI with and without contrast were negative. The patient

responded to treatment with Doxycycline 100 mg po bid and Demerol.

DISCUSSION

Human Monocytic Ehrlichiosis (HME) was first described in 1987 and occurs primarily in the southeastern and south central regions of the country [5, 6]. Human granulocytic anaplasmosis (HGA), is an emerging tick-borne infection of humans in the United States, was first described in 1994 in Minnesota then has been found in the upper midwestern states, northeastern states, and northern California [7]. During 1986 to 1997, health departments and other diagnostic laboratories reported over 1200 cases of human ehrlichiosis to CDC. Approximately two-thirds of them were cases of HME [8].

E. chaffeensis and *A. phagocytophilia* cause HME and HGA, respectively. HME has been linked to the bites of *Amblyomma Americanum* (Lone Star Tick) [9, 10], and HGA has been closely linked to the bites of *Ixodes Scapularis* (blacklegged tick) [7] and *Ixodes Pacificus* (western blacklegged tick). The *Dermacentor Variabilis* (dog tick) has also been suggested in the transmission of both [11]. *Ixodes ricinus* is the primary vector in Europe.

The same ticks that transmit these diseases are also responsible for the transmission of *Borrelia burgdorferi* and *Babesia microti*, the agents of Lyme disease and babesiosis, respectively. Since co-infections have been documented, patients who have been diagnosed with one tick-associated illness are at an increased risk and should also be tested for another tick-borne infection [12,13]. Seroconversion usually occurs between two and four weeks after infection. Persons who have been positive for borreliosis also may carry antibodies to *B. microti*, *E. chaffeensis*, or *A. phagocytophilia*, as in our case.

The prevalence of tick bites is particularly high during the warmer months between April and September, the season for adult *Amblyomma americanum* and nymphal *Ixodes scapularis* ticks and a period when persons are more active outdoors, as in our case.

The symptoms of ehrlichiosis may resemble symptoms of various other infectious and non-infectious diseases. These clinical features generally include fever, headache, fatigue, and muscle aches. Other signs and symptoms may include nausea, vomiting, diarrhea, cough, joint pains, confusion, and occasionally rash. The lack of a rash distinguishes them

from Rocky Mountain spotted fever and Lyme disease; lack of upper respiratory and gastrointestinal symptoms distinguishes them from influenza. Symptoms typically appear after an incubation period of 5-10 days following the tick bite. Laboratory findings indicative of ehrlichiosis include low white blood cell count (WBC), low platelet count, and elevated liver enzymes.

Case definitions used by state health departments for surveillance for these diseases were first adopted by the Council of State and Territorial Epidemiologists (CSTE) in 1996 and were revised in 2000 to incorporate the use of newer laboratory methods for case confirmation [14]. A confirmed case of HA is a clinically compatible illness with either:

- a four-fold change in antibody titer by indirect immunofluorescence assay (IFA) in acute and convalescent phase serum samples,
- PCR amplification of HA DNA from a clinical sample, or
- a smear that is positive for morulae in the granulocytes and a single IFA titer of >1:64.

A probable case is defined as a clinically compatible illness with a single IFA titer of >1:64 or the presence of morulae within infected granulocytes.

In our case, there was no decreased WBC or platelet count but A. phagocytophila IgM ? 1:1280, B. burgdorferi IgM 3.7 index decreased neutrophils, anemia and elevated liver enzymes. It was a confirmed case of HA in combination with Lyme disease.

The clinical picture, including symptoms (fever, body aches and hepatomegaly) and lab results (elevated lymphocytes and monocytes, elevated liver enzymes, elevated atypical white blood cells and positive monospot test) also speaks for the possibility of a superimposed infectious mononucleosis later at the time of admission. However, infectious mononucleosis is a disease of adolescents and young adults, with a peak incidence at ages 15-17. By the time most people reach adulthood, antibodies against EBV can be detected in their blood. In the U.S., up to 95% of adults aged 35-40 have antibodies directed against EBV [15]. Also, positive monospot tests are sometimes encountered in patients with liver complications [16]. And in any case, infectious mononucleosis is a self-limited disease with no

specific treatment.

Rheumatoid factor was positive in our case. This is not strange since it has been reported to temporarily correlate with Lyme disease activity [17,18].

CONCLUSION

Co-infection with tick-transmitted diseases is common. Patients who have been diagnosed with one tick-associated illness should have more extensive laboratory testing if the clinical picture is untypical or multiple tick-associated illnesses are suspected. Rheumatoid factor, atypical lymphocytes and monospot test may be falsely positive in such cases.

CORRESPONDENCE TO

Mohammad Sami Walid, MD, PhD 840 Pine Street, Suite 840 Macon, GA 31201 Phone: 478-743-7092 ex. 266 Fax: 478-738-3834 mswalid@yahoo.com

References

1. Snorre Stuen, Ingrid Van De Pol, Karin Bergström, and Leo M. Schouls, Identification of *Anaplasma phagocytophila* (Formerly *Ehrlichia phagocytophila*) Variants in Blood from Sheep in Norway // *Journal of Clinical Microbiology*, September 2002, p. 3192-3197, Vol. 40, No. 9.
2. Dumler, J. S., A. F. Barbet, C. P. J. Bekker, G. A. Dasch, G. H. Palmer, S. C. Ray, Y. Rikihisa, and F. R. Rurangirwa, Reorganization of genera in the families Rickettsiaceae and Anaplasmataceae in the order Rickettsiales; unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia*, and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and "HGE agent" as subjective synonyms of *Ehrlichia phagocytophila*. *Int. J. Syst. Evol. Microbiol.*, 2001, 51:2145-2165.
3. Paul D. Mitchell,* Kurt D. Reed, and Jeanie M. Hofkes "Immunoserologic Evidence of Coinfection with *Borrelia burgdorferi*, *Babesia microti*, and Human Granulocytic *Ehrlichia* Species in Residents of Wisconsin and Minnesota" // *Journal Of Clinical Microbiology*, Mar. 1996, p. 724-727.
4. Micha Loebermann, Volker Fingerle, Matthias Lademann, Carlos Fritzsche, Emil C. Reisinger "Borrelia burgdorferi and *Anaplasma phagocytophilum* Coinfection" // *Emerging Infectious Diseases*, Feb, 2006.
5. Anderson, B. E., J. E. Dawson, D. C. Jones, and K. H. Wilson. 1991. *Ehrlichia chaffeensis*, a new species associated with human ehrlichiosis. *J. Clin. Microbiol.* 29:2838-2842.
6. Dawson, J. E., B. E. Anderson, D. B. Fishbein, J. L. Sanchez, C. S. Goldsmith, K. H. Wilson, and C. W. Duntley. 1991. Isolation and characterization of an *Ehrlichia* sp. from a patient diagnosed with human ehrlichiosis. *J. Clin. Microbiol.* 29:2741-2745.
7. Bakken, J. S., J. S. Dumler, S.-M. Chen, M. R. Eckman, L. L. Van Etta, and D. H. Walker. 1994. Human granulocytic ehrlichiosis in the upper Midwest United States: a new species emerging? *JAMA* 272:212-218.
8. Centers for Disease Control and Prevention "Human Ehrlichiosis in the United States: Epidemiology" April 5,

2000.

9. Anderson, B. E., K. G. Sims, J. G. Olson, J. E. Childs, J. E. Piesman, C. M. Happ, G. O. Maupin, and B. J. B. Johnson. 1993. *Amblyomma americanum*: a potential vector of human ehrlichiosis. *Am. J. Trop. Med. Hyg.* 49:239-244.

10. Ewing, S. A., J. E. Dawson, A. A. Kocan, R. W. Barker, C. K. Warner, R. J. Panciera, J. C. Fox, K. M. Kocan, and E. F. Blouin. 1995. Experimental transmission of *Ehrlichia chaffeensis* (Rickettsiales: Ehrlichieae) among white-tailed deer by *Amblyomma americanum* (Acari: Ixodidae). *J. Med. Entomol.* 32:368-374.

11. Chen, S.-M., J. S. Dumler, J. S. Bakken, and D. H. Walker. 1994. Identification of a granulocytotropic *Ehrlichia* species as the etiologic agent of human disease. *J. Clin. Microbiol.* 32:589-595.

12. Magnarelli L A, IJdo J W, Anderson J F, Padula S J, Flavell R A, Fikrig E. Human exposure to a granulocytic ehrlichia and other tick-borne agents in Connecticut. *J Clin Microbiol.* 1998; 36:2823-2827.

13. Magnarelli L A, Dumler J S, Anderson J F, Johnson R C,

Fikrig E. Coexistence of antibodies to tick-borne pathogens of babesiosis, ehrlichiosis, and Lyme borreliosis in human sera. *J Clin Microbiol.* 1995;33:3054-3057.

14. CDC, 2000. Ehrlichiosis (HGE, HME, Other or Unspecified): 2000 Case Definition. Atlanta, GA: Centers for Disease Control and Prevention: Division of Public Health Surveillance and Informatics.

15. National Center for Infectious Diseases: Epstein-Barr Virus and Infectious Mononucleosis, Centers for Disease Control and Prevention, 10/26/2006.

16. Kenneth Wener, M.D., Mononucleosis Spot test, MedlinePlus, US National Library of Medicine 6/9/2005.

17. Kujala GA, Steere AC, Davis JS. IgM rheumatoid factor in Lyme disease: Correlation with disease activity, total serum IgM, and IgM antibody to *B. burgdorferi*. *J Rheumatol.* 1987; 14:772-6.

18. Goebel KM, Krause A, Neurath F. Acquired transient autoimmune reactions in Lyme arthritides: Correlation between rheumatoid factor and disease activity. *Scand J Rheumatology Suppl.*1988; 75: 314-7.

Author Information

Mohammad Sami Walid, MD, PhD

Research Fellow, Medical Center of Central Georgia

Mohammed Ajjan, M.D.

Internal Medicine, Medical Center of Central Georgia

Nalini Patel, M.D.

Infectious Diseases, Medical Center of Central Georgia