



Case report

Ehrlichiosis mimicking acute leukemia

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ABSTRACT

Human monocytic ehrlichiosis is a tickborne disease with a spectrum of presentations ranging from asymptomatic, mild to fatal. Ehrlichiosis can transiently cause white blood cells abnormalities that mimic leukemia/lymphoma and cases have been, on rare occasions, initially mistaken for hematological malignancies. We report a case of *Ehrlichia chaffeensis* infection suspected to be acute promyelocytic leukemia at presentation, prompting therapy with all-trans-retinoic acid. Physicians should keep tickborne transmitted illnesses on the differential in patients presenting with pancytopenia, especially in endemic areas.

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Introduction

Human monocytic ehrlichiosis (HME) due to *Ehrlichia chaffeensis* (*E. chaffeensis*) is the most common severe tickborne illness in the United States with an overall fatality rate of 2–3% [1]. A typical presentation includes fever, headache, generalized weakness, pancytopenia, and elevated serum transaminases level [2]. HME also can cause transient white blood cells changes that could be mistaken for acute leukemia [3]. We report a case of HME suspected to be acute promyelocytic leukemia at presentation.

Case report

A 57-year-old female presented in September to a community hospital in Kansas with three days of intractable headache described as “the worst migraine” she had experienced. She also reported chills, nausea, and vomiting. Her past medical history is significant for breast cancer diagnosed five years prior, in remission after partial mastectomy, radiation and hormone therapy. She also has hypothyroidism on levothyroxine, and migraine headaches maintained on preventive topiramate and divalproex. At initial presentation, she was febrile but hemodynamically stable. Initial labs showed: white blood cells (WBC) 1.73k/uL, hemoglobin 14.3 g/dL, platelets 80k/uL, AST 45 U/L, total bilirubin 0.4 mg/dL, creatinine 1.4 mg/dL, LDH 433 U/L, fibrinogen 133 mg/dL, and APTT 37.5 s. Blood and urine

cultures remained negative. Brain computed tomography (CT) and magnetic resonance imaging (MRI) were unremarkable besides ethmoid sinusitis. She was started on ceftriaxone and received one dose of intravenous amikacin. On hospital day 3, WBC further decreased to 0.58k/uL, and platelets decreased to 25 k/uL. A bone marrow biopsy was performed, and she was started on all-trans-retinoic acid (ATRA) for the concern of acute promyelocytic leukemia (APL). She received plasma and platelet transfusions and was transferred to our facility's intensive care unit with a concern of APL and disseminated intravascular coagulation (DIC).

The patient is a married anesthesiologist living in Kansas, without recent travels or known tick bites, but had been exposed to a friend with shingles. She visited an archeology dig in Arizona several months prior to presentation. She also reported performing endotracheal intubation on patients with various exposures at work. She lives on a small farm and is exposed to cattle and sheep. Upon transfer to our facility, she was febrile (temperature 38.7 C), tachycardic (pulse 128 beats per min) and blood pressure was 107/57 mmHg. She was tired but alert and interactive. Neck was supple, neural exam was non focal and cardiopulmonary exam was otherwise unremarkable. She was noted to have an erythroderma over the face and back, scattered macular rash on anterior chest and urticaria-like lesions on the abdomen thought to be from recent platelet transfusion. Labs upon transfer to our facility showed: WBC 0.9k/uL, hemoglobin 9.9 g/dL, platelets 37k/uL, AST 148 U/L, ALT 93 U/L, total bilirubin 0.4 mg/dL, alkaline phosphatase 79 U/L and APTT 26.6 s. D-dimer was elevated at 26,718 ng/mL and CT of the chest identified an acute pulmonary embolus. Serological tests were negative for: Rocky Mountain Spotted Fever, Tularemia, Bartonella, Q-fever, Tuberculosis, Histoplasma, Coccidioides, Hepatitis B and C, and HIV. Polymerase chain reaction (PCR) tests for Epstein-Barr virus (EBV),

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Table 1
Laboratory tests.

Variable (normal range)	Admission to hospital 1	Transfer to hospital 2	Day 11 (discharge)
Hemoglobin (12–16 g/dL)	14.3	9.9	9.8
WBC (4–11 k/uL)	1.73	0.9	6.9
ANC (1.5–6 k/uL)	1.54	0.77	2.5
ALC (1–4.8k/uL)	NA	0.1	4.1
Platelets (150–400 k/uL)	80	37	184
ALT (0–37 IU/L)	45	93	37
AST (0–37 IU/L)	NA	148	24

NA: not available, WBC: white blood count, ANC: absolute neutrophil count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, INR: international normalized ratio

Cytomegalovirus (CMV) and Primate Erythroparvovirus 1 (previously Parvovirus B19) were negative. Respiratory multiplex PCR panel (BioFire) was negative as well.

Peripheral blood smear showed teardrop cells, no schistocytes, markedly decreased platelets, smudge cells and vacuolization of neutrophils. Antimicrobials were changed to acyclovir, meropenem, linezolid, doxycycline, and micafungin empirically. Bone marrow aspirate showed hypocellularity (20%), decreased erythropoiesis and granulopoiesis with 2% blasts.

Flow cytometry was negative for leukemia, therefore ATRA was discontinued on hospital day 5. On hospital day 6, *Ehrlichia/Anaplasma* PCR panel on blood (Mayo Medical Lab) was positive for *E. chaffeensis* and negative for *Anaplasma*, *Ehrlichia ewingii/canis* and *Ehrlichia muris euclairensis*. *Ehrlichia chaffeensis* IgG was < 1:64 (IgM was not tested). The patient improved significantly on treatment with doxycycline 100 mg IV twice daily. Other antimicrobials were stopped in few days, and she was transferred to the medical floor on hospital day 10. She finished a 10-day course of doxycycline and was discharged on day 11 with normal WBC and platelets (Table 1). *Ehrlichia chaffeensis* IgG was repeated 4 weeks after discharge and was positive at 1:1024.

Discussion

Ehrlichia are Gram-negative, obligate intracellular bacteria first described to cause human disease in 1986 in a patient with fever, hypotension, confusion, acute renal failure, coagulopathy, and gastrointestinal hemorrhage [4]. The genus *Ehrlichia* contains five species associated with human disease to date, namely *E. chaffeensis*, *E. ewingii*, *E. muris*, *E. muris euclairensis* (previously *E. muris-like agent*), and *E. canis* [4–6]. Although *Anaplasma phagocytophilum* used to be classified under *Ehrlichia* genus, it was reassigned to the genus *Anaplasma* in 2001 [7]. *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum* target white blood cells, residing in the cytoplasm of macrophages and granulocytes respectively, and occasionally visible in a peripheral blood smear as morula (cytoplasmic vacuoles filled with bacteria) (Fig. 1).

Ehrlichia chaffeensis is considered an emerging zoonosis. HME is endemic in the southeastern and southcentral regions in the United States where the tick vector *Amblyomma americanum* (Lone star tick) (Figs. 2–3), is prevalent [8]. The incubation period ranges from 5 to 14 days after a tick bite. When symptomatic, fever is the most common presenting symptom followed by headache, malaise, and myalgia. Gastrointestinal symptoms include nausea, vomiting and diarrhea and are more common in children. About one third of patients develop a rash. Cough and shortness of breath, meningitis, and confusion can manifest as well. Severe cases reported include toxic shock-like picture with acute respiratory distress syndrome (ARDS),

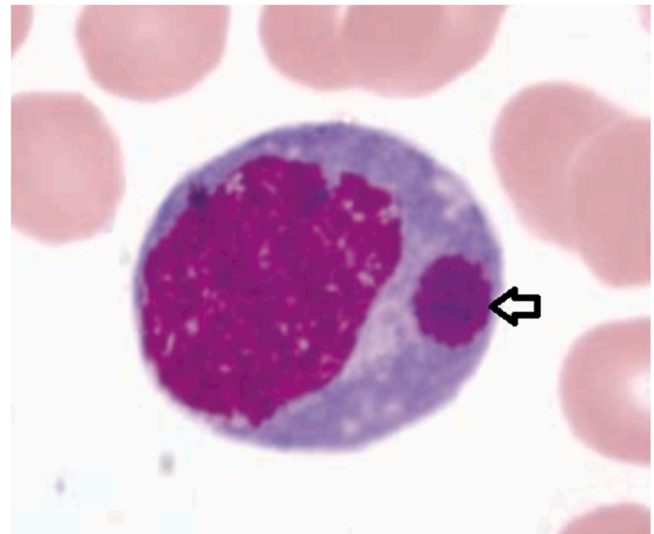


Fig. 1. Wright stain of peripheral blood smears showing an intramonocytic morula (arrow) associated with *Ehrlichia chaffeensis* infection. From CDC [6].

coagulopathy with DIC-like picture and hemorrhage, as well as hemophagocytic lymphohistiocytosis (HLH) [6].

The most common laboratory findings are leukopenia, thrombocytopenia, and elevated liver enzymes [2]. Elevated serum creatinine can also be seen. Whole blood PCR is helpful in diagnosis early during infection. The sensitivity and specificity of assays is variable. The reported sensitivity of whole blood PCR in patients with HME is 52–87% [9]. Indirect immunofluorescence antibody assays usually take 7–10 days from start of symptoms to turn positive, with reported cross-reactivity between *E. chaffeensis* and *A. phagocytophilum*. IgG antibodies are more specific than IgM and a four-fold increase in IgG titers is diagnostic of acute infection. Conventional blood smear microscopy is often not sensitive or specific enough to accurately differentiate between species. Presumptive diagnosis of HME and the decision to treat empirically should be individualized based on clinical presentation, clues from the medical history such as outdoor activities or tick bite, and laboratory abnormalities as well as geography and season. Differential diagnosis of HME includes human granulocytic anaplasmosis, Rocky Mountain spotted fever, viral illnesses (mononucleosis, Colorado tick fever, West Nile virus, early phase of hepatitis A), thrombotic thrombocytopenic purpura, and hematologic malignancies.

HME can transiently cause immune dysregulation and lymphocyte abnormalities resulting in false positive analysis on flow cytometry and gene rearrangement, leading to false diagnosis of leukemia [3,10]. In our case, the patient was transferred to our facility with a presumptive diagnosis of acute promyelocytic leukemia to be seen by hematology and started on therapy with ATRA. Since our region is endemic for ehrlichiosis, the team appropriately ordered tickborne diseases serologies and PCR panel and a repeat bone marrow exam showed hypocellular marrow without evidence of leukemia. The patient improved with doxycycline therapy. Another case of HME mimicking leukemia was reported in 2005 of a 20-year-old, Amish female presenting with fever, chills, hypotension, and malaise. A bone marrow biopsy revealed large sized lymphocytes with irregular nuclear membranes. Flow cytometry of the bone marrow cells revealed 8–10% of phenotypically abnormal T-cells suggestive for T-cell lymphoma/leukemia [3]. The patient improved with IV doxycycline and a repeat bone marrow aspiration one week later was normal (morphology and flow cytometry). It is suggested to repeat examination of abnormal initial bone marrow tests for

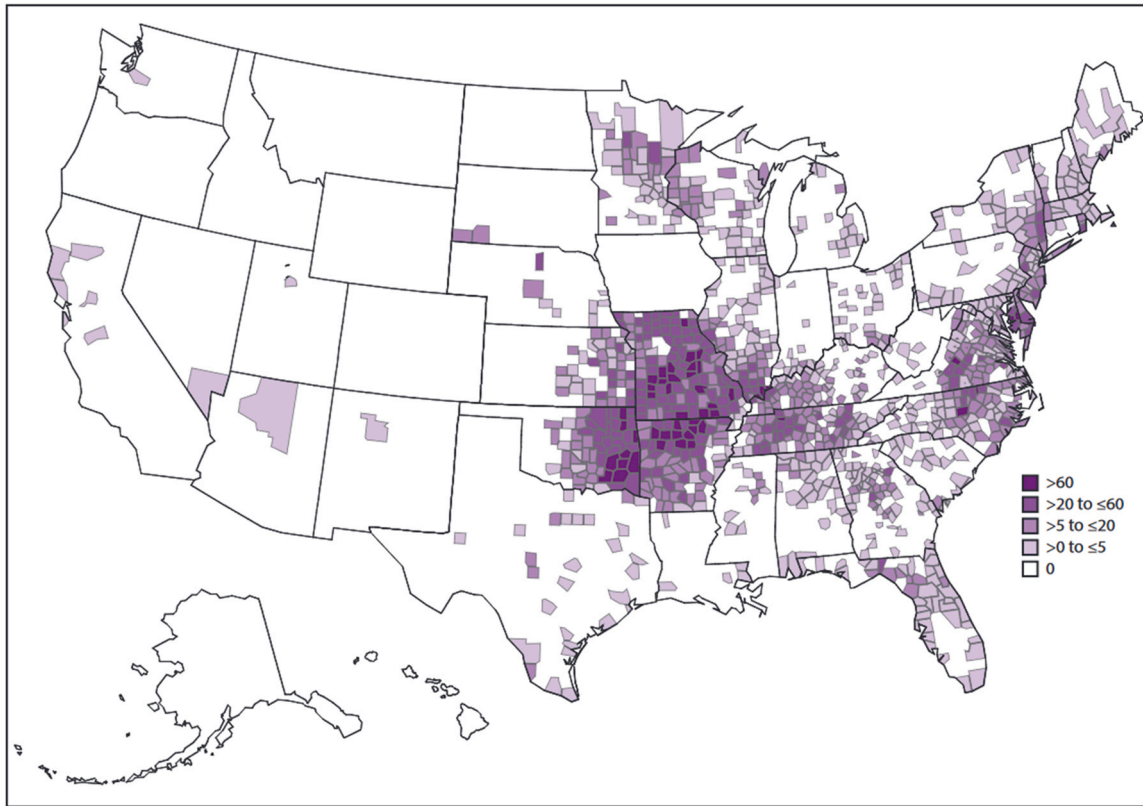


Fig. 2. Reported incidence rate of *Ehrlichia chaffeensis* infection, by county – United States, 2000–2013. From CDC [6].



Photo/CDC

Fig. 3. Adult female *Amblyomma americanum* (Lone star tick). From CDC [6].

confirmation before considering active treatment for leukemia/lymphoma in patients with confirmed ehrlichiosis.

In summary, HME presents with pancytopenia and could mimic hematological malignancy. Physicians should keep this infection on the differential of leukopenia in endemic regions and during the tick

season. A high index of suspicion should prompt empirical Ehrlichia therapy as response is usually dramatic.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

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