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Ehrlichiosis in Southern Ohio: Two case reports and a review of the literature

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1. Background

"Ehrlichiosis" is a generic name for infections caused by small gram-negative obligate intracellular bacteria within the genus Ehrlichia (1, 2). There are at least three species of bacteria within this genus in the United States responsible for ehrlichiosis. Of these, *Ehrlichia chaffeensis* is the most common agent to infect humans (3). Due to this organism's predilection for infecting monocytes the clinical disease-state caused by *E. chaffeensis* has also been identified as either "Human Monocytic Ehrlichiosis" or "Human Monocytotropic Ehrlichiosis" (HME) (2, 4).

The primary vector for *E. chaffeensis* in the US is the lone star tick, *Amblyomma americanum* (5). *A. americanum* feeds on many host species, but the primary reservoir of *E. chaffeensis* is the white-tailed deer (*Odocoileus virginianus*) (3). Similar to other tick-borne diseases, the incidence of HME directly correlates with the local prevalence of arthropod vectors and vertebrate reservoirs (2). HME typically occurs across the South Central, Southeastern, and Mid-Atlantic states, corresponding to regions where white-tailed deer and lone star ticks are prevalent (5). Cases of HME have been reported in all states where *A. americanum* is present (6).

While Ohio was once at the periphery of *A. americanum's* range, the increase in Ohio's white-tailed deer population has led to the tick's migration northward (7). Southern Ohio in particular, has been identified as having a high preponderance of *E. chaffeensis* infected ticks (8). Despite this, few prior cases of HME have been reported from Southern Ohio counties.

HME typically presents as an acute febrile illness. The clinical manifestations of HME are often vague and non-specific, typically consisting of flu-like symptoms (2). However, patients with HME may exhibit moderate to severe illness, with up to 50-70% requiring hospitalization (5). Up to 17% of patients develop life-threatening complications; severe disease is more common in immunocompromised patients (2). Death can occur as early as the second week of illness and has been reported in approximately 1-3% of cases (2,5). HME is associated with hemophagocytic lymphohistiocytosis (HLH), a rare, life-threatening immunological disorder, which further confounds the diagnosis (9).

Given the non-specific nature of HME, history and laboratory abnormalities provide important diagnostic clues. Patients in regions where these infections are known to exist, who present during tick season with fever, leukopenia and/or thrombocytopenia, and increased serum transaminase levels, should have ehrlichiosis included in the differential diagnosis (1).

2. Epidemiology

The first confirmed report of ehrlichiosis in Ohio was in 2006 (8). However, the first human case of ehrlichiosis in the US was described in 1986 (2). The agent responsible, *E. chaffeensis*, was isolated and identified as a novel pathogen in 1991 (10). Ehrlichiosis became a nationally notifiable disease in 1999 (5). The occurrence and incidence rates of HME have steadily increased since it became a reportable disease. Per the Centers for Disease Control and Prevention (CDC), in the year 2000 only 200 cases were reported nationally. In 2019 the number of reported cases increased to 2093 (11). In Ohio the incidence rate (IR) increased from 1.4 cases per million in 2015, to 1.97 cases per million in 2019 (11).

In contrast, per the US Nationally Notifiable Diseases Surveillance System (NNDSS) a total of 4,613 cases of *E. chaffeensis* were reported between 2008 and 2012 (5). The incidence rate (IR) was 3.2 cases per million persons per year (5). In the same reporting period 40 cases were identified in

Photo 1. Photo credit: *Amblyomma americanum*, the Lone Star tick. (From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 8683. Photo credit: James Gathany)

Ohio, representing a reported IR of 0.7 per million persons per year (5). Subsequently, from 2012 through 2016 there were 6,786 cases reported to NNDSS, and the national IR was 4.46 cases per million per year (11). Prospective studies in endemic areas have suggested the true incidence of HME is much higher than what has been established due to under-diagnosis and under-reporting and may be between 100-200 cases per million (2). Despite the increasing numbers of HME cases, public awareness of ehrlichiosis is low. For example, a survey of U.S. patients revealed that only 1.4% were familiar with ehrlichiosis, compared with more than 50% for Lyme disease (12).

Most reported cases of HME are in adult patients (13). The frequency of cases is highest among males, people older than 50 years, and Caucasians (2). Although cases of HME can occur during any month of the year, most cases occur during the summer months with a peak in cases typically occurring in June and July (6). This corresponds to periods of abundant tick populations and increased outdoor recreational pursuits. Approximately 75% of patients with HME recall having a tick bite (3).

3. Case Presentations

Patient A

A 50 year-old Caucasian female presented in the second week of May, 2016 at an outpatient health center in Pike County, Ohio. Her primary complaints were fever of 3 days duration accompanied by nausea, severe body aches, and headache. Two days prior to the onset of her symptoms she removed two ticks from her torso. She was uncertain how long the ticks had been attached prior to removal.

She admitted to diffuse joint warmth and aching, headache, sore throat, bilateral ear pain, pain with swallowing, lower abdominal aching, and cough forceful enough to cause her to vomit. She denied rash, neck pain, or neck stiffness. Her past medical history was negative for chronic medical problems.

Allergies to medications included sulfa, which caused rash. She was a nonsmoker. She used one to two servings of alcohol per day and denied the use of illicit drugs. She was using acetaminophen and ibuprofen as needed for fever and body aches.

On initial exam she had a temperature of 38.5C (101.3F), blood pressure of 122/83 mm/Hg, pulse of 124 beats per minute, respiratory rate of 15 breaths per minute, and an oxygen saturation on room air of 94%. She appeared ill and flushed but did not appear toxic. Her neck was supple without nuchal tenderness or rigidity. She had moderate pharyngeal erythema without exudates. Lymphatic exam demonstrated bilateral anterior cervical tenderness without enlarged cervical lymph nodes. Dermatologic examination showed welts at the sites of her tick bites. No rash was visible otherwise. She had suprapubic tenderness but no abdominal findings otherwise. She had no organomegaly. Her joints were diffusely tender but were without redness, warmth, or swelling. The remainder of her exam was unremarkable.

A rapid strep assay was negative. Urinalysis via visual inspection of a reagent dipstick showed a specific gravity > 1.030, with a pH of 5.5, trace bilirubin, trace blood, and the urine protein was > 300 mg/dL. Leukocytes and nitrites were both negative. The patient was not on her menses.

Additional lab tests obtained at the time of her office visit were as follows:

Complete Blood Count	Normal
White blood cell count: 3.2 x 10^3/uL	(3.8 – 10.8 x 10^3/uL)
Hemoglobin: 13.7 g/dL	(11.7 – 15.5 g/dL)
Hematocrit: 40.7%	(35.0 – 45.0%)
Platelet count: 93 x 10^3/uL	(140 – 400 x 10^3/uL)

Comprehensive metabolic profile	Normal
Glucose: 119 mg/dl	(65 – 99 mg/dL)
Blood Urea Nitrogen: 13 mg/dL	(7 – 25 mg/dL)
Serum creatinine: 0.86 mg/dL	(0.50 – 1.05 mg/dL)
Sodium: 138 mmol/L	(135 – 146 mmol/L)
Potassium: 3.7 mmol/L	(3.5 – 5.3 mmol/L)
Chloride: 108 mmol/L	(98 – 110 mmol/L)
Carbon Dioxide: 22 mmol/L	(19 – 30 mmol/L)
Calcium: 8.6 mmol/L	(8.6 – 10.4 mg/dL)
Protein: 6.6 g/dL	(6.1 – 8.1 g/dL)
Albumin: 3.9 g/dL	(3.9 – 5.1 g/dL)
Globulin 2.7 g/dL	(1.9 – 3.7 g/dL)
Bilirubin 0.8 mg/dL	(0.2 – 1.2 mg/dL)
Aspartate aminotransferase: 80 U/L	(10 – 35 U/L)
Alanine aminotransferase: 49 U/L	(6 – 29 U/L)
Alkaline phosphatase: 99 U/L	(33 – 130 U/L)

Hepatitis serologies

Hepatitis A IgM: nonreactive
Hepatitis B surface antigen: nonreactive
Hepatitis C antibody: nonreactive

Repeat CBC and hepatic transaminases obtained 2 weeks after her initial visit were normal. Convalescent *E. chaffeensis* antibody titers were as follows:

E. chaffeensis IgG: < 1:256
E. chaffeensis IgM: 1:160

Patient B

A 68 year-old Caucasian male presented in the second week of June, 2016 as an outpatient to a health center in Pike County, Ohio. His complaints included severe chills, extreme weakness, and vomiting of three days duration. He participated in an outdoor track meet 3 days prior to being seen. Subsequently, he began experiencing progressive anorexia, sweats, and chills with rigors. For several days prior to the track meet he was aware of diminished energy and exertional dyspnea. He had been hiking in the woods one week prior and sustained several tick bites. He removed the ticks as soon as he found them, however he was uncertain how long they had been attached prior to removal.

On review of systems he admitted to mild sore throat, loose stools, and joint stiffness. He denied skin rash, headache, or neck stiffness. His medical history was remarkable for coronary artery disease with stent placement, hypertension, and hyperlipidemia. Medications included atorvastatin calcium 10 mg daily, and enalapril maleate 5 mg daily. Allergies to medications were denied. The patient was a non-smoker and denied the use of alcohol or drugs.

Upon initial assessment he had a temperature of 37.9C (100.3F), pulse of 57 beats per minutes, blood pressure of 135/63 mm/Hg and a respiratory rate of 18 breaths per minute. Pulse oximetry on room air was equal to 97%.

The patient appeared ill but nontoxic. The remainder of his physical exam was entirely unremarkable.

Because of his history of coronary artery disease, an electrocardiogram was obtained; it demonstrated no signs of ischemia, and no conduction abnormalities.

Lab tests obtained the day of his encounter were as follows:

Complete Blood Count	Normal
White blood cell count: 6.1 x 10^3/uL	(3.8 – 10.8 x10^3/uL)
Hemoglobin: 14.1 g/dL	(11.7 – 15.5 g/dL)
Hematocrit: 41.6%	(35.0 – 45.0%)
Platelet count: 110 x 10^3/uL	(140 – 400 x 10^3/uL)

Comprehensive metabolic profile	Normal
Glucose: 113 mg/dl	(65 – 99 mg/dL)
Blood Urea Nitrogen: 19 mg/dL	(7 – 25 mg/dL)
Serum creatinine: 1.20 mg/dL	(0.50 – 1.05 mg/dL)
Sodium: 137 mmol/L	(135 – 146 mmol/L)
Potassium: 4.2 mmol/L	(3.5 – 5.3 mmol/L)
Chloride: 104 mmol/L	(98 – 110 mmol/L)
Carbon Dioxide: 23 mmol/L	(19 – 30 mmol/L)
Calcium: 8.7 mmol/L	(8.6 – 10.4 mg/dL)
Protein: 6.2 g/dL	(6.1 – 8.1 g/dL)
Albumin: 3.9 g/dL	(3.9 – 5.1 g/dL)
Globulin 3.2 g/dL	(1.9 – 3.7 g/dL)
Bilirubin: 1.5 mg/dL	(0.2 – 1.2 mg/dL)
AST: 94 U/L	(10 – 35 U/L)
ALT: 70 U/L	(6 – 29 U/L)
Alkaline phosphatase: 76 U/L	(33 – 130 U/L)

Upon recognition of lab abnormalities including thrombocytopenia and elevated transaminases, antibody titers were obtained for *E. chaffeensis*. The results were as follows:

E. chaffeensis IgG < 1:64

E. chaffeensis IgM 1:20

Convalescent *E. chaffeensis* antibody titers were obtained 3 weeks after his initial visit. Those results are as follows.

E. chaffeensis IgG 1:512

E. chaffeensis IgM < 1:20

4. Discussion

4.1 Clinical Presentation

The typical symptoms of patients with HME are neither sensitive nor specific for the disease. Symptoms typically begin 5 – 11 days post-exposure, though symptoms may occur as late at 21 days after the tick bite (14). Most patients seek medical care within the first 4 days of illness. Fever is common, occurring in 97% of patients (2). Headache occurs in 80% of patients, myalgias in 57% of patients, and arthralgias in 41% of patients (2). Rash occurs in 21% of adults with HME and in 66% of pediatric patients (2). When a rash is present it may be macular, maculopapular, petechial, or mixed. Rash typically occurs a median of 5 days after illness onset (13, 15). The rash usually involves the trunk and extremities but typically spares the face, palms, or soles (13). Central nervous system involvement including meningitis or meningoencephalitis, occurs in approximately 20% of patients and may be associated with seizures and coma (1, 2).

Children typically present with non-specific gastrointestinal symptoms (9). A diffuse rash similar in appearance to toxic shock syndrome has been reported in up to 30% of cases, more commonly in children than adults (9). When left untreated or when treatment is delayed, severe complications may occur and include adult respiratory distress syndrome, disseminated intravascular coagulation syndrome, hepatitis, and acute renal failure. Immunocompromised patients can develop fulminant disease, opportunistic nosocomial infections, and sepsis (1).

While the clinical manifestations of *E. chaffeensis* infection are nonspecific, laboratory abnormalities provide important diagnostic clues. Marked thrombocytopenia is one of the pathognomonic findings in HME, which is usually detected in 70% to 90% of patients during their illness (2). Mild to moderate leukopenia with a decrease in lymphocytes is observed in 60% - 70% of patients in early illness. Elevated hepatic transaminase levels are detected in approximately 90% of patients (2). Hyponatremia has been reported in as many as 50% of adult patients and 70% of pediatric patients (2).

In patients with neurologic manifestations, cerebrospinal fluid (CSF) pleocytosis is identified in approximately 60% of patients (2). The CSF white count is typically less than 100 cells per cubic millimeter, and protein levels may be mildly elevated. Most samples have a lymphocytic predominance (2).

4.2 Differential Diagnosis

The differential diagnosis of ehrlichiosis at the onset of the disease is extensive due to the non-specific nature of presenting symptoms and signs. If a history of tick bite and outdoor activities exist with symptoms including headache, myalgia, malaise, and fever considerations should include other tick-borne febrile illnesses, such as Rocky Mountain Spotted Fever, Relapsing Fever, Tularemia, Lyme Borreliosis, Colorado Tick Fever, and Babesiosis (2). Other infectious diseases that share clinical and laboratory findings of Ehrlichiosis, particularly if the patient presents with a rash or is severely ill, include: meningococcemia, toxic shock syndrome, influenza, bacterial sepsis, Kawasaki disease, collagen vascular disease, typhus, typhoid fever, Q fever, enteroviral infection, immune thrombocytopenia purpura, and bacterial endocarditis (2). Severe cases have been mistaken for thrombotic thrombocytopenia purpura, appendicitis, or fulminant viral hepatitis (15). Heartland virus disease, a recently identified tick-borne viral infection, also transmitted by the lone star tick, can closely resemble ehrlichiosis (15).

4.3 Case Definition

To meet the confirmed case definition of HME, a case must meet both clinical and laboratory criteria (5). Clinical criteria include an acute onset of fever and one or more of the following symptoms or signs: headache, myalgia, malaise,

anemia, leukopenia, thrombocytopenia, or elevated hepatic transaminases (16).

Laboratory findings are used to identify a clinical case of HME as either confirmed or probable. Criteria for a confirmed case of *E. chaffeensis* include one of the following: serologic evidence of a fourfold change in immunoglobulin G (IgG) specific antibody titer to *E. chaffeensis* antigen by indirect immunofluorescence assay (IFA) between paired serum samples (one taken in the first week of illness and a second 2-4 weeks later); detection of *E. chaffeensis* DNA in a clinical specimen via polymerase chain reaction (PCR) assay; demonstration of ehrlichial antigen in a biopsy/autopsy sample by immunohistology methods; or isolation of *E. chaffeensis* from a clinical specimen in cell culture (16, 17).

The probable case definition for *E. chaffeensis* infection includes clinical criteria and one of the following: serologic evidence of elevation of IgG or IgM antibody reactive with *E. chaffeensis* antibody by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or assays in other formats, or identification of morulae (intracytoplasmic inclusions) in monocytes or macrophages by microscopic examination (5, 17).

4.4 Laboratory Testing

Because of its high specificity (60%-85%) and sensitivity (60%-85%) diagnosis of ehrlichial infection by PCR has become the test of choice for confirming serology indicating ehrlichiosis (5). PCR of whole blood is widely available, has a rapid turnaround time, and enables diagnosis of infection in up to 85% of cases (2). PCR sensitivity is adversely affected by definitive treatment. Therefore, blood samples should be obtained before or at the initiation of therapy (1).

The diagnostic gold standard for confirming *E. chaffeensis* infection is serologic testing of IgM and IgG antibodies via IFA (2). Paired sera collected during a 3 – 6 week interval from initial presentation is preferred. A 4-fold increase in IgG antibody titers, when comparing acute and convalescent serum, confirms the diagnosis of HME (16).

For those patients who did not have serologic testing at the time of initial assessment it is important to obtain a convalescent-phase serum sample, as this may be the only laboratory evidence to support the diagnosis (5).

The development of novel laboratory assays based on antigen or antibody detection is currently being investigated. Several *Ehrlichia* specific tandem repeat proteins (TRP) have been molecularly characterized from sera of patients with acute HME. TRPs are immunoreactive and species-specific, making them potential targets for immunodiagnostic point-of-care assays (9).

Adults and Children ≥ 100 pounds	Doxycycline 100 mg twice daily
Children < 100 pounds	Doxycycline 2.2 mg/kg twice daily
Pregnant women Patients unable to use doxycycline	Rifampin 20 mg/kg twice daily; maximum daily dose is 600 mg

Table 1. Human Monocytotropic Ehrlichiosis Treatment Regimens.

4.5 Treatment

Doxycycline is the recommended treatment of HME (2, 18). Empiric treatment of patients with doxycycline is essential as soon as HME is suspected (1). Treatment should never be withheld pending laboratory confirmation (15). The adult dosage is 100 mg orally twice daily (2, 18). Treatment within the first five days of illness has been shown to decrease severity of disease in patient when compared with patients who received antibiotics later in the course of illness (5). Doxycycline is extremely effective and the response to treatment is usually prompt, with improvement noted within 24 – 48 hours (1). A specific duration of therapy is not well defined, though most authorities recommend continuing antibiotics for 3-5 days after lack of fever, (3, 18) and perhaps longer (e.g., total of 10-14 days) if there is CNS involvement (2). Post treatment relapse has never been reported in patients treated with doxycycline (1).

Doxycycline is also the treatment of choice for children irrespective of age (18, 19, 20). The recommended dosage is 2.2 mg/kg body weight per dose administered twice daily, for children weighing less than 100 pounds (45.4 kg) (2, 18). There is some empiric evidence supporting the use of rifampin in children unable to receive doxycycline (20). Rifampin is also the suggested treatment option during pregnancy (2). The recommended rifampin dose is 20 mg/kg per day given in 2 divided doses, with a maximum dose of 600 mg per day (20).

In vitro susceptibility testing has established that *E. chaffeensis* is resistant to most other classes of antibiotics, including aminoglycosides, fluoroquinolones, penicillins, macrolides and ketolides, and sulfa-containing drugs (1, 2). Of note, treatment with sulfonamides may be associated with the development with more severe ehrlichial disease (15).

Preventive antibiotic therapy for ehrlichial infection is not indicated for patients who have had recent tick bites and are not ill (2, 18). Treatment of asymptomatic persons seropositive for HME is not recommended regardless of past treatment status (15). IFA can persist in the absence of clinical disease for months to years after primary infection; therefore,

serologic tests cannot be used to monitor response to treatment for *E. chaffeensis* infection (15). It is unknown whether patients who recovered from HME are immune or susceptible to reinfection (2).

4.6 Prevention

The primary strategy for prevention of HME is avoidance of tick bites and the immediate removal of ticks when present. People who live in endemic areas should wear light-colored clothing during outdoor activities (4). This enables individuals to see crawling ticks. Adults who are at high risk of getting bitten by ticks should wear full coverage clothing treated with permethrin, and apply chemoprophylactic repellants such as n, n-diethyl-m-toluamide (DEET) to exposed skin (2, 5). Individuals should thoroughly inspect their body, hair, and clothes for ticks, after activity in tick-infested areas, and should promptly remove any attached tick. It is not known how long A. americanum must remain attached before it can transmit E. chaffeensis to a host (4).

Since dogs can transport ticks that carry ehrlichia species pet owners should use veterinary ectoparasite repellants to prevent ticks from attaching to and feeding on pets (5). Tick checks should also be performed regularly on pets after returning from possible tick-infested areas.

4.7 Reinfection and immunity

Immunity to primary *E. chaffeensis* infection in humans has not been investigated.

It is unknown whether patients who recovered from HME are immune or susceptible to reinfection (2).

4.8 Other infections

A single tick bite has the potential to transmit multiple infections. In addition to Ehrlichia species, *A. americanum* can transmit *Franciscella tularensis*, the etiologic agent of tularemia (21). There is increasing evidence of *A. americanum's* role as a vector of *Rickettsia rickettsia,* the etiologic organism of Rocky Mountain Spotted Fever, which is particularly concerning because of its high mortality rate (22). It has also been linked with Southern Tick Associated Rash Illness (STARI), as well as two emerging diseases, Bourbon virus and Heartland virus (23).

4.9 Alph – gal syndrome

While not truly a disease, the bite of *A. americanum* can trigger the alpha-gal syndrome (AGS) (23). AGS, commonly referred to as mammalian meat allergy, is characterized by an IgE – mediated allergic reaction to galactose-α-1,3-galactose (α-Gal) (24). The presentation of allergic reactions in AGS is delayed, and typically occurs within several hours after the consumption of mammalian meat or other animal-based food products. Symptoms of AGS vary, range in severity from mild reactions, including pruritis and urticaria, to severe and life-threatening, including angioedema and anaphylaxis. Most patient present with gastrointestinal complaints (23).

4.10 Climate change

It has been proposed that continued temperature rise would expand suitable ranges for many tick species northward. Since the beginning of the 20th century, temperatures in Ohio have risen more than 1.5°F, and temperatures in the 2000s and 2010s were warmer than in any other historical period (25)**.** As the climate warms and average saturation vapor pressure increases, higher vapor pressure (humidity) conditions have become more common, particularly during warmer times of year (26). Warmer temperatures play a critical role in the tick life cycle by impacting the development of eggs and engorged states and affecting tick questing activity (27). Vapor pressure (humidity) is also a critical factor for tick survival. Ticks have a high surface-to-volume ratio and can desiccate quickly when temperatures are high, and humidity is reduced (28). It is important to note that 2016, the year these cases occurred, was one of the hottest on record, and one of the wettest on record for Southern Ohio (25). It is likely that environment factors were ideal for tick reproduction and activity.

4.11 Outcome and Follow-up

Patient A was empirically treated with doxycycline hyclate 100 mg twice a day orally for 10 days. She sought care at a local emergency room 2 days after being seen due to ongoing fever. In the ER she received IV hydration and a prescription to treat nausea.

Her fever broke shortly after being seen in the ER. The remainder of her symptoms resolved within 3 days.

Patient A met the case definition of probable HME based on her symptoms and a known history of tick bite, associated with serologic testing demonstrating the presence of *E. chaffeensis* IgM antibodies.

Patient B was empirically treated with doxycycline, as well. He became afebrile within three days of starting the antibiotic. His other symptoms resolved within the first week of treatment.

Patient B met the case definition of confirmed HME based on his symptoms, a known history of tick bite, and a four-fold increase in convalescent *E. chaffeensis* IgG titers.

4.12 Learning Points

1. HME is increasing in incidence, as the lone star tick's geographic distribution expands. The increasing incidence and geographic distribution of infection due to *E. chaffeensis* suggests that health-care providers in previously unaffected areas may begin to see patients present with HME.

2. Patients in regions where these infections exist who present during tick season with fever, leukopenia and/or thrombocytopenia, and increased serum transaminase levels should have HME included in their differential diagnosis.

3. Prompt recognition of infections, with early initiation of antibiotics, can help decrease morbidity and mortality related to HME.

4. Doxycycline is the treatment of choice for HME regardless of patient age.

5. A high index of suspicion is required to order appropriate lab testing to confirm the disease.

Conflicts of Interest:

Authors declare no conflicts of interest

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