

Human Monocytic Ehrlichiosis

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CASE PRESENTATION

A 56-year-old white man with a history of Wegener granulomatosis (WG) presented in May 2003 with 6 days of sinus congestion, fever, malaise, myalgias, and red eyes. The appearance of these symptoms in the context of his previous WG immediately led to hospitalization. On admission, his serum creatinine level was discovered to be 3.8 mg/dL (336 $\mu\text{mol/L}$) (patient's baseline, 1.9 mg/dL [168 $\mu\text{mol/L}$]; normal range, <1.3 mg/dL [115 $\mu\text{mol/L}$]), heightening concern about a potential WG flare.

The patient's presentation with WG 16 months earlier had been characterized by 2 months of nasal and sinus congestion, followed by episcleritis, tongue ulcers, and a nondestructive polyarthritis involving small and large joints. He had also developed digital ischemia with splinter hemorrhages and elevation of hepatic transaminase levels (aspartate and alanine aminotransferase levels [AST and ALT] >1000 U/L; normal range, <7-40 U/L). Biopsy of a solitary left upper lobe lung mass had demonstrated necrotizing, granulomatous inflammation. A serum sample had tested positive for antineutrophil cytoplasmic antibodies (ANCA) by immunofluorescence, with a cytoplasmic ANCA staining pattern and an antigen specificity for proteinase 3.

See also Patient Page.

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A 56-year-old man with a history of Wegener granulomatosis presented with 6 days of sinus congestion, fever, malaise, myalgias, episcleritis, and a morbilliform rash. An exacerbation of Wegener granulomatosis was the principal concern because of the frequency of flares in that disease. The patient developed acute renal failure, thrombocytopenia, transaminitis, and, finally, severe myocarditis that led to congestive heart failure. Additional history-taking and the evolution of his clinical features led to empirical treatment with doxycycline for human monocytic ehrlichiosis (HME). The diagnosis of HME was confirmed by both a polymerase chain reaction assay for *Ehrlichia chaffeensis* and by the demonstration of morulae within peripheral blood mononuclear cells. The patient improved promptly following institution of doxycycline, and his cardiac function returned to normal over a period of 4 months.

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Despite daily treatment with cyclophosphamide and high-dose glucocorticoids, the patient's renal function had continued to decline for 4 weeks after the start of therapy, requiring hemodialysis when his serum creatinine reached 8.3 mg/dL (734 $\mu\text{mol/L}$). The patient had discontinued dialysis after 6 weeks and achieved a new baseline serum creatinine of 1.9 mg/dL.

Remission of his WG was induced by treatment with cyclophosphamide and prednisone for 5 months. He then switched to azathioprine, 100 mg/d, for remission maintenance. In addition to conventional WG treatment, the patient also participated in a randomized, double-blind trial of etanercept (a soluble inhibitor of tumor necrosis factor [TNF]) vs placebo for maintenance of WG remission.^{1,2} At the time of his current admission, the patient was receiving azathioprine, 100 mg/d; his experimental medication (either etanercept, 25 mg twice per week, or placebo); trimethoprim-sulfamethoxazole (1 single-strength tablet per day) for *Pneu-*

mocystis prophylaxis; and lisinopril, 10 mg/d. He had discontinued glucocorticoids for 9 months and his ANCA serum samples had been negative for 8 months. He was married and worked for a communications company. He reported a remote history of smoking and occasional alcohol consumption. He had traveled to Maryland's eastern shore in search of retirement properties 2 weeks before admission.

The patient denied shortness of breath, cough, arthralgias, neck stiffness, abdominal pain, nausea or vomiting, chest pain, and dysuria. On physi-

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cal examination, he had a maximal temperature of 40°C, a pulse of 104/min, a blood pressure of 91/54 mm Hg, and an oxygen saturation of 96% on room air. He had ocular erythema consistent with episcleritis. The patient had no oral thrush, tongue ulceration, or nasal bleeding. There was no evidence of lymphadenopathy. His cardiac examination revealed a normal S₁ and S₂ with no murmurs, rubs, or gallops, and his lungs were clear to auscultation. The abdomen was nontender and showed no signs of organomegaly. The musculoskeletal examination was remarkable for absence of synovitis. The skin had a faint but diffuse, confluent macular rash over the arms, trunk, and face that spared the palms and soles and blanched on pressure. There were no splinter hemorrhages. The neurological examination was nonfocal. The patient's laboratory results on admission were remarkable for a sodium level of 129 mEq/L (normal range, 135-148 mEq/L), creatinine level of 3.8 mg/dL, AST level of 36 U/L, ALT level of 22 U/L, albumin level of 3.8 g/dL (normal range, 3.5-5.3 g/dL), and an erythrocyte sedimentation rate of 12 mm/h (normal range, <20 mm/h). A urinalysis with microscopy showed 2+ protein, no red blood cells, 5 to 10 white blood cells per high-power field, and no casts. A chest radiograph was normal. For comparison, the results of blood work obtained 2 weeks prior to admission (for monitoring of WG) are shown

in TABLE 1, along with results obtained during subsequent hospitalization.

Early Hospital Course

The patient's inactive urine sediment partly assuaged concerns about a WG flare. The patient's azathioprine and experimental medication were suspended because of concern about a possible opportunistic infection. Trimethoprim-sulfamethoxazole and lisinopril were also discontinued because of his declining renal function. He was treated with intravenous fluids for acute-on-chronic renal failure, presumed secondary to prerenal azotemia. Despite ongoing fever, empirical antibiotics were not begun because there was no clear infectious source. Blood and urine cultures remained negative.

On hospital day 2, the patient developed voluminous, watery diarrhea that was nonbloody. *Clostridium difficile* toxin assays of stool were negative. His fevers persisted, his serum creatinine level rose to 4.5 mg/dL (398 μmol/L), and he developed brownish nasal crusts without epistaxis. By hospital day 3 the patient's serum creatinine level had stabilized but he had developed significant elevations of his hepatic transaminases and a decreased platelet count (Table 1). The transaminitis heightened concern about a potential WG flare because the patient's AST and ALT concentrations had been elevated at the time of his WG diagnosis. On hospital

day 3, the ANCA assay by immunofluorescence was reported as negative.

On hospital day 4, the patient became progressively dyspneic. A chest radiograph showed mild pulmonary congestion but no focal infiltrates. His intravenous fluids were stopped, but the dyspnea continued to worsen. His oxygen saturation was 93% on room air, and an arterial blood gas measurement demonstrated a pH of 7.4, a PO₂ of 66.0 mm Hg, and a PCO₂ of 29.0 mm Hg. An electrocardiogram indicated normal voltage and no signs of ischemia or pericardial inflammation. The patient's cardiac enzymes, however, were strikingly elevated: serum troponin I level was >200 ng/mL (normal range, 0.0-0.5 ng/mL) and creatine kinase was 1842 U/L (normal range, 24-195 U/L), with a creatine kinase-MB isoenzyme of 99 ng/mL (normal range, 0-5 ng/mL). An echocardiogram showed left ventricular systolic dysfunction and an ejection fraction of 10%. The patient was transferred to the cardiac care unit.

Diagnostic Considerations and the Case Breaker

Because of the frequency with which WG recurs, the principal concern at the time of the patient's hospital admission was a flare of that disease. Following the initial control of WG with conventional therapies in approximately 90% of patients, between 60% and 80% eventually experience disease flares.²⁻⁴

Table 1. Pertinent Laboratory Test Results 2 Weeks Before Hospitalization and After Admission

Laboratory Test	Hospital Day*							
	-14	1	4	5	6	8	9	16
Body temperature, °C	36.2	39.9	37.0	37.1	37.0	36.0	36.0	36.4
Sodium, mEq/L	141	129	135	129	131	137	135	138
Creatinine, mg/dL	2.0	3.8	3.3	3.4	3.6	2.4	2.0	2.1
AST, U/L	26	36	286	536	NA	934	143	37
ALT, U/L	19	22	74	114	NA	948	525	106
White blood cell count, ×10 ³ /μL	7.7	3.5	2.9	3.0	3.1	4.4	5.6	7.8
Platelet count, ×10 ³ /μL	410	169	77	81	85	99	222	401
Total CK, U/L†	NA	NA	1842	2062	1318	NA	NA	NA
CK-MB, ng/mL†	NA	NA	99	77	30	8	NA	NA
Troponin I, ng/mL†	NA	NA	>200	173.69	58.4	NA	NA	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; NA, not analyzed because laboratory test not performed.

SI conversion: To convert creatinine to μmol/L, multiply values by 88.4.

*Day 1 was the day of hospital admission. Patient received doxycycline on hospital days 5 through 16.

†Normal ranges for total CK, CK-MB, and troponin I are 24 to 195 U/L, 0 to 5 ng/mL, and 0 to 0.5 ng/mL, respectively.

Renal disease, the most feared complication of WG, may progress swiftly; the rise in the patient's creatinine level from baseline prompted appropriate alarm. Many features of his acute presentation, particularly renal dysfunction, episcleritis, brown nasal crusts, and transaminitis, were consistent with a WG flare. (Significant hepatic inflammation is not typical of WG,⁵ but the patient had manifested this complication at the time of his WG diagnosis.) Urine sediment without hematuria or red blood cell casts and the presence of only baseline proteinuria both argued against recurrent WG.

The absence of many features of his previously active WG supported a non-WG cause of his current clinical presentation. The patient had neither epistaxis nor bloody nasal crusts, both of which suggest active nasal inflammation, a hallmark of WG. The nasal crusts observed in the hospital were likely related to the effects of dry hospital air superimposed on damaged nasal mucosa from his previously active disease. In addition, the patient had no arthritis, digital ischemia, or pulmonary lesions, and his erythrocyte sedimentation rate was normal. Finally, several features of his current illness, particularly the fever, chills, rash, and diarrhea—which did not develop until hospital day 2—marked a significant departure from his original WG presentation. Wegener granulomatosis may be associated with anemia through several mechanisms (eg, alveolar hemorrhage, anemia of end-stage renal disease, or the effects of medications), but thrombocytopenia is distinctly uncharacteristic of WG. On the contrary, because platelets are acute-phase reactants, thrombocytosis is the rule for patients presenting with generalized WG.

In addition to a WG flare, the remainder of the differential diagnosis centered around possible infections. The major considerations included a variety of viral illnesses that might have led to dehydration and prerenal azotemia, and a group A streptococcal infection, which might have caused the decline in renal function via poststreptococcal glomerulonephritis.⁶ On further inquiry, how-

ever, the patient's wife recalled that during the couple's trip to the eastern shore of Maryland, she had found and removed a tick from her skin. This suggested a tick-borne disease as a possible etiology for the patient's illness. Serological assays for *Borrelia burgdorferi* (Lyme disease) and *Rickettsia rickettsii* (Rocky Mountain spotted fever) and polymerase chain reaction (PCR) assays for human monocytic ehrlichiosis (HME; caused by *Ehrlichia chaffeensis*) and human granulocytic anaplasmosis (HGA; *Anaplasma phagocytophilum*) were obtained. When the patient began to develop increasing respiratory distress on hospital day 4, these results were still pending. Doxycycline, 100 mg/d, was instituted empirically because of the strong suspicion that ehrlichiosis was the cause of the patient's illness. The assay result for HME was reported later as positive (and the HGA PCR result as negative). Review of the patient's peripheral blood smear from the day of hospital admission showed several monocytes containing characteristic cytoplasmic bacterial inclusions (morulae) (FIGURE 1A).

Response and Resolution

The patient's fever abated immediately with the institution of doxycycline; he had no further fever after receiving his first dose. His abnormal laboratory measurements, including cardiac enzymes, serum creatinine, and platelet count, also improved promptly. The AST and ALT continued to rise after initiation of therapy but resolved prior to discharge. Delayed improvement in liver function tests is known to occur after the start of effective antiehrlichial therapy in HME. This is believed to be secondary to lingering inflammation within the hepatic lobules and subsequent hepatocyte death. The patient started a medical regimen for heart failure (lisinopril and atenolol) and was discharged from the hospital 11 days after admission. Blood tests performed 1 week after discharge (day 16 in Table 1) showed rapid resolution of laboratory abnormalities. Serial echocardiograms at 1 week, 6 weeks, and 4 months after discharge showed ejection fractions of 35%, 45%, and 55%, respectively.

DISCUSSION

Human Monocytic Ehrlichiosis Bacteriology and Pathophysiology

A group of human infections previously known merely as "ehrlichiosis" results from the bite of infected ticks. The name of this disorder derives from that of the causative agent, *E chaffeensis*. The genus *Ehrlichia* was named to honor the famous German bacteriologist Paul Ehrlich, who did not actually contribute to its discovery or characterization. The infectious organisms, members of the recently reorganized family Anaplasmataceae,⁷ are obligate intracellular bacteria. Human pathogens in this family include organisms in the genera *Ehrlichia* and *Anaplasma*: *E chaffeensis*, *Ehrlichia ewingii*, and *A phagocytophilum*. These *Rickettsia*-like bacteria infect either the monocyte/macrophage line (*E chaffeensis*) or neutrophils (*E ewingii* and *A phagocytophilum*).⁸ Comparisons of the major features of the organisms that cause ehrlichioses (and anaplasmosis) are shown in TABLE 2. The life cycle of *E chaffeensis* involves both mammalian and tick reservoirs (FIGURE 2).

Epidemiology and Ecology

The CDC recorded at least 1508 cases of HME in the United States through 2003. That the disease is not reportable in all states probably leads to substantial underreporting.^{11,12} In highly endemic regions such as southeastern Missouri,¹³ recent studies have estimated the annual incidence rates of HME to be as high as 158 cases per 100 000 population. Cross-sectional seroprevalence studies have detected antibody titers to *E chaffeensis* of at least 1:80 in 13% of children and at least 1:160 in 3% of children living in the midwestern "tick belt." This seroprevalence rate, which remains high even with more stringent cutoffs for positive results, suggests that subclinical infections are common.¹⁴

The distribution throughout areas of the southeast, south-central, and mid-Atlantic regions corresponds to areas where *Amblyomma americanum* (Lone Star) ticks, the vectors of *E chaffeensis*,

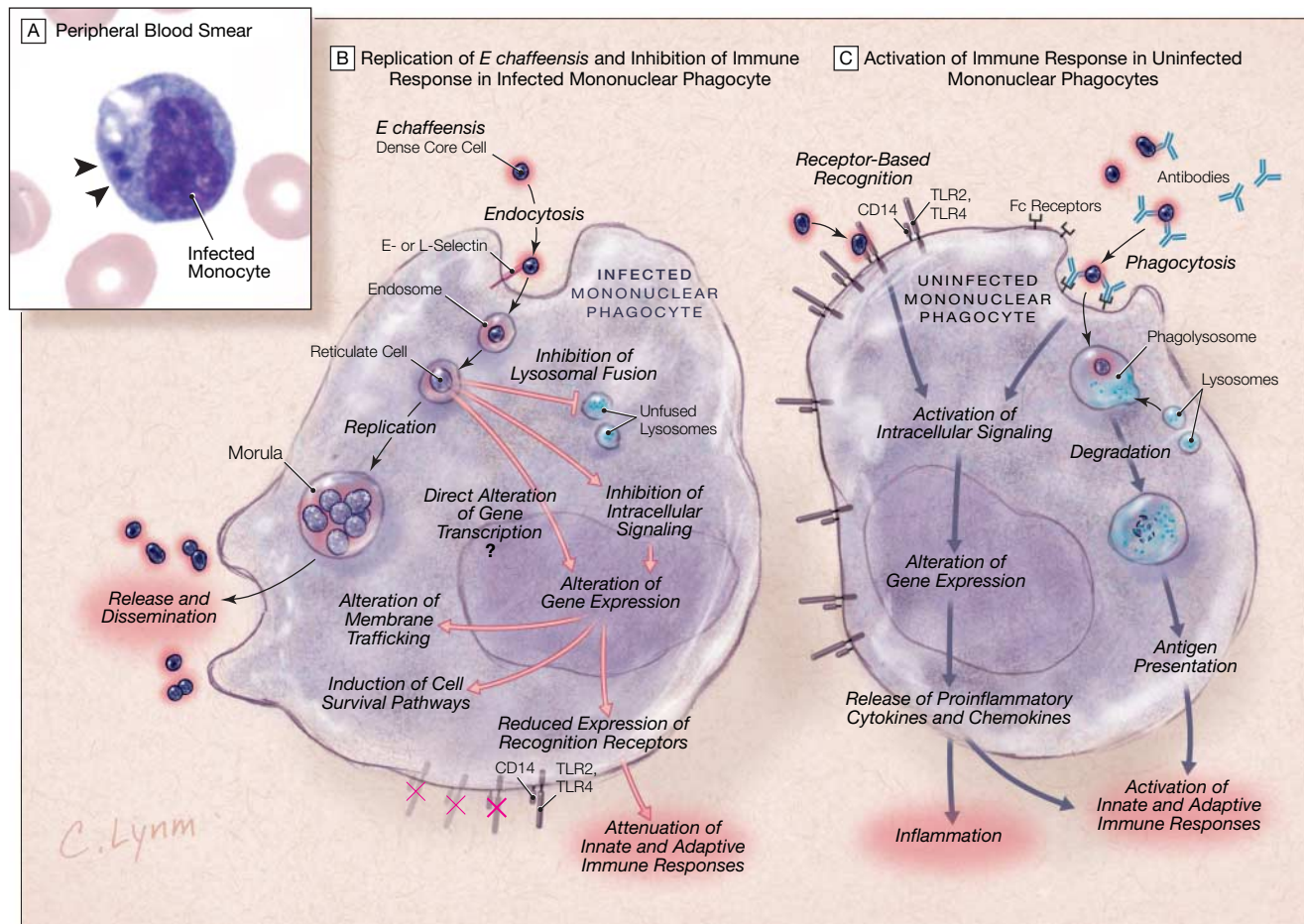
are abundant^{15,16} (FIGURE 3). White-tailed deer (*Odocoileus virginianus*), the major animal reservoir of *E chaffeensis*, are persistently bacteremic with the organism but do not develop clinical signs of infection.^{15,17} As with our patient, who became ill in May, most infections occur between May and July, corresponding to the peak feeding times of Lone Star ticks. Although ticks in both the adult and nymphal stages are

known to bite humans between April and August, transmission is thought to occur most often after bites of adult ticks.¹⁵ The tick bites themselves are generally asymptomatic and may go unnoticed. The skin lesions that result from differing species of ticks, however, may differ based on the pathogen inoculated. For example, the classic erythema migrans lesion associated with Lyme disease (transmitted by

the *Ixodes scapularis* tick, as opposed to *A americanum*) is caused by inflammation at the site of *B burgdorferi* inoculation, followed by radial extension as the spirochete spreads through the dermis. Human monocytic ehrlichiosis is not associated with a similar skin lesion.

Men are more frequently diagnosed with HME than women by a ratio of more than 2 to 1, presumably because

Figure 1. Peripheral Blood Smear and Replication of *Ehrlichia chaffeensis* and Cellular Response



A, Peripheral blood smear obtained on hospital day 1 showing a monocyte with 2 vacuoles (morulae) that contain *E chaffeensis* clusters (arrowheads) (Wright stain; original magnification $\times 240$). B, *E chaffeensis* infects mononuclear phagocytes in blood and in tissues. In the absence of an immune response, the bacterium is internalized via endocytosis. After entry, dense core cells differentiate into reticulate cells that are suspected to be the metabolically active and replicative stage. By poorly understood mechanisms, *E chaffeensis* directs early endosomes containing the bacteria into a receptor-salvage pathway that precludes lysosomal fusion. Likewise, infection alters signal transduction pathways and is associated with significant changes in host cell gene transcription. These events lead to global down-regulation of innate immune response pathways and receptor expression, intracellular vesicular trafficking, and activation of antiapoptotic survival mechanisms. The net effect is a more hospitable environment for intracellular replication. Replicated bacteria are released by cell lysis or exocytosis to infect other mononuclear phagocytes nearby or at disseminated sites. C, With emerging immune response, the bacteria are opsonized by anti-*E chaffeensis* antibodies, bound to Fc receptors, and phagocytosed. Ligation of antibody-bound *E chaffeensis* to Fc receptors triggers G-protein-coupled intracellular signaling that results in destruction of the bacterium, degradation and presentation of antigens for maturing adaptive immune response, and activation of innate immune pathways. This process leads to the production of proinflammatory cytokines and chemokines. Such responses are ultimately beneficial to the host by activation of crucial CD4- and CD8-mediated immunity dominated by IFN- γ . However, induction of proinflammatory mediators, including TNF- α , has the potential to cause transient local tissue and organ injury or systemic manifestations.

of increased recreational and occupational exposure. All individuals are potentially susceptible to HME, however, if they live, work in, or visit rural or suburban areas with deer. Although the average age is about 48 years, severe and fatal infections have occurred in children as well.^{13,15,18,19} Infections recorded in regions without *A americanum* ticks, such as California, suggest alternate vectors.²⁰

Clinical Features

The clinical manifestations of HME and HGA are similar, ranging from mild febrile illnesses to multisystem organ failure.¹⁵ The most typical presentation of either infection is fever, often accompanied by headache, rigors, myalgias, and malaise. None of these features distinguishes HME or HGA from other nonspecific febrile illnesses.^{8,15} Evidence of systemic involvement is helpful in diagnosis: up to 50% of patients have nausea, vomiting, diarrhea, or abdominal pain. Twenty-five percent of HME patients have cough or other evidence of respiratory tract involvement, and 20% have central nervous system involvement without obvious involvement of other organ systems.²¹ Certain laboratory abnormalities are

also characteristic. The presence of hyponatremia, cytopenias (particularly leukopenia and thrombocytopenia), and elevated hepatic transaminase levels are typical of the ehrlichioses.¹³

Leukopenia, which involves both neutrophils and lymphocytes, usually resolves after the first week of illness with or without treatment.²¹ The frequency of cytopenias in HME cannot be explained by direct bacterial lysis of infected cells because only a minority of leukocytes is infected and the bacteria infect neither platelets nor erythrocytes.^{8,15} Cytopenias are also not explained by hematopoietic suppression or hypoplasia, because most examinations reveal hypercellular or normocellular bone marrow.²² The frequent detection of macrophage-rich inflammatory infiltrates within the liver, often accompanied by hemophagocytic cells, implicates macrophage activation as the mechanism for both the cytopenias and the frequency of increased serum transaminase levels.²³ Inflammatory foci are found within the livers of patients with HME, with lobular hepatitis, apoptotic hepatocytes, necrosis, and a paucity of infected cells.²⁴ The etiology of hyponatremia in HME is uncertain but may be related to compensatory changes in re-

sponse to cytokine-mediated increases in vascular permeability.

More than 40% of recognized HME infections require hospitalization.^{13,21} Severe complications of HME include meningoencephalitis, acute respiratory distress syndrome, a septic or toxic shock-like syndrome, renal failure, coagulopathy, and multiorgan failure.^{8,15} Myocardial involvement has been documented only rarely in HME.^{15,25,26} The case fatality rate is approximately 2% to 3%.²³ Fulminant HME can occur in the setting of human immunodeficiency virus infections, organ transplantation, cancer, or immunosuppressive therapy.^{8,15,24,27-34} Severe infections and death, however, may also occur in nonimmunocompromised individuals.^{15,19,35-37}

An association between trimethoprim-sulfamethoxazole treatment and fulminant infection has been demonstrated with rickettsial diseases, although the mechanism by which this occurs is not known. Two cases of HME in healthy young adults taking trimethoprim-sulfamethoxazole^{38,39} were associated with fulminant infections, suggesting that our patient's disease severity may have been heightened by his trimethoprim-sulfamethoxazole regimen.

Table 2. Selected Epidemiological, Ecological, and Serological Features of Ehrlichioses⁸⁻¹⁵

	Human Monocytic Ehrlichiosis	Human Anaplasmosis (Granulocytic Ehrlichiosis)	Ehrlichiosis "Ewingii"
Organism	<i>Ehrlichia chaffeensis</i>	<i>Anaplasma phagocytophilum</i>	<i>Ehrlichia ewingii</i>
Vector	Lone Star tick (<i>Amblyomma americanum</i>)	Deer tick/black-legged tick (<i>Ixodes scapularis</i>), western black-legged tick (<i>Ixodes pacificus</i>)	Lone Star tick (<i>Amblyomma americanum</i>)
Animal host	White-tailed deer, dogs, foxes, wolves, coyotes	White-footed mouse, other mammals	White-tailed deer, dogs, foxes, wolves, coyotes
Cells infected	Monocytes	Neutrophils	Neutrophils
Time of year	Spring/summer	Spring/summer	Spring/summer
Location	Southeastern, south-central, and mid-Atlantic United States	Upper Midwest and northeast United States, California, Europe	Southeastern, south-central, and mid-Atlantic United States*
Reported cases	>1500	>1700	~8
Known tick exposure, %	80-90	45-85	90
Mortality rate, %	2.7	0.5-1.0	None reported
Reported cases, male, %	67	56	100
Laboratory diagnosis			
Acute phase	PCR, blood smear examination	PCR, blood smear examination	PCR, blood smear examination
Convalescent phase	Serology (seroconversion)	Serology (seroconversion)	No specific serology

Abbreviation: PCR, polymerase chain reaction.

*There have been approximately 20 cases of *E ewingii* in humans identified in the mid-Atlantic states (J.S.D., unpublished data). The presence of *E ewingii* in ticks and infected dogs in the mid-Atlantic has been documented.^{9,10}

To our knowledge, HME has not previously been reported in any patient with WG. In the clinical trial in which our patient was a participant,^{1,2} he had been assigned to receive etanercept. Thus, our patient was receiving an immunosuppressive regimen that included both etanercept, a soluble TNF inhibitor known to be associated with an increased risk of atypical infections,⁴⁰ and azathioprine, an inhibitor of T and B lymphocyte function. Although TNF is an important cytokine in the immunologic response to *Rickettsia* species and other infectious pathogens,⁴¹ its specific role in the host response to *Ehrlichia* species remains unclear. Recent animal models of HME suggest a detrimental role for excessive TNF- α , a finding not entirely consistent with the

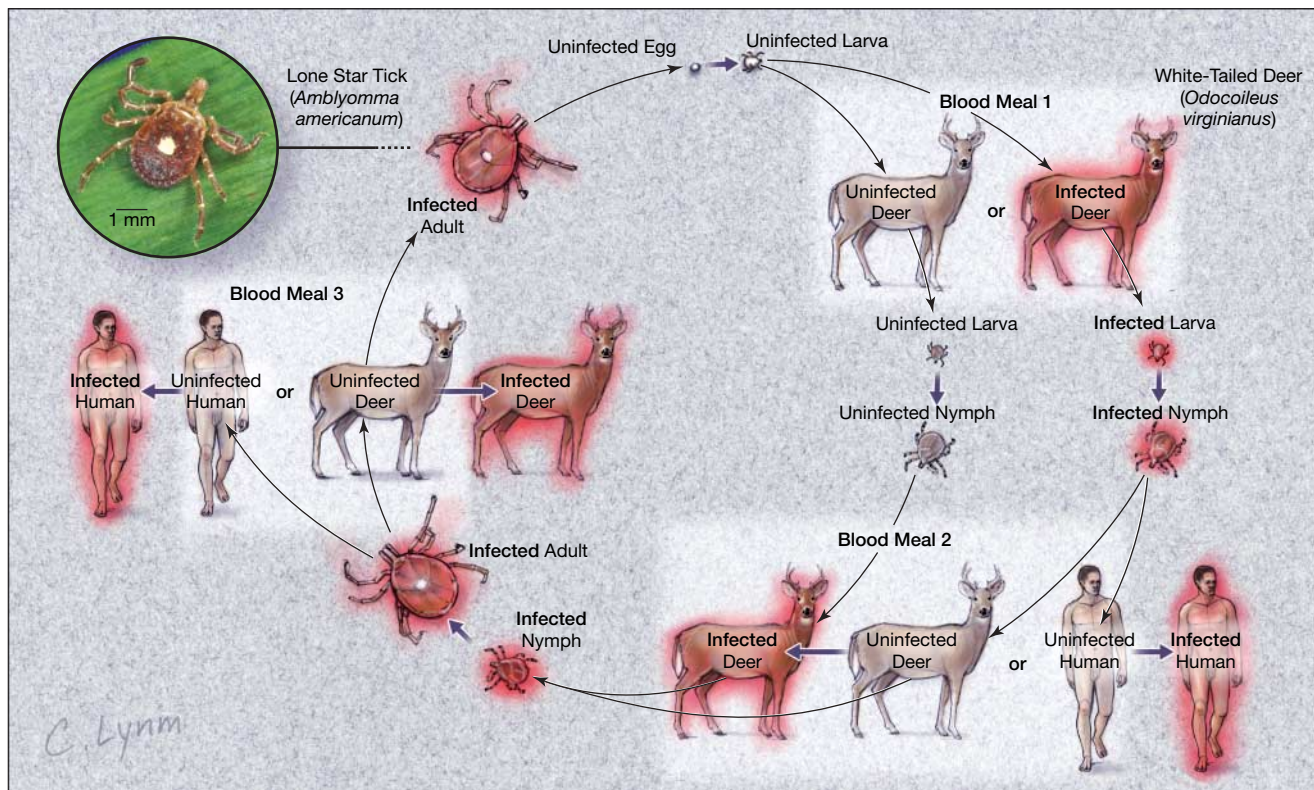
presentation herein.⁴² In a murine model of HME,⁴³ a synergistic role for TNF- α and interferon- γ has been demonstrated in protection against mortality. Use of a TNF- α antagonist by our patient may have contributed to the increased severity by diminishing the induction of innate and adaptive immunity. Loss of TNF- α alone does not increase mortality in mice, however, and a role for this cytokine in human *E chaffeensis* infections has not yet been investigated.

After attachment via surface receptors and internalization into monocytes/macrophages, *E chaffeensis* evades lysosomal fusion of the parasitophorous vacuoles, thereby escaping destruction and surviving within the cell.^{44,45} The bacteria propagate within vacuoles, forming inclusions known as morulae

(Figure 1). Host cells are altered by the intracellular infection in various ways (Figure 1B). For example, initially *E chaffeensis* diminishes the proinflammatory response of the host by altering the cell surface expression of Toll-like receptors (TLR2 and TLR4) and CD14.⁴⁶ However, once opsonized by antibody, *E chaffeensis* interacts with mononuclear phagocytes via Fc receptors and triggers an intense proinflammatory cytokine response (Figure 1C).^{42,47} Excessive cytokine production contributes to the toxic and septic shock-like presentations, respiratory failure, and acute respiratory distress syndrome observed in HME.^{15,35,42}

The pathophysiologic mechanisms of myocarditis in HME appear to differ from those of Rocky Mountain spot-

Figure 2. Transmission of *Ehrlichia chaffeensis* by Tick Vector (*Amblyomma americanum*)



Noninfected larvae obtain blood from a bacteremic vertebrate reservoir host (eg, white-tailed deer), become infected, and maintain ehrlichiae when the tick molts into the nymphal stage (trans-stadial [stage-to-stage] transmission). Infected nymphs may transmit *E chaffeensis* to susceptible reservoir hosts or incidentally to humans during acquisition of blood. Infected adult ticks, having acquired ehrlichiae either by trans-stadial transmission from the infected nymphal stage or during blood meal as noninfected nymphs on infected deer, may also pass *E chaffeensis* to other susceptible reservoirs or humans. Transovarial transmission (transmission to the eggs and into larvae) has not been demonstrated, and eggs and unfed larvae are presumably not infected. White-tailed deer (*Odocoileus virginianus*) are the predominant reservoir for *E chaffeensis*, although canids (eg, foxes, coyotes) are alternate reservoirs. White-tailed deer can maintain a subclinical *E chaffeensis* bacteremia for months and are hosts of all 3 stages of Lone Star ticks, its predominant vector. Photo provided by James Gathary/Centers for Disease Control and Prevention.

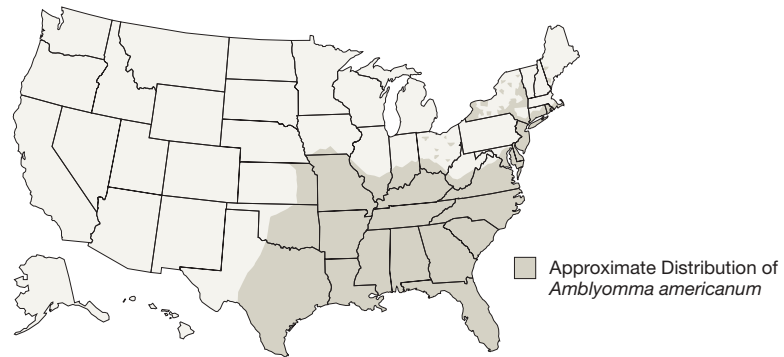
ted fever (caused by *R rickettsii*) and other rickettsioses. *Ehrlichia chaffeensis*, in contrast with *R rickettsii*, does not infect endothelial cells in vivo.²³ The common link between cardiac involvement in these 2 infections is infiltration of the myocardium by inflammatory cells. Although true vasculitis with endothelial cell loss, vascular wall necrosis, and thrombosis can occur in Rocky Mountain spotted fever, the more common histopathologic manifestation is myocardial inflammatory cell infiltrates with edema,^{48,49} as observed with *E chaffeensis* infections.²³ It is possible that *E chaffeensis*-activated macrophages infiltrating the myocardium produce proinflammatory cytokines or induce their production by other cells.^{42,47} Activated macrophages (eg, via interferon- γ) can lead to hepatitis and hepatic necrosis.^{24,42,50} A similar mechanism could also occur within myocardial inflammatory infiltrates containing *E chaffeensis*-infected monocytes.

Diagnosis

The diagnosis of HME requires a compatible clinical history and laboratory evidence of infection. Supportive laboratory evidence includes a single IgG antibody titer of at least 256; seroconversion from negative to positive antibody status (with a minimum titer of 64), a 4-fold rise in titer during convalescence, recovery of *E chaffeensis* in culture, or detection of *E chaffeensis* nucleic acids in blood or cerebrospinal fluid by PCR.^{15,51} Although our patient had a late acute-phase *E chaffeensis* antibody titer of 1024, the majority of patients (60%-97%) are seronegative during the acute phase.^{8,13,21} Thus, therapeutic decisions must often be based on a high index of clinical suspicion and laboratory evidence of the infection, such as PCR assays and peripheral blood smears.

Diagnosis by PCR is faster than enzyme immunoassay and has a sensitivity of 60% to 85%,^{13,52} but the potential for false-positive results is high.¹⁵ Examination of the peripheral blood smear for the typical intracytoplasmic morulae in monocytes is not informative in most cases. Morulae are detected within monocytes

Figure 3. Lone Star Tick and Its Geographic Distribution¹⁶



Approximate geographic distribution of *Amblyomma americanum* in the United States.

in only about 3% of patients with HME.^{8,23,53} In our patient, the identification of *E chaffeensis* morulae within peripheral blood monocytes confirmed the results of PCR and validated the empirical use of doxycycline. Examination of buffy-coat smears might increase the likelihood of morulae detection, but no comparative studies of buffy-coat examinations vs routine peripheral blood smears have been performed.

Differential Diagnosis

Because HME presents with nonspecific findings, the differential diagnosis is broad. Presentations with multiorgan disease invoke sepsis, toxic shock syndrome, meningococemia, typhoid fever, and endocarditis as potential diagnoses. Noninfectious mimics of HME include Kawasaki disease, thrombotic thrombocytopenic purpura, hematologic malignancies, collagen vascular diseases, and, as demonstrated herein, systemic vasculitis. Given a history of animal, tick, or vector exposure, the differential diagnosis must also include Rocky Mountain spotted fever, murine typhus, relapsing fever, Lyme disease, tularemia, West Nile fever, Colorado tick fever, babesiosis, Q fever, leptospirosis, and, in Europe, tick-borne encephalitis. Our patient illustrates the importance of considering ehrlichiosis in patients who present with fever, generalized aches, cytopenias (particularly leukopenia and thrombocytopenia), and abnormal liver function.

Treatment

No controlled prospective evaluations of therapy for HME or HGA have been conducted. However, empirical data, retrospective analyses, and in vitro studies indicate that doxycycline is the drug of choice.^{21,54} Rifampin, effective in vitro, has been associated with some success in treatment of HGA in pregnant women. Because the outcome of HME is dependent on early identification and early effective therapy, a high degree of clinical suspicion is critical to selecting the most appropriate antimicrobial regimen. Therapy is usually advocated for at least 3 to 5 days after defervescence or approximately 10 days total. However, in states such as Maryland, where the prevalence of Lyme disease is high, clinicians often use a 2-week course of doxycycline because of the possibility of simultaneous infection with *B burgdorferi*, which requires a second tick bite because this organism infects the *I scapularis* tick (Figure 3), not *A americanum*.

Prognosis

Most patients with HME respond favorably to treatment, especially if therapy is administered early in the course of the infection.^{13,21} The typical response to doxycycline is rapid defervescence within 24 to 48 hours. After 1 dose of doxycycline, our patient had no more fever. Most laboratory changes also resolve rapidly, with return of the white blood cell and platelet counts to normal within several days.²¹ Although the objective clini-

cal signs respond rapidly, symptoms such as fatigue may persist for weeks or even months. The medical basis for the persistent manifestations is unclear. There is no evidence of persistent *E chaffeensis* infection in humans, and treatment for disease beyond the acute infection is not indicated.^{8,13,15}

CONCLUSION

Human monocytic ehrlichiosis is a disease that can cause severe infections or death yet provides few specific clinical clues to diagnosis. Awareness of this disorder, recognition of its particular risk factors (eg, travel to endemic regions, tick bites), and understanding the spectrum of known presentations and complications of HME are all critical to making the diagnosis promptly and achieving a favorable outcome. The syndrome of fever, generalized aches, cytopenias, and elevated liver function measurements may be particularly useful in triggering suspicion of HME. Even in the absence of an obvious vector exposure or travel history, empirical doxycycline therapy may be lifesaving for patients in whom there is a reasonable clinical suspicion of HME.

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