Is Human Granulocytic Ehrlichiosis a New Lyme Disease? Review and Comparison of Clinical, Laboratory, Epidemiological, and Some Biological Features

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Human granulocytic ehrlichiosis (HGE) and Lyme disease are caused by infectious agents transmitted by deer ticks (*Ixodes scapularis*). Because of the shared tick vector and increased seroprevalence of HGE in patients with Lyme disease, there is some confusion about the identity of these infectious agents and the clinicopathologic spectrum of the disease. HGE is an acute febrile illness associated with leukopenia, thrombocytopenia, and increased serum activities of hepatic transaminases. In contrast, Lyme disease is most often subacute, with the frequent presence of erythema migrans rash and infrequent leukopenia, thrombocytopenia, or elevated serum hepatic transaminase activities. Some ehrlichia infections in animals and humans may become persistent, and *Ehrlichia*-mediated defects in host defense and immune suppression can allow secondary and opportunistic infections. Because of these properties of *Ehrlichia* species, their role in modifying the clinical course of Lyme disease may be hypothesized and should be tested.

Ehrlichioses are zoonotic diseases that are transmitted to humans and animals usually by the bite of infected ticks [1]. In the last decade, after the serendipitous observation of *Ehrlichia*-like structures in the blood of a patient with suspected Rocky Mountain spotted fever, two distinct previously unrecognized tick-borne infections that are caused by *Ehrlichia* species were discovered [2, 3]. The reasons for the sudden emergence of these infections are not entirely understood, but it must be partly attributed to the repopulation of habitats previously devoid of ticks by appropriate host animal species such as deer, small rodents, and humans [4, 5]. In addition, the application of modern molecular methods toward identification of noncultivatable, difficult-to-cultivate, and fastidious bacterial pathogens has made a significant contribution to the rapid identification and recognition of these previously unknown human pathogens [6, 7].

Ehrlichiae and Pathogenesis of Ehrlichiosis

Obligate intracellular bacteria in the genus *Ehrlichia* infect mostly leukocytes or other cells derived from the hematopoietic system upon introduction into the mammalian host [1–3]. Pathogenesis of the diseases caused by ehrlichiae is not well understood; however, ongoing research has identified surface-exposed protein adhesins that mediate attachment to host phagocytic cells [8]. Once attached, the ehrlichiae gain entrance to the phagocyte and reside within a phagosome after active inhibition of phagosome-lysosome fusion mediated by ehrlichial proteins [9]. The individual bacterial cells within the vacuole then divide by binary fission to produce a "microcolony" recognized in Wright-stained blood smears as morulae.

The ehrlichiae damage and lyse host cells by unknown mechanisms to release large numbers of infectious ehrlichiae that then attach to and infect neighboring phagocytic cells. Inhibition of phagosome-lysosome fusion is reversed by IFN-γ, a cytokine that is likely to be critical for recovery from the acute infectious process [10]. The cause of leukopenia and thrombocytopenia is likely to be related to peripheral consumption, sequestration, or destruction since most bone marrow examinations reveal hypercellular or normocellular findings [11].

Human Granulocytic Ehrlichiosis

In 1987 Maeda et al. [12] reported the first case of human infection in the United States by an *Ehrlichia* species, initially misinterpreted as *Ehrlichia canis*. Subsequent serological, epidemiological, clinical, and microbiological studies showed that the disease, then known simply as human ehrlichiosis and now as human monocytic ehrlichiosis, was caused by a new species, called *Ehrlichia chaffeensis* [6]. Although few examples of this organism in blood smears have been reviewed, the evidence shows that it has a strong predilection for mononuclear phagocytes in blood and in tissues.

It was suspected that all ehrlichiosis in humans in the United States was caused by this organism until some patients in the upper midwestern states were noted to have *Ehrlichia*-like morulae only within peripheral blood granulocytes, mostly neutrophils [7, 13]. All tests to prove that this agent was a simple variant of *E. chaffeensis* failed, and subsequent PCR amplification of the 16S ribosomal RNA gene directly from the blood

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Table 1. Comparison of the clinical features of human granulocytic ehrlichiosis (HGE) and Lyme disease.

Clinical feature	Percentage of patients with indicated disease and clinical feature	
	HGE[†]	Lyme disease[‡]
Erythema migrans rash	0	85
Fever	98	42
Diaphoresis	98	11
Chills	96	23
Headache	80	42
Fatigue/weakness	17	49
Myalgia	98	31
Arthralgia	27	36
Neck stiffness	22	21
Anorexia	37	14
Nausea	39	5
Vomiting	34	4
Cough	29	10

NOTE. Data were adapted from [15, 17, 18].
[†] $n = 18–59$.
[‡] $n = 224$.

of one infected patient showed that the causative agent of this new "granulocytic ehrlichiosis" was nearly identical to *Ehrlichia equi* and *Ehrlichia phagocytophila* [7]. This finding was particularly revealing in that these two veterinary pathogens are both granulocytic ehrlichiae that were best known to infect predominantly horses in California and ruminants in Europe, respectively.

The novelty of this infection in humans was confirmed when patients convalescent from granulocytic ehrlichiosis developed antibodies that reacted in high titers to both *E. equi* and *E. phagocytophila* [13, 14]. Moreover, *E. equi* and *E. phagocytophila* antibodies were used to detect the organisms by immunohistology in the tissues of a patient who died [13].

Clinical and epidemiological investigation of the new human granulocytic ehrlichiosis (HGE) revealed that most patients have an acute nonspecific febrile illness characterized by myalgias, headache, malaise, and occasionally gastrointestinal or respiratory symptoms and signs; rash is rare [13, 15–17] (table 1). HGE is associated with leukopenia, thrombocytopenia, mild elevations in hepatic transaminase activities, and deer tick bites [15, 17, 19]. The nonspecific clinical manifestations and laboratory findings of HGE are indistinguishable from those observed in patients with human monocytic ehrlichiosis (*E. chaffeensis* infection).

Subsequent evaluation of the accumulating numbers of patients with HGE has revealed a moderately severe, nonspecific febrile illness that is often described as flu-like [15, 17]. The incubation period ranges between 5.5 and 11 days, and the median age of patients is between 45 and 60 years; males outnumber females by 2:1. Most patients are acutely ill, and between 17% and 54% are hospitalized.

Particularly severe illness requiring intense supportive therapy develops in up to 7%; among ~150 identified cases, four fatalities have been identified (author's unpublished data) [13, 20]. Therapy with doxycycline results in rapid clinical improvement, usually within 48 hours. Approximately 20%–25% of patients have antibodies reactive with *E. equi* at the time of acute illness, and these antibodies may persist for >3 years [15].

Early therapy may abrogate antibody development and confound serological diagnosis (author's unpublished data). Diagnosis during the acute phase of illness is probably best accomplished by PCR amplification of HGE-agent DNA from blood [21]. Culture is still a research tool, and screening of peripheral blood smears for typical neutrophilic morulae is probably very insensitive [2, 16, 17].

HGE occurs mostly during May, June, and July, with a secondary peak in October, November, and December [15, 17]. So far, most cases have been identified in Wisconsin, Minnesota [15], New York [16, 17], Connecticut [20], and Massachusetts [22], although individual cases have been recognized in California, Pennsylvania, Maryland, Florida, and Arkansas [2]. Passive case collection in northwestern Wisconsin reveals rates as high as 14.2 and 16.1 cases per 100,000 population in Sawyer and Washburn counties, respectively [15].

The Overlap of HGE and Lyme Disease

The striking geographic and seasonal distribution is remarkably similar to that of Lyme disease (table 2). In fact, recent studies have shown the presence of the HGE-agent DNA in *Ixodes scapularis* ticks in Wisconsin and Connecticut [5, 19, 23]. This finding is somewhat expected, as the closely related *E. phagocytophila* is known to be transmitted by *Ixodes ricinus* [26], the major vector of Lyme disease in Europe [27].

However, the potential overlap in vectors and geographic distributions has led to the speculation that coinfections with *Borrelia burgdorferi* and the HGE agent might occur. So far,

Table 2. Comparison of the epidemiological and demographic characteristics of human granulocytic ehrlichiosis (HGE) and Lyme disease in the United States.

Characteristic	HGE	Lyme disease
Vector	*Ixodes scapularis, Ixodes pacificus* (?)	*Ixodes scapularis, Ixodes pacificus*
Reservoir	Small mammals (*Peromyscus, Microtus* [?])	Small mammals (*Peromyscus, Microtus*)
Peak season	May–July	May–July
Incubation period	5–11 d	7–10 d (interval to erythema migrans)
Patients		
M:F ratio	2:1	1:1
Age	Older (median, 43–60 y)	Younger (disease 1.7 × more frequent in those ≤15 y)

NOTE. Data were adapted from [4, 15, 17, 23–25].

serological studies seem to confirm this since ~10% of patients with serologically, culture-, and PCR-confirmed early Lyme disease have serological evidence of HGE. Likewise, ~10% of patients with HGE also have serological evidence of recent Lyme disease or babesiosis, also acquired after deer tick bites [19, 28–30]. The apparent reservoir for HGE also seems to be small mammals, particularly white-footed mice (*Peromyscus leucopus*) in the northeastern and upper midwestern states [23, 24, 31].

The potential for coinfections and clinical confusion among these tick-borne diseases exists because of these ecological and epidemiological circumstances. Since HGE is most currently recognized only as an acute febrile illness, a critical comparison of the clinical and laboratory features of HGE and early Lyme disease would be useful as a tool for clinical differentiation. This is particularly true since amoxicillin, which is ineffective as therapy for HGE [15], is often used as a primary antimicrobial agent for early Lyme disease.

The major clinical finding in HGE is that of an acute febrile illness with occasional involvement of the gastrointestinal, renal, or respiratory systems (table 1) [15]. The onset of erythema migrans rash in patients with Lyme disease is frequently detected 7–10 days following the tick bite [32], and the incubation period for HGE is similar [15]. However, clear erythema migrans has never been documented in a case of HGE or babesiosis. In fact, rash is infrequent and poorly characterized in HGE.

In contrast, the onset of illness in Lyme disease is often indolent, lacking significant fever, headache, myalgia, or other constitutional symptoms early on [32]. Fever, headache, diaphoresis, chills, and myalgias are much more frequent in HGE than in Lyme disease and are usually detected at presentation. Although present in less than half of HGE patients, anorexia, nausea, vomiting, and cough are very infrequent with Lyme disease. Fatigue is more often present with Lyme disease.

The laboratory findings in Lyme disease are infrequently of diagnostic aid if the clinical findings are not highly suggestive [33]. However, leukopenia, thrombocytopenia, anemia, and elevations in hepatic transaminase activities are seen in at least 50% of patients with HGE and in <20% of patients with Lyme disease [15, 32] (table 3).

Diagnostic tests for each entity are distinct. However, the pitfalls of serological diagnosis and the relative insensitivity of PCR and culture often force a clinician to rely entirely upon clinical features for the diagnosis of Lyme disease, particularly in geographic regions where the infection is not highly prevalent. Likewise, the fact that most physicians are relatively unfamiliar with ehrlichioses and the lack of widely available diagnostic tests for HGE mandate a clinical diagnosis unsupported by evidence to implicate a specific microbial etiology.

The current paradigm for serological confirmation of Lyme disease calls for demonstration of the presence of *B. burgdorferi* antibodies by an EIA method and, if they are found, the result is confirmed by immunoblot analysis on the basis of defined criteria [34, 35]. Even with these criteria, it is evident that a substantial proportion of patients with Lyme disease will also have serological evidence of HGE [19, 28–30].

Table 3. Comparison of selected laboratory findings in human granulocytic ehrlichiosis (HGE) and early Lyme disease.

Laboratory finding	Percentage of patients with indicated disease and laboratory finding	
	HGE[†]	Lyme disease[‡]
Leukopenia	50	(Rare)
Thrombocytopenia	92	(Rare)
Anemia	50	12
Elevated alanine or aspartate transaminase activity	91	19

NOTE. Data were adapted from [15, 17, 32].
[†] $n = 18–59$.
[‡] $n = 79$.

In fact, recent results of *B. burgdorferi* immunoblot tests performed on sera from patients in New York State with PCR- and serology-confirmed HGE indicate that some patterns diagnostic of Lyme disease occur in the absence of any clear evidence of *B. burgdorferi* infection [36]. Clearly, to identify coinfections with *B. burgdorferi* and the HGE agent, alternative diagnostic methods that directly detect specific bacterial components or cultivate the agents in clinical samples will be needed.

The Implications of Coinfection

One alternative to circumvent these confusing diagnostic studies calls for the broad use of doxycycline as the therapeutic agent when the diagnosis is uncertain or if coinfection is suspected. While this approach will generally achieve the desired therapeutic result, the opportunity to learn more about the clinicopathologic process that results from coinfections will be lost. Why is specific etiologic diagnosis important, and what is the relevance of these potential coinfections to human health?

The complete spectrum of Lyme disease is still not known. Suspected chronic Lyme disease is not proven in many patients who are treated empirically on the basis of highly nonspecific clinical findings that could be easily attributed to multiple etiologies. Long-term therapy under these uncertain circumstances can lead only to uncertain conclusions.

Whether therapy-refractory Lyme disease, seronegative Lyme disease, or other forms of severe chronic Lyme disease occur at a high frequency is controversial. A potential explanation for some of these clinical scenarios might include chronic or persistent coinfections with other tick-borne agents that act independently or in concert with *B. burgdorferi*. While these speculations are still unproved, the historical background and accruing data suggest that this hypothesis may be at least partly true [19, 28–30, 37].

Ehrlichioses as Immunosuppressive Infections

Tick-borne fever was first described in Europe in 1932 as a disease of goats that was a cofactor for disease in animals that were infected with the louping ill tick-borne encephalitis virus [38]. Such animals became ill and died of the encephalitis virus infection only when coinfected with the agent of tick-borne fever. It was later discovered that tick-borne fever was caused by a granulocytic ehrlichia now known as *E. phagocytophila* and was transmitted by *I. ricinus* ticks [26].

Since then, numerous examples of severe and fatal coinfections that occur concurrently with or immediately following tick-borne fever have been identified. Most severe have been the disseminated forms of staphylococcal infections, called pyemia, which kill ~2% of the overall sheep population of Great Britain yearly [39]. In addition, severe pulmonary bacterial [40], chlamydial [41], and viral infections [42] are also known to occur in conjunction with *E. phagocytophila* infection. Investigation of this phenomenon has revealed that *E. phagocytophila* infection results in host defense defects that are multifactorial. There are decreases in CD4 and CD8 cell counts [43] and defects in lymphoproliferation of isolated lymphocytes [44] and in neutrophil emigration and phagocytosis [45, 46].

These findings have important relevance to human disease. The agent of HGE is antigenically indistinguishable from and genetically nearly identical to *E. phagocytophila* [7, 14]. In fact, *E. equi* is a biological equivalent of the HGE agent [7, 14, 47, 48]. Among the four recognized fatalities associated with HGE, none of the patients apparently died from ehrlichiosis, but each had pathological findings at postmortem examination that implicated acquired defects in host defense function.

The first fatal case occurred, in spite of empirical broad-spectrum antibacterial therapy, after exsanguination due to severe candidal esophagitis and disseminated candidiasis [13]. The second patient was in remission from chronic lymphocytic leukemia, had previously undergone a splenectomy, and was receiving high-dose corticosteroid therapy at the time of onset of HGE. He exsanguinated from an esophageal ulcer caused by severe herpesvirus infection and was also found to have cryptococcal pneumonia [13].

The third patient died of severe invasive pulmonary aspergillosis [20]. A fourth patient died from a sudden cardiac arrhythmia secondary to myocarditis of unknown etiology (author's unpublished data). If these findings indicate the potential for the HGE agent to allow opportunistic infections secondary to *Ehrlichia*-mediated host defense abnormalities, the risk of more severe concurrent HGE and Lyme disease might be high.

Ehrlichiae are also known to be capable of long-term persistent infection [3, 49]. This is probably an adaptation for survival in an enzootic horizontal transmission cycle between ticks and mammalian reservoirs. *E. canis,* the agent of canine monocytic ehrlichiosis, is well known to persist in the blood of animals in spite of aggressive tetracycline therapy [49]. Many dogs that were previously subclinically infected die in the third phase of chronic ehrlichiosis that seems to be refractory to antimicrobial therapy. *E. phagocytophila* can be transmitted to naive goats by blood transfusion from goats that have recovered from tick-borne fever 2 years previously [50].

It is now well recognized that some ehrlichiae that infect humans may demonstrate some of the same attributes. *E. chaffeensis* was detected in a postmortem examination of liver tissue from a patient who was infected 68 days previously and was treated with full courses of both doxycycline and chloramphenicol [51]. Human monocytic ehrlichiosis is now recognized as a cause of persistent, long-term fever of unknown origin [52]. An *E. canis*–like organism was recently cultivated from the blood of an asymptomatic person from Venezuela who was probably infected for >1 year [53]. Recently, the agent of HGE was detected up to 30 days after onset of illness in the blood of patients who had recovered from HGE [54]. In sum, *Ehrlichia* species have the capability to establish long-term infections in humans.

As yet, no definite evidence of long-term infection or of increased severity or refractoriness of Lyme disease can yet be attributed to concurrent HGE. Carefully designed, case-controlled studies will be required to evaluate these possibilities, and emerging data seem to suggest that patients with concurrent Lyme disease and HGE or babesiosis fare worse than those with Lyme disease only [18, 37].

Thus, the opportunity to study alternative hypotheses concerning the etiology and pathogenesis of the condition now considered chronic Lyme disease may result in a substantial revision of our critical thinking concerning the causative agents. It may also aid in the design and implementation of therapies to reduce the morbidity associated with diseases transmitted to humans by the ubiquitous tick.

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