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ORIGINAL ARTICLE

Presenting Symptoms and Delayed Diagnosis of Ehrlichiosis

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Abstract

Objective: To describe the presenting symptoms, outcomes, and time to diagnosis of ehrlichiosis cases treated at Mayo Clinic, Jacksonville, Florida.

Patients and Methods: We conducted a retrospective analysis of all patients with ehrlichiosis who were treated at Mayo Clinic in Florida from January 1, 2018, to November 1, 2021. Ehrlichiosis was diagnosed via positive serologic or polymerase chain reaction tests. Abstracted variables included patient demographic characteristics, presenting symptoms, outcomes, and time to diagnosis.

Results: Out of 67 patients with ehrlichiosis who were treated at our institution during the study period, 22 were included in our analysis. These patients had diverse presenting symptoms; fever and malaise were common, and severe cases included altered mental status and septic shock. Laboratory test findings included thrombocytopenia, as well as elevated liver enzyme levels and abnormal kidney function. The time to diagnosis varied among the cases studied, with a median time from admission to diagnosis of 4 days.

Conclusion: Prompt treatment with doxycycline was effective, but delayed diagnosis remains a challenge. Our findings underscore the importance of considering ehrlichiosis in differential diagnoses, especially in endemic areas, and emphasize the need for early intervention to prevent severe outcomes.

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Ehrlichiosis, a zoonotic tick-borne disease, is primarily caused by *Ehrlichia chaffeensis*, but may also be caused by other species such as *Ehrlichia ewingii* and *Ehrlichia muris eauclairensis*.[1,2] *Ehrlichia chaffeensis* is a Gram-negative obligate intracellular bacterium and is closely associated with arthropod vectors and vertebrate hosts. Ehrlichiosis is primarily transmitted through tick bites by the lone star tick (*Amblyomma americanum*) and black-legged ticks, depending on the *Ehrlichia* species. The disease has been classified into 4 categories according to their infectious causes: (1) *E chaffeensis* ehrlichiosis, (2) *E ewingii* ehrlichiosis, (3) *Anaplasma phagocytophilum* ehrlichiosis (formerly human granulocytic anaplasmosis), and (4) indeterminate ehrlichiosis/anaplasmosis, which includes infections caused by the recently identified *E muris eauclairensis*. Ehrlichiosis has a wide spectrum of clinical manifestations. Most symptoms are nonspecific and flulike, such as fever, malaise, and pancytopenia, mimicking other common illnesses. However, symptom severity may escalate rapidly, leading to acute kidney and liver failure, necessitating hospitalization.

Diagnosis of ehrlichiosis requires a comprehensive approach because of its nonspecific clinical presentation. It requires a compatible health history, in addition to evidence of infection via laboratory testing. Diagnostic techniques include serologic analysis (IgM and IgG antibodies by indirect immunofluorescence assay), polymerase chain reaction (PCR) amplification of the bacterial genome, immunohistochemical staining, and the identification of intracytoplasmic basophilic inclusion bodies (morulae) in peripheral blood or buffy coat smears. Identification of morulae

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in monocytes (for human monocytic ehrlichiosis) or neutrophil granulocytes (for human granulocytic ehrlichiosis) is particularly indicative of infection. Polymerase chain reaction is considered the standard for diagnosis because of its high specificity and rapid turnaround time.[3] Serologic testing is more widely accessible and can confirm infection retrospectively but may show delayed positivity, limiting its role in acute diagnosis. Most cases are identified by using PCR because of its speed and accuracy, whereas serologic testing is often used to confirm cases or support a diagnosis. Polymerase chain reaction is the most sensitive and specific method of detection during the first week of infection, whereas serologic testing is the preferred method after this period. During the early phase of the infection, serologic test results are often negative because antibody titers often do not reach detectable levels in the first days after illness onset.

In regions where ehrlichiosis is common, prompt exclusion of the disease in differential diagnoses is crucial.[4] Antibiotic treatment, complemented by symptom management, can effectively restore liver and kidney functions, if administered in a timely manner.[5,6] However, delays in diagnosis and treatment may lead to severe complications and death. Because the presenting symptoms of ehrlichiosis are varied and nonspecific, timely diagnosis is challenging. Moreover, reports on the presenting symptoms and disease course of ehrlichiosis are limited. Therefore, we aimed to characterize the presenting symptoms, outcomes, and time to diagnosis for patients with ehrlichiosis who were treated at our institution. Our findings have the potential to enhance awareness, improve early diagnosis, and highlight the simplicity yet effectiveness of prompt treatment for managing this potentially life-threatening condition.

PATIENTS AND METHODS

This study was approved by Mayo Clinic Institutional Review Board (21-012423). All patients provided authorization for research use of their health records. We retrospectively reviewed the electronic health records of all scratch pediatric and adult patients with ehrlichiosis who were treated at Mayo Clinic, Jacksonville, Florida, from January 1, 2018, to November 1, 2021. Ehrlichiosis was diagnosed through positive serologic or PCR test results. All PCR and serologic tests were performed by Mayo Clinic Laboratories, performing all laboratory tests in a manner consistent with Clinical Laboratory Improvement Amendments regulatory standards. Polymerase chain reaction testing was performed with real-time PCR, a qualitative assay, and the results were reported as either negative or positive for *Ehrlichia/Anaplasma* species. Serologic testing included immunofluorescence assay (antibody titer $\geq$1:64), and a positive result suggested current or previous infection.

Patients were excluded due to incomplete data in their health records. We abstracted the following variables: patient age, sex, body mass index (BMI [calculated as the weight in kilograms divided by the height in meters squared]) values, geographic area of residence (ie, rural, suburban, or urban), presenting symptoms, and the presence of headache and/or fever. Furthermore, we evaluated serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and creatinine as markers of liver and kidney function, as well as platelet levels. Elevated serum creatinine level was defined as a creatinine level greater than 1.35 mg/dL, and acute kidney injury was defined as an increase in creatinine level by 0.3 mg/dL. Both kidney and liver function were evaluated at the time of admission and discharge, which we defined as normal or elevated at admission and normal, improved, or elevated at discharge. Normal laboratory test values per Mayo Clinic Laboratories reference standards were defined as follows: creatinine, 0.59 to 1.04 mg/dL; ALT, 7 to 45 U/L; AST, 8 to 43 U/L; white blood cell count, 3.4 to 9.9×10^9/L; and bilirubin, less than 1.2 mg/dL.

Categorical variables were summarized as frequency (%), and continuous variables (eg, patient age, BMI values, and time to diagnosis) were summarized as median (range).

RESULTS

Study Population and Demographic Characteristics

We initially identified 67 patients with ehrlichiosis who were treated at Mayo Clinic,

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Jacksonville, Florida, during the study period. After excluding 45 patients because of incomplete data in their health records, our analysis included 22 patients (Figure 1). The median (range) age at diagnosis was 62 (17-89) years (Table 1), with a distribution of 4 patients younger than 50 years, 14 between 50 and 69 years, and 4 aged 70 years or older. Most patients were male, with a male-to-female ratio of 2.7:1. The median (range) BMI value for this cohort was 25.3 (22.0-34.4). Ehrlichiosis cases were reported in rural (n=5, 23%), suburban (n=8, 36%), and urban (n=9, 41%) settings. The most cases (n=16, 73%) were reported between April and September. Two infections were associated with occupational exposure, and only 5 patients (23%) were able to recall a specific moment of a tick bite while engaging in outdoor activities and before onset of symptoms.

Clinical Presentation

The most common symptoms observed at the time of admission included fever, generalized weakness, headache, and chills (Figure 2). A severe course of the disease, characterized by symptoms such as altered mental status and confusion, was noted for 7 patients. Additionally, 2 patients had seizures and 2 had septic shock, necessitating admission to the critical care unit. Other reported symptoms included nausea/vomiting, localized rash, neck stiffness, poor appetite, and night sweats. Notably, 14 patients (64%) reported headaches, and 19 patients (86%) had fever at admission.

Laboratory Test Findings

All 22 patients had PCR and serologic tests performed, of whom 20 had positive serologic test results and 12 had positive PCR test results (Figure 1). White blood cell counts varied among patients; 5 patients (23%) had leukopenia at the time of admission, 5 (23%) had leukocytosis, and the other 12 (55%) had normal white blood cell counts. Notably, 15 patients (68%) had new-onset thrombocytopenia, which resolved for 12 patients (80%) during their hospital stay (Table 2). The median platelet count at admission was 127.5×10^9/L. Elevated bilirubin levels were noted for 3 patients (14%). Hemoglobin levels were available for 21 patients (95%). Among them, 8 patients (38%) had anemia at the time of admission. Anemia worsened during the course of hospitalization for 5 patients (63%) but did not require transfusion.

Liver Function Assessment. Liver enzyme levels, specifically AST and ALT, at admission varied widely among the patients in our cohort. Aspartate aminotransferase levels ranged from 15 to 638 U/L, whereas ALT levels spanned from 11 to 848 U/L. Most patients (n=14, 64%) had elevated liver enzyme levels (Table 2). At discharge, 10 patients (45%) had considerably improved liver function test results, 2 (9%) continued to have elevated liver enzyme levels, and 3 (14%) did not have liver function tests performed at discharge. The continuously elevated liver enzyme levels in 2 patients were not related to use of any medications, such as acetaminophen.

Kidney Function Test. Serum creatinine levels varied from admission to discharge among the patients in our cohort. Most patients (n=12, 55%) did not have acute kidney injury at admission, but 10 (45%) did have acute kidney injury (Table 2). Among these 10 patients, 6 (60%) improved during their

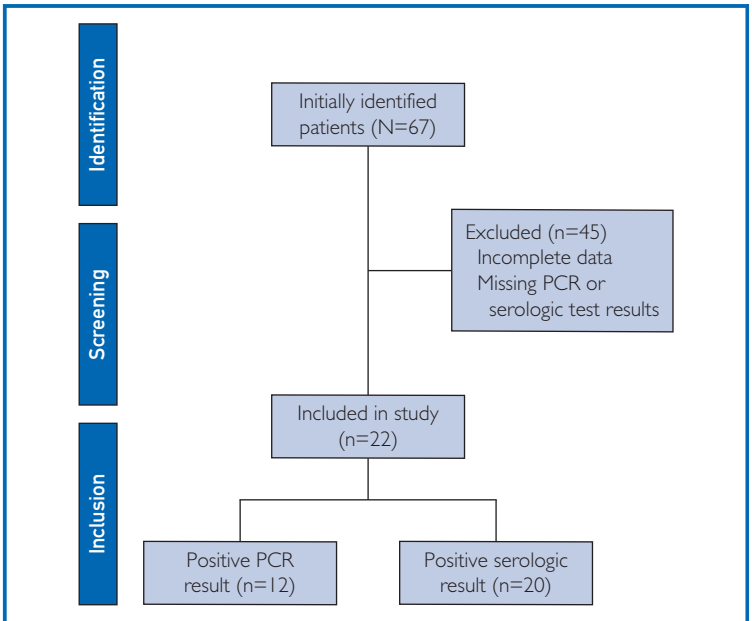

FIGURE 1. Flow diagram of patient selection for analysis. Some patients had positive results with both PCR and serologic testing. PCR, polymerase chain reaction.

TABLE 1. Patient Characteristics (N=22)

Characteristic	Value[a]
Age (y)	62 (17-89)
Sex	
Male	16 (73)
Female	6 (27)
Body weight (kg)	83.3 (57.4-108.0)
Body mass index (kg/m^2)	25.3 (22.0-34.4)
Care type	
Inpatient	15 (68)
Outpatient	7 (32)
Residence type	
Rural	5 (23)
Suburban	8 (36)
Urban	9 (41)

[a]Categorical variables summarized as n (%) of patients; continuous variables (age, body weight, and body mass index) summarized as median (range).

hospitalization course, but 2 (20%) had worsening kidney function. Creatinine levels at admission were not available for 2 patients. At discharge, 11 patients (50%) had serum creatinine levels measured, and 9 (82%) of these patients had normal creatinine levels.

Time to Diagnosis

The time from admission to diagnosis of ehrlichiosis varied among patients and ranged between 0 and 44 days, with a median time to diagnosis of 4 days (Figure 3). Most patients (n=19, 86%) had a time to diagnosis of 10 days or less, although 3 patients (14%) had a time to diagnosis of longer than 10 days. Five patients (23%) had a time to diagnosis of 0 days.

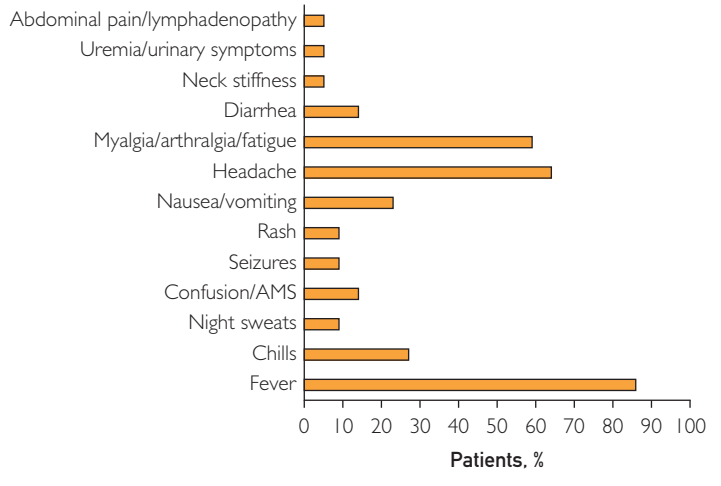

FIGURE 2. Presenting symptoms of ehrlichiosis cases treated at Mayo Clinic. AMS, altered mental status.

Treatment and Response

All patients were treated with doxycycline. Treatment duration varied from 7 to 14 days, and most patients received a daily dose of 200 mg doxycycline. Six patients (27%) received doxycycline on the day of testing or after diagnostic results were available, and 16 (73%) received doxycycline before diagnostic testing was performed.

DISCUSSION

The diagnostic challenge of ehrlichiosis is highlighted by its diverse and nonspecific clinical presentation, which can mimic a range of both infectious and noninfectious illnesses. This challenge is exacerbated by the clinical manifestations of ehrlichiosis, which can range from a mild febrile illness to severe systemic disease leading to multisystem organ failure.[7] Another challenge for clinicians is the considerable delay in symptom onset after a tick bite, often ranging from 7 to 10 days.[8] This delay can lead to a crucial diagnostic gap because patients may not recall or even be aware of the tick bite. This lack of awareness underscores the importance of obtaining a comprehensive patient health history that should extend beyond the usual inquiries about chronic diseases and recent viral or bacterial exposures, especially for patients with a wide range of symptoms. To improve diagnostic accuracy, clinicians must seek details about the patient's recent activities, including trips to endemic areas, outdoor activities, and occupational environments that may increase exposure to tick bites.

This thorough approach to obtaining a comprehensive patient health history is vital because the initial symptoms of ehrlichiosis (fever, chills, malaise, low back pain, and headache) are not unique and may easily be mistaken for many other medical conditions. This may lead to a sepsis-based treatment approach rather than a treatment approach specific to the underlying cause, further delaying timely diagnosis and appropriate treatment. As the disease course progresses, more

TABLE 2. Abnormal Laboratory Test Findings at Admission and Recovery at Discharge (N=22)

Laboratory test finding	No. (%) of patients	
	At admission	Recovered at discharge
Thrombocytopenia[a]	15 (68)	12 (80)
Acute kidney injury[b]	10 (45)	8 (80)
Elevated AST level[c]	14 (64)	8 (57)
Elevated ALT level[d]	13 (59)	6 (46)

[a]Defined as a platelet count of <150,000/μL.
[b]Defined as an increase in serum creatinine concentration by 0.3 mg/dL from baseline.
[c]Defined as a serum AST level of >43 U/L.
[d]Defined as a serum ALT level of >45 U/L.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

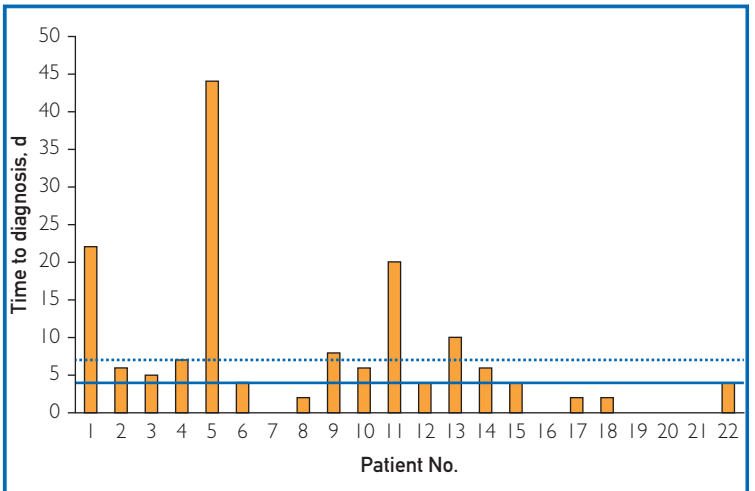

FIGURE 3. Time to diagnosis for patients with ehrlichiosis. Solid line indicates the median time to diagnosis, and dashed line indicates the mean time to diagnosis.

severe and diffuse symptoms, such as arthralgia, myalgia, lymphadenopathy, gastrointestinal tract symptoms, rash, and neurologic and respiratory symptoms emerge, which further complicates the clinical picture.[8,9]

Approximately 57% of patients with ehrlichiosis require hospitalization, and life-threatening complications develop in 11% of patients.[10] In our cohort of patients, 68% of ehrlichiosis diagnoses occurred while the patient was hospitalized, and 36% of patients had a potentially life-threatening condition at the time of admission. Signs of multiorgan dysfunction were noted for 27% of patients. Doxycycline was the primary treatment administered, which was effective in most cases.

The laboratory test findings for ehrlichiosis, although somewhat characteristic, are not definitive on their own for an ehrlichiosis diagnosis, which may also perpetuate delayed diagnoses. The most specific laboratory indicator of ehrlichiosis among our patients was thrombocytopenia and less frequently mild to moderate leukopenia and anemia. This is consistent with previous studies reporting that leukopenia and thrombocytopenia are the most frequently observed abnormalities in ehrlichiosis.[11,12] The incidence of leukopenia for patients with ehrlichiosis ranges from 60% to 70%, and thrombocytopenia occurs in 70% to 90% of patients.[9] Although the simultaneous presence of leukopenia and thrombocytopenia is highly indicative of ehrlichiosis, both of these conditions may be absent if laboratory testing is conducted later in the disease course. Because white blood cells and platelets have a different pace of decreasing and recovering during the ehrlichiosis disease course, ehrlichiosis should not be excluded as a differential diagnosis even if these 2 cell lineages are at a normal level.[13]

Hepatic involvement is common in the ehrlichiosis disease course. Nutt and Raufman[14] reported that among 8 patients with ehrlichiosis, 87.5% had elevated liver enzyme levels that improved with treatment. Aguero-Rosenfeld et al[15] reported that 81% of patients with ehrlichiosis had hepatic dysfunction and elevated liver enzyme levels. Similarly, 64% of patients in our cohort had abnormal liver function; therefore, elevated liver enzyme levels appear to be an important diagnostic indicator of ehrlichiosis. During the course of treatment, abnormal liver function improved in 57% of patients. However, bilirubin level did not appear to be associated with symptom severity. To exclude reasons other than ehrlichiosis for the increased liver enzyme levels, we also abstracted creatine kinase, lactate, and C-reactive protein levels from the health records of all patients included in the study, but these results were in most cases unavailable.

Kidney function was impaired for 10 patients in our cohort but improved for 6 during hospitalization. Although altered kidney function is apparent for some patients with ehrlichiosis, attributing this outcome solely to *Ehrlichia* species infection may be premature. Comprehensive data are needed to establish whether changes in kidney function are a direct consequence of *Ehrlichia* species infection or secondary to other factors commonly present during severe systemic infections. Kuriakose et al[10] reported that patients with ehrlichiosis who were admitted to the intensive care unit had a higher incidence of kidney failure than did those who did not require admission to the intensive care unit. Two case reports described ehrlichiosis-associated nephrotic syndrome in adults, including nephrotic syndrome with minimal change disease[16] and mixed cryoglobulinemia with secondary membranoproliferative glomerulonephritis.[17] Acute kidney injury resulting from rhabdomyolysis in a patient with ehrlichiosis and concomitant statin use was also reported.[18] In our cohort, acute kidney injury was generally mild and usually resolved before discharge, except for 2 patients with severe acute kidney injury. One of these patients required 4 sessions of hemodialysis and subsequent follow-up with nephrologists. The other patient required hemodialysis and had stage 3 chronic kidney disease at last follow-up.

Our study was limited by its retrospective design and relatively small sample size of 22 patients, which may not adequately represent the full spectrum of ehrlichiosis clinical manifestations. Without a control group for comparison, definitively attributing our clinical findings, such as changes in kidney and liver function, solely to ehrlichiosis is also challenging. Other contributing factors or underlying conditions may have influenced these outcomes.

CONCLUSION

Our findings highlight the importance of early detection and management of ehrlichiosis to prevent progression to severe outcomes. Delayed diagnosis of ehrlichiosis is an important challenge for clinicians. Presenting symptoms such as fever, malaise, and body aches can easily be mistaken for other conditions, leading to an initial misdiagnosis. This misstep can escalate into severe clinical scenarios, such as prolonged hospital stays, acute kidney injury, liver failure, and sepsis. Considering ehrlichiosis in the differential diagnosis for patients with presenting symptoms of fever, thrombocytopenia, and leukopenia, especially for those who live in endemic areas, can prompt earlier use of doxycycline and potentially improve patient outcomes. We advocate for increased awareness of the clinical presentation and disease progression of ehrlichiosis among health care professionals to ensure timely diagnosis, expedite treatment, and ultimately improve patient outcomes.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

ETHICS STATEMENT

This study was approved by Mayo Clinic Institutional Review Board (21-012423). All patients provided authorization for research use of their health records.

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Abbreviations and Acronyms: **ALT,** alanine aminotransferase; **AST,** aspartate aminotransferase; **BMI,** body mass index; **PCR,** polymerase chain reaction

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