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Human monocytic ehrlichiosis complicated by hemophagocytic lymphohistiocytosis and multi-organ dysfunction syndrome

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Abstract

Human monocytic ehrlichiosis can manifest as a disease causing multi-organ failure. Rarely, it can cause secondary hemophagocytic lymphohistiocytosis (HLH). Early diagnosis and initiation of treatment for both ehrlichiosis and HLH is lifesaving. Therefore, clinical suspicion of HLH must remain high in the setting of an ehrlichiosis infection.

Keywords

Ehrlichiosis; Hemophagocytic Lymphohistiocytosis

Human monocytic ehrlichiosis[1] (HME), caused by *Ehrlichia chaffeensis*, is an uncommon tick-borne infection endemic to parts of the United States. Although HME typically presents as a mild-moderate illness it can cause severe multi-organ failure, primarily in immunosuppressed individuals (1). Rarely, HME can cause secondary hemophagocytic lymphohistiocytosis[2] (HLH). Here, we present a case of an immunocompetent middle-aged woman who developed severe multi-organ failure and meningoencephalitis due to *E. chaffeensis* infection that was complicated by HLH.

A 41-year-old woman with no significant past medical history was transferred to our institution with 1 week of fevers, malaise, and progressively worsening mental status. Her husband reported a recent camping trip in northern Illinois during which she sustained a tick bite. At the referring hospital, she was found to have distributive shock, acute kidney injury, and encephalopathy. She underwent lumbar puncture showing 144 white blood cells with 71% neutrophils and a negative Gram stain. Broad spectrum antibiotics including doxycycline were started prior to transfer.

On arrival to our institution, she was spontaneously awake but not responsive. Physical examination revealed petechiae over the eyelids. Notable laboratory findings are

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[1]Human monocytic ehrlichiosis (HME)

[2]Hemophagocytic lymphohistiocytosis (HLH)

summarized in Table 1. Evaluation of a bone marrow aspirate demonstrated a hypercellular bone marrow and increased histiocytes with hemophagocytosis as seen in Figure 1.

The patient's clinical and laboratory findings met 6 of the 8 the criteria (diagnostic) for HLH with fevers > 38.5 °C, peripheral blood cytopenias, hypertriglyceridemia, hemophagocytosis in the bone marrow, elevated ferritin, and decreased NK cell activity. Treatment was initiated with prednisone (1 mg/kg) and intravenous immunoglobulin (IVIG, 500 mg/kg) for 3 days (2). Laboratory markers including ferritin, lactate dehydrogenase, and transaminase levels decreased rapidly with treatment.

During her course, the patient remained severely encephalopathic. EEG demonstrated severe encephalopathy without focal seizures, and MRI of the brain revealed diffuse T2/flair enhancement consistent with encephalitis.

Additional results included serum antibody titers for *E. chaffeensis*: IgG > 1:1024 and IgM = 1:20. Titers of *Rickettsia rickettsii* were IgG > 1:1024 and IgM < 1:20. The *Rickettsia* IgG sent from the referring hospital was similarly elevated at 1:512, suggesting previous exposure to *Rickettsia*. Cerebrospinal fluid from repeat lumbar puncture returned positive for *E. chaffeensis* by DNA PCR, confirming the diagnosis of *Ehrlichia* meningoencephalitis.

The patient completed a 14-day course of doxycycline. Several days after completing the antibiotic course, her encephalopathy resolved. Her course was complicated by severe critical illness myopathy; she was discharged to a rehabilitation facility.

E. chaffeensis is an obligate intracellular bacterium transmitted by the lone star tick *Amblyomma americanum*. It is endemic to parts of the United States including the southern regions extending north to Illinois and the upper Midwest.

HME can be fatal in immunocompetent patients and manifests as a multisystem disease, with 42% of cases requiring hospitalization and a case-fatality rate of 3% (3). Early diagnosis is essential, as prognosis worsens if treatment with doxycycline is delayed. HME should be considered in patients who report tick exposure. Specific laboratory tests for HME include DNA PCR and acute and convalescent antibody assays. In the largest case series to date published by Otrock *et al.* in 2015, less than half of their patients had cerebrospinal fluid studies positive for *E. chaffeensis* (4).

HME is rarely a cause of secondary HLH. Otrock *et al.* identified 5 cases of adult HLH secondary to *E. chaffeensis* infection of 76 HLH cases reviewed. In our patient, therapy with prednisone and IVIG for 3 days (2) resulted in rapid improvement in inflammatory markers. Treatment of HLH in addition to doxycycline therapy proved lifesaving in this case.

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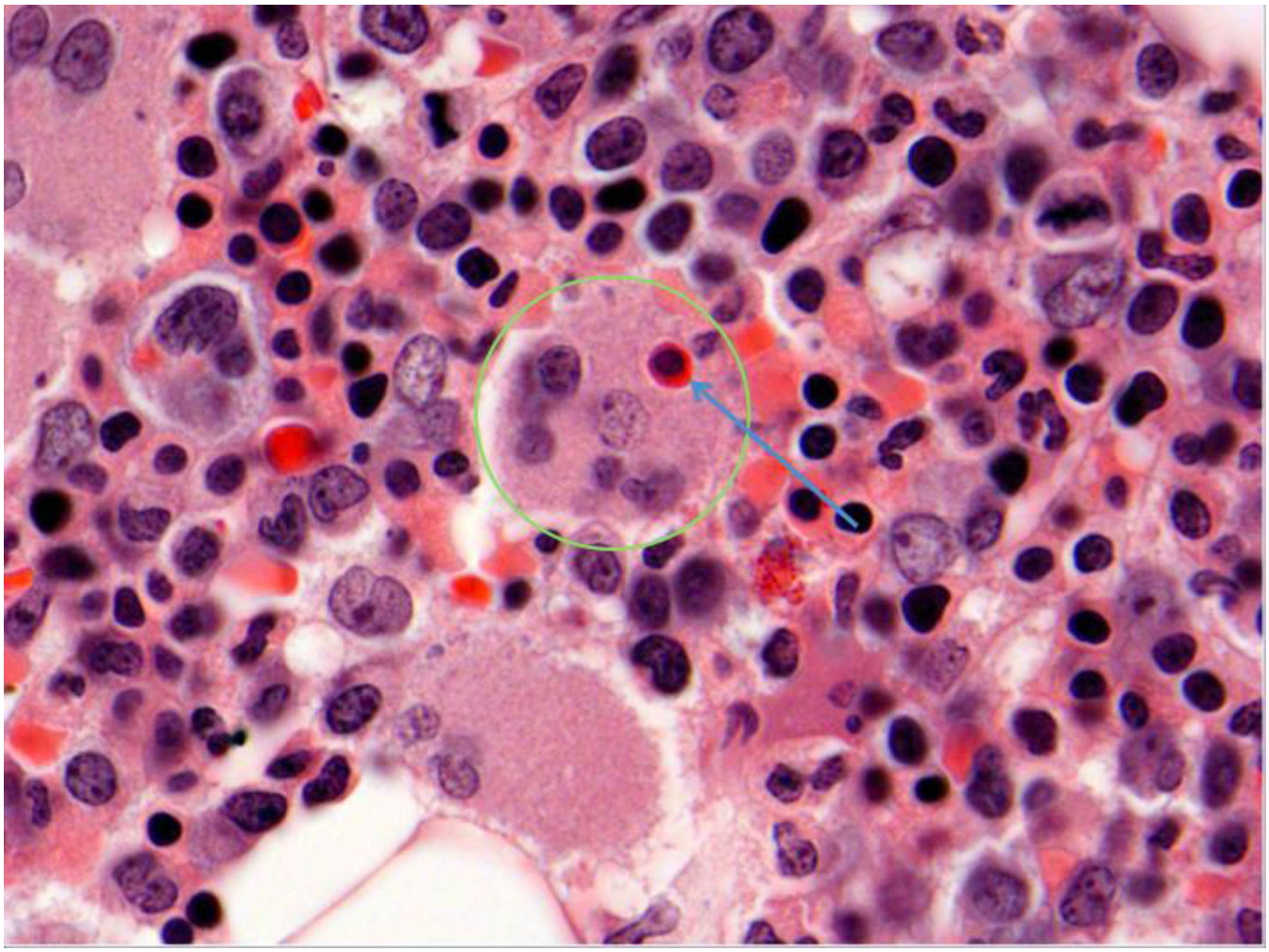

Figure 1.
Section of bone marrow core biopsy demonstrating hemophagocytosis. A histiocyte (green circle), characterized by indistinct nuclear borders and eosinophilic cytoplasm, can be seen englufing an erythoid/RBC precursor (blue arrow).

Table 1

Laboratory evaluation

Laboratory test	Patient's value on admission	Patient's value on day 14	Institutional reference range
Hemoglobin	8.4 g/dL	7.0 g/dL	11.6 – 15.4 g/dL
Platelet count	27 k/uL	131 k/uL	140 – 390 k/uL
White blood cell count	4.2 k/uL	8.1 k/uL	3.5 – 10.5 k/uL
White blood cell differential *	67%N, 19%L, 14%M	Not rechecked	
D-dimer	3465 ng/mL	1987 ng/mL	0 – 230 ng/mL
Fibrinogen	156 mg/dL	371 mg/dL	200 – 393 mg/dL
Lactate dehydrogenase	3137 unit/L	440 unit/L	0 – 271 unit/L
Aspartate transaminase	464 unit/L	18 unit/L	0 – 39 unit/L
Alanine transaminase	138 unit/L	24 unit/L	0 – 52 unit/L
Alkaline phosphatase	246 unit/L	139 unit/L	34 – 104 unit/L
Total bilirubin	3.2 mg/dL	0.8 mg/dL	0 – 1.0 mg/dL
Prothrombin time	9.2 s	11.8 s	9.2 – 13.0 s
Ferritin	13,257 ng/mL	577 ng/mL	11 – 307 ng/mL
Triglycerides	829 mg/dL	Not rechecked	< 100 mg/dL
NK Cell (%)	2 %	Not rechecked	4–25%
NK Cell (abs.)	< 20 cells/uL	Not rechecked	70–760 cells/uL

* Neutrophils = N, Lymphocytes = L, Monocytes = M