IDCases 20 (2020) e00813

Contents lists available at ScienceDirect

IDCases

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Case report

# Ehrlichiosis Presenting as Hemophagocytic Lymphohistiocytosis in an Immunocompetent Adult

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ARTICLE INFO

*Article history:*
Received 6 May 2020
Received in revised form 8 May 2020
Accepted 8 May 2020

*Keywords:*
Ehrlichiosis
Hemophagocytic Lymphohistiocytosis
Human Monocytic Ehrlichiosis
Tick-Borne Illness
Secondary HLH

ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a fatal, immunologic syndrome characterized by dysregulated tissue inflammation. HLH can be either primary or secondary; with the latter typically resulting from an infection. Diagnosis requires five or more of the following: fever, splenomegaly, cytopenia, hypertriglyceridemia, hemophagocytosis via biopsy, low natural killer (NK) cell activity, elevated ferritin and soluble CD25 level (sCD25). We present a case of HLH related to ehrlichiosis.

In order to mount an effective immune response against microbes such as *Ehrlichia* chaffeensis, the host must have preserved NK cell function. Being that HLH Is characterized as a state of depleted NK cell function, It is crucial to investigate the role NK cell function has in the setting of HLH on the infectivity of *Ehrlichia* species.



## Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening, immunologic syndrome that is characterized by excessive inflammation and tissue injury. The suspected mechanism is thought to be from a lack of the body's innate ability to down regulate mechanisms of inflammation [1]. In HLH, macrophages are believed to become activated and secrete excessive amounts of cytokines. Additionally, T lymphocytes and natural killer (NK) cells are unable to clear the activated macrophages. This leads to a dysregulation of the natural feedback loop that occurs in the immune system.

HLH is divided into two major categories: primary and secondary. Primary HLH is most commonly seen in the pediatric population and is associated with a variety of inherited immunodeficiencies and genetic mutations. Secondary HLH is the byproduct of a triggering event, the most common of which is infection. The diagnostic criteria for HLH was developed in 2004 by the Histiocyte Society for HLH Diagnosis [2]. These criteria include: fever > 38.5 °C, splenomegaly, cytopenia, hypertriglyceridemia (fasting >265 mg/dL), hemophagocytosis in bone marrow, spleen, lymph nodes, or liver, low/absent NK-cell activity, ferritin >500 mg/dL, and an elevated soluble CD25 (sCD25) level. The diagnosis of HLH is made if the patient satisfies at least five of the above criteria.

Ehrlichiosis is a tick-borne infection, with different subtypes of infection caused by different species of *Ehrlichia*. Human Monocytic Ehrlichiosis (HME) is the specific subtype of ehrlichiosis found in Missouri and nearby states, with the etiologic agent being *Ehrlichia chaffeensis*. *E. chaffeensis* is transmitted via the lone star tick (*Amblyomma americanum*). Missouri is recognized as one of the states with the highest incidence of HME, with most cases occurring in May-August. The incubation period for ehrlichiosis caused by *E. chaffeensis* lasts 5-14 days. Common presenting symptoms are nonspecific including fever, headache, myalgia, malaise. Less commonly, gastrointestinal and respiratory symptoms can be observed. Rash is present in only 30% of adult cases. Laboratory findings typically include a combination of leukopenia (usually with pronounced lymphopenia), thrombocytopenia, elevated hepatic transaminases, hyponatremia, anemia, elevated creatinine kinase (CK), and elevated lactate dehydrogenase (LDH). Reactive lymphocytosis, or improvement in lymphocyte count, is routinely observed with successful treatment. Rarely morulae, or intracellular inclusions, may be observed in monocytes of the

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https://doi.org/10.1016/j.idcr.2020.e00813

blood, cerebrospinal fluid, or bone marrow phagocytes which would confirm the diagnosis. Diagnosis is typically made with a serum polymerase chain reaction (PCR) for *E. chaffeensis*; serologic testing is available but less useful and requires 4-fold rise in convalescent titers for confirmation. Treatment is with doxycycline primarily, although tetracycline and rifampin may be used [3,4].

We review the case of a patient who was admitted to a tertiary academic medical center with headaches, fevers, and neutropenia and ultimately found to have HLH secondary to ehrlichiosis. This case report reviews the current literature on *Ehrlichia*-induced HLH and also explores possible mechanisms to explain the pathophysiology of *Ehrlichia*-induced HLH.

## Case Report

A 63-year-old Caucasian male from Missouri with a past medical history of hypertension, coronary artery disease, hypothyroidism, and chronic low back pain was admitted to the general medicine service as a transfer for further evaluation and management of fever, headache, and neutropenia during the month of July. Prior to initial presentation, the patient had reported a ten-day history of severe headaches with febrile episodes as high as 103 °F. In addition to these complaints, the patient was noted to have a progressively worsening cough with clear sputum production. He was evaluated at his primary care physician's office and given a course of levofloxacin which did not improve his symptoms. At the outside hospital the patient was noted to have a white blood cell count of 1,920 cells/uL (with lymphopenia), platelet count of 42,000 cells/uL, and lactate of 2 mg/dL. The patient was administered four liters of normal saline as a bolus for initial fluid resuscitation. Vancomycin and piperacillin-tazobactam were initiated for empiric broad-spectrum antimicrobial therapy. Prior to transfer, the patient also underwent computed tomography (CT) imaging of his chest, abdomen, and pelvis which noted mild hepatosplenomegaly and mild perinephric fat stranding. The patient was subsequently transferred to a tertiary academic center for further evaluation.

On arrival, additional history was obtained in which the patient denied any sick contacts, recent travel outside of the state of Missouri, history of intravenous drug abuse, consumption of non-pasteurized dairy, or consumption of raw/undercooked meat. The patient did note that he lived within 100 feet of a large lake, admitted mosquito exposure, and the use of well water since 2005. Physical examination was significant for neck pain with flexion, however the patient did note that he had baseline neck pain from previous neck surgeries. Furthermore, the exam also revealed bibasilar crackles on lung auscultation, abdominal distention, and a small, circumferential, vesiculopapular rash on the left gluteal region. Laboratory studies were remarkable for leukopenia of 1,540 cells/uL, hemoglobin of 10.9 g/dL, platelet count of 35,000 cells/uL, serum creatinine of 2.96 mg/dL, aspartate aminotransferase 98 units/L, and alanine aminotransferase 64 units/L. The white blood cell count differential was notable for neutropenia (1,370 cells/uL), lymphopenia (120 cells/uL), and monocytopenia (30 cells/uL). Other relevant laboratory evaluation included an elevated LDH of 535 units/L and elevated CK of 3,972 units/L.

He was started on empiric coverage for potential meningitis with vancomycin, meropenem, doxycycline, and acyclovir. Additionally, urine Legionella antigen and fourth generation human immunodeficiency virus (HIV) 1/2 antigen and antibody screen were ordered and returned negative. The patient's stay was complicated by oliguric acute kidney injury, persistent neutropenia and thrombocytopenia. A renal ultrasound was obtained which incidentally reported splenomegaly. Despite initial management, the patient developed acute hypoxemic respiratory failure necessitating transfer to the medical intensive care unit and intubation. Following stabilization, a battery of testing was performed including: ADAMTS13 level, Epstein-Barr virus serology (EBV), serum Cytomegalovirus PCR (CMV), Borrelia serology, Rocky Mountain Spotted Fever serology, and Lyme Disease serology – all of which returned negative. Peripheral smear was ordered which demonstrated pancytopenia with rare atypical lymphocytes and no schistocytes, making microangiopathic hemolytic anemia unlikely. The patient ultimately underwent lumbar puncture; CSF analysis demonstrated protein 80 mg/dL (elevated), glucose 133 mg/dL, no white cells, and red cells 48 cells/uL. A meningitis multiplex PCR panel was negative.

To further evaluate his profound thrombocytopenia, hematology/oncology was consulted. Per hematology/oncology recommendations serum triglycerides, ferritin, and sCD25 levels were obtained due to concern for HLH. These were elevated at 617 mg/dL, 860.7 pg/uL, and 1648 pg/mL (reference range <1033 pg/mL) respectively. Given the constellation of fever, splenomegaly, elevated triglycerides, elevated ferritin, and elevated sCD25 levels the diagnosis of HLH was

**Table 1**
Comparison of Documented Cases of *Ehrlichia* Induced Hemophagocytic Lymphohistiocytosis in Immunocompetent Adults.

| Author | Patel et al. | Otrock et al [5] | Otrock et al [5] | Otrock et al [5] | Otrock et al [5] | Pandey et al [7] | Kumar et al [8] | Kaplan et al [9] | Badireddy et al [10] | Provenzano et al [12] |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | 65 | 47 | 59 | 52 | 62 | 74 | 63 | 41 | 74 | 47 |
| Gender | Male | Female | Female | Female | Male | Male | Male | Female | Male | Male |
| Fever (Present or Absent) | Present | Present | Present | Present | Present | Present | Present | Present | Present | Present |
| Splenomegaly (Present or Absent) | Present | Absent | Absent | Absent | Present | Absent | Present | Absent | Absent | Absent |
| Absolute Neutrophil Count (cells/microliter) | 1390 | 1210 | 600 | 100 | 3900 | N/A | 1300 | N/A | N/A | N/A |
| Hemoglobin (grams/deciliter) | 10.9 | 8.6 | 10.6 | 7.9 | 8.8 | N/A | 8 | 8.4 | 10 | N/A |
| Platelets (cells/microliter) | 35,000 | 65,000 | 41,000 | 25,000 | 20,000 | 16,000 | 19,000 | 27,000 | 16,000 | 22,000 |
| Triglycerides (milligram/deciliter) | 617 | 710 | 307 | 650 | 516 | 147 | 436 | 829 | 387 | 1,234 |
| Ferritin (picogram/microliter) | 860.7 | 10,002 | 2,863 | 47,290 | 84,676 | 12,369 | 70,097 | 13,257 | 12,000 | >15,000 |
| Hemophagocytosis by Bone Marrow Biopsy (Yes or No) | N/A | No | Yes | Yes | N/A | Yes | N/A | Yes | Yes | Yes |
| Soluble CD25 Receptor Level (pg/mL) | 1648 | 51,973 | N/A | >575,000 | N/A | N/A | N/A | N/A | N/A | 52,212 |
| Low/Absent NK Activity Level | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Ehrlichia Diagnosis Method | Serum PCR | Serum PCR and CSF PCR | Serum PCR | Serum PCR and CSF PCR | Serum PCR | Unclear | Serum PCR | Serum Titers and CSF PCR | Serum PCR | Serum PCR and CSF PCR |
| Clinical Outcome | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered |

made. Later in the patient's hospital course his serum *Ehrlichia* PCR was positive, and the patient's antimicrobial regimen was de-escalated to doxycycline with continued improvement in the patient's condition. Of note the patient's lymphopenia resolved prior to discharge, in addition his anemia and thrombocytopenia also improved. The patient was ultimately diagnosed with HLH secondary to ehrlichiosis, and discharged on oral doxycycline to complete ten total days of therapy.

## Discussion

Secondary HLH has been well documented in the literature, however secondary HLH as a result of ehrlichiosis has a very limited number of reported cases available for review. A 2015 case series reviewed 76 cases of HLH at a single Midwestern academic tertiary care center, and was able to identify only five cases of *Ehrlichia*-induced HLH [5]. Of the five cases of *Ehrlichia*-induced HLH, four cases were reported to be in adult patients and one was in an adolescent patient. Despite being a rare etiology of HLH, *Ehrlichia* should be considered as a possible cause of secondary HLH especially in areas that are endemic to *Ehrlichia* species. Moreover, early identification of *Ehrlichia* as the etiology of HLH is critical as patients who received doxycycline therapy greater than eight days after the onset of symptoms had increased mortality [6].

In addition to the four adult patients in the aforementioned case series, to date there have been six additional case reports of *Ehrlichia*-induced HLH in adults [7–12]. All of the immunocompetent patients in these case reports were also noted to recover once the underlying diagnosis of ehrlichiosis was made and doxycycline therapy was initiated. Of note, a patient reported by Naqash et al was immunocompromised prior to the diagnosis of *Ehrlichia*-induced HLH and did not recover from this condition. A summary of the patients reported to have *Ehrlichia*-induced HLH can be seen in Table 1. Outside of these rare case reports of *Ehrlichia*-induced HLH, there is little discussion of *Ehrlichia* as a possible cause of this life-threatening immunologic syndrome.

Infection is considered to be the most common etiology of secondary HLH with EBV being identified as the causative viral agent in most cases [2,13,14]. A review of 2197 cases of secondary HLH identified 50.4% of cases being the result of an infection [14]. Of the 1108 cases caused by infection, 68.8% of cases were the result of a viral infection (EBV and HIV being the most common viruses). Bacterial infections only accounted for 9.4% of all cases of secondary HLH with *M. tuberculosis* being the most common bacterial pathogen. *Ehrlichia* was not identified as a common cause of secondary HLH.

A hallmark of HLH is absent or low-level NK cell activity and an elevated level of soluble CD25 receptors (sCD25R) also known as interleukin 2 receptors (IL-2R). NK cells are innate-like lymphocytes which mount an immunologic response to pathogens via a conserved T-cell receptor [15,16]. Gram negative, lipopolysaccharide (LPS) negative, alpha-proteobacteria such as *Ehrlichia* are detected by NK cells via direct recognition of microbial lipids [17]. Additionally, NK cells have been identified to be specifically involved in immunity against microbial pathogens that lack toll-like receptor (TLR) specific ligands, such as *Ehrlichia* [6]. *Ehrlichia chaffeensis* represents a microbe which lacks a TLR specific ligand and requires NK cell activity for the host to mount an immune response, and HLH represents a state of reduced NK cell activity. Therefore, it may be reasonable to conclude that HLH is a state in which *E. chaffeensis* is able to flourish due to diminished NK cell activity. However, at this time additional studies would need to be conducted to isolate the effect that *E. chaffeensis* has on host NK cells in the setting of HLH.

Furthermore, NK cells have also been identified to have a role in the prevention of cellular injury during secondary ehrlichiosis. NK cells have been shown to promote the production of Forkhead box P3 (Fox3+) regulatory T (Treg) cells and cytokine transforming growth factor β (TGF-β), both of which prevent tissue injury [18]. Additional studies have demonstrated that NK cells promote the production of Treg cells via interleukin-2 (IL-2) [19]. HLH represents a state where there is diminished/absent NK cell activity. Therefore, it is possible that the cellular damage observed in *Ehrlichia*-induced HLH may be propagated by diminished NK cell activity, and by proxy the diminished production of Treg cells. The relationship between NK cell activity, Treg cell production, and cellular injury from ehrlichiosis, in the setting of HLH will need additional investigation.

## Conclusion

HLH represents a constellation of findings that are characterized by an absent or low level of NK cell activity and an elevated level of soluble CD-25 receptors. The established literature has demonstrated that host immune response to *Ehrlichia chaffeensis* depends on preserved NK cell function. Furthermore, it appears that NK cells also stimulate Treg cell function which play a crucial role in prevention of cellular injury by *Ehrlichia chaffeensis.* The diminished NK cell activity state in HLH may represent a setting in which *Ehrlichia* is able to flourish. Therefore, it is imperative to further evaluate the role that the absence of NK cell activity in HLH has on the infectivity of *Ehrlichia* species.

## Ethics Approval and Consent to Participate

Care was taken to ensure that the patient identifiers were removed in the process of creating this case report, and patient's family was made aware of this case report.

## Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Availability of data and materials

Not Applicable.

## Funding

There are no sources of funding to report for this case report.

## CRediT authorship contribution statement

**Tarang Pankaj Patel:** Writing - review & editing. **Phillip Beck:** Writing - review & editing. **Dennis Chairman:** Project administration, Conceptualization, Supervision. **Hariharan Regunath:** Project administration, Conceptualization, Supervision.

## Declaration of Competing Interest

The authors declare that they have no competing interests.

## Acknowledgements

Not Applicable.

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