American Journal of Medical Case Reports, 2021, Vol. 9, No. 11, 557-563
Available online at http://pubs.sciepub.com/ajmcr/9/11/11
Published by Science and Education Publishing
DOI:10.12691/ajmcr-9-11-11

Ehrlichia chaffeensis-associated Hemophagocytic Lymphohistiocytosis: A Case Series and Literature Review

Tasaduq Fazili[1,*], Ekta Bansal[1], Dorothy Garner[1], Vijayendra Bajwa[1], Harpreet Kaur[2], Charles Schleupner[1]

[1]Virginia Tech Carilion School of Medicine, Section of Infectious Diseases, Department of Medicine, Carilion Clinic, Roanoke, VA 24014, USA
[2]Virginia Tech Carilion School of Medicine, Department of Medicine, Carilion Clinic, Roanoke, VA 24014, USA
*Corresponding author: tnfazili@carilionclinic.org

Received July 04, 2021; Revised August 09, 2021; Accepted August 17, 2021

Abstract **Introduction:** Hemophagocytic lymphohistiocytosis (HLH) is an uncommon condition characterized by abnormal, excessive immune activation resulting in severe cytopenias from an uncontrolled inflammatory response. It can be primary/ familial or secondary/sporadic. Infections, particularly viral infections are a common cause of secondary HLH. HLH due to Human monocytic ehrlichiosis (HME) is very rare, hence we are reporting our cases. **Objective:** To review cases of Ehrlichia-associated HLH at our institution and perform a literature review regarding this entity. **Methods:** We reviewed cases of Ehrlichia-associated HLH for the previous two years at our institution (Carilion Clinic). We then performed a review of the published literature on it, using Pubmed. **Results:** Over the past two years, five cases of Ehrlichia-associated HLH were diagnosed at our hospital. The average age of the patients was 67 years with predominantly males. All the patients were pancytopenic, and a majority had abnormal liver function tests. Diagnosis of ehrlichiosis was made by serum polymerase chain reaction (PCR) assay on blood. Patients had further testing done because of lack of clinical improvement. All patients had significantly elevated ferritin levels. Bone marrow biopsy samples of all patients showed findings of hemophagocytosis. All, but one, patients were treated with doxycycline and a combination of etoposide and dexamethasone. Three patients recovered while two died. On review of medical literature, we found a total of only 36 cases of Ehrlichia-associated HLH, including our five cases. There were 19 adults and 17 children. Both population groups showed varying degrees of pancytopenia. Splenomegaly was relatively uncommon, seen in less than one-third of the patients. Ferritin and triglyceride levels were routinely elevated. Bone marrow biopsy showing hemophagocytosis was the confirmatory test in all patients. A significant number of patients, both adults and children, required a combination of doxycycline and chemotherapy (etoposide and dexamethasone) to achieve clinical cure. Children had a better prognosis than adults, with one child and four adults succumbing to their illness. **Conclusions:** Ehrlichia-associated HLH is a rare but emerging disease entity. In endemic areas, a high degree of suspicion is required to diagnose ehrlichiosis and HLH resulting from it. Early diagnosis and prompt initiation of treatment for HLH is key to a favorable outcome.

Keywords: *Ehrlichia, hemophagocytic lymphohistiocytosis, HLH*

Cite This Article: Tasaduq Fazili, Ekta Bansal, Dorothy Garner, Vijayendra Bajwa, Harpreet Kaur, and Charles Schleupner, "*Ehrlichia chaffeensis*-associated Hemophagocytic Lymphohistiocytosis: A Case Series and Literature Review." *American Journal of Medical Case Reports*, vol. 9, no. 11 (2021): 557-563. doi: 10.12691/ajmcr-9-11-11.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon condition characterized by abnormal, excessive immune activation resulting in severe cytopenia from an uncontrolled inflammatory response. It is broadly divided into two categories - primary or familial and secondary or sporadic. Infections are a common cause of secondary HLH, in particular, viral infections. Human monocytic ehrlichiosis (HME) has been rarely recognized as an etiology for HLH. As HME is a common zoonotic infection with increasing incidence, predominantly in the Mid-Atlantic, South Central and Southeastern United States, it is important for clinicians to recognize this rare presentation as delayed diagnosis can lead to worse outcomes. We report five cases seen at our institution within last 2 years and review the literature regarding this entity.

2. Case 1

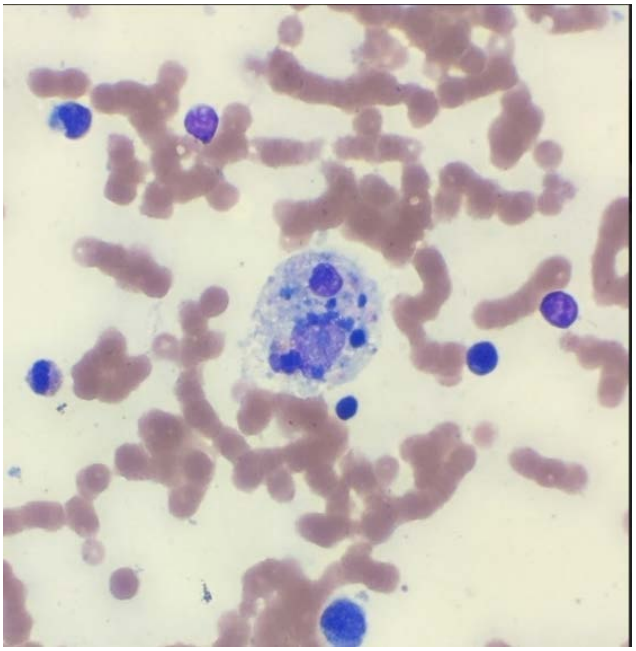

Figure 1. Bone marrow biopsy showing features of hemophagocytosis

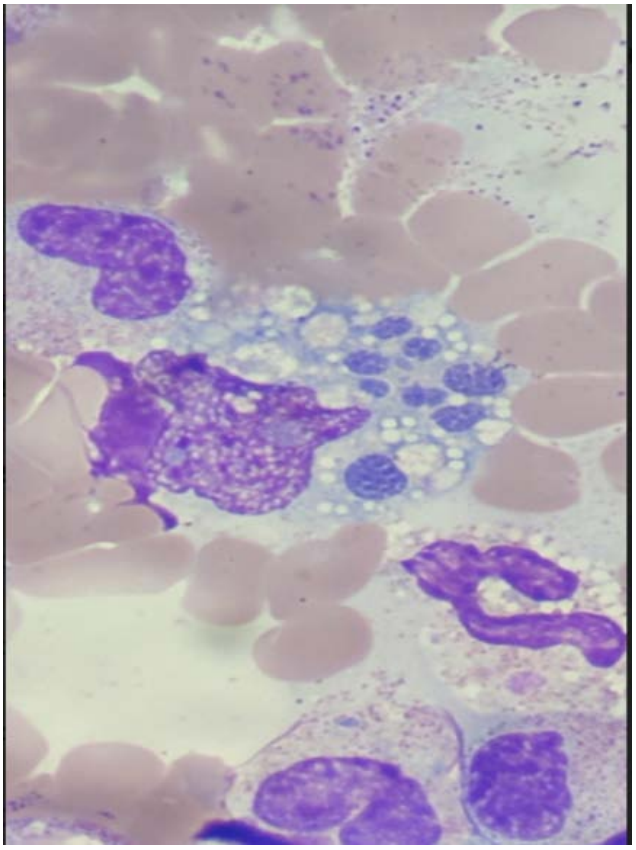

Figure 2. Peripheral blood smear showing presence of morula in a monocyte

A 72-year-old female with ulcerative colitis in remission presented with one week of generalized weakness and severe abdominal pain. At presentation, she was afebrile, tachycardic and hypotensive. Laboratory studies revealed a white blood cell count (WBC) of 11.7 K/uL, a platelet count of 34 K/uL, hemoglobin=13.1 g/dL, aspartate aminotransferase (AST)=182 IU/L, and alanine aminotransferase (ALT)=93 IU/L. She was also found to have acute renal failure (creatinine 3.23 mg/dL) with an anion gap lactic acidosis (9.9 mmol/L). Broad-spectrum antibiotics were started. She underwent an exploratory laparotomy, however with no acute findings. Her clinical course worsened, and she developed fever and coagulopathy. (INR=3.1, fibrinogen=68 mg/dL). Additional laboratory studies were remarkable for a ferritin of 31,754 ng/mL, LDH of 1215 IU/L, triglycerides of 368 mg/dL and developed leucopenia. Doxycycline was empirically initiated at 100 mg twice daily. Due to multi-organ dysfunction, persistent fevers, cytopenia with elevated ferritin levels, a bone marrow biopsy was performed which demonstrated hemophagocytosis (Figure 1) and peripheral blood smear showed monocytic cells with morulae (Figure 2). *Ehrlichia chaffeensis* DNA PCR was positive from the blood. A diagnosis of HLH was made and therapy was initiated with etoposide and dexamethasone. She remained critically ill and continued to decompensate. A comfort care approach was ultimately adopted due to family request, and she expired.

3. Case 2

A 77-year-old male with chronic atrial fibrillation, benign prostatic hypertrophy, obstructive sleep apnea and hypertension was transferred to our center due to worsening thrombocytopenia of 19k/uL and persistent encephalopathy. The patient had presented 9 days prior to a community hospital after a fall with altered mental status. His initial laboratory studies were significant for mild leukopenia WBC=4.1 K/uL, mild thrombocytopenia platelet count=137 K/uL and hyponatremia serum sodium=132 mmol/L. The assessment of stroke-like symptoms was negative. He subsequently developed fever with temperature up to 103.3^{o}F and was empirically started on broad spectrum antibiotics (including doxycycline) for possible meningitis. CT scans of the chest, abdomen and pelvis were unremarkable. The patient subsequently developed acute kidney injury with an elevation in creatinine to 2 mg/dL.

A lumbar puncture showed a cerebrospinal fluid (CSF) WBC=72/mm^3 (95% lymphocytes), RBC=1/mm^3, glucose of 75 mg/dL and protein of 120 mg/dL. CSF was negative for bacterial and viral pathogens. An acute molecular panel for tick borne diseases sent on the blood revealed a positive PCR for *Ehrlichia chaffeensis*. Additional laboratory studies showed a ferritin elevated to 2320 ng/ml and a triglyceride of 164mg/dl. With high clinical suspicion of HLH, a bone marrow biopsy was performed which confirmed evidence of hemophagocytosis. Patient was continued on doxycycline alone (without steroids/etoposide) and showed marked clinical improvement. He was subsequently discharged home to complete a two-week course of doxycycline.

4. Case 3

A 56-year-old female with past medical history of fibromyalgia presented to the emergency department at her local community hospital with a six-day history of

fevers, headache, myalgia, nausea and vomiting. Upon presentation, she was found confused, febrile with temperature 102 F, tachycardic and hypotensive, with a faint petechial rash on her abdomen and lower extremities. Her initial lab studies were remarkable for leukopenia (WBC=0.8 K/uL), thrombocytopenia (platelets=26 K/uL), acute renal insufficiency (creatinine 1.35mg/dl), and elevated liver enzymes (AST=373 IU/L, ALT=84 IU/L). She was transferred to our center for further management. She underwent a lumbar puncture (LP) with normal CSF studies. Peripheral blood smear showed an inclusion body consistent with a morula, suggestive of Ehrlichiosis. This was later confirmed by a positive polymerase chain reaction (PCR) for *Ehrlichia chaffeensis* sent from the blood. Doxycycline was started at 100 mg twice a day. However, she continued to worsen clinically and developed respiratory failure requiring intubation.

Given her thrombocytopenia and persistently elevated liver enzymes, with a significantly elevated ferritin (47,547 ng/uL) and triglycerides (452 mg/dL), there was a strong suspicion for hemophagocytic lymphohistiocytosis (HLH). A bone marrow aspiration was performed, which confirmed evidence of hemophagocytosis. Aggressive HLH therapy was begun with dexamethasone and etoposide. She ultimately improved, completed her course of antibiotics, steroids and etoposide, and was discharged to a skilled nursing facility for rehabilitation.

5. Case 4

A 64-year-old male with chronic atrial fibrillation, diabetes mellitus type 2, chronic kidney disease and hypertension presented to a local community hospital with fever, dizziness, malaise and anorexia. He was found to be in acute renal failure (creatinine=2.45 mg/dl) with an acute myocardial infarction and subsequently transferred to our hospital for further management. On presentation, he was febrile with temperature upto 102 F and tachycardic with heartrate in 120s. His lab work was significant for leukopenia (WBC=2.3 K/uL), thrombocytopenia (platelets=41 K/uL) and elevated liver enzymes (AST=157 IU/L, ALT=136 IU/L). After admission, his respiratory status worsened, and he was ultimately intubated. Doxycycline was started twice a day for presumed tickborne illness.

A positive polymerase chain reaction (PCR) for *Ehrlichia chaffeensis* sent from the blood resulted positive. Additionally, bone marrow biopsy was also performed in view of the persistent leukopenia and thrombocytopenia which revealed evidence of hemophagocytosis. Diagnosis of HLH was made and therapy with corticosteroids and etoposide was initiated. Unfortunately, he developed multiorgan failure and was subsequently transitioned to palliative care, where he expired.

6. Case 5

A 68-year-old male with rheumatoid arthritis, on weekly methotrexate, presented with malaise and decreased urine output for one week duration. Initial lab studies were remarkable for leukopenia (WBC=2.4K/uL), thrombocytopenia (platelets=12K/uL) , acute renal failure (Creatinine 6.6 mg/dL), elevated AST of 173 IU/L and hyperbilirubinemia (direct bilirubin 6.4 mg/dL). *Ehrlichia chaffeensis* was detected by PCR from the blood and doxycycline was started 100mg twice a day. Bone marrow biopsy, performed because of persistent leukopenia and thrombocytopenia, showed evidence of hemophagocytosis. He was diagnosed with HLH and etoposide and corticosteroids were initiated. He briefly required renal replacement therapy. His renal failure and hepatic dysfunction ultimately resolved. He completed the course of doxycycline in the hospital and was discharged home in stable condition, to continue chemotherapy and steroid taper.

7. Discussion

HME is a common zoonotic illness predominantly seen in the mid-Atlantic, south-central and southeastern United States [1]. The main pathogen is *Ehrlichia chaffeensis*, which was first described to cause human disease in 1986, in a man from rural Arkansas [2]. Human Ehrlichiosis is spread by the lone star tick (*Amblyomma americanum*) and the distribution of cases follows the range of this tick along with the white-tailed deer. The typical case involves a male patient with significant outdoor exposure in an endemic region during the summer months. The number of ehrlichiosis cases due to *E. chaffeensis* has increased steadily in the past few years [3]. Symptoms of HME are often nonspecific and include fever, malaise, fatigue, myalgia, and headache in the early stages. Children more commonly present with rash than adults. If untreated, the disease can progress to meningoencephalitis, renal failure, a bleeding diathesis and eventually multiorgan system failure and death.

The diagnosis of HME is predominantly clinical, based on history and physical examination. If there is a high clinical suspicion, treatment should not be delayed for confirmatory testing. Initial labs are usually notable for pancytopenia and elevated serum transaminases [3]. Additional confirmatory testing includes a Wright-stained peripheral blood smear, which may reveal the intracytoplasmic inclusions known as morulae, located within monocytes. This is relatively infrequently positive during HME, found only in 1-25% of patients [4,5]. Inclusion bodies are found more often in immunosuppressed patients and those with a high burden of disease [4,5,6]. The recommended test for diagnosis of an acute infection is PCR with sensitivities reported to range between 60-85% [3,4,5]. Serodiagnosis is a sensitive method of confirmation, which is indicated by a 4-fold change in antibody titers to a minimum of 1:64. Serum titers are not useful in the acute diagnosis because only 22-44% have a high titer within the first week of illness, but up to 100% will become positive 14 days (about 2 weeks) after onset of illness [3,4,5].

The treatment of choice for both adults and pediatric patients is doxycycline continued for at least 3 days after the subsidence of fever with evidence of clinical improvement, typically for a 5–7-day course [3]. In patients who are allergic to or cannot tolerate doxycycline,

rifampin could be used as an alternative agent. Chloramphenicol is a reasonable option but is not readily available in the US. There are extremely limited clinical data for the use of levofloxacin, which is not recommended as a treatment option at this time.

HLH is a rare syndrome associated with uncontrolled activation of the mononuclear phagocytic system, which results in an uncontrolled hyper-inflammatory response and phagocytosis of hematopoietic cells by the activated macrophages [7]. There is no single diagnostic test for HLH; a combination of clinical and laboratory abnormalities is used to make the diagnosis, with the presence of at least five of the following eight criteria [8]:

- Fever of at least 38.5°C
- Splenomegaly
- Cytopenias affecting at least 2 lineages (hemoglobin < 10 g/dl, platelets < 100,000/µL, absolute neutrophil count < 1000/µL)
- Triglycerides greater than 265 mg/dL or fibrinogen less than 150 mg/dL
- Serum ferritin greater than 500 ng/mL
- Hemophagocytosis in bone marrow, liver, spleen, or lymph node
- Low or absent NK cell activity
- Elevated CD 25 (soluble interleukin 2 receptor value) above lab reference range.

HLH can be broadly categorized into primary/familial HLH, or secondary/sporadic HLH. Familial HLH is seen in infants and young children with genetic defects of lymphocyte cytotoxicity, which result in lack of the normal downregulation of activated macrophages and lymphocytes.

Table 1. Clinical features and laboratory values of patients with Ehrlichia-induced HLH (adults)

Reference	Age (years)	Gender	Fever	Splenomegaly	ANC (cells/µL)	Hemoglobin (g/dL)	Platelets (cells/µL)	Triglycerides (mg/dL)	Ferritin (pg/µL)	Hemophagocytosis on bone marrow	Soluble CD25 Receptor level (pg/ml)	Ehrlichia diagnostic method	Treatment	Clinical Outcome
[9]	74	Male	Yes	No	N/A	10	16,000	387	12,000	Yes	N/A	Serum PCR	Doxy	Recovered
[10]	47	Female	Yes	No	1210	8.6	65,000	710	10,002	No	51,973	Serum and CSF PCR	Doxy, methylprednisolone	Recovered
[10]	59	Female	Yes	No	600	10.6	41,000	307	2,863	Yes	N/A	Serum PCR	Doxy	Recovered
[10]	52	Female	Yes	No	100	7.9	25,000	650	47,290	Yes	>575,000	Serum and CSF PCR	Doxy, dexamethasone	Recovered
[10]	62	Male	Yes	Yes	3900	8.8	20,000	516	84,676	N/A	N/A	Serum PCR	Doxy, dexamethasone	Recovered
[11]	77	Male	Yes	No	1700	7.5	40,000	700	79,101	N/A	N/A	Serum PCR	Doxy	Died
[12]	66	Female	Yes	No	2900	12.2	22,000	358	>40,000	Yes	N/A	Serum PCR	Dexamethasone, etoposide	Died
[13]	74	Male	Yes	No	N/A	N/A	16,000	387	12,369	Yes	N/A	Serum PCR	Doxy	Recovered
[14]	63	Male	Yes	Yes	1300	8	19,000	436	70,097	N/A	N/A	Serum PCR	Doxy, anakinra, prednisone	Recovered
[15]	41	Female	Yes	No	N/A	8.4	27,000	829	13,257	Yes	N/A	Serum serology and CSF PCR	Doxy, prednisone, IVIG	Recovered
[16]	47	Male	Yes	No	N/A	N/A	22,000	1,234	>15,000	Yes	52,212	Serum and CSF PCR	Doxy	Recovered
[17]	65	Male	Yes	Yes	1390	10.9	35,000	617	860.7	N/A	1648	Serum PCR	Doxy	Recovered
[18]	49	Male	Yes	Yes	N/A	N/A	56,000	N/A	1,369	Yes	4027	Serum serology and PCR	Doxy	Recovered
[18]	62	Female	Yes	No	N/A	11.2	43,000	N/A	5,877	Yes	8,213	Serum PCR	Doxy, dexamethasone, etoposide	Recovered
Our cases														
	72	Female	No	No	1100	13.7	34000	368	31754	Yes	N/A	Serum PCR	Doxy, etoposide, dexamethasone	Died
	77	Male	Yes	No	4100	10.5	19000	137	2320	Yes	N/A	Serum PCR	Doxycycline	Recovered
	56	Female	Yes	No	1600	9.9	30000	452	47547	Yes	N/A	Serum PCR	Doxycycline, Etoposide, dexamethasone	Recovered
	64	Male	Yes	No	2300	14.9	41000	530	6829	Yes	N/A	Serum PCR	Doxycycline, Etoposide, dexamethasone	Died
	68	Male	Yes	No	2400	12.5	12000	285	55593	Yes	N/A	Serum PCR	Doxycycline, Etoposide, dexamethasone	Recovered

PCR - Polymerase chain reaction; CSF -Cerebrospinal fluid; N/A = Not applicable; Doxy –Doxycycline; IVIG=Intravenous immunoglobulin.

Table 2. Clinical features and laboratory values of patients with Ehrlichia-induced HLH (pediatrics)

Reference	Age (years)	Gender	Fever	Splenomegaly	ANC (cells/µL)	Hemoglobin (g/dL)	Platelets (cells/µL)	Triglycerides (mg/dL)	Ferritin (pg/µL)	Hemophagocytosis on bone marrow	Soluble CD25 Receptor level (pg/ml)	Ehrlichia diagnostic method	Treatment	Clinical Outcome
[19]	10	Male	Yes	Yes	N/A	10.2	50,000	287	>10,000	Yes	N/A	Serum PCR	Doxy, dexamethasone	Recovered
[20]	10	Female	Yes	No	1825	12.3	103,000	N/A	3,517	N/A	4,692	Serum serology	Doxy, steroids	Recovered
[20]	13	Male	Yes	No	N/A	11.1	66,000	605	31,022	Yes	4,545	Serum serology and CSF PCR	Doxy, dexamethasone, etoposide, cyclosporine	Recovered
[21]	9	Male	Yes	No	N/A	8.2	68,000	161	>40,000	Yes	3,022	Serum PCR	Doxy, dexamethasone, etoposide	Recovered
[11]	16	Female	Yes	No	400	11.9	37,000	319	85,517	Yes	N/A	Serum PCR	Doxy, dexamethasone	Recovered
[11]	9	Female	Yes	No	500	10.2	28,000	314	36,282	Yes	4,336	Serum PCR	Doxy, dexamethasone, etoposide	Recovered
[11]	7	Female	Yes	Yes	N/A	8.4	51,000	401	3,183	N/A	10,143	Serum PCR	Doxy	Recovered
[11]	11	Male	Yes	No	800	9.9	15,000	340	21,187	N/A	13,505	Serum PCR	Doxy	Recovered
[11]	7	Female	Yes	No	N/A	7.9	44,000	126	44,095	N/A	11,072	Serum PCR	Doxy	Recovered
[22]	8	Female	Yes	Yes	Pancytopenia (no values reported)			N/A	1860	Yes	N/A	Serum PCR	Doxy	Recovered
[22]	3	Female	Yes	No	Pancytopenia (no values reported)			N/A	52,280	Yes	N/A	Serum PCR	Doxy, dexamethasone, etoposide	Recovered
[22]	7	Female	Yes	Yes	Pancytopenia (no values reported)			N/A	44,095	N/A	11,072	Serum PCR	Doxy, dexamethasone, etoposide	Died
[22]	1.3	Female	Yes	Yes	Pancytopenia (no values reported)			N/A	7,048	N/A	N/A	Serum PCR	Doxy	Recovered
[22]	15	Male	Yes	No	Pancytopenia (no values reported)			N/A	85,517	Yes	N/A	Serum PCR	Doxy, dexamethasone	Recovered
[22]	7	Female	Yes	No	Pancytopenia (no values reported)			N/A	3,183	N/A	10,413	Serum PCR	Doxy	Recovered
[22]	10	Male	Yes	No	Pancytopenia (no values reported)			N/A	21,187	N/A	13,505	Serum PCR	Doxy	Recovered
[22]	9	Female	Yes	Yes	Pancytopenia (no values reported)			N/A	36,282	Yes	5,689	Serum PCR	Doxy, dexamethasone, etoposide	Recovered

PCR - Polymerase chain reaction; CSF -Cerebrospinal fluid; N/A = Not applicable; Doxy –Doxycycline.

Secondary HLH is well described in the literature as a result of infections, malignancies and underlying rheumatologic conditions. It most commonly occurs as a result of viral infections, including Epstein-Barr Virus (EBV), cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV), varicella-zoster virus (VZV), measles virus, human herpes virus 8 (HHV-8), H1N1 influenza virus, parechovirus, and human immunodeficiency virus (HIV-1). In a review of more than two thousand cases of secondary HLH, half were attributed to an infectious etiology [7]. Two thirds of the cases caused by infection were due to viruses, with EBV and HIV-1 being the most common. Bacterial infections were implicated in less than 10% of all cases of secondary HLH, with *Mycobacterium tuberculosis* being the most common etiologic agent.

Ehrlichia-induced HLH is exceedingly rare. In the past 2 years we experienced increasing number of HLH cases due to HME which were initially thought only to represent ehrlichiosis clinically. Therefore, we report a series of five cases seen at our center and review the literature to help clinicians recognize this uncommon disease entity. We used Pubmed to conduct a literature search using the terms Ehrlichia, hemophagocytic lymphohistiocytosis, hemophagocytosis, hemophagocytic syndrome and Human Monocyctic Ehrlichiosis. Including our five cases, a total of 36 cases of Ehrlichia-induced HLH in the English literature were detected [9-22]. Of these, 19 cases were in adults (Table 1) and 17 in children (Table 2).

Among the adult patients, there were more males than females (11 out of 19; around 60%). The ages ranged from 41-77 years, with a mean age of 61 years. All but one patient had fever as a presenting clinical feature. Only 4 patients had splenomegaly on clinical examination. The average absolute neutrophil count was 1946 cells/µL, the average hemoglobin value was 10.3 g/dL while the average platelet count was 30,600 cells/µL. Ferritin values were elevated in all patients, with a wide range from 860 to 84,000 pg/µL, with an average of 28,000 pg/µL. All but one patient had an elevated triglyceride level, with an average of 470 mg/dL. Out of the 15 patients who had a bone marrow examination performed, all but one had evidence of hemophagocytosis. Only 6 patients had soluble CD25 receptor antibody levels measured: all these were elevated, ranging from 1600 to > 575,000 pg/ml. The diagnosis of Ehrlichiosis was made by serum PCR in all cases. In addition, 4 patients also had a CSF PCR positive for Ehrlichia, and 2 patients also had a positive serum serology. Eight patients were treated with doxycycline alone, while 10 patients received doxycycline along with immunosuppressive agents, and one patient received only immunosuppressive medications. That one patient

eventually expired. The most common immunosuppressive combination used was dexamethasone and etoposide, consistent with the 1994/2004 HLH treatment protocol [8]. Most patients had a favorable outcome and recovered (15/19; around 80%), while 4 patients died.

Among children, female sex predominated (11 out of 17 patients). There were ten children under the age of 9 years, with seven from age 9-18. All patients presented with fever. Similar to adults, splenomegaly was present in a minority of patients, pancytopenia and bone marrow hemophagocytosis was a common feature, and the diagnosis of ehrlichiosis was made primarily with a positive PCR from the blood. Curiously, the ferritin level ranged and averaged higher than adults, with a mean of around 30,000 pg/uL, and range of 1860 – 85000 pg/uL. The mortality rate was lower among children, with only 1 out of 17 succumbing to the illness.

Combining the two populations, some basic conclusions can be drawn. Both populations have varying degrees of anemia, thrombocytopenia and neutropenia, and pancytopenia is more often present than not. Soluble CD25 receptor antibodies could play an expanded, albeit expensive role in diagnosis of HLH. Ferritin and triglyceride are commonly elevated though less specific. Splenomegaly was only present in 10 out of 36 total patients and may not be as useful a clinical feature in diagnosis. Bone marrow biopsy is almost always confirmatory and pathologic evaluation should be standard of care in patients with suspected HLH, in particular in patients that don't show improvement clinically or biochemically. Early diagnosis and prompt initiation of doxycycline is a major factor in disease outcome. Some patients recovered just with treatment of their underlying Ehrlichiosis with doxycycline. However, a significant number of patients, both adults and children, required concurrent chemotherapy using etoposide and dexamethasone to achieve clinical improvement. We were not able find any clinically distinguishable features between these two groups, likely due to the small sample size. Children appear to have better outcomes than their adult counterparts.

Secondary HLH due to Ehrlichiosis has a better prognosis than primary HLH, which carries with it a substantial mortality rate [7]. This curious sequela of the common tick-borne illness, human monocytic ehrlichiosis, has potentially drastic implications on patient outcomes and recovery from the disease. In endemic areas, a high degree of suspicion is required to identify ehrlichiosis and start empiric doxycycline therapy while awaiting further testing. Secondary HLH due to *Ehrlichia* should be kept in the differential as a complication of the infection, appropriate testing promptly ordered, and treatment begun at the earliest for patients who meet the diagnostic criteria. This is especially important as several laboratory features of Ehrlichia can overlap with HLH, and delay in diagnosis and treatment initiation can lead to a worse outcome. We hope that clinicians will be better informed to diagnose and treat this disease after this review.

Abbreviations

HLH – Hemophagocytic lymphohistiocytosis
HME – Human monocytic Ehrlichiosis
PCR – Polymerase chain reaction
CSF – Cerebrospinal fluid
WBC – White blood cell
AST – Aspartate transaminase
ALT – Alanine transaminase
CT – Computerized tomography
NK – Natural killer
CD – Clusters of differentiation

References

[1] Chapman AS, Bakken JS, Folk SM, Paddock CD, Bloch KC, Krusell A, Sexton DJ, Buckingham SC, Marshall GS, Storch GA, Dasch GA, McQuiston JH, Swerdlow DL, Dumler SJ, Nicholson WL, Walker DH, Eremeeva ME, Ohl CA; Tickborne Rickettsial Diseases Working Group; CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichiosis, and anaplasmosis--United States: a practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep*. 2006 Mar 31; 55(RR-4): 1-27.

[2] Maeda K, Markowitz N, Hawley RC, Ristic M, Cox D, McDade JE. Human infection with Ehrlichia canis, a leukocytic rickettsia. *N Engl J Med.* 1987 Apr 2; 316(14): 853-6.

[3] Dumler JC, Madigan JE, Pusterla N, and Bakken JS. Ehrlichioses in Humans: Epidemiology, Clinical Presentation, Diagnosis, and Treatment. *Clin Infect Dis* 2007; 45: S45-51.

[4] Horowitz HW, Aguero-Rosenfeld ME, McKenna DF, et al. Clinical and Laboratory Spectrum of Culture-Proven Human Granulocytic Ehrlichiosis: Comparison with Culture-Negative Cases. *Clin Infect Dis*. 1998; 27: 1314-7.

[5] Standaert SM, Yu T, Scott MA, et al. Primary Isolation of Ehrlichia chaffeensis from Patients with Febrile Illnesses: Clinical and Molecular Characteristics. *J Infect Dis* 2000; 181:1082-8.

[6] Paddock CD, Folk SM, Shore GM, et al. Infections with Ehrlichia chaffeensis and Ehrlichia ewingii in Persons Coinfected with Human Immunodeficiency Virus. *Clin Infect Dis* 2001; 33: 1586-94.

[7] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet.* 2014 Apr 26; 383(9927): 1503-1516.

[8] Henter J, Horne AC, Arico M, Egeler M, Filipovich A, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124-131.

[9] Badireddi S, Joshi M. Hemophagocytic Lymphohistiocytosis: An Unreported Complication of Ehrlichiosis in Adults. *Chest* 2012; 142(4_Meeting Abstracts): 415A.

[10] Otrock Z, Gonzalez M, Eby C. *Ehrlichia*-induced hemophagocytic lymphohistiocytosis: A case series and review of literature. *Blood Cells, Molecules and Diseases* 2015(55): 191-193.

[11] Otrock Z, Eby C, Burnham C. Human ehrlichiosis at a tertiary-care academic medical center: Clinical associations and outcomes of transplant patients and patients with hemophagocytic lymphohistiocytosis. *Blood Cells, Molecules and Diseases.* 2019 (77): 17-22.

[12] Naqash A, Yogarajah M, Vallangeon B, Hafiz M, Patel D, Kolychev E, Lebron D, Liles D. Hemophagocytic lymphohistiocytosis (HLH) secondary to *Ehrlichia chaffeensis* with bone marrow involvement. *Ann Hematol* 2017; 96: 1755-1758.

[13] Pandey R, Kochar R, Kemp S, Rotaru D, Shah S. Ehrlichiosis presenting with toxic shock-like syndrome and secondary hemophagocytic lymphohistiocytosis. *J Arkansas Med Scociety*. 2013; 109: 280-282.

[14] Kumar N, Goyal J, Goel A, Shakoory B, Chatham W. Macrophage activation syndrome secondary to human monocytic ehrlichiosis. *Indian J Hematol Blood Transfus* 2014; 30(Suppl 1): S145-S147.

[15] Kaplan R, Swat S, Singer B. Human monocytic ehrlichiosis complicated by hemophagocytic lymphohistiocytosis and multi-organ dysfunction syndrome. *Diagn Microbiol Infect Dis.* 2016; 86(3): 327-328.

[16] Provenzano J, Kamerzell T, Reda E, Hawkinson D, Sharpe M. Diagnosis and treatment of hemophagocytic lymphohistiocytosis

in adult patient with ehrlichiosis. *Case Rep Intern Med* 2015; 2(2): 44.

[17] Patel P, Beck P, Chairman D, Regunath H. Ehrlichiosis presenting as hemophagocytic lymphohistiocytosis in an immunocompetent adult. *ID Cases* 2020; 20: e00813.

[18] Higuita N, Yuen C. Hemophagocytic lymphohistiocytosis secondary to *Ehrlichia chaffeensis* in adults: A case series from Oklahoma. *Am J Med Sci* 2020; S0002-9629(20) 30396-7.

[19] Burns S, Saylors R, Mian A. Hemophagocytic lymphohistiocytosis secondary to *Ehrlichia chaffeensis* infection: A case report. *J Pediatr Hematol Oncol* 2010; 32: e142-e143.

[20] Hanson D, Walter A, Powell J. *Ehrlichia*-induced hemophagocytic lymphohistiocytosis in two children. *Pediatr Blood Cancer* 2011; 56: 661-663.

[21] Cheng A, Williams F, Fortenberry J, Preissig C, Salinas S, Kamat P. Use of extracorporeal support in hemophagocytic lymphohistiocytosis secondary to Ehrlichiosis. *Pediatrics* 2016; 138(4): e20154176.

[22] Cabler S, Hogan P, Fritz S, Bednarski J, Hunstad D. Incidence and treatment of hemophagocytic lymphohistiocytosis in hospitalized children with *Ehrlichia* infection. *Pediatr Blood Cancer* 2020; 67: e28436.