CASE REPORT

Human monocytic ehrlichiosis-associated haemophagocytic lymphohistiocytosis treated successfully with doxycycline and dexamethasone: a case report and review of the literature

Hafiz Javed[1], Arfa Ahmad[2], Abdul Rehman[3], Mohammed Saad[4]

Abstract

Human monocytic ehrlichiosis (HME) is a tick-borne infection caused by Ehrlichia chaffeensis. Haemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome characterized by immune activation, most commonly described in children with primary HLH. HME-induced HLH is an extremely rare clinical entity and treatment recommendations are mostly based on case reports, small case series and expert opinion based on extrapolation of data from children with primary HLH. Hereby, we report the case of a 68-year-old male who presented with symptoms of fever and was diagnosed with HLH secondary to HME. He was treated successfully with a 21-day course of doxycycline 100 mg twice daily and dexamethasone 20 mg once daily for 2 weeks, followed by a gradual taper over the next 6 weeks. This case highlights the potential role of doxycycline in combination with high-dose steroids in the management of patients with HLH secondary to HME.

Keywords: Ehrlichiosis, Haemophagoytic Lymphohistiocystosis, Tick-Borne Diseases..

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Introduction

Human monocytic ehrlichiosis (HME) is a tick-borne infection caused by Ehrlichia chaffeensis and spread by the lone star tick, Ambylomma americanum.[1] Haemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome characterized by immune activation, most commonly described in children with primary HLH.[2] HME-induced HLH is an extremely rare clinical entity, and treatment recommendations are mostly based on case reports, small case series and expert opinion depending on extrapolation of data of children with primary HLH.[3] Hereby, we report the case of a 68-year-old male, who presented with fever and shortness of breath and was diagnosed with HLH secondary to HME. He was successfully treated with a prolonged course of doxycycline and high-dose dexamethasone. The present case study highlights the potential of doxycycline in combination with high-dose steroids for the management of patients with HLH secondary to HME.

[1,3]Department of Medicine, TidalHealth Peninsula Regional, Salisbury, United States of America. [4]Department of Haematology and Oncology, TidalHealth Peninsula Regional, Salisbury, United States of America.

Correspondence: Abdul Rehman. **Email:** abdul.rehman_aku@yahoo.com

ORCID ID: 0000-0002-8398-7810

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Case Report

A 68-year-old male presented to the emergency department of TidalHealth Peninsula Regional hospital (Salisbury, MD, United States of America) on 6th June, 2024 with a 10-day history of high-grade fever. He had a past medical history of rheumatoid arthritis for which he was on maintenance tocilizumab therapy. He resided in a woody, suburban area of the state of Maryland in the United States. On initial evaluation, he was tachycardiac, tachypnoeic, hypoxic and febrile. His physical examination was remarkable for bilateral inspiratory crackles and hepatosplenomegaly. His laboratory investigations revealed anaemia (haemoglobin 8.4 g/dL), thrombocytopenia (platelet count 25/mm3), transaminitis (aspartate aminotransferase 105 U/L) and acute kidney injury (serum creatinine 1.8 mg/dL). He was empirically started on piperacillin-tazobactam and vancomycin for presumed sepsis. He was admitted to the medical care service for further evaluation and management. Initial evaluation for a source of infection, including a chest radiograph and urinalysis, did not reveal evidence of bacterial infection. After admission to the medicine service, the infectious diseases team was consulted and computed tomography (CT) scans of chest, abdomen and pelvis with contrast were obtained. CT scans were only notable for hepatosplenomegaly and bibasilar atelectasis. Given profound thrombocytopaenia, the haematology team was also consulted. A screening panel for disseminated intravascular coagulation (DIC) revealed an elevated international normalized ratio of (INR) 1.3, an elevated D-dimer of 3.91 mg/mL, and decreased fibrinogen of 145 mg/dL. A peripheral smear was reviewed by the haematologist but no schistocytes were

Table-1: HLH-2004 diagnostic criteria and H-Score for our patient.

HLH-2004 diagnostic criteria	Our patient
Fever for >7 days	Febrile for >7 days
Splenomegaly	Hepatosplenomegaly on CT abdomen
Bicytopenia—two of: haemoglobin <9 g/dL, platelets <100/mm^3, neutrophils <1000/mm3	Thrombocytopenia (platelet count 25) and anaemia (haemoglobin 8.4 g/dL)
Triglycerides ≥ 265 mg/dL and fibrinogen ≤ 150 mg/dL	Triglycerides 580 mg/dl and fibrinogen 145 mg/dL
Low or absent natural killer (NK) cell activity	Not done
Ferritin >500 ng/mL	>7,500 ng/mL
Soluble CD25 ≥ 2,400 U/mL	>46,141 pg/mL
Haemophagocytosis on biopsy	Not documented
H-Score parameter	**Score**
Known immunosuppression	Yes (+18)
Temperature, °F	>102.9°F (+49)
Organomegaly	Hepatosplenomegaly (+38)
Number of cytopenias	2 lineages (+24)
Ferritin	>6,000 ng/mL (+50)
Triglycerides	>354 mg/dL (+64)
Fibrinogen	≤250 mg/dL (+30)
Aspartate aminotransferase	≥ 30 U/L (+19)
Haemophagocytosis	Not seen (0)
Total score	292 points
Interpretation	>99% probability of HLH

HLH=Haemophagocytic lymphohistiocytosis; NK=natural killer

seen. The patient continued to spike fevers despite being on vancomycin and piperacillin-tazobactam for 72 hours. The infectious diseases team ordered serologies for tick-borne illnesses, including Anaplasma phagocytophilum, Ehrlichia chaffeensis, Babesia microti, Rickettsia spp. and Borrelia burgdorferi. Given the patient's overall condition, empiric treatment with doxycycline was also started. However, despite this, the patient's condition worsened, and he developed severe encephalopathy along with acute respiratory distress syndrome, necessitating endotracheal intubation.

After being transferred to the intensive care unit, patient underwent CT head without contrast which was concerning for right transverse sinus thrombosis. A CT head with contrast and magnetic resonance venography (MRV) were subsequently performed, done, confirming right transverse sinus thrombosis (Figure 1). Given multiorgan failure, worsening cytopenias and continued fever, ferritin level and triglycerides were checked, which were markedly elevated. The possibility of HLH was considered, and a bone marrow aspiration and biopsy was performed. The Soluble CD25 level was also sent, which resulted at >46,141 pg/mL. Based on the HLH 2004 criteria4, a diagnosis of HLH was made, as detailed in Table 1, and intravenous dexamethasone 20 mg once daily was started. The Patient's tick-borne serologies also came back negative for all tested pathogens. However, the infectious diseases team recommended continuing doxycycline, given the high pre-test probability of tick-borne illness, and ordered serum polymerase chain reaction (PCR) testing for Ehrlichia and Anaplasma. Serum PCR for Ehrlichia was positive. The Patient also required

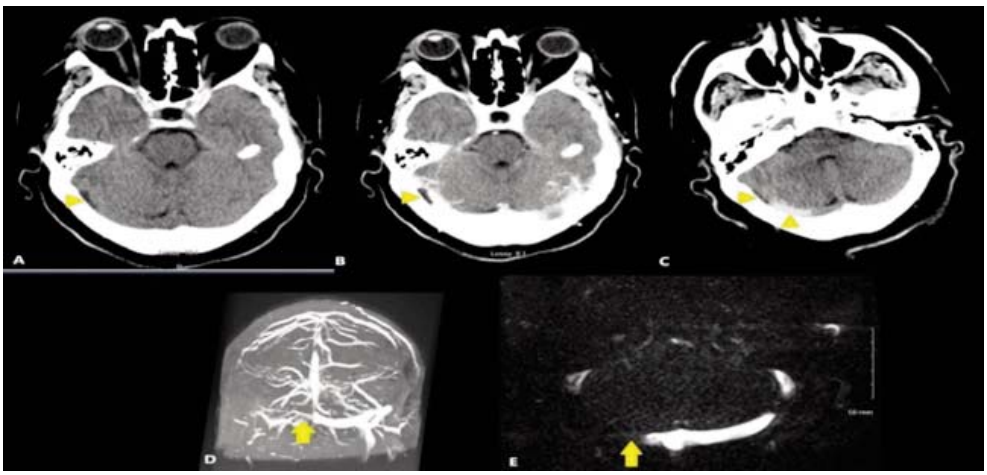

Figure-1: Images of head CT (computed tomography) and MRI (magnetic resonance imaging) demonstrating right transverse sinus thrombosis in our patient. (A) CT head without contrast demonstrating a hypodensity in the expected location of the right transverse sinus (arrowhead). (B) and (C) CT head with contrast demonstrating a filling defect within the right transverse sinus (arrowheads). (D) and (E) MRV (magnetic resonance venography) images show non-visualization of the right transverse sinus (arrows), concordant with CT findings, and confirming right transverse sinus thrombosis.

temporary haemodialysis for acute renal failure. Subsequently, his fever and overall condition improved, and he was transferred to the medical floor. Unfortunately, the bone marrow aspirate was deemed to be haemodiluted and the biopsy was predominantly osteocartilage without marrow, precluding meaningful interpretation. Given that the patient was already improving on doxycycline and dexamethasone, a second bone marrow examination was not pursued. The Patient's renal function tests gradually improved and he no longer required haemodialysis. He was discharged home on a 21-day course of doxycycline 100 mg twice daily and a slow taper of dexamethasone over the following 6 weeks. At a 3-month follow-up visit, the patient was doing well, with no signs of HLH recurrence.

Discussion

HME-induced HLH is a rare clinical entity and its management is mostly based on extrapolation of data from paediatric patients with primary HLH.[2,3] The HLH-2004 diagnostic criteria were initially developed for paediatric patients with primary HLH, but their performance was later validated for adult patients with HLH.[4] Our patient met 6 out of 8 criteria for HLH, which was sufficient for making a diagnosis of HLH. Moreover, the H-score was 292 points, suggesting a >99% probability of HLH.

Secondary HLH in adults is most commonly due to infections and therefore, infectious work-up has a central place in diagnostic evaluation. In our patient, a diagnosis of HME might have been missed if serum PCR testing had not been ordered, especially since serology can be negative in the early stages of disease.[3] It is crucial to exclude infections before initiating treatment for HLH, particularly etoposide, since starting therapy without addressing an underlying infection can have disastrous consequences.[5] In one extreme case, a paediatric patient was treated with cytotoxic agents and referred for haematopoietic stem cell transplant, only to later be diagnosed with disseminated leishmaniasis.[6]

In the published literature, doxycycline, dexamethasone, etoposide, anakinra, intravenous immunoglobulin and other immunosuppressive drugs have been reported for the treatment of HME-associated HLH.[7-10] The reported dosage of doxycycline varies widely, with one study describing a 10-day course8 and another utilizing a prolonged taper over 8 weeks.[10] In this case, we used doxycycline 100 mg twice daily for 3 weeks along with dexamethasone 20 mg once daily for 2 weeks followed by a slow taper over the following 6 weeks. In the absence of high-quality evidence, the duration and dosage of therapy should be tailored to the patient's severity of illness and response to treatment.

The mortality rate of overall tick-borne illness-related HLH has been reported to be approximately 16%.[3] An exact estimate of HME-associated HLH is difficult to obtain but is likely in the same range, based on the published literature.[3,5,7-10] In the present case, we had a favourable outcome with a 3-week course of doxycycline and 2-week course of high-dose dexamethasone therapy followed by a slow taper over the following 6 weeks.

Conclusion

HME-associated HLH is a rare clinical entity that is characterized by hyperactivation of macrophages driven by infection with Ehrlichia chaffeensis. This case highlights successful treatment of HME-associated HLH with doxycycline and high-dose steroids. Clinicians managing adult patients with secondary HLH should always exclude infections as an underlying aetiology. When HME-induced HLH is confirmed, doxycycline and high-dose steroids should be considered first-line therapy before resorting to etoposide or other immunosuppressive agents.

Informed consent: was obtained from the patient for publication of his case report.

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Disclaimer: This case report has never been published in any format before..

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HJ, AA, AR & MS: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.