

Tropical Infection Induced Hemophagocytic Lympho-Histiocytosis

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Abstract

Tropical infections include Dengue, Malaria, Scrub Typhus, Leptospirosis, Typhoid and some other fevers, lead to high morbidity and mortality. Many of these cases have multi-organ dysfunction and require intensive care unit care. Hemophagocytic Lympho-Histiocytosis (HLH), represent a severe hyper-inflammatory condition, can complicate the clinical course of tropical fevers.

Methods: Here we report the clinico-pathological features, laboratory data, treatment and outcome of 3 cases of tropical fever (2 scrub typhus and 1 dengue) complicated by HLH.

Results: All three patients satisfied the HLH-2004 diagnostic criteria. They had fever, acute respiratory distress syndrome, liver dysfunction and encephalopathy. In view of no response to empirical antibiotics and clinical instability, immunosuppressive therapy with dexamethasone was started. Following which all patients had a complete recovery.

Conclusion: HLH should be suspected in severe cases of tropical infections especially if there is no response to disease specific treatment. An early immunosuppressive therapy can do miracle.

Introduction

HLH is a rare and potentially fatal syndrome of pathologic immune dysregulation characterized by clinical signs and symptoms of extreme inflammation. Based upon the cause, HLH may be primary (familial or associated with immune deficiency syndromes) mainly occurring in pediatric age or secondary to infection, malignancy, or autoimmune condition.^[1,2] The diagnosis of this condition is based upon the 'clinical and laboratory criteria' developed by HLH study Group of the Histiocyte Society 2004; having 5 out of 8 of the following: (1) fever, (2) splenomegaly, (3) peripheral cytopenias (affecting at least 2 of 3 cell lineages), (4) hypertriglyceridemia (>265 mg/dL) and/ or hypofibrinogenemia (<1.5 g/dL), (5) hemophagocytosis in bone marrow, spleen, lymph nodes, or liver (6) serum ferritin >500 mg/L, (7) low or absent natural killer cell activity, (8) increased soluble CD25 concentration (a chain of soluble IL-2 receptor) >2400 U/ml.^[3]

Infection induced HLH has been seen most frequently with viral (most commonly Epstein-Barr virus) and numerous bacterial and parasitic infections.^[4,5]

Only a few cases of Tropical Fevers (including Dengue, Scrub typhus, Malaria, Enteric fever and Leptospira) complicated by HLH have been reported in the literature.^[6-9] We report 3 cases of tropical fever presenting to the emergency department complicated by HLH.

The clinico-pathological features, laboratory data, treatment and outcome of the all 3 cases (2 scrub typhus and 1 dengue) are presented in (Table 1).

Cases description

Case 1

A 28 years old man presented on September 9, 2015 with high grade fever for 7 days, rapidly progressive dyspnea for 3 days and altered sensorium for 1 day. On general physical examination, GCS was E3V2M5, BP of 100/60, PR of 124/min, RR of 32/min, temperature 38.4 °C and oxygen saturation (SpO₂) was 80% on room air. He had no pallor, cyanosis, clubbing, pedal edema, jugular venous distension, lymphadenopathy, skin rashes or eschar. Systemic examination revealed bilateral diffuse crackles in chest, liver was palpable 2 cm below costal margin and tip of spleen was palpable. Central nervous system examination did not show signs of meningeal irritation or any focal neurological deficit and cardiovascular examination was unremarkable. Investigation showed a hemoglobin (Hb) of 10.4 g/dl; total leucocyte count (TLC) of 12 x 10⁹/l; platelet counts of 55 x 10⁹/l, creatinine level 2.5 mg/dl; total bilirubin of 1.5 mg/dl; aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) of 198 IU/l, 103 IU/l and 526 IU/l respectively; serum lactate dehydrogenase (LDH) of 1362 IU/L; International Normalisation Ration (INR) of 1.08; and fibrinogen of 2.13 g/l. Arterial blood gas (ABG) analysis revealed PaO₂/FiO₂ ratio of 116 and a chest X ray (CXR) showed diffuse bilateral lung infiltrates. Liver was 18.6 cm and spleen was 13.3 cm in size on ultrasonography.

Patient was intubated and put on mechanical ventilation with acute respiratory distress syndrome (ARDS) protocol. He was empirically started on ceftriaxone and doxycycline. An IgM serology for scrub typhus was positive. Rapid kit test and peripheral smear for Malaria, serological tests for Leptospirosis (IgM antibody),

Table 1: Clinico-pathological characteristics, laboratory data, treatment and outcome of 3 adult patients with tropical infection induced HLH (2 scrub typhus and 1 dengue)

Patient characteristic	Case 1	Case 2	Case 3
Age (years), gender	28 years, male	40 years, male	25 years, male
Presenting complaints and duration	Fever for 7 days, rapidly progressive dyspnea for 3 days and altered sensorium for 1 day	Fever for 10 days and rapidly progressive dyspnea for 7 days	Fever for 7 days, rapidly progressive dyspnea for 2 days and altered sensorium for 1 day
Haemoglobin	7.4	9.9	8.4
TLC	14,200	7,000	18,200
Platelets	57,000	66,000	54,000
Creatinine (mg/dl)	2.5	1.6	1.4
Bilirubin (mg/dl)	1.5	4.3	3.0
AST/ALT/ALP (IU/L)	198/103/526	631/131/312	3314/1779/245
LDH	1362	5115	4849
INR	1.08	1.0	1.12
Fibrinogen level (g/L)	2.13	2.3	3.88
Serum ferritin (mg/l)	1,823	2,000	17,190
Serum triglyceride (mg/dl)	763	674	304
PaO ₂ :FiO ₂ ratio	116	105	106
Chest X ray findings	Diffuse bilateral lung infiltrates	Diffuse bilateral lung infiltrates	Bilateral lung infiltrates, mainly involving lower zones
Liver and spleen size on ultrasonography	Liver- 18.6 cm Spleen- 13.3 cm	Liver- 18 cm Spleen- 13 cm	Liver- 18.5 cm Spleen- 11.9 cm
Bone marrow biopsy	Hemophagocytosis	Hemophagocytosis	Hemophagocytosis
Cultures of blood, urine and bone marrow	Sterile	Sterile	Sterile
Tropical infection work up	Scrub typhus IgM serology positive	Scrub typhus IgM serology positive	Dengue IgM serology positive
HIV serology	Negative	Negative	Negative
Empirical antimicrobial therapy	Ceftriaxone and doxycycline	Ceftriaxone and doxycycline	Ceftriaxone and doxycycline
Immunosuppressive therapy	Dexamethasone	Dexamethasone	Dexamethasone
Outcome	Improved	Improved	Improved

Dengue (NS1 Ag, IgM and IgG antibody), Widal, Visceral Leishmaniasis (RK 39 antibody), hepatitis B surface antigen, anti-hepatitis C virus antibody, HIV ELISA gave negative results. Blood and urine cultures were sterile. A diagnosis of scrub typhus with multi-organ dysfunction was established. However patient did not improve, and his clinical and laboratory parameters further worsened. He had continuous high grade fever with increasing ventilator requirement. PaO₂/FiO₂ ratio decreased to 88 with increased lung infiltrates on repeat CXR, Hb dropped to 7.4, TLC increased to 14.2 x 10⁹/l and thrombocytopenia persisted (57 x 10⁹/l). Initially a possibility of ventilator associated pneumonia was kept and ceftriaxone was changed to imipenem after sending cultures for endotracheal aspirate, blood and urine. Despite this, patient did not improve. All cultures were sterile and serum procalcitonin was normal (0.1 ng/ml). A possibility of secondary HLH was kept in view of persisting high grade fever, cytopenias and hepatosplenomegaly. Serum ferritin was 1823 mg/l, serum triglyceride was 763 mg/dl and bone marrow examination showed hemophagocytosis. Patient was started on dexamethasone on September 24. A dramatic improvement

was observed, fever subsided and patient was extubated on September 27. Hb, TLC and platelet counts improved (10.4 g/dl, 10.4 x 10⁹/l and 207 x 10⁹/l respectively); serum creatinine normalised (0.5 mg/dl); and AST, ALT and ALP decreased (56, 78 and 209 respectively); serum creatinine normalised (1.0 mg/dl); and AST, ALT and ALP decreased (51, 64 and 257 respectively). Patient had made a complete recovery on a follow up visit at the medicine outpatient department 15 days after the discharge.

Case 2

A 40 years old man presented on October 25, 2015 with high grade fever for 10 days and rapidly progressive dyspnea for 7 days. On physical examination, GCS was E4V5M6, BP of 100/60, PR of 100/min, RR of 26/min, temperature 39 °C and oxygen saturation (SpO₂) was 76% on room air. He had pallor but no cyanosis, clubbing, pedal edema, jugular venous distension, lymphadenopathy, skin rashes or eschar. Respiratory system examination revealed bilateral diffuse crackles. Per abdomen, liver was palpable 3 cm below costal margin and spleen was just palpable on deep inspiration. Central nervous system and

cardiovascular examination was normal. Investigation showed an Hb of 9.9 g/dl; TLC of $7 \times 10^9/l$; platelet counts of $66 \times 10^9/l$; creatinine level of 1.6 mg/dl; total bilirubin of 4.3 mg/dl, AST, ALT and ALP of 631 IU/l, 131 IU/l and 312 IU/l respectively; LDH of 5115 IU/L; INR of 1.0; and fibrinogen of 2.3 g/l. ABG revealed PaO₂/FiO₂ ratio of 105 and a CXR showed diffuse bilateral lung infiltrates. Liver was 18 cm and spleen was 13 cm in size on ultrasonography.

Patient was started on ceftriaxone, doxycyclin and high flow oxygen supplementation. An IgM serology for scrub typhus was positive. Rapid kit test and peripheral smear for Malaria, serological tests for Leptospirosis (IgM antibody), Dengue (NS1 Ag, IgM and IgG antibody), Widal, Visceral Leishmaniasis (RK 39 antibody), viral hepatitis (hepatitis A virus IgM, hepatitis E virus IgM, hepatitis B surface antigen, anti-hepatitis C virus antibody), HIV ELISA gave negative results. Blood and urine cultures were sterile. Serum ferritin was 2000 mg/l, serum triglyceride was 674 mg/dl and bone marrow examination showed hemophagocytosis.

A diagnosis of scrub typhus with HLH and multi-system involvement was made. Initially patient was managed with antibiotics alone. However during hospital stay, he developed altered mental status, which was managed with a short course (3 days) of dexamethasone. Investigation showed a Hb improved (10.9 g/dl, $7.4 \times 10^9/l$ and $232 \times 10^9/l$ respectively); serum creatinine normalised (1.0 mg/dl); and AST, ALT and ALP decreased (51, 64 and 257 respectively).

Patient had made a complete recovery on a follow up visit at the medicine outpatient department 10 days after the discharge.

Case 3

A 25 years old man presented on November 19, 2015 with high grade fever for 7 days, rapidly progressive dyspnea for 2 days and altered sensorium for 1 day. On physical examination, patient was agitated with GCS of E3V4M5, BP of 127/70, PR of 128/min, RR of 32/min, temperature 38.8 °C and SpO₂ was 96% on oxygen supplementation with Fio₂ 0.5 and flow 12 l/min. He had no pallor, cyanosis, clubbing, pedal edema, jugular venous distension, lymphadenopathy, skin rashes or eschar. Respiratory system examination revealed bilateral diffuse crackles, predominantly on basal regions. Per abdomen, liver was palpable 2 cm below costal margin and spleen was not palpable. Central nervous system examination did not show signs of meningeal irritation or any focal neurological deficit and cardiovascular examination was unremarkable. Investigation showed a Hb of 12.9 g/dl; TLC of $18.2 \times 10^9/l$; platelet counts of $54 \times 10^9/l$; creatinine level of 1.4 mg/dl; total bilirubin of 3.0 mg/dl; AST, ALT and ALP of 3314 IU/l, 1779 IU/l and 245 IU/l respectively; LDH of 4849 IU/L; INR of 1.12; and fibrinogen of 3.88 g/l. ABG revealed PaO₂/FiO₂ ratio of 106 and a CXR showed bilateral lung infiltrates mainly involving lower zones. Liver was 18.5 cm and spleen was 11.9 cm in size on ultrasonography.

Patient was intubated and put on mechanical ventilation with ARDS protocol. He was started on ceftriaxone and doxycyclin.

An IgM serology for Dengue was positive. Rapid kit test and peripheral smear for Malaria, serological tests for Leptospirosis (IgM antibody), Scrub Typhus (IgM antibody), Widal, Viral Hepatitis (hepatitis A virus IgM, hepatitis E virus IgM, hepatitis B surface antigen, anti-hepatitis C virus antibody), HIV ELISA gave negative results. Blood and urine cultures were sterile. A diagnosis of severe Dengue with multi-organ involvement was made. However patient did not respond, and he had continuous high grade fever with persisting altered sensorium and ventilatory requirement.

Hb dropped to 8.4. A possibility of secondary HLH was kept in view of persisting fever and development of bicytopenia. Serum ferritin was 17190 mg/l, serum triglyceride was 304 mg/dl and bone marrow examination showed hemophagocytosis. Patient was started on dexamethasone followed by improvement of clinical and laboratory parameters. Patient had made a complete recovery on a follow up visit at the medicine outpatient department 7 days after the discharge.

Discussion

Tropical fevers are defined as infections that are prevalent in, or unique to tropical and subtropical regions of the world. Some of these occur throughout the year and some especially in rainy and post-rainy season. These fevers mainly include infectious diseases like Leptospirosis, Enteric fever, Malaria, Dengue and Scrub typhus (can be remembered as mnemonic LEMDS). Most of these tropical infections have overlapping clinical features, multi-system involvement often requiring intensive care unit care and advance life support measures like vasopressor support, mechanical ventilation, hemostatic resuscitation and renal replacement therapy and have an increased morbidity and mortality.^[10]

Infections are a major trigger for adult HLH, an appropriate targeted antimicrobial therapy is a cornerstone of management. Patients who are clinically stable and respond to treatment of the underlying infection may be able to avoid HLH-specific treatment. However, for severely ill patients, initiation of HLH-specific therapy should not be delayed while awaiting resolution of an underlying infection. In general, treatment entails the suppression of an overactive immune system.

The current treatment protocol of adult or acquired HLH is based on the pediatric HLH-94/-2004 protocol.^[1,2] Not all patients with acquired HLH need to be started on the full protocol. Immunosuppressive agents (including corticosteroids, intravenous immunoglobulin, rituximab, cyclosporine alone or in combination) are mainstay of treatment for most of the acquired HLH and infection triggered HLH responds well with corticosteroid alone. However if the disease worsens or does not respond rapidly, full therapy must be initiated quickly.^[11,12]

HLH is a life threatening condition and is often missed in adults. It is diagnosed with an immediate need for treatment due to imminent respiratory, hepatic, renal, or hematopoietic failure, without a definitive diagnosis as to whether HLH has a hereditary background (degranulation assay and/or mutation analysis reports pending). Control of overt inflammation is of utmost importance.^[2]

It should be suspected in patients with tropical fevers, especially in the presence of multi-organ failure, persistent high fever and variable cytopenia. Respiratory distress is frequently present and respiratory insufficiency represents a negative prognostic sign and may need assisted ventilation. Early diagnosis and early effective therapy could reduce the mortality.

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