Hemophagocytic Lymphohistiocytosis

Dr. (Wg Cdr) V Mathew

Senior Consultant Physician, GKNM Hospital, Coimbatore.

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal condition, in which the body's own inappropriate hyperimmune response, leads to Hypercytokinemia (cytokine storm syndrome). It may be primary (underlying genetic mutations) or secondary triggered by infections malignancy or haematological disorders, or immune-suppressed states. Among viral infections, it is most commonly associated with EBV, CMV and HHV 8 infections (29%), other infections (20%), malignancies (27%), and rheumatological disorders (7 %)

The diagnostic criteria set forth by the Histiocyte Society for inclusion in the International Registry for Hemophagocytic Lymphohistiocytosis (HLH) is

a. Fever -7 or more days of temperature as high as 38.5 C
b. Splenomegaly - palpable spleen > 3cm below the costal margin
c. Cytopenia– counts below the specified range in at least 2 of the following lineages
    1. Absolute neutrophil count of less than 1000 /microlitre
    2. Platelet count of less than 100000 /microlitre
    3. Hemoglobin level of less than 9.0g/dl
d. Hypofibrinogenemia or hypertriglyceridemia fibrinogen < 150mg /dl, hypertriglyceridemia > 265 mg /dl
e. Hemophagocytosis – tissue demonstration from lymph node, spleen or bone marrow without evidence of malignancy.
f. Low or absent NK cell activity.
g. Serum ferritin > 500mcg/ l
h. Soluble CD 25> 2400U/ml – but not very sensitive.

Skin findings are noted in more than half of patients such as scaly and waxy lesions and rashes on the scalp and behind the ear.

Other findings include swollen or hemorrhagic gums, abdominal pain, vomiting, diarrhoea and weight loss.

Clinically HLH is characterised by high fever, lymphadenopathy, hepatosplenomegaly, liver dysfunction, pancytopenia, hyperferritinemia, hypofibrinogenemia, coagulopathy and neurological manifestations. (Cerebral HLH – seizures, ataxia, hemiplegia, mental status changes.

Treatment: Initial therapy HLH -2004 protocols, dexamethasone, etoposide, cyclosporine and methotrexate.

Another option is emapalumab – a monoclonal antibody in primary HLH in adults and in children with refractory or progressive disease.

Alemtuzumab may be an effective Salvage agent.

IV IG

Case Report

66-year-old male, known DM & HT for over ten years on regular treatment and follow-up. No vices. Admitted to a local hospital from 14/1/2020 to 17/1/2020 with complaints of fever, body aches, lab reports- cytopenia TC 2400, Platelet 1, 51,000 treated as viral fever, symptomatically – improved.

Recurrence of fever, chills, mild cough –admitted to GKNM hospital on 17/1/2020

Clinically mild fever nil else positive

Investigation Hb 9.6, TC 2500, platelets 1, 40, 000, ESR 71mm/hr, RFT, RBS normal LFT- A-G reversal rest normal. Dengue/scrub typhus. – Negative.

Blood c/s – No growth; CXR – Normal; USG Abdomen -Normal

Continued to have low-grade fever chills (100-101F)

Empirical antibiotics (ceftriaxone)

Repeat TC 2100 Rpt Blood, urine cultures sent, Echo –Normal, ANA- Neg, Sr PSA -N

Rpt TC 1700 – Antibiotics escalated

CECT Chest and Abdomen- Normal; Culture no growth.

Hematologist opinion - to investigate HLH

Sr ferritin increased by 4798, LDH 1098: triglycerides, uric acid, fibrinogen, PT-INR, APTT- normal.

Possibilities considered -HLH – Secondary infection, autoimmune or lymphoproliferative disorder.

Bone marrow - Aspiration and biopsy done - 24/1/20

Mild lymphoplasmacytic, Biopsy –mild histiocytosis no malignancy; rest –Normal

Septicemia panel – nil significant

Bone marrow cultures have no growth.

Immunohistochemistry negative.

ENA profile – negative, anti-TPO negative

Started on low-dose steroids – (25/1/20) Anti platelets withheld. Showed improvement, fever spikes reduced. TC, Platelets improved.

Discharged on 31/1/2020 on oral steroids and supportive-

Planned TEE /PET scan on follow-up if required.

Re admitted- 5/2/2020 with recurrence of fever.

TC 2100, Hb 8.9gm, Platelets 112000, RFT /LFT Normal.

LP done. CSF – acellular; ADA-Normal; fungal stain- negative

CSF autoimmune panel- Negative

Repeat 3 sets of cultures – no growth

Procalcitonin- normal, ferritin- 15985, LDH-1577, triglycerides- 237

PET CT scan was done – hypermetabolic marrow in the axial and appendicular skeleton, no active disease elsewhere.

Reviewed by hematooncologist and hematopathologist. Suggested repeat bone marrow biopsy.

Attenders wanted to go to a higher center. They continued on low-dose steroids and were discharged on 8/2/20.

Vitals stable.

Admitted to higher center 9/2/20

Evaluated- D/D considered 1) malignancy 2) infection 3) connective tissue disorder 4) HLH secondary to malignancy/ infection/ connective tissue disorder.

Bone marrow – features of hemophagocytosis

Diagnosis- HLH based on HLH 2004 criteria

a. Fever >38.5 degrees Celsius (positive)
b. Splenomegaly(negative)
c. Peripheral blood – cytopenia, 2 off the following

   Hb < 10 gm%

   Platelets < 10000 (positive)

   Absolute neutrophil count < 1000 (yes)
d. Hypertriglyceridemia fasting > 265mg (yes)

   And or hypofibrinogenemia <150mg
e. Low or absent NK cell activity (not done)
f. Ferritin >3000 ng (yes)

g. Elevated CD25 > 44

HLH secondary was considered.

Bone marrow tissue gene Xpert – for mycobacterium tuberculosis – trace positive. Other infective aetiology – negative

Initiated on category 1 weight-based ATT on 12/2/20 and dexamethasone 10mg/sq.m (HLH 2004 protocol) from 15/2/20

Developed upper GI bleed – hematemesis and Malena

UGI scopy (after elective intubation for the procedure) fresh clots but no definite source of bleeding.

Sigmoidoscopy, CT angiogram – normal

Developed neutropenic sepsis (TC 200) hospital-acquired pneumonia- antibiotics escalated.

Progressively developed respiratory distress, ARDS – intubated

Worsening hypotension, ischemic hepatitis- drug-induced

ATT modified - His counts remained persistently low despite multiple transfusions etc. Initiated on IVIG for 5 days

No improvement – developed anuria and fluid overload – (AKI - secondary to sepsis/ ATN)

Initiated on dialysis (SLED)- did not improve, and succumbed to his illness

Died 29/2/2020

The case was presented on account of its rarity.

(Incidence is reported to be 1.2 cases per million – However, these figures have increased over time due to improved awareness and detection.)

"There is only one good, knowledge and one evil, ignorance."

-SOCRATES

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