HLH - Unusual Trigger and Positive Outcome

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH), is an uncommon, aggressive and life threatening syndrome of excessive immune activation. We report an unusual case of HLH, in a 34 year old male, who was admitted with Subarachnoid hemorrhage and cerebellar contusion in a Neurosurgical Intensive care unit, whose trigger is not clear.

Case Report

34 year old gentleman was admitted in Neurosurgical ICU of tertiary care centre at Chennai in April 2016 with subarachnoid hemorrhage (SAH) and left cerebellar contusion following an assault. Patient was treated conservatively with antiedema (Injection mannitol) and antiepileptic (Injection phenytoin) drugs. Since seizures were not controlled with single antiepileptic agent, leviteracetam and clobazam were added. On day 6 of admission, patient developed high grade fever. Repeat CT Brain done showed complete resolution of cisternal bleed. Patient was transferred under general medicine due to persistent fever which was high grade associated with chills and rigors, continuous in nature; dysuria was present. There was no associated complaints of cough, expectoration, abdominal pain, loose stools, skin rash, nausea or any bleeding manifestations.

Fig. 1: Erosions and hyperpigmented lesions over arm and chest

On examination, patient was febrile with temperature of 102°F. General and systemic examination revealed no abnormality. Clinically urinary tract infection was suspected and he was started on Inj. cefaperazone with sulbactum. Patient continued to have persistent fever spikes and hence a possibility of CNS infection was also suspected and lumbar puncture was done. CSF Sugar and Protein were abnormal (Sugar – 106 mg/dl; Protein – 61 mg/dl) CSF WBC were 35 /Cumm and RBC were 2150 /Cumm, suggesting a diagnosis of SAH / ? Partially treated bacterial meningitis and antibiotics were changed to vancomycin and ceftriaxone. Urine culture report showed Enterococcus faecalis which was covered with above treatment.

Fig. 2: Erosions over lip

Patient continued to have persistent fever spikes and total WBC counts were on decreasing trend (18400 -14100 - 8300 - 6300 - 2000) associated with anaemia (bicytopenia). Possibility of hemophagocytosis was considered. Ferritin 8291 ng/dl (Normal-28-397) and Triglycerides 411 mgs/dl were elevated. USG Abdomen done revealed splenomegaly. Liver enzymes were elevated (SGOT -234 IU /SGPT- 168 IU); On day 19 patient started developing rashes all over the body (Figures 1 and 2). Bone marrow aspiration was done and revealed marked hypocellular marrow with suppressed erythropoiesis. Only early erythroids were seen. Some erythroblasts showed large basophilic intranuclear inclusions and cytoplasmic budding, suggestive of Parvo virus infection. Macrophages – Present, some show Hemophagocytosis, suggestive of Pure Red Cell Aplasia (PRCA) with hemophagocytosis (Figures 3 and 4). Patient was treated as per HLH 2004 protocol with Inj. Dexamethasone 8 mg twice a day, Inj. Etoposide 250 mg once a day and T. Cyclosporin 175 mg twice a day. Rashes worsened over next 3 days and were maculopapular with ulceration of mucus membranes suggesting Steven Johnson's Syndrome probably secondary to phenytoin. Dermatologist opinion was obtained. Skin rashes improved after phenytoin

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Received: 25.06.2017; Accepted: 24.07.2017

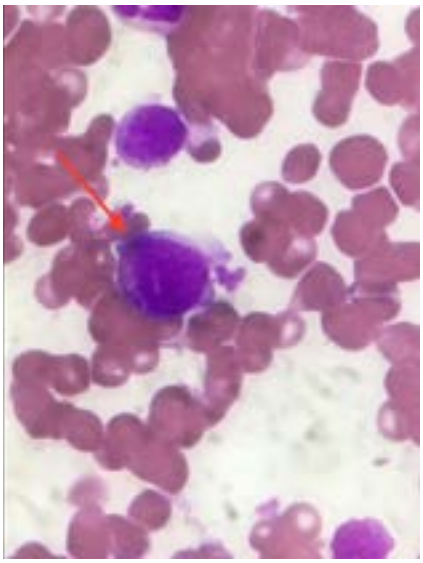

Fig. 3: Pro erythroblast with intranuclear inclusion

was stopped. Parvo Virus IgM was done and found to be negative. Patient condition improved over the next few days.

Our Patient had the following

- Fever
- Splenomegaly
- Decrease in two cell lines
  Hemoglobin – 9.1 gms %
  WBC – 1600 / cu mm
- Hypertriglyceridemia
- Increased ferritin levels
- Bone marrow aspirate showing hemophagocytosis

2009 HLH diagnostic criteria[1]

Identification of a HLH-associated gene mutation: (PRF_1, $UNC_{13}D$, STX_{11}, $STXBP_2$, $Rab_{27}A$, SH_2D_1A, or $BIRC_4$)

Or

Three of the following four clinical criteria: a) Fever >38.5°c (b) Splenomegaly (c) Peripheral blood cytopenia : at least two cell lines (d) Hepatitis

and

One of the following four laboratory criteria:

a. Hemophagocytosis in bone marrow, spleen, lymphnode or Liver

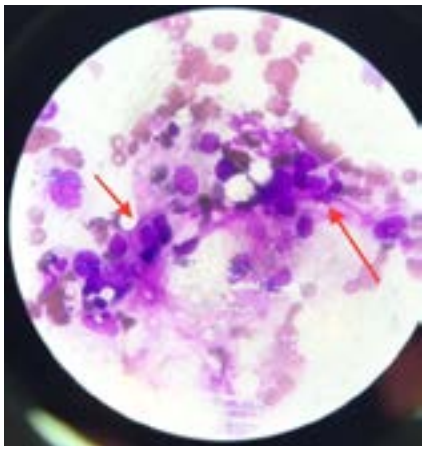

Fig. 4: Hemophagocytes

b. Ferritin >500 ng/mL

c. Elevated soluble CD25

d. Low or absent NK cell activity

Supportive criteria : (a) Hypertriglyceridemia (b) Hypofibrinogenemia (c) Hyponatremia

Discussion

Hemophagocytosis, is an aggressive and life threatening syndrome of excessive immune activation. It is the engulfment of hematopoietic cells by activated macrophages acting outside of usual immune system regulations.[2] It can occur as a familial or sporadic disorder. Though infection is a common trigger both in those with primary and secondary HLH, there can be other causes like malignancy, connective tissue disorder. The excessive inflammation is thought to be caused by a lack of normal downregulation of activated macrophages and lymphocytes. The most common viral trigger is Epstein-Barr virus and it is very rarely associated with Parvo virus infection.[3] In our case bone marrow showed erythroblasts with intranuclear eosinophilic inclusions and pure red cell aplasia is suggestive of Parvovirus B19 infection.[4] Drugs like amoxicillin induced hypersensitivity reaction causing hemophagocytosis has been published in literature before.[5] So the possibility of phenytoin being the trigger cannot be ruled out. Our patient was treated as per HLH 2004 protocol (Table 1). Clinically our patient had shown improvement, Cell counts normalized. Patient is on follow up and there is no recurrence as of now.

Table 1: Treatment Protocol[1]

Sl. No.	Drug	Dose and Duration
Initial therapy		
1	Etoposide	150mg/m², Intravenous, twice a week for week 1-2; once a week for week 3-8
2	Dexamethasone	10 mg/m²/day for initial 2 weeks, 5 mg/m²/day during wee 3-4, 5-2.5mg/m²/day week 4-6 1.25 mg/m²/day week 7-8.
3	Cyclosporin A	Initiate 6 mg/kg daily (2 divided doses)if kidney function is normal. Aim is to achieve trough levels around 200microgram/L.
Maintenance Therapy		
1.	Etoposide	150 mg/m2 intravenous, every second week.
2.	Dexamethasone	Pulses every 2nd week, 10 mg/m² for 3days.
3.	Cyclosporin A	Dose is adjusted to achiever blood levels around 200 mcg/L

Conclusion

Early diagnosis and aggressive adequate treatment is the key in managment of HLH. HLH should be suspected when there is cytopenia, high grade persistent fever and organomegaly. In conclusion a diagnosis of HLH was made in a patient who was admitted for subarachnoid hemorrhage and the probable trigger could be parvo virus or phenytoin or both.

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