

## Hemophagocytic Lymphohistiocytosis in a Young Child

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Hemophagocytic lymphohistiocytosis (HLH) is a multisystem disorder mediated by cytokine storm and is characterized by fever, pancytopenia and organomegaly coupled with laboratory features like hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and transaminitis. Etiology can be genetic or acquired such as infections, malignancy and autoimmune disorders. Diagnosis, identification of underlying etiology and management of HLH remain tough clinical puzzles to sort out for the managing physician. We report a clinicopathological conference of a three-year-old boy who had such a presentation and succumbed during the hospital stay.

**Keywords:** *Aspergillosis, Disseminated intravascular coagulation, Pancytopenia, Pneumonia.*

**H**istory and examination: A 3-year-old boy was admitted with fever and progressive pallor of 2 months duration. He was asymptomatic till 2 months ago, when he started developing high grade fever with intermittent spikes once every day. He would be relatively well in between two fever spikes. Fever was associated with progressive pallor requiring one blood transfusion 20 days back. He had documented thrombocytosis (platelet count: 7 lakhs/mm<sup>3</sup>) at that time. There was no history of localizing features for fever. Past history, developmental history and immunization history were not contributory. There was history of one sibling death at birth for which there was no obvious cause. Examination revealed significant pallor. There was absence of icterus, edema, clubbing, cyanosis, lymphadenopathy, and rash. He was febrile at admission. He weighed 9.5 Kg (expected 14 kg), and had a height of 84 cm (expected 92 cm) and occipitofrontal circumference (OFC) of 46 cm. Abdominal examination showed hepatosplenomegaly with liver of 3 cm below costal margin and spleen of 2 cm below costal margin. Chest, cardiovascular, neurological and joint examinations were normal.

**Investigations:** Investigations revealed anemia and polymorphonuclear leucocytosis with normal platelet counts (**Table I**). Peripheral blood film showed microcytic hypochromic erythrocytes with hypersegmented polymorphs and there were no features of hemolysis. Erythrocyte sedimentation rate (ESR) was raised and he had hypoalbuminemia and high aspartate transaminase levels. Extensive infection workup (**Box I**) was negative except for a positive serology for Epstein Barr virus (EBV)

viral capsid antigen (VCA) IgM. Fine needle aspiration cytology (FNAC) from axillary lymph node was suggestive of reactive lymphoid hyperplasia. Bone marrow had no evidence of leukemia or hemophagocytosis. Chest X-ray (CXR) was normal and ultrasound abdomen showed hepatosplenomegaly. Contrast enhanced computerized tomography (CECT) of chest and abdomen showed hepatosplenomegaly, bilateral pleural effusion and underlying lung collapse. Immunological work up was normal except for low C4 levels (**Box I**).

**Course and management:** Possibility of infections and malignancy was kept at admission. The index child was started on intravenous Ceftriaxone, Cloxacillin and oral Doxycycline. He developed increasing lymph nodes, worsening respiratory distress and lethargy with progressive neutropenia during hospital stay. Chest X-ray done during second week of hospital stay showed patchy areas of collapse and consolidation. Antibiotics were changed to injectable Vancomycin and Imipenem. In view of very high serum ferritin, a possibility of Hemophagocytic lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS) was kept and he was given pulse intravenous Methylprednisolone 30 mg/kg/day for five days. There was a brisk response in fever and respiratory distress. Size of liver, spleen and lymph nodes decreased. He was subsequently shifted to oral prednisolone 2 mg/kg/day. He started developing fever again on day 2 of oral steroids. He was restarted on IV Methylprednisolone and as he did not show a significant response, he was given a dose of intravenous immunoglobulin (IVIg). He responded in terms of

**TABLE I** SERIAL HEMATOLOGICAL AND BIOCHEMICAL PARAMETERS OF THE INDEX PATIENT DURING THE HOSPITAL STAY

Day of hospital stay	Day 2	Day 7	Day 16	Day 22	Day 28
Total leucocyte counts (cells/mm <sup>3</sup> )	17,600	8,500	4,500	16,000	300
Differential counts (P/L/M/E)#	59/31/10	06/77/16/01	48/31/20/01	26/56/15/01	Too low
Hemoglobin (g/dL)	8.1	6.0	9.3	9.9	5.9
Platelets (cells/mm <sup>3</sup> )	1.95 lakhs	1.27 lakhs	4.82 lakhs	13,000	1000
ESR*	62	-	59	-	02
CRP* (mg%)	254	234	248	436	279
Blood Urea/ Creatinine (mg/dL)	15/0.5	17/0.5	18/0.5	214/ 2.0	193/ 2.7
ALT/AST* (U/L)	155/ 26	76/ 25	190/ 37	482/ 63	53/ 33
Total proteins/ albumin (g/dL)	7.9/ 2.7	6.8/ 2.1	7.0/ 2.2	5.7/ 1.9	3.9/ 2.3
Serum ferritin (ng/mL)	-	44,638	16,500	-	5258
Fasting triglycerides (mg/dL)	93	441	-	189	-
PT/ APTT* (sec)	19/ 28	18/ 25	16/ 25	21/ 39	19/ 38
Fibrinogen (g/L)	4.83	3.9	-	0.60	2.18
Urine albumin <sup>§</sup>	1+	-	-	-	2+
Urine microscopy	WBC casts+	-	-	-	-
RBCs/hpf	-	-	-	-	10-15

# Differential counts in order of polymorphs, lymphocytes, monocytes and eosinophils; \*ESR: Erythrocyte Sedimentation Rate, CRP: C Reactive Protein, ALT: Alanine Transaminase, AST: Aspartate Transaminase, PT: Prothrombin time, APTT: Activated Partial Thromboplastin time; <sup>§</sup>Urine albumin by dipstick assay.

reduction in fever and respiratory distress. He developed sudden onset severe respiratory distress and shock on day 20 of admission. Chest X-ray showed enlarged globular heart and echocardiography revealed significant multiloculated pericardial effusion causing tamponade. Emergency pleuropericardial window was created under general anaesthesia. Intra-operative findings were thickened pericardium with multiple loculations and 200 ml of seropurulent fluid was drained. Pericardial tissue histopathology was suggestive of fibrinous pericarditis. Vasopressors, Fluconazole and Clindamycin were added. However, he kept on worsening with development of oliguric renal failure requiring three cycles of peritoneal dialysis. He also needed multiple packed red cell and platelet transfusions. He succumbed to refractory shock with multiorgan dysfunction on day 30 of hospital stay. Postmortem cerebrospinal fluid examination was normal.

**Unit's final diagnosis:** Hemophagocytic lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS), Systemic JIA (SJIA)

**Discussion (Clinical discussant):** Diagnosis of HLH is not in doubt in the index child as he did satisfy five clinical criteria for HLH: fever, splenomegaly, cytopenia involving two cell lines, high fasting triglycerides and high serum ferritin [1]. He also showed brisk response to steroids in terms of reduction in fever, respiratory distress and

increase in platelet counts. HLH is a syndromic diagnosis and no single clinical finding or lab test is diagnostic of this condition [1]. However, ferritin levels more than 10,000 ng/ml have been found to be 98% specific for HLH in children [2]. Absence of hemophagocytosis in various tissues does not exclude HLH [3].

There are various genetic and acquired factors, which can cause HLH and frequently one can get more than one underlying cause [1]. Usually, HLH occurs in a genetically predisposed individual when one or more acquired factors like infections, malignancies and/or rheumatological diseases act as trigger. Presence of EBV VCA IgM positivity suggests acute EBV infection, which is the most common acquired cause known to precipitate HLH [4]. The parameters odd for EBV HLH in the index child are prolonged duration of fever, polymorphonuclear leucocytosis, thrombocytosis, very high ESR and fibrinogen at admission. Hence, to explain prolonged features of inflammation prior to presentation as HLH, I would like to discuss other underlying causes.

Coming to rheumatological conditions, SJIA is a strong possibility as the index child had typical fever pattern, serositis, hepatosplenomegaly, polymorphonuclear leucocytosis and thrombocytosis at the onset. Absence of arthritis does not exclude SJIA. HLH/MAS can be seen at first presentation in SJIA [5] and prolonged

**Box I** INVESTIGATIONS FOR PROLONGED PYREXIA IN THE INDEX PATIENT

Blood cultures: Sterile on day 1, 5, 7, 16, 21  
 Urine cultures: Sterile on day 1, 5, 22  
 Blood fungal cultures: Sterile  
 Fungal serology: Negative  
 Gastric lavage for AFB: No AFB seen  
 Brucella/HIV/ Parvovirus serology: Negative  
 IgM scrub typhus: Negative  
 EBV serology (VCA IgM): Positive  
 Pericardial fluid analysis: No cells, no organism on Gram stain, Bacterial and fungal cultures sterile, AFB smear and cultures sterile

*Investigations for malignancy*

FNAC axillary node: Cellular; Reactive population of lymphoid cells with scattered histiocytes and tingible body macrophages. There were no atypical cells or hemophagocytosis. Stain for AFB was negative  
 Bone marrow examination: Smears were cellular with myeloid to erythroid ratio of 3.4:1. Erythropoiesis was normoblastic and megakaryocytes were adequate on smears. Differential counts in marrow were normal and blasts were 2%. There was no significant hemophagocytosis. No microorganisms were noted. Trepine biopsy was normal and there was no granuloma and lymphoid aggregates.

*Immunological work-up*

Antinuclear antibody by indirect immunofluorescence: Negative  
 Anti-neutrophil cytoplasmic antibody (ANCA): Negative  
 Perforin expression: Normal by flow cytometry  
 Nitroblue Tetrazolium test (NBT): Normal reduction  
 C3, C4\*: 162 mg (50-150 mg), 4 mg (20-50 mg)  
 Lymphocyte subsets\*: CD3- 71.7% (43-76%), CD19- 14.9% (14-44%), CD56- 9.5% (4-23%)

\*Numbers in parenthesis indicate the normal ranges for the age.

preceding inflammation suggests a diagnosis of SJIA. So, we have evidence of HLH in this child with underlying SJIA and acute EBV infection being a trigger.

Is it possible that this child had a genetic predisposition to develop HLH? Genetic causes of HLH include familial HLH, HLH associated with immunodeficiency syndrome with albinism, X-linked lymphoproliferative disorder (XLP) and X-linked inhibitor of apoptosis deficiency. Apart from younger age at presentation, differentiation between genetic and acquired causes based on clinical presentation alone is difficult [6]. XLP is associated with EBV-related HLH, lymphoma and hypogammaglobulinemia. HLH in XLP cannot be differentiated from HLH of secondary

etiologies [7]. A considerable proportion of EBV HLH patients have been shown to have underlying genetic defects [8]. It is impossible to rule out underlying genetic causes with the available investigations.

During third week, this child had recurrence of fever, respiratory distress and pericardial effusion, low ESR, high CRP, and transaminitis. He went on to develop pancytopenia, renal dysfunction, shock, coagulopathy and low fibrinogen. Fibrinous pericarditis as seen in this child has been described in a few cases of HLH [9]. Similarly, renal involvement here could be multifactorial, related to shock as well as to cytokine nephropathy [10].

This child also had unexplained low C4. Congenital C4 deficiencies are associated with autoimmune diseases [11]. SJIA, in contrast, is an autoinflammatory condition and it is not commonly known to be associated with low C4. Terminal events seem to be worsening of MAS with multiorgan dysfunction syndrome (MODS). However, it is difficult to exclude a diagnosis of nosocomial sepsis. So HLH/MAS with MODS with an underlying SJIA, with trigger being an acute EBV infection seems likely in this child.

**Open Forum**

*Pediatrician 1:* Diagnosis of SJIA/MAS does not seem to be in doubt in the index case. Although arthritis is required for the diagnosis of SJIA by the classification criteria, there is a subset of patients who develop arthritis years after onset of fever. Preterminally, we can see falling ferritin and there is progressive cytopenia. So, there is a high chance that this child would have acquired nosocomial infection, especially fungal.

*Pediatric Hematologist:* The context here seems to be what is the cause of HLH, whether it is familial or SJIA. Histology cannot pinpoint the etiology of HLH. Steroids when used alone for treating HLH can lead to transient response and without Etoposide, there can be a recurrence (12).

*Pediatrician 2:* In a child with prolonged fever, thrombocytosis and hyperferritinemia with values in several thousands, the differential diagnosis narrows down to SJIA. The trouble in the index child is that this child presented with a complication of SJIA right at the onset. So, as I look at it, this child had SJIA with MAS and he succumbed to MAS.

*Adult physician 1:* How frequent is JIA under age of five? Do we believe that seropurulent pericardial effusion with 200 ml of fluid was related to SJIA/HLH?

*Pediatrician 3:* There is no doubt about diagnosis of SJIA. In this patient, once Methylprednisolone worked

and after that whatever happened, looks like a secondary infection.

*Clinical discussant:* SJIA is predominantly a disease of under-fives. Arthritis, if present, would have made diagnosis of SJIA easier. MAS can be the initial presentation of SJIA. Infections are associated with an increase in ESR and CRP. The index child, had a raised CRP but the ESR was very low. This could explain MAS as the predominant cause for preterminal worsening. Nosocomial infections continue to be another possibility for preterminal worsening and are a major cause of mortality in HLH/MAS.

*Adult physician 2:* I do not believe that HLH got any better in this child. There was a progressive fall in counts and what happened after steroids and IVIg, was just a mild decrease in inflammation.

#### PATHOLOGY PROTOCOL

Antemortem pericardial biopsy showed fibrin rich exudates with paucity of inflammatory cells and was reported as fibrinous pericarditis. There were no granulomas or malignancy in the pericardial biopsy.

This was a partial autopsy and the prosector noted gangrene of right little finger and right toe, rashes over abdomen and anal excoriation. No excess fluid was seen in the serous cavities. Discolored and hemorrhagic mucosa and serosal exudates were seen in ileum, ileocecal region and large intestine. Ulcerations of variable sizes (0.5 to 5 cm diameter) with hemorrhagic base and dirty exudates were seen involving the entire caecum and terminal part of the small intestine. Microscopically, small intestine showed extensive hemorrhagic ulceration of the entire mucosa with involvement of muscle causing myocytolysis and no preserved epithelium was seen. Many fungal profiles and thrombi were seen in blood vessels in the intestinal wall. There was hardly any inflammatory reaction. In addition, colonies of bacteria were seen in the small and large intestine, both on serosal and mucosal aspects. The esophagus and stomach showed large kissing ulcerations. Some of them appeared hemorrhagic with greenish exudates in base and sharp outline (**Fig. 1a**). **Fig 1b** highlights the septate fungal profiles infiltrating into gastric mucosa causing ischemic necrosis. Periodic acid–Schiff (PAS) and Grocott's stain showed septate fungal profiles with acute angle branching. There was absolute paucity of inflammatory cells in the ulcerated area. The section from appendix showed preserved lymphoid follicles.

Surface of the liver showed multiple superficial nodular whitish lesions of 0.5 to 5 cm diameter. Microscopic examination revealed fibrinous exudate with

sheets of fungal profiles extending into the parenchyma, causing infarction (**Fig. 1d**). Fungal profiles were also identified in the portal vein. Vessels surrounding the mesenteric perinodal tissue and lymph node sinusoids showed fungal thrombi.

Liver was grossly enlarged with exaggerated mottling. Microscopic examination of the liver showed diffuse micro- and macro-vesicular steatosis, sinusoidal dilatation and congestion. Reticulin framework was maintained and there was no fibrosis in the portal tract. Further magnification showed focal cholestasis in liver and prominence of Kupffer cells. There was no hemophagocytosis in liver.

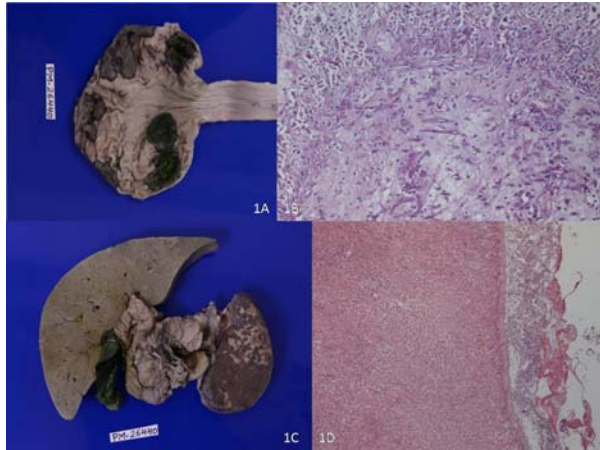
Spleen was enlarged (weight 80 grams) and showed multiple geographic infarcts (**Fig. 1c**). Infarcts with hemorrhagic borders were confirmed on microscopy. There was evidence of perisplenitis. The preserved white pulp could be seen around the splenic arterioles and surrounding parenchyma showed macrophage proliferation. In addition, lot of nuclear debris was seen around the arterioles. However, no evidence of hemophagocytosis was noted.

Lymph nodes showed presence of lymphoid tissue, benign sinus histiocytosis, expansion of sinuses and congested vessels. However, no evidence of hemophagocytosis was noted here too. There was relative depletion of B cells in some of the follicles; however, T cells were preserved.

Lungs weighed 180 grams and were subcrepitant to feel. There was patchy pleural thickening with subpleural hemorrhages (**Fig. 2a**). Thymus could not be delineated. Tracheobronchial tree showed diffuse ulcerations with greenish brown dirty exudates. There was no evidence of pulmonary thrombus. Microscopic sections showed fibrinous pleuritis with proliferation of macrophages in the pleura confirmed by CD68 stain. Other parts of lungs showed exudation of macrophages within alveolar spaces with colonies of bacteria occupying almost all alveoli (**Fig. 2b**). PAS stain showed faint positivity within the bacterial colonies. Gram's stain identified them as red indicating gram negative colonies.

Kidneys were swollen with flea bitten appearance and pin point hemorrhages and weighed 130 grams. The cut surface showed microinfarcts. In addition, there were fibrin thrombi in the glomerular capillary loops and there was no evidence of glomerulonephritis.

The heart weighed 70 grams and showed features of fibrinous pericarditis. The endocardium appeared opaque on left side inflow and outflow portion with dilatation. Microscopically there was evidence of pericarditis with



**FIG. 1** (a) Gross photograph showing punched out bile stained ulcers in the stomach; (b) Microphotograph showing ulcerated mucosa with septate fungal profiles in stomach (H&Ex20X); (c) Gross photograph showing bile stained liver and splenic infarct; (d) Microphotograph showing septate fungal profiles over capsular surface of liver infiltrating parenchyma (H&Ex10X).

scattered inflammatory cells and macrophage proliferation. Sections from myocardium showed subendocardial and parenchymal calcifications. One section from the heart revealed fungal thrombi within the veins as well as arteries of the pericardium.

Biopsy of the skin showed intact epidermis and infarcted adnexal structures. There were congested vessels with fibrin thrombi within them, indicating it to be a part of disseminated intravascular coagulation (DIC). Testes also showed fibrinoid necrosis and fibrin thrombi within vessel lumen.

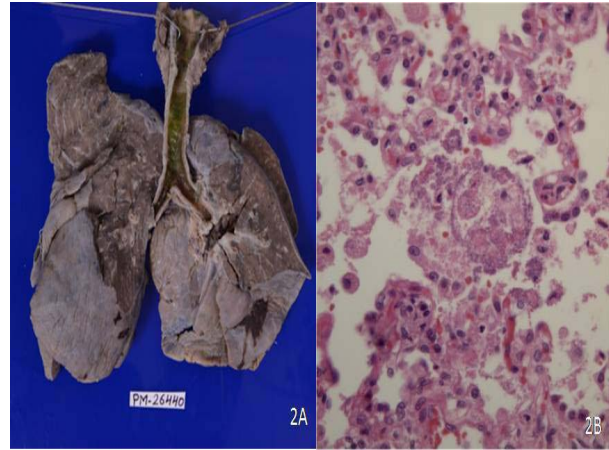
The final autopsy diagnosis in this 3-year-old boy diagnosed as SJIA is

- Primary gastrointestinal aspergillosis with serosal spread and dissemination to lymph nodes, mesentery, liver and pericardial vessels
- Splenic infarct secondary to thrombosis
- Evidence of DIC in skin, kidneys and testes
- Gram negative lobar pneumonia with tracheobronchial ulceration, pericarditis and pleuritis.

### Open Forum

*Adult physician 1:* Thrombocytopenia which occurred in this patient is probably related to DIC secondary to infection.

*Pediatrician 2:* The primary diagnosis would still be SJIA/MAS with nosocomial fungal sepsis.



**FIG. 2** (a) Gross photograph of both lungs with consolidation and greenish exudate in tracheobronchial tree; (b) Microphotograph showing bacterial colonies within the alveoli without inflammation (H&Ex20X).

Hemophagocytosis would have disappeared with treatment. MAS in this setting has a very high mortality which can be reduced by using Anakinra (13), an interleukin-1 receptor antagonist, which is currently not available in India.

*Pediatrician 3:* Is this kind of massive *Aspergillus* enteritis common and is there any way to make an antemortem diagnosis?

*Pathologist 1:* Antemortem diagnosis can be made with help of galactomannan and fungal PCRs, but there are issues of false positivity in them too.

*Adult physician 2:* We see lot of histiocytes in the pericardium and lymph nodes. Is it not usual for a fungal infection to produce a histiocytic response? What is the explanation for GI mucosal infarcts and myocardial calcification?

*Chairman:* There are some questions which are yet to be answered. But in conclusion, it appears that the index child had SJIA to start with and later on succumbed to multiple secondary infections.

### DISCUSSION

The clinical course in the index child reiterates the fact that HLH is a syndromic diagnosis and all diagnostic criteria may not be present initially [14], delineating the importance of serial follow up. Absence of hemophagocytosis in various tissues does not exclude a diagnosis of HLH/MAS as it is not always present at the initial marrow examination and serial examinations may reveal its presence [14,15]. We could not demonstrate hemophagocytosis in index

child even at autopsy. This could have been due to treatment with steroids and IVIg. In an autopsy series of 27 children with HLH, three did not have hemophagocytosis in post-mortem histopathology because of treatment with immunosuppressive drugs [16].

Underlying causes for HLH could be genetic or acquired [4]. In a majority of cases, HLH occurs secondary to one or more acquired triggers in a setting of genetic predisposition [4, 17]. EBV is said to be the most common acquired trigger as was seen in a Japanese registry where more than 40% cases of childhood HLH were related to EBV infection [18]. Mean age at presentation in this registry was 3.9 years [18]. Genetic mutations have been identified in a significant proportion of patients with HLH who have an identifiable acquired trigger [17].

MAS is a term used to describe hemophagocytosis in association with a rheumatological disorder [19]. In a study done to compare features of 27 SJIA/MAS patients with 90 familial HLH and 42 virus-associated HLH patients, absolute neutrophil count > 1800 cells/mm<sup>3</sup> at onset and CRP >90 mg/L were found to indicate MAS/SJIA [6]. Once recognized, early aggressive therapy for MAS is essential as mortality in SJIA/MAS is reported to be around 8% in a multicentric study of 362 patients [20]. High dose corticosteroids, cyclosporine, anakinra and IVIg constitute front-tier therapeutic choices in SJIA/MAS [21].

Independent predictors of early fatal outcome in HLH have been found to be platelet count < 75,000 cells/mm<sup>3</sup> and activated partial thromboplastin time > 33 seconds [22]. Commonest cause of mortality in HLH is related to HLH itself [23]. However, bleeding risks and therapy related complications such as infections are additional causes. Invasive fungal infections were noted in six of 14 fatalities in childhood HLH in a retrospective review and two of them had disseminated *Aspergillus* infections at autopsy [24]. Index child probably developed disseminated *Aspergillus* infection and gram-negative bacterial pneumonia secondary to prolonged hospitalization and immunosuppressive therapy.

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