Hemophagocytosis Associated with Hepatitis A and E Coinfection in a Young Child

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Abstract We report and discuss a unique case of hemophagocytosis associated with hepatitis A and E coinfection in a young child which has never been reported earlier in children. Its varied presentation is emphasized and possible management options and outcome are discussed.

Keywords Children · Hemophagocytosis · Hepatitis

A previously well 6 year old female child presented with high grade fever (104°F) for 7 days. She developed jaundice, excessive sleepiness and altered behaviour 3 days prior to presentation. On examination, she was febrile, drowsy and had pallor, icterus, firm tender hepatomegaly (liver span—12 cm) with ascites. Investigations showed raised total bilirubin (6.2 mg/dl), hypoalbuminemia (2.4 mg/dl), elevated serum liver enzyme levels (AST 4860 IU/l, ALT 2940 IU/l), hemoglobin of 10.4 mg%, normal coagulation profile and presence of specific IgM antibody to hepatitis A virus and hepatitis E virus. A diagnosis of hepatitis A and E with hepatic encephalopathy stage 2 was established. Child was started on supportive therapy. However, fever continued to persist. Blood and ascitic cultures were sterile. Urine

culture showed the growth of *E.coli*. Child was started on broad spectrum antibiotics according to culture and sensitivity report. Despite this fever persisted. Child also developed splenomegaly, increasing ascites and macular rash all over. Repeat laboratory parameters showed anemia (hemoglobin—6.2 mg/dl), raised D-dimer (15.3 mg/l) and fibrin degradation products (>800 ng/ml) with normal leucocytic count ($7,600 \times 10^5 \text{ mm}^3$) and platelet count ($1.8 \times 10^5 \text{ mm}^3$). Hyperbilirubinemia (7.3 mg/dl) and hypoalbuminemia persisted but liver enzymes gradually showed a falling trend (AST 156 IU/l, ALT 101 IU/l). Malaria, typhoid, leptospirae, dengue, tuberculosis, rickettsial, fungal and other viral infections like hepatitis B and C, HIV were ruled out by appropriate investigations. Antinuclear antigen was negative. A bone marrow examination revealed increased number of histiocytes with evidence of hemophagocytosis. She also had elevated serum ferritin level (1,923 ng/ml) and triglycerides (548 mg%). Thus, a diagnosis of hemophagocytosis associated with hepatitis A and E coinfection was established as per the diagnostic guidelines of HLH-2004 protocol (Table 1) [1]. Child was started on dexamethasone following which she became afebrile. After 5 days of afebrile period, parents took discharge against medical advice. After discharge, child had a fulminant clinical course and died after 3 days.

Hemophagocytosis has been described with a variety of viral, bacterial and protozoal infections. However, it is a rare complication in hepatitis A and hepatitis E virus infections with 13 and 1 cases, respectively reported in adults till date [2, 3]. It is unreported in pediatric age group. Moreover, there is no report of hemophagocytosis associated with hepatitis A and E co-infection as in our patient.

The precise pathogenesis remains unclear. Uncontrolled activation of cellular immune system by antigens causing excessive production of interferon gamma, and other

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Table 1 Diagnostic criteria for HLH fulfilled

The diagnosis of HLH can be established if one of the either 1 or 2 below is fulfilled.	
1. A molecular diagnosis consistent with HLH.	NA
2. Diagnostic criteria for HLH fulfilled (5 out of 8 criteria below).	Yes
<i>A. Initial criteria</i>	
<u>Clinical criteria</u>	
• Fever	Yes
• Splenomegaly	Yes
<u>Laboratory criteria</u>	
• Cytopenias (affecting ≥ 2 of 3 lineages in peripheral blood): Hemoglobin (< 9 gm/dL), Platelets ($< 100 \times 10^9/L$) and Neutrophils ($< 1.0 \times 10^9/L$)	No
• Hypertriglyceridemia (> 265 mg/dL) and/or Hypofibrinogenemia (< 150 mg/dL)	Yes
<u>Histopathologic criteria</u>	
• Haemophagocytosis in bone marrow, spleen or lymph nodes No evidence of malignancy.	Yes
<i>B. New diagnostic criteria</i>	
• Low or absent NK-cell activity	NA
• Ferritin ≥ 500 $\mu\text{g/L}$	Yes
• Soluble CD 25 ≥ 2400 U/mL.	NA

NA Not available

cytokines which act on a variety of cells, resulting in macrophage activation and tissue damage is the probable mechanism.

The clinical and laboratory features are variable. Pancytopenia/bicytopenia may not manifest in all patients as was the isolated anemia in our case. The level of serum ferritin may be variable ranging from 1,000 ng/ml to >11akh ng/ml [1].

Although intravenous immunoglobulin (IVIg), steroids, plasmapheresis and cytotoxic agents have been tried in the therapy of viral infection associated hemophagocytosis with varying success rates, there is no standard therapy [1, 2, 4]. IVIg therapy was not administered in the index case due to financial constraints. Cytotoxic agents were not given as patient had infection associated hemophagocytosis and showed some initial response to steroids. Subsequently chemotherapy could not be administered as parents took child against medical advice. The prognosis of viral

infection associated hemophagocytosis is highly variable, with a frequently fatal outcome, as in our patient.

Acknowledgment Conflict of Interest None.

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