Introduction:
Dengue, transmitted by the mosquito Aedes aegypti affects millions of people worldwide every year. Hemophagocytic lymphohistiocytosis (HLH), a potentially fatal condition that is often under recognised contributing to its high mortality and morbidity. Early recognition is crucial for any efforts at curative therapy. Virus-associated hemophagocytic syndrome is a disorder characterized by a benign histiocytic proliferation with marked hemophagocytosis in the background of a systemic viral infection. Infection-associated hemophagocytic syndrome carries a high mortality. Hemophagocytic lymphohistiocytosis (HLH) is a serious condition and may prove fatal if not detected early and treated appropriately. Diagnosis of HLH is challenging and usually missed as clinical and laboratory findings are nonspecific. It should be suspected with prolonged fever beyond seven days associated with splenomegaly, hyperferritinemia, worsening cytopenias and development of multiorgan dysfunction. A proportion of patients recovered with supportive therapy, however most required interventions with corticosteroids, intravenous immunoglobulin or chemotherapy. We report 3 cases of dengue associated HLH. Among them 2 patients were treated with steroid with good outcome, and one died from MODS.

Key words: Haemophagocytic Lymphohistiocytosis, Dengue, Methylprednisolone, MODS

Viral infections mostly implicated in association with HLH are Epstein-Barr virus infection, adenovirus infection, and viral hepatitis. We report 3 cases of dengue associated HLH with their management and outcome. The following cases were diagnosed during the outbreak of Dengue Fever between the month of June and September, 2019 admitted at Popular Medical College Hospital.
On day 3 of admission patient developed breathlessness and patient WBC count was 19.5 K/μL. Ultrasound imaging showed mild splenomegaly (measured length 13.5 cm), free fluid in abdomen and edematous pancreas and bilateral pleural effusion. Chest X-ray showed pneumonitic changes in both lung fields.

Serum ferritin level done at day 3 of admission was 8040 ng/ml. Serum procalcitonin level was 3 ng/dl which indicate sepsis. D-dimer was slightly high but APTT was normal. Serum Triglyceride was 456 mg/dl (<150 mg/dL).

Urine and blood cultures were negative. Negative Weil Felix screening test for rickettsial infections, Rapid-test anti-dengue virus IgM antibody was positive but anti-dengue IgG was nonreactive, which is suggestive of primary dengue infection.

Although bone marrow examination was not done, diagnostic criteria of HLH were met: fever, splenomegaly, cytopenia, hypertriglyceridaemia and hyperferritinaemia. Diagnosis was made Dengue Fever Group C complicated with HLH with pancreatitis and pneumonia. Intravenous Methylprednisolone was initiated on 10th day of illness (500mg/ daily), was continued for 3 days and then was changed to oral methylprednisolone 16 mg twice daily for another 5 days. After good clinical improvement the patient was discharged after 8 days of hospital stay. A follow up checkup after 2 weeks showed all results of blood tests were normal.

**Patient 2**

A 24 year old male from Cumilla with Dengue NS1 positive presented in September 2019 with fever for 6 days and respiratory distress for 3 days. Initial laboratory investigations showed bicytopenia (Leukopena 3.67 K/μL and Thrombo-cytopena 26,000) and transaminases (ALT 399 U/L, AST 673 U/L). Ultrasound imaging showed hepatomegaly (15 cm) and mild splenomegaly (measured length 12.6 cm). Chest X-ray showed feature of pneumonitis. He received empirical antibiotics although later all microbiological investigations were negative. Dengue serology was positive for both IgG and IgM, indicative of secondary dengue infection.

Serum ferritin and Serum Triglyceride level were 6620 ng/ml and 332 mg/dl respectively.

Diagnosis was made Dengue Fever Group C complicated with pneumonitis and HLH on the basis of fever, splenomegaly, cytopenia, hypertriglyceridaemia and hyperferritinaemia.

Three days course of Inj. Methyl Prednisolone 250 mg IV daily was given. Resolution of fever, followed by other symptoms and normalization of all blood results occurred. No oral substitution of Prednisolone was given to the patient.

**Patient 3**

A 60 year old diabetic and hypertensive male from Maniknagar, Dhaka with Dengue NS1 positive presented in august 2019 with fever for 5 days and yellow discoloration sclera, vomiting, disorientation, pain abdomen for 2 days. Significant findings on examination were fever of 103, hypotension, epigastric and right hypochondriac tenderness, deeply icteric and feature of hepatic encephalopathy (Flapping tremor, disorientation).

Initial laboratory investigations showed bicytopenia (Leukopenia 3.60 K/μL and thrombocytopena 13,000/μL), transaminase (ALT 5200 U/L, AST 6873 U/L), bilirubin 19.10 mg/dL, s. albumin 2.86g/dL, renal impairment (creatinine 6.08 mg/dL, urea 160 mg/dL), Lipase 5461 u/L PT 18 sec (control 12sec), APTT 43sec (control 32 sec), D-dimer 4.17, FDP 13.68 (RV <5), Fibrinogen was normal and ABG showed metabolic acidosis.

Ultrasound imaging showed mild splenomegaly (measured length 12.7 cm), free fluid in abdomen and edematous gallbladder. Chest X-ray showed bilateral pleural effusion. Serum procalcitonin level was 95.21ng/dl and lactate was 108.1mg/Dl which indicate severe sepsis.

Dengue serology IgM antibody was positive but anti-dengue IgG was non reactive, which is suggestive of primary dengue infection. All microbiological investigations for secondary infection (Blood, urine and stool culture) were negative. Viral screening (HAV, HBV, HCV and HEV) were negative. Serum ferritin and Serum Triglyceride level were 4524ng/ml and 365 mg/dL respectively.

Diagnosis was made as Dengue Fever Group C complicated with Expanded Dengue Syndrome and MOD (hepatitis, pancreatitis, AKI) and HLH on the basis of, splenomegaly, cytopenia, hypertriglyceridaemia and hyperferritinaemia.

Patient was managed at intensive care unit with board spectrum antibiotic, steroid (Methyle Prednisolone 500 mg IV daily for 3 days), aphaeretic platelet transfusion, Haemodialysis. But patient condition deteriorated further and patient died after 9 days of hospital admission.

**Discussion:**

HLH is a disease with major therapeutic and diagnostic difficulties. The diagnosis HLH was based on five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridaemia and/or hypofibrinogenemia, and hemophagocytosis). In 2004 three additional criteria were introduced by the Histioctye...
Society; low or absent NK-cell-activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels. Five of these eight criteria must be fulfilled for a diagnosis of HLH. The NK cell activity and soluble IL2 receptor quantitation tests are not done in routine clinical practice.

Bone marrow examination could not be done in our 3 cases. These patients fulfilled five out of the eight criteria - high grade fever, splenomegaly, cytopenia, hypertriglyceridaemia, hyperferritinaemia and accordingly were diagnosed as case of secondary HLH clinically and biochemically. HLH may be primary (familial) and secondary. Secondary HLH develop due to over activation of immune system. Secondary HLH has been associated with a variety of viral, bacterial, fungal and parasitic infections as well as collagen vascular diseases and malignancies particularly T-cell lymphomas. The term reactive HLH has been suggested when HLH is associated with an identifiable infectious or non-infectious etiology to distinguish it from the familial form. Infection has been found to be associated with HLH in half of all reported cases.

Early recognition and diagnosis of HLH might enable physicians to start the steroid treatment in optimal time, leading to better clinical outcome. Although the mechanism of HLH remains unclear, current accepted theory suggests that inappropriately proliferating and activated T-cells may induce macrophage activation with inadequate intracellular killing of phagocytes. Many studies suggested the important roles of perforin and natural killer (NK) cells in the HLH subtypes.

In DF the febrile phase lasts up to seven days. With prolonged fever, secondary bacterial infection should be excluded and dengue associated HLH should be suspected. Steroid and immunoglobulin are the mainstay of treatment of HLH. Severe or fatal complications may ensue if dengue associated HLH is unrecognized. Cases received methyl prednisolone due to early recognition of dengue associated HLH based on the presence of persistent fever, splenomegaly, cytopenia, hypertriglyceridaemia and hyperferritinaemia. Case 1 and 2 were successfully recovered with treatment but case 3 did not survived due to development of MOD and Expanded dengue syndrome which encountered the aggressiveness of HLH if not early detected and treated accordingly.

Defervescence occurs between D3 and D7 and in DHF this period is associated with critical phase and plasma leakage. Secondary dengue infection (two sequential infections by different serotypes) is also a risk for severe dengue. We found one case was associated with secondary infection.

Some studies observed that primary dengue infections were as much at risk of severe DHF and dengue associated HLH. Case 1 and 3 were associated with primary infection. So, both primary and secondary infection with DF can cause HLH.

It would be important to differentially diagnose dengue-associated HLH from severe dengue hemorrhagic fever. Early recognition and initiation of steroid would be crucial for the successful treatment of dengue fever complicated by HLH. Dengue virus needs to be investigated as an important triggering factor for HLH.

**Conclusion:**
Dengue associated HLH must be suspected in the presence of persistent fever beyond day 7, splenomegaly, worsening cytopenias, shock and MOD beyond plasma leakage phase. Exclusion of SIRS and secondary infection is important before initiation of corticosteroids. Early recognition has a significant impact on the management and outcome. Dengue associated HLH may indicate a severe form of dengue infection, and dengue virus needs to be recognized as an important causative agent for HLH.

**Limitation:**
BM biopsy needs to be performed to demonstrate hemophagocytosis.

Identification of Dengue virus serotype is very crucial to determine the relationship.

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**Consent:** The patient’s informed signed consent was obtained.

**References:**


