An Unique Case of Dengue and Typhoid Coinfection Resulting in Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is rare, uncommon and life threatening condition characterised by dysfunction of cytotoxic T and natural killer cells and abnormal immune activation, leading to tissue destruction. We report a case of 17 year old with primary diagnosis of Dengue and Typhoid coinfection causing excess immune activity, leading to HLH. Initial management was based on dengue fever. Subsequent blood test revealed a Typhoid coinfection. In spite of treatment for coinfection, patient's clinical condition deteriorated. On further evaluation, HLH was diagnosed. Evaluation fulfilled the criteria of HLH and steroid therapy was added, to which the patient showed improvement. There are many causes of HLH as primary and secondary. It has noted to occur with dengue and typhoid infection individually, but here we represent an unique case of HLH occurring in a dengue and typhoid coinfection ,which has never been reported.

Keywords: HLH, Coinfection, Dengue Fever, Typhoid Fever.

INTRODUCTION

Dengue fever is caused by a virus transmitted through the bite of the mosquito Aedes aegypti. There are four serotypes of the virus. Clinical features include fever, myalgia, bone pain, and fatigue. The severity of the disease varies, from mild symptoms to developing complications like dengue hemorrhagic fever and dengue shock syndrome. Typhoid fever is another common bacterial infection caused by Salmonella typhi and is characterised by fever, anorexia, generalised fatigue, abdominal pain, and diarrhoea. Gastrointestinal symptoms can also be present in dengue fever. Laboratory parameters for both infections reveal leukopenia, thrombocytopenia, deranged liver function tests like elevated alanine transaminase (ALT), and splenomegaly. Because of the similarities in presentation and laboratory findings, there may be a delay in the diagnosis if coinfection exists. Delay in the initiation of appropriate antibiotics for enteric fever in dengue coinfection can result in significant morbidity and mortality.[2,3,4]

HLH is a rare immune mediated disorder which can be primary or secondary. Primary HLH is seen in younger age group, whereas secondary HLH can occur either in children or adult age group following triggers which include infections, autoimmune diseases and haematological malignancy.[1] It is characterised by immune dysfunction and uncontrolled inflammation due to abnormal macrophage activation and cytokine release. Lab parameters reveal bicytopenia, liver dysfunction, coagulopathy, hyperferritinemia, hypertriglyceridemia and elevated lactate dehydrogenase; splenomegaly is also seen.

CASE REPORT

A 17-year-old female presented to the emergency department with complaints of fever lasting 14 days, with 3 days of the afebrile phase. The fever recurred with cough and expectoration for 3 days, loose stools, and vomiting for 5 days. Patient has been taking symptomatic treatment for the same. Outside done investigation showed dengue NS1 positivity. On presentation, patient was febrile. Pallor and severe dehydration was present. Pulse rate of 126 beats per min, BP of 70/50 mmHg. Systemic examination revealed tenderness in right hypochondrium, right iliac and right lumbar region. Other system examination was normal. Fluid resuscitation was started along with inotropic support in view of low BP. Routine blood investigations were sent and revealed pancytopenia. Liver function test revealed hyperbilirubinemia, transaminitis, hypoalbuminemia. Dengue serology was repeated and blood culture was sent, which showed Dengue NS1and IgM positivity. The USG abdomen showed splenomegaly and minimal ascites. Patient was treated as Dengue Shock Syndrome (DSS) with adequate fluid management, inotropic support and other conservative treatment. Human albumin was given to improve the blood volume. One unit of whole blood transfusion was done in view of pancytopenia. In spite of adequate resuscitation, patients blood pressure was persistently low and hence alternate diagnosis was suspected. Patient was screened for coinfection, autoimmune causes and other alternative diagnosis. Widal test revealed *Salmonella typhi* positive for 'O' & 'H' antigen in 1:320 dilution. Third generation cephalosporin was started. Blood culture also reported *Salmonella typhi* growth that was sensitive to ongoing antibiotics. As the fever spikes were persistent, no improvement in blood counts along with the elevated ferritin and splenomegaly, HLH was suspected. Serum ferritin, triglycerides and LDH were sent, which were 971.26 ng/

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Test/date	26/12/22	27/12/22	28/12/22	29/12/22	30/12/22	31/12/22	1/1/23	2/1/23
HB	8.5	7.6	7.5	7.0	7	8.8	8.9	9
PCV	25.2	23	22.3	22	22.6	24.8	26.9	30
WBC	1320	1482	1764	1547	2345	3892	4510	4921
PLT	59,000	56,000	43,000	26,000	14,000	28,899	40,347	74,000

Table-1: Complete blood count

Test / Date	26/12/22	28/12/22	30/12/22	01/01/23	02/01/23
Total bilirubin (mg/dL)	2.1	3.6	3.3	2.3	1.3
Direct bilirubin (mg/dL)	0.9	1.5	1.5	1.5	0.7
Total protein (g/dL)	4.0	4.1	4.1	4.3	4.7
Albumin (g/dL)	1.9	1.9	2.0	2.5	3.2
SGPT (IU/L)	65	51	66	66	88
SGOT (IU/L)	159	170	254	199	155
ALP (IU/L)	55	112	127	179	214
GGTP (IU/L)	83	111	124	220	200

SGPT- serum glutamate pyruvate transaminase, SGOT- Serum glutamic oxaloaceic transaminase, aLP- Alkaline Phosphatase, GGTP- Gamma Glutamyl TransPeptidase

Table-2: Liver function test

Test/ Date	26/12/22	28/12/22	30/1/22	01/01/23	02/01/23
Urea (mg/dL)	13	12	12	15	12
Creatinine (mg/dL)	0.5	0.5	0.4	0.5	0.5
Uric acid (mg/dL)	1.8	1.5	2.8	3	3.1
Sodium (mEq/L)	138	136	139	138	142
Potassium (mEq/L)	3.01	3.1	3.3	3.47	3.41
Chloride (mEq/L)	109	108	106	109	107

Table-3: Renal function test

ml, 545 mg/dL and 713 U/L, respectively. HLH diagnostic criteria were fulfilled. Patient was planned for bone marrow biopsy but deferred in view of low platelet count and clinical improvement. Patient was started on IV steroids for one week and later changed to oral steroids. Inotropic support gradually tapered off. Clinically, the patient improved, and blood counts increased; she was discharged after about two weeks in the hospital.

DISCUSSION

Dengue fever can occur alone or as a coinfection with various other bacterial infections. The complexity of diagnosing a coinfection predisposes the patient to significant morbidity and mortality. It is known that dengue fever can cause reduced T cell proliferation, which makes the patient more susceptible to coinfection.[8] There may also be intestinal endothelial damage or hemorrhage, resulting in dengue virus interaction with other organisms.[9] There is a breakdown of the intestinal mucosal barrier in dengue fever, which further increases the risk for gramme-negative sepsis.[8] The initial presentation of fever with thrombocytopenia in the above-reported case led to the diagnosis of dengue fever as our initial diagnosis. But persistent fever along with loose stools and further evaluation led to the diagnosis of co-infection with typhoid fever. Management of dengue shock syndrome along with antibiotics susceptible to typhoid infection showed a reduction in fever spikes. In spite of treatment, BP was persistently low, and laboratory parameters didn't show improvement, which is why HLH was suspected.

HLH is an immune-mediated inflammatory disorder characterised by macrophage activation and phagocytosis of blood cells. In dengue fever, virus-infected T cells produce inflammatory cytokines, which contribute to the development of HLH. Other infections causing HLH include Adenovirus, Hanta virus, Human Immunodeficiency virus, Staphylococcus aureus, Campylobacter, Mycoplasma, Candida, Cryptococcus etc. Criteria for the diagnosis of HLH include satisfaction of 5 out of 8 criteria: fever, splenomegaly, bicytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, soluble IL-2 receptor >2400 U/mL, and a bone marrow biopsy showing hemophagocytosis. Our patient was satisfied with the following: fever, splenomegaly, bicytopenia, hypertriglyceridemia, and hyperferritinemia. A bone marrow biopsy was not performed in our case because other criteria for diagnosing HLH were met and the patient had thrombocytopenia.

Treatment of HLH is primarily focused on suppressing hyperinflammatory reaction and activated immune cells, eliminating trigger, supportive therapy.[5,6] Immune suppression can be achieved by administering corticosteroids, immunoglobulins, immuno modulators like cyclosporine, monoclonal antibodies like rituximab. Corticosteroids are the first choice in HLH, dexamethasone is preferred over prednisolone because of its better CNS penetration.[7] We

started our patient on intravenous dexamethasone for one week and changed to oral steroids for one more week and slowly tapered off. Patient responded to steroids, antibiotics and conservative treatment.

CONCLUSION

Dengue fever should be evaluated for coinfection when the clinical improvement is diminished. Dengue and typhoid fever individually is very well known in the past to cause HLH. HLH should be suspected at the earliest sign of persistent fever and failure of patient's improvement even after adequate therapy. Delay in diagnosing coinfections and rare complication like HLH in dengue fever will increase the risk for mortality and morbidity. Hence screening for coinfection and complications of dengue like myocarditis, encephalitis and HLH should be done. Prompt treatment helps in early recovery and to reduce the mortality and morbidity. Suppression of cytokine storm by corticosteroids is essential in the management of HLH.

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