Case Report

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Oncology Section

Oral Etoposide for Dengue Induced Haemophagocytic Lymphohistiocytosis Presented as Acute Liver Failure

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ABSTRACT

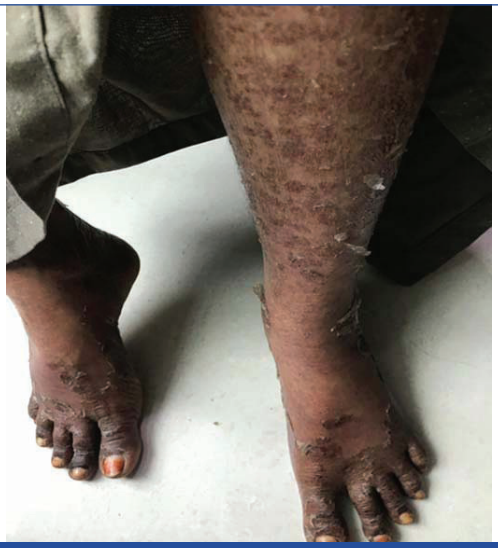
Dengue fever is not an uncommon arboviral infection in lieu of tropical geography. The gravity of the disease ranges from an Outpatient Department (OPD) visits for febrile illness to haemorrhagic complications like shock. Hereby, authors report a case of a 33-year-old female patient with no prior morbidities. Initial fever episodes due to dengue resulted but she deteriorated clinically with second wave of continuous fever spikes. On evaluation, a diagnosis of Haemophagocytic Lymphohistiocytosis (HLH) was made. The patient was treated with steroids and oral etoposide following which patient recovered completely. Although, scarce occurrence of HLH following viral illness needs strong suspicion, prompt investigation and management to avoid potentially life-threatening complications. On a case-to-case basis HLH protocol can be modified to make an OPD base treatment by switching to oral etoposide.

Keywords: Chemotherapy, Cytopenia, Haemophagocytic syndrome, Macrophage activation syndrome

CASE REPORT

A 33-year-old female with no significant past history of any major illness, presented with a history of fever of two days duration to a primary healthcare setting. Patient was clinically stable and was given symptomatic care. Fever persisted for two more days during which in treatment regimen of antibiotics (third generation) cephalosporins were administered. Even so, patient developed petechial and purpuric rashes on both lower limbs associated with generalised erythema. Following antibiotic course there was no progression of rashes. The rashes started to exfoliate in next three days. The initial fever diagnostic work up showed positivity for Immunoglobulin M (IgM) and Immunoglobulin G (IgG) for dengue [Table/Fig-1]. Ensuing two days, jaundice, vomiting with abdominal distension was developed (on 5th day of admission) and the patient was referred further evaluation and strategised management. In further tests, Liver Function Tests (LFT) showed hyperbilirubinaemia with bilirubin of 16.1 mg/dL, Aspartate Transaminase (AST) and Alanine Transaminase (ALT) 10 times the upper limit of normal. Initially diagnosis made was dengue related hepatitis/drug induced liver injury and was managed conservatively. However, LFT progressively worsened and stigma of enlisted differential diagnosis was considered.

Patient started developing new onset of fever spikes at high-grade (temperature around 102°F). Peripheral smear for malarial parasite was negative. IgM for hepatitis A and hepatitis E were negative. Urine examination did not show features of urinary tract infection. Leptospira serology, Weil-Felix serology were negative. Human Immunodeficiency Virus (HIV), HBsAg and Anti HCV were negative. Blood culture, urine culture were negative. C-reactive Protein (CRP) was very high indicating and active inflammatory process (58.86 mg/L). Note CRP value on different days not available due to logistic imidiations. Serum procalcitonin was negative aided in ruling out bacterial sepsis.



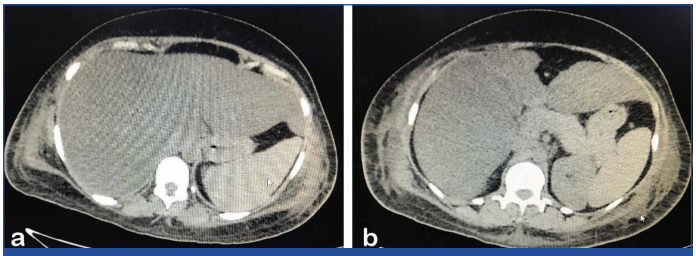
[Table/Fig-1]: HLH syndrome rashes over lower limbs. Dry scaly skin was observed as patient was scratching it due to itchy sensation (pictures were taken after the rashes started to respond).

At this stage carbapenem antibiotics were started and even after which patients persisted to have fever. Along with fever spikes, patient's blood counts started declining progressively. The trend of LFT and haemogram is shown in the table below [Table/Fig-2]. Because of the rapidly falling haemoglobin, haemolysis was alleged but the serum Lactate Dehydrogenase (LDH) was very high (>5000 u/L). Even so, reticulocyte count was normal. Peripheral smear did not reveal any signs of hemolysis. Further, diagnostic tree included direct and indirect Coomb's tests, which were negative. But at this time clinically patient had progressive abdominal distension, Computed Tomography (CT) abdomen was done which showed massive haepatomegaly, splenomegaly and mild pancreatitis with minimal ascites [Table/Fig-3a,b].

Parameter/Day of illness	Day 7	Day 8	Day 10	Day 11	Day 12	Day 13	Day 14	Day 17	Day 19	Day 24	Day 30
Haemoglobin (gm/dL)	9.5	9.5	8.3	7.9	7.4	7.0	7.8	6.5	7.6	8.5	8.9
Total leucocyte count (cells/cumm)	4200	3200	3200	3700	3500	3400	4100	4200	3100	4000	12300
Platelet (lacs cells/cumm)	1.9	1.5	1.0	1.0	0.75	0.6	0.35	0.6	0.9	2.3	5.6
Total/Direct bilirubin (mg/dL)	14/9.5	16.1/9.4	18/10.6	19.2/11.3	19.1/10.1	19/11	17.5/9.3	14.6/7.9	10.9/6.0	6.2/3.3	3.1/1.6

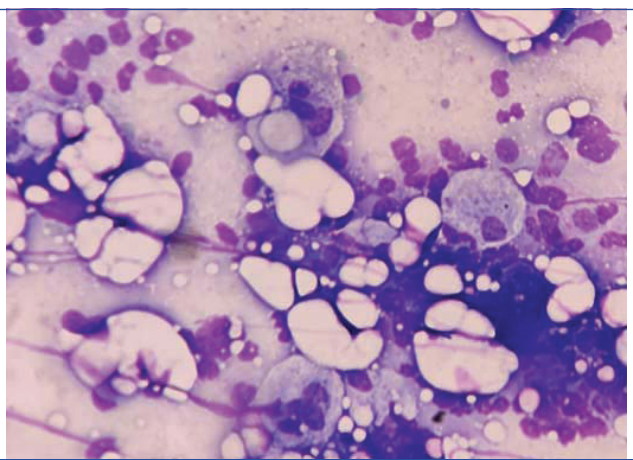
Aspartate Transaminase (AST) and Alanine Transaminase (ALT) (U/dL)	619/319	442/307	872/353	1027/355	949/373	682/364	307/317	183/252	137/224	116/222	76/120
Serum albumin (g/dL)	2.6	2.5	2.3	2.3	2.3	2.2	2.2	3.2	3.3	4.1	4.2
Serum ferritin (ng/dL)	2565	Not repeated									1453
Serum lactate dehydrogenase (U/dL)	5072	4620	5560	-	-	6730	-	3979	-	1160	-
Serum fibrinogen (mg/dL)	115	Not repeated again									

[Table/Fig-2]: Trend of haemogram and liver function test.
CRP-value on different days not available due to logistic imidiations



[Table/Fig-3]: a) Computed tomography abdomen showing haepatomegaly, splenomegaly and mild pancreatitis with minimal ascites; b) Showing bulky pancreas suggesting pancreatitis.

Computed tomography abdomen as followed by serum amylase and lipase test which were elevated since 7th day [Table/Fig 2]. Patient was managed for pancreatitis palliatively. Determinative evaluation for pancreatitis showed no evidence of hypercalcaemia. However, serum triglycerides were elevated (>800 mg/dL). And with a very high LDH, high triglycerides, organomegaly and pancytopenia with persistent fever spikes, Haemophagocytic Lymphohistiocytosis (HLH) was put forth as provisional diagnosis. Blood test revealed that serum ferritin was 2565 ng/dL and fibrinogen was low (115 mg/dL). Bone marrow aspiration and biopsy were done to confirm the diagnosis. Haemophagocytic Syndrome (HScore) for HLH showed >90% indicating the positive scale probability for HLH. Bone marrow aspiration showed myeloid hyperplasia, microscopically and a few macrophages engulfing lymphocytes [Table/Fig-4]. After bone marrow biopsy report and confirmation of diagnosis of HLH, Cerebrospinal Fluid (CSF) cytology was done which came out to be negative. And patient was started on steroids and oral etoposide [Table/Fig-5]. For the logistic issues, we considered oral etoposide treatment regimen. Patient completed full protocol with last five months taking oral etoposide, dexamethasone and following-up on online consultations. All antibiotics and antifungals were stopped. Patient gradually improved with improvement in blood counts and normalising liver functions in the first one month itself, ascites resolved. Patient clinically got better with resolution in pain abdomen and abdominal distension. A follow-up after two weeks showed improvement in clinical and diagnostic parameters with signs of improvement. Recent follow-up in month of February 2022 showed patient was still in remission with no signs of cytopenia or organomegaly. That will make a follow-up period of nearly two years.



[Table/Fig-4]: Bone marrow aspiration showing haemophagocytes (H&E stain, 100X).

Time interval	Dexamethasone	Etoposide	Cyclosporine
Weeks 1 and 2	10 mg/m^2 daily	150 mg/m^2 twice a week	-
Weeks 3 and 4	5 mg/m^2 daily	Oral once weekly (Modified from intravenous)	-
Weeks 5 and 6	2.5 mg/m^2 daily	Oral once weekly (Modified from intravenous)	-
Week 7	1.25 mg/m^2 daily	Oral once weekly (Modified from intravenous)	-
Week 8	Taper dose to zero	Oral once weekly (Modified from intravenous)	-
Week 9-24	Alternate weeks 10 mg/m^2	-	6 mg/kg daily in divided doses (not given)
Week 10-23	-	Oral 150 mg/m^2 on alternate week (Modified from IV)	-

[Table/Fig-5]: HLH 94 treatment protocol (modification for this case, for oral etoposide from week three onwards) [1].

DISCUSSION

Dengue fever is not very uncommon viral infection caused by *Flaviviridae* group of viruses and is spread by Aedes mosquitos [2]. Dengue fever is aboriginally in tropical countries. Infection varies in severity ranging from self-limiting febrile episodes to haemorrhagic complications and shock. Clinically manifests by acute onset of, moderate high-grade fever, myalgia, retro-orbital pain, petechial rashes over skin and mucosal surfaces (wet purpuras). In severe cases major haemorrhagic complications like gastrointestinal bleed, intracranial bleed and shock are noted [3]. Occurrence of hepatitis, encephalopathy and multi organ dysfunctions are among common complications noted. Although, very rare, the viral infection had been noted for causing immune dysfunction and lead to development of haemophagocytic lymphohistiocytosis [4].

Haemophagocytic lymphohistiocytosis is an aggressive disorder with excessive immune activation [2]. Acquired cases are noted to be secondary to autoimmune diseases, haematological malignancies and infections. The disease manifests with fever and multiple organ dysfunctions. This has a very aggressive course and mimics Multiorgan Dysfunction Syndrome (MODS) secondary to most infections [4]. The management for both are different. With a high level of suspicion, the disorder can be diagnosed and managed promptly to avoid lethality's. In this case of 33-year-old female who developed HLH following two weeks of dengue fever. With appropriate management patient had an uneventful recovery. Idiosyncrasy of this case is treatment with oral etoposide after induction chemotherapy of one months and this was planned in view of the issues of travel associated with peak of the pandemic of coronavirus. This case report adds to narrow cases of HLH complicating dengue fever that are available in literature. And this case also adds to proposition of oral etoposide regimen among non high-risky HLH cases. HLH is a multisystem disorder, commonly mistaken for sepsis and its complications. Most common in paediatric age group [2]. Primary HLH occur due to disorders of immune system. Secondary HLH is due to haematological malignancies, solid organ tumours, lymphomas, autoimmune disorders, rheumatological disorders,

acquired immunodeficiency and infections. Among infections, viral (especially Epstein Barr virus, Cytomegalovirus, Parvovirus B-19), tuberculosis, parasitic and fungal infections are common if considered as high-risk factor for HLH.

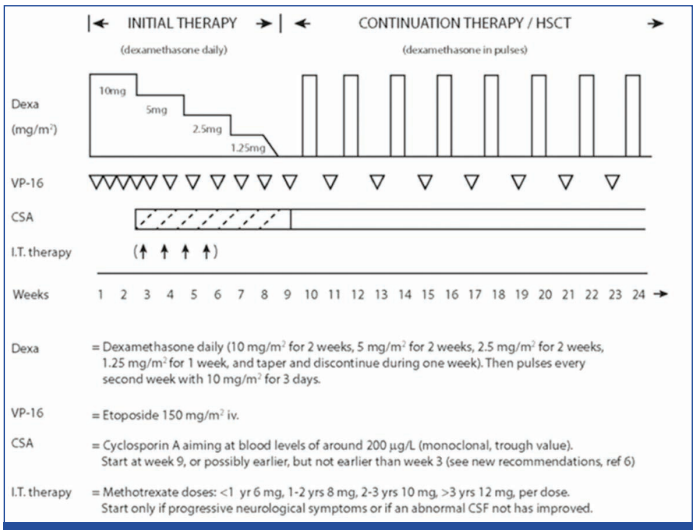
This disorder is characterised by excessive macrophage activation and cytokine release due to a failure in natural killer cell function in its underlying molecular pathogenesis [5]. This results in immune dysregulation and unchecked inflammation; to be précised. Patients with HLH are acutely ill with fever, organomegaly in the form of hepatosplenomegaly, hepatitis, coagulopathy, effusions, lymphadenopathy; as in this case. Most common freaky biochemical results are deranged liver function tests, bicytopenia, hyperferritinaemia, hypofibrinogenaemia, hypertriglyceridaemia, elevated LDH [Table/Fig-6]. Increase in IL-2/CD25 receptor is also observed [6].

Modified 2009 HLH criterion	Present case patient
Atleast five of following are mandatory	
Fever >38.5	+
Splenomegaly	+
Cytopenia	
Haemoglobin <9 gm/L	+
Platelet <100×10^9	+
ANC <1×10^9	
Hepatitis	+
Atleast one of the following	
Ferritin elevation above 500	+
Soluble CD 25 elevation	Not done
Haemaphagocytosis seen on tissue biopsy	+
Low Natural Killer (NK) cell activity	Not done
Supportive but not mandatory	
Hypertriglyceridaemia	
Hypofibrinogenaemia	+
Hyponatraemia	

[Table/Fig-6]: Comparing modified HLH criterion 2009 with present case [7].

Dengue associated HLH is commonly seen in children, with few reports in adults [5]. It has been more commonly noted in patients with dengue haemorrhagic fever, as in present case who has petechial rashes over lower limbs [8]. Dengue infected T-cells produce cytokines leading to uncontrolled histiocytic activity followed by increased production of cytokines, interferon-γ and TNF-α, that in turn plays a role in the pathogenesis of HLH [9]. Till date, only three serotypes of dengue viruses have been chalked up to cause HLH (DEN1, DEN3 and DEN4) [10]. Earlier published databased on postmortem studies, proposed that haemophagocytosis was present in the terminal stages of dengue virus infection [11]. As the febrile period in dengue lasts for three to seven days, ongoing fever after eight days with persistence of cytopenia and multiorgan dysfunction is an alarm for the clinician to revise the diagnosis and also considered HLH [12]. On review of other cases, dengue associated HLH usually presented in the second week of illness [13]. In present patient, the diagnosis was established on day 20 of illness. Criteria for diagnosis of HLH was considered as per previous published guidelines and treatment protocol for HLH in adults according to HLH 94 by American Society of Haematology (ASH) [1,14]. Glucocorticoids are the initial agents in the management of HLH [15]. Dexamethasone ispreferred steroid because of higher penetration through blood brain barrier. Other agents include etoposide, intrathecal methotrexate and cyclosporine as shown in the HLH 94 protocol. In the present case report, patient received corticosteroids (dexamethasone) with intravenous etoposide for the first one month as per HLH 94 regimen and showed complete response by one month.

Incidentally this case presented to us during May 2020 when the first wave of pandemic of coronavirus was at the peak and travelling from interiors of Andhra Pradesh state of India to hospital in Hyderabad was immensely difficult owing to strict nationwide lockdowns and the possibility of offering oral etoposide along with oral dexamethasone was considered. HLH 94 protocol was followed with dexamethasone and oral etoposide after the initial one month of intravenous etoposide considering that bioavailability of oral etoposide is dose-dependent with mean oral absorption is around 50% [15]. Review of literature mentions that daily doses greater than 200 mg need to be divided (BID) as pharmacokinetics are saturable [7,16]. Her dose was 200 mg considering the body surface area of 1.5 m^2 [Table/Fig-7].



[Table/Fig-7]: Treatment protocol for HLH in adults according to HLH 94 [1].

Since, patient did not need Central Nervous System (CNS) directed therapy which mandates hospital visits for intrathecal methotrexate, this plan was deemed appropriate. Considering the poor outcome with macrophage activation syndrome or HLH modification of chemotherapy protocols are rarely practiced unless patient develops complications of chemotherapy or become refractory case of HLH. The regimen proposition is utilising oral etoposide in case of non CNS involved case of HLH.

CONCLUSION(S)

The first learning point in this case are not just high index of suspicion required in case of tropical diseases where symptoms may mask evaluation of HLH. Secondly, this case also gives an opportunity in adversity where in because of coronavirus disease lockdown we could study utilisation of oral etoposide instead of intravenous etoposide. This could be especially applicable to cases where patient is unfit to travel. For example, small cell lung cancer where three days of consecutive intravenous etoposideis administered every 21 days. Lung cancer patient may unfit to travel for three consecutive days to hospital and three days admission adds to total cost. If day second and three etoposide can be administered orally it will save efforts and money. This case also serves as basis of offering oral etoposide instead intravenous etoposide in case travel logistics are limited on case-to-case basis under regular follow-up visits.

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