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Therapeutic challenges in a case of Dengue infection leading to Hemophagocyticlymphohistiocytosis (HLH) syndrome in the background of dialysis dependent Lupus Nephritis and COVID 19 infection- A case report and review of the literature

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Abstract:
Hemophagocyticlymphohistiocytosis(HLH) syndrome is an aggressive and life-threatening syndrome of excessive but ineffective immune activation. It most frequently affects infants from birth to 18months of age, but the disease is also observed in children and adults of all ages. HLH can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupts immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases. Though EBV is the most common viral infection known to cause HLH, dengue-induced HLH is being largely reported. Treatment options are limited for HLH syndrome. HLH is responsible for high risk of morbidity and mortality.We report a case of HLH in a 47 year old female presenting with fever, hepatosplenomegaly and pancytopenia caused after Dengue infection in the background of dialysis dependent lupus nephritis and history of COVID 19 (omicron) infection with fatal outcome.

Keywords: *Hemophagocyticlymphohistiocytosis syndrome, Dengue, Lupus nephritis, COVID 19 infection.*

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I. Introduction

Hemophagocyticlymphohistiocytosis (HLH) syndrome is a potentially life-threatening condition, characterized by hyperinflammation due to the uncontrolled proliferation of activated lymphocytes and histiocytes secreting large amounts of inflammatory cytokines[1]. HLH is classified into primary (genetic) or secondary(acquired). Primary HLH typically occurs during infancy or early childhood and is rapidly fatal if remaining untreated. Few primary HLH may occur during adolescence and in young adults. Secondary HLH is usually caused by viral infection, autoimmune disease, or neoplastic condition[2]. Epstein-Barr virus (EBV) is recognized to be one of the most common causes of infection- associated HLH and is associated with poor outcome[3]. Case reports are there for COVID 19 infections patients developing HLH syndrome and some leading to fatal outcome.[4] On the other hand Lupus or other rheumatologic diseases are risk factors for HLH. Infection with the dengue virus is increasingly recognized as an important cause of secondary HLH. Severe infection is associated with a high mortality and in those who developed secondary HLH may be as high as 43%.[5] Severe dengue infection complicated by HLH may require interventions such as systemic corticosteroids, intravenous immunoglobulin, or chemotherapybut have limited benefits.[6]

We report a case of Dengue infection leading to Hemophagocyticlymphohistiocytosis (HLH) syndrome in the backround of Dialysis dependent Lupus Nephritis and COVID19 infection with a fatal outcome.

II. Case Report

A 47 years old Hindulady with a BMI of 30 hailing from West Bengal was admitted from ER with the history of post hemodialysis hypoglycaemia, severe hypotension and altered sensorium. She had a history of fever 2 days back. She was shifted to ICU after initial resuscitation. Noradrenaline infusion was started. Small fluid bolus was given with USG guided IVC assessment. 25D infusion was started with close CBG monitoring.

High flow oxygen was given through non-rebreathing facemask. Relevant investigations were sent. Arterial line was placed in right radial artery for invasive BP monitoring. Broad spectrum antibiotics were started with Meropenem and Teicoplanin after sending all cultures.

Now in her past history she was a diagnosed case of SLE since 2009 and was on low dose steroids for arthralgia and skin manifestation. Since 2012 she had subnephritic proteinuria with highdsDNA levels. MycofenolateMofetil was added with tapered dose but she never had complete disease remission. Her serum creatinine started rising after COVID 19 infection (omicron variant) in January, 2021 but she never required dialysis.Her proteinuria started rising with rising dsDNAinspite of continuing immunosuppression. In October 2022 she was admitted with hypertensive emergency, volume overload, heart failure and anuric state. After 25days of hospitalisation and 17 session of HD she got discharged inoliguric state with the advice of maintenance HD, triple antihypertensive medicines.

Owing this admission her BP got stabilised, vasopressors were tapered off with stable CBG &normal sensorium but required BiPAP support . Her initial routine investigation showed pancytopenia - Hb-7.2 gm/dl, TLC- 1.3($\times10^9$/L), Platelet counts- 65($\times10^9$/L). CRP was 68.88 mg/L, INR-1.36,Urea -80 mg/dl, Creatinine-4.84 mg/d, eGFR-9.7.(Table 1) Her Dengue NS1 came as strongly positive and IgM for dengue was negative. She was managed conservatively. We kept platelet in reserve. Inj. filgrastim was started. One unit PRBC was transfused. And she was further evaluated for pancytopenia. On Day 2 of admission we got further reports as serum ferritin -11700µg/L, Vitamin B12>1000pg/ml, Triglyceride-485mg/dl,LDH-438mg/dl, Reticulocyte count- 0.5%, LFT showed AST-97U/L, ALT-183U/L, GGT-104U/L, Albumin-2.4g/L. D-Dimer was 4823µg/L;Fibrinogen was-454g/L. She was suspected for Hemophagocyticlymphohistiocytosis syndrome. Bone marrow biopsy was planned. She was started with inj. Dexamethasone 16 mg/day in two divided doses (as 10mg/m^2 /day). In the meanwhile her general condition started worsening again. She developed fever up to 103 degree F. Her FiO2 requirement was increased to 60%. Repeat CRP on day3 was raised to 344. NT-proBNP was>25000pg/ml. Echocardiography showed LVEF-30% with generalised wall motion hypokinesia. She was given SLED. Her antibiotic was escalated further. Atypical coverage along with Antifungal coverage was given. On day 4 her TLC was 0.6($\times10^9$/L), Platelet was 17($\times10^9$/L). She was transfused with 6 units of Platelet. Buffy coat transfusion was planned in view of TLC -0.2($\times10^9$/L) on day 5. Seven unit of buffy coat was transfused. Bone marrow biopsy showed hypocellular marrow with features of hemophagocytosis. (Figure 1& 2)

She responded to Dexamethasone in view of decreased ferritin and decreased triglyceride level but her TLC count remained critical. On Day7 she had gum bleeding and also there was blood in Ryle's tube aspirate. Platelet transfusion was given. She started to become drowsy. She was intubated and put on mechanical ventilation to protect her airway. The situation further worsened when she had blood in ET tube. She developed ARDS. Lung protective ventilation was given. She had very high FiO2 and PEEP requirements. On day 8 she had few episodes of convulsion that was managed with Inj. Midazolam. CT scan brain was planned but couldn't be done due to high transport risk. Further platelet transfusion was given, PRBC transfusion was done. Instead of every effort; on Day 10 her condition deteriorated further and she developed cardiac arrest and expired.

Table 1: Laboratory results

Parameters	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Hemoglobin (g/dl)	7.2		9.5	7.9	8.9	8.0	7.9	7.3	6.5	7.9
Hematocrit	22		29.5	25.6	28.2	25.3	25.3	23.9	20.8	26.2
White cell ($\times10^9$/L)	1.3		1.4	0.6	0.2	0.4	0.3	0.4	0.4	0.1
Platelet ($\times10^9$/L)	33		65	35	60	55	53	55	32	75
INR	1.36							1.07		1.0
APTT				57.6				26.4		40.3
CRP	68		344		266					
ALT (U/L)	61					22				
AST (U/L)	183					189				
LDH (U/L)	438				337					
Ferritin (µg/L)		11700				5290				
Fibrinogen(mg/dl)		454				408				
Trigyceride(mg/dl)		485				185				265
Urea (mg/dl)	80				67					
Creatinine(mg/dl)	4.84				3.57					

Figure 1

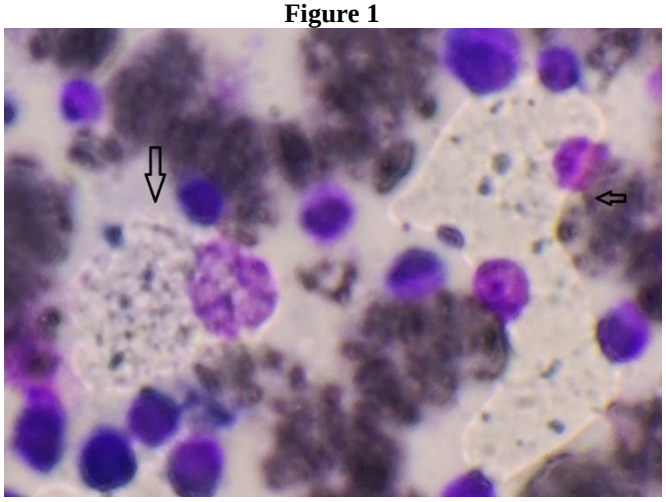
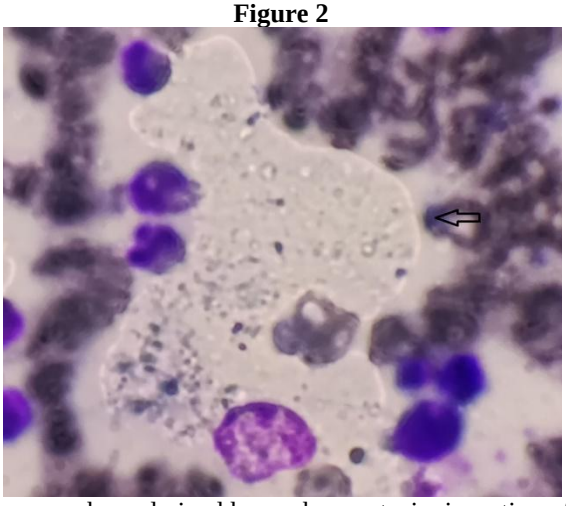


Figure 2



(Figure 1 & Figure 2 showing macrophage derived hemophagocytosis- ingestion of intact cells and cell debris.)

III. Discussion

HLH is a hyperinflammatory condition which is characterized by macrophage activation with phagocytosis of blood cells in the bone marrow and cytokine storm, leading to organ dysfunction and death[2]. Viral infections are a common trigger of HLH but the exact mechanisms by which viruses are implicated in the pathogenesis of HLH remain unproven. It was postulated that viruses, as potent modulators of immune system, may contribute to the development of HLH through evasion of interference with cytokine balance, immune recognition, and inhibition of apoptotic pathways.[7]

Dengue virus belongs to the genus flavivirus within the Flaviviridae family. There are four distinct serotypes. The complications of dengue fever (DF) range from thrombocytopenia, and sepsis, to shock syndrome. Patients with severe dengue are also at risk of developing secondary HLH, which would further contribute to the high mortality.[8]HLH in dengue infection remains a diagnostic challenge and can be misdiagnosed as sepsis because of the nonspecific, overlapping clinical features.

As per HLH-2004 diagnostic criteria, HLH is diagnosed when at least five out of the eight criteria listed are fulfilled. These criteria are fever, splenomegaly, cytopenia affecting at least two of three lineages in peripheral blood, ferritin ≥500 μg/L, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer (NK) cell activity, and high level of soluble interleukin-2 receptor alpha chain (CD25).[9] Our patient fulfilled six criteria out of eight; actually the remaining two criteria i.e. NK cell activity and soluble IL2 receptor(CD25) couldn't be evaluated due to lack of feasibility

Hyperferritinemia is strongly associated with HLH, and a cut-off value of >10,000mcg/L is 90% sensitive and 96% specific for its diagnosis. It also correlates with disease activity. Hyperferritinemia observed in patients with dengue infection is suggestive of highly active disease with increased risk of hyperinflammation and coagulation disturbances[10]. Our patient had a very high ferritin level of 11700μg/L that may correlate with the severity of her illness.

HScore is another criterion used for the diagnosis of HLH. A cut-off of 168 points reveals a sensitivity of 100% and a specificity of 94.1%[11]. Our patient had a very high HScore of 307 that predicts >99% probability of HLH syndrome.

The bone marrow in HLH shows macrophage-derived phagocytosis of blood cells.Hemophagocytosis is neither sensitive nor specific for HLH. Diagnosis should not be delayed looking for this single criteria.But when present give adjunct to the diagnosis.[12] The bone marrow biopsy of our patient showed hypocellular marrow with hemophaocytosis.

We have seen case reports of COVID 19 patients developing HLH syndrome and some leading to a fatal outcome.[4] On the other hand Lupus or other rheumatologic diseases are risk factors for HLH. More precisely the form of HLH that occurs primarily in patients with juvenile idiopathic arthritis or other rheumatologic diseases are called as macrophage activation syndrome(MAS) . Some authors call this "reactive hemophagocytic syndrome.[13] Our patient had advanced lupus nephritis and also had a history of COVID 19 infection with omicron variant in the recent past. So, Dengue along with lupus and recent COVID 19 infection might have provided some complex immunological interplay to further complicate our case.

The treatment approach of HLH is targeted first toward the inciting event, which may be a viral infection, autoimmune disorder, or malignancy. Corticosteroids are often used as an initial agent in the treatment of HLH, whereas other treatment options include etoposide, intravenous immunoglobulin, and intrathecal methotrexate.[14] Treatment of severe EBV-associated HLH with dexamethasone and etoposide had resulted in a reduction of mortality among patients who received treatment.[15] There are numerous published case reports of successful outcome in the use of dexamethasone in patients with severe dengue that developed HLH.[16]Allogenic stem cell transplantation is reserved for refractory cases.[17] In our case we used inj. dexamethasone at a dose of 10mg/m^2/day. Though there was some response in term of lowering ferritin and triglyceride level but other factors may have haltered the recovery. Our patient developed ARDS, ventricular dysfunction, bleeding manifestation, altered sensorium with an existing dialysis dependent malfunctioned kidney. So we failed to prevent multi organ failure and the untimed death of our patient.

IV. Conclusion

HLH is an immunologically mediated inflammatory response to viral infections, immune disorders, and malignancy. HLH induces cytokine storms, and the bone marrow shows lymphohistiocytic reaction and macrophagichemophagocytosis. Though EBV is the most common viral infection known to cause HLH, dengue-indued HLH is being largely reported. Association of HLH with dengue fever is an indicator of severe disease and predicts high mortality. HLH is diagnosed using the HLH-2004 and HScorecriteria. Treatments are available in the form of corticosteroids, intravenous immunoglobulin, and etoposide.

We need further research on pathophysiology of HLH syndrome and also to search for other potential treatment options to treat this deadly disease. Currently researches are going on different aspects of HLH syndrome like whether we can combine ATG and Etoposide for better effects. Can we develop therapies to specially target the dendritic cells and T cells which are driving HLH? -we have to wait for the answer.

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