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CASE REPORT

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Dengue fever complicated by hemophagocytic lymphohistiocytosis: Report of 2 cases and bone marrow findings

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Abstract

Hemophagocytic lymphohistiocytosis is a rare but severe complication of dengue infection which carries a high mortality. This report highlights the importance of early recognition of this condition as prompt appropriate treatment improves outcomes.

KEYWORDS

bone marrow biopsy, dengue fever, hemophagocytic lymphohistiocytosis, severe dengue

1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) 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). The latter 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 cause of infection-associated HLH and is associated with a poor outcome.[3]

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%.[4] Severe dengue infection complicated by HLH may require interventions such as systemic corticosteroids, intravenous immunoglobulin, or chemotherapy.[5] Here, we report 2 cases of dengue-associated HLH with good outcomes following prompt diagnosis and treatment.

2 | CASE 1

A previously well, 33-year-old male presented on day 2 of illness with fever, myalgia, and headache. He had a past history of dengue infection 5 years ago. Clinically, he was hemodynamically stable and well hydrated. Acute dengue infection was confirmed by positive NS-1 antigen assay (SD Bioline Dengue Duo kit).[6] In the ward, he received intravenous fluid and symptomatic treatment. There was no evidence of plasma leakage or hypotensive episode throughout the hospitalization. His blood pressure ranged from 110-130 mm Hg (systolic) and 60-75 mm Hg (diastolic), and the heart rate was ranging between 70 and 85 beats per minute. There was no evidence of organomegaly on physical examination.

His fever recurred on the 4th hospital day (day 5 of illness) with temperature recorded at 39.6°C after an initial defervescence (Figure 1). Further investigations showed platelet count of 60×10^9/L with an increasing triglycerides and decreasing fibrinogen. The serum ferritin was raised at 8364mcg/L (Table 1). Serial blood cultures were negative. A clinical suspicion of HLH was strongly considered as the HScore was 176 with HLH probability of 62%.[7] A bone marrow examination was performed which showed a normocellular marrow with increased number of histiocytes, and evidence of hemophagocytosis (Figure 2).

Intravenous dexamethasone at 10 mg/m^2/d was started on receipt of the results (day 5 of patient's illness). The serum ferritin peaked on day 7 of illness (17492mcg/L) before falling on the following day (9185 mcg/L). He responded well

to dexamethasone as evidenced by resolution of fever and recovery of blood counts with no evidence of organ dysfunction. As a result, dexamethasone was discontinued on day 8 of illness, and he was discharged well.

3 | CASE 2

A 23-year-old lady, with no prior medical illness presented with fever, headache, vomiting, and diarrhea of 4 days duration. Upon arrival to the hospital, she was in hypovolemic shock with a blood pressure of 60/42 mm Hg and heart rate of 122 beats per minute. She was resuscitated with graded crystalloid fluid boluses of 25 mL/kg in total which had resulted in the successful resolution of hypotension. Initial full blood count revealed leukopenia (3.38 × 10^9/L) and thrombocytopenia (109x10^9/L). Clinical suspicion of dengue fever was suspected and a rapid NS-1 antigen (SD Bioline Dengue Duo kit) was requested and shown to be positive.[6]

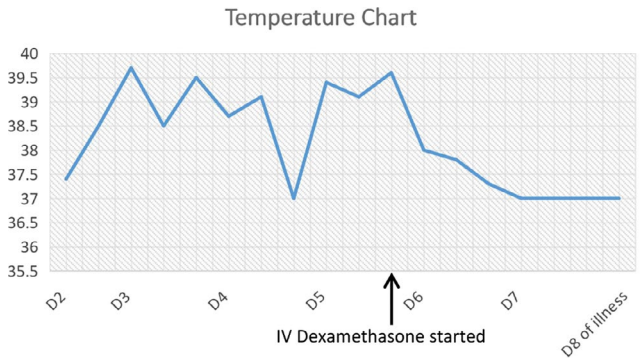

FIGURE 1 Temperature trend of Case 1

She was admitted and noted to have a persistent fever lasting to day 8 of illness (Figure 3). On day 6 of illness, her temperature was maximal at 40°C. Serial blood investigations were undertaken (Table 2) which showed a threefold increase in the liver function tests. The serum ferritin level was also markedly elevated (38 068 mcg/L), whereas triglyceride and fibrinogen levels were within the normal range (Table 2). A clinical suspicion of HLH was suspected as the HScore was 200 with HLH probability of 88%.[7] Hence, she was started on intravenous dexamethasone 10 mg/m^2/d. A bone marrow aspiration and trephine biopsy was performed which revealed a hypocellular marrow with hemophagocytic activity (Figure 4).

Her fever resolved 3 days following administration of dexamethasone (day 9 of her illness), along with improvements in liver enzymes and serum ferritin levels. Dexamethasone was stopped on day 13. Thereafter, she made a full recovery.

4 | DISCUSSION

Dengue virus is the cause of dengue infection which belongs to the genus flavivirus within the *Flaviviridae* family. The dengue virus (DENV) has 4 distinct serotypes, namely DENV-1, DENV-2, DENV-3, and DENV-4. There are nearly

TABLE 1 Laboratory results of Case 1

	Day of illness						
	D2	D3	D4	D5	D6	D7	D8
Hemoglobin (g/L) [12-15]	13.5	12.8	14	13.7	13.8	15	13.9
Hematocrit [36-46]	37	35	38	38	37	40	38
White cell (×10^9/L) [4-10]	9	8.4	6.7	6.7	8.6	16.2	17
Platelet (×10^9/L) [150-410]	36	52	105	60	114	118	190
ALT (U/L) [5-33]	120	115	100	92	73	72	53
AST (U/L) [5-32]	96	93	90	92	110	106	56
LDH (U/L) [135-214]	240	250	368	633	853	1013	531
Ferritin (µg/L) [13-150]		4295		8364	14 985	17 492	9185
Fibrinogen (g/L) [2.2-3.9]		2.6		2.3	2.6	2.5	2.0
Triglyceride (mmol/L) [1.7-2.3]		1.4		2.1	1.7	2.8	2.4
Creatinine (µmol/L) [44-80]	77	78	82	87	75	74	63

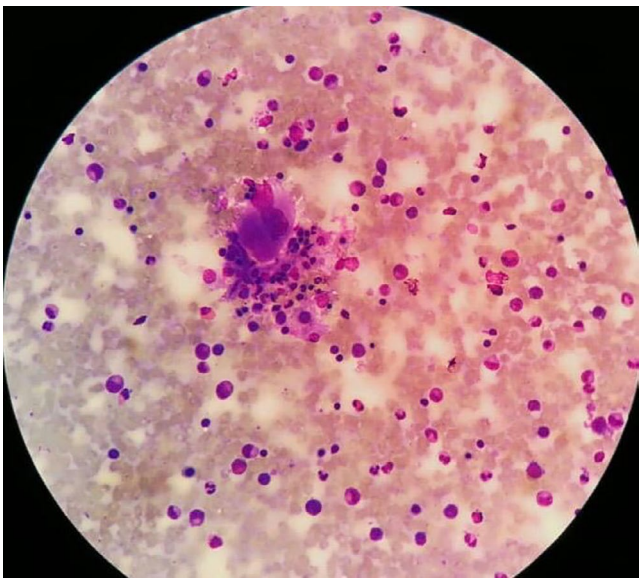

FIGURE 2 Bone marrow aspirates examination showed a normocellular marrow with evidence of hemophagocytosis

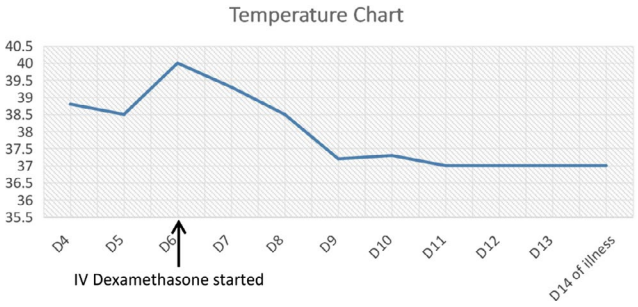

FIGURE 3 Temperature trend of Case 2

50 million cases of dengue infection and 500,000 individuals are hospitalized with dengue hemorrhagic fever each year, mainly in tropical countries.[8] Severe dengue is the leading cause of death related to dengue infection; caused by severe hemorrhage, plasma leakage, fluid accumulation, respiratory distress, or organ impairment.[9] A local study showed a significant number of DENV-2 infected patients developed severe dengue more frequently as compared to other serotypes.[10] Patients with severe dengue are also at risk of developing secondary HLH which would further contribute to the high mortality.[4]

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.[2,11,12] 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.[11]

HLH in dengue infection remains a diagnostic challenge and can be misdiagnosed as sepsis because of the nonspecific, overlapping clinical features. The diagnosis of HLH requires fulfillment of at least 5 of the 8 criteria as listed: fever, splenomegaly, cytopenia affecting at least 2 of 3 lineages in peripheral blood, ferritin $\geq$ 500 μg/L, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent NK-cell activity, and high level of soluble CD25.[12] Markedly raised serum ferritin level is strongly associated with HLH, and a cutoff value of $>$ 10,000mcg/L was 90% sensitive and 96% specific for HLH.[13] Hyperferritinemia observed in patients with dengue infection is suggestive of highly active disease with increased risk of hyperinflammation and coagulation disturbances.[14] This emphasizes the need for closer monitoring in dengue virus-infected patients with hyperferritinemia.

In case 1, HLH was suspected due to resurgence of high-grade fever after an initial defervescence, along with the raised serum ferritin level and abrupt thrombocytopenia. Persistence of fever beyond 7 days and worsening liver functions also suggested the possibility of HLH, as seen in case 2. Both patients were started on intravenous dexamethasone in view of high clinical suspicion of HLH and responded well with resolution of fever and improving blood parameters. Therefore, early recognition and diagnosis of dengue-associated HLH and prompt intervention could have contributed to the favorable outcome in these patients.

Both patients described in this case report underwent bone marrow biopsy which showed presence of hemophagocytic activity. These findings were supportive of our diagnosis of hemophagocytic lymphohistiocytosis due to dengue infection. The typical histopathological findings of HLH include diffuse accumulation of lymphocytes and mature macrophages, which occasionally exhibit hemophagocytosis.[15] Of note, the sensitivity and specificity of hemophagocytosis for HLH were 83% and 60% respectively.[16] Therefore, a negative initial bone marrow specimen should not delay diagnosis and initiation of HLH treatment.

Corticosteroids are often used as an initial agent in the treatment of HLH, whereas other treatment options include etoposide, intravenous immunoglobulin, and intrathecal methotrexate.[17] Treatment of severe EBV-associated HLH with dexamethasone and etoposide had resulted in a reduction of mortality among patients who received treatment.[18,19] There are numerous published case reports of successful outcome in the use of dexamethasone in patients with severe dengue that developed HLH.[20,21] Randomized control trials on the use of such agents in the treatment of dengue fever complicated by HLH are urgently needed in evaluating its role in management.

TABLE 2 Laboratory results of Case 2

	Day of illness										
	D4	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**
Hemoglobin (g/L) [12-15]	11.3	12.9	12.2	12.9	12.0	10.8	10.3	10	9.7	9.8	9.9
Hematocrit [36-46]	33.4	37	34	35	33	29	29	28	28	28	29
White cell ($\times 10^9$/L) [4-10]	3.38	3.6	2.3	5.5	10.6	11.2	13.2	11.9	12.3	13.0	12.0
Platelet ($\times 10^9$/L) [150-410]	109	90	66	59	96	121	187	252	304	378	450
ALT (U/L) [5-33]	21	27	67	175	344	281	248	271	243	234	176
AST (U/L) [5-32]	43	67	219	527	919	398	187	162	125	96	57
LDH (U/L) [135-214]	296	338	822	1808	1964	1681	1396	1148	961	687	575
Ferritin (μg/L) [13-150]			38 068	58 855	60 348	41 843				6775	
Fibrinogen (g/L) [2.2-3.9]			1.8	2.1	1.7	1.4					
Triglyceride (mmol/L) [1.7-2.3]			1.5	1.1	1.4	2.2					
Creatinine (μmol/L) [44-80]	67	57	57	51	50	42			39	45	

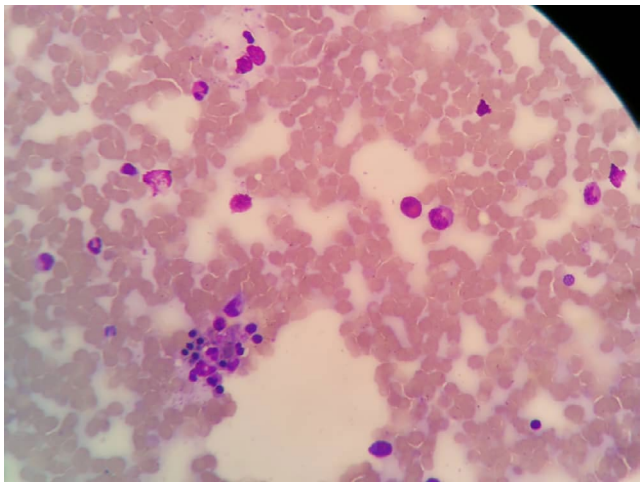

FIGURE 4 Bone marrow aspirates examination showed a hypocellular marrow with hemophagocytic activity

5 | CONCLUSION

HLH is an uncommon but severe complication of dengue infection. Clinicians should have a high index of suspicion of HLH in patients with dengue infection especially if there is a recurrent fever after defervescence or persistent fever >7 days, any cytopenias, or extremely high serum ferritin. Early recognition of this condition and use of corticosteroids is a major contributing factor in improving clinical outcome.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

CYC: preparation of the manuscript and involved in management of the patient. MR, MZ: data curation, assisted in writing manuscript, and involved in patient care. ELCO: proofread and correction of the final manuscript.

ETHICAL APPROVAL

Written informed consent was obtained from the patients for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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REFERENCES

1. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *Eur J Pediatr*. 2007;166(2):95-109.
2. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516.

3. Goudarzipour K, Kajiyazdi M, Mahdaviyani A. Epstein-barr virus-induced hemophagocytic lymphohistiocytosis. *Int J Hematol Stem Cell Res*. 2013;7(1):39-42.
4. Kan FK, Tan CC, von Bahr GT, et al. Dengue Infection Complicated by Hemophagocytic Lymphohistiocytosis: Experiences From 180 Patients With Severe Dengue. *Clin Infect Dis*. 2020;70(11):2247-2255.
5. Wan Jamaludin WF, Periyasamy P, Wan Mat WR, Abdul Wahid SF. Dengue infection associated hemophagocytic syndrome: Therapeutic interventions and outcome. *J Clin Virol*. 2015;69:91-95.
6. Wang SM, Sekaran SD. Early diagnosis of Dengue infection using a commercial Dengue Duo rapid test kit for the detection of NS1, IGM, and IGG. *Am J Trop Med Hyg*. 2010;83(3):690-695.
7. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9):2613-2620.
8. Guzman MG, Halstead SB, Artsob H, et al. Dengue: A continuing global threat. *Nat Rev Microbiol*. 2010;8(12):S7-S16.
9. World Health Organization, Regional Office for the Eastern Mediterranean. Dengue and severe dengue. World Health Organization. Regional Office for the Eastern Mediterranean; 2014.
10. Suppiah J, Ching SM, Amin-Nordin S, et al. Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: A retrospective observational study. *PLoS Negl Trop Dis*. 2018;12(9):e0006817.
11. Brisse E, Wouters CH, Andrei G, Matthys P. How Viruses Contribute to the Pathogenesis of Hemophagocytic Lymphohistiocytosis. *Front Immunol*. 2017;8:1102.
12. Henter JI, Horne AC, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131.
13. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2008;50(6):1227-1235.
14. van de Weg CA, Huits RM, Pannuti CS, et al. Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. *PLoS Negl Trop Dis*. 2014;8(10):e3214.
15. Rosado FGN, Kim AS. Hemophagocytic lymphohistiocytosis. *Am J Clin Pathol*. 2013;139(6):713-727.
16. Goel S, Polski JM, Imran H. Sensitivity and specificity of bone marrow hemophagocytosis in hemophagocytic lymphohistiocytosis. *Ann Clin Lab Sci*. 2012;42(1):21-25.
17. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052.
18. Imashuku S, Kuriyama K, Sakai R, et al. Treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in young adults: a report from the HLH study center. *Med Pediatr Oncol*. 2003;41(2):103-109.
19. Kogawa K, Sato H, Asano T, et al. Prognostic factors of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children: report of the Japan Histiocytosis Study Group. *Pediatr Blood Cancer*. 2014;61(7):1257-1262.
20. Chung SM, Song JY, Kim W, et al. Dengue-associated hemophagocyticlymphohistiocytosis in an adult. *Medicine (Baltimore)*. 2017;96(8):e6159.
21. Ray S, Kundu S, Saha M, Chakrabarti P. Hemophagocytic syndrome in classic dengue fever. *J Glob Infect Dis*. 2011;3(4):399-401.

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