Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatrics

Dengue Fever Complicated by Hemophagocytic Lymphohistiocytosis (HLH) in Children: Case Reports

Lubna Ahmed[1*], Fatema-Tuz-Jahura[2], Afsana Tasnim Tisha[3], Kaniz Fathema[4], Yesmin Tanjin Jahan[5], Shabnam Shahidullah[6], Md. Zakirul Islam[7], Md. Abdul Mannan[8]

[1]Junior Consultant, Department of Pediatrics, Sarkari Karmachari Hospital, Dhaka, Bangladesh
[2]MD-Resident, Department of Pediatrics, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[3]Assistant Registrar, Department of Pediatrics, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[4]Junior Consultant, Department of Pediatrics Gastroenterology & Nutrition, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[5]Assistent Professors, Department of Pediatrics Hemato-Oncology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[6]Assistant Professor (Pediatrics Nephrology), Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[7]Professor & Former Head, Department of Pediatrics, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[8]Professor & Former Head, Pediatrics Intensive Care Unit (PICU), Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh

DOI: https://doi.org/10.36347/sjmcr.2025.v13i01.018 | **Received:** 22.11.2024 | **Accepted:** 27.12.2024 | **Published:** 13.01.2025

***Corresponding author:** Lubna Ahmed
Junior Consultant, Department of Pediatrics, Sarkari Karmachari Hospital, Dhaka, Bangladesh

Abstract **Case Report**

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon systemic inflammatory syndrome that can happen secondary to numerous conditions. It rarely occurs due to dengue infection causing significant mortality and morbidity even with appropriate treatment. In both case- 1 & 2, HLH was suspected due to high grade fever, bicytopenia and worsening of liver function along with raised serum ferritin level. Both patients described in this case report underwent bonemarrow biopsy which showed presence of hemophagocytic activity. Both patients were started on intravenous methylprednisolone and responded well withresolution of clinical symptoms and blood parameter. Therefore, early recognition and diagnosis of dengue associated with HLH and prompt treatment have favourable outcome in these patients. After diagnosing HLH, our patient were started with intravenous methylprednisolone for 3 days and followed by oral prednisolone with gradually tapered over 6 weeks. Both patients had an excellent response to treatment solely with intravenous methylprednisolone. The outcome is further poor if the diagnosis of HLH is delayed or left untreated. These report highlights the importance of early recognition of this condition as prompt appropriate treatment improves outcomes.

Keywords: Hemophagocytic Lymphohistiocytosis, Dengue Fever, Cytopenia, Bone Marrow Biopsy.

INTRODUCTION

Dengue fever (DF) may be complicated by hemophagocytic lymphohistiocytosis (HLH). Steroid administration is highly effective against this hematologic complication and other viral infections. We present a rare case of DF-associated HLH that improved with steroid-sparing supportive care. Initial symptoms include fever, headache, myalgia, and arthralgia, and a rash begins on the trunk 3–4 days after onset. Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening condition, characterized by hyperinflammation due to the uncontrolled proliferation of activated lymphocytes and histiocytes secreting large amount ofinflammatory cytokines [1]. HLH may be inherited (primary) or secondary (acquired)to severe infections, malignancies, or rheumatologic conditions [2]. HLH issporadically seen in clinical practice and is a rare complication of dengue characterized by persistent fever, pancytopenia, hepatosplenomegaly, and increased serum ferritin level. The overlap in clinical features makes diagnosing HLH in a dengue patient difficult, necessitating a bone marrow examination [3]. Most cases resolve spontaneously within about a week without complications. However, infants, the elderly, pregnant women, and people with diabetes and renal failure are at higher risk of developing severe illness that may lead to death. In DF, the presence of warning signs such as persistent vomiting, abdominal pain, hepatomegaly, elevated hematocrit, ascites/pleural effusion, mucosal bleeding, thrombocytopenia, and fatigue increases the

risk of severe disease, which may lead to dengue hemorrhagic fever or dengue shock syndrome [3]. 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]. We report 2 pediatric cases of dengue associated HLH with good outcomes following prompt diagnosis and treatment.

CASE 1

A 9-month-old girl was admitted to a tertiary care hospital, Dhaka, Bangladesh with high grade continued fever for 4 days and persistent vomiting for 3 days. There was no history of cough, breathing difficulty, abdominal pain, crying duringmicturition, loose motion, skin or mucosal bleeding, convulsion or loss of consciousness. On admission she was febrile, mildly pale, hemodynamically stable and had hepatomegaly. Initial blood investigation revealed a positive dengue non-structural protein 1 (NS1) antigen andin complete blood count (CBC), white blood cell count (WBC) 6900/cumm, neutrophils 55%, lymphocytes 39%, hemoglobin level was 11.9 gm/dl with a hematocrit of 31.7% and the platelet count was 58000/cumm. Her CRP was 6 mg/dl, aspartate aminotransferase (AST) level was 1155 U/L, and the alanine aminotransferase (ALT) level was 477 U/L. After the initial workup, she was diagnosed with expanded dengue syndrome. She was treated with oral acetaamiophen on an as needed basis to control fever and fluid management according to dengue national guideline of Bangladesh. 2 days after admission, she had continuous fever, distended abdomen, persistent thrombocytopenia, AST was 1739 U/L, ALT was 842 U/L, serum ferritin was 11720 ng/ml (normal 7-142 ng/ml), fibrinogen was 96 mg/dl (normal 200 -400 mg/dl), triglyceride was 285 mg/dl and blood culture and sensitivity report was no growth.A clinical suspicion of HLH was suspected and bone marrow examination was performed which showed activated macrophage containing erythrocytes, leucocytes, platelet and their precursor resembling hemophagocyte. Based on these investigation findings, she was diagnosed as HLH. Then she was started with intravenous methylprednisolone over 3 days followed by oral prednisolone with gradual tapered over 6week. The fever settled within 24hour after starting methylprednisolone, along with clinical and hematological improvement in CBC, liver enzymes and serum ferritin level. She was discharged after 2 weeks hospital stay and completely recovered while reviewed in this hospital after 6 weeks.

CASE 2

A 19- months-old girl was admitted in same tertiary hospital with high grade fever for 6 days and persistent vomiting for 4 days. On admission she was febrile, edematous, capillary refilling time was 2 second, blood pressure was90/60 (within normal limit), abdomen distended, hepatomegaly and ascites present. Initial blood investigation revealed dengue IgM And IgG was positive. In complete blood count she had a white cell count 16000/cumm, neutrophil 18%, lymphocyte 70%, hemoglobin level was 9.6 gm/dl, hematocrit was 28.3% and platelet was 30,000/cumm. Her alaninine aminotransferase (ALT) was 1012 U/L, aspartate aminotransferase (AST) was 3748 U/L. After initial workup she was diagnosed with expanded dengue syndrome. She was managed with oralacetaminophen and routine fluid management. The following day an ultrasonogram revealed thickened gallbladder, pleural effusion and moderate ascites, fever persist. On blood parameter, there was thrombocytopenia, gradual drop in hemoglobin level, serum ferritin level was 41,500 ng/ml (7-142ng/ml), fibrinogen was 186 mg/dl (200-400 mg/dl), blood CS no growth and bone marrow biopsy revealed features of significant hemophagocytic activity. Based on these investigation findings, she was diagnosed to have HLH. Then she was started with intravenous methylprednisolone 30 mg/kg for 3 days and then oral prednisolone with gradual tapered over 6 weeks. Her fever resolved within 48 hours following administration of methylprednisolone (on day 9 of her illness) along with improvement of liver enzyme and serum ferritin. She was discharged after 7 days hospital stay and completely recovered while follow-up after 6 weeks.

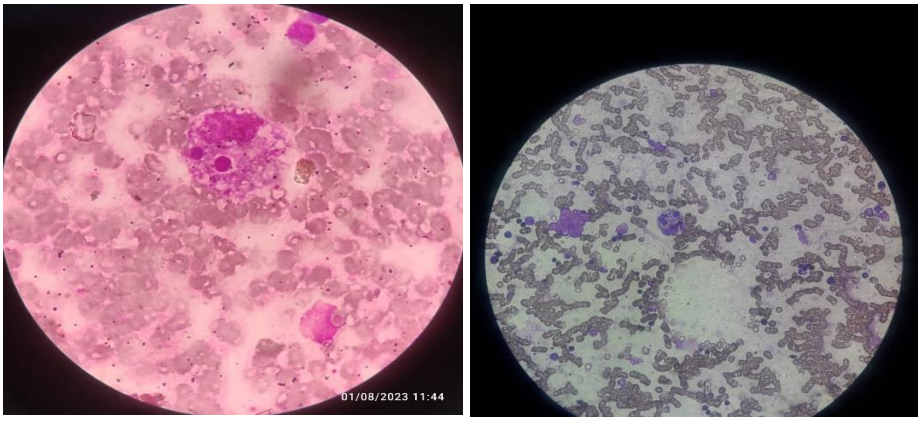

Figure 1 & 2: Bone marrow contains some activated macrophage containing erythrocytes, leucocytes, platelet and their precursor resembling hemophagocyte

DISCUSSION

Dengue fever is caused by the dengue virus, which belongs to the family Flavi-viridae genus Flavi virus andis transmitted to human by Aedes mosquitoes, mainly Aedesaegypti [6]. The clinical spectrum of dengue viral infection includesundifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF) and expanded dengue syndrome or isolated organopathy [7]. Severe dengue is the leading cause of death leading to dengue infection; caused by severe hemorrhage plasma leakage, fluid accumulation, respiratory distress, or organ impairment [8]. A study showed a significant number of DENV-2 infected patients developed severe dengue more frequently as compared to other serotypes [9]. Patient with severe dengue are also at high risk of developing secondary HLH which wouldfurther contribute to the high mortality [4]. HLH is a rare, potentially fatal hyperinflammatory and hemophagocytic syndrome causing severe hypercytokinemia with excessive activation of lymphocytes and macrophages associated with numerous conditions [10]. The disease is seen in all ages and has no predilection for age and sex [11]. There are two main types of HLH; primary or familial HLH associated with genetic predisposition and secondary or reactive HLH associated with other medical conditions, including infective, autoimmune, and malignant conditions [12]. HLH is uncommon manifestation in dengue and the diagnosis of HLH is difficult in dengue due to the overlap of the clinical features [13]. The pathogenesis of HLH was first thought to result from the inability to clear infections in immunodeficient patients [14]. However, HLH in immunocompetent patients disproved that theory later, and the identification of cytotoxic pathway mutations as the primary cause of genetic HLH has elucidated the mechanism of this disease. All forms of HLH are thought to be due to impairment in the function of cytotoxic T lymphocytes and natural killer (NK) cells, associated with a potentially fatal cytokine storm and hyperferritinemia [15]. HLH in dengue infection remains a diagnostic challenge and can be misdiagnosed as sepsis because of the nonspecific, overlapping clinical features [16]. The diagnosis of HLH is based on thediagnostic criteria as revised for HLH-2004 [17].

The diagnosis of HLH can be established if either (1) or (2) is fulfilled:

1. A molecular diagnosis consistent with HLH (i.e reported mutation found in either PRF1 or MUNC13-4)

2. Diagnostic criteria for HLH fulfilled (i.e at 5 of the 8 criteria listed below):

I. Persistent fever
II. Splenomegaly
III. Cytopenias (affecting at least 2 lineages in the peripheral blood)

Hemoglobin <90g/L (in infants <4 weeks: < 100g/L)
Platelet <100X 10⁹/L
Neutrophils< 1.0X10⁹/Liv. Hypertriglyceridemia and/or hypofibrinogenemia

- ✓ Fasting TG ≥3.0mmol/L(i.e ≥265mg/dl)
- ✓ Fibrinogen≤1.5g/L

IV. Hemophagocytosis in bonemarrow, spleen or lymphnode; no evidence of malignancy
V. S. Ferritin ≥500mcg/L (i.e 500ng/ml)
VI. Low or absent natural killer cell activity (acc. to local lab. Ref.)
VII. Increased serum sIL2Rα (acc. to local lab ref.)

Markedly raised serum ferritin level is strongly associated with HLH and a cut off value>10,000 mcg/L was 90% sensitive and 96% specific for HLH [18]. Hyperferritinemia observed in patients with dengue infection is suggestive of highly active disease with increased risk of hyper inflammation and coagulation disturbances [19]. This emphasizes the need for closer monitoring in dengue virus infected patients with hyperferritinemia [20]. In both case- 1 & 2, HLH was suspected due to high grade fever, bicytopenia and worsening of liver function along with raised serum ferritin level. Both patients described in this case report underwent bone marrow biopsy which showed presence of hemophagocytic activity. Both patients were started on intravenous methylprednisolone and responded well with resolution of clinical symptoms and blood parameter. Therefore, early recognition and diagnosis of dengue associated with HLH and prompt treatment have favourable outcome in these patients. The typical histopathological findings of HLH include diffuse accumulation of lymphocytes and mature macrophages, which occasionally exhibit hemophagocytosis [21]. Therefore, negative initial bone marrow specimen should not delay diagnosis and initiation of HLH treatment. The management principles of HLH includes suppression of hyper inflammation, elimination of activated immune cells, elimination of triggers, supportive therapy (neutropenia, coagulopathy), and replacement of defective immune system [15]. Suppression of hyper inflammation and the elimination of activated immune cells can be achieved with corticosteroids, intravenous immunoglobulins, cyclosporine A, and monoclonal antibodies such as alemtuzumab and rituximab [22]. Corticosteroids are the first choice to suppress hypercytokinemia. The first line option is dexamethasone, since dexamethasone crosses the blood brain barrier better than prednisolone, suppress the central nervous system inflammation more effectively [23]. Subsequent hematopoietic stem cell transplantation is recommended for patient with familial disease, with a proven molecular diagnosis, or with severe persistent, or reactivated disease [12]. Regarding disease associated HLH, some have recovered spontaneously with supportive treatment only. However, in most cases, pulse doses of methylprednisolone or dexamethasone have been used to suppress the hyper inflammation state [24]. HLH directed treatment with dexamethasone and etoposide showed substantially reduced mortality in potentially fatal viral infections associated with HLH

[25]. Primary HLH has a near 100% fatality without adequate treatment [26]. Secondary HLH is a rapidly fatal disease. Most patient die of bacterial or fungal infections due to prolonged neutropenia, multi organ failure or cerebral dysfuntion [11]. Therefore, prompt treatment initiation is essential for patient´s survival. Sometimes initial treatment may be necessary to prevent early fatalities, even though the diagnostic workup has not been completed. After diagnosing HLH, our patient were started with intravenous methylprednisolone for 3 days and followed by oral prednisolone with gradually tapered over 6 weeks. Both patients had an excellent response to treatment solely with intravenous methylprednisolone.

CONCLUSION

These two cases highlight the importance of suspecting HLH as a potential complication when persistent fever, cytopenias and abnormal liver enzymes present. In dengue infection associated with HLH, early diagnosis and prompt initiation of appropriate immunosuppressive therapy such as methylprednisolone is a major contributing factor in improving clinical outcome and good prognosis. Although different immunosuppressive agents have been used, our cases suggest that methylprednisolone can be an effective treatment option for HLH associated with dengue infection.

Abbreviations

HLH: Haemophagocytic lymphohistiocytosis
HSCT: Haemopoietic stem cell transplantation
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
DF: Dengue fever
DHF: Dengue haemorrhagic fever

Acknowledgements

We would like to thank Prof. Dr. Sirajul Islam, hematologist for the images of the bone-marrow specimens. Published with written consent of the patient.

Author Contributions

All authors were involved in managing the patient and generating the concept. All authors made an intellectual contribution and wrote the paper. All the authors have read and approved the final manuscript.

Conflict of interest: The authors have no conflicts of interest

Ethical Approval

Written informed consent was obtained from the patient's legal guardian for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

REFERENCES

1. Janka, G. E. (2007). Familial and acquired hemophagocytic lymphohistiocytosis. European journal of pediatrics, 166, 95-109.
2. Gupta, S., & Weitzman, S. (2010). Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. Expert review of clinical immunology, 6(1), 137-154.
3. Wiwanitkit, V. (2015). Haemophagocytic lymphohistiocytosis and dengue. Acta Clinica Belgica, 70(1), 72-72.
4. Kan, F. K., Tan, C. C., von Bahr Greenwood, T., Khalid, K. E., Supramaniam, P., Hed Myrberg, I., ... & Henter, J. I. (2020). Dengue infection complicated by hemophagocytic lymphohistiocytosis: experiences from 180 patients with severe dengue. Clinical Infectious Diseases, 70(11), 2247-2255.
5. Jamaludin, W. F. W., Periyasamy, P., Mat, W. R. W., & Wahid, S. F. A. (2015). Dengue infection associated hemophagocytic syndrome: Therapeutic interventions and outcome. Journal of Clinical Virology, 69, 91-95.
6. Martina, B. E., Koraka, P., & Osterhaus, A. D. (2009). Dengue virus pathogenesis: an integrated view. Clinical microbiology reviews, 22(4), 564-581.
7. Ministry of Health Sri Lanka. Guidelines on Management of Dengue Fever & Dengue Haemorrhagic Fever in Adults. 2010. p.1–39.
8. World Health Organization, Regional Office for the Eastern Mediterranean. Dengue and severe dengue. World Health Organization. Regional Office for the Eastern Mediterranean; 2014.
9. Suppiah, J., Ching, S. M., Amin-Nordin, S., Mat-Nor, L. A., Ahmad-Najimudin, N. A., Low, G. K. K., ... & Chee, H. Y. (2018). Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: A retrospective observational study. PLoS neglected tropical diseases, 12(9), e0006817.
10. Gupta, S., & Weitzman, S. (2010). Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. Expert review of clinical immunology, 6(1), 137-154.
11. Janka, G. E. (2012). Familial and acquired hemophagocytic lymphohistiocytosis. Annual review of medicine, 63(1), 233-246.
12. Henter, J. I., Horne, A., Aricó, M., Egeler, R. M., Filipovich, A. H., Imashuku, S., ... & Janka, G. (2007). HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatric blood & cancer, 48(2), 124-131.
13. Wiwanitkit, V. (2015). Haemophagocytic lymphohistiocytosis and dengue. Acta Clinica Belgica, 70(1), 72-72.
14. Deane, S., Selmi, C., Teuber, S. S., & Gershwin, M. E. (2010). Macrophage activation syndrome in

autoimmune disease. International archives of allergy and immunology, 153(2), 109-120.
15. La Rosée, P., Horne, A., Hines, M., von Bahr Greenwood, T., Machowicz, R., Berliner, N., ... & Henter, J. I. (2019). Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood, The Journal of the American Society of Hematology, 133(23), 2465-2477.
16. Henter, J. I., Horne, A., Aricó, M., Egeler, R. M., Filipovich, A. H., Imashuku, S., ... & Janka, G. (2007). HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatric blood & cancer, 48(2), 124-131.
17. Petty, R. E., Laxer, R. M., Lindsley, C. B., Wedderburn, L. R., Mellins, E. D., & Fuhlbrigge, R. C. (2021). Macrophage activation syndrome. In: Grom, A. A., Schulert, G, editors. Text book of pediatric rheumatology. 8th edition. Philadelphia: Elsevier; p.567-574.
18. Allen, C. E., Yu, X., Kozinetz, C. A., & McClain, K. L. (2008). Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatric blood & cancer, 50(6), 1227-1235.
19. van de Weg, C. A., Huits, R. M., Pannuti, C. S., Brouns, R. M., van den Berg, R. W., van den Ham, H. J., ... & Kallas, E. G. (2014). Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. PLoS Neglected Tropical Diseases, 8(10), e3214.
20. Fardet, L., Galicier, L., Lambotte, O., Marzac, C., Aumont, C., Chahwan, D., ... & Hejblum, G. (2014). Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis & rheumatology, 66(9), 2613-2620.
21. Goel, S., Polski, J. M., & Imran, H. (2012). Sensitivity and specificity of bone marrow hemophagocytosis in hemophagocytic lymphohistiocytosis. Annals of Clinical & Laboratory Science, 42(1), 21-25.
22. Janka, G. E., & Lehmberg, K. (2013). Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology 2013, the American Society of Hematology Education Program Book, 2013(1), 605-611.
23. Janka, G. (2009). Hemophagocytic lymphohistiocytosis: when the immune system runs amok. Klinische Pädiatrie, 221(05), 278-285.
24. Ray, U., Dutta, S., Mondal, S., & Bandyopadhyay, S. (2017). Severe dengue due to secondary hemophagocytic lymphohistiocytosis: a case study. IDCases, 8, 50-53.
25. Gao, C., Cai, Y., Zhang, K., Zhou, L., Zhang, Y., Zhang, X., ... & Li, F. (2020). Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. European heart journal, 41(22), 2058-2066.
26. Kan, F. K., Tan, C. C., von Bahr Greenwood, T., Khalid, K. E., Supramaniam, P., Hed Myrberg, I., ... & Henter, J. I. (2020). Dengue infection complicated by hemophagocytic lymphohistiocytosis: experiences from 180 patients with severe dengue. Clinical Infectious Diseases, 70(11), 2247-2255.