Haemophagocytic lympohistiocytosis: a rare manifestation of dengue fever

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) or haemophagocytic syndrome is a rare disorder that is associated with high mortality. Manifestations are often non-specific, mimicking many common conditions that include infections, autoimmune disease and even neoplasms. It is characterised by cytopenia, hepato-splenomegaly, hyperferritinemia, hypertriglyceridemia, and haemophagocytosis. The underlying pathogenesis is not completely known but is believed to be due to activated but ineffective host immune responses in susceptible patients after external trigger such as virus infections. Associations with other micro-organisms have also been reported. We report a case of HLH that was associated with dengue fever, an infection that is still endemic in many parts of the world.

Keywords: Haemophagocytosis, dengue infection, leucopaenia, anaemia

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening condition that is still not well understood. HLH has been categorised as primary to denote the presence of an underlying genetic disorder or secondary in the presence of underlying disorders. [1] It has also been referred as autosomal recessive familial haemophagocytic lymphohistiocytosis, familial erythrophagocytic lymphohistiocytosis and viral-associated haemophagocytic syndrome. [1] It is more common in the paediatric population and has been strongly linked to genetic abnormalities. In adult, HLH is often associated with infections or other underlying disorders. The most commonly reported virus to be associated with HLH is *Epstein Barr virus* (EBV*)*. However, other infections have also been associated with HLH. HLH often presents with clinical features similar to many conditions that include infections. Unless suspected, the diagnosis is often missed or delayed resulting in undesirable outcomes. [1, 2] We report the rare case of HLH triggered by a dengue infection in a 28-year-old previously well lady.

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CASE REPORT

A 28-year-old previously well lady was admitted with six days of abdominal discomfort,

fever, sore throat, vomiting and diarrhea. Examination was unremarkable except for fever and bilateral enlarged congested tonsils. Laboratory investigations revealed leucopenia (1.7 x 10^9/L), thrombocytopaenia (86 x 10^9/L), hypokalaemia (3.3 mmol/L) and deranged cholestatic liver profiles (ALT: 67 U/L, ALP: 239 U/L, GGT: 414 U/L) with normal serum bilirubin. She later developed blanching macular rashes on both arms. Dengue serology was negative (IgG, IgM and NS antigen). As her condition improved, she was discharged for outpatient review the following week.

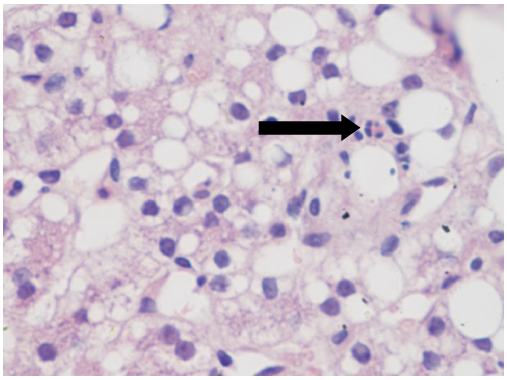

Fig. 1: Liver biopsy showing haemophagotcytosis (arrow) (H&E stain, 40x).

She represented the following day with abdominal discomfort, jaundice, myalgia and worsening of the rash. Repeat investigations showed persistent leucopaenia and improving thrombocytopaenia (104 x 10^9/L). Her liver profiles was worsening (Bilirubin: 94 umol/L, ALT: 309 U/L, ALP: 271 U/L, GGT: 745 U/L, Albumin: 31 gm/L, Protein 62 gm/L) and elevated high CRP (2.85 mg/dL). Hepatitis A, B and C serology, Widal-Weil Felix, CMV and EBV IgM and autoantibodies were all negative. Blood and urine cultures were negatives. A repeat dengue serology this time was positive. An abdominal ultrasound scan showed thickened gallbladder (~8mm) with pericholecystic fluid, multiple small calculi and sludge without ductal dilatation and splenomegaly (14.3cm).

Despite treatment for acute cholecystitis, she continued to have swinging fever, persistent leucopenia with lymphocytosis and deranged liver profiles. Haemophagocytic syndrome was suspected based on the presence of five criteria (HLH 2004) before histological proofs. Serum ferritin (8,125.7 ug/L), LDH (1,095 U/L) and triglyceride (4.76 mmol/L) were all elevated. She was immediately started on treatment for HLH to avoid further deterioration. She was given two doses of intravenous immunoglobulin and three days of intravenous methylprednisolone, after which she became afebrile. Her cytopaenias and ferritin (7,758 ug/L) improved. A liver biopsy after commencing therapy showed haemaphagocytosis, confirming the diagnosis of HLH triggered (Figure 1). She was discharged on 60mg prednisolone and her serum ferritin, pancytopenia and liver profiles had all normalized by two weeks after discharge. She remained well on follow-up with prednisolone tailed off.

DISCUSSION

HLH first described in 1939 is a rare life-threatening hyper-inflammatory syndrome caused by severe hypercytokinemia due to highly stimulated but ineffective immune process. [1-3] Since the introduction of the HLH diagnostic criteria, the number of cases reported in the literature has been increasing.

The underlying pathogenesis is due to the triggering of the cellular immune system

with resultant activation of macrophages and stimulation of the benign histiocytes. [1-3] This leads to dysregulated hyperstimulated immune processes with resultant cytokine storms and histiocytes proliferations. Natural Killer cell activities are also reduced or absent. The exact aetiology is not known but involvements of genetic defects and external agents have been proven. Infections, autoimmune disorders, immune deficiencies disorders, malignancies and post-renal or liver transplantations are more commonly associated with HLH in adult patients. [1-3]

Many organisms have been reported to trigger HLH with EBV being the most implicated infective trigger. [1, 3] Other organisms reported to be involved include the herpes virus (CMV, HSV, Varicella Zoster virus), measles virus, human herpes-8 virus, HIV, brucella species, mycobacterium tuberculosis, gram-negative bacteria, parasites such as leishmaniasis and fungus. [1] Interestingly, despite the high incidence of dengue infection, in some regions with an estimated 50 to 100 million cases of dengue reported by the World Health Organisation each year, the overall number of cases of dengue-associated haemaphagocytosis or HLH reported is still limited. [7-16] However, it is possible that the association is under-recognised. The associations with dengue virus range from mild dengue fever to severe dengue haemorrhagic fever. Even association with dengue fever in the convalescent phase has been reported. [13] However, in this case, it is possible that haemaphocytosis had been there in the acute phase of infection except it was only diagnosed later. In our setting with a small population, this was the only case of dengue infection that was complicated by HLH out of 405 cases reported over a four-year period (2008 to 2011) period, giving an overall incidence of 0.25%.

Diagnosis of HLH is based on the updated "HLH-2004": fever, splenomegaly, bicytopaenia, hypertriglyceridemia and/or hypofibrinogenemia, haemophagocytosis, low/absent NK-cell-activity, hyperferritinemia (>500 mcg/L), and high-soluble interleukin-2 -receptor levels (CD25, the alpha chain of sIL -2 receptor). Presence of at least five criteria is diagnostic for HLH. [1, 2] Positive for molecular markers of HLH is also diagnostic. Ferritin level of 3,000 mcg/L or more has been suggested to be very specific. [1] Like most centres, we do not have the more sophisticated tests and we did not perform any of the latter tests.

The predominant clinical features include fever (91%), hepatomegaly (90%), splenomegaly (84%), neurologic symptoms (47%), rash (43%) and lymphadenopathy (42%). [1] Such features are also seen in common febrile illnesses. In severe cases, multiorgan failures can be the initial presentations. Liver dysfunction is typically cholestatic and despite this being a common feature, liver dysfunction is not included as a diagnostic criterion. With manifestations that mimic infective disorders, it is now believed that a proportion of patients who have died in the intensive care units labeled as sepsis are probably in fact HLH. This is supported by the fact that two third of HLH diagnosis are made post-mortem.

The management of HLH depends on the severity of the conditions. [1] For mild case, it is possible that it may resolve once

the triggering factors have been resolved or treated. However, urgent referral to the haematolo-oncologists who are more familiar with this condition is recommended. Treatment that includes immunochemotherapy based on the HLH-2004 protocol should be commenced immediately once diagnosis is made to reduce the risk of progression to multi-organ failure. In our case, we did not to wait to see if the HLH will resolve on its own as we already had two deaths previously from HLH. We also did not wait for histological confirmation to avoid any delay.

In conclusion, our report highlighted a rare manifestation of dengue infection. Given that infections such as dengue fever are still endemic, it is important for clinicians to be aware of HLH and its association with common infections. Any delay in treatment can lead to undesirable outcomes, including death.

REFERENCES

1: McClain KL. Hemophagocytosis lymphohistiocytosis. UpToDate 19.3. Available from http://www.uptodate.com/contents/hemophagocytic-lymphohistiocytosis (Accessed 15th April 2013).

2: Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48:124-31.

3: Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis. 2000; 6:601-8.

4: Kapdi M, Shah I. Dengue and haemophagocytic lymphohistiocytosis. Scand J Infect Dis. 2012 Jan 21.

5: Larbcharoensub N, Aroonroch R, Kanoksil W, et al. Infection-associated hemophagocytic syndrome among patients with dengue shock syndrome and invasive aspergillosis: a case series and review of the literature. Southeast Asian J Trop Med Public Health. 2011; 42:1106-12.

6: Ray S, Kundu S, Saha M, Chakrabarti P. Hemophagocytic syndrome in classic dengue Fever. J Glob Infect Dis. 2011; 3:399-401.

7: Ramachandran B, Balasubramanian S, Abhishek N, Ravikumar KG, Ramanan AV. Profile of hemophagocytic lymphohistiocytosis in children in a tertiary care hospital in India. Indian Pediatr. 2011; 48:31-5.

8: Soler Rosario Y, Garcia R, Fernandez Sein A. Dengue virus associated hemophagocytic syndrome in children: a case report. Bol Asoc Med P R. 2010; 102:49-54.

9: Jain D, Singh T. Dengue virus related hemophagocytosis: a rare case report. Hematology. 2008; 13:286-8.

10: Lu PL, Hsiao HH, Tsai JJ, et al. Dengue virus-associated hemophagocytic syndrome and dyserythropoiesis: a case report. Kaohsiung J Med Sci. 2005; 21:34-9.

11: Tan LH, Lum LC, Omar SF, Kan FK. Hemophagocytosis in dengue: Comprehensive report of six cases. J Clin Virol. 2012 Jul 10.

12: Joshi R, Phatarpekar A, Currimbhoy Z, Desai M. Haemophagocytic lymphohistiocytosis: a case series from Mumbai. Ann Trop Paediatr. 2011; 31:135-40.

13: Lei HY. Transient hemophagocytic activity in dengue immunopathogenesis. J Formos Med Assoc. 2009; 108:595-8.

14: Jain D, Singh T. Dengue virus related hemophagocytosis: a rare case report. Hematology. 2008; 13:286-8.

15: Srichaikul T, Punyagupta S, Kanchanapoom T, Chanokovat C, Likittanasombat K, Leelasiri A. Hemophagocytic syndrome in Dengue hemorrhagic fever with severe multiorgan complications. J Med Assoc Thai. 2008; 91:104-9.

16: Veerakul G, Sanpakit K, Tanphaichitr VS, Mahasandana C, Jirarattanasopa N. Secondary hemophagocytic lymphohistiocytosis in children: an analysis of etiology and outcome. J Med Assoc Thai. 2002; 85:S530-41.