Case report

Hemophagocytosis in dengue: Comprehensive report of six cases

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ARTICLE INFO

Article history:
Received 13 November 2011
Received in revised form 3 May 2012
Accepted 8 June 2012

Keywords:
Hemophagocytosis
Dengue
Hyperferritinemia

ABSTRACT

Hemophagocytic syndrome is a potentially fatal disorder. It is being increasingly reported but remained under-recognized in dengue. Most reported cases were in association with plasma leakage and shock but multi-organ impairment was also observed. We describe the time-lines of 6 cases of confirmed dengue with varying severities of hemophagocytosis. All had persistent fever, cytopenia and elevated transaminases with markedly elevated ferritin levels during and beyond the plasma leakage phase. Acute renal failure and central nervous system manifestation were observed in two patients. Morphological hemophagocytosis was demonstrated in three patients. All survivors showed clinical and biochemical resolution of hemophagocytosis indicating its transient nature. Persistence of fever and cytopenia together with multi-organ dysfunction, out of proportion to and beyond the plasma leakage phase should prompt clinicians to consider this phenomenon.

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1. Why is the case series important?

Hemophagocytic syndrome (HPS) is a potentially fatal disorder caused by an aberrant immune response. It is a final common pathway of a cytokine storm induced by the uncontrolled proliferation and activation of the macrophages in the reticulo-endothelial system causing systemic inflammatory response and multi-organ dysfunction. Reactive HPS is associated with infections, autoimmune disorders or malignancies. HPS has been reported in dengue patients. It had varying impact on dengue manifestation, management and outcome. This association between dengue and HPS is under-recognized. We describe the time-line of hemophagocytic activity (HA) in a series of adult dengue cases between 2008 and 2011.

2. Description of cases

2.1. P1

A 16-year-old girl was admitted on day 5 of fever (D5) with epigastric pain, vomiting, diarrhoea and skin rash. She had petechiae and tender epigastrium. Her initial laboratory investigations were consistent with the critical phase of dengue. With adequate fluid replacement she was stable but developed pleural effusion and ascites.

After D7, intravenous fluid therapy was discontinued. Despite good peripheral perfusion, she remained unwell with persistent fever and tender hepatomegaly, mild gum bleeding, progressive bi-basal crepitations and a confluent rash. She was treated as pneumonia. Laboratory investigations showed rising transaminases and persistent pancytopenia (Fig. 1). Her C-reactive protein was normal. Abdominal ultrasound showed acalculus cholecystitis, ascites and bilateral pleural effusion. On D16, her ferritin level was 28,060 ng/mL. Bone marrow aspiration and trephine biopsy on D17 demonstrated hemophagocytosis. She improved without specific therapy for HPS.

2.2. P2

A 16-year-old girl presented on D6 of illness. She had fever and anorexia followed by vomiting, epigastric pain, per-vaginal bleeding and lethargy on D4. At presentation, she was febrile, her blood pressure was 123/64 mmHg but she had peripheral hypoperfusion, tender hepatomegaly. Following intravenous fluid replacement her peripheral perfusion improved but was persistently febrile. Ecchymoses, persistent per vaginal bleeding and a progressive drop in haemoglobin were observed. Blood and blood product transfusions were given.

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1386-6532/5 – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jcv.2012.06.005

On D7, she became fluid overloaded and required assisted ventilation. Intravenous fluid therapy was reduced. On D8 ultrasound examination revealed acalculous cholecystitis, pleural effusion and ascites. She remained febrile. The fever improved after a pulse-dose of methylprednisolone given on the suspicion of HPS. However, this was discontinued due to concerns of sepsis. Subsequently, fever recurred and the haemoglobin dropped despite repeated blood transfusions. No sources of bleeding could be identified.

Her transaminases remained elevated and renal function deteriorated. After weaning the sedation she was obtunded and a CT-brain showed cerebral oedema. On D12 the diagnosis of HPS was reconsidered as her ferritin level was elevated (Fig. 2). Bone marrow biopsy on D13 demonstrated hemophagocytosis. She was given Immunoglobulin-G therapy for 3 days, followed by pulse methylprednisolone for another 3 days tapering with prednisolone. Renal replacement therapy was commenced on D14. She recovered fully.

2.3. P3

A 43-year-old woman presented on D6 of fever with anorexia, prolonged menstrual bleeding and progressive lethargy followed by an episode of generalised tonic–clonic seizures. Her temperature was 38.8 °C, and she was dehydrated with a blood pressure of 103/57 mmHg and pulse rate of 106/min. She had undiagnosed diabetes mellitus (blood glucose 17.4 mmol/L, HBA1c 7.4%). A bolus of 20 ml/kg of normal saline was given over 1 h. She was then referred to a second hospital.

On arrival, she still had signs of peripheral hypoperfusion with compensated metabolic acidosis. In addition to plasma leakage, significant bleeding from menstruation was suspected. Over the next 12 h, with further fluid resuscitation and transfusion of 15 ml/kg of fresh whole blood and blood products, her haemodynamic status improved.

Soon after this, her condition deteriorated with recurrence of fever, oliguria, metabolic acidosis and raised transaminases and ferritin levels (Fig. 3). Pulse methylprednisolone was initiated for suspected HPS. Haemodialysis was initiated and non-invasive ventilation commenced. However, 40 min into haemodialysis, she developed hypotension and restlessness. She was mechanically ventilated. Maximal inotropes were added but had no effect. Metabolic acidosis and hypotension persisted despite fluids, blood products and pulses of methylprednisolone. She died 60 h after admission.

2.4. P4

A 20-year-old man with glucose-6-phosphate-dehydrogenase deficiency was admitted on D4 of illness. He had fever, nausea and stable haemodynamic status. Leukopenia, thrombocytopenia and elevated transaminases were present (Fig. 4). He progressed to have epigastric pain, vomiting, a petechial rash, pleural effusion and ascites on D5. There was no evidence of intravascular haemolysis. His transaminases worsened with elevated ferritin. He was discharged well on D9 without specific therapy for HPS (Table 1).
Table 1
Summary of important clinical and laboratory features in P1–P6.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Dengue confirmatory tests</th>
<th>Plasma leakage</th>
<th>Shock</th>
<th>Persistent fever</th>
<th>Acute renal failure</th>
<th>CNS manifestations</th>
<th>Highest measured ferritin (mg/L) (day)</th>
<th>Bone marrow evidencea</th>
<th>Treatment for HPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>16</td>
<td>IgM seroconversion</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>28,060 (D16)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>P2</td>
<td>16</td>
<td>NS1Ag positive and IgM seroconversion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>36,484 (D12)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>P3</td>
<td>43</td>
<td>IgM and IgG positive D6 seroconversion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>154,300 (D8)</td>
<td>ND</td>
<td>No</td>
</tr>
<tr>
<td>P4</td>
<td>20</td>
<td>NS1Ag positive and IgM seroconversion</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>55,640 (D7)</td>
<td>ND</td>
<td>No</td>
</tr>
<tr>
<td>P5</td>
<td>34</td>
<td>NS1Ag positive and IgM seroconversion</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>37,678 (D6)</td>
<td>ND</td>
<td>Yes</td>
</tr>
<tr>
<td>P6</td>
<td>36</td>
<td>NS1Ag positive, IgM and IgG positive D7 seroconversion</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>20,569 (D7)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CNS: central nervous system; HPS: hemophagocytic syndrome.
ND: not done.

a Bone marrow evidence of hemophagocytosis.

2.5. P5

A 34-year-old man was admitted on D4 of fever with anorexia, vomiting and stable haemodynamic status. He had leukopenia and thrombocytopenia (Fig. 5). With fluid therapy he maintained a stable haemodynamic state, but was unwell with persistent fever, vomiting and epigastric pain. He developed pleural effusion and ascites on D5. His transaminases and ferritin level were elevated. He was given pulse methylprednisolone therapy on D5. His fever resolved and was discharged on D9.

2.6. P6

A 36-year-old woman presented on D7 of fever with vomiting, epigastric pain, lethargy and rash and heavy menstrual bleeding for 6 days. She was unwell with a temperature of 38.6 °C, blood pressure of 100/50 mmHg and pulse rate of 90/min. She had warm peripheries, generalised rash, petechiae and tender epigastrium. Blood tests showed bi-cytopenia, raised transaminases, hypertriglyceridemia, hypofibrinogenemia and ferritin levels (Fig. 6). She was given fluid replacement, norethisterone and pulse methylprednisolone. Bone marrow aspiration and trephine biopsy on D8 demonstrated hemophagocytosis. There was no clinical and radiographic evidence of plasma leakage. She was discharged well on D11 with tapering dose of prednisolone.

2.7. Note

Blood cultures, HBsAg and HCV Ab and leptospirosis serology were negative for all patients.

Autoimmune screen was negative for all patients except P3. Sputum cultures were negative for P1 and P2. Paired serology for chlamydia, legionella, mycoplasma and HIV Ab tests were negative for P1. Epstein-Barr virus IgM for viral capsid antigen and cytomegalovirus PCR, Widal-Weil-Felix test and Mycoplasma antibodies were negative for P4, P5 and P6. No malarial parasites were found in peripheral blood film.

3. Other similar and contrasting cases in the literature

Dengue-related hemophagocytosis was first described in post-mortem marrows.13 Although most cases reported in the literature were in association with plasma leakage and shock, two recent cases did not show evidence of plasma leakage, similar to one of our patients.9,10 Most of these cases were recognised because of the persistence of fever and cytopenia beyond the expected period

![Fig. 5](image_url) Trend of laboratory results of P5. D: day of illness; WBC: total white blood count (×10^9/L); PC: platelet count (×10^12/L); AST: aspartate transaminase (IU/L); Fe: ferritin (mg/L). All units are converted to Log10 scale in the figure.

![Fig. 6](image_url) Trend of laboratory results of P6. D: day of illness; WBC: total white blood count (×10^9/L); PC: platelet count (×10^12/L); AST: aspartate transaminase (IU/L); Fe: ferritin (mg/L). All units are converted to Log10 scale in the figure.

for dengue. Srichaikul described patients with shock and multi-organ impairment in association with HPS, similar to those in our series.14 Interestingly, bone marrow evidence of HA was detected as early as D5 of illness in a patient with classical dengue and bicytopenia which is a frequent observation in dengue.15 In this case, ferritin level was only 2374.9 ng/ml on D4, not as high as in our patients which were done at a later phase. Of note, using in vitro assay, thrombocytopenia during the acute phase of dengue was found to be associated with increased phagocytosis of platelets.15

The difference between our series and previous reports is that we describe the time-line of HA, in relation to the plasma leakage phase of dengue.

4. Discussion

This case series describes for the first time the temporal relation of HA to the plasma leakage phase of dengue and its impact on the clinical manifestation and outcome. Plasma leakage was evident between D5 and D7 of illness in all patients except P6. Cytopenias and elevated AST in Figs. 1–5 appeared to overlap with plasma leakage and continued into convalescence. When ferritin levels were measured earlier in P3–P6 (Figs. 3–6) these two parameters correlated with raised ferritin levels. Figs. 4–6 show reducing levels of ferritin coincided with decreasing levels of AST and recovery of cytopenias. All patients had ferritin levels >20,000 mg/L, way above >10,000 mg/L, the level considered pathognomonic for HPS.16–18 Two patients had in addition, acute renal failure and central nervous system manifestations. Morphological hemophagocytosis was demonstrated in three cases, on day 8 of illness and beyond. Four patients received pulse methylprednisolone, and one of them received immunoglobulin therapy. Of these four patients, one died. Spontaneous resolution was observed in two patients, after a prolonged clinical course in one. While dengue infections were confirmed in all cases, bacterial sepsis and other common causes of reactive hemophagocytosis were excluded. All survivors showed resolution of clinical and biochemical markers for hemophagocytosis indicating transient HA phenomenon in dengue.19

Chaiyaratana et al. interpreted raised ferritin levels as markers of acute phase reactions and a predictor of dengue hemorrhagic fever. In contrast, the ferritin levels of at least ten times higher in our patients could be explained by the phenomenon of hemophagocytosis. This is further supported by findings in bone marrow biopsies. Immune dysregulation was postulated to be the cause of elevated transaminases that peaked during the convalescent phase in adult dengue patients.21 Our findings support the possibility of HA, a form of immune dysregulation, playing a role in the pathogenesis of hepatic dysfunction. However HA is a transient and self-limiting activity in dengue,21 but disease modifying agents such as methylprednisolone and/or immunoglobulin may be beneficial in those with severe complications.8,14

5. Conclusion

This case series demonstrates the variability of HA in its duration and severity in dengue. Clinicians should consider this phenomenon when there is persistent fever and cytopenia together with multi-organ dysfunction, out of proportion to and beyond the plasma leakage phase of dengue. Further studies are needed to determine the role of hemophagocytosis in dengue pathogenesis, clinical manifestation and outcome. It may have a major implication in the management and classification of dengue.

Competing interests

None.

Ethical approval

Ethics committee approval is waived for anonymous case reports.

Acknowledgements

The author thanks Nursing and medical staff of University Malaya Medical Centre, Sultanah Aminah Hospital, Johor Baru and Sunway Medical Centre, Selangor.

References