

Severe Dengue with Hemophagocytosis Syndrome

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Abstract

Dengue is known to cause high morbidity and mortality worldwide. In recent years, there have been increasing cases of dengue fever associated with a rare complication: hemophagocytic syndrome (HPS), which is a dangerous disorder that carries high mortality. It is associated with infections, autoimmune disorders, and malignancies. Prolonged duration of fever and cytopenia together with multi-organ dysfunction out of proportion to the plasma leakage phase should alert clinicians to consider this condition. In this case study, we highlight a 45-year-old woman with underlying diabetes who was admitted due to dengue fever with warning signs. Her conditions deteriorated quickly: she had spontaneous bleeding, evidence of plasma leakage, severe hepatitis, and coagulopathy on the 11th day of illness. With the support of other blood results, such as raised serum ferritin and lactate dehydrogenase, she was diagnosed with severe dengue with hemophagocytosis syndrome. She responded well to intravenous dexamethasone and recovered on the 19th day of illness.

Introduction

Dengue has been recognized recently as one of the most significant public health threats, causing high morbidity and mortality worldwide. Although death due to dengue is 99% avoidable, every year around 20,000 deaths are estimated to occur in more than 100 countries.

One of the causes of severe dengue presentation is hemophagocytic syndrome. Hemophagocytic syndrome (HPS), or hemophagocytic lymphohistiocytosis (HLH), is a potentially fatal disorder caused by an abnormal immune response.¹ Reactive HPS is associated with infections, autoimmune disorders, and malignancies. The infectious agents that have been previously linked with HPS are the Epstein-Barr virus, influenza virus, mycobacteria, cytomegalovirus, and human immunodeficiency virus, to name a few. In recent years, there have been increasing cases of dengue fever associated with HPS reported in the literature. However, this condition is still considered rare and under-recognized. Prolonged duration of fever and cytopenia together with multi-organ dysfunction out of proportion to the plasma leakage phase should alert clinicians to consider this condition.

This case illustrates a severe case of dengue infection with multi-organ dysfunction associated with hemophagocytosis syndrome, which was managed successfully due to early recognition of this condition.

Case presentation

We report a case of a 45-year old woman with underlying hypertension and diabetes mellitus who presented on day 5 of illness to the health clinic with a high grade fever associated with chills, rigor, myalgia, arthralgia, and headache. NS1Ag taken was positive. On day 9 of illness, she was referred to the hospital for dengue fever with warning signs because she developed vomiting and loose stool. She denied any bleeding tendencies. On the day of admission, the patient's vital signs were stable with no evidence of organomegaly. The initial full blood count showed leucopenia ($1.29 \times 10^3/\mu\text{L}$) and thrombocytopenia ($74 \times 10^3/\mu\text{L}$). The hematocrit was slightly raised (41%), but the hemoglobin was normal (12 g/dL). The liver function tests showed slightly raised aspartate transaminase (AST; 276 mmol/L) and alanine transaminase (ALT; 35 mmol/L). The patient was initially admitted into the general ward and managed with fluid therapy.

On day 2 of admission, her condition deteriorated. She had spontaneous gum bleeding, persistent vomiting, and dizziness. Her blood pressure was 135/86 mmHg, heart rate 80 beats per minute, and temperature 37.5 °C. Her respiratory rate was 36 per minute with reduced air entry in the right lower zone. Chest x-ray showed bilateral pleural effusion, and arterial blood gases showed compensated metabolic acidosis. There were sudden increased in the liver

enzymes: AST (276→2154), alkaline phosphatase (ALP) (66→109), and ALT (35→205). The coagulation profile was also prolonged with INR of 1.3 and APTT of 75. She was treated as having severe dengue with hepatitis, plasma leakage, and coagulopathy, and thus transferred to the intensive care unit.

The patient was transfused with 4 units of platelets, 4 units of fresh frozen plasma, and 1 pint whole blood and was commenced on non-invasive ventilation. An IV N-acetylcysteine (NAC) regime was given for the severe hepatitis. The increased liver enzyme levels raised the possibility of hemophagocytosis syndrome, which was later confirmed with high serum ferritin (31013 g/dL) and lactate dehydrogenase (LDH; 3627 U/L). The patient was then started on IV dexamethasone. She continued to improve with this management and was discharged on day 19 of illness with slightly raised liver enzymes.

Outcome and follow-up

Repeat blood investigation one week after discharge showed normalized liver function.

Discussion

We describe an unusual, severe presentation of dengue infection associated with hemophagocytosis with multi-organ dysfunction. There have been other cases reported worldwide.^{2,3} To our knowledge, there has been one case series of eight dengue cases associated with hemophagocytosis syndrome reported in Malaysia by Tan et al (2012). Our case was similar to previous cases^{4,5} in that the patient presented with multi-organ dysfunction and highly elevated liver enzymes.

The time of presentation in this case was on the 10th day of illness, which is consistent with most HPS cases reported.⁶ There are underlying diseases or disorders that increase the risk of HPS. This patient has underlying diabetes mellitus. It has been reported that this is one of predisposing factors for HPS.⁷

The elevated transaminases that peak during the convalescent phase in dengue patients are postulated to be due to immune dysregulation. Hemophagocytic activity (HA), a form of immune dysregulation, plays a role in the pathogenesis of hepatic dysfunction. Direct hepatocyte damage by the

virus, immune factors, and apoptosis of cells due to oxidative stress have all been suggested as possible mechanisms for liver cell damage. The limitation in this case was that a bone marrow biopsy was not done in our patient to confirm the hemophagocytic activity because the patient refused. Bone marrow biopsies in other HPS cases showed normal maturity of all cell lineages and infiltration by activated macrophages filled with other blood cells (Stabile et al., 2006). Another feature that supported the diagnosis in this patient was elevated lactate dehydrogenase, which was observed in almost all cases with hemophagocytosis syndrome.⁶

Another hallmark feature of HPS is elevated ferritin level. There is an argument that the increase in ferritin level is a marker for an acute phase reactant.⁸ However, our patient's highest ferritin level was 49637 ug/L, noted on day 12 of illness. This was far above 500 µg/L, which is the level considered as criteria for HPS diagnosis.¹ This supported the diagnosis of HPS in this patient's case.

Specific treatment guidelines for dengue fever associated with HPS syndrome do not exist. The general rule of treatment for acquired HPS is to identify the cause and institute specific treatment for it, which may suffice to arrest the development of HPS. Since there is no specific treatment for dengue fever other than fluid therapy, the main aim of treatment in cases associated with HPS is to suppress the inflammatory response and control cell proliferation. For less severe cases, corticosteroids and/or intravenous immunoglobulins or cyclosporine A may be adequate, but for high-risk cases, etoposide therapy is recommended. However, the most important step is to start treatment early; a delayed initiation of treatment is the greatest barrier to a successful outcome. **Our patient was given IV dexamethasone at day 11 of illness, as soon as HPS was suspected by rapidly rising transaminitis, high ferritin, and the patient clinically deteriorating. Early initiation of at least dexamethasone treatment may halt the inflammation. She improved very well with the treatment. Pulse dosages of methylprednisolone or dexamethasone have been used to suppress the hyperinflammatory state.** Other case reports⁵ also showed improvement of conditions with the same treatment, except for one case in Tan et al. (2008),

where the patient died despite receiving methylprednisolone. This could be due to a more severe presentation of the illness where the steroid was not sufficient or a delay in the initiation of treatment.

The use of NAC in non-acetaminophen acute liver failure (ALF), however, is controversial. A randomized, double-blind, placebo-controlled study had shown that intravenous NAC improved transplant-free survival and was well tolerated in non-acetaminophen ALF when given at an early stage.⁹ None of the other

cases reported the use of NAC as part of the management of dengue infection associated with HPS.

Learning Points

Hemophagocytosis syndrome associated with dengue infection can result in severe multi-organ failure.

Early recognition of the condition with prompt treatment gives a good prognosis for the patient.

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