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Case Report

Dengue Associated Secondary Hemophagocytic Lymphohistiocytosis Affecting a 6-Year-Old Child: Case Report

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Submitted: 25 April, 2023

Accepted: 26 May, 2023

Published: 29 May, 2023

ISSN: 2373-9819

OPEN ACCESS

Keywords

- Dengue; Hemophagocytic Lymphohistiocytosis; Cytokine Storm; Cytokine Release Syndrome; Infection; Hepatitis; Splenomegaly; Prolonged Fever

Abstract

Dengue fever is a mosquitoborne infectious disease endemic in over 100 countries around the world with its incidence growing in a progressive manner in the last five decades. Is cause of thousands to millions hospital admissions with a gargantuan economic burden and high mortality rate. Among the complications that dengue can cause the Hemophagocytic Lymphohistiocytosis is one of great concern since it's a complex and severe hyperinflammation status that mimics the same cause of its expression making it difficult to catch and retarding his proper recognition and treatment. Hereby we document a case of this disease expressed on a previously healthy 6 year-old female patient whose dengue infection was so severe that needed intensive care management with vasoactive drugs and diuretics.

After a short period of wellness began newly with fever, pancytopenia, hepatitis, and inflammatory response symptoms. A Dengue associated Hemophagocytic Lymphohistiocytosis syndrome was suspected and treated with intravenous corticosteroids on a 3-day scheme at no signs of malignancy with excellent response. The health care professionals must know about this not novel entity in order to reach an efficient diagnosis and treatment mostly, but not only, those in tropical and sub-tropical regions of the word were dengue virus is endemic.

INTRODUCTION

Dengue fever is a mosquito-borne infectious disease endemic in over 100 countries around the world, especially South-East Asia, the Americas, the Western Pacific, and Africa [1]. Its incidence has been growing in a progressive manner in the last five decades as much as 30 times, with an actual estimation of 500 million people in risk of infection only in the Americas continental region [2,3]. Mexico is considered an endemic region for the Dengue infection being the state of Guerrero one of the most prevalent localities [4].

The Cytokine Storm Syndrome, the generic term for Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome, is a severe and life-threatening condition mediated by the overproduction of inflammatory cytokines (TNF-alpha, INF-y, IL-1, IL-6 and IL-18) and chaotic immune cells activation, most of them being macrophages, leading to new humoral stimulation that overfeeds this cycle. The distinction between these two terms depends mainly on their etiology, being the Macrophage Activation Syndrome, a disorder developing from autoimmune or rheumatic diseases and the Hemophagocytic group from genetic (primary) causes or infectious/oncologic (secondary) causes, in which Dengue plays a role [5]. We report a female child that developed dengue infection-associated Hemophagocytic Lymphohistiocytosis (DenHLH) successfully treated in a regional hospital in one of Mexico's most prevalent dengue infection areas. This is the first case report regarding this syndrome in the Mexican population.

CASE REPORT

Female 6-year-old patient whose illness begins on April the 11th, 2023, with a non-measured fever and tension headache, 24 h later with poor appetite and myalgias adds the symptoms specter. Attends her local health clinic where is found with a high fever of 39° and treated with acetaminophen. 4 days later re-attends the health clinic with persistent fever, reason why is admitted and treated with intravenous liquids with paraclinic studies showing a platelet recount of 10 x 103, Hb 10.5 g/dl, Htc 31.5%, concentration index of 3.1 and positive IgM for dengue virus. At the fifth day begins with facial edema, abdominal pain, ecchymosis, petechial lesions and bleeding gums, reason why is transferred to the local hospital where is found with lower platelet counts of 8000 c/mcl), cholestatic syndrome with a total bilirubin count of 5 mg/dL due to direct bilirubin of 3.2 mg/dL

and a PCR count of 2.85 mg/dL. Due to this severity is that she is transferred via helicopter to our hospital.

At hospital arrival the patient was found with a clear airway, short of breath, tachycardia, hypotension and a petechial exanthem. Low intravenous liquids among norepinephrine and bi-positive airway pressure were initiated as initial intensive management and access to de Pediatric ICU. During the time at the pediatric ICU the patient was found with several manifestations owing to an Expanded Dengue Syndrome expressed as splenomegaly, severe hepatitis with alithiasic cholecystitis and pleural effusion found by ultrasound, for which diuretics and anti-ammonium therapy with lactulose, neomycin and metronidazole were needed. The fever ceased on the ninth day after its debut and on the fourth day of hospital stay was admitted to the pediatric hospital sector with a marked improvement in her hemodynamic, respiratory, hepatic and hematic systems.

Fever recrudescence of 38.5°C initiated on the 11th day after symptoms debut, accompanied with inflammatory response symptoms, hepatitis and a new fall in all blood cell lines (Hb 7,5 g/dl, Htc 23,7%, Leu 3,8 x109/L, platelets 50 x103/L, AST 250 mg/dL, ALT 184 mg/dL, LDH 1839 mg/dL). A DaHLH was suspected as cause of the this second-disease type manifestation because of the prolonged fever, hepatosplenomegaly history along with the new-onset pancytopenia and a 3 day-scheme of intravenous dexamethasone at a 15 mg/day/dose was initiated as treatment. Euthermia and normal vital signs were achieved 12 hours after the start of the dexamethasone and pancytopenia and hepatitis corrected at the 48 hours. She was discharged eleven days after our hospital admission.

DISCUSSION

Hemophagocytic lymphohistiocytic early diagnosis has always been a clinical challenge, due to its overlap with other inflammatory patterns such as sepsis. The actual diagnostic score accepted as the international referent is the 2004 Histiocyte Society criteria, with the presence of five out of eight criteria (fever, splenomegaly, hyperferritinemia, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis, absent Natural Killer (NK) cell activity, and high-soluble interleukin-2-receptor levels), being the most common signs/symptoms of the sustained fever, splenomegaly, lymphadenopathy, coagulopathy, cytopenia, skin rash and hepatomegaly with liver dysfunction [6]. The fact that most of these features are also common in many other syndromes is a problem, p.e. Dengue infection is a common cause of fever, bicytopenia, hepatomegaly with liver dysfunction and skin rash, but it's even worse for those medical centers and physicians that don't have the means for some complex laboratory tests p.e. seric ferritin, fibrinogen, natural killer cell activity, interleukin-2 receptor (CD25) levels or bone marrow histopathology. In our case the diagnosis was suspected by the long-lasting fever, splenomegaly, severe anemia and high-level lactate dehydrogenase and, since most of the blood test weren't available at that time, we decided to classify it as a Secondary Hemophagocytic Lymphohistiocytic (sHLH) after the blood smear didn't show any blast in order to start therapy.

Most of the scientific sources about DenHLH are case reports, however, a meta-analysis and systematic review made by Nam et al. demonstrates that the pooled mean duration of hospitalization in DenHLH is 21.3 days with a range of 2-85 days and the mean duration from admission to diagnosis of 4.97 days [6,7]. Our patient stayed in our medical center for 11 days with the diagnosis identified on the eight day. Treatment regimens, apart from the supportive and intensive care, include the use of steroids, including methylprednisolone and dexamethasone, etoposide, methotrexate, human intravenous immunoglobulin, among others, as means of reaching immunosuppression or/and immune modulation. Our patient had a positive response to dexamethasone, same that was chosen in order to diminish the typical steroids side effects versus methylprednisolone.

CONCLUSIONS

Hemophagocytic syndromes, being primarily or from secondary origin, are complex, severe and poorly known entities whose existence and prompt identification is imperative to the nowadays health care givers, not only in high income countries but also for professionals working in regions with lower economic status in order to act swiftly and change the affected prognosis.

RECOMMENDATIONS

Being the dengue infection so prevalent in so many parts around the globe it is almost impossible to consider that its related hemophagocytic lymphohistiocytosis syndrome has low numbers. With this in mind, all physicians that live and attend people in tropical countries have to have a particular insight and knowledge about tropical infectious diseases and their complications, including infectious related hemophagocytic syndromes.

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