Primary Dengue Fever Associated with Hemophagocytic Syndrome: A Report of Three Imported Cases, Bordeaux, France

Emmanuel Ribeiro¹, Somar Kassab², Thierry Pistone¹, Marie-Catherine Receveur¹, Pierre Fialon³ and Denis Malvy¹

Abstract

The dengue virus is responsible for a wide range of symptoms that can be classified into two distinct syndromes: classical dengue fever and severe dengue fever. Among the complicating forms, hemophagocytic syndrome (HPS) has been previously reported in case series of patients with secondary dengue fever outside of endemic settings. Of note, the occurrence of HPS has not yet been included among the criteria for defining severe dengue fever. We herein present three patients with HPS related to confirmed primary dengue virus infection. Clinicians should therefore consider hemophagocytosis as a complication during severe dengue infection in naïve patients.

Key words: dengue fever, hemophagocytic syndrome, travellers

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Introduction

Dengue fever is an arboviral infection transmitted by Aedes mosquitoes that represents a growing public health problem in the tropics and subtropics (1). Dengue viruses (DENV) are classified into four antigenically distinct serotypes designated DENV-1 to DENV-4. Although most infections are asymptomatic, all four DENV serotypes can cause a spectrum of disease ranging from “flu-like illness” (dengue fever, DF) to life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The latter have been predominantly argued to occur in patients with secondary dengue infection. The pathophysiology of severe dengue disease appears to be multifactorial; it involves interactions between viral characteristics, immune features and the host genetic background (2).

Infection-associated hemophagocytic syndrome (HPS) is a potential fatal disorder caused by a cytokine storm secondary to an aberrant immune response (3). HPS has a prominent link with a variety of viral, bacterial, fungal and parasitic infections. Reactive HPS has been previously reported in case series of patients with secondary dengue outside of endemic settings. We herein present three patients with hemophagocytic syndrome related to confirmed primary dengue virus infection.

Case Reports

Patient 1

A 44-year-old woman experienced a febrile exanthematous eruption with diffuse arthralgia and myalgia four days after returning from Senegal (travel duration, 2 weeks in mid-September, 1998). This trip was her first in a tropical country. She had been immunized against yellow fever in late May, 1998 and received daily antimalarial chemoprophylaxis with chloroquine plus proguanil. During her stay, essentially under rural conditions (Babagarage, 200 kms south from Dakar), she reported episodes of diarrhea that spontaneously resolved. On admission, a clinical examination was remarkable for hepatomegaly, splenomegaly and...
two types of inflammatory axillary lymphadenopathy. The laboratory findings disclosed leukopenia (2,000 cells/mm\(^3\); normal range: 4,000-10,000), thrombocytopenia (55,000/mm\(^3\); normal range: 150,000-400,000) and hepatic cytolysis at 15N together with increased serum levels of ferritin (9,600 μg/L; normal range: 11-306) and triglycerides (3.04 mmol/L; normal range: 0.8-1.8).

A bone marrow examination revealed macrophagic activation, as evidenced by the detection of many activated macrophages, phagocytes and thrombocytes. No etiologic features were identified concerning a parasitic, bacterial or neoplastic contribution. The serodiagnosis was negative for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) and human herpesvirus 8 (HHV8) and showed a cicatricial presentation of hepatitis A virus (HAV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella zoster virus (VZV) and parvovirus B19-specific antibody titers. An arboviral disease serology examination demonstrated circulating IgM anti-dengue antibodies on immunoenzymology in two consecutive serum sample analyses performed on October and December (index values: 2.5 and 2.9, respectively). A final diagnosis of primary dengue fever complicated by hemophagocytosis was confirmed. The patient’s general condition improved after a two-week regimen of corticotherapy.

**Patient 2**

A 38-year-old man had stayed in southeast Thailand for 15 days in late March, 2009. This trip was his first planned trip to the tropics. He denied having received any antimalarial preventive measures. In mid-July, 2010 confirmed seroconversion for dengue virus infection with negative results for specific IgM antibodies (OD = 0.138 vs. OD control = 0.108) and positive results for specific IgG antibodies (OD = 0.306 vs. OD control = 0.059). Moreover, a serotype evaluation of the same serum sample indicated the presence of specific DENV-1 neutralizing antibodies.

**Patient 3**

A 25-year-old woman had lived in Burkina-Faso since June 2009 for humanitarian purposes, her first stay in the tropics. She did not receive any antimalarial preventive measures. In late October, 2009, she developed a febrile illness (body temperature, 39°C). Probabilistic antimalarial

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**Figure.** Hemophagocytosis in bone marrow aspiration of patient 2 (A) and patient 3 (B) infected with dengue virus associated hemophagocytic syndrome (May-Grünewald Giemsa staining, × 1,000).
treatment (dihydroartemisinin plus piperaquine) was started. Following disease onset, she was repatriated to France. On admission, a physical examination revealed diffuse petechiae, extensive areas of exanthematous skin eruption and splenomegaly. A laboratory examination showed pancytopenia with a white blood cell count of 1,900/mm³, a hemoglobin level of 10.6 g/dL (normal range: 12-16) and a platelet count of 39,000/mm³. A favorable clinical and biological recovery was observed within one week.

**Laboratory-confirmed dengue**

(important when non sign of plasma leakage)

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**Table.** Guidelines Edited by World Health Organization (WHO; 2009) for Diagnosis and Classification of Dengue Fever (Adapted from (4))

<table>
<thead>
<tr>
<th>CRITERIA FOR DENGUE ± WARNING SIGNS</th>
<th>CRITERIA FOR SEVERE DENGUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probable Dengue</strong></td>
<td><strong>Warning Signs</strong></td>
</tr>
<tr>
<td>Live in/ travel to dengue endemic area.</td>
<td>Abdominal pain or tenderness</td>
</tr>
<tr>
<td>Fever and 2 of the following criteria</td>
<td>Persistent vomiting</td>
</tr>
<tr>
<td>• Nausea, vomiting</td>
<td>Clinical fluid accumulation</td>
</tr>
<tr>
<td>• Rash</td>
<td>Mucosal bleed</td>
</tr>
<tr>
<td>• Aches and pains</td>
<td>Lethargy, restlessness</td>
</tr>
<tr>
<td>• Tourniquet test positive</td>
<td>Liver enlargement &gt; 2 cm</td>
</tr>
<tr>
<td>• Leukopenia</td>
<td>Laboratory: increase in</td>
</tr>
<tr>
<td>• Any warning sign</td>
<td>hematocrit concurrent with rapid</td>
</tr>
<tr>
<td></td>
<td>decrease in platelet count</td>
</tr>
</tbody>
</table>

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Classical dengue fever and severe dengue fever. Based on the 1997 World Health Organization (WHO) classification of dengue fever, severe infections may be missed if the criteria are strictly applied to travellers (4, 5). The 2009 guidelines for the classification of dengue fever include severe systemic involvement among the criteria for severe dengue fever (Table (6). Of note, the occurrence of HPS has not yet been included among the formal criteria for systemic injury defining severe dengue fever. Among complicating forms of the disease, DHF and DSS are frequently reported in patients with secondary infections, assuming that antibody-dependant enhancement increases the viral load. Antibody-dependant enhancement has been linked to the presence of non-neutralizing levels of dengue virus-reactive IgG induced by primary infections. The activation, proliferation and secretion of cytokines in tissues by memory T lymphocytes are postulated to add to the inflammatory milieu during secondary infections (7). The level of DENV-specific T cell activation is correlated to the disease severity and is associated with the production of high interferon (IFN)-γ and tumor necrosis factor (TNF)-α levels. Indeed, the overproduction of cytokines and the generation of autoantibodies can counteract platelets and endothelial cells (7). As a result, an aberrant host immunologic response is thought to generate the rapid onset of capillary leakage accompanied by thrombocytopenia and altered homeostasis (7-9).

Several case series have provided evidence that DHF/DSS is associated with severe reactive HPS, beyond a critical prognostic issue. Of note, most reported cases of dengue associated-HPS involve DHF patients living in endemic areas (10-14). Few reports have highlighted the occurrence of HPS in patients with primary dengue infection (15). In our series, all cases involved confirmed primary dengue infections in naïve travellers. The first two patients met the criteria for severe dengue fever with significant liver injury. The third patient met the criteria for dengue virus in-

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**Discussion**

Dengue virus is responsible for two distinct syndromes:
fection with warning sign criteria (mucosal bleeding). All patients sufficiently fulfilled the criteria for HPS diagnosis (16).

HPS is well recognized to be associated with infections, most frequently those caused by viruses. In addition, HPS mechanisms are characterized by the dysregulation of the natural killer (NK) and T-cell functions, resulting in the aberrant activation of T lymphocytes. Monocytes/macrophages are then recruited to cytokine overproduction, leading to the subsequent development of hemophagocytosis (17, 18). The diagnosis of HPS is based on clinical, laboratory and histopathological findings. Diagnostic guidelines were proposed by the Histioocyte Society in 1991 (19) and updated in 2007 (16). The main clinical symptoms are fever and splenomegaly. The hallmark laboratory finding is cytopenia. Other relevant parameters include an elevated ferritin level, hypertriglyceridemia and/or hypofibrinogenemia, and immunological criteria include an increased level of soluble CD25 and a decreased NK cell function (16).

A causal relationship between hemophagocytosis and the severity of dengue infection has been hypothesized (7). Indeed, the pathogenesis of HPS closely resembles the features of DHF/DSS. Consistently, hemophagocytosis is regarded as a cause of thrombocytopenia (16, 19). Serum ferritin is a marker of macrophage activation in vivo and is distinctly highly elevated in patients with DHF (1, 8, 20). Consequently, a cut-off level for ferritin of >1,200 μg/L has been proposed as a predictor of DHF in the early stage of dengue fever (21). In our case series, we noted that all serum ferritin levels were dramatically increased over the value of 7,000 μg/L. These findings suggest that an inflammatory cytokine burden develops during dengue infection, which determines the activation of monocyte/macrophage subsets. Activated macrophages achieve the phagocytosis of antibody-coated platelets and contribute to the development and progression of thrombocytopenia (7). Likewise, Nelson et al. proposed that hemophagocytosis plays a part in the late-stage patterns of dengue virus infection (13). Therefore, markers of mononuclear cell activation should be assessed for prognostic value during dengue infection or when severity criteria are met (6).

In conclusion, clinicians should consider hemophagocytosis as a complication during severe dengue infection in naïve patients. Likewise, the occurrence of HPS deserves further consideration as a firm criterion of organ injury defining severe dengue infection. As this severe condition requires specific therapy, bone marrow aspiration should be carried out in dengue patients presenting with a prolonged fever and surrogate markers for HPS.

The authors state that they have no Conflict of Interest (COI).

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References