Case Report

Autoimmune features caused by dengue fever: a case report

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ABSTRACT

Dengue virus is the most important mosquito-borne viral disease in the world. Co-circulation of the four types of dengue viruses and expansion of dengue epidemic gave rise to infection enhancement and a big expansion of clinical aspects of the disease. Herein we report a case of a 25-year-old white woman with dengue fever and numerous associated autoimmune features. Our patient had proteinuria, an extensive right pleural effusion, a thin pericardial effusion and ascites. She had a low C3 level and positive antinuclear antibody; cryoglobulins were also positive. The numerous autoimmune features of this patient were a diagnostic challenge, since she was a young woman and could be easily mistaken for a rheumatologic patient in a newly open disease. Dengue infection probably was a triggering event causing an abnormal immune response. Therefore, dengue should be suspected in patients with hematological disorders and autoimmune features in endemic regions or those who have travelled to those regions.

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Introduction

The dengue virus is a RNA virus belonging to the Flavirviridae family and is the most important mosquito-borne viral disease in the world. There are four dengue viruses transmitted mainly in tropical countries and virulence seems to be quite variable among them. Classically, infection may be clinically asymptomatic or results in undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). However, the co-circulation of the four types of dengue viruses and expansion of dengue epidemic gave rise to infection enhancement and, consequently, not only significant number of severe forms – including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) – but also an increasing number of “unusual complications”.

The major pathophysiological hallmark that distinguishes DHF/DSS from DF is plasma leakage as a result of increased vascular permeability. That feature is observed instead of hemorrhagic events with secondary hypoalbuminemia or hypoproteinemia, accompanied by thrombocytopenia, altered haemostasis, and, usually, evidence of liver damage (indicated by increased aspartate aminotransferase and alanine aminotransferase). In DHF, but not in DF, there is an enhanced immune response in a host, most of them with a secondary infection, resulting in the formation of circulating immune complexes, complement activation, increased histamine release and massive release of cytokines into the blood, which can give origin to many unusual clinical features.

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Case presentation

A 25-year-old white woman was admitted to our hospital in May 2007 with a two-week history of fever, myalgia, headache and a few petechial lesions on the lower extremities. She took acetaminophen at standard doses as instructed in another service. On the seventh day of symptoms she developed disabsortive diarrhea, nausea, painful enlargement of the abdomen, edema in the legs, dyspnea and orthopnea. She had given birth five months before. She reported the occurrence of many cases of dengue infection in the area where she lived and State of São Paulo Department of Health data showed a dengue outbreak caused by dengue 3 serotype virus (DENV 3) in many regions, including that specific area.

At admission, fourteen days after the beginning of her first symptoms, she presented high temperature, tachycardia (120 bpm), tachypnea and blood pressure of 100 x 70 mmHg. Clinical examination revealed right prominent pleural effusion, ascites, epigastric discomfort, tender hepatomegaly and splenomegaly, soft edema and a few petechiae on the legs. There were no signs of active bleeding and the tourniquet test was negative. Her history of previous infectious diseases and recent trips was also negative. Laboratory results at admission showed leucopenia, thrombocytopenia, elevated aspartate aminotransferase, alanine aminotransferase levels and γ-glutamyltransferase levels, hypoalbuminemia, proteinuria, and elevated C-reactive protein (7.62 mg/dL, [normal range < 0.5mg/dL]) and lactate dehydrogenase (Table 1). Extensive right pleural effusion was observed by chest X-ray (Fig. 1) and computed tomography also showed a thin pericardial effusion, which was subsequently confirmed by

<table>
<thead>
<tr>
<th>Variable / (unit) / [normal range]</th>
<th>Admission</th>
<th>Day 4</th>
<th>Discharge</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%) [37-47]</td>
<td>37.6</td>
<td>28.8</td>
<td>30</td>
<td>33.2</td>
</tr>
<tr>
<td>White cells (per mm³) [4,000-10,000]</td>
<td>3,750</td>
<td>3,340</td>
<td>5,130</td>
<td>7,670</td>
</tr>
<tr>
<td>Neutrophils (per mm³) [2,000-8,000]</td>
<td>2,150</td>
<td>1,560</td>
<td>2,110</td>
<td>4,540</td>
</tr>
<tr>
<td>Lymphocytes (per mm³) [1,000-4,000]</td>
<td>840</td>
<td>1,000</td>
<td>2,240</td>
<td>2,320</td>
</tr>
<tr>
<td>Platelet count (per mm³) [150-400,103]</td>
<td>95,000</td>
<td>94,000</td>
<td>325,000</td>
<td>299,000</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L) [≤ 34]</td>
<td>353</td>
<td>170</td>
<td>49</td>
<td>21</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L) [≤ 27]</td>
<td>370</td>
<td>209</td>
<td>53</td>
<td>29</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L) [≤ 104]</td>
<td>206</td>
<td>162</td>
<td>-</td>
<td>117</td>
</tr>
<tr>
<td>γ-glutamyltransferase (U/L) [≤ 42]</td>
<td>177</td>
<td>134</td>
<td>-</td>
<td>93</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>20.2</td>
<td>36.4</td>
<td>13.0</td>
<td>12.6</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (sec)</td>
<td>39.5</td>
<td>50.7</td>
<td>28.6</td>
<td>30.2</td>
</tr>
<tr>
<td>Albumin (g/dL) [3.4-4.8]</td>
<td>2.6</td>
<td>1.8</td>
<td>-</td>
<td>3.9</td>
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<tr>
<td>Cryoglobulin</td>
<td>Positive</td>
<td>-</td>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td>C3 (g/L) [0.9-1.8]</td>
<td>-</td>
<td>0.39</td>
<td>-</td>
<td>1.89</td>
</tr>
<tr>
<td>C4 (g/L) [0.1-0.4]</td>
<td>-</td>
<td>0.33</td>
<td>-</td>
<td>0.46</td>
</tr>
<tr>
<td>ANA titers</td>
<td>-</td>
<td>1/320</td>
<td>-</td>
<td>Negative</td>
</tr>
</tbody>
</table>

ANA, antinuclear antibodies.

Fig. 1 - Chest X-ray at admission (A) and 2 weeks after hospital discharge (B).
echocardiography. Abdominal ultrasound and computed
tomography revealed hepatomegaly, splenomegaly, and ascites
but no lymphadenopathy was seen. Analyses of ascites and
pleural effusion performed two days following admission
revealed a lymphomonocytic exudate with elevated levels of
adenosine deaminase (ADA) of 39.8 and 49.6 U/L, respectively
(normal range ≤ 40 U/L). Microbiological studies (for bacterial,
mycobacterial, and fungal infections) were negative. Cytological
analyses of the pleural effusion showed cells suggestive of “LE
cells”. Bacterial and parasitological examination of feces showed
no pathological findings. A 0.55 g/day proteinuria was quantified.

At admission, low C3 (0.39 g/L) and normal C4 levels were
observed. A positive detection of antinuclear antibody showed a
“mitotic spindle” fluoroscopic pattern. Cryoglobulins were also
positive while antibodies to native DNA were negative. Serologic
tests for Epstein-Barr virus, toxoplasmosis, syphilis, cytomegalovirus,
HIV, and hepatitis B and C were negative. Dengue serological tests
were performed and included dengue IgM capture enzyme-linked
immunosorbent assay (Panbio – Queensland, Australia) positive and
dengue virus IgM- and IgG specific tests (Dengue DuoCassette, PanBio), both IgM
and IgG positives. These serological findings were strongly
suggestive of recent dengue virus infection. Due to the advanced
time of acute infection, a detection of dengue non-structural
protein 1 (NS1) was not indicated.

Treatment was symptomatic with administration of
crystalloids, fresh frozen plasma and vitamin K. Because a
secondary bacterial infection could not be ruled out she also
received antibiotics. During the first week of hospitalization
patient had fever, impaired respiration and one episode of
vaginal bleeding. At that time, she developed prolonged
thrombin time, a drop in hemoglobin levels, and fibrinogen
consumption (85.5 mg%, [normal range 220-495 mg%]) (Table 1).

Her clinical condition and laboratory tests improved during
the second week and on discharge her clinical symptoms
had almost disappeared. A relative lymphocytosis and
reticulocytosis were observed during the recovering phase.
At the first follow-up visit, she presented complete recovery and
laboratory tests had normalized, including negative
antinuclear antibodies.

Discussion

We have reported the case of a patient presenting with
autoimmune features as an unusual complication of dengue
virus infection. The severity of dengue infection is usually
correlated with the size of the dengue-infected cell mass as
shown many times by high titers of circulating virus in early
illness blood samples or by persisting high concentrations
in blood of dengue viral RNA and dengue non-structural
protein 1 (NS1). This protein also parallels cellular dengue
infection. High levels of markers of immune activation and
severity of dengue infection have led to the hypothesis
of an autoimmune response, mainly as a result of cross-
reactivity between anti-NS1 to host proteins, endothelial
cells and platelets, mediating complement activation and
triggering plasma leakage. Molecular mimicry could be
involved in the pathogenesis of this autoimmune activation.

Dengue infection may also lead to a wide range of
hematological disorders, including thrombocytopenia,
bone marrow suppression, platelet dysfunction, activation
of fibrinolysis and disseminated intravascular coagulation (DIC). Our patient met the WHO criteria
for DHF and showed abnormalities compatible with
bone marrow suppression, and DIC, although major
hemorrhagic manifestations were not observed. The
probable immunological mechanism was suggested by
the wide spectrum of laboratorial abnormalities: a low level
of C3 complement, positive antinuclear antibodies, positive
cryoglobulins and elevated ADA in serum. Prolonged
symptoms from dengue infections, such as we observed, are
not common and could lead to diagnostic difficulties. Plasma
leakage is the hallmark of DHF and occurs late during the
acute infection at or near defervesence and is coincident
with the clearance of virus. It could be demonstrated by
hypoaalbuminemia and cavitary effusions. We were able to
detect specific antibody production against dengue virus
during the phase of DHF, probably also coincident with
lowering of virus titers.

The numerous autoimmune features of this patient were
diagnostic challenge, since she was a young woman and
could be easily confounded with a rheumatologic patient
in a newly open disease. Dengue infections can be a triggering
event causing abnormal immune response leading to atypical
symptoms or autoimmune diseases, such as systemic lupus
erythematosus. Therefore, this infection should be included
in differential diagnosis of patients with hematological
disorders and autoimmune features in endemic regions or
with those who have traveled to them.

Conclusion

Our patient demonstrated anemia, thrombocytopenia,
leucopenia and abnormal coagulation studies (prolonged
activated partial thromboplastin time and thrombin
time and low fibrinogen levels) in combination with features
of autoimmune disorders such as elevation of C-reactive
protein, low complement levels, positive cryoglobulins,
and positive antinuclear antibodies. The description of
the case that at first resembled a systemic autoimmune
disease, including systemic lupus erythematosus and
cryoglobulinemia, was subsequently confirmed as part of
dengue hemorrhagic fever manifestations. Due to the high
frequency of these features in the clinical practice and
the increasing incidence of dengue fever, we think that
clinicians should include dengue infection in
the differential diagnosis of patients with hematological
disorders and autoimmune features. Besides, to our
knowledge, this is the first report of such autoimmune
features in dengue infection.

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Conflict of interest

All the authors declare to have no conflict of interest.

REFERENCES