Can Ngoc Dang, Satoshi D. Ohdachi, Nghia Xuan Nguyen, Tien Duc Pham, Bazartseren Boldbaatar, Hiroshi Satoh, Yasuhiro Yoshikawa, Shigeru Morikawa, Keiko Tanaka-Taya, Richard Yanagihara, and Kazunori Oishi

Author affiliations: National Institute of Infectious Diseases, Tokyo, Japan (S. Arai, K. Araki, H. Satoh, S. Morikawa, K. Tanaka-Taya, K. Oishi); Institute of Ecology and Biological Resources, Hanoi, Vietnam (S.T. Nguyen, C.N. Dang, N.X. Nguyen, T.D. Pham); National University of Mongolia, Ulaanbaatar, Mongolia (B. Boldgiv); National Institute of Biological Resources, Seoul, South Korea (D. Fukui); Hokkaido University, Sapporo, Japan (S.D. Ohdachi); Institute of Veterinary Medicine, Ulaanbaatar (B. Boldbaatar); Chiba Institute of Science, Chiba, Japan (Y. Yoshikawa); and University of Hawaii at Manoa, Honolulu, Hawaii, USA (R. Yanagihara)

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References


Address for correspondence: Satoru Arai, Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Toyama 1-23-1, Shinjuku, Tokyo 162-8640, Japan; email: arais@nih.go.jp

Possible Cause of Liver Failure in Patient with Dengue Shock Syndrome

To the Editor: We report a rare hepatic ultrasonograph finding for a patient with liver failure associated with dengue virus (DENV) infection. This finding might shed light on the pathogenesis of liver involvement in this disease.

In March 2006, a 10-year-old previously healthy boy was hospitalized for a 3-day history of fever, headache, and nausea/vomiting. Fever subsided on the day of admission, but the patient was in shock (blood pressure 80/40 mm Hg) and had gastrointestinal bleeding and hematuria. Physical examination showed an obese, confused patient with generalized petechiae and hepatomegaly. The initial diagnosis was dengue shock syndrome (DSS). The patient was intubated and received intravenous fluid infusion, packed red blood cells, ceftriaxone, sodium bicarbonate, and ranitidine before being transferred to King Chulalongkorn Memorial Hospital in Bangkok. The patient’s blood pressure increased to 130/90 mm Hg after the initial fluid resuscitation (28 mL/kg free flow), and systolic pressure remained at ≥130 mm Hg until transfer.

Laboratory examinations found 14,930 leukocytes/mm³, hemoglobin 16.4 g/dL, hematocrit 48.2%, platelet 18,000/mm³, blood urea nitrogen 33 mg/dL, creatinine 1 mg/dL, sodium 128 mEq/L, potassium 6.2 mEq/L, chloride 91 mEq/L, CO₂ 5 mEq/L, total bilirubin 6.9 mg/dL, direct bilirubin 3.9 mg/dL, aspartate transaminase 3,507 IU/L, alanine transaminase 2,775 IU/L, prothrombin time 43 seconds (international normalized ratio 3.4), and partial thromboplastin time 93.5 s (control 28.7 s). Blood and urine cultures showed negative results. Serum was positive for IgM against DENV. Unfortunately, we did not investigate other viral causes of liver failure.

DSS with liver failure was diagnosed and treated with intravenous fluid, sodium bicarbonate, omeprazole, fresh frozen plasma, platelet transfusion, vitamin K, and recombinant factor VIIa concentrate (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark). Despite stable blood pressure over the next 6 days, liver enzymes continued to rise with progressive jaundice (online Technical Appendix, wwwnc.cdc.gov/EID/article/19/7/12-1820-Techapp1.pdf). Hepatic ultrasonograph on the second
day after admission showed totally reversed direction of portal venous blood flow away from the liver (Figure, panel A), becoming bidirectional on the following day and, finally, reverting to normal direction (although with low velocity) 3 days later (Figure, panel B). Despite improved hemodynamic status, progressive encephalopathy and gastrointestinal bleeding developed and were unresponsive to treatment. Six days later, the patient died of pulmonary hemorrhage and progressive respiratory failure.

DENV infection is one of the most prevalent emerging infectious diseases affecting children and one of the leading causes of liver failure in tropical countries (1,2). Although liver involvement in patients with dengue hemorrhagic fever is well known, the mechanism for DENV-induced liver injury is still a mystery. Liver autopsy specimens of terminal DSS patients generally showed massive or focal necrosis with little or no recruitment of polymorphonuclear cells or lymphocytes (3,4). Ultrasonograph images from patients with liver failure caused by acetaminophen poisoning or hepatitis B indicate increased portal vein flow and normal flow velocity to the damaged liver (5). Decreased portal vein flow velocity and reversal of the flow direction is seen in the terminal stage of hepatic cirrhosis and a few other conditions such as hepatic sinusoidal obstruction (hepatic veno-occlusive disease), arteriportal fistula, extrahepatic portal vein thrombosis, and hepatic venous outflow obstruction (6). This finding is unusual in other instances of toxin- or virus-induced liver failure and might contribute to the understanding of the mechanism of liver involvement in patients with DENV infection.

We previously reported increased portal vein congestion during the toxic stage of DENV infection (7). At defervescence, the portal vein was dilated and blood flow velocity was decreased. This finding is usually observed for patients with high resistance in the hepatic sinusoidal capillary network, such as those with liver cirrhosis, and is correlated with the degree of portal venous hypertension (8). We postulate that DENV infection of the liver might affect the sinusoidal endothelial or Kupffer cells in a way that causes obstruction to the hepatic sinusoidal capillary lumen resulting in decreased portal venous blood flow and flow to the liver and, when severe, shunting of portal blood away from the liver (hepatofugal flow). Because portal venous blood comprises 75% of total hepatic blood (6), this condition coupled with decreased hepatic arterial blood flow as a consequence of shock might have led to severe and irreversible liver damage in this patient. This hypothesis can be further supported by a pathology study of the skin in patients with DENV infection, which showed endothelial swelling and extrusion of its plasma membrane into the capillary lumen, resulting in narrowing of the capillary lumen (9). Of note are the similarities between clinical findings in patients with DENV infection and sinusoidal obstruction syndrome such as hepatomegaly, ascites, right pleural effusion, swelling of the gall bladder wall, and decreased velocity or reversed direction of portal blood flow (10).

In conclusion, we report a case of liver failure from DENV infection with reversal of portal venous blood flow. We postulate that hepatic sinusoidal obstruction coupled with shock might be the underlying mechanism of liver failure in this disease.

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Publication of this case report was approved by the ethic committee, Faculty of Medicine, Chulalongkorn University.

Apichai Khongphatthanayothin, Atchara Mahayosnond, and Yong Poovorawan

Author affiliations: Bangkok Hospital Medical Center, Bangkok, Thailand (A. Khongphatthanayothin); and Chulalongkorn University, Bangkok (A. Khongphatthanayothin, A. Mahayosnond, Y. Poovorawan)

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References


Address for correspondence: Yong Poovorawan, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Rd., Pratumwan, Bangkok 10330, Thailand; email: yong.p@chula.ac.th

Spotted Fever Group Rickettsiae in Questing Ticks, Central Spain

To the Editor: The number of spotted fever group (SFG) rickettsiae that cause diseases in humans is rapidly increasing (1,2); infections have been described in ticks and humans in Spain (3,4). However, in Castilla-La Mancha, central Spain, where recreational parks and hunting estates are abundant and humans may be exposed to infected ticks, information on such infections is not available. Therefore, it is worthwhile to characterize Rickettsia spp. found in this area for epidemiologic studies and proper diagnosis of possible rickettsial diseases.

In this study, we obtained 148 questing adult ticks, representing the most abundant species in the area: 12 Dermacentor marginatus, 8 Rhipicephalus turanicus, 41 R. sanguineus, 41 R. bursa, 33 Hyaalomma marginatum, 11 H. marginatum, and 33 H. maritimum. The ticks were collected from the vegetation at natural sites in Castilla-La Mancha during fall 2009 and spring–summer 2010 (Figure, panel A) and in Questing Ticks, 2009;22:123–40. The results showed that 27 (18.2%) of the 148 ticks analyzed were positive for Rickettsia spp. Of these, 11 were confirmed as R. massiliae in Rh. sanguineus, Rh. turanicus, and Rh. pusillus, 3 as R. raoultii in D. marginatus, and 2 as R. sibirica subspp. mongolitominae in H. marginatum and Rh. pusillus (Figure, panel B). These species had >99% pairwise nucleotide sequence identity to reference strains R. massiliae MTU5 (GenBank accession no. NC_009900), R. slovaca 13-B (accession no. NC_016639), and R. sibirica subspp. mongolitominae HA-91 (accession no. AHZB00000000) genome sequences for all genes analyzed, and the only R. raoultii reported sequences (accession nos. JQ792107, JQ792166, JQ792134, and NR_043755 for ompB, ompA, gltA, and 16S rRNA, respectively). The sequences obtained in this study were deposited in the GenBank under accession nos. KC427998–KC428040.

Multilocus sequence analysis of ompA-ompB sequences (Figure, panel B) and in silico PsfI and Rsal restriction analysis of ompA sequences also confirmed the identity of the Rickettsia spp. identified in this study. As previously shown (7,8), multilocus analysis with ompA-ompB sequences was highly informative about the...
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Technical Appendix

Table. Serial clinical and laboratory data for patient with liver failure and dengue shock syndrome.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3–4</th>
<th>4–5</th>
<th>5–6†</th>
<th>6–7</th>
<th>7–8</th>
<th>8–9†</th>
<th>9–10</th>
<th>10–11</th>
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<tr>
<td>Heart rate</td>
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<td>100</td>
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<td>100</td>
<td>110</td>
<td>100–60</td>
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<td>BP, mm Hg‡</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>48.2</td>
<td>24.6</td>
<td>30.7</td>
<td>33.6</td>
<td>27.8</td>
<td>26.9</td>
<td>28.7</td>
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</tr>
<tr>
<td>ALT</td>
<td>2,775</td>
<td>4,490</td>
<td>4,720</td>
<td>3,098</td>
<td>2,011</td>
<td>1,723</td>
<td>1,725</td>
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<tr>
<td>AST</td>
<td>3,507</td>
<td>11,660</td>
<td>&gt;7,000</td>
<td>8,440</td>
<td>4,082</td>
<td>3,099</td>
<td>2,600</td>
<td>968</td>
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<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.9</td>
<td>9.7</td>
<td>12.2</td>
<td>21.6</td>
<td>24.1</td>
<td>34.8</td>
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<tr>
<td>Direct</td>
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<td>6.0</td>
<td>14.1</td>
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<tr>
<td>PT, INR</td>
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<td>2.4</td>
<td>NA</td>
<td>2.3</td>
<td>2.3</td>
<td>2.1</td>
<td>NA</td>
</tr>
</tbody>
</table>

*BP, blood pressure; ALT, alanine transaminase; AST, aspartate transaminase; PT, prothrombin time; INR, international normalized ratio; NA, not available.
†Dates when liver ultrasonography (Figure) was performed.
‡1 episode of BP 81–85/52–54 mm Hg occurred for 15 minutes, 12 hours after hospital admission; otherwise, the lowest systolic BP was 108 mm Hg.