Dengue Fever Complicated by Acute Acalculous Cholecystitis and Hemophagocytic Lymphohistiocytosis Despite Negative PCR

Takako KOBAYASHI, Masayuki OKI and Hideki OZAWA

Division of General Internal Medicine and Family Medicine, Department of General and Acute Medicine, Tokai University School of Medicine

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Objective: To report a case of dengue fever complicated by acute acalculous cholecystitis (AAC) and hemophagocytic lymphohistiocytosis (HLH), despite initial negative polymerase chain reaction (PCR) results.
Methods: We describe the clinical course of a 40-year-old woman who returned from Indonesia with a persistent fever and rash. The diagnosis was established through clinical evaluation, serological testing, and abdominal imaging. The study conformed to the principles outlined in the Declaration of Helsinki.
Results: Although the initial dengue PCR result was negative, subsequent NS1 and IgM antibody test results were positive. The patient developed severe complications, including AAC, characterized by gallbladder wall thickening, and HLH, indicated by marked fever, splenomegaly, hypofibrinogenemia, hyperferritinemia, and high soluble IL-2 receptor levels. Despite these symptoms, the patient was managed conservatively. Planned percutaneous transhepatic gallbladder aspiration was canceled because of spontaneous improvement observed on ultrasonography. The patient recovered fully without corticosteroid or platelet transfusions and was discharged on day 14.
Conclusion: Given the potential for false-negative PCR results during the acute phase of dengue, multimodal serological testing is essential. This case demonstrates that severe atypical complications, such as AAC and HLH, can be resolved with supportive care alone, avoiding invasive procedures, immunosuppressive therapy, and platelet transfusion.

Key words: Dengue fever, acute acalculous cholecystitis, hemophagocytic lymphohistiocytosis, false-negative PCR, conservative management

INTRODUCTION

Dengue fever is a systemic viral infection transmitted by *Aedes* mosquitoes that affects approximately 390 million people annually [1]. While it typically presents as an acute self-limiting febrile illness, atypical manifestations occur in up to 15.8% of cases and are often classified as Expanded Dengue Syndrome (EDS) [2]. Among these atypical presentations, acute acalculous cholecystitis (AAC) and hemophagocytic lymphohistiocytosis (HLH) are recognized but often mismanaged complications. Recent data indicate that the prevalence of AAC in dengue ranges from 6% to 52%, whereas HLH occurs in approximately 3% of cases, rising to 22% in severe dengue [3, 4]. The mortality for dengue-associated HLH is high, with a pooled rate of approximately 20% [5].

Definitive diagnosis via reverse-transcriptase polymerase chain reaction (RT-PCR) is highly effective within the first five days of illness; however, it is not widely recognized that PCR can yield false-negative results during the acute phase if the viral load begins to decline [6]. In such instances, a critical diagnostic window exists where only immunoglobulin M (IgM) antibody testing or NS1 antigen detection can be used to identify dengue infection [7]. Misdiagnosis at this stage may lead to unnecessary surgery for AAC, which poses hazardous bleeding complications given the profound thrombocytopenia and bleeding risk or inappropriate high-dose steroids for HLH [4].

Furthermore, while prophylactic platelet transfusion is commonly employed, recent large-scale multicenter randomized controlled trials have demonstrated that it is not superior to supportive care and may be associated with adverse events such as fluid overload [8]. Here, we report a unique case of dengue fever with multiple severe atypical complications that resolved successfully with conservative management.

PATIENTS AND METHODS

This study conforms with the principles outlined in the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from the patient for publication of this case report. A 40-year-old woman with no significant medical history presented to our institution with persistent fever and rash. Detailed clinical examinations, laboratory investigations, and diagnostic imaging, including abdominal computed tomography and ultrasonography were performed. Patient management decisions were based on clinical deterioration, laboratory parameters, and imaging findings.

Masayuki OKI, Division of General Internal Medicine and Family Medicine, Department of General and Acute Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-91-9372 E-mail: okixx007@tokai.ac.jp

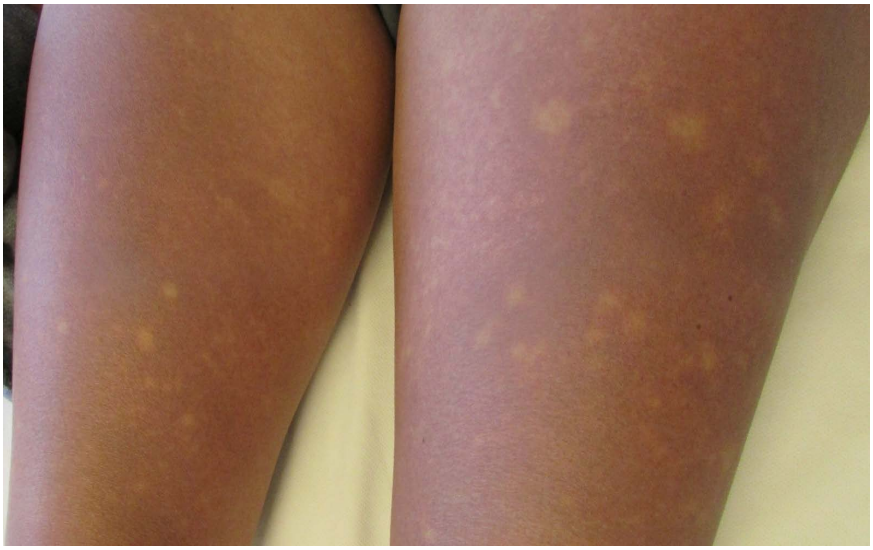

Fig. 1 Physical findings showing the characteristic "island of white in a sea of red" maculopapular rash on the limbs.

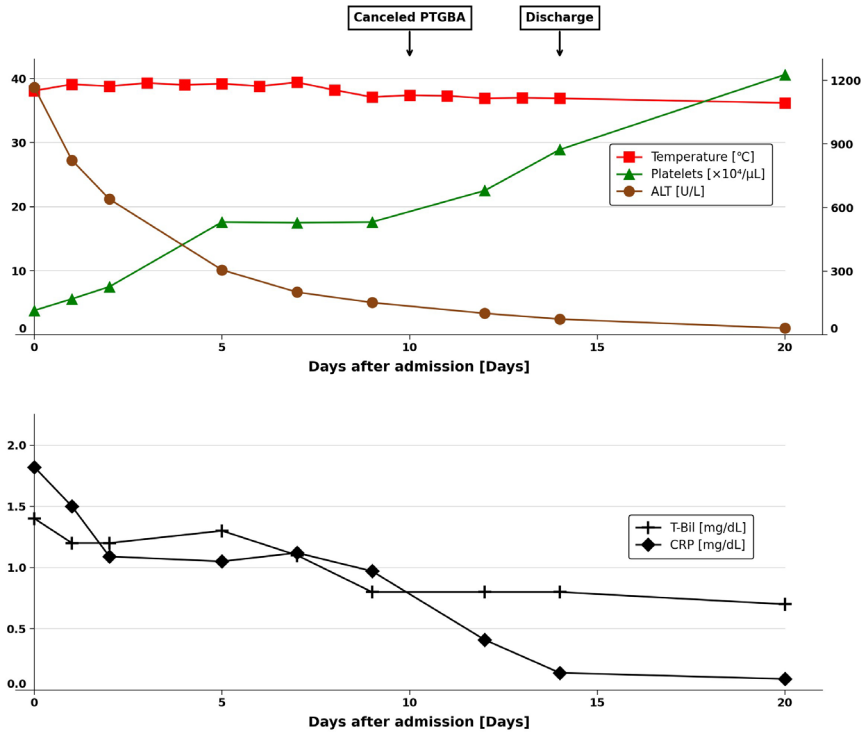

Fig. 2 Clinical course and laboratory trends showing the timeline from return to Japan to discharge. Key data points include recurrent fever spikes, the nadir of platelets at 38,000/μL, peak alanine aminotransferase (ALT) of 1,167 U/L, and the cancellation of percutaneous transhepatic gallbladder aspiration (PTGBA) on Day 10, as ultrasound showed spontaneous recovery.

RESULTS

Clinical Course

Fourteen days prior to admission, the patient reported multiple mosquito bites while traveling to Indonesia. Upon return to Japan, she developed a fever (39°C). PCR testing for dengue was performed at a quarantine station, and the result was negative. Seven days before admission, her fever recurred at 39°C accompanied by a maculopapular rash. Although the rash initially faded, a 40°C fever returned two days before hospitalization.

On admission, her temperature was 38.1°C. Physical examination revealed petechiae on her limbs and the characteristic "island of white in a sea of red" maculopapular rash (Fig. 1). She exhibited significant tenderness in the right hypochondrium with a positive Murphy's sign.

Laboratory Findings

Laboratory investigations revealed profound thrombocytopenia (38,000/μL), severe hepatitis with aspartate aminotransferase (AST) at 5,588 U/L and alanine aminotransferase (ALT) at 1,167 U/L (Fig. 2),

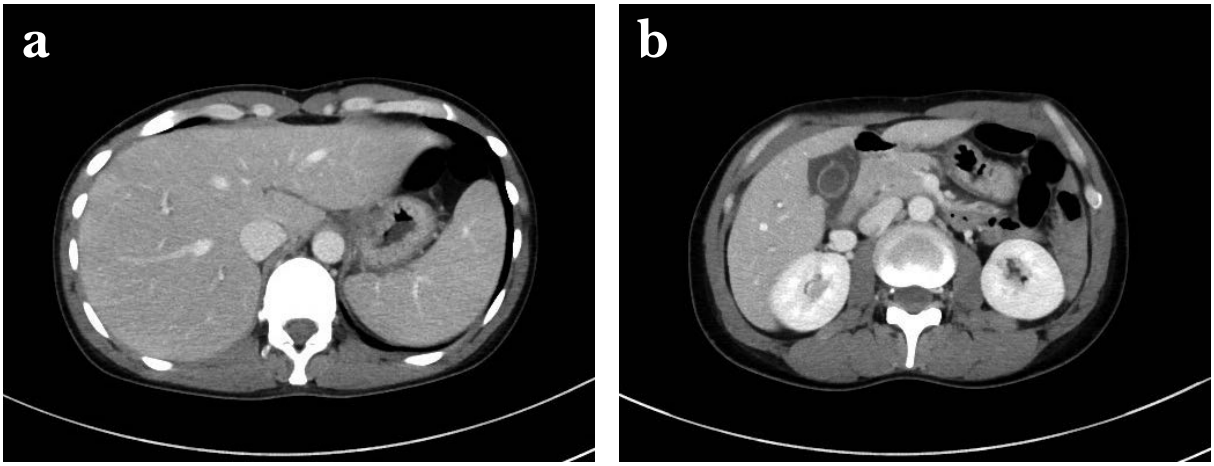

Fig. 3 Abdominal computed tomography on admission revealed hepatosplenomegaly and a periportal collar sign.

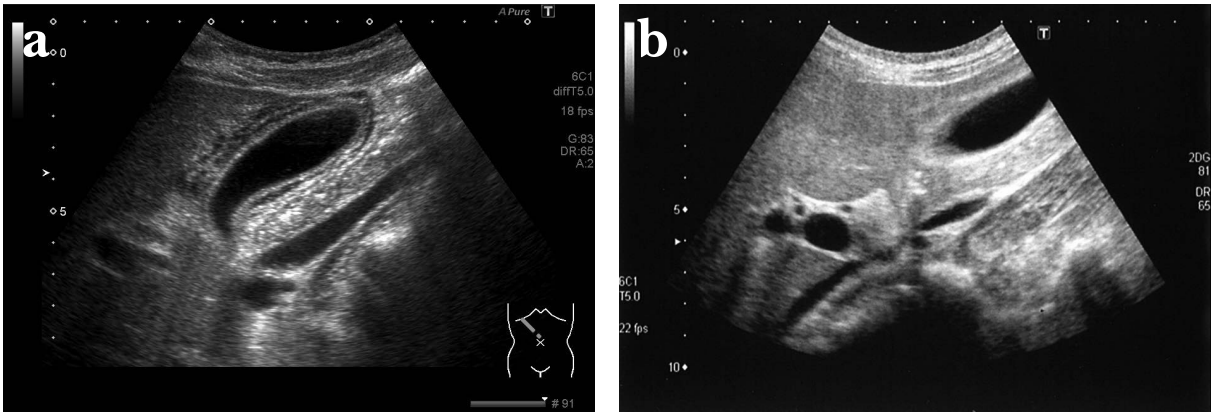

Fig. 4 Abdominal ultrasonography on admission (4a) showing 7 mm gallbladder wall thickening and double wall sign, which significantly improved by Day 10 (4b).

and markedly elevated ferritin at 49,850 ng/mL. Fibrinogen levels were reduced to 148 mg/dL and soluble IL-2 receptor (sIL-2R) levels were elevated to 3,940 U/mL. These findings fulfill the clinical diagnostic criteria for HLH [9]. Despite earlier negative PCR results, both dengue NS1 antigen and IgM antibodies were positive upon admission, confirming dengue viral infection [7].

Imaging Findings

Abdominal computed tomography (CT) revealed hepatosplenomegaly and a periportal collar sign (Fig. 3a, b). Ultrasonography showed gallbladder wall thickening of 7 mm and a double-wall sign (Fig. 4a), consistent with acute acalculous cholecystitis [4].

Management and Clinical Course

Conservative management was initiated using intravenous fluid replacement and close clinical monitoring. Although percutaneous transhepatic gallbladder aspiration (PTGBA) was scheduled for day 10 due to persistent abdominal symptoms, follow-up ultrasonography showed spontaneous improvement in gallbladder wall thickening and resolution of the double-wall sign (Fig. 4b). Consequently, the drainage procedure was discontinued. The patient's condition continued to improve without corticosteroid therapy or platelet transfusion. She was discharged on day 14 in a stable condition with complete resolution of fever, normalization of laboratory parameters, and improvement in imaging abnormalities.

DISCUSSION

This case highlights four principal clinical challenges encountered in managing atypical presentations of dengue.

First, this case demonstrates the limitations of PCR testing. PCR sensitivity peaks during the initial acute phase, but decreases significantly after 5 days [6]. Exclusive reliance on PCR may lead to missed diagnoses, as observed in this patient at a quarantine station. Utilizing a combination of the NS1 antigen, IgM antibodies, and PCR achieves a diagnostic sensitivity of greater than 90% within the first ten days of illness [7]. These findings underscore the need for multimodal serological testing when PCR results are negative; however, the clinical suspicion of dengue remains high among travelers returning from endemic areas.

Second, AAC in dengue infection primarily arises from increased vascular permeability and plasma leakage into the gallbladder wall rather than from direct bacterial infection [4, 10]. Management of dengue-related AAC is generally conservative, emphasizing fluid management and supportive care instead of surgical intervention. In contrast to AAC of other etiologies, dengue-associated AAC is typically self-limiting and responds well to supportive care [11]. Cholecystectomy is generally contraindicated because of the elevated risk

of bleeding due to severe thrombocytopenia. Invasive interventions should be reserved for patients with suspected gallbladder gangrene or perforation [4]. The Tokyo Guidelines 2018 (TG18) for acute cholecystitis enable a stratified risk assessment. In this patient, no TG18 negative predictive factors for poor prognosis were identified; the total bilirubin was 1.4 mg/dL, below the 2.0 mg/dL threshold, and both consciousness and respiratory function were preserved [12]. The absence of these risk factors, together with the significant hemorrhagic risk of invasive procedures, supported the decision to prioritize supportive care and antimicrobial therapy over immediate surgical or drainage interventions [12, 13]. This approach prevented iatrogenic complications and resulted in a clinical resolution.

Third, the patient met the diagnostic criteria for HLH, a severe hyper-inflammatory syndrome, with an estimated mortality rate of 20% [5]. A bone marrow biopsy was not performed in this case, despite meeting HLH diagnostic criteria, due to several clinical factors. The patient's severe thrombocytopenia (platelet nadir: 38,000/μL) and bleeding diathesis posed a significant hemorrhagic risk for invasive procedures [14]. The patient also met six of the eight HLH-2004 diagnostic criteria (fever, splenomegaly, thrombocytopenia, hypofibrinogenemia, hyperferritinemia, and elevated soluble interleukin-2 receptor), which is sufficient for diagnosis without requiring bone marrow confirmation [9]. Additionally, hemophagocytosis is not always present in infection-associated HLH, and its absence does not exclude the diagnosis [15]. Although HLH is commonly treated with high-dose corticosteroids, this case demonstrates that resolution can be achieved with supportive care alone even when multiple severe complications are present [9]. Clinicians should consider the risks of immunosuppressive therapy against the potential for spontaneous recovery in patients with dengue-associated HLH.

Fourth, despite a nadir platelet count of 38,000/μL, the patient did not receive a prophylactic platelet transfusion. Recent multicenter randomized controlled trials indicated that prophylactic platelet transfusion does not provide greater protection against clinical bleeding than supportive care in patients with dengue thrombocytopenia [8]. Platelet transfusion carries significant risks such as fluid overload, anaphylaxis, and transfusion-related acute lung injury. The patient's complete recovery without transfusion was consistent with the current evidence-based recommendations that support conservative observation-based management.

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