CHEST

A 47-Year-Old Returning Traveler With Shock

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A 47-year-old man with no significant past medical history, originally from Indonesia, was brought to the ED of an urban US medical center after being found collapsed on the sidewalk in respiratory distress and with an altered sensorium. Upon arrival to the ED, he was tachypneic, with increased work of breathing and an oxygen saturation of 88% on 100% nonrebreather mask, so he was immediately intubated. Following intubation, he became profoundly hypotensive, requiring aggressive crystalloid resuscitation and vasopressor support. Broad-spectrum antimicrobials were administered, including ceftriaxone, vancomycin, levofloxacin, and oseltamivir. Further history elicited subsequently from family members revealed that the patient had returned from a 2-week vacation in Indonesia 6 days prior to presentation. According to relatives, he appeared to be in his usual state of health upon his return and was not seen by anyone thereafter, but in the interim he reportedly had an episode of epistaxis, and text messages received from him became progressively more bizarre.

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Physical Examination Findings

Upon evaluation by the ICU team, the patient was normotensive and tachycardic while receiving vasopressors, and his rectal temperature was 39.5°C. His oxygen saturation was 100% on volume assist control ventilation set to a tidal volume of 500 mL, respiratory rate of 16 breaths/min, F_{IO_2} of 70%, and positive end-expiratory pressure of 5 cm H_2O. The patient was an obese man sedated on the ventilator. There were no cutaneous lesions or scleral icterus. There was no lymphadenopathy or nuchal rigidity. Cardiopulmonary examination was unremarkable. The abdomen was benign, without organomegaly. There was no clubbing or edema. He was noted to have coffee-ground material in his nasogastric tube and to be bleeding from his arterial catheter site.

Diagnostic Studies

Initial laboratory values revealed a normal leukocyte count. His hemoglobin and hematocrit levels were 17.2 g/dL and 53.6%, respectively. The platelet count was 84,000. Chemistry values were remarkable for hyponatremia, hypokalemia, and hyperglycemia, with a creatinine level of 2.3 mg/dL and serum bicarbonate concentration of 13 mmol/L. The anion gap was 26. Initial venous blood gas results showed a pH of 7.26, with a lactate level of 13.2 mmol/L. There was a mild transaminitis: alanine aminotransferase, 90 U/L; aspartate aminotransferase, 179 U/L. Coagulation parameters were significant for a normal prothrombin time and prolonged activated partial thromboplastin time of 46.3 s. Urinalysis showed hyaline casts. Subsequent laboratory testing in the ICU demonstrated a drop in the platelet

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TABLE 1] Laboratory Data

Laboratory	Reference Range (Adults)	Admission	Day 3 (ICU) Before RRT	Day 6 (ICU) After RRT	Day 15 (Ward) Off MV	2 Wk After Discharge
WBC count, K/μL	4.5-11	7.7	3.3	9.2	9	6.5
Hemoglobin, g/dL	13.5-17.5	17.2	11.8	9.5	9.4	9.3
Hematocrit, %	41-53	53.6	35.5	26.5	26.8	28
Platelet count, K/μL	130-400	84	7	117	166	294
pH	7.32-7.42	7.25	7.28	7.65	7.36	…
Pco_2, mm Hg	38-50	32	29	23	38	…
Po_2 (Fio_2), mm Hg	30-50	34[a]	196 (70%)	81 (40%)	42 (40%)[a]	…
Lactate, mmol/L	0.5-2.2	13.2	2.4	4.3	0.9	…
Sodium, mEq/L	136-146	123	130	130	132	139
Potassium, mEq/L	3.5-5.3	3.3	4.7	3.1	5.6	4.5
Bicarbonate, mmol/L	23-32	13	16	24	18	20
BUN, mg/dL	8-22	24	57	52	92	14
Serum creatinine, mg/dL	0.4-1.6	2.3	7.1	6	6.7	2.3
Aspartate aminotransferase, U/L	5-40	179	17,435	1,212	219	18
Alanine aminotransferase, U/L	5-50	90	3,561	964	348	22
Lactate dehydrogenase, U/L	90-225		8,153	1,538	627	215
Total bilirubin, mg/dL	0-1.5	0.8	1.3	5.1	9.9	1
Conjugated bilirubin, mg/dL	0-0.3		0.8	3.4	4.8	0.4
Prothrombin time, s	10.3-12.6	12.5	20.2	15.6	…	11.7
International normalized ratio	…	1.1	1.8	1.4	…	1.0
Activated partial thromboplastin time, s	26-35	46.3	56.1	40.7	…	39.1
Fibrinogen, mg/dL	233-394	226	…	223	…	…

MV = mechanical ventilation; RRT = renal replacement therapy.
[a]Venous sample.

count to a nadir of 7,000, prolongation of both prothrombin time and activated partial thromboplastin time coupled with decreased fibrinogen, and worsening of renal function with persistence of metabolic acidosis despite rapid normalization of lactate level. Aspartate aminotransferase reached a maximum of 17,435 U/L accompanied by marked elevation in alanine aminotransferase and bilirubin. The patient's laboratory results are summarized in Table 1. Ultimately, blood and urine cultures revealed no growth. Evaluation of the peripheral smear for parasites was negative, as were rickettsial and leptospirosis serologies as well as blood polymerase chain reaction for *Neisseria* meningitidis. The chest radiograph showed clear lungs. Head CT scan was normal. Echocardiography showed normal ventricular and valvular function.

What is the diagnosis?

Diagnosis: Dengue hemorrhagic fever with toxic shock syndrome

Dengue, a single-stranded RNA flavivirus of which there are four serotypes, is responsible for a spectrum of clinical syndromes in humans ranging from mild to life-threatening. Usually acquired via the bite of the *Aedes* mosquito in endemic areas, dengue has been declared the most rapidly spreading mosquito-borne viral disease in the world by the World Health Organization. In the last half-century, the incidence of dengue has increased 30-fold, driven in large measure by urbanization and the evolution of travel and tourism. Although still a disease of the developing world, especially the Caribbean Basin, Southeast Asia, and Central and South America, dengue cases and outbreaks continue to be reported in the United States, mostly in the southern and western regions. Nevertheless, the vast majority of cases encountered in the continental United States have occurred in the context of travel to endemic countries. Of interest with respect to this patient, in 2007 Indonesia reported a record 150,000 cases of dengue.

Most dengue infections are believed to be subclinical, and the infected person acquires lifelong immunity to the infecting serotype. Symptomatic dengue becomes clinically manifest after an incubation period of 3 to 7 days and typically results in the classic constellation of "break-bone fever"—headache, rash, malaise, and body aches. Laboratory abnormalities in uncomplicated cases may be limited to leukopenia. The majority of symptomatic individuals experience steady improvement with conservative measures, such as antipyretics and oral hydration, and are, therefore, not hospitalized. The differential diagnosis includes viral, bacterial, and parasitic pathogens capable of similar presentations and depends on the region in which infection is believed to have occurred (Fig 1). Laboratory confirmation is important for epidemiologic purposes and may be especially valuable in regions not accustomed to patients infected with dengue. Reverse transcriptase polymerase chain reaction can be used to amplify viral RNA in an acute-phase serum specimen collected within 5 days of symptom onset. Likewise, enzyme-linked immunosorbent assay can detect dengue NS1 protein during the viremic phase. Alternatively, and more pragmatically, the diagnosis can be established by detecting dengue IgM antibodies by enzyme-linked immunosorbent assay in a convalescent-phase serum specimen collected at least 4 days after the onset of compatible symptoms.

During the febrile phase of symptomatic dengue infection, which typically lasts 2 to 7 days, the patient may exhibit warning signs of progression to severe disease characterized by increased capillary permeability and consequent distributive shock (dengue shock syndrome [DSS]), usually accompanied by serious bleeding complications (dengue hemorrhagic fever [DHF]). Among the clinical warning signs are hepatomegaly, alteration of consciousness, mucosal bleeding, and "third space" accumulation of fluid. Concurrent elevation of hematocrit and fall in platelet count at this juncture is an ominous finding that reflects hemoconcentration and a predisposition to bleeding, respectively. A positive tourniquet test, whereby numerous petechiae appear after a sphygmomanometer cuff is inflated on the arm and then released, raises the index of suspicion for incipient DHF. The moment of defervescence marks the onset of the critical phase, which lasts 24 to 48 h and may be characterized by transition to recovery or progression to DHF/DSS. Patients with warning signs are often hospitalized for close observation, supportive care, and IV hydration. Even with early and appropriate intervention, the course taken by a particular patient depends on both host and viral characteristics; higher risk for progression is conferred by female sex, young age, high BMI, and certain dengue strains. The severe trajectory is also more likely in those who have been previously infected with a different serotype in a phenomenon blamed on incomplete immunity that, although not protective, facilitates viral entry and spread, thereby enhancing the inflammatory cascade. Rather than direct viral toxicity, the pathogenesis of DHF/DSS is believed to involve virally mediated cytokine activation leading to endothelial dysfunction and permeability. The resultant clinical entity behaves in a manner reminiscent of septic shock with disseminated intravascular coagulation. Patients may initially compensate and manifest a narrowed pulse pressure without overt hypotension. Further deterioration, however, results in refractory hypotension with multiorgan dysfunction syndrome complicated by GI or other life-threatening hemorrhage in the context of consumptive coagulopathy and severe thrombocytopenia. Inability to protect the airway due to profound encephalopathy frequently mandates endotracheal intubation. The presence of pulmonary edema may reflect overzealous fluid administration in the setting of a porous endothelium, viral myocarditis causing left ventricular systolic dysfunction, or noncardiogenic fluid as part of ARDS.

The management of the patient with DHF/DSS is entirely supportive, since no specific therapy for the

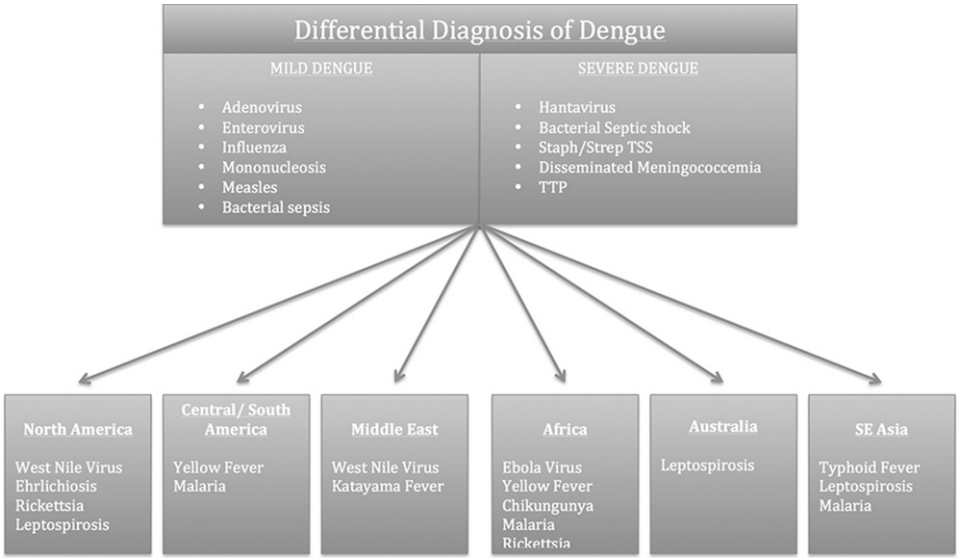

Figure 1 – *Differential diagnosis of dengue infection. The list includes clinical entities to be considered irrespective of the patient's region of exposure as well as infections to be added to the differential diagnosis based on geography (arrows). TSS = toxic shock syndrome. TTP = thrombotic thrombocytopenic purpura.*

dengue virus currently exists. The most severe cases warrant transfer to the ICU in an effort to provide organ support while awaiting the onset of recovery. Timely recognition of those at risk for deterioration has enabled many countries in which dengue is endemic to reduce the overall case fatality rate to < 1%. The mainstay of therapy for patients with evidence of hypoperfusion with or without hypotension is resuscitation with IV isotonic crystalloid. Close monitoring of vital signs, perfusion parameters, and serum hematocrit is essential to avoiding both inadequate fluid administration and the deleterious effects of volume overload. Clinicians should always be on alert for concomitant hemorrhagic shock even in the absence of overt bleeding and be prepared to begin packed RBC transfusions in patients who are hypoperfused without initial hematocrit elevation and in those whose hematocrit falls out of proportion to the hemodilutional effects of crystalloid. Institutional massive transfusion protocols may need to be invoked, which often call for concurrent administration of fresh frozen plasma and platelets. It is important to recognize that in the setting of increased capillary permeability, the associated elevation of serum hematocrit may complicate recognition of occult bleeding and thus delay vital transfusions. In DHF/DSS, serum hematocrit plays an important role as both an indicator of increased capillary permeability if initially elevated and a therapeutic target in the management algorithm. In addition to fluid and blood product administration, the intensive care of the patient with DHF/DSS may involve renal replacement therapy, initiation of vasopressors, and ultimately reversal of inadvertent volume overload.

Clinical Course

This patient's dengue virus antibodies of both IgM and IgG class were positive, thus establishing the diagnosis. The patient's hypoxemia rapidly resolved following initiation of mechanical ventilation. In the course of his ICU stay, the patient required numerous transfusions and renal replacement therapy for acute tubular necrosis. He was eventually weaned off vasopressors and extubated on ICU day 7. Platelet count, coagulation parameters, and transaminases normalized. Recovery of kidney function led to the discontinuation of renal replacement therapy. He was transferred from the ICU and ultimately discharged home from the hospital.

Clinical Pearls

1. *Dengue virus clinical syndromes run the gamut from a self-limited febrile illness to life-threatening shock and hemorrhage.*
2. *The possibility of dengue toxic shock syndrome should be entertained in recent arrivals from endemic areas presenting with distributive shock, especially if complicated by bleeding and thrombocytopenia.*
3. *Early recognition of increased capillary permeability is crucial in suspected dengue infection.*
4. *The role of the ICU in the management of severe dengue includes optimization of circulating volume,*

close monitoring of perfusion parameters, judicious blood transfusions, and provision of organ support.

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Suggested Readings

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