SAGE Open Medical Case Reports
Volume 11: 1–6

DOI: 10.1177/2050313X231220808
journals.sagepub.com/home/sco
Sage

Fatal outcome of dengue fever with multi-organ failure and hemorrhage: A case report

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Abstract

Dengue fever is a prevalent viral disease caused by a single-stranded positive RNA virus belonging to the Flaviviridae family, genus flavivirus. It is characterized by fever, headache, myalgias, leukopenia, rash, and plasma leakage, which may progress to compensated or uncompensated shock and multi-organ failure. Liver involvement is a common feature of Dengue fever and is usually manifested by nausea, vomiting, abdominal discomfort, anorexia, hepatomegaly, and elevated serum transaminase levels. Severe disease is associated with laboratory parameters such as mean Platelet count $<$ 20,000/mm, Aspartate Transaminase Levels $>$45 IU, and lymphocytes $<$1500. The Expanded Dengue Syndrome (EDS), a term coined by World Health Organization in 2012, refers to an atypical presentation of Dengue fever that manifests with generalized impacts on normal physiology. This case report presents a 29-year-old male with EDS who presented at a Tertiary Care Hospital in Karachi and died a week later due to liver failure.

Keywords

Dengue fever, multi-organ failure, hemorrhage, fulminant liver failure, acalculous cholecystitis, lymphadenopathy, hepatomegaly

Date received: 22 June 2023; accepted: 23 November 2023

Introduction

Dengue fever is a viral disease that has been a significant public health problem globally for several decades. The condition stems from a single-stranded positive RNA virus belonging to the family Flaviviridae, genus flavivirus. The Dengue virus has four identified serotypes labeled DENV-1, DENV-2, DENV-3, and DENV-4 and is transmitted by the vector, female Aedes Mosquito, mainly Aedes aegypti and Aedes albopictus.[1] It is now endemic in over a hundred countries, including The Americas, South-East Asia, and Western Pacific regions.[2]

Dengue virus has an incubation period of 3–7 days, followed by symptoms that can appear in three distinct phases; a febrile phase (2–7 days and persists throughout the illness), a critical phase (3–7 days when the disease may disseminate and involve different organ systems), and finally the convalescent, or recovery phase.[3]

The disease is characterized by fever along with two of the following associated symptoms; (1) headache, (2) myalgias, (3) leukopenia, and (4) rash.[3] Dengue hemorrhagic fever (DHF) is among the clinically complicated pictures which may present with a severe fever, hemorrhage with or without hepatosplenomegaly, and occasionally circulatory failure.[1] Dengue Shock Syndrome (DSS) is another variant characterized by hypotension and accompanying chills and agitation.[4] The term Expanded Dengue Syndrome (EDS) was coined by WHO in 2012 when the clinical presentation became vague and showed generalized impacts on normal physiology, which could not be confined to a specific clinical spectrum.[5] Dengue fever has three phases: febrile, critical, and recovery. The febrile phase lasts 2–7 days and includes high fever, headache, retro-orbital pain, myalgia, and arthralgia. The critical phase, lasting 24–48 h, has increased vascular permeability, plasma leakage, and warning signs such as

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abdominal pain, vomiting, and mucosal bleeding. Severe cases may progress to DSS or DHF. The recovery phase involves fluid reabsorption, diuresis, and convalescence. Fatigue and malaise may persist for several weeks after recovery.[6] Liver involvement is among the mainstay features of DF.[3] Dengue virus blunts physiologic hepatic functioning by diverse mechanisms involving direct disruption of hepatocytes and Kupffer cell function and indirectly by immune system impairment via a cytokine surge mediated by t-cells and circulatory failure causing ischemic liver injury.[7] Liver injury in DF is usually manifested by nausea, vomiting, abdominal discomfort, and anorexia concurrent with the findings of hepatomegaly and elevated serum transaminase levels.[8]

A recent DF outbreak occurred in Pakistan from January 1st to September 27th, 2022, with around 25,932 people being afflicted and 62 deaths reported by the National Institute of Health in Islamabad.[9]

Case presentation

A 29-year-old Pakistani male was presented to the Emergency Department of a Tertiary Care Hospital in Karachi on October 19th, 2022, with an altered level of consciousness for 1 day and a history of fever, vomiting, and abdominal pain for the past 5 days.

On history, the fever was high grade with chills and rigors. The pain was aching, localized to right hypochondrium, aggravated with vomiting, and did not relieve with paracetamol. He then gradually developed an altered loss of consciousness and speech impairment which progressively worsened. The patient was admitted to another hospital for 4 days before being referred to the current setup after noticing behavioral alterations. Anti-HBs test, Anti-HAV IgM, and Anti-HEV IgM showed that Hepatitis A, B, and E infections were negative.

On the third day of illness, a Panbio Dengue immunochromatography assay, and an immunochromatographic test for Malaria were utilized, and both yielded a negative result. A chest X-ray was also performed as shown in Figure 1.

Upon receiving the patient in the emergency department, pulse and blood pressure were recorded as 63 beats/min and 94/50 mmHg. He was physically assaulting family and staff members alike, along with displaying resistance to therapeutic care by removing cannulas and nasogastric tubes and to taking medicine. On evaluation by the Psychiatry Department, he was under the impression of delirium. The laboratory investigations are reported in Table 1, which evidently reports deranged Liver Function values. The patient was injected with 1 l of Ringer's lactate to stabilize his vitals and was then advised admission to the Medical High-dependency care Unit (HDU).

The patient was received in Medical HDU, not oriented. The abdomen was examined to be flat, with the lower edge of the liver palpable 1 cm below the costal margin with moderate tenderness in the right hypochondrium, no splenomegaly was appreciated, however, with signs of free fluid present with positive shifting dullness. Pupils were found to be equally reactive to light bilaterally.

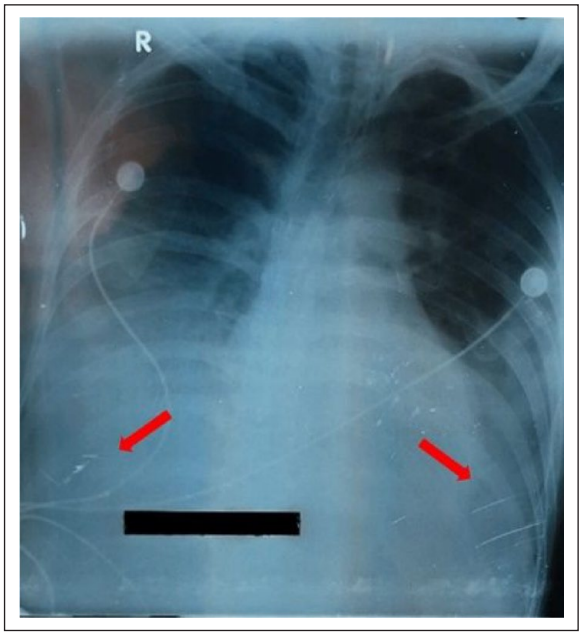

Figure 1. Chest X-ray on the third day of illness showing bilateral pleural effusion.

The patient was shifted to Medical Intensive Care Unit (ICU) on the sixth day of illness and was being treated along the lines of Fulminant Liver Failure. The progressive fluctuations in hemoglobin levels, Total Leukocyte count, Platelet count, and electrolyte levels since before and during admission to the ICU are tabulated in Table 1.

The patient was subjected to the treatment regimen, which included Meropenem 1 gm IV × TDS, Omeprazole 40 mg IV × OD, N-acetylcysteine 150 mg/kg in five divided doses, loading dose of 150 mg/kg in 100 ml 5% dextrose water over 15 min with the maintenance dose of 12.5 mg/kg/h over 4 h and third dose of 6.25 mg/kg/h over 16 h, Mannitol 200 ml IV stat then 100 ml IV × OD (3 days) and Syrup Lactulose 30 ml BD.

On the eighth day of illness, a Dengue IgM Antibody test was performed on the patient, which yielded a positive result. The test was conducted using the Calbiotech Inc. (Catalog No. DE051M) ELISA test system, an enzyme-linked immunosorbent assay designed to detect IgM antibodies to Dengue virus in human serum or plasma.

An ultrasound of the entire abdomen was also performed with the following findings:

- The liver, pancreas, spleen, and kidneys were normal in size.
- The gallbladder wall was appreciated to be thick and hypoechoic, measuring 1.0 cm, with no masses or calculi apprehended. The common bile duct was found to be 0.4 cm in diameter, and the findings were indicative of acute acalculous cholecystitis.

Table 1. Lab reports of the patient before and after hospital admission.

	Reference values	10/17/12	10/19/22	10/20/22	10/21/22	10/22/22	10/23/22	10/24/22	10/25/22	10/26/22	10/27/22
Parameters											
Hematologic tests and coagulation profile											
Hb (G/dl)	13.5–17.5 (male)/12.0–15.5 (female)	14.9	14.5	13.5	11.5	11.3	7.3	5.9	8.0	7.8	6.9
RBC count (million/mm^3)	4.5–5.5 (male)/4.0–5.0 (female)	5.31	5.00	4.80	4.00	4.00	2.00	2.10	2.80	2.70	2.40
HCT (%)	38.8–50.0 (male)/34.9–44.5 (female)	40.7	39.50	37.00	30.90	31.10	16.10	17.10	22.40	21.90	20.70
MCV (fl)	80–96	76.6	78.7	77.9	76.9	77.2	79.3	80.7	80.0	80.5	86.3
MCH (Pg)	27–31	28.1	27.9	28.4	28.6	28.0	26.6	27.8	28.6	28.7	28.8
MCHC (Gm/dl)	32–36	36.6	35.4	36.5	37.2	36.3	33.5	34.5	35.7	35.6	33.3
TLC (10^3/ul)	4.0–11.0	55	16.1	11.3	9.7	5.8	6.5	4.9	7.1	5.5	2.2
Neutrophils (%)	40–75	70	55	66	60	63	82	82	87	74	66
Lymphocytes (%)	20–45	26	19	15	21	27	12	10	11	14	19
Basophils (%)	0.5–1.0	2	—	0	0	0	0	0	0	0	0
Platelets (10^3/ul)	150–400	329	74	53	48	40	45	57	69	110	154
RDW- SD (fl)	35–45	—	36.9	37.7	38.8	40.0	40.4	46.9	45.5	48.1	52.8
MPV (fl)	7.5–11.5	—	—	10.8	—	—	12.9	—	—	11.6	10.9
RDW-CV (%)	11.5–14.5	—	12.0	12.7	13.0	13.4	13.9	16.1	15.6	16.4	17.0
PT (seconds)	11–13	—	22.8	22.8	20.2	50.7	18	13.4	24.1	>120	11.3
INR	0.8–1.2	—	2.21	2.21	1.95	1.95	1.73	1.28	2.33	—	1.08
APTT (seconds)	28–40	—	—	—	50.7	20.2	39.7	37.3	—	>120	—
Biochemistry values											
pH (mmHg)	7.35–7.45	—	—	7.475	—	7.49	7.42	7.429	—	7.379	7.214
pCO2 (mmHg)	35–45	—	—	30.0	—	25.8	26.6	46.0	—	43.0	63.9
HCO3 (mmHg)	22–26	—	—	24.2	—	22.3	19.1	29.5	—	24.7	22.0
CRP (mg/dl)	<0.5	—	—	14.5	14.5	—	38.9	—	72.6	72.7	66.4
BUN (mg/dl)	7–20	29	18	12	11	12	—	31	38	59	69
Creatinine (1.6mg/dl)	0.6–1.3	1.1	1.0	0.8	1.0	1.0	0.7	2.2	2.9	2.8	2.9
Electrolytes											
Na+ (mEq/l)	135–145	136	131	126	125	124	118	119	123	129	136
K+ (mEq/l)	3.5–5.0	4.3	4.2	3.7	3.9	3.6	3.6	3.6	4.1	4.3	5.3
Cl− (mEq/l)	95–105	98	97	95	90	88	81	83	88	93	98
Ca+2 (mg/dl)	8.5–10.5	—	—	7.3	7.3	6.5	6.4	6.5	6.8	6.8	—
Mg+2 (mg/dl)	1.7–2.4	—	—	2.1	1.9	1.7	2.4	2.9	3.0	3.1	—
Phosphorus (mg/dl)	2.5–4.5	—	—	0.7	0.6	0.9	1.5	1.6	2.5	3.1	—
Liver function tests											
Total bilirubin (mg/dl)	0.1–1.2	3.0	7.3	8.1	8.5	8.5	104	11.2	12.6	11.6	9.8
SGPT (U/l)	0–40	4301	2899	2326	1611	1321	898	656	606	462	268
ALP (U/l)	40–130	243	358	358	290	290	268	223	266	315	270
Protein A/G ratio											
Total Protein (G/dl)	6.0–8.3	—	—	—	5.9	—	—	5.1	—	—	—
Albumin (G/dl)	3.5–5.0	—	—	—	3.0	—	—	2.6	—	—	—
Globulin (G/dl)	2.3–3.5	—	—	—	2.9	—	—	2.5	—	—	—
A/G Ratio	1.2–2.2	—	—	—	1.02	—	—	1.04	—	—	—

A/G: albumin/globulin; ALP: alkaline phosphatase; aPTT: activated partial thromboplastin time; BUN: blood urea nitrogen; CA: calcium; CL: chloride; CRP: C reactive protein; fl: Femtoliter; G/dl: Grams per deciliter; hb: hemoglobin; hco3: bicarbonate; HCT: hematocrit; INR: international normalized ratio; K: potassium; LC: total leucocyte count; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; TMCV: mean corpuscular volume; mEq/l: milliequivalent per liter; mg/dl: milligrams per deciliter; Mg: magnesium; mmHg: millimeters of mercury; MPV: mean platelet volume; NA: sodium; Pco2: partial pressure of carbon dioxide; pg: Picograms; pH: potential hydrogen; PT: prothrombin time; RBC: red blood cell; RDW: SD red cell distribution width-standard deviation; RDW-CV: red cell distribution width-Coefficiant of variation; SGPT: serum glutamic pyruvic transaminase; U/l: units per liter; ul: microliter.

- Gross ascites were evident, along with bilateral gross pleural effusions secondary to lung collapse.

The patient became tachypneic and tachycardic with a drop in Glasgow Coma Scale due to which the patient was electively intubated on the seventh day.[10] The patient gradually developed scrotal swelling, which was evaluated by the Urology Department on the 12th day of illness. The department commented on the patient having generalized body swelling which predisposed to scrotal swelling. The patient was currently on a mechanical ventilator and required only scrotal support and elevation for relief. He also developed an abnormal breathing rhythm which was found secondary to blockage of the endotracheal tube with blood clots signifying massive internal hemorrhage. Four packs of Fresh Frozen Plasma, six packs of platelets, and one bag of Packed Cell Volume were transfused to combat the deteriorating hemodynamics of the patient. The patient succumbed to the disease at 10:18 A.M. on the thirteenth day due to hemorrhage secondary to multi-organ failure, as a complication of Dengue fever.

Discussion

Dengue virus is an enveloped RNA virus belonging to the Flaviviridae family, causing infections in tropical and subtropical regions with numbers surmounting to 50 million annual infections. Seventy percent of the population liable to infection is located in Southeast Asia and the Western Pacific.[11] Four different serotypes of the virus have been reported (DENV 1–4), implicating a more serious reinfection when caused by a different serotype.[12,13]

Dengue fever may clinically manifest across four categories, as classified by WHO.

(1) Uncomplicated Dengue fever which is characterized by typical viral features of pyrexia with no complications.

(2) High-grade Dengue fever that is associated with body aches and classifies as the typical "breakbone fever" of Dengue.

(3) Typical Dengue fever complicated by bleeding diathesis and may fall under two categories—DHF without shock and DSS; and

(4) EDS which encompasses multiple organ systems and a plethora of clinical manifestations.[14]

Liver involvement is among the most common complication of Dengue fever; nevertheless, a retrospective study by Kulkarni et al. revealed that only 0.3%–1.1% of the population developed acute liver failure while elevated aspartate transaminase and alanine transaminase were documented in 63%–97% and 45%–96% of the afflicted.[3,15] This signifies that while a modest degree of liver involvement may be noticed in most infected patients, only a few develop life-threatening complications.

A spectrum of atypical organ involvement may occur in EDS that has been reported in various cases and merit discussion. Concurrent intracerebral hemorrhage and subacute thyroiditis were reported in a 20-year-old male in Punjab, Pakistan, in 2011.[16] Characterized by alteration in the mental status and headaches, intracerebral hemorrhage is a well-known yet rare finding in Dengue fever. It may be further complicated if hemorrhage occurs in the pituitary gland, causing pituitary apoplexy, reported in two patients by Wildemberg et al.[17,18] Acute Kidney Injury, and more commonly, gastro-hepatic involvement and acute pancreatitis have also been reported as complications of EDS. A case report highlighting these derangements in a 6-year-old Tamil female has been published by Thadchanamoorthy et al.,[19] elaborating on the prodigious complications that Dengue virus could impose. Apart from intracerebral bleeding, neurological complications such as seizures, altered mental and behavioral features, spinal involvement, and headaches also encompass 0.5%–20% of all cases, with total systemic complication rates surpassing less than 1%.[20] A case report published by Kaushik et al.[21] highlights such a case in a 48-year-old female in India, where DF was complicated by spinal intradural hemorrhage. Recent studies have also revealed noticeable myocardial involvement in patients with Dengue fever. A considerable number of patients with DF have been reported by Wali et al.[22] to present with concurrently reduced Left Ventricular contractility and an Ejection Fraction of less than 40%. Patients have also been discovered on autopsy to be suffering from subclinical myocarditis in the clinical setting of DF.[23]

The end-organ failure that features EDS is the culmination of Dengue shock predisposed by extreme internal exsanguination.[24] A similar phenomenon can be noticed in the case presented above, where internal blood loss led to EDS and ultimately the death of the patient. Despite blood transfusions, the ensuing effects of tissue hypoxia could not be reversed, hence emphasizing the importance of timely blood restoration and prevention of massive hemorrhage. The importance of timely fluid resuscitation and blood transfusion, along with scrutinized monitoring for end-organ damage and deteriorating functionality of the patient, can be reiterated in this case.

Gautam et al. present a similar case in which a 22-year-old male presented to the emergency department with high-grade fever, vomiting, abdominal pain, yellowish skin discoloration, and neurological symptoms. Despite initial management with fluid therapy and inotropic support, the patient's condition deteriorated. He was diagnosed with acute liver failure, renal injury, thrombocytopenia, coagulopathy, and pulmonary hemorrhage. Dengue infection was confirmed, and despite efforts to control bleeding and organ dysfunction, the patient succumbed to respiratory failure on

the 6th day of hospitalization.[25] Ralapanawa et al. published a case report about a 17-year-old healthy male who had contracted Dengue fever. The patient was initially stabilized in the ICU for suspected DHF, but later experienced severe hemoptysis, respiratory distress, and a drop in oxygen saturation. Despite intubation, the patient's condition rapidly deteriorated and his blood pressure became unrecordable. Emergency investigations revealed significant hemorrhage, leading to the patient's demise from extensive pulmonary hemorrhage.[26]

Conclusions

Our case emphasizes the lethality of Dengue fever and its complications when the case is brought into clinical attention once hepatic encephalopathy has developed. Infection by Dengue virus was proven practically days after signs and symptoms developed, which was a significant contributory factor toward the poor outcome in this patient. Fulminant Hepatic Failure ensued with significant capillary leak and overt bleeding which manifested acutely before the patient expired.

Acknowledgements

The authors are very appreciative to the patient for the opportunity to learn as well as thankful to the hospital for providing support for completing this report.

Author contribution

H.U. and R.W. Substantial contributions to the conception or design of the work. Drafting the work or revising it critically for important intellectual content N.K., M. S. H., and H. H. S. Drafting the work or revising it critically for important intellectual content. Final approval of the version to be published.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written Informed Consent was obtained from the legally authorized representative of the deceased subject for the publication of this case report.

Provenance and peer review

Not commissioned, externally peer reviewed.

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