

# Different Presentations of Expanded Dengue Syndrome: A Case Series and Review of Literature

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## ABSTRACT

Expanded dengue syndrome (EDS) is an atypical presentation of dengue fever with the involvement of various organ systems. We present five cases of EDS with varying features. The first and second patients had concurrent infection with falciparum malaria and vivax malaria, respectively, which made the diagnosis and treatment challenging. The third patient had coinfection with scrub typhus. The fourth patient was diagnosed with long-segment myelitis of the brain stem. The final patient in this series had a rare presentation consistent with post dengue hemophagocytic lymphohistocytosis (secondary HLH). There is no direct correlation between the severity of dengue and the type of organ involvement, and even without the classical features of dengue, serious complications can arise. In conclusion, it is of utmost importance to have a high index of suspicion and be well-informed of the different presentations and coinfections associated with EDS.

**Keywords:** Acute kidney injury, Acute respiratory distress syndrome, Coagulopathy, Hemophagocytic lymphohistocytosis, Hypoxia, Myocarditis, Transverse myelitis.

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## BACKGROUND

Dengue is the most rapidly spreading mosquito-borne viral disease in the world, which is caused by a flavivirus known as dengue virus (DEN). It is a small single-stranded RNA virus comprising of four distinct serotypes (DEN 1–4), which is transmitted by Aedes mosquitoes. In 2003, eight countries including Bangladesh, India, and Sri Lanka reported dengue cases. Today, it is endemic in over 100 countries with a higher prevalence in Southeast Asia. Nearly 400 million cases of dengue are reported annually at present. “Asian” genotypes of DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections.

The classical presentation in dengue is fever and thrombocytopenia. In 1997, the World Health Organization (WHO) classified dengue into undifferentiated fever, dengue fever, and dengue hemorrhagic fever.<sup>1,2</sup> Dengue hemorrhagic fever was subdivided further into grades I–IV. Grade I is the presence only of easy bruising or a positive tourniquet test in someone with fever, grade II is the presence of spontaneous bleeding into the skin and elsewhere, grade III is the clinical evidence of shock, and grade IV is a shock so severe that blood pressure (BP) and pulse cannot be detected.<sup>2</sup> Grades III and IV are referred to as “dengue shock syndrome”. In 2009, WHO classified dengue fever into two groups: uncomplicated and severe.<sup>3</sup> Severe dengue is defined as that associated with severe bleeding, severe organ dysfunction, or severe plasma leakage while all other cases are uncomplicated.

More recently, the presentation of dengue fever has been varied with the involvement of several organ systems. This kind of atypical presentation and concurrent coinfections make the diagnosis and the treatment challenging. Therefore, WHO, in 2012, introduced a new term known as expanded dengue syndrome (EDS).<sup>2</sup> In this article, we describe our experience of unusual or atypical manifestations of dengue along with a review of relevant literature.

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## MATERIALS AND METHODS

### Patients Review

Between July 2019 and December 2019 (6 months), we performed a retrospective analysis of all serologically confirmed cases of EDS as per WHO definition criteria, who were admitted to the Medica Superspecialty Hospital, Kolkata. All cases of classical dengue fever, dengue hemorrhagic fever, and dengue shock syndrome without any atypical features were excluded from this study. Clinical, laboratory, and relevant radiological reports were collected and analyzed. Treatment details and outcomes were duly recorded.

## Literature Review

The review of literature was performed using the PUBMED and GOOGLE SCHOLAR search of the keywords “dengue”, and “atypical” or “rare” or “unusual”, as well as “expanded dengue” in the abstract or title of the article. All relevant articles were screened and the reviewed literature was discussed in the present article.

## CASE DESCRIPTIONS AND RESULTS

Five patients with EDS were identified and hospitalized during the study period. All of the patients had confirmed positive immunoglobulin (Ig)M for dengue. A summary of each case is detailed below.

### Case 1

A 14-year-old woman without known comorbidities was admitted to an outside hospital with intermittent high-grade fever, hematemesis, and bloody diarrhea for 3 days. Initially, she was found to have falciparum malaria and started on intravenous (IV) cefixime, artemether (80 mg), and lumefantrine (480 mg). She was transferred here due to persistent fever, abdominal pain, and hypotension on November 11, 2019. On admission, she was drowsy and febrile. Her vitals were as follows: body weight 77.7 kg, BP 100/70 mm Hg, pulse 120/minute, respiratory rate (RR) 20/minute, and SpO<sub>2</sub> 90% on room air. Pallor was present, although there was no active bleeding at presentation. On the systemic examination, her abdomen was soft but tender. Other systemic findings were within the normal limit.

She was started on IV meropenem and injectable antimalarial chemotherapy along with other supportive medications. The significant investigation results included total leukocyte count (TLC) 28000/mm<sup>3</sup>, hemoglobin (Hb) 10.2 g/dL, platelet count 40000/mm<sup>3</sup>, creatinine 3.13 g/dL, sodium (Na) 128 mEq/L, serum glutamic oxaloacetic transaminase (SGOT) 4694 U/L, serum glutamic pyruvic transaminase (SGPT) 1070 U/L, lipase 2155 U/L, international normalized ratio (INR) 2.57, and D-dimer >10,000. Serological testing confirmed falciparum antigen (Ag) positive, dengue NS1 Ag reactive, and dengue IgM reactive. She was electively intubated in view of impending respiratory failure. She continued to require multiple blood product transfusions due to coagulopathy and ongoing bleeding and also required hemodialysis because of severe metabolic acidosis and subsequent anuria. Despite maximum supportive care, she eventually succumbed to her illness on November 11, 2019.

### Case 2

A 66-year-old man with hypertension and chronic kidney disease (CKD) presented with low-grade intermittent fever with chills and rigor, dry cough, and 3–4 episodes of vomiting for 10 days on October 22, 2019. On examination, he was febrile. His BP was 140/90 mm Hg, pulse 88/minute, RR 16/minute, SpO<sub>2</sub> 99% on room air. On systemic examination, he had decreased bilateral vesicular breath sounds and bilateral rhonchi. Other systemic findings were noncontributory. He was started on IV ceftriaxone, oral doxycycline, and other supportive medications.

On investigation, TLC was 4200/mm<sup>3</sup> (neutrophil 77%, lymphocyte 14%), Hb 12.1 g/dL, platelet 110000/mm<sup>3</sup>, creatinine 2.08 g/dL, SGOT 28 U/L, SGPT 16 U/L, and INR 1.16. Dengue IgM was reactive. Despite therapy, he continued to have intermittent low-grade fever. On October 23, 2019, he had hemoptysis and melena. Further blood reports showed a platelet count of 60000/mm<sup>3</sup>,

with peripheral smear growing trophozoites and ring form of *Plasmodium vivax*. MP-Dual Ag for *P. vivax* was positive. Chloroquine was started and he was shifted to the high-dependency unit for further monitoring. His general condition and blood parameters gradually improved. He was discharged in afebrile, stable condition on October 26, 2019.

### Case 3

A 20-year-old man without known comorbidities presented with high-grade intermittent fever for 12 days along with facial puffiness and shortness of breath for 4 days. Initially he was admitted to a local hospital and was treated with IV ceftriaxone and oral ciprofloxacin. As the fever was persistent and he developed shortness of breath, he was shifted to our hospital for further management on October 09, 2019. On examination, he was febrile with a BP of 100/70 mm Hg, pulse 114/minute, RR 38/minute, and SpO<sub>2</sub> 97% on room air. Pallor was present, along with right inguinal lymphadenopathy and a single erythematous erosive lesion over the right thigh. Other systems were found to be normal.

He was started on IV meropenem, oral doxycycline, and other supportive medications. Significant investigation reports were as follows: TLC 8640/mm<sup>3</sup> (N 55%, L 41%), Hb 10.9 g/dL, platelet 95000/mm<sup>3</sup>, C-reactive protein (CRP) 207 mg/L, SGOT 244 U/L, SGPT 184 U/L, total bilirubin 3.3 mg/dL, albumin 2.2 g/dL, and creatinine 1.47 g/dL. Urine routine examination revealed + proteinuria. Ultrasound whole abdomen showed mild hepatosplenomegaly, bilateral mild pleural effusion with reactive periportal, and peripancreatic lymph nodes. Echocardiography revealed mild generalized wall hypokinesia with a small pericardial effusion and an ejection fraction of 50%. Further investigations showed a reactive dengue IgM as well as a reactive scrub typhus IgM. He responded well to medical management and blood parameters improved (TLC 7300/mm<sup>3</sup>, Hb 13.2 g/dL, and platelet 157000/mm<sup>3</sup>). He was discharged in a hemodynamically stable and afebrile condition on October 14, 2019.

### Case 4

A 39-year-old man, without any known comorbidities, was admitted with complaints of acute onset rapidly progressive weakness of both lower limbs for 1 week along with overflow urinary incontinence, slurring of speech, and dysphagia for 3 days. He had a preceding history of fever. On examination, he was afebrile with the following vitals: BP 102/72 mm Hg, pulse 64/minute, RR 18/minute, and SpO<sub>2</sub> 97% on room air. Central nervous system (CNS) examination revealed a Glasgow coma scale score of 15/15 with hoarse speech, neck rigidity, bilateral ptosis (right > left), and mild restriction of abduction of the left eye. Lower limb examination revealed bilateral complete loss of power (0/5) with loss of all sensory modalities. Upper limb examination was normal on both sides.

Magnetic resonance imaging of the brain and cervical spine showed long-segment myelitis with the involvement of the brain stem. Cerebrospinal fluid (CSF) study showed lymphocytic pleocytosis (Cell count 18/μL, L 95%), glucose 80 mg/dL, protein 64 mg/dL, and adenosine deaminase 5.4 IU/L. CSF for anti-neuromyelitis optica (anti-NMO) IgG, tuberculosis polymerase chain reaction (TB-PCR), and herpes simplex virus PCR (1 and 2) were found to be negative. Blood for dengue IgM was reactive. He was started on IV methylprednisolone. As there was no motor improvement after 5 days of IV methylprednisolone, IV Ig therapy was planned.

Due to financial constraints, the patient's family did not give consent for IVIg therapy. He was discharged on July 29, 2019.

**Case 5**

A 27-year-old man without any known comorbidity was admitted on September 06, 2019, with intermittent high-grade fever with severe headache and body ache for 5 days. Dengue NS1 Ag was reactive. On examination, he was afebrile with BP 102/72 mm Hg, pulse 64/minute, RR 18/minute, and SpO<sub>2</sub> 97% on room air. All other systemic findings were normal. He was conservatively managed with IV fluid therapy, antipyretics, and other supportive medications. Blood reports showed Hb 14.1 g/dL, platelet 140000/mm<sup>3</sup>, TLC 2000/mm<sup>3</sup> (N 59%, L 36%), CRP 9 mg/L, SGOT 409 U/L, SGPT 156 U/L, dengue IgM, and IgG reactive.

He continued to have a daily high-grade fever without any obvious source of infection, and further blood reports showed persistent thrombocytopenia with normal inflammatory markers. Postdengue hemophagocytic lymphohistocytosis (secondary HLH) was suspected. Further investigation showed Hb 16.4 g/dL, platelet 22000/mm<sup>3</sup>, TLC 6600/mm<sup>3</sup> (N 45%, L 38%), CRP 13 mg/L, SGOT 1907 U/L, SGPT 445 U/L, ferritin >25000 ng/mL, and lactate dehydrogenase 2644 U/L. Hematology opinion was taken, and IV dexamethasone was started in view of HLH. Gradually he became afebrile; blood parameters including complete hemogram and liver function test started improving. He was discharged on September 14, 2019, in afebrile hemodynamically stable condition. After discharge, the dose of steroid was gradually tapered off during follow-up and now he was doing well (Table 1).

**DISCUSSION**

Expanded dengue is a terminology developed in the WHO guidelines of the year 2012 to describe cases that do not fall into either dengue shock syndrome or dengue hemorrhagic fever. These patients present with unusual manifestations due to severe organ involvement, such as the liver, kidneys, CNS, or heart. The pathogenesis of different organ involvements in dengue is shown in Figure 1.<sup>4</sup>

**Gastrointestinal/Hepatic Manifestations**

The most commonly documented feature has been reported to be asymptomatic transaminitis, followed by acute cholecystitis (often acalculous). This is probably due to hypoxic or immunological injury.<sup>5,6</sup> Patients may also present with acute pancreatitis.<sup>7</sup> In our

case series, our first patient presented with severe transaminitis and upper gastrointestinal (GI) bleeding along with other features of dengue hemorrhagic fever. Patient 3 also presented with transaminitis, hyperbilirubinemia, and hypoalbuminemia along with hepatosplenomegaly on imaging. He responded well to treatment and his liver functions normalized at discharge. Patient 5 had transaminitis along with HLH, which responded to corticosteroids. Although the presence of transaminitis and hyperbilirubinemia is a potential risk factor for acute liver failure, none of our patients developed this dreaded complication. Upper GI bleeding is a relatively rare manifestation associated with dengue hemorrhagic fever.

**Renal Manifestations**

Acute kidney injury (AKI) may be due to immunological cause or direct injury from the dengue virus. Other uncommon presentations may include hemolytic uremic syndrome, proteinuria, or nephrotic syndrome. AKI in dengue is associated with higher morbidity and mortality. Our first patient developed AKI secondary to hemorrhagic shock requiring hemodialysis and eventually expired. Our third patient also developed mild AKI with proteinuria, but responded to supportive care and did not require renal replacement therapy. Other causes of AKI may be hypotension or rhabdomyolysis.

**Brain/CNS Manifestations**

Both central and peripheral nervous systems may be involved in EDS. However, it is less common with an incidence of 1–5%. The possible clinical pictures include stroke, paralysis, encephalitis, meningitis, seizures, neuropathies, Guillain Barre syndrome, and Miller Fischer syndrome. The term dengue encephalitis is defined as dengue with CNS manifestations in the presence of dengue RNA, IgM, or NS1 Ag in CSF with no other pathogens. One of the rare neurological features of dengue is acute transverse myelitis. In our series, patient 4 presented with acute transverse myelitis, which did not respond to corticosteroid therapy. IV Ig was planned but could not be administered due to financial constraints. Few case reports have documented well the success of steroids and immunoglobulins in the treatment of transverse myelitis in dengue fever. Although the exact mechanism of neurological injury in dengue is unknown, likely causes are neutropenia and immunological effector direct invasion by the dengue virus.

**Table 1:** Patients details, organ involvement, and outcomes

Case No.	Age/Sex	Comorbidity	Presentation	Organ involvement	Concurrent disease	Hospital stay	Outcome
1	14/F	—	Fever, hematemesis, melena, abdominal pain	Liver Kidneys Lungs	Falciparum Malaria	3	Death
2	66/M	HTN CKD	Fever, dry cough, vomiting	Lungs	Vivax Malaria	5	Alive
3	20/M	—	Fever, facial puffiness, dyspnea	Liver Heart Kidneys	Scrub typhus	6	Alive
4	39/M	—	Fever, weakness of both lower limbs, slurring of speech	Central Nervous System	—	7	Alive
5	27/M	—	Fever, headache, body ache	Liver Bone marrow (HLH)	—	9	Alive



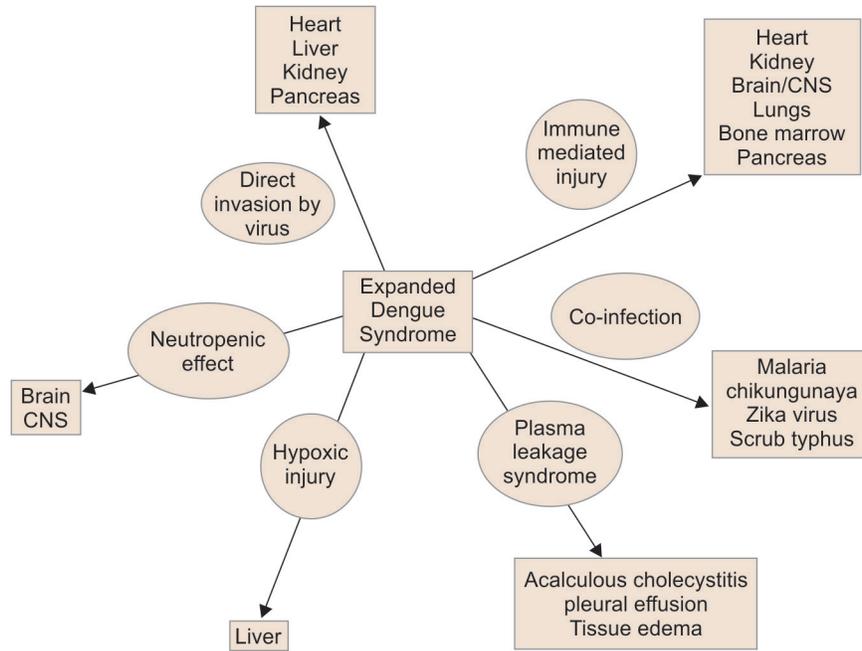


Fig. 1: Pathogenesis of expanded dengue syndrome

### Cardiovascular Manifestations

Arrhythmia is not uncommon, with sinus bradycardia reported as the most common type.<sup>8</sup> Other arrhythmias described in dengue are sinoatrial nodal block, atrioventricular nodal block, complete heart block, paroxysmal supraventricular tachycardia, and atrial fibrillation among others. Most arrhythmias are transient and were reported to recover spontaneously. Dengue myocarditis can occur and is often asymptomatic and self-limiting. The incidence of myocarditis has been estimated to be around 10–15%. However, there are some case reports of fatal outcomes due to dengue myocarditis. The pathogenesis of cardiac injury is postulated to be from acute inflammation due to the virus or direct invasion of virus particles in cardiac muscles. Other rarer cardiac features of EDS may be pericarditis, pericardial effusion, and cardiomyopathy.

### Bone Marrow/Lymphoreticular Manifestations

Although rare, EDS can present with hematological features, such as splenomegaly, disseminated intravascular coagulopathy, cytopenia, or lymphadenopathy. HLH is a rare complication but well-documented. Usually it carries a poor prognosis, but often responds to corticosteroids.<sup>9</sup> One of our patients (patient 5) had persistent thrombocytopenia with markedly elevated transaminases. A diagnosis of HLH was confirmed after further investigations. As per the current literature, IV corticosteroids were administered with satisfactory results.<sup>10</sup>

### Pulmonary Manifestations

Specific respiratory involvement in dengue may be characterized by acute respiratory distress syndrome (ARDS) or pulmonary hemorrhage. In our case series, one patient (patient 1) had ARDS as a part of multi-organ failure, while another (patient 2) had hemoptysis secondary to pulmonary hemorrhage. While the mortality of ARDS in dengue is high, the patient with pulmonary hemorrhage recovered well with supportive management. Patient 3 had mild

bilateral pleural effusions. However, pleural effusion by itself is not considered a part of EDS.

### Others

Some of the uncommon features of EDS involving other systems are acute parotitis, visual disturbances, fatigue, hallucinations, psychosis, and alopecia (Table 2).

### Coinfections

Concurrent infections with malaria, chikungunya, leptospira, and Zika virus have been reported.<sup>11</sup> Coinfection with malaria can be as high as 20% if the population is endemic to it. The most common is *Plasmodium falciparum*, but *P. vivax* coinfection is also documented. Two of our patients were coinfecting with *P. falciparum* and *P. vivax*, respectively. The severity of the disease was far greater with falciparum malaria concurrent infection. The course of the patient with concurrent vivax infection was relatively benign. Zika virus infection is very similar to dengue fever and often difficult to distinguish. Simultaneous infection with scrub typhus is rare and only anecdotal case reports exist.<sup>12</sup> Patient 3 was diagnosed with both EDS and scrub typhus. Her course was benign and she recovered well with supportive care.

### CONCLUSION

EDS is a well-known entity that can present with GI, cardiac, renal, hematological, neurological, or respiratory manifestations. Coinfections with malaria, chikungunya, or scrub typhus are also prevalent. The nature and course of this syndrome depend on the severity of the clinical presentation. There is no direct correlation between the severity of dengue and the type of organ involvement, and even without the classical features of dengue, serious complications can arise. In conclusion, it is of utmost importance to have a high index of suspicion and be well-informed of the different presentations and coinfections associated with EDS.

**Table 2:** Different manifestations of expanded dengue syndrome

System	Manifestations	Percentage
Gastrointestinal/Hepatic	Asymptomatic Transaminitis	20–50% [9–10, 33]
	Hepatitis	NR [8–9, 33]
	Acute liver failure	1–15% [15]
	Acalculous cholecystitis	20–38% [9–11]
	Acute pancreatitis	13% [9, 12–14]
Renal	Upper/lower GI bleeding	NR [16–17]
	Acute kidney injury	7–14% [9, 18–22]
	Hemolytic uremic syndrome	NR [8]
	Hypokalemia	NR [8–9, 33]
	Proteinuria	NR [8–9, 18–19]
Brain and CNS	Nephrotic syndrome	NR [18–19]
	Encephalitis/meningitis	0.5–5% [9, 25–28, 34]
	Stroke (ischemia/hemorrhage)	0.1% [24, 33]
	Febrile seizures (children)	5% [28]
	Neuropathies (GBS/MFS)	0.1–5% [8, 24, 33]
Cardiac	Acute transverse myelitis	0.5–5% [29–32]
	Optic neuritis/cranial nerve palsy	NR [8, 35–39]
	Arrhythmia	10–30% [42–47]
	Myocarditis	9–15% [48–55]
	Pericarditis/pericardial effusion	NR [55–57]
Bone marrow/lymphoreticular	Infection-associated hemophagocytic syndrome/hemophagocytic lymphohistiocytosis	NR [33, 61–71]
	Thrombotic thrombocytopenic purpura	NR [72–73]
	Splenomegaly	8–21% [8, 59–60]
	Lymph node infarction	NR [8]
Respiratory	Acute respiratory distress syndrome	NR [74–77]
	Pulmonary hemorrhage	NR [78]
	Pneumonitis/bronchiolitis	NR [74]
Musculoskeletal	Myopathy/myositis	NR [8, 37, 41]
	Rhabdomyolysis	NR [19, 23]
Others	Visual disturbances, Acute parotitis, Fatigue, Hallucinations, Psychosis, Alopecia	NR [8, 33, 79–80]

NR, not reported

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