Expanded dengue syndrome with small–medium-vessel vasculitis: A case report

Augustine Jose, Minakshi Dhar, Prasan Kumar Panda, Sanjeev Kishore

ABSTRACT

Expanded dengue syndrome (EDS) is a well-described entity in the literature (after 2009), with various new atypical presentations being identified each year. We report a case of 38-year-old man who presented to the emergency department with high-grade, intermittent fever for 7 days along with myalgia and headache. He had multiple painless palpable purpura over both lower limbs and breathlessness from the 4th day of fever. On admission, purpura progressed in the severity and dry impending gangrene of the toes of both feet developed. Blood cultures turned out to be sterile, and other infectious markers (malaria, scrub typhus, and chikungunya) were negative except for dengue serology (enzyme-linked immunosorbent assay-immunoglobulin M [ELISA-IgM]). Skin biopsy confirmed to be cutaneous small-vessel vasculitis. The respiratory distress was due to myocarditis (supported by raised NT-pro-BNP levels) and pulmonary edema. He also had possibly hemolytic anemia due to microangiopathy. Although there are many EDS cases of dengue myocarditis reported till date, dengue resulting in widespread endothelial activation and extensive vasculitis (small vessel due to purpura and medium vessel due to gangrene) is a rare phenomenon.

Key Words: Gangrene, leukocytoclastic vasculitis, myocarditis, severe dengue

INTRODUCTION

Dengue is a flaviviral disease, which is expanding in its clinical presentation as it goes on affecting larger populations. The classically described features of dengue include thrombocytopenia, hemorrhagic manifestations, hepatocellular injury, leukopenia, and capillary leak syndrome including pleural effusion, hypovolemic shock, and ultimately organ failure.[1] In 2009, WHO adopted a new classification of dengue disease, with “severe dengue” encompassing additional organ manifestations.[2] Following the recognition of emerging atypical manifestations of dengue, WHO coined the term “expanded dengue syndrome (EDS),” which includes various clinical features pertaining to different organ systems.[3] Interestingly, along the timeline, dengue has evolved from dengue fever to dengue shock syndrome and its complications and subsequently, to the varieties of organ involvement as EDS.

Among the cardiovascular involvement in dengue EDS, myocarditis is the most common type described.[4] The blood vessel is a major target for end-organ damage in dengue, leading to capillary leak. There have been a few reported cases of dengue with thrombotic microangiopathy, one describing the kidney injury and another resulting in disseminated intravascular coagulation (DIC) and peripheral gangrene.[5,6] However, medium-vessel vasculitis (as gangrene) without DIC is not reported. Cutaneous small-vessel vasculitis (CSVV), mostly idiopathic, is rarely due to virus infections and presents as palpable purpura.
Dengue virus as a trigger for this vasculitis has also not been well defined.

In this article, we describe a case of dengue fever with various end-organ damages as EDS such as myocarditis, possibly thrombotic microangiopathy, CSVV as purpura, and medium-vessel vasculitis with impending peripheral gangrene.

**CASE REPORT**

A 38-year-old man, forest guard, resident of a hilly station of Himalayas, having schizophrenia for the past 15 years, being on antipsychotics: aripiprazole and trihexyphenidyl, presented to the emergency department with high-grade, intermittent fever for 7 days along with myalgia and headache. Following 4 days of fever, he developed multiple painless rashes over the soles of both feet and ankles. The rashes were reddish at the onset and later blackened. There was no gangrene formation or bleeding tendency. He reported breathlessness on exertion and later on in the supine position, but not paroxysmal nocturnal dyspnea. Breathlessness was associated with progressive bilateral leg edema and generalized weakness. He had decreased urine output for 1 day. There was no other history of any localizing symptoms. There was no history of substance use, alcohol intake, smoking, or any other comorbidity except above psychiatry illness. He was evaluated in an outside hospital where dengue NS1 antigen (on day 3 of illness) was positive along with low platelet count (40,000/mm³).

On examination, he was thin built but pale and edematous, afebrile, mildly drowsy, and disoriented. Vitals were unstable: heart rate 128 bpm, regular with satisfactory pulse volume; blood pressure 98/60 mm Hg with pulse pressure 48 mmHg; tachypneic (respiratory rate 30/min) with arterial oxygen saturation of 86% on ambient room air and 92%−95% on 4 L of O₂ therapy (hypoxemia). Along with bilateral pitting pedal edema, there were multiple palpable but nontender purpuric rashes present on both feet ranging in size from 2 mm to 8 mm, with fine scaling and postinflammatory hyperpigmentation with confluence toward the terminal aspect and impending gangrene [Figure 1a]. All peripheral pulses were felt. Jugular venous pulse was not elevated. Chest examination demonstrated bilateral basal fine crackles and occasional wheezes. S1 and S2 were normal but with equal intensity (Tic-Tac rhythm like), and gallop/murmur was not present. Abdominal examination demonstrated mild tenderness over the right hypochondrium and epigastrium, but no palpable liver and spleen. Other systemic examinations were unremarkable.

From day 3 of admission (day 9 of illness), he started experiencing severe pain in both feet, which now showed darkening in color and was tender to touch, suggesting impending dry gangrene superimposed on the purpuric rashes [Figure 1a and b]. All peripheral arterial pulsations were normal, including the toe movements, and there was hyperesthesia of feet.

A probable diagnosis of EDS (because of outbreak season) with myocardium, vessels, skin, and kidney involvements was made.

Electrocardiography showed sinus tachycardia. Chest X-ray revealed features suggestive of early pulmonary edema [Figure 1d]. Initial arterial blood gas analysis showed compensated respiratory alkalosis. Hemogram on day 8 of the illness revealed anemia (Hb, 9.4 g/dL) with a normal mean corpuscular volume (MCV) and corrected reticulocyte count of 2.8, leukocyte count (7900/mm³), and thrombocytopenia (platelet count, 30,000/mm³) with a peripheral smear showing normochromic normocytic picture and reactive lymphocytes. Serum lactate dehydrogenase concentration was increased (457 U/L; reference normal <248 U/L in males). Erythrocyte sedimentation rate was 44 mm/h, and highly sensitive C-reactive protein fraction was 14.2 mg/L. Fibrin degradation products were 12 mg/L, and D-dimer was <0.5. ADAMTS13 levels, serum complement levels, and immunoglobulin levels could not be tested due to technical constraints and resource-limited setting. Kidney function tests suggested acute kidney
injury. Liver function tests showed hyperbilirubinemia, predominantly conjugated (total bilirubin: 2.83 mg/dL/direct: 1.33 mg/dL), with mild transaminitis and hypoalbuminemia. NT pro-BNP levels were highly raised (3114.7 pg/mL; normal range <300 pg/mL); however, transthoracic echocardiogram did not reveal any abnormality. Blood cultures turned out to be sterile, and other infectious markers (malaria, scrub typhus, and chikungunya) were negative, except for dengue serology (ELISA-IgM). Serology for hepatitis B, hepatitis C, and human immunodeficiency virus was negative.

Doppler ultrasonography of both lower limbs demonstrated normal flow precluding arterial or venous occlusion. A skin biopsy was obtained from the area of purpuric rash, which revealed foci in the upper dermis with perivascular infiltration by polymorphonuclear cells with mild edema and nuclear fragmentation, suggestive of leukocytoclastic vasculitis or CSVV [Figure 2a and b].

The final diagnosis of EDS with myocarditis, thrombotic microangiopathy, medium-vessel vasculitis (as impending peripheral gangrene), and CSVV (as purpura) was made.

He was given oxygen supplementation, titrated intravenous crystalloids, inotropic support (dobutamine), titrated diuretics, and other supportive measures. Intermittent continuous positive end-expiratory pressure support was given. Antipsychotic medications were withheld as per the advice by the psychiatrist. Antiplatelets were added after platelet counts were in the normal range.

Over the course of hospital stay, he improved symptomatically, tachycardia and respiratory distress settled, urine output increased with hydration, platelet counts improved, and features of purpura and impending gangrene improved. At the time of discharge, antipsychotic therapy was added as per the opinion of the psychiatrist. On follow-up visit after 7 days, his impending gangrene was not progressing and sloughing had started [Figure 1c], and he was followed up in the department of plastic surgery. Recently, in a follow-up after 2 months of dengue, he is doing his normal daily activities.

**DISCUSSION**

The case of dengue fever described above shows various end-organ involvements such as symptomatic myocarditis, hemolytic anemia, palpable purpura, and CSVV. Dengue fever is well known to cause myocarditis with a reported prevalence ranging from 9% to 15% from various studies. However, most cases are asymptomatic. Myocarditis, as component of EDS, occurs early as end-organ damage. With high vigilance toward breathlessness (or orthopnea) in patients of dengue, all myocarditis cases should be detected and treated early to prevent undue morbidity and mortality.

Thrombotic microangiopathy is a part of thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome, and dengue has been reported to have triggered it warranting exchange transfusion, corticosteroids, and rituximab therapy. A case of TTP associated with dengue was described in a pregnant woman at 16 weeks of gestation, who was treated successfully with plasma exchange and fresh frozen plasma. In our case, we suspect microangiopathic hemolytic anemia. However, peripheral smear finding was not supportive of thrombotic microangiopathy, but diagnosis could not be ruled out.

Dengue-associated vasculitis is a “vasculitis associated with probable etiology” as per the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Here, the site and characteristics of pathology are not clearly defined due to the rare phenomenon. Medium-vessel vasculitis presenting as gangrene is not reported, although DIC is being reported with dengue and gangrene. The predominant cutaneous manifestation associated with dengue infection is a maculopapular rash with the purpuric component.

CSVV is mostly idiopathic and presents as palpable purpura. Few virus infections such as herpes and influenza A have been identified as etiological factors. Only a few cases of cutaneous vasculitis associated with dengue infection have been reported previously. Hence, dengue inciting gangrene and purpura without DIC deserves a recognition and may be added to the spectrum of EDS. CSVV can be induced by a variety of causes, including drugs, infections, connective tissue diseases, and malignancies. The American College of Rheumatology provides a classification criterion for CSVV, according to which, the presence of three of the following five criteria can diagnose CSVV with a specificity of 84%.

i. Onset after 16 years of age

ii. History of taking a medication at the onset of symptoms that may have been a precipitating factor.
iii. The presence of palpable purpura
iv. The presence of a maculopapular rash
v. A biopsy demonstrating granulocytes around an arteriole or venule.

Our case clearly fulfills four of these criteria, including a histopathological evidence. Dengue virus infection resulting in CSVV is a rare entity. The management of CSSV is mainly control of the underlying trigger as it resolves spontaneously in most cases similar to our case too. However, dengue has been recognized as a trigger for central nervous system vasculitis and subsequent ischemic stroke in a pediatric case and for retinal vasculitis and subsequent visual defects in an adult. Our patient did not demonstrate any symptoms consistent with these.

In conclusion, the available evidence is sufficient enough to support the assumption of dengue fever resulting in widespread endomyocardial/endothelial activation (myocarditis, thrombotic microangiopathy, and vasculitis), leading to myocardial failure, anemia, purpura, and impending distal dry gangrene of limbs, respectively. It acknowledges various atypical manifestations of dengue such as myocarditis, thrombotic microangiopathy, and dengue-associated vasculitis as part of EDS. It adds high index of suspicion and vigilance to treating physicians for possible end-danger complications during the dengue season.

Declarations of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Research quality and ethics statement:
The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines, notable the CARE guideline, during the conduct of this research project.

REFERENCES
1. WHO. Dengue Haemorrhagic Fever: Diagnosis, Treatment, Prevention and Control, 2nd ed. Geneva: World Health Organization; 1997.
2. WHO and TDR. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009.
3. WHO: Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Hemorrhagic Fever. World Health Organization, Regional Office for South-East Asia; 2011. Revised and Expanded Edition; 2011. Available from: https://apps.who.int/iris/handle/10665/204894. [Last accessed on 2019 Dec 01]
4. Kadami DB, Salvi S, Chandran A. Expanded dengue. J Assoc Physicians India 2016:64:59-63.
5. Bhargava V, Gupta P, Kaunthia R, Bajpai G. Dengue fever-induced thrombotic microangiopathy: An unusual cause of renal failure. Indian J Nephrol 2017;27:321-3.
6. Nair BT, Sanjeev RK, Tarik jot SB. Peripheral gangrene in a case of severe dengue. Niger J Clin Pract 2016;19:150-2.
7. Neeraja M, Lakshmi V, Teja VD, Lavanya V, Priyanka EN, Subhada K, et al. Unusual and rare manifestations of dengue during a dengue outbreak in a tertiary care hospital in South India. Arch Virol 2014;159:1567-73.
8. Miranda CH, Borges Mde C, Matsuno AK, Vilar FC, Gali LG, Volpe GJ, et al. Evaluation of cardiac involvement during dengue viral infection. Clin Infect Dis 2013;57:812-9.
9. Li Y, Hu Z, Huang Y, Li J, Hong W, Qin Z, et al. Characterization of the myocarditis during the worst outbreak of dengue infection in China. Medicine (Baltimore) 2016;95:e4051.
10. Gavali AS, Shelgaonkar J, Bartakke S. Thrombotic thrombocytopenic purpura in a case of dengue fever: A rare presentation. Indian J Crit Care Med 2017;21:226-8.
11. Deepanjali S, Naik RR, Mailankody S, Kalaimani S, Kadiravan T. Dengue virus infection triggering thrombotic thrombocytopenic purpura in pregnancy. Am J Trop Med Hyg 2015;93:1028-30.
12. Desruelles E, Lamary I, Roulier M, Goursaud R, Mahé A, Castanet J, et al. Cutaneous-mucous manifestations of dengue. Ann Dermatol Venereol 1997;124:237-41.
13. Caballero AA, Olmedo OA, Oddone VR. Manifestaciones cutaneas del dengue. Piel 2009;24:520-3.
14. Cohen C, Trapuck C. Leukocytoclastic vasculitis associated with cutaneous infection by herpessviruses. Am J Dermatopathol 1984;6:561-5.
15. Lee HL, Shin DH, Choi JS, Kim KH. Leukocytoclastic vasculitis associated with influenza A virus infection. J Korean Med Sci 2012;27:1601-3.
16. Barraza M, Gonzalez R, Santacruz JG. Dengue y vasculitis leucocitoclastica. Univ Med 2006;47:278-83.
17. Ishikawa H, Okada S, Katayama I, Mazaki H, Nagatake T, Hasebe F, et al. A Japanese case of dengue fever with lymphocytic vasculitis: Diagnosis by polymerase chain reaction. J Dermatol 1999;26:29-32.
18. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, Garcia-Fuentes M. Cutaneous vasculitis in children and adults. Associated diseases and etiologic factors in 303 patients. Medicine (Baltimore) 1998;77:403-18.
19. Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Arthritis Rheum 1990;33:1065-7.
20. Nanda SK, Jayalakshmi S, Mohandas S. Pediatric ischemic stroke due to dengue vasculitis. Pediatr Neurol 2014;51:570-2.
21. Chan DP, Teoh SC, Tan CS, Nah GK, Rajajopalan R, Prabhakaragupta MK, et al. Eye Institute Dengue-Related Ophthalmic Complications Workgroup. Ophthalmic complications of dengue. Emerg Infect Dis. 2006;12:285-9.