Case Report

An unusual association of disseminated staphylococcal infection in dengue fever

Sruthi Haridas[1], Renoy A Henry[2], Abhishek C Menon[3], Anup Menon[3], L Sasikala[4], Akash Thomas Oommen[4]

From [1]Consultant, Department of General Medicine, PVS Hospital, Calicut, [2]Associate Professor, [3]Assistant Professor, [4]Professor, Department of General Medicine, Amrita Institute of Medical Sciences, Kochi, Kerala, India

ABSTRACT

Dengue fever is an important mosquito-borne disease with a highly variable clinical spectrum, ranging from self-limiting mild illness to expanded dengue syndrome (EDS). While the immune-pathogenesis of dengue virus (DENV) infection had been studied thoroughly, the exact mechanism remains elusive. The transient suppression of host innate immunity by DENV might be the likely reason for dengue-associated co-infections and/or superinfections. In addition, the dual infection can worsen the clinical outcome of Dengue fever. We are reporting a case of disseminated staphylococcal infection in a 31-year-old healthy male with a recent dengue infection. Blood culture showed methicillin-sensitive *Staphylococcus aureus*. Selective IgM deficiency has been proved in this patient, which might explain, the occurrence of disseminated staphylococcal septicemia. This case report highlights the importance of early detection of atypical features and the emerging entity called EDS.

Key words: Brain abscess, Expanded dengue syndrome, Multi-organ dysfunction, *Staphylococcus aureus*

Dengue fever is currently an important public health issue in many tropical areas leading to high morbidity and mortality. In the past 50 years, the incidence of dengue has increased by 30-fold. One study estimates that approximately 390 million dengue infections occur annually, with 96 million of these presenting clinically [1,2]. Due to complex immunologic reactions between host genetic factors, pre-existing comorbidities, and viral strains, a fatality has been reported in some cases despite a timely diagnosis. In addition, in the last decade, the emergence of dengue has been associated with unusual manifestations and coinfections. The World Health Organization coined the term "expanded dengue syndrome" (EDS) in 2011, to describe unusual manifestations involving severe damage to the liver, kidneys, bone marrow, heart, brain, which do not fall into either dengue hemorrhagic fever or dengue shock syndrome [1]. Dengue patients are often predisposed to bacterial infections [3-5]. The incidence of *Staphylococcus aureus* co-infection and its complications are increasing sharply due to increased use of intravascular devices, dengue virus (DENV) related immunosuppression, and increased resistance of *S. aureus* strains to antibiotics [6].

We report herein a case of disseminated staphylococcal infection in a dengue patient, caused by methicillin-sensitive strain leading to bacteremia and widespread metastatic abscesses.

Access this article online	
Received - 29 July 2021 Initial Review - 14 August 2021 Accepted - 25 August 2021	Quick Response code
DOI: 10.32677/ijcr.v7i9.3015	

CASE REPORT

A 31-year-old, healthy male from Kerala, presented with intermittent high-grade fever for 1 week which was associated with severe headache, myalgia, and a depressed sensorium. He was diagnosed to have dengue fever 2 weeks back and was treated elsewhere on an in-patient basis till a week before the presentation. No history of arthralgia, rash, seizures, neck pain, cough, shortness of breath, chest pain, vomiting, abdominal pain, dysuria, and increased urinary frequency. There was no recent history of travel.

Upon presentation to the emergency department, patient was drowsy and febrile (101.4°F) with tachycardia of 120 beats/min and blood pressure of 100/80 mm of Hg. Neurological examination showed signs of meningeal irritation, left hemiparesis (Grade 4, MRC), and bilateral extensor plantar response. Examination of the cardiovascular, respiratory system, and abdomen were unremarkable.

Initial blood investigations showed hemoglobin 14.7 g/dL, white blood cell count 21.41 × 10^9/L, platelet 137 × 10^9/L, and hematocrit 42.6% with elevated inflammatory markers, high blood sugars, deranged renal and liver function tests. Dengue serology was positive (IgM [40.7] and IgG [74]) (Table 1). Urine examination revealed pyuria and haematuria. Ultrasound of the abdomen done showed features of cystitis. With a presumptive diagnosis of sepsis with multiorgan dysfunction, urinary tract

Correspondence to: Dr. Sruthi Haridas, Consultant Physician, Department of General Medicine, PVS Hospital, Calicut, Kerala, India. E-mail: shruthyh543@gmail.com

infection, meningoencephalitis, hyperglycaemic crisis, in the background of recent dengue fever, he was admitted to the medical intensive care unit. A Magnetic resonance imaging (MRI) brain with contrast showed two cerebral abscesses (frontal and occipital) with hemorrhagic transformation and septic embolization in the bilateral cerebral hemispheres and cerebellum (Fig. 1). Cerebrospinal fluid analysis suggested a partially treated meningitis (10 segmented cells, proteins 38 mg/dl, glucose 134 mg/dl, adenosine deaminase 0.7, and sterile cultures).

The patient was managed with intravenous (IV) antibiotics (Meropenem), fluid resuscitation, insulin infusion, and other supportive measures. A detailed cardiology evaluation including transoesophageal echocardiogram was performed and this showed normal left and right ventricular function, mild pericardial effusion, and ruled out any vegetations. Meanwhile, blood and urine cultures showed methicillin-susceptible *S. aureus* (Table 1). Based on the sensitivity report, IV Flucloxacillin was added and Meropenem was continued. But the patient continued to have high-grade fever (101–102°F) and tachycardia. Therefore, thyroid function tests were also done. It showed elevated Free T4 (2.16 ng/dL), normal Free T3 (2.35 ng/dL) with low thyroid-stimulating hormone (TSH) (0.067 mIU/mL), and normal antibody levels (anti-thyroglobulin and anti-thyroid peroxidase antibodies), suggestive of subacute thyroiditis. Thyroid scintigraphy was performed which confirmed the diagnosis (Fig. 2).

Table 1: Initial investigation results (on admission)

Investigations	Results
Hemoglobin (g/dL)	14.7
Hematocrit (%)	42.6
White blood cells (K/uL)	21410
Differential count (%)	N94 L3.9
Platelet (K/uL)	137
Erythrocyte sedimentation rate (mm/h)	66
C-reactive protein (mg/dL)	341.8
Procalcitonin	94.9
Sodium (mmol/L)	129.3
Potassium (mmol/L)	5.2
Calcium (mg/dL)	8.6
Albumin (g/dL)	2.43
Globulin (g/dL)	4.38
AST (IU/L)	57.3
ALT (IU/L)	61.3
ALP (IU/L)	94
Prothrombin time (control)	18.7/ 14.6
INR (s)	1.35
Urea (mg/dL)	96.7
Creatinine (mg/dL)	1.96
Random blood sugar (mg/dL)	527
HbA1C	7.6
Serum Osmolarity (mOsm/Kg)	310
Serum Ketone (mg/dL)	Negative
Dengue Immunoglobulin M (IgM)	Positive (40.7)
Dengue IgG	Positive (>74)
Blood culture	*S. aureus* sensitive to Oxacillin [MIC 0.5 µg/mL], Trimethoprim-sulfamethoxazole [MIC <= 10 µg/mL Resistant to Benzylpenicillin, Levofloxacin, Erythromycin, Clindamycin
Urine culture	*S. aureus* 10^5 cfu/ml sensitive to Cloxacillin/Oxacillin, Nitrofurantoin, Co-trimoxazole, Clindamycin Resistant to Levofloxacin, Penicillin G

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, INR: International Normalized Ratio, *S. aureus: Staphylococcus aureus*

The patient was started on beta-blockers. Nevertheless, the patient's sensorium deteriorated and had continuous high-grade fever (101°F) spikes. At this point, an ultrasound abdomen was repeated, and it revealed a hypoechoic lesion in the spleen and kidney. For detailed evaluation, a multiphase contrast computed tomography of the abdomen and chest was done. This revealed splenic abscess, with septic embolization in the lung, liver segment VII along with moderate pericardial effusion (Fig. 3). In view of multiple abscesses and septic emboli, Flucloxacillin was switched to Vancomycin. With the guidance of ultrasonography, pigtail catheterization and drainage of the splenic abscess was done (500 mL). Serial assessment and monitoring of the size of the splenic abscess, pericardial effusions were done with radiology and cardiology assistance. With the above-mentioned management, the patient showed significant improvement clinically. Further evaluation for autoimmune/vasculitic etiology were normal, except for isolated IgM deficiency, with normal level of other immunoglobulin types [IgM – 28.6 mg/dL (normal range, 40–230 mg/dL), IgA – 154 mg/dL (normal range, 70–400 mg/dL), IgG – 1748 mg/dL (normal range, 700–1600 mg/dL)].

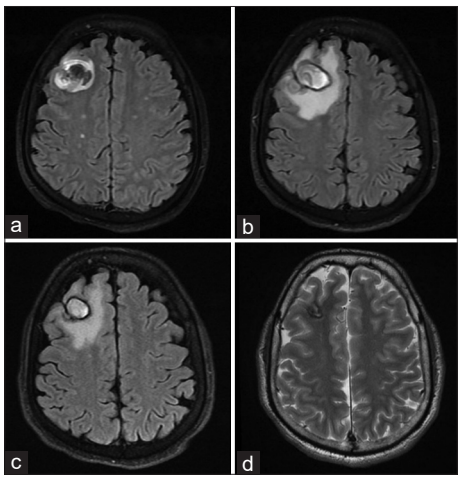

Figure 1: Magnetic resonance image of brain. (a) Day 1: T2-weighted fluid-attenuated inversion recovery (FLAIR) signal showing intra-parenchymal hemorrhagic foci in the right frontal lobe; (b) Week 4: T2-weighted FLAIR signal showing an increase in perilesional edema with lesion size status quo; (c) Week 6: T2-weighted FLAIR signal showing a reduction in size of abscess and perilesional edema; (d) T2-weighted signal showing significant resolution

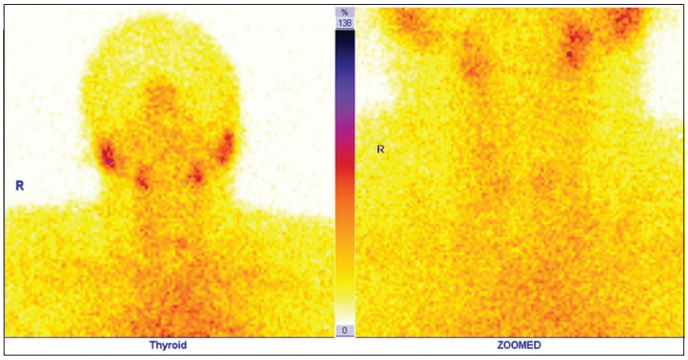

Figure 2: Thyroid scintigraphy with technetium Tc-99 m consistent with sub-acute thyroiditis

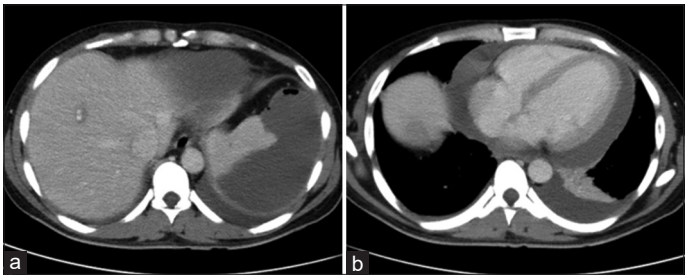

Figure 3: Computed tomography abdomen (a) Splenic abscess and liver (segment VII) abscess; (b) Moderate pericardial effusion

After 4 weeks, as repeat MRI brain showed perilesional edema with lesion size being status quo, anti-edema measures and prophylactic anti-epileptics were added. IV Meropenem was de-escalated to IV Ceftriaxone at a meningitic dose and Vancomycin was continued. After 5 weeks, a review ultrasound of the abdomen showed a significant reduction in the size of the splenic abscess. Follow-up screening ECHO showed no evidence of pericardial effusion. At discharge after 6 weeks of hospitalization, the patient was clinically better. MRI brain showed a significant reduction in the size of the abscess and perilesional edema (Fig. 1). Renal/liver and thyroid functions normalized and euglycemia were attained. IV antibiotics were changed to oral Trimethoprim-Sulfamethoxazole. He was serially followed up on an outpatient basis and at 20 weeks, the lesion in the brain showed a complete resolution.

DISCUSSION

Dengue fever is a common febrile illness caused by infection with one of the four DENV, transmitted by *Aedes aegypti* or *Aedes albopictus* mosquitoes. There is increasing evidence that dysfunctional innate and adaptive immunity are involved in the immune-pathogenesis of severe dengue, leading to multisystemic and unusual clinical manifestations [1,7]. Atypical manifestations observed in this patient were predominantly neurologic symptoms. There were no neurological abnormalities in the acute phase of dengue fever. However, the patient had neurological symptoms, which were probably caused by the staphylococcal co-infection, rather than dengue infection. The patient also had hepatic and splenic involvement (hepatitis, sub-capsular splenic abscess, and sub-capsular hepatic abscess), pericardial effusion, pre-renal acute kidney injury, sub-acute thyroiditis, and stress-induced hyperglycemia.

Various mechanisms have been proposed to explain co-infections in dengue fever. The more likely mechanism is the relative immunosuppression caused by the virus. It can also occur via the disruption of the digestive epithelial barrier by DENV, through endothelial damage or intestinal hemorrhage; or can be a mere temporal coincidence [8]. Some other viruses like measles virus, influenza, parvovirus B19, and cytomegalovirus are also known to induce transient immunosuppression *in vitro* and *in vivo*. In this study, a healthy, young individual, with a recent history of hospitalization for dengue fever, has developed disseminated staphylococcal sepsis and septicemia. IV cannulation, while the patient was admitted with dengue fever, might be the possible source of staphylococcal infection. Isolated IgM deficiency proved, in this case, could be a manifestation of immune dysregulation associated with dengue infection. Selective IgM deficiency is a rare immune disorder, associated with B-cell and T-helper cell dysfunction, and is characterized by a deficiency of serum IgM, with normal levels of other immunoglobulin isotypes. It is associated with susceptibility to *S. aureus*, encapsulated pathogens, and viral infections [9]. *Escherichia coli*, *Salmonella* sp., *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, *Aspergillus*, *Candida tropicalis*, and *Herpes viruses* have also been reported simultaneously with DENV infection [3,10].

To the best of our knowledge, this is the first case report of complete recovery in a patient with disseminated staphylococcal infection following dengue fever who was successfully treated by a multidisciplinary approach. A case report published from Malaysia by Ngoi *et al*. reported the case of a 50-year-old lady with systemic hypertension and diabetes mellitus, who presented with typical symptoms of dengue fever but later succumbed to septic shock caused by hypervirulent methicillin-sensitive *Staphylococcus aureus* [6]. Another case report from Brazil published by Araujo *et al*. discussed the case of a 14-year-old healthy male, who presented with high-grade fever, mental confusion, headache, visual blurring, petechial rash, and myalgia, one month after recovery of dengue infection. The patient had multi-organ dysfunction, with renal failure, coagulopathy, respiratory failure, and refractory shock, dying after 2 days of admission. Blood cultures were sterile. Dengue serology was positive. An autopsy was obtained which showed *S. aureus* sepsis, multisystemic septic embolization, and massive tissue colonization in the heart, brain, and kidneys. Swabs from serosal fluids grew oxacillin-sensitive *S. aureus* [3].

CONCLUSION

In the current scenario, the field of infectious disease is a mystery, with a variegated agent-host response. Dengue fever is an example

of unusual manifestations. The dysregulated immune response associated with DENV infection can lead to severe disease, EDS, and bacterial co-infection or superinfection, worsening the outcome of dengue fever. Persistent fever, rising white blood cell count, and signs and symptoms uncommon for DENV infection should prompt evaluation for bacterial coinfection. Case studies like this may contribute to increased awareness of the unusual manifestations and immune-pathogenesis of bacterial co-infections in dengue fever.

REFERENCES

1. World Health Organization. Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. New Delhi, India: World Health Organization Regional Office for South-East Asia; 2011. p. 196.
2. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, *et al*. The global distribution and burden of dengue. Nature 2013;496:504-7.
3. Araújo SA, Moreira DR, Veloso JM, Silva JO, Barros VL, Nobre V. Fatal staphylococcal infection following classic dengue fever. Am J Trop Med Hyg 2010;83:679-82.
4. See KC, Phua J, Yip HS, Yeo LL, Lim TK. Identification of concurrent bacterial infection in adult patients with dengue. Am J Trop Med Hyg 2013;89:804-10.
5. Trunfio M, Savoldi A, Viganò O, D'Arminio Monforte A. Bacterial coinfections in dengue virus disease: What we know and what is still obscure about an emerging concern. Infection 2017;45:1-10.
6. Ngoi ST, Lee YW, Niek WK, Kan FK, AbuBakar S, Ponnampalavanar SS, *et al*. Atypical presentation of methicillin-susceptible *Staphylococcus aureus* infection in a dengue-positive patient: A case report with virulence genes analysis. Pathog Basel Switz 2020;9:1-6.
7. Malavige GN, Jeewandara C, Ogg GS. Dysfunctional innate immune responses and severe dengue. Front Cell Infect Microbiol. 2020;2020: 590004.
8. Srikiatkhachorn A, Kelley JF. Endothelial cells in dengue hemorrhagic fever. Antiviral Res. 2014;0:160-70.
9. Gupta S, Gupta A. Selective IgM deficiency-an underestimated primary immunodeficiency. Front Immunol. 2017;8:1056.
10. Salam N, Mustafa S, Hafiz A, Chaudhary AA, Deeba F, Parveen S. Global prevalence and distribution of coinfection of malaria, dengue and chikungunya: A systematic review. BMC Public Health 2018;18:710.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Haridas S, Henry RA, Menon AC, Menon A, Sasikala L, Oommen AT. An unusual association of disseminated staphylococcal infection in dengue fever. Indian J Case Reports. 2021;7(9):391-394.