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Variable presentations of dengue fever with diagnostic dilemma: A case series

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ABSTRACT

Dengue is a viral fever in humans which is caused by 4 serotypes of the flavivirus. It is spread by the bite of the infected *Aedes* mosquitoes. The acute febrile illness is often associated with multisystem involvement with complications. The case series presented here depicts atypical manifestations of dengue which may present with hypoplastic anemia, hepatitis, pancreatitis, and encephalopathy. The cases were diagnosed based on history of dengue with subsequent persistence of pancytopenia, presence of hepatitis, pancreatitis, and encephalopathy with serological evidence of dengue and after ruling out other possible etiologies supported by laboratory evidence of investigations. The bone marrow revealed pancytopenia with hypocellular marrow causing hypoplastic anemia, transaminitis and rise of lipase and amylase with symptoms diagnosed hepatitis, pancreatitis, and finally impairment of consciousness with electroencephalogram proved encephalopathy. The importance of the case series lies in the fact that atypical manifestations may occur in dengue patients challenging the physicians and early detection may avoid unnecessary treatment and complications.

Key words: Dengue; Hypoplastic anemia; Hepatitis; Pancreatitis; Encephalopathy

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INTRODUCTION

India is dangerously grounded on the brink of an explosion of tropical infectious diseases. What is more concerning is the variety of presentation of such infectious diseases which bear a close resemblance to other systemic diseases. Dengue is one such infection which is being reported at an alarming rate across all states of India. Dengue fever incidence has dramatically grown throughout the World in times of recent decades as mentioned by WHO from505430 patients in 2000 to5.2 million as in 2019.[1] The term expanded dengue syndrome encompasses neither dengue shock syndrome nor dengue hemorrhagic fever. It stands for the various atypical manifestations of the infection involving the brain, heart, pancreas, and bone marrow. Here, three such non-typical cases of dengue infection are presented entailing the bone marrow, pancreas, and central nervous system, respectively.

CASE SERIES

Case 1

A 35-year-old non-diabetic, non-hypertensive, non-addict male teacher by occupation presented with exertional breathlessness for the past 5 months with fatiguability for a similar duration. He had a history of fever 6 months back with myalgia and arthralgia and was diagnosed as dengue fever based on fever and positive NS1 antigen and immunoglobulin (Ig) M dengue antibody positivity whereas IgG dengue antibody was non-reactive. The patient recovered from fever with persistent anemia, leukopenia, and thrombocytopenia which were evident from past investigation documents five and half months earlier as he was discharged 15 days after admission during suffering from dengue fever. The reports of complete blood count showed hemoglobin (Hb) - 9.4 g/dl, total

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leukocyte count (TLC) - 3500/mm^3, and platelet count of 1.15 lakhs/mm^3 with normocytic, normochromic anemia, packed cell volume (PCV) - 40.5, and erythrocyte sedimentation rate - 23 mm 1st h. There was no definite history of bleeding manifestations during prior admission nor was there any history of shortness of breath which started 15 days after discharge, being gradually progressive with orthopnea, without paroxysmal nocturnal dyspnea, or any swelling of any part of the body. There was no history of morning facial puffiness, hematuria, frothy urine, bowel irregularity, or any history of jaundice. There was no history of any exposure to drugs, toxins, chemicals, or any history of fever. There was no history of recurrent infections in the form of rhinitis, sinusitis, and otitis, and the patient was non-vegetarian. There was no history of bleeding from any site.

On examination, the patient was alert conscious and cooperative with propped-up decubitus. There was severe pallor without any icterus, lymphadenopathy, but there was a presence of mild pitting pedal edema with engorged pulsatile jugular venous pressure. Pulse was 104/bpm with blood pressure (BP) - 100/70 mmHg on both upper limbs with normal temperature. There were no rashes on the skin surface except the soft palate which showed few petechial spots.

There were no hepatosplenomegaly and ascites. There were bibasal fine creps. S1 and S2 were audible without any murmurs and examination of other systems was unremarkable.

Investigations revealed Hb - 7.8 g/dl, TLC - 2800/mm^3, and platelet count of 42 thousand/mm^3. PCV was low (38.1) with normal mean corpuscular volume (86.7 fl), mean corpuscular hemoglobin concentration, and red cell distribution width. There was normocytic normochromic anemia with pancytopenia. IgG and IgM cytomegalovirus (CMV) antibody, IgM viral capsid antigen (VCA), Epstein–Barr virus nucleic acid (EBNA), serology for hepatitis viruses, and human immunodeficiency virus (HIV) 1 and 2 antibody were negative. Random blood sugar (RBS) and renal function test (RFT) were normal with normal liver function tests (LFTs), vitamin B12, and RBC folate assays. UGIE and colonoscopy done during previous admission for anemia were also checked. Ultrasonography (USG) WA, chest X-ray PA view, and 2D echocardiography with color Doppler were normal with negative ANA HEP 2. Dengue IgG was positive by GAC enzyme-linked immunosorbent assay (ELISA).

A provisional diagnosis of hypoplastic anemia was made due to the presence of pancytopenia and bone marrow was advised for histopathology and biopsy which showed multiple hypocellular fat spaces with minimal erythroid and myeloid components with occasional megakaryocytes and plasma cells with cellularity of <25%. Reticulocyte count was <20,000/mm^3 with absolute neutrophil count <500/mm^3 diagnosing severe hypoplastic anemia based on Camitta Criteria (Figure 1).

The patient was put on supportive treatment with frusemide injection SOS, rest, propped up position, and moist oxygen SOS. Drugs precipitating aplasia and IM injections were avoided. As platelet counts progressively decreased to 10,000/mm^3, 6 units platelet transfusion was done with barrier nursing and broad-spectrum antibiotics were given for the prevention of infection. The patient was referred to higher hematology setup where he is undergoing treatment with antithymocyte globulin and cyclosporine.

As dengue serology was reactive and the patient developed persistent pancytopenia post-dengue fever, he was diagnosed with post-dengue severe hypoplastic anemia which is a rare presentation of dengue fever.

Case 2

A 22-year-old male patient with no known comorbidities presented with complaints of intermittent high-grade fever for 7 days and pain abdomen for 5 days before admission. His fever was sudden in onset, intermittent in nature, associated with headache and arthralgia, and relived on taking paracetamol tablets. He also complained of pain abdomen, originating in epigastric region, progressing to generalized pain abdomen. There was neither any history of nausea or vomiting nor any bladder bowel involvement nor any history suggestive of any rheumatological disease. On admission, he was febrile and hemodynamically stable. On examination, no skin rashes, no lymphadenopathy nor any hepatosplenomegaly was found. Other systemic examinations also had no significant findings. His initial

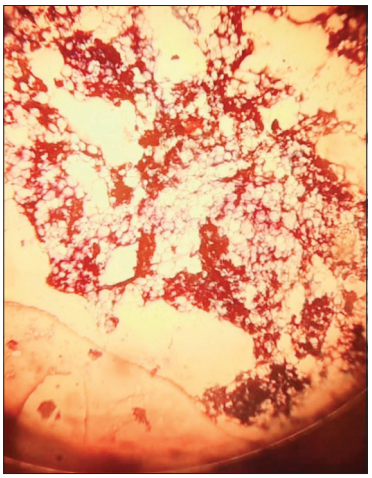

Figure 1: Bone marrow showing hypocellularity of case 1 of dengue hypoplastic anemia

blood reports showed hemoglobin – 14.3 g/dl, TLC – 9350/cumm, platelet count of 1,76,000/cumm, and PCV – 39.2. His Serum Glutamic Oxaloacetate Transaminase (SGOT) was 262 IU/L, serum glutamic-pyruvic transaminase (SGPT) – 167 IU/L, and total bilirubin – 1.2 mg/dl with conjugated fraction of 0.4 mg/dl. Serum amylase level was 253 IU/L and serum lipase was 599 IU/L. Ferritin levels were found to be 1500 mg/dl as a part of positive acute phase reactants. His RFT was normal. Among the fever panel that was sent out, dengue NS1 came as positive for this patient. However, USG whole abdomen done for this patient revealed a mild diffuse thickening of the gall bladder wall. He was started on conservative management with fluid therapy and other supportive treatment. His fever and pain abdomen had subsided from day 2 of admission. Serial estimation of the liver enzymes, serum amylase, and serum lipase showed a gradual reduction with a value of SGOT – 55 IU/L, SGPT – 131 IU/L, serum amylase – 116 IU/L, and serum lipase – 141 IU/L on day 7 of admission. A repeat USG W/A done showed similar findings. Dengue IgM done on D5 of admission was found to be reactive. Incidental finding of hypovitaminosis D was found for this patient. The patient was finally discharged in a hemodynamically and clinically stable condition.

Case 3

A 63-year-old non-diabetic, non-hypertensive, non-addict male, fruit seller by occupation presented with fever for the past 2 days with chill and rigor with headache, bodyache, myalgia without any history of vomiting, and bladder bowel complaints. There was no skin rashes, joint pain, or any history of bleeding from any site. There was retro orbital pain without any history of jaundice. The patient was disoriented in time, place, and person 12 h after admission.

On examination, there was no pallor, icterus, lymphadenopathy, or skin rashes. Temperature was 101.0° F with tachycardia and hypotension with BP -90/60 mmHg. There were no hepatosplenomegaly and ascites. On examination of the neurological system, the neck was supple with no abnormalities in cranium and spine or no signs of meningeal irritation. Plantar was bilateral extensor. There was no flapping tremor and examination of other systems was unremarkable.

A provisional diagnosis of viral encephalitis was made with differentials of septic and metabolic encephalopathy.

Investigations revealed normal hemoglobin with normal TLC, but platelets were reduced (90,000/mm^3). PCV was 32.3 with normocytic normochromic morphology with reduced platelets on smear. Fever profile in the form of MP slide and dual Ag, NS1 Ag, Typhi Dot M, IgM and IgG CMV ab, EBNA and IgM VCA, urine CS, and blood CS aerobic single hand were sent. RBS and RFT (sodium, potassium, urea, and creatinine) revealed mild hyponatremia (sodium - 130 meq/l). Hepatitis A, B, C, D, E, and HIV serology were non-reactive and LFT revealed mild transaminitis. Chest X-ray, ECG, and echocardiography were normal with IVC collapsibility showing hypovolemia guiding fluid therapy. USG WA was normal. Fever profile showed NS1 positivity by ELISA (46.2) with rest of the reports being normal. Electroencephalogram revealed encephalopathy with normal computed tomography of the brain (Figure 2) and magnetic resonance imaging of the brain. Cerebrospinal fluid results (CSF) showed normal glucose, mild elevation of protein (60 mg/dl) (n - 15–40 mg/dl), and normal chloride. CSF cellularity was 70 cells/mm^3 with lymphocyte predominance with normal CSF ADA. CSF CBNAAT and herpes simplex virus (HSV) DNA polymerase chain reaction did not reveal any abnormality. Dengue IgM done 7 days after fever revealed positivity by MAC ELISA.

A diagnosis of dengue encephalitis was made. Treatment was started with IV fluids NS with IVC collapsibility guiding fluid therapy with initial rate of 6 mL/kg/h. The patient was kept in propped-up position with moist oxygen inhalation as arterial blood gas revealed hypoxemia. Ryle's tube and catheterization were done and IV fluid adjustment was performed by urine output monitoring and IVC collapsibility in inspiration and expiration. Injection ceftriaxone and doxycycline with acyclovir injection were started and after scrub typhus IgM and leptospira IgM were negative, doxycycline was stopped and acyclovir was also stopped after CSF did not reveal culture positivity for HSV DNA. CSF culture, urine culture, and blood culture were normal with mild rise of procalcitonin.

The patient started to improve 5 days after admission; Ryle's tube and catheter were removed subsequently; and

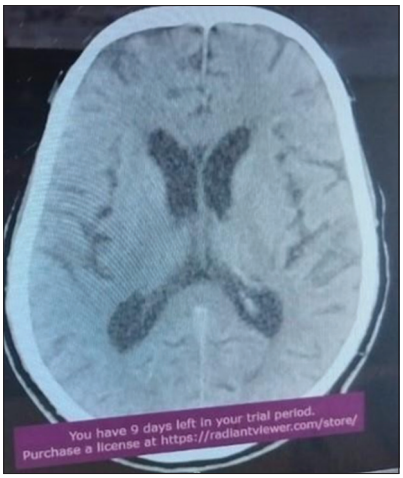

Figure 2: Computed tomography brain showing normal finding of Case 3 dengue encephalopathy

the patient was on oral feeding 8 days after admission. Temperature became normal 7 days after admission after which injection paracetamol was stopped and oral paracetamol SOS was started. Injection ceftriaxone was stopped 8 days after admission, platelet counts improved to 1.9 lakhs/mm^3 with normal serum electrolytes, and the patient was discharged 15 days after admission with advice for follow-up in Medicine and Neuromedicine outpatient department.

DISCUSSION

Dengue fever affects multiple systems of the body with fatal outcomes. The case series presented here depicts unusual manifestations of dengue fever. Expanded dengue syndrome, a term coined by the WHO in 2012, encompasses such manifestations. The pathogenesis of this syndrome has been explained by mainly two mechanisms: The antibody-dependent enhancement process and the Th4 lymphocyte activation along with gamma interferon production. The first case presented as severe aplastic anemia following an episode of dengue fever 6 months before admission. He presented with petechial spots in soft palate and pancytopenia. It was diagnosed by dengue IgG by ELISA and bone marrow study after excluding other causes of hypoplastic anemia. Viruses, including arboviruses have often been implicated for bone marrow failure which is primarily mediated by virus-induced inhibition of replication of hematopoietic stem cells. Dengue infection commonly presents with thrombocytopenia and neutropenia and the bone marrow shows marked hypocellularity with an aberrant megakaryopoesis.[2] After the 7th day, viral infection lymphocytes show an abnormal vacuolization. Reticulocytopenia, lymphocytopenia, thrombocytopenia, and granulocytopenia appear in this order.[3] It is postulated that both the immunological process and direct viral assault to bone marrow instigate dengue-associated aplastic anemia. Our second case is a dengue-induced hepatitis and pancreatitis in an immune-competent young male. Hepatic involvement is the most common systemic manifestation in dengue infection. It can present with mild hepatic dysfunction to fulminant liver failure[4,5] Mechanisms of liver injury in dengue may be attributed to the direct effects of the virus or host immune response on hepatocytes, circulatory insufficiency, or hypoxia caused by capillary leak within the liver or hypotension.[6] The presence of at least two of the following three criteria is required for diagnosis of acute pancreatitis: Acute onset of persistent, severe epigastric pain often radiating to the back, elevation in serum lipase or amylase to 3 times or greater than the upper limit of normal, and radiological evidence of acute pancreatitis on imaging (contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal USG).[7] Our patient met the clinical and biochemical criteria sufficing the diagnosis of acute pancreatitis owing to dengue fever after ruling out other infective, metabolic, drug induced, or iatrogenic causes. Pancreatic enzymes showed a downward trend around the 5th day; these data are alike to those described in the Kumar et al., case report where after 1-week serum amylase and lipase were reduced.[8] Radiological evidence of distended gall bladder has been reported as a common finding in dengue infection as in our case. In our third case, dengue encephalopathy was seen in a case of seropositive dengue infection. Neurological manifestations of dengue fever have been increasingly reported over the past few years. Dengue encephalopathy is a well-acknowledged finding, the incidence ranging from 0.5% to 6.2%.[9] It can be due to variety of causes, such as hepatic malfunction, cerebral edema, cerebral hypo-perfusion any intracranial bleed due to thrombocytopenia or due to direct virus-associated neuronal injury.[10] This case emphasizes the extent to which brain injury that can be present in dengue infection.

CONCLUSION

Dengue affects different systems of the body causing complications. Atypical manifestations often misguide primary care physicians causing diagnostic and treatment delay. The case series presented here is important as hypoplastic anemia, hepatitis, pancreatitis, and encephalopathy are atypical manifestations of dengue with importance of history particularly in the first case of hypoplastic anemia where initial NS1 Ag and IgM antibody positivity with persistence of pancytopenia and IgG antibody positivity during subsequent visit diagnosed the case. The second and third cases presented with hepatitis, pancreatitis, and encephalopathy. Further studies are needed to elucidate the exact incidence and prevalence of atypical manifestations of dengue.

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