Case Report:

Dengue Fever Complicated by Sickle Cell Crisis with Multiple Splenic Infarcts

Dr. B Saroj kumar prusty [1] Dr. Kiran Kumar Ramineni [2] Dr. Abhijeet Ingle [3]
Dr. Krishna Mohan reddy G[4] Dr. Safina Perveen [1] Dr. Majed abdul basit momin [3]

Abstract:

Dengue infections typically present with fever and thrombocytopenia. Although good number of patients improve with supportive care, few can have a fulminant course with multiorgan dysfunction. In endemic zone co-occurring illness like Sickle cell disease can contribute to poor outcome. Various splenic complications of Sickle cell disease include massive splenomegaly with sequestration, large infarcts and abscess requiring splenectomy. We report an interesting case of dengue fever, who developed shock and acute abdomen during hospital stay. Further evaluation revealed multiple splenic infarcts with correlating histopathology and etiological work up including hemoglobin electrophoresis helped in the de novo detection of the underlying sickle cell trait.

Keywords: Sickle cell trait, sickle cell disease, dengue fever, splenectomy

International Journal of Human and Health Sciences Vol. 05 No. 04 October'21 Page : 519-524
DOI: http://dx.doi.org/10.31344/ijhhs.v5i4.367

Introduction:

Dengue fever is a mosquito borne tropical infection caused by flavivirus. The epidemiology of dengue fevers in the Indian subcontinent has been very complex and has substantially changed over the past six decades in terms of prevalent strains, and severity of disease. The classical clinical presentation of dengue virus infection is well known; however, several atypical clinical presentations have also been reported [1].

Sickle cell trait is an inheritable condition with heterozygous allele which usually has asymptomatic or milder course of disease. Under stressful conditions there may be decompensation and significant clinical complications can manifest. The disease of the Asian haplotype is generally milder because of the mutation occurring against a genetic background which is likely to inhibit sickling[2]. We report a case of dengue fever which had a complicated course because of underlying sickle cell trait which was previously undiagnosed.

Case Report:

A 30-year-old male presented with complaints of high grade fever for six days associated with chills, myalgia, lethargy, headache, mild right hypochondrial pain with multiple episodes of vomitings. He did not have any significant past medical history. He was alert and conscious. Vital signs were temperature of 38.3 degree Celsius, pulse rate of 108 beats per minute regular rhythm, normal volume with normal capillary refill time and warm peripheries, blood pressure of 110/70 mm of Hg, respiratory rate of 20 breaths per minute and SpO_2 of 97% under room air. There was no evidence of cutaneous or mucosal rashes or hemorrhagic lesions. Abdominal examination revealed mild right hypochondrial tenderness, mild ascitis without hepatomegaly. Respiratory and cardiovascular system examination was unremarkable. He did not have any focal

1. **Department of Critical care**, Yashoda Hospitals, Malakpet Branch, Hyderabad, Telangana State, INDIA.
2. **Depatment of Neurology,** Yashoda Hospitals, Malakpet Branch, Hyderabad, Telangana State, INDIA.
3. **Department of Laboratory Medicine,** Yashoda Hospitals, Malakpet Branch, Hyderabad, Telangana State, INDIA.
4. **Department of Medicine,** Yashoda Hospitals, Malakpet Branch, Hyderabad, Telangana State, INDIA.

Correspondence to: Mustafa Dogan, MD. Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Ophthalmology. 03200, Afyonkarahisar, Turkey E-Mail: *mustafadogan@yahoo.com*

Table :1 Laboratory data

S. No.	Laboratory parameters	Test Results					
1	**Day of illness**	6th day of illness	9th day of illness - Day 0 of splenectomy	2nd day of post splenectomy	5th day of Post splenectomy	10th day of Post splenectomy	**Biological reference interval**
	Haemogram						
	Hemoglobin	**15**	**7.8**	**8.5**	**9.7**	**11.2**	12 - 15 gm%
	HCT	**48**	**27**	**27**	**29**	**34**	36 - 45 %
	MCV	80	90	90.6	88	86	83 - 101 fl
	MCH	33	32	30.4	31	32	27 - 32 pg
	MCHC	34	33	33.5	32	32	31.5 - 34.5 gm%
	White Blood Cells	**6700**	**24000**	21500	**15400**	10,000	4000 - 11000 / cumm
	Platelets	**0.54**	**1.2**	4.8	**7.2**	6.24	1.5 - 4.5 lakhs/cumm
2	ESR	10					0 - 15 mm end of one hr
3	Reticulocyte count	**1.5%**	**6.0%**	3%		2.0%	0.2 - 2.5 %
4	LFT						
	Total Bilirubin	1	**4.7**	2	**1.8**	1.2	0.2 - 1.3 mg/dl
	Direct	0.2	**0.8**	0.4	**0.6**	0.2	0 - 0.3 mg/dl
	Indirect	**0.8**	**3.9**	1.6	**1.2**	1	0 - 1 mg/dl
	SGOT	646	**542**	187	**94**	57	14-60 U/L
	SGPT	328	**284**	163	**75**	55	0-35 U/L
	Alkaline Phosphatase	172	168	102	**98**	78	38 - 126 U/L
5	S. Creatinine	0.9	**1.6**	1.2	1.12	0.9	0.7 - 1.2 mg/dl
6	S LDH	90	**1380**	436		110	120-246 U/L

neurological deficits or neck stiffness. Basic laboratory investigations on day 6 of illness revealed hemoglobin of 15gm/dl, hematocrit of 48%, white blood cell count 6700/cu mm, thrombocytopenia of 54,000/cmm and increased transaminases level suggestive of mild hepatitis (Table 1).

Patient was admitted to the intensive care unit, with a provisional diagnosis of Dengue fever with warning signs like abdominal tenderness, lethargy and vomiting. Further etiological work up confirmed dengue with strongly positive IgM titer. Other possible differentials such as malaria, leptospirosis and scrub typhus were negative. Ultrasonography of the abdomen revealed mild ascites with gall bladder wall edema and bilateral minimal pleural effusion suggestive of polyserositis. Treatment was initiated with hydration guided by hematocrit levels, ultrasound based volume status on inferior venacava status (IVC status) and other supportive measures.

On day 9 of illness the patient developed left upper abdominal pain with left hypochondrial tenderness, tachycardia and hypotension with complaining of passing brown coloured urine. Ultrasound abdomen was repeated and showed multiple heterogeneous areas of hypodense lesions in the spleen. Patient was suspected to have multiple splenic infarcts with diffuse altered echotexture and moderate perisplenic collection. Patient was provisionally diagnosed to have multiple splenic infarcts with splenic rupture leading to perisplenic hematoma. Hemoperitoneum was confirmed by ultrasound guided diagnostic aspiration. Subsequent laboratory evaluation showed fall in hemoglobin level, with disproportionate elevation of indirect bilirubin, increased reticulocyte count and increase in LDH , suggestive of hemolysis (Table–1) possibly due to splenic syndrome secondary to hemoglobinopathy disorder of sickle cell. However, there were no sickle cells found in peripheral smear. Sickling test and hemoglobin electrophoresis were advised . In view of splenic rupture, perisplenic hematoma and hemodynamic instability, the patient was taken up for emergency laparotomy. Intraoperative findings were

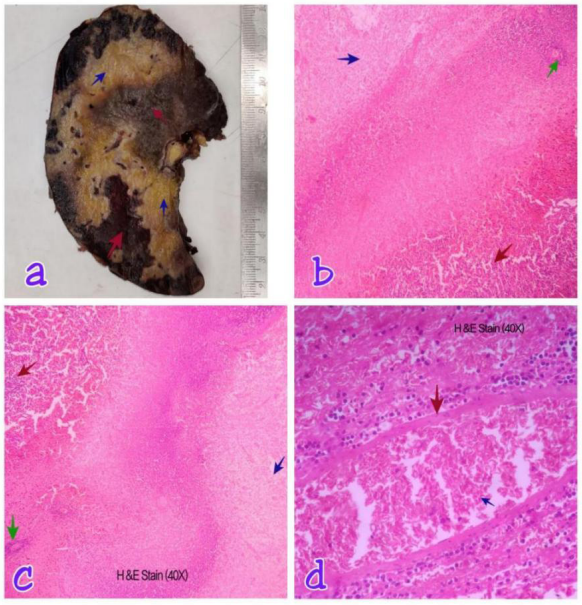

Figure1: Splenectomy specimen cut section & Microscopic findings

Figure1a: Spleen cut section show yellowish areas (blue arrow) with brownish areas in between (red arrow)

Figure1b &c: Microscopic examination (H&E stained 40X) areas of necrosis (blue arrow), congested blood vessels (green arrow) and preserved splenic parenchyma

Figure 1d: Microscopic examination (H&E stained 40X) blood vessels engorged with sickled RBCs

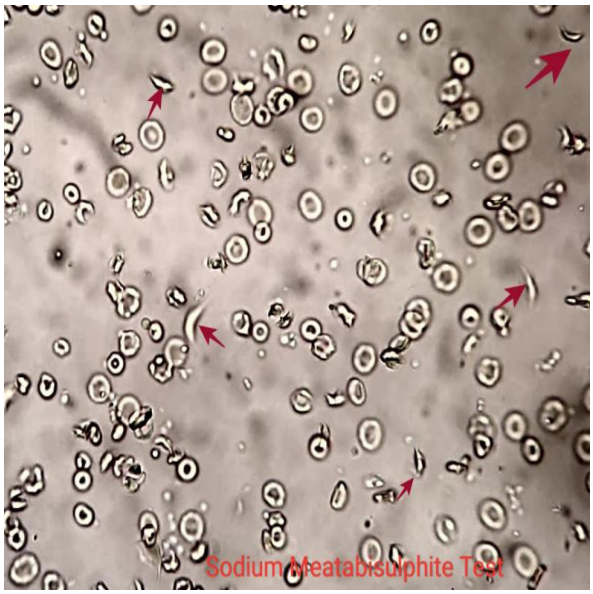

Figure : 2 Sickling Test (2% sodium metabisulphite) show positive sickle cells

Table 2: Hemoglobin electrophoresis (HPLC)

Investigation	Observed Value	Unit	Biological Reference Interval
HEMOGLOBIN A	**75.1**	**%**	95-98%
HEMOGLOBIN A2	2.8	%	2.0-3.7
HEMOGLOBIN F	0.7	%	0.1- 1.2
HEMOGLOBIN S	**20.7**	**%**	0.0-0.0
HEMOGLOBIN D	0.0	%	0.0-0.0
HEMOGLOBIN C	0.0	%	0.0-0.0
Unknown unidentified	0.7	%	0.0-2.0

hemoperitoneum (1.5L hemorrhagic peritoneal fluid) with subcapsular splenic bleed with soft, congested, fragile patchy

brownish colored spleen. Splenectomy was done. The patient was hemodynamically stabilized by transfusing Intravenous fluids, blood and blood products. Patient was shifted to a medical ICU post operatively for monitoring vitals and kept on ventilator support. As the patient was further stabilized hemodynamically and tolerated the spontaneous breathing trial on the second postoperative day, the patient was weaned off from the ventilator.

Gross examination of spleen showed markedly congested capsule and focal irregular brownish and geographic whitish areas. On serial slicing cut sections showed geographic yellowish areas with brownish areas in between (Figure 1a). Microscopic examination showed large areas of coagulative necrosis rimmed by markedly congested blood vessels, neutrophilic infiltrates consistent with multiple splenic infarcts (Fig – 1b&c). Congested blood vessels engorged with sickled RBCs (Fig – 1D)

Sickling test in peripheral blood performed using 2% Sodium metabisulphite was positive for delayed sickling (after 24 hours incubation) (Figure 2).

Hemoglobin electrophoresis by High Performance Liquid Chromatography method (HPLC) showed hemoglobin S of 20.7 %, suggestive of Sickle cell trait (Table 2)

Post splenectomy platelet count and WBC counts increased as a physiological response, mentioned in (Table – 1). He was started on Tablet Aspirin 75mg once daily and discharged successfully on seventh postoperative day in stable condition. During follow ups he maintained improvement and was independent for all activities of daily living. Post splenectomy vaccination was completed. Based on the clinical features supported with

laboratory and histopathology evidence, final diagnosis of sickle cell vaso-occlusive crisis resulting in multiple splenic infarcts (called as splenic syndrome) in a de novo detected sickle cell trait during acute dengue fever was made.

Discussion:

The case presented here is a young male who presented with acute febrile illness, with thrombocytopenia, polyserositis, hepatitis and warning signs of abdominal pain, vomiting, lethargy, fluid accumulation, and increased hematocrit. In hospital evaluation, confirmed the diagnosis of dengue fever with warning signs. He had a complicated course and developed acute onset left hypochondrial pain, hypotension, pallor, thought of patient developed severe dengue, but the multiple heterogeneous areas of hypodense lesions in the spleen (multiple splenic infarcts), perisplenic blood collection (splenic rupture), and altered splenic echotexture in rapid bedside ultrasound with brown coloured urine, with features of hemolysis from laboratory values of fall in hemoglobin, increased indirect bilirubin, LDH, and reticulocyte count, led to high clinical suspicion of acute hemolytic anemia with splenic syndrome, secondary to sickle cell disease. Evaluated by hemoglobin electrophoresis, peripheral smear and spleen biopsy while Emergency laparotomy with splenectomy, which confirmed the diagnosis of Sickle Cell trait (SCT). High clinical suspicion and emergency surgical management, helped in better outcome, otherwise abdominal pain, shock status, hepatitis could have been easily misinterpreted as part of Severe dengue illness.

Dengue fever is a viral illness caused by RNA Flavivirus, transmitted by *Aedes aegypti* mosquito. Indian subcontinent is endemic for dengue because of the tropical climate. Dengue virus has five identified serotypes. Most of the Dengue cases are asymptomatic or cases with mild symptoms only. The actual incidence of Dengue in endemic countries like India is unknown because of under reporting of mild symptomatic cases [3] . The clinical presentation of dengue can vary from mild dengue fever with or without warning signs to severe dengue with multiorgan dysfunction leading to death. As per world health organization (WHO-2009) criteria for warning signs, may be any one of the following, includes, abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement more than 2 centimeter, and an increase in hematocrit (HCT) accompanied by decrease platelet count. Criteria for severe dengue, any one of following includes, severe plasma leakage leading to dengue shock syndrome and fluid accumulation with respiratory distress, severe bleeding, and severe organ involvement including the liver (AST or ALT levels more than 1000) the central nervous system (impaired consciousness), the heart and other organs[4]. Our patient presented as Dengue with warning signs at the time of admission, later developed a clinical picture similar to severe dengue, but turned out as sickle cell trait (SCT) complicated with splenic syndrome, previously not diagnosed.

Sickle cell trait (SCT) is usually less severe with minimal or no manifestations [5]. SCT is diagnosed by detecting the presence of HbS (20-40 %), and HbA (80-60 %) on hemoglobin electrophoresis. The peripheral smear in SCT has normal RBC morphology, with the exception of a few target cells, however a sickling test with 2% sodium metabisulphite yields a positive result. SCT does not cause vaso-occlusive crisis, unlike that of sickle cell disease. The susceptibility of red blood cells to sickle depends on the concentration of HbS. However, patients with sickle cell trait could have the same presentation as sickle cell anemia if they are exposed to conditions that favor sickling and vaso-occlusive crisis. Conditions include less oxygen content of the inspired air (hypoxia), cardiac & pulmonary status, dehydration, infections, hypothermia or hyperthermia and release of inflammatory cells. The HbS will result in the clogging of tiny capillary vessels most especially in the bones and organs by sickled red blood cells. Development of splenic infarcts in SCT is reported with high altitude hypoxemia and infections [5]. In our case, at the time of crisis , on 9th day of illness, routine peripheral smear was negative for sickle cell, but a sickling test using 2% sodium metabisulphite showed positive sickle cells after 24 hr incubation(delayed sickling). Further hemoglobin electrophoresis confirmed the SCT.

Dengue fever complicated by Sickle cell crisis with Multiple splenic infarcts in SCT has not been reported in India. However, there are reports of severe dengue with deaths in patients of sickle cell disease and trait from central and south America. The highest frequency of sickle cell disease is found in tropical regions particularly Sub-Saharan Africa, few tribal regions of India

and the middle east[6]. Dengue infection in sickle cell Anemia (HbSS) has poor outcomes [7]. The data available on association of sickle cell disease and dengue infection is based on case series and some retrospective studies. Existing literature suggests that the risk of fatal dengue may be higher among patients with a relatively mild genotype (hemoglobin SC - HbSC), although exact incidence and extent of risk is unclear[6]. The evidence of poor outcomes in sickle cell disease patients infected with dengue can be extrapolated to the following mechanism. Patients with HbSC are more susceptible to fatal dengue because red blood cells (RBC) are more prone to dehydration secondary to potassium loss from RBCs. This leads to a greater propensity for dense cell formation compared to HbSS (sickle cell disease) [6]. The higher mean cell hemoglobin concentration (MCHC) in these dense cells causes both an increase in Hemoglobin S polymerization and may reduce the time for sickling. The dengue virus either alters the HbSC red blood cell rheology by triggering dehydration or changes the endothelial adhesivity resulting in a massive vascular leak syndrome and intravascular dehydration which further leads to massive sickling[8] .

Neo-angiogenesis is the other possible mechanism which could explain a higher morbidity in HbSC patients[8]. Endothelial cells of blood vessels produced by neo-angiogenesis become more permeable in response to inflammatory cytokines such as High mobility group box 1 (HMGB1) . The increased expression of HMGB1 protein is well described in sickle cell vaso-occlusive crises [9] . Same protein is thought to play an important role in dengue shock syndrome resulting in massive vascular leakage and intravascular dehydration [10]. The RBCs and endothelium are probably the common targets for both Dengue and Sickle cell disease [11]. Massive splenic infarction which is arbitrarily defined as infarction involving more than 50% of the spleen size is almost unknown among adults with Sickle cell trait, but there are reports of massive splenic infarcts in patients with sickle cell disease, and hemoglobin SC disease, seen particularly in association with stress, hypoxia or following air travel especially in unpressurized aircrafts [12].

Here in our case because of dengue with warning signs, might have complicated the undiagnosed SCT with multiple splenic infarcts, acute hemolysis, and splenic rupture with a possible mechanism of severe intravascular dehydration in spite of fluid resuscitation due to worsening capillary leak syndrome. Clinical picture was confused with severe dengue, however early high index of clinical suspicion and diagnosis have saved the patient .

Conclusion:

Multi organ dysfunction is known to occur in dengue infection. Co-existing previously undiagnosed pathologies like sickle cell trait may contribute to acute deterioration. High index of clinical suspicion for timely diagnosis of comorbidities and close monitoring help in the appropriate management of complicated dengue cases.

Source of Fund: Not applicable

Conflict of Interest: None declared

Ethical clearance: Written consent has been obtained from the patient.

Authors contribution:

Concept and design: Dr. B Saroj kumar prusty(SKP) , Dr. Kiran Kumar Ramineni (KKR), D**r. Safina Perveen (SP) Dr. Majed abdul basit momin (MBM)**

Major revision of the article: SKP, KKR, MBM

Final approval of the article: SKP, KKR, MBM,AI, KMR and SP.

References:

1. Gupta N, Srivastava S, Jain A, Chaturvedi UC. Dengue in India. Indian J Med Res 2012;136(3):373–90.
2. Serjeant GR, Ghosh K, Patel J. Sickle cell disease in India: A perspective. Indian J Med Res 2016;143(1): 21-4.
3. Das S, Sarfraz A, Jaiswal N, Das P. Impediments of reporting dengue cases in India. J Infect Public Health 2017;10(5):494-8.
4. Guzman, M., Gubler, D., Izquierdo, A. et al. Dengue infection. Nat Rev Dis Primers 2016;16055(8): 1-25.
5. Sears DA. The morbidity of sickle cell trait. The American Journal of Medicine 1978;64(6): 1021-36.
6. Wilder-Smith A, Leong WY. Risk of severe dengue is higher in patients with sickle cell disease: a scoping review. J Travel Med 2019;26(1): 937-41.
7. Moesker FM, Muskiet FD, Koeijers JJ, Fraaij PL, Gerstenbluth I, van Gorp EC et al. Fatal dengue in patients with sickle cell disease or sickle cell anemia in Curaçao: two case reports. PLoS Negl Trop Dis 2013;7(8):e2203.
8. Rankine-Mullings A, Reid ME, Moo Sang M, Richards-Dawson M, Knight-Madden JM. A Retrospective Analysis of the Significance of Haemoglobin SS and SC in Disease Outcome in Patients with Sickle Cell Disease and Dengue Fever. EBio Med 2015; 2(8): 935–9.
9. Xu H, Wandersee NJ, Guo Y, Jones DW, Holzhauer SL, Hanson MS et al. Sickle cell disease increases high mobility group box 1: a novel mechanism of inflammation. Blood 2014;124(26): 3978-81.
10. Ong SP, Lee LM, Leong YFI, Ng ML, Chu JJH. Dengue Virus Infection Mediates HMGB1 Release from Monocytes Involving PCAF Acetylase Complex and Induces Vascular Leakage in Endothelial Cells. PLoS One 2012;7(7):e41932.
11. Iversen PO, Abisay M, Seleki F, Majigo M, Luzzatto L, Makani J. Sickle cell disease, malaria and dengue fever: a case of triple jeopardy. Journal of Travel Medicine 2019;26(7):1-2.
12. Al-Salem, AH. Splenic complications of sickle cell anemia and the role of splenectomy. ISRN Hematol 2011;2011: 864257.