A Rare Combination in Dengue Fever: Acute Pancreatitis With Normal Enzyme Levels

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ABSTRACT
Dengue is one of the most important emerging viral disease of humans in the world afflicting humanity in terms of morbidity and mortality. Currently the disease is endemic in all continents except Europe. We present a rare combination of events in dengue fever in form of Acute Pancreatitis (rare complication),which was clinically and radiologically proven but with Normal Amylase and Lipase levels. Neither the pathogenesis of acute pancreatitis in dengue nor the normal enzyme levels in acute pancreatitis are clearly understood, but various mechanisms are postulated. The challenges faced in the diagnosis of Acute Pancreatitis, awareness and timely recognition of this complication are very important for proper management especially in Dengue fever.

KEYWORDS: Dengue fever, Acute Pancreatitis, Amylase, Lipase

INTRODUCTION
Dengue fever is an arthropod-transmitted viral disease having the greatest epidemiological, social, and economic impact. It is an increasing threat to global public health. Dengue is a self limiting acute mosquito transmitted disease characterized by fever, headache, muscle, joint pains, rash, nausea and vomiting. Dengue Fever (DF) is caused by an arbovirus and spread by Aedes mosquitoes. The first evidence of occurrence of DF in the country was reported during 1956 from Vellore district in Tamil Nadu. All the four serotypes i.e. Dengue 1,2,3 and 4 have been isolated in India. As Aedes aegypti breeding is more common in urban areas the disease was observed mostly prevalent in urban areas but now prevalent in rural areas too. In 2015 till OCT 15 a total of 64058 cases were confirmed and a total of 135 deaths occurred[1].

Severe dengue (Dengue Hemorrhagic Fever- DHF and Dengue Shock Syndrome-DSS) is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Various common complications of severe dengue are myocarditis, encephalitis, acute motor weakness, Guillane–Barre like syndrome, acute liver failure, lupus erythematosus, hemophagocytic syndrome, acute kidney injury etc[2]. Acute pancreatitis is a very rare complication of DF. Here, we report a case of Acute Pancreatitis Fatally Complicating Dengue Fever with Normal Enzyme Levels.

CASE REPORT
A 36 year old male who was non alcoholic, non diabetic and non hypertensive ,thin individual presented to acute medical care with complaints of fever 20 days back, high grade lasted for two days and subsided. It was associated with abdominal pain, abdominal distention and vomiting. His pain in abdomen was acute in onset and severe in intensity, localized to epigastrium which was radiating to back. There was bilious vomiting of 4-5 episodes. There was no history of headache, myalgia, sore throat, cold/cough, rash, petechiae, jaundice, breathlessness, diarrhea or decreased urine output, constipation, obstipation, trauma or drug history. On examination, he was conscious, oriented, Icteric, no rash or petechiae and afebrile .All is vitals are stable except Blood Pressure-150/90 mm Hg. Systemic examination is normal except distention of abdomen with diffuse tenderness more in epigastric region, with no organomegaly and sluggish bowel sounds.

Following investigations were done: Hemoglobin - 12.3 g/dL, Hematocrit - 39 vol%, Total Leukocyte count -15500 cells/cumm, Platelets -2,67,000cells/µL, Coagulation profile is in normal limit.NS1 antigen for dengue - Positive (suggestive of acute severe infection with dengue virus with thrombocytopenia) , Salmonella typhi O & H, Salmonella paratyphi A & B – titres are in normal limits .MP QBC – Negative. Serum Total Bilirubin – 4.5mg/dl ,Direct – 3.64mg/dl, AST -92 U/L , ALT – 43 U/L,ALP – 383 U/L,
Serum Albumin – 2.3 g/dl. Serum Amylase -28 U/L ,Serum Lipase -42 U/L .Renal Function Tests and Electrolytes are in normal limits. Viral Screening for HIV, HBsAg, HCV were non reactive, ECG showed Incomplete Right Bundle Branch Block. Chest X-ray is normal.(Fig 1.) Ultrasound abdomen revealed -mild ascites and right minimal pleural effusion. GB well distended and pancreas appeared normal(obliterated vision due to bowel gas). X-Ray Erect abdomen is normal.

Provisionally the diagnosis of Dengue Fever With Hepatitis With the possibility of Acute Pancreatitis was made and patient was Empirically started on following treatment : -Nil By Mouth, Ryles tube was inserted. Intravenous fluids 0.9% NS/DNS at 100mL/h along with parenteral antibiotics – Injection Ciprofloxacin 400mg intravenous (IV) 12th hourly , Injection Metronidazole 500mg IV 8th hourly were started. Supportive treatment with Injection Pantoprazole IV infusion @ 8mL/hr, Injection Ondesetron 4mg IV 8th hourly, Injection Tramadol 40 mg slow IV 12th hourly were given. On 2nd day of admission, patient still complained of abdominal pain. A computerized tomography (CT) of abdomen was done to rule out diagnosis of pancreatitis. CT abdomen revealed: Mildly bulky pancreas showing heterogenous attenuation with mild peripancreatic fat stranding and fluid. F/S/O Acute Pancreatitis (MCTSI – 6).(Fig 2.) To rule out other causes of Pancreatitis following investigations were done:-Serum Calcium and Fasting Lipid Profile were in normal range. Serum LDH – 1828 IU/L.

Treatment was continued with bowel rest, hydration, pain control and hepatoprotective drugs. On Day 3 , patient complained of breathlessness. On examination patient was tachypneic, bilateral rales were heard .ABG and X-ray were taken which revealed hypoxemia and diffuse alveolar infiltrates. PaO2/FiO2 ratio – 168 mm Hg. So, the diagnosis of ARDS was entertained and patient was given mechanical ventilator support with change of antibiotics to Injection Metronidazole 500mg IV 8th hourly for 7 days later continued with Injection Tigecycline 50 mg IV 12th hourly and Injection Colistin 1 MU IV 8th hourly for 10 days and patient was successfully weaned off the ventilator on Day 21.Patient was discharged on 28th day. So, finally it was diagnosed as Dengue Fever complicated with Hepatitis and Acute Pancreatitis with ARDS.

DISCUSSION

Dengue is the most important arthropod-borne viral disease, and it is a major public health problem in subtropical and tropical regions. Dengue is an arthropod borne single-stranded RNA virus belonging to family Flaviviridae and transmitted by vector Aedes aegypti. There are four serotypes of dengue virus–DENV-1, DENV-2, DENV-3, and DENV-4. Dengue virus manifests as minor flu-like illness to critical disease. Dengue Fever has three phases: a febrile phase, critical phase, and recovery phase. The critical phase usually consists of severe increase in capillary permeability, shock from plasma leakage, severe hemorrhage, and organ impairment. Our case met the WHO criteria (2012) of case definition of Dengue with warning signs[3]. Critical phase of dengue is usually highlighted by leucopenia (<5000/cumm), low platelet counts, and a rising hematocrit due to plasma leakage. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase as a stress response . In addition, severe organ involvement may develop such as severe hepatitis, encephalitis, myocarditis, and/or severe bleeding, without obvious plasma leakage or shock [4].

But on presentation our patient had leukocytosis, normal platelet count, normal hematocrit and hepatitis. This may be explained by the fact that the patient had a mild plasma
leakage only which may be responsible for a baseline normal hematocrit value. Leucocytosis can be due to stress response due to the disease condition itself.

There are various atypical presentations of Dengue fever: Neurological :- Encephalopathy, Acute motor weakness, Seizures, Neuritis, Guillain-Barre syndrome, Hypokalemic paralysis, Acute viral myositis, and Acute encephalitis Gastrointestinal:- Acute hepatic failure, Coagulation disturbances, Hepatitis, Pancreatitis Cardiac :- Myocarditis, Sinoatrial block, and Atroio-ventricular dissociation Others :- Systemic lupus erythematosus, Uveitis, Acute kidney injury, Acute inflammatory colitis, Kawasaki disease, Hemophagocytic syndrome, which have been documented in the literature[2].

Till date, there have been only a few case reports of acute pancreatitis complicating Dengue Fever from across the world. Our patient also had dengue fever which was complicated by acute pancreatitis with a normal serum amylase and lipase and ultrasound findings but evidenced by CECT abdomen. Hyperlipasemia and enlarged pancreas have been known to occur in Dengue Fever, but acute pancreatitis is an atypical and rare presentation[3,6,7,8]. The largest described series was in an Dengue Hemorrhagic Fever outbreak in Taiwan in 2002 were pancreatitis (defined by a lipase level threefold greater than the upper limit of normal) was diagnosed in three patients with acute Dengue Hemorrhagic Fever, other few isolated cases have been described in Thailand, Indonesia, Noumea (New Caledonia), Colombia, India[9].

The exact pathogenesis of pancreatic involvement in dengue is not known. But it can be due to result of direct invasion by the virus itself causing inflammation and destruction of pancreatic acinar cells, pancreatic damage due to dengue shock syndrome or acute viral infection causing an autoimmune response to pancreatic islet cells and development of edema of the ampulla of Vater with obstruction to the outflow of pancreatic fluid[9,10]. In our case, we presume it is due to direct invasion of virus.

An infectious agent should be suspected as the cause of AP if the characteristic syndrome due to the infectious agent is present, which is seen in 70% of cases [11]. Criteria suggested for associating pancreatitis with an infective etiology include : (a) Finding the organism in pancreas or pancreatic duct, which is ‘Definitive criteria’. (b) Culture of the organism from the pancreatic juice or blood or serological evidence combined with characteristic clinical or epidemiological setting ‘Probable criteria’ and (c) Culture of the organism from other body sites or serological evidence of infection, which is ‘Possible criteria’ [12].

The diagnosis of acute pancreatitis is made based on relevant clinical features including severe abdominal pain, nausea, vomiting and elevation of pancreatic enzymes with serum amylase and/or lipase levels usually three times the upper limit of normal[13,14]. Abdominal imaging with CT, magnetic resonance imaging (MRI), or trans abdominal ultrasonograph (US) can be helpful in confirming the diagnosis of pancreatitis or ruling out other etiologies of acute abdominal pain that may cause mild elevations of serum pancreatic enzymes[13].

Lipase is a 48 kD pancreatic enzyme that is involved in digestion. Lipase level increases within four to eight hours of acute pancreatitis, peaks at 24 hours, and remains elevated for one to two weeks, typically longer than amylase levels [13,15,16].

Lipase is more sensitive and specific than amylase in diagnosing acute pancreatitis, with a negative predictive value of 94% to 100% [15,16]. Therefore, normal lipase level in the setting of acute abdominal pain is often used to rule out a diagnosis of acute pancreatitis. Lactate dehydrogenase (LDH), one of the 11 criteria of the Ranson score, has also been studied independently. Chen and coworkers [17] found that in 42 patients with acute pancreatitis, serum LDH activity was significantly higher in severe than in mild attacks. Other conditions that can raise LDH levels include hemolysis, severe infections , sepsis, brain infarcts, meningitis, encephalitis, pulmonary infections and infarcts, liver diseases, pancreatitis, muscle injury and myositis, HIV and many others[18]. Our patient was admitted with a Dengue fever complicated with clinical picture and radiographic findings consistent with acute pancreatitis despite normal lipase and amylase levels throughout the hospital course. In the case of our patient, the etiology of acute pancreatitis was due to dengue fever which is a rare presentation. A literature search yielded two cases of asymptomatic acute pancreatitis with normal lipase levels similar to our patient. However, neither reported the likely etiology for acute pancreatitis [15,16].

CONCLUSION

This is an unusual and the first case reported with combination of Dengue fever complicated with Acute pancreatitis with normal amylase and lipase levels with ARDS . This case proves once again that, clinical judgment should never be replaced by laboratory studies for appropriate diagnosis ,even though they are useful for confirmation of the diagnosis. Timely recognition and understanding the pathogenesis can help deal with complex systemic manifestations and proper management.

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