Dengue Infection: A Hidden Cause of Acute Insult in a Case of Acute on Chronic Liver Failure in Endemic Area

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Abstract: Acute on chronic liver failure (ACLF) can be precipitated by several factors such as bacterial infection, alcohol intake, viral hepatitis, surgery, etc. Identification of precipitating factor is an important part of management of ACLF. A middle aged gentleman was presented with features of acute liver failure and after through history and investigations, he was diagnosed as acute on chronic liver failure. Chronic liver disease was first diagnosed after this event of acute insult. Precipitating factor of ACLF was dengue fever in this case report. Therefore, in endemic area of dengue infection, dengue serology tests which are not routinely done should be advised to identify dengue infection as an acute insult in ACLF.

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Case report
Fifty-year-old non-diabetic, non-hypertensive gentleman, who was on alcohol (more than three standard drinks per day) for last 15 years, was admitted with fever, abdominal distension, and jaundice for 10 days duration, and altered sensorium for last 3 days duration. He had no history of any herbal medication or binge of alcohol intake before onset of jaundice and also he did not have any history of melena or haematemesis during or before this event. On admission, he was hemodynamically stable but disoriented. Pulse rate and blood pressure were 116/min and 110/82 mm Hg respectively. On physical examination, he had anaemia, jaundice, pedal edema, fever and grade III hepatic encephalopathy but no palmar erythema, spider nevi (angiomata), gynaecomastia. On abdominal examination, he had free fluid in abdomen, and respiratory system and cardiovascular system were normal. Initially he was treated in local hospital and then referred to our hospital for further evaluation and management.

After taking history and physical examinations, provisional diagnoses were acute liver failure (ALF) (in view of jaundice followed by ascites and grade III hepatic encephalopathy within ten days of onset of jaundice), acute on chronic liver failure (ACLF) (suspected aetiology of chronic liver disease was alcohol, and suspected

| Investigations                         | Test value at the time of admission | Laboratory value at the time of follow-up visit |
|----------------------------------------|-------------------------------------|-----------------------------------------------|
| Haemoglobin                            | 8.9 g/dl                            | 10.6 g/dl                                     |
| White blood cell (WBC) count           | 9,000/cu mm                         | 7,000/cu mm                                   |
| Platelet count                         | 128,000/cu mm                       | 152,000/cu mm                                 |
| Prothrombin time                       | 25.8 s                              | 18.7 s                                        |
| Mean normal prothrombin time           | 12.3 s                              | 12.3 s                                        |
| International normalized ratio          | 2.16                                | 1.55                                          |
| Total bilirubin                        | 10.5 mg/dl                          | 3 g/dl                                        |
| Direct bilirubin                       | 5.3 mg/dl                           | 1.2 g/dl                                      |
| Aspartate aminotransferase             | 94 U/l                              | 72 U/l                                        |
| Alanine aminotransferase               | 99 U/l                              | 46 U/l                                        |
| Albumin                                | 2.3 g/dl                            | 2.7 g/dl                                      |
| Creatinine                             | 1.63 mg/dl                          | 0.92 mg/dl                                    |
| Sodium                                 | 133 mmol/l                          | 136 mmol/l                                    |
| Potassium                              | 2.9 mmol/l                          | 3.7 mmol/l                                    |
| Ammonia                                | 197 µmol/l                          | not done                                      |
| Procalcitonin                          | <0.10 ng/ml                         | not done                                      |
| C-reactive protein (CRP)               | 26.4 mg/l                           | 9.5 mg/l                                      |
| Blood smear for malaria parasite       | not found                           | not done                                      |
| Glycosylated (HbA1c)                   | 5.6%                                | not done                                      |
| pH(Arterial blood gas analysis)         | 7.423                               | not done                                      |
| Lactate                                | 2 mmol/l                            | not done                                      |
acute insult was infection and/or alcohol) and acute severe alcoholic hepatitis (in view of alcohol intake for last 15 years).

On the day of admission, laboratory examinations of blood (Table 1) showed: total leukocyte count 9,000/cu mm, hemoglobin 8.9 g/dl, platelet count 128,000/cu mm, mean corpuscular volume 114.8 fl, creatinine 1.63 mg/dl, Na\(^+\) 133 mmol/l, K\(^+\) 2.9 mmol/l, procalcitonin < 0.10 ng/dl, arterial ammonia 197 µmol/l, prothrombin time 25.8 s (control: 12.3 s), and international normalized ratio (INR) 2.16.

His liver function test (LFT) showed following abnormalities: total bilirubin 10.5 mg/dl, aspartate aminotransferase (AST) 94 U/l, alanine aminotransferase (ALT) 53 U/l, albumin 2.3 g/dl, alkaline phosphatase (ALP) 99 U/l. Blood, urine and ascitic fluid culture showed no growth. Chest X-ray (PA – posteroanterior view) and echocardiography were normal. HBsAg, IgM anti Hbc, total anti Hbc, anti HCV, anti HAV IgM and anti HEV IgM were non-reactive (Table 2). At the time of hospital admission his MELD score and CTP score were 29 and 13 respectively (Table 3).

Contrast enhanced computed tomography of brain was done in view of altered sensorium and showed no abnormality but ultrasonography (USG) abdomen identified following abnormalities: course echotexture of liver, splenomegaly and moderate ascites.

| Table 2 – Serology tests at the time of admission |
| Tests | Result |
|-------|--------|
| Anti HAV IgM | non-reactive |
| Anti HEV IgM | non-reactive |
| HBsAg | non-reactive |
| IgM anti Hbc | non-reactive |
| Total anti Hbc | non-reactive |
| Anti HCV antibody | non-reactive |
| Dengue IgM antibody | reactive |
| NS1 antigen test | positive |
| Malaria antigen test | negative |

HAV – hepatitis A virus; HEV – hepatitis E virus; HBsAg – hepatitis B surface antigen; HCV – hepatitis C virus

| Table 3 – Different scoring system at the time of admission |
| Score | Value |
|-------|-------|
| MELD score | 29 |
| MELD\(_{\text{Na}}\) score | 30 |
| Child-Pugh-Turcotte score | 13 (class C) |
| APASL ACLF research consortium (AARC) score | 11 |

APASL – Asian Pacific Association for the Study of the Liver; MELD – Model for End-stage Liver Disease
Stool was sent for occult blood test in view of anaemia and revealed positive result. Stool culture was not done because he did not have any history of loose stool. Upper GI (gastrointestinal) endoscopy showed grade II oesophageal varices but no active bleeding or presence of any red colour sing, mild portal hypertensive gastropathy without red spots, and no gastric varix.

After abdominal USG and upper GI endoscopy, acute liver failure was excluded from provisional diagnosis. Initially we thought it was a case of acute on chronic liver failure (ACLF) (aetiology of CLD – chronic liver disease – was alcohol; acute insult was alcohol intake in view of no bacterial growth in blood, urine and ascitic fluid culture and normal blood procalcitonin value).

Dengue serology was advised in view of dengue outbreak in our area (dengue endemic area) and report showed that dengue IgM antibody and NS1 antigen were positive. After this blood report our final diagnosis was ACLF (aetiology of CLD was alcohol and acute insult was dengue infection).

He was treated conservatively and improved symptomatically. Twenty-two days after admission, he was discharged in stable condition and advised to come for follow-up after 2 weeks from the date of discharge.

Discussion
ACLF definition was first proposed by Asian Pacific Association for the Study of the Liver (APASL) in 2009 and again modified in 2014. According to APASL (2014), “ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dl (85 micromol/l) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%) which is complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality” (Sarin et al., 2014). According to World Gastroenterology Organization (WGO), “ACLF is a syndrome in patients with CLD with or without previously diagnosed cirrhosis characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the international normalized ratio), and one or more extra hepatic organ failures, that is associated with increased risk for mortality within a period of 28 days and up to 3 months from onset” (Jalan et al., 2014). In our case, patient was suffering from chronic liver disease which was undiagnosed before incidence of acute insult. Aetiology of CLD was alcohol intake, and acute insult was dengue infection. Our case was diagnosed as acute on chronic liver failure by following the APASL diagnostic criteria of ACLF.

ACLF management needs treatment of underlying precipitating factor, organ failure support and other supportive care. Treatment plan depends on MELD score; when MELD score < 30, ACLF is treated by supportive care but if MELD score ≥ 30, patient should be sent for urgent liver transplantation evaluation (Sarin et al., 2014; Sarin and Choudhury, 2016). Organ failure is not a contraindication for transplantation, except when patient needs cardiac or pulmonary support or has rapidly progressing organ failure at day four or seven (Sarin et al., 2014).
APASL ACLF research consortium (AARC) score of ACLF (based on MELD and lactate) is highly specific and sensitive to assess prognosis and has better predictive value than MELD or CLIF-SOFA score (Sarin et al., 2014). ACLF grade (based on CANONIC study) predicts mortality and patients with grade 3 ACLF show the poor prognosis compared with ACLF grade 1 and 2 (Moreau et al., 2013). Chronic Liver Failure Consortium ACLF score (CLIF-C ACLF score) showed a significantly higher predictive accuracy than MELD, MELD-Na and Child-Pugh-Turcotte score after ACLF diagnosis. Number of organ failure is also a predictor of morbidity and mortality in ACLF.

Liver enzymes are elevated in 30% of the cases of dengue fever (Lee et al., 2012). Dengue related acute liver failure has been described in few case reports and majority of them are reported in children and young age group (Subramanian et al., 2005). Cirrhotic patients usually do not have classical features of dengue and associated with poor prognosis. Dengue should be suspected as a cause of liver failure in endemic areas where no precipitating factor is identified (Kulkarni et al., 2019). Therefore, in endemic areas, dengue can cause acute insult on chronic liver disease resulting in ACLF. In our study, dengue was responsible for worsening of chronic liver disease.

**Conclusion**

Dengue infection is commonly presented with uncomplicated dengue fever. Dengue infection can cause asymptomatic elevation of liver enzymes and rarely acute liver failure. Like other hepatic complications, dengue infection can be responsible for acute insult on chronic liver failure leading to ACLF. So in dengue endemic area if patient is presented with acute hepatic decompensation or ACLF, dengue serology test should be done along with other investigations to rule out dengue infection as an acute insult.

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