A Case of Acute-on-Chronic Liver Failure (ACLF) Due to An Uncommon Acute And Chronic Event

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Acute on Chronic Liver Failure (ACLF) is an acute worsening of patients with chronic liver disease resulting in liver failure. Usually these patients have cirrhosis as the underlying liver disease with alcohol being the most common etiology. Common hepatic illnesses causing acute worsening in Indian patients of ACLF include alcoholic hepatitis, acute viral hepatitis related to hepatitis E virus and acute flare in chronic hepatitis B. We report an adult case of ACLF due acute viral hepatitis related to hepatitis A virus infection superimposed on nonalcoholic steatohepatitis without cirrhosis. (J CLIN EXP HEPATOL 2018;8:95-97)

Acute on Chronic Liver Failure (ACLF) has been defined by the Asia-Pacific Association for the Study of Liver (APASL) as acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.¹ There is an East versus West divide in the underlying chronic liver disease and the etiology of acute precipitating events in patients with ACLF. As per the APASL criteria patients with chronic liver disease not amounting to cirrhosis such as chronic hepatitis B and Nonalcoholic Steatohepatitis (NASH) can also present as ACLF after a superadded acute insult¹ whereas the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines would include only patients with established cirrhosis as the underlying chronic liver disease in ACLF.² Similarly, the common acute precipitating events are either superadded acute hepatitis E or flare of chronic hepatitis B in Asian patients with ACLF in

contrast to alcohol and extra-hepatic infection/sepsis as the acute events in the data from West. Alcohol and hepatitis B virus are the common causes of chronic liver disease in ACLF in India, with a small fraction constituted by the cryptogenic cirrhosis related to burnt out NASH.³ Hepatitis A Virus (HAV) is an infrequent cause of acute viral hepatitis in adults and hence an uncommon cause of acute precipitating event in adult patients with ACLF.^{3,4}

We report an adult patient with ACLF with HAV related acute viral hepatitis as the acute precipitating event in an asymptomatic patient with NASH not amounting to cirrhosis liver.

CASE REPORT

A 34-year-old, non-alcohol consumer male with a body mass index of 24.4 kg/m², belonging to good socio-economic status with no addictions or co-morbid illnesses, presented with one month history of jaundice preceded by a prodrome of nausea, vomiting and fever for 2 days. Ascites and pedal edema appeared 3 weeks after the onset of jaundice. Investigations done in the first week of his illness showed Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) levels >20 times of Upper Limit of Normal (ULN), with bilirubin 14 mg/dL (conjugated 10 mg/dL), serum Alkaline Phosphatase (ALP) < 1.5 times ULN, serum albumin 3.4 g/dL and prothrombin time prolonged by 3 s. IgM anti-HAV antibody was positive and hepatitis B surface antigen, anti-Hepatitis C Virus (HCV) and IgM anti-hepatitis E virus antibodies were negative. Ultrasonography (USG) of abdomen showed enlarged, hyperechoic liver with thickened gallbladder wall and no free fluid. Over a period of next three weeks though his AST and ALT levels decreased, his serum bilirubin remained high (18 mg/dL) and

Keywords: NASH, NAFLD, cryptogenic cirrhosis, hepatitis A virus, ACLF
Received: 18 January 2017; **Accepted:** 25 August 2017; **Available online:** 1 September 2017

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Abbreviations: AASLD: American Association for the Study of Liver Diseases; ACLF: Acute on Chronic Liver Failure; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; APASL: Asia-Pacific Association for the Study of Liver; EASL: European Association for the Study of the Liver; HAV: Hepatitis A Virus; HCV: Hepatitis C Virus; NAFLD: Non-alcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; ULN: Upper Limit of Normal; USG: Ultrasonography
<http://dx.doi.org/10.1016/j.jceh.2017.08.006>

Figure 1 (a) Liver biopsy showing disarray of the lobular architecture with portal expansion by fibrosis and foci of macrovesicular steatosis (Hematoxylin and Eosin, 40 $\times$). (b) Higher magnification showing macrovesicular steatosis and ballooning degeneration (Hematoxylin and Eosin, 200 $\times$). (c) Masson trichrome stain showing portal fibrosis and pericellular zone 3 fibrosis. Intracanalicular cholestasis and cholestatic rosettes are also noted (100 $\times$). (d) Focal area showing reticulin collapse (Reticulin stain; 100 $\times$); Inset showing Kupffer cells containing PAS positive diastase resistant lipofuscin like material (Periodic acid Schiff with diastase stain, 400 $\times$).

prothrombin time was prolonged by 9 s. USG done at one month of illness showed mild hepatomegaly, hyperechoic liver with mildly heterogenous echotexture and fuzzy outline with portal vein diameter of 11.7 mm, thickened edematous gallbladder wall and ascites.

Upper gastrointestinal endoscopy did not show esophageal varices. With the diagnosis of ACLF with HAV related acute viral hepatitis as acute insult, patient was worked up for etiology of chronic liver disease and secondary causes of hepatic steatosis. He was negative for HBsAg, anti-HBc (total), anti-HCV and auto-immune markers (ANA, AMA, SMA, LKM) and his total IgG levels, iron studies, serum ceruloplasmin and serum tissue transglutaminase antibody levels were normal. Transjugular Liver Biopsy (TJLB) was done which showed disarray and distortion of the lobular architecture. The portal tracts showed moderate expansion with fibrosis along with mild lymphocytic inflammatory infiltrate (Figure 1a). Porto-portal bridging fibrosis along with occasional porto-central bridging was also noted. There was macrovesicular steatosis along with few foci of lobular inflammation (2–4/ $\times$ 20 field) and mild hepatocellular

ballooning (Figure 1b). There was centrilobular pericellular fibrosis (Figure 1c). These features suggest a possibility of NASH with incomplete nodule formation not amounting to cirrhosis. In addition, foci of reticulin collapse along with accumulation of Kupffer cells containing PAS positive diastase resistant lipofuscin like material (Figure 1d; inset) were also noted alongside intracanalicular and intrahepatocytic cholestasis and cholestatic rosettes (Figure 1b) suggesting an acute injury over and above the background of NASH. Patient was managed with ursodeoxycholic acid and diuretics, and on follow up over three months his ascites disappeared, prothrombin time normalized, and there was progressive improvement in AST, ALT, bilirubin and albumin levels.

DISCUSSION

ACLF is a distinct entity separate from decompensated cirrhosis because of an acute precipitating event and a potential component of reversibility.¹ Development and improvement of ACLF depends on severity of the acute event and stage of underlying chronic liver disease. The

index case had ACLF due to HAV related acute viral hepatitis on underlying NASH not amounting to cirrhosis. With the resolution of acute hepatitis, patient improved over a period of three months and came back to his original compensated chronic liver disease. While his liver functions were severely deranged he did not have evidence of extrahepatic organ failure resulting in good outcome as multi-organ failure is a better predictor of mortality than liver failure in ACLF.^{5,6}

As per the APASL consensus, NASH but not simple steatosis, irrespective of stage of fibrosis, has been included as an underlying chronic liver disease in ACLF.¹ NASH is usually suspected in an obese, diabetic subject especially if he or she is older than 40 years. Our patient was non-diabetic, non-obese and was aged 34 years but TJLB showed presence of underlying NASH with advanced fibrosis. Compared to the data from the West, the prevalence of obesity and diabetes mellitus is less common in Indian patients with Nonalcoholic Fatty Liver Disease (NAFLD).^{7,8} There are limited data on the prevalence of NAFLD from India but studies suggest that nearly a quarter of general population is affected and 20–50% of these patients have NASH.⁹ This pool of patients may develop ACLF depending on severity of underlying NASH and severity of acute insult. Cryptogenic cirrhosis, many of which may be due to NASH,¹⁰ accounts for 1–36% cases of underlying chronic liver disease in ACLF in India.^{3,4,11} To the best of our knowledge there is no data worldwide on NASH without cirrhosis as chronic liver disease in ACLF.

In India, HAV infections occur in most individuals by childhood with seroprevalence of anti-HAV antibodies as high as 80–98% beyond 5–10 years of age.¹² Hence, HAV infection as a acute precipitant of ACLF in adults is relatively uncommon, accounting for only 0–2% of ACLF cases in adults^{3,4} compared to 28–42% in children.^{13,14} However, presumably due to access to better sanitation and hygiene, seroprevalence of anti-HAV antibodies has been shown to be declining in urban upper class populations of India with a high seroprevalence being seen only after 35 years of age.¹⁵ Hence, more adults are now susceptible to acute HAV infection, resulting in a 3-fold increase in proportion of HAV as cause of acute hepatitis in adults.¹⁶

The current case highlights the importance of considering both uncommon acute and chronic events in the etiological work-up of ACLF, and provides evidence for inclusion of asymptomatic chronic liver diseases like NASH, even in the absence of cirrhosis, as etiology of the chronic event.

CONFLICTS OF INTEREST

The authors have none to declare.

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