Editorial

Autoimmune hepatitis related acute and acute on chronic liver failure: lost in translation

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Autoimmune hepatitis (AIH) presents as a chronic necro-inflammatory liver disease in a vast majority of patients. An acute presentation occurs in about 25% of those patients, manifesting as fulminant hepatitis with or without liver failure (1). Establishing diagnosis of AIH is a challenge for clinicians but is of critical importance as it is a treatable condition with favorable prognosis. Both initial and subsequent simplified diagnostic criteria for classical AIH have been standardized by consensus (2,3). However, these criteria were designed to differentiate AIH from other causes of chronic liver disease, not to address diagnostic considerations of ALF. In addition to that, patients with acute presentation were not included in development of these criteria. Kessler *et al.* compared clinical and histopathological features of acute fulminant and chronic presentation and suggested that patients with acute presentation differ clinically, biochemically, and histologically from patients with more typical presentation. Despite the differences in pattern of necroinflammation, both groups exhibited variable degree of fibrosis (stage I–IV) (4). It is important to consider AIH in differential diagnosis, especially when patients present with an acute hepatitis or fulminant hepatic failure.

Differential diagnosis of patients presenting with acute or sub-acute onset of jaundice, coagulopathy and encephalopathy is wide. It could be drug or toxin induced acute liver injury, acute viral hepatitis, or acute presentation of any of the following; alcoholic hepatitis, AIH, hepatitis B virus (HBV) infection, primary sclerosing cholangitis (PSC), and Wilson disease (5). In past years, a distinct entity called acute on chronic liver failure (ACLF) has been recognized. In 2009, the Asian Pacific Association for the Study of the Liver (APASL) provided the first consensus on ACLF, defined as "an 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" (6). The 2014 definition was further expanded to include" high 28-day mortality" (7). The acute insult may occur at any time during the course of chronic liver disease and does not represent a terminal event. An acute event could be the first presentation of prior unknown chronic liver disease, which refers to the cohort analyzed in the study of Anand *et al.* (8). In such cases, the acute change is most commonly due to extrahepatic bacterial infection or systemic inflammatory response syndrome (SIRS), followed by alcohol consumption. Other precipitants include drug induced toxicity, gastrointestinal hemorrhage, major surgery, transjugular portosystemic shunt, and large-volume paracentesis without albumin infusion. The precipitating factor remains unknown in a proportion of these patients (5). Drug toxicity has not been well studied as a precipitating factor. According to experts, prescribed or over the counter medications may be poorly tolerated by patients with cirrhosis; hence potential hepatotoxins should be avoided in patients with liver cirrhosis (9,10).

Previously published research has identified acute presentation of AIH as a distinct entity different from chronic presentation of AIH (4,11). However, the cohort of acute AIH analyzed in different research model included patient with variable degree of features of chronicity and fibrosis (MHN-5); which were identified upon initial presentation. The cohort analyzed in Anand *et al.* study was very ambiguous and heterogeneous; it included a

few patients with viral hepatitis and drug induced liver injury but reported them as "flare of chronic AIH causing ACLF". None of the patients in that cohort had prior diagnosis of AIH or use of immunosuppression therapy. Anand *et al.* has presented their study cohort as a separate entity different from acute AIH. In fact, acute flare of AIH causing ACLF is not different from acute presentation of AIH; the diagnosis should have been based upon criteria proposed by Starvitz *et al.* (11). This issue raises a few concerns about the inclusion criteria of cohort in the Anand *et al.* study. (I) Inclusion criteria were less stringent as they used simplified AIH score of ≥6 and/or histopathology suggestive of AIH to diagnosis of AIH. Whereas Stravitz *et al.* used simplified AIH ≥6 points as suggestive of, and ≥7 points considered diagnostic of, AIH (11). Moreover, point distribution of histopathologic categories as 0, 1 and 2 are lacking. It seems that almost 40–50% of patients did not meet histopathological criteria of AIH in ALF as defined by Stravitz *et al.*; (II) indication of corticosteroid therapy remains unclear; (III) distribution of sepsis and SIRS is lacking, although they are the most common inflammatory precipitants of chronic liver disease. Histopathological features associated with SIRS-related hepatitis are not well studied. It is prudent to define such patients prior to establishing diagnosis of AIH-ALF or AIH-ACLF; (IV) Anand *et al.* have shown significant survival improvement in the corticosteroid group, which in turn was not significant compared to group without sepsis and no corticosteroid therapy. The authors have published outcome of ACLF patients with or without infection (12). ACLF patients without infection or SIRS and without any specific treatment including antibiotics had significant improvement in survival. Thus, benefit of corticosteroid therapy remains controversial. Furthermore, treatment with corticosteroids in highly susceptible ACLF cohort is not without risk.

Some patients with indeterminate ALF or ACLF without prior known history of chronic liver disease may be suspected of having an autoimmune pathogenesis on the basis of positive autoantibodies and other clinical clues like female gender and hyperglobulinemia for example. However, even in patients with demographic and laboratory evidence of AIH, the diagnosis of ALF usually remains tentative since autoantibodies are non-specific; histology is not conclusive and the entity is so rare that diagnostic criteria have not been codified by consensus. Stravitz *el al.* has reported similar histopathological findings in patients with acetaminophen toxicity, acute HBV infection and other etiologies. Outcomes for such patients without evidence of infection or SIRS are relatively good with supportive care.

In conclusion, ACLF is a very heterogeneous entity and acute presentation of AIH is a minor component. Exclusion of common factors such as infection, SIRS, toxins and acute viral hepatitis (A, B, E, EBV, herpes, and others) are mandatory prior to establishing diagnosis of AIH. Unfortunately, SIRS associated histopathological features are not well studied. Histopathological features of acute hepatitis due to viruses or toxins including prescription medications, herbs, and others are overlapping and indistinguishable from AIH. Stravitz *et al.* have nicely proposed clinical and histological features of AIH presenting with acute liver failure and such patients may or may not have features of chronicity at the time of presentation. Thus, diagnosing them as "acute flare of chronic AIH" upon first presentation in the absence of prior known diagnosis of AIH as opposed to acute presentation of AIH is a matter of debate.

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