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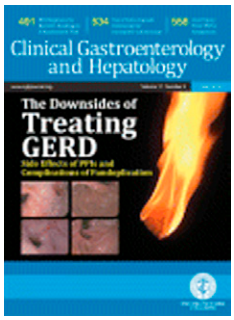

Acute exacerbation among chronic hepatitis C patients: Tip of the iceberg that deserves more attention

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Title: Acute exacerbation among chronic hepatitis C patients: Tip of the iceberg that deserves more attention

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Chronic hepatitis C (CHC) infection is a global epidemic with nearly 200 million people infected worldwide, and is one of the leading indications for liver transplantation.[1] While acute exacerbation of chronic hepatitis B (defined as intermittent elevation of ALT levels to >10 times upper limit of normal and >2 times the baseline value) is well characterized [2], little is known about acute exacerbation among patients with CHC (ae-CHC). In this month's issue of *Clinical Gastroenterology and Hepatology,* Sagnelli and colleagues compared 82 consecutively, prospectively enrolled treatment naïve CHC patients who developed symptomatic acute exacerbation (case) with 82 sex, age, and hepatitis C virus (HCV) genotype-matched controls who did not develop acute exacerbation (control). [3] The authors defined ae-CHC as at least a 5-fold increase in ALT values from baseline values in patients with known CHC. Compared to controls, patients with ae-CHC had higher mean AST (672 +/- 788 IU/dL vs. 51 +/- 55 IU/dL), ALT (1,063 +/- 1,038 IU/dL vs. 71 +/- 68 IU/dL), total bilirubin (15.87 +/- 7.15 mg/dL vs. 0.7 +/- 0.4 mg/dL), and higher proportion of IL-28B CC genotype (40.2% vs. 24.4%). Most importantly, patients with ae-CHC had more rapid progression of liver fibrosis and higher hepatic activity index scores than the control group on repeat liver biopsy. While concurrent acute viral hepatitis (hepatitis A, hepatitis B, hepatitis D, hepatitis E, and EBV) was excluded as the cause of ae-CHC, the possibility of acute super infection of hepatitis C was not evaluated. Previous studies attempted to address this issue through evaluating for the presence of mixed genotypes, and by assessing for risk factors that would predispose to acute hepatitis C infection.[4, 5] While acute reinfection with different strains of HCV is uncommon, when it does occur it can present in a similar fashion to ae-CHC .[6-8]

There is currently no consensus over the definition of ae-CHC, and prior studies utilized different ALT cutoffs to categorize reactivation events. The current study may reflect one end of a spectrum of ae-CHC presentation. Acute exacerbation of CHC was first reported by Sheen et al. in 1996[4]. Using definitions similar to that used for acute exacerbation of hepatitis B at the time, the authors reported an annual incidence of 11.9% for ae-CHC; 55% of the episodes were asymptomatic and only detected during routine follow-up lab tests. In the current study, the most common pattern of symptomatic acute exacerbation was a single episode lasting less than 5 months, which occurred in 50 of the 82 patients. It is common practice to monitor liver function tests (LFT) at 6-month intervals among patients with stable CHC, raising the possibility that ae-CHC with subsequent resolution during the 6-month interval may be under diagnosed. Furthermore, it is well-known that ALT levels fluctuate in patients with CHC, and thus a mild increase in ALT (as new onset or resolving acute exacerbation) during the 6 month interval can be considered normal. While patients with ae-CHC in the current study had documented HCV infection for a mean of 9 years prior to exacerbation, many patients had marked increases in LFT indistinguishable from acute hepatitis C. Similar to the case of chronic hepatitis B, severe acute exacerbation could manifest and resemble acute hepatitis in previously asymptomatic patients.[2] One major difference is that patients with acute hepatitis C can clear the infection spontaneously[9] whereas none of the patients in the current series with symptomatic acute exacerbation achieved spontaneous viral clearance.

In the current study, HCV genotype 2 accounted for 46.4% of patients with acute exacerbation. Previous studies have estimated that genotype 2 accounts for about 22% of the HCV population in Italy[10], suggesting that genotype 2 may be associated with higher risk of ae-

CHC. The association of HCV genotype 2 with increased risk of acute HCV exacerbation has been previously reported, mostly as letters to the editors. In another published study from Italy, Rumi et al. evaluated 100 consecutively enrolled CHC patients with genotype 2c and 106 with genotype 1b where acute exacerbation flares were defined as ALT $\geq$ 400 IU/L or a maximum/minimum ALT ratio of $\geq$ 8.[5] Patients with HCV genotype 2c had significantly higher rates of acute exacerbation compared with HCV genotype 1b (55.6 per 1000 person-years vs. 15.0 per 1000 person-years; p = 0.001). In their multivariate logistic regression analysis, HCV genotype 2c was an independent predictor of developing ae-CHC (OR 6.49, 95% CI 2.56-16.44) compared to genotype 1b.

A known cause of acute exacerbation or reactivation of hepatitis B or C is immunosuppression.[2, 11] In a recent retrospective study by Mahale, et al. 340 CHC patients with underlying malignancies and received immunosuppressive or chemotherapy were evaluated to determine the prevalence and risk factors for developing ae-CHC.[12] Among the entire cohort, 11% developed ae-CHC , and underlying hematologic malignancies (vs. solid malignancies) and chemotherapy regimens containing rituximab were associated with greater risk of developing ae-CHC. Genotype 2 was also found in another small case series to be a risk factor for ae-CHC in patients with B-cell lymphoma who received rituximab containing regimens.[13] The current study excluded patients with concurrent autoimmune hepatitis and those taking potentially hepatotoxic medication within 6 months of enrollment. However, specific information regarding potential exposure to immunosuppressive therapy was not included.

A subset of patients in the current study had repeat liver biopsies: 23 in the case group and 31 in the control group, with the mean interval between the baseline and repeat biopsies of 5.85 and 5.05 years, respectively. Patients with ae-CHC had significantly worse liver disease on repeat biopsy than the control group (an increase of $\geq$2 points in hepatic activity index: 60.9% vs. 9.7%, $p < 0.005$; an increase of $\geq$2 points of Ishak scores: 78.3% vs. 38.7%, $p < 0.005$). In the study by Rumi et al.[5], where a different definition of acute exacerbation was used and most patients were asymptomatic, an increase of $\geq$2 point of Ishak scores was found on repeat liver biopsy in 63% of patients with ae-CHC but only 19% in those without an exacerbation event (p=0.003) . The findings of these 2 studies demonstrate that acute exacerbation events were associated with more aggressive liver disease regardless of symptoms and this may have implications on the decision of anti-viral therapy.

Polymorphisms in the IL-28B gene were recently found to be a major predictor of response to interferon-based anti-viral therapy and outcomes of acute hepatitis C. The favorable IL-28B CC genotype was associated with spontaneous clearance of acute hepatitis C regardless of symptoms. [9] The current study found that IL-28B CC was more common in patients with symptomatic acute exacerbation compared to controls (40.2% vs 24.4%, $p<0.05$). A total of 32 case and 38 control patients were subsequently treated with pegylated interferon and ribavirin with a sustained virological response rate of 81.2% and 60.5% respectively. However, the differences in achieving sustained virological response stratified by genotype and IL-28 status did not reach statistical significance due to the small sample size.

What can we conclude from the current study? It adds to emerging evidence that ae-CHC, symptomatic or asymptomatic, is more common in genotype 2 patients. This study also

confirms the previous finding that patients with ae-CHC have more rapid progression of liver disease and hence should be treated more aggressively. The IL-28B CC genotype was more common in patients with ae-CHC, and patients with ae-CHC responded favorably to the pegylated interferon/ribavirin combination therapy. Symptomatic ae-CHC usually resolves within 6 months, and this study clearly shows that it might be difficult to differentiate from acute hepatitis C. Larger studies utilizing a standardized definition of ae-CHC inclusive of both symptomatic and asymptomatic patients may better characterize the true prevalence and natural history of acute exacerbation. So when you see your next patient with acute hepatitis C with unknown history who does not develop spontaneous resolution, is this an acute C or an acute exacerbation of chronic hepatitis C?

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