

New-onset ascites as a manifestation of virologic relapse in patients with hepatitis C cirrhosis

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Background: Chronic hepatitis C is the most common cause of cirrhosis in industrialized countries. Successful treatment of chronic hepatitis C in patients with advanced fibrosis or cirrhosis has significant benefits, including improvements in inflammation, fibrosis, and portal hypertension, with prevention of esophageal varices and clinical decompensation.

Case: In this report, we present two patients with well-compensated hepatitis C cirrhosis who achieved an end-of-treatment response on a direct-acting antiviral therapy-based triple regimen for hepatitis C virus, but subsequently presented with new-onset ascites associated with virologic relapse.

Conclusion: We propose that the development of ascites in this setting is due to the adverse impact of inflammation of the virologic relapse on portal hypertension. Our observation that ascites formation can be a manifestation of virologic relapse has potentially important clinical implications, as it highlights not only the importance of close monitoring of cirrhotic patients after achieving end-of-treatment response but also the impact of active inflammation on the severity of portal hypertension.

Keywords: chronic hepatitis C, cirrhosis, virologic relapse, portal hypertension, ascites

Introduction

Chronic hepatitis C (CHC) is currently the most common cause of cirrhosis in industrialized countries. In the US, there are currently approximately 4 million CHC-infected people, and it is projected that 1.76 million with untreated CHC will develop cirrhosis over the next 40–50 years.¹ Successful treatment of CHC has significant benefits. In advanced fibrosis or cirrhosis, sustained virologic response (SVR) has been shown to be associated with improved inflammation and fibrosis within 6 months after therapy compared to relapsers and nonresponders.² In a retrospective study of CHC patients who achieved SVR, 56% had improved fibrosis stage within 3 years, and 64% of cirrhotic patients had fibrosis regression to stages 1–3.³

In compensated cirrhotic patients undergoing antiviral therapy, SVR is associated with improved portal hypertension. Significant decrease in the hepatic venous pressure gradient was seen in cirrhotic patients achieving SVR compared to those who did not respond.⁴ Achievement of SVR also prevents the development of esophageal varices and clinical decompensation.^{5,6} Among CHC patients with advanced hepatic fibrosis, SVR is associated with lower all-cause mortality, liver-related mortality, and need for transplantation.⁷

In this report, we describe two well-compensated cirrhotic patients who achieved end-of-treatment response on a direct-acting antiviral therapy-based triple regimen.

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Both presented after completing therapy with new-onset ascites and virologic relapse. Due to the adverse impact of inflammation on portal hypertension, we speculate that the sudden onset of inflammatory activity associated with relapse contributed to the development of ascites.

Case 1

A 53-year-old woman with CHC genotype 1, biopsy-proven cirrhosis, and previous partial response to polyethylene glycosylated (PEGylated) interferon and ribavirin was started on telaprevir-based therapy. Cirrhosis was well compensated, without ascites or edema before and during therapy. Pretreatment laboratory evaluation revealed albumin 4.4 g/dL, aspartate aminotransferase (AST) 115 U/L, alanine aminotransferase (ALT) 120 U/L, alkaline phosphatase 191 U/L, total bilirubin 1.1 mg/dL, hemoglobin 16.3 g/dL, platelet count 183,000/ μ L, and hepatitis C virus (HCV) viral load 3,210,000 IU/mL. Upper endoscopy was negative for varices. Therapy was complicated by anemia requiring ribavirin dose reduction and erythropoietin therapy and rash that resolved after discontinuation of telaprevir. Viral load was 110 IU/mL at treatment week three and undetectable at week eight. PEGylated interferon and ribavirin were discontinued after 48 weeks of therapy. HCV viral load remained undetectable from week eight until the end of therapy. Laboratory evaluation at week 45 revealed albumin 2.7 g/dL, AST 125 U/L, ALT 67 U/L, total bilirubin 1.3 mg/dL, hemoglobin 10.1 g/dL, and platelet count 49,000/ μ L. Weight at the end of therapy was 132 lb (60 kg). One month after discontinuation of therapy, the patient presented with 5 lb weight gain (weight 137 lb) and new-onset ascites. Evaluation revealed albumin 3.1 g/dL, AST 77 U/L, ALT 44 U/L, total bilirubin 0.8 mg/dL, blood urea nitrogen (BUN) 8 mg/dL, creatinine 0.7 mg/dL, hemoglobin 13.5 g/dL, platelet count 105,000/ μ L, and virologic relapse with HCV viral load of 228 IU/mL. Abdominal magnetic resonance imaging (MRI) revealed a cirrhotic morphology, abdominal ascites, and recanalization of the umbilical vein and left retroperitoneal varices consistent with portal hypertension. The patient refused diagnostic paracentesis. An echocardiogram was obtained, which revealed normal left ventricular systolic and diastolic functions and right ventricular systolic pressure, with no sign of pulmonary hypertension. Ascites rapidly responded to sodium-restricted diet and diuretic therapy (spironolactone 50 mg, furosemide 20 mg daily). Repeat laboratory evaluation after control of ascites revealed an albumin level of 3.9 g/dL. Repeat viral load 3 months after the end of therapy was 528,810 IU/mL.

Repeat abdominal MRI 7 months after therapy cessation showed no ascites.

Case 2

A 61-year-old woman with CHC genotype 1, biopsy-proven cirrhosis, and previous nonresponse to three courses of interferon-based therapy was started on telaprevir-based therapy. Cirrhosis was well compensated, without evidence of ascites or hepatic encephalopathy. Upper endoscopy was negative for esophageal varices. Laboratory evaluation revealed albumin 2.7 g/dL, AST 132 U/L, ALT 81 U/L, alkaline phosphatase 394 U/L, total bilirubin 0.8 mg/dL, hemoglobin 13.3 g/dL, platelet count 156,000/ μ L, and HCV viral load 71,600 IU/mL.

After initiation of telaprevir-based therapy, the patient achieved rapid virologic response. Side effects of therapy included anemia, requiring ribavirin dose reduction and erythropoietin therapy. Treatment was noteworthy for stable hypoalbuminemia, with albumin level 2.1 g/dL without edema or ascites. She completed 12 weeks of telaprevir-based therapy, but therapy was discontinued at treatment week 31 due to a severe facial rash requiring systemic steroids for 2 days. HCV viral load remained undetectable from treatment week four until the end of therapy. Laboratory evaluation at the end of therapy revealed albumin 2.1 g/dL, AST 64 U/L, ALT 32 U/L, alkaline phosphatase 347 U/L, total bilirubin 1.3 mg/dL, hemoglobin 10.8 g/dL, and platelet count 80,000/ μ L. Weight at the end of therapy was 122 lb.

The patient presented 1 month later with 8 lb weight gain (weight 130 lb) over 2 weeks, new ankle edema, and abdominal distention. Abdominal ultrasound showed moderate ascites. HCV viral load was undetectable, albumin 2.9 g/dL, AST 71 U/L, ALT 37 U/L, alkaline phosphatase 309 U/L, total bilirubin 1.5 mg/dL, BUN 13 mg/dL, and creatinine 0.7 mg/dL. The patient refused diagnostic paracentesis. An echocardiogram was obtained, which revealed normal left and right ventricular function, with no sign of pulmonary hypertension. Sodium-restricted diet and diuretics (spironolactone 50 mg, furosemide 20 mg daily) were started, with prompt resolution of edema and ascites. Three months after the end of therapy, HCV viral load was 203 IU/mL, and on repeat 69,900 IU/mL, confirming relapse. Albumin level was 2.6 g/dL, AST 91 U/L, ALT 55 U/L, alkaline phosphatase 348 U/L, total bilirubin 1.1 mg/dL, BUN 12 mg/dL, creatinine 0.6 mg/dL, hemoglobin 13.5 g/dL and platelet count 140,000/ μ L. Diuretics were tapered, then discontinued at posttreatment week 20 with continued control of ascites. Albumin level remained stable at 2.6 g/dL.

Discussion

Well-compensated cirrhosis was present in both patients prior to interferon-based therapy. Except for the expected side effects of therapy, both patients tolerated therapy and were free of ascites throughout therapy. Both developed ascites within 1 month of discontinuation of therapy. Both patients were on no other medications and had no other medical problems. Besides weight gain, abdominal distention, and ankle edema, neither patient had any other symptoms, including abdominal pain, fever, shortness of breath, or cough. In the first patient, virologic relapse was immediately detected. The viral load was only 228 IU/mL at the onset of ascites and subsequently rose to 528,810 IU/mL by 3 months post-treatment. In the second patient, serum HCV ribonucleic acid (RNA) was undetectable at the onset of ascites, but was subsequently detected.

Inflammation plays a significant role in the development and maintenance of portal hypertension. In chronic hepatitis B, inflammation is associated with increased liver stiffness, which predicts the presence of portal hypertension in chronic liver disease.^{12,13} Liver stiffness, which correlates with portal pressures in patients with recurrent hepatitis C following liver transplantation, has been reported to be increased by active inflammation.

Treatment of active inflammation in cirrhotic patients due to alcohol, hepatitis B, and autoimmune-mediated injury leads to a decrease in the severity of portal hypertension and marked clinical improvement. Portal hypertension, assessed by the hepatic venous pressure gradient, is higher in patients with alcoholic cirrhosis with concurrent acute alcoholic hepatitis than in patients without acute alcoholic hepatitis,¹⁴ and corticosteroid therapy leads to marked clinical improvement. Similarly, patients with end-stage liver disease secondary to chronic autoimmune hepatitis and hepatitis B may demonstrate marked clinical improvement following appropriate therapy. Although fibrosis may regress with effective therapy, it occurs over a prolonged period. The time course of clinical improvement and decrease in portal hypertension is more closely associated with resolution of inflammatory activity. In contrast, the acute development of inflammation superimposed upon chronic disease, such as superinfection of well-compensated cirrhotic patients with hepatitis E, frequently leads to rapid clinical decompensation.¹⁵

Despite the benefits of SVR in CHC cirrhosis, interferon-based therapy is associated with significant risk. In a retrospective analysis of cirrhotic patients awaiting liver transplantation, treated patients had significantly higher rates of bacterial infections and septic shock compared to

controls,¹⁶ and 13% of patients treated with eltrombopag for thrombocytopenia to enable treatment with PEGylated interferon and ribavirin developed hepatic decompensation events (mostly ascites) during therapy.¹⁷ Recently, it has been reported that up to 4.4% of cirrhotic patients receiving telaprevir or boceprevir with PEGylated interferon and ribavirin will experience hepatic decompensation during therapy.¹⁸ The mechanism for the development of ascites during therapy remains to be determined. However, the development of hypoalbuminemia leading to decreased oncotic pressure is a possible factor.¹⁹

The development of ascites in our patients with initial virologic response was unexpected, due to the early beneficial effects of successful therapy on portal pressures.⁴ Although at the end of therapy aminotransferase levels remained elevated in both patients, the level of aminotransferase levels is poorly correlated with inflammatory activity in CHC.¹⁰ Levels during therapy with telaprevir and PEGylated interferon may remain elevated despite a virologic response in up to 67% of patients with elevated ALT levels at baseline.¹¹ Although levels decrease to a greater extent compared to placebo in patients treated with telaprevir-based therapy, no information is available on the percentage of normalization and its correlation with SVR at the end of therapy.

Hypoalbuminemia has been found to be a predictor of development of adverse events during triple therapy. Although the development of hypoalbuminemia may have predisposed our patients to ascites, it was not due to the adverse effects of active therapy, as both first developed this complication one month after therapy had been discontinued. Rather, we propose that the development of ascites after completion of therapy was due to the adverse impact of acute inflammation associated with virologic relapse on portal pressures. Possible support for this proposal is provided by the changes in wedged hepatic vein pressure gradient in patients who relapse following antiviral therapy.⁴ Although comparison of pre- and posttreatment measurements was not provided, there appears to be an increase in the wedged hepatic venous gradient in patients who relapse versus no significant change in those who do not respond to antiviral therapy. Histologic findings of acute hepatitis C infection vary based on the timing. Early biopsies may show mixed cholestatic and portal/lobular inflammation, while late biopsies show milder nonspecific portal/lobular inflammation.²⁰ Although ascites preceded the detection of relapse by 2 months in the second patient, a false negative test result due to a low viral load is possible. In addition, it has also been shown that in early relapse, HCV RNA may be detected in the liver before becoming detectable

in the serum.^{8,9} We suspect that active hepatic inflammation contributing to increased portal pressures was present at the time ascites developed. We propose that the rapid improvement and ability to discontinue diuretic therapy the second case was a result of the spontaneous improvement in portal pressure due to decreased severity of inflammatory activity.

Although further studies are needed to confirm the association between virologic relapse and the development of ascites in a cirrhotic patient, our observation has potentially important implications. It highlights the importance of closely monitoring cirrhotic patients after completion of therapy and assessing for relapse in those who present with new-onset ascites. It also highlights the potential impact of active inflammation on the severity of portal hypertension. Finally, it raises the possibility that patients with decompensated cirrhosis due to CHC might clinically improve with effective antiviral therapy, as is the case with hepatitis B cirrhosis. This question will hopefully soon be addressed with the rapid improvement in interferon-free, direct-acting antiviral regimens.

Author contributions

Deborah Lim Chua – study concept and design, drafting of the manuscript, critically revised the manuscript and approved the final version. Thomas Hahambis – acquisition of data, critically revised the manuscript and approved the final version. Samuel Sigal – study concept and design, study supervision, critical revision of the manuscript for important intellectual content and approved the final version.

Disclosure

The authors report no conflicts of interest in this work.

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