Case Report

Resolution of refractory hepatic hydrothorax in patients with hepatitis C virus cirrhosis after treatment with direct-acting antiviral agents

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Abstract:

Hepatic hydrothorax (HH) is a transudative pleural effusion that complicates advanced liver cirrhosis. Cases refractory to medical treatment in the form of salt restriction and diuretics are labeled refractory hepatic hydrothorax (RHH) and may require transjugular intrahepatic portosystemic shunts (TIPSS) or even liver transplantation. Renal impairment is common in advanced liver disease, worsens its prognosis, and makes the management of HH more challenging. Successful antiviral therapy reduces some of the complications of cirrhosis secondary to hepatitis C virus (HCV) infection. We herein report two cirrhotic patients with chronic kidney disease who developed RHH which resolved after the successful treatment of their HCV infection with direct-acting antivirals (DAAs). In cases of RHH associated with HCV cirrhosis, a trial of DAAs is warranted before resorting to TIPSs or liver transplantation.

Keywords:

Chronic kidney disease, cirrhosis of liver, direct-acting antiviral agents, refractory hepatic hydrothorax

Hepatic hydrothorax (HH) is a transudative pleural effusion of at least 500 ml in a patient with liver cirrhosis in the absence of primary cardiac or pulmonary disease. It occurs in about 5% of the patients with advanced cirrhosis, is mostly right sided, and can compromise respiration.[1,2] Spontaneous bacterial empyema occurs when HH becomes infected in a manner analogous to spontaneous bacterial peritonitis (SBP). Treatment modalities for HH include salt restriction and diuretics, repeated pleurocentesis, pleurodesis, the insertion of a permanent chest tube, surgical repair of the diaphragmatic leak, peritoneovenous shunts, and transjugular intrahepatic portosystemic shunts (TIPSS).[1-3] These interventions are fraught with complications and, even when successful, are associated with a high mortality. Liver transplantation is the definitive therapy in those who otherwise qualify for it.[1-4] The following is a description of two patients with hepatitis C virus (HCV) cirrhosis and chronic kidney disease (CKD) who experienced full resolution of their refractory HH (RHH) after achieving a sustained virologic response (SVR) with direct-acting antivirals (DAAs).

Case Reports

Case 1

A 50-year-old female with end-stage renal disease (ESRD), secondary to amyloidosis on hemodialysis, presented to the emergency department (ED) with dyspnea for 4 days. Her medical history included cirrhosis secondary to HCV genotype 1a infection, two failed kidney

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transplants, and posttransplant diabetes mellitus. Her chest examination suggested the presence of a large right-sided pleural effusion.

Chest X-ray [Figure 1] showed massive right pleural effusion. Computed tomography scan of the chest and abdomen revealed small ascites and splenomegaly but no evidence of parenchymal lung pathology. Her characteristics and laboratory details are shown in Table 1. A pigtail pleural catheter was inserted and the right lung fully re-expanded after intermittent drainage of the effusion. Pleural fluid analysis results were consistent with a transudate. Echocardiogram revealed normal left ventricular ejection fraction with mild left ventricular hypertrophy and diastolic dysfunction.

Attempts at treating her effusion with frequent hemodialysis and ultrafiltration were unsuccessful as she had frequent and symptomatic hypotension. She was discharged home 9 days following the removal of the pleural catheter but returned to the hospital the following week with dyspnea. Chest X-ray showed reaccumulation of the right pleural effusion. Again, there was no evidence of intravascular fluid overload.

She was readmitted 3 weeks later with worsening right pleural effusion and severe dyspnea. A pleural catheter was reinserted, again with repeated drainage of the pleural fluid for the following 3 weeks.

A 24-week course of ombitasvir, paritaprevir, and ritonavir plus dasabuvir was started and was well tolerated. HCV-RNA became negative 2 weeks after discharge. After 2 more weeks, she still had a moderately large effusion on X-ray and was mildly symptomatic. Her dyspnea progressively improved and resolved. Three months after DAA initiation, the right pleural effusion had diminished and completely resolved over the following 6 months [Figure 2]. She had no further hospital admissions or ED visits during the subsequent 9 months [Figure 3]. HCV-RNA quantification was 875,091 IU/ml before the initiation of antiviral therapy and became undetectable at 12 and 24 weeks' posttreatment confirming SVR. Her most recent laboratory values are shown in Table 2.

Case 2

A 39-year-old male with liver cirrhosis secondary to HCV genotype 4 infection presented to the ED with low blood pressure, New York Heart Association class 2 dyspnea, and nonproductive cough. He had been diagnosed with HCV infection 8 years earlier and with cirrhosis 3 years later. Around that time, he was found to have 2+ proteinuria by dipstick and microhematuria. Urine protein/creatinine ratio was 0.16 g/g. Renal biopsy reportedly revealed Type 1 membranoproliferative glomerulonephritis (MPGN). Although proteinuria increased over the following 3 years, it never exceeded 2.24 g/24 h. His serum creatinine remained stable mostly between 110 and 130 μmol/l (glomerular filtration rate [GFR] 53–60 ml/min by the four-variable Modification of Diet in Renal Disease equation).

His liver cirrhosis was complicated by ascites, encephalopathy, coagulopathy, and pancytopenia. Furosemide and spironolactone were prescribed for massive ascites and severe peripheral edema with a partial response. HCV infection was treated with a 24-week course of sofosbuvir and modified dose of ribavirin but failed to achieve SVR. He was subsequently diagnosed and treated for nonocclusive portal vein thrombosis and SBP.

In June 2015, he was started on ledipasvir–sofosbuvir. A month later, he developed dyspnea and cough and was found to have a large right pleural effusion. Thoracentesis

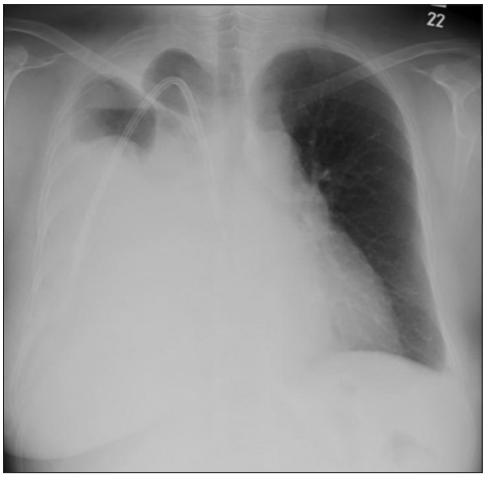

Figure 1: Chest radiograph in patient 1 showing right-sided pleural effusion at presentation

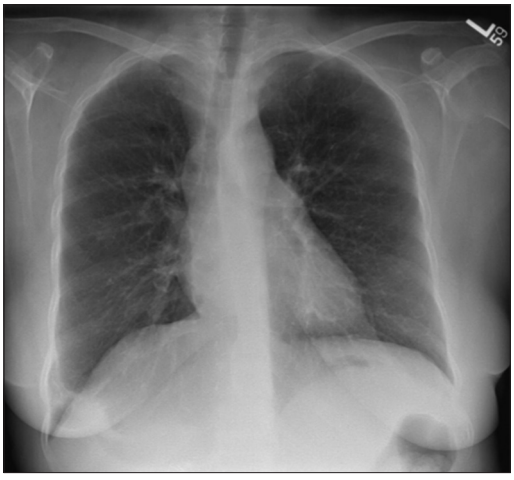

Figure 2: Normal X-ray chest after 12 months of starting direct-acting antiviral agents in the patient 1

was performed with improvement in his symptoms. Pleural fluid analysis results are not available, but he was diagnosed with HH. He had chronic anasarca but not orthopnea or paroxysmal nocturnal dyspnea. A previous echocardiogram had been reported as normal.

Over the following several months, he had multiple emergency room visits and one hospitalization for RHH [Figure 4] requiring repeated thoracenteses. He completed 24 weeks of therapy and achieved SVR. Before treatment, his HCV-RNA quantification was 126,908 IU/ml and became negative at 12 and 24 weeks' posttreatment.

Follow-up chest X-rays demonstrated the resolution of the hydrothorax and full re-expansion of the right lung [Figure 5]. During the subsequent 10 months, he had no visits to the ED or hospital admissions [Figure 4]. Initial and follow-up laboratory data are shown in Table 2.

Table 1: Patient characteristics before the initiation of successful direct-acting antiviral therapy of hepatitis C virus infection

	Patient 1	Patient 2
Sex	Female	Male
Age	50	39
Etiology of ESLD	HCV	HCV
Child-Pugh score	8	11
Child-Pugh class	B	C
MELD-Na score	23	15
CKD duration (years)	>24	>3
CKD stage	5D	G3b, A3
CKD etiology	Amyloidosis	HCV-related MPGN
Dialysis	Yes	No
HCV genotype	1a	4
HCV quantification	875,091	216,908
Previous DAA	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin
Duration	2 days	24 weeks
Comments	Rash and angioedema	Failed
Ascites	small	large
Hepatic encephalopathy	No	Yes
Variceal bleeding	No	No
Successful DAA regimen	Ombitasvir, paritaprevir, ritonavir and dasabuvir	Ledipasvir-sofosbuvir

ESLD=End-stage liver disease, HCV=Hepatitis C virus, MPGN=Membranoproliferative glomerulonephritis, MELD=Model for end-stage liver disease, CKD=Chronic kidney disease, DAA=Direct-acting antiviral

Table 2: The laboratory values before and after successful antiviral therapy of hepatitis C virus

Direct-acting antivirals	Patient 1		Patient 2	
	Before	At last follow-up	Before	At last follow-up
Serum albumin (g/l)	34.4	37	15	27
Bilirubin (μmol/l)	15	4	11	7.4
INR	1.1	1.1	1.6	1.4
Serum creatinine (μmol/l)	HD (434)	HD (446)	114	122
Weight (kg)	65	67	119	116.7
MELD-Na score	23	22	15	13
Child-Pugh score	8	5	11	8
Child-Pugh class	B	A	C	B

DAA=Direct-acting antivirals, MELD=Model for end-stage liver disease, INR=International normalized ratio, HD= Hemodialysis

Discussion

HH is an uncommon manifestation of portal hypertension. It occurs in about 5% of patients with advanced cirrhosis. The diagnosis of HH is made in a cirrhotic when a pleural effusion (transudate) develops in the absence of primary cardiopulmonary conditions.[1,5] When it persists in spite of sodium restriction and the use of maximally tolerable doses of diuretics, it is labeled RHH.[1] These cases undergo repeated thoracentesis initially but may require TIPSS or liver transplantation for long-term management.[2,6] Unfortunately, liver transplantation is a major and expensive operation with limited availability worldwide, and many patients are excluded because of their age, associated comorbidities, or the lack of deceased donor organs.

The introduction of DAA promises to change the natural history of HCV-related liver disease and its associated complications and may obviate the need for liver transplantation in certain patients. DAAs have become the treatment of choice for chronic hepatitis C infection, and they achieve SVR in >90%.[7-11]

Recent studies suggest that patients achieving SVR experience improvement in their liver function reflected by a decrease in their model for end-stage liver disease (MELD) scores and Child–Turcotte–Pugh (CTP) scores.[12-15] However, the full impact of successful DAAs on the complications of cirrhosis remains largely undocumented.[13] Extended follow-up will be required to determine the long-term effects on health-related quality of life, occurrence of hepatocellular carcinoma, and survival.[7]

The use of DAAs in patients with advanced CKD and hemodialysis has lagged with patients of normal or mildly impaired renal function because of safety concerns. Recent trials have provided several effective and safe DAA treatment options in that population.[16,17]

HH is a serious complication of advanced cirrhosis. So far, no cases of complete resolution of RHH have been reported in the literature with treatment by DAA. We herein report the effect of successful antiviral therapy on two cases of RHH in the setting of HCV-related liver

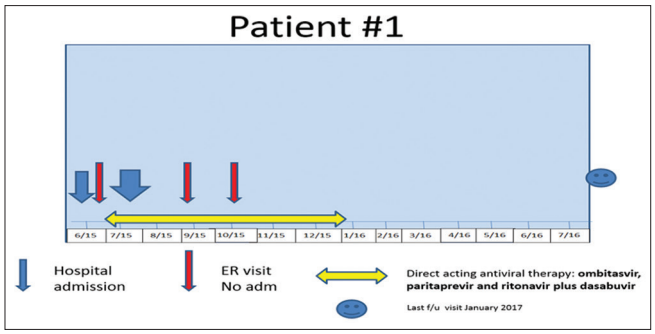

Figure 3: Hospitalizations and Emergency Room visits for patient 1 before, during, and after direct-acting antiviral therapy. ER visits leading to hospitalizations are not shown

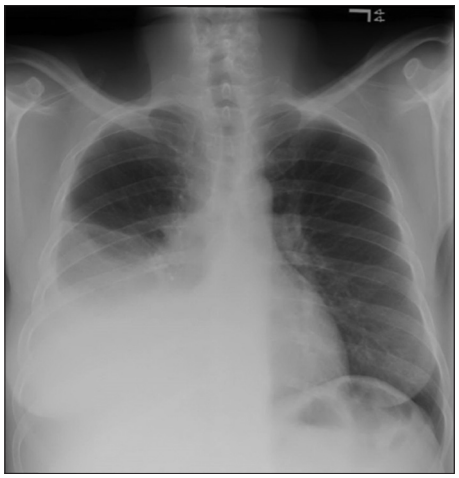

Figure 4: Chest X-ray of patient 2 at presentation showing right-sided pleural effusion

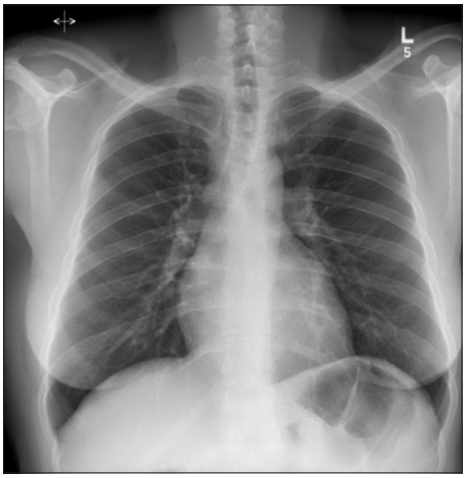

Figure 5: Chest X-ray of patient 2 after 14 months of initiation of direct-acting antivirals showing disappearance of pleural effusion

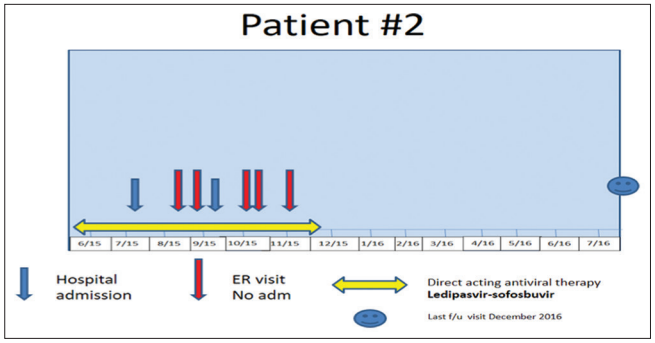

Figure 6: Hospitalization and Emergency visits for patient 2 during and after direct-acting antiviral therapy. ER visits leading to hospitalizations are not shown

cirrhosis. Both patients had CKD. The first patient had long-standing ESRD and two failed kidney transplants, while the second patient had stage 3 CKD secondary to MPGN. RHH was diagnosed in the first patient after intravascular fluid overload was excluded. Our second patient had total body fluid overload and the hydrothorax without evidence of intravascular overload or nephrosis. In both patients, RHH resolved after achieving SVR. This has not been reported in the literature hitherto.

Our first patient had cirrhosis of liver secondary to HCV infection genotype 1a and was hemodialysis dependent. It was difficult selecting a suitable DAA regimen for this patient. The guidelines suggest avoiding paritaprevir (NS3-4A protease inhibitor)-containing regimens in decompensated cirrhosis.[17] Meanwhile, sofosbuvir-containing regimens are not recommended for patients with ESRD and those with GFR <30 ml/min. After discussing the different treatment options with the patient and in view of the absence of severe impairment of hepatic synthetic function, it was felt reasonable to proceed with a trial of ombitasvir, paritaprevir, and ritonavir plus dasabuvir with close monitoring of liver function tests.[17,18]

The second patient had HCV cirrhosis secondary to genotype 4 infection and stage 3 CKD secondary to Type 1 MPGN, with GFR ranging between 53 and 60 ml/min. This patient was successfully treated with ledipasvir–sofosbuvir. Ledipasvir–sofosbuvir is considered a good choice for treating HCV genotype 4-infected patients with or without cirrhosis and with decompensated cirrhosis.[7,17] HH developed after the initiation of DAA but resolved over the following several months. This patient had severe hypoalbuminemia, massive ascites, significant peripheral edema, and a modest response to combination diuretics. Although he had proteinuria, he was not nephrotic and his renal function remained stable over the following 2 years.

In the first patient, clinical and radiological improvement was noted after 12 weeks of therapy. In the second patient, the improvement was evident by the end of his 24-week DAA course. In both, the resolution of the HH was virtually complete by the end of the 1st year. In the two patients, there was a decline in their MELD-Na and CTP class consistent with improvement in liver function. The impact of the response to DAA on the

utilization of health-care resources was evident in both patients [Figures 3 and 6]. The observed time course suggests that a period of 6 months from the start of DAA therapy may be required for judging its impact on the course of RHH and deciding about the need for further interventions.

Conclusion

In conclusion, we report two cases of RHH that resolved after DAA induced SVR. The improvement started within months from the start of treatment and was completed by the end of the year. We therefore suggest that in HCV cirrhotic patients and HH, successful treatment with DAA may lead to its resolution and help avoid the need for more risky and costly interventions such as TIPSS and liver transplantation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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