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Case Report

An unusual survival for 6.5 years with end-stage hepatitis C related advanced liver cirrhosis following sustained virologic response with direct antiviral agents – A case report from A low-resource setting.

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Abstract

Advanced chronic liver disease is frequently complicated by hepatic encephalopathy (HE), hepatorenal syndrome, and spontaneous bacterial peritonitis; predictors of poor prognosis that significantly reduce survival. While orthotopic liver transplantation (OLT) remains the definitive treatment, it is often inaccessible in resource-limited settings. We present the case of a 70-year-old retired hospital attendant with hypertension who developed decompensated liver cirrhosis secondary to chronic hepatitis C virus HCV infection. She presented with portal hypertension, grade 4 HE, hepatorenal syndrome, and spontaneous bacterial peritonitis. She remained in grade 3 to 4 HE for approximately three months and in grade 2–3 HE for an additional two months. Despite profound hepatic decompensation and a high Model for End-Stage Liver Disease-Sodium (MELD-Na) score of 48 (indicating a 71% three-month mortality) and a Child-Pugh score of 15 (Class C), she responded remarkably to intensive conservative management. After six months of inpatient care, which included direct-acting antiviral therapy, anti-failure therapy, and seizure management, she recovered from hepatic coma. She received a six-month course of direct-acting antivirals (DAAs)daclatasvir and sofosbuvir and achieved sustained virologic response. Over six and a half years later, she remains in good health with preserved cognition and normal blood pressure and has been under annual surveillance for hepatocellular carcinoma. This case underscores the transformative potential of DAAs in improving survival even among severely decompensated HCV-related cirrhotic patients. It highlights the need for expanded access and subsidization of DAAs in low-resource settings, where liver transplantation is not feasible, and emphasizes the role of aggressive, supportive management in bridging the treatment gap.

Keywords: Hepatic Encephalopathy; Liver Cirrhosis; Hepatitis C; Decompensated End-stage Liver Disease.

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Introduction

Hepatitis C viral infection is a frequent cause of chronic liver disease, particularly in the developing world. It has a chronic course and is pathologically characterized by systemic inflammation, hepatic necroinflammation, and bridging fibrosis in the liver.[1,2], resulting in cascading complications ranging from portal hypertension, variceal bleeding, hepatorenal syndrome, and hepatic encephalopathy.[1–3] In addition to the chronic liver disease it causes, the Hepatic C virus leads to many extrahepatic complications, such as atherosclerotic coronary heart disease, mixed cryoglobulinemia, membranous glomerulonephritis, insulin resistance, diabetes, hepatic steatosis and, sarcopenia.[3–6] However, the introduction of direct-acting antivirals (DAAs) in 2011 revolutionized the treatment of hepatitis C infection. [3,4]. The high cost of DAAs precludes many from benefiting from the use of these drugs, particularly in the developing world [4, 5]. The DAAs reduce hepatic fibrosis, portal hypertension, and inflammation and improve liver function, positively affecting the extrahepatic complications of chronic hepatitis C infection [6]. However, many general and primary healthcare practitioners are unaware of this. [7, 8]

Hepatic encephalopathy (HE) is a neuropsychiatric complication associated with advanced cirrhosis. It is mediated by portal hypertension and portal-systemic shunting, which are both consequences of advanced liver disease.[3,7]. These represent the decompensation of a previously compensated and asymptomatic liver cirrhosis. It manifests as a spectrum of neurocognitive dysfunctions with symptoms ranging from disorientation to coma. [3,4] It is a frequent cause of hospital admission in patients with end-stage liver disease, and its appearance facilitates early mortality.[7–15]. There are two types, overt and covert hepatic encephalopathies, which constitute an integral part of the spectrum of neurocognitive impairment in cirrhosis (SONICS).[13,14] The prevalence of hepatic encephalopathy is approximately 30–45% in patients with advanced chronic liver disease. 6] Covert hepatic encephalopathy (CHE) is an independent risk factor for death and hospitalization. This renders the patient debilitated and incapable of self-care. In addition, it compromises the health-related quality of life with cirrhosis. [1,2]

The pathophysiological mechanisms underlying HE include hyperammonemia, proinflammatory milieu, gut dysbiosis, and neurotransmitter dysfunction, culminating in brain edema, which is the hallmark of HE. [13,14]

This case report highlights an uncommon clinical vignette of complete recovery from persistent grade 3–4 hepatic encephalopathy that lasted for more than 12 weeks. Transplant-free survival of more than 6 years with subsequent normalized blood pressure while off antihypertensives in a resource-limited setting is quite unusual.

Case Report

The patient is a retired hospital attendant in her 70s with background hypertension who has been on follow up for > 10 years. During a routine follow-up clinic visit, she complained of a vague right upper quadrant abdominal pain, no constitutional symptoms were observed during the visit. The significant findings were pitting leg edema and hepatomegaly 14 cm below the right coastal margin, firm and nodular, with a blunt edge. Splenomegaly was not observed. She tested positive for Hepatitis C antibody. Liver function tests were then requested. Tests for hepatitis B and human immunodeficiency viruses all resulted in negative results.

Three days later, she re-presented with leg swelling, abdominal swelling and pain, restlessness, and fever to the emergency room. She has no history of diabetes and does not consume alcohol. In addition, the patient did not abuse drugs and never had an occupational needlestick injury or a history of blood transfusion. The systemic review was unmarketable. There was no known history of hepatitis C viral infection or liver disease among family members. Significant exam findings at the time were a fever of 38.6 centi-grades, palmar erythema, and pitting leg edema up to the mid-shin and abdominal distension

and generalized tenderness, marked peritoneal stretch tenderness, hepatomegaly 14 cm below the right costal margin, and firm, nodular, blunt-edged, and moderate ascites. The Glasgow coma score (GCS), initially 15/15 at presentation with flapping tremors observed, subsequently worsened to 6/15 within 48 hours of admission. An assessment of decompensated chronic liver disease, hepatitis C Virus (HCV) infection-related, complicated by grade 4 hepatic encephalopathy precipitated by spontaneous bacterial peritonitis (SBP) was made. One week into admission, the patient developed hepatorenal syndrome (HRS) type1 as evidenced by the rapid deterioration in renal action as reflected by rising serum creatinine and urea. Her GCS would go on to hover around 4/15 to 10/15 over the next 4 months. Preliminary laboratory evaluation revealed a positive hepatitis C virus antibody.

The hepatitis C viral count was 173,300 copies/mL, the international normalized ratio (INR) was 15.4, and the prothrombin time was 81 seconds. [9-11] Abdominal ultrasound revealed features of chronic liver disease with portal hypertension. Preliminary laboratory values revealed the following results: Na^+117 mmol/L(low), K^+ 3.4 mmol/l, CL^-88 mmol/L, $HCO_3$21 mmol/L, Creatinine 257 umol/L(elevated). Liver function test revealed ALT, 34 U/L(normal); AST, 103 U/L(elevated): ALP, 343 IU/L: Gamma GT, 194 U/L(elevated); conjugated bilirubin 28 umol/L(elevated); total bilirubin, 71 umol/L(elevated); total protein, 66 g/L(normal); albumin, 18 g/L(low). Alpha-fetoprotein varied from 20.53 ng/L to 34.7 I.U./mL Platelet count was 142 × 10^3/uL, PCV was 33.6%, and WBC was 4.79 × 10^3/uL; the differential counts were within normal limits. Assessment of fibrosis by Fibroscan^R (elastography) showed severe fibrosis. Her Model for end-stage liver disease MELD-Na Score was 48 (90-day mortality estimated at 66% Child-Pugh score Class C (15 points); 3-month mortality was 71%). Random blood sugar was 9 mmol/L.

She received daclatasvir and sofosbuvir for 6 months. The viral load declined from 173,330 copies/mL to < 67 copies/mL. The final viral load on 07 April 2022 was< 32 copies/mL. While on admission, which spanned 6 months, she was managed with DAA, antibiotics, which included parenteral levofloxacin, metronidazole, and ceftriaxone, as indicated. The other drugs included intravenous fluids, propranolol, silymarin, lactulose, and paraldehyde. Oxygen therapy was initiated when she began to desaturate at Spo2 of 80% post-ictal, which subsequently improved to 98%. The anti-failure regimen was intensified, and rectal washouts were performed when indicated. She had an appropriate dosage of salt-poor albumin infusion as indicated. Nutritional rehabilitation was instituted. Several episodes of seizures were observed during her hepatic coma and were managed with paraldehyde. She was successfully managed for hepatorenal syndrome and spontaneous bacterial infection using the abovementioned antibiotics and albumin infusion. Her GCS, which at some point hovered around 4/15, gradually improved to 15/15 by the sixth month of admission. Physiotherapy was then initiated when contractures and sarcopenia began to profoundly manifest around the fourth month into admission and were continued post-discharge until she became self-ambulant.

Her electrolyte, urea, and creatinine levels normalized as she improved 6 weeks into admission, except for hyponatremia, which persisted. She had never undergone dialysis or received a liver transplant. Given the severe fibrosis, as confirmed by the Fibrous scan, she was placed under 6-monthly surveillance to monitor for possible malignant transformation using a liver ultrasound scan and serum alpha-fetoprotein (See figure 1). Approximately 2 years post-discharge, the total platelet decreased to 94,000; abdominal ultrasonography revealed an echogenic liver fatty infiltration. She had an episode of variceal bleeding 4 years post-discharge, which was endoscopically confirmed to be varices; however, she declined banding due to her apprehension for the procedure. Hence, the patient was conservatively managed with propranolol, rabeprazole, hematinic, and simvastatin.

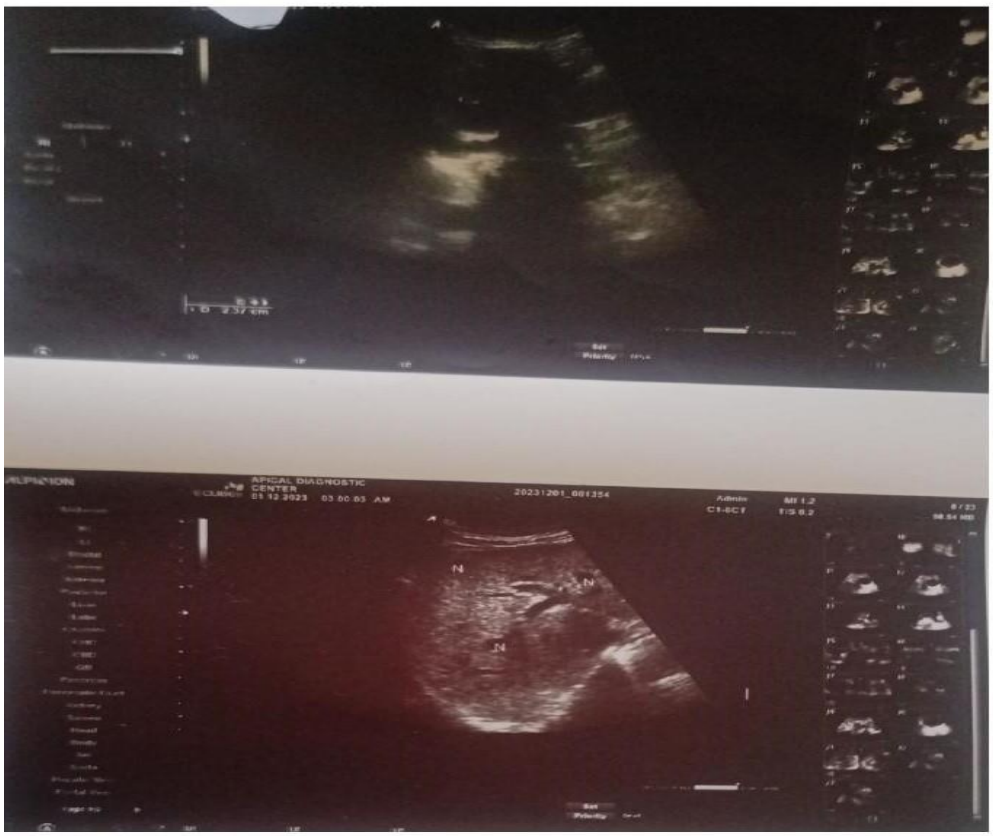

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Figure 1. Recent ultrasound of the liver.

The following were her most recent laboratory parameters as of 05 November 2023 – INR 1.2 (average), platelet count 100,000 (low), alpha-fetoprotein 122 ng/mL (high), electrolyte urea and creatine are all normal, fasting blood sugar 4.6 mmol/L. The fasting lipid profile parameters were all normal except for HDL, which was 25 mg/dL (low); an abdominal ultrasonography scan revealed liver cirrhosis with dysplastic nodules and a right renal cyst. Elastography consistently revealed severe fibrosis.

In her most recent follow-up (25th October 2024), besides the mild leg swelling bilaterally, as evidenced by mild pitting led edema, patients had no complaints. Her electrolytes, urea, and creatine were all within normal limits. Alpha-fetoprotein showed > 400ng/ml(high), serum albumin 28g/l(low). The latest full blood count showed a platelet count of 94,000 and an INR of 1.5. In this regard, she was scheduled for a liver biopsy but that suffered some setbacks as the family was unwilling.

Discussion

The long-term prognosis of the DAA as regards disease progression and survival in patients with advanced decompensated HCV-related CLD remains debatable[2] and untested in northeastern Nigeria. However, several studies continue to show that achieving sustained viral response SVR with the DAAs reduces all-cause mortality and liver-related deaths.[16,17].

DAAs became available in the region only recently. However, they are still beyond the reach of the majority of patients due to their exorbitant cost and limited availability. In addition to cost as a barrier, most patients present very late.[18]. Market survey shows that the 3-month dose of sofosbuvir/daclatasvir hovers around $106 to $300 as of September 2024 in Nigeria, where the monthly minimal wage is about $43. Furthermore, most studies which evaluated the clinical outcomes of patients with advanced decompensated HCV related CLD after treatment with DAA followed them for periods ranging from 24-36 months.[1,19,20]. And in those studies, the participants were either in Child-Pug class A or B.[1] as against the index case who was in Child-Pugh class C which we have followed up on for 6 years and still going forward.

Hepatic encephalopathy, a late and severe complication of advanced liver cirrhosis, is a significant cause of morbidity and death, connoting a poor prognosis.[7,11,13,14,21]. Going by her iMELD-Na and Child-Pugh score, liver transplantation was indicated as the standard of care even though this is relative. However, being in a low-income and poor-resource setting where no orthotopic liver transplant facility operates, she was precluded from it. In view of this limitation, we intensified conservative medical therapy. Timely OLT has a critical relationship with posttransplant survival and reduces pretransplant mortality.[15] The median survival probability following the first episode of HE is warranting hospital admission in the background of decompensated liver cirrhosis in a multicenter Australian study was 44% and 35% at 12 and 24months, respectively.[15]. Considering this background, the survival of our patient for such a long duration is indeed uncommon hence it is being reported.

Advanced fibrosis despite virological clearance increases the risk of Hepatocellular carcinoma HCC which is usually aggressive in 12.7- 28.8%, and it is the most common complication following SVR using DAA. [10]

In an American-based study, patients with grade 3–4 HE at the time of wait-list registration for liver transplant had a significantly higher risk of dying than patients without HE.[8]. In addition, the multivariate Cox proportional hazards modelling of 90-day wait-list mortality in this study found a hazard ratio [HR] of 1.65, 95 % confidence interval [CI] 1.44–1.89; $P < 0.001$).[8]. Furthermore, the study did reveal that the female gender carries a relatively higher risk of death when compared to men.[8].

HRS type 1 is a severe complication of end-stage liver disease and has a very poor prognosis and a median survival of 2 weeks.[13] Additionally, it is a functional type of renal dysfunction associated with a rapid and progressive decline in renal function characterized by renal vasoconstriction.[13] In a prospective American study involving patients with decompensated liver cirrhosis, a 90-day mortality rate of 57% emerged despite receiving standard care.[14]

Spontaneous bacterial peritonitis is often a common trigger for HRS, which was observed in this index case report. Liver transplantation is the standard, definitive treatment. However, our region has no OLT facilities; hence, she did not receive them. However, we intensified the conservative care by using salt-poor albumin infusion and antibiotics, viz., parenteral levofloxacin 500mg daily and intravenous metronidazole 500mg 8 hourly for 2 weeks and other support care. This underscores the importance of aggressively containing HRS triggers, particularly in resource-limited settings where OLT facilities do not exist.

This study is limited in its design by being a case report, reporting the outcome in only a single patient. The strength of this study lies in the fact that the patient is still being followed prospectively for 6 years

now after a 6-month hospitalization and treatment. Lastly, the lack of liver biopsy is also a limitation in this study.

Conclusion

DAA improves the prognosis and survival of patients with hepatitis C viral infection-associated cirrhosis, even in the presence of advanced decompensated cirrhosis and old age. In this regard, we advocate the timely and aggressive initiation of DAA in such patients to reduce the incidence of complications and prevent disease progression in resource-limited settings. The findings from this case study speak to public health authorities, particularly in the developing world, to improve access to DAA for patients with hepatitis C viral infection who, in most cases cannot afford them and to provide training and awareness among doctors in public and private healthcare facilities that DAAs offer tremendous benefits regarding survival, even in the presence of end-stage liver disease. Due to the shortage of specialist gastroenterologists, it is also necessary for the healthcare authorities to consider initiating a policy that spells the training of medical practitioners in our hospitals across the country especially in the suburban and rural areas and the general outpatient clinics on how to evaluate and manage uncomplicated chronic HCV infection to in other to reduce the morbidity and mortality arising from this disease.

The monitoring and evaluation of patients cured of HCV-related CLD is advocated. Finally, we recommend more public health education on screening and sensitization on the preventive measures against the spread of viral Hepatitis C and B.

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