# Regression of hepatocellular carcinoma after treatment with Sofosbuvir — A case report

Shafaq Mahmood, Aleesha Gul, Tayyaba Saif

## Abstract

Spontaneous regression (SR) of hepatocellular carcinoma (HCC) is a rare event. Several factors have been suggested as the underlying mechanism but the exact pathogenesis is not understood. The role of sofosbuvir in HCC regression has not been established yet. We report here a case of a 59 years old male who developed HCC secondary to chronic HCV infection. He failed treatment with interferon but the tumour regressed completely after treatment of hepatitis C with sofosbuvir and ribavirin for 48 weeks.

**Keywords:** Hepatocellular carcinoma, Spontaneous neoplasm regression, Hepatitis C, Sofosbuvir.

## Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer related deaths and the fifth most common malignant tumour worldwide. Chronic infection with hepatitis C virus (HCV) plays a key role in development of HCC.[1] With curative treatment, 5-year survival rate of more than 50% has been reported for an early stage tumour. However, due to late presentation, majority of the patients have a dismal prognosis. No effective curative therapy exists for an advanced stage carcinoma and the survival rate is less than 1 year.[2]

Spontaneous regression (SR) of HCC is a rare phenomenon with a reported incidence rate of 1 in 140,000 cases. Several factors have been suggested as likely mechanisms leading to SR of HCC, but the exact pathogenesis is still not confirmed. The correlation between HCC regression and direct-acting antivirals (DAAs), specifically sofosbuvir, is still unestablished and needs to be explored.[3] We present here a case of advanced HCC secondary to chronic HCV infection who failed treatment with combined interferon and ribavirin therapy but showed complete regression of the tumour upon subsequent treatment of HCV with sofosbuvir and ribavirin.

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## Case Report

A 59 years old male had a history of Hepatitis C (genotype III-a) acquired through a needle prick injury in 2000 and later developed HCC diagnosed in September 2014. The patient had received pegylated interferon and ribavirin alternatively for 6 years that was unsuccessful as he did not achieve sustained virological response (SVR) to the combination therapy.

The patient was a binge drinker till the end of 2013. In August 2014 he presented with a 2 month history of high grade fever, malaise, weight loss and pain in right hypochondrium. On investigation his HCV viral load at that time was 2041287 IU/mL. Alpha fetoprotein (AFP) was markedly raised to 256 IU/mL. Abdominal imaging which included Biphasic computed tomography (CT) scan of the liver and magnetic resonance imaging (MRI) abdomen with contrast was performed (Figure-1). On the basis of MRI findings and markedly raised AFP levels, he was diagnosed as a case of HCC. He was started on anti-HCV treatment with sofosbuvir 400mg once daily and ribavirin 600mg twice daily on 5th-Oct-2014. He was then referred to India for liver transplant. He had a live donor offspring daughter 26 years of age who consented to be live donor for him. He was admitted to liver transplant clinic on 16th- Nov-2014. By this time he had completed 6 weeks of combination therapy with sofosbuvir and ribavirin. His pre-transplant laboratory investigations revealed an AFP level dropped from 256 IU/mL to 93.04 IU/mL. HCV RNA became undetectable. Triple phase contrast enhanced CT scan abdominal angiography was also performed which revealed cirrhotic liver with a focal rounded arterial phase enhancing lesion measuring 8mm in segment 4A of liver getting isodense to liver parenchyma in venous phase. He also had his PET MRI done which showed no demonstrable metabolically active suspicious abnormality in the whole body to suggest any metastasis. The patient refused to undergo liver transplant and was discharged on 18th-Nov-2014. He

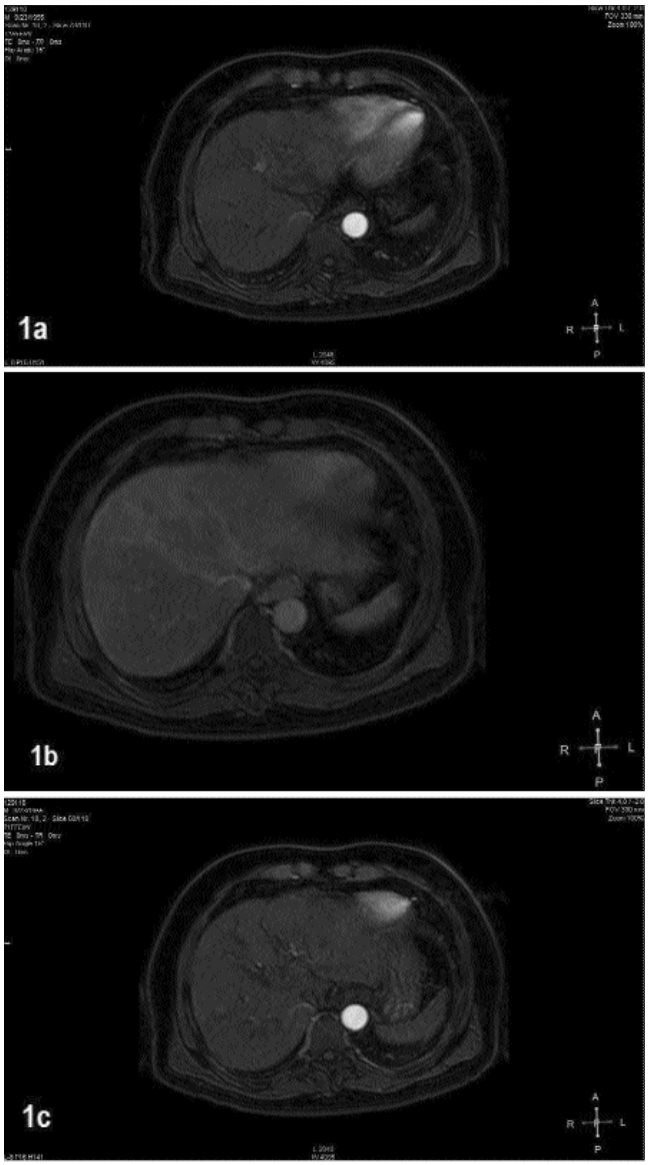


**Figure-1:** (MRI Abdomen with contrast): a) Focal abnormality in segment 4A of the liver adjacent to a porto-billiary triad measuring around 14mm which had strong enhancement on the arterial phase; b) and washes out on the delayed venous phase with capsular enhancement characteristic for HCC; c) Another peripheral segment 8 lesion measuring 1.3 cm had characteristic arterial enhancement with venous washout.

was advised monthly AFP and follow up.

After completing 6 months of treatment, he had his HCV PCR done in April 2015 where his HCV RNA was again found to be detectable (Viral load 40,494 IU/mL). AFP level was 22.9 IU/mL. As he was not interferon naïve, the treatment was continued for another 6 months, as recommended for the chronic non-responder patients.[4] After completion of 48 weeks of treatment in October 2015, his end of treatment response (ETR) was negative. AFP level was 10.0 IU/ml. MRI abdomen with contrast revealed complete regression of tumour and no space occupying lesion (SOL) could be identified in the liver (Figure-2). His last follow up after 12 weeks revealed undetectable HCV RNA and the patient was thus able to achieve SVR. Consent of the patient was taken prior to the writing of the manuscript.

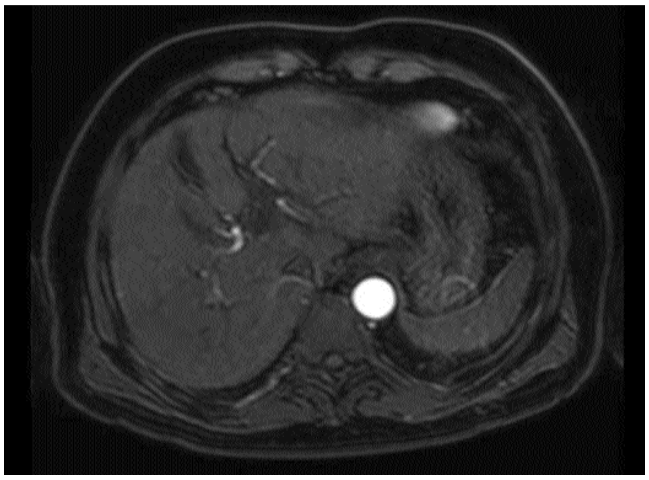

**Figure-2:** (MRI abdomen with contrast) No liver SOL is seen. No abnormal enhancement is seen corresponding to the nodular lesion detected in previous MRI in segment 4A and 8.

## Discussion

SR of HCC is a rare event with an estimated incidence rate of 0.4%. HCC regression is defined as the partial or complete regression of HCC in the absence of any specific anti-neoplastic therapy, namely chemotherapy and/or locoregional therapy.[3] To our knowledge, less than 100 cases of SR of HCC have been reported since its first description by Johnson and colleagues in 1972.[5] Majority of the patients were men above 60 years with some underlying liver pathology and markedly raised AFP levels.[6] Our patient was a 59 years old male with chronic HCV infection and high serum AFP levels (256 IU/mL). Tumour size was small (14mm) as compared to previous case reports.

The underlying mechanism leading to SR is still not confirmed. However, various causative factors including tumour hypoxia, systemic inflammatory responses, abstinence from alcohol or smoking, consumption of herbal medicines, high fever and massive bleeding have been proposed in the literature before.[6] Jonathan et al in his systematic review of 75 patients with SR of HCC identified tumour hypoxia (28%) and systemic inflammatory responses (33%) as the two most common

mechanisms responsible for SR. Whereas, in rest of the patients (38%) the cause was unknown.[5]

The role of anti-HCV therapy in regression of HCC is previously unexplained and very few cases have been documented in the literature before. Recently, Tebit et al[7] and Martin et al[3] reported regression of HCC in patients with chronic HCV infection upon treatment with sofosbuvir, a new generation direct acting anti viral agent (DAAs). The combination of sofosbuvir and ribavirin has shown to slow down the progression of HCC by maintaining an increased SVR rate in patients with chronic HCV infection.[8] However; the exact mechanism is not understood. The pharmacologically active form of sofosbuvir (GS-461203) acts as a chain terminator by inhibiting HCV NS5B RNA-dependent RNA polymerase causing a significant reduction in viral load. Whereas, the anti-viral effect of ribavirin is achieved through the inhibition of p38 mitogen-activated protein kinases (MAPK) phosphorylation pathway. These proposed pharmacological mechanisms might be responsible for the anti-tumour effect of these drugs as suggested by Tebitet al.[7]

In our patient, HCC regression was attributed to treatment with sofosbuvir and ribavirin as none of the previously mentioned factors could be established in this case. After one month of combination therapy, the tumour in segment 4A regressed in size from 14mm to 8mm and no tumour stain uptake was appreciable in previously cancerous segment 8 of the liver. The tumour completely regressed upon completion of treatment after 48 weeks and no liver SOL was seen.

In our patient, liver biopsy was not considered mandatory as the diagnosis of HCC was confirmed on findings of abdominal imaging and markedly raised AFP levels. We reviewed several case reports in the literature as well in which histological examination was not performed and the diagnosis was solely made on radiological and laboratory findings.

## Conclusion

The role of antiviral therapy in regression of HCC still remains an open ended question. In order to develop better understanding of this effect, much more detailed, comprehensive and large scale studies along with molecular/genetic tests are required. Not only would it enable us to understand the exact underlying mechanism of SR, but will also help to formulate new treatment strategies for HCC.

**Disclaimer:** The abstract has not been presented or published in a conference, or published in an abstract book.

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