CASE REPORT

An unfortunate failure: multifocal hepatocellular carcinoma in a non-cirrhotic patient with chronic hepatitis C treated with ledipasvir/sofosbuvir

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the third highest cause of cancer mortality worldwide. Risk factors include chronic liver disease and cirrhosis of various causes including chronic hepatitis B and C. In cases of chronic hepatitis C virus (HCV), HCC usually does not manifest unless the liver has become cirrhotic. Fortunately, novel treatments for hepatitis C including ledipasvir/sofosbuvir can cure patients from their disease and as a result, may never develop cirrhosis and therefore, be at much lower risk of developing HCC. We present a patient with chronic HCV genotype 1a who was successfully treated with ledipasvir/sofosbuvir with documented sustained viral response, but 6 months later was found to have multifocal HCC with virus reactivation with no evidence of cirrhosis on imaging or biochemical testing. While novel antiviral agents for HCV lead to >90% cure rate, cure is defined as sustained viral response of only 12 weeks. This brings to light a new patient population who may require further follow-up than 3 months to ensure viral clearance. Furthermore, this patient developed HCC despite initial viral clearance and no evidence of cirrhosis, indicating possible oncogenic potential of HCV that is independent of cirrhosis that necessitates further investigation.

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the third highest cause of cancer mortality worldwide [1]. In cases of chronic hepatitis C virus (HCV), HCC usually does not manifest unless the liver has become cirrhotic. We present a patient with chronic hepatitis C genotype 1a who was successfully treated with ledipasvir/sofosbuvir, but 6 months later was found to have multifocal HCC with virus reactivation with no evidence of cirrhosis on imaging or biochemical testing.

2. Case

A 69-year-old African American male with past medical history of hepatitis C, chronic atrial fibrillation on warfarin, hypertension, and cholelithiasis presented with hematochezia and was admitted for acute blood loss anemia. History was significant for melena and hematochezia of three months duration as well as recent 12 lb weight loss. He was unsure of how he contracted hepatitis C, but denied any history of intravenous drug use or tattoos. He was a former alcohol consumer and had quit drinking 11 years ago. He was treated 6 months prior to admission with ledipasvir/sofosbuvir for 3 months with documented sustained viral response. On physical exam, he had no stigmata of cirrhosis and his vitals were stable.

His initial hemoglobin was 6.6 g/dL. He was transfused 2 units packed red blood cells and had an upper endoscopy which revealed a large bleeding duodenal ulcer that was subsequently clipped. The same day, the patient had further episodes of hematochezia and drop in hemoglobin from 8.5 to 7.6 g/dL, so he had repeat upper endoscopy which showed slow oozing from the ulcer which was not amenable to intervention. He was given 1 more unit packed red blood cells and within the next 24 h, the patient's hemoglobin stabilized and the bleeding stopped.

Incidentally, it was noted that the patient had a recent right upper quadrant ultrasound as outpatient 1 month prior to admission which showed a 3.8 cm hepatic mass. Due to patient's history of hepatitis C, magnetic resonance imaging was performed. This revealed a 3.9 cm low T1, high T2 lesion in the right lobe of the liver which corresponded to the lesion seen on ultrasound. This lesion did not demonstrate intrinsic post-contrast enhancement, but did have rim enhancement and peripheral parenchymal enhancement. Also seen was a similar smaller 1-cm lesion in the left lobe anteriorly which was not well seen on post-contrast imaging. Additional smaller lesions were seen at the posterior aspect of the right liver, with only minimal non-enhancing components (Figure 1). Differential diagnoses at this point included abscess, hemorrhage, and atypical HCC.

Figure 1. Magnetic resonance image of liver, coronal view. A 3.9-cm by 3.2-cm by 2.6-cm lesion is seen in the right lobe of the liver that is low T1, high T2. A similar 1-cm lesion is seen in the left lower lobe more inferiorly.

Alpha-fetoprotein level was 4078.7 ng/mL (normal: 0.0–8.0 ng/mL). Hepatitis C viral load was also checked, which was positive and quantitatively 4,900,000 IU/mL.

Once the patient's bleeding duodenal ulcer had stabilized, he was discharged and referred to surgical oncology for consultation. Due to the patient's multiple comorbidities, it was concluded that patient would not be a surgical candidate and was referred to interventional radiology for possible chemoembolization of the larger hepatic mass. A computed tomography scan with angiography was then done 2 months after initial presentation which showed multiple ill-defined enhancing masses with largest measuring 10.5 cm in the right hepatic lobe with neovascularity (**Figure 2**). Also noted was an area of arterial enhancement in right anterior portal vein consistent with tumor thrombus. Lastly, two right lung nodules were noticed and considered likely metastases. The patient received left hepatic artery intra-arterial chemoembolization with

doxorubicin by interventional radiology. He had no immediate post-procedural complications, but unfortunately was lost to interventional radiology follow-up.

3. Discussion

While novel agents for treating HCV genotype 1 leads to 95% cure rate, there is still a chance of failure. This case demonstrates the development of multifocal HCC in a non-cirrhotic patient who was successfully treated for HCV after achieving sustained virologic response. The typical progression of chronic HCV without treatment leads to cirrhosis in up to 20% of cases, with 1–4% of these progressing to HCC [1]. The etiology of HCC is known to be complex, with multiple factors coming into play when it comes to disease progression and patient prognosis. The hypothesis of pathogenesis of HCC in itself is multifaceted, including

Figure 2. Computed tomography of the abdomen with contrast, sagittal view. Within the right hepatic lobe, there are multiple focal ill-defined enhancing masses with associated neovascularity. The entire area of enhancement dimensions are 10.5 cm by 7.5 cm by 6.3 cm.

identified mechanisms such as activation of multiple oncogenic pathways, DNA damage checkpoints, and inflammation and oxidative stress [2]. Furthermore, cirrhosis in itself has been hypothesized to be a checkpoint leading to HCC. Our patient had no biochemical or radiological evidence of cirrhosis, which further suggests that HCV may have independent oncogenic properties. This elucidates the point that HCC without cirrhosis may have different biochemical features when compared to HCC with cirrhosis that may indicate different treatment is needed [3]. As more patients go on to use novel agents for eradicating HCV, this may give rise to a new patient population whose HCV is successfully treated, but still go on to develop HCC. This may necessitate more frequent follow-up than 12-week intervals to monitor sustained viral response as well as determining guidelines for active surveillance.

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Informed consent

Written informed consent was not obtained from the patient for publication of this case report as patient was lost to follow up and was unable to be reached.

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