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CASE REPORT

A Call To Action: Cholangiocarcinoma in the Setting of Sustained Hepatitis C Virologic Response – Case Report and Review of Literature

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Abstract

The incidence of cholangiocarcinoma, an aggressive malignancy with poor prognosis, is increasing. Hepatitis B and C have been well established as predisposing factors for this malignancy. The availability and efficacy of treatment for hepatitis C infection has led to a substantial reduction in viral hepatitis-related cholangiocarcinoma mortality. Despite treatment, the potential for developing cholangiocarcinoma continues to exist for patients with underlying cirrhosis.

We present a patient who was effectively treated for hepatitis C with direct-acting antiviral therapy eight years prior. He presented with malaise, fatigue, and an unintentional weight loss of 40 pounds. Imaging revealed a metastatic malignancy, and a liver biopsy confirmed the diagnosis of cholangiocarcinoma and the absence of underlying cirrhosis in the background liver. This case highlights the persistent risk of developing cholangiocarcinoma despite achieving sustained virological response to treatment for hepatitis C. We review the associated literature and briefly discuss the predisposing conditions that might result in such an outcome. We also encourage the need for long-term surveillance for such patients and the importance of conducting more multi-center studies to identify at-risk patients and develop cost-effective screening protocols.

Keywords: Cholangiocarcinoma, Sustained virologic response, Occult hepatitis C infection, Direct-acting antivirals

1. Introduction

After hepatocellular carcinoma, cholangiocarcinoma (CCA) is the most common primary hepatic malignancy.[1–3] The incidence of CCA in the U.S. population is 1.26/100,000.[4] A retrospective review conducted in Japan between 1980 and 1997 was one of the earliest studies to demonstrate an association of chronic hepatitis B and hepatitis C infections with CCA.[5] Since then, several studies have corroborated an association of viral hepatitis with CCA.[6–8] Since these studies used Hepatitis C (HCV) antibody seropositivity as a marker of infection, it remains unclear whether the risk of CCA is ameliorated in patients who are successfully treated for HCV versus those who are not treated for HCV.[9]

Treatment with direct-acting antivirals (DAA) leads to sustained virological response (SVR) in 99 percent of patients.[10] Similar to the outcomes seen in individuals with hepatitis B, successful SVR with DAA therapy is postulated to reduce the risk of CCA by lowering the viral load, inflammation, and fibrosis.[11–13] While only a small number of CCA cases have been documented in patients who had achieved SVR, these typically occurred in the context of preexisting cirrhosis.[14] Here, we present a case of CCA in the setting of a treated Hepatitis C infection without preexisting cirrhosis and briefly

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review factors associated with an increased risk of cancer after SVR.

2. Case presentation

A 74-year-old man presented with malaise, fatigue, and an unintentional weight loss of 40 pounds over a six-month duration. Past medical history was remarkable for uncontrolled type 2 diabetes mellitus and end-stage renal disease s/p deceased donor renal transplant implantation four years ago and currently on immunosuppressive therapy. The patient additionally had a history of hepatitis C infection (genotype 1b) eight years prior. He had successfully achieved SVR with Ledipasvir/Sofosbuvir therapy. A screening colonoscopy three years prior to presentation was within normal limits.

Physical examination was significant for an ill-appearing man with temporal wasting. Neither skin lesions nor peripheral lymphadenopathy was present. Abdominal, lung, and chest examinations were unremarkable.

Laboratory tests were significant for hemoglobin of 12 g/dL (Reference range: 12.6–17.4 g/dL). Serum bilirubin was 0.4 mg/dL (Reference range: 0.2–1.3 mg/dL), and alkaline phosphatase was 250 U/L (Reference range: 38–126 U/L). Serum LDH and uric acid were within normal limits. CT abdomen and pelvis with intravenous contrast (Fig. 1A, B, C, and D) showed multiple, new ill-defined, irregular hypodense masses within the left hepatic lobe with mild rim enhancement. Enlarged periportal lymph nodes and multiple bulky celiac axis nodes were noted. Contrast-enhanced MRI of the abdomen (Fig. 2A and B) showed enlarged liver with a mildly nodular contour. Multiple ill-defined T2, slightly hyperintense, and T1 hypointense lesions with mild peripheral enhancement and central necrosis were demonstrated throughout the left and medial right hepatic lobes. Necrotic lymphadenopathy was seen in the left supra celiac, hepatic portal, and periportal regions. There was an enhancing nodular mass at the gastric cardia/gastroesophageal junction. These findings were suspicious for metastatic hepatic lesions and metastatic lymphadenopathy of a primary gastrointestinal source versus cholangiocarcinoma with intrahepatic metastases.

CEA was within normal limits (2.3 ng/mL), and AFP and CA 19–9 were elevated to 38 ng/mL and 279 U/mL, respectively. Hepatitis C viral load was undetectable. There was no serologic evidence of acute or chronic hepatitis B infection. Upper gastrointestinal endoscopy showed a grossly normal esophagus with a non-malignant appearing nodule in the gastric antrum (Fig. 2C) and the absence of gastroesophageal junction or gastric cardia masses, as was suggested by MRI. Non-bleeding duodenal ulcers with no stigmata of bleeding were seen (Fig. 2D). Biopsies obtained from the gastric nodule and duodenal ulcers were negative for malignancy. CT-guided biopsy of the left lobe liver mass (Fig. 3) showed a poorly differentiated adenocarcinoma that stained positive for CK7 and CK20 and negative for Hepatocyte Paraffin-1 (HepPar-1). The surrounding liver parenchyma showed mild nonspecific chronic hepatitis with minimal fibrosis and absence of steatosis. Thus, a diagnosis of CCA was made. CT chest with contrast (Fig. 1E) for staging showed several right-sided predominant pulmonary nodules and small left-sided pleural-associated nodules, consistent with Stage IV CCA.

The patient was deemed to be a poor candidate for multi-drug chemotherapy in the setting of poor functional status. Guardant360 testing was negative for targetable alterations. Single-agent capecitabine therapy was initiated but had to be discontinued due to persistent vertigo and nausea. The patient decided to pursue hospice care and unfortunately passed a few weeks thereafter.

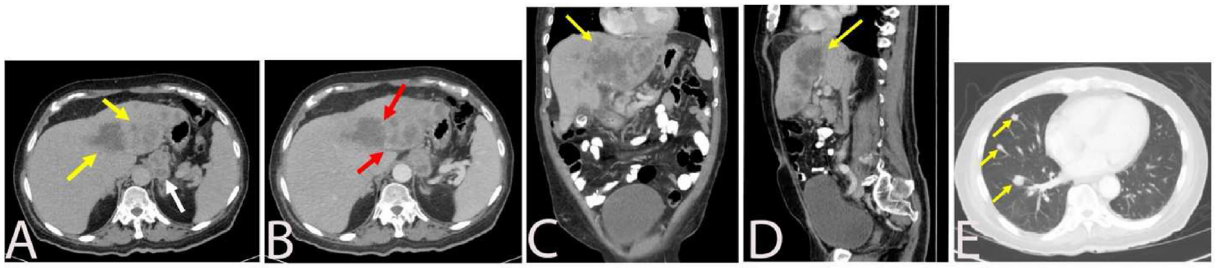

Fig. 1. A,B,C and D are images of CT abdomen with intravenous contrast. A is an axial image in the portal venous phase showing multiple, ill-defined, hypodense lesions in the left hepatic lobe and medial right hepatic lobe with irregular margins (yellow arrows). A conglomerate of enlarged celiac lymph nodes are also seen (white arrows). B is a delayed image demonstrating subtle rim-enhancement of the hepatic lesions (red arrows). Image C and D show the hepatic lesions (yellow arrows) in coronal and sagittal views respectively. E is an image of CT chest with contrast showing metastatic nodules in the right middle and lower lobes (yellow arrows).

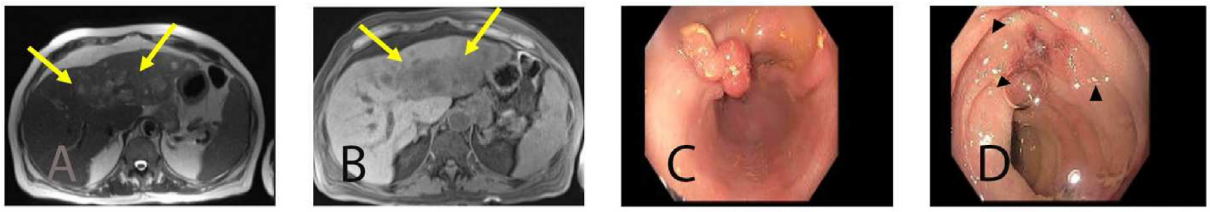

Fig. 2. A and B are axial T2-weighted and T1-weighted post-contrast abdominal MRI images demonstrating multiple, centrally necrotic, peripherally enhancing, ill-defined, mass lesions in the liver (yellow). C and D are upper endoscopy images showing non-malignant appearing nodule in the gastric antrum and multiple superficial ulcers in the third part of the duodenum respectively.

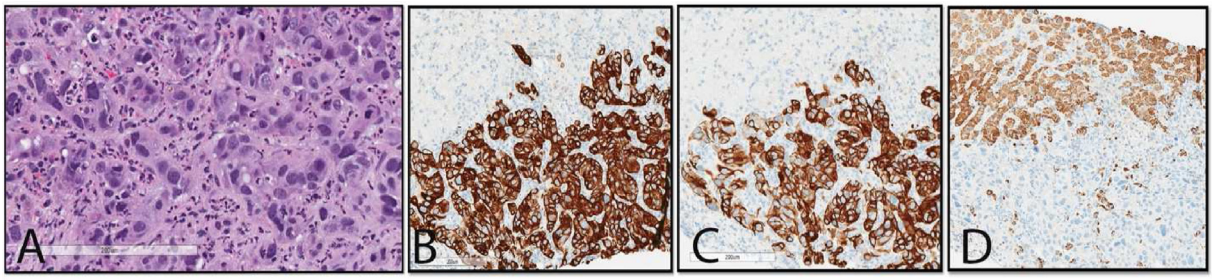

Fig. 3. Image A demonstrates histology of the left lobe liver mass obtained by CT guided biopsy. It shows a highly pleomorphic, poorly-differentiated tumor with nuclear pleomorphism and irregularity of the tumor cells (large purple nuclei) admixed with the much smaller inflammatory cells. CK 7 (Image B) and CK 20 (Iamge C) immunohistocheical stains highlight the tumor cells, whereas the liver parenchyma cells are negative. Conversly, the HepPar1 immunohistochemical stain (Image D) highlights the liver parenchyma, but does not stain the tumor cells.

3. Discussion

Sustained virological response (SVR) is the gold standard for hepatitis C cure, defined as undetectable HCV-RNA in serum 12 weeks after stopping antiviral medication.[15] The ability to achieve SVR in the great majority of patients has led to a significant reduction in liver-related morbidity and mortality, as well as the risk of diabetes and future cardiovascular events.[16] However, even with SVR, the risk of developing CCA and hepatocellular carcinoma (HCC) remains, especially in the presence of cirrhosis. The pro-inflammatory milieu, gut dysbiosis, and persistent endotoxemia have been proposed to exacerbate that risk in these patients.[17] The literature on cholangiocarcinoma occurring in HCV-treated patients without cirrhosis is limited to case reports, case series, and small studies (refer to Table 1). In this article, we present a case of CCA in a patient without cirrhosis whose hepatitis C had been successfully treated. We also review the literature to identify patients at risk of developing CCA and requiring long-term surveillance after SVR.

Various mechanisms have been proposed to explain the phenomenon of tumor occurrence following successful SVR. These include viral persistence, the persistence of steatosis, and immunologically driven chronic inflammation.[15,18–20] DAA treatment-induced modification of natural killer function and dysregulation of anti-tumor response from an abrupt decrease of HCV viral load are other speculated mechanisms.[21]

Viral persistence, also known as occult HCV infection (OCI), has a reported 15% incidence in DAA-treated patients and an even higher incidence in genotype 3 HCV infection.[15] In such cases, HCV-RNA can be detected in liver tissues despite negative serologic titers.[18] Whitcomb et al., in histological evaluation of allograft liver biopsies following SVR, demonstrated necro inflammatory activity and detectable HCV RNA in most of the specimens.[22] This residual HCV-RNA can potentially trigger fibrotic progression and impede fibrosis regression.[15] Immunologically driven chronic inflammation is also postulated to be associated with hepatocarcinogenesis, as demonstrated by Saldarriaga et al., in which some degree of portal lymphocytic inflammation persisted even after successful hepatitis C treatment. This was hypothesized to be the result of a dysfunctional immune response caused by the previous chronic HCV infection.[19]

Nkontchu et al. examined the histopathological changes in the distant non-tumoral liver of patients who developed a peripheral intrahepatic cholangiocarcinoma (ICC) in the absence of cirrhosis or bile duct disease. Macro vesicular steatosis (77%) and mild or moderate iron overload (66%) or both (20%) were consistently observed in the liver biopsies, and these pathologies are thought to

Table 1. Summarizes the studies that described the development of cholangiocarcinoma (CCA) in patients who were successfully treated for hepatitis C infection.

Author	Type of study	Age of patient	Baseline liver biopsy	Treatment modality	Was SVR achieved?	Biopsy of surrounding liver tissue at the time of CCA diagnosis	Duration from SVR to CCA development	Was the patient included in HCC surveillance?
Saldarriaga et al.[19]	Retrospective study	Unknown, female	Well-developed bridging fibrosis	DAA	Yes	Fibrosis	35 months	Yes
Shinkawa et al.[27]	Case report	65-year-old male	Moderately active hepatitis with severe fibrosis	IFN therapy	Yes	Minimal activity with mild fibrosis	7 years	No
Barua et al.[28]	Case report	62-year-old male	Evidence of cirrhosis on CT scan/MRI (Treatment delay - 15 years after Hepatitis C diagnosis)	DAA	Yes	Unclear	5 weeks	NA
Nagano et al.[29]	Case report	64-year-old male	Chronic active hepatitis with septal fibrosis	IFN therapy	Yes	Liver cirrhosis	4 years (2 HCCs and 1 CCA)	Unclear
Sanchez-Azofra et al.[10]	Retrospective study	59-year-old male	F3 Fibrosis on Transient elastography (TE)	DAA	Yes	Unclear. Increase in the TE value was noted at the time of CCA diagnosis	20.4 months; Excessive alcohol intake	Yes (Per EASL guidelines)
Pons et al.[26]	Prospective multicenter study	2 patients (Incidence: 0.3%)	Unclear	DAA	Yes	Unclear	Unclear	Yearly TE
Cerban et al.[30]	Case series	5 patients						
		45-year-old female	Cirrhosis	DAA	Yes	Unclear	6 months	Yes
		62-year-old female	Cirrhosis	DAA	Yes	Minimal activity with moderate fibrosis (F3)	12 months	Yes
		59-year-old female	F2 fibrosis on TE	Prior treatment with IFN & Ribavirin without SVR; 2 years later received DAA therapy & ribavirin	Yes	Refused liver biopsy	4 months	Yes
		65-year-old male	Cirrhosis	DAA	Yes	Unclear	36 months	Yes
		78-year-old male	Cirrhosis	Prior treatment with IFN & Ribavirin without SVR. Subsequent DAA therapy	Yes	Unclear	24 months	Yes
Tsumura et al.[31]	Case report	56-year-old male	Unclear	IFN therapy	Yes	Cirrhosis/fibrosis	13 years (Double HCC-CCA)	Unclear

Tamai et al.[32]	Case series	Average age - 74.3 years, 2 males and 1 female	Unclear	Unclear	Unclear	Chronic hepatitis C in 1 case, fatty liver in 1 case, and alcoholic liver disease in 1 case	Unclear	Unclear
Osawa et al.[33]	Case report	35-year-old male	Unclear	DAA; Diagnosed 20 years ago, 2 unsuccessful IFN therapies	Yes	Mild chronic hepatitis and steatosis	1 year	Unclear
Vakiti et al.[21]	Case series	60-year-old male	F4 fibrosis	Prior failed IFN & Ribavirin therapy; Treated with DAA	Yes	Cirrhosis	1 year	Yes
		73-year-old female	F0/1 fibrosis	DAA	Yes	Unclear	6 months	No
		69-year-old male	Cirrhosis	Prior failed IFN & Ribavirin therapy; Treated with DAA	Yes, after retreatment in 2 years	Unclear	1 year	Yes

DAA: Direct-acting antiviral agents; IFN: Interferon therapy; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; F0−F4 describe METAVIR fibrosis stage according to Fibro Scan; EASL: The European Association for the Study of the Liver.

contribute to persistent inflammation and fibrosis in the liver.[20] In line with these observations, a recent case−control study suggested that statins may reduce the extrahepatic cholangiocarcinoma risk and improve survival.[23]

As described in Table 1, most of the patients in the literature who developed CCA after a successful SVR had underlying cirrhosis, steatosis, or a longer duration of chronic hepatitis C infection. However, our patient had only mild inflammation reactionary to the neoplastic process, without any evidence of cirrhosis, fibrosis, or steatosis. This makes the development of CCA unique in this case. We suspect that immunosuppression might have allowed HCV viral load to persist in the liver despite serological clearance, leading to ongoing inflammation, neoplastic transformation, and, ultimately, CCA.

Screening strategies vary across the world. Asian Pacific Association for the Study of the Liver (APASL) recommends 6-monthly surveillance in all patients up to 2 years after SVR, followed by 6-monthly surveillance of METAVIR fibrosis stage F3−F4 and annual surveillance of F0−F2.[24] However, the current AASLD guidelines do not provide surveillance recommendations for patients without cirrhosis in the context of SVR after DAAs.[25] Since our patients did not fall under the umbrella of HCC surveillance per AASLD guidelines, we urge the need for developing a cost-effective surveillance strategy for patients without cirrhosis who achieve SVR.

In order to mitigate the risk of developing hepatic malignancies in noncirrhotic patients, we recommend evaluating metabolic risk factors, monitoring AFP levels, and screening for ongoing alcohol use. Pons et al. noted serum albumin $\geq$4.4 g/dL, Liver Stiffness Measurement (LSM) < 10 kPa or LSM between 10 and 20 kPa but albumin <4.4 g/dL at follow-up to be associated with a decrease in the incidence of hepatic malignancy.[26] Therefore, monitoring certain biomarkers, such as albumin levels and liver stiffness measurement, during follow-up visits may be beneficial.

4. Conclusion

This case demonstrates the development of CCA in a patient who had previously achieved SVR for hepatitis C. The uniqueness of this case lies in the fact that the background liver lacked the traditional risk factors for neoplastic transformation, including cirrhosis, fibrosis, or even steatosis. This patient would not meet the standard screening criteria for surveillance for hepatic malignancy. Therefore, for similar patients, if CCA does occur, it may be diagnosed late when treatment options are limited.

Further multi-center prospective studies are needed to elucidate the risk factors for CCA and HCC, and to formulate evidence-based surveillance protocols in non-cirrhotic patients who achieve SVR.

Conflict of interest

The authors declare no conflict of interest.

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