Intrahepatic Cholangiocarcinoma in a Patient with Hepatitis C: A Cautionary Tale

SOUMITRI BARUA, AB, MD'21; SOPHIE SPRECHT-WALSH, LPN; ZOE WEISS, MD; JAMES N. BUTERA, MD; KHALDOUN ALMHANNA, MD, MPH; SUSAN HART, MD; JAEL RODRIGUEZ, MD; LYNN E. TAYLOR, MD

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INTRODUCTION

Delayed treatment of hepatitis C virus infection (HCV) can lead to cirrhosis and may increase the risk of associated malignancies including hepatocellular carcinoma (HCC) and less commonly, intrahepatic cholangiocarcinoma. Stigma and misunderstanding surrounding alcohol and/or substance use disorders (SUD) can delay or prevent access to life-saving direct-acting antiviral (DAA) therapies, despite the large body of evidence supporting HCV treatment in people with SUD. We present a case of fatal intrahepatic cholangiocarcinoma in an HCV-infected patient who received unrestricted access to treatment for three malignancies and other chronic health conditions but for whom treatment of HCV was delayed due to SUD.

CASE REPORT

A 62-year-old African American male presented in October 2017 to the co-located HCV clinic at his methadone maintenance program for a second opinion regarding treatment of chronic HCV. Past medical history was notable for transitional papillary cell bladder carcinoma with transurethral resection of bladder in 2006, prostate cancer with transurethral resection of prostate and radiation in 2007, diffuse large b-cell lymphoma (DLBCL) stage III status post six cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine sulfate [Oncovin®], prednisone) through which he missed no doses or scheduled treatments, diabetes mellitus type two, hypertension, alcohol dependence, opioid use disorder and injection drug use (IDU) on methadone maintenance since January 2008. In February 2002 he was diagnosed with HCV. He was first referred to hepatology for HCV evaluation and treatment in February 2011. In March 2011 liver biopsy was performed, with one cylindrical core fragment measuring 1.8 cm by 0.1 cm demonstrating fibrosis stage 1 of 4. Right upper quadrant ultrasound revealed cirrhosis in February 2013.

The patient attended eight hepatology appointments from 2011 to 2018 and underwent repeated liver imaging as ordered. From the interferon into the DAA era, HCV treatment was deferred by his hepatologists due to ongoing alcohol and illicit opioid use. For example, in September 2015, his physician documented, "patient understands that sobriety from IDU as well as alcohol are a requirement for treatment of HCV, given that after investing in treatment we want to help him protect his liver from any further damage as much as possible." Similarly, between 2016 and 2017, the patient saw his primary care physician (PCP) eight times, at all of which the patient was informed that he could not access HCV treatment due to alcohol misuse.

The patient reported that he tried to discontinue alcohol but developed alcohol withdrawal seizures. He had been given lists of local resources to help him 'detox,' by a social worker at the request of his PCP. The patient declined outpatient pharmacologic treatment for alcohol use disorder. Regarding his tobacco dependence, he was counseled by his PCP on the benefits of nicotine replacement therapy, began using the nicotine patch in January 2017, and decreased to 4–5 cigarettes per day from one pack per day by July 2017.

During these years, the patient continued to receive primary and subspecialty care and be followed for his other malignancies. Urology monitored for recurrence of his bladder and prostate cancers. The patient's oncologist saw him two to three times annually to monitor for DLBCL recurrence. There was no deferral or denial of cancer treatment due to SUD.

At initial HCV evaluation at the HCV program embedded within his methadone program on October 10, 2017, physical examination was significant for a firm liver edge palpable 3 cm below the right costal margin, lack of palpable spleen, and trace ankle edema. Laboratory studies were notable for albumin 4.0 mg/dl, total bilirubin 0.6 mg/dL, AST 56 units/L, ALT 39 units/L, platelets 169,000/ L, INR 1.1, Cr 0.79, HCV viral load 857, 032 IU/mL and HCV genotype 1a. Testing for HIV was negative, hepatitis B virus (HBV) serologies showed isolated core antibody reactivity, and hepatitis A total antibody was reactive. The infectious disease-trained physician reviewed medical records at the patient's request. Diagnosis of cirrhosis was discussed with him, including the impression per the last hepatic ultrasound in April 2017 indicating hepatomegaly (likely from alcohol and diabetes-related steatosis) and cirrhosis. Benefits of DAA therapy

leading to sustained virologic response (SVR) were reviewed, including lowering risk for decompensated cirrhosis and other HCV-associated conditions and extrahepatic manifestations. It was explained that men with alcohol use disorder and chronic HCV were at highest risk for HCC, and that SVR reduced the risk of developing HCC; SVR is associated with a greater than 70% reduction in the risk of HCC, and a 90% reduction in the risk of liver-related mortality and liver transplantation.[1-2] The patient and physician discussed the deleterious effects of alcohol on the liver and overall, and the risks of HCV reinfection and transmission with continued IDU. They developed a plan for risk reduction to be reviewed on an ongoing basis. The patient was eager to initiate DAAs.

The HCV physician contacted the patient's hepatologist, PCP and oncologist, recommending prompt HCV treatment. All agreed that this physician could treat the patient's HCV. The HCV physician remained in close contact with the patient's PCP, hepatologist and oncologist from this point onward. On October 20, 2017, ten days after initial HCV assessment, the patient began DAA treatment with sofosbuvir/velpatasvir (Epclusa), for 12 weeks. He achieved SVR in April 2018.

Five weeks following SVR, in May 2018, the patient had a computed tomography (CT) scan of the abdomen in the setting of "abdominal pain and alcohol intoxication" in the emergency department. CT demonstrated a nodular liver contour, compatible with cirrhosis, with a 2 cm indistinct hypoattenuating segment II lesion, plus a 6 mm right lower lobe ground glass pulmonary nodule. The recommendation was for liver protocol magnetic resonance imaging (MRI) or CT for further evaluation and, "continued attention to patient's annual lung cancer screening CT." Prior CT for lung cancer screening in 2016 did not show this nodule.

August 2018 MRI of the abdomen demonstrated a poorly defined lesion within segment II of the liver which displayed intrinsic T1 hypointensity and mild T2 hyperintensity. The arterial phase was not acquired due to patient intolerance. There was evidence of extensive washout on delayed phase imaging with multiple satellite nodules. The region of washout measured 3.0 x 1.6 x 2.0 cm. Findings were considered highly suspicious for malignancy in the left hepatic lobe; further characterization required the arterial phase, not performed as the patient could not tolerate that portion of imaging. Three-phase CT liver examination was recommended given shorter length of acquisition time.

In September 2018, CT scan of the abdomen revealed re-demonstration of a 1.7 x 2.1 cm peripherally enhancing ill-defined lesion in hepatic segment II without definitive evidence of washout on delayed phase imaging, corresponding to the left hepatic lobe indeterminate lesion on August MRI. Further evaluation with histologic correlation was recommended. Ultrasound-guided diagnostic biopsy of the left hepatic lobe lesion sized 0.5 x 2.1 x 0.1 cm revealed adenocarcinoma compatible with pancreaticobiliary primary.

The patient's findings were deliberated at his hospital's Oncology multidisciplinary tumor board in October 2018, and consensus opinion favored surgical resection of the mass with lymph node dissection for presumed intrahepatic cholangiocarcinoma. The patient underwent staging laparoscopy where he was found to have carcinomatosis with disease near the superior mesenteric artery. Two omental biopsies were positive for adenocarcinoma consistent with the original biopsy. Celiac lymph node biopsy showed metastatic poorly differentiated adenocarcinoma with extensive extranodal involvement.

The patient was deemed to have stage IV disease and was started on combination gemcitabine and cisplatin. He was followed by palliative care during his treatment and continued with methadone maintenance. In February 2019, scans showed disease progression and he was switched to modified FOLFOX (leucovorin, fluorouracil, and oxaliplatin). Unfortunately, the patient clinically deteriorated. He opted to stop active treatment and enroll in hospice. He died in May 2019.

DISCUSSION

Hepatocellular carcinoma (HCC) and cholangiocarcinoma are the most common primary liver cancers. HCV is a causal agent of HCC, with risk of HCC developing once cirrhosis develops. HCC is the fasting-rising cause of cancer-related death in the U.S.[3-4] There are three types of cholangiocarcinomas: extrahepatic, intrahepatic and combined. Intrahepatic cholangiocarcinoma is less common than HCC.[5] The incidence ratio of HCC to intrahepatic cholangiocarcinoma is 13.7 to 1 infected with either HBV or HCV.[6] The association of HCV with intrahepatic cholangiocarcinoma may be under-appreciated compared to the association with HCC.[7] Although the mechanism of intrahepatic cholangiocarcinoma development is unclear, one theory is that HCV in bile duct epithelium leads to chronic inflammation and tumorigenic processes. HCV RNA has been detected in intrahepatic cholangiocarcinoma biopsy specimens. A meta-analysis of patients with HCV and intrahepatic cholangiocarcinoma demonstrates a statistically significant positive association with HCV and incidence of intrahepatic cholangiocarcinoma; the pooled odds ratio (OR) of intrahepatic cholangiocarcinoma was 3.38 (95% CI, 2.72 to 4.21), while the pooled OR of extrahepatic cholangiocarcinoma was 1.75 (95% CI, 1.00 to 3.05).[7] HCV carries a poor prognostic prediction for intrahepatic cholangiocarcinoma.[8] Surgical resection is the preferred treatment but is contraindicated in patients with bilateral, multifocal disease and distant metastases, as in this patient.[9]

Beyond hepatic malignancies, there are extra-hepatic oncologic manifestations of HCV. HCV is a lymphocytic virus associated with several lymphoproliferative disorders, including DLBCL, the most common type of B cell

non-Hodgkin lymphoma.[10] Continued stimulation of lymphocyte receptors by HCV antigens, viral replication in B cells, and damage of B cells are potential mechanisms of pathogenesis of DLBCL in HCV-infected patients.[11] Our patient continued to receive consistent follow-up care for DLBCL recurrence after completing chemotherapy in 2014. While the pathogenesis of this malignancy continues to be investigated, one cannot say for certain that ongoing HCV infection, first detected in 2002, did not impact development of DLBCL in this patient. In the setting of both HCV and NHL, it is imperative to retard progression of liver disease by treating with DAAs.[12] For some types of NHL, achieving SVR leads to better 10-year survival rates compared with those not treated with antivirals or controls.[13] For patients with NHL, treating concurrent HCV with DAAs may induce NHL remission in up to 75% of cases.[13-15] Some oncology programs around the U.S. are now routinely including HCV treatment within their protocols.

Treating the infection has become the easy part of HCV care, as DAAs can safely cure most patients in 8 to 12 weeks. Staging fibrosis and treating cirrhosis over time can be more challenging. The patient's 2011 liver biopsy was 1.8 x 0.1 cm in size. While non-invasive measures to stage fibrosis have become standard of care in HCV, liver biopsies were routinely performed in the interferon-era. A specimen of at least 2.5 cm in length is required to stage hepatic fibrosis in HCV, or else disease severity may be under-staged, as may have occurred with this patient.[16] Note, he was diagnosed with cirrhosis in 2013, two years after initial staging biopsy.

IDU, opioid use disorder, alcohol misuse and HCV often coexist.[17] People who use drugs are disproportionately affected by HCV. The burden of HCV-related disease in this group continues to grow at alarming rates and represents a major cost to the healthcare system. People who inject drugs (PWID) carry the highest burden of HCV, with almost half of PWID worldwide living with HCV.[17-21] IDU is the main route of transmission in middle- and high-income regions.[17-21] High levels of HCV treatment and cure for PWID can reduce HCV incidence and prevalence.[22-27] Therefore, expanding preventive efforts, testing, diagnosis, treatment and cure among this population is critical. As early as 2014, for example, the Veterans Administration, the largest provider of HCV care in the U.S., abolished HCV treatment candidacy based on substance use: "There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment."[28]

Rather than excluding PWID, national and international guidelines including those of the American Association for the Study of Liver Diseases (AASLD)/Infectious Disease Society of America and World Health Organization, endorse prioritizing PWID for HCV treatment to improve individual and public health.[29-30] Benefits of treating HCV early include thwarting development of cirrhosis, end-stage liver disease and HCC, and stemming disease spread.[28, 31-32] Decreasing the infectivity of the transmitting population is essential to achieve HCV elimination.[29-30] While historic concerns about treating HCV in PWID include risk of reinfection and sub-optimal adherence, a robust body of evidence demonstrates DAA efficacy among PWID both on opioid agonist therapy and not, as well as HCV treatment as prevention benefits among PWID to eliminate HCV.[22,33-35] Reported rates of reinfection after SVR among PWID are low – 3.8-6.2/100 person-years, and may be exacerbated by slow scale-up of HCV treatment for this population.[36] Concerns about reinfection rates in other subpopulations, such as surgeons and HIV-infected men who have sex with men, have not impeded HCV treatment. Additionally, HCV treatment of PWID is cost-effective, particularly when the prevention benefits are considered.[22]

AASLD and the World Health Organization do not require treatment of alcohol use disorders before HCV treatment, nor HCV treatment restrictions for persons with alcohol use disorders. HCV and alcohol act synergistically in causing more severe liver injury than seen with either disease alone. Persons with coexisting alcohol disorders are at a higher risk for HCV-related complications.[17,37] Curing HCV is easier than 'curing' alcohol disorders; pharmacotherapy for alcohol misuse is limited, and behavioral interventions are not always successful. SVR rates are similar in drinkers and nondrinkers.[38]

While physicians caring for patients with tobacco dependence recommend tobacco cessation and treat tobacco dependence, potential life-saving therapies for the treatment of lung cancer or asthma are not withheld from smokers. Diabetes medications are not withheld from those who are overweight and do not adhere to dietary recommendations. Substance use criteria are not used to restrict access to antiretroviral therapy for HIV/AIDS. The 2020 standard of care requires that PWID and people with alcohol use disorders not experience delays in accessing potentially life-saving DAA medications due to provider-level misperceptions not supported by evidence. Addiction is a chronic relapsing and treatable brain disease to be treated with respect and compassion.

The HCV epidemic exposes racial and socioeconomic health care disparities. More than half of HCV-infected people in U.S. have incomes lower than twice the poverty level and less than a high school education. Native Americans and Alaskan Natives have the highest incidence. People who are African American account for 25% of those with chronic HCV but 11% of the population.[39-40] Multiple studies identify a racial/ethnic disparity with respect to HCV diagnosis, referral and treatment initiation. Implementing universal screening and treatment will help overcome these inequities.[41]

CONCLUSION

Intrahepatic cholangiocarcinoma is an aggressive HCV-associated malignancy. Further research as to the impact of SVR on intrahepatic cholangiocarcinoma incidence and incidence of other HCV-associated malignancies is needed. Early DAA treatment is now universally recommended except for those with short life expectancy that cannot be remediated by HCV therapy or liver transplantation. Interferon-era concerns about treating HCV in drug-involved patients should not be perpetuated. Evidence-based national and international guidelines supporting prioritization and HCV treatment scale-up for this population.[31-32]

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Authors

Soumitri Barua, AB, MD '21, The Warren Alpert Medical School of Brown University, Providence, RI.

Sophie Sprecht-Walsh, LPN, CODAC Behavioral Health, Providence, RI.

Zoe Weiss, MD, Division of Infectious Diseases, Brigham and Women's Hospital and Massachusetts General Hospital.

James N. Butera, MD, Department of Medicine, The Warren Alpert Medical School of Brown University, Division of Hematology-Oncology, Rhode Island Hospital, Providence, RI.

Khaldoun Almhanna, MD, MPH, Division of Hematology/Oncology, The Warren Alpert Medical School of Brown University; Lifespan Cancer Institute, Rhode Island Hospital, Providence, RI.

Susan Hart, MD, CODAC Behavioral Health, Eleanor Slater Hospital, Cranston, RI.

Jael Rodriguez, MD, Department of Internal Medicine, Warren Alpert Medical School of Brown University; Division of General Internal Medicine, Rhode Island Hospital/The Miriam Hospital.

Lynn E. Taylor, MD, CODAC Behavioral Health and University of Rhode Island, Providence, RI.

Correspondence

Lynn E. Taylor, MD
letaylor@uri.edu