Hepatocellular Carcinoma in HIV-Infected Women: Two Case Reports

MICHELLE L. WESTBROOK, MS; SHIKHA GARG, MD; STACEY CHAPMAN, RN; SUSAN CU-UVIN, MD; KAREN T. TASHIMA, MD; LYNN E. TAYLOR, MD

ABSTRACT

With the widespread availability of highly active antiretroviral therapy (HAART), and increased life expectancy among HIV-infected individuals, liver-related mortality has emerged as the leading cause of non-AIDS-related death. The incidence of hepatocellular carcinoma (HCC), a sequela of chronic liver disease, is rising among HIV-infected individuals. While women are increasingly and disproportionately affected by HIV, little is known about HCC in HIV-infected women given HCC's predilection for men. In 2007, 2 out of 398 HIV-infected women seen at a Rhode Island HIV clinic were diagnosed with HCC. Of 351 HIV-infected individuals with HCC described in the published literature, 12 (3.4%) were women. These 2 cases add to the existing literature on this topic.

KEYWORDS: HIV, Hepatocellular Carcinoma, Women

INTRODUCTION

With the widespread availability of highly active antiretroviral therapy (HAART) and increased life expectancy among HIV-infected individuals, liver-related mortality has emerged as the leading cause of non-AIDS-related death.[1,2] The incidence of hepatocellular carcinoma (HCC), a sequela of chronic liver disease, is rising among HIV-infected individuals and is being driven by coinfection with hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol and tobacco.[2-6] HCC is an aggressive malignancy, with a median survival of 6-8 months from time of diagnosis among HIV-infected individuals.[3,7-9] In the general population, men are three times as likely as women to be diagnosed with HCC.[4,7-13] Most observational cohort studies describing HCC in the setting of HIV infection lack data on women. Consequently, little is known about HCC in HIV-infected women.

In 2008, 398 (33%) of 1203 HIV-infected patients at the Miriam Hospital Immunology center, a Rhode Island HIV care center, were female. One hundred thirty-two (33%) of the 398 women were coinfected with chronic HCV. Two of these women were diagnosed with and subsequently died from HCC. These two cases may reflect a rise in HCC incidence among HIV-infected women as they increasingly live into their post-menopausal years. This may suggest a need for greater attention to HCC prevention and screening among HIV-infected women, historically thought to be at low risk.

CASE REPORTS

Case 1

A 47-year-old Hispanic woman was diagnosed with HIV infection in 1994, and with HCV in 1996. Additional medical history included major depressive disorder (MDD), alcohol abuse, non-injection cocaine use and tobacco dependence. She denied history of injection drug use (IDU). A highly active antiretroviral therapy (HAART) regimen consisting of lamivudine, zidovudine, and nelfinavir was initiated in 1998 when her $CD4^+$ cell count was 342 cells/µl. She experienced a robust immunologic response to treatment, achieving a peak $CD4^+$ cell count of 1400 cells/µl in 2006. From 2004 onward she maintained a non-detectable HIV RNA level and a $CD4^+$ cell count above 400 cells/µl. Despite multiple referrals to an on-site HIV/viral hepatitis coinfection clinic, she did not present for her first HCV visit until March 2000. Evaluation of HCV revealed genotype 1a infection with HCV RNA level of 2,820,000 copies/mL. She did not return for further HCV care until 2003. At that time, she displayed clinical evidence of cirrhosis with spider angiomas, palmar erythema and rash consistent with cryoglobulinemia. Laboratory evaluation revealed a platelet count of 176 X 10^9 cells/L, INR 1.20, albumin 3.3 g/dl, total bilirubin 0.9 mg/dl, aspartate aminotransferase (AST) 120 IU/L, and alanine aminotransferase (ALT) 119 IU/L. Abdominal ultrasound revealed an enlarged spleen but no focal masses or ascites. Despite recommendations that she initiate HCV treatment, she declined therapy due to concern for adverse effects. She did discontinue alcohol use. She agreed to surveillance for HCC with bi-annual abdominal imaging. After a liver biopsy performed at her insistence confirmed a histologic diagnosis of cirrhosis, she agreed to initiate pegylated interferon alfa 2a plus ribavirin in January 2007. She developed cytopenias but otherwise tolerated therapy well. Due to virologic non-response, treatment was discontinued at week 12 and she was referred for early consideration for future liver transplantation.

In November 2007, a screening abdominal magnetic resonance imaging (MRI) obtained as part of the transplant evaluation process revealed 14 mm and 22 mm lesions in the left hepatic lobe. Alpha-fetoprotein (AFP) was found to be elevated to 351 IU/mL from a value of 34 IU/mL two years prior. Biopsy of the liver lesions in January 2008 confirmed a diagnosis of HCC. Her HIV at that time was well-controlled with a CD4+ cell count of 633 cells/µL and an HIV viral

load of <75 copies/mL. She underwent radio-frequency ablation in January 2008, but by March 2008 she had developed a new hepatic mass. She was then diagnosed with biopsy-confirmed breast cancer in April 2008. In July 2008, her AFP rose to 56,766 IU/mL and abdominal MRI revealed numerous hypervascular hepatic masses and metastases to the abdominal wall. After extensive discussions with the patient, and per her wishes, she entered Hospice care. In September 2008, 8 months after her HCC diagnosis, she died at the age of 61. At the time of her death, her CD4+ cell count was 451 cells/mL and HIV RNA level was <75 copies/mL.

Case 2

A 42-year-old African and Native-American woman was diagnosed with HIV and HCV in March 2000. Additional medical history included MDD, hypertension and chronic renal insufficiency secondary to HIV-associated nephropathy. She had a longstanding history of polysubstance addiction, with ongoing injection drug use (IDU) of heroin and cocaine, heavy alcohol use and tobacco addiction. Her initial HIV parameters revealed a $CD4^+$ cell count of 308 cells/μL and HIV viral load of 1,385 copies/mL. She was intermittently adherent to a HAART regimen of lamivudine, stavudine and nelfinavir. Initial HCV evaluation in September of 2000 revealed genotype 1a infection with a viral load greater than 1,000,000 copies/mL. Additional laboratory evaluation at that time revealed a platelet count of 90 X 10^9 cells/L, INR 1.2, albumin 2.6 g/dl, total bilirubin 0.6 mg/dl, AST 78 IU/L, and ALT 94 IU/L. Emphasis was placed on assisting her in abstaining from alcohol and tobacco, and adhering to HAART. She declined further evaluation and treatment of her HCV, including liver biopsy and referral to coinfection clinic, until September 2007. At initial visit, her Child-Turcotte-Pugh score was 7. She declined HCV treatment and further assistance with alcohol and tobacco cessation but agreed to HCC surveillance.

In September 2008, the patient was hospitalized due to abdominal pain. AFP was found to be elevated to 143 IU/mL from a previous value of 2 IU/mL two years earlier. At that time, her CD4+ cell count was 211 cells/mL, HIV viral load was 10,534 copies/mL, and she was on hemodialysis for end-stage renal disease. A triple phase abdominal computer axial tomography (CAT) scan revealed two hypervascular liver lesions, 2.1 x 1.6 cm and 1.1 cm in size, with early arterial enhancement and venous washout consistent with HCC. Due to the superficial location of the liver lesions with minimal surrounding healthy liver tissue, biopsy of the lesions was felt to be associated with a high bleeding risk and the patient did not want a liver biopsy. Based upon clinical, laboratory, and radiographic findings, a diagnosis of HCC was made. In consultation with the oncology service, she was felt not to be a candidate for ablation, resection or chemotherapy, as these therapies would likely be minimally effective and decrease her quality of life. The patient concurred and requested palliative care services. Four months later she discontinued hemodialysis, and died in February 2009 at the age of 51, five months after HCC diagnosis. At the time of her death her CD4+ count was 211 cells/μL and her HIV viral load was 10,534 cells/mL.

DISCUSSION

Women account for more than 25% of newly diagnosed HIV infections in the United States, and roughly 55% of HIV infections worldwide.[14-16] As HIV-infected women age, they are at an increased risk of morbidity due to concurrent illnesses, including liver disease. Based upon risk factors and geographic distribution, HIV-infected women have elevated rates of alcohol consumption[17], coinfection with HCV[18,19], coinfection with HBV[18,20] and tobacco use[5,6] compared to HIV-uninfected women, all drivers of HCC development. With HCC incidence rates increasing among U.S. women,[10] preventive care, including vaccination for HBV among susceptible persons, and strategies to reduce alcohol and tobacco use; screening for viral hepatitis to detect infection early in the disease course; and treatment for persons chronically infected with HCV or HBV are needed to help reverse this trend.

Of 316 HIV-infected individuals with HCC reported in previous studies[4,7,9], only 12 (3.4%) were women. Two additional cases of HCC in HIV/HCV coinfected women were identified at our center in 2008 out of 132 total HIV/HCV coinfected women. Although it is possible that these 2 cases herald a rising incidence of HCC in this population, surveillance data is lacking to support such a supposition. Recent data indicate that a high percentage of at-risk HIV-infected individuals are not being screened for HCC despite a survival benefit seen with screening.[21] Thus, HCC may remain undiagnosed in HIV-infected women or be diagnosed too late in its course to permit consideration of liver transplantation or tumor resection.

The 2010 American Association for the Study of Liver Diseases guidelines endorse ultrasonographic liver imaging every 6-12 months for HCC screening for individuals with cirrhosis secondary to HCV infection, alcohol use, genetic hemochromatosis, and primary biliary cirrhosis. Imaging is also recommended for individuals with chronic HBV infection, with interval follow-up based upon age, sex, ethnicity, and family history.[22] While these guidelines pertain to both HIV-infected and uninfected individuals, no guidelines have been developed to specifically address HCC surveillance in the setting of HIV infection.

Although there have been no randomized controlled trials to show that screening for HCC in patients with HIV improves survival,[23] modeling studies have suggested that screening should improve resectability and liver transplantation rate.[23] A recent large retrospective study involving HIV/HCV coinfected patients from 22 centers around the world found that median survival for individuals undergoing HCC screening was 12.8 months, versus 3.7 months for

individuals who had not undergone HCC screening.[21] HCC screening was also shown to be associated with better liver function and earlier HCC stage, as well as a higher eligibility for liver transplantation and more frequent use of effective HCC therapies.[21] In this study, 43% of HIV/HCV coinfected individuals with HCC were identified as never having been screened for HCC prior to diagnosis.[21]

Our 2 cases illustrate that HIV-infected women may survive HIV infection, only to die of HCC. Although data on HCC screening in HIV infection are limited, recent studies have demonstrated a survival benefit with screening, as well as improved eligibility for more effective treatment options.7,24 Whether HCC incidence in HIV-infected women is rising requires further study. A crucial next step is improved HCC surveillance in HIV-infected populations.

Acknowledgements

This publication resulted (in part) from Dr. Taylor's research supported by Award Number K23DA020383-01 from the National Institute on Drug Abuse. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health. This research has been facilitated by the infrastructure and resources provided by the Lifespan/Tufts/Brown Center for AIDS Research, an NIH funded program #P30 AI42853; and by the Center for Drug Abuse and AIDS Research (CDAAR), an NIH funded program #P30 DA013868. Funding was also provided in part by (Garg) Lifespan/Brown/Tufts: NIAID 5T32AI007438-17.

The authors would like to acknowledge the patients, physicians and nurses of the Immunology Center at the Miriam Hospital, as well as, Charles C. J. Carpenter, MD, and Norbert Bräu, MD, for their review of the manuscript. The authors would also like to acknowledge Wendy Henderson, MD, from the NIH and Fizza Gillani, PhD, for data support.

References

1. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. Aug 14-28 2006;166(15):1632-1641.
2. MacDonald DC, Nelson M, Bower M, Powles T. Hepatocellular carcinoma, human immunodeficiency virus and viral hepatitis in the HAART era. *World J Gastroenterol.* Mar 21 2008;14(11):1657-1663.
3. Garcia-Samaniego J, Rodriguez M, Berenguer J, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol.* Jan 2001;96(1):179-183.
4. Berretta M, Zanet E, Di Benedetto F, et al. Unusual presentation of metastatic hepatocellular carcinoma in an HIV/HCV coinfected patient: case report and review of the literature. *Tumori.* Jul-Aug 2008;94(4):589-591.
5. Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *J Natl Cancer Inst.* Dec 15 2004;96(24):1851-1856.
6. Dubois G, Braillon A. Hepatocellular carcinoma: again, tobacco is the first enemy. *Int J Epidemiol.* Oct 2010;39(5):1399.
7. Brau N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol.* Oct 2007;47(4):527-537.
8. Giordano TP, Kramer JR, Souchek J, Richardson P, El-Serag HB. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. *Arch Intern Med.* Nov 22 2004;164(21):2349-2354.
9. Clifford GM, Rickenbach M, Polesel J, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *Aids.* Oct 18 2008;22(16):2135-2141.
10. CDC. Hepatocellular Carcinoma- United States 2001-2006. *Morbidity and Mortality Weekly Report.* 2010;59(17):517-520.
11. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. *J Hepatol.* Jun 2005;42(6):799-805.
12. Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *Aids.* Nov 19 2004;18(17):2285-2293.
13. Pineda JA, Romero-Gomez M, Diaz-Garcia F, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology.* Apr 2005;41(4):779-789.
14. Orenstein R, Tsogas N. Hepatitis C virus and human immunodeficiency virus co-infection in women. *J Am Osteopath Assoc.* Dec 2001;101(12 Suppl Pt 2):S1-6.
15. CDC. HIV Surveillance Report, 2008. June 2010;20. http://www.cdc.gov/hiv/topics/surveillance/resources/reports. Accessed July 1, 2010.
16. WHO. HIV/AIDS Programme: Highlights 2008-2009.
17. CDC. Health Behaviors of Adults: United States, 2005-2007. In: Services UDoHaH, ed. Vol 10: Centers for Disease Control and Prevention; 2010:143.
18. Feldman JG, Minkoff H, Landesman S, Dehovitz J. Heterosexual transmission of hepatitis C, hepatitis B, and HIV-1 in a sample of inner city women. *Sex Transm Dis.* Jul 2000;27(6):338-342.
19. Frederick T, Burian P, Terrault N, et al. Factors associated with prevalent hepatitis C infection among HIV-infected women with no reported history of injection drug use: the Women's Interagency HIV Study (WIHS). *AIDS Patient Care STDS.* Nov 2009;23(11):915-923.
20. Rodriguez-Mendez ML, Gonzalez-Quintela A, Aguilera A, Barrio E. Prevalence, patterns, and course of past hepatitis B virus infection in intravenous drug users with HIV-1 infection. *Am J Gastroenterol.* May 2000;95(5):1316-1322.
21. Nunez MK, L; Barreiro, P; Nelson, M; Vispo, M; Page, E; Fox, R; Bini, E; Sherman, N; Brau, N. Screening for Hepatocellular Carcinoma (HCC) in HIV/HCV-Coinfected Patients: Impact on Staging, Therapy and Survival. Paper presented at: 17th Conference on Retroviruses and Oppurtunistic Infections; February 16-19, 2010, 2010.
22. Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. *Hepatology.* July 2010;000(000):1-35.
23. Koteish A, Thuluvath PJ. Screening for hepatocellular carcinoma. *J Vasc Interv Radiol.* Sep 2002;13(9 Pt 2):S185-190.
24. Henderson WA, Shankar R, Gill JM, et al. Hepatitis C progressing to hepatocellular carcinoma: the HCV dialysis patient in dilemma. *J Viral Hepat.* Jan 2010;17(1):59-64.

Authors

Lynn E. Taylor, MD, is an Assistant Professor of Medicine, Dept. of Medicine, Division of Infectious Diseases, Warren Alpert Medical School of Brown University.

Karen T. Tashima, MD, is a Professor of Medicine, Division of Infectious Diseases, Warren Alpert Medical School of Brown University.

Susan Cu-Uvin, MD, is an Associate Professor, Obstetrics and Gynecology and Medicine, Warren Alpert Medical School of Brown University.

Shikha Garg, MD, served as a Miriam Hospital research T32 Fellow.

Stacey Chapman, RN, is a research nurse and clinic coordinator, Division of Infectious Diseases at The Miriam Hospital.

Michelle L. Westbrook, MS, served as a research assistant at The Miriam Hospital.

Disclosures

Dr. Taylor is an infectious disease reviewer for UpToDate and consults for TheBody.com.

The authors and/or their spouses/partners have no financial interests to disclose.

Correspondence

Lynn E. Taylor, MD
The Miriam Hospital
164 Summit Ave.
CFAR/RISE Building, Room 156,
Providence RI 02906
401-793-4705, alt phone 401-793-2928
LTaylor@Lifespan.org