Hepatocellular Carcinoma in an HIV Patient "Cured" of Hepatitis C Virus

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A 66-year-old man presented in August of 2005 with increased abdominal girth, early satiety, decreased oral intake/anorexia, and an approximately 12-pound weight loss over the past month. He complained of new right upper quadrant pain for the past 5 days.

His medical history was relevant for a diagnosis of AIDS in 1996, when he presented with thrush and a CD4 count of 24 cells/dL. He was simultaneously assessed for hepatitis C virus (HCV) and was found to be positive for genotype 4. At the time of diagnosis, he was drinking alcohol heavily and was clinically depressed. He underwent surveillance examination for HCV with a liver biopsy in 1997 and was found to be cirrhotic, though he had preserved biochemical parameters (see Table 1). The patient declined HCV treatment in favor of controlling his depression and alcohol abuse. He was vaccinated against hepatitis A/B, started on antiretrovirals, and followed regularly by his HIV physicians. His liver function was monitored with regular liver function tests (LFTs). He was advised to cease all alcohol intake. The patient was recurrently referred for HCV in 2001 after a period of sobriety and initiated treatment with interferon alfa-2b (Intron A, Schering) for a period of 40 weeks. His pretreatment HCV viral load was 24,300 copies/mL, which was lowered to under 600 with immediate response to therapy, one month after initiating treatment. After 4 weeks, he was found to have an undetectable viral load but could not tolerate the side effects and treatment was discontinued (Table 2). Interestingly, his HCV remained undetectable and he was returned to the care of his HIV physicians.

The patient was closely followed-up with almost monthly visits in 2004–2005. However, no surveillance with alpha-fetoprotein (AFP) tests or abdominal imaging was performed (AFP last checked >5 years previous; ultrasound >1 year previous). The patient's highly active antiretroviral therapy (HAART) regimen consisted of abacavir sulfate plus lamivudine (Epzicom, Glaxo-SmithKline)/ritonavir (Norvir, Abbott)/atazanavir sulfate (Reyataz, Bristol Myers-Squibb). His most recent CD4 count was 10^9 cells/dL and his viral load was less than 400 copies/mL. He was described as "thin" with normal abdominal exam in December of 2004, but in March of 2005 as "thin" with "prominent" abdomen. In August of 2005, he was described as "cachectic" with a "distend abdomen, ventral hernia" upon admission.

He underwent paracentesis, which showed evidence of portal hypertension (SAAG >1.1). Of more concern was the bloody nature of the fluid and increased AFP levels measured (>21,000 ng/mL). Cytology was negative and abdominal ultrasound revealed no irregularities. This was followed by magnetic resonance imaging with ferridex (Figure 1), which revealed a large dominant mass, as well as smaller masses distributed throughout the liver, consistent with hepatocellular carcinoma (HCC). The patient was subsequently referred to a hospice.

Literature Review

It is well known that all patients with cirrhosis are at risk for the development of HCC, which is the fourth most common cancer worldwide. The risk of developing HCC does vary with the etiology of the underlying liver disease.[1] Patients with cirrhosis secondary to chronic viral infections such as hepatitis B and C have a risk of developing HCC at a rate of 3–5% per year. Alcoholic cirrhosis incurs an intermediate risk of 1–4% per year. Cirrhosis secondary to primary biliary cirrhosis and Wilson disease appears to incur the lowest risk for developing HCC. In the United States, the dominant etiology of cirrhosis is from chronic hepatitis C and alcohol abuse, with the percentage of cases expected to increase over the ensuing decades. Additionally, there is a growing body of evidence that patients with HIV/HCV coinfection have a rate of

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Table 1. Laboratory Values Over Disease Course

Year	AST, U/L	ALT, U/L	Alk P, U/L	T Bili, mg/dL	HCV VL, copies/mL	HIV Labs	AFP, ng/mL	PIVKA	Liver Biopsy	Imaging
1997	–	–	–	–	2×10^6	–	–	–	Refused tx due to depression/EtOH	–
1998	–	–	–	–	–	–	–	–	Done (see below)	–
1999	–	–	–	–	–	CD4:24 VL:<400	–	–	Done (see below)	–
2000	–	–	–	–	2×10^4	–	–	–	Chronic HCV infection Moderate activity fibrosis Stage 4 = cirrhosis Stage 3 = portal inflammation Moderate interface activity No change from previous biopsies	–
8/00	279	234	213	0.8	<600	–	26	–	–	–
2001	48	33	239	0.6	<600	–	4	–	–	17 cm echogenic liver, 15 cm spleen, no ascites, no masses
2002	87	100	107	0.6	–	CD4:109 VL <50	–	–	–	None
2003	60	91	162	0.6	–	–	–	–	–	None
2004	49	100	133	1.3	–	–	31	–	–	None
2005	101	56	246	0.4	<10	CD4:104 VL: <400	22131	3.6	–	U/S: liver 20 cm, no biliary dilation, new pelvic ascites, no masses MRI: Small liver, mass 16 × 10 × 10 cm in seg 5-6-7 with decreased ferridex uptake, + arterial enhancement. Additional 2-cm masses in seg 3-4-5-8. RHV thrombus. No adenopathy, splenomegaly

AFP=alpha fetoprotein; Alk P = alkaline phosphate; ALT= alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PIVKA = protein induced by Vitamin K absence; RHV = right hepatic vein; T Bili = total bilirubin; VL = viral load.

progression to cirrhosis that is more rapid than HCV monoinfected patients.[2,3] However, there are conflicting reports regarding the increased rate of HCC development in HIV/HCV coinfected patients with cirrhosis.[4,5]

HCC screening recommendations in patients with cirrhosis exist outside the United States. The European Association for the Study of the Liver (EASL) recommends biannual abdominal ultrasound and AFP level measurements.[6] Most tertiary care centers consider this guideline the standard of care.[7] The combination of AFP monitoring and ultrasound has a sensitivity and specificity of 79% and 87%, respectively.[8] Because as many as 20% of HCC cases do not produce AFP and ultrasound is operator-dependant, additional tests will be required to improve the detection of HCC. More recently, there has been criticism of the value of AFP in screening for HCC and a proposal to abandon its use.[9] In fact, the latest American Association for the Study of Liver Diseases (AASLD) guidelines regarding HCC surveillance in patients with cirrhosis do not mandate the use of AFP.

Current investigations center on finding better tumor markers for HCC. New tumor markers such as protein induced by vitamin K absence (PIVKA), vascular endothelial growth factor, and Glypican 3 are currently being studied.[10,11] The value of these tests has yet to be determined, and they are not widely available. Improving the imaging of liver lesions is also important in the detection of HCC. Many centers are investigating triple phase computed tomography (CT) and contrast magnetic resonance imaging (MRI) and are achieving better sensitivity (up to 100% for lesions >2 cm), but the specificity appears to be variable.[12,13] CT scanning as a screening tool is considered cost-effective in patients who are transplant eligible.[14] All patients undergoing preoperative workup for liver transplant also undergo evaluation with triple phase CT scanning or contrast MRI. Despite these improvements, almost one third of patients are understaged.[15,16]

Only 20–30% of patients with HCC are diagnosed at a time when the tumors are amenable to surgical resection or liver transplantation.[17] This means that the large majority of patients will have to undergo noncurative therapies (Table 3). Although most of the options are still in their nascent stages of investigation, some have entered the mainstream and enough data have accumulated to demonstrate survival benefits.

Systemic chemotherapy has advanced little since the 1970s, when doxorubicin was first advocated for treatment of HCC. Numerous trials using doxorubicin monotherapy showed an approximate 18% response rate.[18] Phase II trials of other chemotherapeutic agents have not demonstrated superiority. Despite this, some advocate the use of cisplatin. Phase II trials of combination chemotherapy with etoposide and epirubicin do

Table 2. Treatment History

Year	Treatment Regimen	HCV VL	Comments
5/01–6/01	Pegylated interferon (no ribavirin) qwk	<600	D/C after 1 mo due to depression
2002	-	<600	SVR

D/C = declined; HCV VL = hepatitis C viral load; SVR = sustained virologic response.

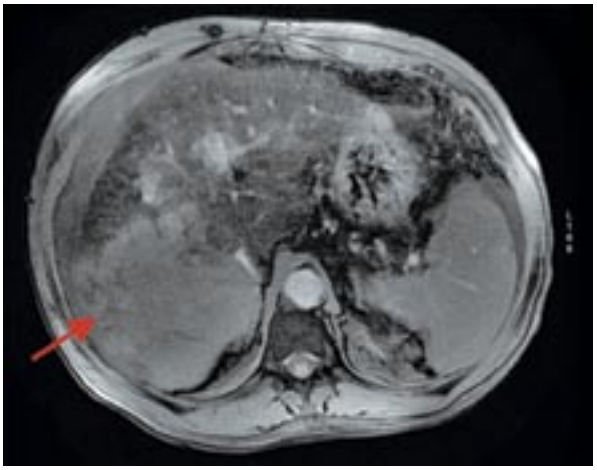

Figure 1. MRI of the abdomen with ferridex.

Table 3. Palliative Therapies for Hepatocellular Carcinoma

- Transcatheter chemoembolization
- Hepatic artery infusion
- Percutaneous interstitial ablation
- Percutaneous ethanol injection
- Percutaneous acetic acid injection
- Radiofrequency ablation
- Microwave coagulation therapy
- Cryosurgery
- Radiation therapy
- Conformational external-beam radiation
- Internal radiation
- Systemic chemotherapy
- Hormonal: tamoxifen, somatostatin
- Immunotherapy: interferon, interleukin-2, alpha-1-thymosin
- Multimodality

demonstrate increased activity against HCC that will need to be verified with additional investigation.[19] The ability to deliver higher doses of chemotherapeutic agents directly into the vasculature supporting the tumor has pushed transarterial chemoembolization (TACE) to the forefront of HCC management. The procedure involves an interventional radiologist accessing the femoral artery to gain access into the celiac trunk and then selective catheterization the hepatic artery, which selectively feeds the tumor. At this point, a chemotherapeutic agent (doxorubicin or cisplatin) attached to a carrier substance (lipiodol) is delivered. Subsequently, gelfoam is used to embolize the artery. This results in high concentration of chemotherapeutics delivered to the tumor and the blood supply subsequently cut off.[20] Llovet and associates[21] have performed a meta-analysis on TACE studies and demonstrated a survival benefit in patients with unresectable HCC. TACE is contraindicated in patients with advanced cirrhosis or portal vein thrombosis because there is risk of inducing liver failure with the procedure.[22,23] Subcutaneous octreotide has been shown is some studies to prolong survival, though the mechanism is unknown and the data are conflicting.[18,24] Brachytherapy in the form of I^{131}-iodiol has been shown to have benefit without the complications of TACE, but requires a six-day hospitalization in isolation to prevent radiation exposure. Radiofrequency ablation (RFA) involves a catheter laparoscopically placed directly into the tumor with delivery of cautery to destroy it. Depending on the approach, RFA often requires general anesthesia and surgical operative time. RFA has been shown to be successful in local control of HCC.[25]

In regard to the current case, important considerations need to be highlighted. It is important to educate general providers that patients "cured" of HCV (ie, sustained virologic response [SVR]) who have cirrhosis are still at appreciable risk for development of HCC. To date, there has been no analysis of the cost of screening of HCC in HIV/HCV coinfected patients. Current screening guidelines recommend checking AFP and abdominal ultrasound every 6 months. Some centers utilize other tumor markers, which should be checked in addition to, not instead of, AFP (they are considered complimentary). If any of these tests are abnormal, additional imaging with contrast CT or MRI needs to be performed, given their high sensitivity and specificity. At this time, staging will determine if the patient is a potential surgical (ie, curative intent) candidate or eligible for palliation only. This patient presented with stage III HCC and was not a surgical candidate. He had Childs B cirrhosis and was thus not a TACE candidate. However, he was symptomatic from the disease and may benefit from octreotide or brachytherapy with I^{131}-iodiol. Untreated patients with this stage of HCC have a life expectancy of approximately 3 months and it is unclear how much additional survival benefit the proffered therapy would provide the patient.

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Review

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The incidence of hepatocellular carcinoma (HCC) has risen dramatically in the United States over the past three decades.[1,2] Registry data from the Surveillance, Epidemiology, and End Results (SEER) Program demonstrated the age-adjusted incidence increased from 1.4 per 100,000 during the time period from 1976 to 1980 to 3.0 per 100,000 from 1996 to 1998.2 Much of the rise in HCC has been attributed to the growing number of patients with hepatitis C virus (HCV) and cirrhosis. Not surprisingly, HCC is increasingly recognized in patients coinfected with HCV and HIV. Swaminath presents a particularly instructive case in which a coinfected patient was diagnosed with HCC after achieving an SVR to antiviral therapy for HCV. The case report raises important issues about HCV in coinfected patients, including the natural history of HCV, the efficacy of antiviral therapy, and surveillance for HCC.

Approximately 15–30% of patients with HIV are coinfected with HCV due to shared routes of transmission for both viruses.[3,4] Rates of HCV were reported to be as high as 85% in HIV-infected injection drug users.[4] HIV coinfection was associated with more severe HCV-related liver injury and an increased rate of progression to cirrhosis compared to HCV infection alone.[5,6] Moreover, coinfected patients who responded to highly active antiretroviral therapy (HAART) had rates of fibrosis progression that were similar to HCV monoinfected patients,[7] highlighting the importance of effective HIV management in this setting. Alcohol abuse, present in the case report, was also associated with HCV progression in coinfected patients. In one study, the projected time to cirrhosis in HCV-infected patients with a CD4 count of 200 cells/μL or higher, who consumed more than 50 g of alcohol daily was only 16 years.[8]

Studies of coinfected patients have shown a shorter interval to the development of HCC than in patients with HCV alone. As illustrated by the case report, HCC develops on a background of cirrhosis in patients with HCV. Other factors that interact with HCV to increase the risk of HCC include alcohol abuse, tobacco use, and diabetes, which serves as a marker for insulin resistance and nonalcoholic fatty liver disease.[9] Pertinent to the present case, alcohol use in excess of 40 g/day and 80 g/day was shown to increase the risk of HCC in HCV patients by two- and four-fold, respectively.[10] Although HIV is associated with the development of Kaposi sarcoma related to human herpes 8 virus infection and with cervical cancer related human papilloma virus,[11] HIV has not been directly implicated in hepatocarcinogenesis.

Retrospective studies suggested that successful antiviral therapy for HCV might reduce the risk of HCC.[12-16] Data from a recent multicenter trial including peginterferon alfa-2a plus ribavirin for the treatment of HCV in coinfected patients showed promising results. Patients with genotype-1 infection had an SVR of 29% and the SVR for those with genotype 2 or 3 was 62%.[17] Hepatic decompensation was observed in a few patients with more advanced cirrhosis. Therefore, coinfected patients with cirrhosis should be selected carefully and monitored closely during antiviral therapy. Clinicians should be familiar with the HAART regimen that patients are taking and avoid the combination of ribavirin and DDI, which was associated with the development of lactic acidosis.

Hepatocellular carcinoma was identified in the patient in the case report after a particularly short, but successful course of treatment for HCV. A number of possible explanations exist. First, the tumor might have been present but unrecognized prior to antiviral therapy, although the four-year interval between treatment and diagnosis of HCC makes this possibility seem unlikely. Second, continued alcohol use could have contributed to tumor development. Finally, HCC might have developed despite an SVR as previously reported.[18-22] In one case, HCC was identified 12 years after SVR.[20] Risk factors for HCC after SVR include advanced fibrosis stage and older age.[21,22] These findings have lead some authors to promote screening for HCC twice per year in high risk patients and once per year in low risk patients for more than ten years after SVR.[23]

The cost-effectiveness of surveillance for HCC was addressed in a position paper by the American Association for the Study of Liver Disease (AASLD).[24] The cost per year of life saved by HCC surveillance in cirrhotic patients was estimated at $26,000 to $112,996, compared to $25,000 per life year saved with colorectal cancer screening. The AASLD also published practice guidelines for HCC surveillance.[25] The guidelines suggest that monitoring should be performed in high risk hepatitis B carriers regardless of the degree of fibrosis and in patients with HCV, alcohol, hemochromatosis and other causes of liver disease, who have evidence of cirrhosis. Additionally, ultrasound and alpha fetoprotein (AFP) was recommended at an interval of 6–12 months. The European Association for the Study of the Liver (EASL) recommended surveillance for HCC by ultrasound and AFP on a 6–12 month basis as well.[26] The EASL also recommends surveillance only in patients who would be considered suitable for treatment of HCC.

The diagnosis of HCC can be established based on cytology or histology. The AASLD guidelines provided recommendations for follow-up and noninvasive criteria for the diagnosis of HCC in cirrhotic patients based on the size and imaging characteristics of a lesion.[25] Accordingly, subcentimeter lesions should be followed at a 3–4 month interval to check for enlargement. Follow-up imaging can revert to the standard interval if stability is documented over 18–24 months. Lesions between 1 and 2 cm in size that show characteristic hypervascularization on two cross-sectional imaging studies meet the noninvasive criteria for HCC. Biopsy was suggested for lesions 1–2 cm in size without characteristic enhancement. Noninvasive criteria for the diagnosis of HCC for lesions greater than 2 cm include hypervascularzation on one dynamic imaging study or an AFP level greater than 200 ng/mL. The patient in the case report met the latter noninvasive criteria with a markedly elevated AFP level and characteristic findings on a contrast-enhanced MRI. Treatment options for HCC are outlined in the literature review accompanying the case report.

In conclusion, HCV is common in patients with HIV and tends to follow a more aggressive natural history than in patients with HCV alone. Management of HCV in coinfected patients includes treatment of HIV when indicated, avoidance of alcohol, and consideration of antiviral therapy consisting of peginterferon and ribavirin. As demonstrated in the case report, HCC can develop in cirrhotic patients even after a SVR, highlighting the importance of HCC surveillance in patients with cirrhosis.

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