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Hepatocellular carcinoma after sustained virologic response in hepatitis C patients without cirrhosis on a pre-treatment liver biopsy

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Abstract

Among hepatitis C patients, lack of cirrhosis and sustained virologic response reduce the risk of hepatocellular carcinoma. Japanese studies document multiple cases of hepatocellular carcinoma among these patients, but only one case has been reported outside of Asia. We identified five patients with hepatitis C in our university-based hepatology practice who developed hepatocellular carcinoma despite sustained virologic response and lack of cirrhosis on their pre-treatment liver biopsy. At the time of hepatocellular carcinoma diagnosis, two remained noncirrhotic, one had clearly progressed to cirrhosis, and two lacked repeat histology. We present these patients in a case series format and discuss several important implications of their cases. Physicians often base screening and treatment decisions on an initial liver biopsy performed years prior. Because fibrosis may advance, and because sustained virologic response and lack of cirrhosis do not fully protect against hepatocellular carcinoma, *future study should further evaluate the risk of hepatocellular carcinoma among hepatitis C patients after SVR.*

Keywords

hepatitis C; hepatocellular carcinoma; interferon; ribavirin; screening; sustained virologic response

INTRODUCTION

Screening for hepatocellular carcinoma (HCC) among cirrhotic patients infected with the hepatitis C virus (HCV) is an established practice, recommended by the American Association for the Study of Liver Disease (AASLD), given the elevated risk for HCC among these patients. [1] Pharmacologic therapy with interferon (IFN) reduces the risk of HCC among patients with

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HCV, including patients with cirrhosis.[2] The magnitude of risk reduction may be larger with sustained virologic response (SVR), defined as an undetectable hepatitis C viral load 24 weeks after treatment. Among patients with cirrhosis, there remains a definite risk of HCC after SVR, and the AASLD recommends that, "...it seems that patients with hepatitis C and cirrhosis who have achieved viral clearance on therapy should, at least for now, continue to undergo surveillance." [1]

Noncirrhotic patients with HCV have a lower risk of HCC, and routine screening among these patients is not recommended by the AASLD, before or after treatment with IFN.[1] Data from Japan demonstrate a finite HCC risk after IFN therapy and SVR among noncirrhotic HCV patients. Among the seven studies in the literature (table 1), a total of 2,482 patients were followed for at least 40 months (and many for longer periods of time). [3],[4],[5],[6],[7],[8],[9] Overall, forty-seven patients (1.9%) developed HCC. Despite prospective screening in most studies, subjects developed HCC after two to six years of screening. Nearly 90% of patients had stage 3 or less fibrosis and would not have been screened under AASLD guidelines. These data may not be generalizable to all patients with HCV who receive antiviral therapy, because Japanese patients with HCV develop HCC at higher annual rates than patients of other backgrounds, [10] and all study patients received IFN monotherapy rather than IFN and ribavirin (RVN).

There are only two reports of HCC in noncirrhotic patients after SVR outside of Japan, and only one of these is outside of Asia. In 2006, Sieja and Everson reported the case of a 50 year-old man with HCV and stage 3 fibrosis, who developed HCC nearly 5 years after IFN therapy and SVR.[11] Researchers in Thailand later reported three cases of HCC among 171 patients with HCV and SVR following IFN treatment who were followed for an average of 35 months. One of these patients was noncirrhotic.[12]

We identified in our university-based hepatology practice five HCV patients who attained SVR following antiviral therapy and later developed HCC despite lack of cirrhosis on the liver biopsy most recently preceding antiviral therapy. Their cases are presented below with a discussion of important points raised by each case. *For staging of fibrosis we used the Batts-Ludwig system,¹³ which is essentially identical to the Metavir system in employing a 0 to 4 score for fibrosis. A score of 0 corresponds to no fibrosis, 1 denotes portal fibrosis (fibrous portal expansion), 2 indicates periportal fibrosis (periportal or rare portal-portal septa), 3 indicates septal fibrosis (fibrous septa with architectural distortion but no obvious cirrhosis), and 4 corresponds to cirrhosis.*

CASE REPORTS

Patient 1 is a man who was 49 years old when he was diagnosed with hepatitis C (genotype 1b) in 1997. His pathology was grade 1, stage 2 on biopsy (3.1cm core) in 2000; *there was grade 1 steatosis. The duration of his infection was not known.* Hepatitis B core antibody was positive; surface antigen and antibodies were negative. *Ferritin level was 602 mcg/L. He was not obese nor diabetic, and an HIV antibody test was negative.* He had a history of alcohol abuse that ended in 1999. He completed a 48-week course of pegylated IFN and RVN in 2003 with resultant SVR. One month after completing treatment, he underwent abdominal CT imaging to evaluate an umbilical hernia and was found to have a 2.8×2.2 cm hypervascular hepatic mass in segment 5. *Transaminase levels were not rising.* A CT-guided biopsy was nondiagnostic, but surgical hepatic wedge resection demonstrated a 3.5 cm, moderately differentiated HCC without vascular invasion. Liver fibrosis at resection (8×6×5cm resected wedge) remained stage 2; *there was grade 1 steatosis. AFP peaked at 268 ng/mL.* He thereafter underwent HCC screening with AFP measurements and CT imaging every three months, and a few months later, he was found to have a small, nonenhancing hepatic lesion on CT. MRI

confirmed a 2 cm enhancing mass at the border between segments 4a and 8, which was treated with radiofrequency ablation. Two additional lesions were later seen, and the patient underwent percutaneous ethanol injection and right hepatic artery embolization. He continues to undergo surveillance every three months, and his viral load remains undetectable. He has been evaluated for liver transplantation.

Patient 2 is a man who was 49 years old when he was diagnosed with hepatitis C (genotype 3) in 1999. His pathology was grade 3, stage 3 on biopsy (2.1cm core) in 2000; *there was grade 1 steatosis. The duration of infection was not known.* He had a history of alcohol abuse that ended several years before HCV diagnosis. Hepatitis B core and surface antibodies were positive; surface antigen was negative. *Ferritin level was 144 mcg/L. He was obese but was not diabetic, and an HIV antibody test was negative.* He underwent treatment with Rebetron for six months in 2000, but did not attain SVR. He completed a second treatment course with 48 weeks of pegylated IFN and RVN in 2003, achieving SVR. HCC screening was performed annually with measurement of AFP and CT imaging. *His transaminases did not rise.* 37 months after completing his second round of treatment, a 4.3×10.4 cm heterogeneous enhancing mass was found in the right lobe of the liver. Two weeks later, the patient underwent right hepatic lobectomy. Pathology demonstrated poorly differentiated HCC without vascular invasion. Liver fibrosis on the resected specimen remained at stage 3. *AFP peaked at 20,648 ng/mL.* Subsequent surveillance has revealed no recurrence of HCC.

Patient 3 is a man who was 54 years old when he was diagnosed with hepatitis C (genotype 1) in 2002. His pathology was grade 2, stage 2 on biopsy (1.4cm×0.9cm, somewhat fragmented sample) at that time; *there was grade 1 steatosis. He was thought to have been infected with HCV approximately 30 years previously.* He had a history of alcohol abuse that ended in 1994. Hepatitis B core and surface antibodies and surface antigen were all negative. *Ferritin level was elevated at 1,692 mcg/L, but this later decreased to 106 mcg/L. He was not obese or diabetic, and an HIV antibody test was negative.* He completed a 48-week course of pegylated IFN and RVN in 2003 and achieved SVR. *His AST and ALT levels did not rise after therapy.* Ten months after completing therapy, he underwent abdominal CT to evaluate hematuria and was found to have a 4.3×4.8 cm enhancing right inferior hepatic mass in segment 6. He underwent partial hepatectomy, and pathology demonstrated a 4 cm, moderately differentiated HCC without vascular invasion. His liver fibrosis on the resected specimen had progressed to stage 4. *His AFP peaked at 3.1 ng/mL.* He continues to receive regular surveillance with AFP measurement and CT imaging, and has had no recurrence. He declined evaluation for liver transplantation.

Patient 4 is a woman who was 63 years old when she was diagnosed with hepatitis C (genotype 2b) in 1997. Her pathology was grade 2, stage 2–3 on biopsy (0.6cm × 0.1cm, fragmented sample, felt possibly to represent a higher stage) in 1999; *she had no steatosis on biopsy. Her duration of infection was thought to have been approximately 20 years.* She had no history of alcohol abuse. Hepatitis B surface antibody was positive, surface antigen negative; hepatitis B core antibody was not performed. *Ferritin level was 114 mcg/L. She was obese and diabetic, but her HIV antibody test was negative.* She underwent treatment with Rebetron for 6 months in 2002. She had initial virologic response but relapsed shortly thereafter and was treated with pegylated IFN and RVN for 48 weeks, finishing treatment in June 2004. She achieved SVR and thereafter underwent regular screening for HCC with AFP measurements and ultrasound imaging. *Her transaminases did not rise.* In December 2004 she was found to have a 2.5 cm mass in segment 7 in conjunction with a rising AFP, *which peaked at 12.4 ng/mL.* This was treated with radiofrequency ablation and further surveillance has revealed no recurrence. Repeat biopsy was not obtained. The patient has been listed for liver transplantation.

Patient 5 is a man who was 62 years old when he was diagnosed with hepatitis C (genotype 2b/4e) in 1990. His pathology was grade 2, stage 3 on biopsy (1.3cm core) in 1998; *there was no steatosis. His duration of infection was thought to be approximately 30 years.* He had no history of alcohol use. Hepatitis B surface antibodies and surface antigen were negative; hepatitis B core antibody was not performed. *Ferritin level was 145 mcg/L. He was obese but not diabetic. An HIV antibody test was not performed.* He underwent interferon therapy in 1991, but was a nonresponder. He was retreated with Rebetron in 2000, but stopped therapy after three months due to side effects. He did, however, achieve SVR, and was subsequently lost to follow-up. *Transaminase levels did not begin to rise until sixty-eight months after completing therapy, when he was noted to have increasing AST levels while being evaluated for abdominal discomfort. CT imaging revealed an 11×9.5 cm enhancing mass occupying most of the right lobe of the liver with right portal vein thrombosis and multiple hypervascular foci thought likely to be malignant disease. AFP peaked at 89.6 ng/mL.* Biopsy was not pursued given the high likelihood of metastatic HCC. The patient opted for conservative management. He received two doses of liposomal doxorubicin, but was unable to tolerate the side effects. The patient transitioned to hospice care, and he died nine months after being diagnosed with HCC.

In total, five HCV patients lacking cirrhosis on the most recent liver biopsy preceding antiviral therapy were diagnosed with HCC following antiviral therapy and the development of SVR. Mean time between SVR and HCC diagnosis was 24.4 months. These data are summarized in table 2. *With a few exceptions, these five patients were generally lacking other apparent risk factors for HCC. One patient was diabetic, and three were obese. Although three of five had grade 1 steatosis on initial liver biopsy, the fibrosis pattern for these three was periportal fibrosis consistent with HCV rather than the pericentral fibrosis typical of nonalcoholic steatohepatitis. No patients had active hepatitis B infection. Only one patient had an elevated ferritin level (while undergoing IFN treatment), but this later normalized. None of the patient had significant increases in their transaminases after therapy, suggesting a lack of other active liver disease.*

DISCUSSION

While Japanese studies document multiple cases of HCC among noncirrhotic HCV patients following antiviral therapy and SVR, this experience has yet to be replicated outside of Asia. In our university-based practice in the United States, we identified five cases of HCC occurring in HCV patients lacking cirrhosis on initial liver biopsy. Not all of these patients remained noncirrhotic at the time of HCC diagnosis, yet treatment and screening decisions were appropriately made on the basis of their initial biopsy. These cases illustrate several salient points regarding HCC screening among patients with HCV.

The first two patients developed HCC in the setting of SVR and non-cirrhotic liver tissue documented at the time of HCC resection. Each of these patients had adequate biopsy specimens at the time of initial biopsy and at the time of HCC resection. Similar cases are well-documented in Japan, but appear to be much less common in other countries. Mechanisms underlying the development of HCC among such patients are not well-understood. [1] IFN reduces the rate of fibrosis progression and may result in regression of fibrosis among HCV patients, [14] suggesting that mechanisms other than, or in addition to, fibrosis likely contribute to HCC development. Multiple cellular pathways have been implicated in the initiation of hepatic dysplasia and hepatocarcinogenesis. [15],[16],[17] Accelerated hepatocyte cycling may result in the development of monoclonal populations of dysplastic hepatocytes [18] with malignant potential. The increase in hepatic regeneration and hepatocyte cycling that occurs after antiviral therapy may activate cellular pathways lying in the pathway of dysplasia, increasing the risk of hepatocarcinogenesis. Alcohol abuse increases the risk of HCC among

HCV patients. [4] Both patients 1 and 2 had a history of alcohol abuse, but neither had been active drinkers for years. Concomitant hepatitis B infection may increase the risk of HCC in patients with HCV; [19] none of our patients had active chronic hepatitis B, and two had evidence of past hepatitis B exposure and clearance. These first two cases suggest that the combination of SVR and stage 3 or less fibrosis may not be fully protective against HCC, *even among patients without other evident causes of liver disease*. Providers should evaluate which patients to screen for HCC on an individualized basis.

The third patient's initial liver biopsy demonstrated stage 2 fibrosis, yet he was diagnosed with HCC in the setting of stage 4 fibrosis less than two years later. His initial biopsy specimen was relatively small (1.4×0.9 cm and somewhat fragmented), so it is possible that he actually had more advanced fibrosis that was not detected at that time. If the initial biopsy was accurate, however, this suggests rapid progression of fibrosis. Although he had been an alcohol abuser in the past, he quit alcohol ten years prior to the diagnosis of HCC. Factors have not been identified which are known to lead to progression of fibrosis by two stages in two years, but this should be further investigated, as identification of patients at risk of rapidly progressive fibrosis could facilitate earlier HCC screening.

Patient 4 demonstrates the difficulties in initiating antiviral therapy when patients have only a remote liver biopsy available. In this case, biopsy preceded treatment by five years, and the patient was diagnosed with HCC shortly after completing antiviral therapy. Had the patient received a repeat biopsy prior to treatment, a higher grade of fibrosis might have been documented, which could have changed screening and treatment decisions. *Not all patients should undergo repeat liver biopsy prior to treatment, but it may be useful among some patients. In particular, among patients with findings consistent with cirrhosis (i.e., lab findings such as hypoalbuminemia and thrombocytopenia, physical examination findings such as ascites and spider angiomas, and endoscopic findings such as varices or portal hypertensive gastropathy), a repeat biopsy could reveal cirrhosis, which might alter surveillance and treatment decisions.*

Patient 5 demonstrates the familiar challenge of patient loss to follow-up. The patient attained SVR but was subsequently out of care for many years, and was diagnosed with HCC after developing related symptoms. Had this patient been routinely seen in hepatology clinic, the laboratory and physical examination sequelae of progressive fibrosis might have been realized, and HCC screening could have been initiated.

Although we identified a relatively small number of patients who developed HCC after SVR, our experience suggests a need to further study such patients. Because these patients are not routinely screened, HCC diagnoses may occur late in the disease, at which point treatment options may be limited. *Although there are not data to support screening all HCV patients after SVR, further study could help identify subsets of patients at higher risk.*

In summary, this case series demonstrates that lack of cirrhosis on initial liver biopsy and achievement of SVR in patients with HCV does not eliminate risk of HCC. Studies should further address these issues *in order to better understand the magnitude of HCC risk among noncirrhotic HCV patients.*

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Table 1
Japanese studies investigating risk of HCC among noncirrhotic HCV patients following IFN therapy and SVR.

Study	Date	Study type	Number of patients with SVR	Mean follow-up prior to and after SVR, months	Number of patients with SVR who developed HCC (%)	Number of patients developing HCC by stage of fibrosis (%)	Annual incidence rate for sustained responders (by stage when available)	Mean number of months from SVR to HCC diagnosis
Enokimura, et al (3)2003	2003	Prospective	142	---	6 (4.2)	---	0.61%	59.2
Iwasaki, et al (4)	2004	Prospective	792	62	23 (2.9)	F1: 4 (17.4) F2: 4 (17.4) F3: 12 (52.2) F4: 3 (13.0)	F0-2: 0.2% F3-4: 2.9%	---
Okanoue, et al (5)	1999	Prospective	316	40-46	3 (0.9)	F3: 3 (100.0)	F1: 0% F2: 0% F3: 1.2% F4: 0%	32.4
Shindo, et al (6)	2001	Prospective	67	≥96	2 (3.0)	---	0.37%	47
Takimoto, et al (7)	2002	Retrospective	201	81.6	---	---	0.29%	---
Tanaka, et al (8)	2000	Prospective	175	59.6	3 (1.7)	---	0.35%	---
Yoshida, et al (9)	1999	Prospective	789	51.6	10 (1.3)	F0/1: 1 (10.0) F2: 1 (10.0) F3: 7 (70.0) F4: 1 (10.0)	F0/1: 0.11% F2: 0.10% F3: 1.29% F4: 0.49%	---
Total	---	---	2,482	---	47 (1.9)	F0/1: 5 (13.9) F2: 5 (13.9) F3: 22 (61.1) F0-F3: 32 (88.9) F4: 4 (11.1)	---	---

Table 2

Characteristics of case series patients.

Patient	Genotype	Fibrosis stage at initial biopsy	Fibrosis stage at time of HCC excision	Years between biopsies	Alcohol use?	Treatment type (duration in weeks)	SVR?	Months from SVR to HCC diagnosis
1	1b	2	2	0	Prior	PEG-IFN/RVN (48)	Yes	1
2	3	3	3	6	Prior	Rebetron (24), PEG-IFN/RVN (48)	Yes	37
3	1	2	4	2	Prior	PEG-IFN/RVN (48)	Yes	10
4	2b	2-3	Unknown	N/A	None	Rebetron (24), PEG-IFN/RVN (48)	Yes	6
5	2b/4e	3	Unknown	N/A	None	Rebetron (24), Rebetron (12)	Yes	68