



HEPATOCELLULAR CARCINOMA DEVELOPMENT IN A PATIENT WITH HCV INFECTION AFTER ERADICATION WITH DIRECT-ACTING ANTIVIRAL AGENTS

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Abstract – Hepatitis C virus (HCV) treatment with Interferon (IFN)-free direct-acting antiviral agents (DAAs) showed high rates of success, leading to substantial changes in this field. However, limited data are available about the evolution of liver disease after HCV eradication. Recently, published studies on the recurrence of hepatocellular carcinoma (HCC) after HCV treatment raised questions on the real benefit of treatment of patients with advanced fibrosis or cirrhosis.

We report a case of a 45-years-old cirrhotic patient successfully treated with DAAs who developed an HCC after HCV eradication.

KEYWORDS: Hepatocellular carcinoma, HCV infection, Direct-acting antivirals.

BACKGROUND

Interferon (IFN)-free direct antiviral agents (DAAs) effectively eradicate hepatitis C virus (HCV) and rapidly improve residual liver functions. The currently available novel combinations of DAAs have completely changed the panorama of hepatitis C treatment. Current HCV eradication rates have exceeded 90% in a very short time¹.

However, an unexpectedly high rate of early recurrence of hepatocellular carcinoma (HCC) has been reported after some weeks of starting treatment. Therefore, HCC risk may not be modified during and after DAA treatment in HCV patients with the advanced liver disease. However, the evidence relating DAA treatment and HCC development/recurrence is still limited, and the mechanism is not well known. Some recently published studies observed a large number of HCC in patients with HCV and cirrhosis treated with DAAs².

Despite successful HCV treatment, patients with very early HCC diagnosed before starting DAAs showed an increase in the probability of recurrence from 17.6 to 21.5% in a few months³. In consideration of the above literature studies, it is possible to observe more frequent cases in clinical practice.

We report a case of HCC early detection after HCV treatment with DAAs in a cirrhotic patient from Sassari, Northwest Sardinia, Italy.

CASE REPORT

We describe the history of a 45-years-old man, affected by HCV (3a genotype) related chronic hepatitis, who was followed-up since 2008 in our Liver Unit as an outpatient. He was monitored with an ultrasound examination and liver blood tests every six months. Antiviral therapy with Peg-Interferon plus ribavirin was started with initial response, followed by a relapse in the same year. Fibroscan evaluation showed the presence of F4 fibrosis. The patient continued his follow-up, with no significant changes until 2015, when he started therapy with DAAs (sofosbuvir plus daclatasvir plus ribavirin). He achieved a sustained virological response (SVR) with a complete clearance of the virus. Six months after the end of therapy, when the virus was still undetectable in the bloodstream, an ultrasound examination of the liver detected a new nodule, 19 mm in the maximum size, located in the



sixth segment (Figure 1). The ultrasound contrast enhancement examination (CEUS) characterized the hepatic nodule as a hepatocellular carcinoma (HCC) since the nodule was hypervascular in the arterial phase and showed a wash out in the parenchymal phase (Figure 1). The patient performed also a contrast enhancement computer tomography (ceCT) with a triphasic study of the liver and a scan of the whole body to better stage the extent of the tumor. According to the result of ceCT scan, there was only one nodule located in the liver without any other secondary lesions. Considering that the patient was in stage 0, according to BCLC (Barcellona Clinic Liver Cancer) staging system, we decided to treat the tumor with radio frequency ablation (Figure 1). We were able to destroy the tumor as confirmed by ceCT scan, performed after a month.

DISCUSSION

In the new era of DAAs, eradication of HCV could be relatively easy and rapid, but actually, a long-term evaluation of the impact on the incidence of HCC is still ongoing. Despite HCV eradication, a close ultrasonography follow-up is mandatory in patients with liver cirrhosis⁴.

Conti et al² showed in 24 weeks follow-up of a cohort of 344 consecutive cirrhotic patients who underwent DAA therapy a sustained virological response in 91% of patients. However, HCC was detected in 26 patients (7.6%, 95% CI: 4.99-10.84): 17 of 59 patients (28.81%, 95% CI: 17.76-42.07) with previous HCC and 9/285 patients (3.16%, 95% CI: 1.45-5.90) without previous HCC. Child-Pugh class ($p=0.03$, OR: 4.18, 95% CI: 1.17-14.8) and history of HCC ($p<0.0001$, OR: 12.0, 95% CI: 4.02-35.74) resulted independently associated with HCC development at multivariate analysis. Among patients with previous HCC, younger age and more severe liver fibrosis were significantly associated with HCC recurrence, both at univariate and at multivariate analysis.

In a very recent Italian study by Menzaghi et al⁵, the risk of HCC development has been evaluated in 1,154 patients treated with DAA. Median follow-up was 16.7 months. Twenty-seven patients developed an HCC including 21 new cases and 6 recurrences. In a multivariate Cox model including age, sex, Metavir, HIV co-infection, HCV genotype, and outcome at 12 weeks only age (HR 1.06, 95% CI 1.01-1.12, by 1 year) and Metavir F4 (HR 4.70, 95% CI 1.08-20.44 as compared to F0-F3) were significantly associated to HCC.

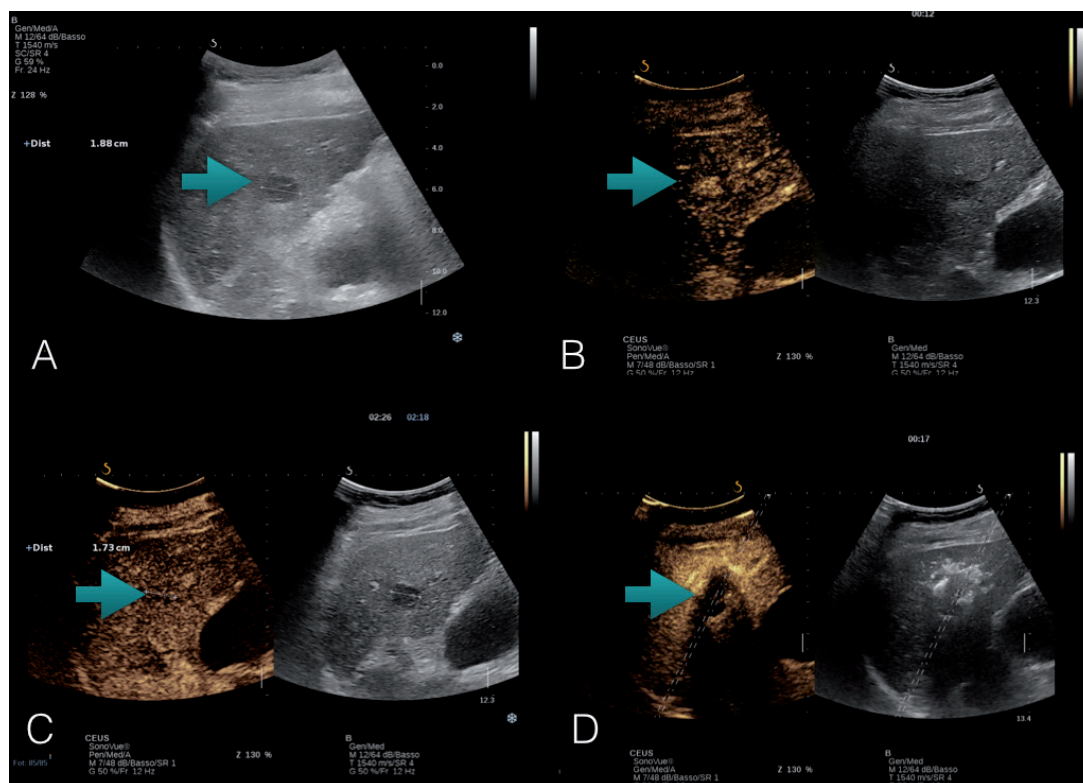


Fig. 1. This figure is subdivided in four panels (A, B, C, D). Panel A shows a hypoechoic lesion located in the sixth segment 19 mm in the maximum size. Panel B shows the hypervascular aspect of the lesion during the arterial phase. Panel C shows the hypovascular aspect during the parenchymal phase. Panel D shows the successful result after radiofrequency ablation since the lesion is avascular in all the phases.

Currently, the main therapeutic approaches in the management of HCC include procedures with ultrasound or angiography guide, surgical resection or orthotopic liver transplantation (OLT).

An important innovation in the field of HCC management is represented by the use of newer molecular approaches such as non-coding RNA and genome-wide association studies, useful to identify new target pathways for the treatment of HCC⁶.

If the early onset of HCC after DAAs will be proved, it would be interesting to evaluate potential molecular variability, with the goal of personalized therapies.

In the last two decades, in respect of typical HCV-infected patients, special populations have been identified for clinical characteristics, such as elderly and HIV-positive patients. HCC represents a new challenge in this particular setting of patients⁷. Due to the poor prognosis, HIV infection represented exclusion criteria of OLT, a few years ago⁸. However, more evidence on the success of liver resection in HIV-infected has become available⁹.

CONCLUSIONS

Despite no definite conclusions can be drawn from a single case report, our findings suggest that in patients with cirrhosis a close monitoring for HCC development should be continued even after HCV eradication. However, more data are needed regarding the possible influence of DAAs on the onset of new HCC and recurrences. Longitudinal evaluation of larger cohorts followed for longer follow-up time could help to clarify the rationale for treating HCV patients with advanced liver diseases. Furthermore, given the complexity of the clinical scenario, there is a need for a multidisciplinary approach. Hepatologists, hepatobiliary/transplant surgeons, oncologists, radiologists, infectious disease specialists, and pathologists should be involved to define tailored interventions after HCV eradication, based on the severity of liver disease.

CONFLICT OF INTERESTS:

The authors declare they have no conflicts of interest regarding the present manuscript.

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