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CASE REPORT

Liver metastasis from neuroendocrine carcinoma after the use of the new direct-action antivirals against hepatitis C virus in a patient with past history of hepatocellular carcinoma

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ABSTRACT

The use of the new direct-action antivirals against hepatitis C virus provides very high viral eradication rates. However, various recently published articles recommend caution with their use after the appearance of some cases of *de novo* tumors (originated in hepatic and extra-hepatic locations) and a possible shorter time period of recurrence of hepatocellular carcinomas previously treated with surgery or loco-regional therapies. The sudden drop of the number of natural killer cells secondary to the use of these new medicines has been suggested as one of the possible mechanisms responsible for this process. However, due to the controversy concerning this subject and the absence of long-term follow-up studies in clinical practice, caution is needed before definitive conclusions are settled. We present the case report of a patient diagnosed of chronic liver disease secondary to hepatitis C virus infection and a past history of hepatocellular carcinoma in complete remission after radiofrequency ablation. He was treated with the new direct-action antivirals reaching sustained viral response. Six months later, the patient was diagnosed with liver metastasis from a small-cell neuroendocrine tumor of unknown primary site.

Key words: Direct-action antivirals. Hepatitis C virus. Natural killer cells. Liver metastasis from a neuroendocrine carcinoma.

INTRODUCTION

The use of the new direct-action antivirals (DAA) against hepatitis C virus infection (HCV) has achieved very high eradication rates (greater than 90% in the majority of articles recently published). In addition to this, DAAs have shown a very good safety profile in clinical studies, which has enabled the treatment of patients with more unfavorable conditions than those treated with interferon in the past (such as patients with advanced liver cirrhosis or previous hepatocellular carcinomas [HCC] successfully treated) (1). However, not all that glitters is gold: with the employment of treatment regimens containing interferon, a drop in the progression of liver fibrosis was shown after viral eradication, and this was associated with a drop in the rate of HCC diagnosed in patients with sustained viral response (2,3). Although we still do not have definitive information concerning this issue with regard to the new DAAs due to the short time that they have been commercialized, some articles published recently associate the use of these medicines with an increased incidence of hepatic and extra-hepatic tumors showing aggressive behavior and with an increased rate of recurrences of previous HCC. With the aim of delving into this subject, we present the following case report.

CASE REPORT

We present the case of a 72-year-old male diagnosed with liver cirrhosis secondary to HCV infection who was being followed up in our outpatient liver clinic since 2000. He was infected by a genotype 1b virus and was naive to antiviral therapy, as he had rejected treatment regimens containing interferon in the past. He also had a past medical history of patent ductus arteriosus surgery during childhood, atrial fibrillation, ischemic coronary events in 2004 requiring the positioning of conventional stents, and also the replacement of an aortic valve by a metallic prosthesis in 2013, being treated since then with oral anticoagulation (Eliquis®). He had also suffered from acute strokes in 2007 and 2013 with complete recovery from both and had chronic obstructive airway disease with a low rate of exacerbations. In May 2014, a liver magnetic resonance imaging (MRI) study was performed in the context of the HCC screening program. A lesion that measured 25 x 17 millimeters in the VI segment was found, and was compatible with a diagnosis of HCC. The patient received radiofrequency ablation, achieving a complete radiological response in the following liver MRI performed four weeks later. After this, the patient underwent clinical and radiological close follow-up every three months with no signs

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of tumor relapse being found. In May 2015, the patient started on an antiviral treatment consisting of ledipasvir/sofosbuvir 90/400 mg (Harvoni®) once a day for 12 weeks, the absence of tumor recurrence having previously been verified in an MRI performed two days before. The patient finished treatment without presenting any adverse events or other complications, and he acquired sustained viral response 12 and 24 weeks after the end of treatment. In October 2015, another MRI was performed, in which the area previously treated with ablation did not reveal radiologic signs of tumor recurrence (Fig. 1). However, three months later, several low-sized lesions, hypo-intense in T1 sequence and slightly hyper-intense in T2 sequence, appeared in a follow-up MRI, some of them showing ring dye-enhancement. Due to these characteristics, these lesions were highly suggestive of liver metastasis. However, the liver area where ablation had been previously applied did not show signs of tumor relapse (Fig. 2). By that time, the hypothesis of liver tumor recurrence of the previous HCC with aggressive behavior was the main diagnosis suspected, although an alternative diagnosis such as liver metastasis of an extra-hepatic unknown primary site could not be discarded. In order to clarify this, a fine-needle aspiration was done to collect cells from one of these liver lesions to perform cytological analysis. This analysis showed metastatic cells from a small-cell neuroendocrine carcinoma (CD 56+, synaptophysin+ in the immunohistochemistry study). A total-body computed tomography was performed, which revealed several lesions located in dorsal and lumbosacral vertebral bodies showing malignant radiological signs compatible with the diagnosis of metastasis. The bone scan and the spine MRI performed later confirmed the findings of the tomography. To date, the exact primary location of the tumor has

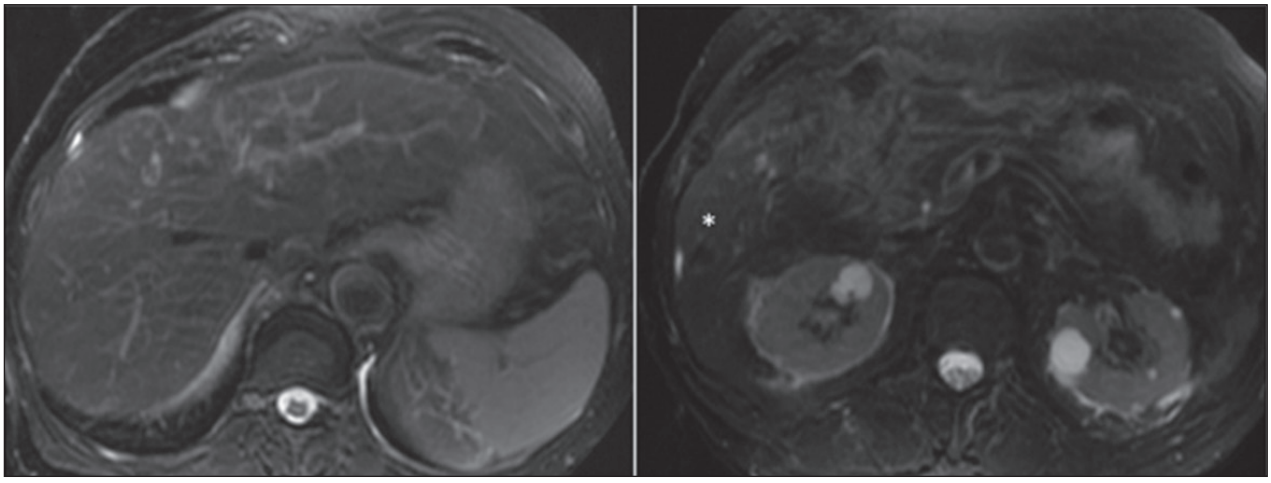

Fig. 1. Axial T2 weighted Liver MRI images obtained three months after the end of DAA treatment. The area previously ablated (*) does not show radiological signs of tumor persistence. No other liver lesions are seen.

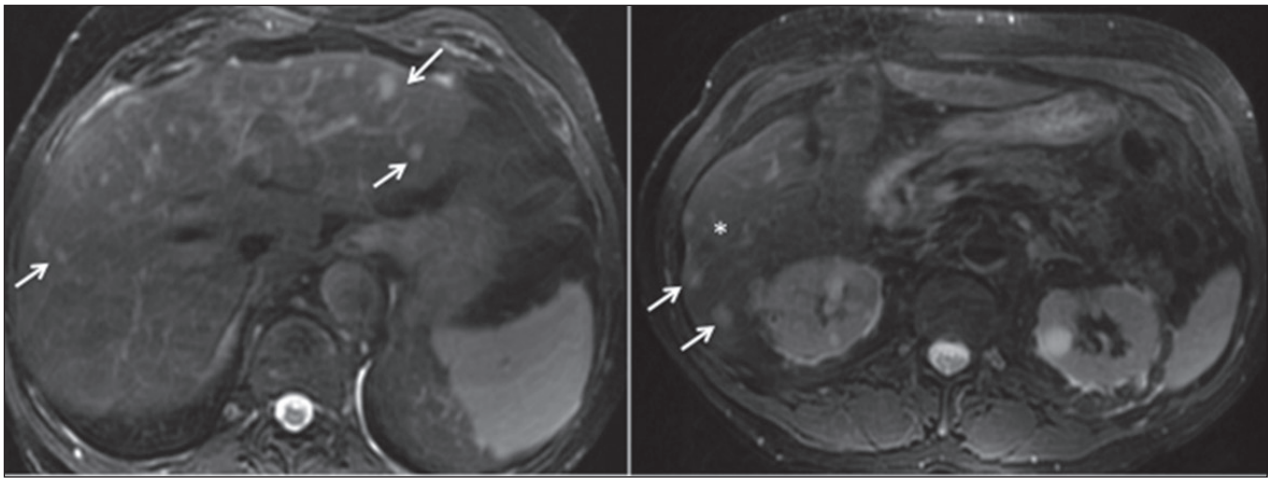

Fig. 2. Axial T2 weighted Liver MRI images obtained six months after the end of DAA treatment. Numerous hyper-intense lesions have appeared throughout liver parenchyma (arrows). The area previously ablated (*) does not show radiological signs of tumor persistence.

not been found; however, the hypothesis of a small-cell lung cancer in a metastatic state is the most probable diagnosis. The patient has received a chemotherapy regimen consisting of carboplatin and etoposide and he has also been administered palliative radiotherapy to control the pain of bone spine metastasis, showing a good clinical response. In the tomography performed six months after starting chemotherapy treatment, all the bone metastasis and the majority of liver lesions had disappeared, with only some minuscule liver metastasis remaining. Due to his good response to treatment, the patient has re-started a new chemotherapy regimen; the results will be evaluated in the near future.

DISCUSSION

The use of the new DAAs has resulted in a revolution in the treatment of HCV infection. However, there are still some unknown issues concerning their medium-long time side effects, and this is due to the lack of experience with them to date. In this sense, the specific role played by the new DAAs concerning the risk of development of new cases of HCC tumors as well as HCC recurrences from previously treated tumors are some of these uncertainties. Nowadays, this controversial point is being intensively debated with arguments in favor of and against this hypothesis (4-7).

One of the most important articles concerning this issue is the study performed by the collaborative group ANRS, in which the conclusions of three prospective cohort studies are summarized concerning the risk of developing HCC recurrence after receiving the new DAAs. The authors of this study conclude that the use of DAAs does not seem to involve a higher risk of HCC recurrence (4). However, opposing evidences have also been published. An example of these is the article published by Reig et al., in which 28% of the patients included in their registry and treated with the new DAAs showed early recurrence of their HCC that was previously treated successfully with radiofrequency ablation, surgical resection or chemoembolization (only one patient received the last treatment), with a mean time tumor recurrence of 3.5 months from the start of the antiviral treatment and with 25% of these recurrences showing aggressive behavior (5). Another study that follows the same line is the one presented by Conti et al (6). This is a retrospective cohort study in which the risks of appearance of *de-novo* HCC tumors and HCC recurrences were analyzed considering the first 24 weeks after finishing DAA treatment (only evaluating patients with negative viral load after treatment). The risk of developing new liver tumors and recurrences of previously treated liver tumors was 3% and 29%, respectively. Despite the fact that the number of HCC recurrences noted by these authors is not higher than the numbers obtained in other studies evaluating patients with HCC tumors treated and evaluated one year after (7), the authors highlight the temporal coincidence of these recurrences, taking place in the brief period time evaluated in the study (around six months). They conclude that DAAs may not increase the total number of HCCs developed but they could play a role in reducing the period for tumor recurrences to appear (6).

One of the theories that has been recently proposed to explain this hypothetical higher risk of recurrence and occurrence of liver tumors after the use of DAAs relies on the fact that during chronic infection of the HCV, natural killer (NK) cells would show an increased activated state compared to the state shown by HCV non-infected patients. In addition to this, these cells would show an increased cytotoxic function against the virus but also against tumor cells. Some authors have suggested that the fast reduction of viral load caused by the new DAAs would cause a fast drop of this hyper-activation state of NK-cells, as well as a fast normalization of their cytotoxic function. This would cause a situation of, at least, partial immunosuppression in which the usual immune surveillance against malignant clones established during the chronic infection phase would be damaged, thus, leading to proliferation and systemic spread of initially dormant malignant cells (8,9). This lack of anti-tumor surveillance would affect the human body systemically, which would also explain the presence of tumors in other locations. This is the case of the article published by Lin et al. in which they describe the sudden onset of two clinical cases of mantle cell lymphoma with aggressive behavior after the use of therapies containing sofosbuvir (Sovaldi®) (10). If this hypothesis is confirmed in the future, the management of patients treated with the new DAAs could change, meaning that patients should undergo close follow-up visits after antiviral treatment in order to obtain an early diagnosis of malignancy with a higher chance of providing curative treatment of the tumor. In this context, it seems important to mention the role of the cytological analysis obtained via the fine-needle aspiration technique to characterize liver lesions that do not show a typical dye-enhancement pattern suggestive of HCC (like the clinical case presented) and whose correct diagnosis defines the treatment and prognosis of the patient.

Finally, the case report we have presented, as well as the patients included in the articles published by Reig and Conti, could be just unfortunate tumor cases unrelated to the antiviral treatment prescribed. However, because of the current uncertainty, and until high quality and long-term evidence with these new therapies is provided, the note for caution suggested by Reig et al. seems, in our point of view, very reasonable.

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