CASE REPORT

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Complete and Sustained Off-Therapy Response to Sorafenib in Advanced Hepatocellular Carcinoma

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ABSTRACT

A 75-year-old Caucasian woman with alcohol-related cirrhosis was admitted to our Unit in October 2012 for the diagnostic evaluation of a focal liver lesion detected by regular surveillance ultrasound. The subsequent dynamic CT and MR led to a diagnosis of infiltrative hepatocellular carcinoma (HCC) of 5 cm in the hepatic segment IV with neoplastic infiltration of the left branch of the portal vein, in absence of extrahepatic metastases. Therapy with sorafenib 400 mg bid was started and the subsequent dynamic CT performed at the 10th month of therapy showed a complete response according to RECIST criteria and mRECIST, while seriated dosages of α-fetoprotein levels showed a progressive reduction up to normalization. After 18 months of therapy, Sorafenib was discontinued due to a grade 3 adverse event. Nonetheless, all subsequent radiological controls, performed over the following two years confirmed a complete off-therapy response despite withdrawal of Sorafenib. After three years the patient is asymptomatic, with a preserved liver function and undetectable solid tumor lesions at dynamic CT.
This case represents one of the few examples of complete response to anti-angiogenic drugs and, to our knowledge, the only case of sustained response, even after the discontinuation of Sorafenib, described so far in the literature.

Key words: hepatocellular carcinoma – HCC – BCLC – sorafenib – complete response.

Abbreviations: AFP: alpha-fetoprotein; AE: adverse event; BCLC: Barcelona Clinic Liver Cancer; CT: computed tomography; HCC: hepatocellular carcinoma; mRECIST: modified response evaluation criteria in solid tumors; PS: Performance status; RCTs: randomized controlled trials.

CASE REPORT

A 75-year-old Caucasian woman with alcohol-related cirrhosis was admitted to our Unit in October 2012 for the diagnostic evaluation of a focal liver lesion detected by regular surveillance ultrasound. Her medical history included heavy smoking (about 40 cigarettes/day), hypertension, and chronic obstructive pulmonary disease diagnosed several years before.

Upon admission the patient was asymptomatic and there was no evidence of hepatic encephalopathy, ascites or peripheral edema. Physical examination was unremarkable, except for hepatosplenomegaly.

Laboratory tests showed mild thrombocytopenia (PLT 103,000x10^3/μL), mild hypoalbuminemia (3.3 g/dL), and α-fetoprotein (AFP) values > 3000 ng/mL (normal values < 5 ng/mL). All other liver function tests were normal and the Child-Pugh score was A6, indicating a good residual liver function.

Esophagogastroduodenoscopy detected the presence of large-size isolated gastric varices (IGV 1) and portal hypertensive gastropathy.

The subsequent dynamic CT and MR led to a diagnosis of infiltrative hepatocellular carcinoma (HCC) of 5 cm in the hepatic segment IV with neoplastic infiltration of the left branch of the portal vein (Fig. 1), in absence of extrahepatic metastases.

Considering the presence of macrovascular invasion, the preserved liver function (Child-Pugh score A6) and the good performance status (PS 1), the patient was allocated in stage C according to the Barcelona Clinic Liver Cancer (BCLC) staging system.

According to the tumor stage, and in absence of absolute contraindications, the patient was given Sorafenib (Nexavar®, Bayer Healthcare Pharmaceuticals-Onyx Pharmaceuticals) at a

dose of 400 mg/bid. The treatment was quietly tolerated during the first months except for the onset of grade 2 diarrhoea in the 4th month, which required a permanent dose reduction to 200 mg/bid.

Dynamic CT performed after the third month of therapy showed a reduction of the HCC lesion size from 5 to 3.7 cm, hypodensity of the lesion at all phases, and a partial recanalization of thrombosis of the right branch of the portal vein. The subsequent dynamic CT performed at the 10th month of therapy showed the absence of hypervascular liver lesions, and the disappearance of the portal vein thrombosis (Fig. 2). Furthermore, seriated dosages of AFP showed a progressive reduction of its values, down to 300, 14, and 2 ng/ml, at 2nd, 3rd and 10th month of therapy, respectively, and afterwards persistently below 10 ng/mL until today.

After 18 months of therapy, in March 2014, Sorafenib therapy was permanently discontinued due to worsening of diarrhoea (grade 3), which was not responsive to dose reduction and to a temporary withdrawal of therapy.

All subsequent radiological controls – the last one performed in January 2016 – evidenced an unchanged radiological picture, confirming a complete off-therapy response according to RECIST criteria and mRECIST, despite the discontinuation of Sorafenib.

After three years the patient is asymptomatic, with a preserved liver function and undetectable solid tumor lesions at dynamic CT.

DISCUSSION

The incidence of HCC is increasing worldwide, being the leading cause of death in patients with cirrhosis [1], and Sorafenib is currently the only approved therapy for the treatment of advanced HCC. With this background, evolution of this case could be of great interest because pivotal randomized controlled trials (RCTs) [2, 3] showed no case of complete response according to RECIST criteria [4] on a total of 758 patients included, both in Sorafenib and placebo arms.

Following the pivotal trials, only a few cases of complete response to Sorafenib have been reported in clinical practice [5-7], and this represents, to the best of our knowledge, the only case of sustained response observed even after discontinuation of Sorafenib.

A limitation of this study lies in the absence of liver biopsy. Nevertheless, according to current guidelines, a biopsy is not essential in our case, because one contrast-enhanced study is sufficient for a confident diagnosis of an HCC with a diameter > 1 cm [8]. In our patient, a dynamic CT showed the

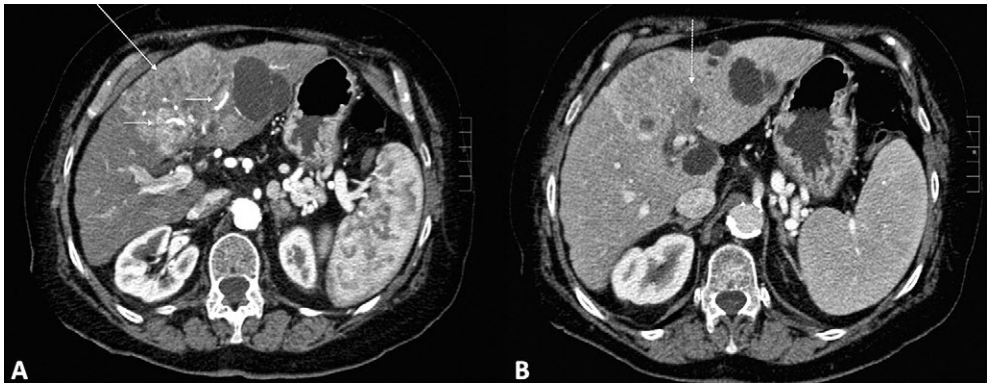

Fig. 1. CT scans of the abdomen performed at diagnosis. A) Arterial phase shows a large enhancing "spread like" hepatocellular carcinoma (HCC) located at IV hepatic segment (arrow), with marked hypertrophy of the feeding arteries (small arrows). B) Hepatic venous phase and delayed phase CT scan shows hypo-isoattenuation of lesion to liver parenchyma with thrombosis of the left portal vein branch (dotted line).

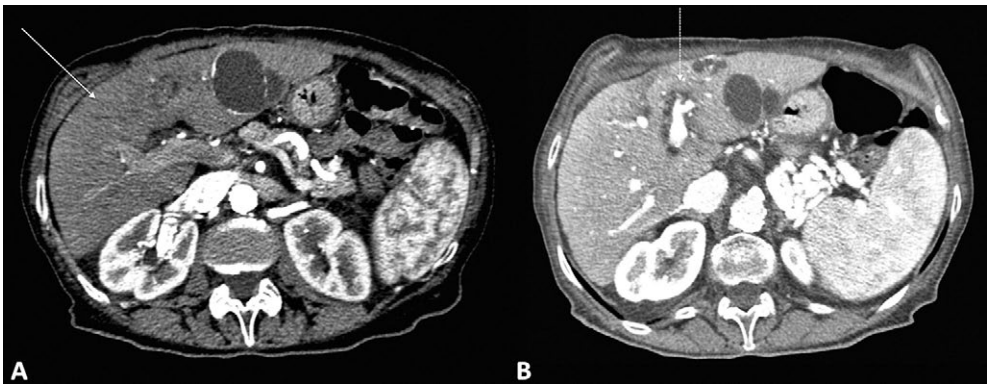

Fig. 2. CT scans of the abdomen performed at the 10th month of therapy. (A) Arterial phase shows that HCC lesion has been replaced by an isoattenuating to liver parenchyma, non enhancing area (arrow). (B) Hepatic venous phase and delayed phase CT scan shows recanalization of the left portal vein branch (dotted line).

typical imaging features, and a subsequent MR confirmed the diagnosis. In addition, although sporadic cases of vanishing HCC have been described so far [9, 10], this hypothesis does not seem appropriate for our case, because a neoplastic thrombosis was already present, and it is well known that this represents one of the worst negative prognostic factors in HCC.

Similarly to other reports, this case of complete response stands as a sporadic clinical evidence of tumour shrinking, resembling that obtained following conventional chemotherapy. This is in contrast with the results obtained in pivotal trials and should lead to a more accurate biological characterization of the neoplasm. Indeed, the natural history of HCC is extremely heterogeneous, due to the complex biological characteristics of the tumor - and most of them are still unknown. Consequently, a subclassification of HCC patients according to their genomic and proteomic profiling will be necessary in the near future, in order to identify and properly select the subset of patients that could experience a greater benefit from targeted agents [11].

In this regard, the histological sample provides important and unique information that currently cannot be replaced by any other test, but the recent trend towards a reduction in HCC biopsies could represent a major obstacle to a personalized approach in liver cancer [12]. Perhaps we do need to take a step back in order to make one forward?

CONCLUSION

This case represents one of the few examples of complete response to anti-angiogenic drugs and, to our knowledge, the only case of sustained response, even after the discontinuation of Sorafenib, described so far in the literature.

Conflicts of interest: None to declare.

Authors' contribution: M.M. wrote, revised the manuscript and participated in patient care. F.S.M. and R.V. participated in patient care and revised the manuscript. F.V. performed radiological assessment.

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