CASE REPORT

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Complete Remission of Advanced Hepatocellular Carcinoma Treated with Sorafenib and Concomitant Appearance of IgG4-related Diseases. A Case Report

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ABSTRACT

Sorafenib is currently the gold standard therapy for palliative treatment of advanced hepatocellular carcinoma (HCC) in patients with compensated liver disease. There are few cases reported in literature describing patients with HCC achieving a complete remission (CR) due to Sorafenib therapy. We report the case of a 62-year old patient who obtained CR despite single, long drug discontinuation and kept it without any maintenance therapy. Furthermore, this is the first case describing the onset of a likely IgG4-related retroperitoneal fibrosis and cholangitis during Sorafenib administration. Further studies are required to define the predictors of a good response to Sorafenib and to codify a therapeutic maintenance regimen for patients who achieve CR.

Key words: Sorafenib – IgG4-related disease – hepatocellular carcinoma – HCC.

Abbreviations: AFP: alpha-fetoprotein; CR: complete remission; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MRI: magnetic resonance imaging; mRECIST: modified Response Evaluation Criteria in Solid Tumors; PET: positron emission technology; 18-FDG: 18-fluorodeoxyglucose.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death in the world [1]. Only 20% of patients with HCC can receive curative local treatment. The prognosis is poor, if untreated, with a mean survival of 7-8 months [2]. Sorafenib is a small-molecule multi-kinase inhibitor. Sorafenib HCC Assessment Randomized Protocol (SHARP) trial and the Asia-Pacific trials demonstrated that Sorafenib was currently the only systemic agent, able not only of improving progression-free survival significantly, but also of enhancing overall survival in patients with unresectable advanced HCC [3, 4]. Sorafenib has become the first-line treatment for patients with advanced HCC and a performance status 1 or 2 according to the Eastern Cooperative Oncology Group (ECOG). However, complete remission (CR) is extremely rare [5]. We report the case of a 62-year old patient with hepatitis C virus (HCV) related cirrhosis and a large HCC treated with Sorafenib who obtained a complete, durable remission 20 months after treatment was withdrawn, despite one treatment interruption due to adverse reactions. The peculiarity of this case is the onset of a likely IgG4 related disease during treatment.

CASE REPORT

A 62-year old Caucasian male was referred to our department from 2008, with a history of hepatitis C virus (HCV), genotype 1b, related cirrhosis by 1990s and a sustained virologic response achieved with peginterferon alfa-2a and ribavirin in 2008. In July 2013 he underwent a liver resection for HCC of the VII-VIII segment. Afterwards, in January 2015, during the evaluation for inclusion in the liver transplantation list, the patient developed a massive relapse of HCC, affecting the V-VIII segments. The HCC diagnosis was based on imaging criteria according to the vascular behavior (Fig. 1 A and B), in addition to a neoplastic infiltration of the right supra-hepatic venous branch, without evidence of portal thrombosis. Alpha-fetoprotein (AFP) increased from a

value of 10.6 ng/mL to 2,484 ng/mL. The patient had several comorbidities: diabetes mellitus, autoimmune thyroiditis, overweight (body mass index=33) and unilateral blindness. The patient's physical condition was good (performance status 0 according to the ECOG) and was ranked as Child-Pugh A. According to the most recent guidelines for HCC diagnosis and treatment, locoregional therapies were excluded [6]. Thus, Sorafenib therapy was started in March 2015, at the dose of 800 mg/die. In July 2015 the patient withdrew from therapy due to severe diarrhea. In July 2016 half-dose therapy (400 mg/die) was resumed, without serious side effects. Since July 2016 the AFP values have been in the normal range. In November 2017, after 32 months from the beginning of therapy (of which 21 months were without any interruption), a contrast enhancement ultrasound showed absence of disease activity without arterial phase uptake of zinc-hexafluoride. A subsequent magnetic resonance imaging (MRI) made in January 2018 confirmed the presence of a nodule of 7x4 cm without typical contrasting behavior for HCC or vascular infiltration. The positron emission technology (PET) scan excluded uptake of 18-fluorodeoxyglucose (18-FDG) on the liver, evidencing a CR from the disease. Due to uncontrollable diarrhea, the dosage of Sorafenib was further reduced in February 2018 (200 mg/day). Since the radiological appearance of HCC nodule remained unchanged (Fig. 1 C and D), in March 2019 Sorafenib therapy was discontinued. Particularly, during Sorafenib administration the patient presented the appearance of peripheral edema, painless eyelid, periorbital swelling, dry eyes associated with CT evidence of retroperitoneal fibrosis (May 2017) (Fig. 2 A and B), increased levels of alanine amino-transferase 86 U/L, aspartate amino-transferase 155 U/L and gamma-glutamyl transferase 188 U/L and altered hepatobiliary MRI excretion. An increase in IgG4 up to 1,378 mg/dL led to the final diagnosis of retroperitoneal fibrosis and cholangitis possibly IgG4-related. The diagnosis of retroperitoneal fibrosis was presumed according to the diagnostic criteria available [7] due to the impossibility of obtaining a histological diagnosis through a retroperitoneal biopsy for several reasons. The patient had a low platelet count ($60*10^3/mm^3$) and altered international normalized ratio (INR 1.81). The retroperitoneal approaches for biopsy excluded both an ultrasound (US) and CT-guided manoeuvres due to the difficult access to the site of retroperitoneal fibrosis; an endoscopic US (EUS) approach was also excluded due to the close contiguity with the aorta and the small size of the fibrosis. Poor benefit steroid therapy was set up and currently the patient is still under evaluation for a possible anti-CD20 off-label therapy. To date this is one of the few cases of patients with advanced HCC experiencing a CR despite one therapy discontinuation and the first case who developed a possible IgG4-related disease while taking Sorafenib.

DISCUSSION

In this case, a patient with HCV cirrhosis and locally advanced HCC was treated with Sorafenib achieving a CR. According to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria, CR correlates with the disappearance of any intra-tumoral arterial enhancement in all target lesions, and partial response with at least a 30%

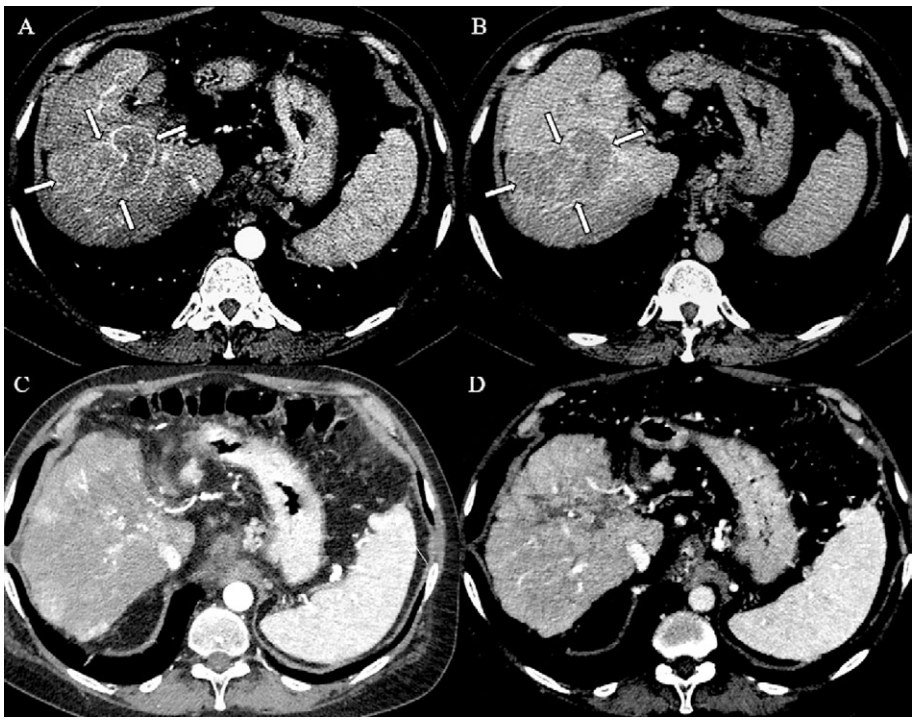

Fig. 1. A, B) Computed tomography images: nodule in the liver segments V-VIII , with a maximum diameter of 8 cm, with hypervascularization in the arterial phase (A) and wash out of contrast media in the venous phase (B), compatible with the accepted imaging diagnosis of hepatocellular carcinoma. C, D) Computed tomography images of the same patient, performed after Sorafenib administration: the images in the same planes as in panels A and B, demonstrate the absence of liver lesions both in the arterial (C) and in the venous phases (D).

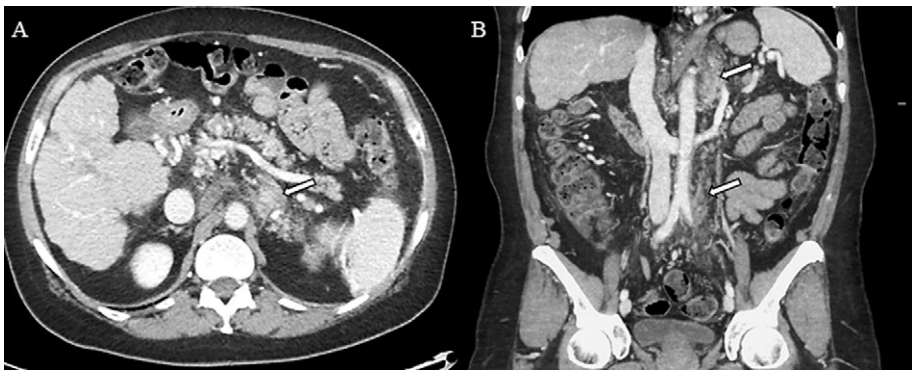

Fig. 2. A, B) Computed tomography images demonstrated inflamed retroperitoneal tissue, especially localized in the left para-aortic space (A) and not extended below the aortic bifurcation (B).

decrease in the sum of the longest baseline diameter of target lesions [8]. After 10 years of research for Sorafenib, there are still no validated prognostic or predictive markers of response to Sorafenib in HCC [9]. Characterizing the biological peculiarities of the tumor could help the identification of those characteristics that make one histological type more responsive to Sorafenib than another. However, according to the available guidelines [6, 10], the diagnosis of HCC is based on the vascular behavior of lesions greater than one centimeter on imaging, whereas biopsies on HCC are less and less carried out, thus limiting biomarkers' evaluation as for the present report [11]. Recent studies have demonstrated that several biomarkers may help to predict a poor response to Sorafenib, such as a fast reduction in serum AFP while des-y-carboxyprothrombin levels following treatment predicts a good response to Sorafenib [12]. A previous study suggested that an early AFP response within the first 4 weeks is a surrogate marker, predictive of progression-free survival and overall survival in HCC patients treated with Sorafenib [13]. However, in our case, after an initial AFP increase in the first 4 months, we assisted to a considerable AFP reduction during Sorafenib administration until a final normalization. Our data, on one hand support the hypothesis that AFP variations may be predictive of response to therapy but on the other suggests, similarly to another report [14], that one month may be insufficient to predict drug response. Moreover, the AFP flare could be due to a tumor flare or necrosis rather than disease progression [15]. Furthermore, we also confirmed previous data reporting a CR more frequent in viral etiologies of liver disease [16]. A particular signature of our case is that CR was obtained despite a long-lasting withdrawal. According to the available literature, there is only one other case of an achieved CR despite one therapy discontinuation lasting 15 days due to drug intolerance during treatment [17]. Our patient discontinued treatment one time (up to 11 months) due to the onset of severe diarrhea that was treated with rifaximin and loperamide, leading to a subsequent therapy resumption with Sorafenib dosage reduction. Thus, the management of adverse drug reactions is essential. Low dose Sorafenib, as also reported in other studies [18], achieved a CR by improving the patient's quality of life. An interesting issue also raised by other authors [19] is whether the increased incidence of reactions may be a predictor of a better HCC response to the drug. Bettinger et al. [20] reported for the first time that diarrhea was an independent positive prognostic factor (HR=0.41; p=0.001) in 112 patients with advanced HCC, a finding also confirmed by other studies [21, 22]. The molecular mechanism of this correlation is unclear; one study supported the hypothesis that Sorafenib might cause diarrhea inducing pancreatic exocrine dysfunction [23]; thus, the onset of diarrhea could be an indicator of adequate response to the drug, being intrinsically related to a pharmacological action. Another open question is whether continuing therapy after CR, with eventual dosage and period adjustments is recommended. There is no strong evidence regarding this point in literature without an unanimous consensus on which approach to adopt since insufficient data are available on the long-term follow-up of these patients after reaching CR. Some authors suggested low dose Sorafenib as maintenance therapy, reporting data that a reduced dosage may be sufficient [24, 25], whereas a recent large study by Zhang et al. [26] showed that there is no benefit in terms of recurrence-free survival and overall survival by keeping the patient on Sorafenib therapy in patients achieving CR. Besides, the patient's quality of life was improved after therapy withdrawal, probably due to the resolution of adverse effects due to therapy [26]. Therefore, discontinuing Sorafenib therapy once CR is achieved seems to be the best cost-benefit option. In our case we discontinued Sorafenib only after an additional 18 months from the first imaging report without active disease. However, further studies are required to understand how to manage these patients in the long-term after the achievement of a complete response. Lastly, our patient also developed a possibly IgG4-related cholangitis and peritoneal fibrosis during treatment. However, this latter diagnosis was not supported by histology since the risk of bleeding related to the sampling of peritoneal fibrosis was unbalanced regarding the benefits, even with an EUS approach [27]. Moreover, data from a previous series [28] of retroperitoneal fibrosis patients showing that inflammatory retroperitoneal fibrosis is frequently not extended below the aortic bifurcation and causing medial ureteral attraction, similar to our case, also supported our decision not to attempt any sampling. In literature there are only two cases of autoimmune disease (Grave's disease) associated with Sorafenib therapy, which was used for other indications (respectively for chordoma and metastatic renal cell carcinoma) [29, 30]. To date, this is the only described case of likely IgG4-related disease during Sorafenib treatment and the only case in which the patient was already affected by an autoimmune disease (thyroiditis).

There is evidence that various tyrosine kinase inhibitors are able to modulate immune responses; in particular these molecules might mediate both beneficial and harmful effects on immune cells and trigger global auto-immunity system, by releasing new tumoral antigens. Thus, it is possible to speculate regarding a possible effect of Sorafenib in unmasking or enhancing the onset of other autoimmune disease [31-32]. The awareness of this possible side effect should increase physicians' attention in early recognition of any autoimmune manifestation, allowing an early diagnosis. Another point that needs to be considered is the role of IgG4 in patients with HCC. A previous study [33] showed that serum IgG4 before HCC resection was significantly elevated in patients with recurrent HCC, thus serving as marker of a Th1-to-Th2 switch and implying an immunological tolerance for the malignancy. According to the authors these changes finally led to an increased risk of HCC recurrence. However, if on one hand an IgG4 dosage before Sorafenib administration is not available and the IgG4-related disease was not confirmed by histology, we still believe that the IgG4 increase reported in the present case was not linked to the sole presence of HCC for several reasons. First, our patient responded to Sorafenib therapy achieving complete response thus meaning that the predictive role for characterizing HCC aggressiveness related to high IgG4 levels was lacking; second, the IgG4 increase reported was related to classical clinical patterns of IgG4-related disease, supporting our diagnosis. Lastly, the data reported by Wu et al. [34] came from HCC patients undergoing resection, without a possible Sorafenib effect in unmasking autoimmune diseases.

CONCLUSIONS

Our case suggests that adverse events during Sorafenib treatment could be markers of therapy efficacy, requiring a correct management in order to continue treatment, eventually at a reduced dosage. Therapy withdrawal for short periods does not seem to influence the response. To date, there is no strong evidence on the long-term management of patients reaching complete response to Sorafenib, although the most beneficial approach seems to be to discontinue Sorafenib. Finally, our case and other previously reported underline a possible Sorafenib effect in unmasking autoimmune disease during treatment, mainly in predisposed patients.

Conflicts of interest: None to declare.

Authors' contributions: G.I., M.R., G. Mazzella and G. Marasco designed the study. G.I., M.R. and G.Marasco acquired and interpreted data. G.I and G.Marasco drafted the manuscript. All authors revised the manuscript and approved the final version.

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