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CASE REPORT

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Long-term response of hepatocellular carcinoma to sorafenib in a patient with HFE-haemochromatosis

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ABSTRACT

In the literature there has been only one case report of cirrhotic patient with hepatocellular carcinoma (HCC) and with a history of hereditary haemochromatosis treated with sorafenib for six months. Herein, we describe a case of a primary non-cirrhotic patient who was incidentally diagnosed with haemochromatosis during prolonged therapy with sorafenib due to HCC. A 53-year-old primary non-cirrhotic man with advanced HCC was treated with sorafenib at 400 mg twice daily since October 2010 following percutaneous ablation treatment of the largest liver nodule. He was seronegative for hepatitis B and C virus. After two years of kinase inhibitor therapy, the liver changes with cirrhotic features suggesting hemochromatosis were discovered on repeated imaging. The diagnosis of associated iron-overload disease was confirmed by genotypic expression — he was homozygous for the *HFE* gene C282Y mutation. Maintaining cancer stabilisation by continuing sorafenib therapy at the fixed standard dose for six years, he has undergone thirty-five phlebotomies until now.

Key words: hepatocellular carcinoma, hemochromatosis, sorafenib

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with increasing incidence, and is the third most frequent cause of cancer-related death worldwide. Most HCC patients present with advanced and multifocal disease at the time of diagnosis and are of poor prognosis. Cirrhosis, which is present in approximately 80–90% of HCC patients, is the most important risk factor for this malignancy regardless of aetiology and may be caused by chronic viral hepatitis, alcoholic liver disease, autoimmune disease, exposure to hepatotoxins, and metabolic disease including haemochromatosis, alpha-1 antitrypsin deficiency, as well as non-alcoholic fatty liver disease associated with obesity, insulin resistance, and type 2 diabetes [1]. Several environmental factors and molecular abnormalities are additional risk factors for this malignancy [1–3]. Co-existence of multiple causes of liver injury increases the risk of HCC development.

Altered iron homeostasis is one of the processes leading, via chronic liver damage, to HCC development [1, 2]. Significant iron deposition, in the absence of hemochromatosis, in cirrhotic livers of various cases of cirrhosis was documented [4]. Hereditary hemochromatosis is an autosomal recessive disorder that leads to progressive iron accumulation, with nonspecific symptoms such as cirrhosis, diabetes mellitus, cardiomyopathy, and endocrinopathy, which typically begin in adulthood. This disease is not uncommon in the Caucasian population. It is associated with an increased risk of HCC, which occurs predominantly in patients with cirrhosis at the time of diagnosis. The genetics of hemochromatosis are complex with strong environmental disease modifiers [5]. Most cases have been linked to mutations in genes

associated with iron homeostasis. There have been three major variants in the high Fe (*HFE*) gene associated with the disease: C282Y, H63D, and S65C. The clinical penetrance of these mutations is highly variable. The homozygosity for the C282Y polymorphism in the *HFE* gene accounts for > 80% of haemochromatosis iron phenotypes in Caucasians, and occurs in 0.3–0.6% of persons of European descent [5]. The clinical penetrance of iron overload in many C282Y homozygotes is mild [6]. The HFE 282Tyr mutation almost completely prevents the formation of a complex between the mutant HFE protein and the transferrin (TF) receptor (TFR), allowing high-affinity TF binding to the TFR. This binding results in an increased cellular uptake of iron [7]. A second missense mutation in the *HFE* gene, H63D, is found in about 4% of patients with hereditary haemochromatosis, but its role in iron overload is still debated [7]. Rare, non-*HFE*-related hereditary iron overload includes defects of genes *TFR2,* which codes for the second TFR, and *HAMP* and *HJV*, which code for hepcidin and haemojuvelin, respectively, which are responsible for juvenile haemochromatosis. Moreover, ferroportin disease (a special dominantly inherited clinical form of iron overload due to JK mutations of the *SLC40A1* gene) and inherited mutations in the ceruloplasmin gene (aceruloplasminaemia), which lead to the impairment of iron release from cells [8, 9]. As well as acquired or environmental, other genetic factors may influence iron absorption or iron stores. For instance, *GNPAT* D519C was reported recently as a factor strongly associated with markedly increased iron stores in C282Y homozygotes [6].

A 19-fold increased risk of HCC among C282Y homozygotes with cirrhosis due to chronic viral hepatitis and alcoholic liver disease was demonstrated [10]. In this study the other *HFE* allele constellations (C282Y/H63D compound heterozygotes, H63D homozygotes) were not associated with the increased risk of HCC.

Sorafenib, an oral multikinase inhibitor with activity against Raf-1, B-Raf, VEGFR-2, PDGFR, and c-Kit receptors, has a potent antiangiogenic and proapoptotic activity and, therefore, presents a marked antitumoral effect, including HCC. Sorafenib has become a standard therapy in advanced HCC on the basis of the results reported by two randomised, placebo-controlled trials: the SHARP (Sorafenib HCC Assessment Randomised Protocol) and the Asia-Pacific trial [11, 12]. In these trials, the median times to progression and overall survival were 5.5 months and 2.8 months, and 10.7 months and 6.5 months, respectively.

Here we present a case of a primary non-cirrhotic patient incidentally diagnosed with hereditary haemochromatosis during prolonged therapy with sorafenib due to advanced HCC.

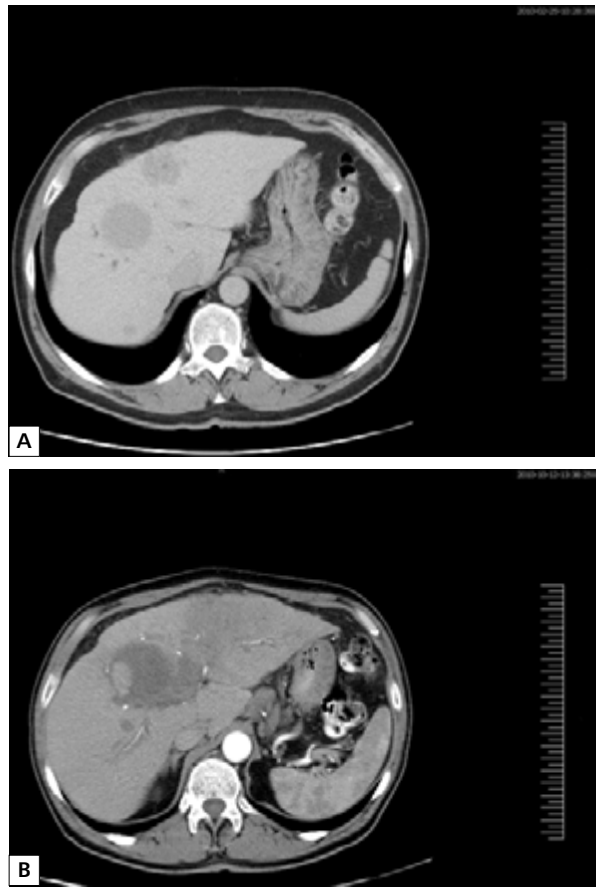

Figure 1. CT liver scans. **A**. Before treatment (Feb. 2010); **B**. At the beginning of sorafenib therapy (the largest nodule in the 8/5 segment of the liver post alcohol injections) (Oct. 2010)

Case report

A 53-year-old, non-cirrhotic man (Child-Pugh class A) with HCC started sorafenib treatment at 400 mg, orally, twice daily in October 2010. Previously, between July and September 2010, he underwent three percutaneous ethanol injections (PEIs) of the largest liver nodule. HCC was revealed incidentally in February 2010 based on ultrasound and computed tomography (CT) during a diagnostic process of alopecia and fatigue (Fig. 1A), and was confirmed by a liver biopsy (Figure 2A and B). At that time, no cirrhosis was found. The patient denied alcohol abuse and hepatitis infection. He had well-controlled hypertension. His father died due to gastric cancer, and his twin was diagnosed with colon cancer. His Eastern Cooperative Oncology Group (ECOG) performance status was 1. Physical examination revealed hepatomegaly and mild skin hyperpigmentation. The liver function parameters were mildly elevated (transaminases ALT and AST, CTC grade 1), alpha-fetoprotein (AFP) level was normal

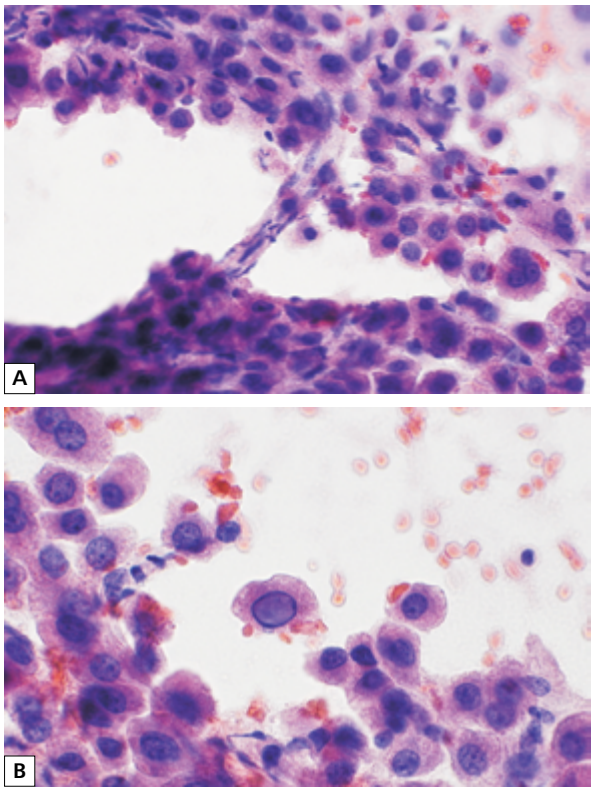

Figure 2. Hepatocellular carcinoma (HCC). **A**. The aspirate is hypercellular, and endothelial cells can be appreciated coursing through the aggregates of neoplastic hepatocytes, H&E 20×; **B**. The cluster of cells shows single cell with prominent intranuclear vacuole, H&E 40×

(2.3 ng/ml). CT scans demonstrated three intrahepatic lesions located in both lobes of 46 × 41 mm (4 segment), 49 × 49 mm (8/5 segment), and 8 mm (7 segment) (Fig. 1B), and enlarged lymph nodes located in the hilus and in the iliac trunk area, up to 23 mm.

Stabilisation of the disease was achieved and confirmed every 3–4, and thereafter every six months by repeating CT of the abdomen. In November 2012, the liver steatosis was described as a new finding on CT scans. Magnetic resonance images (MRI), performed in February 2013, presented significantly decreased signal in the liver, like in haemochromatosis, as well as cirrhosis features, and iron deposits in the pancreas. Estimated serum ferritin level was 3095 ng/ml, and serum iron was slightly elevated. Genotypic expression of the iron-overload disease was confirmed by real-time PCR — the patient was homozygous for the *HFE* gene mutation C282Y. The screening test for a HCV infection was negative, and the serum level of anti-HBs antibodies was normal. At that time, the patient's AFP serum level was 3.37 ng/mL. Continuing sorafenib therapy at the standard dose, the patient has undergone thirty-five phlebotomies until now, and dietary modification was advised. Ferritin level within a therapeutic target of 50–100 μg/L was achieved. The last MRI documenting stabilisation of the HCC disease was done in December 2016.

In November 2014 the patient was successfully treated due to a heart attack with balloon angioplasty on second obtuse marginal (OM 2) branch and drug-eluting stent implantation (DES) on the left anterior descending artery. He is being administered acetylsalicylic acid, clopidogrel, lercanidipine hydrochloride, carvedilol, nebivolol, and indapamide.

Hand-foot skin reaction (HFSR) (grade 2, resolved to grade 1) was the only adverse event he experienced during sorafenib therapy. He remains in good condition, and his ECOG performance status is 1. The liver function parameters continue to be mildly elevated (transaminases ALT and AST; CTC grade 1), and glucose and AFP levels are within the normal range.

Discussion

The case reported here presents HCC developed in the absence of cirrhosis, an event generally infrequent, also in haemochromatosis individuals. A meta-analysis that included nine studies (1102 HCC cases and 3766 controls), mainly from European populations, provides evidence that the *HFE* C282Y polymorphism confers increased genetic susceptibility to HCC but not to liver cirrhosis [7]. This analysis did not find an association of H63D mutation with HCC. The role of HFE C282Y as well as compound heterozygosity for C282Y/H63D in an increased HCC risk, but not liver cirrhosis, was confirmed recently in an updated systematic review and meta-analysis of 5758 cases and 14,741 controls [13]. Additionally, H63D polymorphism in developing non-cirrhotic HCC in the African population.

The relationship between iron and HCC is complex [14]. Iron can act as a modulating co-factor in a range of chronic liver diseases and can accelerate the development of liver injury, fibrosis, cirrhosis, and ultimately HCC. Pollicino et al. [15] reported a case of a 43-year-old man with HFE-haemochromatosis, seronegative for hepatitis B and C infections, who developed HCC in the absence of severe liver damage. An occult HBV infection was found based on the molecular analyses, performed on both tumoural and non-tumoural liver tissue specimens taken at the time of orthotopic liver transplantation due to HCC recurrence. The authors suggested that the combination of haemochromatosis and occult HBV infection might have led to a sequence of cellular events that determined the development of HCC even in the absence of cirrhosis.

HCC arising in non-cirrhotic liver in genetic haemochromatosis has already been a subject of case reports [2, 16]. Co-existence of HCC and haemochromatosis in a patient receiving sorafenib is a rare real-life condition,

with scarce clinical data. So et al. [17] reported a patient with a 25-year history of hereditary haemochromatosis, with cirrhosis and unresectable metastatic HCC, who had a rapid and clinical response during six months of sorafenib therapy, and this effect was maintained for six months after therapy discontinuation. His serum AFP level was found to be 13.599 ng/mL. This patient tolerated the therapy well, except for the onset of grade 1 diarrhoea, which was well controlled without dose reduction. Our patient is the second reported case treated with sorafenib due to HCC coexisting with haemochromatosis.

The question arises whether a test for haemochromatosis should be incorporated into the initial work-up in our patients. Universal screening for haemochromatosis is not recommended [18]. On the other hand, the majority of patients with haemochromatosis, without timely appropriate treatment, develop hepatic fibrosis and cirrhosis due to hepatic iron accumulation. Thus, in the case of haemochromatosis it is recommended that ultrasound surveillance are conducted at intervals of 3–6 months [19–21]. In this case, advanced serum ferritin level assessment and prior diagnosis of haemochromatosis would provide earlier introduction of treatment, and consequently might reduce the risk of damage of the liver and other organs. Serum ferritin measurement, as was used in our patient, is the most useful parameter in the diagnosis and monitoring of iron loading disease. There are, however, several clinical conditions that are associated with high ferritin, including inflammation, cell necrosis, neoplasms, and alcohol consumption [5]. Among other serum iron parameters, namely low (or normal) total iron-binding capacity (TIBC) or as an alternative to TIBC unsaturated iron binding capacity (UTIBC) and high serum iron, elevated transferrin saturation index (TSI) along with hyperferritinaemia are the principal biochemical findings in haemochromatosis [5]. Of note, in this patient the serum AFP level continues to be within normal range.

Hepatic resection, liver transplantation, and ablative therapies, including open and percutaneous radiofrequency (RFA) and PEI, are, according to the guidelines, the first-line treatment options for HCC [19, 22]. Ablation methods are recommended in cases of unresectable early HCC. The preferred method of local treatment in this group of patients is RFA or, less popular in clinical practice, PEI, which was used in our advanced HCC case. Patients with intermediate and advanced HCC undergo different TACE (transarterial chemoembolisation) modalities, such as selective TACE or drug-eluting beads (DB-TACE), or systemic therapy. Recently, transarterial radioembolisation (TARE) using microspheres of Yttrium-90 is being introduced. Moreover, recent approaches combine TACE with RFA or TACE with sorafenib [19, 23]. The role of radiotherapy in HCC needs further evaluation [24].

Disease stabilisation, as achieved in our patient, is typical with sorafenib therapy for HCC. Except for the above case of the patient described by So et al., the phenomenon of complete response of HCC following sorafenib therapy has been reported by others [25]. Further advances in the identification of biomarkers predicting prognosis of HCC and response to sorafenib or other treatments for this condition may facilitate more personalised treatment in such oncological patients [26, 27].

The toxicity profile of sorafenib therapy is generally mild and manageable. The most common adverse effects of sorafenib are diarrhoea, fatigue, weight loss, and HFSR or palmar-planar erythrodysesthesia syndrome. However, serious toxicities, mostly diarrhoea and HFSR, led to discontinuation of sorafenib treatment in 11% of patients entered into randomised trials [11, 12]. In the presented case of HCC associated with haemochromatosis with evidence of active liver disease, no worsening of liver function was observed, and a full standard dose of sorafenib could be maintained for six years of the therapy.

In conclusion, HCC coexisting with haemochromatosis in a patient without cirrhosis is rare. Sorafenib is an effective and well-tolerated long-term therapy in HCC patients with associated haemochromatosis. This iron-overload disease should be kept in mind in patients who develop HCC.

References

1. Dongiovanni P, Romeo S, Valenti L. Hepatocellular carcinoma in nonalcoholic fatty liver: Role of environmental and genetic factors. World J Gastroenterol 2014; 20: 12945–12955. doi: 10.3748/wjg.v20.i36.12945.
2. Greene CM, Varley RB, Lawless MW. MicroRNAs and liver cancer associated with iron overload: therapeutic targets unraveled. World J Gastroenterol 2013; 19: 5212–5226. doi: 10.3748/wjg.v19.i32.5212.
3. Zheng N, Wei W, Wang Z. Emerging roles of FGF signaling in hepatocellular carcinoma. Transl Cancer Res 2016; 5: 1–6. doi:10.3978/j.issn.2218-676X.2016.01.05.
4. Geramizadeh B, Ghazanfari Y, Nikeghbalian S, Malekhosseini S-A. A single center study comparing the stainable iron depositions in 1000 explanted cirrhotic livers of different causes. Hepat Mon 2015; 15: e33710 doi: 10.5812/hepatmon.33710.
5. Zoller H, Henninger B. Pathogenesis, diagnosis and treatment of hemochromatosis. Dig Dis 2016; 34: 364–373.
6. Barton JC, Chen W, Emond MJ et al. *GNPAT* p.D519G is independently associated with markedly increased iron stores in *HFE* p.C282Y homozygotes. Blood Cells Mol Dis 2017; 63: 15–20.
7. Jin F, Qu L-S, Shen X-Z. Association between C282Y and H63D mutations of the HFE gene with hapatocellular carcinoma in European populations: a meta-analysis. J Exp Clin Cancer Res 2010; 29: 18.
8. Kono S. Aceruloplasminemia. Curr Drug Targets 2012; 13: 1190–1199.
9. Musci G, Polticelli F, Bonaccorsi di Patti MC. Ceruloplasmin-ferroportin system of iron traffic in vertebrates. World J Biol Chem 2014; 5: 204–215.
10. Cauza E, Peck-Radosavljevic M, Ulrich-Pur H et al. Mutations of the HFE gene in patients with hepatocellular carcinoma. AM J Gastroenterol 2003; 98: 442–447.
11. Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma a phase III randomized, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25–34. doi: 10.1016/S1470-2045(08)70285-7.

12. Llovet JM, Ricci S, Mazzaferro V et al. SHARP investigators study group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378–390. doi: 10.1056/NEJMMoa0708857.
13. Ye Q, Qian B-X, Yin W-L, Wang F-M, Han T. Association between the HFE C282Y, H63D polymorphisms and the risk of non-alcoholic fatty liver disease, liver cirrhosis and hepatocellular carcinoma: an updated systematic review and meta-analysis of 5,758 cases and 14,741 controls. PLoS One 2016; 11: e0163423.
14. Tirnitz-Parker JE, Glanfield A, Olynyk JK, Ramm GA. Iron and hepatic carcinogenesis. Crit Rev Oncol 2013; 18: 391–407.
15. Pollicino T, Vegetti A, Saitta C et al. Hepatitis B virus DNA integration in tumour tissue of a non-cirrhotic HFE-haemochromatosis patient with hepatocellular carcinoma. J Hepatol 2013; 58: 190–193. doi: 10.1016/j.jhep.2012.09.005.
16. Britto MR, Thomas LA, Balaratnam N, Griffiths AP, Duane PD. Hepatocellular carcinoma arising in non-cirrotic liver in genetic haemochromatosis. Scand J Gastroenterol 2000; 35: 889–893.
17. So BJ, Bekaii-Saab T, Blooston MA, Patel T. Complete clinical response of metastatic hepatocellular carcinoma to sorafenib in a patient with hemochromatosis: A case report. J Hematol Oncol 2008; 1: 18–20. doi:10.1186/1756-8722-1-18.
18. Crownover BK, Covey CJ. Hereditary hemochromatosis. AM Fam Physician 2013; 87: 183–190.
19. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908–943.
20. van Meer S, de Man RA, Siersema PD, van Erpecum KJ. Surveillance for hepatocellular carcinoma in chronic liver disease: evidence and controversies. World J gastroenterol 2013; 19: 6744–6756.
21. Vanclooster A, Wollersheim H, Vanhaecht K et al. and on behalf of the Haemochromatosis working group. Key-interventions derived from three evidence based guidelines for management and follow-up of patients with HFE haemochromatosis. BMC Health Serv Res 2016;16: 573.
22. Villanueva A, Scientist R, Newell P et al. Inherited hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 2010; 24: 725–734.
23. Wang G, Liu Y, Zhou Sh et al. Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. Hepatol Int 2016; 10: 501–510.
24. Park HC, Yu JI, Cheng JC et al. Consensus for radiotherapy in hepatocellular carcinoma from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014): current practice and future clinical trials. Liver Cancer 2016; 5:162–174.
25. Katafuchi E, Takami Y, Wada Y et al. Long-term maintenance of complete response after sorafenib treatment for multiple lung metastases from hepatocellular carcinoma. Case Rep Gastroenterol 2015; 9: 285–290. doi: 10.1159/000438746.
26. Lee YS, Kim BH, Kim BC et al. SLC15A2 genomic variation is associated with the extraordinary response of sorafenib treatment: whole-genome analysis in patients with hepatocellular carcinoma. Oncotarget 2015; 6: 16449–16460. doi: 10.18632/oncotarget.3758.
27. Shin JW, Chung Y-H. Molecular targeted therapy for hepatocellular carcinoma: current and future. World J Gastroenterol 2013; 19: 6144–6155. doi: 10.3748/wjg.v19.i37.6144.