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CASE REPORT

A Rare Case of Metastatic Pancreatic Hepatoid Carcinoma Treated with Sorafenib

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Abstract
Background Hepatoid carcinoma (HC) is a rare histopathological tumor type with prominent features of hepatoid differentiation, and while most of the reported cases are of gastric origin, ten cases of pancreatic HC have been reported to date. The majority of HC cases are metastatic at presentation, mainly to the liver, lymph nodes, and lungs. They are aggressive, invading, and proliferating in the venous and lymphatic systems, with a behavior similar to that of hepatocellular carcinoma. Diagnosis is challenging: alpha-Fetoprotein, the most useful marker, is not always positive.

Methods We present the first case of metastatic pancreatic HC treated with sorafenib, an oral multikinase inhibitor approved for advanced hepatocellular carcinoma that has antiangiogenic, pro-apoptotic, and raf-kinase inhibitory properties.
Results The patient, a 37-year-old male, was diagnosed with hepatoid carcinoma of the pancreas that had metastasized to liver, lungs, and lymph nodes. The cytokeratin (CK) profile was useful for the diagnosis: Both the hepatoid and adenocarcinoma components of the tumors were CK18+, CK19+, and CK20+/−, whereas normal and neoplastic hepatocytes are CK18+, CK19−, and CK20−. Amylase, lipase, and liver enzyme levels were elevated, but bilirubin was normal. Treatment with sorafenib resulted in more than 7 months of progression-free survival. Therapy was discontinued after 8 months when his bilirubin level increased dramatically. Signs of liver failure resolved temporarily with insertion of a biliary stent, but his condition deteriorated and he died 3 months later, 1 year after diagnosis.
Conclusion In the absence of evidence-based experience with this rare and aggressive tumor and given its similarities with hepatocellular carcinoma, sorafenib should be considered as a possible treatment.

Keywords Pancreatic hepatoid carcinoma · Sorafenib · Liver metastasis · Antiangiogenic therapy

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Introduction

Hepatoid carcinoma (HC) is a rare tumor with prominent features of hepatic differentiation, often mixed with areas that are more characteristic of tumors of the underlying primary site [1]. Its occurrence has been reported in as many as 15 different sites; however, the total number of cases is very small. At this writing, only a dozen pancreatic

HC cases have been reported [2–11]. Tumor cells can show one of several histological patterns (trabecular, medullary, and glandular) and varying degrees of differentiation, ranging from well-differentiated with a morphology typical of hepatocytes to less differentiated and irregular forms. They are known to occur most frequently in the stomach, and while the limited number of pancreatic HC cases in the literature precludes defining a prognosis, HCs of the gastrointestinal tract in general have an unfavorable course. The majority have already metastasized at discovery, most frequently to the liver, lymph nodes, and lung. Their aggressiveness derives from a propensity to proliferate in lymphatic and venous vessels that mimics the behavior of hepatocellular carcinoma (HCC) [12].

No unified standard for the diagnosis of pancreatic HC exists. alpha-Fetoprotein (AFP) is the most useful marker, but it is not always positive and it is important to note that AFP may also be expressed in pancreatic ductal carcinoma, acinar cell carcinoma, islet cell tumors, and poorly differentiated pancreatic adenocarcinoma, not otherwise specified. For this reason, the diagnosis is based principally on the histological appearance of hematoxylin and eosin stained material, especially when the primary tumor is known.

Sorafenib is a multikinase inhibitor that exerts pro-apoptotic and growth inhibitory effects by acting on targets localized in tumor cells (c-RAF, BRAF, V600E BRAF, c-KIT, and FLT-3) and antiangiogenic effects by acting on the tumor vasculature (c-RAF, VEGFR-2, VEGFR-3, and PDGFR-β). It is approved for use in advanced renal cell carcinoma and HCC [13].

Case Report

This case concerns a 37-year-old male former smoker brought to medical attention for an epigastric abdominal mass in May 2008. The patient was admitted to general surgery and underwent a whole-body CT scan. The abdominal/thoracic CT scan revealed the presence of an 11-cm-long solid lesion at the body of the pancreas (Fig. 1a), celiac and periaortic lymph node lesions (6.5 and 8.9 cm), and a liver almost completely

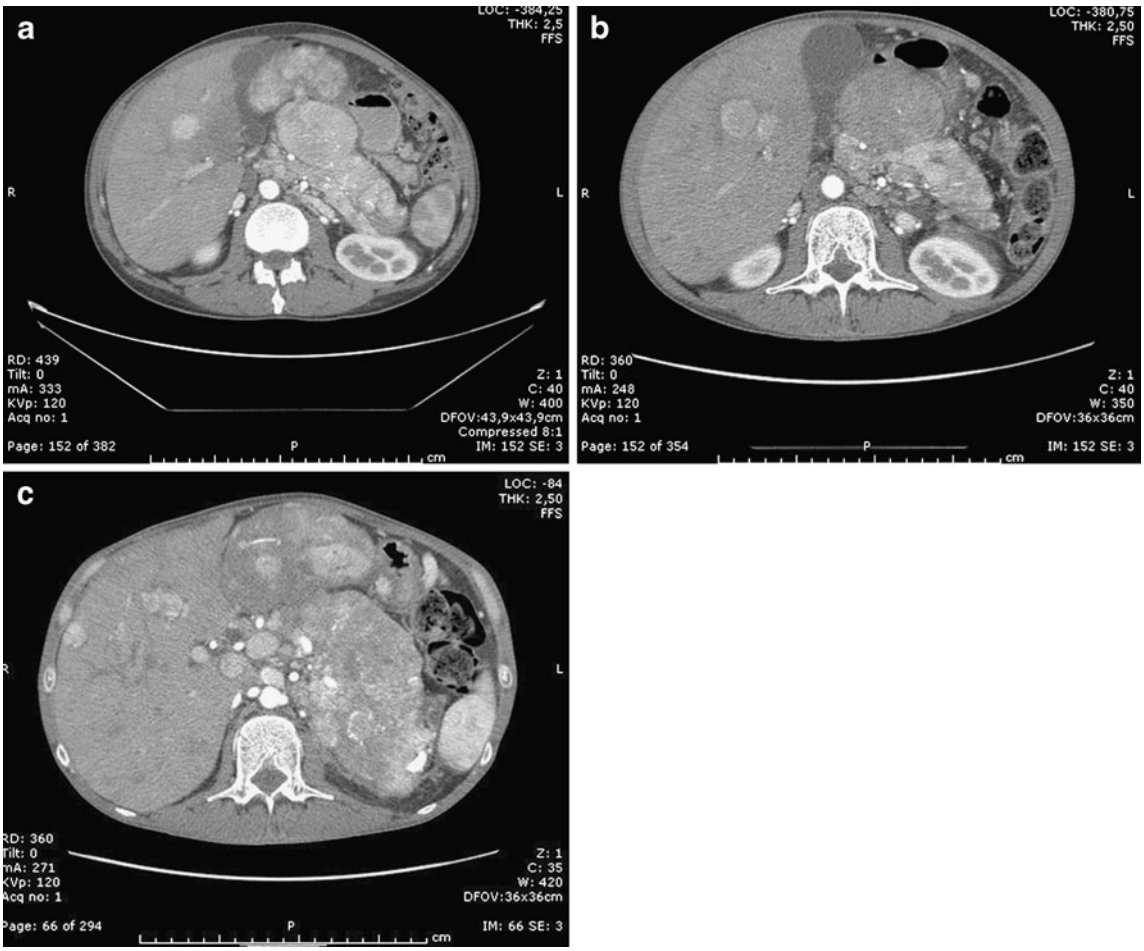

Fig. 1 Abdominal CT scans of the 11-cm-long solid lesion in the pancreas, taken **a** before treatment; **b** after 3 months on sorafenib therapy, revealing a reduction of arterial enhancement; and **c** after 6 months on therapy, showing a slight reappearance of arterial enhancement

replaced by numerous lesions, the largest of which measured 14 cm (Fig. 2a). The liver lesions showed characteristic hypervascularity (strong arterial enhancement and late portal washout) associated with a hypodense peripheral halo. Several bilateral nodules and mediastinal adenopathies were found in the lungs. The blood tests showed elevated transminases (ALT 463 U/l), alkaline phosphatase (313 U/l), gamma-GT (226 U/l), and elevated amylase and lipase, while bilirubin levels were normal. Levels of carcinoembryonic antigen (CEA) and CA 19.9 were normal, while alpha-fetoprotein was nearly so at 11 mcg/l (the ULN being 10 mcg/l). A slight increase in prothrombin time ratio and decrease in albumin were recorded. Markers for hepatitis B and C and HIV serology were negative. The Child–Pugh class was A. Moderate abdominal pain was managed with low-dose opioid. A percutaneous liver biopsy was performed under ultrasound guidance. Histopathological analysis revealed "malignant epitheliomorphic neoplasm compatible with HC" (Fig. 3). Immunohistochemistry was positive for pan-cytokeratin (CK), CK7 (Fig. 4), CK18 (Fig. 5), OCH1E5 (Fig. 6) and negative for CK20, low molecular weight CK, chromogranin (Fig. 7), synaptophysin, and polyclonal CEA. The pathology slides for this case were also reviewed at the reference center for hepatobiliary surgery at the National Cancer Institute in Milan, Italy, to confirm the diagnosis.

In July of 2008, considering disease spread, the overall conditions and onset of liver failure (mild ascites, hypoalbuminemia, and increase in total bilirubin by 1.59 mg/dl), we discussed the possibility of starting treatment. The patient refused classical chemotherapy but agreed to therapy with sorafenib, approved in Italy for treatment of advanced-stage HCC in patients with Child–Pugh class A. The literature contains no data regarding the activity of systemic agents in this rare disease. A dosage of 400 mg was administered b.i.d. Albumin and diuretics (potassium canrenoate, Union Health Srl, Rome) were administered intravenously.

In October of 2008, CT revealed stable disease with reduction in the intensity of arterial phase enhancement in lesions in the pancreas (Fig. 1b) and liver (Fig. 2b) and a

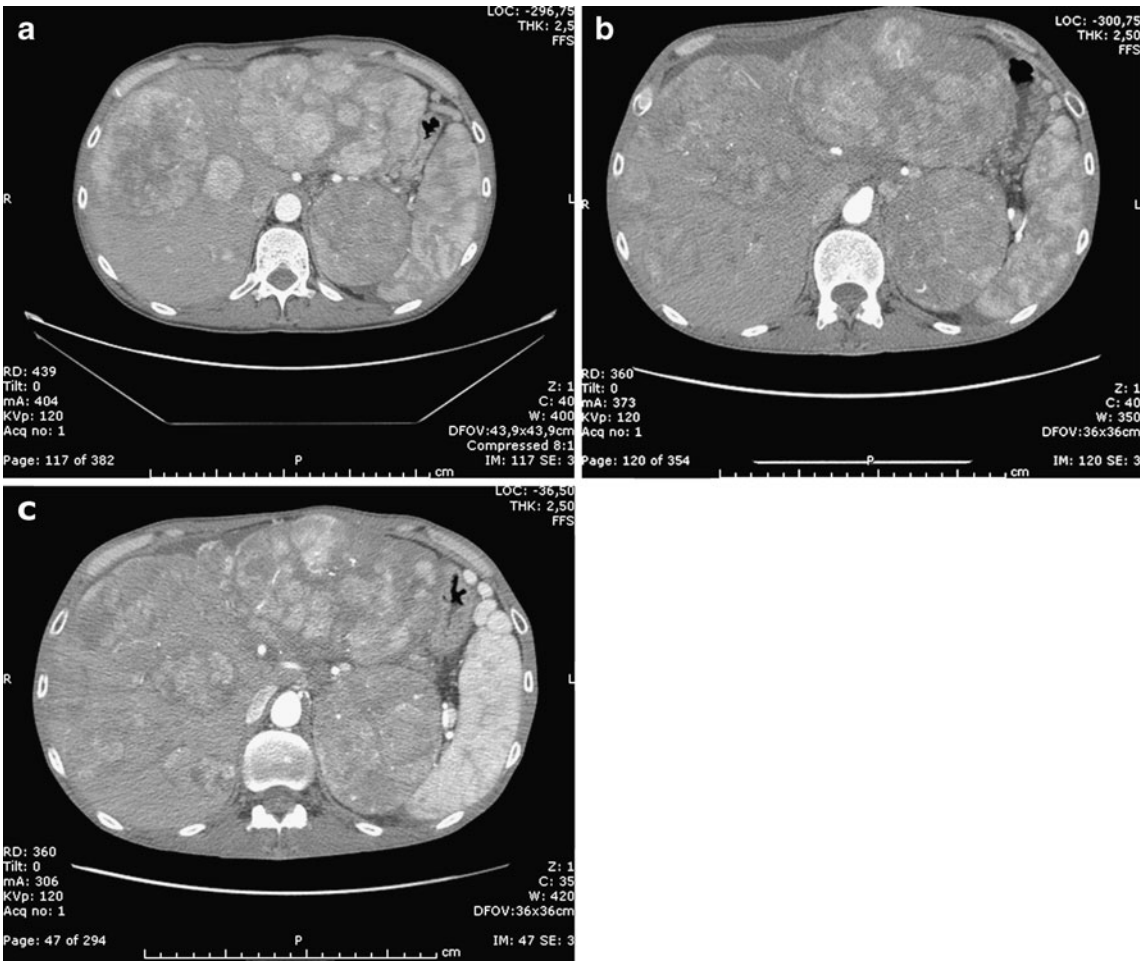

Fig. 2 Abdominal CT scans of the numerous lesions in the liver, the largest of which are 14 cm. **a** Before treatment; **b** after 3 months on sorafenib therapy, revealing a reduction of arterial enhancement; and **c** after 6 months on therapy, showing a slight reappearance of arterial enhancement

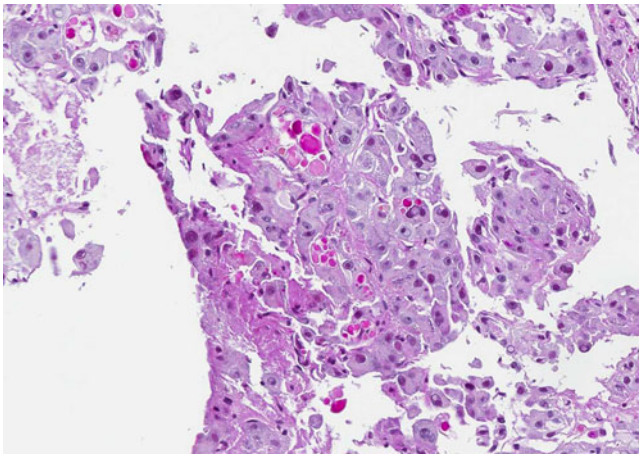

Fig. 3 Hematoxylin and eosin staining (×20)

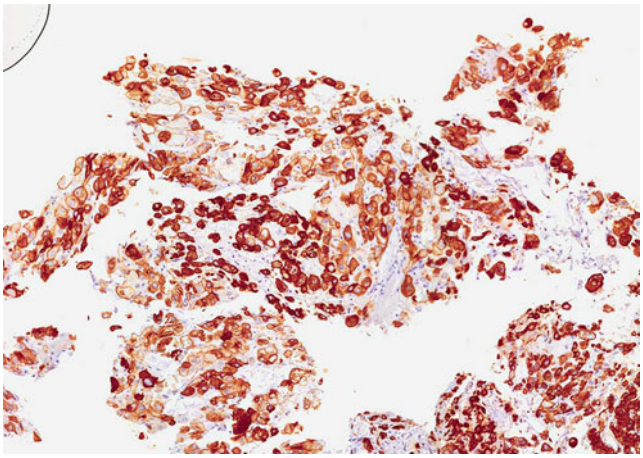

Fig. 5 CK 18 staining (×10)

slight increase in ascites. Abdominal pain was managed with 40 mg of oxycodone daily (Oxycontin, Mundipharma Pharmaceuticals S.r.l., Milan, Italy), his weight had remained constant, and therefore therapy was continued. Total bilirubin increased to 3.68 mg/dl in August but decreased to 0.7 mg/dl in January 2009. Sorafenib was well tolerated, with grade 2 hand and foot syndrome being the only toxicity.

A CT scan in January of 2009 confirmed stable disease but revealed a slight increase in arterial phase enhancement (Figs. 1c and 2c). On February 26th, we decided to stop the treatment when total bilirubin had reached 5.77 mg/dl. On March 13th, a metallic biliary stent was deployed endoscopically. Bilirubin levels decreased to 1.8 mg/dl by April 2nd, but after a few weeks, the total bilirubin level increased progressively up to 17.23 mg/dl and stabilized near 10 mg/dl in May 2009. Blood ammonia levels increased, provoking hepatic encephalopathy, and the patient died at home on June 10th, 1 year after diagnosis (Figs. 8 and 9).

Discussion

Hepatoid carcinomas should be distinguished from metastatic liver cancer so that appropriate therapy can be selected; however, they are often difficult to identify based on histomorphological characteristics alone. HC and HCC share numerous clinicopathological features, such as hepatoid morphology, high serum AFP levels and AFP-positive staining in histology, polyclonal CEA (canalicular pattern), and alpha-1 antitrypsin [14–19]. Thus, HC may closely resemble or even be indistinguishable from HCC, making differential diagnosis challenging, especially when the primary tumor is unknown and the diagnosis must be established from a liver biopsy. Although there is no universal marker capable of differentiating between the two by immunohistochemistry, we found the profile of CK expression to be helpful. In our case, both the hepatoid and adenocarcinomatous tumor components were CK18+, CK19+, and CK20+/−, whereas normal and neoplastic hepatocytes are known to be CK18+, CK19−, and CK20− [6, 14, 15, 20].

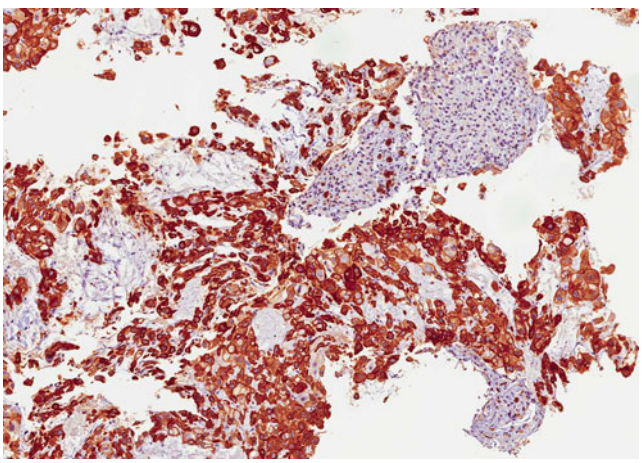

Fig. 4 CK 7 staining (×10)

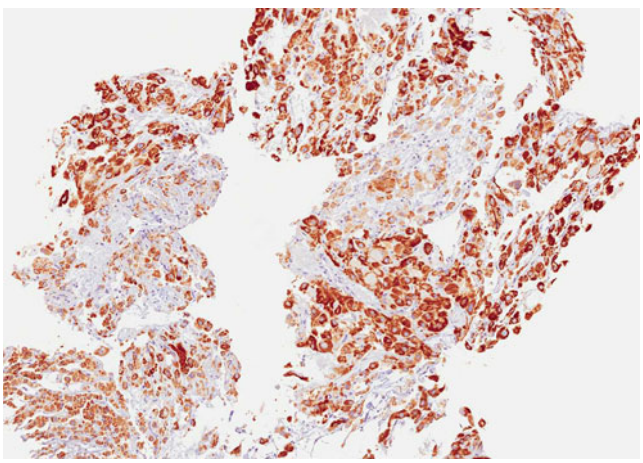

Fig. 6 OCH1E5 staining (×10)

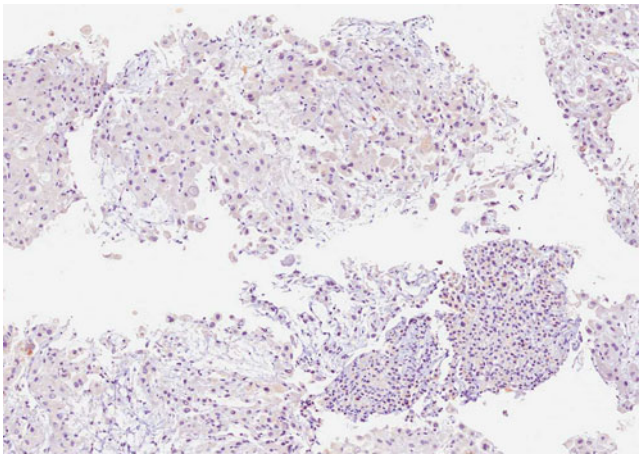

Fig. 7 Chromogranin staining (×10)

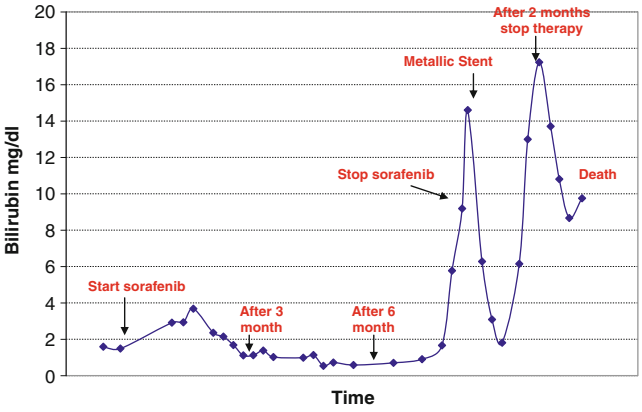

Fig. 9 Values of total bilirubin at beginning, during, and after treatment with sorafenib

Although this case was defined by pathologists as HC, it has some features that are not consistent with hepatoid pancreatic tumors described in the literature. The tumor was positive for OCH1E5 (HepPar1), which is often negative in HC and positive in HCC. Most, but not all, cases have been associated with high serum AFP levels. Clinically, the neoplasm is characterized by a predilection for older patients, a very aggressive course, and poor survival (several months) when metastatic [8] (case 2) [9, 10], rather than when localized [2–8] (case 1). Our patient was young and appeared to have a slower disease course, in spite of extensive metastases to the liver and early involvement in lymph nodes. However, his age and especially the absence of risk factors would also make HCC less likely. Metastases to the pancreas occur in less than 5% of HCC cases [21].

Regarding possible origins of pancreatic HCs, the liver, endocrine-, and exocrine pancreas all develop from a common foregut endoderm; it may be that liver-specific genes are de-repressed in the pancreas during carcinogenesis, resulting in a partial hepatic phenotype that manifests as hepatoid carcinoma. Alternatively, the existence of a common progenitor cell for both the pancreas and the liver is suggested by the anatomy and development of the pancreatic and hepatic buds during embryogenesis and a large body of evidence supports the idea that transformation of pancreas cells into liver cells and vice versa may occur in adult life [9, 22–28]. Some pancreatic adenocarcinomas present the focal hepatoid differentiation cited above. Whether pancreatic HCs originate from a common progenitor cell of the pancreas and liver remains to be confirmed.

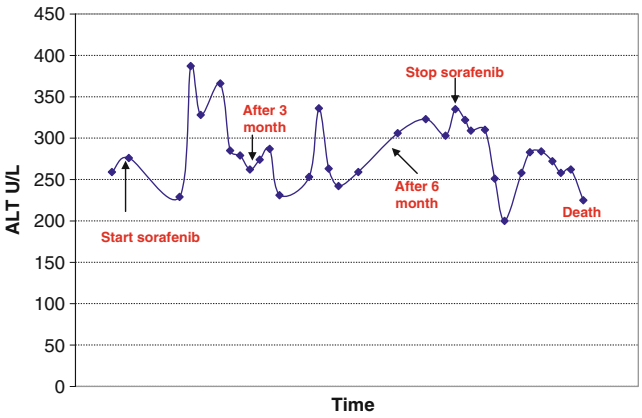

Fig. 8 Values of ALT at beginning, during, and after treatment with sorafenib

Chemotherapeutic agents have limited effectiveness against tumors of the pancreas or liver. Patients with pancreatic cancer may occasionally experience diminished symptoms on therapy with classical drugs like fluorouracil. Gemcitabine has demonstrated activity in patients with pancreatic cancer that make it a useful palliative agent [29] and the standard of care for advanced disease; however, it should be used with caution in patients with hepatic insufficiency. Unfortunately, HCC is only minimally responsive to systemic chemotherapy. Doxorubicin-based regimens appear to have the greatest efficacy, with response rates of 20% to 30%, but no impact on overall survival. No standard therapy has been established for treating hepatoid tumors. Our patient experienced prolonged clinical benefit with an overall survival of 1 year, comparable to the median survival achieved in the registration study of sorafenib for HCC (10.7 months) [30].

In conclusion, we report the first case of metastatic HC (of probable pancreatic origin) in an otherwise healthy young man treated with the multi-target tyrosine kinase inhibitor sorafenib. The decision to treat was based on uncertainty regarding the diagnosis and the activity of sorafenib in HCC, lack of guidelines and an effective standard of treatment in advanced disease, and the patient's class A liver function and desire to undergo this type of treatment. Treatment at 400 mg b.i.d. provided disease control for 8 months, which was confirmed by imaging and

biochemical data. Sorafenib is indicated for treatment of HCC, and considering the similarities between HCC and HC, this drug could be considered as first-line therapy in advanced-stage hepatoid tumors not amenable to local therapy.

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