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CASE REPORT

Sorafenib-Induced Acute Pancreatitis: Case Report and Review of the Literature

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the third leading cause of cancer-related death worldwide [1]. The reported annual incidence of HCC is rising in most countries, mostly due to the increasing burden of chronic hepatitis B and hepatitis C virus (HCV), along with the prevalence of other risk factors such as excessive alcohol consumption. Although new HCV therapies have proven effective, they are often expensive and not always universally accessible. Additionally, the increased incidence of non-alcoholic fatty liver disease secondary to obesity and diabetes contribute to new cases of HCC, especially in developed countries such as the USA [2–4].

The Barcelona Clinic Liver Cancer (BCLC) Classification is the gold-standard guideline for managing patients with HCC [5]. Early stages of HCC can be successfully managed with different treatment modalities, including hepatic resection, liver transplantation, and ablative therapies. Intermediate stages can be treated with chemoembolization. Advanced HCC carries a poor prognosis with a mean survival time of 4–6 months. Given that liver metabolism is not altered in patients with Child-Pugh stage A and B liver disease, sorafenib was introduced as a feasible therapeutic option for advanced stage HCC patients deemed ineligible for curative treatment [6].

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Since its US Food and Drug Administration (FDA) approval in December 2005, sorafenib has been used for the treatment of metastatic renal cell carcinoma (RCC) and HCC [7]. Sorafenib is an inhibitor of multiple classes of receptor tyrosine kinases including platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR)-2 [8]. These pathways play central roles in cell proliferation and apoptosis, vasculogenesis, and metastasis [9]. By inhibiting these receptor pathways, sorafenib aims to slow tumor growth and delay disease progression. Sorafenib therapy has been shown to slow disease progression by an average of 4.2 months and prolong survival by a mean of 3 months longer than placebo [10].

Most trials on sorafenib have shown a favorable safety profile. The most commonly reported side effects of sorafenib treatment include diarrhea (30%), dermatologic toxicity (rash, hand-foot skin reaction in 30% of patients), hypertension (15%), and hyperlipasemia/hyperamylasemia (30–40% average incidence rate) [11, 12]. Acute pancreatitis is a rare side effect of sorafenib with an incidence rate of <1% and has occurred most commonly in patients being treated for metastatic renal cell carcinoma (Table 1). Most side effects are reported to occur within 3 weeks of initiating treatment [18].

We present the case of a 53-year-old man with HCC who had been taking sorafenib 200 mg twice daily for 3 weeks, but stopped therapy after suffering from a lower extremity rash. Three days after stopping therapy, he suffered from acute pancreatitis. This is the first reported case of a patient suffering from acute pancreatitis secondary to sorafenib treatment that occurred after the patient had already stopped therapy.

Due to the increased frequency of sorafenib use among patients with unresectable hepatocellular carcinoma, our purpose was to analyze the literature for reported cases of sorafenib-induced pancreatitis. The goal of our literature review was to determine how many cases have been reported,

Table 1 Previous case reports of sorafenib-induced pancreatitis in comparison to our case report

Reference (oldest ➔ newest)	Age (years)/ gender	Malignancy	Treatment	Duration of treatment prior to development of pancreatitis	Amylase/ lipase level (U/L)	Duration until resolution of pancreatitis
Amar [13]	53/F	Metastatic RCC	Sorafenib 400 mg BID	3 weeks	1361/99	2 weeks Therapy discontinued
Li [2]	80/M	Metastatic RCC	Sorafenib 400 mg BID	4 weeks	156/>200	9 days Therapy restarted with recurrence at 6 months, then discontinued
Saadati [7]	53/M	HCC	Sorafenib unknown dose	4 weeks	118/484	Not specified Therapy discontinued
Koboyashi [14]	71/M	Metastatic RCC	Sorafenib 400 mg BID	2 weeks	973/2733	3 weeks Therapy discontinued
Sevin [15]	69/F	Metastatic RCC	Sorafenib 400 mg BID	10 days	244/1014	5 days Started sunitinib 6 weeks later
Olayode [16]	68/M	Metastatic RCC	Sorafenib 200 mg BID	11 days	148/805	2 days Restarted, remained asymptomatic at 10 weeks
Wang [17]	76/F	HCC	Sorafenib 400 mg QD	6 weeks	124/>3000	5 days Restarted, remained asymptomatic at 6 weeks
Chou [12]	56/M	HCC	Sorafenib 200 mg QD	6 days	1388/3685	7 days Therapy discontinued
Our case	53/M	HCC	Sorafenib 200 mg BID	3 weeks	148/4379	5 days Therapy discontinued

RCC renal cell carcinoma, *HCC* hepatocellular carcinoma

the average age of reported cases, the sorafenib doses of patient's suffering from pancreatitis, the time lag between starting treatment and becoming symptomatic, and the time until resolution of symptoms.

Case Report

A 53-year-old Caucasian male presented to the emergency department because of a 2-day history of abdominal pain and jaundice. His past medical history included HCC, decompensated liver cirrhosis secondary to hepatitis C and chronic alcoholism, gastroesophageal reflux disease, and type 2 diabetes mellitus. He was diagnosed with hepatitis C 17 years ago, but was not started on antiviral therapy until 1 year ago because the patient was lost to follow-up. However, even once he completed treatment with pegylated interferon alpha and ribavirin, he was deemed treatment unresponsive because his HCV RNA levels remained elevated. HCC with main portal vein invasion was diagnosed 3 months prior to the current admission using abdominal computed tomography (CT)-guided liver biopsy.

According to the BCLC staging system (Fig. 1), a diagnosis of advanced stage HCC with Child-Pugh class B symptoms [no encephalopathy, mild to moderate ascites, alanine aminotransferase (ALT) 26, aspartate aminotransferase (AST) 45, total bilirubin 1.9, albumin 2.4, prothrombin time (PT) 12.3, amylase 50, lipase 240] was made. He started receiving palliative treatment with oral sorafenib at 200 mg twice daily.

Three weeks after starting sorafenib, he developed a lower extremity rash and stopped taking the medication as instructed

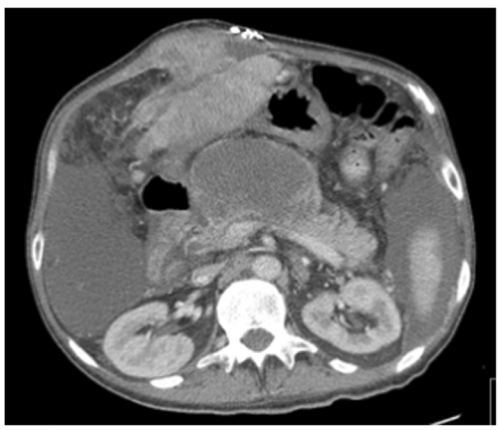

Fig. 1 Abdominal computed tomography with oral and intravenous contrast, axial view, showing no evidence of pancreatic tumors or calcifications, ductal dilation, and no gallstones in the common bile or pancreatic ducts

by his oncologist. Three days after stopping the medication, he developed acute epigastric pain and jaundice that triggered his presentation to the emergency department.

On admission, he reported a 1-day history of abdominal pain in the epigastric region that radiated to the back, dull, intensity 8/10 exacerbated by eating but no alleviating factors. He endorsed 1 day of nausea and increased jaundice. He had no recent history of alcohol or illicit drug use and had not received steroids recently. He had a cholecystectomy for symptomatic cholelithiasis decades prior.

Physical examination showed a cachectic male with skin jaundice and scleral icterus. He had palpable tenderness in the epigastric region, without rebound. There was dullness to percussion in the lower abdominal quadrants. The remainder of the physical exam was unremarkable, including vital signs and other peripheral stigmata of liver cirrhosis. Laboratory tests showed the following: white blood cell count 13,100 U/L, glucose 125 mg/dL, lactate dehydrogenase (LDH) 300 mg/dL, serum total bilirubin 5.3 mg/dL (normal, 0.2–1.3 mg/dL), ALT 17 U/L (normal, <40 U/L), AST 62 U/L (normal, <35 U/L), PT 19.1 s (normal, 9.5–11.7 s), blood urea nitrogen (BUN) 27 mg/dL (normal 6–20 mg/dL), creatinine 1.0 mg/dL (normal 0.6–1.2 mg/dL), albumin 1.5 g/dL (normal, 3.7–5.3 g/dL), amylase 148 U/L (normal, 28–100 U/L), and lipase 4379 U/L (normal, 8–58 U/L). The results of other laboratory tests and chest x-ray were unremarkable. On the basis of clinical symptoms and elevated lipase level, a diagnosis of acute pancreatitis was made.

After admission, abdominal CT with oral and intravenous contrast showed no evidence of pancreatic tumors or calcifications, ductal dilation, and no gallstones in the common bile or pancreatic ducts (Fig. 1). There was mild to moderate ascites and peripancreatic edema. The patient's Ranson criteria and BISAP scores were zero, suggesting a mild case of pancreatitis with a <1% risk of mortality from pancreatitis, despite his comorbidities. Given his high surgical risk, prior cholecystectomy, and lack of common bile duct stones on abdominal imaging, ERCP was not performed.

We reviewed his medication history to rule out other potential causes of his acute pancreatitis. He had taken spironolactone, furosemide, and lactulose to control his liver disease, gabapentin for pain-control from his HCC, and omeprazole for gastroesophageal reflux disease, as well as insulin for managing his type 2 diabetes mellitus. Among these drugs, spironolactone has been reported to cause nausea, vomiting, and abdominal pain without causing pancreatitis. This was unlikely given the acute elevation in amylase and lipase seen in our patient. Furosemide can cause pancreatitis, but our patient had been taking a low dose (20 mg once daily) for over 6 months, making it a less likely culprit. Omeprazole can rarely cause pancreatitis, but our patient had been taking a low dose (40 mg once daily) for several years.

Therefore, sorafenib was highly suspected to have caused our patient's acute pancreatitis. Due to his adverse reactions to sorafenib, including lower extremity rash and acute pancreatitis, along with radiologic and clinical evidence of disease progression to stage D, Child-Pugh C, sorafenib therapy was discontinued indefinitely and he was referred to hospice. By the end of his 5-day admission, the patient's symptoms had mostly resolved and his lipase level trended back down to a level of 475 mg/dL. One month post-discharge, the patient's performance status has stabilized (ECOG 3) [19], and he is continuing to receive supportive medical management.

Method

The databases Medline/Pubmed, Web of Science, Scopus, ProQuest, Science Direct, and Springer were searched using the terms "sorafenib" and "pancreatitis," both as basic and MeSH terms. The authors assessed titles and abstracts for reports of sorafenib-induced pancreatitis in the following: (1) published in English, (2) full text available, (3) human subjects, (4) case reports, and (5) patients only receiving sorafenib chemotherapy. Full text articles were obtained; pertinent information was extracted and organized in tabular form (Table 1). Articles that did not meet these criteria were excluded. Figure 2 provides an outline of the methodology used to retrieve articles for this review. Since all studies included in this review are case reports, the quality of the studies was not assessed further using other criteria such as the Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

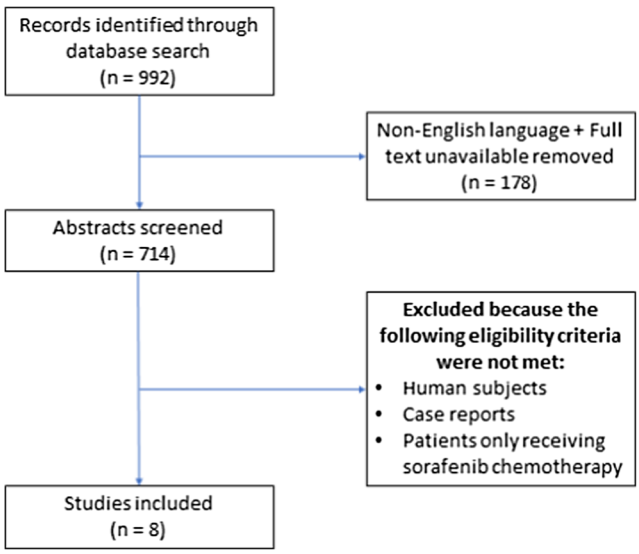

Fig. 2 Flow diagram for article screening and selection

Results

As outlined in Fig. 2, nine reports were included in this review—eight previous case reports as well as our case report. These nine cases are summarized in Table 1. Six of the nine cases presented were men, and three were seen in women. The age of patients affected ranged from 53 to 80 years old (mean age 64.3 years). Five patients had received sorafenib for metastatic RCC and four had received it for HCC. The duration of sorafenib treatment prior to the onset of acute pancreatitis ranged from 6 days to 6 weeks, with an average onset of 20.1 days. The average duration of treatment until patients suffer symptoms of acute pancreatitis is 3 weeks. There does not appear to be a relationship between the type of cancer (metastatic RCC vs. HCC) and pancreatic enzyme level. Similarly, there does not seem to be a relationship between the sorafenib dose and the pancreatic enzyme level.

Discussion

Each of the sorafenib-induced pancreatitis cases reported to date (Table 1) has had a relatively benign course, with symptoms resolving anywhere from 2 days to 3 weeks, with an average recovery of 7.6 days. The sorafenib dose and duration of therapy did not always correlate to the time to symptomatic resolution. However, patients eligible to receive these medications are often immunocompromised and with poor baseline performance status. Given the already high risk of infection and complications in hospitalized patients, close monitoring and prevention of such episodes is crucial in improving quality of life in these patients. Approximately 55% of patients may be able to reinitiate therapy after controlling for adverse events, but most reports agree that if a second event occurs or disease progresses to Child-Pugh C or BCLC stage D, treatment cessation is recommended.

All previous case reports of sorafenib-induced pancreatitis have occurred in patients who were still taking sorafenib at the time of admission. Despite our patients' elevated enzymes, it is highly possible that his peak level had already occurred prior to presenting with abdominal pain. The half-life of sorafenib is 25–48 h, so he still would have had high serum levels of the medication in his system despite discontinuing therapy 3 days prior to his emergency room visit. This made sorafenib a viable culprit for his acute pancreatitis.

Causes of Elevated Lipase

Hyperlipasemia, or excess levels of the pancreatic enzyme lipase, is a commonly used marker for pancreatic inflammation. In acute pancreatitis, lipase levels can increase up to three times the upper limit of normal (approximately 70 U/L) [20]. Despite its frequent use as a clinical indicator of pancreatitis, it is important to recognize other causes of hyperlipasemia. Lipase may be increased in malignancies of the liver, pancreas, or stomach, infections of the gall bladder, renal failure, and as a side effect of many medications [20]. Hyperlipasemia itself does not cause symptoms, but if elevated as a component of one of the previously mentioned conditions, can be affiliated with a variety of clinical symptoms.

The patient presented in the case report had no evidence of metastatic involvement of his stomach or pancreas, infection, or other critical illness, and his renal function was unimpaired. Although his HCC had progressed, which could explain his elevated lipase, his baseline lipase level prior to starting therapy with sorafenib was approximately 400 U/L. As a result, the measured value on this admission was more than ten times higher than his baseline. Additionally, his acute epigastric pain and peripancreatic edema on abdominal CT were highly suggestive of acute pancreatitis and used to formulate a clinical diagnosis. Although it is highly likely that his HCC contributed to his recent weight loss, anorexia, fatigue, and chronic abdominal pain, the acute worsening of these symptoms over the span of 24–48 h is suspected to be attributed to new-onset acute pancreatitis.

Sorafenib

Although the etiology of sorafenib-induced pancreatitis is not completely understood, pancreatic ischemia secondary to sorafenib's anti-angiogenic effect on VEGFR is suspected to be a major contributor [2, 3]. VEGFR may play a role in maintaining pancreatic capillaries and regulating the cell cycle of pancreatic acinar cells [21]. As a result, the inhibition of VEGFR may induce pancreatic ischemia and necrosis [22]. Given sorafenib's half-life of 25–48 h, the prolonged inhibition of VEGF could provide a potential explanation for the delayed presentation of many patients suffering from sorafenib-induced pancreatitis. Although serum VEGF levels are elevated in acute pancreatitis, there is no relation between the serum VEGF level and severity or prognosis [16, 23].

A second possible explanation for sorafenib's effect on the pancreas is that it can result in gastrointestinal dysmotility. Thus, duodenal contents can reflux into the pancreatic duct, resulting in the premature activation of zymogens within pancreatic acinar cells and subsequent autodigestion of pancreatic tissue [13].

Other possible mechanisms include chemical-induced vasoconstriction, direct injury of vessel wall, intravascular coagulation, and increased endothelial permeability [12]. Despite the potential plausibility of these different mechanisms in causing acute pancreatitis in patients taking sorafenib, other trials have shown conflicting evidence regarding these hypotheses. Additionally, numerous factors have been demonstrated to affect the rate of sorafenib clearance, including genetic variations in CYP liver

enzymes [24, 25], gender, diet, and concurrent medication use [12, 26–29]. It would be beneficial for further studies to evaluate the relative impact of these mechanisms in predisposing patients to sorafenib-induced pancreatitis, especially given the increased utility of sorafenib and other tyrosine-kinase inhibitors in treating patients with multiple oncologic diseases [12, 15, 27]. In the meantime, clinicians must be aware of individual patient characteristics that may affect the metabolism of medications like sorafenib and therefore increase the risk of acute pancreatitis in these patients.

Early clinical trials of patients receiving sorafenib treatment have shown a dose-response relationship between sorafenib dose and elevations in pancreatic enzyme levels [14, 17]. Pancreatic enzymes typically begin rising 4 to 7 days after starting treatment with sorafenib [12]. However, based on cases reported to date, the temporal association can range from 6 days to 6 weeks. It has been suggested that lipase levels could be monitored after starting treatment as a predictor for future pancreatitis risk while taking sorafenib. However, given the frequency of hyperlipasemia as a side effect of sorafenib and relative infrequency of acute pancreatitis, the expense and time of clinical monitoring are unlikely to be beneficial. We recommend that informing patients of the side effects associated with sorafenib is critical and that anyone experiencing abdominal pain while receiving treatment should seek clinical assessment. Similarly, clinicians should have a low threshold to evaluate patients taking sorafenib for radiologic evidence of acute pancreatitis as a potential cause.

Conclusion

Our case report presents the first instance of a patient suffering from sorafenib-induced pancreatitis 3 days after discontinuing sorafenib. This case highlights that monitoring patients for side effects from this medication, TKIs, and other antineoplastic agents in general is important given their prolonged half-life and thus potential to cause toxicity at any time while the medication is still in the patients' system.

Ultimately, pinpointing a potential causation between the inhibition of different cell pathways and their associated clinical outcomes is an area for future study. Sorafenib is an important therapeutic consideration for patients with renal cell and hepatocellular carcinoma. However, given the prevalence of patients suffering from adverse effects of this medication, clinical awareness of its side effects is important for early recognition and treatment of complications, as well as for considering medication cessation.

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Compliance with Ethical Standards

Consent Informed consent was obtained from the patient for publication of this case report and any accompanying images.

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