Pazopanib-induced asymptomatic radiological acute pancreatitis: A case report

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Abstract. The universal clinical use of multi-targeted tyrosine kinase inhibitors (TKIs) in patients diagnosed with advanced renal cell carcinoma (RCC) has significantly prolonged their estimated survival times and their quality of life. However, several adverse side-effects associated predominantly with the inhibition of the vascular endothelial growth factor receptor by these drugs may prove to be potentially life-threatening. One adverse event that is only rarely observed with the use of TKIs in this clinical setting is acute pancreatitis. In the present study, to the best of our knowledge, the first case of asymptomatic radiological acute pancreatitis associated with the use of pazopanib in monotherapy in a patient with RCC is presented. In addition, a comprehensive review of the literature on this topic is provided, and certain potential measures that may aid in early diagnosis and treatment are discussed.

Introduction

Renal cell carcinoma (RCC) accounts for 2% of all malignant tumors worldwide, with clear-cell RCC (ccRCC) being the most common subtype. Conventional cytotoxic drugs and radiation therapy have demonstrated low efficacy in the treatment of RCC (1). However, the development of an improved understanding of the molecular basis of renal cell carcinogenesis has permitted the development of multikinase inhibitors that predominantly target angiogenesis (2). In patients with a high risk or intermediate risk according to Memorial Sloan Kettering Cancer Center (MSKCC) criteria (3), or in patients with a symptomatic primary lesion, advanced metastatic disease may be managed with cytoreductive nephrectomy in operable patients, and subsequent first-line therapy with multi-targeted tyrosine-kinase inhibitors (TKIs) that block vascular endothelial growth factor receptor (VEGFR)-mediated cellular signaling pathways, such as sunitinib or pazopanib (4-6). These latest drugs provide a median overall survival time of 28.3 months for patients treated with pazopanib, and 29.1 months for those treated with sunitinib, with 20 or 24% of patients remaining alive at 5 years follow-up, respectively (7).

Multi-targeted TKIs that are employed in RCC share a class of adverse effects associated mainly with inhibition of the VEGFR, consisting predominantly of hypertension, arterial thromboembolic events, cardiomyopathy, hemorrhage, wound healing complications, proteinuria, gastrointestinal perforation, hand-foot syndrome, and diarrhea. To date, acute pancreatitis has been reported as a rare adverse event associated with VEGFR TKIs (8). A recent meta-analysis evaluating the risk of pancreatitis in patients treated with multi-targeted TKIs versus non-TKI arms in randomized clinical trials (RCTs) demonstrated that subjects in the TKI group were at higher risk of suffering from acute pancreatitis (8). However, the majority of cases were attributed to the use of sunitinib, and only one case occurred in a patient with non-small cell lung cancer (NSCLC) treated with the combination of pazopanib and pemetrexed (8). Increases in the levels of asymptomatic lipase and amylase associated with the use of pazopanib have also been observed (9). Nevertheless, to the best of our knowledge, asymptomatic acute pancreatitis has never been reported associated with the use of pazopanib in monotherapy in patients with RCC. In the present study, to the best of our knowledge for the first time in the literature, a case of a 67-year-old man with metastatic RCC who developed progressive acute pancreatitis during first-line, single-agent treatment with pazopanib, which was resolved after discontinuation of the treatment, is reported.

Case report

The case of a 67-year-old male patient diagnosed with a right RCC with splenic, bilateral lung and left adrenal metastases is

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Abbreviations: RCC, renal cell carcinoma; TKIs, tyrosine-kinase inhibitors (TKIs); VEGFR, vascular endothelial growth factor receptor; CT, computerized tomography; RCT, randomized clinical trial

Key words: renal cell carcinoma, tyrosine kinase inhibitors, toxicity, pazopanib, acute pancreatitis

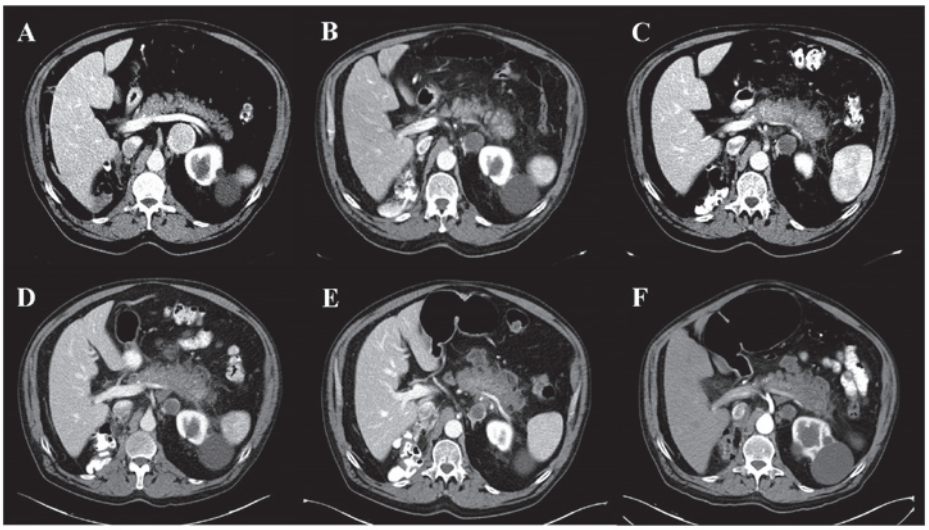

Figure 1. Serial contrast-enhanced CT imaging of a 67-year-old male patient with pazopanib-induced asymptomatic radiological acute pancreatitis. (A) At baseline, no alterations of the pancreas were identified. (B) At 2 months following the initiation of treatment with pazopanib, CT imaging revealed focal acute edematous pancreatic tail and body pancreatitis. (C) A worsening of the pancreatitis is shown in the posterior revaluation, and therefore treatment with pazopanib was maintained. After initiating treatment with sorafenib, (D) stabilization of acute pancreatitis was observed, which was maintained (E and F) on further examinations

reported. The patient's past medical history revealed chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), thalassemia minor and previous polypectomy of three tubulovillous colon polyps. At the outset, the patient was prescribed treatment for COPD with roflumilast, fluticasone propionate, tiotropium bromide, inhaled budesonide and terbutaline on demand, and continuous positive airway pressure for OSA. Prior to starting treatment, the patient had none of the major risk factors associated with pancreatitis: There was no current habit of smoking or alcoholism, no dyslipidemia, diabetes mellitus or hypercalcemia, no previous history of cholelithiasis, biliary-pancreatic infections or abdominal surgery, and prior radiological studies had excluded the presence of cysts or pancreatic metastasis (Fig. 1A).

After having been diagnosed with a right renal mass, the patient underwent a right radical nephrectomy with a confirmatory pathology report of Furhman grade II ccRCC (pT3b N0 M1; stage IV). At 4 weeks after recovery from surgery, the patient initiated treatment with first-line pazopanib (800 mg administered daily). At 2 months following the initiation of treatment, the patient consulted for hand-foot syndrome in his hands (grade 1) and feet (grade 2), according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.03). At this stage, the blood test revealed grade 2 hypertransaminasemia and grade 1 amylase elevation (113 mg/dl; Fig. 2). Blood analysis revealed a glucose level of 133 mg/dl, and the level of lipase was within its normal range. The patient denied having any of the symptoms of acute pancreatitis or liver dysfunction. The computerized tomography (CT) scan revealed a focal acute edematous pancreatic tail and body pancreatitis, as well as fat striation, compatible with acute pancreatitis with a Balthazar Score of grade C (Fig. 1B). A partial response of the patient's metastatic disease was also observed. Due to the complete absence of signs and symptoms of a clinically meaningful acute pancreatitis, and considering the important clinical and radiological benefits that had been obtained since the initiation of pazopanib, a course of subsequent continuation of treatment was decided.

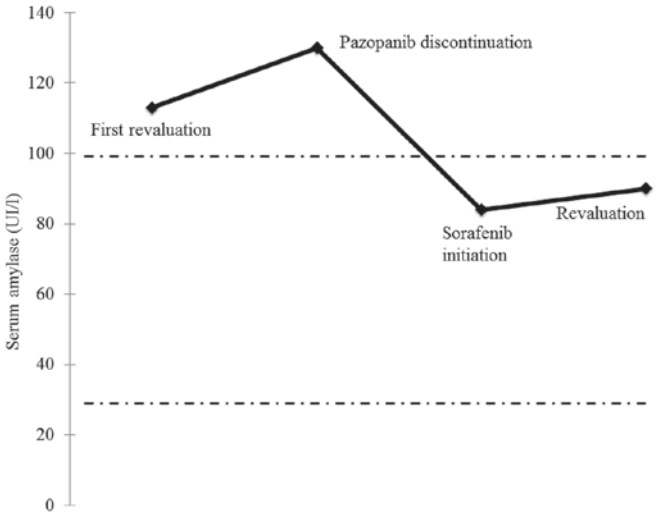

Figure 2. The changes noted in the serum amylase levels. Asymptomatic acute pancreatitis was diagnosed 2 months after initiation of the treatment, with increasing levels of serum amylase noted until pazopanib discontinuation. Decreasing levels and normalization of serum amylase levels were observed after holding pazopanib, and under sorafenib treatment.

In the following radiological evaluation, given a marked worsening of the patient's condition, as noted in the radiological images (Fig. 1C) and the serum analysis of pancreatitis (Fig. 2), treatment with pazopanib was discontinued. After three more weeks, the patient underwent a further clinical and radiographical evaluation. An abdominal CT scan revealed stable acute pancreatitis (Fig. 1D), although the tumor disease was now characterized by loco-regional progression of the splenic and left adrenal metastases. An improvement in the amylase and transaminases levels was observed (Fig. 2). For that reason, it was decided to resume active treatment. Considering

the clinical and radiological benefits initially obtained from the VEGF TKI treatment, a second-line treatment was initiated, and treatment with sorafenib (400 mg twice daily) was decided.

At 10 days after resuming treatment, the patient experienced an incapability to walk due to grade 3 hand-foot syndrome, and so a dose reduction to 200 mg sorafenib, to be administered twice a day, was decided upon. Topical treatment for the skin lesions with a mixture of retinoic acid, triamcinolone acetonide, urea and propylene glycol was started, with consequent amelioration, allowing deambulation. During follow up, stabilization of the signs of pancreatitis upon radiological and analytic examination was identified (Figs. 1E and 2). The last CT scan performed two months after sorafenib initiation revealed retroperitoneal and liver metastatic progression, with no changes in the appearance of the pancreas observed on performing radiology (Fig. 1F). The patient maintained grade 1 hand-foot syndrome, with no other toxicities of grade >2 associated with sorafenib, and therefore the dose administered was scaled up to the full dose (400 mg twice a day).

After three more months, during the last follow-up visit, the patient remained on sorafenib and presented stable metastatic disease, with no radiological changes in pancreatic features and with mild skin toxicity.

The patient gave his informed consent authorizing the publication of this case report.

Discussion

In the present study, the case of a male patient with metastatic RCC who developed acute pancreatitis that was diagnosed as an asymptomatic finding during his first CT scan evaluation, two months after pazopanib initiation, was described.

The efficacy of pazopanib is similar to that of other TKIs used as first-line treatment in metastatic RCC, such as sunitinib (10). The toxicity profile of pazopanib in patients with advanced RCC accounts for hand-foot syndrome, rash, stomatitis, dysgeusia, dyspepsia, anorexia, nausea, vomiting, diarrhea, fatigue, weight loss, hair color change, alopecia, hypertension, increased mean arterial blood pressure, and liver function abnormalities (11). No evidence of clinically important differences in the quality of life when comparing pazopanib with a placebo has been identified (12). Furthermore, a randomized, controlled, double-blind cross-over trial of pazopanib versus sunitinib demonstrated patients' preference for pazopanib over sunitinib (13).

Santoni *et al* (14) published a systemic review and meta-analysis of gastrointestinal events in patients with solid tumors who received sorafenib, sunitinib and pazopanib, including RCC, NSCLC, hepatocellular carcinoma, breast cancer, neuroendocrine tumors, gastrointestinal stromal tumors and soft tissue sarcomas (14). These authors described anorexia, diarrhea and nausea as the main gastrointestinal adverse side-effects observed, but no cases of acute pancreatitis were observed. By contrast, a meta-analysis evaluating the risk of specifically developing acute pancreatitis associated with multi-targeted TKIs has recently been published (8). In that study, phase II and phase III RCTs in patients with different tumor origins comparing arms with TKIs versus non-TKI treatment were included. The incidence of pancreatitis in the two groups was specifically analyzed. A significantly higher risk of pancreatitis was observed in the TKI group (25 of 5,569 patients) compared with the control group (7 of 5,009 patients). The majority of the cases occurred in patients on sunitinib. Only one patient of the 5,569 in the TKI arm, receiving treatment with pazopanib, developed pancreatitis. However, that subject was diagnosed with advanced NSLC, and received a combination regimen with pemetrexed and pazopanib, so it remains unclear whether acute pancreatitis was induced by pazopanib, by pemetrexed, or by both drugs in combination (8). A case of isolated amylase and lipase level elevation associated with the use of pazopanib in a patient with metastatic RCC was also reported; however, that patient exhibited neither symptoms nor radiological signs of pancreatitis (9).

The toxicity shown by pazopanib when used to treat sarcomas has been further investigated by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC study 62043), with cardiovascular, gastrointestinal and hepatic disorders, myelosuppression and proteinuria being the major adverse effects (15). The occurrence of pneumothorax, heart failure, venous thrombosis, pulmonary embolism and hypothyroidism is rare, although these are potentially serious adverse effects also associated with pazopanib treatment (16). A case of pazopanib-induced acute pancreatitis in a patient with cutaneous angiosarcoma was also recently reported (17). However, no previous reports of pancreatitis, when pazopanib has been administered as single agent, have been reported for patients diagnosed with RCC.

To the best of our knowledge, the present study has described the first case of development of asymptomatic acute pancreatitis associated with a single agent, pazopanib, in a patient with metastatic RCC. Previous radiological studies did not reveal any disorder in the patient's pancreas prior to pazopanib administration. However, a radiologically evident, but clinically asymptomatic, acute pancreatitis 2 months after initiation of pazopanib treatment was apparent. The condition was confirmed by serum analysis (i.e. an elevation in the amylase level), and the continuation of pazopanib following the initial diagnosis of pancreatitis was associated with the worsening of radiological pancreatitis. Resolution of the inflammation was achieved by withholding the medication, revealing a temporal and dose-accumulation association between both factors (acute pancreatitis and pazopanib treatment). The presumed pathophysiological mechanism for this rare adverse effect would include the ability of pazopanib (and, potentially, of other VEGFR TKIs) to affect the pancreatic cells, or, more likely, the vascular endothelial receptors in the vessels of the pancreas, causing ischemia of the pancreatic tissue (18).

Given the fact that asymptomatic pancreatitis is a rare example of toxicity associated with pazopanib and a follow-up CT scan is performed every 8-12 weeks, the present authors suggest monitoring amylase and lipase levels at baseline and during treatment with pazopanib and other antiangiogenic TKIs. In those patients who show increasing levels of acute pancreatitis-associated enzymes, an abdominal CT scan should be performed in order to rule out rapidly progressing acute pancreatitis. According to the present case study, switching to

a different TKI may be feasible as an option, since it seems to be more likely to be a specific drug-associated, rather than a class-associated event.

As shown in the present case report, multi-targeted VEGFR TKIs are the standard of care against advanced RCC, since the administration of these drugs is capable of resulting in a marked change in the life expectation of patients with this disease, with a median overall survival of ~28-30 months for patients treated with pazopanib and sunitinib. However, VEGFR TKIs are also associated with rare, but potentially life-threatening, adverse events, such as hemorrhage and cardiovascular events. Although acute pancreatitis has not been a commonly suspected toxicity in patients receiving pazopanib, evidence that has shown the possibility of developing this condition with sorafenib, and the findings of the present case study following pazopanib treatment may change the way in which patients on these drugs are monitored, and perhaps serum markers of pancreatitis may be added to routine clinical practice. In case of confirming acute pancreatitis associated with a particular drug, switching to a different VEGFR TKI may maintain the clinical benefits, leading to an improvement in, or maybe even resolving, the pancreatitis.

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