EJMO

DOI: 10.14744/ejmo.2017.10820
EJMO 2017;1(2):115–117

Case Report

Sunitinib-Associated Acute Pancreatitis: A Case Report

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Abstract

Sunitinib is a multikinase inhibitor used for the treatment of metastatic renal cell carcinoma. Acute pancreatitis associated with sunitinib is rare. Presently described is a case of a 79-year-old man with metastatic renal cell carcinoma who developed acute pancreatitis following the initiation sunitinib treatment. The development of acute pancreatitis secondary to sunitinib should be considered in patients presenting with abdominal pain after the administration of sunitinib.

Keywords: Pancreatitis, renal cell carcinoma, sunitinib

Cite This Article: *Karakurt Eryilmaz M, Yalcin Musri F, Kivrak Salim D, Tazegul G, Coskun H. Sunitinib-Associated Acute Pancreatitis: A Case Report. EJMO. 2017; 1(2): 115-117*

Renal cell carcinoma (RCC) is responsible for 80 to 85 percent of primary renal neoplasms. At diagnosis, approximately 25 percent of individuals have distant metastases or advanced locoregional disease. Vascular endothelial growth factor (VEGF) is the most important growth factor that is involved in tumor angiogenesis, and it plays a significant role in the growth and progression of RCC.[1] VEGF pathway inhibitors are important agents in the treatment of advanced or metastatic RCC. They are also preferred agents for treatment of patients who have progressed after prior therapy. The small molecule tyrosine kinase inhibitors (TKI) including sunitinib, pazopanib, sorafenib and axitinib block the intracellular domain of the VEGF receptor (VEGFR).[2]

Sunitinib is an oral multikinase inhibitor, inhibits the VEGFR-1, VEGFR-2, the platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-kit) oncogene. Sunitinib demonstrated improvement in progression-free survival (PFS) and overall-survival (OS) compared to patients treated with interferon (IFN)-α in the first line treatment of patients with metastatic RCC.[3,4] The most common side effects associated with sunitinib include hypertension, fatigue, nausea, diarrhea, skin discoloration, and myelosuppression.

Herein, we present a case of 79 year-old man with metastatic renal cell carcinoma who developed acute pancreatitis following sunitinib initiation.

Case Report

A 79-year-old man was admitted with rectal bleeding in November 2014. Colonoscopy revealed an ulcerous-vegetative mass located in distal rectum. The biopsy of rectal mass revealed well- differentiated adenocarcinoma. F-fluorodeoxyglucose [(18) F-FDG)] positron emission tomography/computed tomography (PET/CT) performed for staging revealed right renal 5.9 centimeter hypermetabolic mass (SUVmax: 5), thickening of the rectal wall and multiple hyper-metabolic metastatic nodules in both lung. Biopsy of renal mass revealed clear cell subtype renal cell carcinoma. Biopsy of lung nodules was consistent with metastasis of renal cell carcinoma. In November 2014, both

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Submitted Date: July 01, 2017 **Accepted Date:** July 30, 2017 **Available Online Date:** August 26, 2017

right radical nephrectomy and total mesorectal excision for rectal cancer were performed in the same session because of synchronous tumors. Pathologic stage of rectal cancer was stage 2B (T4aN0M0) according to the 7th edition tumor-node-metastasis (TNM) staging system. Adjuvant radiotherapy was no administered for rectal cancer because renal cell carcinoma was metastatic. Patient was started on adjuvant interferon (IFN)-alpha treatment (3 million units (MIU)/m^2 subcutaneously, 3 days a week). He had progression of the lung metastasis after three months of IFN-alpha. For this reason, sunitinib 50 mg daily was initiated on February 2015. His medical history revealed type 2 diabetes mellitus and hypertension. In addition to sunitinib, patient's medications included metoprolol 50 mg daily, ramipril 2.5 mg daily, repaglinide 1 mg three times daily and metformin 1000 mg twice daily. Approximately after 10 days of sunitinib initiation, he was admitted to hospital for hypertensive episodes occurred at home. Blood pressure was around 130/80 mm/Hg, he was hospitalized for follow-up. After 2 days of hospitalization, patient developed severe epigastric pain, nausea and vomiting. Physical examination revealed tenderness in epigastric region. Patient had no previously history of pancreatitis, alcohol consumption, and family history of pancreatitis. Laboratory studies demonstrated elevated amylase (713 U/L; reference range, 28–100) and lipase (925 U/L; reference range, 13–60). His triglyceride (131 mg/dL; reference range, 50–200) and corrected calcium (9 mg/dL; reference range, 8,8–10,2) levels were within normal limits. Abdominal ultrasonography revealed a diffusely enlarged pancreas compatible with acute pancreatitis but there were neither gallstones nor biliary duct dilatation. Sunitinib was stopped following the diagnosis of acute pancreatitis. He was treated with conservative therapy including stopping oral intake, starting intravenous hydration and analgesics. Over the next four days, patient's symptoms improved, and he was able to resume oral intake. Serum amylase and lipase levels trended down following conservative therapy (Fig. 1). Two weeks later, he was discharged without complications. Sunitinib was not started again.

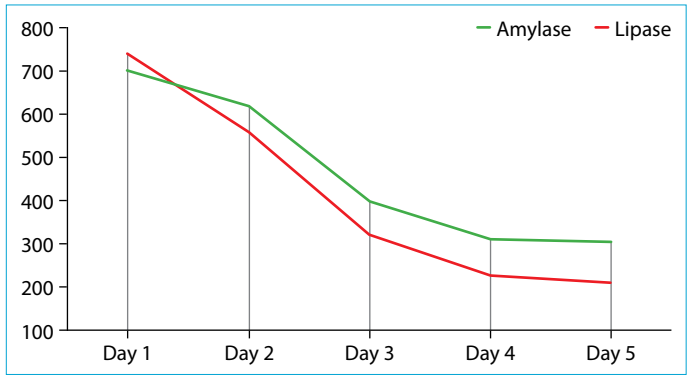

Figure 1. Patient's amylase and lipase levels were significantly reduced after sunitinib cessation and conservative treatment for pancreatitis.

Discussion

Sunitinib is widely used in the treatment of advanced renal cell carcinoma in first line. Overall, sunitinib is well tolerated and toxicities are manageable. Most common sunitinib related toxicities include cardiovascular effects (hypertension, thromboembolism, left ventricular dysfunction) and non-cardiovascular effects (proteinuria, bleeding, delayed wound healing, gastrointestinal perforation, fatigue, thyroid dysfunction, hand-foot skin reaction, and dysphonia).[5] Rarely, sunitinib has been associated with QTc prolongation, reversible posterior leukoencephalopathy, and osteonecrosis of the jaw.[6–8]

Asymptomatic transient elevations in serum amylase and serum lipase have been reported in patients treated with sunitinib, although overt pancreatitis appears to relatively rare.[9] In the literature, several reports exist regarding patients who developed acute pancreatitis while on TKI such as sunitinib, sorafenib and axitinib.[10–12] Recently, a meta-analysis demonstrated a significant increase in the risk of all grades of pancreatitis with VEGFR-TKI compared to controls. Additionally, study showed a trend for greater the risk of severe pancreatitis (grade ≥3), but that was not statistically significant.[13]

Pathogenesis of TKI-induced acute pancreatitis is not well documented but possible cause is considered as inhibition of VEGF pathway. The inhibition of VEGF leads to pancreatic acinar cell apoptosis and release of autodigestive enzymes.[14] Another possible cause is decrease in gastrointestinal motility by TKI. Decreased gastrointestinal motility causes reflux of duodenal contents into the pancreatic duct thereby pancreatic enzymes are activated.[11]

Acute pancreatitis is an inflammatory condition of the pancreas, characterized clinically by abdominal pain and elevated levels of lipase and amylase. The gallstones and chronic alcohol consumption are responsible for 60 to 75 percent of cases of acute pancreatitis. Additionally, hypertriglyceridemia, hypercalcemia, and infections are less common causes of acute pancreatitis. Some medications such as tetracyclines, sulfonamides, furosemide and corticosteroids are associated with pancreatitis. Initial management of a patient with acute pancreatitis consists of supportive care with intravenous fluid resuscitation, pain control, and nutritional support.[15]

In summary, we report a patient with acute pancreatitis occurring after 10 days sunitinib treatment. We think that the

cause of pancreatitis was sunitinib because no evidence was found supporting other causative factors for pancreatitis. Clinicians should be aware of this rare side effect, sunitinib should be prompt discontinued and effective conservative therapy should be started in these patients.

Disclosures
Peer-review: Externally peer-reviewed.
Conflict of Interest: None declared.

References

1. Ishikawa Y, Aida S, Tamai S, Akasaka Y, Kiguchi H, Akishima-Fukasawa Y, et al. Significance of lymphatic invasion and proliferation on regional lymph node metastasis in renal cell carcinoma. Am J Clin Pathol 2007;128:198–207. [CrossRef]
2. Iacovelli R, Sternberg CN, Porta C, Verzoni E, de Braud F, Escudier B, et al. Inhibition of the VEGF/VEGFR pathway improves survival in advanced kidney cancer: a systematic review and meta-analysis. Curr Drug Targets 2015;16:164–70. [CrossRef]
3. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24. [CrossRef]
4. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584–90.
5. Kollmannsberger C, Soulieres D, Wong R, Scalera A, Gaspo R, Bjarnason G. Sunitinib therapy for metastatic renal cell carcinoma: recommendations for management of side effects. Can Urol Assoc J 2007;1:S41–54.
6. Bello CL, Mulay M, Huang X, Patyna S, Dinolfo M, Levine S, et al. Electrocardiographic characterization of the QTc interval in patients with advanced solid tumors: pharmacokinetic-pharmacodynamic evaluation of sunitinib. Clin Cancer Res 2009;15:7045–52. [CrossRef]
7. Costa R, Costa R, Costa R, Junior GM, Cartaxo HQ, de Barros AC. Reversible posterior encephalopathy syndrome secondary to sunitinib. Case Rep Oncol Med 2014;2014:952624. [CrossRef]
8. Fleissig Y, Regev E, Lehman H. Sunitinib related osteonecrosis of jaw: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:e1–3. [CrossRef]
9. Britten CD, Kabbinavar F, Hecht JR, Bello CL, Li J, Baum C, et al. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. Cancer Chemother Pharmacol 2008;61:515–24. [CrossRef]
10. Ruinemans GM, Balemans C, Mattijssen V, Wiersma-van Tilburg AJ, Smit HJ. Fatal necrotizing pancreatitis during combined treatment with erlotinib and sunitinib. Lung Cancer 2010;70:364–5. [CrossRef]
11. Li M, Srinivas S. Acute pancreatitis associated with sorafenib. South Med J 2007;100:909–11. [CrossRef]
12. Péron J, Khenifer S, Potier V, Vitry T, Pasquet F, Rassat R, et al. Axitinib-induced acute pancreatitis: a case report. Anticancer Drugs 2014;25:478–9. [CrossRef]
13. Ghatalia P, Morgan CJ, Choueiri TK, Rocha P, Naik G, Sonpavde G. Pancreatitis with vascular endothelial growth factor receptor tyrosine kinase inhibitors. Crit Rev Oncol Hematol 2015;94:136–45. [CrossRef]
14. Pezzilli R, Corinaldesi R, Morselli-Labate AM. Tyrosine kinase inhibitors and acute pancreatitis. JOP 2010;11:291–3.
15. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet 2015;386:85–96. [CrossRef]