



Sorafenib-induced pancreatitis

Talat Ayyildiz^{a*}, Taner Aydin^b, Ahmet Tarik Eminler^c, Cinar Yildirim^c, Kader Irak^c, Murat Kiyici^c, Selim Gurel^c, Selim Giray Nak^c, Macit Gulten^c, Enver Dolar^c

^a Department of Gastroenterology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

^b Department of Internal Medicine, Faculty of Medicine, Uludag University, Bursa, Turkey

^c Department of Gastroenterology, Faculty of Medicine, Uludag University, Bursa, Turkey

ARTICLE INFO

ABSTRACT

Article History

Received 03 / 09 / 2014

Accepted 19 / 10 / 2014

* Correspondence to:

Talat Ayyildiz
Department of Gastroenterology,
Faculty of Medicine,
Ondokuz Mayıs University,
Samsun, Turkey
e-mail: talatayy@gmail.com

Sorafenib is an inhibitor of multikinase proteins which is used for metastatic renal cell carcinoma and advanced stage hepatocellular carcinoma. Its side effects include serum amylase and lipase elevations anticipated to occur within first weeks of treatment but clinically and radiologically evident acute pancreatitis develops rarely. Five cases of acute pancreatitis have been reported in literature until date. The case we described here is the sixth case of clinically diagnosed acute pancreatitis.

Keywords:

Hepatocellular carcinoma
Pancreatitis
Sorafenib
Tyrosine kinase inhibitor

© 2015 OMU

1. Introduction

Sorafenib is an inhibitor of multikinase proteins which was approved in 2005 for the treatment of metastatic renal cell carcinoma by oral route. Sorafenib was shown to extend life expectancy by 3 months in patients with advanced stage hepatocellular carcinoma (HCC) which led to its use in this group of patients. The most common side effects associated with sorafenib use include rash, hand-foot skin reaction, alopecia, fatigue, diarrhea, nausea, anorexia and hypertension (Ratain et al., 2006; Escudier et al., 2009).

A few cases of sorafenib-induced pancreatitis have been reported in literature. As shown in Table 1, our case is the sixth case of clinically diagnosed acute pancreatitis and the second case with respect to development of pancreatitis in the setting of hepatocellular cancer (Amar et al., 2007; Li and Srinivas, 2007; Saadati and Saif, 2010; Kobayashi et al., 2011; Sevin et al., 2013).

2. Case

A sixty two-year-old male presented to the emergency department with nausea accompanied by pain which had initially occurred 2 days ago in the epigastric region and extended to the low back in a belt-like fashion and radiated to the left shoulder. Diagnostic investigations conducted 2 years ago for low back pain revealed a mass in the liver and subsequent biopsy result was consistent with HCC; also metastasis to lumbar vertebrae was detected. Hepatitis B surface antigen (HBsAg) was positive. Transarterial chemoembolisation (TACE) was performed for the liver mass which was followed by abscess formation requiring antibiotherapy administration after drainage by catheterization. Then, laminectomy was performed for a new-onset compression fracture of L3. While the patient was being followed by the Medical Oncology department with stable disease, Sorafenib tablets (2x400 mg/day) were started for the patient 3 months ago. His medical history includes

Table 1. Summary of reported cases of Sorafenib-induced pancreatitis

Reference	Age	Sex	Malignancy	Dose of Sorafenib	Duration of treatment prior to pancreatitis	Lipase (U/L)	Amylase (U/L)
Amar et al.	53	Female	Metastatic renal cell carcinoma	400 mg twice daily	3 weeks	99	1361
Li and Srinivas	80	Male	Metastatic renal cell carcinoma	400 mg twice daily	4 weeks	>200	156
Saadati and Saif	53	Male	Hepatocellular carcinoma	Not reported	Not reported	484	118
Kobayashi et al.	71	Male	Metastatic renal cell carcinoma	400 mg twice daily	2 weeks	2733	973
Sevin et al.	69	Female	Metastatic renal cell carcinoma	400 mg twice daily	10 days	1014	244

chronic atrial fibrillation with no alcohol consumption. His medications included fentanyl transdermal patch, etodolac, hyoscine butylbromide and diltiazem which he used for about 2 years. Vital findings were normal. Initial laboratory workup gave the following results: serum amylase 620 IU/L, lipase 734 IU/L, urinary amylase 6.425 IU/L, Haemoglobin 9.60 g/dL, white blood cells 4.890 K/ μ L, platelet count 112 K/ μ L, triglycerides 178 mg/dL, total cholesterol 134 mg/dL, AST 72 IU/L, ALT 27 IU/L, alkaline phosphatase 289 IU/L, total bilirubin 5.5 mg/dL, direct bilirubin 4.4 mg/dL, urea 53 mg/dL, creatinine 2.1 mg/dL, CRP 19.8 mg/dL and calcium 7.3 mg/dL. Liver cirrhosis was classified as Class A according to the Child-Pugh score (Child and Turcotte., 1964; Pugh et al., 1973). Abdominal ultrasound examination did not show any pathological findings such as stones or sludge (mud) in the bile ducts and gallbladder. Pancreas could not be evaluated firmly. The patient was hospitalized based on a clinical diagnosis of acute pancreatitis. At the time of presentation, his creatinine values were elevated due to acute renal failure. An abdominal computed tomography examination conducted for renal assessment about 1 week after his presentation indicated that pancreas was normal and a lesion (10x12 cm) with heterogeneous density which occupied the posterior of the left lobe almost entirely and a cystic formation (4x6 cm) located in the inferior segment of the right lobe (subsegment 6) containing millimetric air sinuses as well as a 2x4 cm hypodense lesion at the level of the hepatic dome which stained peripherally were observed. In the perihepatic region, freely moving fluid was detected in the perisplenic and both paracolic regions measuring 5 cm at its highest point in the pelvis. Intra-abdominal fat planes showed considerable dirty shadowing (Fig.1). During clinical follow-up, Sorafenib was discontinued after his hospitalization but all other medications were continued.

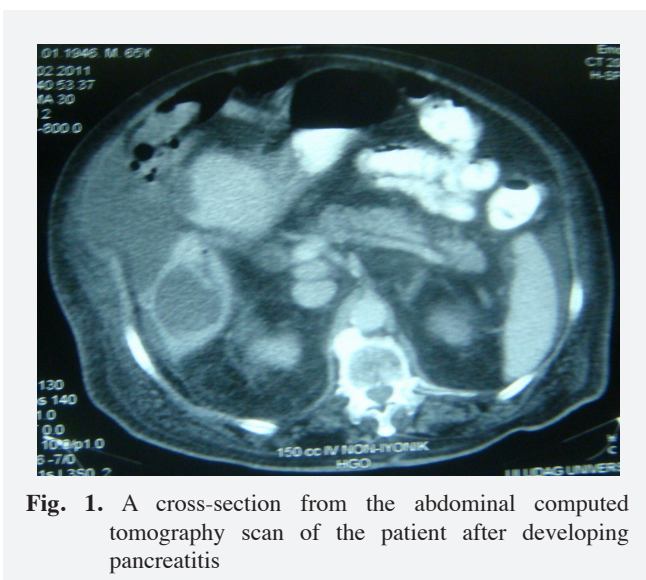


Fig. 1. A cross-section from the abdominal computed tomography scan of the patient after developing pancreatitis

Escherichia coli grew in the culture of the sample obtained from intra-abdominal loculated fluid. Treatment with intravenous ceftriaxone 2x1 g and metronidazole 3x500 mg was administered for 14 days. Also, intravenous fluids and analgesics were given. No additional intervention was undertaken because abscess formation in the liver was well-organized. The patient was discharged with improvement of general condition.

3. Discussion

During embryonic pancreas development, vascular endothelial growth factor (VEGF) stimulates growth of islet cells. VEGF expression is inversely related to acinary cell growth. VEGF has been shown to play a prominent role in the development of pancreas in animal models.

Sorafenib is a small molecular inhibitor and binds to the receptors of serine/threonine Raf-1 kinase and several tyrosine kinases including vascular endothelial growth receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR), FMS-like tyrosine kinase-3 (FLT-3) and c-kit (Ratn). Ras/Raf/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) (MEK) pathway has a key role in cell proliferation and apoptosis and VEGFR-2/PDGFR signaling cascade is involved in vasculogenesis, angiogenesis, tumor cell motility and metastasis (Wilhelm et al., 2004).

Sorafenib was approved by the Food and Drug Administration (FDA) in USA in 2005 for the treatment of renal cell carcinoma. Subsequently, approval was granted also for treatment of advanced hepatocellular cancer and shown to extend average life expectancy of these patients by 3 months (Llovet et al., 2008).

Cases of pancreatitis were observed in 3 patients in Sorafenib phase I studies. In these 3 patients, development of acute pancreatitis was considered to be independent of dosage. Pancreatitis developed at 3 and 6 weeks while receiving 2x100 mg/day in two of the patients and at 8 months while receiving 2x400 mg/day in the third patient. All patients recovered within 10-14 days after discontinuation of the drug (Strumberg et al., 2005).

In a study by Hyodo et al. (2012) elevations of lipase and amylase occurred with an incidence of 55.7% and 38.2% among 131 patients receiving Sorafenib 400 mg twice daily. The majority of these elevations were seen within the first 3 weeks and all of them resolved spontaneously. Additionally, there were no clinical or radiological findings which were suggestive of pancreatitis (Hyodo et al., 2012).

Pancreatic ischemia at the earlier phase of acute pancreatitis is important for development of pancreatic necrosis. Possible mechanisms contributing to the process include chemical-induced vasoconstriction, direct damage to vessel wall, intravascular coagulation and increased

endothelial permeability (Klar et al., 1990). Mitogen-Activated Protein Kinase (MAPK) is a downstream effector of Ras/Raf/MEK/ERK pathway and found to be activated in acute pancreatitis (Murr et al., 2003). A marked elevation in serum VEGF level was noted in patients with acute pancreatitis but its association with the severity or prognosis of the disease could not be established (Ueda et al., 2006). Why Sorafenib induces acute pancreatitis when in fact it was anticipated to have a protective effect against this condition owing to its inhibitory action on Raf pathway and VEGFR remains a question to be answered.

Acute pancreatitis is a complicated condition associated with release of autodigestive enzymes and originates from apoptosis of acinary cells. Sorafenib causes reflux of duodenal contents into pancreatic duct by inducing gastrointestinal motility abnormalities. Thus, it prematurely activates zymogens which are inactive digestive enzymes contained in pancreatic acinary cells and results in release of active enzymes into the pancreatic tissue and autodigestion. This explains why pancreatitis develops after at least 3 months of

drug intake and shows a mild prognosis and reversible nature (Li and Srinivas, 2007).

Management of sorafenib-induced acute pancreatitis includes discontinuation of drug therapy, administration of analgesics for pain, prevention of acute renal failure and intravenous fluid replacement. As in the case of our patient, complete resolution of acute pancreatitis within 10-14 days was reported in all patients after discontinuation of sorafenib.

It is known that acute pancreatitis mostly develops in relation to alcohol consumption and cholelithiasis. Other causes of pancreatitis include infections (viral and bacterial), pancreatic carcinoma, trauma, hypertriglyceridemia, scorpion stings and snake bites and a variety of medicines (sunitinib, chemotherapeutic and antiretroviral drugs, diuretics, NSAIDs, methyl dopa and tetracyclines). In light of emerging literature, we believe that it would be wise to add sorafenib to antineoplastic agents that potentially induce pancreatitis. It should be borne in mind that patients presenting with abdominal pain might develop pancreatitis if their treatment regimen includes sorafenib.

REFERENCES

- Amar, S., Wu, K.J., Tan, W.W., 2007. Sorafenib induced pancreatitis. *Mayo Clin. Proc.* 82, 521.
- Child, C.G.III., Turcotte, J.G., 1964. Surgery and portal hypertension. In: *The liver and portal hypertension*, Child, C.G., Eds, W.B. Saunders, Philadelphia. P.50.
- Escudier, B., Eisen, T., Stadler, W.M., Szczylik, C., Oudard, S., Staehler, M., Negrier, S., Chevreau, C., Desai, A.A., Rolland, F., Demkow, T., Hutson, T.E., Gore, M., Anderson, S., Hofilena, G., Shan, M., Pena, C., Lathia, C., Bukowski, R.M., 2009. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J. Clin. Oncol.* 27, 3312-3318. doi: 10.1200/JCO.2008.19.5511.
- Hyodo, I., Adachi, M., Tsukamoto, T., Murai, M., Naito, S., Akaza, H., 2012. Serum pancreatic enzyme elevation under treatment with sorafenib. *Gan. To. Kagaku. Ryoho.* 39, 1651-1656.
- Klar, E., Messmer, K., Warshaw, A.L., Herfarth, C., 1990. Pancreatic ischaemia in experimental acute pancreatitis: Mechanism, significance and therapy. *Br. J. Surg.* 77, 1205-1210.
- Kobayashi, Y., Kanemitsu, T., Kamoto, A., Satoh, M., Mori, N., Sekii, K., Yoshioka, T., Itatani, H., Fujimoto, T., 2011. Painless acute pancreatitis associated with sorafenib treatment: A case report. *Med. Oncol.* 28, 463-465. doi: 10.1007/s12032-010-9479-2.
- Li, M., Srinivas, S., 2007. Acute pancreatitis associated with sorafenib. *South Med. J.* 100, 909-911.
- Llovet, J.M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J.F., de Oliveira, A.C., Santoro, A., Raoul, J.L., Forner, A., Schwartz, M., Porta, C., Zeuzem, S., Bolondi, L., Greten, T.F., Galle, P.R., Seitz, J.F., Borbath, I., Häussinger, D., Giannaris, T., Shan, M., Moscovici, M., Voliotis, D., Bruix, J., 2008. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 359, 378-390.
- Murr, M.M., Yang, J., Fier, A., Gallagher, S.F., Carter, G., Gower, W.R. Jr., Norman, J.G., 2003. Regulation of kupffer cell TNF gene expression during experimental acute pancreatitis: The role of p38-MAPK, ERK1/2, SAPK/JNK, and NF-kappaB. *J. Gastrointest. Surg.* 7, 20-25.
- Pugh, R.N., Murray-Lyon, I.M., Dawson, J.L., Pietroni, M.C., Williams, R., 1973. Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.* 60, 646-649.
- Ratain, M.J., Eisen, T., Stadler, W.M., Flaherty, K.T., Kaye, S.B., Rosner, G.L., Gore, M., Desai, A.A., Patnaik, A., Xiong, H.Q., Rowinsky, E., Abbruzzese, J.L., Xia, C., Simantov, R., Schwartz, B., O'Dwyer, P.J., 2006. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 24, 2505-2512. doi:10.1200/JCO.2005.03.6723.
- Saadati, H., Saif, M.W., 2010. Sorafenib-induced acute pancreatitis. *JOP.* 11, 283-284.
- Sevin, A., Chen, A., Atkinson, B., 2013. Tyrosine kinase inhibitor induced pancreatitis. *J. Oncol. Pharm. Pract.* 19, 257-260. doi: 10.1177/1078155212457968.
- Strumberg, D., Richly, H., Hilger, R.A., Schleucher, N., Korfee, S., Tewes, M., Faghiih, M., Brendel, E., Voliotis, D., Haase, C.G., Schwartz, B., Awada, A., Voigtman, R., Scheulen, M.E., Seeber, S., 2005. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J. Clin. Oncol.* 23, 965-972.
- Ueda, T., Takeyama, Y., Yasuda, T., Matsumura, N., Sawa, H., Nakajima, Kuroda, Y., 2006. Vascular endothelial growth factor increases in serum and protects against the organ injuries in severe acute pancreatitis. *J. Surg. Res.* 134, 223-230. doi:10.1016/j.jss.2005.12.032.
- Wilhelm, S.M., Carter, C., Tang, L., Wilkie, D., McNabola, A., Rong, H., Chen, C., Zhang, X., Vincent, P., McHugh, M., Cao, Y., Shujath, J., Gawlak, S., Eveleigh, D., Rowley, B., Liu, L., Adnane, L., Lynch, M., Auclair, D., Taylor, I., Gedrich, R., Voznesensky, A., Riedl, B., Post, L.E., Bollag, G., Trail, P.A., 2004. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* 64, 7099-7109. doi:10.1158/0008-5472.CAN-04-1443.