

Pazopanib-Induced Asymptomatic Necrotizing Pancreatitis Diagnosed on ¹⁸F-FDG PET-CT Scan

Abstract

Multi-targeted tyrosine kinase inhibitor (TKI) pazopanib approved for the treatment of advanced soft tissue sarcoma (STS) has prolonged the estimated survival times and quality of life of patients. However, several adverse effects associated predominantly with the inhibition of the vascular endothelial growth factor receptor by these drugs may prove to be potentially life-threatening. One such rare adverse event with the use of pazopanib is acute pancreatitis. We present a case of asymptomatic necrotizing pancreatitis induced by pazopanib treatment for metastatic STS detected on ¹⁸F-FDG PET-CT imaging.

Keywords: *FDG PET-CT, pancreatitis, pazopanib, tyrosine kinase inhibitors*

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Introduction

Soft tissue sarcomas (STSs) are a rare, heterogeneous group of mesenchymal origin solid tumors. Treatment in localized resectable STS includes wide excisional surgery with or without radiotherapy. The use of chemotherapy or targeted therapy, in particular pazopanib, is reserved for unresectable and advanced metastatic disease, for disease palliation.^[1] Pazopanib is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors, and c-Kit, approved for treating metastatic STS and renal cell carcinoma.^[2,3] Multi-targeted tyrosine kinase inhibitors (TKIs) are associated with adverse effects such as hypertension, arterial thromboembolic events, hemorrhage, wound-healing complications, hand-foot syndrome, diarrhea, asymptomatic elevation in pancreatic enzymes seen in a third of patients, and rarely associated with acute pancreatitis (~1% of patients).^[4-6] Acute pancreatitis associated with TKIs has been reported to be clinically silent; thus, imaging can play a role in its early diagnosis and guide timely and appropriate management.^[6] We present an interesting case of incidentally detected pazopanib-induced asymptomatic necrotizing pancreatitis in a patient with

metastatic STS detected on ¹⁸F-FDG PET-CT imaging.

Case Report

A 67-year-old man, nonsmoker, nonalcoholic, diagnosed with high-grade pleomorphic spindle cell STS (right thigh), underwent surgical resection and radiation. After disease-free interval of 6 months, the patient developed lung metastasis detected on ¹⁸F-FDG PET-CT scan. Pazopanib therapy was initiated at a dose of 800 mg/day. After 3 months, follow-up ¹⁸F-FDG PET-CT scan showed disease progression. In addition, a new interesting incidental finding was detected involving diffuse hypodensities collections surrounding pancreas demonstrating diffuse FDG activity (SUVmax 5), with area of necrosis in head of pancreas and adjacent peripancreatic fat stranding, all features suggesting necrotizing pancreatitis (Balthazar grade E) [Figure 1a and c-e]. As the patient had no specific complaints of abdominal pain, further laboratory evaluation with serum amylase and lipase was not done. Based on FDG PET-CT scan findings along with no associated risk factors for pancreatitis in this patient, such as gall stone, excessive alcohol consumption, hypertriglyceridemia, hypercalcemia, and being clinically asymptomatic, a suspicion of pazopanib-induced subclinical pancreatitis was considered. In view of disease progression, pazopanib was discontinued

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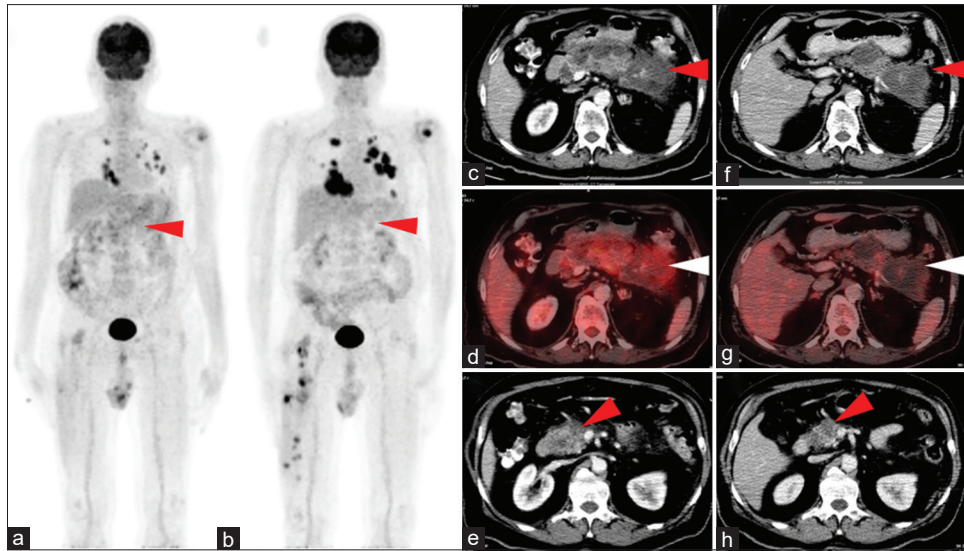


Figure 1: ¹⁸F-FDG PET-CT scan on pazopanib: MIP (a), transaxial CECT and fused (c and d) images show incidental finding of diffuse hypodensities-collections surrounding pancreas demonstrating diffuse FDG activity (SUVmax 5) with area of necrosis in pancreatic head (e) and adjacent fat stranding. FDG PET-CT scan 2 months after discontinuing pazopanib: MIP (b), transaxial CECT and fused (f-h) images show significant decrease in inflammatory FDG activity and extent of hypodensities surrounding pancreas

immediately and chemotherapeutic regimen including endoxan, methotrexate, and celecoxib was administered. After 2 months, the patient developed right inguinal swelling, and ¹⁸F-FDG PET-CT scan was performed demonstrating further disease progression. However, there was a significant decrease in inflammatory metabolic activity and extent of hypodensities collections surrounding pancreas, suggesting resolving pancreatitis, also confirming its benign inflammatory nature [Figure 1b and f-h].

Discussion

STSs represent approximately 1% of adult cancers comprising more than 100 subtypes. Major site of occurrence is limb/limb girdle (60%) or intra-abdominal (20%). Around 10% of patients are metastatic at diagnosis (more commonly lung). Depending on tumor grade, 30%–50% of patients die due to advanced metastatic disease. Cytotoxic chemotherapy is the mainstay treatment for metastatic STS. Targeted therapy has gained importance in the salvage setting in chemotherapy refractory cases. Of these, pazopanib is approved for the treatment of multiple subtypes of advanced STS and known to improve progression-free survival based on the results of a double-blind, placebo-controlled randomized phase III PALETTE trial.^[1] Pazopanib toxicity profile in the treatment of advanced metastatic sarcomas has been 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 major adverse effects.^[7] Acute pancreatitis is reported as a rare adverse event associated with VEGFR TKIs and sometimes is difficult to diagnose as patients are

asymptomatic.^[8] A meta-analysis in 2015 evaluating risk of pancreatitis in patients treated with TKIs versus non-TKI arm in randomized clinical trials demonstrated higher risk of acute pancreatitis in the TKI group.^[7] However, most cases were attributed to TKIs such as sunitinib and sorafenib showing asymptomatic elevation of serum lipase–amylase levels in one-third of patients, with rare association of acute pancreatitis in around 1% only.^[5,6,9] In our report, the 67-year-old man, case of metastatic STS on pazopanib monotherapy, developed asymptomatic necrotizing subclinical pancreatitis incidentally detected on follow-up ¹⁸F-FDG-CECT imaging. The patient had no known risk factors for pancreatitis, and after discontinuation of pazopanib treatment in view of disease progression, follow-up PET-CT imaging showed features of resolving pancreatitis, thus making the likelihood of pazopanib-induced pancreatitis more evident.

Mechanism of pazopanib-induced pancreatitis has several theories and needs further research. One possible mechanism is pazopanib-induced microvascular ischemia due to its antiangiogenic effect, placing patient at risk for pancreatic inflammation. Another theory suggests that TKIs decrease gastrointestinal motility may cause duodenal reflux and activation of pancreatic enzymes. It is also possible that the loss of acinar cells due to VEGF inhibition induces an increase in pancreatic enzymes. It is known that pazopanib association with increase in pancreatic enzymes is not dose dependent.^[9,10] In the event of pancreatitis following TKI administration, treatment should be discontinued promptly and an alternate treatment should be considered.^[11]

¹⁸F-FDG PET-CT is a noninvasive modality to assess treatment response and extent of disease in STS. In sarcoma staging, whole-body PET-CT scan helps detect metastases

at unexpected sites, outside standard field of view of CT and MRI.

Hence, along with oncologists, even radiologists and nuclear medicine physicians should be aware of pancreatitis being a possible adverse event of pazopanib therapy, sometimes clinically silent, and recognize its features on FDG PET-CT scan to guide prompt management and prevent potential complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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