Available online on 15.05.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research



Open Access Full Text Article

Case Report

# Sitagliptin-induced Pancreatitis: A case report and plausible mechanism

Kamel El-Reshaid *, Shaikha Al-Bader **, Zaneta Markova ***

* Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait

** Department of Medicine, Nephrology unit, Amiri hospital, Ministry of health, Kuwait

*** Department of radiology, Qutaina medical center, Kuwait

Article Info:

Article History:

Received 19 March 2021;
Review Completed 12 April 2021
Accepted 17 April 2021;
Available online 15 May 2021

Cite this article as:

El-Reshaid K, Al-Bader S, Markova Z, Sitagliptin-induced Pancreatitis: A case report and plausible mechanism, Journal of Drug Delivery and Therapeutics. 2021; 11(3):1-3
DOI: http://dx.doi.org/10.22270/jddt.v11i3.4679

*Address for Correspondence:

Dr. Kamel El-Reshaid, Professor, Dept. Of Medicine, Faculty of Medicine, Kuwait University,P O Box 24923, 13110 Safat, Kuwait

## Abstract

Drugs are rare cause of acute pancreatitis (AP) with an estimate incidence of 0.1-2%. We present an 63-year-man 1 week history of severe and progressive epigastric pain that radiates to the back and is worse on lying down, who was found to have lipase of more than 813 IU/L. The patient denied current alcohol use. Abdominal ultrasound and abdominal computed tomography scan did not show gallstones or biliary duct abnormalities. For his type-2 diabetes mellitus, he was taking Gliclazide and Metformin for years and Sitagliptin was the only drug added 6 months ago. He was managed conservatively with intravenous fluids, pain medications, and control of diabetes with insulin. Within 3 days, he improved dramatically and was discharged on diabetic diet and Gliclazide 120 mg daily with Lantos 10 units at night. He was instructed to avoid oral hypoglycemia agents from the dipeptidyl-peptidase IV inhibitors (DPP-4i) group. Three weeks later, repeat computed tomography scan of the abdomen showed normal pancreas. On follow up; and up to 1 year, he did not have subsequent AP. The most plausible mechanism of such late-development of rare drug-induced AP is late-encounter with triggering factor/s for Sitagliptin in genetically-predisposed individuals.

Keywords: CT scan, diabetes mellitus, DPP-4i, metformin, pancreatitis, Sitagliptin.

## INTRODUCTION

As compared to biliary tract obstruction and alcohol, drugs are rare cause of acute pancreatitis (AP), with an estimated incidence of 0.1-2% [1]. The true incidence of AP is not known as the evidence is derived mainly from random case reports. Tradionally; case reports with the strongest evidence are those that exclude common etiologies, provide the time interval between the start of treatment with the suspected drug and the development of AP, document response to withdrawal of the drug, and demonstrate recurrent AP upon rechallenge with the drug. However, certain drugs may not satisfy the previous type I hypersensitivity or idiosyncratic reaction in AP and may present with AP months after initiation of treatment. Sitagliptin (S) is one of them and the dramatic improvement of the AP following its withdrawal and lack of subsequent recurrence are the mainstay of diagnosis [2]. In our case report, we present a patient with S-induced AP and discus the possible mechanism of such phenomenon.

## THE CASE:

A 63-year-man presented with 1 week history of severe and progressive epigastric pain that radiates to the back and is worse on lying down. It was associated with recurrent vomiting that did not relieve the pain as well as abdominal distension and constipation. He did not have fever, itching and skin rash. He did not experience similar pains in the past. The patient has type 2-diabetes mellitus (2DM) for more than 20 years which was controlled with Gliclazide (Diamicron MR) 120 mg on daily basis with Metformin (Glucophage) 1000 mg twice daily. In the past 6 months, his DM was uncontrolled and hence S was added in the Metformin tablet as Janovomet (50/1000 mg) twice daily. On his initial presentation; he was in distress of abdominal pain yet not short of breath. He was afebrile and blood pressure was at 110/70 mm Hg with postural hypotension. He had tender and rigid abdomen with diminished bowel sound. Laboratory investigations showed peripheral leukocytic count at 16 X 109/L with 90% neutrophils with normal platelets counts and hemoglobin. Serum sugar was 10 mmol/L. Serum urea, creatinine, electrolytes and liver functions were normal including albumin and bicarbonate. Serum TSH, cholesterol and triglycerides were normal. Serum amylase was elevated at 370 IU/L (Normal: 25-130) as well as serum lipase at 814 IU/L (Normal: 13-60). Urine routine and microscopy revealed 1 (+) glucose yet without ketoneuria, proteinuria, hematuria and pyuria. Ultrasound examination of the abdomen showed an enlarged and edematous pancreas with ill-defined margins. The gall bladder and common bile duct were normal and without stones. Computed tomogram of the abdomen confirmed the findings and confirmed the absence of gall stones and tumor (Figure 1). The patient was treated conservatively with

nasogastric suction, intravenous fluids, broad-spectrum antibiotic prophylaxis and narcotics for pain control. Serum glucose was controlled with insulin drip. Gliclazied and Janovomet were discontinued. Within 3 days, the patient had improved dramatically an oral feed were restarted. He was discharged on diabetic diet and Gliclazide 120 mg daily with Lantos 10 units at night. He was instructed to avoid oral hypoglycemia agents from the dipeptidyl-peptidase IV inhibitors (DPP-4i) group. Three weeks later, repeat CT scan of the abdomen showed normal pancreas (Figure 2). On follow up; and up to 1 year, he did not have subsequent AP.

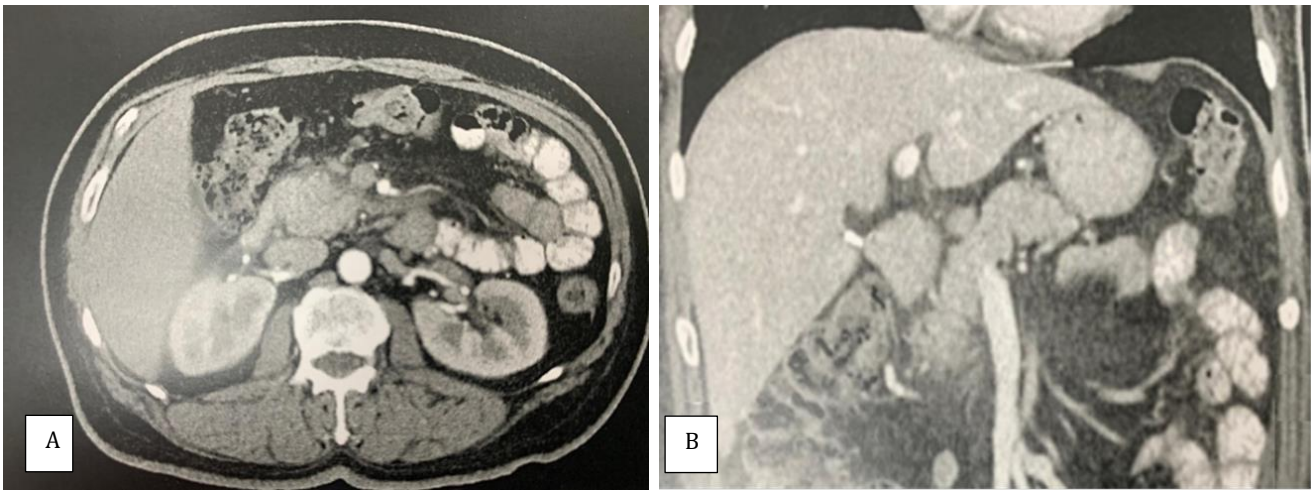


Figure 1: Axial (A) and coronal (B) planes of CT scan of the patient's abdomen, on his initial assessment, showing an enlarged pancreas (Arrow) with indistinct margins and reduced density (due to oedema) with surrounding fat stranding.

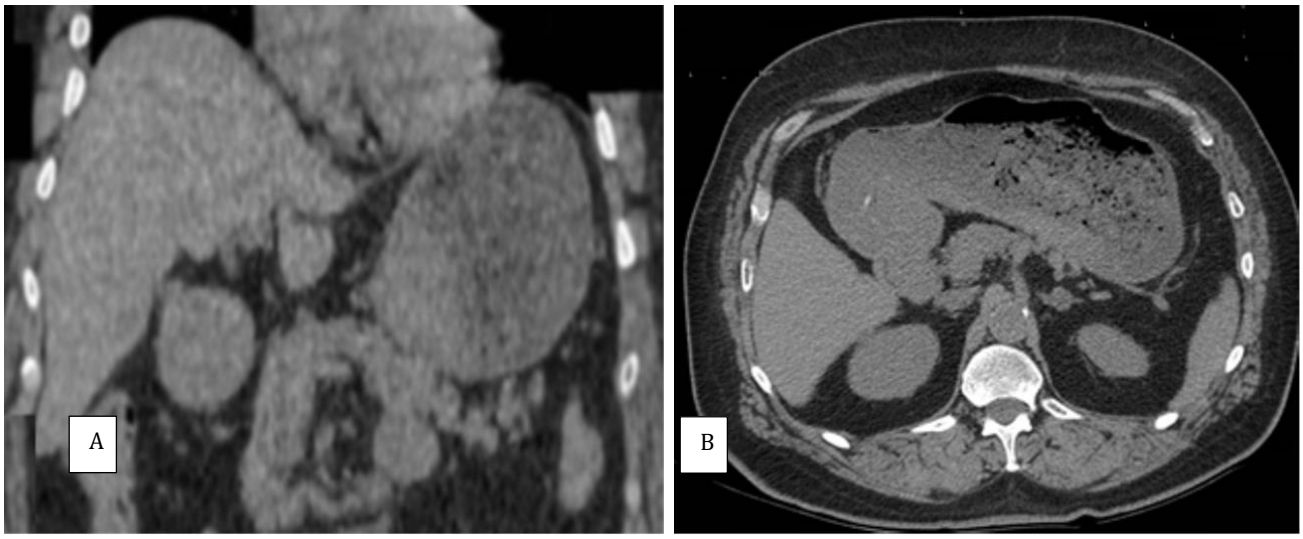


Figure 2: Axial (A) and coronal (B) planes of CT scan of the patient's abdomen, 3 weeks after discontinuation of Sitagliptin treatment, showing normal pancreas (Arrow).

## DISCUSSION

Acute pancreatitis (AP) is a common emergency resulting from inflammation of the pancreas. Diagnosis is established with the cardinal features of acute upper abdominal pain radiating to the back and worse with lying down, Elevated pancreatic enzymes with Amylase or lipase > 3 X upper limit of normal in patients with chronic pancreatitis, or amylase, or lipase > 2 X upper limit of normal in acute ones, and characteristic features on imaging [3]. The mechanism involves premature activation of enzymatic precursors in the acinar cells triggering a self-digestive inflammatory cascade. Pancreatic enzymes such as trypsinogen are synthesized and stored in an inactive – hence harmless – form, and are activated upon release into the lumen of the duodenum via the action of enterokinases [4]. Premature activation may occur for a variety of reasons with gall stones and alcohol being the most common. Toxins (alcohol and organophosphate insecticides), drugs (steroids, thiazides, beta-blockers, protease inhibitors, and azathioprine), metabolic (hypercalcemia, obesity, hypothyroidism and hypertriglyceridemia), structural damage to pancreatic duct post-ERCP and infections (mumps) account for the rest [5]. DPP-4is have been introduced in treatment of T2DM in 2006. They are widely used since they effectively control blood sugar, pose a low risk of hypoglycemia, and are neutral for

weight [6]. DDP-41s inhibit DPP-4, an enzyme that inactivates glucagon-like peptide-1 (GLP-1), leading to prolongation of the half-life of GLP-1 in the body. GLP-1 stimulates glucose-dependent insulin release from the pancreatic islets leading to decreased blood glucose levels. In addition they slow gastric emptying, and inhibit inappropriate post-meal glucagon release [6]. However, a potential association between DPP-4i treatment and pancreatitis and pancreatic cancer was suggested in 2009, based on studies in rats carrying the human islet amyloid polypeptide transgene treated with S, in which increased pancreatic ductal turnover, ductal metaplasia, and isolated pancreatitis were observed [7]. Moreover, in September 2009, The United States Food and Drug Administration (FDA) Adverse Event Reporting System has reported cases of acute pancreatitis that were likely provoked by DPP-4i use, including necrotizing or hemorrhagic pancreatitis, which can be life threatening [8]. Since the FDA believed that there may be an association with S and AP it recommended the manufacturer (Merck pharmaceuticals) to revise S- prescribing information to alert healthcare professionals to this potentially serious adverse drug event [9]. Recently, a meta-analysis study, suggested only a small absolute increased risk for pancreatitis with DPP-4i therapy compared with placebo [10]. The drawback of the latter study was that it was a retrospective study on a rare event. The late development of AP in small proportions of S-treated patients is intriguing. The most plausible theory; is an initial change in pancreatic cells by S which was documented in animal studies [7]. The latter change will predispose to AP after exposure to future triggering-factor/s in genetically predisposed patients. In Conclusion; AP among S-treated patients is a rare yet cautious long-term monitoring is essential since it is not an idiosyncratic or type 1 hypersensitivity reaction.

## REFERENCES:


1. Balani AR, Grendell JH. Drug-induced pancreatitis: incidence, management and prevention. Drug Saf. 2008; 31:823-837.
2. Alkayali T, Ricardo J, Busari K, Saad I. Sitagliptin-induced Pancreatitis: Chronic Use Would Not Spare You the Complication. Cureus. 2020; 12:e7389.
3. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013; 108:1400–1415.
4. Dominguez-Munoz JE, Malfertheiner P, Ditschuneit HH, Blanco-Chavez J, Uhl W, Buchler M, et al. Hyperlipidemia in acute pancreatitis. Relationship with etiology, onset and severity of the disease. Int J Pancreatol 1991; 10:261–267.
5. Whitcomb DC, Yadav D, Adam S, et al. North American Pancreatic Study Group. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatol. 2008; 8:520–531.
6. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35:1364–1379.
7. Matveyenko AV, Dry S, Cox HI, et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. Diabetes 2009; 58:1604–1615
8. FDA Issues Caution for Januvia and Janumet for Acute Pancreatitis. September 28, 2009.
9. "Januvia for type 2 diabetes". Merck & Co. Archived from the original on 2012-09-07.
10. Buse JB, Bethel MA, Green JB, Stevens SR, Lokhnygina Y, Aschner P, Grado CR, Tankova T, Wainstein J, Josse R, Lachin JM, Engel SS, Patel K, Peterson ED, Holman RR; TECOS Study Group. Pancreatic Safety of Sitagliptin in the TECOS Study. Diabetes Care. 2017; 40:164-170.