The European Research Journal

http://www.eurj.org

Case Report

Acute pancreatitis and type 2 diabetes mellitus: who is guilty?

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ABSTRACT

Many factors play a role in the etiology of acute pancreatitis and its pathogenesis is not fully understood. Dipeptidyl peptidase 4 (DPP-4) inhibitors are a new group of agents for the treatment of Diabetes Mellitus (DM). There are some controversies about specific adverse events such as pancreatitis and hypersensitivity reactions. A 50-year-old morbid obese woman presented with upper abdomen pain after the eating food, nausea and vomiting. She was diagnosed with type 2 diabetes mellitus 7 years ago. Vildagliptin had been added to her treatment six months ago. Abdominal examination revealed epigastric tenderness with guarding. Laboratory data revealed elevated pancreatic enzymes. Abdominal computed tomography (CT) showed features of pancreatitis. Vildagliptin was stopped and patient's symptoms had diminished in parallel with normalization of pancreatic enzymes; and at the 5th day patient was discharged with healthy condition. She was free of symptoms and all laboratory data were normal at the 30th day after discharge. It is important to keep in mind that diabetic patients have an increased risk of pancreatitis which may be related to obesity, hyperlipidemia and/or drugs.

Eur Res J 2015;1(2):74-77

Keywords: Diabetes mellitus, acute pancreatitis, dipeptidyl peptidase 4 inhibitors, morbid obesity

Introduction

Alcohol and gallstones are the etiology of chronic pancreatitis in many adults. Other etiologic factors are biliary sludge and microlithiasis, smoking, hypertriglyceridemia, hypercalcemia, drugs, obesity, diabetes, infections and toxins, trauma, pancreas divisum, vascular disease, pregnancy and idiopathic [1]. Patients with diabetes mellitus have a 2 fold increase in the risk of pancreatitis due to factors such as obesity, gallstones, elevated triglycerides, and medications [2, 3]. Obesity increases risk of pancreatitis and pancreas carcinoma due to increased inflammation [4]. Incretin mimetics, glucagon-like peptide-1 receptor (GLP-1R) agonists and DPP-4 inhibitors are new anti-diabetic agents which can cause pancreatitis as side effect. Postmarketing events of acute pancreatitis have been reported in patients receiving sitagliptin, vildagliptin, or saxagliptin. Most of the cases with pancreatitis are reported with sitagliptin among DPP-4 inhibitors; although there are a few case reports related to vildagliptin, too. In this paper, we report a case of acute pancreatitis which may be associated DPP-4 inhibitors, obesity or DM itself.

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Received: 23.03.2015; Accepted: 05.06.2015: Published Online: 04.07.2015

Case Report

A 50-year-old woman presented with upper abdomen pain after the eating food, nausea and vomiting. She was diagnosed with type 2 diabetes mellitus for 7 years, and had been treated with acarbose 150 mg/day, glimepiride 3 mg/day and metformin 2000 mg/day. Six months before this admission she had had an HbA1c level of 7.8 % and vildagliptin, 50 mg twice daily, had been added to her treatment. The patient had no history of alcohol, smoking or gallbladder disease. On physical examination, her weight was 100 kg, height was 150 cm and body mass index was 44.4 kg/m². Abdominal examination revealed epigastric tenderness with guarding. Laboratory findings revealed elevated pancreatic enzymes, increased white blood cells (WBC), and normal triglycerides levels (Table 1). Abdominal CT showed features of pancreatitis (pancreatic enlargement and peri-pancreatic pollution) and gallbladder was free of stones (Figures 1 and 2); intra-extrahepatic bile duct and choledoc diameters were also normal. We conclude the diagnosis of acute pancreatitis on the basis of these findings. Vildagliptin and all other oral anti-diabetic drugs were stopped and patient is started on insulin treatment. She was treated conservatively for pancreatitis. On the next day, amylase and lipase levels had decreased. On the 5th day, a repeat abdominal CT showed that pancreas size was normal and there was no pollution around of the pancreas (Figure 3); amylase and lipase levels have also returned to normal; thus, the patient was discharged. On her control visit at the 30th day after discharge the patient was free of symptoms and all laboratory data were within normal limits.

Discussion

Acute pancreatitis is a disease with a wide spectrum of severity and complications, with different incidences among populations. The etiology of acute pancreatitis is multifactorial including gallstones, chronic alcohol abuse, hypertriglyceridemia, obesity, diabetes mellitus, viral hepatitis and drugs [2].

Two large studies reported that patients with type 2 DM have 1.49-2.83 fold increased risk of acute pancreatitis compared to nondiabetics [2, 3]. The exact cause of the increased risk of pancreatitis in diabetic patients is unclear, however, the known risk factors for pancreatitis appear more frequently in diabetic patients.

Table 1. Basal and follow-up laboratory data.

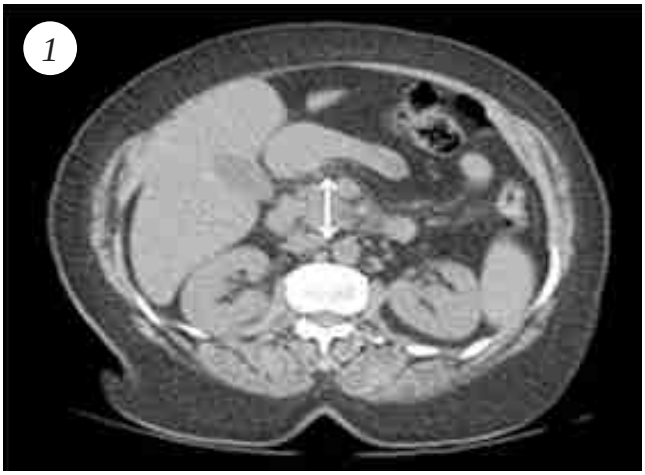
Parameters	1.day	5.day	30.day
WBC (4-10 109/L)	10,1	6,7	8,5
AST (15-37 U/L)	61	16	13
ALT (30-65 U/L)	106	43	15
GGT (5-38 U/L)	272	42	57
Alkaline Phosphatase (30-120 U/L)	255	105	116
Triglyceride (0-200 mg/dl)	110	89	121
Amylase (25-115 U/L)	963	49	53
Lipase (0-60 U/L)	347	40	38

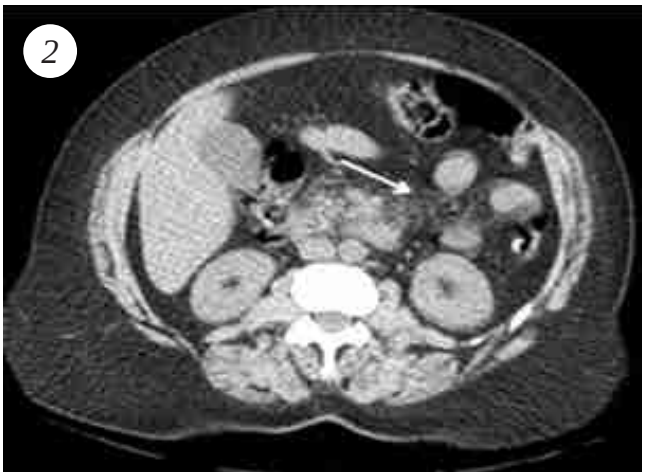
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyltransferase

Although it is a controversial topic, some post-marketing reports, raised the possibility of an increased risk of pancreatitis with incretin based therapies especially related GLP-1 agonists and sitagliptin [5-7]. Between 2006 and 2009 there were 88 post marketing reports of severe pancreatitis associated sitagliptin [8]. A study evaluating the US Food and Drug Administration Adverse Event Reporting System data notifying a 6-fold increased risk of pancreatitis in patients taking exenatide or sitagliptin has attracted attention about pancreatitis side effect related to these drugs [9]. However, in another analysis, which comprised 20.312 patients treated with a DPP-4 inhibitor and 13.569 patients treated with either placebo or a comparator. There was no evidence of an increase in the incidence of pancreatitis with DPP-4 inhibitor therapy [10]. The most common adverse effects of vildagliptin are headache, nasopharyngitis, cough, dizziness and increased sweating. Uptoday we could find three pancreatitis case reports related to vildagliptin in the literature [7, 10, 11]. The mechanisms of pancreatitis related with incretin mimetics are uncertain. Some animal studies revealed that sitagliptin increased pancreatic ductal replication, ductal metaplasia and rarely induced pancreatitis in mouse model [12, 13].

Obesity increases risk of acute and chronic pancreatitis because of chronic inflammation [4, 14]. In addition to this, obesity also affects the mortality, local or systemic complications of acute pancreatitis as a prognostic factors. Interestingly, obese patients have better prognosis than non-obese patients after pancreatitis, which is called "obesity paradox" [15].

Our patient had obesity, type 2 DM and DPP-4 inhibitor usage as risk factors for pancreatitis. The acute pancreatitis developed in this patient while being treated with vildagliptin but the presence of a causal relation could not be determined. Two of case reports have reported early pancreatitis within a month after vildagliptin [7, 11] and another reported pancreatitis after 6 months [10]. Our patient had pancreatitis after 6 months. Appearance of pancreatitis after vildagliptin, and resolving of sypmtoms, physical and imaging findings and normalization of laboratory data rapidly after its discontinuation, suggest that pancreatitis may have been caused by vildagliptin. In the light of above





Figures 1 and 2. Basal axial CT images showing pancreatic enlargement and peri-pancreatic pollution.

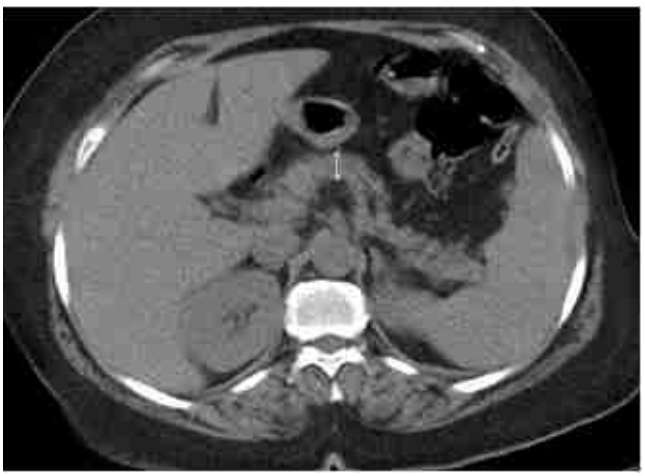


Figure 3. Postpancreatic axial CT: Pancreas size is normal and there is no pollution.

mentioned limited data, because time frames upto appearance of pancreatitis is different, we assume that vildaglipitin related pancreatitis may be an idiosyncratic effect.

In conclusion, DPP-4 inhibitors may also be considered besides the classic risk factors of pancreatitis in patients with DM. We assume that antidiabetic treatment must be individualized keeping also in mind that each diabetic patient may have a diverse risk factor(s) for pancreatitis.

Informed Consent

Written informed consent was obtained from patient who participated in this case report

Conflict of interest

The authors declared no conflict of interests

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