Clinical Medicine Insights: Case Reports

CASE REPORT

A Case of Severe Acute Necrotizing Pancreatitis after Administration of Sitagliptin

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Abstract: A 55-year-old Japanese man with a 3-year history of type 2 diabetes mellitus was admitted to our hospital for upper abdominal pain. Control of diabetes mellitus was good with voglibose and metformin, with sitagliptin added to this regimen 8 months prior. His pancreatic enzyme levels were elevated, and abdominal computed tomography (CT) showed diffuse pancreatic swelling with fluid accumulation and ascites of CT grade 3. The patient was diagnosed with severe acute pancreatitis. There were no obvious causes for pancreatitis except the recently administered sitagliptin. Since incretin-related drugs entered the market, the number of incretin-related drugs prescriptions rapidly increased and so did the incidence of pancreatitis. There are several reports suggesting the correlation between incretin-related drugs and pancreatitis, such as a report based on data obtained from the United States Food and Drug Administration (FDA) which revealed a significant correlation between the administration of exenatide or sitagliptin and pancreatitis. However, there also is a report that denied the evidence for such in a large cohort study. The relation between incretin based drugs and pancreatitis is still controversial.

Keywords: diabetes mellitus, DPP-4 inhibitor, sitagliptin, pancreatitis

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs are incretin-based drugs; these drugs have found widespread use as a new class of anti-hyperglycemic agents effective for treating diabetes mellitus. GLP-1 is reported to slow food absorption, improve insulin production by the pancreas, and increase beta cell mass, whereas DPP-4 inhibitors act by delaying the breakdown of GLP-1. Both types of agents lower glucose levels without weight gain and with a reduced risk of hypoglycemia, representing clear advantages over other glucose-lowering agents.[1] These beneficial aspects in addition to ease of use, particularly in the case of the DPP-4 inhibitors, has accelerated their worldwide use. As these are newly developed drugs, their long-term side effects are still unknown. However, concerns regarding the association between the use of these drugs and pancreatitis and pancreatic or thyroid cancers have increased, and need to be investigated.

Case Report

A 55-year-old Japanese man with type 2 diabetes mellitus was admitted to our hospital with a 24 hour history of upper abdominal pain. At a previous visit to another hospital, he had been diagnosed with gastric ulcer and prescribed a histamine H2 blocker. However, his symptoms worsened, with increased back pain and frequent vomiting. At the time of the diagnosis, his type 2 diabetes mellitus had been controlled with 0.6 mg of voglibose and 500 mg of metformin per day, both initiated 3 years before. In addition with that, 50 mg of sitagliptin per day had been added to his treatment regimen 8 months earlier, and diabetes mellitus was in good control with HbA_{1c} below 6.5%. His latest fasting glucose and glycosylated hemoglobin levels were 111 mg/dL and 6.2%, respectively. He had no history of chronic pancreatitis, pancreatic tumor, hypercalcemia, or habitual alcohol use. Hyperlipidemia had also been diagnosed at the same time of the diabetes mellitus diagnosis, however was well controlled with 10 mg of atorvastatin.

On physical examination, his height, weight, and body mass index were found to be 175 cm, 77.2 kg, and 25.2 kg/m^2, respectively. His body temperature, blood pressure, and heart rate were 38.1 °C, 172/88 mmHg, and 98 beats/min, respectively. Upper abdominal tenderness was observed without mass or rigidity. C-reactive protein level was 0.1 mg/dL, and white blood cell count was 21800/μL. His pancreatic and liver enzyme level were elevated at the hospitalization (amylase level, 3581 IU/L; pancreatic amylase level, 3435 IU/L; elastase-1 level, 6749 ng/dL, aspartate aminotransferase level, 266 IU/L; and alanine aminotransferase level, 137 IU/L). Abdominal computed tomography (CT) revealed elevated adipose tissue concentration in the pancreas, duodenum, and transverse colon. Ascites was present on the liver surface, abdominopelvic cavity, peripancreatic area, and posterior pararenal extraperitoneal space; furthermore, a gallstone was detected (Fig. 1A). The Acute Physiology, Age, and Chronic Health Evaluation

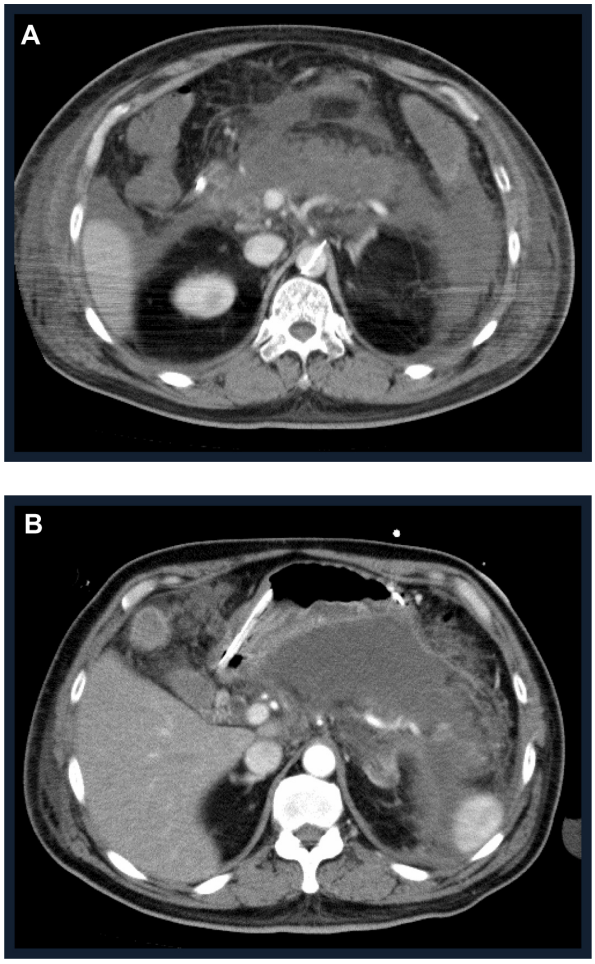

Figure 1. A computed tomography (CT) scan of the abdomen on admission revealed peripancreatic inflammatory changes, with ascites on liver surface, abdominopelic cavity, peripancreaticposterior pararenal extraperitoneal space (**A**). A CT scan of the abdomen on 13th day after hospitalization revealed poorly enhanced areas in the body and tail of the pancreas consistent with necrosis and cyst formation (**B**).

(APACHE) score was 6 points, Systemic Inflammatory Response Syndrome (SIRS) score was 3, and CT scan severity index was grade 3. He was diagnosed with severe acute pancreatitis.

Clinical Course

His condition was complicated by severe systemic inflammation, disseminated intravascular coagulation, and respiratory insufficiency, which required treatment comprising intravenous fluid therapy, administration of antibiotics and pancreatic enzyme inhibitors systemically and via an arterial catheter, use of a respirator, and continuous hemodiafiltration in the intensive care unit. Three days after admission, total bilirubin increased. However, CT revealed no signs of common bile duct dilatation, choledocholithiasis, or gallstone incarceration. Hyperbilirubinemia improved a few days after treatment for pancreatitis, and there was no recurrence of pancreatitis or hyperbilirubinemia during hospitalization; therefore, we eliminated pancreatitis by gallstone.

Extensive inflammation and necrosis were observed, and the pancreatic cyst was resistant to therapy, requiring nearly 3 months of daily drainage and weekly necrectomy (Fig. 1B). On day 87 after admission, an oral diet was started. In spite of the improvement in pancreatitis, his insulin levels gradually decreased, with serum and urine C-peptide concentrations of 0.52 ng/mL and 38.6 μg/day, respectively. The delta C-peptide level after glucagon loading was 0.31 ng/mL (serum C-peptide levels before and 6 min after glucagon stimulation were 0.38 and 0.69 mg/dL, respectively). At that time, a diagnosis of pancreatic diabetes was made. His diabetes mellitus was well controlled with a total insulin injection of 28 units per day. He was discharged from hospital 111 days after admission. There is no recurrence of pancreatitis for 14 months after discontinuation of sitagliptin.

Discussion

Acute pancreatitis is known to be fatal, with a mortality rate of nearly 10% if severe disease is not diagnosed and if appropriate treatments are not initiated immediately.[2] Even in cases in which diagnosis and treatment are rapid, severe pancreatitis can prove life threatening. Various causes for pancreatitis include alcohol consumption, gallstones, idiopathic chronic pancreatitis, endoscopic retrograde cholangiopancreatography or endoscopic sphincterotomy, trauma, malignancy, autoimmune hypercalcemia, hyperlipidemia, or certain drugs, of which alcohol and gallstone are the 2 primary causes in Japan.[3] Our patient did not have a history of alcohol intake within the few months prior to hospitalization. In addition, he had no history of a medical condition that could cause acute pancreatitis, except hyperlipidemia, which was well controlled with atorvastatin for the past 3 years. Because abdominal CT revealed gallstones and bilirubin was elevated after hospitalization, we first suspected gallstone pancreatitis. However, neither CT nor ultrasound imaging indicated biliary ductal dilatation involving the common bile duct. Hyperbilirubinemia improved only a few days after treatment for pancreatitis had begun, suggesting that bilirubinemia might have developed as a result of the spread of inflammation from pancreatitis. In addition, there was no recurrence of pancreatitis for 14 months without gall stone treatment.

Medications are also known to cause pancreatitis, with a frequency of 1.4% to 2.0%.[4] There are several reports describing pancreatitis associated with metformin and atorvastatin. In the Japanese guidelines for pancreatitis published in 2010, metformin and atorvastatin are not included. However, as one of the HMG-CoA reductase inhibitors group, pravastatin is classified within class I (medications in which at least 1 case report described a recurrence of acute pancreatitis with a rechallenge with the drug).[5] An exhaustive search of the literature revealed only 6 and 5 cases of pancreatitis associated with atorvastatin[6–11] and metformin, respectively.[12–16] In most of these cases, drugs were administered for less than a year. With the increased use of incretin-related drugs, a few cases of acute pancreatitis that had been suspected to be related with DPP-4 inhibitors or GLP-1 agonists have been reported. To the best of our knowledge, only 4 cases of pancreatitis related to sitagliptin and vildagliptin have been reported (Table 1). One patient was treated with sitagliptin for 8 weeks;[17] 2 other patients were switched from sitagliptin to vildagliptin 2 weeks or 6 months before;[18,19] and 1 patient received combined therapy of sitagliptin and exenatide for a few weeks.[20] Raschi et al reported a significant correlation between GLP-1, DPP-4 inhibitors, and pancreatitis, on the basis of the information in the FDA database.[21] Among these drugs, sitagliptin and exenatide are reported to have a

Table 1. Reports of pancreatitis cases related with DPP-4 inhibitors.

Case	Age	Sex	DPP-4 inhibitor	GLP-1	Duration	Other OHA	CT grade	Ref.
1	53	F	Sitagliptin	N/A	8 weeks	Metformin, gliclazide	1	17
2	76	F	Sitagliptin	Exenatide	Few weeks	N/A	3–4	18
3	74	M	Sitagliptin → vildagliptin	N/A	2 weeks	Glimepirid, pioglitazone	1	19
4	61	F	Sitagliptin → vildagliptin	N/A	5 weeks	Metformin	2	20

strong correlation with pancreatitis. The average duration from administration of sitagliptin and exenatide to onset of pancreatitis was 444 days and 515 days, respectively, which was similar to that in our case in which pancreatitis was diagnosed 8 months after the administration of sitagliptin.

Animal studies showed that GLP-1-based treatments induced pancreatitis in a rat model of type 2 diabetes, with medications such as sitagliptin increasing pancreatic ductal replication and acinar-to-ductal metaplasia.[22–24] Exenatide has also been found to induce pancreatic acinar inflammation, with abnormal acinar cells and a high frequency of cell death.[25] Further, in type 2 diabetes patients, pancreatitis is 6-fold more likely to be reported in association with sitagliptin or exenatide than with other therapies.[23] These drugs are also suggested to be correlated to pancreatitis and increased risks for pancreatic and thyroid cancers. However, Dore et al. reported that no evidence was found for an increased incidence of pancreatitis in a large cohort of patients treated with either exenatide or sitagliptin, compared to those treated with metformin or glyburide.[26]

Conclusion

There are many case reports and studies suggesting that GLP-1 agonists and DPP-4 inhibitors, which are widely used and promoted for the treatment of type 2 diabetes, could have serious accidental and unexpected side effects. We reported a case of acute necrotic pancreatitis in which a DPP-4 inhibitor had been administered 8 months before. While the DPP-4 inhibitor was suspected to be the cause of pancreatitis, the correlation between incretin-based drugs and pancreatitis remains controversial.

Author Contributions

Conceived and designed the experiments: MS. Analysed the data: MS. Wrote the first draft of the manuscript: MS. Contributed to the writing of the manuscript: MS, NH. Agree with the manuscript results and conclusions: MS, NH, AY, KK, GY. Jointly developed the structure and arguments for the paper: MS, NH. Made critical revisions and approved final version: MS, NH. All authors reviewed and approved of the final manuscript.

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Competing Interests

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