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# Mildly symptomatic liraglutide-induced acute pancreatitis in a patient with type 2 diabetes mellitus: a case report

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## Abstract

**Background:** Acute pancreatitis (AP) represents a serious clinical challenge as it can threaten the patient's life if it is missed or improperly managed. Liraglutide is one of the glucagon-like peptide 1 receptor agonists (GLP1-RA) which represent a novel class of antidiabetic medications in the Egyptian market. Hereby, we report a case of liraglutide-induced acute pancreatitis with atypical presentation.

**Case presentation:** A 53-year-old Egyptian male patient with diabetes presented to the emergency department with abdominal discomfort and vomiting without significant abdominal pain. Serum lipase and amylase were elevated more than three folds the upper normal limit (NUL 300 and 110 U/L respectively); abdominal ultrasonography was inconclusive, but contrast-enhanced computed tomography was diagnostic. A diagnosis of liraglutide-induced AP was built after exclusion of other causes. After admission, his medications were modified and improved clinically after 1 week.

**Conclusion:** Mildly symptomatic AP in diabetic patients is a clinical challenge as it can be missed. Therefore, in certain clinical situations, AP should be suspected in patients administrating liraglutide particularly for those with autonomic neuropathy.

**Keywords:** Liraglutide, Acute pancreatitis, Type 2 diabetes mellitus, Case report

## Background

Acute pancreatitis (AP) is conventionally diagnosed by the presence of two of the three following criteria: characteristic abdominal pain, elevated serum amylase and/or lipase more than three folds the upper normal limit, and characteristic abdominal imaging findings [1]. Gallstones and alcohol are the leading causes of AP; however, other causes such as hypertriglyceridemia, hyper/hypocalcemia, autoimmune, infection, neoplasm, genetics, trauma, endoscopic retrograde cholangiopancreatography (ERCP), and drug-induced pancreatitis (DIP) are increasingly recognized. More than 500 drugs were reported to induce AP [2]; hereby, we report a case of DIP with atypical presentation.

## Case presentation

A male patient 53 years old experienced mild abdominal discomfort and repeated vomiting for 1 week before admission with gradual onset and progressive course preceded by nausea, anorexia, excess flatus, and chronic constipation (1–2 times/week). He had type 2 diabetes mellitus (T2D) and hypertension (8 and 2 years ago respectively), with no history of fever, alcohol consumption, or drug intake rather than his daily medications that included insulin degludec 26 U OD, liraglutide 1.8 mg OD, metformin 500 mg BID for T2D, and lisinopril 10 mg OD for hypertension, and no past history of infectious diseases, blood transfusion, surgery, ICU

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admission, or alcohol consumption with irrelevant family history.

Physical examination showed body weight 108 kg, BMI 34.5 kg/m$^2$, waist circumference 124 cm, positive acanthosis nigricans sign, ABP 130/75 mmHg, pulse 105/min, temperature 38.2 °C, and respiratory rate 20/min. Abdominal examination showed marked diffuse abdominal distension with epigastric tenderness on palpation and negative shifting dullness sign. Chest and heart examination showed no abnormal signs. The right foot showed a small uncomplicated pressure ulcer.

Laboratory tests are done as shown in Table 1. Abdominal ultrasonography (US) revealed excess colonic gas, sluggish bowel motion, no gall bladder ( GB) stones

**Table 1** Laboratory parameters of the patient before and throughout acute pancreatitis

| Parameter | 3 months before | Day 0 in ER | 3rd day | 8th day |
|---|---|---|---|---|
| **Lipase (U/L)** | 74 | 1880 | 867 | 290 |
| **Amylase (U/L)** | 66 | 1060 | 450 | 124 |
| **ESR (mm/h)** | 10 | 75 | 45 | 23 |
| **CRP (mg/L)** | 6 | 124 | 37 | 10 |
| **Creatinine (mg/dL)** | 1 | 1.4 | 1.2 | 1.12 |
| **BUN (mg/dL)** | 16 | 20 | 18 | 18 |
| **Calcium (mg/dL)** | 8.9 | 10.1 | 9.15 | 9.45 |
| **Phosphorus (mg/dL)** | 4.1 | 4.51 | 4.35 | 4.2 |
| **Magnesium (mg/dL)** | 2.1 | 2.15 | 2.19 | 2.2 |
| **Ferritin (ng/ml)** | 42 | 90 | 75 | 70 |
| **ALT (IU/L)** | 36 | 100 | 73 | 47 |
| **AST (IU/L)** | 28 | 71 | 36 | 22 |
| **GGT (IU/L)** | 44 | 119 | 81 | 51 |
| **Albumin (g/dL)** | 4.6 | 4.5 | 4.6 | 4.6 |
| **Alkaline phosphatase (IU/L)** | 36 | 58 | 38 | 38 |
| **Total bilirubin (mg/dL)** | 1.1 | 1.2 | 1 | 1.1 |
| **Lipid profile (mg/dL)** | | | | |
| **TC** | 132 | 199 | 187 | 156 |
| **TG** | 144 | 146 | 131 | 145 |
| **HDL-C** | 47 | 46 | 35 | 50 |
| **LDL-C** | 57 | 124 | 126 | 67 |
| **VLDL-C** | 29 | 29 | 26 | 29 |
| **WBCs ($\times 10^3$)** | 7.9 | 16.3 | 7.9 | 7.4 |
| **RBCs ($\times 10^6$)** | 4.69 | 4.59 | 4.46 | 4.75 |
| **HB (g/dL)** | 13.6 | 13.3 | 13.4 | 13.1 |
| **Hct (%)** | 40.3 | 40.4 | 38.7 | 41.5 |
| **MCV (fL)** | 85.9 | 88 | 86.8 | 87.4 |
| **MCH (pg)** | 29 | 29 | 30 | 27.6 |
| **MCHC (g/dL)** | 33.7 | 32.9 | 34.6 | 31.5 |
| **RDW (%)** | 12.8 | 13 | 13.1 | 13.3 |
| **PLT ($\times 10^3$)** | 350 | 320 | 306 | 336 |
| **MPV (fL)** | 8.2 | 8.1 | 8.4 | 7.9 |
| **Segment (%)** | 55.8 | 53.3 | 53.4 | 53.4 |
| **Lymphocyte (%)** | 23 | 29.9 | 30.3 | 31.4 |
| **Monocyte (%)** | 10.6 | 10.3 | 10.1 | 9.2 |
| **Eosinophil (%)** | 9.4 | 5.7 | 5 | 5 |
| **Basophil (%)** | 1.2 | 0.8 | 1.2 | 1 |

or dilated intrahepatic biliary radicles (IHBR), homogenous bright liver parenchyma and normal kidneys with difficult visualization of the pancreas, and no ascites or lymphadenopathy. The provisional diagnosis was acute pancreatitis, but it was uncertain due to the absence of the characteristic pain and inconclusive abdominal US. Multiphasic contrast-enhanced computed tomography (CECT) of the abdomen was done and revealed a diffuse enlarged pancreas with heterogeneous enhancement of the parenchyma, irregular contour with peripancreatic edema, and fat strands. There were no necrotic signs, abnormal fluid collection, pseudocyst, or mass. CT severity index (CTSI) score was 2. A diagnosis of liraglutide-induced acute pancreatitis was built.

Three months prior to the attack, the patient was on oral antidiabetic drugs (glimepride 6 mg OD and vildagliptin/metformin 50/1000 BID) with HBA1c that was 9.23% out of target complicated with right foot neuropathic ulcer and diabetic gastroparesis symptoms such as chronic constipation and persistent fullness. The treatment was modified to basal insulin degludec 10 IU with gradual up-titrated dose according to the fasting plasma glucose till reaching 26 U OD plus GLP1-RA (liraglutide) with gradual up-titrated dose from 0.6, 1.2, to 1.8 mg OD added on metformin 500 mg BID according to the American Diabetes Association guidelines (ADA 2020) [3]. Prior to liraglutide initiation, the patient was secured against GLP1-RA contraindication such as a history of liraglutide allergy, pancreatitis or pancreatic cancer, medullary thyroid carcinoma (MTC), or multiple endocrine neoplasia (MEN) 2 in the patient or his family. Improved self-monitoring blood glucose (SMBG) readings and lowered HBA1c to 7.71% with weight loss of 2.7 kg over the last 3 months were noticed.

After admission, the patient started soft enteral feeding, prophylactic antibiotic with basal-bolus insulin regimen of insulin degludec and insulin aspart with frequent assessment of serum plasma glucose, electrolytes, and arterial blood gases.

After 3 days, the patient exhibited slight improvement of serum lipase, amylase, and inflammatory markers with the abdominal US that showed a moderate colonic distension with a slight improvement of the bowel motion without pain on probing. Five days later, CECT was repeated and showed essentially normal pancreatic status with improved laboratory findings (Table 1). Our patient had liraglutide-induced mildly symptomatic acute pancreatitis. The most challenging risk was the absence of significant pain which represents an alarming symptom.

## Discussion

Despite the proven safety and efficacy in the management of T2D, GLP1-RA have been associated with AP particularly exenatide and to lesser frequency liraglutide [4]. The majority of patients exhibited a mild self-limited disease, but about 20% may have moderate to severe AP. Traditionally, accurate history taking and pancreatic amylase, lipase, and inflammatory markers in addition to the abdominal US are the pillars of AP diagnosis; however, CECT is required only if the diagnosis is uncertain [5]. Many scores are traditionally used to detect the severity and prognosis of AP such as Ranson criteria (1974), Glasgow-Imrie score (1978), Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS II) (1984), Sequential Organ Failure Assessment (SOFA), CT severity index (CTSI), Bedside Index of Severity in Acute Pancreatitis (BISAP) score (2008), and Japanese Severity Score [6].

Our patient experienced liraglutide-induced AP without the characteristic pain pattern that may be attributed to diabetic autonomic neuropathy. The absence of pain represents a serious clinical challenge with probable missed diagnosis of AP. Funch et al. [7] found that liraglutide was not associated with an increased risk of AP, but they reported concerns regarding the limited numbers, rarity of outcomes, and unmeasured confounding factors and ethnicity issue. The US Food and Drug Administration (FDA) and European Medicine Agency reviewed the existing data about GLP1-RA, and till now, they did not get a final conclusion regarding a causal relationship between GLP1-RA and AP; therefore, they keep safety risks for these drugs. Both agencies called for more research on this issue [8]. Clinical trials of liraglutide revealed more cases of AP in the liraglutide arms than the control arms. However, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the recent meta-analyses did not consider AP as a major adverse effect of liraglutide [9, 10].

## Conclusion

Acute pancreatitis represents a potential complication of liraglutide. Therefore, in certain clinical situations, assessment of pancreatic enzymes for patients administrating liraglutide is required to avoid missed diagnosis and subsequent serious complications of AP that may threaten patients' lives particularly in diabetic patients with autonomic neuropathy.

### Abbreviations

AP: Acute pancreatitis; T2D: Type 2 diabetes mellitus; GLP1-RA: Glucagon-like peptide-receptor agonists; ERCP: Endoscopic retrograde cholangiopancreatography; DIP: Drug-induced pancreatitis; US: Ultrasonography; IHBR: Intrahepatic biliary radicles; CECT: Contrast-enhanced computed tomography; CTSI: CT severity index; ADA: American Diabetes Association; MTC: Medullary thyroid carcinoma; MEN: Multiple endocrine neoplasia; SMBG: Self-monitoring blood glucose; FDA: The US Food and Drug Administration

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**Authors' contributions**
Author 1 "M.A.G" carried out the conception and literature review, analyzed and interpreted the patient's data, and wrote the final manuscript. Author 2 "A.H.E" contributed in the laboratory work and critical revision of the draft and shared in the final manuscript writing. The authors read and approved the final manuscript.

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**Consent for publication**
Written consent to publish was obtained from the patient prior to submission and is available.

**Competing interests**
None

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## Publisher's Note