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CASE REPORT

Diabetic Ketoacidosis and Hypertriglyceridemia-induced Pancreatitis: Can the Perfect Storm Happen Twice?

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Abstract

This case report describes the recurrence of diabetic ketoacidosis (DKA) leading to hypertriglyceridemia-induced pancreatitis. Hypertriglyceridemia is present in 2−5% of patients with diabetic ketoacidosis. Hypertriglyceridemia-induced pancreatitis occurs in up to 4% of patients with diabetic ketoacidosis and is a well-reported complication. This is the first case report to the author's knowledge, where the same patient had two separate episodes of acute pancreatitis that have been attributed to diabetic ketoacidosis and resultant severe hypertriglyceridemia, etiology determined to be medication non-compliance. DKA and acute pancreatitis can co-exist, and hypertriglyceridemia has been the predominant pathogenetic link between the two conditions. We also describe the pathophysiology and treatment of hypertriglyceridemia-induced pancreatitis in diabetic ketoacidosis.

Keywords: Diabetic ketoacidosis, Insulin therapy, Intravenous insulin therapy, Hypertriglyceridemia, Acute pancreatitis, Anion gap metabolic acidosis, Diabetes Mellitus, Medication nonadherence, Non compliance, Dyslipidemia

1. Introduction

Acute pancreatitis is one of the most common causes of hospitalization for a gastrointestinal cause in the United States. The most common causes are alcohol abuse, gall stones, and hypertriglyceridemia.[1] Diabetic ketoacidosis (DKA) is an important complication of diabetes mellitus, arising predominantly from a lack of medication compliance. In DKA, with the body driving itself into a predominantly catabolic phase due to a relative absence of insulin in the bloodstream, there is often moderate to severe hypertriglyceridemia.[2] DKA and acute pancreatitis can co-exist, and hypertriglyceridemia has been the predominant pathogenetic link between the two conditions.[3] Hypertriglyceridemia-induced pancreatitis occurs in up to 4% of patients with diabetic ketoacidosis and is a well-reported complication.

2. Case presentation

The patient is a 32-year-old male with a medical history of type 2 diabetes mellitus and dyslipidemia presented to the emergency department with a two-day history of abdominal pain. He initially noticed the pain after a heavy meal, and the pain has since been continuous and progressive. The pain became very sharp, a ten-on-ten intensity, radiating to his back, worsened with leaning back or trying to lie down. He reported being excessively nauseous, with a few episodes of non-bloody, non-bilious vomiting. He denied any recent changes in his diet, binge drinking, recent hospitalizations, or medication changes. His home medications included fenofibrate 48 mg daily, metformin 500 mg two times a day, insulin glargine 30 units at bedtime, and insulin lispro 7 units three times a day with meals. He reported being occasionally non-compliant with his medications, especially insulin, due to forgetfulness

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and lack of motivation. He says he is on an average American diet and is non-compliant with the diabetic diet advised to him by his primary care physician. He reported following a sedentary lifestyle, with very minimal physical activity or exercise. On presentation, his vital signs were temperature of 98.9-degree Fahrenheit, heart rate of 91 beats per minute, blood pressure 127/84 mmHg, and respiratory rate of 18 per minute. He appeared to be in distress from the pain, sitting in the leaning forward position. On physical examination, he was alert and oriented. His lungs had good air entry and were clear to auscultation bilaterally. He was tachycardic, S1 and S2 heard, with no appreciable murmurs. On abdominal examination, there was epigastric tenderness with voluntary guarding. There was no lower extremity edema.

Chart review revealed that two years prior, the patient had a hospitalization with similar complaints and was treated for diabetic ketoacidosis which was complicated by hypertriglyceridemia and pancreatitis. Similarities in laboratory tests and treatment plan between the 2 episodes are as discussed below. He was admitted 2 year ago with nausea, vomiting, epigastric abdominal pain. Labs revealed hyperglycemia at 400 mg/dl, elevated anion gap of 16, elevated lipase level. He was admitted to ICU for management of Diabetic ketoacidosis with intravenous insulin drip. Ultrasound abdomen was suggestive of pancreatitis, no gall stones. The next day morning his lipid panel was back, with elevated triglycerides level at 2330 mg/dl and hemoglobin A1c at 10. Laboratory tests this admission revealed a normal complete blood count, blood glucose level at 256 mg/dL, an elevated anion gap of greater than 17, and an elevated beta-hydroxybutyrate of 74.50 mg/dL. A fasting triglyceride level on admission was 5223 mg/dL (worse compared to first episode). The hemoglobin A1c level the next day was noted to be at 11.7. Lipase level was 257 IU/L. Relevant admission labs have been summarized in Tables 1 and 2. Ultrasonography of the abdomen revealed a normal-appearing gall bladder and no dilation of the common bile duct. The differential diagnoses for high anion metabolic acidosis would include lactic acidosis, ketoacidosis like uncontrolled diabetes or starvation, methanol or ethylene glycol ingestion, and aspirin toxicity. In this patient, because of prior history of uncontrolled diabetes, diabetic ketoacidosis was the most likely diagnosis. Because of the character of abdominal pain, and an elevated lipase level that was more than three times the upper limit of normal, a diagnosis of acute pancreatitis was made. The most common etiology for acute pancreatitis includes gall stones, alcohol, hypertriglyceridemia, and certain medications like valproic acid, sulfonamides, diuretics, tetracycline, azathioprine. In this patient, ultrasonography of the abdomen failed to reveal any evidence of cholelithiasis, and the patient has no history of significant alcohol abuse. Hypertriglyceridemia was presumed to be the most likely etiology of pancreatitis in this patient. The patient was treated with aggressive intravenous hydration with normal saline and was started on an intravenous insulin drip at a rate of 0.1 units/kg/hour. A low rate was chosen for the insulin drip because of the patient's relative euglycemia despite the high anion gap metabolic acidosis. The patient's basal metabolic profile was closely followed, and the insulin drip was titrated to maintain euglycemia whilst ensuring the resolution of the acidemia. The insulin drip was eventually bridged to subcutaneous long-acting insulin therapy with insulin glargine after 48 h. The patient's triglyceride levels improved to 237 mg/dL. On the prior admission, he was managed similarly with insulin drip, intravenous hydration with improvement in triglycerides level, was discharged home on insulin and fenofibrate that he reported being non-compliant with, which triggered the current episode.

The patient was discharged home on hospital day 6, on an insulin regimen with insulin glargine 30 units at bedtime, insulin lispro 7 units three times a day with meals, and oral Fenofibrate 48 mg daily. Medication adherence was reinforced. The patient was advised to follow a diabetic diet that is low in cholesterol. Lifestyle modifications were advised and written instructions for a structured exercise program were given to the patient. The patient was given a referral to an endocrinology clinic where he has been following up periodically since discharge. He has not had hospitalizations for diabetic ketoacidosis since then.

Table 1. Pertinent labs.

	Reference range	Day 1	Day 3
Blood glucose (mg/dl)	70−110	256	163
Anion gap (mEq/L)	8−16	17	8
Beta-hydroxybutyrate (mg/dl)	0.00−4.16	74.50	19.50
Lipase (International unit/L)	9−50	523	86
Triglycerides	<150	5223	237
Hemoglobin A1c	<5.7	11.7	N/A
Sodium (mEq/L)	135−145	130	132

Table 2. Arterial blood gas levels.

	Reference Range	Day 1
pH	7.35−7.45	7.18
pCO2 (mmHg)	35−48	22
Bicarbonate (mmol/L)	22−30	14

Interpretation: Metabolic acidosis with respiratory compensation.

3. Discussion

Diabetic ketoacidosis is a complication of diabetes and is characterized by the triad of hyperglycemia resulting from relative insulin deficiency, leading to ketosis, and high anion gap metabolic acidosis. It is a dreaded complication in patients with type I diabetes, and less commonly in those with type 2 diabetes mellitus. Prior undiagnosed diabetes, noncompliance to medications and insulin injections (as in the case discussed above), and acute illness or infections are the major etiologies.[4] Lack of insulin results in lipolysis in adipose tissue with the release of free fatty acids. Increased delivery of free fatty acids to the liver leads to the high output of very-low-density lipoproteins, which, when coupled with the inhibition of lipoprotein lipase in peripheral tissues, results in hypertriglyceridemia. Hypertriglyceridemia is a relatively rare cause of acute pancreatitis, accounting for 1−4% of the total number of cases.[5] Triglyceride levels greater than 1000 mg/dl are considered to be a significant risk factor and if present on disease presentation, is usually enough to make hypertriglyceridemia the presumed etiology. Triglycerides themselves do not appear to be toxic, it is the breakdown of triglycerides into toxic fatty acids (FA) by pancreatic lipases that causes lipotoxicity during acute pancreatitis. The severity of acute pancreatitis in patients with hypertriglyceridemia is dependent on both the inflammatory response caused by pancreatitis itself, and the injury caused by lipotoxicity from triglyceride hydrolysis. All these can damage the pancreatic tissue, cause inflammation leading to acute pancreatitis. The triad of diabetic ketoacidosis, resultant hypertriglyceridemia, and acute pancreatitis is a rare occurrence but is described well in prior case reports.

Shaikh et al. described the case of a 27-year-old male with hypertriglyceridemia-associated pancreatitis and diabetic ketoacidosis, who was successfully managed with intravenous insulin drip.[6] Huang et al. described a retrospective case series of six patients who presented with the triad of DKA, hypertriglyceridemia, and acute pancreatitis. The patients were treated with plasmapheresis, hydration, and intravenous insulin therapy.[7] Donelli et al. described the case of a 37-year old Chinese man who had a similar presentation and a triglyceride level greater than 7000 mg/dL on admission. This patient was treated with therapeutic plasma exchange, establishing the safety and efficacy of the same for treating extremely high elevation of triglyceride levels.[8] There are no head-to-head comparisons of plasma exchange therapy with traditional intravenous insulin therapy alone for the management of this condition. However, current evidence dictates that insulin therapy alone has provided a cure in most of the patients as per the above described case reports. This is especially important considering that plasma exchange therapy is expensive and may not always be readily available.

4. Conclusion

1. The triad of diabetic ketoacidosis, resultant hypertriglyceridemia, and acute pancreatitis exists and is a high mortality condition. Hence a triglyceride level should be obtained in all patients who present with diabetic ketoacidosis and acute pancreatitis.
2. This triad requires early and prompt treatment with intravenous insulin therapy. More expensive therapeutic options such as plasma exchange have not been proven to be superior yet.
3. Medication adherence should be reinforced in such patient populations as recurrence is a real possibility in cases of continued medication nonadherence.
4. Current guidelines recommend fibrate therapy in patients with elevated triglyceride levels.[9] However, fibrates increase the risk of gall stone production, thereby, predisposing patients to the development of acute pancreatitis. A review by Preiss et al. proposed that statin therapy may be effective in reducing the risk of pancreatitis in patients with mild to moderate elevations in triglyceride levels.[10]
5. However, due to the recurrent and severe nature of the patient's triglyceride levels, and imaging revealed no signs of gall stones, we chose fibrate therapy in this patient.

5. Patient consent

Informed consent is obtained from the patient. The case report has been fully explained to the patient and all the questions have been answered to patient satisfaction. The patient has agreed to participate in this case report. A version of a case report to be submitted or published (including tables/labs) was given to the patient for review and it

has been submitted after the patient agreed to it. No personal health information or patient identifiable details/data was used in the case report.

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Conflict of interest

The authors have no conflict of interest to declare.

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