Acute pancreatitis secondary to hypertriglyceridemia precipitated by diabetic ketoacidosis in a previously undiagnosed ketosis-prone patient with diabetes mellitus

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ABSTRACT

Diabetic ketoacidosis is a potentially fatal complication of diabetes mellitus that may result in hypertriglyceridemia. Rarely, the resulting hypertriglyceridemia may precipitate acute pancreatitis. We report a case of acute pancreatitis secondary to hypertriglyceridemia precipitated by diabetic ketoacidosis and postulate that this unusual presentation is due to the patient being prone to ketosis.

KEYWORDS Diabetes; hypertriglyceridemia; ketoacidosis; ketosis-prone; pancreatitis

Diabetic ketoacidosis (DKA) is a potentially fatal complication of diabetes mellitus (DM) that is most often caused by trauma, infection, or neglect to administer insulin.¹ Patients with DKA may present with polydipsia, polyuria, nausea, vomiting, confusion, and abdominal pain, which may be the first symptom experienced.² Complications associated with DKA include cerebral edema, acute kidney failure, acute respiratory distress syndrome, and, rarely, severe hypertriglyceridemia.³ Hypertriglyceridemia is an uncommon cause of acute pancreatitis linked to 1% to 4% of cases.⁴ Here, we report the case of a previously undiagnosed middle-aged ketosis-prone diabetic man with acute pancreatitis secondary to hypertriglyceridemia caused by DKA.

CASE REPORT

A 33-year-old obese white man without significant past medical history presented to our emergency department with 2 days of progressively worsening sharp epigastric pain (9/10) with radiation to the right upper quadrant. He also had a fever to 101.3°F, thirst, nausea, and nonbloody, nonbilious vomiting for 1 day. He reported no alcohol use, history of gallstones, trauma, or new medication use. His mother was diagnosed with DM in her 30s. On presentation, his temperature was 99°F with a blood pressure of 125/75 mm Hg, his heart rate was 85 beats/min, and his respiratory rate was 16 breaths/min on room air (97% oxygen saturation). The abdomen was nondistended, but severe tenderness was

present in the epigastric region with a negative Murphy's sign and no rebound tenderness. Bowel sounds were present.

The serum amylase was 547 U/L (normal 19–105 U/L) and lipase was >400 U/L (upper detectable level, normal 22.0–51.0 U/L). A complete blood count with differential was unremarkable. His bicarbonate was 17 mmol/L (normal 22–30 mmol/L) with an anion gap of 17 mmol/L. His venous blood gas pH was 7.28. His blood glucose level was 310 mg/dL (normal 70–110 mg/dL). Although the patient's urinalysis was negative for ketones, a plasma beta-hydroxybutyrate was 5.554 mmol/L (normal 0.02–0.27 mmol/L). The total triglycerides were 2845 mg/dL (normal 10–170 mg/dL), and total cholesterol was 400 mg/dL (normal 0–200 mg/dL) with observable lipemia in the lab test tubes. Hemoglobin A1c was 13.5% (normal 4.2%–5.8%), correlating to an estimated average glucose of 340 mg/dL.

The patient was given normal saline intravenously with continuous insulin drip and repletion of electrolytes such as potassium and phosphorus as needed. Labs were rechecked throughout admission (*Table 1*). Twenty-two hours after admission, the anion gap had closed and the patient was switched to subcutaneous insulin titrated to body mass with an insulin sliding scale.

Forty-six hours after admission, the anion gap was 13 and plasma beta-hydroxybutyrate was 3.772 mmol/L. He was maintained on his subcutaneous insulin regimen and was started on a clear liquid diet, which he tolerated. Seventy hours after admission, the anion gap was 8 mmol/L with lower beta-

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Table 1. Laboratory values for the patient throughout admission with respect to diabetes ketoacidosis and transient hyperlipidemia^a

Lab test	Upon admission	22 hr	46 hr	72 hr
Bicarbonate (mmol/L)	17	22	20	24
Anion gap (mmol/L)	17	10	13	8
Beta-hydroxybutyrate (mmol/L)	5.554	NR	3.772	2.569
Total triglycerides (mg/dL)	2845	486	309	274
Total cholesterol (mg/dL)	400	NR	214	NR
Serum glucose (mg/dL)	310	176	156	NR

^aNR indicates not recorded.

hydroxybutyrate and total triglycerides. At this time, a soft, regular diet was started and gemfibrozil 600 mg was given twice per day. His pain was down to 1/10 and abdominal tenderness to palpation had disappeared. One week later, workup of the patient's DM showed results most consistent with A- β + ketosis-prone DM (Table 2).

DISCUSSION

An association between DKA and acute pancreatitis exists. Nair et al investigated 100 consecutive episodes of DKA revealing 11 patients (11%) with acute pancreatitis on presentation.⁵ However, the triad of DKA with hypertriglyceridemia-induced acute pancreatitis occurs in 4% of cases.⁶ Furthermore, it is a remarkably rare first presentation of DM in adults.

DKA results from an absolute insulin deficiency or lack of hormonal response to insulin. Not only does this cause termination of the citric acid cycle and ketogenesis to provide nutrients to vital organs, but it also results in decreased inhibition of hormone-sensitive lipase.⁶ This leads to increased lipolysis and levels of circulating nonesterified fatty acids, which are raw materials for very low-density lipoproteins.⁶ Furthermore, reduced peripheral tissue lipoprotein lipase results in increased

serum very low-density lipoproteins and subsequent lipemia and hypertriglyceridemia.^{7,8}

Ketosis-prone diabetes is a ubiquitous, heterogeneous syndrome denoted by patients who do not encompass the typical phenotype of autoimmune type 1 DM but may nevertheless present with DKA or unprovoked ketosis.⁹ The A β classification of Balasubramanyam et al is a novel approach to considering ketosis-prone diabetes.¹⁰ Under this system, autoantibodies to glutamic acid decarboxylase (GAD-65) or tyrosine phosphatase-like protein IA-2 (IA-2) assess autoimmune destruction of islet cells and C-peptide levels determine the functionality of the pancreatic β cells. One longitudinal study of patients under the A β classification demonstrated that particular groups were more ketosis prone than others (Table 3).¹¹ However, the mechanisms that trigger these patients to develop DKA are poorly defined.⁹ Our patient, a 33-year-old obese man, does not fit the traditional mold of a type 1 DM patient. His workup revealed results consistent with A- β + DM (autoantibodies were below the 99th percentile with normal pancreatic beta cell functioning) with a 54% chance of being a ketosis-prone diabetic (Table 3). This could account for his presentation.

Several hypotheses have been proposed for why patients with A- β + diabetes may paradoxically go into DKA despite adequate C-peptide levels, as documented in the review by Balasubramanyam et al.¹⁰ Upon review of the literature, we identified a lack of discussion of ketosis-prone diabetes in case reports reporting the triad of DKA, hypertriglyceridemia, and acute pancreatitis. Consideration of this rare clinical presentation in this light may help improve anticipatory guidance, personalized medical care, and management of acute presentations.

The treatment of this condition involves standard DKA management including aggressive fluid resuscitation initially with 0.9% normal saline and then 5% dextrose with 0.45% normal saline, insulin via a continuous drip at first before transition to subcutaneous administration, and repletion of electrolytes.¹² The patient should undergo bowel rest. When the patient is tolerating a clear liquid diet, initiating a fibrate to lower triglyceride levels is of particular importance.^{13–15} Under other circumstances, the severity of triglyceridemia has necessitated urgent plasmapheresis.^{13,16} Such measures should not be undertaken in cases such as the one presented when standard care is sufficient and limits resource utilization. However, our patient did main-

Table 2. Laboratory results of the patient's workup for diabetes mellitus most consistent with A- β + ketosis-prone diabetes mellitus

Lab test	Result	Normal range	Interpretation
C-peptide (ng/mL)	5.5	1.1–4.4	Pancreatic beta cell function intact
GAD-65 autoantibody (U/mL)	<5.0	0.0–5.0	Insignificant autoantibody levels to GAD-65
IA-2 autoantibody	Negative	Negative	Insignificant autoantibody levels to islet cells

GAD indicates glutamic acid decarboxylase.

Table 3. A β classification of ketosis-prone diabetes mellitus reflecting antibody production, β cell function, and percentage of patients who develop ketones^a

Classification	Antibody present?	β -cell function present?	Percentage ketosis-prone
A+ β +	Yes	Yes	8%
A+ β –	Yes	No	18%
A– β +	No	Yes	54%
A– β –	No	No	20%

^aFrom Umpierrez et al.¹¹

tain elevated ketones at discharge despite clinical improvement, closed anion gap, and downtrending triglycerides. Given the patient's highly elevated hemoglobin A1c (13.5%) and probable ketosis-prone diabetes state (not previously diagnosed), the authors postulate that his homeostasis may include asymptomatic intermittent/persistent ketosis. Furthermore, persistently elevated glucose can precipitate glucolipotoxicity, the combined effects of which are documented to be deleterious to pancreatic beta-cell function and survival, possibly exacerbating the patient's condition.¹⁷

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