Case Study

Acute Pancreatitis in Association with Diabetic Ketoacidosis in a Newly Diagnosed Type 1 Diabetes Mellitus Patient; Case Based Review

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Abstract
Patients with newly detected type 1 diabetes mellitus come to the fore with initial presentation of diabetic ketoacidosis (DKA). Among the several risk factors, acute pancreatitis (AP) is an uncommon cause. DKA may mask coexisting AP, which occurs in at least 10-15% cases. AP is more likely to be associated with a severe episode of DKA with marked acidosis and hyperglycemia. Here we present the clinical and biochemical profile of a 12 year old type 1 diabetes girl presenting with DKA complicated by AP. Prompt diagnosis of AP in DKA or vice versa is important for proper management. The management requires diligent correction of dehydration and hyperglycemia, while monitoring neurological status and blood chemistry. It is imperative to monitor and avoid potentially fatal complications of the combined entity, including cerebral edema, thromboembolism, acute respiratory distress syndrome and rhabdomyolysis. Exclusion of acute pancreatitis in cases with persistent abdominal pain in this scenario is vital.
**Introduction:**

Diabetic ketoacidosis is an acute metabolic complication reflective of extremes of abnormal insulin homeostasis mainly in type 1 diabetes mellitus (T1DM). It has an estimated mortality of 2-10%. Acute pancreatitis (AP) coexisting with diabetic ketoacidosis (DKA) as a cause or result has been reported previously. In these reports, the diagnosis of AP was based solely on clinical features and associated elevations in serum pancreatic enzymes without any confirmatory radiographic (CT scan) findings. Several case reports emphasizing the development of diabetic coma as a rare complication of severe AP also noted that some of these patients had no preexisting diabetes. Other reports documented an association of AP with hyperosmolar nonketotic diabetic coma.

During severe episodes of DKA, insulin deficiency increases free fatty acid (FFA) and amino acids release from adipose tissue and muscle respectively and increased counter-regulatory hormones causes increased gluconeogenesis and glycogenolysis in the liver. Elevated FFA taken up by liver leads to increased production of very low density lipoprotein (VLDL) cholesterol, which causes hypertriglyceridemia. Hypertriglyceridemia is an uncommon cause of acute pancreatitis accounting for 1-4% cases, especially when the serum triglyceride (TG) level exceeds 1000 mg/dl. These transiently elevated levels of serum triglyceride are believed to precipitate acute pancreatitis. DKA is known to mask the clinical features of acute pancreatitis, with acute pancreatitis reported in 10–15% of patients.

We report a case of newly diagnosed T1DM presenting with DKA and AP. We also hereby review the pathogenesis and clinical implications of such an uncommon association.

**Case Report:**

A 12 year old girl presented to emergency department with 6-8 episodes of non bloody, non bilious vomiting over past 2 days, associated with severe, continuous non radiating epigastric pain and lethargy of 24 hours duration. She had 2 bouts of loose motion on the day of presentation. Upon admission, the patient weighed 55 kg with height of 161 cm and body mass index 21.2 kg/m². She was drowsy with heart rate of 100/minute, blood pressure- 100/60 mm hg in right arm supine position, respiratory rate of 26/minute with kussmaul’s acidic breathing and body temperature of 100.4°F. Physical examination revealed dehydrated tongue with decreased skin turgor without any evidence of eruptive or tuberous xanthoma and xanthelesma. There was soft, tender epigastrium with sluggish bowel sounds without any mass or skin discoloration. Neurologically she was drowsy, pupils equal in size and normally reactive with no focal neurologic deficit.

Initial laboratory parameters included neutrophilic leucocytosis, random blood glucose 320 mg/dl, HbA1C 13.8%, sodium- 138 meq/l, potassium- 4.5 meq/l, chloride- 95 meq/l, cholesterol- 320 mg/dl, low density cholesterol- 156 mg/dl (estimated by homogenous enzymatic colorimetry method), triglyceride- 1020 mg/dl, normal renal and liver function tests with urine strongly positive for ketones (4+). Arterial blood gas (ABG) analysis revealed pH- 7.2, pCO2- 13 mm Hg, HCO3- 9 meq/l.
With a provisional diagnosis of T1DM with DKA, patient was aggressively hydrated and treated with intravenous insulin. On the second day she had normalization of ABG, but there was no improvement in neurological status with aggravated abdominal pain. Follow up laboratory analysis revealed amylase levels of 440 U/ l, lipase- 560 U/ l. Contrast tomography (CT) of abdomen revealed diffusely inflamed and swollen pancreas without any fluid collection confirming the diagnosis of AP. This was AP grade C, according to Balthazar CT severity index (Figure 1). Patient was managed conservatively measures like nil by mouth, nasogastric aspiration, intravenous fluid, insulin and monitoring of her vital clinical and laboratory parameters.

On 3rd day, she was conscious with laboratory parameters revealing fasting blood sugar of 124 mg/ dl, triglyceride- 340 mg/ dl, cholesterol- 181 mg/ dl, LDL- 101 mg/ dl. The patient commenced oral intake and multiple subcutaneous insulin injections. At this stage her fasting C-peptide was 0.2 ng/ ml (N- 1.1- 4.4 ng/ ml), anti GAD antibody titer- 1.5 U/ml (N- 0-0.9) and anti IA-2 antibody titer- 0.8 U/ ml(N- 0-0.4 U/ml), confirming the diagnosis of T1DM. On 6th day the child was asymptomatic with a normal abdominal examination and normalization of serum amylase and lipase levels( 50 & 35 U/ L respectively). Repeat CT abdomen at this point showed significant improvement. Follow up clinical examination at 2 months revealed body weight of 63 kg with BMI 24.3 kg/ m², good glycemic control (FBS- 102 mg/ dl, PPBS- 135 mg/ dl, serum triglyceride- 225 mg/dl) and normal pancreatic ultrasonography

**Discussion:**

Our patient presented with an episode of DKA complicated by AP. Although transient hyperglycemia (50-70%) and glycosutra (30%) are not uncommon in AP, permanent diabetes mellitus is exceedingly rare in children (14) and is relatively infrequent in adults occurring in 1-15% of affected adults. Pancreatic diabetes accounts for less than 1% of all cases of diabetes mellitus.

Serum levels of pancreatic enzymes are dependent on the rate of entry of these enzymes into circulation from pancreatic acini and clearance or metabolism by the kidneys. Because the pancreas accounts for 95% of serum lipase, in contrast to 40% to 50% for amylase, serum lipase is considered a more specific marker for pancreatitis than amylase. Nair et al observed that the specificity of elevated amylase (at three times the normal level) was 97% for diagnosing acute pancreatitis; while the specificity of elevated lipase (at the same level) was only 91%, indicating high amylase as a critical marker of acute pancreatitis. The magnitude of lipase elevation appears to correlate with degree of acidosis, where as hyperamylasemia is nonspecific. A normal serum amylase level does not rule the possibility of a coexisting acute pancreatitis. Noticeably, normoamylasemia is possible in about 50% of patients with hypertriglycerideremia induced pancreatitis. The mechanism is believed to be the interference with in vitro determination of the actual amylase level by disturbance of the calorimetric methods. Serial dilutions of the sample could reduce interference of light transmission by hyperlipidemia serum. In our patient both lipase and amylase levels were elevated.
Acute pancreatitis can induce hyperglycemia and ketosis in a patient with diabetes mellitus and hence may be a primary event rather than a sequel to DKA\textsuperscript{19-21}. Nonspecific elevations of amylase and/or lipase without clinical evidence of pancreatitis have been reported in 24.7%–79% of DKA cases\textsuperscript{18}. At least in those patients with continuous abdominal pain, it is prudent not to ignore it as a clinical component of DKA but to proceed further with amylase, lipase, and triglyceride estimations, and when one of these is markedly raised (>3 times amylase and lipase or > 1000 mg of triglyceride), a CT scan of the abdomen should be performed\textsuperscript{12}.

In DKA, insulin deficiency activates lipolysis in adipose tissue releasing increased free fatty acids, which accelerates formation of VLDL in the liver. In addition, reduced activity of lipoprotein lipase in peripheral tissue decreases removal of VLDL from the plasma, resulting in hypertriglyceridemia\textsuperscript{22}. Moderate hypertriglyceridemia is common during episodes of DKA (23). However, severe hypertriglyceridemia, defined as TG level > 2000 mg/ dl is rare. Hypertriglyceridemia can cause AP by generation of cytotoxic free fatty acids in the pancreatic circulation\textsuperscript{12,24,25}. This results in vascular endothelial cell damage, sludging of red cells, pancreatic ischemic injury and inflammation.

Although no convincing clinical data exist, few possible explanations for hyperlipasemia in DKA can be offered. One explanation is that lipase with a molecular mass of 46–52 kD is removed from circulation by glomerular filtration and then subsequently reabsorbed to be metabolized by renal tubules\textsuperscript{26,27}. In DKA there is moderate hypovolemia with a reduced glomerular filtration rate\textsuperscript{28, 29}. Therefore, less efficient handling of lipase by the kidney is conceivable, which leads to elevations in serum levels even without overt renal failure. Another possibility is the release of nonpancreatic lipolytic enzymes into the circulation\textsuperscript{30}. Two potential nonpancreatic sources for lipase in DKA are the stomach and liver, organs involved in DKA\textsuperscript{6,31,32}. The currently used lipase assays is 1-oleolyl-2,3-diacetylglycerol, a substrate more readily metabolized by nonpancreatic lipolytic enzymes\textsuperscript{27,30}. Another possibility is that in recent onset diabetics immunological destruction of β cells might spill over and cause damage to the pancreatic acini, releasing lipase into circulation\textsuperscript{30,33}.

Prompt diagnosis of AP in DKA or vice versa has several clinical implications\textsuperscript{12}. Firstly AP can aggravate the severity of ketoacidosis by worsening the depletion of intravascular volume thus necessitating more aggressive fluid replacement. Secondly, AP can also alter glucose homeostasis, thus making control of hyperglycemia more difficult. Thirdly, once the ketoscidosis is controlled, oral feeding may be resumed, which may be detrimental in some patients with AP. Patients with DKA may experience abdominal pain even in absence of acute pancreatitis as a result of gastritis, gastric atony or hepatomegaly and distension of liver capsule\textsuperscript{34-36}. Abdominal pain is a common feature of both these conditions. AP, therefore needs to considered in a child with DKA and severe abdominal pain failing to resolve rapidly with the correction of acidosis and dehydration\textsuperscript{14,37}.
Abdominal ultrasound is a particularly useful tool in supporting the diagnosis AP. Pancreatic enlargement and hypoechogenicity on ultrasound is virtually diagnostic of AP\textsuperscript{34}. Abdominal CT, particularly contrast enhanced is an excellent tool for identifying AP and its complications\textsuperscript{38,39}. CT is the imaging modality of choice in patients with unconfirmed AP, in those who fail to respond to conservative therapy or have suspected complications. Nevertheless, 20% of children with a mild clinical form of pancreatitis have a normal CT scan and is not a sensitive method for detecting gall stones, unless they are calcified\textsuperscript{40}. Ranson’s prognostic criteria are not applicable to assess the severity of AP in DKA because they overestimate the severity\textsuperscript{12}. Severity index based on CT findings proposed by Balthazar et al appears to better correlate with outcome (A- Normal Pancreas, B- Enlargement, C- Inflammation of pancreas and fat, D- Single fluid collection, E- ≥ 2 fluid collection)\textsuperscript{41}.

**Conclusion:**
Diabetes mellitus secondary to AP is extremely rare in children. It is important to consider AP in the differential diagnosis of any child with severe prolonged abdominal pain, particularly in association with DKA. AP is more likely to be associated with a severe episode of DKA with marked acidosis and hyperglycemia. Elevation of serum lipase and amylase occur in DKA, and elevation of lipase levels appears to be less specific than amylase levels for the diagnosis of AP in the diagnosis of DKA. The concurrent diagnosis of these 2 conditions has several important clinical implications. Early imaging of the pancreas is recommended.

**References:**


