경증 고중성 지방혈증을 가진 당뇨병성 케톤산증 환자에서 발생한 급성 췌장염

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조은애 · 박창환

Concurrent Diabetic Ketoacidosis and Acute Pancreatitis in Mild Hypertriglyceridemia: An Enigmatic Triangle

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Hypertriglyceridemia (HTG) is a well-established cause of acute pancreatitis (AP). Diabetic ketoacidosis (DKA) leads to lipolysis and HTG, and can result in AP. Triad of AP, DKA, and HTG is rare and not fully understood. Usually AP is associated with severe HTG with serum triglyceride (TG) level over 1,000 mg/dL. However, we experienced two cases of AP in DKA with mild HTG with TG level less than 200 mg/dL. Herein, we report these unusual cases and provide a review of the literature about the triad of DKA, HTG, and AP.

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INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease of the pancreas characterized by epigastric pain and elevated serum pancreatic enzymes more than 3 times the upper normal value. While the mortality in mild pancreatitis is known to be less than 1%, it is up to 10% in necrotizing pancreatitis, and is about 25-30% in infectious necrotizing pancreatitis.¹ Assessment of severity and etiology, prediction of prognosis, and subsequent intensive care at the time of diagnosis is crucial

for successful treatment of AP.

Hypertriglyceridemia (HTG) is a well-known cause of AP. In a recent systematic review, HTG was attributable to 9% of AP and incidence of AP in patients with HTG was about 14%.² However, little is known about the triad of diabetic ketoacidosis (DKA), HTG, and AP, hence it is referred to as “the enigmatic triangle”. DKA is a condition of profound insulin deficiency, leading to hyperglycemia, ketogenesis and lipolysis, resulting in hypertriglyceridemia.

The risk of AP increases with serum triglyceride (TG) levels

over 500 mg/dL, and it increases markedly with TG levels over 1,000 mg/dL.³ AP associated with mild HTG in non-alcoholics is rare. We herein report two unusual cases of AP in DKA with only mild HTG and provide a review of the literature on the triad of DKA, HTG, and AP.

CASE

1. Case 1

A 48-year-old woman presented to the emergency department with abdominal pain, nausea, and vomiting that started 4 days prior with worsening of general condition in last 2 days. She had a 12-year history of type 2 diabetes and had been taking metformin, glimepiride, dipeptidyl peptidase-4 (DPP-4) inhibitor, and sodium-glucose co-transporter-2 (SGLT2) inhibitor for 1 year, but her glucose control was poor. She had been refusing insulin therapy. She had no history of hypertension. Her family history was unremarkable. She denied tobacco or alcohol use.

On admission, her blood pressure was 160/60 mmHg, heart rate was 110 beats/min, respiratory rate was 22 breaths/min, and body temperature was 36.2°C. The patient was mildly confused, and physical examination revealed severely dehydrated tongue, decreased skin turgor, and tenderness in the epigastrium and left upper quadrant abdomen. Her body mass index (BMI) was 24.0 kg/m² (height 167 cm and body

weight 67 kg).

Laboratory findings showed elevated white cell count of 31,000 /μL, pH 6.8, bicarbonate 1.2 mmol/L, anion gap 23.8 mmol/L, ketone body >13,000 μmol/L, glucose 346 mg/dL, glycated hemoglobin 8.7%, osmolality 294 mOsm/kg, blood urea nitrogen (BUN) 24.5 mg/dL, creatinine 0.99 mg/dL, sodium 129 mEq/L, total calcium 7.1 mg/dL, amylase 1,029 U/L, lipase 85 U/L, TG 174 mg/dL, and C-reactive protein (CRP) 2.92 mg/dL. Urine dipstick test was positive for ketone (3+), sugar (3+), protein (1+), and RBC (2+). Liver function tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin were within normal range.

Computed tomography (CT) of the abdomen was performed and showed edematous change of the pancreatic tail with surrounding fat stranding (Fig. 1), which was considered as mild acute pancreatitis in CT severity index. No gallstone or choledocholithiasis was found in the CT. Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) were not performed because the patient refused to undergo these exams. The diagnosis of DKA, acute interstitial edematous pancreatitis, with concurrent mild HTG was made. She had no organ failure (modified Marshall score for organ dysfunction was 0 [4]). According to revised Atlanta classification,⁴ she had mild acute pancreatitis. The patient was transferred to intensive care unit (ICU) and treated with vigorous hydration, intravenous insulin, and analgesics. There

Fig. 1. (A) Computed tomography of the abdomen showed edematous change of the pancreatic tail and (B) reticular stranding of the surrounding fat.

was no sign of infection and therefore antibiotics were not used. Her condition improved and she was transferred to ward after 4 days. Her abdominal pain improved gradually and oral feeding was started from the 4th day of admission. She was discharged with subcutaneous insulin after 10 days. She has been followed upon discharge and remains well without further episodes of DKA and AP.

2. Case 2

A 54-year-old woman presented to the emergency department with drowsy mental state. Two days ago, she received treatment at a local clinic because of abdominal pain,

Fig. 2. Computed tomography of the abdomen demonstrated pancreatic parenchymal edema with a single fluid collection around the pancreatic tail.

headache, and general weakness but her general condition worsened over the 2 days. She had a 10-year history of type 2 diabetes and hypertension, but had been taking her medications irregularly. She denied tobacco or alcohol use.

On admission, the initial assessment showed confused mentality with blood pressure at 70/40 mmHg, heart rate at 140 beats/min, respiratory rate at 22 breaths/min, and body temperature at 36.9°C. Physical examination of the abdomen showed epigastric tenderness but no guarding, rigidity, or Murphy's sign. Her body BMI was 25 kg/m² (body weight 60 kg and height 155 cm).

Laboratory exams showed white cell count of 3,200 /μL, pH 7.2, bicarbonate 10.6 mmol/L, anion gap 22.4 mmol/L, glucose 300 mg/dL, glycated hemoglobin 14.2%, osmolality 295 mOsm/kg, BUN 39.8 mg/dL, creatinine 0.92 mg/dL, sodium 133 mEq/L, potassium 3.0 mEq/L, total calcium 7.6 mg/dL, amylase 529 U/L, lipase 2,214 U/L, TG 197 mg/dL, and CRP 11.88 mg/dL. Urine dipstick test was positive for ketone (3+), sugar (2+), protein (1+), and RBC (2+). Liver function tests showed elevated AST of 50 U/L and ALP of 310 U/L, but normal ALT, r-GTP, and bilirubin levels.

Abdominal CT scan with contrast showed edematous change of the pancreas with a single fluid collection around the pancreatic tail (Fig. 2), which was consistent with mild acute pancreatitis in CT severity index. No gallstone or choledocholithiasis was identifiable in the CT. The patient was diagnosed with DKA, acute interstitial edematous pancreatitis, and concurrent mild HTG. Her modified Marshall score for organ

Fig. 3. (A) Endoscopic ultrasound showed non-dilated common bile duct without stones (arrow), (B) edematous pancreas with a fluid collection in the pancreatic head (arrowhead), and (C) the gallbladder without sludges or stones.

dysfunction was 3 (systolic blood pressure <90 mmHg, pH <7.3). According to revised Atlanta classification,⁴ she had moderately severe acute pancreatitis.

The patient was transferred to ICU for adequate management. Vigorous hydration, continuous intravenous insulin infusion, and analgesics were started. Her systolic blood pressure raised to 100 mmHg within 6 hours after hydration. Her health status improved and she was transferred to ward after 3 days. In an attempt to rule out radiolucent stones in the biliary tree as a possible cause of acute pancreatitis because her AST and ALP were elevated, EUS was performed after 3 days. EUS revealed edematous pancreas with some fluid collections in the parenchyma, but no stones in the biliary tract and the gallbladder (Fig. 3). After 3 days, oral diet was started while her abdominal pain was controlled with analgesics. She was discharged with subcutaneous insulin after 8 days and remains well without further episodes of DKA and AP until now.

DISCUSSION

We report two cases of AP associated with DKA with only mild HTG. The patients had poor glycemic control and developed DKA. Both patients had TG level under 200 mg/dL, which is generally not considered as the level for the cause of AP.⁵ Imaging studies showed no other causes for AP and both patients denied alcohol consumption. According to revised Atlanta classification, the severity of AP was mild in one patient and moderately severe AP in another patient. Both patients recovered well after aggressive hydration and insulin therapy.

The association between DKA, HTG, and AP has been reported infrequently in several case reports.^{6,7} In DKA, insulin deficiency activates lipolysis in adipose tissue and results in release of free fatty acids (FFA). Increased delivery of FFA to the liver leads to excessive very low density lipoproteins (VLDL) formation. In addition, the activity of lipoprotein lipase in peripheral tissue is decreased and removal of VLDL from the plasma is reduced, resulting in HTG.⁶

The exact mechanism of HTG induced AP has not been fully elucidated. The most widely accepted hypothesis proposes that excessive FFAs, which are hydrolyzed from TGs by pancreatic

lipase, result in toxic injury to acinar cell and capillary endothelium, leading to pancreatic ischemia. Also, high chylomicron concentration results in pancreatic capillary hyperviscosity and leads to ischemia and acidosis.⁵

HTG is defined by fasting serum TG level above 150 mg/dL. HTG is classified into different severity categories: mild (serum TG levels of 150 to 199 mg/dL), moderate (200 to 999 mg/dL), severe (1,000 to 1,999 mg/dL), and very severe ($\geq 2,000$ mg/dL).⁸ While more studies are needed to define the exact TG level causing AP, AP usually occurs when the TG level is more than 1,000 mg/dL. TG levels over 500 mg/dL raises high degree of suspicion that HTG is the cause of AP, especially when TG level estimation is delayed.⁵

Little is known about the mechanism of AP in DKA. Nair and Pitchumoni⁷ reported three cases of AP in DKA patients with HTG and suggested the hypothesis that DKA leads to HTG and AP occurs as a result. However, we experienced two cases of AP in DKA patients with mild HTG. In both cases, serum TG levels were checked on the day of presentation. In a prospective study evaluating the incidence and prognosis of AP in 100 DKA patients, AP occurred in 11 patients.⁹ Among these patients, the cause of AP was classified as: HTG in four patients (36.4%) because TG levels were above 1,000 mg/dL, alcohol in two (18.2%), drug induced in one (9%), and idiopathic in four (36.4%). The TG levels in the patients who were classified as idiopathic were all below 500 mg/dL (range, 145-447 mg/dL). Therefore, it is questionable whether HTG in DKA causes AP or DKA per se is a rare cause of AP and HTG is an epiphenomenon. More studies are needed in focusing the exact mechanism of AP in DKA.

The triad of DKA, HTG, and AP has the potential of poor prognosis because it is considered to be associated with more severe hyperglycemia, acidosis, and intravascular volume depletion. Bouchaala et al.¹⁰ recently reported 50% mortality in four cases of AP in DKA patients. Other studies also found higher Ranson criteria and APACHE II scores in AP with DKA patients compared to non-DKA patients.⁹⁻¹² However, the clinical course of AP including the length of stay and in-hospital mortality did not differ significantly among DKA patients and non-DKA patients.^{11,12} The patients in our case

report had mild AP according to CT severity index. Transient organ failure was found in one of our patients, but she recovered well after treatment. Nair et al.⁹ also reported that AP in DKA appeared to be mild in their study. Prospective, large-scale studies are warranted with regard to the severity of the concurrent DKA, HTG, and AP.

Diagnosis of AP in DKA is somewhat challenging. Our patients complained of abdominal pain and had elevated level of amylase more than 3 times the upper normal value. However, it is common for patients with DKA to complain of abdominal pain. Serum amylase, lipase, or TG levels are elevated frequently in these patients.⁹ Therefore, it is the clinician's suspicion and adequate evaluation that makes the correct diagnosis.

In conclusion, AP can occur in DKA patients with only mild HTG. The exact mechanism of this enigmatic triad is still unknown. Although the treatment of AP in DKA does not differ and the clinical course seems to be mild, clinicians should pay attention to this triad until further large-scale studies are performed to evaluate the prognosis, as only 15-20% of patients with AP experience serious disease.

요약

고중성 지방혈증은 잘 알려진 급성 췌장염의 원인 중 하나이다. 당뇨병성 케톤산증, 고중성 지방혈증 및 급성 췌장염이 연관이 있다는 것은 알려져 있으나, 이 세 가지 질환의 연관성이 어떠한 기전에 의해 발생하는지 정확히 알려지지 않았다. 보통 중성지방이 1,000 mg/dL 이상으로 상승하였을 때 급성 췌장염의 위험도가 증가한다고 알려져 있다. 그러나 본 저자들은 당뇨병성 케톤산증 환자에서 중성지방이 200 mg/dL 미만임에도 급성 췌장염이 발생한 증례를 경험하여 이를 보고하고자 한다.

국문 색인: 당뇨병성 케톤산증, 급성 췌장염, 고중성 지방혈증

Conflicts of Interest

The authors have no conflicts to disclose.

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