Acute Necrotizing Pancreatitis Caused by Iatrogenic Hypercalcemia

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INTRODUCTION

Acute pancreatitis is a reversible inflammatory disease of the pancreas that usually follows a mild and self-limited course. Although extremely rare, hypercalcemia is a possible cause of acute pancreatitis. There are only a few reported cases, all of which were mild and self-limited. Here we report a patient with iatrogenic hypercalcemia-induced necrotizing pancreatitis that progressed to serious adverse events such as biliary obstruction, peripancreatic fluid collection with walled-off necrosis, and acute cholecystitis. The patient was successfully treated with appropriate endoscopic and radiologic interventions, and recovered well.

Keywords: Pancreatitis, Acute necrotizing pancreatitis, Hypercalcemia, Calcium compounds

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Gallstones and alcohol consumption are well-known causes of acute pancreatitis, which usually follows a mild and self-limited course. Although extremely rare, hypercalcemia is a possible cause of acute pancreatitis. There are only a few reported cases, all of which were mild and self-limited. Here we report a patient with iatrogenic hypercalcemia-induced necrotizing pancreatitis that progressed to serious adverse events such as biliary obstruction, peripancreatic fluid collection with walled-off necrosis, and acute cholecystitis. The patient was successfully treated with appropriate endoscopic and radiologic interventions, and recovered well.

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INTRODUCTION

Acute pancreatitis is a reversible inflammatory disease of the pancreas that usually follows a mild and self-limited course. However, in approximately 15-20% of cases, acute pancreatitis progresses to serious adverse events, which may be life-threatening.¹

Gallstones and alcohol consumption are the leading causes of acute pancreatitis, accounting for 60-70% of cases. Other well-known causes of acute pancreatitis include post-endoscopic retrograde cholangiopancreatography (ERCP), abdominal trauma, post-operative state, adverse drug effects, sphincter of Oddi dysfunction, pancreatic cancer, periampullary diverticulum, pancreatic divisum and hereditary pancreatitis.²⁻⁴

Although not common, hypercalcemia can cause acute pancreatitis if serum calcium levels increase rapidly. To date, few cases have been reported, all of which were self-limited and treated easily by conservative treatment including fasting, in-
travenous hydration, and removal of the predisposing factor.\textsuperscript{5,7} Here we report a case of extensive necrotizing pancreatitis caused by excessive intravenous calcium supplementation.

**CASE**

A 26-year-old woman came to the emergency center of our hospital complaining of dizziness. Hours before the symptom started, she took 15 tablets of calcium channel blocker that she had mistaken for sleeping pills.

Her mental status was slightly drowsy, but orientations to time, person, and place were intact. At presentation, she had no gastrointestinal symptoms other than dizziness. Her initial blood pressure was 85/49 mmHg and heart rate was 101 beats/min. Initial laboratory data (normal range or value in parentheses) were as follows: white blood cell count, $9.4 \times 10^3$ (4.0-10.0) x $10^3$ /mm$^3$; hemoglobin, 12.9 (12.0-16.0) g/dL; platelet count, 336 $\times 10^3$ (150-350 $\times 10^3$) /mm$^3$; corrected serum calcium 8.94 (8.6-10.2) mg/dL; phosphorus, 6.3 (2.5-4.5) mg/dL; blood urea nitrogen, 18 (10-26) mg/dL; creatinine, 2.13 (0.70-1.4) mg/dL; aspartate aminotransferase, 36 (0-40) IU/L; alanine aminotransferase, 21 (0-40) IU/L; alkaline phosphatase, 59 (40-120) IU/L; γ-glutamyl transferase, 105 (5-36) IU/L; total bilirubin, 1.3 (0.2-1.2) mg/dL; amylase, 40 (30-110) IU/L, and lipase, 17 (13-60) IU/L.

Normal saline hydration was used for volume resuscitation, and intravenous vasopressors (norepinephrine and epinephrine) were continuously infused to maintain blood pressure. In addition, glucagon, lipid emulsion and large doses of calcium compounds (calcium chloride and calcium gluconate) were intravenously administered during the initial 48 hours in the emergency center to treat calcium channel blocker intoxication.\textsuperscript{8} Her vital signs stabilized and dizziness improved.

On day 3 after admission, the patient complained of sudden-onset severe epigastric pain and fever. Epigastric tenderness and decreased bowel sounds were noted on physical examination. Laboratory tests showed increased levels of serum pancreatic enzymes (amylase, 550 U/L; lipase, 1,679 U/L) and corrected serum calcium (17.24 mg/dL). Leukocytosis had developed in a neutrophil-dominant pattern in 94.6% of the total white blood cell count (19.4 $\times 10^9$ /mm$^3$). Abdominal computed tomography (CT) showed diffuse swelling of the pancreas with non-enhancing low attenuating regions, suggestive of necrotizing pancreatitis. Extensive peripancreatic fluid collection was also observed (Fig. 1).

After being referred to the Department of Gastroenterology, she fasted and empirical broad-spectrum antibiotics were administered.

On day 11 after admission, she became icteric and her serum total bilirubin level increased to 4.3 mg/dL. ERCP was performed and a narrowed distal common bile duct was documented on cholangiography. A 10-Fr plastic stent was inserted into the narrowed common bile duct, following which her serum bilirubin level gradually decreased (Fig. 2).

On day 19 after admission, she complained of diffuse abdominal pain and fever. Follow-up CT showed walled-off necrosis and a large amount of peripancreatic fluid collection. Endoscopic ultrasonography (EUS) was performed using a linear echo-endoscope (GF-UCT260; Olympus Medical, Tokyo, Japan), and EUS-guided cystogastrostomy was performed using a partially covered self-expandable metal stent. After stent insertion, turbid fluid with necrotic debris gushed out (Fig. 3).

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*Fig. 1. Abdominal computed tomography showed diffuse swelling of the pancreas with non-enhancing low attenuating regions, suggesting necrotizing pancreatitis.*

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out through the stent. Fever and diffuse abdominal pain showed considerable improvement after the EUS-guided cystogastrostomy procedure (Fig. 3).

On day 22 after admission, abdominal pain of the right upper quadrant and fever recurred. Murphy’s sign was positive on physical examination. After CT, acute cholecystitis was highly suspected and percutaneous transhepatic gall-bladder drainage (PTGBD) was performed. Her symptoms were relieved after the PTGBD procedure (Fig. 4).

The patient eventually recovered well after supportive treatment and interventional procedures. The internal stents and PTGBD catheter were successfully removed within 3 months after their insertion. She was symptom-free and discharged 73 days after her admission. She has been regularly monitored at an outpatient clinic for the past 16 months since her discharge, and no additional events have been observed (Fig. 5).

Fig. 2. Endoscopic retrograde cholangiogram showed distal common bile duct narrowing (A). Endoscopic sphincterotomy was performed and a 10-Fr plastic stent was placed in the narrowed bile duct (B).

Fig. 3. Abdominal computed tomography showed an increased amount of peripancreatic fluid collection extending along both pararenal spaces (A). Endoscopic ultrasonography-guided cystogastrostomy was performed (B). A fully covered metal stent (5 cm in length and 8 mm in diameter) was inserted and turbid fluid with necrotic debris gushed out. Endoscopic nasocystic catheter was additionally inserted for drainage of a large amount of necrotic debris (C).
DISCUSSION

Although not common, hypercalcemia can cause acute pancreatitis. Mithöfer et al. reported that acute pancreatitis occurred in rats after the administration of a calcium compound. As hypercalcemia developed, an increased in serum amylase and tissue trypsinogen activation peptide levels was observed along with edema formation and leukocytic infiltration in the pancreatic tissue.

The molecular mechanism underlying hypercalcemia-induced pancreatitis is yet to be elucidated. However, there are two suggested explanations. First, de novo activation of zymogens by hypercalcemia; the activated zymogens, including trypsin, destroy acinar cells and autodigest the pancreatic tissue, resulting in subsequent pancreatitis. Second, hypercalcemia can cause formation of pancreatic calculi and protein plug by modifying pancreatic secretion, resulting in pancreatic duct obstruction and subsequent pancreatitis. It has been suggested that other causes of acute pancreatitis, such as alcohol consumption, pancreatic ductal hypertension, ischemia, hyperlipidemia, and viral infection, also induce pancreatitis by increasing intracytoplasmic calcium levels.

There are many medical conditions known to cause pancreatitis by increasing serum calcium levels, including advanced malignancies with bone metastasis, multiple myeloma, vitamin D toxicity, sarcoidosis, and familial hypocalciuric hypercalcemia. Although primary hyperparathyroidism is a well-known cause of hypercalcemia and the serum calcium levels of patients are usually high, the prevalence of acute pancreati-
Iatrogenic Hypercalcemia-induced Acute Necrotizing Pancreatitis

To the best of our knowledge, this is the first report of necrotizing pancreatitis caused by iatrogenic hypercalcemia. In this case, necrotizing pancreatitis could be life-threatening at presentation. However, the patient successfully recovered with supportive treatment and appropriate interventional procedures.

Although there are few reported cases of acute pancreatitis that developed as an adverse event of excessive calcium supplementation, all of them followed a self-limited course and improved with conservative treatment, including fasting and removal of the predisposing factor. Pronisceva et al. reported a case of a 42-year-old woman complaining of vomiting and abdominal pain. She was diagnosed with acute pancreatitis, which was caused by hypercalcemia because of oral calcium supplementation. Calcium level in blood was returned to normal after cessation of calcium supplementation, and her symptoms were improved. Feyles et al. reported a case of a 6-year-old boy with pseudohypoparathyroidism. He had been treated with calcium and vitamin D supplementation. He was admitted for acute pancreatitis, and his serum calcium level was high. Hypercalcemia induced by over-supplementation of calcium and vitamin D was thought to be the cause of his acute pancreatitis. His condition improved after calcium level in blood was returned to normal.

Physicians should learn from our case to pay special attention while administering calcium supplements for treating patients. Serum calcium levels must be periodically monitored and should be checked more frequently if intravenous calcium supplements are used. The possibility of acute pancreatitis and even necrotizing pancreatitis should be considered if the patient complains of abdominal pain and newly developed hypercalcemia. Severity should be assessed immediately, and appropriate management including interventional procedures should be considered.

요 약

급성 췌장염은 대부분의 경우 보존적 치료만으로 수 일 이내에 호전되는 경과를 보이며, 전체의 60-70%가 담석, 음주에 의해 발생하는 것으로 알려져 있다. 드물지만 고갈슘혈증에 의해서도 급성 췌장염이 발생할 수 있으며, 의인성 고갈슘혈증 또한 급성 췌장염을 유발할 수 있다. 지금까지 보고된 의인성 고갈슘혈증에 의한 급성 췌장염의 증례는 모두 성인으로, 수일간의 보존적 치료 및 혈중 간질 농도의 정상화를 통해 합병증 없이 호전되었다. 저자들은 27세 여성이서 의인성 고갈슘혈증에 의해 발생한 급성 고 máu성 췌장염과 여러 합병증에 관한 증례를 문헌 고찰과 함께 보고하고자 한다.

국문 약어: 췌장염, 급성 고혈증 췌장염, 고갈슘혈증, 간질 복합체

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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