A Case of Calcium Resistant Pancreatitis

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Abstract

Gallstones and alcohol abuse are two of the most common causes of acute pancreatitis in the US. Aggressive fluid hydration and pain management are the mainstays of management. In some cases, however, symptoms and electrolyte derangements cannot be fixed until the underlying triggering cause is addressed. We present a case of a 39-year-old male with a significant alcohol abuse history presenting with an episode of acute pancreatitis and elevated triglyceride and low calcium levels. Curiously, despite aggressive calcium repletion, levels did not respond. It was only when the triglyceride levels began to normalize did the calcium levels begin to respond.

Introduction

Gallstones and alcohol abuse are two of the most common causes of acute pancreatitis (AP) in the US. Other common causes include hypertriglyceridemia, autoimmune pancreatitis, post-endoscopic retrograde cholangiopancreatography, gain of function mutations, pancreatic duct injury, and medication-induced [1]. Normal serum Calcium (Ca) ranges between 8.5 to 10.2 mg/dL and both hypercalcemia and hypocalcemia can lead to certain clinical symptoms. Acute hypocalcemia can cause papilledema, long QT interval, and neuromuscular irritation, whereas chronic forms can manifest as ectopic calcification, extrapyramidal symptoms, parkinsonism, and dementia. Symptoms of hypercalcemia, on the other hand, depend on the severity of hypercalcemia; mild forms (<12 mg/dL) may be asymptomatic, or have nonspecific symptoms like constipation, fatigue, and depression. Chronic and slowly progressive elevation may be well tolerated, but an acute increase can result in polyuria, polydipsia, and sensorium changes. Up to 88% of hospitalized patients with AP have concurrent hypocalcemia (prevalence 15–88%), which correlates with the severity of their illness [2]. Magnesium deficiency may contribute to the pathogenesis of hypocalcemia in patients with AP. Despite normal serum magnesium concentrations, patients with AP and hypocalcemia frequently have magnesium deficiency [3]. One possible mechanism of hypocalcemia seen in AP includes the autodigestion of mesenteric fat by pancreatic enzymes, causing the release of free fatty acids, ultimately leading to the formation of calcium salts [4]. Elevated levels of urinary and salivary amylase are important markers of disease severity [5].

Clinical Course

A 39-year-old male with a past medical history of significant alcohol abuse (up to 15 beers and 10-15 shots of vodka daily) and seizure disorder (on lamotrigine) presented to the hospital for worsening abdominal pain associated with nausea and non- bloody / non-bilious vomiting. Diagnostics on arrival were pertinent for hypertriglyceridemia >4,425 mg/dL, hypocalcemia 5.3 mg/dL, hypokalemia 3.1 mmol/L, hyponatremia 128 mmol/L and elevated lipase of 839 U/L. Abdominal ultrasound was significant for hepatomegaly and cholelithiasis without biliary or pancreatic duct dilation. CT and MR imaging, however, did show evidence of peripancreatic fat stranding and fluid (without drainable collection) (Figure 1).

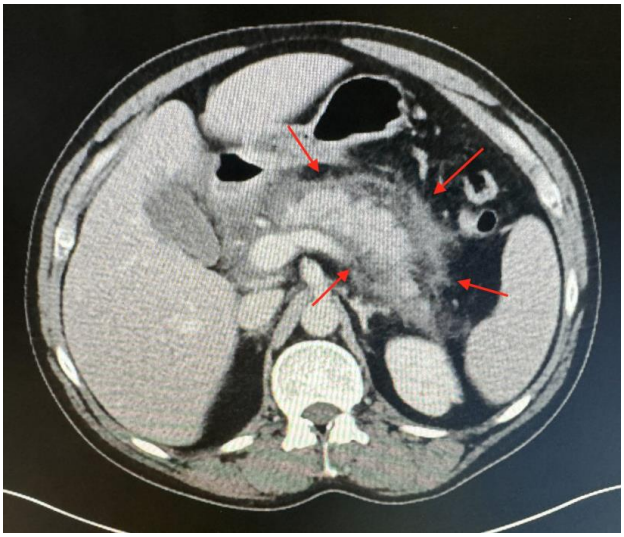

FIGURE 1: CT imaging of the abdomen with arrows depicting peripancreatic fat stranding and free fluid; concerning for AP.

Patient received aggressive fluid resuscitation and was placed on an insulin drip for the first 48 hours for persistent hypertriglyceridemia. He was replenished with up to 5000mg of IV calcium gluconate over the first 24 hours with minimal changes in serum levels. It was only after triglyceride levels began to normalize did Ca begin to rise. He was given approximately 20,000 mg of IV calcium gluconate over his hospital stay (roughly 96 hours). Basic metabolic panels done every four hours showed consistent signs of treatment-resistant hypocalcemia with calcium levels less than 8.0 mg/dL as seen in Table 1 and Figure 2.

TABLE 1
Table depicting the relationship over time (from admission to discharge) of TG to Ca levels.

	Triglycerides (TG) (mg/dL)	Calcium (Ca) (mg/dL)
0hr (admission)	> 4425	5.2
24hr	1133	6.2
48hr	588	6.6
72hr	278	8.1
96hr (discharge)	232	8.7

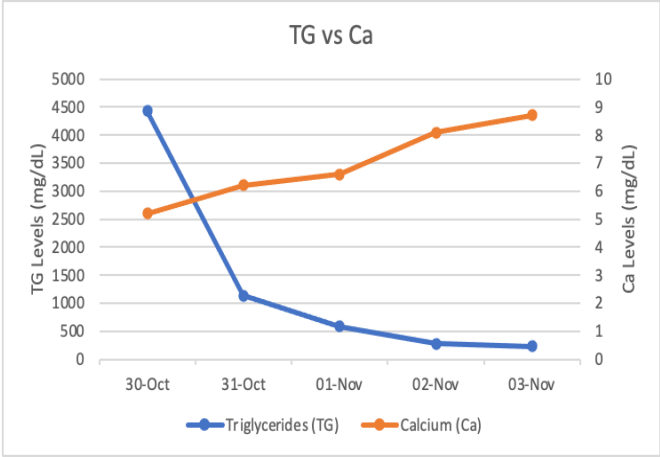

FIGURE 2: Graph depicting the gradual rise of Ca as TG levels (mg/dL) decrease over hospital stay

Discussion

Diagnostic Criteria

AP is one of the most common causes of gastrointestinal-associated hospitalizations in the United States. Hypertriglyceridemia is the third most frequent cause of AP, accounting for approximately 5% of all cases. As per a study conducted in China, the annual admission rate of hypertriglyceridemia-induced pancreatitis (HTGP) had increased from 14.3% to 35.5% [6]. A TG level of above 1000 mg/dL is often used to define hypertriglyceridemia as the source of AP; for every 100 mg/dL rise in serum TG level above 1000 mg/dL, there is approximately 4% increase in the incidence of AP. Nevertheless, there is a greater but lower risk of HTGP at lower levels of triglycerides (TG), making it important to check the levels of TG on admission to identify hypertriglyceridemia as either the sole reason or a cofactor. This is because HTGP is often more severe as compared to other causes [7]. As per the diagnostic criterion established in Japan, two of the following three manifestations are to be met for a diagnosis of AP: characteristic upper abdominal pain, elevated levels of pancreatic enzymes, and findings of ultrasound, computed tomography, or magnetic resonance imaging suggesting AP. Due to high specificity and sensitivity, measurement of blood lipase levels is usually recommended and is considered superior to other pancreatic enzymes. Blood amylase levels can be elevated in diseases other than pancreatitis and because of its low specificity should be used with caution. The cut-off level of pancreatic enzymes for the detection of AP has not yet been determined due to a lack of adequate evidence and consensus to date [8]. The diagnosis of AP continues to evolve. A few patients can develop severe AP resulting in major complications and increased morbidity and mortality, hence signifying the importance of increased recognition of such patients.

Scoring Systems

Several scoring systems specific to pancreatitis have been described that correlate with subsequent morbidity and mortality. Ranson score was introduced in 1974 by Dr John Ranson and includes variables on admission and within 48 hours. These variables include: age older than 55, white blood cell count more than 16000/microL, blood glucose greater than 200 mg/dL, lactate dehydrogenase level greater than 350 IU/dL, and aspartate aminotransferase level more than 250 IU/dL. The variables during initial 48 hours include: hematocrit decrease more than 10% points, serum blood urea nitrogen increase greater than 5 mg/dL, Ca levels less than 8 mg/dL, PaO2 less than 60 mmHg, base deficit greater than 4 mEq/L, and fluid sequestration less than 6 L. As per the original study of Ranson criteria, the presence of 3 or more variables was associated with 62% mortality [9]. Other commonly used scoring systems used in AP include Acute Physiology and Chronic Health Evaluation (APACHE II), Bedside Index of Severity in AP (BISAP), and Modified computed tomography severity index (MCTSI) [10]. The APACHE score was developed in 1981 and is confined to critically ill patients admitted to the ICU. The three key actors making up this scoring system are acute physiology scores, age scores, and chronic health scores, with point scores from 0-71 [11].

Pathophysiology

Hypocalcemia is used to evaluate the severity of pancreatitis as per Ranson's criteria. Various animal studies have indicated that hypocalcemia can be a negative prognostic indicator in pancreatitis patients. The exact cause of this remains unclear, however. Several theories have been proposed, including reduced basal levels of parathyroid hormone [12], normal parathyroid hormone levels but an inadequate response to hypocalcemia [13] [14], unresponsiveness of parathyroid hormone receptors [15] [16], hypomagnesemia [17] [18], and formation of extravascular calcium soaps [19] [20]. The theory of calcium soap formation, although widely accepted, has been challenged due to the insufficient quantities found in patients with severe pancreatitis [19]. Other potential causes such as abnormal levels of glucagon [21] [22], calcitonin [23] [24], or other hormones have been suggested, but these have not been consistently observed [16]. Hypocalcemia has also been linked to a decrease in protein-bound calcium due to hypoalbuminemia, but ionized calcium levels also decline [13] [15].

It is being observed that severe hypocalcemia in acute pancreatitis is more likely in patients with extremely high levels of TG in their blood [25]. The association between high TG levels and AP is reported to be around 20-30% [26] [27]. These patients may also have very high levels of free fatty acids (FFAs) in their blood, and in some cases, measurements exceeding 4 mEq/L, the highest being ever recorded in humans.

FFAs can bind to Ca, leading to the theory that FFA-calcium complexes could cause hypocalcemia. This idea is based on anecdotal human observations and in vitro experiments. One study showed that high plasma FFA levels caused a decrease in serum calcium concentration. However, it is still unclear whether the calcium bound to FFAs is effectively removed from the active ionized calcium pool or if it remains available in a complex form. High levels of Ca can also promote pancreatic injury; bile acids and ethanol can lead to the pathologic release of Ca from the endoplasmic reticulum. Persistent hypercalcemia can lead to continuous trypsinogen activation resulting in the vacuolization and death of acinar cells [4].

Imaging

In terms of imaging, abdominal ultrasound is recommended for patients with first presentation, and suspicion of AP, to look for the presence of calculi, gas, biliary dilatation, and fluid collection. CT scan allows for analysis of pancreatic morphology and to determine the extent and severity of the disease. MRI is used in cases of limitations or contraindications to CT scans and in patients with presentation of AP but negative CT results. CT scan reveals an enlarged pancreas with normal relative enhancement and regular peripancreatic fat, or ground glass opacity due to an inflammatory process. The presence or absence of necrotic tissue differentiates between acute edematous and necrotic pancreatitis [28]. The role of imaging in AP has substantially increased. The 2012 revision of the Atlanta classification signifies accurate characterization of collections that complicate AP. As per the Atlanta classification, the disease has been classified into two phases, an early phase lasting for a week and a late phase respectively. The late phase can extend for months and it is during this phase that the assessment of local complications with imaging may be crucial for management. Although a CT scan is the first choice in acutely ill patients with AP, an MRI is more appropriate for discovering necrotic debris, which may change the management [29].

Management

The management of AP is divided into three major areas which are hydration, pain control, and nutrition. The initial treatment for AP, as per ACG guidelines, consists of aggressive hydration, especially in the first 12-24 hours as it may have little benefit after that. Unless there are any renal or cardiovascular comorbidities, 250-500mL per hour of an isotonic crystalloid solution, preferably Lactated Ringer's, needs to be administered. Although there is conflicting evidence of the type of fluid to be used, Lactated Ringer's vs normal saline, limited evidence does suggest Lactated Ringer's reduces intensive care unit admissions and hospital stays [30]. Abdominal pain is the most common symptom in AP and opioids are considered effective and safe in controlling pain [31]. Previously it was believed that keeping the patient nil per os was the best way forward when dealing with AP in an attempt to decrease the stimulation of an already inflamed pancreas. Current evidence, however, demonstrates that early feeding may be the best approach. Oral feeding can be initiated within 24 hours if the pain is decreasing and there is no nausea, vomiting, or ileus [32]. Multiple varieties of diets have been proven efficacious including low fat, normal fat, and soft or solid consistency; starting with a clear liquid diet is not required [33]. In patients who cannot tolerate oral feeds, enteral instead of parenteral is recommended in moderately severe and severe AP, nasogastric and naso-enteral enteral feeding are comparable in safety and efficacy [34] [35]. The use of antibiotics when suspecting an extra pancreatic infection is highly recommended as these infections are associated with an increase in mortality.

Amongst the causes of AP, hypertriglyceridemia is one of the main culprits behind pancreatitis accounting for 1-35% of all cases of AP [36]. General measures to tackle hypertriglyceridemia as a cause of AP is to treat the pancreatitis with supportive measures and pain control, diet should be restricted in terms of fat until the TG levels are < 1000mg/dL, and discontinuing any medication that might be increasing TG levels [37]. Additional options in treating hypertriglyceridemia in patients with AP and signs of hypocalcemia, as in our patient, lactic acidosis, or worsening systemic inflammation include plasmapheresis and IV insulin administration. Insulin has several beneficial effects on TG metabolism and has been shown to help lower serum TG levels. This is achieved by increasing the activity of lipoprotein lipase (LPL). This enzyme accelerates the breakdown of chylomicrons and very low-density lipoproteins (VLDL) into glycerol and free fatty acids (FFAs). Additionally, insulin inhibits hormone-sensitive lipase in adipocytes, the enzyme responsible for releasing fatty acids from adipose tissue into the bloodstream. In cases of severe AP with high TG levels, the primary goal of insulin therapy is to counteract the stress-induced release of fatty acids from adipocytes, encourage the storage of TG within adipocytes, enhance fatty acid metabolism in insulin-sensitive cells, reduce peripheral insulin resistance, and primarily correct hyperglycemia. In studies involving mice, insulin has also been shown to reduce the severity of AP and improve recovery [38] [39]. For individuals with hypertriglyceridemia-induced pancreatitis, keeping TG levels below 500 mg/dL (5.6 mmol/L) can potentially speed up the process of clinical recovery [40]. In an experiment by Rattner et al., fatty acids were injected into rats to induce necrotizing pancreatitis; a time-dependent decrease in calcium was observed. The severity of pancreatitis correlated to the degree of hypocalcemia [41].

Hypocalcemia is a component of Ranson's scoring system used for evaluating the severity of pancreatitis. Multiple studies on animal models have demonstrated that low levels of calcium in the blood serve as an unfavorable indicator for the prognosis of individuals with pancreatitis [42]. There has not been any research conducted on the impact of correcting hypocalcemia in patients with pancreatitis, but studies performed in other groups of patients with hypocalcemia correction have not yielded beneficial results in favor of correcting hypocalcemia with parenteral calcium infusion. One study with liver transplant patients demonstrated that the likelihood of experiencing biochemical AP following transplantation was elevated in relation to the quantity of intravenous CaCl given during the pre-anhepatic phase and the surge in serum calcium within the first 2 hours after reperfusion of the liver graft [43]. Another study looking at septic patients in the ICU noted that the use of

IV Ca was linked to an elevated risk of death and a deterioration in organ function [44]. Calcium infusion may result in skin tissue death. When administering it intravenously, it should be exclusively through a central venous catheter. Severe hypocalcemia can have many associated life-threatening complications including, but not limited to, arrhythmias, seizures, tetany, and other neurological/psychological disorders. Patients with hyperphosphatemia should not receive calcium, as it can lead to the formation and buildup of calcium phosphate deposits in different tissues [4].

Conclusion

Various factors can affect the development and progression of acute pancreatitis. Aggressive fluid hydration, pain management, and early feeding when tolerable are current recommendations for management. Electrolyte derangements may not be able to be corrected unless the triggering mechanism is addressed. As with our case, the patient's hypocalcemia remained resistant to treatment until his TG levels had begun to normalize. Other electrolytes, such as magnesium and phosphorus, should also be monitored and managed as they may also be deranged in patients with a history of alcohol abuse. Currently, the administration of insulin to normalize TG levels is not part of current guidelines, but in our case, had a substantial improvement in his clinical course and recovery. Further investigations should be performed into the efficacy of treating hypertriglyceridemia-induced pancreatitis with such therapy to help prevent life-threatening complications.

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