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CASE REPORT

Hypercalcemia – An enigmatic cause of acute pancreatitis

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ABSTRACT

Background: Acute pancreatitis (AP) continues to be one of the common abdominal emergencies encountered in tertiary care hospitals. The majority of AP is caused by gall stones and alcohol. Hypercalcemia though uncommon has been reported to cause AP, recurrent AP, and chronic pancreatitis (CP).
Aim: The aim of this study was to describe hypercalcemia-induced AP in different settings.
Materials and Methods: In total 100 patients with AP, admitted from January 2021 to December 2021 at our center, etiologies were biliary (36%), alcohol (19%), idiopathic (21%), alcohol plus Biliary (5%), post-endoscopic retrograde cholangiopancreaticography (7%), drug-induced (6%), hypercalcemia (3%), and dengue infection (3%). Overall mortality was 11%.
Results: In three patients with hypercalcemia-induced pancreatitis, causes of hypercalcemia were multiple myeloma, parathyroid adenoma leading to hyperparathyroidism, and hypervitaminosis D in association with hyperthyroidism.
Conclusion: Hypercalcemia-induced AP is not a rare phenomenon and should be actively investigated to prevent further attacks of AP and progression to CP.
Relevance for Patients: Hypercalcemia is a potentially treatable cause of AP and its identification will not only help to treat and prevent further episodes of pancreatitis but also to manage underlying diseases leading to hypercalcemia.

1. Introduction

Acute pancreatitis (AP) continues to be one of the common abdominal emergencies encountered in tertiary care hospitals. Etiologies of AP include gall stones, alcohol, drugs, infections, trauma, hypertriglyceridemia, and hypercalcemia among others. Gall stones and alcohol contribute to the majority of AP. Hypercalcemia though uncommon has been reported to cause acute, recurrent acute pancreatitis (RAP), and chronic pancreatitis (CP). Usual causes of hypercalcemia include hyperparathyroidism (PHPT), malignancies including multiple myeloma, vitamin D toxicity, sarcoidosis, familial hypocalciuric hypercalcemia (FHH), and total parenteral nutrition [1-5]. Acinar cells of the pancreas are initiating site of pancreatic injury [6]. Hypercalcemia-induced pancreatitis may be calcium-sensing receptor (CaSR) dependent or independent; however, exact mechanism is still to be elucidated [7,8]. Raised intracellular calcium activates calcineurin, leading to intracellular activation of pancreatic enzymes (e.g., trypsin) and activation of NF-kb resulting in pancreatic injury and systemic inflammatory response syndrome [9-11].

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2. Materials and Methods

A hundred patients with AP were admitted to the gastroenterology ward of a tertiary care hospital for 1 year (January to December 2021). Etiologies of AP were biliary in 36 %, alcohol in 19%, alcohol and Biliary in 5%, post endoscopic retrograde cholangiopancreatography in 7%, drug-induced in 6%, hypercalcemia in 3%, dengue infection in 3%, and idiopathic in 21%. A genetic study was not performed for hereditary pancreatitis. We report a case series of three patients with AP induced by hypercalcemia in different settings. Calcium levels of all patients (corrected for albumin) and ionized calcium in selected patients were measured and were either within normal range or lower except in these three reported cases. Baseline parameters of these cases are illustrated in Table 1.

3. Results

3.1. Case 1

A 62-old-year female presented with acute, severe pain abdomen for 5 days, located in the upper part of the abdomen and radiating to the back. The pain was associated with bilious vomiting and decreased urine output. There was no history of jaundice, fever, breathing difficulty, or similar episodes of pain in past. She had no history of alcohol, drug, or complementary and alternative medicine (CAM) intake. She had no history of any surgical intervention. Non-contrast CT scan showed pancreatic edema and (peri) pancreatic fat stranding without any collection. The patient had elevated corrected calcium with reversal of albumin/globulin ratio (0.32), hypercalcemia, renal dysfunction, and anemia at presentation. These findings led to the diagnosis of hypercalcemia-induced AP in the setting of multiple myeloma. Later was confirmed by qualitative immunotyping, bone marrow aspiration, and serum protein electrophoresis (Table 2). The patient treated for multiple myeloma with clinical improvement without any recurrence in 6 months follow-up.

3.2. Case 2

This 44-year lady presented with a history of epigastric and right hypochondrial pain for 4 days. The pain was acute onset, severe, non-radiating, and aggravated by food intake. The pain was associated with nausea, and vomiting without a history of constipation or obstipation. The patient had a history of breathlessness for 2 days without any history of cough, palpitation, pedal swelling, or decreased urine output. No history of drug or CAM intake or significant family history of pancreatitis or symptoms related to hypercalcemia. Contrast-enhanced CT demonstrated acute necrotizing pancreatitis with intra-pancreatic non-enhancing fluid collection in the head, body, and tail region (modified CT severity score 10/10).

She had elevated ionized calcium 1.82 mmol/L (1.120–1.320 mmol/L) and corrected serum calcium, elevated intact

Table 1. Baseline parameters of hypercalcemia induced pancreatitis cases.

Parameters	Case 1	Case 2	Case 3	Normal range
Age (Years)	62	44	45	-
Sex	Female	Female	Female	-
Hemoglobin	4.3	11	8.8	11–15 g/dl
Total leukocyte count	5700	24000	4200	400010000/micro L
Platelets	114	234	169	150–450/micro L
Alanine aminotransferase	17	25	105	10–40 U/L
Aspartate aminotransferase	25	28	108	9–37 U/L
Alkaline phosphatase	171	2000	332	110–310 U/L
Total protein	9.0	7.3	6	6.4–8.5 g/dl
Albumin	2.2	3	3	3.2–5.5 g/dl
Bilirubin	0.2	0.3	0.4	0.1–1.2 mg/dl
Sodium	139	134	141	135–145 mmol/L
Potassium	4.6	4.6	4.7	3.5–5.5 mmol/L
Creatinine	7.2	0.9	0.6	0.5–1.4 mg/dl
Urea	134	51	45	15–45 mg/dl
Serum calcium	10.4 (Corrected-11.84)	12.6 (Corrected-13.4)	12.5 (Corrected-13.3)	8.5–11 mg/dl
Phosphate	7.3	2.5	2.3	2.5–7.0 mg/dl
Total cholesterol	51	106	150	150–250 mg/dl
Triglycerides	70	156	136	10–200 mg/dl
High-density lipoprotein	13	24	39	35–61 mg/dl
Low-density lipoprotein	24	29	36	60–160 mg/dl
Lipase	1507	1631	1432	5.6–60 U/L
Amylase	1209	2970	1987	28–100 U/L

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Table 2. Results of serum protein electrophoresis of case 1.

Parameter	Findings	Normal value
M band	Detected	Absent
K light chain	94.05	3.3–19.4 mg/dl
Lamda light chain	6.42	5.71–26.3 mg/dl
Ig G	1609	700–1600 mg/dl
Ig M	12.0	40–230 mg/dl
Ig A	5239	70–400 mg/dl
Total protein	8.3	6.4–8.3 g/dl
Albumin	2.12	3.97–4.95 g/dl
Alpha 1 globulin	0.38	0.21–0.35 g/dl
Alpha 2 globulin	0.58	0.51–0.85 g/dl
Beta 1 globulin	4.43	0.34–0.52 g/dl
Beta 2 globulin	0.43	0.23–0.47 g/dl
Gamma globulin	0.35	0.8–1.35 g/dl

parathyroid hormone (iPTH) (>2500 [14–65 pg/ml]), and low vitamin D (25 OH) −6.3 (18.5–24 ng/ml). Ultrasonography neck revealed a solid hypoechoic 2.7 cm lesion with lobulated irregular margins posterior to the left lobe of the thyroid gland (parathyroid adenoma). Removal of parathyroid adenoma led to normalization of serum calcium and the patient did well in the 2-month follow-up.

3.3. Case 3

This 45-year female presented with pain epigastrium for 2 days, which was acute onset severe, non-radiating, aggravated by food, and partially relieved by analgesics. No history of jaundice, fever, breathlessness, decreased urine output, or any drug or CAM intake. The patient had a history of weight loss and palpitations over 2 months. CECT abdomen showed AP with marked peripancreatic and omento-mesenteric nodular fat stranding and mild peripancreatic fluid collections. She had a history of weight loss and palpitations for the past 2 months. She had tachycardia, goiter, and acral tremors. She had elevated serum calcium (12.5 mg/dl [corrected Ca 13.3 mg/dl]), low iPTH (3.6 pg/ml [14–65 pg/ml]), and high (>100 [18.5–24 ng/ml]) vitamin D levels. She had hyperthyroidism (T3-2.64 pmol/L, T4-19.13 pmol/L, thyroid-stimulating hormone −0.005 mIU/L). The patient denied any history suggestive of taking vitamin D either in medicinal or inadvertent form, no feature suggestive of lymphoma or any granulomatous disorder, and her angiotensin converting enzyme level was 71 (Normal 8–51). The cause of hypervitaminosis D (HVD) could not be ascertained; however, exposure to the sun as stated by the patient could be the probable cause of HVD. The patient received treatment for HVD and hyperthyroidism along with dietary restriction of calcium and vitamin D and improved.

4. Discussion

Hypercalcemia has been reported to be causative in 1.5–8% of cases of AP and the majority occur in the setting of hyperparathyroidism [12]. In our 100 patient population of AP during 1 year, the frequency of hypercalcemia-induced pancreatitis was 3% with multiple myeloma, PHPT, and HVD/hyperthyroidism contributing to 1% each.

Although approximately 21% of newly diagnosed symptomatic myeloma patients show elevated serum calcium levels [13], reported cases of AP in patients with *multiple myeloma* are surprisingly rare. PHPT has been associated with AP, RAP, and CP and the overall frequency of pancreatitis in PHPT ranges between 3% and 13% [14,15]. The exact frequency of pancreatitis in settings of HVD and hyperthyroidism could not be found in the literature as most reports are in the form of case reports.

Usually, there is a decrease in serum calcium found frequently in AP and may be attributed to fat saponification, transient hypoparathyroidism, hypomagnesaemia, and hypoalbuminemia. The corrected value of serum calcium and ionized calcium in selected patients was either within the normal range or lower except in these three reported cases. Albumin-corrected value of serum calcium and/or ionized calcium should be used to have a real estimate of calcium level. Treatment approaches such as rapid hydration, calcitonin spray, and corticosteroids are used to acutely lower the serum calcium levels in cases of severe hypercalcemia (serum calcium levels >14 mg/dL) to prevent or treat episodes of cardiac arrhythmia. Calcium levels in all 3 patients were <14 mg/dL suggesting moderate hypercalcemia, where acute lowering of serum calcium is not required usually; however, all patients were given adequate intravenous fluid as required in case of AP and were monitored regularly with serial calcium measurement and electrocardiogram for arrhythmia.

In our first case, serum total calcium was 10.4 mg/dl, while the corrected value was 11.84 mg/dl suggestive of hypercalcemia and contributed in addition to reversal of albumin/globulin ratio, renal dysfunction, and anemia for diagnostic work up of multiple myeloma. Renal failure, anemia, bony lesions, and hypercalcemia are frequent features of multiple myeloma. Myeloma cell-derived cytokines may induce osteoclastic actions resulting in elevated serum calcium levels [16].

The etiology of hypercalcemia in case 2 was evaluated with findings of raised iPTH and low serum vitamin D3 levels. Imaging of her neck revealed a solid hypoechoic 2.7 centimeters lesion with lobulated irregular margins posterior to the left lobe of the thyroid gland (parathyroid adenoma). These findings suggested PTH-dependent hypercalcemia. FHH is a rare autosomal dominant condition resulting from mutation in the CaSR gene causing decreased receptor activity. It is very difficult to distinguish FHH from PHPT in absence of a family history of hypercalcemia. Obtaining serum calcium levels from 1st-degree relatives of the patient would have been beneficial in this regard; however, it was not done. Genetic analysis for CaSR gene mutation was also not performed in this case. Finding a solitary adenoma in a patient with FHH has been reported and this fact, further, complicated the distinction between FHH and

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PHPT; however, the patient responded well to the removal of her parathyroid adenoma during 2 months follow-up which favors the final diagnosis of PHPT due to parathyroid adenoma as FHH patients usually do not respond to sub-total parathyroidectomy or removal of adenoma.

In our 3rd case, either HVD or hyperthyroidism could have caused hypercalcemia; however, HVD appears more plausible as hyperthyroidism may be associated with mild-to-moderate hypercalcemia in approximately 20% of patients [17], but severe hypercalcemia, leading to symptoms, is rare [18]. HVD usually results from iatrogenic or inadvertently excess intake of vitamin D, overproduction of vitamin D metabolites in granulomatous disease, lymphoma/malignant lymphoproliferative diseases [19], and extremely rarely from exposure to the sun (bed-tanning). Our patient denied any history of medicinal intake including in the form of eye drops which could have resulted in HVD. A rare loss of function mutation in the vitamin D 24-hydroxylase (CYP24A1) gene may result in persistently high levels of active vitamin D metabolites even in absence of iatrogenic or inadvertently excess intake of vitamin D [20,21]; however, the genetic analysis of CYP24A1 mutation was not done in our case and cause of HVD could not be ascertained except speculations of sun exposure.

5. Conclusion

Hypercalcemia-induced pancreatitis is not rare. Hypercalcemia and underlying disease must be carefully evaluated in every case of AP and especially idiopathic. Evident hypercalcemia may lead to catastrophic outcomes, and hence, it is necessary to clearly identify the situation not only to treat and prevent further episodes of pancreatitis but also to manage underlying diseases.

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Conflict of Interest

All authors declare no conflicts of interest.

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