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From Abdominal Groans To Psychic Moans: A Curious Case Of Hypercalcemia

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Abstract:
Characterised by a myriad of etiologies, acute pancreatitis occurring in the setting of hypercalcemia is rare. It is crucial to recognise the wide range of symptoms and signs of hypercalcemia in this regard. After having managed the patient according to standard protocols for pancreatitis and specific measures directed at reducing serum calcium levels, it is imperative to warrant an aggressive search for the etiology of hypercalcemia. This is pivotal in ultimately deciding management strategies and guiding further definite treatment plans. Here, we present a unique case of hypercalcemia, which on amalgamating clinical, biochemical, radiological and pathological clues, ultimately unraveled a rather enigmatic presentation of a common disease entity.

Keywords*: hypercalcemia, acute pancreatitis, tuberculosis, granulomatous diseases, hyperparathyroidism.*

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I. Introduction:

Acute pancreatitis (AP) continues to be one of the common abdominal emergencies encountered in tertiary care hospitals. Etiologies of AP include gall stone disease, alcohol, drugs, infections, trauma, hypertriglyceridemia, and hypercalcemia among others. Gall stones and alcohol contribute to the majority of the cases of AP. Hypercalcemia, though uncommon has been reported to cause acute, recurrent acute pancreatitis, and chronic pancreatitis. Usual causes of hypercalcemia include primary hyperparathyroidism (PHPT), malignancies including multiple myeloma, vitamin D toxicity, sarcoidosis, familial hypocalciuric hypercalcemia, granulomatous diseases and total parenteral nutrition. Granulomatous diseases, such as sarcoidosis and tuberculosis (TB), can disrupt the calcium phosphate homeostasis leading to hypercalcemia independently of PTH levels by promoting an overproduction of calcitriol within granulomas due to activated macrophages that express 1-α-hydroxylase. Despite sarcoidosis being the usual culprit among granulomatous diseases, hypercalcemia in TB patients remains a significant clinical concern, with rates ranging from 2.3% to 28% [(1)]. Calcitriol plays a crucial role in the regulation of granulomatous inflammation and influences the cell-mediated immunity in tuberculosis. Tuberculosis (TB) is widely prevalent in India and its varied manifestations are well known. Hypercalcemia in the setting of TB may range from the usual asymptomatic presentation to the rarer, but more florid symptoms attributable to raised serum calcium levels. Here we present a case of tuberculosis associated hypercalcemia presenting as acute pancreatitis.

II. Case Presentation:

A 55-year-old female, presented to our emergency with the chief complaints of abdominal pain since 2 days and altered sensorium since 1 day. The patient was apparently normal 2 days back, after which she experienced abdominal pain which was sudden in onset, progressive in nature, localized predominantly to the epigastric region. There was a history of altered sensorium characterised by confusion and disorientation since 1 day. There was no associated with headache, fever or seizures. There was a history of non-passage of stools for 1 day. On repeated probing, the relatives gave a history of use of over-the-counter medications (antacids and antipyretics.) for low grade intermittent undocumented fever and dyspepsia for the last 1.5 months. There was no significant weight loss, night sweats. There was no history of decreased urine output. There was a history of pulmonary tuberculosis 15 years back for which patient completed 6 months of anti-tubercular treatment (ATT). There was no history of diabetes, hypertension, peptic ulcer disease or any other known chronic co morbidities.

On examination, she had a pulse of 110/minute (regular, normal volume), blood pressure (BP) of 110/70 mm Hg, an axillary temperature of 100°F and appeared drowsy and dehydrated. There was tenderness in the upper abdomen, without any palpable lump or organomegaly; with sluggish bowel sounds. Examination of other systems did not reveal any specific abnormality. Investigations in the emergency (Day 1) showed

deranged kidney function tests, elevated serum lipase and amylase with hypercalcemia **(Table 1)**. Ultrasonography of the abdomen revealed a bulky pancreas with raised cortical echoes in bilateral kidneys with CMD being maintained. The arterial blood gas analysis showed elevated ionic calcium level, with the ECG showing a short QT interval. A provisional diagnosis of Acute pancreatitis with acute kidney injury with metabolic encephalopathy secondary to hypercalcemia was made. Intravenous (IV) fluids and analgesics were initiated as per standard protocols in combination with intravenous calcitonin for 48 hrs (in view of persistent hypercalcemia), following which she experienced symptomatic relief with a concurrent improvement of the renal functions and normalisation of the serum calcium levels by Day 5 of admission.

TABLE 1: Table showing trends of various biochemical parameters on Day 1, Day 3 and Day 5 of admission to the hospital.

	Day 1	Day 3	Day 5
Hb (gm/dl)	13.2	12.8	13.0
TLC(per mm^3)	12400	9800	8600
Polymorphs (%)	70	68	65
Platelets (lakh)	2.36	2.56	2.8
Urea (mg/dl)	88	64	40
Creatinine (mg/dl)	**2.8**	**1.8**	**1.0**
T.Bil/ D.bil (mg/dl)	1.5/.7	1.4/0.7	1.2/0.6
AST (U/L)	64	54	52
ALT (U/L)	53	43	41
ALP (U/L)	165	170	168
TP/SA (gm/dl)	6.4/3.9	6.8/3.5	6.9/3.2
Amylase and lipase (U/L)	**650/1012**	**450/800**	**120/345**
Na/K	133/3.8	134/4.2	138/3.9
Calcium	**13.2**	**12.8**	**10.2**

Abbreviations: Hb: Haemoglobin, TLC: Total leucocyte count, TBil: Total bilirubin, DBil: Direct Bilirubin, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, TP/SA: Total protein/Serum albumin;

Delving further into the possible cause for hypercalcemia, investigations revealed a low iPTH level (8 pg/ml) suggesting a non-PTH-dependent etiology for the same. The 25(OH)Vitamin D (18.2 ng/ml) were low coupled with an elevated $1,25(OH)_2$ Vitamin D (194 pg/ml) and 24 hour urinary calcium (408 mg/day) levels. Serum and urinary protein electrophoresis, serum free light chain assay, skeletal survey, thyroid function tests were normal. Parathyroid hormone related peptide (PTHrP) was not available at our institute. Reduced PTH levels, raised $1,25(OH)_2$ Vitamin D and low 25(OH)Vitamin D were all suggestive of a granulomatous pathology. **(Table 2)** The Serum ACE levels were marginally elevated at 84 mcg/L. In view of pancreatitis with deranged KFT, a NCCT of the abdomen was planned to look for local complications which revealed a bulky pancreas with fat stranding and heterogeneity suggestive of acute pancreatitis. Multiple enlarged peripancreatic, mesenteric, and retroperitoneal lymph nodes were noted **(Figure 1 & 2)**. An endoscopic-ultrasound guided FNAC of the peripancreatic lymph nodes was done which FNAC showed scattered lymphocytes with epitheloid cells forming a granuloma the stain for AFB being positive. Moreover, CBNAAT was positive for M. Tuberculosis. **(Figure 3 & 4)**

A final diagnosis as Hypercalcemia-induced acute pancreatitis secondary to granulomatous disease (Tuberculosis) was made. Anti-tubercular therapy (ATT) was initiated and the patient is being closely followed-up. She is well-compliant and currently onto her 5^{th} month of ATT. She is completely asymptomatic, with her serum calcium levels and renal function parameters being well within the normal range.

TABLE 2: Table showing various biochemical parameters pertaining to the evaluation of hypercalcemia

iPTH	**8** (15-63pg/ml)	24 hour urinary calcium	**408** (<300 mg/day)
PTHrP	N/A	Serum ACE	**84** (9-70 mcg/L)
25 (OH) Vitamin D	**18.2** (30-60 ng/ml)	SPEP/UPEP/FLCA/Skeletal survey	Negative
1,25 (OH)2 Vitamin D	**194** (16-60 pg/ml)	TFT	Normal

Abbreviations: iPTH: Intact Parathyroid hormone, PTHrp: Parathyroid hormone-related peptide, N/A: Not available, ACE: Angiotensin-converting enzyme, SPEP: Serum protein electrophoresis, UPEP: Urine protein electrophoresis, FLCA: Free-light chain assay, TFT: Thyroid function test.

Figures 1&2: Transverse and coronal non-contrast computed tomography scans showing multiple enlarged peripancreatic, mesenteric and retroperitoneal lymph nodes.

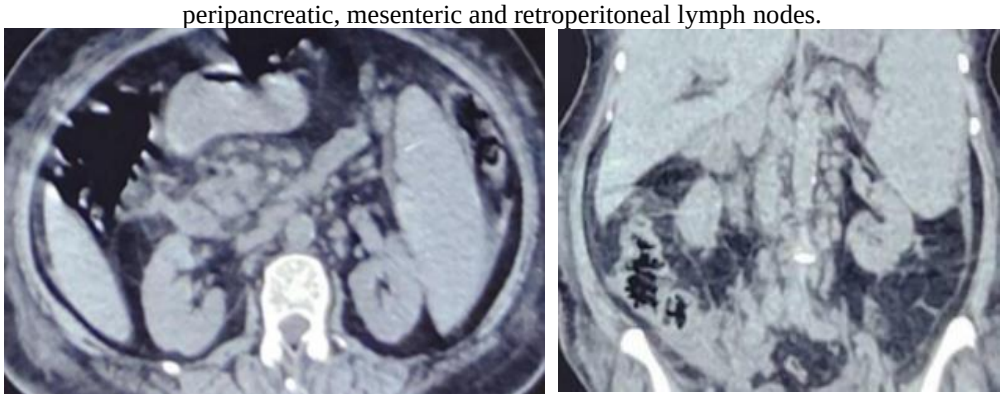


Figure 3 : FNAC showing granuloma with epitheloid cells and lymphocytes.

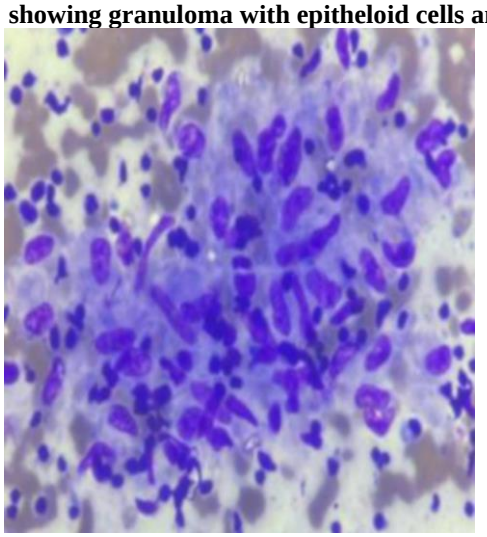
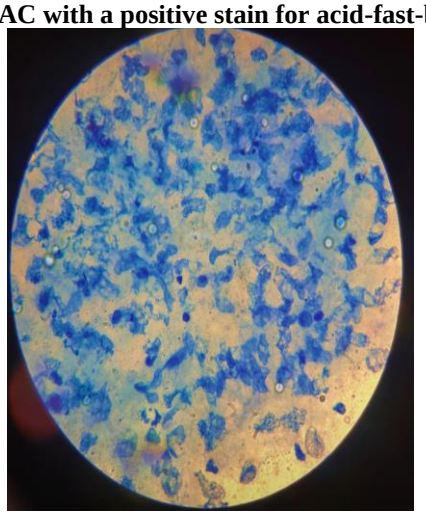


Figure 4: FNAC with a positive stain for acid-fast-bacilli (AFB)



III. Discussion:

In our report, we describe a case of hypercalcemia presenting as acute pancreatitis accompanied with metabolic encephalopathy in the background of abdominal lymphadenopathy. Normalisation of the serum calcium levels was associated with an improvement in pancreatitis as well as sensorium. This was followed by a thorough search for the etiology of hypercalcemia through judicious integration of history and clinical assessment, laboratory data, radiological investigations and eventually pathological confirmation. This is a rare case in which pancreatitis was the first manifestation of abdominal tuberculosis induced hypercalcemia and responded well to ATT.

The overall incidence of acute pancreatitis in the general population is estimated to be around 13 to 45 cases per 100,000 people per year. While hypercalcemia is a recognized cause of pancreatitis, it is relatively rare. Hypercalcemia has been reported to be causative in 1.5–8% of cases of AP and the majority occur in the setting of hyperparathyroidism [(2)]. Usually, there is a decrease in serum calcium found frequently in AP and may be attributed to fat saponification, transient hypoparathyroidism, hypomagnesaemia, and hypoalbuminemia. Hypercalcemia in the setting of acute pancreatitis is seldom seen. Hypercalcemia can lead to pancreatitis through several mechanisms: elevated calcium levels may directly damage pancreatic acinar cells by activating digestive enzymes prematurely; high calcium can cause ductal obstruction by precipitating calcium salts, increasing pressure and inflammation in the pancreas. Reduced blood flow due to altered vascular tone may also contribute to ischemia and tissue damage. Furthermore, hypercalcemia disrupts fat metabolism, leading to toxic free fatty acids that harm pancreatic cells. Lastly, hormonal influences, such as increased parathyroid hormone-related peptide (PTHrP), can exacerbate inflammation, highlighting the complex relationship between hypercalcemia and pancreatitis [(3)]. Hypercalcemia is known to occur in granulomatous disease most commonly sarcoidosis and tuberculosis [(4,5)]. The incidence of hypercalcemia in tuberculosis varies from 2% to 25% depending on the geographical area where the study was conducted and is depended on multiple other factors such as the intake of calcium, Vitamin D, and exposure to the sun [(6-10)]. Mechanism of hypercalcemia in tuberculosis is considered to be due to the extra-renal production of $1,25(OH)_2D_3$ by alveolar macrophages and T lymphocytes possibly CD8 T lymphocytes [(11)]. However, hypercalcemia independent of the following mechanism is also reported. Activated Vitamin D plays an important role in the regulation of granulomatous inflammation and influences the cell-mediated immunity to tuberculosis. If produced in large quantities, there may be spillage into the systemic circulation causing severe hypercalcemia [(12)].

IV. Conclusions:

Pancreatitis in the setting of hypercalcemia is an uncommon entity.
TB presenting as hypercalcemia induced pancreatitis is rare.
Prompt recognition of etiology was pivotal in guiding appropriate management strategies for the patient.

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