Severe Hypercalcaemia as a Consequence of Parathyroid Crisis - A Case Report

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Abstract
A 36-years old man presenting with the complaint of sudden severe upper abdominal pain, vomiting and polyuria with raised serum creatinine (2.74 mg/dl), serum calcium (19.68 mg/dl) and intact parathyroid hormone (iPTH) (2014.70 pg/ml) level. His ultrasound image of neck region demonstrated hypoechoic mass (12x10 mm) at left inferior parathyroid gland. Parathyroid scintography reported positive for parathyroid adenoma (left lower). He underwent medical management followed by parathyroidectomy. Optimum serum calcium concentration is essential for homeostasis and function of multiple organ systems. Severe hypercalcaemia is rare but life threatening complication of primary hyperparathyroidism (PHPT). In order to prevent mortality, it is necessary to provide immediate appropriate treatment by correcting hypercalcaemia and dehydration.
Keywords: Hypercalcaemia; Parathyroid Adenoma; Parathyroid Crisis; Parathyroid Hormone (PTH); Primary Hyperparathyroidism (PHPT)

1. Introduction

Hypercalcaemia is a clinical disorder that most generally results from malignancy or primary hyperparathyroidism (PHPT) [1-4]. Other causes incorporate tertiary hyperparathyroidism, familial hypocalciuric hypercalcaemia, hyperthyroidism, drug impacts, sarcoidosis, tuberculosis, and immobilization [1]. Hypercalcemic emergency (severe hypercalcaemia) doesn't have a definite definition, albeit stamped height of serum calcium, typically in excess of 14 mg/dl, is related with intense signs and side effects of hypercalcaemia. The symptoms are as often as possible vague reflecting of multi-organ involvement with gastrointestinal, renal, neuromuscular and focal sensory system dysfunction [5].

Primary hyperparathyroidism is the unregulated over production of parathyroid hormone (PTH), bringing about strange calcium homeostasis. Parathyroid emergency is likewise known as parathyroid crisis; an uncommon and possibly lethal inconvenience of primary hyperparathyroidism (PHPT), wherein patients usually have severe hypercalcaemia with signs and side effects of various organ dysfunctions. Patients frequently show metabolic encephalopathy, renal insufficiency, gastrointestinal manifestations and cardiovascular dysrhythmia [6]. Prognosis is poor: mortality is almost 100% in non-operable cases and 20% cases in which parathyroidectomy is performed [7]. Therefore proper evaluation, early diagnosis and appropriate therapy are vital.

2. Case Report

A-36 years old man, married, known to be non-diabetic, normotensive hailing from Gulshan, Dhaka, admitted in Department of Medicine, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh with the complaints of sudden severe upper abdominal pain and repeated vomiting for 4 days. The pain was diffuse, constant, radiated to the back, aggravated by taking meal and partially relieved by leaning forward position and antispasmodic. Patient noticed several episodes of vomiting for one day before hospital admission. Vomiting was non-projectile, contained ingested food materials, not mixed with blood or bile and not associated with food intake or headache. He also noticed nausea, anorexia, weakness and lethargy during the course of illness. On query; patient gave the history of frequent passage of large volume urine for last 3 days, which was more than 3 liter/24 hours, associated with dryness of mouth and increased with water intake. His bowel habit was normal. There was no history of hematemesis, melaena, red color urine, sense of burning micturition, depression, unconsciousness, palpitation, weight loss, cough, fever, joint pain, rash, gall stone disease or head injury. Patient was non-alcoholic but ex-smoker with 20 sticks of cigarette/day. He belongs to a family of middle socioeconomic condition. There was no significant family history or any contributing drug history related to this illness. On examination; patient was ill looking, moderately dehydrated and felt comfort on leaning forward position. His pulse rate was 88 beats per minute, blood pressure was 100/60 mm of Hg, respiratory rate was 16 breaths per minute and temperature was recorded 98.8˚F (at the time of examination). Anaemia, jaundice, cyanosis, bony tenderness, ascites were absent. His abdomen was tender over epigastric region. Upper border of liver dullness present over 5th intercostal space along right mid-
clavicular line. Bed side dipstick test of urine was negative for glucose and albumin. Biochemical assays revealed no abnormal findings in complete blood count (CBC) and urine routine microscopic examination (R/M/E) along with normal physiological level of serum electrolytes, serum alanine transaminase (ALT) and serum phosphate. Patient’s serum creatinine was initially rising (highest recorded level was 2.74 mg/dl) which was gradually decrease to normal limit after conservative management; indicated that it was acute kidney injury (AKI). Ultrasonography (USG) of whole abdomen revealed features of acute pancreatitis, mild fatty change in liver, relatively larger and swollen kidney with mild acute renal parenchymal disease. Initial urinary amylase was 626 U/L (normal level up to 500 U/L) and serum lipase was 1323 U/L (normal level: 23-300 U/L); consisting with acute pancreatitis. Serum calcium level was initially 12.8 mg/dl (normal limit is 8.5-10.5 mg/dl) which was increasing gradually and highest recorded value was 19.68 mg/dl. Serum intact parathyroid hormone (iPTH) level was 2014.70 pg/ml (normal value is 9-80 pg/ml), which indicated primary hyperparathyroidism. A twelve lead electrocardiogram (ECG) tracing showed cardiac arrhythmia, while endoscopy of upper gastrointestinal tract (GIT), plain X-ray abdomen A/P view in erect posture and X-ray skull A/P view were normal. USG of neck region and parathyroid scintigraphy showed features of left lower parathyroid adenoma (Figure 1 and Figure 2).

The patient was finally diagnosed as a case of acute kidney injury, acute pancreatitis due to hypercalcaemia a consequence of primary hyperparathyroidism (PHPT) as a result of left lower parathyroid adenoma (Parathyroid crisis). The patient was transferred to the coronary care unit (CCU) for observation of cardiac arrhythmia and symptomatic treatment. To decrease the serum calcium concentration the patient received; Inj. Salmon Calcitonin (200 IU/ml) 6 IU/kg - 8 hourly, given by subcutaneous route; Inj. Zoledronic Acid (4 mg/5 ml) mixed with 100 ml Normal Saline infused intravenously over 1 hour; Inj. Hydrocortisone (20 mg) 1 amp was given through intravenously every 6 hourly. In addition; intravenous normal saline was infused accordingly for correcting dehydration.

The initial treatment was successful and follow up on 4th day of hospitalization showed general well-being like- nausea, anorexia, weakness, and lethargy were improved; dehydration and polyuria were corrected; serum calcium level became normal. Surgical exploration of the neck was carried out on 7th day of hospitalization and thereafter the serum parathyroid hormone (PTH) level had been reduced to 60.8 mg/dl (4 days after surgery). A parathyroid adenoma of 12 × 10 × 10 mm, with a weight of 4.8 g was found and removed. The remaining parathyroid glands were found normal in size and left untouched. Histological examination revealed the parathyroid adenoma (Figure 3). Serum calcium and the intact parathyroid hormone (iPTH) levels were normalized. The patient was discharged 6 days after surgery with advice and has so far been followed up for a 12-month period without any sign symptoms of recurrence or other endocrine disorders.
**Figure 1**: Ultrasound image demonstrates a hypoechoic mass, 12 × 10 × 10 mm, inferior and posterior to the left lobe of the thyroid, consistent an enlarged left inferior parathyroid gland.

**Figure 2**: Parathyroid scintigraphy reported positive for parathyroid adenoma (Left lower).
3. Discussion

In this report, we portrayed an instance of a youngster with serious hypercalcaemia with intact parathyroid hormone (iPTH) level was over abundance of 2014.70 pg/ml. Diagnostic evaluation confirmed the presence of a huge (4.8 g) parathyroid adenoma. Hypercalcaemia and hyperparathyroidism were settled quickly following initial medical management and finally adenoma resection. We believe that our patient's findings reflect the most severe clinical manifestations of primary hyperparathyroidism (PHPT). While, PHPT brought about by parathyroid adenoma is normal, this case is novel for a few reasons. To begin with; severe hypercalcaemia is uncommon in PHPT. In this case level of serum calcium was 19.68 mg/dl. This degree of hypercalcaemia results only when PHPT is exceptionally severe (as in this case) or when tertiary hyperparathyroidism develops (like autonomous hyperparathyroidism, hypersecretion after long-standing renal insufficiency etc). Vasoconstriction initiated by severe hypercalcaemia is a significant contributing reason for the acute renal failure as saw in this understanding. The resultant decrease in glomerular filtration rate (GFR) probably

Figure 3: Histopathology report of parathyroid tissue reveals parathyroid adenoma.
represented his normal serum phosphate level, which are commonly low to normal, typical in PHPT. In this setting of hypercalcaemia where primary or tertiary hyperparathyroidism is suspected, doctors ought to search other etiologies (for example malignancy, thiazide or lithium use, milk-antacid disorder, hypervitaminosis D and granulomatous infection). Secondly, the especially raised iPTH (>2000 pg/ml) usually observed in secondary or tertiary hyperparathyroidism. In a new arrangement of 80 patients with primary hyperparathyroidism from parathyroid adenoma, the most elevated announced PTH concentration was 2578 pg/ml [7].

Third, the size of this patient's parathyroid adenoma was quite large [12 × 10 × 10 mm (Figure 1)]. In primary hyperparathyroidism, adenoma size is an important determinant of disease severity, but the reason for such large variation (100-fold) in size is unknown. Two recent studies reported normal parathyroid glands weights from 62.4 ± 31.6 mg [8] and from 42.6 ± 20.3 mg [9], respectively. It was reported that, the mean parathyroid adenoma weight was 553.7 ± 520.5 mg [10]. This patient's parathyroid adenoma weighed 4.8 g, making it significantly larger than most reported parathyroid adenomas. Adenomas weighing more than 60 g have been rarely reported [10, 11]. Fourth, this patient endured acute kidney injury, doubtlessly because of severe hypercalcaemia (19.68 mg/dl). Serum calcium concentrations from 12.0 to 15.0 mg/dl have been appeared to diminish GFR by direct vasoconstriction and natriuresis prompting volume exhaustion and pre-renal azotemia [12]. Additionally, aquaporin-2 downregulation along with tubulointerstitial injury resulting in impaired osmotic gradient formation may preclude effective urine concentrating mechanisms [13]. Rather than an exceptional case of primary hyperparathyroidism, most of this patient's clinical features are more consistent with parathyroid carcinoma. Parathyroid carcinoma accounted for only 0.74% of more than 22000 cases of ‘primary hyperparathyroidism’ in a large retrospective study. Total serum calcium concentrations were >14 mg/dl in more than 66% of carcinoma cases [8]. Nephrolithiasis, nephrocalcinosis and impaired kidney function were found in 32-80% of patients with parathyroid carcinoma compared with 4-18% in benign primary hyperparathyroidism [14]. In this case, there was no evidence of malignancy.

Hypercalcemic emergency is described by severe hypercalcaemia, generally with a serum calcium >3.5 mmol/l (>14 mg/dl), with related sign and symptoms involving different organ systems and patients frequently show metabolic encephalopathy, renal insufficiency, gastrointestinal manifestations, cardiovascular dysrhythmia and a normochromic normocytic anaemia [15-21]. Malignancy is the most widely recognized reason for hypercalcemic emergency, which results from hypersecretion of PTH related polypeptide or from bone resorption identified with osseous metastasis [16].

Severe hypercalcaemia is a medical emergency and underlying therapy depends to the etiology. Therapy is aimed at increasing renal excretion of calcium and decreasing bone resorption [15-17]. Patients with hypercalcaemic crisis are volume depleted and initial therapy should be intravenous hydration with isotonic saline. The conventional use of loop diuretics to promote calciuresis is currently under scrutiny as this may exacerbate extracellular volume depletion through concomitant sodium diuresis [16, 17]. Bisphosphonates, which directly inhibit osteoclast activity, are the most
effective of the pharmacological agents that decrease bone resorption. Pamidronate has gained acceptance as the drug of choice since it is the most potent bisphosphonate and has the fewest side effects [16].

For patients with parathyroid crisis, surgical procedure should be implemented, after preliminary medical management. Recent studies involving urgent parathyroidectomy has suggested excellent results with perioperative mortality of less than 5% [18-21]. As for all patients with PHPT, around 85-90% of patients with parathyroid crisis have a solitary adenoma [18-21]. It was reported that, serum parathyroid hormone (PTH) levels decrease quickly after parathyroidectomy, while serum calcium level normalized within a few days [17-18]. The adjustment of serum calcium and PTH is complemented by improvement of bone-pain, renal insufficiency, cardiac dysrhythmias and mental status changes. Complete resolution of the metabolic derangements including improvement of bone, renal and hematological abnormalities may take six to twelve months [17-18].

4. Conclusion
Hyperparathyroidism must be considered at the top among the differential diagnosis for severe hypercalcaemia in all age groups. These patients may present with a wide range of clinical symptoms related to metabolic derangements of multiple organ systems. Initial medical management should aim to lowering serum calcium by increasing renal excretion of calcium and reducing bone resorption. Patients should undergo urgent parathyroidectomy. Surgical resection results in prompt correction of serum calcium and parathyroid hormone level along with gradual resolution of the metabolic consequences of severe hypercalcaemia.

Conflicts of Interest
The authors declare no conflicts of interest regarding the publication of this case report.

Ethical Approval
Our institutions do not require ethical approval for reporting individual cases or case series.

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