Case Report

Inappropriate Supplementation of Vitamin D and Calcium Resulting in Hypercalcemic Crisis and Acute Pancreatitis in a Patient with Primary Hyperparathyroidism

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Abstract

Objectives: **To report a case of inappropriate supplementation of vitamin D and calcium inducing hypercalcemic crisis and acute pancreatitis in a 30-year-old man with primary hyperparathyroidism. These life-threatening complications of hyperparathyroidism and the co-occurrence of thyroid nodular disease are discussed.**

Methods: **Detail clinical description, laboratory, pathology and medical imaging findings are presented.**

Results: **Following a pathological right humerus fracture the patient was prescribed alpha-calcidiol and calcium supplementation. Two months later he presented with hypercalcemic crisis. Serum calcium was 16.8 mg/dL and PTH was 2465 pg/ml. Acute pancreatitis complicated the picture and forced the delay of emergency parathyroidectomy. After 3 days of stabilizing measures and lowering serum calcium level, neck exploration was performed and a cystic parathyroid adenoma removed.**

Conclusions: **Fragility fractures in a young patient should always lead to complete work up for secondary causes of osteoporosis. In that context, if the patient presents acutely ill with gastrointestinal symptoms, body aches, and muscle weakness, hypercalcemia of primary hyperparathyroidism is to be ruled out and association of of acute pancreatitis and hypercalcaemic crisis is to be kept in mind. In such cases, early diagnosis followed by appropriate emergency measures to correct hypercalcemia and acute pancreatitis is critical for reducing the high morbidity associated with the condition. Successful parathyroidectomy quickly relieves the symptoms and prevents recurrence.**

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Key Words: *Hypercalcaemic crisis; acute pancreatitis; parathyroid adenoma; parathyroidectomy*

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Introduction

Hypercalcemic crisis of hyperparathyroidism is a life threatening endocrine emergency. Signs and symptoms are usually proportional to the severity and the rapidity of onset of hypercalcemia, and the crisis mostly occurs in hyperparathyroidism due to an adenoma or carcinoma.[1] In acute primary hyperparathyroidism, 1-8% of patients may develop pancreatitis,[2-5] which further aggravates the picture. In such cases, the need for emergency parathyroidectomy calls for suitable and timely decisions. Here, we report the case of a 30-year-old man with primary hyperparathyroidism due to a large cystic parathyroid adenoma who presented with hypercalcemic crisis and acute pancreatitis. Prompt parathyroidectomy was successfully performed and symptoms were quickly relieved.

Case Presentation

A 30-year-old man had experienced intermittent joint pain of both knees for approximately 2 years. During this period, he gradually developed bilateral pelvic pain and left talalgia. Two months before admission, he fell off a motorcycle and was seen in a local hospital. X-ray and CT images revealed right humerus fracture, and suggested diffuse osteoporosis and osteitis fibrosa cystica with bent deformity of femoral bones. Serum proteins and electrolytes were normal except for hypercalcemia (12.8mg/dL). Without further examination, the patient was prescribed calcium carbonate (600mg/d) and α-calcitrol (0.5μg tid). A month later, he began to experience fatigue, anorexia, nausea, epigastralgia and weight loss. As

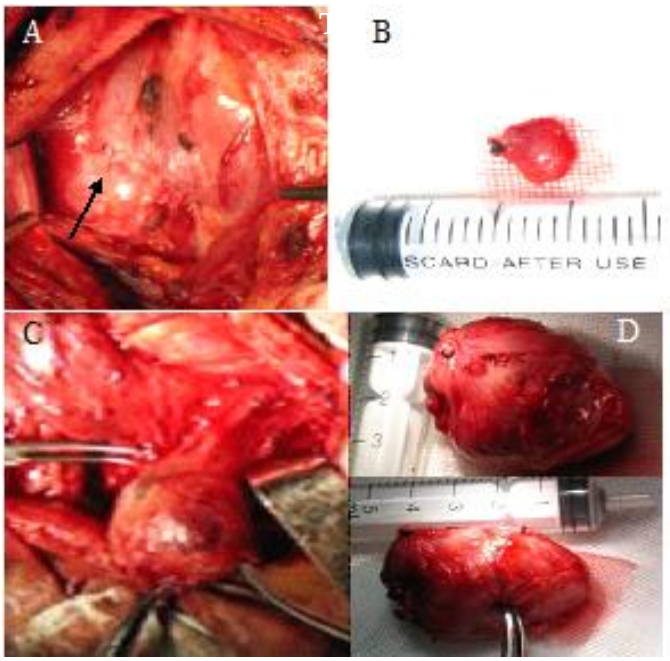
symptoms worsened, he consulted our emergency department 2 months after his accident.

The patient's past medical history was unremarkable except for peptic ulcer disease four years previously; no alcoholism or history of pancreatitis, gallstones, constipation, urolithiasis, hematuria or hypertension was reported; there was no family history of endocrinopathy.

On admission the patient looked cachectic and exhibited a waddling gait; blood pressure was 140/85mmHg, pulse 120/min, T 37.4°C, RR 28rpm. A firm, round, 4cm-mass, was palpated near the left lower pole of the thyroid. Blood tests revealed normochromic normocytic anemia (8.5g/dL), high serum calcium (16.8mg/dL) with hypophosphatemia (0.53mg/dL). Urine calcium was 17.57mmol/24h (7.5-25mmol/24h); serum PTH was 2465pg/ml (15-65pg/ml); alkaline phosphatase was 1025U/L (35-105U/L); serum creatinine, electrolytes, and thyroid function were normal.

Treatment was promptly initiated with IV fluids, furosemide, clodronate (300 mg), cimetidine (200 mg) and calcitonin (50 units s.c. q6h). Ultrasound examination of the neck showed a 4.6 x 2.8 x 3.2 cm round, well-circumscribed, hypoechoic, complex mass, extending from below the left lower pole of the thyroid, with a 3.5cm cystic component. A smaller 1.2cm hypoechoic nodule was detected on the right lower thyroid lobe. Neck CT suggested a partially cystic left parathyroid adenoma, with no cervical lymphadenopathy.

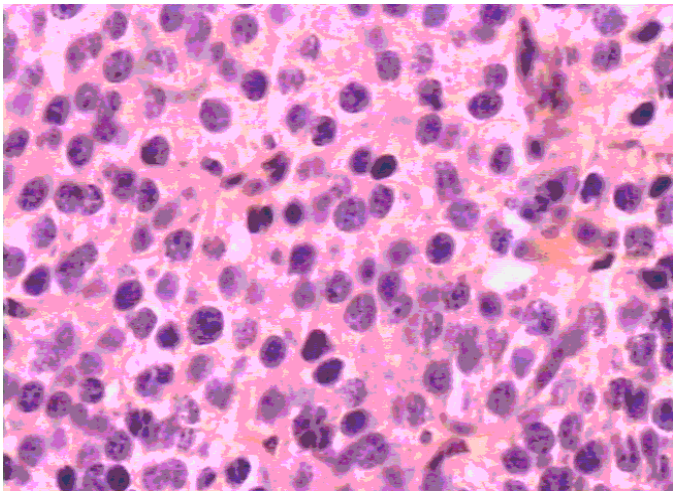
Figure. 1. Intraoperative findings. (A) A thyroid nodule (arrow) at the lower pole of the right lobe of thyroid. (B) resected thyroid nodule, 1.0 x 0.8 x 1.0 cm. (C) Large left inferior parathyroid mass. (D) resected parathyroid mass, 8.52 g, 4.6 x 2.8 x 3.2 cm.



Eight hours after admission, the patient developed vomits and midepigastric pain radiated through to the back. Epigastric tenderness and rebound with abdominal distension was evident. Serum amylase was 1635 units/L (normal 28-120 units/L). Abdominal CT showed normal biliary tree, diffusely enlarged pancreas and ascitis, suggestive of acute pancreatitis. After 3 days of supportive measures, including gastrointestinal decompression, IV octreotide (50μg/h), cefoperazone (1.5g tid), and aggressive IV hydration, serum calcium had decreased to 11.5 mg/dL, and serum amylase to 37 units/L.

At this point, bilateral neck exploration was carried out. A 1cm right lower pole thyroid nodule was resected (**Figure 1**). The two right parathyroid glands appeared normal. The 4x2x3cm ovoid mass at the lower pole of the left thyroid lobe was aspirated and yielded 20ml of clear fluid where PTH levels reached 6,500,000 pg/mL. Pathology examination confirmed it as a parathyroid adenoma **(Figure 2**). After removal, serum PTH concentrations dropped to normal level in 10 minutes, followed by a reduction of serum calcium to 10mg/dL 12h after surgery (**Figure 3**).

Figure 2. Histological examination of resected large parathyroid mass revealed a benign adenoma by light microscope, HE X200.



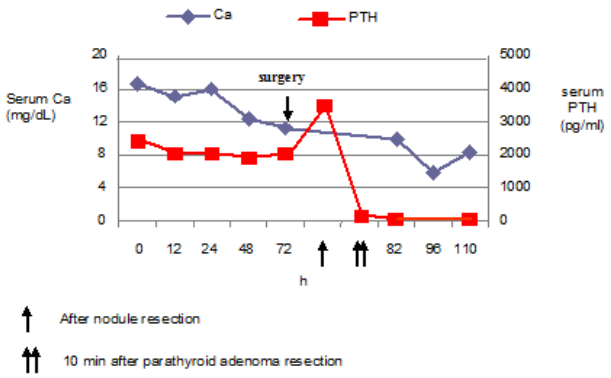
Two days after surgery, serum calcium fell to 5.9mg/dL (**Figure 3**), and the patient showed positive Chvostek's and Trousseau's signs, all of which reversed quickly with intravenous calcium and magnesium. Oral calcium and vitamin D supplements were sufficient to normalize serum calcium and the patient was subsequently discharged. Six month after surgery the patient remained asymptomatic with normal serum PTH, calcium and phosphate.

Discussion

We describe here the case of a young man who presented with hypercalcemic crisis after inappropriate supplementation with alpha-calcidiol and calcium in the presence of primary hyperparathyroidism. Retrospective series have suggested

that less than 2% of patients with primary hyperparathyroidism develop parathyroid crisis.[5] In our case, the patient had osteoporosis, which was readily recognized; however, hypercalcemia and evidence of osteitis fibrosa cystica were overlooked and the diagnosis of hyperparathyroidism was not initially considered.

Figure 3. Serum calcium and PTH levels at admission, before and after surgery. Intraoperative PTH values were as follows: time of neck incision, 3465; 10 minutes after cystic parathyroid adenoma resection 144. Serum calcium decreased to 10mg/dL 12 h after surgery. Two day later, serum calcium further decreased to 5.9mg/dL, to normalize after 2 days and stabilized in low-normal range.



Calcium and vitamin D supplementation in patients with stable hyperparathyroidism is recommended because of the high prevalence of vitamin D deficiency in this group of patients, which with poor calcium intake has been associated with higher PTH levels, worsening bone disease, larger adenomas, and more severe post-surgical hypocalcemia, including «hungry bones» syndrome.[6-8] However, hyperparathyroid patients on vitamin D and calcium supplementation must be closely monitored for worsening of their hypercalcemia and levels of hypercalciuria associated with urolithiasis or nephrocalcinosis. The vitamin D analogue prescribed to our patient, calcidiol, does not require hepatic 25-hydroxylation, has rapid onset of action and stronger hypercalcemic effect. This too may have contributed to the severity of hypercalcemia.

Hypercalcaemic crisis and acute pancreatitis

Acute pancreatitis occurs in small proportion of hypercalcemic hyperparathyroid patients. Mixter *et al* reported acute pancreatitis in 7% of 155 hyperparathyroid patients in 1962.[4] Subsequent series, found this complication in 2.9% (Mayo Clinic, 1967), 8% (Spain, 1988), and 4.6% of primary hyperparathyroid patients (Germany, 2008).[1,4] Because many patients are asymptomatic, the prevalence of pancreatitis might be underestimated. It has been hypothesized that elevated serum calcium levels in hyperparathyroidism may result in calcium deposits in pancreatic ducts and blocking of pancreatic secretion. Backflow of pancreatic secretions would damage pancreatic tissues leading to pancreatitis.[9,10] The occurrence of severe acute pancreatitis in a hyperparathyroid patient with normocalcemia may be explained by pancreatic saponification and calcium binding to pancreatic tissue, which can produce spuriously low serum calcium concentrations.

Hypercalcaemic crisis and immediate parathyroidectomy

In cases of primary hyperparathyroidism, surgical exploration of the neck and removal of hyperfunctional parathyroid tissue should be undertaken as soon as patient conditions stabilize. In a 35-years retrospective study of 43 patients with hypercalcaemic crisis (serum calcium of $\geq$15mg/dL), hypercalcemia was successfully reversed by parathyroidectomy with excellent long-term survival.[11] In our case, acute pancreatitis presented an additional challenge to deciding the proper time for surgery, resulting in a most reasonable and necessary 72 hours delay.

During surgery, the removed lesions are usually sent for frozen section examination for histological validation. In addition, given the short serum half-life of PTH (3-6min), its concentrations should be evaluated about 10 minutes after removal of the suspected lesions.[12] A rapid drop of serum PTH not only confirms the diagnosis, but also assures the surgeon that no hyperplastic parathyroid gland or adenoma is left behind.

Hyperparathyroidism with thyroid disease

Co-occurrence of hyperparathyroidism and thyroid nodular disease varies, with a prevalence ranging from 18% to 84.3%.[13] Thyroid carcinoma has been reported in 3.1%~15% of patients with primary hyperparathyroidism. This association was evaluated in a retrospective study of 487 patients with either primary (n = 241) or secondary (n = 246) hyperparathyroidism. Thyroid nodular disease was present in 38.2% of patients with secondary hyperparathyroidism versus 51.5% of patients with primary hyperparathyroism, suggesting an increased prevalence of nodular goiter in the context of hyperparathyroidism more pronounced in primary disease. As calcium itself has been considered a potential goitrogenic factor, the higher prevalence of goiter in primary vs. secondary hyperparathyroidism is consistent with the fact that calcium levels are elevated only in the former.[13]

The patient in this report lived in an iodine deficient region, which puts him at increased risk of developing goiter. Therefore we can only hypothesize that hypercalcemia may have been a contributing factor to the development of goiter.

Post-parathyroidectomy hypocalcemia

In our patient, bone pain and elevated serum alkaline phosphatase reflected osteitis and suggested significant bone disease. After surgery, once serum PTH normalizes, calcium and phosphate quickly re-deposit into tissues, particularly bones, resulting in hypocalcaemia without hyper-phosphatemia (unlike postsurgical hypoparathyroidism). This case remind us that profound hypocalcemia should be

anticipated after parathyroidectomy for primary hyperparathyroidism, and therefore vitamin D and calcium supplements should be administered generously postoperatively particularly in patients with evidence of significant parathyroid related osteitis. A rapid decline of serum calcium after removal of an adenoma can lead to life threatening arrhythmias, systolic and diastolic dysfunction. An IV infusion of calcium after successful removal of parathyroid adenomas may be necessary in order to allow gradual and controlled decline of serum calcium. Phosphate and magnesium levels should also be monitored and replacement given if needed.

Conclusion

In this report, we highlight the importance of including primary hyperparathyroidism in the differential diagnosis when assessing patients with fragility fractures and osteoporosis. In our case, failure to identify the cause of this young man's osteoporosis, and providing unmonitored calcium and vitamin D supplementation, resulted in hypercalcaemic crisis, complicated with acute pancreatitis. As exemplified in this case, after early intensive care management, surgical exploration of the neck and removal of the hyperfunctioning parathyroid tissue should be performed without delay. Pathological diagnosis of removed tissue, and monitoring of serum PTH, calcium, phosphate and magnesium levels should follow. Finally, aggressive postoperative intravenous calcium infusion followed by oral calcium and vitamin D supplements will help prevent severe postoperative hypocalcemia.

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