CASE REPORT

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Hypercalcaemic Crisis as a Rare Presentation of Hyperthyroidism

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Abstract

Hyperthyroidism is a well known cause of hypercalcaemia but hypercalcaemic crisis is very rare. The underlying mechanisms are still not clear. Thyroid hormone may have a role in stimulating bone turnover. A 63-year-old lady presented with decreased level of consciousness with background history of vomiting, loss of apetite and weight loss. Her blood investigations revealed severe hypercalcaemia with raised T3, T4 and low TSH. A final diagnosis of Graves' disease was made and patient was treated conservatively for correction of calcium with diuretics and intravenous fluids; and antithyroid treatment was started. She improved and was discharged.

Keywords: Hypercalcaemia, hypercalcaemic crisis, hyperthyroidism.

Introduction

Hyperthyroidism is a disease characterised by increased level of thyroid hormone in the body, leading to symptoms and signs including palpitation, tremor, weight loss in spite of having good appetite, and complications related to the increased metabolic rate. Thyroid hormone also regulate bone metabolism. Hyperthyroidism has been associated with mild-to-moderate hypercalcaemia in approximately 20% of patients[1].

A mild-to-moderate rise in calcium level is often seen but it rarely exceeds 3.0 mmol/l in hyperthyroidism[2,3]. Hypercalcaemia is defined as a calcium level exceeding 3.5 mmol/l and patient often has symptoms including multiple kidney stones, constipation, and muscle weakness[4]. Severe hypercalcaemia or hypercalcaemic crisis is very rare[5]. Only a few cases of hyperthyroidism associated hypercalcaemic crisis have been reported[6-8]. It was thought that thyroid hormone can directly stimulate bone turnover, elevate serum calcium, as well as urinary and fecal calcium excretion[2,9,10].

We are presenting a case of hyperthyroidism associated hypercalcaemic crisis and the effect of thyroid hormone on metabolism of calcium, phosphate, parathyroid hormone (PTH), and 1,25-dihydroxy cholecalciferol [1,25 $(OH)_2 - D_3$] is reviewed.

Case report

A 63-year-old female was admitted to our hospital with complaints of low backache for 4 months, decreased appetite and weight loss of approximately 5 - 6 kg for 1 month, recurrent episodes of nausea and vomiting for 20 days and decreased level of consciousness for 5 days. There was no history suggestive of fever, seizure episodes, recurrent episodes of diarrhoea/constipation, chronic cough with expectoration, headache, ear discharge, fall, trauma, visual disturbances, burning urination, and increased frequency of urine or decreased urine output. There were no similar episodes in past. Patient was on non-steroidal anti-inflammatory drugs (NSAIDs) (on and off) for backache for 4 months. Past history for diabetes, hypertension and anti tubercular treatment was absent.

On general examination, patient was thin built, lying on bed with GCS of E3V2M5, pulse was 106/min regular, rhythmic, normo-volumic and all peripheral pulses were palpable. Her blood pressure was 122/76 mmHg and respiratory rate was 14/min. Patient was afebrile. No obvious neck swelling was noted. Her breast examination was normal. Respiratory, cardiovascular and abdominal examinations were within normal limit. On nervous system examination, patient was in altered sensorium with GCS of E3V2M5. Neck rigidity and Kerning sign were absent. Sensory and motor examination could not be done.

Her arterial blood gas (ABG) analysis showed ionized calcium 1.860 mmol/l (normal range1.150 - 1.330 mmol/l) and other electrolytes were normal.

Serum calcium was raised significantly to 12.6 mg/dl (corrected calcium with total albumin was 14 mg/dl); whereas serum sodium, potassium and magnesium values were normal. Her serum creatinine was 1.7 mg/dl (normal range 0.5 - 1.4 mg/dl), blood urea 101 mg/dl (normal range 15 - 45mg/dl), total protein 6.5 gm/dl (normal range 6 -8.5 gm/dl), albumin 2.5 gm/dl (normal range 3.2 - 5.5 gm/dl) and alkaline phosphate 257 U/L (normal range 53 - 141 U/L). Her urine and stool examinations were normal.

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NCCT head and CSF analysis was normal. Thyroid profile showed T3 - 3.20 ng/ml (normal 0.60 - 1.81 ng/ml) T4 - 19 µg/ml (5.01 - 12.45 µg/ml) and TSH < 0.01 µIU/ml (normal - 0.35 - 5.50 µIU/ml). Antithyroid peroxidase antibody (anti TPO) was raised 34 IU/ml (normal range 0 - 20 IU/ml).

Serum phosphate level was 4.3 mg/dl (normal range 3.5 - 6.5 mg/dl). Her parathyroid hormone (PTH) level was 15 pg/ml (normal range 14 - 72 pg/ml). Urinary Bence-Jones protein was negative. No 'M' peak was seen on serum electrophoresis. Vitamin D and alkaline phosphatase level were 232 nmol/l (normal - 75 - 250 nmol/l) and 257 U/L (normal range 53 - 141 U/L) respectively.

Her electrocardiogram showed normal sinus rhythm with slightly increased QT interval. X-ray chest, Lumbosacral spine, skull and hip were normal (Fig. 1). Ultrasonography of bilateral thyroid lobes showed mildly increased blood-flow and vascularity without any nodules or irregular margins. Ultrasonography of abdomen and pelvis was normal. Dual energy X-ray absorptiometry showed T-score of -1.5 at lumbar spine and mild osteoporosis noted at neck of femur with T-score of -2.5.

To look for cause of hypercalcaemia, history was reviewed in order to find out any intake of oral medication (in the form of oral calcium supplement). To look for any evidence

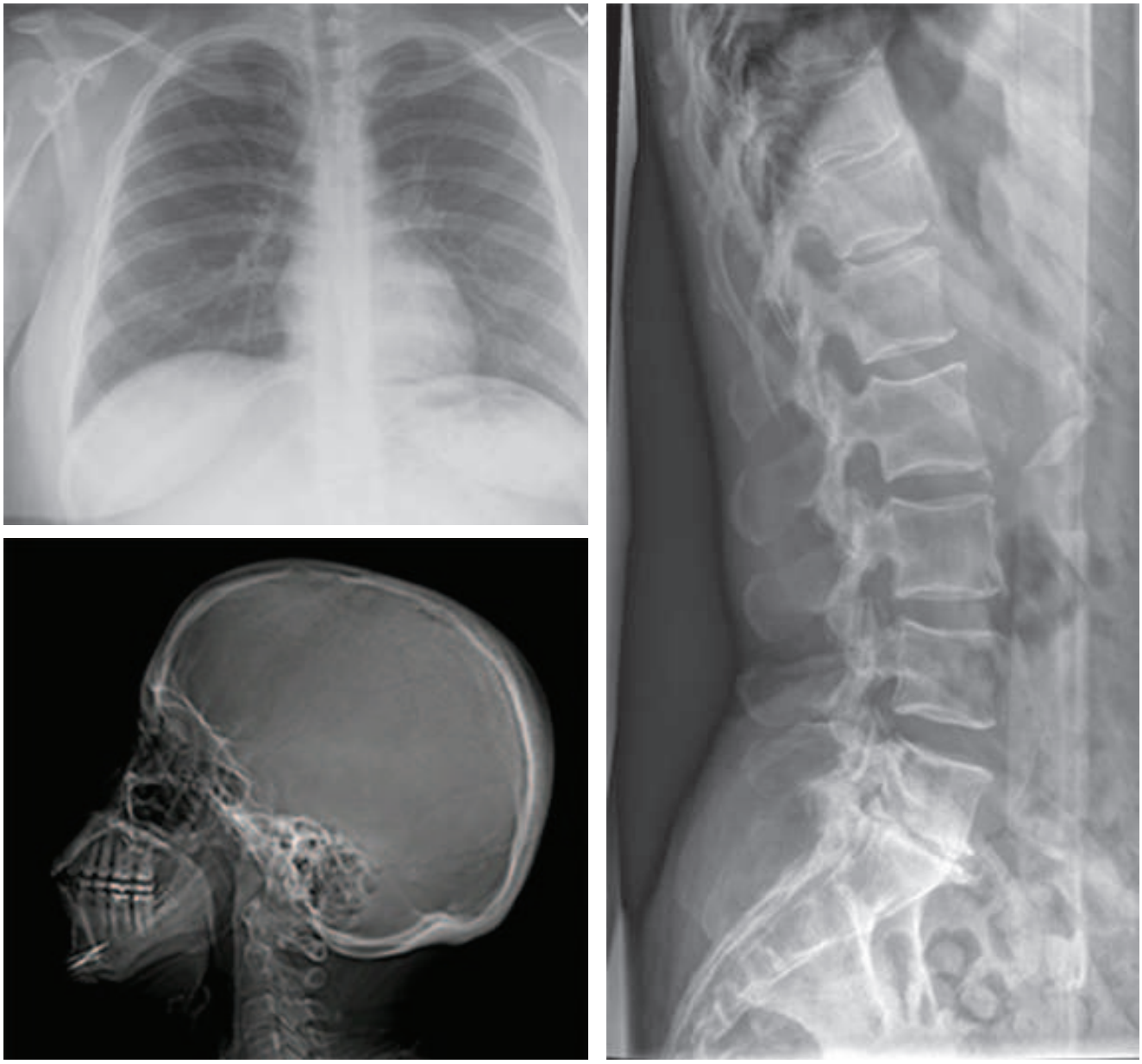

Fig. 1: *X-ray chest, skull and lumbo-sacral spine.*

of malignancy, CECT abdomen and thorax was done, which was normal. Her tumour markers CA 125, CA 19 - 9, cancer embryo antigen (CEA) and alpha feto protein (AFP) was normal.

Based on these findings of low TSH with raised anti TPO and low bone marrow density on DEXA scan, a diagnosis of Grave's disease associated hypercalcaemia was made. Patient was managed conservatively with intravenous fluids (5,000 ml over 24 hour) and diuretics (furosemide) 20 mg IV, 8 hourly to control hypercalcaemia. She was started on tab carbimazole 10 mg, 1 tab TDS with long acting beta-blocker, propranolol 40 mg OD. Her serum calcium and ionized calcium lowered down in 24 hours and normalised by 5th day. Patient regained consciousness as her serum calcium normalised. Her renal function returned to normal level by day 5 (creatinine 0.7 mg/dl and urea 22 mg/dl). Patient was discharged on day 8 with serum calcium of 9.8 mg/dl. She was advised to take tab carbimazole 10 mg, 1 tab TDS along with plenty of fluids.

After 1 month her serum calcium was 9.2 mg/dl, phosphate 3.8 mg/dl with T3 - 1.51 ng/ml (normal - 0.60 - 1.81 ng/ml) T4 -11.05 µg/dl (5.01 - 12.45 ug/ml) and TSH 0.23 µIU/ml (normal - 0.35 - 5.50 µIU/ml). After 6 months her serum calcium was 9.6 mg/dl, phosphate was 4.10 mg/dl and thyroid profile was T3 - 1.10 ng/ml, T4 - 7.80 ng/ml and TSH 1.16 IU/ml.

Discussion

Normal calcium level in body is well regulated by parathyroid hormone, vitamin D and calcitonin from bone, gut and kidney. Normal level of calcium is 8.8 to 10.7 mg/dl, mild hypercalcaemia is 10.8 to 12 mg/dl, moderate is 12 to 14 mg/dl and severe hypercalcaemia is > 14 mg/dl[11]. A hypercalcaemic crisis is an emergency situation with a severe hypercalcaemia, generally above 14 mg/dl (or 3.5 mmol/l)[12]. The main symptoms of a hypercalcaemic crisis are hypercalcaemia with altered sensorium, abdominal pain, and constipation. 90% cases of hypercalcaemia in elderly are due to hyperparathyroidism and malignancy[13].

Pathophysiology of hypercalcaemia in hyperthyroidism is poorly understood. It is thought that thyroid stimulating hormone (TSH) itself had a bone protective effect suggesting that suppressed TSH levels also play a role in hypercalcaemia. TSH have osteoblastic and T3 have osteoclastic activity[10]. The molecular mechanisms by which a hyperthyroid state effects bone includes increased sensitivity of β adrenergic receptors to catecholamines as well as increased sensitivity of bone to PTH[14,15]. Another clinical study demonstrated increased cortical porosity and resorption in hyperthyroid patients as compared to healthy controls[16]. Serum IL-6 and its soluble receptor positively correlate with thyroid hormone level in hyperthyroid patients. Thyroid hormone directly increases the sensitivity of bones to IL-6, which promotes osteoclastic differentiation via increasing the expression of the receptor activator of nuclear factor kB ligand (RANKL)[2,17]. Adrenaline and glucocorticoid hormones are also dysregulated contributing to a hypercalcaemic state[6,18].

Primary hyperparathyroidism and malignancy were ruled-out in our case by normal PTH and normal ultrasonography of neck, CECT abdomen and thorax and normal tumour markers. Osteolytic bone diseases such as multiple myeloma, Paget disease, or bone metastases were excluded based on normal ALP, PTH and urinary Bence-Jones protein and absence of 'M' peak on serum electrophoresis. Medication related hypercalcaemia was ruled-out as there was no suggestive history of intake of vitamin D and calcium in any form and her vitamin D level was also normal. Hence the final diagnosis of hyperthyroidism causing hypercalcaemia was made. Rapid correction of calcium after rehydration and diuretic therapy resulted in immediate regain of consciousness and her calcium levels were maintained within normal limits with anti-thyroid treatment.

The primary treatment for hyperthyroidism-associated hypercalcaemia is to control the hyperthyroid status. The rapid improvement in the symptoms is due to quick rehydration; however, antithyroid therapy improves the hyperthyroid symptoms and maintains the blood calcium level[19]. In this patient, FT3 and FT4 were normalised after 2 months. Although hypercalcaemia often leads to decreased serum phosphate levels[20], low PTH levels may cause increased reabsorption of phosphate in the kidney tubules. Previous studies have shown that hypercalcaemic patients can have low to normal serum phosphate levels[21].

Conclusion

Hyperthyroidism-associated hypercalcaemia crisis is a rare complication in hyperthyroid patients; however, this cause should not be ignored after excluding other causes of hypercalcaemia. Timely treatment of hypercalcaemia is a critical step for rapid control of symptoms and saving the life of the patients. Nevertheless, treatment of hyperthyroidism is required to maintain the blood calcium level.

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