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Hypercalcemia as an Unusual Manifestation of Recurrent Graves' Disease: A Case Report

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Abstract

Malignancy and primary hyperparathyroidism are the most common causes of hypercalcemia, a common biochemical abnormality. In clinical practice, hyperthyroidism may be disregarded as a less frequent cause of parathyroid hormone (PTH)-independent hypercalcemia. We describe the case of a 58-year-old woman who had persistent moderate hypercalcemia and recurrent Graves' disease.

The patient had a history of Graves' disease, which was first treated with carbimazole and then thyroid lobectomy. Due to inadequate treatment compliance, the patient later experienced a relapse. Thyrotoxicosis was confirmed by laboratory testing, which showed elevated FT3 and FT4 levels and suppressed TSH. Excluding primary hyperparathyroidism, calcium levels with suppressed PTH ranged from 116 to 124 mg/L. Malignancy and other secondary causes of hypercalcemia were ruled out by thorough investigations.

After receiving intravenous hydration and antithyroid medication, the patient's calcium levels gradually returned to normal. Following definitive treatment with a total thyroidectomy, euthyroidism was restored and serum calcium levels fully returned to normal.

This case emphasizes the importance of taking hyperthyroidism into account when making a differential diagnosis for PTH-independent hypercalcemia. By controlling thyrotoxicosis, early detection of this association may avoid needless investigations and enable appropriate management.

Introduction

Hypercalcemia is a common biochemical abnormality, most frequently caused by primary hyperparathyroidism and malignancy. Less commonly, endocrine disorders such as hyperthyroidism may be responsible for PTH-independent hypercalcemia. Although the association between hyperthyroidism and hypercalcemia has been described, it remains underrecognized in routine clinical practice We report the case of a women presenting with persistent moderate hypercalcemia in the setting of recurrent Graves' disease related to residual thyroid tissue following prior lobectomy. This case highlights the importance of considering hyperthyroidism as a cause of PTH-independent hypercalcemia, even in the absence of severe calcium elevation, and highlights the need for systematic thyroid function testing in the evaluation of unexplained hypercalcemia.

Case Presentation

A 58-year-old woman was referred to our endocrinology department for the management of uncontrolled hyperthyroidism associated with unexplained hypercalcemia. Her medical history was notable for Graves' disease diagnosed in 2011, initially treated with carbimazole (30 mg/day) for one year, followed by a left thyroid lobectomy with benign histology. A relapse of hyperthyroidism occurred in 2014 for which carbimazole was reintroduced ; however treatment adherence was poor. Her past medical history also included type 2 diabetes mellitus treated with metformin, hypertension treated with amlodipine/valsartan, dyslipidemia treated with rosuvastatin, and a non-documented cardiopathy. There was no history of prolonged immobilization, lithium, thiazide , diuretics ,long term vitamin D supplementation or calcium intake . There was no personal or family history of malignancy, hyperparathyroidism, or granulomatous disease.

The patient present with progressive asthenia and significant unintentional weight loss estimated at 21% over three months. Physical examination revealed a patient in fair general condition, afebrile and normotensive, non signs of dehydration with a low body mass index. Cardiovascular examination showed a regular heart rate of 82 beats per minute. Cervical examination revealed a stage II goiter predominantly involving the right thyroid lobe with consistency homogeneous, without cervical lymphadenopathy. The remainder of the physical examination was unremarkable.

Thyroid Evaluation

laboratory investigations in our patient confirmed thyrotoxicosis with suppressed thyroid-stimulating hormone (<0.008 mIU/L), elevated free thyroxine (FT4 3.44 ng/dL), and free triiodothyronine (FT3 8.22 pg/mL). Thyroid autoimmunity testing revealed markedly elevated TSH receptor antibodies (21.64 U/L; <1.75), anti-thyroid peroxidase antibodies (896.4 IU/mL) which confirm active Graves' disease.

Thyroid ultrasonography was performed (Figure 1) which showed the absence of the left thyroid lobe, consistent with prior lobectomy, with a hypervascular residual thyroid tissue in the left thyroid bed. The right thyroid lobe was enlarged, heterogeneous, and markedly hypervascular on Doppler examination, containing featuring two nodules: a mixed predominantly solid nodule measuring 26 × 17 mm classified as EU-TIRADS III, and a smaller subcapsular nodule classified as EU-TIRADS II. No suspicious cervical mass or lymphadenopathy were identified.

The evaluation was further completed with thyroid scintigraphy (Figure 2) that showed an enlarged right thyroid lobe with diffuse increased radiotracer uptake and a markedly elevated technetium uptake rate (TcTU 41%), inappropriate for the suppressed TSH level. A hypofunctioning nodule corresponding to the EU-TIRADS III lesion was identified. These findings were consistent with nodular Graves' disease on the remaining thyroid tissue.

As a part of the etiological workup, fine-needle aspiration cytology of the hypofunctioning nodule was performed with cytology classified as Bethesda category IV (follicular neoplasm). The patient was started on carbimazole 40 mg/day, leading to progressive biochemical improvement.

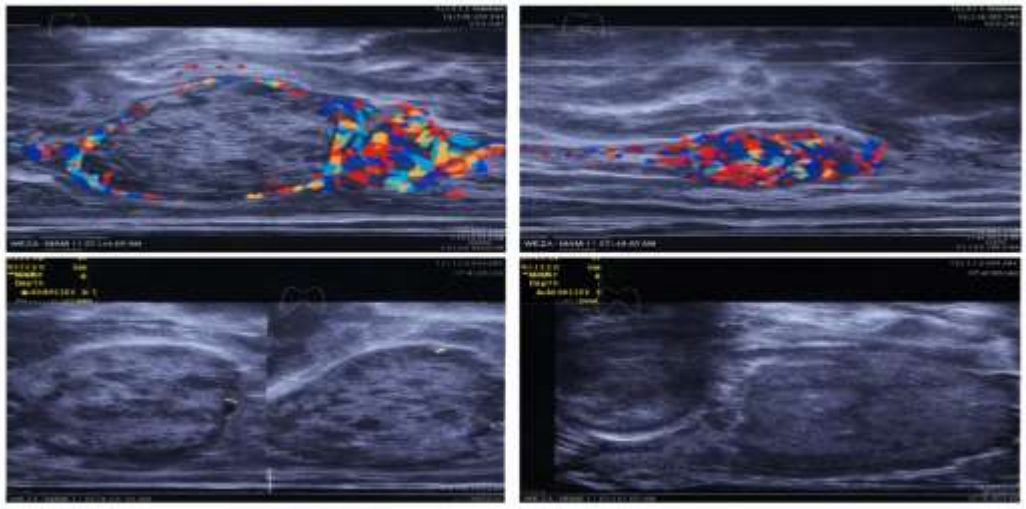

Figure 1 Thyroid ultrasound with color Doppler : revealed a heterogeneous and markedly hypervascularized thyroid gland , associated with a nodular lesion in the inferior pole of the right lobe , consistent with nodular Graves disease

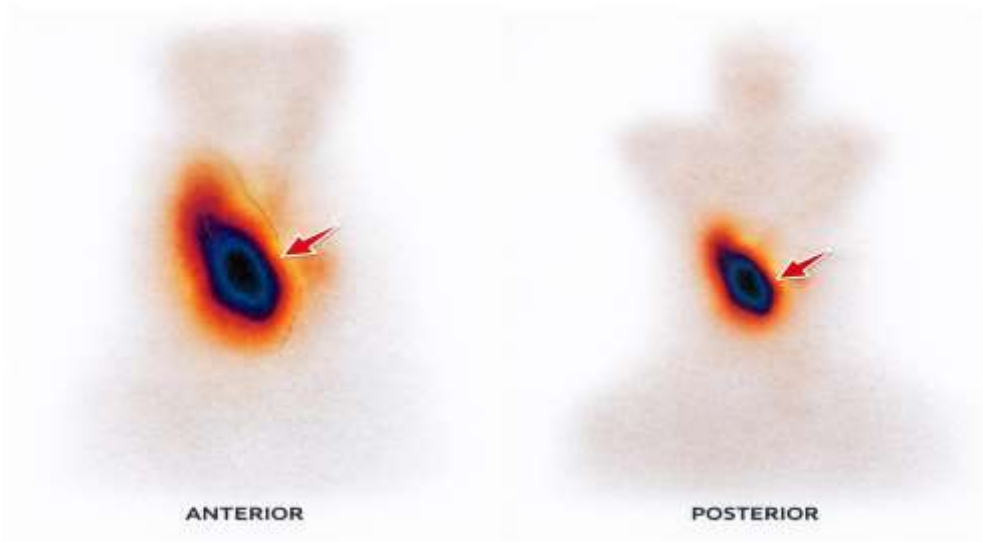

Figure 2 Anterior thyroid scintigraphy: diffuse increased uptake uptake in the right thyroid lobe with a focal hypo functioning nodular area . Residual uptake in the left thyroid bed is consistent with thyroid remnant after prior lobectomy

Hypercalcemia Assessment

As a part of assessment of hyperthyroidism-related systemic involvement, serum calcium was measured confirmed persistent hypercalcemia, with total serum calcium values ranging from 116 to 124 mg/L. Serum albumin levels were within the normal range, and corrected calcium values remained elevated. The patient was started on intravenous hydration, leading to improvement in serum calcium levels. At hospital discharge and before surgery, serum calcium levels were around 97mg/dl (Figure 3)

An extensive etiological workup was performed. Parathyroid hormone (PTH) was suppressed (7.13 pg/mL), excluding primary hyperparathyroidism. Serum phosphorus was normal, and 24-hour urinary calcium excretion was low-normal. Vitamin D deficiency (10 ng/mL) and hypomagnesemia (16 mg/dl) were identified . PTH-related peptide was undetectable.

To exclude an underlying malignancy, evaluation for hematological malignancy showed negative Bence-Jones proteinuria and a non-contributory serum protein electrophoresis. Given the patient's weight loss and inflammatory syndrome, malignancy was extensively investigated. Contrast-enhanced computed tomography of the cervico-thoraco-abdomino-pelvic regions revealed no solid organ tumors or osteolytic lesions. Mammography and breast ultrasonography showed only benign findings. No granulomatous disease was identified, and infectious workup was negative.

Bone involvement assessment revealed elevated alkaline phosphatase levels (369 IU/L) and bone mineral density showing osteoporosis at the lumbar spine and osteopenia at the femoral necks. She was referred to rheumatology for osteopenia management.

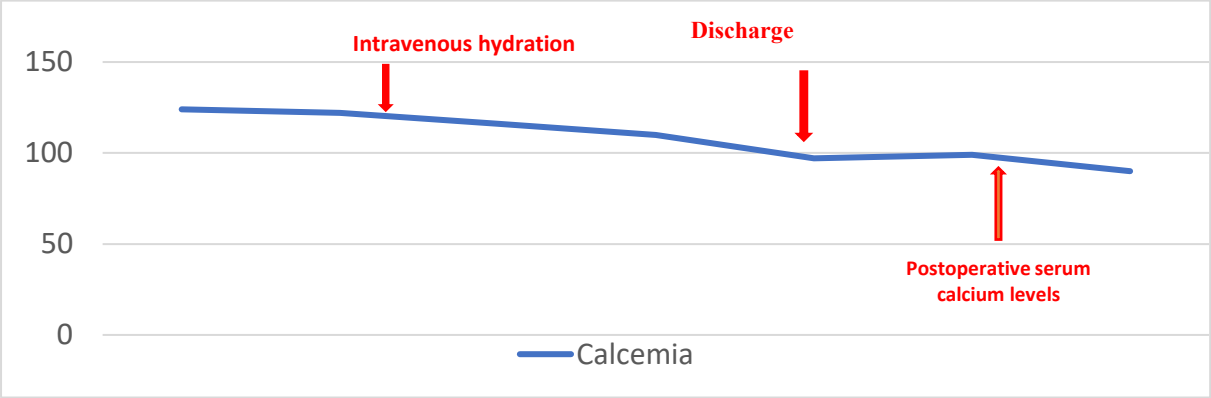

Figure 3: Serum calcium levels before and after intravenous hydratation and surgery

Treatment and outcome

Following medical control of hyperthyroidism and achievement of near-euthyroidism, serum calcium levels progressively normalized. The patient subsequently underwent total thyroidectomy. Histopathological examination revealed diffuse and multinodular goiter with features of Graves' disease, without evidence of malignancy.

Postoperatively, she was started on levothyroxine replacement therapy. At one-month follow-up, mild hypercalcemia persisted, with normalization of PTH levels. At three months, serum calcium levels fully normalized without specific calcium-lowering therapy (Figure 3). A final multidisciplinary evaluation concluded that hypercalcemia was most likely secondary to prolonged uncontrolled thyrotoxicosis.

Discussion

Frequency of hypercalcemia induced hyperthyroidism

According to several studies , hypercalcemia associated with hyperthyroidism in generally mild . Kaur et al reported that hypercalcemia related to Graves' disease is usually mild and rarely the main presenting feature (3) in addition ,Chen et al. reviewed reported cases of hyperthyroidism associated hypercalcaemic crisis and emphasised that serum calcium levels in most hyperthyroid patients remain moderately elevated, typically below 3 mmol/L, in contrast levels exceeding 3.5 mmol/L are exceptional (1).

In our patient, hypercalcaemia was moderate and persistent, with repeated corrected calcium levels ranging from 116 to 122 mg/L, without features of hypercalcaemic crisis. This biochemical profile is consistent with the literature .

Pathophysiological mechanisms

The pathophysiology of hypercalcemia in hyperthyroidism remains incompletely understood and is likely multifactorial. Several mechanisms have been proposed:

1. Increased bone resorption : thyroid hormones directly stimulate osteoclastic activity leading to accelerated bone turnover and calcium release into the circulation.
2. Enhanced bone sensitivity to regulatory mediators: thyrotoxicosis increases skeletal responsiveness to parathyroid hormone and catecholamines, amplifying bone resorption even in the presence of suppressed PTH levels.
3. Cytokine-mediated osteoclast activation: thyroid hormones augment sensitivity to interleukin-6 , promoting osteoclast differentiation through increased RANKL, and intensifying bone remodeling.
4. Hyperadrenergic state : α-adrenergic stimulation increased renal calcium excretion leading to hypercalciuria) and β-adrenergic stimulation stimulate osteoclast activation and bone resorption

Biochemical markers of bone turnover such as alkaline phosphatase (ALP), bone-specific ALP, and PINP may be elevated, reflecting high bone remodeling activity.

Clinical symptoms

Clinical symptoms of hypercalcaemia in hyperthyroid patients are often nonspecific and may overlap with symptoms of thyrotoxicosis itself. Reported symptoms include asthenia, weight loss, gastrointestinal disturbances polyuria, and neuropsychiatric complaints (1,3) . It is important to highlight dehydration and gastrointestinal symptoms were identified as aggravating factors for calcium elevation (1).

In our case, our patient presented with marked asthenia and significant weight loss (21% over three months) in the context of long-standing Graves' disease. Although she did not exhibit severe neurological or cardiac manifestations of hypercalcaemia, the association of weight loss, inflammatory syndrome, and osteometabolic abnormalities initially suggested the possibility for malignant or systemic disease, consistent with the diagnostic challenge frequently reported in the literature (1).

Etiological features

According to the literature hypercalcaemia occurring in a hyperthyroid patient should be considered a diagnosis of exclusion. Primary hyperparathyroidism and malignancy remain the most common causes of hypercalcaemia overall and must be systematically ruled out before attributing calcium abnormalities to thyrotoxicosis (1).

However , Hyperthyroidism-related hypercalcaemia has been described in various etiological settings, including: Graves' disease, which represents the most frequently reported association (3,5) , Toxic multinodular goitre and toxic adenoma, where moderate hypercalcaemia with suppressed parathyroid hormone has also been observed (1) , of note mixed clinical contexts where dehydration, renal dysfunction, vitamin D deficiency, or medications may contribute (1,2)

Our patient had Graves' disease with nodular involvement of the remaining thyroid lobe. The hypercalcaemia was PTH-independent, PTH-related peptide, extensive negative workup for malignancy, granulomatous disease, and multiple myeloma were negative. These findings strongly support hyperthyroidism as the most likely cause of hypercalcaemia in this case, in line with previously published reports.

Management and Prevention of hypercalcemia induced hyperthyroidism

Across published reports, control of thyrotoxicosis is the main treatment for hypercalcaemia associated with hyperthyroidism (1,3). Normalisation of serum calcium levels typically follows restoration of euthyroidism, even without specific anti-hypercalcaemic therapy. Recommandation of management strategies depend on the severity of hypercalcaemia : Mild or asymptomatic hypercalcaemia: oral hydration and initiation of antithyroid drugs are usually sufficient (1).Moderate or symptomatic hypercalcaemia: intravenous saline hydration is recommended, with consideration of calcitonin or loop diuretics after adequate rehydration (1).Severe hypercalcaemia or crisis: aggressive intravenous hydration, calcitonin, bisphosphonates, cardiac and renal monitoring are required (1,2).

In our case, the patient was treated with oral and intravenous hydration combined with carbimazole, contributing to progressive correction of calcium levels as euthyroidism was achieved. She did not require calcitonin or bisphosphonate therapy, given to her moderate calcium elevation. Definitive treatment with total thyroidectomy was followed by sustained improvement in calcium metabolism, in agreement with outcomes reported in the literature.

Preventive measures described in published reports include early and effective control of hyperthyroidism, maintenance of adequate hydration, avoidance of medications that may exacerbate hypercalcaemia (thiazide diuretics or lithium), and close biochemical monitoring during thyrotoxic phases . These principles are particularly relevant in patients with recurrent or poorly controlled disease, as illustrated by our patient's clinical history (4,5) .

Role of micronutrition

Micronutrition may play a supportive role in the overall management in hyperthyroidism-related hypercalcaemia and should be considered supportive rather than therapeutic. Vitamin D deficiency is common in hyperthyroid patients and may worsen bone demineralization , in contrast supplementation should be cautious and limited to correction of deficiency, particularly during active hypercalcaemia . In addition correction of hypomagnesaemia is recommended, as magnesium deficiency may exacerbate neuromuscular symptoms and metabolic imbalance.(4,6)

In our patient, correction of vitamin D and hypomagnesaemia may have contributed to metabolic stabilization without worsening hypercalcemia.

Conclusion and Clinical implications

Hypercalcemia is a rare but recognized complication of hyperthyroidism. Although usually mild it may occasionally be the presenting manifestation of graves' disease recurrence. This case highlights the importance of considering hyperthyroidism as potential cause of unexplained hypercalcemia, once primary hyperparathyroidism and paraneoplastic causes been excluded. Recognizing this association may help avoid unnecessary investigation and allow timely, targeted treatment .

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