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Severe Symptomatic Hypercalcaemia in Recurrent Graves' Disease: When Thyrotoxicosis Is Not the Whole Story

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Abstract

Hypercalcaemia is a recognised but usually mild complication of thyrotoxicosis. We describe a 66-year-old woman with recently relapsed Graves' disease who presented with profound asthenia, anorexia, marked weight loss, progressive functional decline, and an acute confusional syndrome. Investigation revealed severe hypercalcaemia with a markedly elevated parathyroid hormone (PTH) concentration and hypophosphataemia, indicating concomitant primary hyperparathyroidism (PHPT). Graves' disease was confirmed by strongly positive thyroid-stimulating hormone (TSH) receptor antibodies and compatible thyroid ultrasonography. The acute confusional syndrome was considered multifactorial, with metabolic and nutritional contributions. Hydration, electrolyte replacement, and intravenous bisphosphonate therapy progressively reduced serum calcium, with clinical improvement. Hypercalcaemia persisted during follow-up, and definitive surgical treatment was proposed; however, surgery had not been performed at the time of reporting. The absence of histopathological confirmation precludes differentiation between parathyroid adenoma, hyperplasia, and carcinoma and represents a limitation of this report.

This case shows that hypercalcaemia in patients with thyrotoxicosis should not be automatically attributed to thyroid hormone excess. Severe or persistent hypercalcaemia requires systematic investigation, and appropriate interpretation of PTH is essential to recognise dual endocrine pathology that overlapping clinical manifestations may otherwise obscure.

Categories: Endocrinology/Diabetes/Metabolism
Keywords: graves' disease, hypercalcaemia, parathyroid hormone, primary hyperparathyroidism, thyrotoxicosis

Introduction

Hypercalcaemia is a recognised biochemical abnormality in patients with thyrotoxicosis and has been reported in approximately 20% of cases [1,2]. It results primarily from increased bone resorption, with secondary suppression of parathyroid hormone (PTH) and reduced circulating 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) concentrations. In most patients, hypercalcaemia is mild and improves following control of thyroid hormone excess; severe symptomatic presentations attributable to thyrotoxicosis alone are uncommon [1]. Severe hypercalcaemia may cause neurological, renal, and cardiovascular complications, making prompt recognition and aetiological assessment essential. Early PTH measurement helps distinguish PTH-dependent from PTH-independent causes, and an elevated or inappropriately normal concentration should prompt investigation beyond thyrotoxicosis alone [3].

Primary hyperparathyroidism (PHPT) is characterised biochemically by hypercalcaemia in the presence of an elevated or inappropriately normal PTH concentration [3]. Its clinical spectrum ranges from asymptomatic biochemical disease to renal, skeletal, gastrointestinal, neuromuscular, and neuropsychiatric manifestations. Coexisting PHPT and Graves' disease has previously been described, including presentations with severe hypercalcaemia and hypercalcaemic crisis [2,4,5]. Earlier observations also documented changes in calcium and PTH concentrations during treatment of hyperthyroidism, illustrating the biochemical interplay between the two conditions [6].

The overlap in clinical manifestations can complicate recognition of these disorders, particularly when thyrotoxicosis provides an apparently plausible explanation for hypercalcaemia. We report a patient with recurrent Graves' disease, severe symptomatic hypercalcaemia, and an acute confusional syndrome, in whom markedly elevated PTH supported concomitant PHPT. The case highlights the diagnostic value of persistent hypercalcaemia despite normalisation of circulating thyroid hormone concentrations and the importance of avoiding attribution of systemic and neuropsychiatric deterioration solely to Graves' disease.

Case Presentation

A 66-year-old woman presented to the Emergency Department with progressive asthenia, anorexia, and cognitive impairment. She had previously been independent but had developed progressive fatigue, apathy,

anorexia, nausea, and vomiting over approximately four weeks. During the two weeks preceding admission, oral intake became severely reduced, with refusal of solid food. She experienced substantial unintentional weight loss of more than 13 kg and progressive difficulty walking. During the week preceding admission, her family noticed confusion and intermittently incoherent speech, as well as urinary and faecal incontinence.

Her medical history included recurrent hyperthyroidism, previously treated in the United Kingdom, hypertension, dyslipidaemia, and hyperuricaemia. She had undergone left nephrectomy following a previous infectious complication. Recurrent hyperthyroidism had been identified 25 days before admission (Day -25; Day 0 = hospital admission), with suppressed thyroid-stimulating hormone (TSH) and markedly elevated free thyroxine (FT4) (Table *1*). Thiamazole was initiated at 5 mg/day on Day -15 and increased to 10 mg twice daily on Day -8. The timeline of events is summarised in Table *2*.

Parameter (unit)	Day -25	Admission (Day 0)	Day 37	October 2026 follow-up	Reference range
Total calcium (mg/dL)	-	15.5 (peak)	11.7	13.7	8.6-10.3
Corrected calcium (mg/dL)	-	-	11.8	-	8.6-10.3
Ionised calcium (mmol/L)	-	-	1.57	-	1.15-1.32
Albumin (g/dL)	-	3.17	4.17	-	3.97–4.94
PTH (pg/mL)	-	630	-	429	15-65
Phosphate (mg/dL)	-	1.0-1.8	1.8	2.2	2.5-4.5
Magnesium (mg/dL)	-	1.2	-	-	1.6-2.6
Creatinine (mg/dL)	-	0.90	1.00	0.70	0.51-1.10
25-hydroxyvitamin D (ng/mL)	-	22.50	-	26.9	30-100
TSH (mIU/L)	<0.01	<0.005	-	<0.005	0.27-4.20
FT4 (ng/dL)	7.75	1.56	-	1.52	0.93-1.70
FT3 (pg/mL)	-	3.40	-	7.0	2.00-4.40
TRAb (IU/L)	-	32.0	-	-	<1.75
Anti-TPO antibodies (IU/mL)	-	462	-	-	<34
Anti-Tg antibodies (IU/mL)	-	1109	-	-	<115

TABLE 1: Laboratory findings before admission during hospitalisation and at follow-up.

Day 0 corresponds to the day of hospital admission. Reference ranges are those of the local laboratory. Corrected calcium was adjusted for serum albumin.

anti-Tg, anti-thyroglobulin; anti-TPO, anti-thyroid peroxidase; FT3, free triiodothyronine; FT4, free thyroxine; PTH, parathyroid hormone; TRAb, thyroid-stimulating hormone receptor antibodies; TSH, thyroid-stimulating hormone; -, not available

Time point	Clinical events, investigations and management
2024	Abdominal ultrasound showed no definite renal calculi; nephrocalcinosis was not explicitly addressed in the report.
Day -25	Recurrent hyperthyroidism identified, with suppressed TSH and FT4 of 7.75 ng/dL.
Day -15	Thiamazole initiated at 5 mg/day.
Day -8	Thiamazole dose increased to 10 mg twice daily.
Day 0	Hospital admission for progressive asthenia, reduced oral intake, substantial weight loss, cognitive impairment and gait disturbance. Total serum calcium was 15.5 mg/dL, PTH 630 pg/mL and 25-hydroxyvitamin D 22.50 ng/mL. Brain CT showed no abnormalities.
Day 1	Thyroid ultrasonography demonstrated diffuse enlargement, heterogeneous hypoechoic parenchyma and increased vascularity.
Days 0-8	Intravenous and oral hydration, intravenous pamidronate 90 mg over three hours, intravenous thiamine and electrolyte replacement. Neither calcitonin nor cinacalcet was administered during this admission. Serum calcium decreased to approximately 10-12 mg/dL, with clinical improvement.
Day 8	Hospital discharge with Endocrinology and Internal Medicine follow-up.
Day 37	Persistent hypercalcaemia: total calcium 11.7 mg/dL, albumin-corrected calcium 11.8 mg/dL and ionised calcium 1.57 mmol/L. Persistent hypophosphataemia, with preserved renal function.
September 2026	Parathyroid scintigraphy showed focal uptake posterior to the inferior aspect of the right thyroid lobe, with pronounced delayed retention, suggesting hyperfunctioning parathyroid tissue.
October 2026	DXA showed T-scores of -4.2 at the wrist, -2.8 at the femoral neck and -2.3 at the lumbar spine (L1-L4). Repeat testing showed total calcium 13.7 mg/dL, PTH 429 pg/mL, creatinine 0.70 mg/dL and 25-hydroxyvitamin D 26.9 ng/mL.
Day 80	Total thyroidectomy and selective parathyroidectomy recommended. Cinacalcet 30 mg twice daily initiated while awaiting surgery.
At the time of reporting	Definitive surgery remained pending; no histopathological diagnosis was available.

TABLE 2: Timeline of clinical presentation, investigations, and management.

Day 0 corresponds to hospital admission.

CT, computed tomography; DXA, dual-energy X-ray absorptiometry; FT4, free thyroxine; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone

At presentation, she was markedly asthenic and required assistance for transfer. She was afebrile and haemodynamically stable, with a blood pressure of 148/61 mmHg and heart rate of 75 beats/min. Neurological assessment demonstrated marked psychomotor slowing, impaired attention and recall, brisk deep tendon reflexes with unsustained ankle clonus, mild symmetrical proximal lower-limb weakness, and a slow gait requiring bilateral support. Brain computed tomography showed no abnormalities, and serum magnesium was within the normal range. The brisk reflexes may have reflected concomitant thyrotoxicosis rather than hypercalcaemia.

Admission laboratory investigations revealed severe hypercalcaemia, with a total serum calcium concentration of 15.5 mg/dL, a markedly elevated PTH concentration of 630 pg/mL, accompanied by hypophosphataemia and hypomagnesaemia. The serum 25-hydroxyvitamin D concentration was 22.50 ng/mL. Renal function remained preserved (Table *1*).

Following recent initiation and escalation of antithyroid treatment, FT4 had decreased substantially during admission, while TSH remained suppressed. Thyroid autoimmunity was strongly positive, with high titres of TSH-receptor antibodies (TRAb), anti-thyroid peroxidase, and anti-thyroglobulin antibodies, confirming Graves' disease (Table *1*).

Thyroid ultrasonography on Day 1 demonstrated diffuse enlargement of the gland, with markedly heterogeneous and hypoechoic parenchyma (Figure *1*) and increased vascularity on power Doppler imaging (Figure *2*). Several small bilateral echogenic or hyperechogenic pseudonodular areas were identified,

although distinction between relatively spared thyroid parenchyma and true solid nodules was limited in the context of diffuse parenchymal abnormalities.

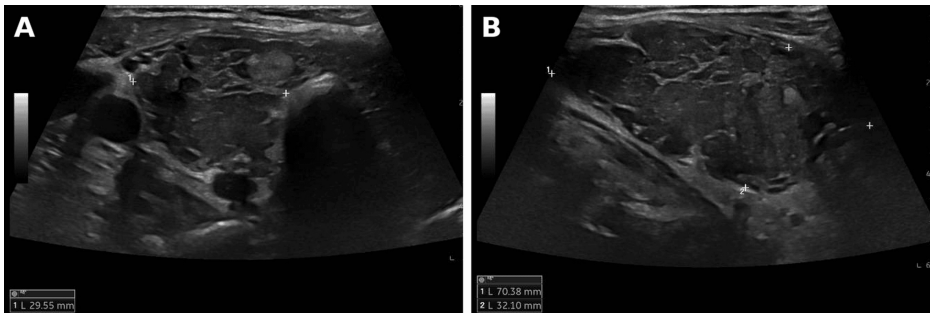


FIGURE 1: Greyscale thyroid ultrasonography (Day 1).

(A) and (B) Diffusely enlarged thyroid gland with markedly heterogeneous, hypoechoic parenchyma and small echogenic pseudonodular areas. The right lobe measured 70 × 32 × 29 mm and the left lobe 71 × 30 × 29 mm (longitudinal × anteroposterior × transverse dimensions). Maximum isthmus thickness was 9 mm. No candidate parathyroid lesion was described in the ultrasound report; a dedicated parathyroid assessment was not documented. Electronic callipers indicate gland measurements.

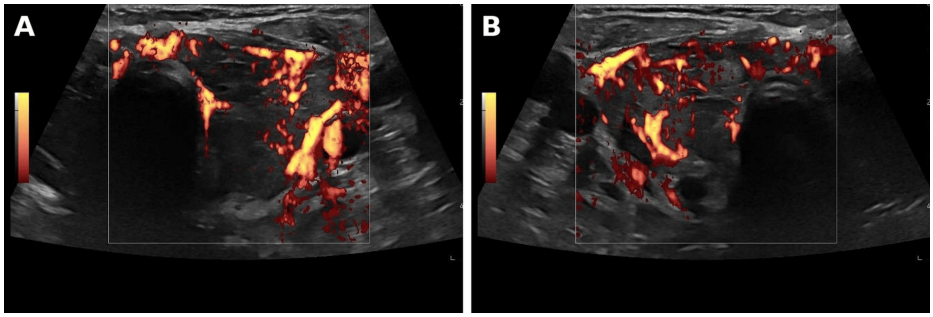


FIGURE 2: Power Doppler thyroid ultrasonography (Day 1).

(A) and (B) Markedly increased parenchymal vascularity, consistent with Graves' disease.

Neurological assessment considered the acute confusional syndrome to be multifactorial, with metabolic and nutritional factors potentially contributing in the context of prolonged reduced oral intake. Intravenous thiamine and electrolyte replacement were therefore administered.

Severe hypercalcaemia was managed with intravenous and oral hydration and pamidronate 90 mg, administered intravenously over three hours. Despite the presence of a solitary kidney, the estimated glomerular filtration rate was approximately 70 mL/min/1.73 m^2 at the time of administration. Neither calcitonin nor cinacalcet was administered during the initial hospitalisation. Serum calcium progressively decreased to approximately 10-12 mg/dL (Table *1*), accompanied by improvement in the patient's overall clinical condition. She was discharged on Day 8 with outpatient Endocrinology and Internal Medicine follow-up.

At outpatient reassessment on Day 37, hypercalcaemia persisted, with elevated total, albumin-corrected, and ionised calcium concentrations, persistent hypophosphataemia, and preserved renal function (Table *1*). The biochemical findings supported a diagnosis of concomitant PHPT [3].

An abdominal ultrasound performed in 2024 showed no definite evidence of renal calculi, although nephrocalcinosis was not explicitly addressed in the report. Subsequent skeletal assessment by dual-energy X-ray absorptiometry in October 2026 showed T-scores of -4.2 at the wrist, -2.8 at the femoral neck, and -2.3 at the lumbar spine (L1-L4).

Parathyroid scintigraphy performed in September 2026 demonstrated focal uptake posterior to the inferior aspect of the right thyroid lobe, with pronounced retention on delayed images, suggesting hyperfunctioning parathyroid tissue.

Repeat laboratory testing in October 2026 demonstrated persistent hypercalcaemia and elevated PTH, with

total serum calcium of 13.7 mg/dL and PTH of 429 pg/mL. Serum creatinine was 0.70 mg/dL, and 25-hydroxyvitamin D was 26.9 ng/mL (Table *1*). On Day 80, total thyroidectomy and selective parathyroidectomy were recommended, and cinacalcet 30 mg twice daily was initiated while awaiting surgery.

At the time of reporting, surgery had not yet been performed. The histopathological diagnosis therefore remained unconfirmed, precluding definitive distinction between parathyroid adenoma, hyperplasia, and carcinoma.

Discussion

Hypercalcaemia has been reported in approximately 20% of patients with hyperthyroidism and is predominantly attributed to increased bone turnover induced by excess thyroid hormone. It is usually mild, although severe presentations attributable to thyrotoxicosis alone have been described [1,2]. In this setting, elevated calcium concentrations should suppress PTH secretion; an elevated or inappropriately normal PTH concentration therefore warrants investigation for a concomitant PTH-dependent disorder [3].

The most informative finding in this case was the dissociation between the response to antithyroid treatment and the severity of the calcium disturbance. FT4 decreased from 7.75 ng/dL on Day -25 to 1.56 ng/dL on admission, when FT3 was also within the reference range at 3.40 pg/mL. Despite normalisation of circulating thyroid hormone concentrations, total serum calcium was 15.5 mg/dL and PTH was 630 pg/mL. Persistent hypercalcaemia on Day 37 and subsequent calcium and PTH concentrations of 13.7 mg/dL and 429 pg/mL in October 2026 further supported concomitant PHPT. Although previous thyroid hormone excess may have contributed to the initial calcium disturbance, it could not adequately explain this PTH-dependent biochemical profile.

Recognition of this distinction was clinically important because the manifestations overlapped. Weight loss, gastrointestinal symptoms, asthenia, proximal weakness, and functional deterioration could have been attributed to recurrent Graves' disease, creating a risk of diagnostic anchoring. Confusion and psychomotor slowing were also compatible with severe hypercalcaemia, although reduced nutritional intake and other metabolic abnormalities may have contributed. The neurological presentation was therefore considered multifactorial, and the contribution of each disturbance could not be established.

Coexisting Graves' disease and PHPT has previously been described. Arem et al. documented changes in calcium and PTH during treatment of hyperthyroidism in two patients, illustrating the biochemical interaction between these disorders [6]. Yokomoto et al. reported a hypercalcaemic crisis with calcium of 19.0 mg/dL, while Baldane et al. described a similarly severe presentation with gastrointestinal and neurological symptoms; both reports described combined thyroid and parathyroid surgery after biochemical stabilisation [4,5]. These observations suggest that thyroid hormone and PTH excess may contribute jointly to hypercalcaemia. Nevertheless, calcium severity alone cannot distinguish isolated thyrotoxicosis from concomitant PHPT, making PTH measurement central to the differential diagnosis.

The marked biochemical abnormalities also warrant consideration of parathyroid carcinoma. Our patient's PTH concentration was approximately 9.7 times the upper limit of normal, alongside calcium exceeding 14 mg/dL. These findings raise suspicion but are not specific for malignancy [7]. The thyroid ultrasound did not describe a candidate parathyroid lesion or adjacent lymphadenopathy, and a dedicated parathyroid assessment was not documented. Subsequent scintigraphy identified hyperfunctioning tissue posterior to the inferior aspect of the right thyroid lobe, but the report provided neither lesion dimensions nor an assessment of local invasion. Moreover, scintigraphic uptake cannot reliably distinguish adenoma from carcinoma [7]. Malignancy therefore remained an unresolved differential diagnosis.

Parathyroid localisation may be challenging in Graves' disease because thyroid enlargement, heterogeneous parenchyma, and pseudonodular changes can complicate ultrasonographic assessment, while increased thyroid tracer uptake may obscure parathyroid abnormalities [2]. Intrathyroidal parathyroid tissue is another consideration when localisation is inconclusive, although this location was not established in our patient [8]. Localisation findings should guide operative planning without being interpreted as confirmation of benign pathology.

When both disorders warrant surgery, combined thyroidectomy and parathyroidectomy can address them during a single operation [8]. In this case, recurrent Graves' disease, marked thyroid enlargement, and symptomatic PHPT provided a rationale for the proposed combined approach over radioiodine, which would not definitively treat PHPT. Cinacalcet was subsequently initiated while surgery was pending. The operative approach must nevertheless reflect the possibility of carcinoma: strong preoperative or intraoperative suspicion favours oncological en bloc resection, including the tumour, ipsilateral thyroid lobe, and involved adjacent tissues, while avoiding capsular rupture [7]. The proposed total thyroidectomy with selective parathyroidectomy should not be equated with such an oncological resection.

This report has several limitations. The urinary calcium-to-creatinine clearance ratio was not obtained,

limiting assessment for familial hypocalciuric hypercalcaemia. The available renal ultrasound predated the current presentation and did not explicitly address nephrocalcinosis. Most importantly, surgery remained pending, preventing confirmation of the underlying parathyroid pathology and assessment of definitive treatment outcomes. As a single case, this report illustrates the diagnostic value of interpreting PTH alongside calcium and thyroid hormone concentrations, but cannot establish the frequency of this association, the relative contribution of each disorder, or the superiority of a particular treatment strategy.

Conclusions

Hypercalcaemia in patients with Graves' disease should not automatically be attributed to thyrotoxicosis. Serum PTH should be measured in every thyrotoxic patient with hypercalcaemia to distinguish PTH-dependent from PTH-independent causes. Hypercalcaemia that persists after restoration of euthyroidism warrants further investigation regardless of its magnitude. An elevated or inappropriately normal PTH concentration should prompt evaluation for concomitant PHPT.

An elevated or inappropriately normal PTH concentration in this setting should prompt evaluation for concomitant PHPT. This case illustrates how overlapping clinical manifestations may complicate recognition of coexisting thyroid and parathyroid disease. However, observations from a single patient cannot establish generalisable conclusions about this association or its optimal management. Although the biochemical findings supported concomitant PHPT, surgery remained pending at the time of reporting; therefore, the underlying parathyroid pathology and the outcome of definitive treatment could not be confirmed.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Sofia Prada, Teresa Pereira, Marinela Major, Fernando Aldomiro

Acquisition, analysis, or interpretation of data: Sofia Prada, Carlota Mello, Teresa Pereira

Drafting of the manuscript: Sofia Prada, Carlota Mello, Teresa Pereira

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Supervision: Marinela Major, Fernando Aldomiro

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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