



Case Report

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# Hypercalcemia Caused By Concomitant Graves Disease and Primary Hyperparathyroidism



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## Summary

Here, we present the clinical course, laboratory results and management and review pertinent literature for a rare case of concomitant Graves' disease and primary hyperparathyroidism associated with hypercalcemia. A 71 years old African American woman presented with generalized fatigue, polyuria, polydipsia, and poor appetite for a few weeks. On admission, laboratory values showed serum calcium level of 12.3mg/dL, albumin of 3.6g/dL, iPTH of 37pg/mL, PTH related peptide of 0.2pmol/L, 25(OH) vitamin D of 65ng/mL, TSH of 0.01uIU/mL, and free T4 of 7.1ng/dL. I-123 uptake and scan of the thyroid showed 44% homogeneous uptake at 24 hours. The patient was initially diagnosed with hypercalcemia related to hyperthyroidism. She received intravenous hydration and was treated with 25.9mCi of I-131 2 months later. The serum calcium remained 10.4-10.7mg/dL (range, 8.6-10.4mg/dL) after freeT4 normalized to 1.58ng/dL. Repeat labs revealed serum ionized calcium of 5.9mg/dL, iPTH of 65pg/mL and 24- hour urinary calcium of 166.4mg, which is consistent with primary hyperparathyroidism. Hypercalcemia in Graves' hyperthyroidism should warrant a thorough investigation for concomitant primary hyperparathyroidism.

## Background

Thyroid and parathyroid disease may coexist [1-3]. Cases of synchronous thyroid pathology have been observed in patients presenting with primary hyperparathyroidism (PHPT), suggesting the importance of preoperative evaluation of thyroid gland [1,2]. We have previously reported the coexistence of thyroiditis and thyroid nodules with parathyroid disorders [4,5] and the development of PHPT after radioactive iodine-131 (RAI) treatment for Graves' hyperthyroidism [6,7]. Wahl et al. [8] found that the prevalence of PHPT was about 1% among 5450 patients referred for thyroid surgery, which can create a challenge in the clinical decision making and management of these patients. It is optimal to deal with both problems in one operative procedure if surgery is required [1]. However, there are fewer case reports or studies emphasizing the importance of searching for PHPT in Graves' disease patients with concomitant

hypercalcemia. Here we report a unique case of hypercalcemia caused by hyperthyroidism and PHPT.

## Case Presentation

A 71 years old African American woman with a past medical history of hypertension, colon cancer and anxiety disorder was admitted to the hospital with generalized fatigue, polyuria, polydipsia, and poor appetite for a few weeks. On examination, she was anxious. Her blood pressure was 118/68mm Hg, heart rate 108, respiratory rate 14, and she was afebrile. Extra-ocular muscles were intact with mild proptosis. The thyroid was normal in size, non-tender, and without bruits. Cardiovascular examination was notable for a 2/6 systolic ejection murmur. The pulmonary, abdominal, and neurologic examinations were unremarkable. There was trace bilateral lower extremity edema.

## Investigation

Laboratory values showed a serum calcium of 12.3mg/dL (range, 8.6-10.4), albumin of 3.6g/dL (range, 3.5-4.8), intact parathyroid hormone (iPTH) of 37pg/mL (range, 15-65), parathyroid hormone (PTH) related peptide of 0.2pmol/L (normal, <2), 25OH vitamin D of 65ng/mL (range, 30-74), thyroid stimulating hormone (TSH) of 0.01uIU/mL (range, 0.45-4.50), and free thyroxine (T4) of 7.1ng/dL (range, 0.82-1.77). I-123 uptake and scan of the thyroid showed 20% and 44% homogeneous uptake at 4 and 24 hours, respectively. Thyroid ultrasound showed a multi-nodular goiter with a dominant 1.8cm complex hyperechoic nodule in the right lower lobe with mild vascularity and no microcalcification. The patient was diagnosed with hypercalcemia related to hyperthyroidism.

## Treatment

She received intravenous hydration and was started on methimazole and propranolol. Prior to discharge, the serum calcium improved to 11.2mg/dL (range, 8.6-10.4) and free T4 improved to 5.53ng/dL (range, 0.82-1.77). Two months later, she was treated with 25.9mCi of I-131.

## Outcome and Follow-Up

Even though the free T4 returned to normal at 1.58ng/dL (range, 0.82-1.77), the serum calcium remained 10.4-10.7mg/dL (range, 8.6-10.4). Repeat labs revealed serum ionized calcium of 5.9mg/dL (range, 4.5 - 5.6), intact PTH of 65pg/mL (range, 15-65), 24- hour urinary calcium of 166.4mg (range, 100-300), and 25(OH) vitamin D of 46.4ng/mL (range, 30-74); those lab values were consistent with the diagnosis of PHPT. She was advised to stay well hydrated and monitor calcium levels with regular follow up as she did not meet the guideline for the parathyroidectomy.

## Discussion

The association between PHPT and thyroid disease, either benign or malignant, has been documented in the literature. Indeed, up to 65% of patients with PHPT have associated thyroid abnormality [9]. However, hypercalcemia caused by the coexistence of hyperthyroidism and PHPT, especially in the absence of previous neck irradiation, is extremely rare [10-12]. Only few cases have been reported in the English literature, and most reports originated from Asia [9]. Hypercalcemia occurs in up to 8% of patients with hyperthyroidism. The increased calcium release into the circulation is due to the increased bone resorption. Hypercalcemia suppresses the secretion of PTH, leading to hypercalciuria, which protects against hypercalcemia but leads to negative calcium balance in hyperthyroid patients [13]. Persistence of hypercalcemia after the normalization of TSH, however, is suggestive of other etiologies for hypercalcemia and work-up of PHPT is warranted. In our case, the diagnosis of Graves' disease is suggested by low TSH, high free T4, and high diffuse I-123 uptake. The diagnosis of primary hyperparathyroidism is suggested by high calcium and non-suppressed iPTH level.

In a retrospective study involving 96 patients admitted for elective hyperthyroidism surgery, 13 were diagnosed with hyperthyroidism associated with PHPT but none showed clinical manifestations of hypercalcemia [14]. Among these 13 patients, 11 had a parathyroid adenoma, and two had parathyroid hyperplasia. In another study conducted by Wagner et al. [15] 13387 patients who were referred to an outpatient department for thyroid diseases were screened for the presence of PHPT. The prevalence of PHPT was significantly higher in patients with thyroid diseases when compared with patients without thyroid disease (26/9017 = 0.29% vs. 4/4370 = 0.09%). Among patients with thyroid disease, the occurrence of PHPT was significantly higher in patients with euthyroid goiter, with the highest prevalence in patients with thyroid carcinoma. These findings suggest that serum calcium should be measured for patients referred to thyroid disease screening.

Arem et al. [10] reported the coexistence of Graves' disease and primary hyperparathyroidism in two patients undergoing medical management of hyperthyroidism. Serum free calcium level was initially markedly augmented - 1.61 and 1.71mM (normal, 1.12 to 1.28). However, the increase in immunoreactive

PTH values was only marginal. Both cases were successfully managed by parathyroidectomy and subtotal thyroidectomy for hyperparathyroidism and thyrotoxicosis, respectively. Thyroid hormone could potentiate the osteoclastic effects of PTH and exacerbate hypercalcemia, which then led to a relative suppression of PTH secretion by the abnormal parathyroid tissue [10]. In our case, hypercalcemia was initially associated with a normal iPTH level of 37pg/mL (range, 15-65), possibly caused by the effect of hypercalcemia potentiated by hyperthyroidism to suppress iPTH in concomitant PHPT. In addition, the initial normal iPTH level suggested PHPT since iPTH level would likely be suppressed if hypercalcemia was caused by hyperthyroidism alone. After the patient received methimazole and radioiodine treatment and became euthyroid, serum calcium values remained high and iPTH increased to abnormal values suggestive of hyperparathyroidism.

## Conclusion

In conclusion, hypercalcemia in patients with hyperthyroidism and normal iPTH levels should warrant a thorough investigation for possible concomitant PHPT. In this case reported here, preferred treatment should be combined thyroidectomy and parathyroidectomy.

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## Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Patient Consent

A written informed consent was obtained from the patient.

## Author Contributions and Acknowledgements

Dr. Wang is the patient's main physician and is the corresponding author.

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