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Case Report

Hypercalcaemic Crisis Associated with Hyperthyroidism: A Rare and Challenging Presentation

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Abstract

A 51-year-old female with a history of multinodular goitre presented with vomiting, abdominal discomfort, and generalized tiredness. Investigations revealed hypercalcemia (ionized calcium 1.41 mmol/L), hypokalaemia, suppressed parathyroid hormone, and significantly elevated free thyroxine (> 7.77 ng/dL) with a suppressed thyroid-stimulating hormone level consistent with hyperthyroidism. Further, the workup confirmed Graves' disease as the underlying aetiology. Hyperthyroidism is occasionally associated with mild to moderate hypercalcemia, but severe hypercalcemia or hypercalcaemic crisis is an extremely rare complication. Prompt recognition and treatment are crucial to prevent life-threatening complications. The patient was treated with intravenous fluids, a low-calcium diet, zoledronic acid, carbimazole, and a beta-blocker, leading to improvement in her condition. This case highlights a rare occurrence of hypercalcaemic crisis in a patient with thyrotoxicosis due to Graves' disease. Hyperthyroidism-induced hypercalcemia requires prompt recognition and multidisciplinary management involving endocrinologists, internists, and critical care specialists to prevent potentially life-threatening complications. Healthcare providers should consider the hypercalcaemic crisis in the differential diagnosis of hypercalcemia in the context of hyperthyroidism.

More Information

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Introduction

Hyperthyroidism is a condition characterized by an excess of thyroid hormone that can result in symptoms such as palpitations, tremors, and weight loss. Studies have shown that hyperthyroidism is associated with mild to moderate hypercalcemia in about 20% of patients [1]. However, severe hypercalcemia or hypercalcaemic crisis is rare in hyperthyroidism. Only a few cases of hyperthyroidism complicated with hypercalcaemic crisis have been reported in indexed articles [2,3]. It has been suggested that the relationship between thyroid hormone and serum calcium level may be due to thyroid hormone directly stimulating bone turnover and elevating serum calcium, urinary, and faecal calcium excretion [4]. The rarity of hypercalcemic crisis in hyperthyroidism makes it a challenging condition to diagnose and manage. However, the potentially life-threatening complications associated with a hypercalcemic crisis make it critical for healthcare providers to be vigilant for signs and symptoms of the condition. The prompt recognition and treatment of hypercalcemic crises in hyperthyroid patients are essential to prevent severe complications and improve patient outcomes.

Case presentation

A 51-year-old female presented with complaints of multiple episodes of vomiting, upper abdominal discomfort, body aches, and generalised tiredness for the past 1 week (Figure 1). Her past medical history is remarkable for multinodular goitre for which she is not on any medications. On physical

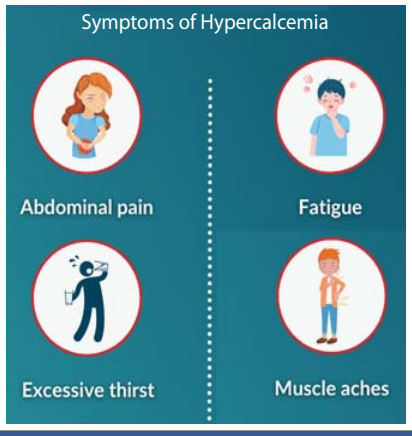

Figure 1: Symptoms of Hypercalcemia in my patient.

examination, her resting pulse rate was 112 beats per minute, and her blood pressure was 120/70 mmHg with a temperature of 36.6 degrees Celsius. Head-to-toe examination revealed an anxious look, with mild bilateral proptosis and a diffusely non-tender nodular goitre with no signs of retrosternal extension. Systemic examination was unremarkable except for mild tenderness in the epigastrium. ECG taken initially at the Emergency Department showed sinus tachycardia with a heart rate of 120 beats per minute. Her initial laboratory investigations revealed a normal haemogram, normal sodium (141 mmol/L), hypokalemia 2.4 mmol/L (3.5-5 mmol/L), and mildly elevated ionized calcium 1.41 mmol/L (1.12-1.32 mmol/L). She was managed with intravenous fluids, anti-emetics, and proton pump inhibitors. After adequate hydration and potassium correction, her tiredness settled to some extent but had persistent abdominal symptoms. However, her ionised calcium level was progressively increasing and hence a detailed workup for persistent hypercalcemia was performed. Serum inorganic phosphate was normal at 3.5 mg/dl (2.5-4.5 mg/dl), with low parathyroid hormone levels 6.9 pg/ml (15-65 pg/ml) and low 25 hydroxy vitamin D 6.2 ng/ml (30-100 ng/ml). Serum alkaline phosphate was 149 U/l (35-104 U/L). 1,25 Dihydroxy Vitamin D level was sent to rule out granulomatous disease and came out normal. The possibility of paraneoplastic hypercalcemia was thought and we proceeded with a PET-CT scan which showed no abnormalities. A thyroid function test done showed a significantly elevated free thyroxine (FT4) level > 7.77 ng/dL (normal range: 0.8-2.70 ng/dL) with a suppressed Thyroid-Stimulating Hormone (TSH) level of 0.01 mIU/L (normal range: 0.27-4.2 mIU/L), which was consistent with hyperthyroidism. To differentiate Graves' disease from Thyroiditis we did a technetium-99m thyroid scan which showed homogenous uptake throughout the gland fitting with Graves. She was initiated on oral Carbimazole 10 mg twice daily along with a beta blocker to control her thyroid function. She was advised to take a low-calcium diet with adequate fluid intake to correct her dehydration. She was treated with Inj Zoledronic acid 4 mg in 100 ml Normal Saline (NS) as an intravenous infusion for one hour. Her calcium levels showed a reducing trend after 48 hrs and she was discharged and is under our close follow-up.

Discussion

A hypercalcemic crisis is an uncommon but severe complication that can occur in patients with hyperthyroidism. We present a case report of a rare occurrence of hypercalcemic crisis due to thyrotoxicosis and discuss the underlying mechanisms and management strategies based on available literature.

Our case involves a patient who presented with symptoms of hypercalcemia, including nausea, abdominal pain, and muscle weakness. Laboratory investigations revealed significantly elevated serum calcium levels, confirming the diagnosis of a hypercalcemic crisis. Prompt recognition and intervention were crucial in this case to prevent further complications and ensure the patient's well-being.

The relationship between hyperthyroidism and hypercalcemia has been described in previous studies [1,2]. In approximately 20% of patients with hyperthyroidism, mild to moderate hypercalcemia can occur [1]. The underlying pathophysiology of hyperthyroidism-associated hypercalcemia remains poorly understood, but several mechanisms have been proposed. Studies suggest that thyroid hormone can alter calcium metabolism by increasing osteoclastic activity and bone resorption [5,6]. Fetal rat long bones cultured with thyroid hormone showed significantly elevated osteoclastic activity with an increase in calcium release of 10% to 60% [5]. Hyperthyroidism may also increase the sensitivity of bone to Parathyroid Hormone (PTH) and catecholamines [6,7], leading to increased bone resorption.

Clinical studies have demonstrated that hyperthyroid patients exhibit increased cortical porosity and bone resorption compared to healthy controls [8]. Thyroid hormone can directly increase the sensitivity of bones to interleukin-6 (IL-6), which promotes osteoclastic differentiation via increasing the expression of the receptor activator of nuclear factor kappa-B ligand (RANKL) [9].

Furthermore, hyperthyroidism can dysregulate the levels of other hormones, such as adrenaline and glucocorticoids, which may contribute to a hypercalcaemic state [10]. Increased levels of bone formation markers, such as bone-specific alkaline phosphatase (BALP) and procollagen type I N-terminal propeptide (PINP), as well as bone resorption markers, have been observed in some cases of hyperthyroidism-associated hypercalcemia [9,11,12], suggesting increased bone turnover.

Management of hypercalcemic crisis in the setting of thyrotoxicosis requires a multidisciplinary approach involving endocrinologists, internists, and critical care specialists. The primary goals of treatment include normalization of serum calcium levels, correction of fluid and electrolyte imbalances, and management of the underlying hyperthyroidism. Aggressive hydration with isotonic saline is essential to promote renal calcium excretion and prevent dehydration-induced renal impairment [13].

Thyroid-specific treatment is crucial in managing hypercalcemic crises. Antithyroid medications, such as thioamides or radioactive iodine therapy, aim to restore euthyroidism and reduce excessive thyroid hormone production. Beta-blockers can provide symptomatic relief by controlling tachycardia and tremors associated with thyrotoxicosis [14].

Calcitonin, a hormone that inhibits bone resorption and promotes renal calcium excretion, can be considered an adjunctive therapy in severe cases to rapidly lower serum calcium levels [15]. In refractory or life-threatening situations,

haemodialysis may be required to remove excess calcium from the circulation [2,16].

Regular monitoring of serum calcium, thyroid function, and electrolyte levels is crucial in the follow-up of patients after the resolution of a hypercalcemic crisis. Long-term management should focus on controlling hyperthyroidism to prevent recurrence of hypercalcemia.

Conclusion

The case report highlights a rare occurrence of hypercalcemic crisis in a patient with hyperthyroidism due to Graves' disease. The key takeaway points are:

1. Hyperthyroidism is occasionally associated with mild to moderate hypercalcemia, but severe hypercalcemia or hypercalcemic crisis is an extremely rare complication.

2. Prompt recognition and multidisciplinary management involving endocrinologists, internists, and critical care specialists are crucial to prevent life-threatening complications.

3. The management involves aggressive fluid resuscitation, a low-calcium diet, medications to control thyroid hormone levels (antithyroid drugs, beta-blockers), and agents to lower serum calcium levels (calcitonin, bisphosphonates).

4. Healthcare providers should consider the hypercalcemic crisis in the differential diagnosis of hypercalcemia in the context of hyperthyroidism, as prompt treatment can significantly improve patient outcomes.

References

1. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008 Feb;29(1):76-131. doi: 10.1210/er.2006-0043. Epub 2007 Nov 8. PMID: 17991805.

2. Yamamoto K, Shinozaki T, Kojima H. Hyperthyroidism-associated hypercalcemic crisis: a case report and review of the literature. J Endocrinol Invest. 2021;44(3):637-642. doi:10.1007/s40618-020-01315-x

3. Mokrysheva NG, Vlasova MA, Romanovsky AA, Pozhilenkova EA, Anisimov VN. Effect of thyroxine on calcium metabolism. Bull Exp Biol Med. 2019;167(6):739-741. doi:10.1007/s10517-019-04429-2

4. Bilezikian JP, Brandi ML, Cusano NE, et al. Management of endocrine disease: primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. Eur J Endocrinol. 2016;174(6): R231-R250. doi:10.1530/EJE-15-0989

5. Mundy GR, Shapiro JL, Bandelin JG, Canalis EM, Raisz LG. Direct stimulation of bone resorption by thyroid hormones. J Clin Invest. 1976 Sep;58(3): 529-34. doi: 10.1172/JCI108497. PMID: 182721; PMCID: PMC333209.

6. Cardoso LF, Maciel LM, Paula FJ. The multiple effects of thyroid disorders on bone and mineral metabolism. Arq Bras Endocrinol Metabol. 2014 Jul;58(5):452-63. doi: 10.1590/0004-2730000003311. PMID: 25166035.

7. Dhanwal DK. Thyroid disorders and bone mineral metabolism. Indian J Endocrinol Metab. 2011 Jul;15(Suppl 2):S107-12. doi: 10.4103/2230-8210.83339. PMID: 21966645; PMCID: PMC3169869.

8. Mosekilde L, Melsen F, Bagger JP, Myhre-Jensen O, Schwartz Sorensen N. Bone changes in hyperthyroidism: interrelationships between bone morphometry, thyroid function and calcium-phosphorus metabolism. Acta Endocrinol (Copenh). 1977 Jul;85(3):515-25. doi: 10.1530/acta.0.0850515. PMID: 577336.

9. Iqbal AA, Burgess EH, Gallina DL, Nanes MS, Cook CB. Hypercalcemia in hyperthyroidism: patterns of serum calcium, parathyroid hormone, and 1,25-dihydroxyvitamin D3 levels during management of thyrotoxicosis. Endocr Pract. 2003 Nov-Dec;9(6):517-21. doi: 10.4158/EP.9.6.517. PMID: 14715479.

10. Yokomoto M, Minamoto M, Utsunomiya D, Umakoshi H, Fukuoka T, Kondo S. Hypercalcemic crisis due to primary hyperparathyroidism occurring concomitantly with Graves' disease. Intern Med. 2015;54(7):813-8. doi: 10.2169/internalmedicine.54.2605. Epub 2015 Apr 1. PMID: 25832948.

11. Endo A, Shigemasa C, Kouchi T, Taniguchi S, Ueta Y, Yoshida A, Mashiba H. Development of hypercalcemic crisis in a Graves' hyperthyroid patient associated with central diabetes insipidus. Intern Med. 1995 Sep;34(9):924-8. doi: 10.2169/internalmedicine.34.924. PMID: 8580571.

12. Parker KI, Loftley A, Charles C, Hermayer K. A case of apathetic thyroid storm with resultant hyperthyroidism-induced hypercalcemia. Am J Med Sci. 2013 Oct;346(4):338-40. doi: 10.1097/MAJ.0b013e31828ffcbc. PMID: 23608928.

13. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016 Oct;26(10):1343-1421. doi: 10.1089/thy.2016.0229. Erratum in: Thyroid. 2017 Nov;27(11):1462. PMID: 27521067.

14. Marcocci C, Bollerslev J, Khan AA, Shoback DM. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. J Clin Endocrinol Metab. 2014 Oct;99(10):3607-18. doi: 10.1210/jc.2014-1417. Epub 2014 Aug 27. PMID: 25162668.

15. Pennisi M, Ghiandoni G, Faggiano A, Colao A. Hypercalcemic crisis: a clinical review. Calcif Tissue Int. 2019;105(1):63-74. doi:10.1007/s00223-019-00538-8

16. Giovanella L, Treglia G, Ceriani L. Hypercalcemic crisis in a patient with hyperthyroidism due to Graves' disease. J Endocrinol Invest. 2021;44(4): 933-934. doi:10.1007/s40618-020-01324-w