JMS Journal of Medical Science

Thyroid storm with simultaneous hypercalcemic crisis – life-threatening complications of unconventional therapy of Graves' disease

Maryla Pelewicz-Sowa
Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Poland
https://orcid.org/0000-0001-8898-7361

Piotr Miśkiewicz
Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Poland
https://orcid.org/0000-0003-4015-6491

Corresponding author: piotr.miskiewicz@wum.edu.pl

Received: 2022-11-18
Accepted: 2023-01-25
Published: 2023-02-09

How to Cite: Pelewicz-Sowa M, Miśkiewicz P. Thyroid storm with simultaneous hypercalcemic crisis – life-threatening complications of unconventional therapy of Graves' disease. Journal of Medical Science. 2023;92(1);e775. doi:10.20883/medical.e775

DOI: https://doi.org/10.20883/medical.e775

Keywords: Thyroid crisis, hyperthyroidism, thyrotoxicosis, hypercalcemia, goiter

ABSTRACT

Thyroid storm is a life-threatening endocrine disorder most often associated with uncontrolled or undiagnosed Graves' disease (GD). As thyroid hormones are involved in bone metabolism, hyperthyroidism may lead to hypercalcemia, usually mild to moderate. However, several cases of hypercalcemic crisis during thyrotoxicosis have been described.

We present a case of severe thyroid storm with simultaneous hypercalcemic crisis resulting from excessive intake of 5% Lugol's iodine solution (5% iodine, 10% potassium iodide, 85% water; 10 drops/day) and vitamin D3 (10000 IU/day) during two months of unconventional treatment in a 78-year-old female with a history of hyperthyroidism in the course of GD. Herbalist/healer prescribed supplements before admission to the hospital. At the clinic, we started therapy with antithyroid drugs (ATDs), inorganic iodide and corticosteroids but without positive effect. The patient's condition kept deteriorating with loss of consciousness. Moreover, the patient suffered from severe complications, including Takotsubo cardiomyopathy and sepsis, requiring intensive care unit. Finally, therapeutic plasmapheresis (TPE) (4 procedures) was required to reduce thyroid hormone levels successfully. Total thyroidectomy was performed, resulting in postoperative hypothyroidism and transient hypoparathyroidism. Treatment with corticosteroids led to transient secondary adrenal insufficiency. Following 2-month of hospitalization, the patient was discharged in stable condition.

Hypercalcemic crisis is a rare but severe complication of thyrotoxicosis; therefore, it should be considered in diagnostic and therapeutic process. Unconventional therapies conducted by "healers" may lead to life-threatening complications. TPE should be considered in patients with thyrotoxicosis resistant to the standard therapy with ATDs, corticosteroids and beta-blockers.

Introduction

Thyroid storm is a life-threatening endocrine emergency resulting from severe thyrotoxicosis. It manifests as multiple organ failure with impaired consciousness, high fever, jaundice, diarrhoea and heart failure, reaching a mortality rate of over 10% [1, 2]. Management of thyroid storm includes immedi-

ate diagnosis followed by intensive treatment with antithyroid drugs (ATDs), corticosteroids, inorganic iodide and antipyretics. Standard therapy focuses on the reduction of thyroid hormone secretion and production, as well as managing systemic and organ-specific signs and symptoms. Severe cases unresponsive to the initial therapy may require therapeutic plasmapheresis (TPE) [3].

Graves' disease (GD) is an autoimmunological thyroid disease most often associated with thyroid storm, usually uncontrolled in the presence of additional triggers, such as iodine contrast agents, thyroidectomy and radioiodine therapy. Rarely, thyrotoxicosis results from other endocrine disorders, such as toxic multinodular goitre, pituitary adenoma or metastatic thyroid cancer [3].

Severe hypercalcemia (>3.0 mmol/L) is another potentially lethal endocrine emergency leading to multiple organ damage. Clinical presentation includes polydipsia and polyuria, nausea and constipation, cognitive impairment, renal dysfunction, pancreatitis, peptic ulceration, hypertension and arrhythmias. It requires urgent correction with intravenous rehydration and bisphosphonates. Hypercalcemic crisis usually originates from primary hyperparathyroidism or malignancy. However, acute hypercalcemia may occur in rare cases due to thyrotoxicosis [4].

Thyroid storm with simultaneous hypercalcemic crisis

A 78-year-old female with a 2-month history of hyperthyroidism diagnosed ambulatory, was referred to the Department of Internal Medicine and Endocrinology due to fatigue, nausea, vomiting, anorexia, abdominal pain, polydipsia, polyuria, weight loss (15 kg) and heart palpitations lasting for one month. Patient had been taking 5% Lugol's iodine solution (5% iodine, 10% potassium iodide, 85% water; 10 drops/day), vitamin D3 (10000 IU/day), vitamin K2, magnesium, selenium, zinc, azarole, coenzyme Q10, and d-ribose supplements prescribed by "herbalist/healer" for 2 months. Laboratory tests revealed thyrotoxicosis with simultaneous hypercalcemia and liver damage (see **Table 1**). Thyroid ultrasound demonstrated substernal multinodular goitre. Diagnosis of thyroid storm and hypercalcemic crisis GD was made (see **Table 2**).

Treatment with thiamazole, dexamethasone, propranolol, sodium perchlorate and rehydration was introduced [3]. Despite the therapy, the patient's condition deteriorated with impaired consciousness and lack of verbal communication. Electrocardiography showed tachycardia, atrial fibrillation, and ST-segment elevation in V2-V3. Coronarography excluded significant coronary artery disease. Based on echocardiography findings and slightly increased cardiac troponin level (5 ng/ml; reference range: <0.06 ng/ml), Takotsubo cardiomyopathy was diagnosed [5]. Treatment with anticoagulants, antiplatelets, digoxin and angiotensin-converting enzyme inhibitors was administered, but the patient's condition kept deteriorating. Head computed tomography excluded any relevant abnormalities. Blood and urine cultures were positive for Klebsiella pneumonia, and therefore patient received targeted antibiotics. As, despite the treatment, free triiodothyronine (fT3) and free thyroxine (fT4)

Table 1. Clinical and laboratory characteristics of a patient with thyroid storm and hypercalcemic crisis on admission before treatment.

Clinical and laboratory characteristics	Results	Reference range
Glasgow coma scale	14	–
Blood pressure, mmHg	140/80	<140/90
Heart rate, beats/min	110	<100
Body temperature, °C	36.6	<37.2
Na^+, mmol/l	147.2	137.0–145.0
K^+, mmol/l	3.34	3.6–5.0
TSH, µIU/mL	<0.005	0.27–4.2
fT3, pmol/l	>50	3.1–6.8
fT4, pmol/l	>100	12–22
TSHR-Ab, IU/l	3.62	<1.8
TPO-Ab, IU/ml	<9	<34
Tg-Ab, IU/ml	273	<115
Total calcium, mmol/l	3.19	2.15–2.6
Ionized calcium, mmol/l	1.44	1.15–1.29
Parathormone, pg/ml	26	15–65
25(OH)D, ng/ml	64.35	30–80
Creatinine, mg/dl	0.67	0.5–1.1
Urea, mg/dl	66	15–48
AST, U/l	78	5–40
ALT, U/l	101	7–56
Urine iodine, µg/l	2338	100–200
Urine calcium, mmol/l	23.9	–

TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TSHR-Ab, thyrotropin receptor antibody; TPO-Ab, anti-thyroperoxidase antibody Tg-Ab, antithyroglobulin antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2. Thyroid storm criteria and patient's score at baseline.

Diagnostic criteria	Points	Patient' score
Temperature, °C		0
37.2–37.7	5	
37.8–38.3	10	
38.4–38.8	15	
38.9–39.3	20	
39.4–39.9	25	
≥40.0	30	
Tachycardia beats/min.		
90–109	5	
110–119	10	10
120–129	15	
130–139	20	
≥140	25	
Atrial fibrillation		0
Absent	0	
Present	10	
Congestive heart failure		
Absent	0	
Mild (pedal oedema)	5	5
Moderate (bibasilar rales)	10	
Severe (pulmonary oedema)	15	
Central nervous system disturbance		
Absent	0	
Mild (agitation)	5	
Moderate (lethargy)	10	10
Severe (seizure, coma)	15	
Gastrointestinal-hepatic dysfunction		
Absent	0	
Moderate (diarrhoea, abdominal pain, nausoea/vomiting)	10	10
Severe (jaundice)	20	
Precipitating event		
Absent	0	
Present	10	10
Total score		45
<25		Storm unlikely
25–44		Impending storm
≥45		Thyroid storm

serum levels remained above the reference range, the patient was qualified for TPE [3]. Acceptable reduction of fT3 and fT4 (to 6.61 pmol/ and 43 pmol/l, respectively) required four procedures (see **Figures 1** and **2**). When the patient stabilized, a total thyroidectomy was performed, resulting in postoperative hypothyroidism and transient hypoparathyroidism. Histopathological examination confirmed the diagnosis of multinodular goitre and excluded any malignancy. Six-week treatment with gradually tapered doses of dexamethasone resulted in secondary adrenal insufficiency. Following three weeks of hydrocortisone replacement therapy, cortisol level increased (10.1 ug/dl, reference range: 5–25 ug/dl) with no additional signs or symptoms of adrenal insufficiency. Therefore, hydrocortisone was withdrawn. The patient was informed that she might require hydrocortisone administration in stress doses. After one month of physical rehabilitation, she was able to eat, drink, sit, and stand up on her own. If accompanied, she could walk a short distance. Following a 2-month hospitalization, the patient was discharged in stable condition.

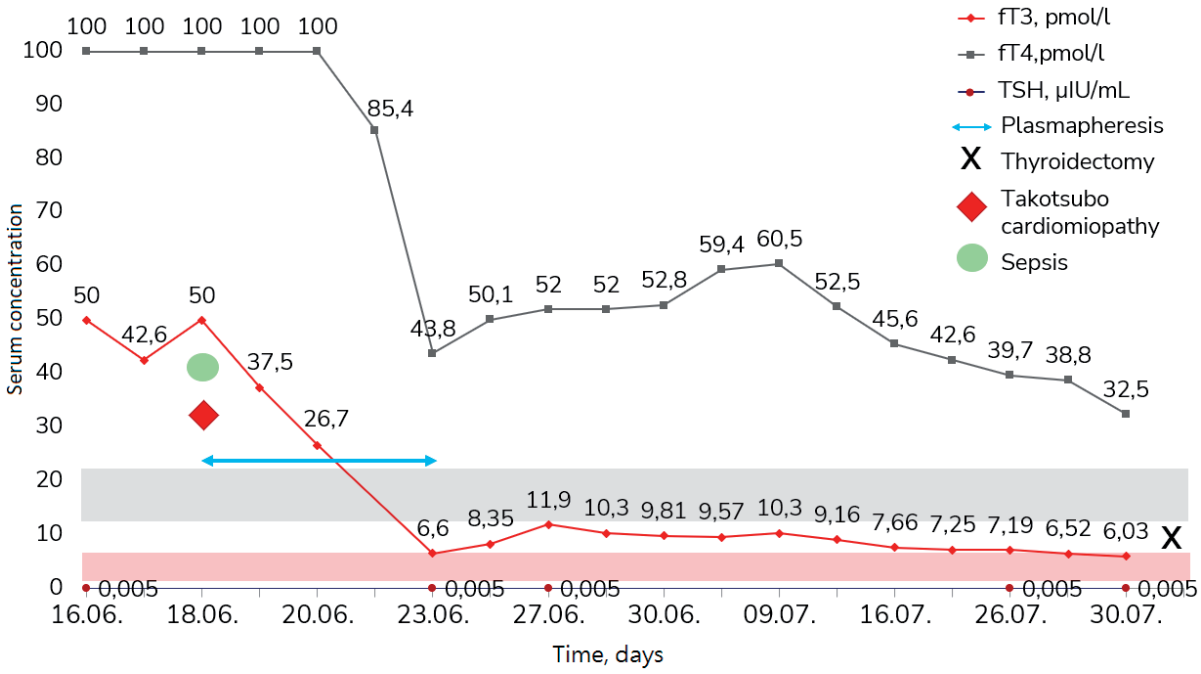

Figure 1. Evolution of thyroid hormone levels in a patient diagnosed with thyroid storm and hypercalcemic crisis. Grey and red lines represent the reference ranges of fT4 and fT3, respectively.

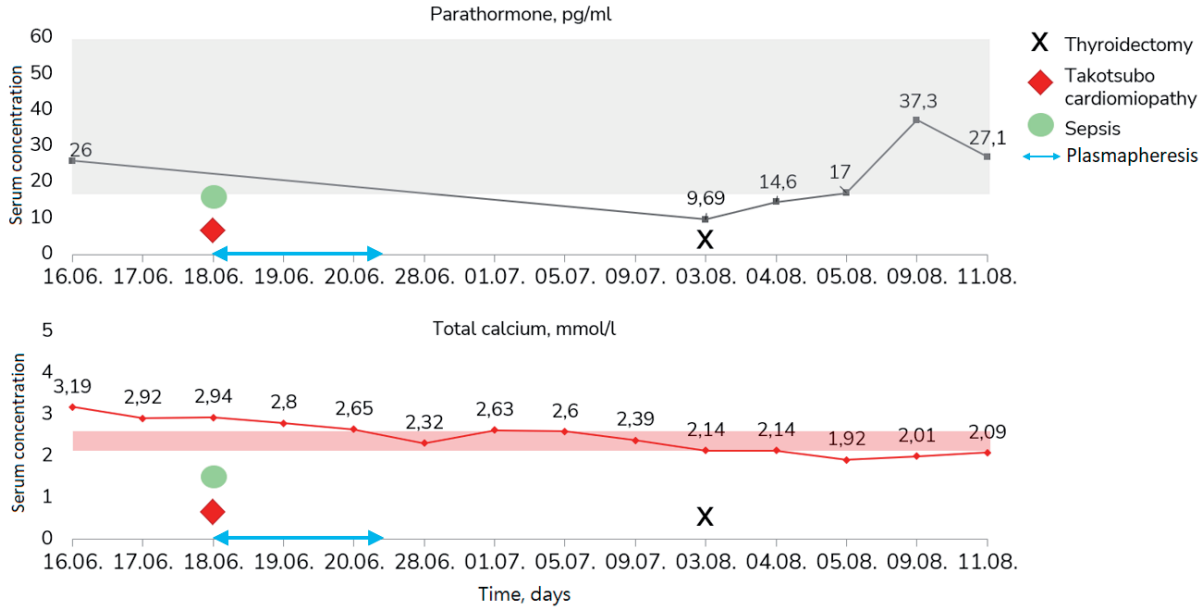

Figure 2. Evolution of parathormone and total calcium levels in a patient diagnosed with thyroid storm and hypercalcemic crisis. Grey and red lines represent reference ranges of parathormone and total calcium, respectively.

Discussion

Uncontrolled or undiagnosed GD is the most common cause of thyrotoxicosis. Thyroid storm is a life-threatening condition characterized by rapid deterioration and diverse clinical presentation depending on the affected organs [6]. The presented case describes occurrence of thyroid storm with simultaneous hypercalcemic crisis in a patient with untreated GD and excessive iodine and vitamin D3 intake.

Hyperthyroidism is associated with hypercalcemia. Thyroid hormones are involved in bone metabolism by increasing bone resorption and

formation, which may lead to elevated serum calcium levels [7]. Mild hypercalcemia (>2.6 mmol/l) was observed in 6% to 20% of patients with hyperthyroidism [8, 9]. However, hypercalcemic crisis due to thyrotoxicosis is rare. Only a few reports described the occurrence of severe hypercalcemia in hyperthyroidism secondary to GD [10–13]. In our case, excessive vitamin D3 intake in the presence of increased thyroid hormone levels could have additionally triggered symptomatic hypercalcemia development [14].

Multiple organ failure is the primary cause of death in patients with thyrotoxicosis. Even following the proper therapy, irreversible disorders, including brain damage, cerebrovascular disease, renal impairment and psychosis, may occur [1]. In our patient, thyroid storm and hypercalcemic crisis led to severe complications, including Takotsubo cardiomyopathy and sepsis. Although the applied treatment successfully saved the patient's life, it also resulted in hypothyroidism, transient hypoparathyroidism and transient secondary adrenal insufficiency. The presented case underlines the harmfulness of unconventional treatments, even with over-the-counter supplements. Overall, two-month hospitalization required cooperation from various departments and specialists. Therefore, managing patients with thyroid storm always requires a multidisciplinary approach involving endocrinologists, neurologists and cardiologists with immediate access to the intensive care unit.

Conclusions

Unconventional therapies conducted by "healers" may lead to life-threatening complications. Thyroid storm can result from incorrect treatment of GD. Hypercalcemic crisis may occur due to thyrotoxicosis and should be considered in the differential diagnosis and therapeutic process. Patients suffering from severe hyperthyroidism resistant to standard therapy with ATDs, corticosteroids and beta-blockers may benefit from TPE.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References

1. Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Monden T, Kouki T, Otani H, Teramukai S, Uehara R, Nakamura Y, Nagai M, Mori M; Japan Thyroid Association. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid. 2012 Jul;22(7):661-79. doi: 10.1089/thy.2011.0334. Epub 2012 Jun 12. Erratum in: Thyroid. 2012 Sep;22(9):979. PMID: 22690898; PMCID: PMC3387770.
2. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. 1993 Jun;22(2):263-77. PMID: 8325286.
3. Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Kanamoto N, Otani H, Furukawa Y, Teramukai S, Akamizu T. 2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (First edition). Endocr J. 2016 Dec 30;63(12):1025-1064. doi: 10.1507/endocrj.EJ16-0336. Epub 2016 Oct 15. PMID: 27746415.
4. Walsh J, Gittoes N, Selby P; Society for Endocrinology Clinical Committee. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Emergency management of acute hypercalcaemia in adult patients. Endocr Connect. 2016 Sep;5(5):G9-G11. doi: 10.1530/EC-16-0055. PMID: 27935816; PMCID: PMC5314807.
5. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. Eur Heart J. 2018 Jun 7;39(22):2047-2062. doi: 10.1093/eurheartj/ehy077. PMID: 29850820; PMCID: PMC5991205.
6. 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.
7. Pantazi H, Papapetrou PD. Changes in parameters of bone and mineral metabolism during therapy for hyperthyroidism. J Clin Endocrinol Metab. 2000 Mar;85(3):1099-106. doi: 10.1210/jcem.85.3.6457. PMID: 10720046.
8. Daly JG, Greenwood RM, Himsworth RL. Serum calcium concentration in hyperthyroidism at diagnosis and after treatment. Clin Endocrinol (Oxf). 1983 Sep;19(3):397-404. doi: 10.1111/j.1365-2265.1983.tb00013.x. PMID: 6627696.

9. Baxter JD, Bondy PK. Hypercalcemia of thyrotoxicosis. Ann Intern Med. 1966 Sep;65(3):429-42. doi: 10.7326/0003-4819-65-3-429. PMID: 4161741.
10. Chen K, Xie Y, Zhao L, Mo Z. Hyperthyroidism-associated hypercalcemic crisis: A case report and review of the literature. Medicine (Baltimore). 2017 Jan;96(4):e6017. doi: 10.1097/MD.0000000000006017. PMID: 28121960; PMCID: PMC5287984.
11. Ozkaya HM, Keskin FE, Haliloglu OA, Senel TE, Kadioglu P. Life-Threatening Hypercalcemia due to Graves' Disease and Concomitant Adrenal Failure: A Case Report and Review of the Literature. Case Rep Endocrinol. 2015;2015:684648. doi: 10.1155/2015/684648. Epub 2015 Mar 24. PMID: 25878906; PMCID: PMC4388017.
12. Korytnaya E, Rao NG, Mayrin JV. An unusual case of hypercalcemia associated with graves' disease and vitamin d deficiency. Clin Med Insights Endocrinol Diabetes. 2011;4:25-8. doi: 10.4137/CMED.S7116. Epub 2011 Jun 1. PMID: 22879791; PMCID: PMC3411504.
13. 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.
14. Norman AW. Intestinal calcium absorption: a vitamin D-hormone-mediated adaptive response. Am J Clin Nutr. 1990 Feb;51(2):290-300. doi: 10.1093/ajcn/51.2.290. PMID: 2407100.