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Role of Cholestyramine in Refractory Hyperthyroidism: A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 52
Final Diagnosis: Refractory iodine induced hyperthyroidism
Symptoms: Neck swelling • shortness of breath
Medication: Cholestyramine
Clinical Procedure: Total thyroidectomy
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course

Background: Hyperthyroidism is a common disease that usually responds to the conventional therapy of anti-thyroidal medications (methimazole or PTU) and beta-blocker. Refractory hyperthyroidism is a rare condition in which hyperthyroidism fails to respond to the above therapy. Cholestyramine has been shown to decrease thyroid hormone level when added to the ongoing anti-thyroidal medications.

Case Report: A 52-year-old woman with past medical history of enlarging goiter presented with obstructive symptoms of worsening shortness of breath and snoring. Admission thyroid function test showed mild hyperthyroidism (suppressed TSH, slightly high FT4, and high normal FT3) that worsened after she received a CT scan with contrast and failed to respond to a 3-week course of high-dose dexamethasone, high-dose carbimazole, and up-titrated propranolol. Five days after cholestyramine was added, her FT4 decreased by 30% and normalized after 12 days. The patient underwent total thyroidectomy as definitive treatment for the hyperthyroidism and for the obstructive symptoms.

Conclusions: Cholestyramine is an effective additional treatment for hyperthyroidism and may be an effective treatment for refractory iodine-induced hyperthyroidism. The possibility of self-remission (natural course) is less likely given the dramatic and rapid response to cholestyramine.

MeSH Keywords: Cholestyramine Resin • Hyperthyroidism • Iodine

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/893821

Background

Iodine transport into the thyroid gland is a crucial step in thyroid hormone biosynthesis. The sodium iodide symporter co-transports 2 sodium ions along with 1 iodide ion, with the transmembrane sodium gradient serving as the driving force for iodide uptake [1]. Perchlorate competitively inhibits iodine uptake and was inhibited by the Na+/K+-ATPase inhibitor.

Hyperthyroidism is a very common disease, most likely secondary to Graves's disease followed by toxic multi-nodular goiter. Iodine-induced hyperthyroidism occurs in patients with underling nodular goiter, a phenomenon referred to as Jod-Basedow syndrome. Iodine-induced hyperthyroidism is usually self-limited and lasts for 1–18 months.

The most important step in management of such patients is the discontinuation of the iodine source, avoiding any additional iodine exposure, and initiation of beta-blocker. Other medical options (e.g., thionamide, lithium, and corticosteroid) may be indicated in severe cases, worsening symptoms, or elderly patients. Medical treatment with Carbimazole and Propylthiouracil is usually very effective in restoring euthyroid status but there are few case reports of refractory (resistant) hyperthyroidism to these conventional therapies. Perchlorate with thionamide may be an effective strategy to minimize the risk of iodine-induced hyperthyroidism when administration of an iodine load (e.g., cardiac catheter) is planned [2]. Surgical treatment is indicated in patients with underling goiter with obstructive symptoms, when the patient is allergic to medical treatment, or when medical treatment is ineffective.

Case Report

A 52-year-old woman with known past medical history of goiter presented to the emergency department with a rapidly growing goiter and shortness of breath. The shortness of breath started 5 days prior to admission and was positional, mainly when lying down and she denied any history of chest pain, lower extremity edema, or fever. The neck swelling started 18 years ago and was progressively and slowly getting worse. She had seen her general practitioner for this condition and was prescribed levothyroxine 25 mcg, which she was taking on a p.r.n. basis, on average 1–2 times per week, with the last dose taken 1 week prior to her admission. She reported long-standing history of worsening loud snoring, fatigue, and excessive daytime sleepiness. She denied any history of palpitation, sweating, weight loss/gain or diarrhea. Otherwise, her past medical/surgical history was non-significant. She denied any allergy to medications. Her vital signs showed BP 110/82, heart rate 86, respiratory rate 18, oxygen sat 96%, weight 86 kg, and height of 164 cm. Her physical examination revealed a non-tender enlarged goiter with negative Pemberton's sign and no visible dilated vein, facial edema, or proptosis. She was admitted under general surgery, given the enlarging goiter with the obstructive symptoms (shortness of breath) and was started on dexamethasone 8 mg po TID and her home dose of levothyroxine 25 mcg po q day was continued.

On hospital day 1, she underwent thyroid ultrasound, which showed a multi-nodular goiter with retro-sternal extension with 2 right thyroid nodules, the largest measuring 6x4x3 cm and 1 left thyroid nodule measuring 5×4×4 cm. All isoechoic heterogonous nodules had ill-defined borders without calcification, with multiple enlarged cervical lymph nodes with benign features. On hospital day 2, initial thyroid function test (TFT) showed TSH of 0.005 (normal 0.27–4.2), FT4 of 25.73 (normal 12–22), FT3 of 6.44 (normal 3.1–6.8), negative thyroid peroxidase and thyroglobulin antibody. Levothyroxine 25 mcg was discontinued (Table.1). Her shortness of breath improved with the dexamethasone but there were no changes in her snoring or fatigue. On hospital day 5, she underwent a CT scan of the neck with contrast, which showed both thyroid lobes were enlarged, with the right lobe measuring 10×6.5×5 cm and left lobe measuring 12.5×7.5×6.5 cm. The gland reached the submandibular region, with left lobe compression and shifting the oropharynx and the trachea to the right side with both lobes displaced. The carotid artery and the internal jugular vein were laterally displaced and extended retrosternally by 5 cm.

On hospital day 8, repeated TFT showed TSH of 0.005, FT4 of 33.31, and FT3 of 6.05. On hospital day 12, another TFT was done by the surgery team, which showed TSH of 0.005 and FT4 of 36.13. No levothyroxine was given for 10 days. After this result, Internal Medicine was consulted and they started carbimazole 30 mg po bid and propranolol 10 mg po tid and the dexamethasone dose was decreased to 8 mg po bid. On hospital day 22, the thyroid function test was repeated and showed TSH of 0.005, FT4 of 39.04, and FT3 of 5.67. Propranolol was increased to 20 mg po tid and compliance to carbimazole intake was confirmed by direct nurse observation. On hospital day 24, she underwent thyroid fine-needle aspiration (FNA) for the right dominant nodule and the results were consistent with a colloid nodule. On hospital day 30, repeated TFT showed TSH of 0.005, FT4 of 47.10, and FT3 of 6.3. At this time, Endocrinology was consulted and I evaluated the case. My impression was underling multi-nodular goiter with hyperthyroidism induced by contrast (Jod-Basedow). She also had refractory hyperthyroidism despite being on a high dose of carbimazole for 3 weeks, as well as propranolol and high-dose dexamethasone. The carbimazole dose was increased to 40 mg po bid and she was started on cholestyramine 4 g po bid, and we increased the propranolol to 40 mg po tid and decreased the dexamethasone to 2 mg po tid. On hospital day 35, repeated TSH was 0.005, FT4 of 30.58, and

Table 1. Trend of thyroid function test results.

Hospital day	TSH (0.27–4.2)	FT4 (12-22)	FT3 (3.1-6.8)	Intervention
2	0.005	25.73	6.44	Home Thyroxine dose D/C'd and started Dexamethasone 8 mg TID
8	0.005	33.31	6.05	Contrast CT done hospital day 5
12	0.005	36.13	N/A	Carbimazole 30 mg bid + Propranolol 10 mg bid + Dexamethasone 8 mg bid
22	0.005	39.04	5.67	Carbimazole 30 mg bid + Propranolol 20 mg bid + Dexamethasone 8 mg bid
30	0.005	47.10	6.3	Carbimazole 40 mg bid + Propranolol 40 mg bid + Dexamethasone 2 mg tid + Cholestyramine 4 g po bid
35	0.005	30.58	4.55	Carbimazole 40 mg bid + Propranolol 40 mg bid + Dexamethasone 2 mg bid + Cholestyramine 4 g po tid
42	0.005	23.3	4.2	Carbimazole 40 mg bid + Propranolol 40 mg bid + Dexamethasone 2 mg bid + Cholestyramine 4 g po tid

FT3 of 4.55. The cholestyramine dose was increased to 4 g po tid, the dexamethasone dose was decreased to 2 mg po bid, and the carbimazole was continued at 40 mg po bid. Her white blood cell count and liver function test result remained stable throughout the hospital stay. On hospital day 42, a repeated TFT showed TSH of 0.005, FT4 of 23.3, and FT3 of 4.2.

On hospital day 43, she underwent total thyroidectomy and the final histopathology report revealed a multi-nodular goiter with no malignancy. Carbimazole and propranolol were discontinued on the day of surgery. On hospital day 44, the dexamethasone was discontinued and the hydrocortisone 20 mg po q.a.m. and 10 mg po q.p.m. were started. On the same day she developed numbness around the mouth and the corrected calcium was 7.3 (normal 8.4–10.2), phosphorous was 5.8 (normal 2.5–4.8), and PTH was 0.164 (normal 1.6–6.9) and she was started on calcium carbonate intravenously and alfacalcidol (one-alfa) 0.25 mcg po bid and cholecalciferol 50,000 IU po q weekly. On hospital day 45, the numbness resolved and calcium carbonate 1200 mg po tid was started, the alfacalcidol was increased to 0.5 mcg po bid, and the corrected calcium was 8.3 with phosphorous of 4.8. On hospital day 46, the hydrocortisone was discontinued and the 8 am cortisol level on the following morning and 5 days after being off hydrocortisone were 26 and 14, respectively, with ACTH level of 19.7 (normal 7.2–63) and stable chemistry (sodium and potassium), without any signs or symptoms of adrenal insufficiency. On hospital day 47, repeated FT4 of 14 and levothyroxine 25 mcg daily was initiated. On hospital day 50, she was discharged home in stable condition with resolution of the shortness of breath and improvement of the snoring without any hoarseness of the voice post-operatively.

Discussion

The surgery team felt that the suppressed TSH was secondary to the thyroxine intake, which they discontinued. But when the repeated TFT of thyroxine came back high, they consulted Internal Medicine. There was no endocrinologist at the hospital and when I joined as locum endocrinologist that month I got involved in this patient's care, which is the reason behind the late Endocrinology consultation.

Iodine contrast used for diagnostic imaging studies contains large amounts of iodine >200,000 µg [3]. Iodine-induced hyperthyroidism has been estimated at around 0.4% and has been shown to be more prevalent in patients with nodular goiter, older age, comorbidities [4]. The effects of excess iodine may last up to several months and are usually self-limited. Anti-thyroidal agents such as carbimazole and propylthiouracil (PTU) have been shown to be effective in accelerating recovery in such patients [5]. Several proposed mechanisms for refractory hyperthyroidism have been published, including drug malabsorption and impairment of intrathyroidal drug accumulation or action [6].

Thyroid hormone is metabolized mainly in the liver by conjugation to glucuronides that enter the enterohepatic circulation [7]. Cholestyramine is an ion exchange resin currently approved for hyperlipidemia treatment. In several previous studies it was shown to interfere with endogenous thyroid hormone absorption, which usually is increased in hyperthyroidism cases. An RCT that assigned hyperthyroid patients to methimazole and propranolol alone groups or in addition to cholestyramine showed those who were assigned to cholestyramine had more rapid decline of thyroid hormone compare to conventional therapy alone [8].

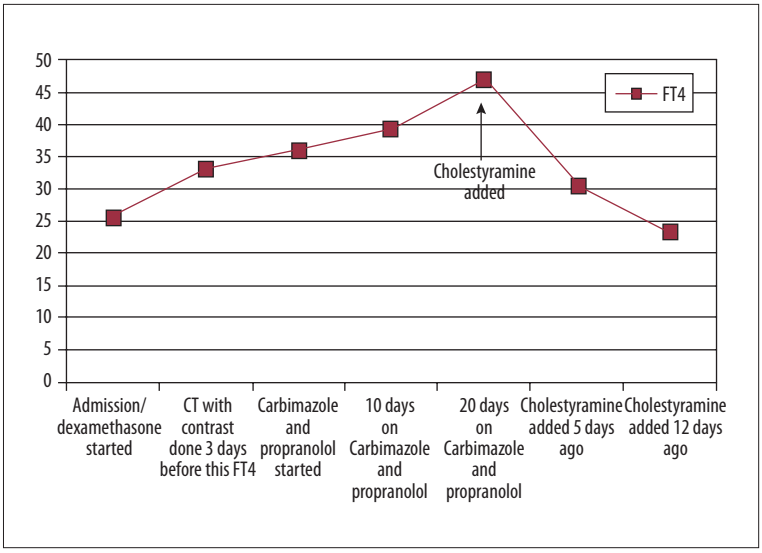

Figure 1. Thyroid function test results according to the hospital course.

A recently published case report showed that high-dose prednisone with lithium is also an effective measure in treatment of refractory hyperthyroidism [6]. Intravenous methimazole was shown to be an effective treatment for 3 hyperthyroid patients who were resistant to oral methimazole [9].

The present patient had no exposure to Amiodarone during or before this hospitalization. Perchlorate has been shown to be beneficial with thionamide in treatment of Amiodarone-induced hyperthyroidism type I and is a potentially effective option for prevention of iodine-induced hyperthyroidism in case of planned large diagnostic iodine administration [10]. Perchlorate was not tried in the present patient given the local unavailability and lack of evidence of its effectiveness in patients with this presentation.

There is a previous case report of 1 patient with refractory Grave's hyperthyroidism, which responded to Cholestyramine [11]. Here, I report the case of a huge multinodular goiter with obstructive symptoms, which was complicated by iodine contrast-induced hyperthyroidism refractory to a 3-week course of conventional therapy consisting of high doses of dexamethasone, carbimazole, and propranolol. Despite this therapy, FT4 continue to get worse. The patient had rapid decrease of FT4 by more than 30% only 5 days after cholestyramine was added to the ongoing therapy and normalized by 12 days (Figure 1). The Grave's disease case and my case both had normalized FT4 7–12 days after initiation of Cholestyramine. The difference between my case and the Grave's disease case is that my patient had isolated FT4 elevation. In both cases, the Cholestyramine dose was 12 g/d.

Surgical treatment (thyroidectomy) was the only suitable definitive treatment for this patient. Thyroidectomy was indicated because the patient had a rapidly growing goiter, with obstructive symptoms and worsening refractory hyperthyroidism. Radioactive iodine treatment is another option as a definitive treatment for hyperthyroidism in general, but would not have been helpful in my case given the large iodine load she had recently received.

Conclusions

To the best of this author's knowledge, this is the first reported case of iodine-induced hyperthyroidism with an isolated high FT4 that was refractory to conventional therapy with dramatic response to cholestyramine. A self-limited course (natural course) of the iodine-induced hyperthyroidism is less likely given the unresponsiveness to the proven effective medical therapy as well as the rapid improvement after cholestyramine was initiated.

Conflict of interests

The author has no conflicts of interests.

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