CASE REPORT
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A Case of Methimazole-Resistant Severe Graves' Disease: Dramatic Response to Cholestyramine

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A 22-year-old woman with severe Graves' disease was referred from a local clinic because of her refractory hyperthyroidism. She presented with exophthalmos, diffuse goiter, and tachycardia. She was treated with a maximal dose of methimazole and a beta-blocker for 2 months. However, her thyroid function test (TFT) did not improve. TFT showed a free T4 level of 74.7 ng/dL and a thyroid stimulating hormone (TSH) level of 0.007 μIU/mL. She was then administered cholestyramine (4 g thrice daily), hydrocortisone (300 mg/day) and methimazole (100 mg/day) which prepared the patient for surgery by reducing the free T4 level (4.7 ng/dL). The patient underwent a total thyroidectomy without experiencing thyrotoxic crisis. This case describes the use of cholestyramine for the first time in Korea in treating Graves' disease and provides limited evidence that cholestyramine can be an effective option.

Key Words: Cholestyramine, Graves' disease, Thyrotoxicosis, Methimazole

Introduction

The most common cause of hyperthyroidism is Graves' disease. It is an autoimmune disorder characterized by a constellation of clinical features including hyperthyroidism, diffuse goiter, ophthalmopathy, and dermopathy.[1] The therapeutic approach to Graves' disease consists of treatment with a beta-blocker, which results in both a rapid amelioration of symptoms and a decrease in thyroid hormone synthesis. Usually Graves' disease responds well to treatment with the antithyroid drugs; propylthiouracil (PTU) and methimazole (MMI) or its pro-drug, carbimazole. If these drugs are not effective, then surgery or radioiodine therapy must be considered. However, radioactive iodine is reluctant to use to women of childbearing age. Furthermore, there is increasing evidence that radioactive iodine can worsen ophthalmopathy resulting from Graves' disease compared to treatment with antithyroid drugs or surgery.[2] In the case of thyroidectomy, the patient's free T4 level needs to be near or at normal before surgery to prevent a post-operative thyroid storm. Thus, adjunctive treatment in the form of beta-blockers, corticosteroids, or inorganic iodide may also be used for more prompt control of symptoms prior to surgery.[3] Nevertheless, we often encounter the patients who are resistant to antithyroid drugs and adjunctive therapy. Certain studies have indicated that bile acid sequestrants, when administered with antithyroid drugs, produce a more rapid decline in serum thyroid hormone levels.[4-6] However, there has been no report in Korea regarding the effect of treatment with cholestyramine. Here, we report a successful case of cholestyramine treatment prior to surgery in a patient resistant to MMI.

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Case Report

A 22-year-old woman was diagnosed at a local clinic with hyperthyroidism in July 2011 and was prescribed propranolol (10 mg once daily) and MMI (5 mg twice daily). At the time, she was not compliant in regularly taking the medications. When she was referred to our hospital in August 2011 for a tonsillectomy, the operation was cancelled due to uncontrolled hyperthyroidism. At that time, her TSH level was 0.01 μIU/mL (0.4-4.0 μIU/mL) and free T4 level was 3.59 ng/dL (0.93-1.7 ng/dL). After 2 years, she was referred again to our general surgery clinic for uncontrolled hyperthyroidism. She claimed that she took antithyroid drugs regularly since August 2011. There was no data about her thyroid function for past 2 years while she was treated at the local clinic. She was administered 15 mg of MMI thrice daily, and 10 mg of propranolol twice daily for a month at an outpatient clinic but her free T4 level did not improve (TSH: 0.011 μIU/mL, free T4: 7.83 ng/dL). The amount of MMI was increased to 20 mg 4 times daily and 10 mg of propranolol twice daily for 2 weeks. Nevertheless, her thyroid function test did not normalized so she was referred to our endocrinology outpatient clinic. She was a smoker (2 packs-years), weighed 52.9 kg and her height was 160 cm (body mass index: 20.66). On physical examination, the thyroid gland was diffusely enlarged, firm, and not tender without a bruit (right lobe major axis: 7 cm, left lobe major axis: 5 cm). She presented with exophthalmos, lid retraction and, lid lag in both eyes without visual disturbance. She complained of general weakness, excessive sweating, heat intolerance, nervousness, and palpitations. Her blood pressure was 140/83 mmHg. An electrocardiogram revealed sinus tachycardia (heart rate: 139 bpm) with no rhythm disturbances. Her serum free T4 and total T3 levels were severely elevated with suppression of serum TSH (free T4 level of 74.7 ng/dL, total T3 level of 23.4 ng/mL (0.65-1.5 ng/mL), and TSH level of 0.007 μIU/mL on the day of admission. TBII was tested 2 months before admission and it was 29.2 U/L (0-9.9 U/L). It wasn't rechecked thereafter). The thyroid scintigraphy scan showed homogeneously increased Tc-99m uptake (thyroid uptake: 29.4%) (Fig. 1). Ultrasound image revealed a diffusely enlarged gland without any nodule or mass. After the patient was admitted, she was administered 3 drops of Lugol's solution thrice daily (0.45 cc in total), 100 mg of MMI (the dose was decided mainly upon the expert's opinion),[7] 120 mg of propranolol, and 300 mg of hydrocortisone daily. PTU was once given but she complained of severe nausea and pruritus after taking it. So it was stopped afterward. Cholestyramine

Fig. 1. Patients scintigraphy scan. This shows diffuse enlargement of both lobes of the thyroid gland with increased Tc-99m uptake.

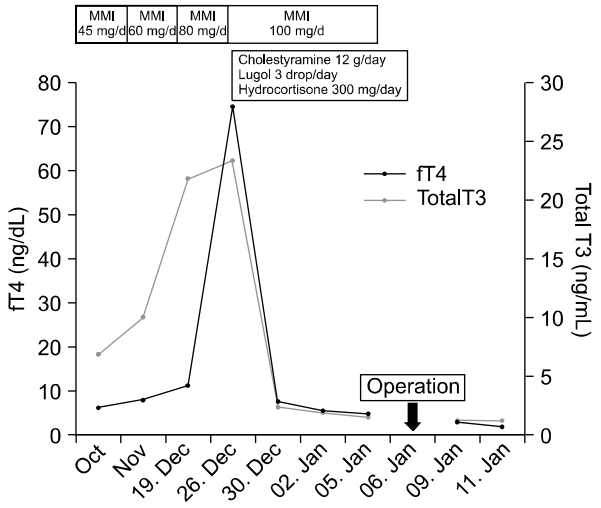

Fig. 2. Interval change of free T4 level and total T3 level following administration of medications (fT4: free T4, MMI: methimazole).

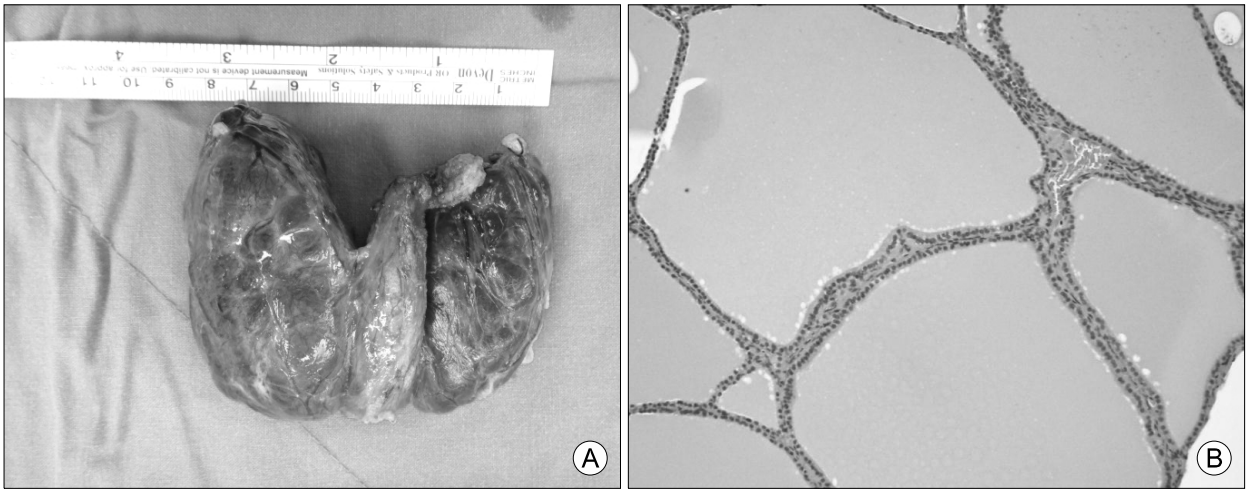

Fig. 3. Histopathologic images of the patients thyroid. (A) The postoperative gross image of the patients thyroid gland. Right lobe (7.0×4.0×3.5 cm), left lobe (5.0×5.0×3.0 cm), isthmus (3.0×2.0×1.0 cm) and pyramidal lobe, weighed 78 g in total. (B) Usually histologic findings of the Graves' disease are hyperplastic, and dilated follicles of variable sizes with scalloping of the colloid, but this case showed decreased scalloping of the colloid.

(4 g thrice daily) was added the day after admission. The patient experienced mild abdominal pain and diarrhea following administration of cholestyramine, but the symptoms were tolerable. Hydrocortisone was tapered 4 days later to 200 mg daily because of the development of non-pitting type edema in both legs. Eventually, the patient's free T4 level started to decline and the day before her thyroidectomy, the free T4 level was 4.7 ng/dL (Fig. 2) (At the same time, her total bilirubin was 1.2 mg/dL [0.1-1.2 mg/dL], AST 12 IU/L [15-40 IU/L], ALT 29 IU/L [0-40 IU/L] and creatinine 0.56 mg/dL [0.6-1.5 mg/dL]). The patient underwent total thyroidectomy 10 days after admission (Fig. 3). The operation was successful without the risk of precipitating thyrotoxic crises. The patient was started on thyroid replacement therapy (levothyroxine 50 mcg/day). Her general condition has remained stable during the 2 months following surgery.

Discussion

Hyperthyroidism resistant to antithyroid drug therapy is rare but potentially life-threatening. Thyroidectomy is one of the definitive approaches used in the treatment of thyrotoxicosis, especially in patients resistant to medical treatment. Surgery is indicated in pregnant hyperthyroid patients intolerant to antithyroid drugs, non-pregnant patients who refuse radioactive iodine therapy, patients resistant or allergic to radioactive iodine or antithyroid drugs, and patients with large or nodular goiter or with a cold nodule in active progressive ophthalmopathy.[8] Moderately severe ophthalmopathy may be a contraindication to treatment with radioiodine, since radioiodine may exacerbate the condition.[9,10] Worsening ophthalmopathy is more common in cigarette smokers than nonsmokers.[10] Thyroidectomy should preferably be performed when the patient is euthyroid in order to decrease perioperative cardiac risk. Adjunctive treatment in the form of beta-blockers, corticosteroids, or inorganic iodine may also be used to achieve a euthyroid state. However, in some cases, additional treatment may be required despite these conventional modalities.

Cholestyramine, an ion exchange resin used to lower serum cholesterol, interferes with the absorption of ingested thyroid hormones and the enterohepatic circulation of endogenous thyroid hormones, whose levels are increased in hyperthyroidism.[11] There are several studies regarding cholestyramine as a medication for thyrotoxicosis. Certain studies have reported a more rapid decline in free T4 and total T3 levels in patients diagnosed with Graves' disease who were treated for 4 weeks with cholestyramine and antithyroid drugs as compared to patients treated with only

antithyroid drugs.[5,12] In addition, Sebastian-Ochoa et al.[6] reported a patient who was resistant to antithyroid drug in whom thyroid hormone levels completely normalized after 1 week of additional treatment with cholestyramine. Furthermore, Kaykhaei et al.[13] suggested that low doses of cholestyramine are effective in producing a rapid and complete decline of thyroid hormone levels in patients with Graves' disease, when used in combination with MMI and propranolol. Based on these reports, cholestyramine was orally administered for rapid preoperative control of severe thyrotoxicosis in a patient who underwent surgery for excision of a toxic goiter due to Graves' disease that was refractory to treatment with propranolol and high doses of MMI.

Mercado et al.[5] reported that once the cholestyramine was discontinued after 2 weeks of the administration, the declining rate of thyroid hormones slowed down. So we think it's worth a try to prescribe cholestyramine when Graves' disease is diagnosed at the first time. The dosage of cholestyramine was variable in reports. It was administered from minimally 1 g twice a day[13] to maximally 4 g four times a day.[4] The treatment period was usually 2 to 4 weeks. Because cholestyramine showed its efficacy even it was minimally administered, we suggest to prescribe small dose of cholestyramine at the time you try it, in case the patient shows adverse effects.

However, it is necessary to consider why the patient was resistant to the antithyroid drugs. Possible reasons may include drug malabsorption, rapid drug metabolism, antidrug antibodies, impairment of intrathyroidal drug accumulation or action, and predominant elevation of T3 rather than T4 levels.[14] Therefore, we closely monitored the management of our patient and found her to be compliant in taking her medications. There was nothing remarkable in her medical history or physical examination to suggest malabsorption. We considered measuring the drug level or detecting anti-drug antibodies in the patient's thyroid tissue, but these tests are not usually available for routine clinical use. Thus, we were not able to determine the MMI level in the patient's thyroid tissue.

The glucocorticoid is known to prohibit conversion of T4 to T3 in peripheral tissues and release of thyroid hormone from the thyroid so it is used as an adjunctive treatment in thyrotoxicosis. But we couldn't find the reference that how much the steroid was able to decrease the level of free T4 and how fast. Empirically, decline of free T4 when the glucocorticoid is used is mild.

The limitation of this case is that the effect of glucocorticoid and that of cholestyramine on free T4 can't be divided.[15] The present case highlights a rare but important, clinical finding in the treatment of antithyroid drug-resistant thyrotoxicosis. Based on our experience with this case, we conclude that in cases of thyrotoxicosis refractory to medical treatment, cholestyramine may be used as an adjuvant to antithyroid drugs for the rapid treatment of patients prior to thyroidectomy when surgery cannot be delayed. A more comprehensive study needs to be conducted in order to validate our findings.

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