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Case Report

Lithium Monotherapy in Graves Thyrotoxicosis

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Abstract

Lithium is not commonly used to treat thyrotoxicosis, and there are few reports in the literature of its use as initial therapy in thyrotoxicosis. We describe the case of a patient with Graves thyrotoxicosis and ophthalmopathy, on a background of autoimmune neutropenia, treated successfully with relatively long-term lithium monotherapy. Lithium was used at a lower dose and longer duration than previously reported on, to good effect. We demonstrate that lithium is an important and useful option for those who are unable to tolerate thionamide therapy.

Key Words: Graves disease, thyrotoxicosis, lithium

Abbreviations: ATD, antithyroid drug; fT4, free thyroxine; LFT, liver function test; RAI, radioactive iodine; T3, 3,5,3′-triiodothyronine; TSH, thyrotropin, thyroid-stimulating hormone; TSH-R, thyrotropin receptor, thyroid-stimulating hormone receptor.

Introduction

Graves disease is characterized by antibody-mediated activation of thyrotropin receptors (TSH-Rs), resulting in the symptoms of hyperthyroidism, including goiter, palpitations, heat intolerance, and tremor [1]; and Graves ophthalmopathy, due to inflammation and fibrosis of TSH-R–presenting tissues in the periorbital spaces. Its symptoms are managed with β-adrenergic blockade, and there are 3 options for achieving euthyroidism: antithyroid drugs (ATDs), radioactive iodine (RAI), and surgical thyroidectomy [1]. The ATDs used are the thionamide class, including methimazole/carbimazole and propylthiouracil. The most serious side effects of these medications are agranulocytosis, aplastic anemia, and liver dysfunction [2]. The National Institute for Health and Care Excellence (NICE) recommends RAI as the first-line therapy for definitive management of Graves hyperthyroidism [3]. ATDs are often used to achieve euthyroidism prior to RAI or thyroidectomy [1].

Rarely, alternative agents such as lithium are needed in the management of hyperthyroidism. Lithium has long been a mainstay in the treatment of bipolar disorder. It has been shown to reduce thyroid hormone release from the thyroid gland, resulting in goiter and clinical hypothyroidism [4]. This may be due to reduction in endocytosis of colloid into the follicular cells, resulting in less thyroid hormone release from the gland. As a treatment then for hyperthyroidism, lithium has been shown to be effective in reducing thyroid hormone levels rapidly [5]. Furthermore, lithium increases retention of RAI in the thyroid gland [6].

Lithium is not commonly used to treat Graves disease due to its potential for toxicity and the effectiveness of conventional antithyroid medications such as carbimazole and propylthiouracil.

We present a case of a patient with Graves disease treated with lithium monotherapy prior to successful radioiodine therapy.

Case Presentation

A 66-year-old woman presented to her general practitioner with a 1-week history of light-headedness, nausea, intermittent palpitations, and weight loss of 3 kilograms. She had no recent viral illnesses, neck swelling or pain, night sweats, or change in bowel habits. Her past medical history includes rheumatoid arthritis, for which she was taking etanercept, with stable disease. She had previously taken hydroxychloroquine, methotrexate, D-penicillamine, sulfasalazine, leflunomide, and prednisolone. She had also been diagnosed with autoimmune neutropenia, with baseline neutrophil count around 1.2×10^9/L (1.2×10^3/μL). There was no family history of thyroid disorders.

Diagnostic Assessment

Serum biochemistry demonstrated thyrotoxicosis: TSH less than 0.01 mIU/L (<0.01 uIU/mL) and free thyroxine (fT4) 82.2 pmol/L (12-22 pmol/L) (6.47 ng/dL [0.8-1.7 ng/dL]). Her other blood tests were unremarkable aside from chronic neutropenia.

She had an urgent endocrine assessment. There was no discernible goiter, no features of eye disease, and no thyroid bruits to auscultation. Due to the neutropenia, the uncertainty of etiology (and thus best treatment option for her thyrotoxicosis), and the laboratory delay in awaiting antibody results, an RAI uptake scan was performed the next day. This showed homogenous distribution of the tracer in keeping with Graves disease (5.9% uptake). Her thyroid receptor antibodies were elevated 17.0 IU/L (0-2.9 IU/L) (17.0 mIU/mL), confirming the diagnosis of Graves disease.

Treatment

The patient is a retired physician, and was fully informed regarding the management options. The decision regarding

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the best management option was complex. She was not keen to commence carbimazole due to its risk of causing agranulocytosis, with her already-borderline neutrophil count. Her medical background is in pediatric oncology, and in her career she saw many presentations of febrile neutropenia; it was of paramount importance to her to avoid any risk of this. As endocrinologists we recognized that there is no evidence that having autoimmune neutropenia would increase her risk of agranulocytosis, and recommended starting carbimazole with close monitoring of her white cell count; however, she had read in the literature about the use of lithium in hyperthyroidism and was keen to trial this. She declined surgical thyroidectomy. On further multidisciplinary team discussion, and with the patient, lithium carbonate 400 mg daily was prescribed with the plan to definitively treat with RAI therapy when biochemically euthyroid.

Prior to having RAI therapy, however, she developed mild proptosis and lid retraction of the right eye, so RAI therapy was postponed pending ophthalmology review. They felt she had only mild thyroid eye disease in her right eye, which was slowly improving while on lithium, and required no additional treatment such as steroids.

Outcome and Follow-up

Her thyroid function steadily improved with lithium therapy over the subsequent 5 months (Table 1 and Fig. 1). The patient unilaterally opted to reduce her lithium dose as her symptoms improved (see Fig. 1). At this time, her serum fT4 started to increase, so she agreed to resume 400 mg. We monitored her serum calcium and lithium levels throughout the duration of therapy (initially weekly, then fortnightly and, once stable, monthly). Her Graves eye disease had become quiescent after a few months. She subsequently underwent RAI therapy, and lithium was discontinued 1 week later. To reduce the risk of exacerbation of thyroid eye disease following RAI, she opted to have a 6-week course of prophylactic oral prednisolone. Within 3 months of RAI, she became biochemically hypothyroid and was started on levothyroxine 100 µg daily.

Discussion

ATDs are commonly used in the medical management of thyrotoxicosis and are generally well tolerated. These medications can rarely cause agranulocytosis, a life-threatening side effect [2]. Our patient had a history of autoimmune

Table 1. Thyroid function tests, serum lithium and serum adjusted calcium over time

	Serum free T4 (12-22 pmol/L)[a]	Serum free T3 (3.1-6.8 pmol/L)[a]	Serum TSH (0.27-4.2 mIU/L)[b]	Serum lithium (0.4-1 mmol/L)[c]	Serum adjusted calcium (2.20-2.55 mmol/L)[d]	Notes
Aug. 25, 2020	82.2	—	<0.01			Presentation
Aug. 26, 2020	71.9	—	<0.01		2.34	
Aug. 27, 2020	75.8	33.1	<0.01			Lithium started
Oct. 1, 2020	87.7	24.1	<0.01		2.41	
Oct. 3, 2020	83.9	22.9	<0.01	0.1	2.33	
Oct. 5, 2020	69.1	—	<0.01	0.2	2.36	
Oct. 7, 2020	70.6	16.4	<0.01	0.4	2.52	
Oct. 9, 2020	63.8	—	<0.01	0.5	2.41	
Oct. 14, 2020	45.3	—	<0.01	0.5	2.39	
Oct. 21, 2020	36.3	—	<0.01	0.5	2.46	
Oct. 28, 2020	32.1	—	<0.01	0.6	2.41	
Nov. 4, 2020	29.5	—	<0.01	0.5	2.46	
Nov. 11, 2020	29.5	—	<0.01	0.5	2.38	
Nov. 18, 2020	27.2	—	<0.01	0.4	2.39	
Nov. 25, 2020	27.5	—	<0.01	0.5	2.43	
Dec. 9, 2020	23.2	—	<0.01	0.5	2.47	
Jan. 6, 2021	20.4	—	<0.01	0.5	2.36	
Feb. 3, 2021	16.3	—	<0.01	0.5	2.33	
March 3, 2021	20.3	—	<0.01	0.4	2.36	
March 31, 2021	27.8	—	<0.01	0.4	2.40	Radioiodine
April 26, 2021	22.1	—	<0.01			
May 12, 2021	18.1	4.2	0.01			
June 8, 2021	7.5	—	5.21		2.27	Levothyroxine started

Abbreviations: T3, 3,5,3′-triiodothyronine; T4, thyroxine; TSH, thyrotropin.
[a]Serum free T4 and T3 conversion factor 0.078 to ng/dL.
[b]Serum TSH mIU/L equivalent to uIU/mL.
[c]Serum lithium mmol/L equivalent to mEq/L.
[d]Serum adjusted calcium conversion factor 4 to mg/dL.

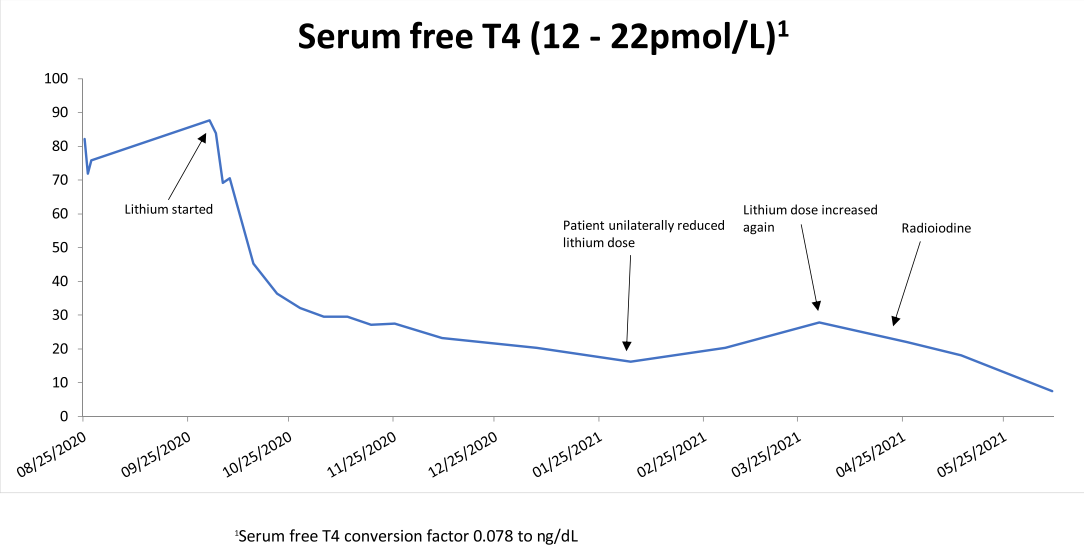

Figure 1. Serum free thyroxine (T4) over time.

neutropenia, and after counseling about the side effects she decided against having conventional ATDs, which led to the use of lithium.

There are only a few reports describing the use of lithium as monotherapy when other ATDs are contraindicated. One report described 6 cases of thyrotoxicosis treated with lithium [7]. In these cases, usual ATDs (methimazole or thyramazole) were either contraindicated due to adverse effect or ineffective in achieving euthyroidism. Each of these patients received 900 mg lithium per day and became euthyroid within 1 month prior to having definitive therapy (RAI or thyroidectomy).

A second study recruited 51 patients with Graves disease with either deranged liver function tests (LFTs) or leukopenia and started patients on lithium monotherapy for 36 weeks [8]. Patients received either 500 mg or 750 mg daily. Those with deranged LFTs were also given a hepatoprotective medication (such as diammonium glycyrrhizinate) and those with leukopenia a medication to increase white cell count (such as granulocyte colony-stimulating factor). A total of 94.0% of patients received propranolol and 37.0% steroids for symptom control. At 36 weeks there was a reported resolution in all patients' symptoms and significant improvement in thyroid function tests in both groups. After 36 weeks, lithium was stopped. At follow-up at week 52, 23.5% of patients had achieved remission, 11.8% had relapsed and restarted lithium, 49.0% had relapsed and received RAI, and 15.7% relapsed and underwent thyroid surgery. This was a small study, but supports it lithium's effectiveness at controlling thyrotoxicosis. These limited data suggest that the role for lithium is prior to definitive treatment in those in whom standard ATDs are contraindicated.

Common to these case reports is the use of high doses of lithium (up to 900 mg daily) to achieve rapid control of thyroid function. One final report used a lower dose. This was a case of a 67-year-old woman with Graves thyrotoxicosis who was started first on methimazole [9]. Her LFTs deteriorated following commencement of methimazole so the clinical team opted to switch to lithium 450 mg daily. She concurrently started hydrocortisone and propranolol. She became biochemically euthyroid in 8 days and remained on lithium monotherapy for more than 1 month prior to RAI therapy. The dose in this case was similar to ours (400 mg daily), supporting the use of a lower dose of lithium effectively. In our case we opted for a lower dose of 400 mg daily for 2 reasons: first, to avoid rapid hypothyroidism developing as this could worsen our patient's eye disease; second, our unit has minimal experience with the use of lithium in this way, which explains why we undertook more regular monitoring of thyroid function tests, calcium, and lithium levels than is usual. We anticipate using less frequent monitoring in the future. In hindsight, we could have monitored TSH-R antibody levels to measure responsiveness. The unplanned reduction in lithium dose by the patient was fortunate at least in showing that when the lithium dose is lowered, the serum fT4 began to increase again.

Furthermore, the previous case studies support lithium's use as an adjunct to RAI. A recent meta-analysis has shown lithium as adjunctive therapy is superior to RAI alone in the control of thyrotoxicosis in Graves disease [10]. The studies in this meta-analysis mostly used lithium therapy for fewer than 7 days, with the longest study using lithium for 3 weeks prior to RAI. The meta-analysis did not show a significant difference in outcomes between those treated fewer than or more than 7 days [10]. Our case suggests that if a prolonged course of lithium is needed, it is safe and equally effective as achieving rapid control.

Lithium is recognized to cause increased uptake of iodine into the gland and reduced thyroid hormone release [4]. This suggests lithium may reduce the release of T4 from the gland when stimulated by the anti-TSH-Rs as occurs in Graves disease. As an adjunct to RAI, lithium likely augments the uptake of the RAI into the gland leading to gland destruction.

There have been limited reports of the use of lithium monotherapy for the initial management of Graves disease. Our case adds to the existing literature, but also confirms that using lower doses of lithium can effectively render a patient euthyroid prior to RAI. Given the potential side effects of lithium, using a lower dose is favorable. Further reports are needed to evaluate the safety and efficacy of low-dose lithium

therapy over longer periods of time. Lithium is an important and useful option for those patients who cannot use conventional ATDs or who do not wish to have definitive therapy.

Learning Points

- Lithium is an effective medical treatment for rapid control of thyrotoxicosis
- Lithium may be used for a longer duration at a lower dose than has previously been used
- Lithium is a viable option for patients in whom conventional ATDs or definitive therapies should be avoided
- Further research on the safety and efficacy of lithium monotherapy is needed

Contributors

All authors made individual contributions to authorship. J.L., O.K., A.C., and F.A. were involved with manuscript submission; O.K. and A.C. were the primary physicians managing the patient; F.A. provided expertise and support with managing the patient. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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