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Refractory Thyrotoxicosis: Report of Two Cases and Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. Authors MSB and MSN designed the study, wrote the protocol and first draft of the manuscript. Author ARS managed the literature searches. Authors WSW and RAR managed the writing-reviewing and supervision. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Thyrotoxicosis occurs in approximately 2% of women and 0.2% of men (1) Patients with thyrotoxicosis usually present with heat intolerance, palpitations, anxiety, fatigue, weight loss, muscle weakness, diarrhea, and in women – irregular menses. Clinical findings may include tremor, tachycardia, lid lag, and goiter. Causes of thyrotoxicosis are Grave's disease, toxic multinodular goiter, thyroiditis and exogenous ingestion of thyroid hormone. In overt thyrotoxicosis, the serum value of TSH is decreased and free thyroxine (T4) or free tri-iodothyronine (T3), or both, are raised. Conventional management of thyrotoxicosis includes antithyroid drugs. (2) Very rarely, patients may be resistant to these modalities and require additional management. Refractory thyrotoxicosis is when patients do not respond to conventional treatments.

Keywords: Thyrotoxicosis; refractory thyrotoxicosis; thyroidectomy.

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1. INTRODUCTION

"In overt thyrotoxicosis the serum value of TSH is decreased and free thyroxine (T4) or free tri-iodothyronine (T3), or both, are raised. Subclinical thyrotoxicosis is defined as the presence of a persistently low serum concentration of TSH, with normal free T3 and T4 concentrations. The presence of raised serum concentrations of thyroperoxidase (TPO) antibodies indicates an autoimmune thyroid disorder and a raised Thyroid stimulating immunoglobulins (TSI) value indicates Graves' disease" [1]. The mode of treatments for thyrotoxicosis is mostly medical management with antithyroid drugs or radioactive iodine ablation. Majority of patients respond to the conventional treatments. We present two cases of overt thyrotoxicosis which were resistant to conventional management who had to undergo surgical management of total thyroidectomy.

2. CASE PRESENTATION

2.1 Case 1

Madam T, a 56 years old lady presented with hyperthyroid symptoms of easy fatigability, excessive sweating and tremor. Her thyroid function test showed free T4 of 48.8 (normal value: 12-22) and TSH of 0.018 (normal value: 0.274.2). She was then started on oral Carbimazole 10mg OD. Her TFT normalised after one month (T4 17.1, TSH <0.08). However she developed allergic reaction of urticaria and periorbital swelling to carbimazole. Her symptoms then recurred (TFT: T4 100 TSH <0.08). Her medication was changed to oral PTU 100mg BD, but unfortunately she developed worsening transaminitis secondary to the PTU. (LFT: ALT 44>845, AST 40>808, ALP 261>579). At this juncture, she was diagnosed as having refractory thyrotoxicosis and was then started on oral Prednisolone 40mg OD, oral Propranolol 40mg TDS, and Cholestyramine 4g TDS. She was then referred for total thyroidectomy and started on Lugol's iodine 10 drops TDS where her best TFT preoperatively showed improvement to TSH <0.01 T4 34.01. Finally the patient underwent total thyroidectomy a few weeks later and histopathological findings came back as nodular hyperplasia.

2.2 Case 2

Madam S, a 52 years old lady with underlying schizophrenia and neurofibromatosis was diagnosed with hyperthyroidism since March 2020. Her initial presentation was palpitations, diarrhoea and hand tremors. At that time, her TFT showed T4 of 80.7 and TSH of <0.01. Ultrasound neck done showed multiple nodules, heterogeneous, normal vascularity, with no retrosternal extension. She was then started on oral Carbimazole 40mg BD. However, despite being compliant to her medications, her TFT worsened (TSH <0.001, T4 80.7). Her thyroid medication was then changed to oral Methimazole 30mg BD, but unfortunately again she became resistant to the medication. TFT at this time showed TSH <0.01 T4 62.4. She was then diagnosed with refractory thyrotoxicosis and subsequently started on oral Prednisolone 15mg BD and Propranolol 20mg BD. However her hyperthyroid symptoms persisted. She was then referred for total thyroidectomy, and oral Lithium 300mg BD was given and completed for three days. Her best TFT preoperatively showed TSH <0.01 T4 5.39. The patient underwent total thyroidectomy and histopathological findings came back as nodular hyperplasia.

3. DISCUSSION

"Conventional management of thyrotoxicosis includes antithyroid medications. Adjunctive treatments include beta-blockers, corticosteroids and inorganic iodide (Lugol's iodine). Beta-blockers and high-dose glucocorticoids-inhibit the peripheral conversion of T4 to T3. Lugol's iodine reduces T3 and T4 by increasing iodine uptake and inhibiting the enzyme thyroid peroxidase, thus attenuating oxidation and organification of thyroid hormones" [2]. "Refractory cases have mostly shown resistance to high-dose thionamides and beta-blockers" [3]. "Rarely resistance to iodine has also been reported in amiodarone-induced thyrotoxicosis" [4].

The management of refractory thyrotoxicosis involves evaluating patient's compliance to medications, and also to rule out malabsorption problems. One of the investigations proposed for this purpose is to measure the drug levels. Measurement of anti-drug antibodies is also suggested as well as iodine measurement of urinary iodine excretion to evaluate iodine contamination [5].

"The definitive treatments for refractory thyrotoxicosis are surgery or radioactive iodine ablation. However, the first step is to achieve euthyroid state prior to surgery to minimize potential complications such as thyroid storm" [6].

All elective surgery should be postponed until euthyroidism or near euthyroid state is achieved.

"In patients who are hyperthyroid and require urgent surgery, rapid control with high dose methimazole or PTU, B-blockers, Lugol's iodine and glucocorticoids are recommended" [7]. "Prednisolone added to antithyroid drugs, has been successfully used to achieve euthyroid state in patients with resistant thyrotoxicosis" [1] and has been tried on both of our patients. It is useful for rapid pre-operative preparation of uncontrolled, resistant thyrotoxicosis.

"Cholestyramine, a bile acid sequestrant has also shown to cause a dramatic decline in serum thyroid hormone levels in Graves associated thyrotoxicosis resistant to conventional treatment" [8]. Cholestyramine works by binding to thyroid hormone in the intestine and decreases their reabsorption [9-11]. We used this drug in our first patient Madam T and managed to lower down her FT4 levels.

"Radioactive iodine ablation of ^{131}I is an effective definitive treatment option for Graves thyrotoxicosis. Retrospective data show that 80-90% will become euthyroid within 8 weeks after a single dose of ^{131}I" [8].

"Last but not least, charcoal plasma-perfusion and plasmapheresis have been used successfully to remove circulating thyroid hormone in a few thyroid storm patients who have failed more conventional therapy" [12]. "Nevertheless it should only be considered for patients in thyroid crisis who have exhausted other therapies and still continue to deteriorate" [13].

4. CONCLUSION

The two patients were resistant to conventional managements including beta-blockers and anti-thyroid drugs. Radioactive iodine or surgery is the definitive modes of treatment in such complex cases. Preoperative thyrotoxicosis is a potentially life-threatening condition that requires medical intervention before surgery. Iodine and steroids can be used if rapid preparation is required or more severe thyrotoxicosis is present. Cholestyramine and lithium can also be used to prepare patients for definitive treatments. The goal of therapy is to render the patient as close as possible to clinical and biochemical euthyroidism before surgery in order to ensure successful outcomes.

CONSENT

As per international or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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