Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign):
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter:
Date of report submission: 9 March 2022

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: Resistant thyrotoxicosis

Case history:

A 42-year-old lady was suffering from relapsing Graves' thyrotoxicosis since 2006. She refused radioactive iodine and defaulted follow up since 2010. She attended emergency department due to febrile illness in 2014. She was found to have hyperthyroidism and thus was restarted on carbimazole. She defaulted follow up again since 2017.

She was diagnosed with breast cancer with neo-adjuvant chemotherapy without immunotherapy given. She was found to have relapse of thyrotoxicosis during pre-operative assessment for mastectomy with free T4 (fT4) 50.1 pmol/l (12-22) and thyroid stimulating hormone (TSH) <0.01 mIU/l (0.27-4.2).

She was referred to our medical unit for early assessment. However, she defaulted appointment and was first assessed in October 2021. She had mild tremor and palpitation and was resumed on carbimazole 10mg twice daily in October 2021. ECG revealed sinus tachycardia and propranolol was initiated. Left mastectomy was scheduled in December 2021. Early follow up was arranged with aim to render biochemical euthyroid before operation.

On follow up in November, patient remained hyperthyroid with fT4 36

pmol/L (7.9-14.4) and TSH <0.03 mIU/L (0.38-0.53). Carbimazole was stepped up to 30mg daily.

She was followed up two weeks later with fT4 mildly improved 30.2, T3 6.9 pmol/L and TSH <0.03 mIU/L, thus carbimazole was further stepped up to 20mg twice daily.

Operation was postponed in view of thyrotoxic state. Echocardiogram was done in December 2021 showing normal left ventricular systolic function with Grade I diastolic dysfunction.

Despite on carbimazole 20mg twice daily, she remained thyrotoxic with fT4 rising trend to 49.6 pmol/L and TSH <0.03 mIU/L despite good drug compliance. Thyrotoxic symptoms worsened including sweaty palm, palpitations, hand tremor and heat intolerance. In view of need for semi-urgent operation, carbimazole was further stepped up to 40mg twice daily for rapid normalization of thyroid function. Cholestyramine 4g twice daily was added after explanation of possible gastrointestinal upset.

On follow up two weeks later, her thyrotoxic symptoms improved with mild palpitation and sweating. She tolerated carbimazole and cholestyramine. Latest thyroid function test showed fT4 40.3 pmol/L and TSH <0.03 mIU/L. She was diagnosed as anti-thyroid drug resistant thyrotoxicosis as she remained thyrotoxic despite putting on maximal carbimazole and cholestyramine.

She was clinically admitted for further management for resistant thyrotoxicosis. Her medications were further titrated up to carbimazole 40mg thrice daily, cholestyramine 4mg thrice daily and Inderal 20mg thrice daily. Lithium 400mg daily and prednisolone 20mg daily were added. Lugol's iodine was not started due to risks of escape phenomenon, rebound thyrotoxicosis and uncertainty of adequate ATD blockade effect in ATD resistance thyrotoxicosis patient.

fT4 further elevated at 49.6 pmol/L and fT3 was 8.3 pmol/L (3.8-6.0). Anti-TG and anti-TPO were normal while anti-thyroid-stimulating-hormone-receptor antibody (anti-TSH-R) was elevated 2.4 IU/l (<1). Ultrasound thyroid showed normal thyroid parenchymal echotexture with no focal thyroid lesion detected. She remained hemodynamically stable. In view of thyrotoxicosis state, mastectomy was delayed. Endocrine surgeon was contacted and agreed for total thyroidectomy and left mastectomy in same session. She was kept on same dose cholestyramine, lithium and prednisolone upon discharge. Carbimazole was tailed down to 40mg twice daily.

Upon follow up, fT4 was decreased with latest value 28.7 pmol/L and

thyrotoxic symptoms subsided. Lithium was stopped.
She was admitted for left mastectomy and thyroidectomy. Inderal was stepped up to four times daily. Lugol's iodine 0.3ml thrice daily was initiated before operation. Intravenous hydrocortisone was given pre-operatively for stress cover. Carbimazole, Lugol's iodine and cholestyramine were signed off after total thyroidectomy and mastectomy. Recurrent hypocalcemia noted with calcium and vitamin D supplements given. Thyroxine supplement was commenced. She was discharged and plan for early follow up for thyroid function and calcium level.

Discussion and literature review

Hyperthyroidism is a common disease and most patients responded well to conventional anti-thyroid drugs. However, a small proportion of patients are resistant to conventional treatments. Drug compliance must be explored before diagnosis of true resistant thyrotoxicosis. Possible mechanisms of resistant hyperthyroidism include malabsorption of drug, rapid metabolization of drug, anti-drug antibodies, impairment of intra-thyroidal drug accumulation or action and predominant elevation of T3 rather than T4 levels. [1] In resistant thyrotoxicosis, second line treatments including cholestyramine, prednisolone and lithium may be considered.

Thyroid hormones are mostly metabolized in the liver by conjugation to glucuronides, which are subsequently excreted via bile and enter the enterohepatic circulation. Cholestyramine is an ion exchange resin currently approved for management of hyperlipidemia. It also interfered with the absorption of ingested thyroid hormone. Cholestyramine can act rapidly and reduce thyroid hormone levels in patients with Graves' hyperthyroidism. It can an effective and well-tolerated second line treatment together with thionamides. [2] Thyrotoxicosis has been inadequately controlled in this case despite adding cholestyramine to carbimazole.

Rapid reduction in serum thyroid hormone concentration has been noted after initiation of corticosteroids. [3] Resistant thyrotoxicosis had been

successfully controlled with corticosteroids. [4] Mechanisms of action had been postulated to be multifactorial. Corticosteroids inhibit the conversion of thyroxine to active triiodothyronine in the peripheral tissue and block the release of thyroxine from the thyroid. Graves' disease is an autoimmune disease with cell-mediated and antibody-mediated actions. In this case, anti-TSH-R was elevated thus corticosteroids can quickly control the hyperthyroidism by its immunosuppressive effect.

Lithium is noted to be an alternative for controlling thyrotoxicosis in resistant thyrotoxicosis since 1970s. Lithium inhibits the release of thyroid hormones and inhibits the synthesis of thyroid hormones. Lithium rapidly control hyperthyroidism and can maintain euthyroid state for up to 6 months in a study investigating eleven patients with a long history of Graves' disease received lithium for 6 months as the sole therapy. [5] Thyrotoxic patients pending definitive treatment who are contraindicated or resistant to thionamides were initiated on lithium in a local study.[6] A satisfactory response, as defined by a fall by 40% or more in fT4 levels and clinical improvement, was achieved in twelve out of thirteen patients within 1 to 5 weeks. A high rate of relapse has been noted after discontinuation of lithium therapy; thus lithium should only be used with the intention to prepare for definitive treatment.

In cases of resistant hyperthyroidism, definitive treatment with either radioactive iodine or total thyroidectomy is preferred early. It is crucial to render patient euthyroid before definitive treatment of thyrotoxicosis to prevent the risk of precipitating thyroid crisis.

Pre-operative management for uncontrolled hyperthyroidism with Lugol's iodine has been advocated. Lugol's iodine increased thyroidal iodide uptake, inhibits thyroid peroxidase which attenuates iodine oxidation and organification, and blocks the release of thyroid hormones. Lugol's iodine significantly reduced plasma thyroid hormone levels and heart rate. [7] Escape phenomenon from the acute Wolff-Chaikoff effect is expected in commencing iodine. It is associated with the decrease in thyroid sodium / iodide symporter activity, thus resulting in a decrease in intra-thyroid iodide concentration. There is a therapeutic window between achieved euthyroidism and escape phenomenon. In a case report with inadvertent prolonged use of iodine, exacerbation of the manifestation of thyrotoxicosis was noted after about 30 days. [8] According to literature

review [9], most of the pre-operative use of Lugol's iodine are for urgent preparation for thyroidectomy in uncontrolled thyrotoxicosis and failed medical therapy, rebound of thyrotoxicosis is not concerned in post-thyroidectomy case.

In summary, this is a case illustrating the use of second line treatment of hyperthyroidism after failure of thionamides. Thyrotoxicosis persisted despite second line treatments, including cholestyramine, corticosteroids, and lithium, have been initiated. Lugol's iodine has thus been used as rescue pre-operative therapy before definite treatment with total thyroidectomy. Surgery was uneventful and patient was now on thyroxine supplement and regular follow up.

Tables and figures (where applicable) (no more than two figures)

Reference (not more than 10)

1. Li H, Okuda J, Akamizu T, Mori T. A hyperthyroid patient with Graves' disease who was strongly resistant to methimazole: investigation on possible mechanisms of the resistance. Endocr J. 1995;42(5):697-704.
2. Tsai WC, Pei D, Wang TF et al: The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. Clin Endocrinol (Oxf), 2005; 62(5): 521–24
3. Ozawa Y, Daida H, Shimizu T, Shishiba Y. Rapid improvement of thyroid function by using glucocorticoid indicated for the preoperative preparation of subtotal thyroidectomy in Graves' disease. Endocrinol Japon 1983; 30: 93-100.
4. Jude EB, Dale J, Kumar S, Dodson PM. Treatment of thyrotoxicosis

resistant to carbimazole with corticosteroids. Postgrad Med J. 1996;72(850):489-491.
5. Lazarus JH, Richards AR, Addison GM, Owen GM. Treatment of thyrotoxicosis with lithium carbonate. Lancet. 1974;2(7890):1160-1163.
6. Ng YW, Tiu SC, Choi KL, et al. Use of lithium in the treatment of thyrotoxicosis. Hong Kong Med J. 2006;12(4):254-259.
7. Calissendorff J, Falhammar H. Rescue pre-operative treatment with Lugol's solution in uncontrolled Graves' disease. Endocr Connect. 2017;6(4):200-205.
8. Leuştean L, Preda C, Ungureanu MC, et al. Jod-Basedow effect due to prolonged use of lugol solution-case report. Rev Med Chir Soc Med Nat Iasi. 2014;118(4):1013-1017.
9. Hope N, Kelly A. Pre-Operative Lugol's Iodine Treatment in the Management of Patients Undergoing Thyroidectomy for Graves' Disease: A Review of the Literature. Eur Thyroid J. 2017;6(1):20-25.

No of words in Case History and Discussion (excluding references):___1241_____

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

_____

(signature of Trainee)

Endorsed by Supervisor *

_____

(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise

Trainees whether further amendments are necessary, review the Originality/Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.