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Case report

Drug-resistant Graves' disease complicated by hypertension and heart failure: a case report and literature review

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Abstract

Background: Thyrocardiac disease, a severe complication of hyperthyroidism, can lead to life-threatening cardiac manifestations such as congestive heart failure, arrhythmias, and pulmonary hypertension. While most patients respond to medical therapy, a subset remains refractory, necessitating alternative interventions.

Case Presentation: A 37-year-old female presented with an 11-month history of weight loss, palpitations, and fatigue. Clinical and laboratory findings confirmed thyrotoxicosis and Class IV congestive heart failure. Despite maximal medical therapy with carbimazole, beta-blockers, diuretics, and other medications, her symptoms persisted with recurrent cardiac failure. She underwent left total and right subtotal thyroidectomy. Postoperatively, the patient developed supraventricular tachycardia and acute pulmonary edema, which were successfully managed with intensive care. At three months post-surgery, thyroid and cardiac parameters had normalized**.**

Conclusion: This case highlights the challenges of managing treatment-refractory thyro-cardiac disease in a resource-constrained environment and underscores the importance of early surgical intervention. A multidisciplinary approach is critical for optimizing outcomes in this high-risk population.

Keywords: Drug resistance, Graves' disease, thyro-cardiac, thyroidectomy, congestive cardiac failure.

Introduction

Hyperthyroidism has a prevalence ranging from 0.4 to 2.5% in iodine sufficient parts of the world, the most common cause being Graves' disease (70–80% of cases), followed by solitary toxic adenoma and toxic multinodular goitre(1,2), Drug-resistant thyrotoxicosis is

defined as failure to achieve biochemical control despite being on optimal dosages of anti-thyroid medication for at least 4-6 months. It occurs in approximately 5-10% of cases (3). Thyro-cardiac disease covers the spectrum of cardiovascular manifestations induced by thyrotoxicosis, including atrial fibrillation, heart failure, and cardiomyopathy, which develop in up to 27% of thyrotoxic patients, with prognosis significantly worsened when resistance to antithyroid drugs occurs (4,5).

This report aims to describe the management challenges and outcomes of a patient with drug-resistant thyrocardiac disease in a resource-constrained environment. It also examines current evidence on the aetiology, pathophysiology, and advanced management strategies of this condition.

Case Report

Patient information

A 37-year-old female caterer was seen in the surgical outpatient clinic with an 11-month history of weight loss, increased appetite, easy fatigability, menstrual irregularity, and darkening of complexion.

Clinical findings

Examination revealed an anxious-looking patient with a resting pulse rate of 120/min, which was regular and of moderate volume. Blood pressure was 170/95 mmHg, and the apex beat was at the 6th left intercostal space, anterior axillary line. First, second, and third heart sounds were audible. There was an anterior neck swelling measuring 8cm x 7cm. It was firm, non-tender, and mobile on swallowing but not on tongue protrusion. Trachea was central with no evidence of retrosternal extension. There was marked bilateral exophthalmos, lid lag, and lid retraction. There was marked facial hyperpigmentation in comparison with the rest of the body.

Diagnostic assessment

The following investigations were carried out: Hb-12.7 g/dl, WBC-5.04 x 10^9/l, Neutrophils-48.3%, Lymphocytes-39.7%, Monocytes-12.0%, Platelets-156 x10^9/l, Fasting blood sugar-3.9 mmol/l, Na+-138.7 mmol/l, K^+-4.4 mmol/l, Urea-7.5mmol/l,Creatinine-105.6mmol/l, Bicarbonate-28.2 mmol/l, Chloride-99.9 mmol/l, Total Protein-65.5 g/l, Albumin-30.9 g/l, T3-14.5 pmol/l, T4-20.4 pmol/l, TSH-<0.005 mIU/l.
Thyroid ultrasound scan showed a left thyroid lobe measuring 4.7 x 2.6 x 3.5cm with a volume of 21.4ml and a right thyroid lobe measuring 4.4 x 2.7 x 4.4cm with a volume of 25.5ml.
The electrocardiogram showed a prolonged P wave, QS wave in lead V1, poor R wave progression in V2 and V3, premature ventricular contraction bigeminy, left ventricular hypertrophy, and T wave abnormality (Figure 1).

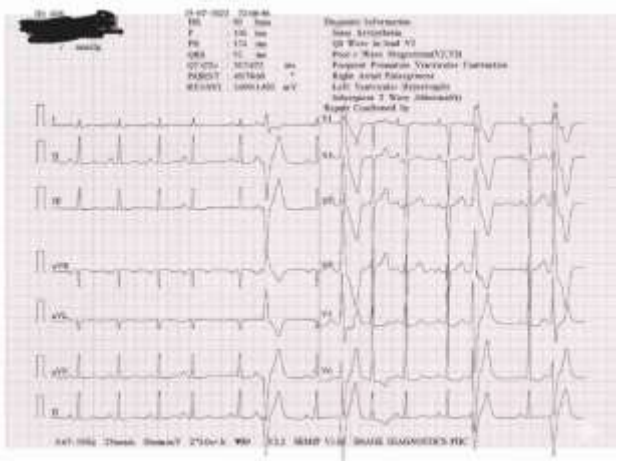

Figure 1: Electrocardiogram showing prolonged P wave, QS wave in lead V1, poor R wave progression in V2 and V3, premature ventricular contraction bigeminy, left ventricular hypertrophy, and T wave abnormality.

Echocardiogram showed hypertensive dilated cardiomyopathy with pulmonary hypertension and left intracardiac clot (Figure 2).

A diagnosis of thyrotoxicosis with New York Heart Association (NYHA) Class IV congestive

cardiac failure and hypertension was made, and multidisciplinary management by surgeon, cardiologist, and anesthesiologist was commenced.

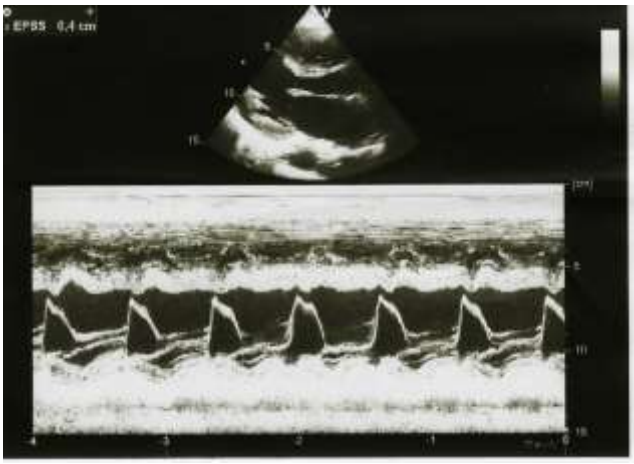

Figure 2: Echocardiogram showing hypertensive dilated cardiomyopathy with pulmonary hypertension and left intracardiac clot.

Therapeutic interventions (Table 1)

The patient continued on treatment for seven months with intermittent resolution of cardiac failure. T3 and T4 levels remained elevated despite use of a maximal carbimazole dosage of 90 milligrams daily (Figure 3).

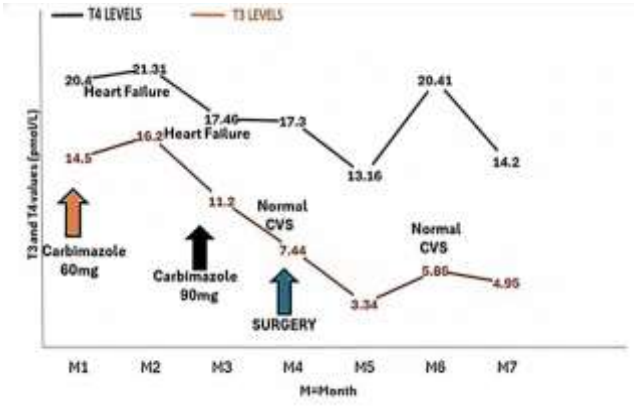

Figure 3: Graph showing T3 and T4 levels over 7 months.

In view of the non-availability of alternative drugs like propylthiouracil, Lugol's iodine, lithium, and cholestyramine, a decision was taken to undertake surgery due to gradually worsening episodes of cardiac failure. This was scheduled for a cardiac failure-free interval and was performed under general anesthesia. After measuring and recording basal blood pressure, heart rate, and arterial oxygen saturation, 1 mg of midazolam was administered to the patient before induction of anaesthesia. She received propofol 1.5 mg/kg in a loading dose, followed by 75 mcg/kg/min and fentanyl 100 micrograms admixture in an infusion. Tracheal intubation was facilitated with succinylcholine 1.5 mg/kg, while atracurium was used for the maintenance of muscle relaxation. She had left total and right subtotal thyroidectomy, preserving approximately 1/8th of the right thyroid gland.

Anaesthesia and surgery were uneventful, and the patient was transferred to the recovery room. Postoperatively, she developed supraventricular tachycardia with pulse rate rising to 244/min, fever (37.9 °C), and blood pressure fluctuation. Acute pulmonary oedema with oxygen desaturation, cough, and expectoration of pink, frothy sputum also supervened. Burch-Wartofsky Score (9) was assessed at 80, and she was placed on 100% oxygen via a non-rebreather mask with intravenous frusemide 100mg stat given to commence treatment of acute pulmonary oedema. She was later placed on mechanical ventilation and weaned off after the third day. The cardiologist reviewed the patient, and intravenous Furosemide 60mg 12 hourly was added to the guideline prescribed drugs, earlier used.

She remained oxygen dependent with alternating bradycardia and tachycardia until the 5th post-operative day when she was gradually weaned off oxygen, achieving and maintaining an oxygen saturation of 95% on room air by the 8th post-operative day. The patient was discharged home on the 10th post-operative day with all vital signs normal.

Follow-up and outcome

Review in the surgical outpatient clinic 3 months after surgery revealed the following parameters: The weight was now 71 kilograms from an initial weight of 61 kilograms. Pulse rate 81/min. BP 135/75 mm Hg. Electrocardiogram - Sinus rhythm, normal QRS complex, normal QRS axis, normal T wave, isoelectric ST segment, and no pathologic Q waves. Echocardiogram - Eccentric left ventricular hypertrophy, no regional wall motion abnormality, mildly thickened mitral valve, but all other valves are normal. No intramural thrombi present, Serum T3-4.95 pmol/l, serum T4-14.2 pmol/l.

Table 1: Medications used in the management of the patient, including dosages, mechanisms of action, and guidelines governing use

Drug	Dosage and Frequency	Indication	Mechanism of Action	Comments	Guidance
Carbimazole	30 milligrams thrice daily.	Alleviation of thyrotoxicosis.	Converted to methimazole in the body and then inhibits thyroid peroxidase to block T_3 and T_4 production.	Agranulocytosis is the major side effect, though rare.	American Thyroid Association [6]
Propranolol	40 milligrams twice daily.	Heart rate control and management of atrial fibrillation.	Beta blockade, inhibition of the conversion of T_4 to T_3	Risk of acute circulatory collapse and worsening of failure. Careful assessment is necessary. Activity may be reduced by increased breakdown due to a hypermetabolic state.	European Society of Cardiology (ESC) [7]
Amlodipine	10 milligrams daily.	Treatment of hypertension.	Calcium channel blockade, vasodilatation	Oedema, dizziness, palpitation and fatigue may occur.	European Society of Cardiology (ESC) [7]
Telmisartan	80 milligrams daily.	Treatment of hypertension.	Renin Angiotensin Aldosterone System inhibition	Hyperkalaemia, dizziness, hypotension, and renal impairment may occur.	European Society of Cardiology (ESC) [7]
Spironolactone	25 milligrams daily.	Treatment of hypertension.	Mineralocorticoid receptor antagonist.	Hyperkalaemia, Hyponatriaemia. Severe allergic reactions may occur.	European Society of Cardiology (ESC) [7]
Digoxin	0.5milligram daily	Rate control in heart failure and atrial fibrillation.	Na^+/K^+ ATPase inhibition in cardiac muscle	Efficacy is reduced by the up regulation of the sodium potassium ATPase	European Society of Cardiology (ESC) [7]

				caused by elevated thyroid hormone. Narrow therapeutic window.	
Rivaroxaban	2.5 milligrams daily	Treatment and prevention of stroke, deep vein thrombosis, and pulmonary embolism.	Selective and competitive inhibitor of Factor Xa	Stop medication 2 days before major surgery.	European Society of Cardiology (ESC) [7]
Bromazepam	3 milligrams twice daily	Alleviation of symptoms of anxiety.	Central nervous system depressant. Potentiates the action of G-Aminobutyric Acid (GABA)	Dependence, Tolerance and withdrawal symptoms may occur with long-term use.	American Thyroid Association [6]
Omeprazole	40 milligrams daily.	Control of hyperacidity.	Proton pump inhibitor.	May impair L-Thyroxine absorption.	National Institute for Health and Care Excellence (NICE) [8]

Discussion

The management of refractory thyrotoxicosis in the presence of significant cardiac manifestations presented a formidable clinical challenge in this patient. The case shows the limitations of medical therapy in severe cases and demonstrates the importance of definitive surgical treatment in a resource-poor environment. There are several reasons why drug treatment proved unsuccessful in this patient. These include late recognition of symptoms, late presentation in hospital, and the non-availability of credible drug alternatives such as propylthiouracil. The mechanism of speculated treatment resistance in this case remains unclear. Drug non-compliance was ruled out because the patient was required to bring along her drugs to each visit for checking. We postulate that persistent high titers of TSH-receptor antibodies (TRAb) could have caused thyroid hyperstimulation that overwhelmed conventional antithyroid drugs (9). This could not be confirmed due to the non-availability of facilities for the TRAb assay. Impaired drug absorption, accelerated drug metabolism due to her hypercatabolic state, and abnormalities in the accumulation or intrathyroidal action of carbimazole are other possible mechanisms of treatment failure (10).

The profound cardiac complications observed in this patient are a direct consequence of the genomic and non-genomic effects of thyroid hormone, which act together to create a vicious cycle. Genomic effects result from long-term exposure to T3 and T4, which remodel the heart via alpha-myosin heavy chain(αMHC), Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase isoform 2a (SERCA2a), and Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels. These cause the heart to become hyperdynamic and prone to fast rhythms. Non-genomic effects occur concurrently and include vasodilatation, low systemic vascular resistance (SVR), and direct ion channel stimulation, which force the heart to operate at maximum capacity continuously. This level of work cannot be sustained indefinitely, and (6,7)

heart failure occurs, manifesting as a high-output state from reduced SVR and subsequent Renin-Angiotensin-Aldosterone System (RAAS) activation, or as a tachycardiomyopathy from sustained tachycardia impairing diastolic filling and causing oxidative stress (6,11). A hypercoagulable state due to activation of factors VIII, IX, and von Willebrand factor is usually present in most patients with established atrial fibrillation.6 Though these clotting factors were not assayed in our patient, the presence of an intracardiac clot on echocardiography requiring anticoagulation with rivaroxaban is strongly suggestive of their activation and elevation.

A comprehensive search of the literature (Table 2, annexed) revealed that 23 cases have been documented worldwide before our report, 21 were female (91.3%), and 2 were male (8.7%). The mean age was 36.09 years while the median was 31.5years. The maximum age was 68 years, and the minimum age was 14 years, making the age range 54 years. The aetiology of hyperthyroidism was Graves' disease in 14 (60.9%) patients, unspecified in 5(21.7%) patients, toxic multinodular goiter in 1(4.3%), and Amiodarone-induced in 1 case (4.3%). A multimodal preparatory regimen was used in most of these patients, consisting of hormonal blockade with high-dose anti-thyroid drugs (carbimazole, methimazole, or propylthiouracil), peripheral T4 to T3 conversion inhibition with dexamethasone, prednisolone, or hydrocortisone, and hormone release inhibition with Lugol's iodine or lithium. Enterohepatic recirculation disruption with cholestyramine to reduce hormone reabsorption was also used in 2 cases (8.7%).

Lugol's iodine, lithium, and cholestyramine were not available for use in the index patient.

Definitive treatment was thyroidectomy in 14 (60.9%) patients and radioactive iodine ablation (RAIA) in 3 (13%) others. Steroid therapy was used in 16 (69.6%) patients either for control of hormone levels pre-operatively or as an adjunct to RAIA. We did not use steroids in our patient because of the potential to worsen heart failure (7). An interesting feature is the use of Anemarrhena Bunge extract for adjunctive and definitive treatment of thyrotoxicosis in one patient (21). This will obviously require further study to assess efficacy.

A review of reported cases shows our patient to be the third such report from Africa, (3) and the only case in which the patient was treated for 3 severe co-morbidities viz thyrotoxicosis, hypertension, and cardiac failure. This triad highlights the complications that may arise from late presentation as well as the challenges resulting from the combination of several different medications. Control of tachycardia and atrial fibrillation by propranolol was made difficult by increased drug breakdown from hyperthyroidism, which also increased renal clearance of digoxin, causing a relative reduction of efficacy. As control of thyroid hormone levels was achieved, the dose of digoxin was reduced to prevent toxicity (28). Spironolactone may interfere with digoxin excretion and trigger toxicity. In concert with Telmisartan, it may also cause significant hyperkaliemia, thus worsening cardiac failure (29). Close monitoring of our patients' electrolyte status was thus necessary and was done daily. Bradycardia and hypotension were other potential complications of multiple drug therapy that required increased alertness on our part.

Emerging Therapies

For cases where surgery is high-risk or is refused by the patient, Therapeutic Plasma Exchange (TPE) provides rapid reduction of thyroid hormones and antibodies and serves as a bridge to definitive therapy (30). Immunomodulatory therapies include Teprotumumab, which is an IGF-1R monoclonal antibody that reduces TRAb in Graves' disease, improving ophthalmopathy and other symptoms (31). Rituximab is a CD20-targeted drug that depletes B-cells and reduces antibody production, with studies showing up to 60% response (10,32,33). Gene therapy using

Thyroid Stimulating Hormone Receptor (TSHR) silencing RNA nanoparticles has been found to produce more than 70% receptor knockdown in murine Graves' disease models (34).

Limitations of the study

This report is limited by the absence of a TRAb assay, the unavailability of alternative drugs such as propylthiouracil, adjunctive medications such as Lugol's iodine, cholestyramine, and lithium, as well as radioiodine, which may have influenced management decisions. Facilities for monitoring drug levels were also nonexistent.

Conclusion

Thyrocardiac disease remains a challenging condition, especially in patients refractory to medical therapy in situations where alternative drugs are not available. This case highlights the need for prompt recognition of drug resistance as well as early and decisive surgical management, which can be life-saving, particularly in low-resource settings. It also underlines the challenges that may arise from multiple drug therapies and interactions. Improvisation and development of therapies effective in resource-challenged environments should also be a priority.

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Ethical considerations

Written informed consent was obtained from the patient for publication of this case report and accompanying images. The study was approved by the Research Ethics Committee of Bayelsa Medical University. Ethical Approval number: BMU/REC/264/25.

Data availability statement

The data that support the findings of this study are available from the corresponding author (AAD), upon reasonable request.

Conflicts of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. No potential conflict of interest relevant to this article was reported.

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Annex 1:

Table 2: Published case reports of drug resistant thyrotoxicosis

Author	Year	Age	Sex	Etiology	Resistance To	Steroid	Other Tx	Effective Tx
EB Jude [12]	1995	46	F	NA	CBZ 60 mg	Prednisolone	NA	Prednisolone and RAIA
EB Jude [12]	1995	30	F	NA	CBZ 30 mg	Prednisolone	NA	Prednisolone and RAIA
Hua Li [13]	1995	23	F	NA	MMZ 20 mg	NA	PTU	Thyroidectomy
Sebastian-Ochoa [14]	2008	32	F	Graves	MMZ 60mg	Dexamethasome	Lugols and Cholestyramine	Cholestyramine + Thyroidectomy
Taimur Saleem [15]	2011	50	F	Graves	CBZ 90 mg and PTU	Prednisolone	Lithium	Lithium and Prednisolone
Yeoree Yang [16]	2015	40	F	Graves	MMZ 45mg		Cholestyramine	Cholestyramine
S. Ahmad [17]	2015	54	F	Graves	CBZ 60 mg	NA	Lugols Iodine	Thyroidectomy and Lugols Iodine
Seung Byung Chae [18]	2016	22	F	Graves	MMZ 20 mg	Hydrocortisone	PTU	Thyroidectomy
R Ramtahal [19]	2016	40	F	Graves	CBZ 80 mg	NA	PTU	PTU
Dinesh Nagi [20]	2016	NA	M	Factitious	CBZ 60mg	Prednisolone	NA	Thyroidectomy
Jiman Kim [21]	2018	29	F	NA	MMZ100 mg	NA	Anemarrhena Bunge	Anemarrhena Bunge
Anastasia Linardi [22]	2018	27	F	Graves	CBZ and PTU	Prednisolone	NA	Prednisolone
Ngoné Diaba Diack [3]	2020	22	F	Graves	CBZ 80 mg, MMZ 40 mg and PTU 800 mg	Prednisolone	Lugols iodine	Thyroidectomy
Ngoné Diaba Diack [3]	2020	19	F	Graves	CBZ 60 mg	NA	Lugols iodine	Thyroidectomy
Krzysztof Lewandowski [23]	2021	56	M	Amiodarone induced	MMZ 40 mg	Prednisolone	IV MMZ	Thyroidectomy
Yusaku Mori [24]	2021	14	F	Graves	MMZ 120 mg	Dexamethasome	Lithium Carbonat	Thyroidectomy

							e 800mg	
A.B.M. Kamrul Hasan [25]	2022	18	F	Graves	CBZ 75 mg	Prednisolone	NA	RAIA
S Lee [26]	2022	31	F	NA	CBZ 80 mg and PTU 1000 mg	Prednisolone	NA	Thyroidectomy
S Lee [26]	2022	43	F	Graves	CBZ 80 mg	Prednisolone	PTU	PTU
S Lee [26]	2022	31	F		CBZ 120 mg	NA	PTU	Thyroidectomy
Fateen Ata [10]	2023	34	F	Graves	CBZ 60 mg PTU 450 mg	Prednisolone		Thyroidectomy
Renzu [27]	2024	68	M	Graves	MMZ 60 mg		Lugol's iodine	Thyroidectomy
Renzu [27]	2024	65	F	Multinodular goitre	MMZ 120 mg	Dexamethasone	Lugol's iodine	Thyroidectomy