CASE REPORT

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A Rare Coexistence of Thyrotoxic Cardiomyopathy and Asthma in Graves' Disease: Clinical Challenges and Management Strategies: A Case Report

Mutiara Lirendra[1], Eva Niamuzisilawati[2], Ega Caesaria[2], Brilliant Van Fitof[2], A Farih Raharjo[3], Adi Bestara[4]

[1]Resident of Internal Medicine, Dr. Moewardi General Hospital / Sebelas Maret University Surakarta, Indonesia
[2]Division of Endocrinology, Diabetes, and Metabolic Diseases, Dr. Moewardi General Hospital / Sebelas Maret University Surakarta, Indonesia
[3]Division of Pulmonology, Dr. Moewardi General Hospital / Sebelas Maret University Surakarta, Indonesia
[4]Division of Cardiovascular Diseases, Dr. Moewardi General Hospital / Sebelas Maret University Surakarta, Indonesia

***Corresponding Author:**
Eva Niamuzisilawati. Division of Endocrinology, Diabetes, and Metabolic Diseases, Dr. Moewardi General Hospital / Sebelas Maret University Surakarta, Indonesia
Email: xxx

ABSTRACT

Graves' disease is the most common autoimmune hyperthyroid disorder. Thyrotoxic cardiomyopathy (TCM) is a rare but potentially lethal complication of thyrotoxicosis, with an incidence of <1%. Beta-blocker is one of the drugs of choice in treating TCM. However, in asthma patient, beta-blocker may induce bronchoconstriction. We report a rare case of a 36-year-old male presented with complaints of shortness of breath, wheezing, cough, and palpitation. The patient had a history of asthma. Physical examination revealed diffuse thyroid enlargement, exophthalmos, tremor, cardiomegaly, irregular heart sounds, rales, wheezing in both lungs, and BMI was underweight. Wayne index was 20 (hyperthyroid) and Burch Wartofsky score was 35 (impending storm). Laboratory results showed low Thyroid-stimulating hormone level and high level of Free-T3, Free-T4, Thyroid-Stimulating Hormone Receptor Antibodies, and N-terminal pro-B-type natriuretic peptide. Chest X-ray showed cardiomegaly. electrocardiogram showed atrial fibrillation RVR. Echocardiography showed segmental wall motion abnormality EF 48%. Patient was diagnosed with Graves' disease with hyperthyroidism, acute asthma exacerbation, Heart failure with mildly reduced ejection fraction NYHA III due to thyrotoxic cardiomyopathy. Patient was treated with methimazole, short-acting beta-agonists, corticosteroid, digitalis, diuretics, anticoagulant, and angiotensin receptor blockers. During follow up, laboratory results, ECG, and clinical symptoms were improved. The management of Graves' disease with hyperthyroidism and TCM focuses primarily on controlling the thyroid hormone levels to prevent further cardiac deterioration. The complex interplay between managing thyroid hormone levels and preventing asthma exacerbation in this patient highlights the need for a multidisciplinary approach to optimize treatment outcomes. Graves' hyperthyroid patients with cardiomyopathy and asthma require holistic, comprehensive, and meticulous drug selection to prevent exacerbation.

Keywords: Graves' disease, hyperthyroidism, asthma, thyrotoxic cardiomyopathy.

INTRODUCTION

Graves' disease is the most common autoimmune hyperthyroid disorder, accounting for 60-80% of hyperthyroid cases. The incidence of Graves' disease is 20-40 cases per 100,000 population per year and is most common in people aged 20-50 years. Graves' disease is more common in women than in men.[1,2] The prevalence of hyperthyroidism in Indonesia is 0.6% in women and 0.3% in men of the total population of Indonesia and is most often caused by Graves' disease.[3] Graves' disease occurs based on an autoimmune process. Thyroid autoantibodies or Thyroid Receptor Autoantibodies (TRAbs) stimulate the Thyroid Stimulating Hormone (TSH) receptor in the thyroid gland, resulting in excessive secretion of thyroid hormone.[4]

Manifestations of hyperthyroidism vary from mild to severe including fatigue, weight loss, palpitations, tremors, and atrial fibrillation. Excessive thyroid hormone levels will affect the cardiovascular system, where uncontrolled hyperthyroidism can cause cardiomyopathy and heart failure. Thyrotoxic cardiomyopathy (TCM) is a rare but potentially lethal complication of thyrotoxicosis, with an incidence of <1%. Graves' disease is most often associated with TCM.[5] TCM causes severe impairment of left ventricular function and can lead to cardiogenic shock.[6]

Early diagnosis of TCM is essential because patients require immediate supportive therapy. The goal of TCM treatment is to restore euthyroidism and manage cardiovascular manifestations. Achieving euthyroid status will improve cardiovascular conditions and provide a better prognosis.[7] Beta-blockers are safe and effective first-line drugs for managing cardiovascular symptoms.[8,9] However, in asthma patients, beta-blockers may induce bronchoconstriction. The use of beta blockers in TCM patients with asthma should be based on individual risk assessment.[10] This case report aims to present a case of Graves' disease with a rare complication of thyrotoxic cardiomyopathy accompanied by asthma.

CASE ILLUSTRATION

A 36-year-old man came to the emergency room with complaints of shortness of breath and wheezing for three days before hospital admission. The symptoms were felt continuously and worsens in the morning, at night, or when exposed to cold temperatures. He also felt shortness of breath when walking more than two meters and sleeps more comfortably with two pillows. He can still speak in full sentences. The patient also complained of coughing for one week ago. The cough is felt to have phlegm but the patient has difficulty expelling the phlegm. He also felt palpitations for two months ago and has worsen in the last week. Palpitations were felt continuously and did not improve with rest. The patient felt hungry often and ate often but lost weight. He has lost about 4-5 kg in the last month. His eyes appeared more prominent. He also felt excessive sweating even though he was sedentary. These complaints have been felt for the past two months. The patient was diagnosed with hyperthyroidism one month ago and was treated with thiamazole 20 mg in the morning and 10 mg at night, propranolol 10 mg three times a day.

Two weeks earlier, the patient was admitted to a private hospital due to a viral infection. Before the scheduled check-up, the patient's asthma relapsed. He has a history of asthma since childhood, but has not had a relapse for almost 20 years. When his asthma relapses, he uses salbutamol. The patient has allergies to dust and seafoods, especially shrimp and crab. There was no history of hypertension and diabetes. The patient defecates 1-2 times a day with normal stool consistency. The patient urinates 4-5 times a day with urine volume of approximately 100-200 ml and clear yellow in colour.

On physical examination, the patient's Body Mass Index (BMI) was 17.9 kg/m^2 (underweight), blood pressure was 123/74 mmHg, heart rate was 110 times/minute, respiratory rate was 30 times/minute, and temperature was 38.7°C. On head examination, atrophy of temporalis muscle and exophthalmos were found in the eyes. The neck examination revealed diffuse thyroid enlargement (Figure 1). Cardiac examination revealed enlarged heart borders and irregular heart sounds. Pulmonary examination revealed rales and wheezing. On extremity examination, tremor was found. The patient's Wayne Index was 20 indicating hyperthyroidism and the Burch Wartofsky Score was 35 indicating impending storm.

Laboratory results showed low TSH level (0.01 uIU/mL) and high levels of Free-T3 (7.99 pmol/l), Free-T4 (46.28 pmol/l), TRAb (>40 IU/L), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (285 pg/ml). ECG showed atrial fibrillation with variable conduction RVR 120

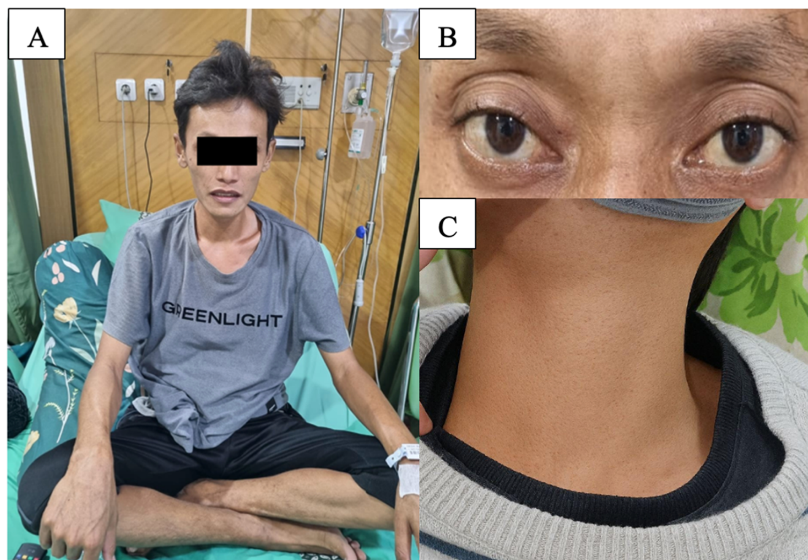


Figure 1. Clinical picture at admission of the patient showing (A) atrophy of temporalis muscle and underweight BMI, (B) exophthalmos, and (C) diffuse thyroid enlargement.

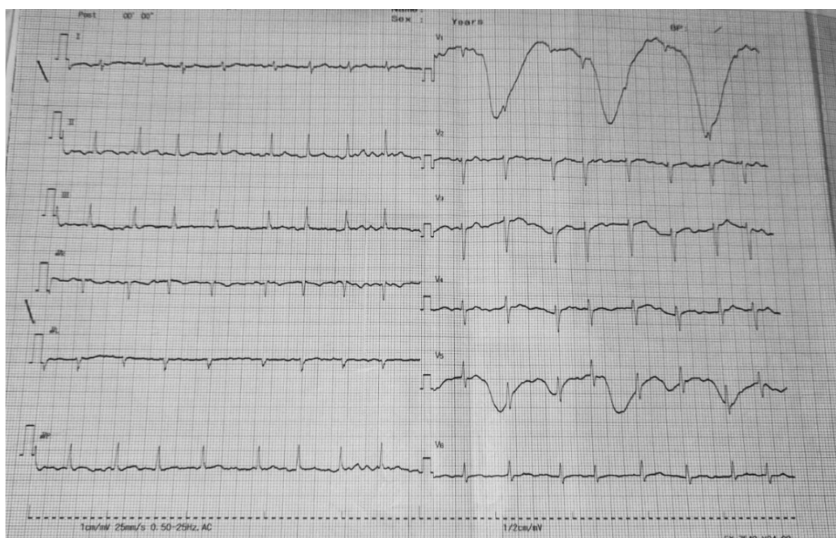


Figure 2. ECG at admission showing atrial fibrillation with variable conduction RVR 120 bpm, normal axis.

bpm, normal axis (Figure 2). Chest X-ray showed cardiomegaly with Cardio-Thoracic Ratio 63% (Figure 3). Echocardiography showed segmental wall motion abnormality with EF 48% (Simpson 46%) (Figure 4).

The patient was diagnosed with Graves' disease with hyperthyroidism, acute asthma exacerbation, and Heart failure with mildly reduced ejection fraction NYHA III due to thyrotoxic cardiomyopathy. He was treated with methimazole 10 mg once daily, valsartan (ARB) 40 mg once daily, spironolactone (aldosterone

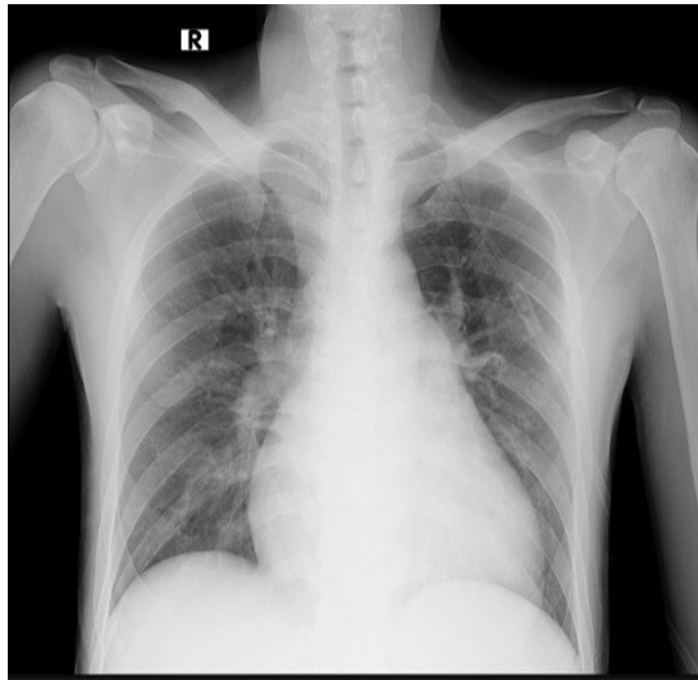


Figure 3. Chest x-ray at admission showing cardiomegaly with CTR 63%.

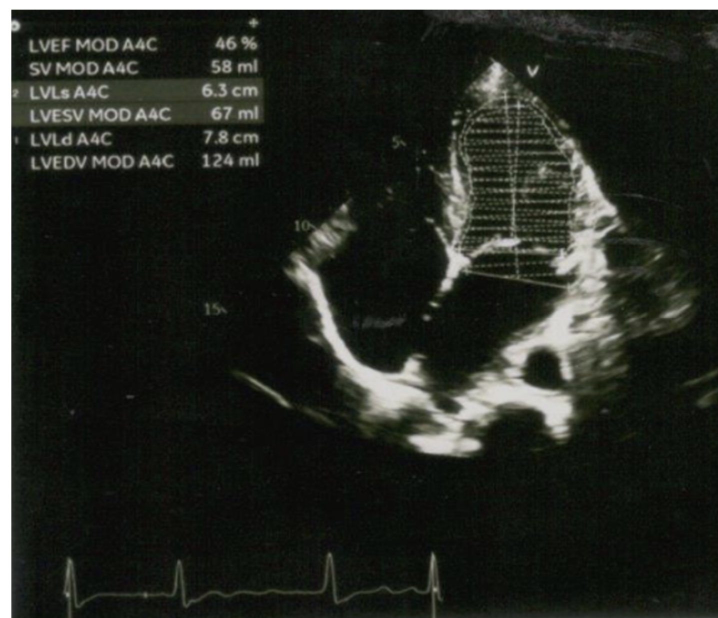


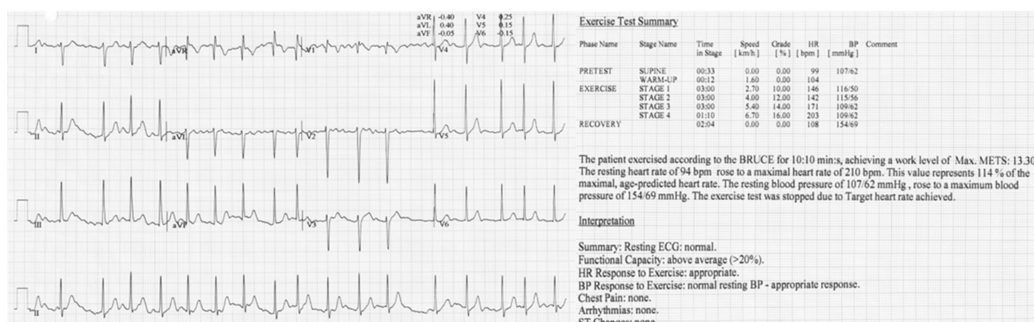
Figure 4. Echocardiography at the second day of hospital stay showing segmental wall motion abnormality with EF 48% (Simpson 46%).

antagonist) 25 mg once daily, furosemide (diuretic) 20 mg once daily, digoxin 0.25 mg once daily, warfarin (anticoagulant) 1 mg once daily, nebulized budesonide and salbutamol every 8 hours. During treatment follow ups, the patient reported that his symptoms had improved significantly. Clinically, the symptoms of hyperthyroidism and TCM gradually subsided. Treadmill test after one month of treatment showed normal resting electrocardiogram (ECG), above average (>20%) functional capacity, and appropriate responses of heart rate and blood pressure to exercise. There were no chest pain, arrhythmias, or ST changes during testing (Figure 5). Serial laboratory results showed decrease of FT4 level and increase of TSH level (Figure 6).

DISCUSSION

Asthma is a disorder in which there is chronic inflammation of the respiratory tract that causes hyperreactivity of the bronchi, characterized by recurrent episodic symptoms of wheezing, coughing, shortness of breath, and tightness in the chest especially at night or early morning, which are generally reversible.[11] In this case, the patient has a history of asthma since childhood but rarely relapses. An acute asthma attack is an episode of sudden worsening of asthma. Triggers for asthma attacks can be caused by a number of factors including allergens, viruses, and irritants. Risk factors for asthma are divided into genetic factors (atopy, gender, race) and environmental factors (dust, food, beta-blocker drugs, excessive emotional expression, cigarette smoke, air pollution, and weather changes).[12] In this case, the triggers for the patient's asthma attack were the use of beta-blocker drugs and cold air. In asthma attacks, bronchodilator drugs and systemic corticosteroids can be given. In this case, the patient was given nebulized budesonide (Pulmicort) and salbutamol (Ventolin) every 8 hours.

Graves' disease is an autoimmune disorder that develops due to the interaction between TRAbs and the TSH receptor resulting in excessive thyroid hormone secretion (hyperthyroidism). Graves' disease is the most common cause of hyperthyroidism and is more common in women with a female to male ratio of 6-7:1. Genetic factors account for 60-80% of the risk of Graves' disease.[13,14] Clinical manifestations of Graves' hyperthyroidism include tremor, palpitations, fatigue, poor concentration, weight loss, sweating, and hyper defecation. Physical signs include tachycardia, hypertension, diffuse thyroid enlargement with thyroid bruit, exophthalmos, atrial fibrillation, signs of heart failure, fine tremor, hyperkinesia, hyperreflexia, warm and clammy skin, palmar erythema, and pretibial myxoedema.[1] In this patient, there were signs and symptoms of hyperthyroidism such as palpitations, excessive sweating, weight loss



Exercise Test Summary

Phase Name	Stage Name	Time in Stage	Speed [km/h]	Grade [%]	HR [bpm]	BP [mmHg]	Comment
PRETEST	SUPINE	00:33	0.00	0.00	99	107/62	
	WARM-UP	00:12	1.60	0.00	104		
EXERCISE	STAGE 1	03:00	2.70	10.00	146	116/50	
	STAGE 2	03:00	4.00	12.00	142	115/56	
	STAGE 3	03:00	5.40	14.00	171	109/62	
	STAGE 4	01:10	6.70	16.00	203	109/62	
RECOVERY		02:04	0.00	0.00	108	154/69	

The patient exercised according to the BRUCE for 10:10 min:s, achieving a work level of Max. METS: 13.30. The resting heart rate of 94 bpm rose to a maximal heart rate of 210 bpm. This value represents 114 % of the maximal, age-predicted heart rate. The resting blood pressure of 107/62 mmHg , rose to a maximum blood pressure of 154/69 mmHg. The exercise test was stopped due to Target heart rate achieved.

Interpretation

Summary: Resting ECG: normal.
Functional Capacity: above average (>20%).
HR Response to Exercise: appropriate.
BP Response to Exercise: normal resting BP - appropriate response.
Chest Pain: none.
Arrhythmias: none.
ST Changes: none.

Figure 5. Treadmill test after one month of treatment.

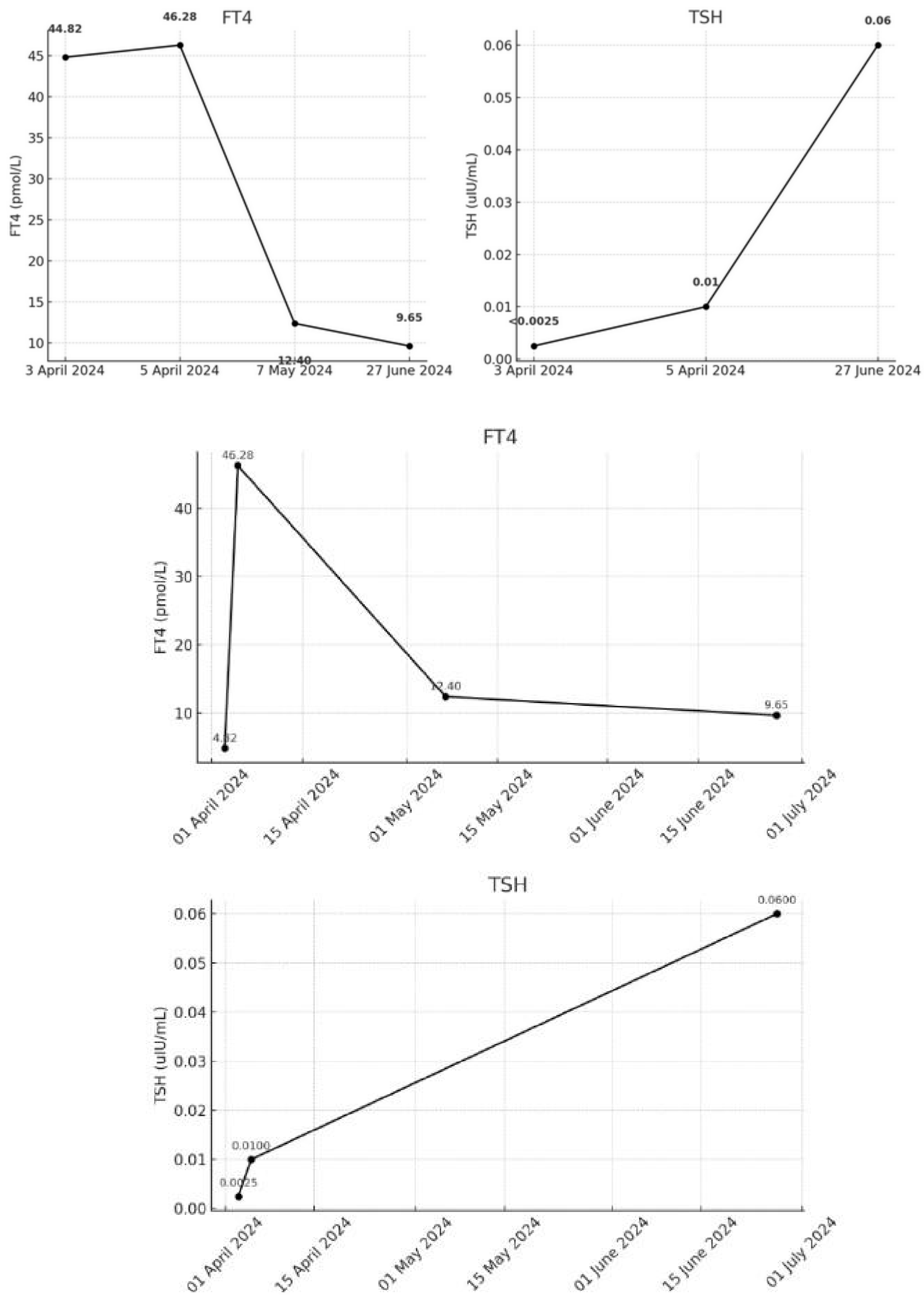


Figure 6. FT4 and TSH levels monitoring at admission, during hospital stay, and follow up: FT4 levels increased from 44.82 pmol/ to 46,28 pmol/l on the fourth day of hospital stay, decreased to 12,4 pmol/l after one month later, and decreased thereafter reaching normal levels. TSH levels were <0,0025 uIU/ml at admission, increased to 0,01 uIU/ml on the fourth day of hospital stay, and returned to normal afterwards

despite increased appetite, diffuse thyroid enlargement, tachycardia, exophthalmos, and atrial fibrillation.

To diagnose hyperthyroidism clinically, the Wayne Diagnostic Index can be used as a reference, which is a simple diagnostic tool. If the total Wayne Index score is >19, the patient is considered to have hyperthyroidism, a score of 11-19 is equivocal, and <11 implies euthyroidism.[15] In this case, the total Wayne Index score is 20 therefore the patient has hyperthyroidism. The diagnosis of hyperthyroidism can be confirmed by determining serum TSH and FT4 levels. A person is considered to have hyperthyroidism if the TSH level is below the reference value and the FT4 level is higher than the reference value. In this case, serum TSH level decreased and FT4 increased, thus meeting the criteria for a diagnosis of hyperthyroidism. The American Thyroid Association recommends that one or more of three methods can be used to diagnose Graves' disease, including TRAb examination, radioactive iodine uptake, or the presence of diffuse increased vascularity on Doppler ultrasonography. TRAb examination has sensitivity of 97% and specificity of 99% for the diagnosis of Graves' disease.[13,16] In this case, TRAb level was elevated, fulfilling the criteria for diagnosis of Graves' disease.

Treatment of hyperthyroid disease may involve antithyroid drugs, radioactive iodine, or surgery. Antithyroid drugs that can be used are methimazole or propylthiouracil (PTU). The duration of action of methimazole is longer and more potent than PTU so it can be given in a single dose per day. The initial dose of PTU is 100-200 mg three times daily and methimazole is 10-30 mg once daily. In this case, the patient was given methimazole 10 mg once daily. Antithyroid drugs is given until the euthyroid state is achieved, usually 1-3 months, then the dose is gradually reduced and continued with the lowest possible maintenance dose. Evaluation of thyroid function is done by monitoring serum FT4 and TSH levels every 4-6 weeks. If serum TSH, FT4, and total T3 levels remain normal after one year, the patient is in remission.[17]

Thyroid hormones affect cardiac muscle cells and the contractile function of the heart. Hyperthyroidism can increase cardiac output and decrease systemic vascular resistance, resulting in systolic hypertension. A shorter cardiomyocyte refractory period can lead to sinus tachycardia and atrial fibrillation which can then complicate into heart failure.[9] In this case, the patient had symptoms of shortness of breath and tachycardia during light activity. Physical and supporting examinations showed rhonchi, cardiomegaly, decreased ejection fraction, and increased natriuretic peptide concentrations. In this case, the patient met the criteria for a diagnosis of NYHA III heart failure with the cause of thyrotoxic cardiomyopathy, in which heart failure is caused by uncontrolled thyroid hormones.

TCM occurs in less than 1% of thyrotoxicosis patients. TCM is characterized by ventricular chamber dilation and decreased cardiac contractility. Identification of TCM should be done promptly because as it is a reversible cause of heart failure and heart function can recover after reaching euthyroid state.[9,18,19] The management of Graves' disease with TCM focuses primarily on controlling the thyroid hormone levels to prevent further cardiac deterioration. Beta-blockers are commonly used in the treatment of TCM due to their ability to control heart rate and reduce the workload on the heart. Beta-blockers are the first choice in TCM cases. However, beta-blockers are contraindicated in this patient due to asthma. Selective beta-blockers may be considered. Other treatment options for TCM include the use of digitalis, diuretics, ARB, and anticoagulants, which can be tailored to the patient's clinical

condition. Digitalis helps in controlling heart rate, diuretics manage fluid overload, ARB provide afterload reduction, and anticoagulants prevent thromboembolic complications associated with atrial fibrillation.[9,20] In this case, the patient was treated with valsartan (ARB) 40 mg once daily, spironolactone (aldosterone antagonist) 25 mg once daily, furosemide (diuretic) 20 mg once daily, digoxin 0.25 mg once daily, and warfarin (anticoagulant) 1 mg once daily. Warfarin is the most widely used anticoagulant drug for stroke prevention in atrial fibrillation. During treatment follow ups, all clinical symptoms, ECG treadmill test, and laboratory results improved significantly.

CONCLUSION

Graves' hyperthyroid patients with thyrotoxic cardiomyopathy and asthma require holistic, comprehensive, and meticulous drug selection to prevent exacerbation. Beta-blocker is one of the drugs of choice for treating TCM. Propranolol is a non-selective beta-blocker that might induce bronchoconstriction in asthmatic patient. Selective beta-blockers should be considered in Graves' hyperthyroid patients with TCM and asthma to prevent exacerbation. The complex interplay between managing thyroid hormone levels and preventing asthma exacerbation in this patient highlights the need for a multidisciplinary approach to optimize treatment outcomes.

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