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Successful antihypertensive therapy with metoprolol in a patient with Graves' disease following Hashimoto's thyroiditis: A Case Report

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ABSTRACT

Introduction: Graves' disease (GD) and Hashimoto's disease (HT) are autoimmune diseases of the thyroid gland, with different pathophysiological mechanisms. In GD, antibodies against the TSH receptor cause hyperthyroidism, while in HT, there are anti-TPO and anti-TG antibodies, which cause hypothyroidism. The case illustrates the diagnostic difficulties in the transition from HT to GD, which can be masked by general symptoms and lead to delays in diagnosis. In hyperthyroidism, arterial hypertension often results from the predominance of the sympathetic nervous system; therefore, treatment with beta-blockers is justified. Treatment of hypertension in the course of GD differs from that of primary arterial hypertension. Case report: The case describes a 37-year-old patient with a history of HT who converted to GD. With disease progression, an increase in blood pressure (HBPM) was observed, despite normal thyroid hormone levels after introduction of thiamazole at 10 mg twice daily. The implementation of metoprolol effectively lowered the blood pressure. Conclusion: Any patient diagnosed with HT should be monitored for the development of symptoms of hyperthyroidism. Cardioselective beta-blockers, such as metoprolol, are effective in treating hypertension secondary to GD and should be considered in any patient with contraindications to propranolol.

Keywords: hypertension; metoprolol; Graves' disease; Hashimoto's disease

1. INTRODUCTION

Graves' disease (GD) and Hashimoto's thyroiditis (HT) are both autoimmune diseases associated with the presence of antibodies directed against thyroid antigens. GD is characterized by the presence of thyrotropin receptor antibodies (TRAb), which stimulate the thyroid-stimulating hormone receptor (TSH-R), leading to hyperthyroidism - elevated levels of free triiodothyronine (FT3) and free thyroxine (FT4), and suppressed thyroid-stimulating hormone (TSH) (Zuhur et al., 2021). GD is the most common cause of hyperthyroidism, affecting around 2% of

women and 0.5% of men. However, HT is associated with the presence of thyroid peroxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-TG), which lead to the destruction of thyroid cells and result in hypothyroidism - reduced FT3 and FT4 levels, and elevated TSH (Takasu et al., 2008). These two diseases differ in their mechanism of action and, consequently, in their clinical effect and symptoms in patients, which has significant consequences for the diagnosis and treatment of patients with these conditions.

Hypertension is a chronic condition characterized by persistently elevated blood pressure in the arteries. It is one of the most important modifiable risk factors for cardiovascular disease, stroke, heart failure, and chronic kidney disease (Fuchs et al., 2020; Burnier et al. 2023). According to ESC guidelines, hypertension is diagnosed if home blood pressure measurements (HBPM) are at least 135 mmHg systolic or 85 mmHg diastolic, or if two separate measurements in the physician's office show a systolic pressure of at least 140 mmHg or a diastolic pressure of 90 mmHg, or in 24-hour ambulatory blood pressure monitoring average systolic pressure is ≥130 mmHg and/or diastolic pressure ≥80 mmHg. It is recommended to maintain blood pressure below 120-129/70-79, if well tolerated (McEvoy et al. 2024).

Arterial hypertension is divided into two categories: primary, which accounts for about 90% of cases, and secondary to other diseases, which accounts for about 10%. The most important modifiable environmental contributors are high salt and alcohol intake, obesity, and low levels of physical activity (Kornitzer et al. 1999). The causes of secondary hypertension include renovascular disease, renal parenchymal disease, congenital adrenal hyperplasia, aortic coarctation, drug and substance use, obstructive sleep apnea, as well as hormonal disorders: primary hyperaldosteronism, pheochromocytoma, Cushing syndrome, hyperthyroidism, and parathyroid conditions (Daly et al., 2022).

Arterial hypertension as a symptom of hyperthyroidism is most likely caused by dysregulation of the autonomic nervous system, with a predominance of the sympathetic component (Girard et al., 1998; Safa-Tisseront et al., 1998). Therefore, beta-blockers (BB), as adrenergic antagonists, are effective in symptomatic therapy in the course of hyperthyroidism. It was believed that the drug dedicated to the symptoms of the adrenergic system in the case of hyperthyroidism is propranolol, a non-selective beta-blocker. However, currently, treatment can be started with cardioselective BB, such as metoprolol (Matsuo et al., 2024). Unlike propranolol, metoprolol does not inhibit peripheral conversion of T4 to T3, but its better tolerability and cardioselectivity make it a valuable option, especially for patients with chronic diseases such as diabetes or asthma.

We present a case of a patient with increasing HBPM and a history of HD that converted to GD, who was successfully treated with metoprolol as hypotensive therapy. This case highlights the diagnostic and therapeutic challenges in patients transitioning from hypo- to hyperthyroidism, as well as the role of cardioselective beta-blockers in hypertension secondary to hyperthyroidism.

2. CASE REPORT

A 37-year-old female patient presented to her primary care physician due to a two-year history of gradually increasing home blood pressure measurements (HBPM) to 180/95 mmHg from initial values of 130/80 mmHg. On physical examination, the patient appeared hemodynamically and respiratory stable, with a blood pressure of 145/89 mmHg and HR 74 beats per minute. The patient has been taking thyrozol 10mg twice daily in the last four months, due to Graves' disease diagnosed 8 months earlier based on positive Thyrotropin Receptor Antibodies (TRAb), a Thyroid-Stimulating Hormone (TSH) level below 0.004 uIU/mL, and an elevated Free Thyroxine (FT4) level of 25 pmol/L. She did not present signs of ophthalmopathy or other clinical symptoms. Notably, until that time, the patient had been treated for several years with levothyroxine 12,5 μg five days a week and 37,5 two days a week - for the management of hypothyroidism coexisting with Hashimoto's thyroiditis. HT was diagnosed several years earlier, because of elevated TSH level, and positive anti-TPO coexisting with clinical symptoms: weight gain, fatigue, and hair loss. Additionally, medical history revealed obesity and insulin resistance.

Laboratory tests performed by the primary care physician revealed euthyroidism, with normal TSH, FT3 and FT4 levels, as well as normal blood count, estimated glomerular filtration rate and glucose level. Thyroid ultrasound (Figure 1.) showed an enlarged gland with heterogeneous echogenicity. Electrocardiogram revealed a regular sinus rhythm, intermediate electrical axis, no ST-T segment abnormalities, and a normal corrected QT interval.

Metoprolol was initiated at a dose of 25 mg once daily, resulting in stabilization of blood pressure at 130/75 mmHg after five weeks.

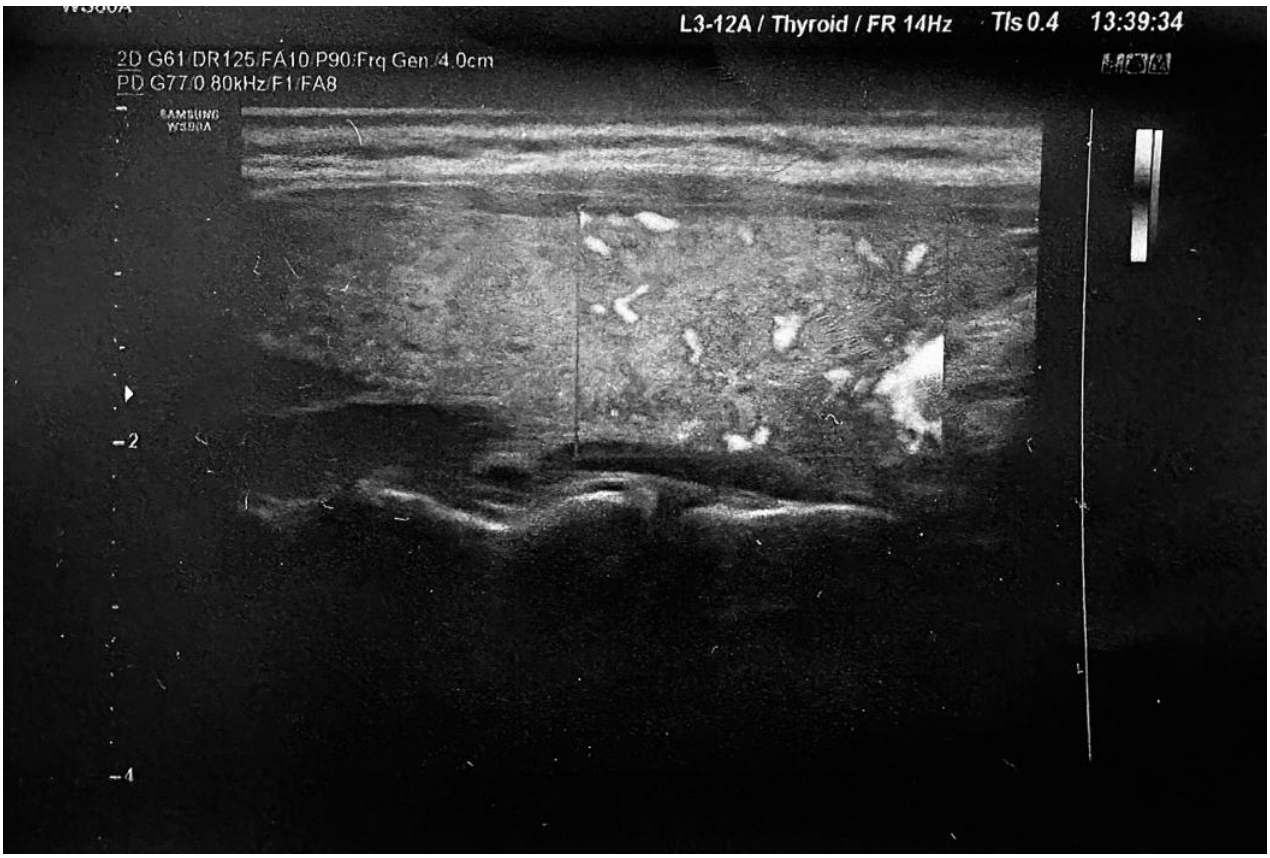

Figure 1. Ultrasound image of the thyroid gland.

3. DISCUSSION

The typical symptoms of hyperthyroidism are primarily the result of increased sympathetic nervous system activity, which causes sympathovagal imbalance and cardiovascular stress response (Chen et al., 2006; Saitoh et al., 1992; Burggraaf et al., 2001). The underlying mechanisms involve thyroid hormones, especially T3, which enhance tissue sensitivity to catecholamines through upregulation of β-adrenergic receptors, increased expression of adrenergic response genes and direct action on autonomic regulatory centers in the brain. T3, which is in excess in this condition, causes an increase in the expression of beta-1 adrenergic receptors, among others, in cardiomyocytes and the nervous system, which leads to a rise in the body's sensitivity to the effects of noradrenaline and adrenaline, and stimulation of the adrenergic system. This is manifested by an acceleration of the heart rate (HR), an increase in the ejection fraction, hypertension (most often systolic), hand tremors, and increased sweating (Bahouth et al., 1991). Other symptoms of hyperthyroidism include: weight loss despite increased appetite, irritability, anxiety, insomnia, difficulty concentrating, arrhythmias such as atrial fibrillation, heat intolerance, muscle weakness (especially in the limbs), increased frequency of bowel movements, menstrual irregularities, increased thirst and frequent urination, hair loss, thin, moist skin, and an enlarged thyroid gland (Goichot et al., 2016; Devereaux et al., 2014; Boelaert et al., 2010). Characteristic symptoms in GD include ocular symptoms such as bulging eyes (exophthalmia), eyelid swelling, diplopia, and eyelid retraction. Typical for this condition is also pretibial myxedema (Bartalena et al., 2014).

The treatment of hypertension secondary to hyperthyroidism differs from that used in primary hypertension, where the first-line therapy typically involves angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretics, calcium channel blockers; beta-blockers are generally reserved for later stages. Beta-blockers as first-line drugs in the treatment of hypertension can be used in specific situations, such as heart failure or ischemic heart disease (where they are used in combination therapy) and in monotherapy for tachyarrhythmia or symptoms of hyperthyroidism (McEvoy et al., 2024). This results from various mechanisms of hypertension development. As mentioned above, in case of hypertension secondary to hyperthyroidism, it is essential to inhibit the hyperreactivity of the adrenergic system, which is most likely responsible for the development of hypertension in this group of

patients. Moreover, many patients with GD present an acceleration of HR (Ertek et al., 2013). Therefore, in the initial therapy, adrenergic blockers, such as beta-blockers, can be used.

The meta-analysis by Guo et al. showed that adding beta-blocker to hypertension monotherapy reduced systolic blood pressure by 4.1 mm Hg and diastolic blood pressure by 3.7 mm Hg. In contrast, combined therapy for hypertension with metoprolol resulted in a reduction of systolic blood pressure by 3.6 mm Hg and diastolic blood pressure by 2.1 mm Hg compared to treatment without beta-blockers (Guo et al., 2023).

The transformation from HT to GD is rare but has been documented (Vassallo et al., 2024; Gonzalez et al., 2018). The symptoms associated with increased HBPM over two years suggest that hyperthyroidism may have been present by our patient, who was treated for hypothyroidism, several months before the diagnosis was made. In patients with HT evolving into GD, symptoms may be misleading, e.g., attributed to chronic fatigue, which delays diagnosis. Therefore, it is essential to monitor patients with HT for signs of hyperthyroidism, especially if there is a need to reduce the dose of levothyroxine (Gonzalez et al., 2018).

HT is mainly characterized by thyroid damage, leading to primary hypothyroidism. Histopathologically, the disease is characterized by lymphoplasmacytic infiltration, formation of lymphoid follicles with germinal centers, and parenchymal atrophy. HT leads to systemic symptoms resulting from thyroid damage (Ralli et al., 2020).

The symptoms of HD may involve fatigue and weakness, weight gain, cold intolerance, dry skin, hair loss, constipation, muscle and joint pain, facial swelling, and hypotension (Kotak et al., 2024). Moreover, psychiatric and neurological symptoms are also possible: depression, concentration and memory problems, mood swings, drowsiness (Wang et al., 2024). The results of the study by Yuan et al., (2023) indicate several local symptoms associated with Hashimoto's thyroiditis, including throat discomfort, neck pain, voice changes, shortness of breath, dysphagia and sleep apnea. Since HT can lead to hypothyroidism, and therefore thyroxine deficiency, in patients with signs and symptoms of hypothyroidism or permanent hypothyroidism, levothyroxine supplementation is necessary (Martinez et al., 2021). It is speculated that selenium supplementation may be beneficial as supportive therapy in the treatment of Hashimoto's thyroiditis (van Zuuren et al., 2013). However, reliable data in this area remain limited.

In some patients, despite previous destruction of the thyroid gland due to Hashimoto's disease, partial recovery of gland function may occur. When combined with the presence of TRAb, this can lead to hyperthyroidism (Essouabni et al., 2024). In patients with HT and sudden normalization or suppression of TSH levels, physicians should consider repeat antibody testing and TRAb screening to exclude transformation to GD.

4. CONCLUSION

The use of a cardioselective beta-blocker, such as metoprolol, may be effective in normalizing blood pressure in patients diagnosed with hyperthyroidism. However, further research is necessary. In patients diagnosed with HD, special vigilance is required, as the development of GD is possible. Physicians should consider the use of cardioselective beta-blockers not only for symptom relief but also for blood pressure control in patients with hyperthyroidism, particularly when standard antihypertensive treatment strategies are ineffective or poorly tolerated.

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Author contributions

Klaudia Miklusiak was author of the concept, involved in gathering the necessary clinical data. Karol Miklusiak and Klaudia Miklusiak performed the initial analysis, drafted the introduction, case report, discussion and conclusion sections.

Informed consent

Written & Oral informed consent was obtained from individual participants included in the study.

Ethical approval

Not applicable.

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data associated with this work are present in the paper.

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