

# Unilateral Thyroid Involvement in Graves' Disease: A rare presentation of Graves' Disease

Nicolas Perini <sup>1,\*</sup>, Letícia Santana de Castro César <sup>2</sup>, Maria Fernanda Maciel <sup>2</sup>, Roberto Bernardo Santos <sup>3</sup>, Danilo Villagelin <sup>2</sup>

<sup>1</sup> Postgraduate Program in Internal Medicine, Universidade Estadual de Campinas, Campinas, São Paulo, Brazil.

<sup>2</sup> Faculty of Medicine, School of Life Sciences, Pontifical Catholic University of Campinas, Campinas, São Paulo, Brazil.

<sup>3</sup> Hospital PUC-Campinas, Pontifical Catholic University of Campinas, Campinas, São Paulo, Brazil.

\* Correspondence: nicolas\_perini@hotmail.com.

**Abstract:** Graves' disease is a rare autoimmune disorder characterized by increased hormone production leading to clinical signs of hyperthyroidism, most cases present with different degrees of TSH suppression, accompanied by elevated FT4. Thyroid scintigraphy commonly reveals an enlarged goiter with diffuse increased iodine uptake. This study presents the case of a 50-year-old woman with a clinical history of Graves' disease presenting with suppressed TSH and elevated FT4 combined with clinical signs of hyperthyroidism (tachycardia and peripheral tremors). Thyroid imaging showed increased unilateral uptake on scintigraphy with no visible nodules on ultrasound. The patient showed an adequate initial response to methimazole, with disease relapses after dose reduction. The patient was able to maintain euthyroidism with continued antithyroid drug use. Single lobe involvement of Graves' Disease is a rare phenomenon attributed to the autoimmune process combined with acquired variations impacting a specific lobe. Clinically, patients are present with different degrees of hyperthyroidism. In most cases, the use of antithyroid drugs provides adequate disease control, with patients subjected to definitive treatment presenting a higher risk of disease recurrence in the contralateral lobe. This report shows a case with a favorable response to continue antithyroid drugs treatment after disease relapse. The findings highlight the rare occurrence of unilateral thyroid gland involvement in Graves' disease. Also, suggest a favorable response to continue antithyroid treatment for patients exhibiting relapses.

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## 1. Introduction

Graves' disease is an autoimmune disease that represents the primary cause of hyperthyroidism in adults [1], affecting 3% of women and 0.5% of men in their lifetime, with peak incidence in the second to fifth decade of life [2]. The physiopathology revolves around T lymphocytes presenting thyroid antigens to B lymphocytes, resulting in the production of thyroid-stimulating immunoglobulin (TRAb) [3]. These bind to the TSH receptor, stimulating hormone production and tissue growth [3]. The excess T3 and T4 levels resulted from the hyperthyroid state cause a wide range of clinical manifestations, with over 80% of presenting tachycardia, heart palpitations, peripheral tremors, heat intolerance, fatigue, diarrhea and menstrual cycles changes occur in around 20% of patients with

only 10% presenting severe cardiac manifestations such as atrial fibrillation and heart failure [4]. Up to 70% of patients may present clinical signs of thyroid eye disease (TED) upon diagnosis [4].

Laboratory diagnosis is determined by TSH, FT4, and FT3 levels. Patients present with various degrees of TSH suppression, accompanied by elevated FT4 and FT3 levels. More than 90% of patients exhibit positive TRAb levels [5]. In terms of imaging, thyroid ultrasound reveals an enlarged goiter in most cases, accompanied by increased vascularity, while thyroid scintigraphy shows diffusely increased radiotracer uptake [6]. This imaging characteristic, combined with clinical and laboratory manifestations of thyrotoxicosis, aids in Graves' disease diagnosis in patients with negative TRAb [5]. Unilateral uptake in a patient with Graves' disease is a rare occurrence, where the patient exhibits clinical and laboratory manifestations of Graves' disease [7]. However, during the scintigraphy, the radiotracer pattern demonstrates one hyperfunctioning thyroid lobe with a hypofunctioning contralateral lobe [8]. In these cases, ultrasound imaging is required to rule out other conditions such as unilateral thyroid hemiagenesis or a large autonomous functioning nodule [8].

In this context, we report the case of a 50-year-old woman with hyperthyroidism with negative TRAb antibodies and unilateral uptake on thyroid scintigraphy, compatible with unilateral Graves' disease.

## 2. Case Report

A 50-year-old female patient with a history of Graves' disease, diagnosed 4 years earlier, was referred to a specialized clinic for thyroid function control. Upon initial clinical assessment, the patient complained of fatigue and weight loss. The physical examination exhibited clinical signs of hyperthyroidism with tachycardia (heart rate: 123 bpm), peripheral tremors with no palpable cervical nodules or goiter, and no signs of TED.

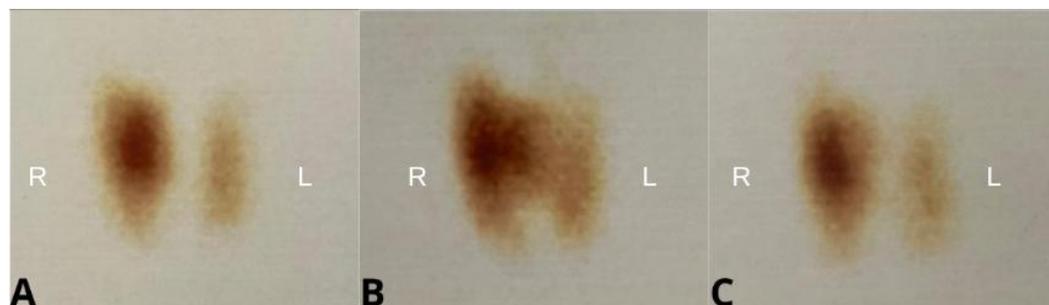
### 2.1 Diagnostic Assessment

Patient had clinical signs of thyrotoxicosis with no prior history of levothyroxine use. Clinical history of exogenous levothyroxine use, laboratory evaluation was compatible with thyroid hyperfunction with suppressed TSH levels (TSH:0.001 mUI/L; reference value 0.27-5.50 mUI/L), slightly elevated free T4 (FT4:1.89ng/dL; reference value 0.93-1.70ng/dL), and negative thyroid biomarkers (Ant TPO:1.5 U/mL; reference value: <9.0 U/mL and Ant Tiroglobulin: <0.9 UI/mL; reference value: <4.0 UI/mL). TRAb levels were negative (1.08; the reference value <1.75- chemiluminescence assay). Thyroid ultrasound revealed a thyroid gland with diffuse heterogenic texture with no nodules, with a right lobe measuring 5.8 cm<sup>3</sup> and left lobe measuring cm<sup>3</sup>, with a 3.8 total volume of 9.6 cm<sup>3</sup> (reference range: 7 to 15 cm<sup>3</sup>). Given the biochemical diagnosis of hyperthyroidism with no visible thyroid nodules ultrasound or suggestive signs of destructive thyroiditis, a Tc99m pertechnetate thyroid scintigraphy to determine Hyperthyroidism etiology, the revealing an increased thyroid volume with increased iodine uptake in the right thyroid lobe, accompanied by decreased uptake in the left lobe, consistent with a hyperfunctioning right lobe (Figure 1).

### 2.2 Treatment

The patient was initially treated with 5mg/day of methimazole, after nine months of methimazole use, the patient exhibited normal thyroid function, with TSH in the upper reference range (TSH:4.86 mUI/L; reference value 0,27-5.50 mUI/L), and FT4 in the lower range (FT4:1.16ng/dL; reference value 0.93-1.70ng/dL) and no clinical signs of Graves orbitopathy. The methimazole dose was reduced to 2.5mg/day. Follow-up imaging was conducted, revealing a patient with a diffuse heterogeneous texture and no visible nodules, and a normal thyroid volume.

**Figure 1.** Tc99m pertechnetate thyroid scintigraphy showing an increased thyroid volume with an increased uptake hyperfunctioning right thyroid lobe. Total uptake 1.8% (normal range 0.4-1.6%). A: Anterior view: Increased Tc99m uptake in the right lobe with and decreased uptake in the left lobe. B: Oblique Anterior Right view. C: Oblique Anterior Left view.



### 2.3 Outcome and Follow-up

After a year of treatment, the patient remained euthyroid with consistent thyroid scintigraphy results showing right lobe hyperfunction and negative TRAb antibodies. Upon physical examination, the patient presented no signs of TED, laboratory evaluation showed maintained euthyroidism, and the methimazole dose was reduced to 5 mg twice weekly. The patient relapsed after an attempt at methimazole dose reduction and was offered definitive treatment with radioiodine or partial thyroidectomy but opted to return to ATD use. Methimazole was adjusted to 5mg/day to maintain euthyroidism.

Four years after initial treatment, the patient remains in an euthyroid state with on-going methimazole use; the patient remains asymptomatic, with no signs of TED.

### 3. Discussion

The literature documents (Table 1) only a few cases of Graves' disease presenting with unilateral involvement of a bilobed thyroid gland, as presented in Table 1[7,8-16], similarly to the bilateral manifestation of the condition, unilateral cases predominantly affect female patients [17]. The involvement of a single lobe cannot be solely attributed to the autoimmune pathology associated with Graves' disease [8]. This atypical presentation may be explained by variations between lobes that may arise from acquired conditions, such as unilateral bacterial or viral inflammation impacting a specific lobe [18]. Other explanations lie in the detection of retroviral sequences in thyroid tissue from affected patients, although the role of these infections in the pathogenesis remains uncertain [7]. Variations in the amino acid structure of thyroid antigens in each lobe may contribute to differing levels of B-cell infiltration within the thyroid gland, which is also implicated in these atypical manifestations [8].

Another hypothesis suggests that variations in local factors, such as NIS receptors, with the description in literature of single lobe mutations in the NIS suppression gene, may influence iodine uptake capacity and, consequently, affect thyroid function [9]. Additionally, distinct lymphatic drainage systems might result in different immune responses in each lobe, leading to uneven disease involvement, given that most bacterial or viral infections in the thyroid spread via lymphatic vessels this distinct drainage system may lead to the exposure of different antigens in each lobe [8]. In the presented case the patient did not present positive autoimmune biomarkers through the follow-up suggesting that this rare manifestation may be the result of local factors in the right lobe such as NIS receptor dysfunction.

Regarding clinical presentation, patients with unilateral Graves' disease present hyperthyroidism symptoms, weight loss, palpitations, diarrhea, tremors, fatigue, heat intolerance, nervousness, and insomnia, with some patients presenting enlargement of the affected lobe that could result in dysphagia [10]. The presence of TED is uncommon, with

few documented cases, but when present, it does not appear to correlate with a higher severity of TED [9,14].

**Table 1.** Summary of Previously Reported Cases of Unilateral Graves' Disease.

References	Age and gender	Affected lobe	Symptoms	Thyroid Eye Disease	TRAb	Treatment	Remarks
[7]	31-year-old female	Right lobe	Night sweat, diarrhea, tachycardia, nervousness, tremor and weight loss	Not present	Elevated 26.2 U/L (normal range 0–10 U/L)	Initially, thiamazole (40 mg/day) and propranolol (20 mg/day). After 6 months, symptoms disappeared and TSH, FT3 and FT4 normalized; continued thiamazole (20 mg/day). After 12 months, thiamazole discontinued. Two years after diagnosis, thyroid HR-ultrasonography was normal and TRAb normalized	Three years after diagnosis and two years after treatment, patients remained euthyroid with no relapse or left lobe involvement
[8]	13 females and 2 males, mean age 47 years	Eight right lobe, seven left lobe	Not mentioned	Not mentioned	Not mentioned	Eight patients treated with antithyroid drugs with good response. One 43-year-old female achieved euthyroid state after 1 year of I-131 ablation	Follow-up not possible in six patients
[9]	63-year-old male	Right lobe	Bilateral exophthalmos, heart failure, diffuse enlargement of right thyroid lobe	Presented bilateral exophthalmos	Not mentioned	Not mentioned	—
[10]	61-year-old female	Right lobe	Weight loss and occasional palpitations, no gland enlargement	Not mentioned	Negative (+7.4%)	Inorganic iodine 30 mg/day for 2 weeks, followed by right hemithyroidectomy. Six months post-surgery, TRAb became positive (+42.4%) with normal TSH and thyroid function tests. Three months later, FT3 and FT4 increased with suppressed TSH. Methimazole 30	Initial radioisotope scintigraphy showed unilateral diffuse <sup>123</sup> I uptake. After surgery, remaining lobe was affected but remission achieved with antithyroid medication

						mg/day initiated, maintenance dose 5 mg/day led to normalization	
[11]	33-year-old female	Right lobe	Fatigue, heat intolerance, sweating, weight loss	Not present	Elevated 9.2 U/L (normal <1.5 U/L)	Thiamazole 40 mg/day achieved complete remission in 4 weeks. Continued 20 mg/day for 6 months, then block-and-replace with 5 mg/day thiamazole and 50 µg/day levothyroxine, normalizing hormones; TRAb reduced to 4.3 U/L	Patient had chronic hepatitis C previously treated with PEG-interferon and ribavirin; remission achieved without contralateral lobe involvement
[12]	39-year-old male	Right lobe	Symptoms and signs of hyperthyroidism	Not mentioned	Positive	Methimazole for 12 months normalized TSH, TRAb and thyroid hormones. After discontinuation, thyroid hormones remained normal but TSH was suppressed	—
[13]	48-year-old male	Left lobe	Weight loss, sweating, jitteriness	Not present	Not mentioned	Beta-blocker and radioiodine ablation. Four months later, symptoms resolved, FT4 normalized, FT3 decreased but remained above upper limit, TSH suppressed	Patient was using citalopram, simvastatin and vitamin D at diagnosis
[14]	30-year-old male	Right lobe	Right-sided thyromegaly, dysphagia, palpitations, insomnia	Right eye proptosis, redness in both eyes (worse on right)	TRAb within reference values	Methimazole 5–10 mg on alternating days, later discontinued for right hemithyroidectomy. Four months later, TSH, FT4 and FT3 normal; TRAb elevated and TSI high. One year later, patient remained euthyroid without methimazole	History of Graves' disease treated for 3 years; relapse after dose reduction; surgery recommended due to high TSI indicating low chance of long-term remission
[15]	43-year-old female	Right lobe	Weight loss with increased appetite, palpitations, right-	Not present	Positive	Methimazole administered with symptom regression and normal status for 4 months	—

			sided neck swelling				
[16]	71-year-old woman	Right lobe	Palpitations	Not present	Positive 3.1 IU/L (normal < 1.5 IU/L)	18-month course of synthetic antithyroid medication with good clinical and biological tolerance; remission achieved after 2 months	—
[16]	75-year-old woman	Right lobe	Palpitations, irritability, diarrhea, heat intolerance, hypertension, weight loss; mildly asymmetrical thyroid	Not present	Positive 4.4 IU/L (normal < 1.5 IU/L)	Full symptom relief after 4 weeks; thyroid function normalized by end of 18-month treatment, indicating remission	History of breast cancer treated with surgery, chemotherapy and radiotherapy

Laboratory evaluation is compatible with hyperthyroidism, with patients presenting elevated FT3 and FT4 levels with different degrees of TSH suppression [9-15]. Thyroid autoimmunity biomarkers, particularly TRAb, are positive in approximately 50% of the cases described [7,8, 16]. Antithyroid drugs (ATD) represent the primary choice of therapy for the management of Graves' disease; similarly, the unilateral Graves' disease follows the same algorithm as bilobular Graves' disease hence the fact that an unilateral manifestation does not impact negatively the response to ATD use with methimazole representing the primary treatment choice in most cases, with some patients requiring the use of blockers for symptom management until euthyroidism is reestablished [17,19]. Remission was achieved in up to 50% of patients after an initial course of antithyroid drug treatment [8,18].

In case of relapse after an initial a second course of ATDs has been demonstrated to be a safe and effective alternative to reestablish euthyroidism for patients with Graves' disease [20]. Definitive treatment with partial thyroidectomy and radioiodine can be used for specific cases unable to achieve euthyroidism with antithyroid drugs or when there are serious side effects or contraindications to ATD use [8]. In two reported cases where the patients were initially treated with partial thyroidectomy, the contralateral remaining lobe became hyperfunctioning during follow-up and required methimazole use to establish euthyroidism [10]. In the reported cases treated with radioiodine, initial positive results were observed with disease control; however, during follow-up, patients experienced either recurrence of the disease or development in the opposite lobe [8,13].

Although the reported cases in the literature are scarce, the existing evidence supports the use of the same rationale for bilateral and unilateral Graves' disease [8,10]. In the presented case, the patient had an adequate initial response to anti-thyroid drugs with thyroid function control, but relapsed after dose reduction, given the patient's refusal to a definitive treatment and the literature evidence supporting a second course of ATD to establish euthyroidism in bilobular Graves' disease[20], the patient was subjected to continue ATD use with adequate thyroid function control. In the revised literature different treatment approaches were utilized, the use of ATD for the same recommended time frame as bilateral Graves' disease was effective in achieving remission with multiple reported cases of contralateral disease after surgical approach, this pattern observed could

indicate that over time the same environmental exposure could lead to an autoimmune reaction affect the contralateral lobe, following this hypothesis the effect of ATD in modulating autoimmune response in the thyroid could explain the possibility of disease and remission in prologued use [21].

Similarly to bilateral Graves' disease, the unilateral form presents a good short-term prognosis with most reported cases presenting adequate thyroid function, although given the possibility of long-term relapse even in patients subjected to definitive treatment, the continued thyroid function assessment should be conducted at six-month intervals during follow-up.

#### 4. Conclusion

The study reports highlight a rare occurrence of a patient exhibiting unilateral thyroid involvement in Graves' Disease. Despite its rarity, single lobe Graves' disease treatment bears strong similarities to the bilateral disease with strong possibilities of disease remission after an initial course of antithyroid drugs. For patients exhibiting relapses, a second prolonged course of ATDs could represent a safe alternative to definitive treatment in establishing euthyroidism.

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