CASE REPORT

Graves' disease, myxedema, and papillary thyroid carcinoma

Doença de Graves, mixedema e carcinoma papilífero de tireoide

Luiz Augusto Marin Jaca, Felipe Ramos Caprini, Maira Rubini Ruiz, Léa Maria Zanini Maciel, Cacilda da Silva Souza

ABSTRACT

Graves' disease (GD) is the leading cause of hyperthyroidism and diffuse toxic goiter in iodine-sufficient geographical areas. GD is associated with classical manifestations such as ophthalmopathy and thyroid dermopathy, in addition to diffuse goiter, which may be the site of carcinomas, as a complication. **Case report:** A 52-year-old woman presented with goiter and symptoms compatible with hyperthyroidism, such as heat intolerance, weight loss, fatigue, increased sweat, tachycardia, fine tremors, increased intestinal transit, anxiety, emotional lability, insomnia, exophthalmos, and pretibial myxedema. A complementary investigation confirmed the diagnosis of hyperthyroidism (high free T4 and total T3 levels and low thyroid-stimulating hormone - TSH levels). Ultrasound images showed diffuse enlargement of the thyroid lobes by approximately 10 times and the presence of three thyroid nodules, one of which was larger than 2 cm with heterogeneous echogenicity and vascularization throughout the nodule; ultrasound-guided fine needle aspiration revealed cytology compatible with Bethesda IV; scintigraphy revealed a low uptake area (cold nodule) amid a diffuse high-uptake goiter. A thyroidectomy was performed, and the anatomical specimen diagnosis revealed papillary thyroid carcinoma in the right lobe, with adjacent parenchyma compatible with GD. Histopathological examination of the skin showed the presence of myxedema compatible with Graves' dermopathy. The patient evolved with the normalization of TSH levels and a reduction of cutaneous manifestations. **Conclusion:** GD abnormalities may not be restricted to the classic clinical manifestations, and a careful investigation may reveal the coexistence of carcinomas.

Keywords: Goiter, Graves' disease, Myxedema, Thyroid carcinoma, Papillary.

RESUMO

A doença de Graves (DG) é a principal causa de hipertireoidismo e bócio difuso tóxico em áreas geográficas com iodo suficiente. DG está associada a manifestações clínicas clássicas como oftalmopatia e dermopatia da tireoide, além do bócio difuso, que pode ser sítio de carcinomas, como uma complicação. **Relato de caso:** Mulher de 52 anos apresentou bócio e sintomas compatíveis com hipertireoidismo como intolerância ao calor, emagrecimento, fadiga, sudorese aumentada, taquicardia, tremores finos, trânsito intestinal aumentado, ansiedade, labilidade emocional, insônia, exoftalmia e mixedema pré-tibial. A investigação complementar confirmou o diagnóstico de hipertireoidismo (níveis elevados de T4 livre e T3 total; níveis baixos de hormônio estimulante da tireoide - TSH). As imagens ultrassonográficas mostraram aumento difuso dos lobos tireoidianos em aproximadamente 10 vezes e a presença de três nódulos tireoidianos, um dos quais, maior que 2 cm, com ecogenicidade e vascularização heterogêneas em todo o nódulo, cuja punção aspirativa por agulha fina guiada por ultrassom revelou citologia compatível com Bethesda IV; e a cintilografia evidenciou uma área de baixa captação (nódulo frio) em meio a um bócio difuso de alta captação. Foi realizada tireoidectomia e o diagnóstico da peça anatômica revelou carcinoma papilífero de tireoide em lobo direito, com parênquima adjacente compatível com DG. O exame histopatológico da pele mostrou a presença de mixedema compatível com dermopatia de Graves. A paciente evoluiu com normalização dos níveis de TSH e redução das manifestações cutâneas. **Conclusão:** As anormalidades da DG podem não estar restritas às manifestações clínicas clássicas, e uma investigação criteriosa pode revelar a coexistência de carcinomas.

Palavras-chave: Bócio, Doença de Graves, Mixedema, Carcinoma papilífero da tireoide.

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https://doi.org/10.11606/issn.2176-7262.rmrp.2022.196486

INTRODUCTION

Graves' disease (GD) is the most common cause of hyperthyroidism and diffuse, toxic goiter in iodine-sufficient geographical areas, with an incidence of 14–50 cases per 100,000 inhabitants per year.[1-3] GD is more common between ages 30 and 60; however, people can be affected at any age, and it is 5–10 times more frequent in women.[2,4] Signs and symptoms of hyperthyroidism are shared with other causes of thyrotoxicosis, such as toxic multinodular goiter and toxic adenoma.[1]

The exact etiology of GD remains unclear, although it is thought to result from a complex interaction between genetic susceptibility and epigenetic factors.[5] In GD, the loss of immune tolerance to thyroid antigens and the autoimmune reaction cause the production of autoantibodies directed against thyrotropin receptor (TSH-R-Abs) by B-cell clones that infiltrate the gland. Different types of TSH-R-Abs can have various actions as thyroid-stimulating antibodies (TSAbs), thyroid-blocking antibodies, or neutral antibodies.[4] Particularly, TSAbs stimulate thyroid hormone production uncontrolled by the hypothalamic-pituitary axis, the proliferation of thyrocytes, and enlargement of the thyroid gland.[4]

GD can also involve organs other than the thyroid, including the eyes, skin, and joints. The extrathyroidal manifestations include Graves' orbitopathy (GO) and, more rarely, thyroid dermopathy [or pretibial myxedema (PTM)] and thyroid acropachy.[1-2,4]

Since these treatments do not directly affect the pathogenesis of the disease, none of the main approaches offered to treat GD are considered ideal, which include pharmacological therapy by inhibiting the production of thyroid hormones through thionamide antithyroid drugs (ATDs), primarily methimazole, and propylthiouracil; surgical removal of the thyroid gland (total thyroidectomy); and radioactive iodine (^{131}I) (RAI)-induced reduction of the thyroid tissue.[5-6]

The present case report seeks to describe goiter with remarkable systemic manifestations and a detailed workup investigation, which can reveal uncommon complications. We underlined PTM as an extrathyroidal manifestation of GD, particularly, the coexistence of papillary thyroid carcinoma, whose increased risk and its management are debated in the literature.

CASE REPORT

A 52-year-old woman was referred for specialized investigation complaining of a rapid increase in volume in the anterior cervical region for five months. She reported dysphagia, weight loss of approximately 40 kg in three months, tremors, palpitations, irritability, heat intolerance, hair loss, increased skin temperature, and exophthalmos. She also complained of a headache that started two months ago, like a migraine but denied changes in bowel and urinary habits. She had had systemic arterial hypertension for 8 years, using losartan, hydrochlorothiazide, amlodipine, and previously prescribed methimazole and propranolol. On physical examination, tachycardia (heart rate of 110 beats per minute at rest), increased skin temperature, and global thyroid enlargement **(Figure 1A)** were noted, with no palpable thyroid nodules on palpation. In the lower limbs, erythema associated with consistent edema (non-pitting) in the pretibial region was observed bilaterally **(Figure 1B–1C)**.

Her laboratory evaluation showed reduced TSH levels [0.006 μU/mL; reference value (RV), 0.4–4.5 μU/mL] and increased free T4 (5.4 ng/dL; RV, 0.9–1.8 ng/dL) and total T3 (593.0 ng/dL; RV, 84.0–172.0 ng/dL) levels, compatible with hyperthyroidism. Thyroid ultrasound showed a global enlargement of the left thyroid lobe (LTL) (74.30 cm^3, 8.50 × 4.10 × 4.10 cm) and right thyroid lobe (RTL) (85.96 cm^3, 8.20 × 4.80 × 4.20 cm). Also, it revealed the presence of three solid nodules (N) with well-defined borders and without halos. Two nodules were hyperechoic with peripheral vascularization, N1 (0.7 × 0.6 × 0.5 cm) in the LTL without calcifications and N2 (1.2 × 1.3 × 0.9 cm) in the RTL with punctiform calcifications. The third N3 (2.8 × 2.3 × 2.4 cm) in the RTL presented with heterogeneous echogenicity and vascularization throughout the nodule without calcifications, whose analysis of the ultrasonography-guided fine needle aspiration (FNA) material received the Bethesda IV classification, compatible with follicular neoplasm. Scintigraphy revealed a diffuse high-uptake goiter and a cold nodule in the projection of the RTL.

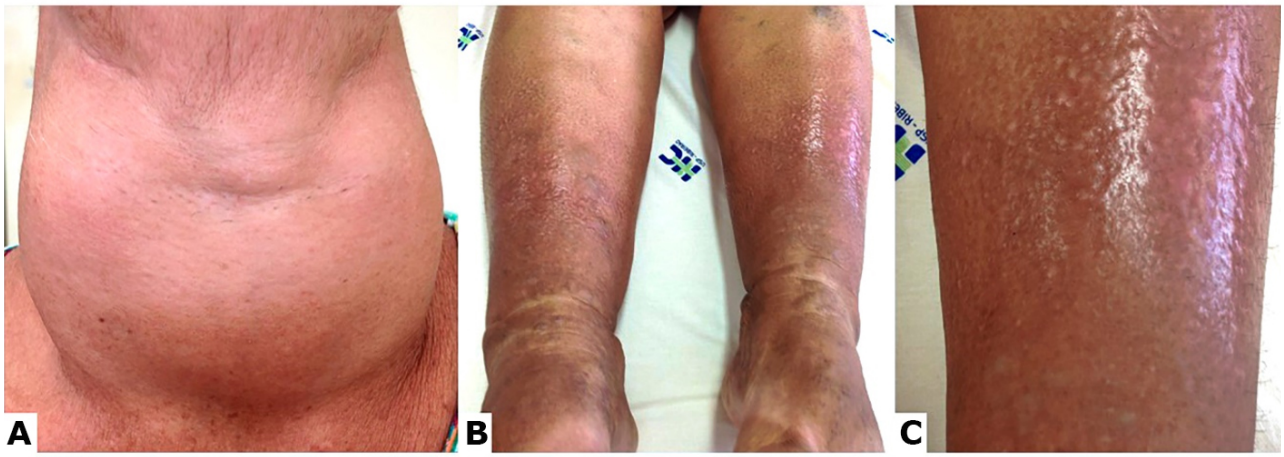

Figure 1: Details of physical examination. **(A)** Diffuse goiter. **(B)** Myxedema: non-pitting edema and erythema in the pretibial region bilaterally. **(C)** Details of cutaneous alterations of myxedema of the lower extremity with an appearance similar to that of orange skin.

Given this association of goiter, GD, and nodules suggestive of follicular neoplasia, after satisfactory control of thyroid function with methimazole, total thyroidectomy was indicated. Anatomopathological examination of the surgical specimen showed the presence of papillary thyroid carcinoma in the RTL, with free surgical margins, and adjacent parenchyma compatible with the alterations observed in GD.

To investigate the persistence of edema in the pretibial region in the postoperative period of thyroidectomy, an evaluation was performed through a skin biopsy of the right pretibial region. Pathological examination of the skin showed myxedema compatible with Graves' dermopathy. The patient developed post-total thyroidectomy hypothyroidism, and sodium levothyroxine was indicated. In subsequent evaluations, TSH values were normalized, and myxedema was reduced in the pretibial region.

DISCUSSION

The onset of goiter and hyperthyroidism symptoms may develop gradually or suddenly, and a wealth of symptoms can be reported by patients. The excess thyroid hormones affect the function of most organs, leading to a wide range of symptoms.[5] Obstructive symptoms caused by bulky goiter and common symptoms of thyrotoxicosis were reported by our patient, among others also frequent: fatigue, muscle weakness, excessive sweating, palpitations, anxiety, insomnia, and gastrointestinal dysfunction.[5]

Cardiac manifestations are more common in thyrotoxicosis of elderly patients compared to those who are younger. Atrial fibrillation occurs in more than 10% of patients aged ≥60 years but is rare in patients with hyperthyroidism who are younger than 60 years.[3] However, alterations in the basal metabolic rate, cardiovascular hemodynamics, and psychiatric and neuropsychological function can be present in mild thyrotoxicosis.[6] Rarely, embolic events, cardiovascular collapse, multisystem involvement, and decompensation caused by thyroid storm in a severely thyrotoxic patient, and death can occur in uncontrolled hyperthyroidism.[6]

In the case report, diffuse goiter, marked manifestations of thyrotoxicosis, and extrathyroidal manifestations, such as exophthalmia and PTM that specifically characterize GD were noted but without thyroid acropachy. Additionally, the investigation clarified the interpretation of the clinical findings and revealed complications.

Functional TSH-R-Abs seem to be predictive of extrathyroidal manifestations. Also, insulin-like growth factor-1 receptor (IGF-1R) antibodies have a potential role in the pathogenesis of these manifestations.[1-2,4]

Ophthalmopathy, the most common extrathyroidal manifestation of GD, occurs in approximately 25%–50% of patients.[2] The common signs of GO include exophthalmos, lid retraction, corneal exposure, edema and hyperemia of the eyelid, conjunctiva and caruncle, with symptoms of photophobia, tearing, and pain, which can cause a substantial negative impact on the quality of life.[1]

As observed in our patient, thyroid dermopathy is an uncommon cutaneous manifestation of GD, which affects approximately 0.5%–4.3% of patients with a history of thyrotoxicosis and 15% of patients with severe GO.[7] Most patients with dermopathy had ophthalmopathy (97.0%).[7] PTM in 20% of cases is associated with thyroid acropachy, mainly in the form of digital clubbing.[1]

PTM was the most prevalent form of thyroid dermopathy. However, the disorder can occur in other areas, such as the upper extremity, areas exposed to trauma or pressure, surgical scars, and vaccination sites.[1,7] The most common presentations are non-pitting edema and plaque formation with characteristic skin thickening. Reddish or pigmented lesions are usually symmetrical, elevated, and firm in the lower extremity with an appearance like that of orange skin. Nodular pretibial dermopathy may also occur. Elephantiasis is less common and occurs in 5% of cases.[1,7]

The pathogenesis and histological features of GO and PTM are similar**.** In both conditions, there is the accumulation of glycosaminoglycans (GAGs), or mucopolysaccharides, and mucin, which leads to the retention of fluid and expansion of connective tissues**.** The TSH receptor in fibroblasts and its interaction with TSH receptor antibodies provokes a cascade of immune processes with cytokine involvement, which results in the activation and proliferation of fibroblasts and mucin production, mainly composed of hyaluronic acid.[1]

GO is a result of infiltration by inflammatory cells, the proliferation of orbital fibroblasts, increased amount of GAG, expansion of fat tissue, and enlargement of extraocular muscles. The increased production of GAG by fibroblasts has critical consequences because its hydrophilic properties attract water, thus contributing to intraorbital edema and congestion. While the expansion of extraocular muscles may prevail in some patients, the enlargement of fibroadipose tissue may represent the main histological alteration in other patients.[1]

In PTM, classic histopathological features consist of an abundant and diffuse distribution of mucin, which separates collagen bundles in the papillary dermis, as large amounts of GAGs are diffusely dispersed in the reticular dermis. Furthermore, hyaluronic acid levels are frequently 6–16 times higher in these lesions than in normal skin.[7]

GD treatment should be tailored in each patient individually according to age, the severity of hyperthyroidism, goiter size, and presence and degree of ophthalmopathy.[5] ATDs have been the most indicated treatments for GD; thyroidectomy and RAI are indicated for refractory cases. [5-6]

In the present case, imaging studies showed diffuse goiter and the presence of nodules, which are frequently found in cases of GD. The prevalence of thyroid nodules in GD, detected on palpation or via imaging modalities, is higher than that in the normal population.[4,8] The incidence of thyroid nodules in GD, ranging from 22% to 45%, has been associated with an increased risk of thyroid cancer.[4,9] Furthermore, the event rate of thyroid cancer associated with nodules in GD ranges from 0.4% to 9.8%. Although the risk of carcinoma developing within a nodule is high in this condition, the treatment of GD with nodules is still debated.[9]

Although not necessary or mandatory, thyroid ultrasound is a sensitive and reliable tool for GD diagnosis, which should be part of the thyroid workup in patients with helpful information. Thyroid ultrasound provides an accurate assessment of the thyroid size for monitoring and therapy planning and allows the detection of thyroid nodules that may not be palpable on physical examination.[2,9]

Thyroid ultrasonography in all patients with GD has been shown to identify more nodules and cancer than palpation and ^{123}I scintigraphy. However, since most of these cancers are papillary microcarcinomas with minimal clinical impact, a combined investigation of several methods, such as FNA biopsy, is recommended in addition to ultrasound with grayscale and color Doppler, for surgical decision-making.[6]

In our patient, clinical, ultrasonographic, and scintigraphic criteria were used to identify high-risk

nodules, further assessed by FNA biopsy and analyzed by cytology. The pattern of sonographic features associated with a nodule confers a risk of malignancy and, combined with nodule size, guides FNA decision-making. Features with the highest specificities on ultrasound for thyroid cancer are microcalcifications, irregular margins, and tall shape, particularly when associated.[10] Further, nonfunctioning or hypofunctioning nodules by RAI scan should be considered for FNA biopsy because they may have a higher probability of being malignant.[6]

Following imaging methods and FNA, thyroidectomy was indicated due to suspicion of papillary carcinoma associated with one larger nodule (>2.0 cm) present in the middle of the diffuse enlargement of the RTL gland in our case. Following the recommendation of the American Thyroid Association and American Association of Clinical Endocrinologists, thyroid nodules larger than 1.0–1.5 cm should be evaluated. If the cytopathology is suspicious or diagnostic of malignancy, surgery is advised after the normalization of thyroid function with ATDs. Surgery should also be considered for indeterminate cytology.[6] Core needle biopsy and molecular testing of cytology specimens may be helpful for evaluating indeterminate thyroid nodules.[10]

Disease-free survival at 20 years is reported to be 99% after thyroidectomy for GD in patients with small (≤1.0 cm) coexisting thyroid cancers.[6] Among thyroid carcinomas arising from the follicular cells, papillary carcinomas occur in 80% of cases, as in our case; and follicular carcinomas occur in 14%, of which 3% is the Hürthle cell subtype.[8]

A systematic review and meta-analysis showed that patients with GD and coexisting thyroid nodules had a fivefold increase in the probability of being diagnosed with thyroid carcinoma compared with those without nodules.[8] The authors recommend considering the screening of nodules in selected patients with GD, although a potential excess in the diagnosis of thyroid papillary microcarcinomas (diameter of ≤10 mm) should be recognized. However, thyroid carcinoma can occur in patients with GD without nodules, and the absence of nodules on ultrasound examination does not reduce the risk of malignancy.[9] Furthermore, a meta-analysis demonstrated a significant increase in the risk of multifocality and multicentricity, in addition to distant metastasis, at the time of diagnosis of differentiated thyroid carcinoma in patients with GD compared with those without GD.[11]

CONCLUSIONS

The clinical manifestations of GD can be striking, and general and specialized physical examination can provide evidence of classical goiter, thyrotoxic manifestations with multisystem involvement, and extrathyroidal manifestations, including GO, and, less often, thyroid dermopathy, as PTM. A detailed investigation can reveal the coexistence of neoplasms in GD. Despite the debates, there are recommendations that can guide the management of these associated conditions.

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Institution name: This work was performed at the Internal Medicine Department, University of São Paulo, Ribeirão Preto Medical School, Ribeirão Preto, São Paulo, Brazil.
Conflict of interest: The authors declare no conflict of interest.
Financial support: none

Author contributions statement

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Felipe Ramos Caprini: Conducting the investigation process, specifically performing the data/evidence collection and final approval of the manuscript.

Maira Rubini Ruiz: Conducting the investigation process, specifically performing the data/evidence collection, and final approval of the manuscript.

Léa Maria Zanini Maciel: Conceptualization and ideas; conducting the investigation process, intellectual participation in propaedeutic and/or therapeutic conduct of the case studied; review and editing, specifically critical review, commentary, and revision, including pre-publication stages; and final approval of the manuscript.

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Editor:
Prof. Dr. Paulo Henrique Manso

Received: apr 19,2022
Approved: may 06, 2022