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Atypical presentation of Graves' disease: About 2 cases

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Abstract

GD may be associated with PTC, especially in the presence of nodules. The pathophysiology remains controversial, with one hypothesis incriminating autoimmunity; Our aim was to report a general review of the literature concerning this atypical association.

Case report: 1st case of a 19-year-old girl followed for GD associated with exophthalmia under well managed treatment, who presents a massive increase of the goitre and a difficulty to control the hyperthyroidism indicating a total thyroidectomy whose histological study is in favour of a multifocal PTC. The 2nd patient was being followed for GD associated with a small thyroid nodule revealed on ultrasound. During follow-up, the patient presented with therapeutic failure, hence the indication for total thyroidectomy, which revealed a micro-PTC

Conclusion: Based on a review of the literature, the prevalence of the association of GD and PTC is estimated at 10 to 15%, with a controversial prognosis, hence the need for rigorous follow-up and active surveillance of atypical cases of GD, especially in the presence of nodules..

Keywords: Graves' disease- autoimmunity - thyroid nodules - treatment resistance-papillary thyroid carcinoma.

Introduction

Graves' disease (DG) is the most common cause of autoimmune hyperthyroidism in adults aged between 20 and 50 years (1), affecting around 2% of women and 0.2% of men worldwide, with an incidence between 20 and 40 cases per 100,000 population per year (2).

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer in the population (3). Despite an increasing incidence, its prognosis remains favorable due to the progress made in diagnosis and management (4).

The increased incidence of carcinoma in patients with thyroiditis suggests that thyroiditis may be a

precancerous condition. The results of a meta-analysis by Dias Lopes & al indicate an increased risk of thyroid cancer in the presence of autoimmune thyroiditis, but without clear pathophysiological evidence (5).

The aim of our presentation is to report atypical cases of Graves' disease associated with nodules without ultrasound atypia revealing PTC.

Presentation of cases

Clinical case 1: A 19-year-old patient with no known medical history was being treated for GD put on carbimazol and propranolol by her referring doctor. She was referred to us following the appearance of exophthalmos after 07 months of treatment, which led to the indication for bolus treatment with corticosteroids and selenium.

During her follow-up, at 18 months of treatment, the patient presented a clinical and biological relapse of her hyperthyroidism with a sudden increase in thyroid volume and ocular pain. Clinically, the patient presented with tachycardia despite a well-conducted treatment, a WHO stage 3 goitre and a hyperthyroidism (6), and exophthalmos with an activity score of 3/7 according to EUGOGO 2021 (7). Biological control revealed overt hyperthyroidism (Table 1).

Thyroid ultrasound revealed a glandular volume of 210 ml (versus 50 ml), with the presence of several bilateral hyperechogenic nodular tissue lesions, the largest measuring 26 mm in diameter, classified as EU-TIRADS III (8). Technetium scintigraphy revealed a warm left lower polar zone compatible with the nodule described on ultrasound (Figure 1).

The patient benefited from assisted medication with an increase in carbimazole to 45 mg/d, a bolus of corticosteroid therapy as indicated by the ophthalmologists, followed by prednisone 60 mg/day for one week with gradual tapering off.

Biological control tests carried out one week after the protocol revealed persistently high levels of thyroid hormones (table 1). To remedy this apparent resistance to carbimazole, 4 g of cholestyramine were added for one week, with persistent hyperthyroidism at FT3, the patient was put on propylthiouracil and referred for endocrine surgery.

Total thyroidectomy was performed without complication. Anatomopathology revealed several whitish nodules in the 2 lobes, clearly identified macroscopically and measuring between 0.2 and 2.5*2.3 cm (fig2). Compatible with PTC invading the thyroid parenchyma without extrathyroidal infiltration. Immunostaining for analysis of exon 15 of the BRAF gene showed the absence of any mutation.

The 1-week postoperative check-up showed no postoperative complications, in particular no signs of hypocalcemia or local complications, and the ophthalmological assessment showed a clear improvement in the oculo-orbital condition. In terms of treatment, the patient was put on L thyroxine, with prednisone tapering off, and was then referred to nuclear medicine for further management.

Clinical case 2: A 57-year-old patient, hypertensive on bi-therapy was referred to our department for management of GD evolving for 03 years having received two cures of synthetic antithyroid drugs, with therapeutic failure after 1 year of treatment.

On clinical examination, the patient was in good health, tachycardic at 95 bpm, overweight, and cervical examination revealed no goiter or thyroid nodule. Biological tests showed TSH to be 0.004 µui/ml and FT4 to be 14.65 pg/ml (1.3*N). On cervical ultrasound, the

gland was normal in size, with an echostructural and Doppler appearance compatible with thyroiditis. There was a single right lower lobar nodule measuring 7 mm, classified 3 according to TIRADS (8).

Therapeutic failure and the presence of the nodule on ultrasound led to thyroid scintigraphy, which was consistent with GD without nodular lesions (fig 3).

The patient was put on propranolol 40 mg/d + carbimazol 20 mg/day. The course was marked by normalization of FT4 two months later. The patient was then referred for endocrine surgery at her request.

A total thyroidectomy was performed, the post-operative course was straightforward, and the pathological examination was in favor of a 5 mm encapsulated thyroid micro-PTC without vascular emboli. The patient was put on inhibiting treatment with L thyroxine and then referred to nuclear medicine for further treatment.

Discussion

Our study had elucidated 2 cases of PTC associated with GD, with the 1st case having difficulty controlling the hyperthyroidism and a massive increase in the goitre revealing multifocal PTC, whereas the 2nd case presented the particularity of the existence of a small cold thyroid nodule of benign ultrasound characteristics.

The existence of an occasional correlation between GD and PTC remains controversial. And the prevalence of this association was estimated at 0.5 to 8.0/100,000 until 1995 (6), Other meta-analyses have revealed a prevalence of 10 to 15% (7), A recent meta-analysis published in 2019 involving 2,582 patients treated by surgery revealed a prevalence of malignancy during GD of the order of 11.5% with extremes of 3.8% to 29.2% (8).

Histologically, papillary thyroid cancer is the most common type. A large retrospective multicentre study by P. Premoli & al. involving 579 patients operated on for thyroid carcinoma, 193 of whom had associated GD, revealed that the classic variant of PTC was the most common and that there was no significant histological difference between the two groups (with or without DG) (9). Another study by Caglar Keskin & al also showed a predominance of the papillary type in 87% of cases (10).

It is accepted that patients with multifocal papillary thyroid cancer have a higher postoperative disease progression than those with unifocal papillary thyroid cancer (11). Premoli's Italian study showed that multifocality was more frequent in the group with DG (27.5%) than in the group without DG (7.5%) ($p < 0.0001$) (9), These results are comparable with those of the study by Ergin & al, whose aim was to determine the aggressiveness of thyroid carcinomas in patients who had undergone total thyroidectomy for GD versus euthyroid goiter. The latter showed a higher number of multifocal carcinomas in the group with GD (12).

The prognosis of PTC in GD is controversial, with some studies showing that GD affects the prognosis of PTC (13) (14), others indicating that thyroid cancer in GD is no more aggressive than in euthyroid patients (15) while other authors show better disease-free survival in patients with PTC associated with GD than in others (16) .

Other more recent studies have stratified this risk according to tumor size. Premoli & al showed that the proportion of patients with recurrent and/or persistent disease at the end of follow-up was significantly higher in the GD group if the tumor was ≥ 1 cm (9).

Recent systematic reviews have analyzed the risk associated with this association and have highlighted an increased risk of PTC associated with high mortality with a high level of evidence for patients with GD and

thyroid nodules compared with patients with GD without nodules, while a moderate risk has been noted for patients with GD with solitary nodules compared with patients with multiple nodules. The same is true for PTC-related mortality in GD patients compared with euthyroid patients (17). This evidence lacks reliability for possible consensual application due to certain limitations attributed mainly to the nature of the retrospective and non-randomized studies.

The detection of thyroid nodules during GD was associated with an increased risk of malignancy, hence the need to emphasize the value of imaging during GD, even if it has no diagnostic value. Recommendations for the management of these nodules lack precision, and surgery remains the gold standard for doubtful cases. Their prognosis is still debated in the literature and lacks specificity for follow-up. Prospective randomised studies are needed to reveal more secrets and highlight the uncertainties that confound clinicians in these special cases.

Conclusion

These presentations demonstrate the importance of rigorous and vigilant follow-up of cases of relapsed GD or GD resistant to standard treatment, especially when they are associated with single or multiple nodules, and should be a warning sign for the practitioner to investigate the aetiology further, in particular a malignant pathology.

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Legend Tables and Figures

Table 1: Changes in thyroid biology during treatment

	18 month's trématent	1 week after starting carbimazol 45 mg +CTC	1 week after adding cholestyramine
TSH (µui/ml)	0.001	<0.0083	
Free T3 (pg/ml)	14.69 (3.6*N)	>20 (>5*N)	8.19 (2.04 *N) introducing PTU
Free T4 (ng/dl)	6.54 (4.2*N)	5,22 (3.37*) N	0.73 (N)

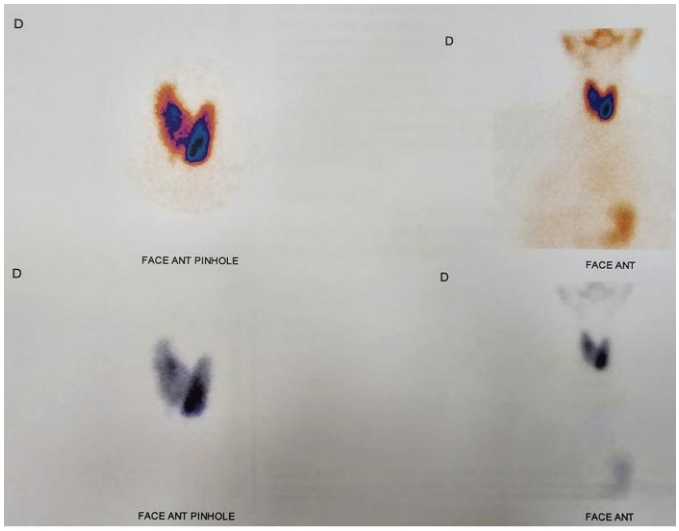

Figure 1: Thyroid scintigraphy showing basedowified goitre with a warm left lower polar nodular formation

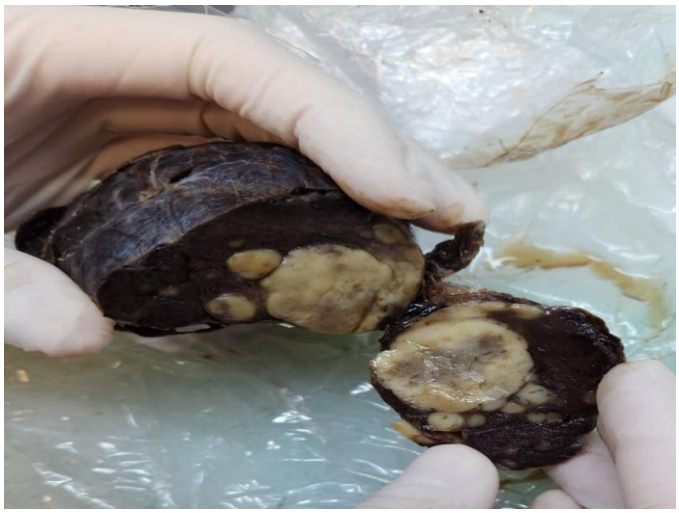

Figure 2: Macroscopic appearance of the thyroid gland showing fleshy nodules

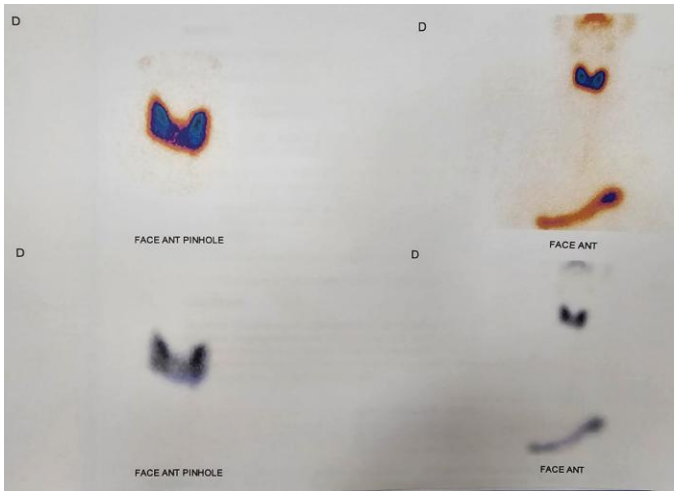

Figure 3: Thyroid scintigraphy showing Graves' disease without nodule.