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Sequential Development of Papillary Thyroid Carcinoma in Unilateral Graves' disease: A Case Report

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ABSTRACT

Background: Unilateral Graves' disease (UGD) is a rare form of Graves' disease (GD) characterized by hyperactivity confined to one thyroid lobe. Although thyroid cancer is associated with GD, its coexistence with UGD is exceptionally rare.

Case Report: A 35-year-old woman with GD, treated with methimazole, became pregnant and remained euthyroid during pregnancy after discontinuing methimazole. Four months after delivery, she was diagnosed with mild hyperthyroidism (TSH=0.05 Thyroid scintigraphy showed increased radiotracer in the right lobe, while an ultrasound revealed a 13×10×8 mm nodule with a hypoechoic, taller-than-wide appearance. A fine-needle aspiration biopsy was suspicious for papillary thyroid carcinoma (PTC), which was confirmed after total thyroidectomy.

Conclusion: unilateral Graves' disease (UGD), similar to the typical form, can occur alongside thyroid cancer. A thorough evaluation of thyroid nodules in UGD using imaging and cytology is essential for accurate diagnosis and timely treatment.

Introduction

Graves' disease (GD) is an autoimmune disorder of unknown etiology, marked by the production of autoantibodies that mainly stimulate the TSH receptor (1). This stimulation generally leads to diffuse thyroid enlargement (goiter) and increased radioactive iodine uptake, with uniform radiotracer distribution across both thyroid lobes on scintigraphy (1,2). However, rare cases of unilateral Graves' disease (UGD) have been reported, in which radiotracer uptake is confined to a single lobe, with suppression of the contralateral gland (3-5).

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, characterized by an excellent prognosis and long-term survival rates (6,7). Although its precise etiology remains unclear, PTC is more frequently observed in individuals with autoimmune thyroid disorders, particularly Graves' disease (8,9).

However, the coexistence of PTC with unilateral Graves' disease is an exceptionally rare condition that is underreported in the medical literature.

Here, we report a unique case of PTC arising in the context of UGD, emphasizing the importance of thorough clinical evaluation in atypical cases of GD.

Case Presentation

A 35-year-old woman (P.F.) was diagnosed with Graves' disease, based on goitrous hyperthyroidism associated with orbitopathy, and was referred for potential modifications in her treatment plan three months after the initial diagnosis. Initial thyroid function tests showed: TSH=0.001 (normal range: 0.3-5.0), T4=19 (normal range: 4.7-12.5), T3=377 (normal range: 70-180), and thyroid hormone binding ratio (THBR)=0.99 (normal range:0.851.1).

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Treatment with methimazole (MMI) 10 mg twice daily was initiated. Euthyroidism was achieved at the next visit, and the MMI dosage was reduced to 5 mg twice daily (Table1). She lost follow-up, and while on 5 mg MMI twice daily, laboratory results revealed: TSH=5.2, T4=7.8, T3=84.6, and THBR=0.91. The MMI dosage was reduced to 5 mg/day. The patient returned with missed periods and a positive HCG test. Methimazole was discontinued, and thyroid function tests (TFTs) in mid-gestation showed: TSH=0.58, T4=12.9, T3=117, and THBR=1.0, with positive TSH receptor antibody (TRAB) at 3.14 IU/L (positive>1.5). Changes in TFTs are shown in Table 1.

The pregnancy proceeded uneventfully, and she returned for a follow-up visit 4 months after delivery. There were no symptoms or signs of hyperthyroidism; however, a thyroid examination revealed a small, 1×1 cm fixed and firm nodule in the right lobe. TFTs showed TSH=0.01, T4=8.35, T3=90, and THBR=0.98. Thyroid ultrasonography and a thyroid scan with 99Tc were performed. Pre-pregnancy ultrasonography suggested a diagnosis of Graves' disease with goiter and hypo echogenicity, but no nodules were present. Post-delivery ultrasound revealed a solid, hypoechoic 13×10×8 mm nodule, taller than wide, in the right lobe, accompanied by multiple smaller (less than 6 mm) spongiform nodules in both lobes (Table1).

The thyroid scan showed increased ^{99}Tc uptake in the right lobe with suppression of the remaining gland (Figure1). Cytological findings from ultrasound-guided fine needle aspiration (FNA) were suspicious for papillary thyroid carcinoma (PTC) (Figure2). The patient underwent total thyroidectomy, and the final pathology report confirmed a 10 mm PTC (Figure3).

The patient was provided written informed consent for publication of this report.

Table1. Longitudinal Data of Thyroid Function, Imaging, and Treatment

	Prior to pregnancy			During pregnancy					Post delivery	
Time (Weeks)	-30	-20	-4	+8	+14	+18	+28	+32	+12	+16
T3 (ng/dl)	377	97.6	84.6	89.1	120	117	90.4	103	90	70.9
T4 (µg/dl)	19	9.5	7.8	6.38	9.75	12.9	12.4	11.9	8.35	7.99
TSH (mIU/L)	0.001	0.1	5.2	3.1	0.35	0.58	0.21	0.53	0.01	0.05
THBR	0.99	0.99	0.91	1.0	1.1	1.0	1.0	0.95	1	0.98
TRAB (IU/L)						3.1				
Thyroid scan (^{99}Tc)									Right lobe uptake with suppression of rest of the gland	
Thyroid ultrasound		Goiter, Hypoechogenecity, Increased vascularity								Same as -20, Solid, Hypoechoic and taller than wide 13×8×10 nodule in the right lobe
Treatment	MMI 10 mg twice daily	MMI 5 mg twice daily	MMI 5 mg daily							

Abbreviations: T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin; THBR, thyroid hormone binding ratio; TRAB, thyrotropin receptor antibody; MMI, methimazole

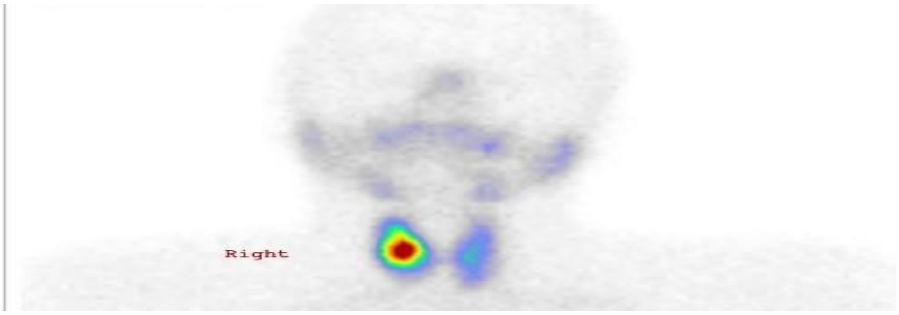

Figure 1. Technetium-99m Thyroid Scintigraphy. Increased uptake in the right lobe with suppression of the left lobe, suggestive of unilateral Graves' disease.

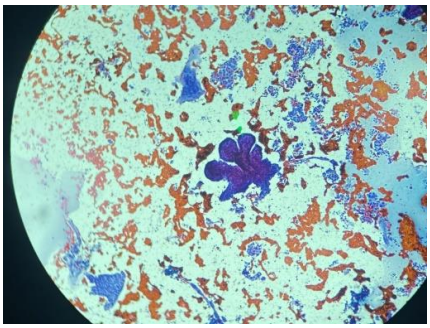

Figure 2. Fine Needle Aspiration Cytology of Suspicious Nodule. The image shows a three-dimensional papillary architecture (center), with overlapping, crowded cells suggesting papillary thyroid carcinoma

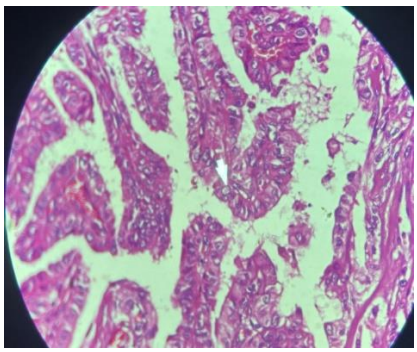

Figure 3. Histopathology of total thyroidectomy. The image demonstrates true papillae with multiple branching, pseudo nuclear inclusions, and large vesicular nuclei (arrowhead), characteristic of papillary thyroid carcinoma.

Discussion

To our knowledge, this is the first reported case of papillary thyroid carcinoma (PTC) arising in the context of unilateral Graves' disease (UGD). UGD is a rare variant of Graves' disease, characterized by hyper function confined to one thyroid lobe, with suppression of the contralateral lobe. The non-routine use of thyroid scintigraphy for diagnosing GD may contribute to the underestimation of UGD prevalence. In this regard, a retrospective study spanning nine years identified 15 cases of UGD, highlighting the underdiagnosis of unilateral Graves' disease (10).

Although several hypotheses have been proposed, including unequal lobar sensitivity to TSH, differences in sodium-iodide symporter (NIS) expression between lobes, and congenital asymmetries of the thyroid lobes, the exact pathophysiology of unilateral GD remains unclear (4).

Evidence suggests that the clinical features and treatment of UGD are comparable to those of classical GD (3). In this case, the patient presented with goiter, hyperthyroidism, and orbitopathy, achieving euthyroidism with MMI. However, thyroid scintigraphy performed postpartum revealed UGD localized to the right lobe. It remains uncertain

whether the GD was unilateral from the onset or evolved over time to become localized.

Notably, the hyper functioning right lobe in this patient became nodular, necessitating differentiation from toxic adenomas (11). This distinction is critical, as toxic adenomas are rarely malignant, whereas cold nodules in the context of GD require evaluation with thyroid ultrasound and fine-needle aspiration (FNA) as indicated. Several factors in this case argue against a diagnosis of toxic adenoma:

- ✓ The thyroid scan showed diffuse uptake in the right lobe without a sharply defined "hot" nodule (Figure1).
- ✓ TSH suppression by a 13 mm nodule is unlikely.
- ✓ Ultrasound findings of the dominant nodule were highly suspicious for PTC.
- ✓ The nodule's evolution on ultrasound was incompatible with a benign or "hot" nodule.

Interestingly, Sharma et al. reported a similar case of Marine-Lenhart syndrome in which a hyper functioning nodule was diagnosed as PTC (12). In their case, a right lobe thyroid enlargement with hyperthyroidism, positive thyroid-stimulating immunoglobulin (TSI), and increased radioiodine uptake in the right lobe were observed. FNA confirmed PTC within a 2.3×2.2×1.3 cm nodule. The thyroid scan was interpreted as a "hot nodule" in the context of GD (12). However, UGD with PTC may have been a more accurate diagnosis, as diffuse uptake without well-defined borders was noted, similar to our case. Moreover, hot nodules are rare in younger populations, and the rapid enlargement of the right lobe further challenges the diagnosis of a benign hot nodule.

Few other cases of UGD have been reported, none associated with cancer Clinical manifestations, including goiter, hyperthyroidism, and positive thyroid autoantibodies, were similar to classical GD (3,11,13,14). Management of UGD has included ant thyroid medications, radioiodine ablation, and, in three cases, hemi thyroidectomy (5,15).

Currently, no specific recommendations exist for treating thyroid nodules or cancers in the context of UGD. The American Thyroid Association (ATA) advises that thyroid nodules discovered in patients with GD should be evaluated similarly to the general population (16). This principle likely extends to patients with UGD. In our case, total thyroidectomy was performed to address both GD and the confirmed PTC.

Conclusion

Thyroid cancer can develop within the context of unilateral Graves' disease. When a nodule is detected in UGD, it is essential to differentiate it from a benign hot nodule. Comprehensive evaluation, including laboratory tests, imaging studies, thyroid ultrasound, and fine-needle aspiration, is critical for accurate diagnosis and appropriate management.

Author contributions

All authors contributed equally to the preparation and reporting of this case. Cytology and pathology review and preparation were performed by M.J. Patient data collection and preparations were conducted by M.K. The initial draft of the manuscript was written by M.K. and A.K. All authors reviewed and provided comments on previous versions of the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest statement

The authors declare that there are no conflicts of interest related to this publication.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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