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A Rare Coexistence of Medullary Thyroid Cancer with Graves Disease: A Case Report and Systematic Review of the Literature

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Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 39
Final Diagnosis: Medullary thyroid cancer
Symptoms: Hyperthyroidism symptoms
Medication: —
Clinical Procedure: Total thyroidectomy
Specialty: Surgery

Objective: Rare disease

Background: Graves disease is occasionally associated with thyroid cancer. The most common histological type of thyroid cancer in patients with Graves disease is papillary followed by follicular. Medullary thyroid cancer and Graves disease have been reported simultaneously only in a few cases in the literature.

Case Report: A case of coexistence of Graves disease and medullary thyroid cancer is described in this report. The patient was diagnosed with Graves disease 8 years ago. Although he had an initial successful treatment with carbimazole, in the last 2 years no steady euthyroid function was achieved. Total thyroidectomy was considered as the optimal treatment. An incidental medullary microcarcinoma with maximum diameter 0.5 cm was identified by pathology report.

Conclusions: Medullary thyroid cancer has been reported in patients with Graves disease in 15 cases, including the current case. Medullary thyroid cancer is aggressive, and a delayed diagnosis would be harmful. Hence, patients with Graves disease should be evaluated regularly by a thyroid specialist.

MeSH Keywords: Carcinoma, Medullary • Graves Disease • Thyroidectomy

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Background

Thyroid cancer is occasionally associated with hyperthyroidism [1]. Among thyroid malignancies, the most common histological type is papillary followed by follicular. Medullary thyroid cancer (MTC) is rarely associated with Graves disease or other forms of hyperthyroidism [2,3]. McFarland et al. demonstrated in 1980 the first case of a patient with Graves disease and MTC [4]. Until 2004, only 11 similar cases were reported in the literature according to the Habra et al. study [5]. We describe the case of a patient with persistent Graves disease who underwent total thyroidectomy. The presence of MTC was shown by histopathologic examination.

Case Report

A 39-year-old male Caucasian patient was diagnosed with Graves disease 8 years before. He also had mellitus diabetes type I, and he was receiving as a treatment a combination of rapid-acting and intermediate-acting insulin. The initial treatment with an antithyroid drug (carbimazole) was successful and the patient was euthyroid for 6 years. At that point, his thyroid function was completely suppressed because of the antithyroid medication [thyroid stimulating hormone (TSH): 48.58 μLU/mL, free thyroxine (FT4): <0.4 ng/dL, free triiodothyronine (FT3): 1.1 pg/mL]. The next 2 years, the carbimazole dosage was modified to stabilize his thyroid function when it was necessary, as adjustment of effective dosage was difficult. Finally, total thyroidectomy was suggested to achieve steadier euthyroid function. The patient agreed and decided to undergo to surgical treatment.

Preoperative ultrasonography showed a diffuse enlarged thyroid gland with cystic degeneration and increased thyroid vascularization. No pathological or suspicious lymph node was detected. A characteristic ultrasonography image is shown in Figure 1A. Lymph node mapping with ultrasonography was not performed because there was no evidence of malignancy preoperatively. Thus, a total thyroidectomy was planned by the surgeon. The preoperative concentration of serum calcium was 9.03 mg/dL, serum phosphorus was 2.5 mg/dL. and parathormone (PTH) was 7.7 pmol/L. The difficulty of the operation was mild, and no complications were noted. A gross anatomy image of the specimen is showed in Figure 1B. The patient's postoperative course was uneventful. The concentration of serum calcium, serum phosphorus, and PTH at first postoperative day were 8.64 mg/dL, 3.4 mg/dL, and 2.3 pmol/L respectively. Hence, the patient was discharged on the second postoperative day. The pathology report showed incidental medullary microcarcinoma in the left thyroid lobe with maximum diameter 0.5 cm and nodular goiter with reverse lesions (Figure 1C, 1D).

Discussion

Coexistence of thyroid cancer and hyperthyroidism has been observed at a frequency ranging from 1.6–21.1% [1]. The prevalence of thyroid carcinoma is increased in patients with Graves disease, especially in those with palpable nodules. The most common histological type of thyroid carcinoma of patients with hyperthyroidism is papillary carcinoma followed by follicular carcinoma. A thyroid malignancy is associated with more aggressive behavior and worse prognosis when it is observed in patients with hyperthyroidism [1].

Medullary thyroid malignancy is aggressive, and a delayed diagnosis could be harmful. MTC could be sporadic estimated at 75% of cases or inherited (MEN2A, MEN2B, familial) estimated at 25% of cases, and is associated with a mutation in proto-oncogene rearranged during transfection (RET). Consequently, it is necessary to obtain a detailed family history. Moreover, suspicious nodules are detected frequently through clinical examination and ultrasonography. Early diagnosis could be achieved in such cases with a fine needle aspiration (FNA) test. If diagnosis of MTC is set preoperatively with the aforementioned process, the assessment of serum calcitonin concentration and carcinoembryonic antigen should be performed. These tumor markers are also useful postoperatively, as they could predict an aggressive MTC [6].

A systematic review of the literature was performed to find similar reported cases. The databases of PubMed, Scopus, and Cochrane library were searched. From inception until March 12, 2019 there were 21 cases described of MTC in patients with hyperthyroidism, including this current case description. Regarding the cause of hyperthyroidism in these cases, it was ascertained that 15 of the patients, suffered from Graves disease. It should be noted, that no pathogenetic mechanism has been described until now explaining the coexistence of MTC and Graves disease. The reported cases of MTC in patients with Graves disease per decade was approximately steady from 1990 until now, although most of the cases (8 cases) were described between 1995–2005. In 5 cases, including the current case, the finding of MTC was characterized as incidental [4,7–9]. In our patient's case the presence of MTC is characterized as incidental because no evidence of MTC were presented preoperatively and the diagnosis was made by pathology. Clinical symptoms were presented in only 3 cases in our review [3,5,10], and included weight loss and diarrhea. In addition, the maximum diameter of MTC was ≥2 cm in 5 patients [3,8,11,12]. Finally, only 3 patients were male [5,10], confirming the scarceness of the current case. A detailed presentation of the systematic review is presented in Table 1.

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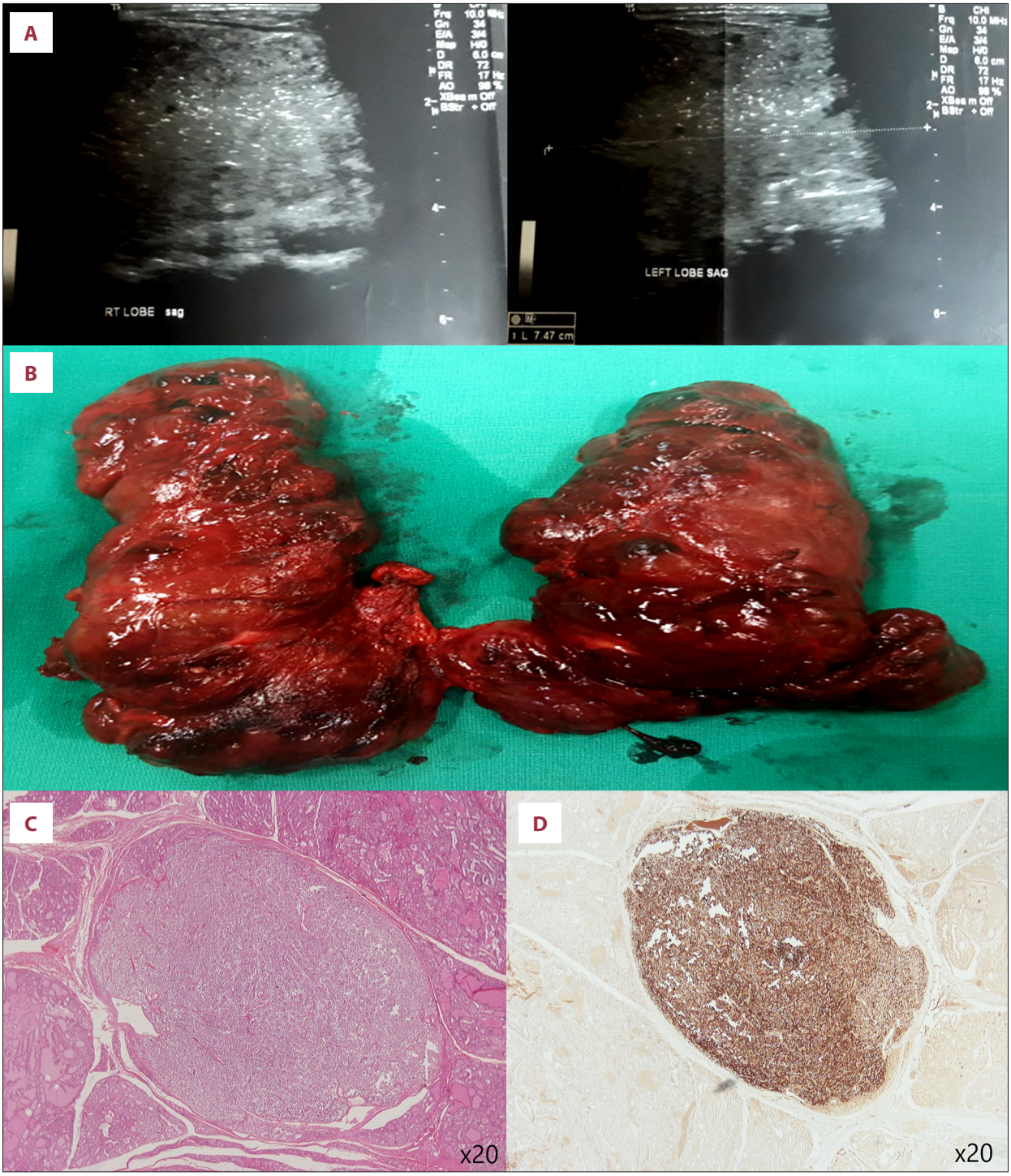

Figure 1. (**A**) Preoperatively ultrasonography image of right and left thyroid lobes. (**B**) Gross anatomy image of thyroid gland. (**C**) Medullary carcinoma of the thyroid. Hematoxylin Eosin 20×. (**D**) Medullary carcinoma of the thyroid. Calcitonin 20×.

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Table 1. Reported cases of patients with Graves disease and MTC.

Decade	First author (Year)	Age	Sex	Tumor size ≥2 (cm)	Presentation
1980–1989	McFarland [4] (1980)	30	Female	No	I
	Schwartz [7] (1989)	40	Female	No	I
1990–1999	Diklic [11] (1991)	50	Female	Yes	N
	Diklic [11] (1991)	33	Female	Yes	N
	Ardito [8] (1997)	50	NA	Yes	Postoperatively
	Brändle [10] (1999)	50	Male	No	CS & N
	Brändle [10] (1999)	33	Female	No	N
2000–2009	Verbeke [12] (2000)	67	Female	Yes	N
	Mazziotti [13] (2001)	30	Female	No	N
	Nakamura [9] (2002)	32	Female	No	I
	Habra [5] (2004)	70	Male	No	CS
	Chao [14] (2004)	NA	NA	NA	NA
2010–2019	Meng [15] (2013)	26	Female	No	N
	Khan [3] (2015)	62	Female	Yes	CS & N
	Sapalidis (2019)	39	Male	No	I

I – incidental; N – nodule; NA – not available; CS – clinical symptoms.

Conclusions

Graves disease should not be considered protective for any thyroid cancer, as it was believed earlier. The simultaneous existence of Graves disease and MTC seems to be very rare. Until now, the coexistence of Graves diseases and MTC seems to be incidentally. Even the presence of MTC in Graves disease is extremely rare; however, a complete clinical and laboratory evaluation in patients with Graves disease should be performed, especially when a multinodular goiter is also presented. Thus, an early diagnosis and appropriate management of MCT could be made.

Conflict of interest

None.

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