

# Nodular Graves' disease with medullary thyroid cancer

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## ABSTRACT

Co-existence of thyroid nodules with Graves' disease has been reported in various studies. 10–15% of such nodules harbor thyroid cancer with papillary thyroid cancer being the commonest. Medullary thyroid cancer (MTC) in nodules associated with Graves' disease is rare. On literature survey, we came across 11 such cases reported so far. We report a 62-year-old female with Graves' disease who also had a thyroid nodule that on fine-needle aspiration cytology and the subsequent postthyroidectomy histopathological examination was reported to be MTC.

**Keywords:** Calcitonin, Graves' disease, medullary thyroid cancer, nodule, total thyroidectomy

## INTRODUCTION

Graves' disease named after Robert Graves, the 19<sup>th</sup> century Irish physician is an autoimmune thyroid disorder and the most common cause of hyperthyroidism.<sup>[1]</sup> Nodules associated with Graves' disease have been reported in various studies with a prevalence rate ranging from 12.8% to 36.6%.<sup>[2–4]</sup> These co-existing nodules in Graves' disease are usually nonfunctional (cold) and rarely functional (warm/hot) when they are referred to as Marine-Lenhart syndrome.<sup>[5]</sup> Ascertaining the pathological nature of these nodules by fine needle aspiration cytology (FNAC) or fine-needle aspiration biopsy has an important bearing on the choice of treatment.<sup>[6]</sup> 10–15% of nodules associated with Graves' disease are reported to be thyroid cancers with papillary thyroid cancer being the commonest histopathology.<sup>[2,3]</sup> The prevalence of medullary thyroid cancer (MTC) in such nodules is rare. On literature review, we came across 11 cases of Graves' disease with nodules harboring MTC.<sup>[6]</sup> We report one such rare association of Graves' disease with MTC in a woman of 62 years.

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## CASE REPORT

A 62-year-old married postmenopausal woman presented to our department with complaints of a painless neck swelling on the right side for the last 20 years with recent onset diarrhea and weight loss despite of increased appetite for the last 3 months. She gave a past history of being under treatment for hypertension and type 2 diabetes mellitus. None of her children, parents, or immediate relatives had a history of neck swellings or neck surgery. There was no history of irradiation to head and neck. Her general physical examination revealed a regular pulse of 80 per min with good volume, her recorded blood pressure was 110/90 mmHg and the recorded body temperature was 98.5°F. The systemic examination was unremarkable. The local examination of the neck revealed a firm round swelling on the right side of the neck of approximately 4–5 cm in the maximum diameter. The swelling moved on deglutition. There was no other visible or palpable swelling in the neck. A high-resolution ultrasound of neck reported a lesion of 3.4 cm × 2.7 cm × 2.2 cm with multiple hyperechoic foci and distal acoustic shadowing with in it. A few level II and level III cervical lymph nodes were also seen on the left side [Figure 1]. Her hemogram, serum calcium and serum phosphorus and parathormone

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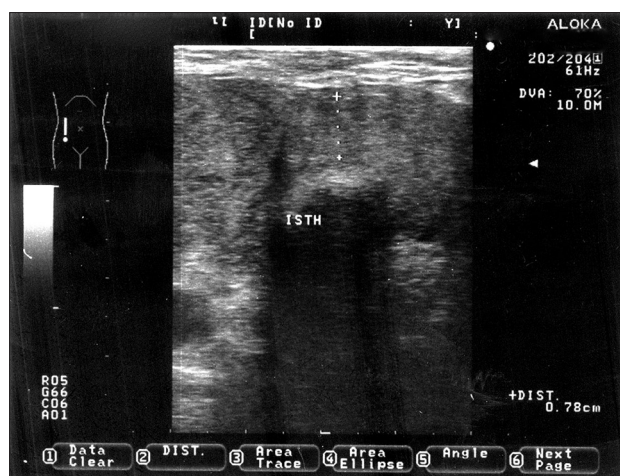
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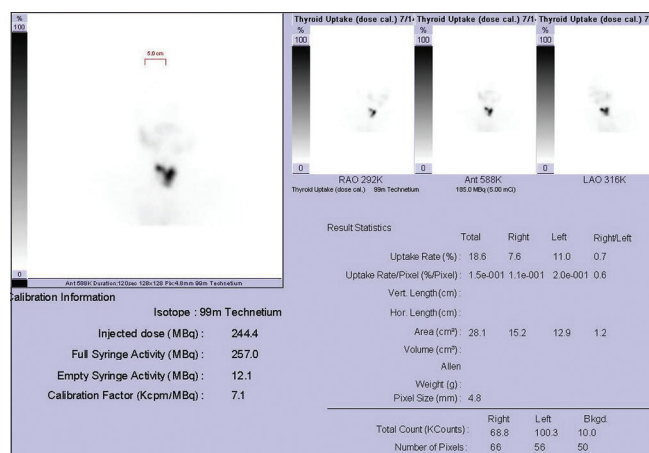
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**Figure 1:** High resolution ultrasonography neck showing a lesion with multiple hyperechoic foci and distal acoustic shadowing

were within normal limits. The free levothyroxine (FT4), free tri-iodothyronine (FT3) were elevated at 0.61 ng/dl (normal: 0.2–0.5 ng/dl) and 2.25 ng/dl (normal: 0.93–1.7 ng/dl) respectively. The thyroid stimulating hormone (TSH) was suppressed at 0.01  $\mu$ IU/ml (normal: 0.27–5.0  $\mu$ IU/ml normal range). Planar thyroid scan done 20 min after intravenous administration of 185 MBq of technetium-99m pertechnetate revealed an enlarged right lobe of the thyroid with increased uptake except in the lower pole, which had grossly decreased tracer uptake. Left lobe of the thyroid was also enlarged with uniformly increased tracer uptake. The salivary glands were poorly visualized. The software calculated thyroid uptake was increased at 18.6% (normal: 0.4–4%). The scan was reported as hyperfunctioning thyroid (Graves' disease) with a nonfunctional (cold) nodule in the lower pole of the right lobe [Figure 2]. A subsequent radioactive iodine-131 thyroid uptakes done with 25  $\mu$ Ci of oral iodine-131 revealed an elevated 24 h uptake of 56.2% (normal: 30%  $\pm$ 10%). FNAC of the thyroid nodule in the right lobe of the thyroid was reported as MTC. The patient was planned for thyroid surgery after achieving euthyroid status with anti-thyroid drugs. Her preoperative serum calcitonin and carcinoembryonic antigen (CEA) levels were reported to be 751 pg/ml (normal, <5.00 pg/ml) and 111.06 ng/ml (normal, 0.00–3.00 ng/ml) respectively. Patient underwent a preoperative contrast-enhanced CT scan (CECT) of neck, chest and abdomen, which revealed an enhancing nodule measuring 4.5 cm  $\times$  2.6 cm with internal calcification at the junction of right lobe of thyroid with the isthmus. A few level II and level III right cervical lymph nodes with the largest measuring 10 mm in the short axis and preserved fatty hilum were seen [Figure 3]. A 9 mm level II cervical lymph node was seen on the left side. CECT of chest and abdomen including the bone window were reported as normal. Total thyroidectomy with right sided selective neck dissection of level II–level VI was performed. Grossly the tumor involved one lobe of thyroid measuring 5 cm  $\times$  4 cm  $\times$  3 cm. On cut section, tumor mass was not infiltrating the capsule and was gray white. The rest of thyroid was grossly unremarkable. On microscopic examination, it showed nests of tumor cells with neuroendocrine features, at places showing clearing of



**Figure 2:** Technetium-99m pertechnetate thyroid scan showing a cold nodule in the lower pole of right lobe with thyroid uptake on 18.6%

cytoplasm with minimal pleomorphism. Thick bands of acellular material, which was eosinophilic were also seen [Figure 4a]. The nonneoplastic thyroid comprised of dilated follicles with pent up secretions with ducts showing eaten up peripheries [Figure 4b]. Surrounding thyroid showed dense lymphoid infiltrate. Lymph nodes (30) were dissected out all of which were free of tumor metastasis (30/30 – ve). The tumor was T3N0M0 (Stage II). Dissected lymph nodes (level II–level VI) in the specimen were free of tumor. A pathological diagnosis of MTC, pT3N0M0 (Stage II) was made. Her immediate postoperative period was uneventful. Two weeks after surgery, the patients developed clinical features suggestive of hypothyroidism. Her serum TSH was elevated at 60.06 uIU/ml. The patient was prescribed 150  $\mu$ g levothyroxine daily that normalized her TSH values. Serum calcitonin and CEA levels repeated 1-month after surgery were reported to be 2 pg/ml and 40.01 ng/ml respectively. Her serum calcium and phosphorus were reportedly normal at 9.48 mg/dl and 4 mg/dl respectively. Currently, the patient is on follow-up with no evidence of local disease or distant metastasis 6 months after curative surgery.

## DISCUSSION

In a multicenter retrospective trial based on 557 consecutive patients who underwent surgery for Graves' disease, thyroid nodules were observed in 25.1% of patients. Small nodules associated with Graves' disease have also been reported in various other studies with a prevalence rate ranging from 12.8% to 36.6%.<sup>[2,3]</sup> The wide range in reported prevalence relates to different methods used in detecting and documenting these nodules. Arguably the overwhelming concern for these nodules harboring malignancy is understandable for reasons of altered management strategy and prognostication from an otherwise nonnodular Graves' disease, which are usually managed with medical treatment or radioactive iodine-131 administration.<sup>[7]</sup> MTC in association with hyperthyroidism is rare. In literature, we came across 15 such cases of which 11 had Graves' disease [Table 1]. The case under report is one of such rare association of MTC with Graves' disease. The patient, a married, postmenopausal,

62-year-old women under treatment for essential hypertension and type 2 diabetes mellitus had been harboring a painless neck swelling for 20 years which she ignored. Her recent onset diarrhea with weight loss despite of good appetite prompted her treating physician to ask for thyroid function laboratory parameters that revealed an underlying hyperthyroid status with a neck swelling. On subsequent investigations, she was diagnosed to have Graves' disease with associated sporadic MTC. In light of the patient having no other malignancy, the elevated calcitonin and CEA were attributed to co-existent MTC. Her female gender was in conformity with reported rate of 80% being females among 11 reported cases of Graves' associated with MTC. Though this patient presented with MTC at the age of 62 years but considering a lapse of 20 years since the swelling it appears that the MTC developed in the existing nodule and her age at that time would have been 42 years. The mean age of patients reported in the literature is 44 years at presentation with a range of 30–70 years [Table 1]. The mean age of sporadic MTC is 46 years compared to 32 and 25 years for MTC associated with MEN 2A and MEN 2B, respectively.<sup>[16]</sup> We did contemplate a RET proto oncogene study in this patient but for logistic reasons were unable to do so. Nevertheless, we had strong reasons based on the negative family history of the patient to believe that this

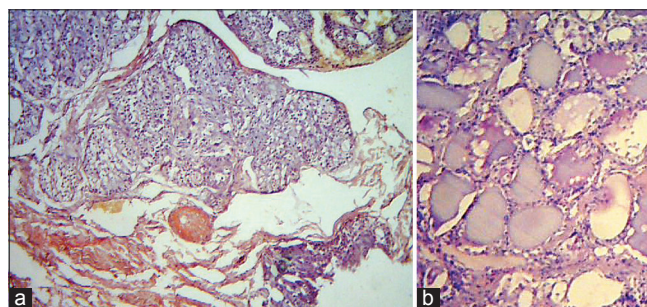
was a nonfamilial sporadic MTC. We also did not find any clinical features, laboratory findings, and imaging lesions suggesting, pheochromocytoma, mucosal ganglioneuromas, etc. RET proto oncogene studies in patients of hyperthyroidism (Graves' disease) with MTC may be selectively done in patients presenting at younger age (25–35 years), having clinical features, laboratory findings, imaging studies suggestive of hyperparathyroidism, deranged catecholamine metabolites, adrenal mass or when there is family history of thyroid nodules/thyroid surgery. The standard treatment of hyperthyroidism (Graves' disease) with MTC should be total thyroidectomy with lymph node dissection.<sup>[17]</sup> Locally advanced MTC with hyperthyroidism (Graves' disease) or those associated with distant metastasis may need adjuvant treatments like external beam radiotherapy, and chemotherapy that may include the tyrosine kinase inhibitors in refractory cases.<sup>[17]</sup> The patient under report had a pathological T3N0M0 (Stage II) disease with postoperatively normalized calcitonin levels accompanied by a significant fall in the CEA levels. The patient did not receive any adjuvant treatment. On follow-up, there is no evidence of loco-regional disease or distant metastasis. She is maintained in a euthyroid status on substitution dose of Levothyroxine.

## CONCLUSION

Rarely, nodules associated with hyperthyroidism (Graves' disease) can be MTC. Total thyroidectomy with lymph node dissection is the treatment of choice in such patients. Serial serum calcitonin



**Figure 3:** Contrast enhanced computed tomography scan neck showing an enhancing nodule with internal calcification at the junction of right lobe of thyroid with isthmus



**Figure 4:** Photomicrograph showing nests of tumor cells with neuroendocrine features, at places showing clearing of cytoplasm with minimal pleomorphism (a). The photomicrograph shows nonneoplastic thyroid comprised of dilated follicles with pent up secretions with ducts showing eaten up peripheries (b)

**Table 1: Nodular Graves' disease with medullary thyroid cancer**

Author	Age (years)	Sex	Mode of presentation	Preoperative (calcitonin pg/ml)	TNM/tumor size (cm)
Brändle <i>et al.</i> <sup>[8]</sup>	50	Male	Diarrhea and nodule	1572	1.0
Brändle <i>et al.</i> <sup>[8]</sup>	33	Female	Cold nodule	1300	1.4
Diklic <i>et al.</i> <sup>[9]</sup>	50	Female	Nodule	NA	3.0
Diklic <i>et al.</i> <sup>[9]</sup>	33	Female	Nodule	NA	6.0
Ardito <i>et al.</i> <sup>[10]</sup>	50	NA	Postoperatively	NA	T4N0M0
Verbeke <i>et al.</i> <sup>[11]</sup>	67	Female	Cold nodule	6268	2.0
Nakamura <i>et al.</i> <sup>[12]</sup>	32	Female	Incidental	110	0.35×0.25
McFarland <i>et al.</i> <sup>[13]</sup>	30	Female	Incidental	NA	1.2
Mazziotti <i>et al.</i> <sup>[14]</sup>	30	Female	Palpable nodule	5125	1.6
Schwartz <i>et al.</i> <sup>[15]</sup>	40	Female	Incidental	NA	0.5
Habra <i>et al.</i> <sup>[6]</sup>	70	Male	Weight loss	18,300	1.1
Current report	62	Female	Diarrhea and nodule	751	T3N0M0

Nodule: Thyroid nodule, NA: Not available, TNM: Tumor, node, metastasis



levels must be incorporated in the routine follow-up protocol of such patients. Advanced Stage III and Stage IV disease may require adjuvant treatment in the form of external beam radiotherapy, chemotherapy, and tyrosine kinase inhibitors. RET proto-oncogene studies can be undertaken in selective patients where clinical and laboratory parameters suggest the possibility of MEN 2A or MEN 2B.

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### Conflicts of interest

There are no conflicts of interest.

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