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Case Report

Medullary Thyroid Carcinoma in the Background of Non-neoplastic Toxic Nodular Goiter

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ABSTRACT

Background/Objective: Medullary thyroid carcinoma (MTC) is an uncommon thyroid cancer (TC), rarely found in hyperfunctioning goiter.
Case Report: We present a case of a woman treated for breast carcinoma (BCA) found to have a benign hyperfunctioning nodular goiter, its likely transformation to MTC, and its treatment. Family history revealed papillary thyroid cancer in her nephew.
Discussion: Most TCs in hyperfunctioning nodules are differentiated carcinomas. Familial MTC or MTC in association with multiple endocrine neoplasia 2 is the expected genetic association in this case.
Conclusion: The association of BCA and MTC may have been coincidental, given the high prevalence of BCA in females. It could have been the result of a common genetic precursor of both tumors and/or treatment modality such as external beam radiation therapy used to treat BCA. This case highlights the importance of considering MTC as a potential diagnosis even in cases of hyperfunctioning nodular goiter. We call for consideration of calcitonin level measurement in the workup of thyroid nodules in select cases. Close follow-up of thyroid nodules, particularly in patients with another primary malignancy, is important because of possible common genotype triggers.

Introduction

Medullary thyroid carcinoma (MTC) accounts for 5% to 8% of all thyroid cancers (TCs).[1] MTC differs from other TC types, originating from parafollicular C cells of the thyroid gland.[2,3] Metastatic disease in MTC is a consequence of disease progression and not uncommonly seen at diagnosis.[2,3] MTC can be associated with other endocrine tumors in multiple endocrine neoplasia 2.[4] Total thyroidectomy is the primary treatment. Neck dissection (ND) is often routinely preformed for known MTC, with criteria for extent of surgery laid out in clinical guidelines.[3] It is rare for a hyperfunctioning benign thyroid nodule to convert to MTC. Here, we share our hypothesis of this rare transformation.

Case Report

A 61-year old female, nonsmoker underwent right modified radical mastectomy for breast carcinoma (BCA) in 2018. There was no history of childhood head and neck radiation. She was referred to endocrinology for abnormal thyroid function tests. Clinically, there were no fine hand tremors, tachycardia, diaphoresis, or compressive symptoms but some weight loss over preceding months. Nontender nodular goiter was palpable, with no

Abbreviations: BCA, breast carcinoma; CEA, carcinoembryonic antigen; CT, computed tomography; FNA, fine needle aspiration; FNAC, fine needle aspiration cytology; LN, lymph node; MTC, medullary thyroid carcinoma; ND, neck dissection; TC, thyroid cancer; US, ultrasound.

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retrosternal extension or cervical lymph nodes (LNs). Biochemically, patient was hyperthyroid (Table 1). Thyroid scan showed a right toxic nodule. Neck ultrasound (US) revealed multiple benign-appearing nodules, largest (3.5 cm) in right lobe (Fig. *A-E*). US-guided fine needle aspiration (FNA) cytology (FNAC) of right thyroid nodule was negative for malignancy. The right nodule had been selected for FNAC because of larger nodule size, heterogeneity, and macrocalcifications. Radioiodine ablation of the thyroid gland was recommended; however, she opted for medical treatment. Antithyroid medication was started. Following chemotherapy, the patient moved to another city, where she received external beam radiation therapy. Records revealed stable thyroid function on carbimazole, as well as remission of BCA.

Five years later, the patient developed progressively worsening shortness of breath. She landed in emergency department of our institute, with compressive symptoms due to large multinodular goiter. Repeat US was not preformed prior to surgery. Total thyroidectomy was performed. No abnormal LNs were visualized at surgery. Histopathology showed MTC occupying both lobes, 5.5 and 3.5 cm in largest dimensions (Supplementary Figure 2 *A-D* and Supplementary File).

Metastatic workup revealed raised serum calcitonin and carcinoembryonic antigen (CEA). Biochemical workup of multiple endocrine neoplasia 2 revealed normal metanephrine, normetanephrine levels, and normocalcemia (Table 2). Postoperative neck computed tomography (CT) scan revealed no residual tumor. A solitary cervical LN at level 2b was noted on right side measuring 19 × 12.3 mm, FNA biopsy of which revealed benign LN tissue. Chest, abdomen, and pelvis CT scan with contrast showed a few bilateral lytic lesions in the ischium and iliac bones. The remaining imaging was unremarkable.

Three months later, CEA level was trending downwards but calcitonin was rising (Table 2). The level of BCA tumor marker CA15-3 was normal at 14.40 (1.5–32.4) U/mL. Bone scan showed no scintigraphic evidence for metastatic bone disease. Fluorodeoxyglucose positron emission tomography and CT scans were negative for metastatic disease. There was redemonstration of nonavid osteolytic areas involving right iliac bone and acetabulum posteriorly without interval change (likely osteoporotic). Rising calcitonin was attributed to occult MTC.

Clinically, patient was functional class 1, well oriented, with no concerning complaints. There were no palpable masses or nodules in the neck. There was no kyphosis or sternal, tibial, or spinal tenderness.

She was continued on thyroxine replacement, which had been initiated after thyroidectomy, as well as vitamin D and calcium supplementation. Intravenous zoledronic acid 5 mg was advised. In 2021, the patient had had a dual-energy x-ray absorptiometry scan, which revealed osteoporosis. She had received oral risedronate, which she stopped due to gastrointestinal intolerance.

In view of presence of presumably unrelated cancers, BCA and MTC, a family history of cancer was revisited. The patient's nephew (sister's son), at age of 15 years, underwent total thyroidectomy and ND in 2001 for papillary thyroid carcinoma, followed by high-dose radioactive iodine therapy.

Table 1
Biochemical Thyroid Profile at Presentation (2018) and Readmission (2022)

Date	2018	December 2022	
Thyroid profile at the time of the first presentation		Thyroid profile on readmission (carbimazole 10 mg daily)	Normal ranges
TSH level, μIU/mL	0.006	0.01	Adults 21-54 y, 0.4-4.2 55-87 y, 0.5-8.9
Total T3 level, μg/dL	3.76	…	1.23-3
Total T4 level, μg/dL	14.9	…	5.5-11
Free T4 level, ng/dL	2.5	0.9	0.89-1.76

Abbreviations: T4 = thyroxine; TSH = thyroid-stimulating hormone; T3 = triiodothyronine.

Highlights

- High suspicion for malignancy in thyroid nodules, irrespective of functional status.
- Periodic surveillance of the nodule in patients with history of another malignancy.
- Calcitonin levels in the work-up of a thyroid nodule for a subset of patients.

Clinical Relevance

Meticulous follow-up should be emphasized in a subject discovered to have a thyroid nodule, particularly in a subject who has another malignancy. This is irrespective of initial investigations being negative for malignancy in the nodule. Genomic studies have shown a link between some breast and thyroid cancer types. Patients could benefit from early definitive therapy.

Discussion

Occult MTC is a rare finding in 0.3% of patients with nodular goiter. TC and hyperthyroidism coexist at a rate of 1.6% to 21.1%.[5] The most common histologic type of TC in patients with hyperthyroidism is papillary carcinoma, followed by follicular carcinoma.[6] MTC, which can behave aggressively, can be sporadic in 75% of cases or hereditary in 25%.[7] Systematic reviews demonstrate that the odds of malignancy in hot nodules are reduced by 49% to 62%, compared with nontoxic nodules. However, the overall rate of malignancy observed in hot nodules is higher than expected.[8] Our case is unique in that it represents a probable conversion of a benign, hyperfunctioning nodule to MTC with compressive symptoms.[2,9] The majority present with cervical lymphadenopathy,[2,9] which our patient did not demonstrate. On initial evaluation, MTC diagnosis may have been missed due to large nodule size or failure to recognize cytology features of MTC. Prior to surgery, repeat US and FNAC were not performed; thus, we do not have data comparing the findings with those performed 5 years earlier. With increasing expertise with FNAC, sensitivity, specificity, and predictive values for ruling out malignancy have improved.[10] Biopsies need to be obtained from multiple sites within a large nodule or from different nodules to reduce risk of false negatives.[10] Cytology diagnosis of MTC can be more challenging. Workman et al[11] compared histopathologically confirmed MTC with preoperative cytologic assessment of index nodule. Of 71 patients, 49% were diagnosed by FNA as definitive, 20% were suspected, and 31% had no indication of MTC. This group (and others) proposed additional testing, such as calcitonin levels, to improve preoperative diagnosis of patients with MTC.[11,12]

Basal and stimulated levels of calcitonin play a vital role in diagnosing, staging, postoperative management, and prognosis of MTC.[13] The sensitivity and specificity of the test are high and are positively correlated with tumor mass.[2,13] The routine measurement of calcitonin in patients with thyroid nodules for preoperative

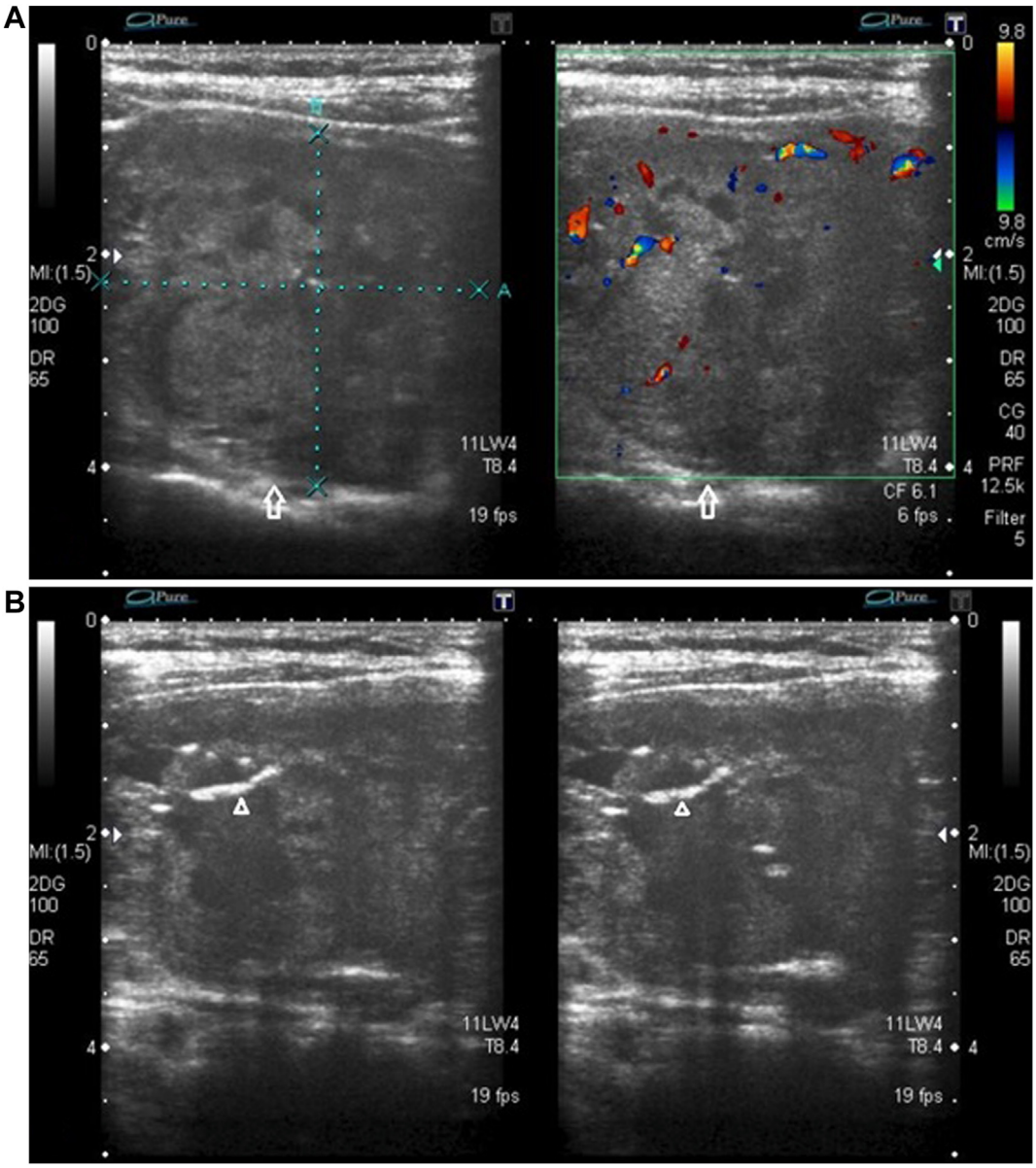

Fig. *A* through *C*, Ultrasound images of the thyroid gland showing bilateral nodular enlargement. Large well-defined heterogeneous rounded complex (with small cysts) nodule in the right lobe, measuring 35 × 33 mm (*A* and *B*, arrows), with multiple coarse calcifications (*B*, arrowheads). Inferiorly, the nodule showed extension into the sternum. Large well-defined rounded nodule (*C*, arrows) in the left lobe with multiple coarse calcifications (*C*, arrowheads). Internal vascularity was also observed on color Doppler imaging. No cervical lymphadenopathy. *D* and *E*, Ultrasound images of the thyroid gland showed an additional nodule in the right lobe (*D*, arrow), which was complex and well-defined with a few benign calcifications within it. *E*, An additional solid-appearing nodule within the isthmus of the thyroid gland (arrow), in keeping with a multinodular goiter.

Table 2
Specific Investigations: Tumor Markers for Medullary Thyroid Carcinoma and Associated Multiple Endocrine Neoplasia 2

Specific investigations	January 2023 (2 wk after thyroidectomy)	April 2023	Normal ranges
Metanephrine level, pg/mL	14.4	…	0-90
Normetanephrine level, pg/mL	121	…	0-190
Calcium level, mmol/L	8.7	…	8.6-10.2
Albumin level, g/dl	4.3	…	3.5-5.2
Vitamin D level, ng/mL	19.1	…	>30
CEA level, ng/mL	385	44.40	<3.0
Calcitonin, level, pg/mL	209	289	0.0-11.5

Abbreviation: CEA = carcinoembryonic antigen.

diagnosis of MTC remains a matter of debate. In a study conducted at a national health care system hospital, patients with nodular thyroid gland were screened for calcitonin levels. The authors concluded that calcitonin screening for early diagnosis is a highly sensitive test. The positive predictive values for basal calcitonin values for preoperative diagnosis of MTC reached 100% for values more than 100 pg/mL.[14] Although, in our patient, suspicion of TC was low given a hot nodule was seen on thyroid scan, nonsinister radiologic features, and FNAC revealing benign disease, a simple calcitonin test, in exceedingly high range, may have urged us to encourage the patient to go for surgical removal of the nodule back in 2018. The European Thyroid Association advocates calcitonin determination in patients with thyroid nodules.[15] This approach has not been adopted by thyroid associations globally.

Tan et al[16] studied the association between BCA and TC risk through a genome-wide association study, supporting a causal link between some types of BCA and TC. Radiation exposure, particularly in childhood, is a proven risk factor for TC.[17] Many proteins, lipids, and genes have been implicated in the effects of radiation on cancer development; however, gaps in knowledge persist. Whether cancers share common genotype triggers, or effects of therapeutics employed for the primary malignancy lead to secondary malignancy, is yet to be definitively ascertained.[17] Our patient had received external beam radiation therapy for BCA, which may have triggered conversion of the benign nodule to malignant disease. This association of BCA and MTC may have been coincidental given the high prevalence of BCA in females.

Family history was intriguing because familial MTC seemed likely. Records of the nephew's workup, however, revealed ongoing treatment for papillary TC, with total thyroidectomy, ND, and high-dose radioactive iodine therapy. This familial association has not been described, reminding us of unknown genetic and environmental factors in pathophysiology of cancers. Our patient's family has been referred to an oncogenetic expert to plan future preventive strategy, including testing for RET sequence variation.

We plan to follow serum calcitonin and CEA levels. If calcitonin doubling time increases, neck reimaging, 3-phase CT, or liver and spine magnetic resonance imaging would be required. At thyroidectomy, LN dissection had not been performed because MTC had not been suspected. Gallium-68 DOTATATE positron emission tomography/CT may be useful for occult MTC diagnosis that is not identified on anatomic imaging.[3]

The lytic lesions are likely related to osteoporosis in this postmenopausal woman, as evidenced by a recent dual-energy x-ray absorptiometry scan consistent with osteoporosis. MTC has a predilection for bones;[1,2] however, bone scan (sensitivity, 50%; specificity, 90%) was not consistent with metastatic disease. A marker for BCA metastasis, CA15-3, remained normal, indicating that the lytic lesions were not related to BCA metastasis. Zoledronic acid 5 mg was administered parenterally, which would serve to address the osteoporosis. Intravenous bisphosphonates have been shown to have antiangiogenic effects on metastatic bone disease.[18]

Conclusion

We recommend careful evaluation and follow-up of patients who have toxic nodules or Graves disease. Such individuals should not be considered protected from TC, as believed earlier. Clinicians need to consider primary thyroid malignancy, as well as metastatic disease, in a thyroid nodule, irrespective of functional status,[19] in patients who have another malignancy. We call for consideration of assessment of calcitonin levels on a case-by-case basis in thyroid nodule workup, particularly those revealing suspicious features clinically and/or radiologically. In MTC, where cytology diagnosis can be challenging, calcitonin screening may serve as useful adjunct in preoperative nodule assessment. Surgery is the mainstay of treatment for MTC. Medications such as cabozantinib and vandetanib can cause disease regression in a subset of patients and improve survival. This has revolutionized the medical treatment of MTC.[20]

Disclosure

The authors have no conflicts of interest to disclose.

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