Concurrent Medullary, Papillary, and Follicular Thyroid Carcinomas and Simultaneous Cushing’s Syndrome

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What Is Known about This Topic?
- Only two cases of concurrent papillary, follicular, and medullary thyroid cancer have been described.

What Does This Case Report Add?
- This is the first reported case of a patient with follicular, papillary, and medullary thyroid carcinoma, and Cushing’s syndrome. Although no associated genetic mutation is currently known, this may very well be the first report of a new syndrome.

Key Words
Thyroid · Papillary carcinoma · Follicular carcinoma · Medullary carcinoma · Cushing’s syndrome

Abstract

Background: Papillary thyroid carcinoma is the most common thyroid cancer (85%). Follicular thyroid carcinoma is the second most common type of thyroid cancer, accounting for up to 10% of all thyroid cancers. Medullary thyroid carcinoma accounts for only 5–8% of thyroid cancers. Concurrent medullary, follicular, and papillary carcinomas of the thyroid gland are extremely rare and reported scarcely. Case Report: A 72-year-old male presented with nonspecific neck pain. The workup revealed a nodular thyroid gland with a follicular lesion on fine-needle aspiration. Total thyroidectomy was performed and pathological examination identified a 25-mm follicular carcinoma, two papillary microcarcinomas, and two medullary microcarcinomas. The genetic workup was negative and no other family members were diagnosed with any endocrinopathy. Two months after surgery, the patient was diagnosed with Cushing’s syndrome that was treated with laparoscopic left adrenalectomy. On 3-year follow-up, the patient is asymptomatic with no evidence of re-
current disease. **Conclusion:** We present a rare case of a patient with follicular, papillary, and medullary thyroid carcinoma, and Cushing’s syndrome. To date, no known genetic mutation or syndrome can account for this combination of neoplastic thyroid and adrenal pathologies, although future research may prove differently.

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**Introduction**

Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are both derived from the thyroid follicular cells. Of the two, PTC is the most common thyroid cancer, accounting for 75–80% of all thyroid cancers [1]. FTC is the second most common thyroid carcinoma and accounts for 10% of thyroid malignancies. Medullary thyroid carcinoma (MTC) is derived from C or parafollicular cells and currently accounts for 4–8% of thyroid cancers. MTC presents as part of the autosomal dominant inherited multiple endocrine neoplasia (MEN) type 2 syndrome or familial MTC in about 20–25% of cases and as a sporadic tumor in the remainder [2, 3].

Concurrent appearance of medullary, follicular, and papillary carcinomas of the thyroid gland in the very same patient is extremely rare and has previously been reported only twice in the English literature [4, 5]. We present the unique case of a simultaneous presence of medullary, follicular, and papillary thyroid carcinoma as well as Cushing’s syndrome in a single patient. We discuss possible genetic associations and review the literature.

**Patient**

A 72-year-old male presented to his primary care physician with neck pain with no other symptoms. Medical history was positive for obesity, ischemic heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, a 3-cm subrenal aortic aneurism, and 100 pack-years of smoking. The patient denied any family history of endocrine malignancy or endocrinopathy. Physical examination revealed a thyroid gland of normal size and contour with no cervical or other lymphadenopathy. No other significant physical findings were recorded. Because of his neck pain, the patient was referred for a computed tomography (CT) scan of the neck. On CT, a left thyroid lobe nodule was identified with no other findings in the neck. Subsequent ultrasonography demonstrated a multinodular goiter with a dominant nodule at the inferior pole of the left lobe measuring 26 × 27 × 28 mm. Fine-needle aspiration of this nodule revealed a follicular lesion (Bethesda classification IV). A 131I thyroid scan showed normal thyroid size without any hot or cold nodules. The patient elected to undergo a total thyroidectomy which was uneventful. Pathological examination of the gland identified a left-lobe well-differentiated follicular carcinoma measuring 25 mm in diameter. In the right lobe, two papillary microcarcinomas were identified with the larger one measuring 3 mm in diameter. In addition, a left-lobe medullary microcarcinoma measuring 4 mm and a right-lobe medullary microcarcinoma measuring 1 mm in diameter were identified. Diffuse and nodular C-cell hyperplasia were also demonstrated.

Two months after surgery, a diagnostic whole-body radioactive iodine scan was performed followed by an ablative dose of 100 mCi of 131I.

To rule out familial MTC, a sequence analysis of the RET proto-oncogene from peripheral blood leukocytes was performed (exons 10, 11, and 13–16) and no mutation was detected.

At follow-up, 2 months after surgery, physical examination revealed facial plethora, supraclavicular fat pads, gynecomastia, hepatomegaly, and edema of the extremities. In the presence of hypertension and diabetes, these findings raised the possibility of Cushing’s syndrome. Both 1- and 8-mg overnight suppression tests revealed borderline nonsuppressible morning cortisol (4.1 and 2.3 μg/dl, respectively) and suppressed ACTH levels (<5.0 pmol/l). Calcium infusion test, serum estradiol, E2, LH, FSH, and testosterone and urinary free cortisol levels were all within normal limits. Urinary dopamine, epinephrine and norepinephrine levels were normal. Abdominal and pelvic CT scan revealed a lobular mass 2 × 2.4 cm superior to the left adrenal, containing a small focal fat density suspected to be an atypical adenoma. An uneventful laparoscopic left adrenalectomy was performed. Histopathology reported an adrenocortical adenoma and myelolipoma. Three weeks after the surgery, blood sugar levels improved, the leg edema disappeared, and the patient lost 7 kg in weight.

On follow-up after 4 years, including annual physical examination, neck sonography, and calcitonin and thyroglobulin levels, the patient is asymptomatic with no evidence of local or systemic recurrence of the thyroid carcinomas. No family members had been diagnosed with any similar pathology or endocrinopathy.

**Discussion**

The thyroid gland is comprised of two main types of epithelial cells. Follicular cells produce thyroid hormone and are the origin of papillary and follicular cancers. Parafollicular cells (C cells) produce calcitonin and are the origin of MTC. The embryonic source of these two cell lines differs: follicular cells arise from endoderm and C cells arise from ectoderm [6].

MTCs comprise 4–8% of all thyroid cancers. Most cases are sporadic (75%). However, 25% are due to autosomal dominant inheritance as part of the MEN 2 syndrome or familial MTC. These inherited tumors are caused by germline point mutations in various regions of the RET proto-oncogene on chromosome 10 [3, 6].
Well-differentiated thyroid carcinomas include PTC and FTC and are sporadic in most cases. PTC can be associated with the V600E BRAF activating point mutation on chromosome 7. Rearrangements of two transmembrane tyrosine kinase receptor genes (RET and NTRK1) have also been shown to be associated with PTC [7]. FTC is associated with several oncogenes – somatic mutations in MET (tyrosine kinase receptor gene), RAS (G protein signal transduction), and a translocation in PPARγ1 (tumor suppressor gene). However, the incidence of these mutations has been estimated to be lower than both PTC and MTC [8].

To date, there is no known common mutation involved in the pathogenesis of all three thyroid tumor types.

The synchronous combination of all three thyroid carcinomas has been described only twice before. In 1992, Gonzalez-Campora et al. [4] described a 27-year-old woman with a combination of a 30-mm follicular carcinoma, a 4-mm medullary carcinoma, and a papillary microcarcinoma. All three carcinomas were anatomically distinct. Thirteen years later, in 2005, Cupisti et al. [5] described a 52-year-old man with a combination of a 50-mm follicular carcinoma, an ipsilateral 15-mm medullary carcinoma, and a contralateral 3-mm papillary microcarcinoma. In both cases, no genetic workup was reported.

In all three cases, the largest (and the indication for surgery) was a follicular carcinoma. The medullary carcinoma was much smaller in all cases and was not even sampled by fine-needle aspiration. Furthermore, in two cases, it was smaller than 5 mm. The rate of incidental MTC is not well established and the optimal treatment of such incidental findings is under debate. Although routine total thyroidectomy and prophylactic central compartment (level VI) lymph node dissection are recommended for all patients with known MTC, the follow-up for patients with incidental MTC is similar to the patients operated upon for known MTC [2, 9]. In a retrospective study of incidental MTCs, Raffel et al. [10] concluded that completion thyroidectomy and neck dissection are not mandatory in patients with tumors smaller than T2 and with no genetic background. In this regard, the presence of incidental MTC in all three cases is important for follow-up planning and scheduling but is not an indication for further surgery. Recent guidelines could not reach a consensus regarding serum calcitonin measurements for every patient with suspected well-differentiated thyroid carcinoma [11]. These cases illustrate this dilemma – elevated serum calcitonin levels identified prior to surgery would have been an indication for prophylactic central neck dissection. That being said, the clinical significance of micromedullary carcinoma is not clear and, thus, the cost-effectiveness of routine calcitonin measurement has not yet been settled [12]. Although preoperative calcitonin levels do correlate with tumor size [13], this is not necessarily the case for all micromedullary tumors. In one study, calcitonin levels were only elevated in tumors larger than 0.5 cm [14].

In contrast to MTC, the incidence of incidental papillary thyroid microcarcinoma is common, well documented and investigated. In up to 50% of the autopsies, papillary thyroid microcarcinoma can be identified. The incidence increases with age and controversy exists regarding the extent of surgery, if at all, required for such lesions [15]. Obviously, the total thyroidectomy performed in all three cases is quite sufficient.

There is no previous documentation in the literature of synchronous FTC, MTC, PTC, and Cushing’s syndrome in the same patient. Ectopic production of corticotropin-releasing hormone by an MTC or its metastases is a rare cause of ectopic Cushing’s syndrome. It has been reported in 0.6% of the patients with Cushing’s syndrome and has been described in sporadic and familial cases [16]. However, our patient had ACTH-independent Cushing’s syndrome.

Another non-MEN genetic endocrinopathy is the Carney complex which is caused by a mutation in PRAKRIA tumor suppressor gene on chromosome 17 or 2 with an autosomal dominant inheritance. It is associated with spotty skin pigmentation, myxomas, schwannomas, and other endocrinopaties. Approximately 15% of these patients are diagnosed with papillary or follicular carcinoma of the thyroid gland. Approximately one fourth of patients with Carney complex have been diagnosed with primary pigmented nodular adrenocortical disease and can present with corticotrophin-independent Cushing’s syndrome [17]. Due to its rarity, our patient was not tested for Carney complex.

In conclusion, we present a rare case of a patient with FTC, PTC, MTC, and Cushing’s syndrome. To date, no known genetic mutation or syndrome can account for this combination of neoplastic thyroid and adrenal pathologies, although future research may prove differently.

Disclosure Statement

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References


