Coexistence of Papillary and Medullary Thyroid Carcinoma: A Rare Entity

Papiller ve Medüller Tiroid Kanseri Birlikteliğ: Nadir Bir Olgu Sunumu

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Abstract
The coexistence of different types of thyroid carcinomas is rather unusual. It has been considered coincidental and linked to the growing incidence of papillary thyroid carcinoma (PTC). This paper presents a case of multifocal PTC and coexistent medullary thyroid carcinoma (MTC) distinct from each other, along with PTC lymph node metastasis. The 44-year-old female patient underwent subtotal thyroidectomy with a pre-operative diagnosis of multinodular goiter. Histological reports revealed PTC in the right lobe and PTC beside a tumoral area morphologically suspicious for MTC in the left thyroid lobe. Immunohistochemistry confirmed the diagnosis of MTC. Post-operative ultrasound and subsequent fine needle aspiration biopsy revealed lymph node metastases of PTC in the right anterior cervical area. Complementary thyroidectomy, central neck dissection, and right modified neck dissection were carried out with subsequent I-131 ablation therapy. In conclusion, the biological behaviors and prognoses of MTC and PTC are different. Therefore, the entity demands a different clinical approach in treatment and follow-up.

Keywords: Papillary thyroid carcinoma; medullary thyroid carcinoma

Özet
Farklı tipteki tiroid karsinomların birlikteliğini oldukça nadir bir durum olarak kabul edilmektedir. Bu durum tesadüfi olarak kabul edilmekte olup, giderek artan papiller tiroid kanseri [papillary thyroid carcinoma (PTC)] insidansı ile ilişkilendirilmektedir. Bu yazida, birbirinden normal tiroid dokusu ile net olarak ayrılan tiroid kanseri [medullary thyroid carcinoma (MTC)] yan sıra multifokal PTC ve PTC lenf metastazı tespit edildi. Kliniğimize başvuran 44 yaşındaki kadın hasta, multinodüler guatr tanısı ile subtotal tiroidektomi operasyonu geçirdi. B [<...>]

Introduction
Papillary thyroid carcinoma (PTC) are the most common of all thyroid cancers (>70%). It originates from follicular thyroid cells and shows multifocal growth in nearly 29% cases. Immunohistochemical results of PTC are positive for thyroglobulin and Thyroid Transcription Factor-1 (TTF-1). PTC cells are negative for calcitonin, Carcinoembryonic Antigen (CEA), and chromogranin. PTC...
shows a high recovery rate. Metastasis to lymph nodes in the neck is seen in over 75% of the large thyroid cancers and 50% of small tumors (1). Medullary thyroid cancer (MTC), derived from the parafollicular calcitonin (CT) producing cells of the thyroid, is the third most common of all thyroid cancers (about 1 to 3 percent). Most of them are sporadic (75%), while approximately 25 percent are familial, as evident in multiple endocrine neoplasia type 2 (MEN2) (2). MTC has a much lower recovery rate than the papillary and follicular types of thyroid cancers, which are “well-differentiated”. Immunohistochemically, the MTC cells stain positive for calcitonin, chromogranin, and CEA and negative for thyroglobulin (1).

Coincidental occurrence of MTC and PTC in the same patient is rare and represents less than 0.5% of all thyroid malignancies. In the last decades, case reports on PTC are have increased, primarily due to the rise in its incidence (3). Generally, the prognosis is determined by the MTC component, which is even poorer. Therefore, the treatment and follow-up should be planned accordingly. Investigators who have studied the biological behavior of MTC in association with PTC did not find any difference in comparison to the solitary MTC cases (4). This case report describes a patient with PTC in the right thyroid lobe, sporadic MTC, and PTC separately in the left thyroid lobe and PTC metastasis to the right cervical lymph nodes.

Case Report

A 44-year-old female (housewife) was admitted to a hospital with swelling on the neck and weakness. The thyroid ultrasound disclosed an enlarged thyroid gland with two nodules in the left lobe (16 mm and 7 mm in greatest dimension) and two nodules in the right lobe (28 mm and 5 mm in greatest dimension). The free thyroxin levels were lower, while the thyroid-stimulating hormone level of the patient was higher than the normal range. Euthyroidism could be accomplished with L-thyroxine replacement therapy, and then the patient underwent right total thyroidectomy and left subtotal thyroidectomy. The histopathological evaluation of the excised material revealed PTC in the right thyroid lobe and PTC besides a tumor area that was considered suspicious for MTC in the left lobe. Subsequently, the patient was admitted to the author’s hospital for further evaluation.

After admission to the author’s hospital, the specimens were re-evaluated. Of the tumoral areas, 1.0 cm PTC and 1.5 cm MTC were identified in the left thyroid lobe, and another 0.9 cm PTC focus was present in the right lobe on histological evaluation. Normal thyroid tissue demarcated the papillary carcinoma area from the medullary one in the left thyroid lobe (Figure 1). Cuboidal cells lined the finger-like projection of PTC (Figure 2a). Pleomorphic diversification of tumor cells and intermediary amyloid-like material helped identify MTC (Figure 3a), and mitotic activity was low. Immunohistochemically, the lesional cells of PTC were positive for thyroglobulin and negative for calcitonin (seen surrounded by normal thyroid tissue (Figure 2b), while the MTC cells stained positive for calcitonin (Figure 3b).

The calcitonin and CEA levels were found to be within normal limits, and RET protooncogene analysis was negative. Postoperative ultrasound revealed a 6 × 4 mm fibrotic tissue with no evidence of residual thyroid tissue on the right side and a 13 × 6 mm residual thyroid tissue on the left side. The right anterior cervical area showed enlarged lymph nodes (16 mm in greatest dimension). Fine needle aspiration biopsy of the nodes revealed PTC metastasis. Whole-body PET scan disclosed increased 18F-FDG uptake in right superior jugular and right superior paratracheal lymph nodes. Central
Neck dissection, modified right neck dissection granting the removal of five lymph nodes, and complementary thyroidectomy were performed. Histology disclosed lymph nodes metastases of the PTC. Postoperative thyroglobulin and calcitonin levels were found to be 46 ng/mL and 25 pg/mL, respectively (normal range 0-55 ng/mL and 0-150 pg/mL, respectively). Post-surgical thyroid ablation as an adjuvant treatment was carried out using I-1–131 in a dose of 150 mCi. The whole body I-131 scan post-treatment showed diffuse and focal activity foci in the thyroid area over the sternal indentation. Six months after the intervention, thyroglobulin and calcitonin levels were detected to be <3 ng/mL and 16 pg/mL, respectively. Subsequently, a 6-month follow-up visit had been scheduled for which the patient did not show up.

Discussion

The coexistence of PTC and MTC is rather unusual and can be observed in two settings, a mixed tumor showing dual differentiation (defined as Mixed Medullary-Follicular Cell Carcinoma-MMFCC), or a collision tumor with well-defined components at distinct locations. The case reported in this paper belongs to the latter category since the two thyroid carcinoma types observed in the same lobe were separated by normal thyroid parenchyma. The coexistence of various degrees of differentiation in different areas within one spotlight of thyroid cancer (MMFCC) is more common. It is a kind of MTC that is positive for calcitonin, and also a kind of follicular (papillary) carcinoma positive for thyroglobulin; its incidence rate is less than 5% of all thyroid tumors (5). Tumors with mixed histological characteristics are more commonly detected in iodine-deficient areas (6).
Collisional MTC and PTC is a rare entity with an incidence of <0.5% of all thyroid tumors. The occurrence of two distinct tumor types, derived from different embryogenic tissues, developing simultaneously in the same patient, is questionable. Several hypotheses have been put forward to explain the coexistence of different thyroid tumor types in the literature. The stem cell theory states that follicular epithelial cells and parafollicular C cells are differentiated from the suprapericardial body which originates from the same stem cell. They may undergo neoplastic transformation in response to common tumorigenic stimuli. Another theory describes that stimulation from one tumor results in the simultaneous inversion of follicular cells and C cells. The collision tumor theory affirms that two independent tumors exist in the same region just by coincidence (7); most authors have accepted this theory in the last two decades.

Several genes and genetic mutations responsible for the development of thyroid cancer have been identified, such as oncogenic tyrosine kinase alterations (RET/PTC, TRK), BRAF mutations, and PAX8/peroxisome proliferator-activated receptor-gamma rearrangement (8,9). Some studies reveal the role of both, RET and BRAF genes in tumorigenesis of the collision tumors (10). RET germline mutation and V804M proto-oncogene mutation have been identified in simultaneous PTC and MTC in several cases. Nonetheless, no definite conclusions have been reached. No common genetic mutation could be detected in the pathogenesis of the two tumor types (10).

Biscolla et al. asserted that 21 of 190 (11.05%) cases of MTC were associated with PTC. However, the epidemiological, clinical, and pathological features of patients with MTC associated PTC and patients with distinct MTC showed no difference (4). Erhamamci et al. found a 0.28% prevalence of simultaneous MTC and PTC in among 1420 differentiated thyroid carcinoma (DTC) patients (4 in 1420) (11). Dionigi et al. reported only 5 cases of simultaneous MTC and multifocal PTC (like the present case) out of 2897 thyroid cancer patients over 15 years (12). It has been suggested that this entity represented a primary tumor with an incidental pathological finding of a second malignancy (13,14).

Wong et al. established that MTC/DTC collision tumors were diagnosed earlier in tumor development than MTC alone, tending to a better prognosis (13). A multicentre Italian study on evaluating 183 PTC/MTC patients concluded that in cases with concurrent MTC and PTC, the priority since this entity has the most severe impact on prognosis (15). In conclusion, the incidence of thyroid cancer, PTC in particular, has increased all over the world in the last three decades and is multifactorial, most likely (3,16). Accordingly, the incidence of medullary and papillary thyroid cancer together, which has been considered coincidental, is decreasing. Although the prognosis of the disease is predominantly defined by the more aggressive MTC component, every malignancy must be treated according to its respective stage and current guidelines.

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