Case Report

Synchronous Medullary Carcinoma, Hurthle Cell Carcinoma and Parathyroid Adenoma: A Unique Case Report and Literature Review

Fatih Kuzu,[1] Ahmet Cinkaya,[2] Mehmet Fatih Ekici,[3] Hilmi Kodaz,[4] Aysenur Deger[5]

[1]Department of Endocrinology, Evliya Celebi Training and Research Hospital, Kutahya, Turkey
[2]Department of Radiation Oncology, Dumlupinar University Faculty of Medicine, Kutahya, Turkey
[3]Department of General Surgery, Evliya Celebi Training and Research Hospital, Kutahya, Turkey
[4]Department of Medical Oncology, Acibadem Hospital, Eskisehir, Turkey
[5]Department of Pathology, Dumlupinar University Faculty of Medicine, Kutahya, Turkey

Abstract

Presently described is the case of a 68-year-old female patient who presented at a general surgery clinic with the complaint of swelling in the throat. Medullary carcinoma, Hurthle cell carcinoma, and parathyroid adenoma were detected. The patient underwent surgery and was followed-up with vitamin D and 1-thyroxine replacement therapy.
Keywords: Hurthle cell carcinoma, medullary carcinoma, parathyroid adenoma

Cite This Article: Kuzu F, Cinkaya A, Ekici M, Kodaz H, Deger A. Synchronous Medullary Carcinoma, Hurthle Cell Carcinoma and Parathyroid Adenoma: A Unique Case Report and Literature Review. EJMO. 2017; 1(1): 34-37

Medullary thyroid carcinoma (MTC) may occur in a sporadic form, or may be observed in a hereditary form as a component of multiple endocrine neoplasia type 2 (MEN2) syndromes. The fact that there is no MTC in another family member does not mean that the case is not familial. For familial MTC, DNA analysis and screening must be performed for RET proto-oncogene mutations. Mutation of this gene has also been demonstrated in papillary thyroid cancers (PTC); however, this is a somatic mutation.[1] It is observed only in the cancerous tissue and is not used in family screening.

There are reports in the literature describing simultaneous papillary carcinoma and MTC in the same thyroid gland.[2–4] There is also a report of the coexistence of MTC, PTC, and primary hyperparathyroidism.[5] To our knowledge, this is the first case report of parathyroid adenoma accompanying Hurthle cell carcinoma and MTC. We also present a review of the literature.

Case Report

A 68-year-old female patient presented at the general surgery clinic with the complaint of swelling in the throat. The patient's history included hypertension and coronary artery disease diagnoses, and she was receiving medical treatment for those diagnoses. There was no history of radiation exposure or family history of thyroid cancer.

Physical examination determined that her weight was 72 kg and her height was 168 cm. Blood pressure was 125/75 mmHg, she had thyroid in stage 1b, and palpation revealed nodule of approximately 2 cm in size with medium stiffness in the right thyroid lobe. Serum biochemical evaluation indicated calcium level of 11.2 mg/dL. Complete blood count

was normal. Hormone testing yielded thyroid-stimulating hormone level of 1.42 uIU/mL and free thyroxine level of 0.78 ng/dL.

A hypoechoic nodule of approximately 17x10x19 mm with rough-to-fine calcific foci was observed at the mid-posterior of the right thyroid lobe in sonographic image. There was an isoechoic nodule approximately 8x6x6 mm in size located at the posterior inferior left thyroid lobe and a heterogeneous hyperechoic nodule approximately 7x5x6 mm in size in the middle posterior section. Result of thyroid fine needle aspiration biopsy of the suspicious nodule in the right lobe was suspicious malignant cytology. The patient underwent total thyroidectomy.

The patient was referred to the department of endocrinology and metabolic diseases in the postoperative period based on the pathology report.

MTC was detected in the right lobe section of thyroidectomy material. Immunohistochemistry revealed positive stain with calcitonin, synaptophysin, neuron specific enolase (NSE), carcinoembryonic antigen (CEA), low molecular weight keratin (LMWK), and cytokeratin 19 (CK19). There was intermittent chromogranin staining. Anti-mesothelial cell antibody staining was negative. Hurthle cell carcinoma with a diameter of 6 mm was detected in the left lobe. Immunohistochemistry showed positive stain with CK19, Galectin-3, thyroglobulin, and LMWK. Chromogranin, calcitonin, synaptophysin, NSE, and CEA stains were negative. A homogeneous, yellowish piece of nodule tissue 22 x 13 x 8 mm in size sent separately by the surgeon was reported to be parathyroid adenoma (Figures 1–5).

Postoperative serum biochemical evaluation produced calcium level of 9.6 mg/dL, phosphorus level of 3.8 mg/dL, parathormone level of 131 pg/mL, and 25-hydroxy vitamin D level of 18 ng/mL. Since the calcium level was normal, high parathormone level was thought to be secondary to vitamin D deficiency. Vitamin D replacement therapy was initiated. Pathological lymph node was not detected in detailed neck ultrasonographic imaging performed for MTC following result of calcitonin level of 4.8 pg/mL (<10 pg/mL). Thyroglobulin level was 0.07 ng/mL and anti-thyroglobulin level was 1 IU/mL. Thyroid function tests were normal with 1-thyroxine replacement. When examining for MEN, computed tomography and adrenal imaging were normal. Catecholamine metabolites were normal in 24-hour urine collection, and RET mutation genetic analysis was negative. The patient was followed-up with vitamin D and 1-thyroxine replacement.

Discussion

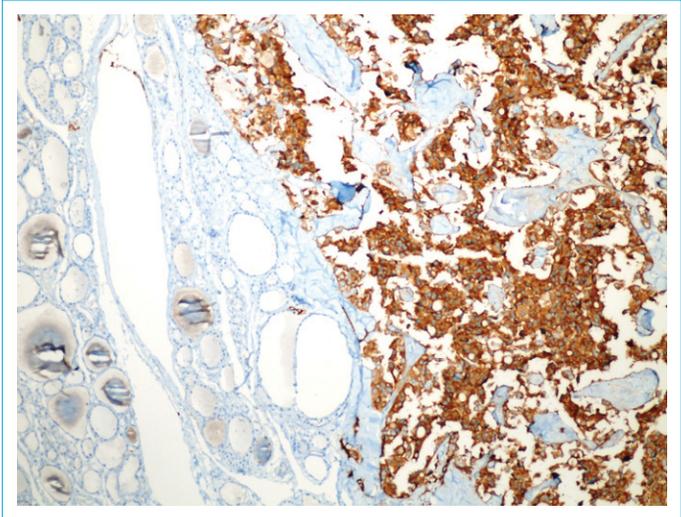MTC is a malignant neoplasm originating from parafollicu-

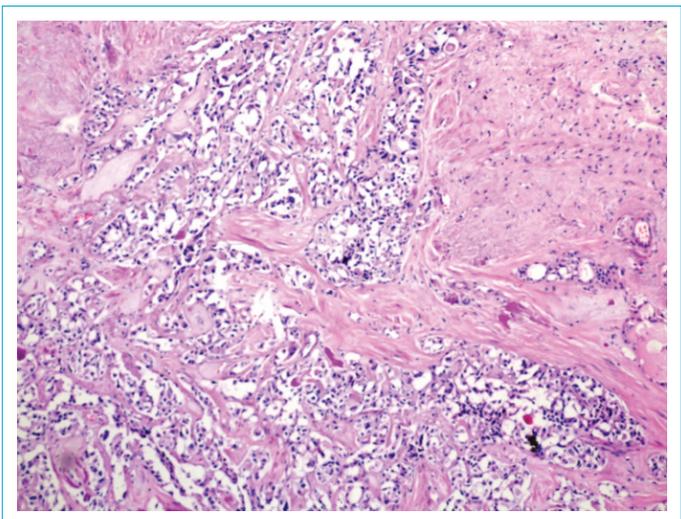**Figure 1.** Diffuse synaptophysin stain reaction in medullary carcinoma tumor cells.

Figure 2. Positive hematoxylin and eosin stain.

lar cells (C cells) of the thyroid gland and morphologically resembles parafollicular cells. MTC represents approximately in 5% of all thyroid cancers. PTC is a malignant epithelial tumor originating from the thyroid follicular epithelium and exhibits characteristic nuclear changes. PTC is the most common malignant neoplasm of the thyroid and constitutes approximately 85% to 90% of the cancers in this organ. Hurthle cell carcinomas are not common; they account for 15% to 20% of all follicular carcinomas. As with follicular adenoma and carcinoma, the separation of Hurthle adenoma and carcinoma is also histologically dependent on the presence of transcapsular and/or vascular invasion.[6]

Though MTC and PTC are considered to be totally different tumors, their pathogenesis is related to the activation of some common oncogenes, such as RET, RAS, and BRAF.
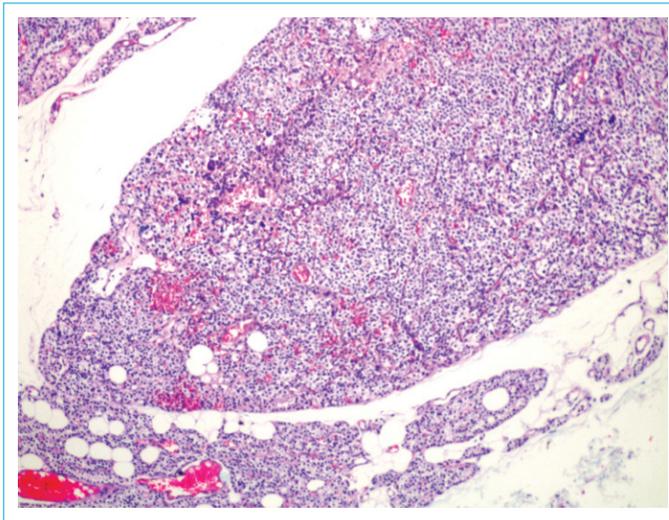
Figure 3. Parathyroid adenoma stained with hematoxylin and eosin with border separating it from peripheral parathyroid tissue.
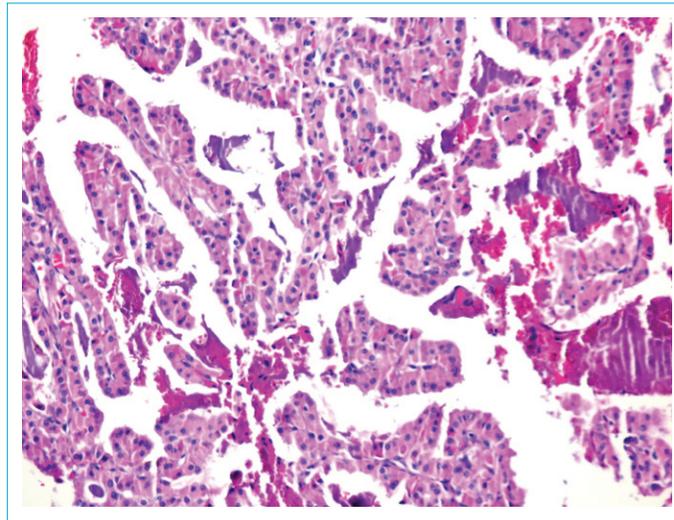

Figure 5. Case 2: Tumor cells in Hurthle cell carcinoma with eosinophilic cytoplasm of oncocytic character. Hematoxylin and eosin x400.
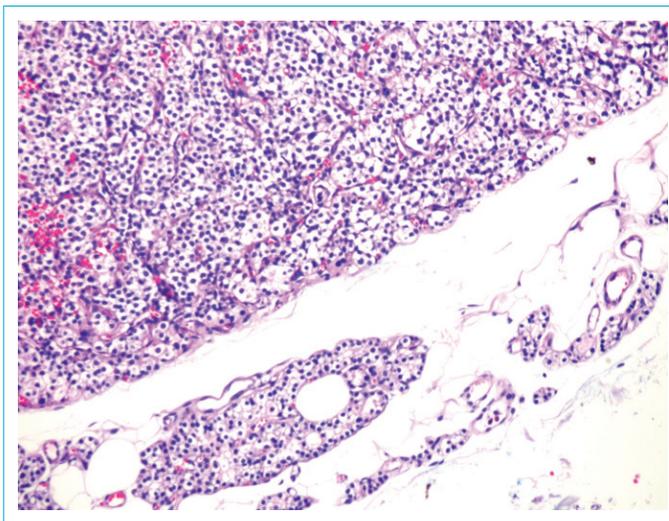

Figure 4. Parathyroid adenoma separated from environmental parathyroid tissue by a thin fibrous capsule. Hematoxylin and eosin x200.

[7] The RET proto-oncogene is activated in both MTC and PTC through different oncogenic mechanisms. The RET gene is not expressed in thyroid follicular cells; however, according to recent data, in approximately 6.8% of cases with PTC, RET/PTC can be activated through chromosomal rearrangement. RET/PTC variants are often formed in radiation-induced papillary cancer.[1, 8] Although RET germline mutations are present in 95% to 98% of hereditary MTC, somatic mutations are present in 40% of sporadic MTC cases. The role of RET in simultaneous MTC and PTC formation has been investigated in several studies; however, the results are contradictory.[7, 9] In some studies, it has been observed that germline mutations of RET may create the tendency for this coexistence. Shifrin et al. reported that a RET V804M

mutation was responsible, and Ciampi et al. detected S981A germline mutation in 1 patient and V804M germline mutation in another of 24 patients with MTC and PTC.[7]

MEN 2C syndrome was described as a new syndrome by Shifrin et al. A total of 40 of 107 family members were found to have V804M RET mutation in their study. Thyroidectomy was performed on 15 members of the family. There was a high prevalence of MTC and concomitant PTC (40%). Occurrence of PHPT was low (13%) and accompanying parathyroid adenoma was seen in only 2 cases. No pheochromocytoma was found. This family is the largest to be reported with this mutation. This syndrome does not conform to the classic familial MTC or MEN2A cancer syndrome. PTC has not been considered an incidental finding and is accepted to be the result of an inherited V804M RET mutation. MEN2C syndrome has been suggested to be the result of V804M RET mutation accompanied by MTC, PTC, and rarely, PHPT.[4, 9]

Another oncogene that can activate both PTC and MTC is the RAS oncogene. It is present in 40% to 50% of follicular thyroid carcinomas and 10% to 20% of the follicular variant of PTC. It is described in 10% to 40% of sporadic MTC cases. Sometimes mutations in the RAS and RET genes can occur in the same tumor.[10]

We found 2 cases similar to ours in the literature. PTC and MTC accompanied by parathyroid adenoma with negative RET gene mutation was observed by Cheung et al.[5] and the coexistence of PTC and MTC was also detected in a patient with secondary hyperparathyroidism following renal transplantation by Behrend et al.[11]

Some cases that clinically suggest sporadic MTC may, in fact, be familial. As such, it is very important to perform ge-

netic examination of the index case for RET mutations. A positive result indicates a familial case and family screening is required. If the mutation screening is negative and the family history is negative, it is considered a sporadic case. In our case, there was the coexistence of Hurthle cell neoplasia, MTC, and parathyroid adenoma. RET mutation result in screening for MEN was negative. Surrenal imaging was normal. Level of catecholamine metabolites in 24-hour urine test was normal. Our case was similar to MEN2C syndrome described by Shifrin; however, because the RET gene mutation was negative the coexistence was thought to be incidental.

The diagnosis, treatment, and follow-up of this case was conducted by a multidisciplinary team of an endocrinologist, an endocrine surgery team, and pathology unit. Genetic diagnosis studies are as valuable as pathological examination, and familial cases can be successfully diagnosed with multidisciplinary study.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Biscolla RP, Ugolini C, Sculli M, Bottici V, Castagna MG, Romei C, et al. Medullary and papillary tumors are frequently associated in the same thyroid gland without evidence of reciprocal influence in their biologic behavior. Thyroid 2004;14:946–52. [CrossRef]

2. Dionigi G, Castano P, Bertolini V, Boni L, Rovera F, Tanda ML, et al. Simultaneous medullary and papillary thyroid cancer: two case reports. J Med Case Rep 2007;1:133. [CrossRef]

3. Machens A, Dralle H. Simultaneous medullary and papillary thyroid cancer: a novel entity? Ann Surg Oncol 2012;19:37–44.

4. Marsh DJ, Learoyd DL, Andrew SD, Krishnan L, Pojer R, Richardson AL, et al. Somatic mutations in the RET proto-oncogene in sporadic medullary thyroid carcinoma. Clin Endocrinol (Oxf) 1996;44:249–57. [CrossRef]

5. Cheung L, Howlett D, El Teraifi H, Kirkland P. Association of synchronous medullary and papillary thyroid carcinomas with primary hyperparathyroidism: first case report and literature review. J Laryngol Otol 2014;128:565–8. [CrossRef]

6. Ciampi R, Romei C, Pieruzzi L, Tacito A, Molinaro E, Agate L, et al. 17. Classical point mutations of RET, BRAF and RAS oncogenes are not shared in papillary and medullary thyroid cancer occurring simultaneously in the same gland. J Endocrinol Invest 2017;40:55–62. [CrossRef]

7. Ciampi R, Mian C, Fugazzola L, Cosci B, Romei C, Barollo S, et al. Evidence of a low prevalence of RAS mutations in a large medullary thyroid cancer series. Thyroid 2013;23:50–7. [CrossRef]

8. Komminoth P. The RET proto-oncogene in medullary and papillary thyroid carcinoma. Molecular features, pathophysiology and clinical implications. Virchows Arch 1997;431:1–9.

9. Moura MM, Cavaco BM, Pinto AE, Leite V. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. J Clin Endocrinol Metab 2011;96:E863–8. [CrossRef]

10. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al; Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567–610. [CrossRef]

11. Behrand M, von Wasielewski R, Brabant G. Simultaneous medullary and papillary microcarcinoma of thyroid in a patient with secondary hyperparathyroidism. Endocr Pathol 2002;13:65–73. [CrossRef]