

A Case of Mixed Medullary and Follicular Cell Carcinoma of the Thyroid

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Abstract

A medullary thyroid carcinoma is a malignant tumor derived from the C-cells of the thyroid. Despite their distinct embryological origin, medullary thyroid carcinomas are exceptionally accompanied by a tumor derived from the follicular cells; this is defined as mixed medullary and follicular cell carcinoma. There have been controversies regarding the origin of this rare mixed thyroid carcinoma questioning whether or not a mixed carcinoma originates from a common cancer stem cell. We present a case of mixed medullary and follicular cell carcinoma in which two thyroid carcinomas were found intermingled in the thyroid as well as in the metastatic cervical lymph nodes. We examined the tumor by immunostaining with thyroglobulin, calcitonin, and thyroid transcription factor-1, and also reviewed the literature and discuss the origin of this rare mixed thyroid carcinoma.

Key words: medullary thyroid carcinoma, follicular thyroid cell, papillary thyroid carcinoma

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Introduction

A malignant tumor derived from the C-cells of the thyroid is defined as a medullary thyroid carcinoma (MTC). MTC is usually composed of a pure population of cells with neuroendocrine differentiation. Amyloid deposition in the parenchyma may be detectable either by the usual Hematoxylin and Eosin (H&E) stain or using a Congo red stain in approximately 80% of cases (1). Most MTCs secrete calcitonin and express carcinoembryonic antigen (CEA), both of which are useful diagnostic immunohistochemical markers as well as clinical markers that can be used to evaluate disease activity. In contrast with rare MTCs, papillary and follicular thyroid carcinomas are the most common thyroid cancers, accounting for more than 90% of all thyroid cancer (1). These tumors derive from the follicular cells of the endoderm. Embryologically, thyroid follicular cells are most likely derived only from the median of a thyroid anlage, while C-cells originate in the ultimobranchial body, corre-

sponding to the fourth (or fifth) pharyngeal pouch (2).

Despite their distinct embryological origin, exceptional cases do exist in practice in which an MTC is accompanied by a tumor derived from follicular cells, namely a follicular or papillary thyroid carcinoma (FTC/PTC). We report here on a case of mixed medullary and follicular cell carcinoma (MMFCC) and review the tumor origin of the mixed thyroid carcinoma.

Case Report

A 43-year-old man was referred to our department with a left thyroid mass and high serum levels of CEA (72.7 ng/mL; reference range <5 ng/mL) in July 2009. Because of this marked elevation of CEA, he underwent upper gastroendoscopy and colonoscopy, both of which were normal. Positron emission tomography-computed tomography (PET-CT) detected a left thyroid mass with a strong fluorodeoxyglucose (FDG) accumulation, but no lung nodules. A thyroid ultrasound showed a solitary hypoechoic mass in the left

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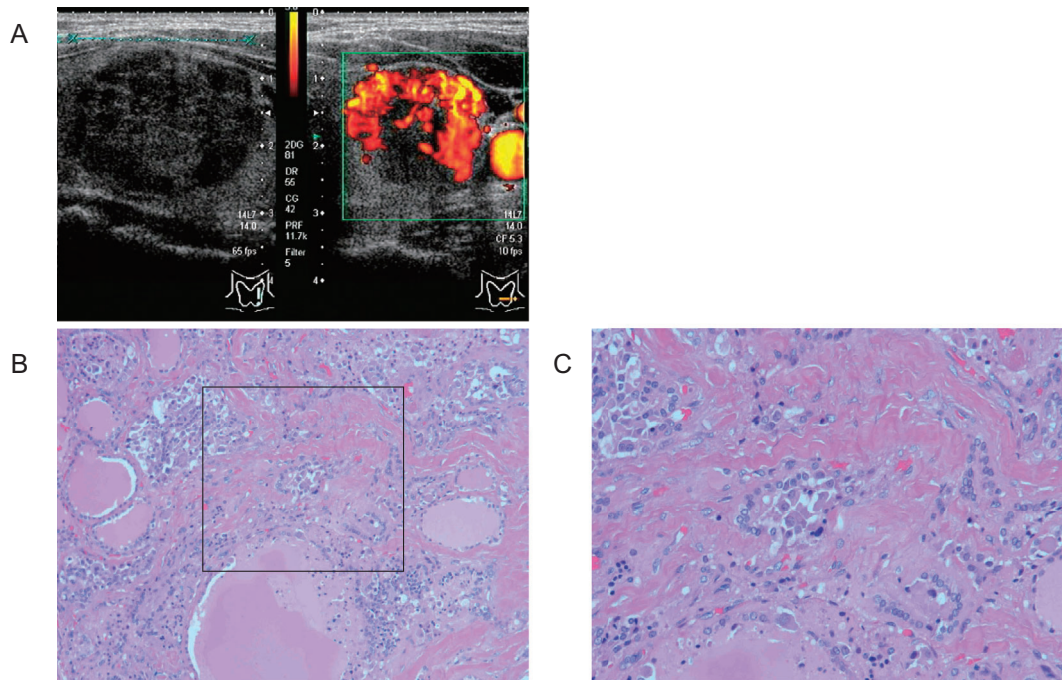


Figure 1. Ultrasound findings of the thyroid tumor (A) and microscopic findings of the carcinoma (B and C). (A) The thyroid tumor in the left lobe was a hypoechoic (left) and hypervascular (right) tumor with an irregular border. (B and C) Eosinophilic, round- to spindle-shaped cell proliferation was associated with amorphous amyloid deposition (B). Note that cells with ground glass nuclei surround the round- to spindle-shaped cells (C). The square in Fig. 1B corresponds to Fig. 1C. Hematoxylin and Eosin staining, $\times 100$ in B and $\times 200$ in C.

lobe with an irregular border and a diameter of approximately 2 cm (Fig. 1A). Fine needle aspiration cytology from the tumor was Class V with a cluster of round, oval and irregularly shaped cells with hyperchromatic nuclei with coarsely granular chromatin. The aspirate was found to contain amyloids, suggesting MTC. The patient's serum levels of calcitonin were markedly elevated (3,600 pg/mL; reference range <100 pg/mL) and his serum levels of calcium, thyroid-stimulating hormone (TSH) and free thyroxine including thyroglobulin (14.3 ng/mL; reference range <30 ng/mL) were normal. His blood pressure was normal, urine concentrations of metanephrine and normetanephrine were not elevated, and there was no mass or FDG accumulation in the adrenal glands. There was no family history of endocrine disorders. We therefore considered a diagnosis of sporadic MTC.

The patient underwent total thyroidectomy and neck lymph node dissection. Postoperative microscopic examination showed that the vast majority of the thyroid tumor was MTC intermingled with a minimal component of PTC (Fig. 1B and C). These two types of cancers with a distinct pathology were also observed in the dissected lymph node (Fig. 2A). Immunostaining with calcitonin (Fig. 2B) and thyroglobulin (Fig. 2C) confirmed H&E findings of mixed thyroid carcinomas. We also stained the lymph node with thyroid transcription factor-1 (TTF-1), which was moderately positive in the MTC and strongly positive in the PTC (Fig. 2D). The patient's postoperative course was uneventful

and his serum levels of CEA and calcitonin decreased to 5 ng/mL and 300 pg/mL, respectively. He underwent radioiodine therapy and has been under careful observation without apparent recurrence of MTC or PTC.

Discussion

MTC accounts for approximately 5-10% of all thyroid carcinomas (1) and very rare ($<0.5\%$ of all thyroid cancers (3)) cases of MTC may display mixed features, with an FTC or PTC component in the primary tumor, in the metastases or in both. The progression and prognosis of the disease are similar to those of MTC, the primary component of MMFCC (1). Similar to conventional FTC/PTC, metastatic lesions of the FTC/PTC component of MMFCC have been shown to accumulate radioactive iodine (4), but no medical therapy has yet proven effective for recurrent or metastatic MTC. Furthermore, the effectiveness of external radiotherapy and chemotherapy for MTC remains controversial.

It remains to be determined whether or not MMFCC derives from a common stem cell. This is because the presentation of MMFCCs can be one of the following: 1) concurrent and synchronous, but with an anatomically distinct MTC and FTC/PTC, 2) an MTC and FTC/PTC that merge with one another (collision tumor), or 3) an MTC and FTC/PTC that are intimately intermingled (true MMFCC) (2).

MMFCC has been described as a "composite thyroid carcinoma" (5) deriving from a theoretical common stem

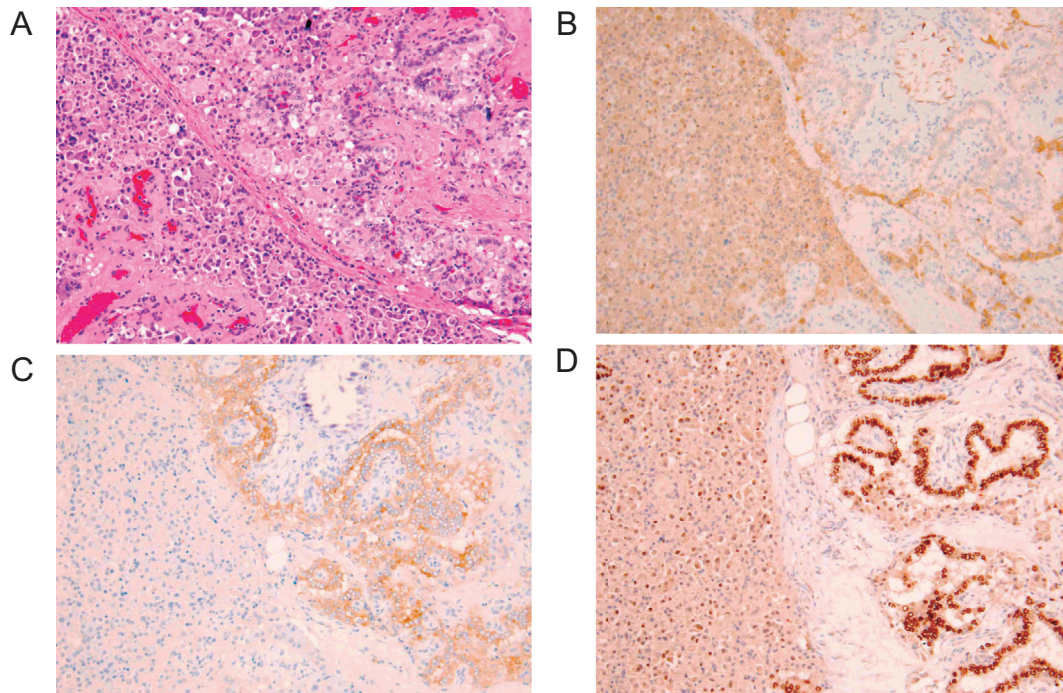


Figure 2. Immunohistochemical findings of the lymph node with MMFCC metastasis. Tissue specimens from the cervical lymph node were stained with Hematoxylin and Eosin staining (A) calcitonin (B), thyroglobulin (C) and TTF-1 (D). ($\times 100$).

cell (6). According to this theory, the ultimobranchial body could be the source of the putative common stem cell because nests of these cells in the thyroid gland have been shown to be immunoreactive for both thyroglobulin and calcitonin (5, 6). To support this theory, the coexpression of both calcitonin and thyroglobulin in individual tumor cells has been cited, at both the protein and mRNA levels in some case reports (3, 5-7).

Considering the high rate of incidental PTC up to 35% of autopsy series (8), one might suppose that concurrent MTC and FTC/PTC in the thyroid may not be so uncommon. Indeed, occult papillary carcinoma has been seen in 13.8% (9) and 19% (10) of cases of overt MTC. In these studies, MTCs were well separated from FTC/PTCs by normal thyroid tissue in all specimens, but were not admixed. Kim et al (10) extensively and critically reviewed cases of MMFCC reported in the English literature, finding that only 11 of 65 patients showed pathological features of both PTC and MTC in the same primary tumor. Therefore, most reported cases involved MTC and PTC components well separated by normal thyroid tissue, which therefore can be regarded as concurrent and synchronous FTC/PTCs in patients with MTCs. By examining genomic DNA from the MTC and FTC/PTC components obtained separately from several patients with MMFCC, Volante et al (7) showed different patterns rearranged during transfection (RET) of proto-oncogene mutation, loss of heterozygosity and X-chromosomal inactivation. Recently, Rossi et al (11) identified two independent mutations present in the RET in the MTC component and BRAF genes in the PTC component. Interestingly, the tissue specimens used in Volante et al (7) were so-called true

MMFCCs, while Rossi et al (11) used concurrent MTC and FTC/PTC. These findings support the different genetic and therefore embryonic origin of these two coexisting carcinomas. The present case is a true MMFCC with clearly distinct expression of calcitonin and thyroglobulin in the MTC and PTC respectively, suggesting different origins of the cancer cells. The expression pattern of TTF-1 did not differ from that seen in conventional PTC and MTC (12), which also supports the different origins of the cancer cells. It currently remains uncertain whether MMFCC is a simple reflection of a serial consequence of concurrent and incidental MTC and FTC/PTC that progressed and mixed together, or a distinct subset of tumors of unique origin from common stem cells.

Here, we report a case of MMFCC in which MTC intermingled with PTC both in the primary thyroid tumor and in the lymph nodes. The present case showed distinct expression of specific tumor marker antigens in an each component, suggesting distinct origins of tumor precursor cells. More cases and more detailed analyses are needed to determine the developmental origin of this rare tumor.

The authors state that they have no Conflict of Interest (COI).

References

1. DeLellis RA, Lloyd RV, Heitz PU, Eng C. Pathology and Genetics of Tumours of Endocrine Organs. IARC Press, Lyon, 2004.
2. Sadow PM, Hunt JL. Mixed medullary-follicular-derived carcinomas of the thyroid gland. *Adv Anat Pathol* 17: 282-285, 2010.
3. Papotti M, Negro F, Carney JA, Bussolati G, Lloyd RV. Mixed

- medullary-follicular carcinoma of the thyroid. A morphological, immunohistochemical and in situ hybridization analysis of 11 cases. *Virchows Arch* **430**: 397-405, 1997.
4. Hales M, Rosenau W, Okerlund MD, Galante M. Carcinoma of the thyroid with a mixed medullary and follicular pattern: morphologic, immunohistochemical, and clinical laboratory studies. *Cancer* **50**: 1352-1359, 1982.
 5. Apel RL, Alpert LC, Rizzo A, LiVolsi VA, Asa SL. A metastasizing composite carcinoma of the thyroid with distinct medullary and papillary components. *Arch Pathol Lab Med* **118**: 1143-1147, 1994.
 6. Ljungberg O, Ericsson UB, Bondeson L, Thorell J. A compound follicular-parafollicular cell carcinoma of the thyroid: a new tumor entity? *Cancer* **52**: 1053-1061, 1983.
 7. Volante M, Papotti M, Roth J, et al. Mixed medullary-follicular thyroid carcinoma. Molecular evidence for a dual origin of tumor components. *Am J Pathol* **155**: 1499-1509, 1999.
 8. Piersanti M, Ezzat S, Asa SL. Controversies in papillary microcarcinoma of the thyroid. *Endocr Pathol* **14**: 183-191, 2003.
 9. Biscolla RP, Ugolini C, Sculli M, et al. Medullary and papillary tumors are frequently associated in the same thyroid gland without evidence of reciprocal influence in their biologic behavior. *Thyroid* **14**: 946-952, 2004.
 10. Kim WG, Gong G, Kim EY, et al. Concurrent occurrence of medullary thyroid carcinoma and papillary thyroid carcinoma in the same thyroid should be considered as coincidental. *Clin Endocrinol (Oxf)* **72**: 256-263, 2010.
 11. Rossi S, Fugazzola L, De Pasquale L, et al. Medullary and papillary carcinoma of the thyroid gland occurring as a collision tumour: report of three cases with molecular analysis and review of the literature. *Endocr Relat Cancer* **12**: 281-289, 2005.
 12. Nonaka D, Tang Y, Chiriboga L, Rivera M, Ghossein R. Diagnostic utility of thyroid transcription factors Pax8 and TTF-2 (FoxE1) in thyroid epithelial neoplasms. *Mod Pathol* **21**: 192-200, 2008.