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MEN2 Syndrome-Related Medullary Thyroid Carcinoma with Focal Tyrosine Hydroxylase Expression: Does It Represent a Hybrid Cellular Phenotype or Functional State of Tumor Cells?

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Case History

A 38-year-old woman presented with abdominal pain, right-sided large thyroid mass with dysphagia, lower backache, and weight gain. During the clinical examination, she was pale and was found to have hypertension. The initial laboratory testing showed a normal thyroid function along with low hemoglobin (7.6 g/dl, normal: 12–15 g/dl). Ultrasound identified a large thyroid mass occupying almost the entire right lobe. No cervical lymphadenopathy was detected. A fine needle-aspiration biopsy of the thyroid mass was scheduled; however, the patient opted for total thyroidectomy given her elevated calcitonin (19930 ng/l; normal: 0–5 ng/l) and CEA (1425 ng/ml; normal: 0–5 ng/ml) levels.

What is your Diagnosis? Figures 1, 2, and 3.

Clinicopathological Diagnosis: MEN2 syndrome-related medullary thyroid carcinoma with focal tyrosine hydroxylase expression.

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The thyroidectomy specimen showed a dominant 5.0 cm well-differentiated neuroendocrine tumor consisting of spindle to epithelioid cells. The tumor displayed a predominant nested growth pattern resembling meningothelial whorls or a zellballen pattern of paragangliomas (Fig. 1). Microcystic change was seen in areas. No amyloid deposition was identified in sections examined. A panel of immunochemical stains was ordered by taking into consideration the differential diagnoses of medullary thyroid carcinoma and paraganglioma of the thyroid gland, as well as a remote possibility of metastatic neuroendocrine neoplasm originating from various sites. The tumor cells were diffusely positive for chromogranin-A and synaptophysin. Calcitonin (Fig. 2 a, b), and monoclonal CEA (mCEA) (Fig. 2 c, d) stained around 90% of the tumor cells. Staining for keratins were variable with focal reactivity for cytokeratin 7 (Fig. 2e) and patchy reactivity for low molecular weight cytokeratin (CAM5.2) (Fig. 2f). Interestingly, focal tyrosine hydroxylase reactivity was identified in up to 10% of the tumor cells (Fig. 3 a, d); however, TTF-1 remained positive in almost all tumors cells including those with focal tyrosine hydroxylase expression (Fig. 3 b, e). No immunoreactivity for GATA-3 (Fig. 3c), CDX-2, and epithelial membrane antigen was seen. Isolated tumor cells revealed positivity for serotonin. In addition to a very few sustentacular cells, focal S100 protein expression was noted in the tumor. The MIB-1 labeling index was 6% in hot spots. A diagnosis of medullary thyroid carcinoma with focal tyrosine hydroxylase expression was rendered. In addition, multifocal medullary thyroid carcinoma was also noted in the contralateral thyroid lobe. This finding raised the possibility of *RET*-driven genetic susceptibility (MEN2 syndrome).

Postoperative laboratory work-up identified primary hyperparathyroidism characterized by increased serum calcium (2.97 mmol/l, normal: 2.15–2.50 mmol/l) and

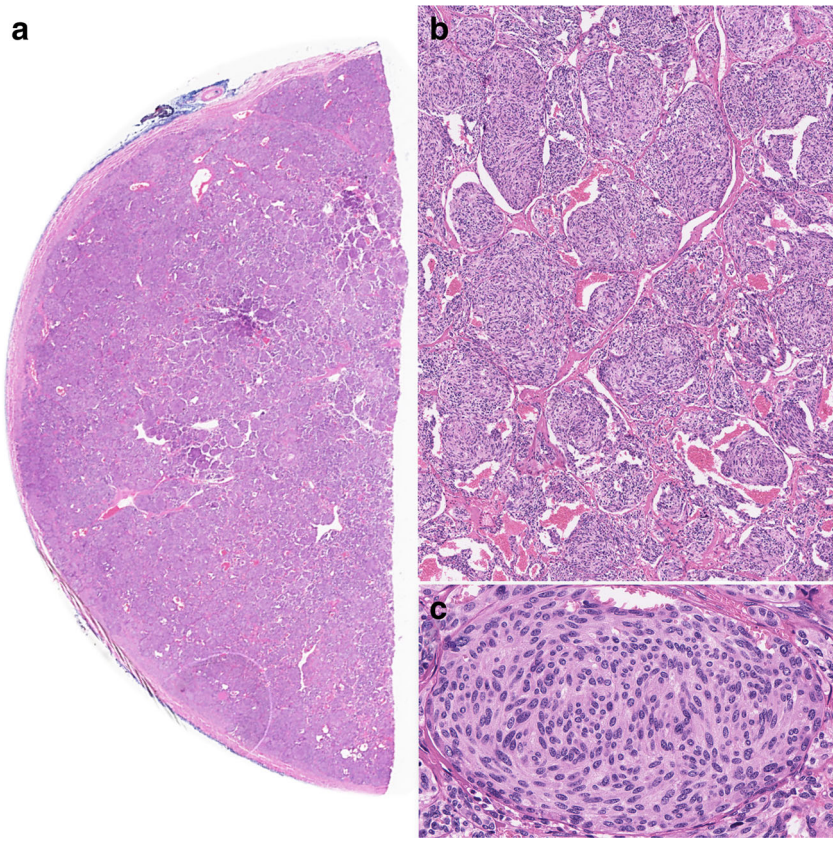

Fig. 1 Histological features of the thyroid mass. The thyroidectomy specimen showed a dominant 5.0 cm well-differentiated neuroendocrine tumor composed of spindle to epithelioid cells (**a**, **b**, **c**). This tumor replaced almost the entire right lobe (**a**). The tumor displayed a predominant nested growth pattern resembling meningothelial whorls or a zellballen pattern of paragangliomas (**b**, **c**)

parathyroid hormone (81 pg/ml, normal: 15–55 pg/ml). Hyperparathyroidism-related lytic bony lesions involving vertebrae, ribs, humeri, pelvis, and sacral body were identified. Sestamibi scan localized an abnormal parathyroid gland in the right inferior neck for which she underwent parathyroidectomy. Postoperative biochemical cure was achieved after the removal of parathyroid adenoma. The interim clinical screening for MEN2 syndrome yielded a 2.8 cm right adrenal mass, consistent with pheochromocytoma. The laboratory work-up showed increased levels of 24-h urine epinephrine (290 nmol; normal: <109 nmol) and norepinephrine (1112 nmol; normal: <473). These findings also shed light to the etiology of her hypertension at the time of the initial presentation. In summary, the clinicopathological findings were considered consistent with MEN2 syndrome (likely MEN2A syndrome given the lack of Marfanoid habitus and identification of parathyroid disease). Unfortunately, the patient was lost to follow-up. Thus, no further germline testing could be performed.

Comment

While medullary thyroid carcinoma is the most common neuroendocrine neoplasm occurring in the thyroid gland, primary neuroendocrine neoplasms of the thyroid gland also encompass several other diagnostic entities including paraganglioma of the thyroid gland (arising from inferior laryngeal paraganglia), intrathyroidal parathyroid neoplasms (adenoma or carcinoma), and odd neuroendocrine neoplasms arising from intrathyroidal thymic remnants [1]. In addition, one should always consider the possibility of a metastatic neuroendocrine neoplasm to the thyroid gland. To complicate this quandary, medullary thyroid carcinomas can present with various cytomorphological features including papillary, pseudopapillary, follicular (glandular), cystic, encapsulated, epithelioid, spindle cell, oncocytic, clear cell, small cell (neuroblastoma-like), giant cell, angiosarcoma-like, paraganglioma-like, and melanin-producing variants [1, 2]. Not surprisingly, the many faces of medullary thyroid carcinoma can pose diagnostic challenges by simulating other diagnostic entities; thus, immunohistochemical confirmation of parafollicular C-cell origin is required in all cases.

Traditionally, calcitonin has been regarded as a diagnostic biomarker of medullary thyroid carcinoma. Several other neuroendocrine neoplasms including but not limited to well-differentiated mediastinal neuroendocrine tumors (carcinoid tumors of the lung or thymus) can show immunoreactivity for either calcitonin and/or calcitonin gene-related peptide [1, 3]. Furthermore, some calcitonin-negative medullary thyroid carcinomas can show immunoreactivity for calcitonin gene-related peptide. However,

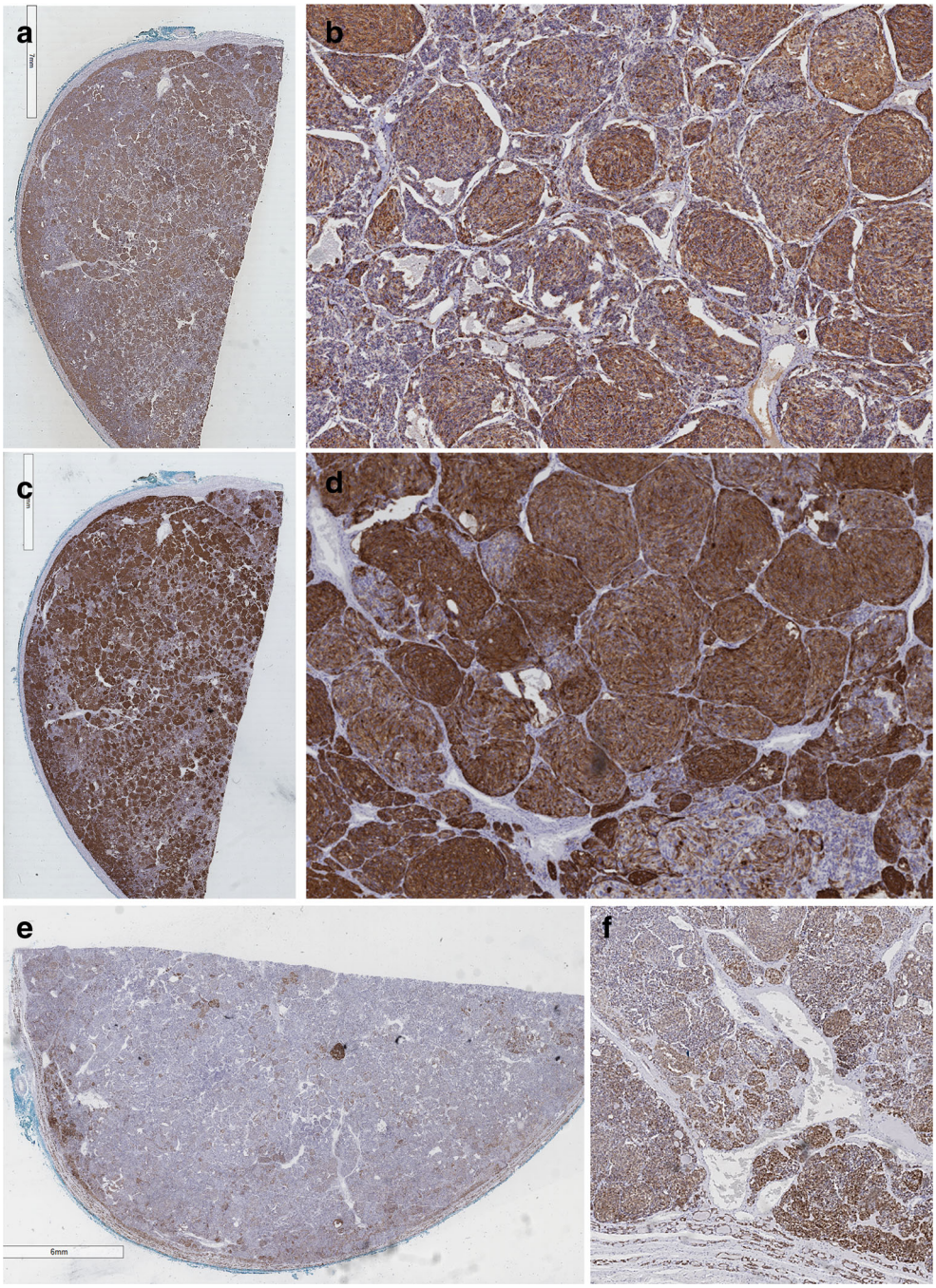

Fig. 2 Calcitonin, monoclonal CEA, and keratin immunohistochemistry in the dominant thyroid tumor. Calcitonin (**a**, **b**) and monoclonal CEA (**c**, **d**) stained around 90% of the tumor cells. Staining for keratins were variable with focal reactivity for cytokeratin 7 (**e**) and patchy reactivity for low molecular weight cytokeratin (**f**)

regardless of calcitonin and/or calcitonin gene-related peptide expression status, an integral diagnostic characteristic of medullary thyroid carcinoma is the reactivity for mCEA, which is often diffuse [1, 3]. Of note, CEA also serves as an invaluable serum biomarker for biochemical surveillance of patients with medullary thyroid carcinoma. Well-differentiated pulmonary neuroendocrine neoplasms with calcitonin expression tend to be either negative or focally positive for mCEA [1, 3]. In the current case, positivity for mCEA and calcitonin, and TTF-1 distinguished parafollicular C-cell origin, and confirmed the diagnosis of medullary thyroid carcinoma.

The presented tumor also revealed scattered serotonin expression. Practicing pathologists often link serotonin expression to an enterochromaffin cell origin. Neuroendocrine tumors of enterochromaffin cell origin often express CDX-2 [1, 3]. In addition, positivity for serotonin has been reported in various endocrine cells (i.e., pulmonary neuroendocrine cells) and neuroendocrine neoplasms including pulmonary neuroendocrine tumors

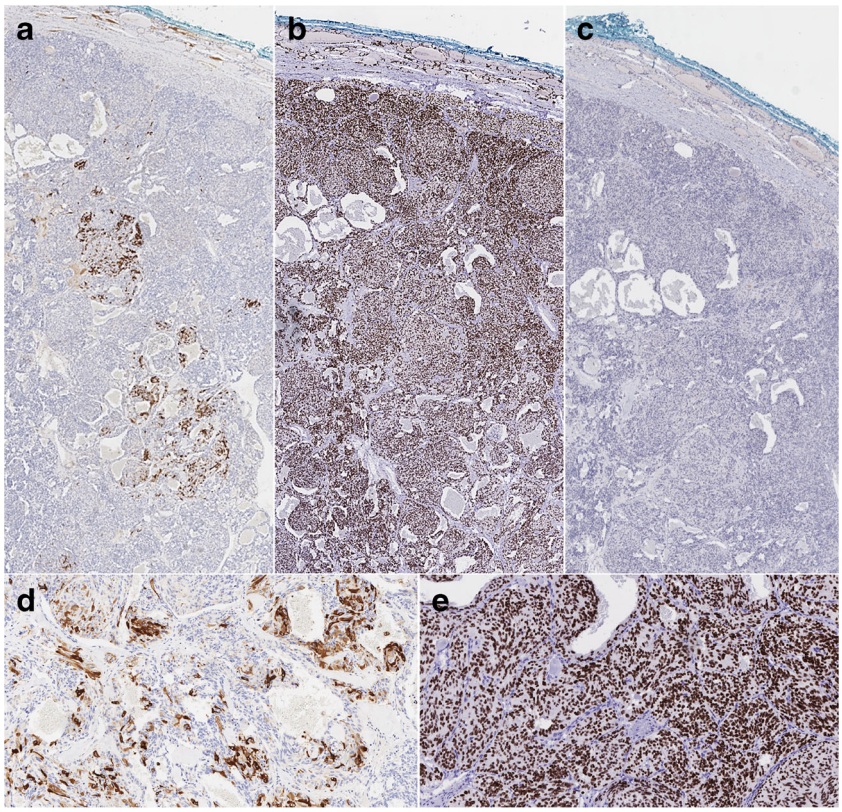

Fig. 3 Tyrosine hydroxylase, TTF-1, and GATA-3 immunohistochemistry in the thyroid tumor. Focal tyrosine hydroxylase reactivity was identified in up to 10% of the tumor cells (**a**, **d**). TTF-1 stained all tumors cells (**b**, **e**). The tumor cells lacked GATA-3 expression (**c**)

(carcinoid tumors), medullary thyroid carcinoma, and paraganglioma [1, 3].

The current case was an excellent mimic of thyroid paraganglioma. In fact, the possibility of paraganglioma should be considered in all keratin- and site-specific transcription factor-immunonegative neuroendocrine neoplasms [1, 3]. The identification of S100-positive sustentacular network is helpful but it is not specific to this diagnostic category as it can also be seen in various neuroendocrine neoplasms [1, 3]. Since a small fraction of epithelial neuroendocrine neoplasm can also be negative for keratins, it is important to combine keratins (at least AE1/AE3 and low molecular weight cytokeratin) with site-specific transcription factors (i.e., TTF-1, CDX-2, PDX-1, etc.). Traditionally, tyrosine hydroxylase reactivity has been linked to neuroendocrine neoplasms arising from paraganglia (i.e., paraganglioma, pheochromocytoma) as tyrosine hydroxylase is considered the rate-limiting enzyme in catecholamine synthesis [1, 3, 4]. Since medullary thyroid carcinomas tend to show a diffuse mCEA expression, focal tyrosine hydroxylase reactivity and focal absence of mCEA reactivity in the presented case may raise the possibility of a hybrid cellular component leading to composite paraganglioma and medullary thyroid carcinoma. However, negativity for GATA-3 (a nuclear transcription factor that can be expressed in paragangliomas) [3] and diffuse positivity for TTF-1 in tyrosine hydroxylase expressing tumor cells makes this possibility unlikely in this case. In addition, previous investigations on TT cell lines (derived from human medullary thyroid carcinoma) have shown that tyrosine hydroxylase can be identified in TT cell lines [5, 6]. In light of these findings, we concluded that the scattered tyrosine hydroxylase positivity likely represent a functional state in a subset of tumor cells in this medullary carcinoma, the biological significance of which is not known.

While the current case should be added to the spectrum of many faces of medullary thyroid carcinoma, practicing pathologists should adopt performing relevant immunohistochemical biomarkers of cellular origin in order to distinguish such presentations. In addition, the presented case underscored the need to use tyrosine hydroxylase in combination with mCEA, TTF-1, and GATA-3 when questioning the distinction of medullary thyroid carcinoma from paraganglioma of the thyroid gland.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Statement This case report does not contain any research studies with human participants or animals performed by any of the authors. Therefore, for this type of manuscript formal consent is not required.

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