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Biological phenomenon of epithelial-Mesenchymal transformation in medullary thyroid cancer: An interesting case phenomenon

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Abstract
Medullary thyroid carcinoma (MTC) is the differentiated thyroid cancer arising from the neoplastic clonal proliferation of parafollicular C-cells within thyroid parenchyma. It is widely believed to be neuroectodermal in origin. We highlight a rare case scenario, wherein the pathological biology of tumour changed to a mesodermal plasmacytoma in the course of followup. Here we discuss this uniquely rare biological phenomenon of MTC exhibiting epithelial- mesenchymal transformation (EMT) at follow-up, drastically changing the course of management.

Keywords: Neoplams, Plasmacytoma, Medullary cancer, Thyroid Gland, Thyroid Nodule

Introduction

Medullary thyroid carcinoma (MTC) is the differentiated thyroid cancer arising from the neoplastic clonal proliferation of parafollicular C-cells within thyroid parenchyma. Morphologically and functionally, its biology is unique amongst endocrine neoplasms. Prognosis is also widely variable from case to case depending on the stage of the disease [1]. MTC has high propensity for regional lymph nodes and distant metastasis. No optimal adjuvant therapies such as radio-iodine, radiotherapy or hormonal suppression are effective unlike in papillary or follicular thyroid cancers. It is widely believed to be neuroectodermal in origin. Here we discuss a rare biological phenomenon of MTC exhibiting epithelial- mesodermal transformation (EMT) at followup, drastically changing the course of management.

Case Details

A 54 year old lady presented with a rapidly growing neck mass with difficulty in swallowing for 5 months. No features of hypo or hyperthyroidism were present. No clinical history of diarrhea, rashes or other paraneoplastic features were elicitable. He was hypertensive and diabetic for the last 4 years.

On examination, a hard grade II multinodular goiter with palpable level II, III, IV, V lymphnodes were found on both sides of the neck. Cross-sectional imaging and ultrasound confirmed thyroid nodules with jugular lymphadenopathy. Fine needle aspiration cytology (FNAC) was suggestive of MTC. Serum calcitonin was 378 pg/mL (reference range: 2- 10 pg/mL). Clinical diagnosis was MTC T3N1bMx. No distant metastases were found clinically and radiologically. No familial or syndromic associations were found.

After preoperative optimization, total thyroidectomy accompanied by central compartment neck dissection and bilateral modified radical neck dissection (Figure 1) was performed. 56 lymph nodes were dissected. Histopathologic report rendered the diagnosis of medullary thyroid cancer characterized by polygonal to spindle shaped cells arranged in trabecular, carcinoid pattern with cells having amphophilic granular cytoplasm, eccentric nuclei and focal amyloid deposits along with lymphovasular invasion (Figure 2). Postoperative period was uneventful. Serum calcitonin fell to 6 pg/mL.

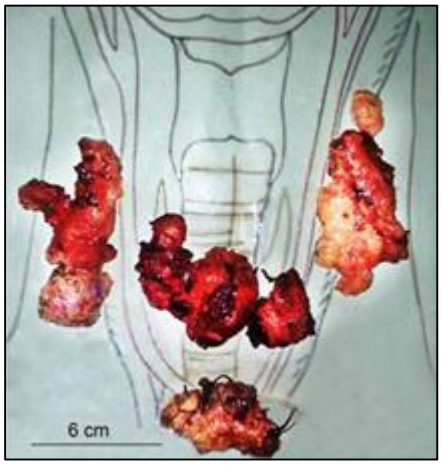

Fig 1: Gross ex vivo specimen showing total thyroidectomy with neck dissection (central and bilateral)

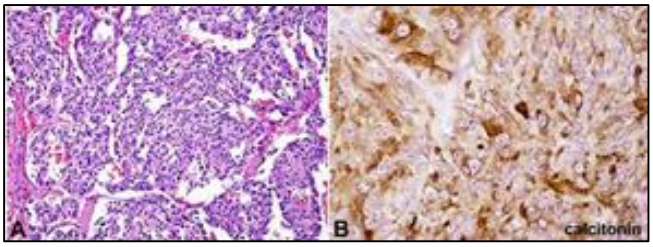

Fig 2: A-Photomicrograph of medullary thyroid carcinoma (H&E; 40X): **B**-Immunohistochemistry for calcitonin 40X)

At 12 months follow-up, the patient complained of hoarseness with a palpable level IV jugular lymph node on the right side. Imaging revealed level IV and V paratracheal lymphadenopathy (Figure 3A). Serum calcitonin was 6 pg/mL. With the working diagnosis of regionally recurrent MTC, a re-exploration was planned. The recurrent mass lesions at the lymph node levels III, VI were excised (Figure 3B). Histological examination of the excised specimens demonstrated an Extramedullary Plasmacytoma (EMP) in the background of focal medullary thyroid carcinoma tissue (Figure 4A). There was no residual thyroid tissue in any of tissue blocks on histologic examination. Immunohistochemistry (Figure 4B) showed CD 138 positivity and calcitonin negativity. Further workup showed positive serum electrophoresis but Bence Jones proteins were negative. Bone marrow aspiration was negative for any multiple myeloma. The patient was treated with external irradiation (33 fractions). The patient was disease free at last follow-up duration of 24 months.

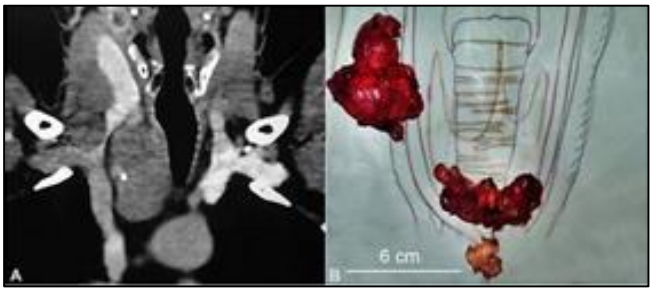

Fig 3: A-CT scan showing paratracheal mass; B - Excision of mass at re-exploration

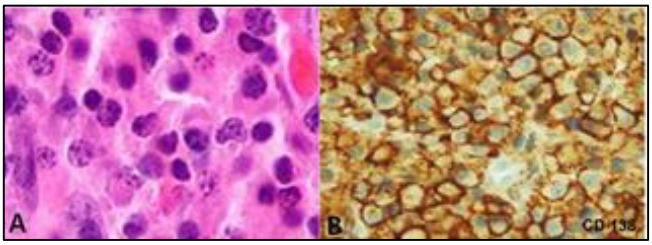

Fig 4: A-Histopathology showing neoplastic plasma cells with anisocytosis (H&E; 50X); **B**- Immunohistochemistry showing intense CD 138 positivity (H&E; 40X)

Discussion

In 1959, Hazard JB described MTC Despite different hypotheses, the most commonly held opinion is that it arises from Calcitonin secreting C-Cells, which are neuroectodermal (from neural crest) in origin [2]. Being part of APUD (amine precursor uptake and decarboxylation) system, MTC cells has potential to secrete multiple polypeptide and protein molecules, often leading to protean paraneoplastic syndromes such as ectopic Cushing's syndrome due to secretion of ACTH hormone. Some latest data from animal tissues show that it is endodermal in origin, but needs more studies to establish the lineage of MTC [3].

In the present case scenario, we found EMP in lymph nodes recurrence of MTC at the follow-up, suggesting EMT from one germ layer of epidermis to mesoderm. The presence of EMP pathology in the background of focal MTC in the recurrent lymph node specimens justifies this EMT hypothesis. This finding was also confirmed by immunohistochemistry showing intense positivity for CD 138 (syndecan 1) a specific mesodermal marker for plasma cell proliferation. An epithelial-mesenchymal transition (EMT) is a biologic process that allows a polarized epithelial cell, which normally interacts with basement membrane via its basal surface, to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype, which includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and greatly increased production of extracellular matrix components [4]. Though, the existing knowledge on EMT is premature, significant inroads have given insights in to its implications both in physiological, pathological and neoplastic biology. The broad consensus, classifies EMT based on its functions in to - Type I EMT which associated with implantation, embryo formation, and organ development are organized to generate diverse cell types that share common mesenchymal phenotype [5]; Type II EMT is associated with wound healing, tissue regeneration, and organ fibrosis [6] and Type III EMT occur in neoplastic cells that have previously undergone genetic and epigenetic changes, specifically in genes that favor clonal outgrowth and the development of localized tumors [7, 8]. These changes, notably affecting oncogenes and tumor suppressor genes, conspire with the EMT regulatory circuitry to produce outcomes far different from those observed in the other two types of EMT. It is still unclear what specific signals induce type 3 EMTs in carcinoma cells. The startling observation of EMT evolving from the background of medullary thyroid cancer was not reported in the literature to the best of our knowledge. This case also highlights the fact that apart from a spectral pattern of

prognosis in MTC ranging from indolent to rapidly spreading, EMT adds another dimension in the natural history of MTC. We speculate that this mechanism might have been underreported. We could not explore the molecular basis of EMT.

Conclusions

Dynamic metaplastic transformations of endocrine tumors necessitates life-long follow-up and counseling. Natural history, management and prognosis of MTC changes with phenomena such as EMT. Active molecular research of involved pathways is required to disclose new therapeutic targets.

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