ABSTRACT

The medullary thyroid carcinomas (MTC) comprise 5-10% of all thyroid carcinomas. It is known to show many cyto-architectural variations. The WHO classification of thyroid tumors includes an entity called mixed medullary-papillary carcinoma, a rare malignancy known to represent <1% of all thyroid malignancies. Fewer than 40 such cases have been reported so far and include tumors showing morphological features of both medullary carcinoma and papillary carcinoma with immunoreactivity for calcitonin and CK19 & thyroglobulin respectively. We report a case of a 27-year-old female with complaints of gradually increasing neck swelling for 2 years, with difficulty in swallowing in the last 2 months. The swelling was more localized towards left. Ultrasound neck revealed a nodule in the left lobe of thyroid with benign features most likely nodular colloid goiter. Thyroid profile of the patient was normal. FNA revealed sheets and follicles lined by both hyperplastic and involutional follicular cells. Few micro follicles showed pleomorphic cells having hyperchromatic nuclei and mild anisonucleosis. A diagnosis of colloid goiter was given on cytology; however, on grounds of suspicion of a neoplastic process, histopathology was advised. The patient underwent total thyroidectomy. Hematoxylin & Eosin stained sections showed features of mixed medullary-papillary carcinoma of the thyroid which was further confirmed on Immunohistochemistry and raised serum calcitonin levels. It is important to know about this entity due to its prognostic implications, association with other endocrine disorders and to prevent any diagnostic dilemmas.

Keywords: Medullary Thyroid Carcinoma, Thyroidectomy, Carcinoma Thyroid

INTRODUCTION

Depending on their embryogenic origin, thyroid carcinomas have been divided into two groups. One arising from neuroectodermal derivation of the fourth branchial arch (parafollicular or medullary carcinoma), and the other of foregut endodermal origin arising from the base of the tongue (follicular and papillary carcinomas). Medullary thyroid carcinoma (MTC) accounts for 5-10% of all the thyroid malignancies. Papillary thyroid carcinoma (PTC) are the most common comprising about 90% of the cases. Mixed medullary-papillary thyroid carcinoma is a rare variant of MTC. It is known to represent less than 1% of all thyroid malignancies. Classification of thyroid tumors by the World Health Organization (WHO) includes mixed medullary-follicular carcinoma. Under this entity tumors showing mixed medullary and follicular components have been observed more often but medullary carcinoma thyroid mixed with papillary carcinoma is rarely seen.

CASE REPORT

A young 27-year-old female patient presented with painless palpable mass in left side of neck, increasing in size over 2 years. The patient had difficulty in swallowing, but no symptoms of toxicity or hypothyroidism. Patient denied a family history of thyroid disorders, radiation exposure or other endocrinopathies. Physical examination showed well-demarcated nodule moving with deglutition. It measured about 7x6 cm and was non-adherent to any adjacent structure or the overlying skin. Serum levels of free triiodothyronine, free thyroxine, and thyrotropin were within normal range. Ultrasound neck showed a nodule in the left lobe of thyroid with hypervascularity suggestive of benign features most likely nodular colloid goiter. Fine needle aspiration (FNA) of
the nodule revealed sheets and follicles lined by both hyperplastic and involutional follicular cells. Few microfollicles showed pleomorphic cells having hyperchromatic nuclei and mild anisonucleosis (Fig.1). A diagnosis of colloid goiter was given on cytology; however, on grounds of suspicion of a neoplastic process, histopathology was advised.

![Image of smear showing follicular cells with occasional cells having enlarged and hyperchromatic nucleus.](image1)

Fig.1 (H&EX 400): smear showing follicular cells with occasional cells having enlarged and hyperchromatic nucleus.

The patient underwent total thyroidectomy with regional cervical lymph node dissection owing to suspicion of malignancy. Specimen was measured and it was 9x7x5cm with outer surface dull and congested (Fig 2). Cut surface showed variegated appearance with multiple cystic nodules showing papillary outgrowths; largest measuring 5x3.5cm; smaller measuring 3x3cm.

![Image of cut surface of thyroidectomy specimen showing variegated appearance with papillary outgrowths.](image2)

Fig.2 Cut surface of thyroidectomy specimen showing variegated appearance with papillary outgrowths.

The microscopic analysis of the tumor is shown in Fig. 3 (a, b &c) Sections showed nodular architecture, composed of cells arranged in nests, trabeculae, solid areas as well as variable sized follicles. These were lined by cuboidal cells having round to oval nuclei with nuclear clearing (ground glass appearance), overlapping and grooving. This typical pattern of micro follicular arrangement and cytological appearance were consistent with follicular variant of papillary thyroid carcinoma (Fig 3a). Other sections showed tumor cells arranged in irregular and solid nests of pleomorphic thyroid cells surrounded by a fibrovascular stroma with abundant amounts of acidophilic homogenous material. The tumor cells were large, polygonal and oval to spindle shaped having pale clear cytoplasm, with eccentrically located round nuclei, prominent nucleoli, and finely granular cytoplasm. These tumor features were consistent with MTC (Fig 3b). Mitotic activity was low, and no area of necrosis or hemorrhage was observed.

![Image of section showing an area of follicular variant of papillary carcinoma with small follicles lined by cells having nuclear clearing, grooving and overlapping.](image3a)

Fig 3a: H&E X 400: section showing an area of follicular variant of papillary carcinoma with small follicles lined by cells having nuclear clearing, grooving and overlapping.

![Image of section showing area of medullary carcinoma with irregular and solid nests of large, polygonal and oval to spindle shaped cells having pale clear cytoplasm, eccentrically located round nuclei, prominent nucleoli, and finely granular cytoplasm surrounded by a fibrovascular stroma.](image3b)

Fig 3b: H&E X 100: Section showing area of medullary carcinoma with irregular and solid nests of large, polygonal and oval to spindle shaped cells having pale clear cytoplasm, eccentrically located round nuclei, prominent nucleoli, and finely granular cytoplasm surrounded by a fibrovascular stroma.

![Image of IHC for CK-19 X 100: Section showing membranous and cytoplasmic positivity for CK-19 in the area of papillary carcinoma.](image3c)

Fig 3c: IHC for CK-19 X 100: Section showing membranous and cytoplasmic positivity for CK-19 in the area of papillary carcinoma.

**DISCUSSION**

The thyroid carcinomas are divided in two groups, based on the proposed cell of origin the groups are, 1. Follicular and papillary tumors arising from follicular cells; and 2. Medullary neoplasms arising from parafollicular cells. The simultaneous occurrence of MTC and PTC in the same thyroid is a rare phenomenon that can occur as a mixed tumor showing dual differentiation or a collision tumor (i.e., a tumor with two separate and different components). In the presented case, lesions with features of MTC and PTC were detected in same locations and were not separated by a normal thyroid tissue. Thus it is a case of a mixed tumor showing dual differentiation. According to WHO, male to female ratio of mixed thyroid carcinoma is 1.3:1. Patients usually present...
with a “cold” thyroid nodule. Some of these mixed thyroid tumors have been shown to occur in kindreds with inherited MTC caused by germline RET mutation. With course of progression lymph nodes are involved. Distant metastasis to lung, liver, mediastinum or bone is also seen. The cellular origin for the simultaneous occurrence of MTC and PTC carcinoma is not exactly established, yet histogenesis of our case may be explained by several hypotheses. One is of common stem cell origin, with the potentiality of dual differentiation of both C cell and follicular cell elements. The second hypothesis is divergent differentiation, in which, some cells of medullary carcinoma differentiate towards a follicular phenotype by the acquisition of additional molecular defects. The third is field effect hypothesis. In other words, a common oncogenetic factor stimulates neoplastic transformation of both C cells and follicular cells. The last hypothesis is that a separate conditional neoplastic transformation takes place in both C cell and follicular cells i.e. collision tumor. It may not be possible to speculate which hypothesis is dominantly operative in such cases.[7]

It is difficult to comment upon the prognosis of such combined thyroid carcinomas as few cases have been reported.[8] Patients with papillary carcinoma have the highest 10 year relative survival while MTC is considered to have a worse prognosis, difficult to cure and more likely to recur.[9] However, according to WHO, prognosis of mixed medullary and follicular thyroid carcinoma depends upon the medullary component. Hence, presence of the medullary component makes the prognosis worse as compared to pure papillary carcinoma.

CONCLUSION
A precise diagnosis of this uncommon variety of mixed thyroid carcinoma is fundamental for both adequate treatments of patient and genetic screening for excluding Multiple Endocrine Neoplasia 2 (MEN2) syndromes and familial medullary thyroid carcinoma (FMTC). Overall, mixed MTC-PTC is a rare clinical entity. Due to its prognostic implications, thorough sampling is important for accurate diagnosis of this type of tumor to avoid diagnostic dilemma.

What this study adds:
1. What is known about this subject?
Mixed medullary papillary thyroid carcinoma represents a rare phenotypically distinct tumor and less than 50 such cases have been reported in the literature.

2. What new information is offered in this study?
Besides being rare the condition is clinically very important as if such a condition is encountered the treatment should be driven by the medullary component, which is more aggressive.

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REFERENCES

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