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SYNCHRONOUS MEDULLARY AND PAPILLARY THYROID MICROCARCINOMA- A CASE SERIES

Pathology

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ABSTRACT

Papillary thyroid carcinoma is one of most common malignant thyroid tumor, while medullary thyroid carcinoma is relatively rare. Both these tumors have different cell of origin and clinical implications. Synchronous papillary and medullary thyroid carcinomas are rare and show medullary component with positivity for calcitonin and component of papillary carcinoma with positivity for thyroglobulin. We describe our experience of three patients with synchronous medullary and papillary thyroid carcinoma detected over a period of 22 years from a tertiary care referral center in India. Numerous hypothesis are proposed to understand the mechanism of this co-occurrence. True mixed carcinoma with dual expression of thyroglobulin and calcitonin are a controversial entity, but all three of our cases show distinct and well defined population of medullary and papillary carcinoma, supporting a different cell of origin of both tumors. It is a diagnostically challenging and important entity in the evaluation of thyroid tumors.

KEYWORDS

Medullary, papillary, thyroid, synchronous.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is one of the most common malignant thyroid tumor which originates from thyroglobulin (TG)-producing follicular cells and represents up to 90% of thyroid malignancies. Medullary thyroid carcinoma (MTC) arises from parafollicular calcitonin (CT)-producing cells and accounts for 5–10% of all thyroid malignancies.1Papillary carcinoma is the most common incidentally detected thyroid cancer with an incidence of 7% in patients with multinodular goiter. Simultaneouspapillary and medullary thyroid carcinoma is rare, It has been reported in 3.6 to 13.8% of all thyroid malignancies by Machens et al and Biscolla et al respectively.2,3 We describe our experience of three patients with synchronous medullary and papillary thyroid carcinoma over a period of 22 years from a tertiary care referral center in India. During this period a total of 87 medullary thyroid carcinoma were diagnosed.

Case 1: A4-year lady presented with history of thyroid enlargement and hypothyroidism for last 10 years. There was no history of compressive symptoms and no family history of thyroid swelling or any malignancy. On physical examination firm thyroid enlargement involving both lobes with nodular surface was observed. No cervical lymph nodes were palpable. No other systemic abnormality was detected. Unguided fine needle aspiration cytology (FNAC)of the thyroid swelling was suggestive of benign thyroid swelling. Pre-operative serum calcitonin was not performed. Patient underwent total thyroidectomy.

Gross features: Total thyroidectomy specimenshowed enlarged right and left lobes. Cut section of left lobe showed a firm whitish irregular lesion measuring 1x0.6 cm. Cut section of right lobe showed complex cystic colloid filled nodule replacing whole of the parenchyma. Isthmus was unremarkable.

Microscopic features: The section from the lesion in the left lobe showed a tumor composed of adjoining areas of medullary carcinoma and papillary microcarcinoma (Figure 1). Areas of medullary carcinoma displayed tumor in nests and sheets. Tumor cells were polygonal and plasmacytoid, displaying mild pleomorphism, granular chromatin and moderate cytoplasm. The adjoining thyroid parenchyma showed C-cell hyperplasia. Papillary carcinoma showed tumor disposed predominantly in follicles and focal papillae. Tumor cells displayed oval nuclei with crowding, overlapping, grooving and nuclear pseudoinclusions. Extrathyroidal invasion was not seen. The right lobe showed colloid nodulewith no evidence of malignancy.

Immunohistochemistry: Medullary carcinoma cells displayed positivity for Calcitonin, CEA, Chromogranin, Cytokeratinand TTF1, and were negative for Thyroglobulin. Foci of C-cell hyperplasia were positive for calcitonin and chromogranin. Papillary carcinoma showed positivity for Thyroglobulin, Cytokeratin, TTF1 and was negative for Calcitonin, Chromogranin and CEA.

Case 2: A 65-years lady presented with a progressively increasing thyroid swelling for 6 months. No features of hypoor hyperthyroidism and no compressive features were present. No family history of similar illness was present. Physical examination showed bilateral multinodular goiter with cervical lymphadenopathy.Serum calcitonin (2000 pg/ml) and serum CEA (66ng/ml) levels were increased. Urine metanephrines and normetanephrine levels were normal. FNAC from thyroid swelling was diagnosed as medullary thyroid carcinoma.Total thyroidectomy with Left Modified Radical Neck Dissection was performed.

Gross features: Total thyroidectomy showed right lobe showed a gray-browntumor measuring 3.5x3x1cms and replacing whole parenchyma. Cut section of left lobe showed a single firm whitish tumor nodule measuring 0.5x0.5 cm.4 lymph nodes were identified in neck dissection specimen.

Microscopic features: The right lobeshowed a tumor disposed in sheets and nests with severe desmoplasia (Figure 2). Tumor cells were moderately pleomorphic,plasmacytoid in appearance with areas of amyloid deposition. An area of the tumor showed sheets of small hyperchromatic cells. The tumor was diagnosed as medullary carcinoma with poorly differentiated areas. Extrathyroidal extension and lymph node metastasis in three out of four lymph nodes was also present. Left lobe nodule displayeda focus of papillary microcarcinoma composed predominantly of papillae lined by cells displaying nuclear clearing, grooving and pseudoinclusions.

Immunohistochemistry: The tumor cells of medullary carcinoma showed expression ofcalcitonin and chromogranin and were negative for thyroglobulin. Foci of papillary carcinoma displayed positivity for thyroglobulin and were negative for calcitonin and chromogranin.

Case 3: A 46-years ladycomplained of gradually increasing thyroid swelling for 4 years. History of low grade fever and on and off productive cough for 4 years was present. No history of hypo/hyperthyroidism, no compressive symptoms and no suggestive family history was present. Physical examination showed thyromegaly with cervical lymphadenopathy. Chest CECT findings were suggestive of centrilobular emphysema and bronchiectasis. Investigations revealed elevated serum calcitonin levels (2000 pg/ml). T3, T4 and TSH were normal. FNAC of cervical lymph nodes was diagnosed as metastatic medullary carcinoma. Total thyroidectomy with central compartment lymph node dissection and bilateral modified radical neck dissection along with superior mediastinal lymph node dissection was performed.

Gross features: Total thyroidectomyshowed solid grayish irregular white nodule measuring 2x1.5 cm in the right lobe. Similar nodules in isthmus measuring 0.5 cm in upper part of isthmus and other measuring 1.5x1 cm at lower part of isthmus were seen. Left lobe showed small whitish nodule measuring 0.3x0.3 cm.55 Lymph nodes

were dissected from neck dissection specimens.

Microscopic features: Right lobe and isthmus displayed foci of medullary carcinoma disposed in nests and follicles with infiltrative pattern. Tumor cells were polygonal in shape and displayed mild atypia, round nuclei, fine chromatin and granular cytoplasm. Focal amyloid was present and desmoplasia was severe. Perineural invasion was also seen. The left lobe nodule displayed papillary microcarcinoma disposed in papillae with nuclear features of overlapping, clearing, grooving and pseudoinclusions with foci of psammomatous calcification. Lymph nodes displayed metastatic medullary carcinoma (17/55).

Immunohistochemistry: The tumor cells of MTC displayed positivity for Calcitonin, Chromogranin and negativity for Thyroglobulin. Papillary carcinoma displayed positivity for Thyroglobulin and negativity for Calcitonin and chromogranin.No definite focus of c-cell hyperplasia was seen.

DISCUSSION

The simultaneous occurrence of MTC and PTC is a rare phenomenon that canbe observed in primarily two settings: a mixed tumourshowing dual differentiation or a collision tumour, with two spatiallydistinct and well-defined components.[4]

We describe three patients with coexisting papillary and medullary thyroid carcinoma. In our experience coexisting papillary carcinoma was seen in approx. 3% of all medullary thyroid carcinoma. In the second and third case of this series, PTC and MTC were in different lobes, and in the first case PTC and MTC were present as contiguous, but well-defined components of the same tumor nodule, thus supporting the collision theory.In published case reports with separation of MTC and PTC by normal thyroid tissue, a coincidental or synchronous co-occurrence has been suggested.4-6These findings support the presence of different origin of both the tumors.The other theories are stem cell and hostage theories. Stem cell theory proposes that a stem cell from the ultimobranchial body which undergoes neoplastic transformation, may give rise to dual (endocrine and neuroendocrine) differentiation in MTC and these cells showimmunoreactivity for both thyroglobulin and calcitonin. Hostage theory is that non-neoplastic follicular cells entrapped by MTC cells are stimulated by trophic factors and acquire genetic defects leading to hyperplastic and subsequently neoplastic transformation.[5,6]

The importance of this finding lies in the fact that the detection of foci of differentiated thyroid carcinoma in the thyroid of a patient with medullary carcinoma may require the addition of radioactive iodine treatment.

The RET proto-oncogene mutation is detected in hereditary medullarycarcinoma cases. Sporadic MTC is associated with mutations in the RET gene in about 50% of cases. Point mutations either at codon 918 (exon 16) or at the cysteine codons of exons 10 and 11 or in exons 13 and 15 have been described in sporadic cases.7,8Rearrangements of the tyrosine kinase receptors RET (ret/PTC) and NTRK1 have been characterized as specific for PTC and have been documented in about 20–40% of cases.9The presence of this oncogenemutation in some of the papillary carcinomacases may form the opinion that the simultaneousoccurrence of these two tumors is associatedwith RET proto-oncogene mutation. Gul et al.detected papillary thyroid carcinoma in one ofthe four familial medullary carcinoma casesof siblings and attributed this co-occurrenceto RET mutation.10 However, RET mutationwas detected in only five of the 26 patients of simultaneousmedullary and papillary carcinoma reported by Machens and Dralle.3 Kim etal. also described the detection of concurrentpapillary thyroid carcinoma in 10 of the 53 patients with medullary thyroid carcinomaas a simple manifestation of incidental papillarycarcinoma and did not indicate a commonetiological factor for these two tumors.11 Genetic evaluation was not performed in our patients.

Medullary carcinoma thyroid has poorer prognosis and different treatment in comparison to well differentiated thyroid carcinoma originating from follicular cells. Detection of coexisting papillary carcinoma may have a definite therapeutic implication. We found coexisting papillary microcarcinoma in 3% of MTC. Thus, for appropriate patient care careful evaluation of peritumoral and adjoining thyroid parenchyma should always be performed in all thyroidectomy specimens

FIGURE 1:

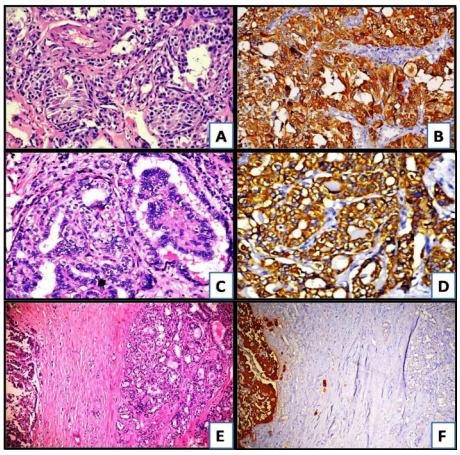

Figure 1: Case 1; MTC displaying spindle and plasmacytoid cells (A: H&E 400X, B: calcitonin immunostain 400X). Typical focus of PTC with nuclear clearing, grooving, pseudoinclusions and positivity for Thyroglobulin (C: H&E 200X, D: thyroglobulin immunostain 400X). MTC on left side and PTC on the right, separated by fibrous stroma (E, H&E 100X). MTC displaying positivity for chromogranin while PTC is negative for it (F, chromogranin immunostain 100X).

FIGURE 2

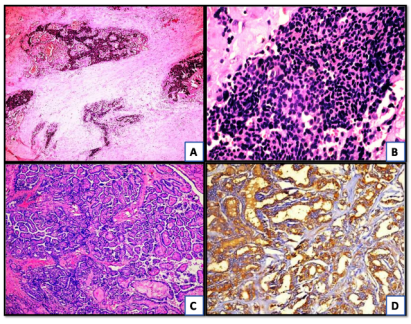

Figure 2: Case 2; MTC displaying small hyperchromatic cell population with severe desmoplasia (A: H&E 100X, B: H&E 400X). Coexisting papillary microcarcinoma and displaying positivity for Thyroglobulin (C: H&E 100X, D: Thyroglobulin 200X)

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