A Patient with Synchronous Follicular (Hurthle Cell), Papillary, and Medullary Thyroid Carcinomas: A Case Report with Literature Review on Possible Incidence and Pathogenesis

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Abstract:
This case report is the fourth case documented of a patient with synchronous Follicular, Papillary, and Medullary Thyroid Carcinoma. There have been several case series in the last two decades that include either concurrent papillary-medullary or follicular-medullary thyroid carcinoma, but only three cases documented for all three of these types of thyroid carcinomas occurring in the same patient. There has been conflicting research on whether the pathogenesis of such synchronicity is coincidental or molecular/genetically linked. Advances in molecular/genetic detection in the last five years has elucidated new evidence that synchronous occurrence of MTC, PTC, and FTC may be coincidental.

Introduction:
Thyroid nodules occur in 4-7% of the adult population, however only 1 in 20 new nodules diagnosed are expected to be malignant. [1] Therefore history and physical examination are extremely important in the diagnosis of thyroid carcinomas. Risk factors include age less than 20 or greater than 60, male gender, rapid growth, pain, history of radiation exposure, family history of thyroid cancer, hard/fixed nodules, lymphadenopathy, vocal cord paralysis, nodule size greater than 4, or upper aerodigestive tract compression. [1] In addition to history and physical exam, thyroid ultrasound and thyroid function tests are helpful. Fine Needle Aspiration (FNA) usually is the first initial invasive diagnostic modality of a thyroid nodule to rule out thyroid carcinoma.

The incidence of thyroid carcinoma in the U.S. is about 3% (48,020 out of 1,596,670) of all cancers in general population during 2011, with women representing 75% and men 25% of the cases.[1] Papillary thyroid carcinoma (PTC), Follicular Thyroid Carcinoma (FTC), Medullary Thyroid Carcinoma (MTC), and Anaplastic/Undifferentiated Thyroid Carcinoma (ATC) are the four major types with frequencies of 75%, 16%, 5%, and 3% respectively.[2] There have been numerous reports of either synchronous MTC and PTC or mixed MTC and FTC variants occurring in the same patient [3, 4], but only three documented cases of a patient having synchronous FTC, MTC, and PTC.[5-7]

The Pathogenesis of PTC is lymphotrophic malignant transformation of thyroid tissue most commonly caused by mitogen-activated protein kinase (MAPK) pathway associated with BRAF mutation[8] and RET proto-oncogene rearrangement/RAS mutation, at 50% and 10-30% of the cases, respectively.[9] Patients with PTC positive for BRAF mutation have been noted to have a more aggressive clinical course, therefore, require a more aggressive treatment algorithm than PTC negative for BRAF. [9]
FTC occurs more frequently in females than males often during the sixth decade of life and associates with chronic TSH elevation. The incidence of occurrence is elevated in the iodine deficient population with little evidence to suggest any hereditary causation. There have been reports of follicular variant of PTC that can look like FTC on FNA cytology due to overlapping cytological features and structures on basis of very limited sample of specimen for analysis. Therefore, surgical pathology is often required to differentiate benign follicular adenoma, follicular variant PTC, or malignant FTC based on capsule/overlapping structural invasion.

MTC is usually preceded by multi-focal para-follicular C-cell hyperplasia, with 75% found as sporadic. Less than 25% is hereditary and is associated with MEN IIA and IIB via RET proto-oncogene rearrangement and RAS germ-line mutation. The National Cancer Institute has published clinical diagnostic criteria that limit the unnecessary genetic testing secondary to the low incidence rate of hereditary MTC and the high cost of screening.

In the last two decades, there has been conflicting evidence that synchronous MTC and PTC occurrences may be linked secondary to presence of RET proto-oncogene rearrangement and activation through either coincidental or genetically linked pathogenesis.

This case report presents the fourth documented case and reviews the current literature regarding possible pathogenesis of these three types of thyroid carcinoma occurring in the same patient as either coincidental or linked.

Case Presentation:
A seventy-two year-old African American female presented with a six-month history of a large left thyroid. The patient denied any compressive symptoms such as odynophagia, dysphagia, dyspnea, hoarseness, or change in voice. The patient also denied temperature intolerance, unintentional weight loss, and previous history of radiation exposure to the head and neck. Past medical history was significant for diabetes mellitus type II and hypertension. There was no family history of thyroid cancer or significant neoplastic disease.

Initial ultrasound of thyroid with fine needle aspiration (FNA) revealed 6.7cm by 5.4cm by 4.2cm solid mass replaced most of the left thyroid gland, and a 0.9cm by 0.9cm by 0.7cm cystic nodule in the right thyroid gland. FNA cytopathology reported Bethesda Category “suspicious for follicular neoplasm” with findings of Hurthle Cell Neoplasia with cytologic atypia.

Left hemi-thyroidectomy was performed and final pathology revealed follicular (Oncocytic/Hurthle Cell) thyroid carcinoma (5.5cm) with a microscopic focus of papillary thyroid carcinoma – follicular variant (1.8mm) confirmed positive for HBME1 on immunostaining. Results and findings were discussed with the patient in the office during the first post-operative follow-up visit, and patient was scheduled for right completion thyroidectomy in 4 weeks.

Subsequently, the patient proceeded with right completion thyroidectomy. The final pathology revealed two microscopic foci of medullary thyroid carcinoma (2mm and 0.8mm) confirmed positive for calcitonin, synaptophysin, and chromogranin A and negative for HBME-1 and thyroglobulin. The final pathology also reported a separate microscopic focus of well differentiated follicular variant of papillary thyroid carcinoma (2mm) confirmed positive for Thyroglobulin and HBME-1 and negative for calcitonin, synaptophysin, and chromogranin.

All tumors were confined to the thyroid and surgical/histopathology margins were clear. This case was discussed at the institution’s tumor board with recommendations made for adjuvant external-beam radiation therapy to follow post-total thyroidectomy radioactive iodine ablation.

Comprehensive histopathology slides were reviewed at our institution’s Department of Pathology & Laboratory Medicine. Below Figures 1 to 3 highlighted features of FTC (Hurthle/Oncocytic Cell Variant), followed by Figures 4 to 6 highlighted features of PTC (Follicular Variant), and finally Figures 7 to 9 highlighted features of MTC stained with Chromogranin A.
Figure 1: Follicular Thyroid Carcinoma (Hurthle/Oncocytic Cell Variant) of the Thyroid, with replacement of normal thyroid tissue by Exclusively Follicular Cells with some features of vascular invasion – Low Magnification (Shown with Arrows)

Figure 2: Follicular Thyroid Carcinoma (Hurthle/Oncocytic Cell Variant) of the Thyroid, Medium Magnification showing trapped Hemoglobin Vascular Invasion by the Follicular Cells (Shown with Arrow)

Figure 3: Follicular Thyroid Carcinoma (Hurthle/Oncocytic Cell Variant) of the Thyroid, at High Magnification showing oxyphlic/Hurthle cell features of pink/granular/irregular shaped cytoplasm and atypical hyperchromatic nucleus (Shown in Arrows)
Figure 4:
Papillary Thyroid Carcinoma (Follicular Variant), at Low Magnification showing classic papillary architecture with thin papillae with fibrovascular cores (Shown in Arrows)

Figure 5:
Papillary Thyroid Carcinoma (Follicular Variant), showing the fibrovascular cores, vascular invasion with trapped hemoglobin. (Shown in Arrows)

Figure 6:
Papillary Thyroid Carcinoma (Follicular Variant), at High Magnification showing nuclear enlargement/thinning of chromatin and elongation/prominent nuclear grooves (Shown in Arrows)
Figure 7: Medullary Thyroid Carcinoma with Chromogranin A Staining, at Low Magnification showing replacement of normal thyroid tissue with Para-follicular C-Cells (Shown with Arrows)

Figure 8: Medullary Thyroid Carcinoma, at Medium Magnification, showing Para-follicular C-Cell Hyperplasia with Chromogranin A staining showing neuroendocrine origin

Figure 9: Medullary Thyroid Carcinoma, at High Magnification, with Chromogranin A showing thinning of chromatin, cytoplasmic hyperplasia with scattered metachromatic granules. (Shown with Arrows)
Discussion:
A report of 3 cases by Rossi et al, 2005[4] was the first study that found two distinct point mutations in the RET and BRAF genes, refuting the previous hypothesis that a common genetic mutation in RET and BRAF genes may be the pathogenesis of synchronous MTC/PTC occurrence. Rossi et al, pointed out two separate exon locations among the three cases confirmed by gene analysis using PCR.

Recent literature [3, 12] has demonstrated that PTC's are inherently multi-centric (not intra-glandular spread) and pathogenesis is due to BRAF and RET oncogene rearrangement. This is different from the RET oncogene germ-line mutation in Hereditary Medullary Thyroid Carcinoma in MEN IIA and IIB based on PCR validation of all the case series reported for synchronous PTC and MTC thyroid carcinoma.[3] Therefore, the new evidence offers support that such synchronicity is coincidental instead of genetically linked.

Follicular Cell Thyroid Carcinoma along with its Hurthle Cell/Oncocytic variants have not demonstrated any genetic association to either BRAF or RET oncogene rearrangements, as described for PTC in a recent study by Musholt, et al 2008. [13] In addition, epidemiologic data has suggested that the increased incidence of FTC in the iodine deficient population is highly correlated with chronically elevated TSH.[14] Therefore, the evidence offers support for the hypothesis that any synchronicity would be coincidental and not genetically linked.

Finally, 75% of MTC cases are sporadic, and less than 25% are genetically linked to RET-Oncogene activation. This would suggest a non-genetically linked pathogenesis in the majority of the cases (3:1 odds ratio).[9]

With insufficient evidence of genetic linkage between FTC, PTC, and MTC, the next logical step would suggest broadening genetic testing and characterization of these three types of thyroid carcinoma to a larger patient population to elucidate the pathogenesis of synchronous occurrence.

The cost of testing and clinical outcome analysis of cancer genetics services has to be taken into consideration. The prevalence of the disease and improvement in clinical outcome (e.g. survival) has to overcome the cost and subsequent treatment change in order for the test to be broadly applied to a wider patient population. The results from genetic testing on thyroid carcinomas can dramatically impact subsequent treatment and test selection. A properly standardized protocol has to be developed prior to applying the genetic testing of thyroid carcinomas to a larger population. For MEN2A/B screening of MTC positive patients, there have been reports of significant false-negative test results in patients younger than 15 years of age.

Currently, there is no guideline on how to standardize genetic characterization of thyroid carcinomas, and the genetic testing results vary from study to study. Hence, the conflicting evidence of synchronous relationship in the previous literature might be confounded by non-standardized genetic characterization on patient population selected with non-validated selection criteria.

Conclusion:
This is the fourth reported case in literature of synchronous FTC, PTC, and MTC occurring in the same patient. A literature review of the past two decades does not reveal sufficient evidence to suggest genetically linked pathogenesis compared to being purely coincidental. Recent studies using molecular/genetic studies failed to demonstrate any correlation between concurrent PTC and MTC.[15] Furthermore, there is insufficient evidence of FTC along with Hurthle Cell/Oncocytic variants to suggest possible genetic linkage to such synchronicity.[14] Therefore, the synchronous occurrence of these three types of thyroid carcinoma in a given patient is likely coincidental based on the current evidence in the literature. Further study is required using a larger patient population with standardized genetic characterization and patient selection criteria in order to generate enough statistical evidence to absolutely validate or disprove the genetic linkage of such synchronicity. [3]
References:


Figures/Acknowledgement:

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