Enigma of Adenoma-carcinoma Sequence in Thyroid Gland: An Interesting Case Report of Multiple Pathologies with Literature Review

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ABSTRACT
Phenomenon of adenoma-carcinoma is well-known in gastrointestinal tract tumors (GIT), but evidence of such sequence in thyroid oncogenic phylogeny is inconsistent. Frequently mixed/hybrid pathologies can occur in the same thyroid gland. We report an interesting case of such mixed tumors with inherent oncological sequence to discuss this issue in thyroid gland.

Keywords: Adenoma, Cowden syndrome, Multiple endocrine neoplasia MEN syndrome, Papillary carcinoma, Thyroid cancer.

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INTRODUCTION
Oncogenetics in thyroid gland is complex, except for multiple endocrine neoplasia (MEN) related medullary thyroid cancer (MTC), evolving from premalignant C-cell hyperplasia. Thyroid gland is ground for plethora of tumors arising from follicular and para-follicular cells. Often, hybrid/mixed tumors, such as MTC with papillary thyroid cancer (PTC), PTC with follicular adenoma (FA) have been reported. Various theories, such as collision, entrapment, etc., are proposed for these hybrid tumors. But, adenoma-carcinoma sequence (ACS) as seen in gastrointestinal tract tumors (GIT) has been untenable in thyroid and remains enigmatic. In this context, we present a case of multiple pathologies within same gland with inherent sequence to add weight to the issue of ACS.

CASE REPORT
A 50-year-old man presented with history of left paramedian anterior neck swelling and difficulty in swallowing since 2 years. It was gradually progressive to attain present size. On neck examination, it was a 4 cm firm multinodular mass in the region of left lobe of thyroid with a healed previous thyroidectomy scar. There was no cervical lymphadenopathy. He underwent right hemithyroidectomy for right solitary thyroid nodule 3 years ago and histopathology was reported as benign follicular adenoma. There was no family history of any thyroid cancer or nodules or multiple endocrine neoplasia related associations or neurocutaneous stigmata (e.g., café-au-lait spots, adenoma sebaceum, lipomas, mucosal neuromas). It was provisionally diagnosed as recurrent sporadic nonsyndromic multinodular goiter (MNG). Fine needle aspiration cytology (FNAC) of the goiter was reported as follicular adenoma. We performed completion left hemithyroidectomy. Postoperative period was uneventful.

Histopathological examination of thyroidectomy specimen revealed combination of adenomatous hyperplasia, follicular adenoma and papillary microcarcinoma (classical variant) in the same specimen (Figs 1 and 2). On follow-up of 12 months, he is asymptomatic and on thyroxine replacement therapy with no evidence of extrathyroidal uptake on radioiodine scan at 6 months postoperatively.

Fig. 1: Microphotograph (H&E, 50× magnification) showing areas of (A) follicular adenoma; (B) foci of papillary microcarcinoma; and (C) adenomatous hyperplasia
DISCUSSION

The oncogenic phylogeny of thyroid nodules, tumors and cancer is complex and not fully understood. Several theories, such as Iodine deficiency, adaptive mutations of thyrotopin receptor (TSHR) due to goitrogens, embryogenetic mechanisms have been proposed to explain thyroid tumorigenesis.\(^5\)\(^6\) The genetic changes commonly found in papillary and follicular thyroid cancer involve ras, p53 and PTC genes.\(^7\) The presence of monoclonal follicles leads to evolution of cancer from the nodules. Even, multiple simultaneous mutations might be involved in thyroid tumorigenesis, though their respective roles is not elucidated.\(^8\) But, we lack robust evidence of this mechanism at genetic level, in literature and left with extrapolative evidence as of now. We have not performed any genetic or clonality studies apart from clinicoinvestigative and histopathological evaluation in the present case. Simultaneous occurrence of multiple tumors with different histopathology in the same gland is referred to as mixed or hybrid or composite tumors. Mixed tumors in thyroid (MTT) gland are uncommon and their origin is either sporadic or syndrome related or familial. Though there are reports of MTT, it is probably under-reported compared to its incidence. The pathogenetic mechanism of MTT remains enigmatic, though several theories, such as common stem cell, collision, hostage theories have been proposed.\(^9\)\(^10\) Collision theory postulates multifocal origin from different cell clones and hostage theory postulates the sequestration of adenomatous areas by another tumor type.\(^10\) The familial non-MTC thyroid cancer (FNMTc) is characterized by PTC or follicular thyroid cancer (FTC) in multiple family members and combination of adenoma-carcinoma is more frequently seen in FNMTc. With more awareness, FNMTc is being increasingly reported in recent literature with an incidence of 3 to 6%.\(^11\) However, the genetics of FNMTc is complex and not well understood. On the other hand, MEN related MTC occurs due to a specific point mutation on chromosome.\(^10\) Mixed tumors in thyroid gland can occur in Carney’s complex, Werner’s syndrome, Cowden syndrome, Gardner’s syndrome, etc., characterized by constellation of multiple endocrine and nonendocrine lesions/tumors affecting multiple organs.\(^12\) These syndrome related/familial thyroid tumors and other
stigmata tend to occur at younger age compared sporadic tumors. But, at 50 years in the present case, we found no syndromic or familial associations and is unlikely to not appear till now. Thus, as seen in this case, a non-MTC, sporadic, non-syndromic MTT with an inherent chronology is suggestive of adenoma-carcinoma sequence similar to GIT. Gastrointestinal tract tumors syndromes with associated thyroid cancer such Gardner’s syndrome, Peutz-Zegher’s syndrome, hereditary non-polyposis coli syndromes are characterized by premalignant villous adenomas progressing to colonic carcinoma. Such premalignant lesion in thyroid was evidenced only in MEN related MTC in the form of C-cell hyperplasia, but not substantiated in MTT or thyroid tumors arising from follicular cell. A multi-step pathologic process of ACS has not been demonstrated convincingly in human thyroid cancer, but indirect evidence is demonstrated in transgenic mice and rodent thyroid tumors. Hyperplasia, adenoma and carcinoma in the same gland could be indicative of sequential oncological changes at genetic level. But, we did not come across any syndromic association in this case. Past head and neck external beam irradiation or radioiodine therapy or occupational radiation hazards could lead to thyroid parenchymal damage and trigger somatic mutations (e.g., ret-PTC mutations) enroute cancer cell clones. But, such scenario was not existent in this case. Mixed tumors in thyroid gland demands thorough clinical evaluation with exclusion of familial/syndromic associations for optimal treatment, counseling and cancer surveillance of patient and the family.

REFERENCES


