Familial thyroid carcinoma: the road less traveled in thyroid pathology – an update

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Abstract

This paper reviews the pathologic and clinicopathologic aspects of thyroid cancers and neoplasms which occur in familial settings. The data and details of C cell lesions are reviewed and a brief overview of the molecular-morphological correlations is presented.

Familial tumors of follicular derivation are also described with a review of the many syndromes associated with these lesions. These tumors which may be papillary, follicular or Hurthle cell can occur solely as thyroid neoplasms without extrathyroidal manifestations or may accompany syndromes in which the extrathyroidal lesions are of primary prognostic importance (e.g. familial adenomatous polyposis). The pathologist may play a critical role in the identification of these syndromes by recognizing particular patterns of thyroid tumors (e.g. cribriform morular variant of papillary carcinoma). These issues are reviewed in this article.

Keywords C cell tumors; familial tumors; syndromic neoplasms; thyroid cancer

The majority of thyroid carcinomas are sporadic and their etiologic factors are not well-established. The one factor that is associated with an increased risk for papillary thyroid carcinoma is ionizing radiation, usually of low to intermediate dose.[1–3] The molecular correlates of the interaction of radiation with follicular epithelial cells have been defined in part and continue to be studied. It is known that rearrangements or translocations in *ret* protooncogene (ret/PTC) are found in about one-third of sporadic papillary carcinomas[4–6]; whereas about 45% of papillary carcinomas harbor mutations in *BRAF* gene.[7–10]

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A minority of thyroid carcinomas are familial and these fall into two main groups: those derived from parafollicular or C cells (i.e., medullary carcinoma) and those of follicular cell origin. Certainly the understanding, both at the clinical and the molecular level of familial medullary carcinoma and related syndromes, is far ahead of our knowledge of familial follicular derived tumors.[11–17]

In general, familial tumors of any organ share certain characteristics (Box 1) including young age at diagnosis, similar tumors affecting other family members, putative precursor lesions and multifocal disease.[16–23]

Medullary carcinoma

Although tumors that today would be diagnosed as medullary carcinoma of the thyroid were seen and described in the early part of the twentieth century they were not recognized as a distinct group. They were classified as either "atypical adenomas" if they were circumscribed and non invasive and as spindle cell carcinomas akin to anaplastic carcinomas if they were infiltrative in growth pattern.

In 1951, Robert Horn described seven cases of a distinctive thyroid tumor which on the basis of morphology illustrated in the photomicrographs were medullary carcinomas MTC; he noted that they were clinically aggressive lesions although the clinical course was less aggressive than that of anaplastic cancers.[27]

Hazard et al. in their classic paper used the diagnostic term "*medullary carcinoma*"; these authors did credit Horn's description and agreed with the intermediate clinical features of this tumor. All the cases in these series occurred in adults; these early papers did not indicate the possibility of a hereditary neoplastic syndrome.[28]

During the mid-twentieth century, other factors not immediately related to the pathology of these tumors were progressing. These included the identification of C cells in the human thyroid (they had been known for decades in animals) and the discovery of the hormone calcitonin (originally termed thyrocalcitonin) by Copp and collaborators.[29] This hormone was noted to have the effect of lowering calcium in experimental animal models and being an antagonist to parathyroid hormone.

In 1961, a case report appeared describing the autopsy of an individual with thyroid tumors, and bilateral pheochromocytomas of the adrenal glands. The author, Sipple, has forever been associated with this syndrome of multiple endocrine tumors.[30]

In the mid-1960s ED Williams postulated (based on a few cases) that this unusual thyroid tumor, medullary carcinoma, might indeed be derived from non-follicular thyroid cells, i.e. the C cells and that the new hormone might be produced by these cells in the thyroid. If so, he theorized that medullary carcinoma could produce calcitonin and this could become a diagnostic and prognostic marker for this neoplasm.[31]

Investigation at the more basic level was concurrently being conducted in many laboratories around the world and by linkage analysis; the 'hot spot' on chromosome 10 was implicated in tumorogenesis of medullary carcinoma. These studies led to the discovery of ***ret*** mutations in the germline of these familial cases as well as in the tumors.[32] The elegance of germline genetic testing with essentially no false positive tests has been a major advance in oncology and has served as the model to be found for many common cancers (unfortunately the genetics of common

Characteristics of familial thyroid carcinoma[13,14,16,23–26]

- Young patients
- Gender incidence equal (contrast to sporadic PTC 3:1 Female: Male ratio)
- Positive family history of thyroid cancer and/or nodules (usually multinodular goiter)
- (Some have positive family history of other endocrine or non-endocrine lesions)
- Multifocal tumors
- Bilateral tumors
- Possible precursor lesions (C-cell hyperplasia)

Box 1

cancers has proven to be quite complex and not as easily followed as medullary carcinoma cases). Multiple point mutations in *ret* can give rise to medullary carcinoma and there have now been studies that show the specific mutations can be correlated with distinct pathologic features, specific patterns of organ involvement, clinical features and prognostic outcomes.[33–40]

Medullary thyroid carcinoma comprises fewer than 10% of all thyroid malignancies. This tumor is of great diagnostic importance because of its aggressiveness, its close association with multiple endocrine neoplasia syndromes (MEN IIa and IIb), and a relationship to C-cell hyperplasia, the putative precursor lesion. While the majority of medullary carcinomas are sporadic, about 10–20% are familial.[25,36,37,41–43]

Clinical features are similar in sporadic and familial cases that are symptomatic. Medullary carcinoma affects patients of any age although most occur in adults at an average age of 50 years. However, in familial cases, children can be affected; also in these instances the age at diagnosis tends to be younger (mean age: about 20 years). Although sporadic medullary carcinomas are seen more commonly in women, familial cases have an equal sex ratio, since an autosomal dominant mode of inheritance is present.[44,45]

In the familial forms there are associated endocrine and/or neuroendocrine lesions, although familial medullary carcinoma alone can occur in some kindreds (most endocrinologists now believe that familial medullary carcinoma without other endocrine lesions is still an MEN syndrome wherein other endocrine lesions are sub clinical and not manifested). Sipple's syndrome [multiple endocrine neoplasia (MEN) type 2 or 2A] is familial and consists of medullary thyroid cancer and C cell hyperplasia, adrenal pheochromocytoma and adrenal medullary hyperplasia, and parathyroid hyperplasia. Although most affected patients will have the complete syndrome, not every patient will manifest each of these lesions. Indeed, parathyroid disease is seen in a minority of affected families (16–25%) Mutations in ***ret*** (different from the ret translocation in papillary carcinoma) are found in the tumors and the germline of patients with familial medullary carcinomas and the MEN type 2 syndromes. Mutations in specific codons have been correlated with clinical behavior and symptomatology in some families.[36,37,45–49]

MEN type 2B consists of medullary thyroid carcinoma and C cell hyperplasia, pheochromocytoma and adrenal medullary hyperplasia, mucosal neuromas, gastrointestinal ganglioneuromas, and musculo-skeletal abnormalities. These patients may have familial disease (over 50% do); some cases arise apparently as spontaneous mutations. These patients have biologically aggressive medullary carcinoma and may succumb to metastases at an early age. MEN 2B shows similarity to von Recklinghausen's disease since in neurofibromatosis similar lesions are found in the gastrointestinal tract, and pheochromocytomas are common. In MEN 2b 96% of the tumors and germline mutations in ret are found on codon 918—an intracellular domain of the ret oncogene.[26,49] The remaining cases show mutation in ret codon 883 and 904 of exon 5, codon 691, also codon 634 of exon 11; and codon 838 of exon 14.[37,45,50,51] Recently, a rare RETK666N DNA variant has been identified in few cases of MEN2 patients and their family members. However, additional studies are need to define its pathogenic potential[52] (Table 1).

Pathology

Medullary carcinoma is usually located in the area of highest C cell concentration, i.e., the lateral upper two-thirds of the gland. In familial cases, multiple small nodules may be detected. The tumors range in size from barely visible to several centimeters. Many medullary carcinomas are grossly circumscribed but some will show infiltrative border. Rarely, gross necrosis and hemorrhage can occur.[48,53–56] They are frequently yellow tan in color resembling pulmonary carcinoids.

By light microscopy the typical medullary carcinoma may be circumscribed or more likely will demonstrate freely infiltrating into the surrounding thyroid. The pattern of growth is of tumor cells arranged in nests separated by varying amounts of stroma. The tumor nests are composed of round, oval, or spindle-shaped

Syndromes associated with medullary thyroid carcinoma[23,37,49]

Syndrome	Clinicopathologic features
MEN 2	Medullary thyroid carcinoma and
Sipple's syndrome	associated C cell hyperplasia
	Adrenal pheochromocytoma and adrenal medullary hyperplasia
	Parathyroid hyperplasia (adenomas)
MEN 2B	Medullary thyroid carcinoma and
	associated C cell hyperplasia
	Adrenal pheochromocytoma and adrenal medullary hyperplasia
	Neuromas of oral cavity, and gastrointestinal tract
	Musculoskeletal abnormalities (Marfanoid habitus)
	Eye lens abnormalities
FMTC	Medullary thyroid carcinoma and
	associated C cell hyperplasia

MEN — multiple endocrine neoplasia; FMTC — familial medullary thyroid carcinoma.

Table 1