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Neuroendocrine Tumors of the Thyroid and Their Mimics

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Abstract
This paper will review neuroendocrine lesions of the thyroid and the differential diagnosis with the most significant such tumor of the thyroid, that is, medullary thyroid carcinoma. A brief overview of the understanding of this tumor's identification as a lesion of C cells and its familial and syndromic associations will be presented. Then, a discussion of the various mimics of medullary carcinoma will be given with an approach to the types of tests that can be done to arrive at a correct diagnostic conclusion. This review will focus on practical "tips" for the practicing pathologist.

Keywords Medullary thyroid carcinoma · Calcitonin · Carcinoembryonic antigen · Hyalinizing trabecular tumor · Intrathyroidal parathyroid · Paraganglioma · Thymic neuroendocrine carcinoma · Calcitonin negative medullary carcinoma · Ewing/PNET of thyroid · Metastatic neuroendocrine tumors to thyroid

One of the most important descriptions of thyroid tumors in the modern era was the "Carcinoma of the Thyroid-Description of a distinct morphologic variant" defined by Dr. Robert Horn in 1951 [1] and subsequently termed "Medullary Carcinoma of the Thyroid" by Dr. J.B. Hazard and colleagues in 1959 [2].

Neither of these authors recognized that this tumor was in fact derived from a second cell in the thyroid which had been known in various animal species (especially, dogs and birds) [3, 4]. They also did not realize that the cell of origin produced the not yet discovered hormone, calcitonin (originally called thyrocalcitonin) [5]. In a matter of a few years however, various investigators had put together a number of pieces of information from anatomy, physiology, and pathology and realized they had discovered a "new" thyroid tumor, derived from what was now known as the C cell and which had an intermediate prognosis between well-differentiated thyroid carcinoma of follicular cell origin and anaplastic thyroid carcinoma [6, 7]. Shortly thereafter, syndromic familial cases were identified, and soon, the genetic basis of these syndromes was defined [8].

Although for the past 50 years, the C cells were considered to be derived from the neural crest, newer embryological studies, especially in mammals that have shown that they are not. Elegant linkage tracking and genetic studies, predominantly in mouse embryos, have shown that C cells are derived from endoderm and travel with the ultimobranchial body into the thyroid [9, 10]. It is possible that in avian species, the C cells arise from neural crest, but in these animals, the ultimobranchial body remains an organ separate from the thyroid. The difference in development may explain the difference in precursor cells of C cells [9, 10].

The pathologist practicing today knows that "medullary carcinoma" of the thyroid is a neuroendocrine carcinoma which produces the hormone calcitonin and that one can perform an immunostain for this hormone proving the diagnosis. In addition, serum measurement of calcitonin can be used diagnostically and most importantly, prognostically in the postoperative setting [11, 12]. There are criteria to assess for precursor lesions, such as C cell hyperplasia, and to predict familial/syndromic disease if multifocal and bilateral lesions (both carcinomas and hyperplasias) are recognized [11, 13].

What problems remain with this tumor for the pathologist diagnosing such a lesion?

The main issue is the recognition of the tumor. In FNA samples, it is estimated that about 3% of cases diagnosed as "atypia of undetermined significance" or "follicular lesion of undetermined significance" (AUS/FLUS-Bethesda system) [14] represent medullary carcinoma (personal

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communication Dr. Richard Kloos), when such samples are tested by molecular analytic methods.

Secondly, the histopathologist may have problems recognizing these tumors since they can show a variety of growth patterns, some of which mimic other thyroid tumors (usually of follicular derivation, i.e., hyalinizing trabecular tumor) or other non-thyroid tumors (i.e., true paraganglioma), parathyroid proliferations, or extrathyroidal malignancies spreading to the gland (usually by a hematogenous route). Most medullary carcinomas show an epithelial (nests or trabeculae) or spindle cell growth or a mixture of these. However, examples of the lesion include those that show true or pseudopapillary growth, follicular pattern, giant cells, clear cell lesions, squamoid lesions, small cell tumors, and oncocytic neoplasms [15–21].

Vignette 1: Oncocytic lesions are especially problematic since such tumors share with medullary carcinoma, trabecular growth, abundant, sometimes granular, cytoplasm, and rounded nuclei with nucleoli. However, the "neuroendocrine" nuclei are not present in oncocytes or Hurthle cells. Caution must be taken in interpreting FNA specimens from oncocytic medullary tumors since cell blocks of oncocytic cells can demonstrate a "stickiness" that can lead to a falsely positive calcitonin immunostain. Our group has seen three such cases in which true oncocytic (Hurthle cell) neoplasms were diagnosed as "malignant-medullary carcinoma"; on histological examination, two were Hurthle cell carcinoma and one, an oncocytic adenoma.

Vignette 2: A 73-year-old man presented with a 3-cm intrathyroidal tumor which was excised and diagnosed as "spindle and giant cell anaplastic carcinoma". He was told he had a dismal prognosis, so he refused therapy and was lost to follow-up. Three years later, he re-presented for an inguinal hernia and he and his physicians were amazed he was alive. He had no evidence of neck recurrence or of metastatic disease. Review of the slides of his thyroid tumor and application of immunostains showed a calcitonin, chromogranin, and CEA-positive medullary carcinoma with tumor giant cells.

Finally, the definition of C cell hyperplasia is still in flux; definitions of the number of C cells in normal human adults have varied from 4 to 6 cells in clusters around a follicle or 50 C cells per one low-powered field [22–27]. Fuchs et al. [28] have recently discussed the problem. Although most pathologists recognize that C cells are more numerous in neonatal and pediatric thyroids, the limits of numbers of C cells that are normal in adult humans remain unclear. Many endocrine pathologists do agree that there are at least two types of C cell hyperplasia, which associated with genetically determined syndromes and which is a precursor lesion to medullary carcinoma (neoplastic C cell hyperplasia) [29] and a second type seen in association with some follicular-derived neoplasms (benign and malignant) [26] and in some cases of Hashimoto thyroiditis [23]. Kaserer et al. [29] have suggested that since the first of these is neoplastic (and many examples exist of cytological atypia in this proliferation), the lesion should be termed "THINC" or "TINC" (thyroid intraepithelial neoplasia of C cells) [29]. The WHO monograph mentions this terminology without completely endorsing it. [30].

In conclusion, it appears that although the normal number of C cells in adult humans is still debated, the cytological changes seen in hyperplastic C cells in genetically defined syndromes can be a helpful clue to the diagnostic pathologist. Neoplastic C cells are abnormal not only in numbers (and they may be nested too), but also in their cytology. large nuclei with pleomorphism [29].

Medullary carcinoma can usually present as an asymptomatic lump in the neck (unless ectopic hormone production gives rise to symptoms associated with that hormone excess); the lesion can be of any size and about half the patients will show evidence of cervical node metastases [11, 13]. Grossly, the lesion is firm, tan-yellow and firm. Many lesions are grossly circumscribed, but not encapsulated. Most tumors are located in the upper half or two-thirds of the thyroid lobes.

Microscopically [12, 30–32], the tumors show a number of different patterns, including the most common one: epithelial with nested or trabecular growth or spindle cell growth; sometimes, mixtures of these are noted (Figs. 1 and 2). However, a variety of different growth patterns are known (Tables 1 and 2). Even though the tumor is circumscribed grossly and microscopically, it usually infiltrates (at least focally), the surrounding thyroid and venous invasion is common. The latter may give the pathologist pause as he/she may think of the possibility of multifocal tumors. Assessing these small areas for endothelial cells will solve that issue. In familial cases, however, multifocality is expected. These foci are larger than intralymphatic, or intravascular nodules. Cytologically, the tumor cells recapitulate the pattern of growth although most tumors will show nuclei of neuroendocrine cells with "salt and pepper" nuclei. Some tumors with an epithelial predominance show tumor cells that resemble plasma cells with eccentric nuclei and basophilic cytoplasm. In these cases, bi-nucleated cells can be found. The cytoplasm itself may be granular. In about 75% of medullary cancers, the stroma contains endocrine amyloid believed to represent, in part, the prohormone, procalcitonin.

About 8–10% of cases will contain intracytoplasmic mucin [33] and some rare tumors have contained melanin [34]. Through 2018, 14 cases of melanin-producing melanoma were documented in the literature [35].

Immunohistochemically, the tumor cells stain for calcitonin, TTF1 (variable 30-75%), PAX 8 (usually weak and anti-body dependent) [36], cytokeratin, and neuroendocrine markers (chromogranin and synaptophysin) [15]. If ectopic

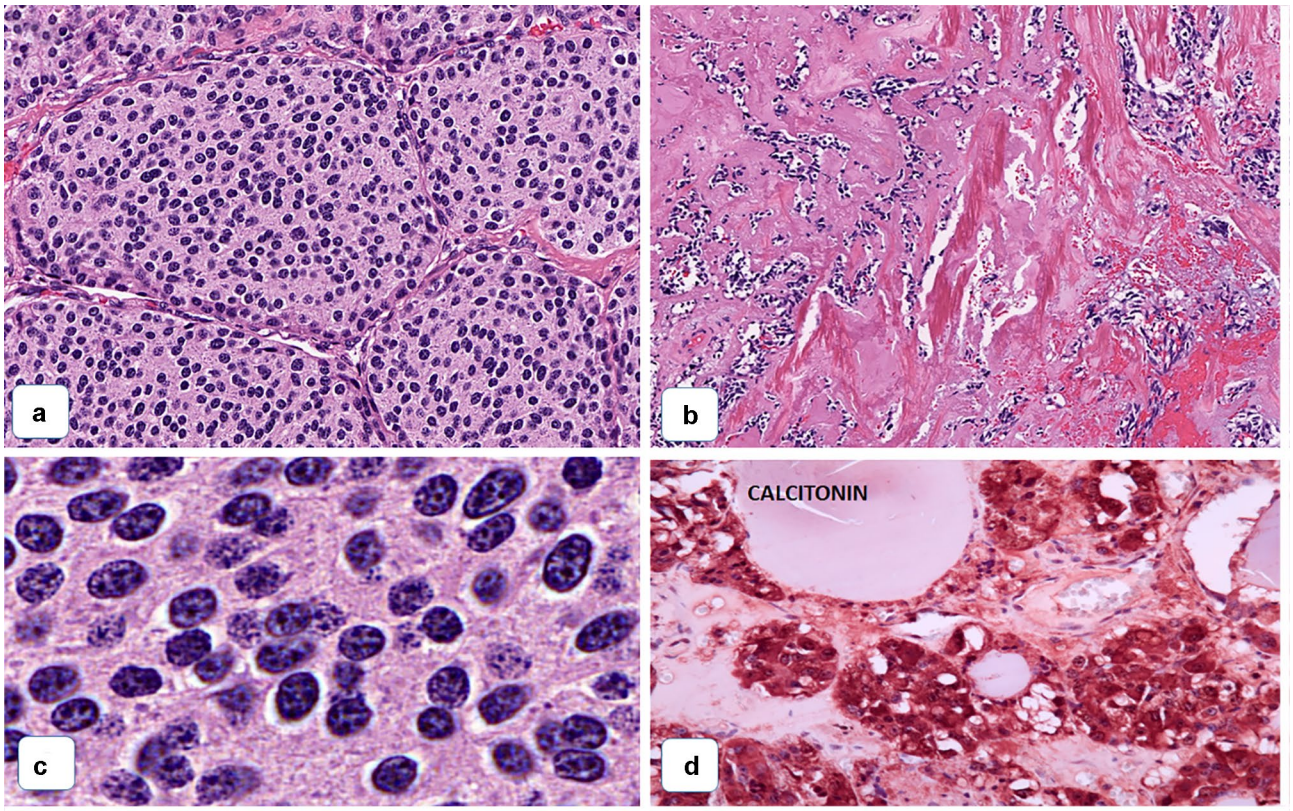

Fig. 1 Medullary thyroid carcinoma. **a** Nested pattern of growth with uniform cytology (H&E; 150). Stromal amyloid is shown (H&E × 100). **b** High power of the "salt and pepper" nuclei (H&E × 400). **c** Calcitonin immunostain in area of follicular growth of medullary carcinoma (immunostain × 200)

hormone production is associated with the tumor, specific staining for those substances may be found. Staining for calcitonin and calcitonin-related peptide (CGRP) can occur in neuroendocrine tumors other than medullary carcinoma. Thus, rare examples of parathyroid carcinoma, and tumors of lung, head and neck area, thymus, and pancreases can

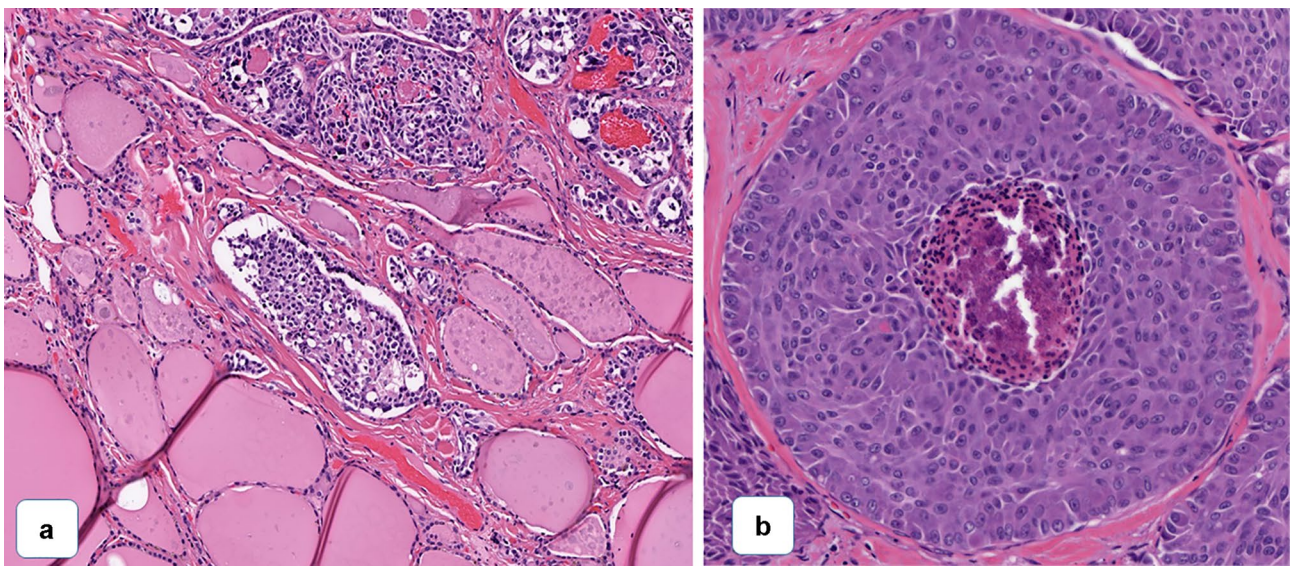

Fig. 2 **a** Medullary thyroid carcinoma. This lesion was circumscribed, but note lymphatic invasion in surrounding thyroid (H&E × 100). **b** Another case showing coagulative necrosis. This tumor showed extrathyroidal extension, nodal and bone metastasis (H&E; × 200)

Table 1 Growth pattern of medullary carcinoma

Epithelial (nests, trabecular)
Spindled
Mixed
Papillary
Pseudopapillary
Follicular (glandular)
Oncocytic
Clear cell
Paraganglioma-like
Giant cell
Squamous
Angiomatous

Table 2 Products of medullary carcinoma

Amyloid
Mucin
Melanin
Hormones (ectopic)

stain for both calcitonin and CGRP [37–39]. Most critically, medullary carcinoma stains for monoclonal CEA (carcinoembryonic antigen) [31]. This finding is so specific as to be diagnostic of a C cell lesion, even in the absence of calcitonin staining on tissue or elevation in the serum. [31].

In familial cases (Table 3), the thyroid often shows multiple and bilateral tumors of varying sizes [29, 30, 32, 40, 41]. The background thyroid will show C cell hyperplasia with the presence of nodules formed by atypical C cells [29, 41] (Fig. 3). Depending on the timing of thyroidectomy, this C cell increase may be the only lesion.

The age at which thyroidectomy is performed in the modern era is influenced by the exact mutation in *ret*. For example, many endocrinologists and endocrine surgeons will recommend thyroid surgery at age 2 or 3 for a patient with MEN 2B and mutation in codon 918 of *ret* [11, 13]. Some clinicians have questioned the recommendation of germline genetic testing in any patient who is found to have a micro or gross medullary carcinoma. If a patient is young (under 35 and has a family history of "thyroid nodules" or "thyroid surgery") or has manifestations of endocrine disorders involving non-thyroid endocrine organs (i.e., adrenal), then it seems reasonable that the cost of such testing is justified.

Medullary microcarcinoma (Fig. 4) can occur in the thyroids of familial cases; however, similar lesions can be found as isolated single tumors in thyroids removed for non-C cell proliferations [40, 41]. As with papillary microcarcinomas, these lesions measure 1 cm or less. These small lesions behave in an indolent manner; a study from Memorial Hospital in New York found that no medullary microcarcinoma metastasized if it measured 5 mm or less. However, tumors larger than 5 mm were, on occasion, associated with nodal metastases [40].

Distinguishing nodular C cell hyperplasia from medullary micro carcinoma can occasionally produce diagnostic

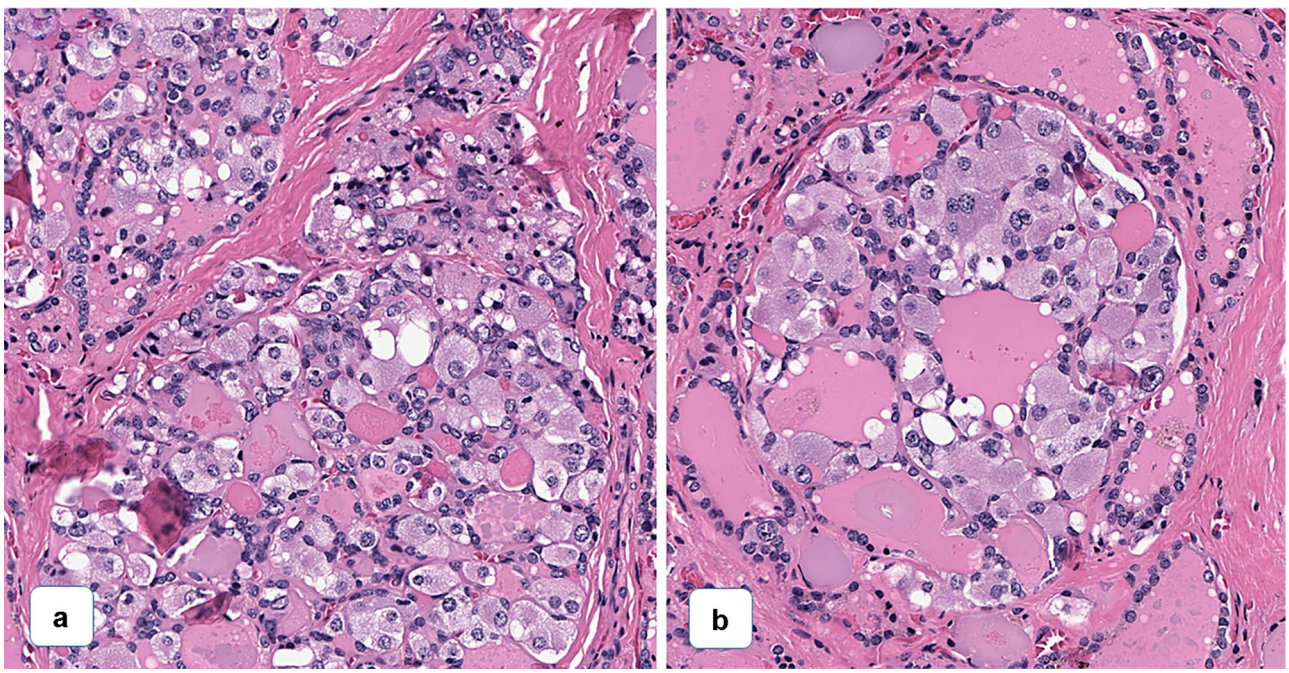

Fig. 3 C cell hyperplasia. **a** Note numerous large plate-like cells close to follicles and in stroma (H&E × 200). **b** Clusters of C cells with voluminous granular cytoplasm around residual follicles with colloid (H&E, × 200)

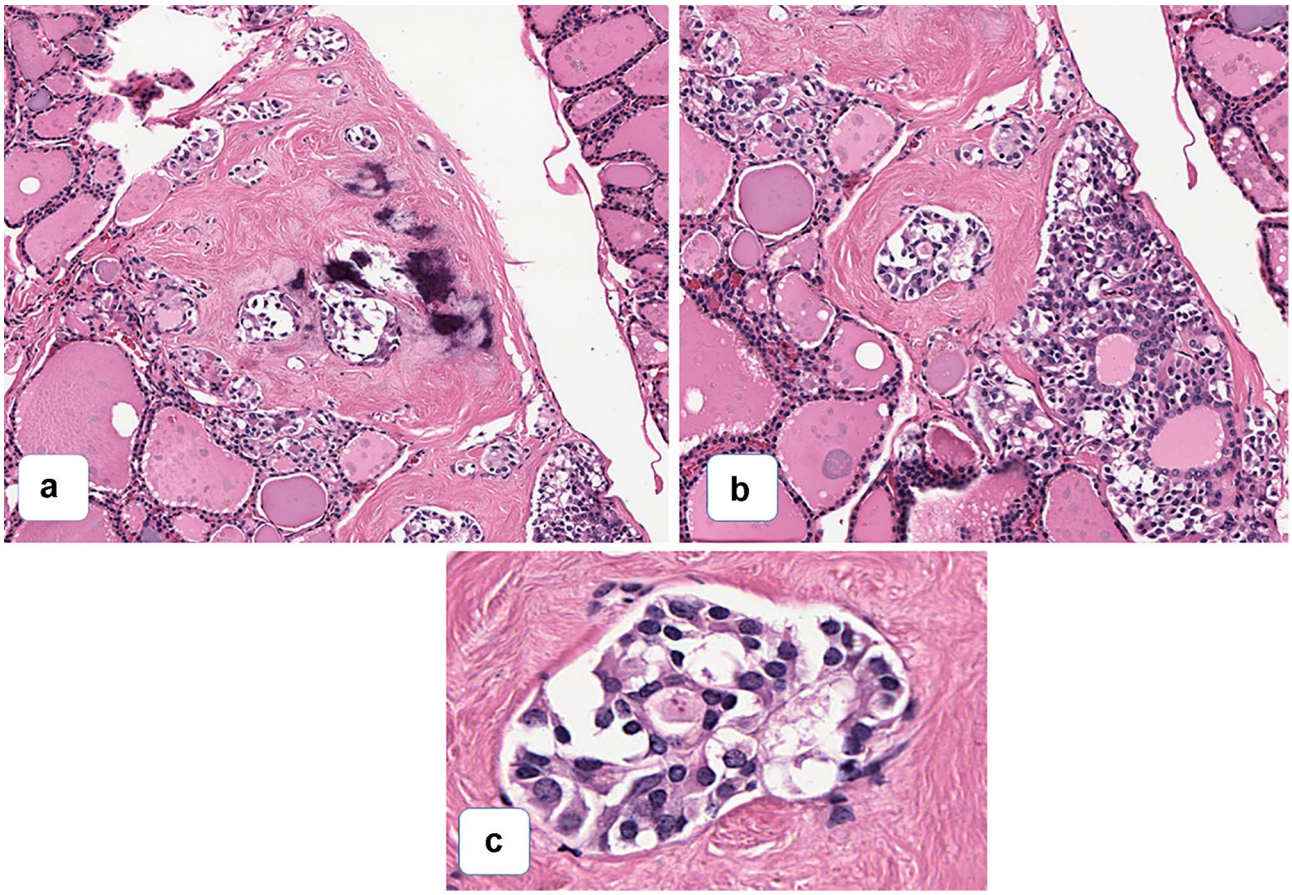

Fig. 4 Micromedullary carcinoma. **a** Incidental finding in a thyroid lobe containing a follicular adenoma (H&E × 10). **b** Higher power shows fibrous stroma and irregular clusters of tumor cells no longer organized around follicles (H&E, × 100). **c** Higher power of medullary carcinoma nest in dense stroma (H&E, × 250)

difficulty. Helpful clues include irregular (non-smooth) outlines at the edge of the lesion, stroll fibrosis and rarely amyloid, and single cells infiltrating the stroma [40]. Immunostaining for laminin and type 4 collagen may be useful to assess basement membrane integrity [41].

The prognosis of medullary carcinoma varies between familial and sporadic cases. Since familial cases are frequently identified by genetic screening because of family history, the tumors are small and may not yet have developed and total thyroidectomy is curative. In sporadic cases, stage of tumor, including size, extra-thyroidal extension, and nodal metastases influence outcome. Pathological features that may show some relationship with prognosis, but not individually at a statistically significant level, are much amyloid, calcification of the amyloid, rare mitoses, absence of necrosis, and greater than 75% of tumor cells staining for calcitonin (these probably reflect the degree of differentiation of the tumor from a functional standpoint). Recent studies [42, 43] have found that a high proliferation index (Ki67) or > 5 mitoses per 10 high power fields and the presence of necrosis are independent adverse prognostic features (Fig. 2).

In metastatic medullary carcinoma, next generation sequencing of the tumor can show specific genetic alterations which may allow targeted therapy.

Table 3 The major syndromes

MEN IIA SIPPLE	MEN IIB (or III)
MTC and CCH	MTC and CCH
Adrenal pheo and AMH	Adrenal pheo and AMH
Parathyroid lesions (25%)	Mucosal and GI neuromas
	Skeletal abnormalities (Marfanoid)
	Ocular lens abnormalities

MTC medullary thyroid carcinoma, *CCH* Ccell hyperplasia, *PHEO* pheochromocytoma, *AMH* adrenal medullary hyperplasia

Intrathyroidal Parathyroid Lesions

Most humans have 4 parathyroid glands and these are located at the upper and lower poles of the thyroid gland [9, 10, 44]. On occasion, one or more parathyroid glands

become trapped within the thyroid during development. There may be just a portion of parathyroid and fat or an entire gland present. If there is no parathyroid disease, such glands produce no medical problem. However, if the intrathyroidal parathyroid undergoes neoplastic transformation, or the patient develops secondary hyperparathyroidism (due to renal failure), the intra-thyroidal lesion will present as a nodule [44, 45]. Ultrasound and clinical evaluation may misinterpret the nodule as of thyroid origin. FNA of such a nodule may be misinterpreted as "follicular neoplasm" or "follicular lesion" assuming it is of thyroid origin. It is only when the lesion is removed with part of the thyroid that the true diagnosis is rendered.

Clues on the FNA sample [14] include the uniformity and monotony of the cells and their absence of pleomorphism. Should the diagnosis of a parathyroid lesion be considering a portion of the FNA, sample can be sent for parathyroid hormone assay and the diagnosis will become obvious. In my experience, these parathyroid adenomas usually involve the lower glands. It is important to remember that this situation is rarer than a surgeon believes since a gland may be only partially intrathyroidal. To be truly considered an intra-thyroidal parathyroid, the entire gland (whether normal or hypercellular) must be surrounded by thyroid tissue. In the lower poles of the thyroid, one can encounter divots, wherein part of the parathyroid is outside of the thyroid histologically, but may be mistaken for an intra-thyroidal gland by the operating surgeon.

Any lesion that can involve the parathyroid glands in their normal location can occur in an intra-thyroidal gland-adenoma, atypical adenoma, hyperplasia, and even carcinoma [44, 45].

Helpful immunostains for distinguishing intra-thyroidal parathyroid proliferations from thyroid lesions, including medullary carcinoma, are parathyroid hormone, chromogranin (both would be positive in parathyroid) and TTF1, calcitonin, and thyroglobulin which would all be

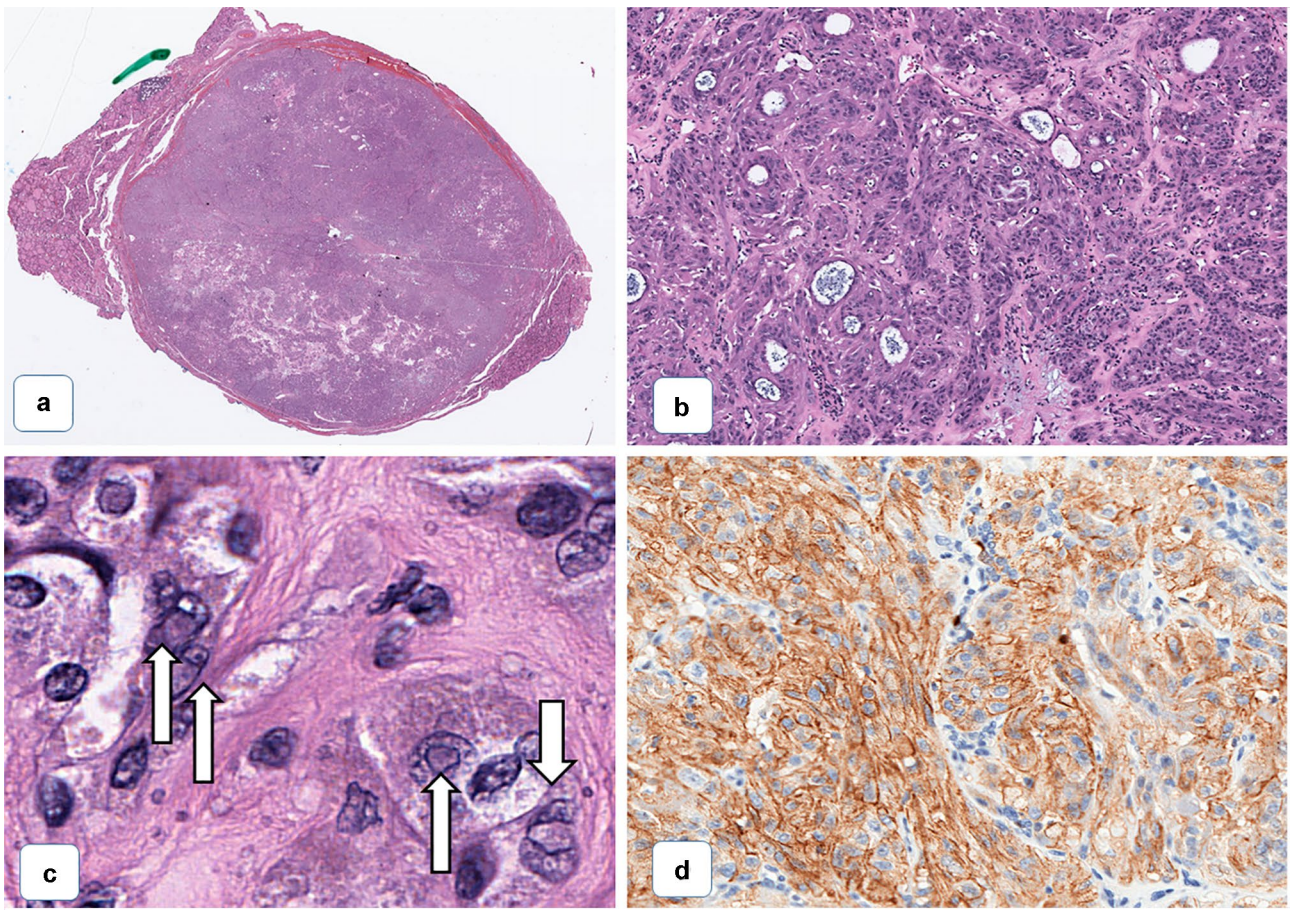

Fig. 5 Hyalinizing trabecular tumor. **a** Low power view of circumscribed tumor (H&E, × 4). **b** Note tumor cells arranged in cords with "empty" follicles. **c** Tumor cells with oval nuclei and prominent inclusions (arrows) (H&E × 400). **d** Ki67 stain shows membranous and peripheral cytoplasmic staining characteristic of this tumor (immunostain, × 100)

negative. One additional helpful stain is GATA3, which stains all parathyroid tissue and is negative in thyroid lesions [30].

Hyalinizing Trabecular Tumor

Although some pathologists persist in considering this unusual lesion as a variant of papillary carcinoma, the overwhelming majority of these lesions (if defined by strict diagnostic criteria) behave in a benign clinical fashion [30, 46–50]. Some cases reported to be associated with metastases (44, 46) have shown focal growth pattern similarity to HTT but have not fulfilled the complete definition. These tumors probably represent papillary or follicular carcinoma with focal HTT pattern [30].

Classically, HTT are usually circumscribed and yellow-tan grossly. The circumscription is recapitulated histologically. They are composed of trabeculae of cells with abundant eosinophilic cytoplasm and large oval nuclei. The latter resemble exaggerated papillary carcinoma nuclei and show prominent inclusions and intranuclear grooves [30] (Fig. 5). The stroma between the trabeculae is fibrous and may resemble amyloid although not quite so eosinophilic and is negative on stains for amyloid. The cytoplasm will contain so-called "yellow bodies" in about 60–70% of the cells.

A characteristic and specific finding for these tumors is peripheral cytoplasmic and membrane staining for Ki67 (with MIBI antibody and if the stain is done at room temperature). No other thyroid tumor has this feature, which is specific for HTT [30]. Huss and Mendelsohn [18] described a series of circumscribed trabecular neoplasms which were calcitonin positive and were indeed medullary carcinomas. In distinguishing HTT from medullary carcinoma (in which trabecular growth is a prominent pattern), several clues are helpful: the nuclei of HTT show exaggerated features of nuclei of papillary carcinoma (Fig. 4) immunostaining will clinch the diagnosis since HTT is positive for thyroglobulin and negative for calcitonin while medullary carcinoma shows the opposite staining pattern. In addition, peripheral cytoplasmic and membrane staining of the cells of HTT with Ki67 is a unique finding in HTT and distinguishes this lesion from all other thyroid tumors [30].

Some HTT contain calcifications resembling psammoma bodies. Hence, the nuclei, the calcification, and some data showing ret/PTC translocations led some pathologists to consider these papillary carcinoma variants [47–50].

Molecular analysis of HTT has been confusing with some early studies showing ret/PTC translocations [47, 50]; more recent reports do not concur with these findings. BRAF V600 E mutations have also not been found [51]. However, recent data show a characteristic rearrangement involving GLIS (PAX8-GLIS 1 or 3 rearrangement) which appears specific for this thyroid lesion [52, 53]. Indeed, large series of these tumors with long-term follow-up have shown a remarkably benign course. The large series from Carney et al. [54] showed that all but one patient had a benign course (no recurrence or metastasis) in up to 48 years of follow-up! (the diagnosis in one patient who developed lung metastases may not have been a classic HTT histologically). Because of these statistics [54–56], the 2017 WHO book [30] on Endocrine tumors termed these lesions "hyalinizing, trabecular tumor", "hyalinizing trabecular neoplasm", or even "hyalinizing trabecular adenoma".

Paraganglioma

True paraganglioma of the thyroid is very rare and this author believes it does not occur. On occasion, one will encounter a paraganglioma that is present within the thyroid, but in my experience, these lesions have always been located at the periphery of the gland. The experienced head and neck or endocrine pathologist will recognize paraganglion tissue in the soft tissue immediately adjacent to the thyroid, but not within it. Should a tumor arise in this tissue, it could easily involve the nearby thyroid and present clinically, radiologically, surgically, and even microscopically as a primary thyroid lesion.

The cell clustering nature of the growth (nests) may mimic some epithelial predominant medullary carcinoma. Immunostaining may guide the pathologist to the correct diagnosis: although both may show tumor cells that stain for chromogranin and synaptophysin, S100 staining the sustentacular cells in paraganglioma [30] and alternatively negative calcitonin will help.

Most of the intrathyroidal paragangliomas reported have behaved in a clinically benign fashion [30]. However, it is important for the diagnostic histopathologist to check for possible genetic [30] predisposition to multifocal paragangliomas and also the possible malignant potential of such lesions [57]. This is true for any paraganglioma no matter its site of origin.

It is beyond the scope of this review to discuss the various genetic signatures that predict risk of malignant behavior in paragangliomas/pheochromocytomas. MEN2, neurofibromatosis type 1, and von Hippel-Lindau syndromes show these types of tumor (usual intra-adrenal) and these are almost always benign (although they may be multifocal) [57].

Those tumors arising in patients with germline mutations in succinate dehydrogenase (SDH), however, do

show malignant (i.e., metastasizing) potential. Of the numerous subtypes of SDH, the one with largest risk of aggressive clinical behavior is SDHB [57, 58].

Vignette 3: A 23-year-old woman presented with a 2.8-cm neck mass clinically and by imaging studies to be in the thyroid, FNA was diagnosed as "neoplasm present" and this was not further defined. Histology of the excised lobe was considered paraganglioma (the lesion was circumscribed without invasion, showed a nested growth pattern, and chromogranin positivity). Three years later, an enlarged neck node on the ipsilateral side of the thyroid tumor was noted by the patient. FNA showed tumor. Review of the original thyroid lobectomy slides included staining for calcitonin and CEA (both were diffusely positive).

SHDB loss or retention can be assessed by immunostaining as this may be a significant clue to familial or potentially malignant disease. It is also likely that loss of staining and likely genetic basis for tumor development may indicate multifocal disease in such patients. In our institution which is a large referral center for paraganglion and adrenal medullary (pheochromocytomas) tumors, the frequency of SDHB loss is about 40% [58]. Familial disease, multifocality, and malignant behavior are fairly common in our institution. It is likely, however, that these statistics represent an outlier because of referral patterns.

Calcitonin Negative Medullary Carcinoma

The concept of calcitonin negative medullary carcinoma (non-secretory medullary carcinoma) has developed over recent decades and is found in isolated case reports or small series [59, 60]. Gambardella et al. [59] summarized the literature up to 2019 and found 51 cases. However, immunostains for calcitonin were often not performed and/or gave weak/focal results. In many cases, CEA stain was positive. This subgroup (calcitonin negative or weak and CEA positive) probably represents medullary cancers, but is non-secretory (serum calcitonin normal) [59].

The so-called small cell medullary carcinoma is the tumor most likely to give negative immunostain results for calcitonin. This author believes one can see areas of small cell pattern in an otherwise calcitonin positive medullary tumor or such a lesion may be found in the thyroid of a patient with known RET germline mutation (and/or a positive family history). Such tumors can be accepted as medullary carcinoma if the tumor cells stain for monoclonal CEA or if that protein is absent, by proving the presence of mRNA for calcitonin by in situ hybridization methods. [31].

Thyroid Tumors of Ewing/PNET Family

Recent reports indicate that some calcitonin negative small cell medullary carcinomas represent an entirely different entity-i.e., an Ewing family tumor showing translocation of EWSR1-Fli1 [61–63]. Some reported cases have been carcinoma with the suggestion raised that the small cell lesion arose via de-differentiation of the papillary neoplasm. The designation CEFTE has been suggested for these lesions (carcinoma of thyroid with Ewing family tumor elements [62, 63]. In addition, strong and diffuse staining for p63 is noted whereas TTF-1, thyroglobulin, and calcitonin are typically negative [62, 63].

Some reported examples are apparently "pure" Ewing/PNET. Immunostain results reported show that all examples have membrane staining for CD99. Those tumors tested by FISH technology have shown the characteristic EWSR1-Fli1 translocation. Many of the patients reported are young males (under 40). The prognosis with appropriate therapy for Ewing tumor is good [62].

Intrathyroidal Thymic Neuroendocrine Tumors

Very rare examples of intrathyroidal tumors of thymic lineage, usually carcinoma, have been described. Of three types of carcinoma that arise in this ectopic thymus are included carcinomas with neuroendocrine differentiation. These lesions show epithelium that stains for CD5 and cytokeratins as well as for common neuroendocrine markers, chromogranin, and synaptophysin [30, 64]. If the lesions are confined within the thyroid and completely excised, the prognosis appears favorable in the limited reported experience.

Metastatic Neuroendocrine Tumors to the Thyroid

In current oncologic practice with the widespread use of targeted chemotherapy, proton beam radiation, and immunotherapy, patients with advanced cancers are surviving longer than in prior decades. The longer survival allows for metastatic spread to unusual sites and one of these is the thyroid. Cytopathologists are identifying metastatic lesions in many organs and the thyroid is no longer an uncommon site of metastases. Tumors of renal, lung, breast, and colonic origin are the most common primary sites as is cutaneous melanoma [65].

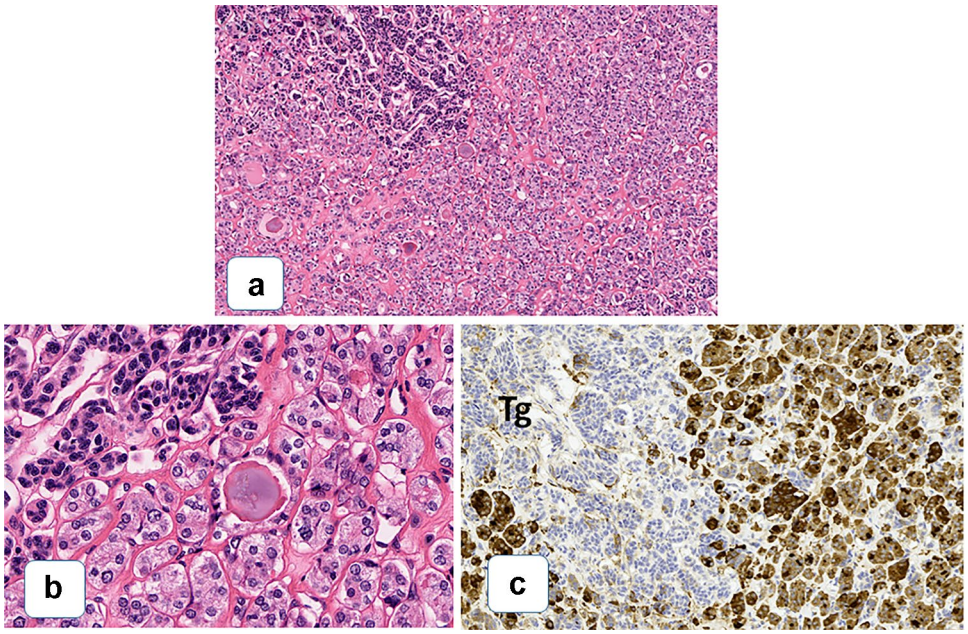

Fig. 6 Metastatic lung neuroendocrine tumor to follicular variant of papillary carcinoma. **a** Upper left shows darker cell groups with right half of photograph showing papillary carcinoma (H&E, × 50). **b** Note dark cluster of neuroendocrine tumor (left) abutting papillary carcinoma (H&E × 150). **c** Thyroglobulin stain features strongly positive reaction on right and negative stain in neuroendocrine tumor (immunostain, × 150)

Neuroendocrine tumors usually of grade 2 or 3 that arise in the lung (most frequent) or the GI/pancreas system can on rare occasions metastasize to the thyroid gland and mimic medullary carcinoma (Fig. 6). There are several small series that have been reported and in most of the patients described the presence of a metastatic lesion was only identified after immunostaining for calcitonin and careful history, or radiological investigation of the patient and his/her history [65–67]. Metastases to the thyroid often are multifocal but on occasion may present as a solitary mass and thus further mimic a thyroid primary. In some cases reported, the neuroendocrine tumor spread to a primary thyroid cancer of follicular derivation, i.e., the neuroendocrine lesion, involved an encapsulated follicular variant of papillary carcinoma. In such cases, the metastatic tumor involves the primary thyroid tumor multifocally, but tends to remain within the recipient lesion [68].

Conclusion

This review has focused on neuroendocrine proliferations especially medullary carcinoma and its related lesions. The differential diagnosis between medullary carcinoma and its mimics in the thyroid has been discussed and illustrated (Table 4). The discussion has focused on practical aspects to aid in the correct diagnoses of these various lesions.

Table 4 The "Down & Dirty" IHC stains for neuroendocrine thyroid tumors

	Medullary Ca	Parathyroid	Paraganglioma	HTT	Ewing's	Thymic Ca
Neuroendocrine Marker (chromogranin CD56)	+	+	+	–	–	–
Calcitonin	+	–	–	–	–	–
CEA (monoclonal)	+	–	–	–	–	–
Cytokeratin	+	±	Usually	+	–	+ CK5
PTH	–	+	–	–	–	–
TTF-1	+ 30%	–	–	–	–	–
S100	–	–	+	–	–	–
GATA3	–	+	–	–	–	–
Ki67 (MIB-1) membrane	–	–	+	–	–	–
CD99 membrane	–	–	–	–	+	–

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