Medullary Thyroid Carcinoma

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Background

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, medullary thyroid carcinoma (MTC) comprises approximately 1–2% of thyroid carcinomas; this value is lower than previous estimates because of the relative increase in the incidence of papillary thyroid carcinoma (PTC) over the past several decades [1]. Looking ahead, the recent reclassification of the noninvasive follicular variant of PTC as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (i.e., not a malignancy) will undoubtedly increase the proportion of thyroid malignancies comprised of MTC in the future [2].

MTC occurs in sporadic and heritable forms. Sporadic MTC (70–80% of cases) typically presents as a solitary thyroid nodule in adults. In contrast, patients with hereditary MTC usually develop multifocal bilateral thyroid tumors, and the age of presentation varies with the syndrome. Hereditary syndromes include multiple endocrine neoplasia (MEN) type 2A, familial medullary thyroid carcinoma (FMTC), and MEN type 2B. Table 9.1 summarizes the clinical and pathologic features of the sporadic and hereditary forms of MTC.

MEN2 syndromes and FMTC show an autosomal dominant mode of inheritance and are associated with pathogenic germline mutations of the *RET* gene, encoded on chromosome 10, that result in constitutive activation of the RET receptor tyrosine kinase.

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Table 9.1 Clinical and pathologic features of hereditary and sporadic medullary thyroid carcinoma

	MEN2A	FMTC	MEN2B	Sporadic MTC
Proportion	~20% of MTC (~80% of hereditary cases)	~4% of MTC (~15% of hereditary cases)	~1% of MTC (~5% of hereditary cases)	70–80% of MTC
		May be considered a variant/ spectrum of MEN2A		
Age at presentation	Early adulthood (third to fourth decades)	Adulthood (fifth to sixth decades)	Infancy/childhood	Adulthood (fifth to sixth decades)
Genetics	Germline *RET* mutation (most commonly exon 10 and exon 11)	Germline *RET* mutation (most commonly exon 10 and exon 11)	Germline *RET* mutation (95% with exon 16 codon M918T mutations; <5% with exon 15 codon A883F mutation)	Somatic *RET* mutations (most commonly codon M918T) in 25–45%
				1–7% of presumed sporadic MTC have germline *RET* mutations
				Somatic *RAS* mutations identified in *RET* wild-type cases
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	N/A
Associated diseases	Pheochromocytoma (50%); hyperparathyroidism (20–35%); variants with cutaneous lichen amyloidosis, Hirschsprung disease	Absence of pheochromocytoma, hyperparathyroidism, or other endocrinopathies	Aggressive MTC with early spread to lymph nodes; pheochromocytoma (50%); mucosal ganglioneuromas; Marfanoid habitus; everted eyelids; thick lips	N/A
Number of thyroid nodules	Usually multicentric/ bilateral	Usually multicentric/bilateral	Usually multicentric/bilateral	Usually a solitary nodule
C-cell hyperplasia	Present	Present	Present	Usually absent

MEN2A multiple endocrine neoplasia type 2A, *FMTC* familial medullary thyroid cancer, *MEN2B* multiple endocrine neoplasia type 2B, *MTC* medullary thyroid carcinoma

Mutations in the extracellular domain of *RET* (e.g., codons 609, 611, 618, 620, and 634) result in kinase activation via ligand-independent receptor dimerization, and mutations in the catalytic domain of *RET* (e.g., codon 918) result in kinase activation independent of ligand or receptor dimerization. There is a strong correlation between specific pathogenic mutations and phenotype, vis-à-vis MEN2 subtype, aggressiveness of MTC, and association with other manifestations such as Hirschsprung disease and cutaneous lichen amyloidosis [1, 3]. Somatic *RET* mutations have been identified in up to 50% of sporadic MTC [4, 5]. Among larger series, between 1 and 7% of patients with presumed sporadic MTCs are found to have hereditary disease, underscoring the importance of germline *RET* mutation testing in all patients diagnosed with MTC [1, 6, 7].

Most cases of MTC demonstrate characteristic cytomorphology, a distinctive immunophenotype, and variable stromal amyloid deposition (Table 9.2). Nevertheless, MTC can show a wide variety of cell shapes, cytoplasmic features, and growth patterns, leading to the description of a large number of MTC variants: papillary (or pseudopapillary), follicular, giant cell, spindle cell, small cell and neuroblastoma-like, paraganglioma-like, oncocytic, clear cell, angiosarcoma-like, squamous cell, melanin producing, and amphicrine (mucin producing) [8]. Recognizing and reporting any specific variant of MTC is not important for clinical management. This morphologic heterogeneity, however, leads to significant diagnostic challenges in the morphologic evaluation of this neoplasm (Table 9.3) [9].

Definition

MTC is a malignant neuroendocrine neoplasm derived from the parafollicular cells (C cells) of the thyroid gland.

Criteria

Aspirates show moderate to marked cellularity.

Numerous isolated cells alternate with syncytium-like clusters in variable proportions.

Cells are plasmacytoid, polygonal, round, and/or spindle-shaped. Long cell processes are seen in some cases.

The neoplastic cells usually show only mild to moderate pleomorphism.

Rare bizarre giant cells may be seen; they can be numerous in the giant-cell variant.

Nuclei are round, oval, or elongated and often eccentrically placed, with finely or coarsely granular ("salt and pepper") chromatin.

Binucleation is common. Multinucleation is less often observed.

Nucleoli are usually inconspicuous but can be prominent in some cells.

Nuclear pseudoinclusions are occasionally noted. Nuclear grooves are rare or absent.

Cytoplasm is granular and variable in quantity. Small red-purple granules are seen with Romanowsky stains in some cases. Rare cases show cytoplasmic melanin pigment.

Table 9.2 Cytologic differential diagnosis of medullary thyroid carcinoma

Tumor	Cytoarchitecture and background	Cytoplasm	Nucleus	ICC/stains	
				Positive	Negative
Medullary thyroid carcinoma	Isolated, dispersed cells and/or syncytium-like clusters; amyloid	Plasmacytoid, epithelioid, giant, spindle-shaped. Red-purple granules with Romanowsky-type stains	Round, ovoid, or elongated, with granular chromatin. INCI and binucleation (some cases)	CT, CEA, NE markers, TTF1, PAX8 (variable), Congo red (amyloid)	TG
Follicular neoplasm	Microfollicles/crowded groups	Scant to moderate	Round, hyperchromatic, variable nuclear enlargement	TTF1, TG, PAX8	CT, CEA, NE markers
Hürthle-cell neoplasm	Isolated, dispersed cells and syncytium-like clusters	Abundant, finely granular (blue-gray with Romanowsky-type stains)	Round and enlarged, with moderate irregularity and prominent nucleolus	TTF1, TG, PAX8	CT, CEA, NE markers
Papillary thyroid carcinoma	Papillae, sheets, microfollicles	Variable, depending on subtype	Enlarged and ovoid with irregular contours, grooves, INCI, and chromatin pallor	TTF1, TG, PAX8	CT, CEA, NE markers
Hyalinizing trabecular tumor	Cohesive clusters associated with hyaline matrix	Epithelioid to spindled	Enlarged, with irregular contours, grooves, INCI, and chromatin pallor	TTF1, TG, Ki67 (membranous)	CT, CEA, NE markers
Poorly differentiated thyroid carcinoma	Crowded groups, isolated, dispersed cells	Scant, occasionally plasmacytoid	Round, with variable enlargement and binucleation; apoptosis; mitosis	TTF1, PAX8, TG (variable)	CT, CEA
Anaplastic thyroid carcinoma	Isolated, dispersed cells and crowded groups. Variable necroinflammatory debris	Epithelioid, spindled, variable sizes	Enlarged, with variable pleomorphism, nucleolar prominence, multinucleation; necrosis/apoptosis; mitotic activity	PAX8 (variable)	TTF1, TG, CT, CEA, NE markers

Tumor	Cytoarchitecture and background	Cytoplasm	Nucleus	ICC/stains	
				Positive	Negative
Melanoma	Isolated, dispersed cells	Epithelioid, spindled, variable sizes. Variable melanin pigmentation	Enlarged, with prominent nucleoli	S100-protein, HMB45, Melan-A, SOX10	CK, CT, CEA, NE markers
Parathyroid	Sheets, cords, acini	Moderate amount, often granular	Round, with granular chromatin	NE markers, PTH, GATA3	CT, CEA, TTF1, TG
Plasmacytoma	Isolated, dispersed cells; amyloid	Moderate amount with eccentric nuclei ("plasmacytoid")	Round, with granular chromatin	CD138, kappa or lambda Ig light chain restriction, Congo red (amyloid)	CT, TTF1, NE markers
Paraganglioma	Isolated, dispersed cells and loose clusters	Moderate to abundant amount of delicate cytoplasm	Round, with granular chromatin, anisonucleosis	NE markers, S100-protein (sustentacular cells)	CK, CT

CEA carcinoembryonic antigen, *CK* cytokeratin, *CT* calcitonin, *ICC* immunocytochemistry, *Ig* immunoglobulin *INCI* intranuclear cytoplasmic pseudoinclusions, *NE* neuroendocrine, *PTH* parathyroid hormone, *TG* thyroglobulin

Table 9.3 Variants of medullary thyroid carcinoma and associated differential diagnostic considerations

MTC variant	Differential diagnosis
Amphicrine (mucin and calcitonin-producing cells)	Secretory carcinoma, metastatic adenocarcinoma
Clear cell	Renal cell carcinoma, follicular neoplasm with clear cells
Follicular/tubular	Follicular neoplasm
Giant cell	Undifferentiated (anaplastic) thyroid carcinoma (UTC)
Melanin-producing/pigmented	Melanoma
Mixed follicular and medullary	Follicular neoplasm
Oncocytic (oxyphilic)	Oncocytic variants of follicular neoplasm and PTC
Papillary/pseudopapillary	Papillary thyroid carcinoma (PTC)
Paraganglioma-like	Paraganglioma, hyalinizing trabecular tumor
Small cell/neuroblastoma-like	Small-cell carcinoma of the lung, lymphoma
Spindle cell	Sarcoma, UTC
Squamous	Squamous-cell carcinoma, UTC, PTC with squamous differentiation/metaplasia

MTC medullary thyroid carcinoma (Adapted from [9]. With permission from Wolters Kluwer Health, Inc.)

Amyloid is often present and appears as dense, amorphous material that resembles thick colloid.

With liquid-based preparations, fine cytoplasmic vacuolization can be prominent.

Cells are typically strongly immunoreactive for calcitonin, CEA, neuroendocrine markers (chromogranin, synaptophysin), and TTF1. Immunoreactivity for PAX8 is variable. Cells are negative for thyroglobulin (aberrant results occasionally occur).

Explanatory Notes

Cytologic preparations from MTC are usually moderately or highly cellular and composed of a mixture of noncohesive cells (Fig. 9.1) and crowded, syncytium-like aggregates (Fig. 9.2) [8–12]. Occasionally, rosette-forming, follicular, and pseudopapillary architecture can be seen. Most aspirates show a mixture of cell morphologies, including polygonal, round, and plasmacytoid shapes (all with round to ovoid nuclei) (Fig. 9.3), as well as spindled cells with elongated nuclei (Fig. 9.4). Tumor cells have a variable amount of cytoplasm, sometimes replete with red-purple granules after Romanowsky-type staining of air-dried smears (Fig. 9.5). A minority of cases demonstrate cytoplasmic vacuoles, melanin-like pigment (Fig. 9.6), and intracytoplasmic lumina (Fig. 9.7) [8]. With liquid-based preparations, fine cytoplasmic vacuolization can be prominent (see Fig. 9.6). Typically, most of the tumor cells demonstrate only mild to moderate nuclear pleomorphism, with occasional cells showing markedly enlarged or bizarre-appearing nuclei [8, 10]. Binucleation is common [8, 10]. Intranuclear pseudoinclusions (indistinguishable from those seen

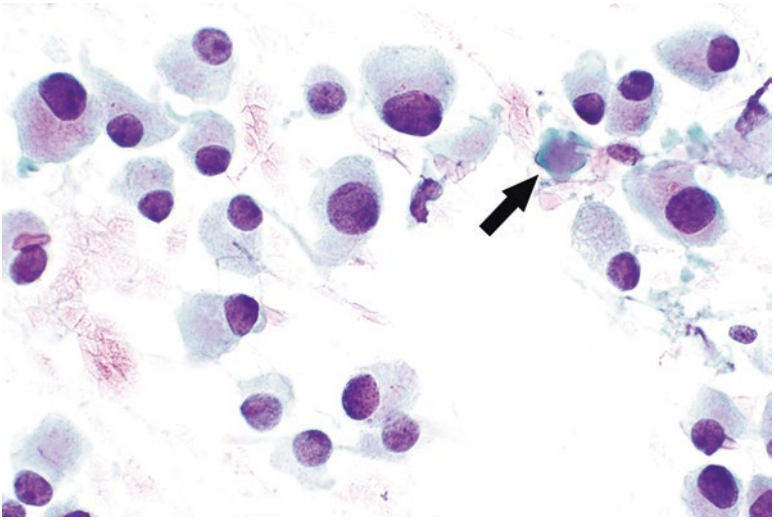

Fig. 9.1 Medullary thyroid carcinoma. Predominantly dispersed plasmacytoid or polygonal cells have granular ("salt and pepper") chromatin and small or indistinct nucleoli. A small fragment of amyloid is present (*arrow*) (smear, Papanicolaou stain).

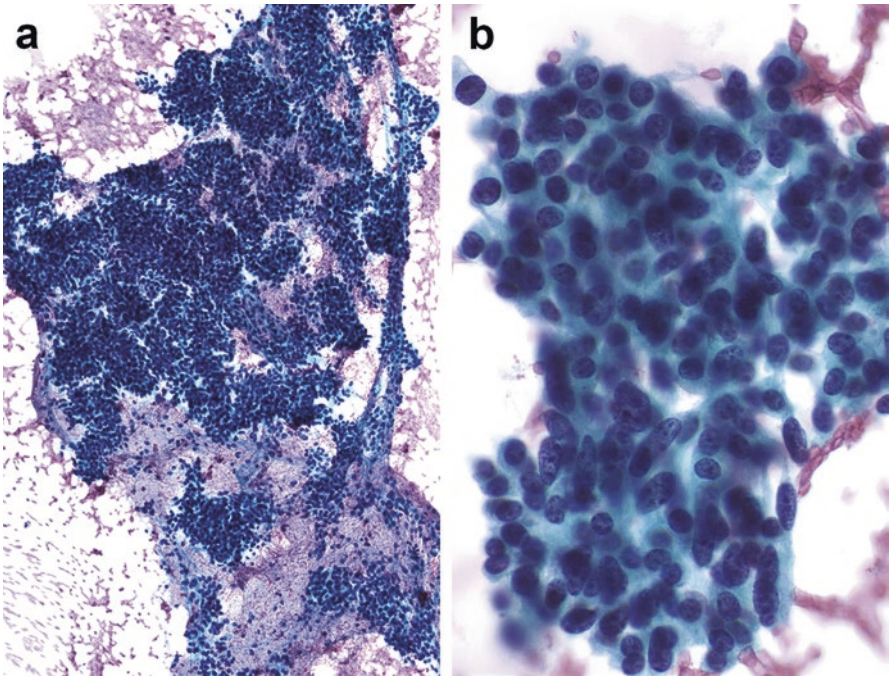

Fig. 9.2 Medullary thyroid carcinoma. (**a**) In some cases a cohesive, syncytium-like pattern of crowded cells predominates, with few isolated cells. (**b**) In this example, tumor cells exhibit less abundant cytoplasm, round to ovoid nuclei, and coarse chromatin. Medullary thyroid carcinomas with this pattern mimic a follicular neoplasm, poorly differentiated thyroid carcinoma, and parathyroid neoplasms (smear, Papanicolaou stain).

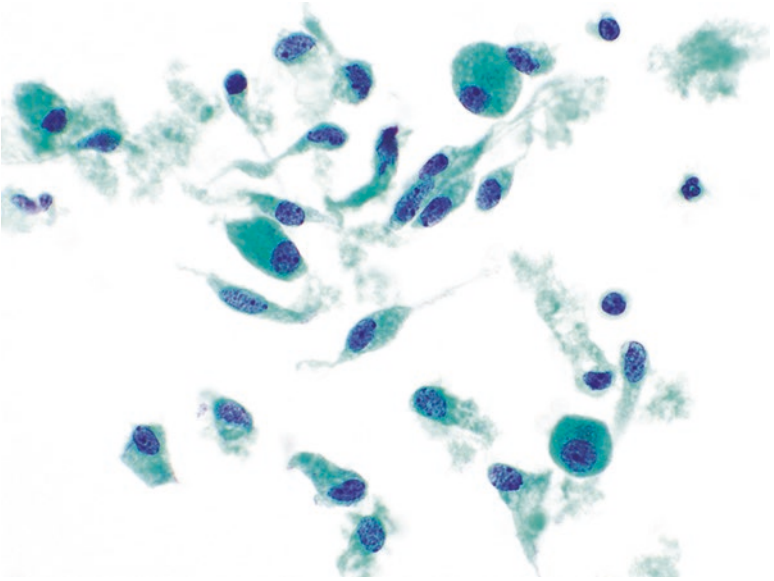

Fig. 9.3 Medullary thyroid carcinoma. A variety of shapes (round, polygonal, plasmacytoid, and spindled) are noted in this noncohesive population of tumor cells (ThinPrep, Papanicolaou stain).

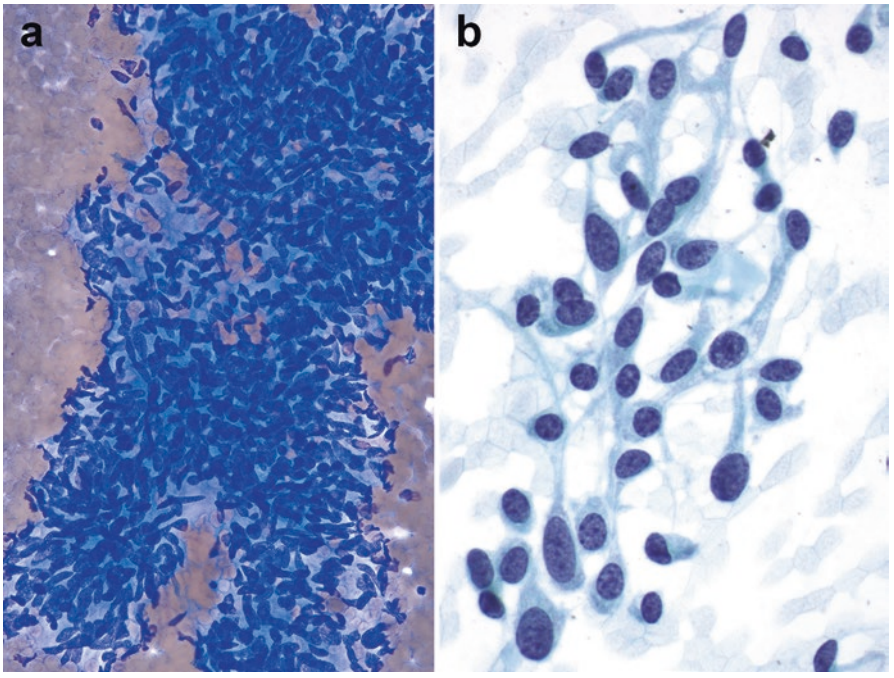

Fig. 9.4 Medullary thyroid carcinoma. (**a**) The spindle-cell variant can have a syncytium-like arrangement (smear, Diff-Quik stain). (**b**) The spindle-cell variant has prominent interdigitating cytoplasmic processes with oval nuclei. Smooth nuclear membranes, granular chromatin, and inconspicuous nucleoli are maintained (smear, Papanicolaou stain).

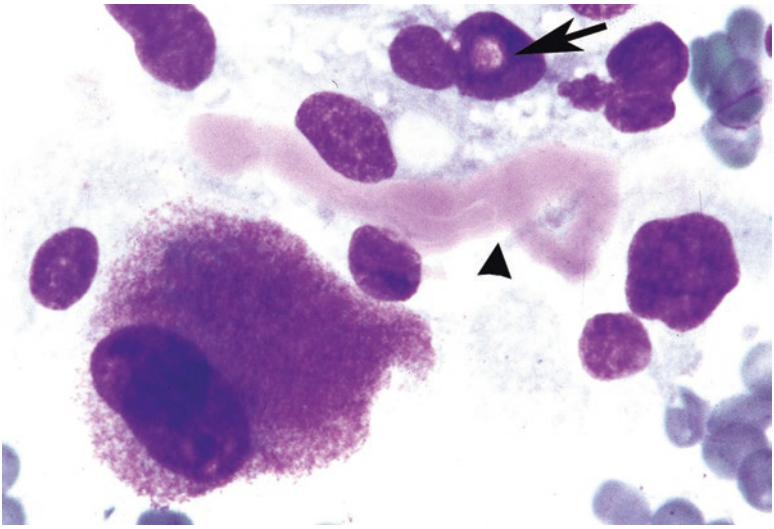

Fig. 9.5 Medullary thyroid carcinoma. A large tumor cell with abundant cytoplasm demonstrates red cytoplasmic granules with a Romanowsky-type stain. Note also the presence of amyloid (*arrowhead*) and a tumor cell with an intranuclear pseudoinclusion (*arrow*) (smear, Diff-Quik stain).

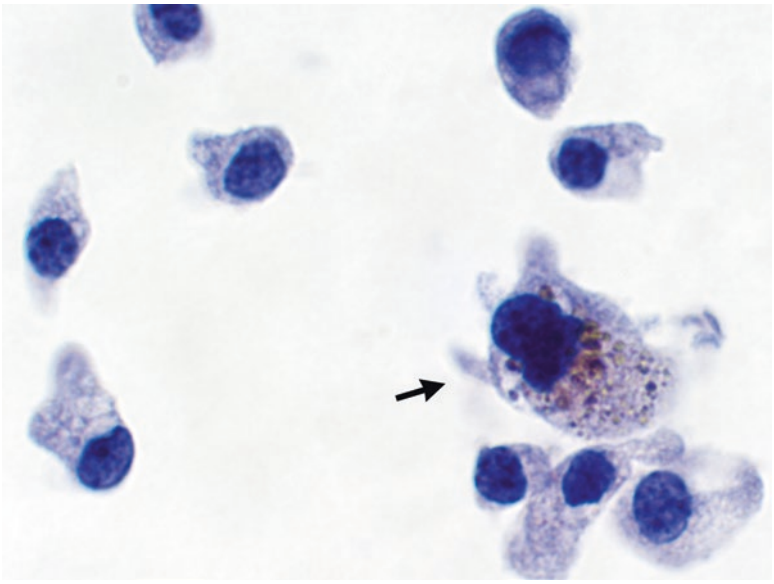

Fig. 9.6 Medullary thyroid carcinoma. Pigmentation and/or melanocytic differentiation can be seen in medullary thyroid carcinoma (*arrow*), which raises the possibility of a metastatic melanoma. Even without pigmentation, melanoma is a mimic of medullary thyroid carcinoma because both often demonstrate an isolated-cell pattern, epithelioid or spindled morphology, and binucleation. Immunocytochemistry on the cell block in this case confirmed the diagnosis of medullary thyroid carcinoma (ThinPrep, Papanicolaou stain).

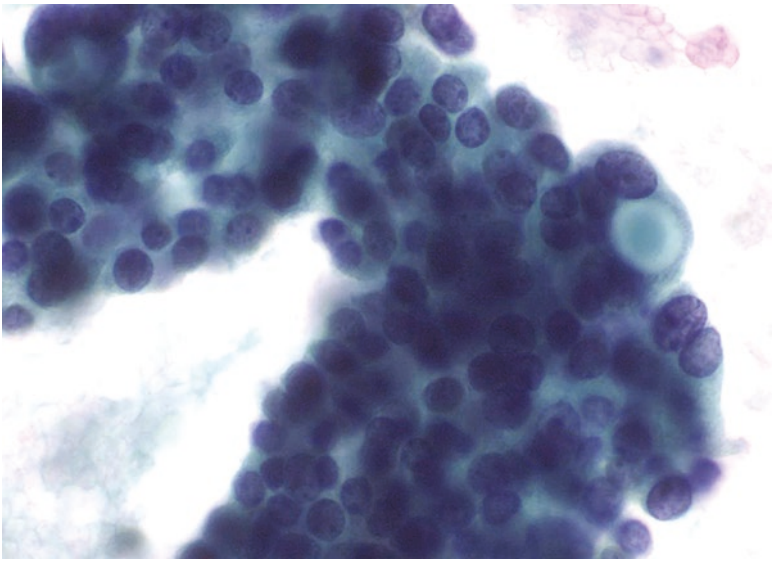

Fig. 9.7 Medullary thyroid carcinoma. Cytoplasmic vacuoles or lumina are occasionally seen in medullary thyroid carcinoma (smear, Papanicolaou stain).

in papillary thyroid carcinoma) are seen in a limited number of cells in ~20–50% of cases (Fig. 9.8) [8, 10, 13]. Nuclear grooves are rare [13]. Rare cases show scant cytoplasm and nuclear molding, resembling small-cell carcinoma (Fig. 9.9). Amyloid is identified in approximately one-third to one-half of MTC aspirates (Figs. 9.10 and 9.11) [8, 10, 14]. It is virtually indistinguishable from colloid without the cellular context and is not diagnostic of MTC by itself, since amyloid may be present in papillary thyroid carcinoma (rarely) and amyloid goiter [15, 16]. Colloid is present in about 30% of MTC aspirates and is more frequent in medullary thyroid microcarcinoma, likely due to incidental colloid sampling from surrounding thyroid follicles [10, 17]. Calcifications (including psammoma bodies) have been reported in approximately 3% of MTC [8, 10].

Diagnosing MTC by FNA can be challenging given its diverse appearances and cytologic overlap with other tumors. Although the sensitivity of FNA for a definitive and specific diagnosis of MTC has been reported to be as high as 89% in a single-institution study, a meta-analysis revealed a substantially lower sensitivity of 56% (range 12–88%), thus highlighting the challenge that MTC poses to the cytologist [10, 18]. Immunocytochemistry (ICC) is extremely helpful for distinguishing MTC from its cytologic mimics (Table 9.2). Most MTCs are immunoreactive for "C-cell markers" (calcitonin, CEA), neuroendocrine markers (synaptophysin, chromogranin) [19–25], and TTF1 [19, 21, 26–28] and are negative for thyroglobulin (Fig. 9.12) [22, 29]. Staining for PAX8 varies considerably among studies (0–75%), with positive cases generally showing only focal immunoreactivity [27, 30–32]. Therefore, TTF1 and PAX8 are not helpful for distinguishing MTC from follicular

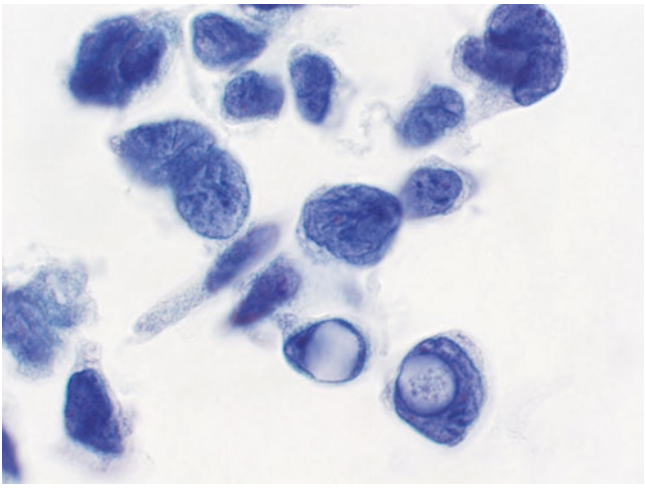

Fig. 9.8 Medullary thyroid carcinoma. Intranuclear cytoplasmic pseudoinclusions can be seen, mimicking papillary thyroid carcinoma (ThinPrep, Papanicolaou stain).

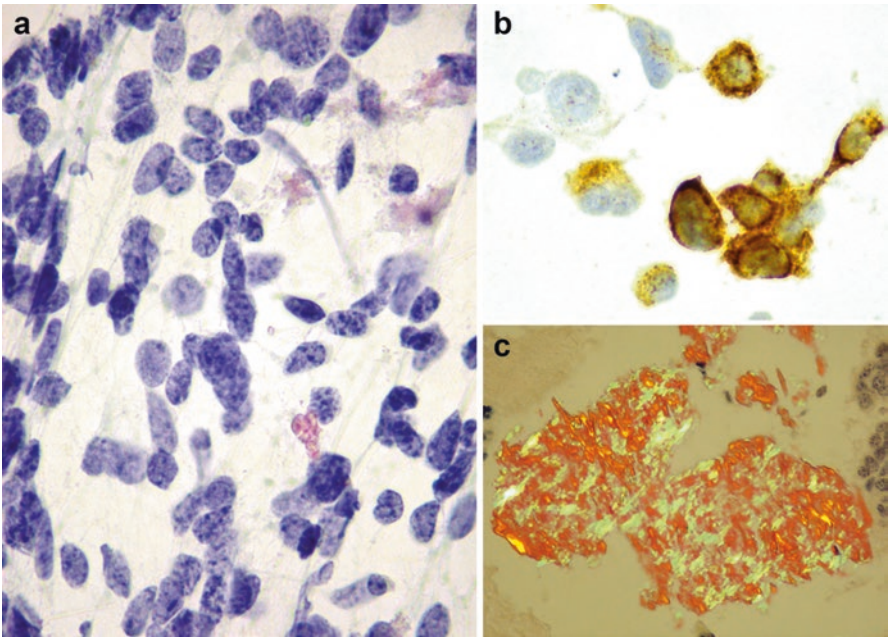

Fig. 9.9 Medullary thyroid carcinoma, small-cell variant. (**a**) Rare cases of medullary thyroid carcinoma exhibit scant cytoplasm and nuclear molding, resembling small cell carcinoma of the lung and other sites (smear, Papanicolaou stain). (**b**) Immunoreactivity for calcitonin and (**c**) Congo red staining for amyloid on cell block preparations support the diagnosis of medullary thyroid carcinoma. Nevertheless, because their immunprofiles can overlap and both tumors can contain amyloid, the distinction requires correlation with clinical findings.

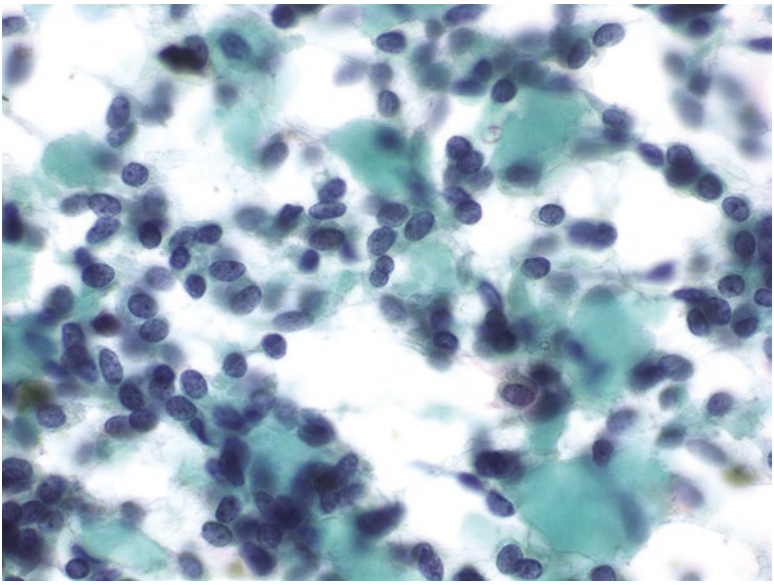

Fig. 9.10 Medullary thyroid carcinoma. In this smear, amyloid is abundant and readily appreciated as a light-green, waxy, amorphous deposit (Papanicolaou stain).

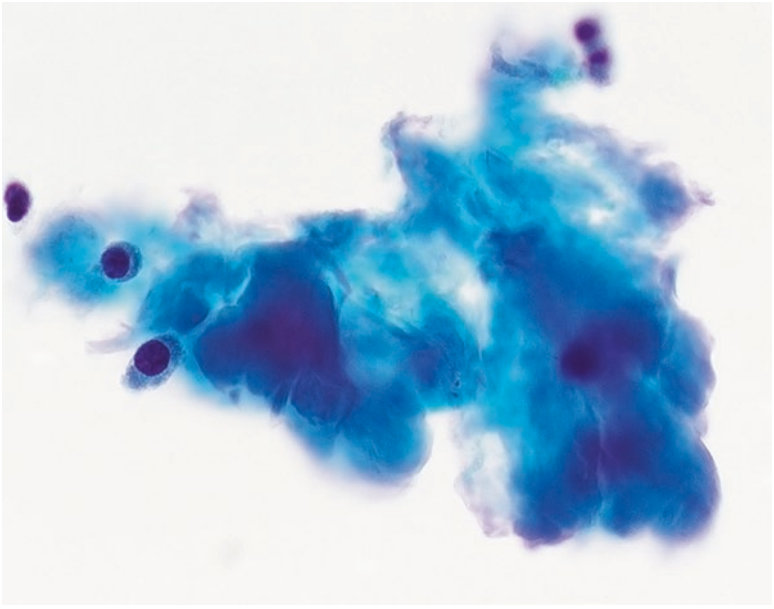

Fig. 9.11 Medullary thyroid carcinoma. Amyloid has the same dense, amorphous, and waxy appearance on liquid-based preparations as it does on smears (ThinPrep, Papanicolaou stain).

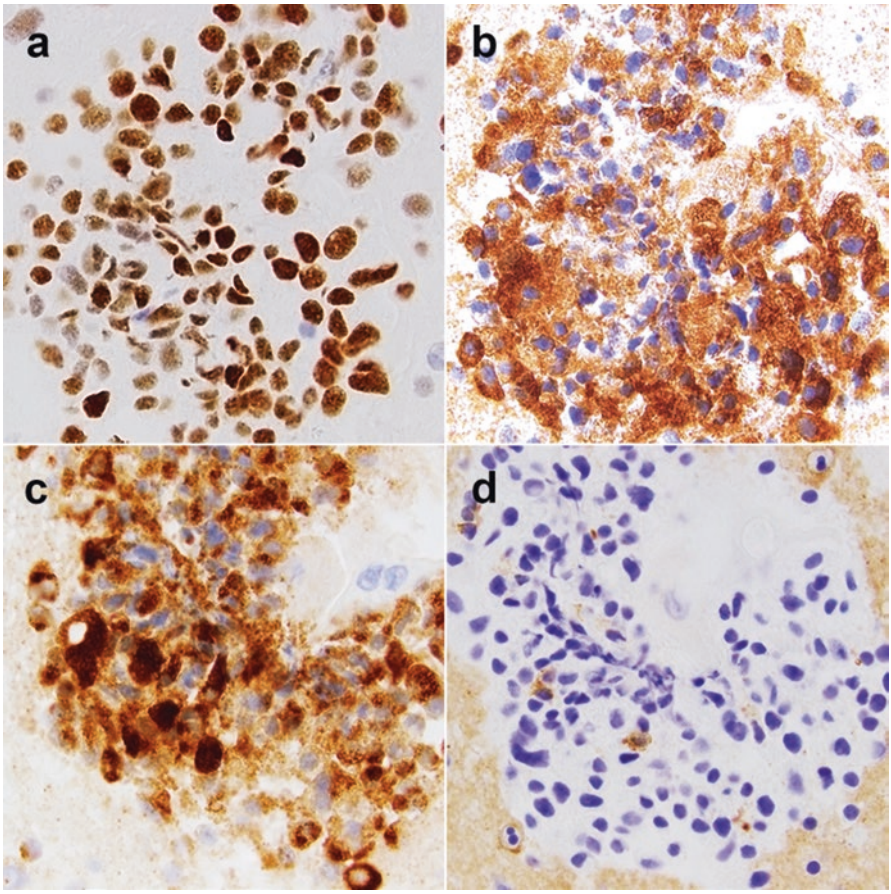

Fig. 9.12 Medullary thyroid carcinoma. The tumor cells (on cell block preparations) are immunoreactive for (**a**) TTF1 (nuclear), (**b**) calcitonin (cytoplasmic), and (**c**) chromogranin (cytoplasmic). (**d**) Tumor cells are negative for thyroglobulin.

cell-derived thyroid neoplasms. A Congo red stain can confirm the presence of amyloid, which supports the diagnosis of MTC in the context of characteristic malignant cells. The measurement of calcitonin levels in needle rinsings (washout fluid) from FNAs of thyroid nodules, thyroidectomy beds, and/or lymph nodes, can be helpful. This is particularly true in patients with elevated serum calcitonin levels and/or when FNA findings are inconclusive for MTC, e.g., when confirmation by ICC is not possible given limited material or equivocal staining results [1, 33]. Overall, this test is reliable, inexpensive, and associated with fast turnaround time. In order to avoid repetition of the FNA for this purpose, calcitonin measurement in FNA washout fluid should be anticipated in all clinically suspected cases of MTC and for all patients with MEN2. The Afirma Gene Expression Classifier (Veracyte, Inc., South San Francisco, CA), in common use for nodules interpreted as atypia of

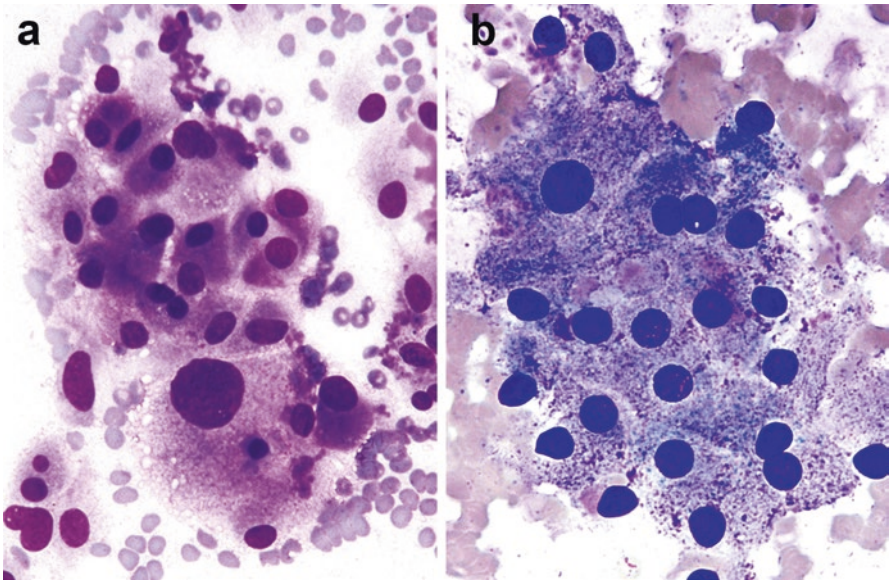

Fig. 9.13 Medullary thyroid carcinoma (*left*) versus Hürthle-cell neoplasm (*right*). (**a**) With Romanowsky-type stains, the cells of some (but not all) medullary thyroid carcinomas are noteworthy for abundant red cytoplasmic granules (smear, Diff-Quik). (**b**) In contrast, Hürthle cells have blue-gray cytoplasmic granules with Romanowsky-type stains (smear, Diff-Quik).

undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) or follicular neoplasm (FN)/suspicious for follicular neoplasm (SFN), includes an MTC classifier that is effective in identifying the MTCs hidden in the substantial population of nodules with indeterminate cytology [34, 35].

The differential diagnosis of MTC includes the full spectrum of follicular cell-derived thyroid tumors (Table 9.2). Aspirates of Hürthle-cell (oncocytic) neoplasms often yield noncohesive cells with abundant granular cytoplasm, resembling some MTCs (Fig. 9.13). Papillary thyroid carcinoma (PTC) and hyalinizing trabecular tumor (HTT) can also mimic MTC by virtue of their intranuclear pseudoinclusions [36]. In particular, certain variants of PTC (tall cell, oncocytic) can have elongated or abundant cytoplasm, similar to that of some MTC cells [37]. Poorly differentiated thyroid carcinoma (PDTC) can resemble MTC; both have similar cytoarchitecture (crowded insular/nested groups and/or noncohesive cells), variable binucleation and chromatin granularity, and occasional plasmacytoid shape (Fig. 9.14) [38]. Like MTC, cells of undifferentiated (anaplastic) thyroid carcinomas (UTC) can have a multitude of appearances, including epithelioid, plasmacytoid, spindled, and giant-cell forms (Fig. 9.15) [39]. Increased mitotic activity, apoptosis, and necrosis should raise concern for PDTC or UTC rather than MTC. For each of the above possibilities, a panel of immunostains (calcitonin, CEA, synaptophysin, chromogranin) helps distinguish MTC from follicular cell-derived thyroid neoplasms.

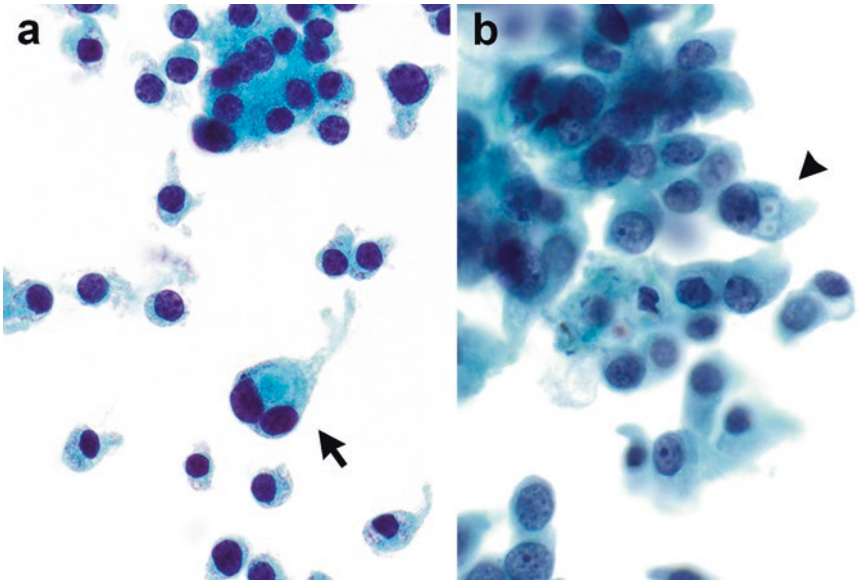

Fig. 9.14 Medullary thyroid carcinoma (*left*) versus poorly differentiated thyroid carcinoma (*right*). (**a**) Medullary thyroid carcinomas often demonstrate an isolated-cell pattern, plasmacytoid cytomorphology, and they occasionally have cytoplasmic lumina (ThinPrep, Papanicolaou stain). (**b**) Poorly differentiated thyroid carcinomas have similar features, and intracytoplasmic lumina are sometimes seen (ThinPrep, Papanicolaou stain).

Additional mimics of MTC include other neuroendocrine lesions in the head and neck, such as paraganglioma and parathyroid adenoma, both of which resemble MTC morphologically, and all are immunoreactive for synaptophysin and chromogranin. Additional immunostains help discriminate MTC (CEA+, calcitonin+, cytokeratin [CK]+) from paraganglioma (CEA-, calcitonin-, CK-, S100-protein+ sustentacular cells) and parathyroid neoplasms/hyperplasia (CEA-, calcitonin-, PTH+, GATA3+) [40, 41]. Metastatic neuroendocrine tumors to the thyroid gland or cervical lymph nodes mimic MTC and can be associated with elevated serum calcitonin levels [42]. In particular, moderately differentiated neuroendocrine carcinomas (atypical carcinoid) of the larynx are frequently positive for calcitonin and/or CEA. In contrast to MTC, however, most laryngeal atypical carcinoids are negative for TTF1 [19]. Correlation with clinical and radiographic findings plays a critical role in distinguishing MTCs from extra-thyroidal neuroendocrine tumors. Of other tumors metastatic to the thyroid, melanoma is a noteworthy mimic of MTC: the variable cell shape, frequent binucleation, nuclear pseudoinclusions, and dispersed cell pattern of many melanomas are features shared by many MTCs. In a patient with a history of melanoma, MTCs can be recognized by their immunoreactivity for cytokeratins and C-cell markers, the lack of staining for melanocytic markers (HMB45, S100-protein, Melan-A, SOX10), and the absence of macronucleoli. MTCs with a prominent spindle-cell pattern resemble mesenchymal lesions; immunoreactivity for CK, calcitonin, and neuroendocrine markers can be used to confirm

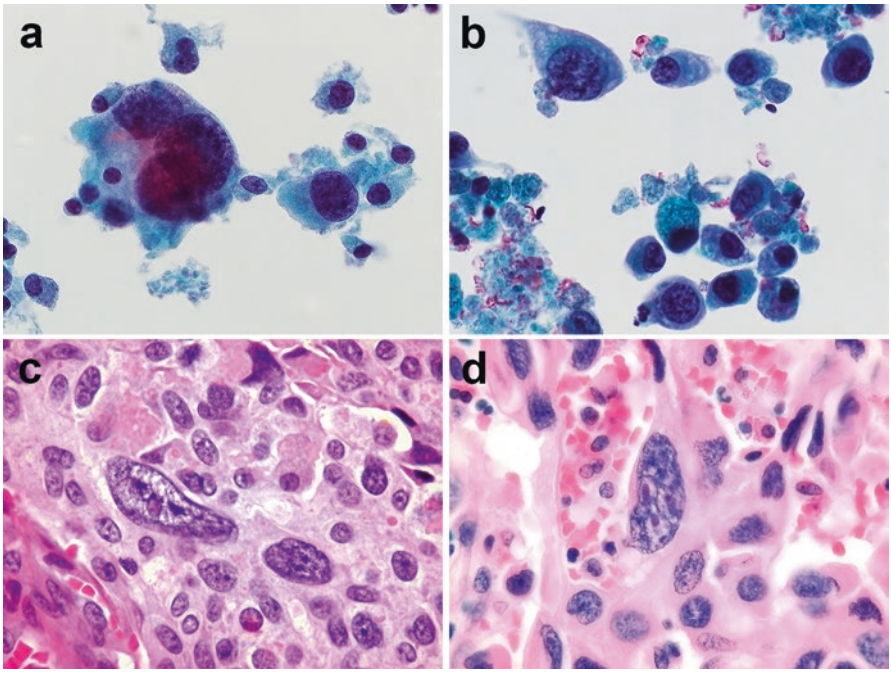

Fig. 9.15 Medullary thyroid carcinoma (*left*) versus undifferentiated/anaplastic thyroid carcinoma (*right*). (**a**) The giant-cell variant of medullary thyroid carcinoma exhibits markedly enlarged, epithelioid tumor cells with pleomorphic nuclei, often admixed with more conventional-appearing tumor cells (ThinPrep, Papanicolaou stain). Multinucleation may be seen, as in this example. (**b**) Note the resemblance to undifferentiated (anaplastic) thyroid carcinoma, which can also exhibit an epithelioid cytomorphology and nuclear pleomorphism (ThinPrep, Papanicolaou stain). This rapidly growing primary thyroid tumor was positive for PAX8 and negative for TTF1, calcitonin, synaptophysin, and chromogranin. Histologic images of medullary thyroid carcinoma (**c**) and undifferentiated thyroid carcinoma (**d**) demonstrate similar nuclear and cytoplasmic features (hematoxylin and eosin stain).

the diagnosis of MTC in this setting [43]. Finally, plasma cell neoplasms resemble MTC because a dispersed cell pattern, "plasmacytoid" morphology, and amyloid deposition are shared by both tumors. Plasmacytomas of the thyroid are exceptionally rare but have been described [44]. Expression of CD138 and immunoglobulin light chain restriction favor a plasma cell neoplasm, whereas expression of C-cell and neuroendocrine markers supports a diagnosis of MTC.

Management

Following a cytologic diagnosis of MTC, preoperative studies should include a neck ultrasound and measurement of serum calcitonin and CEA. Systemic imaging studies may be indicated for patients with clinical or laboratory evidence of metastatic disease. Genetic testing for germline *RET* mutations should also be performed, and

patients with hereditary MTC should be evaluated for pheochromocytoma and hyperparathyroidism prior to thyroid surgery [1]. For patients with pheochromocytoma, alpha/beta-adrenergic blockade and resection of the adrenal tumor should precede thyroidectomy for MTC. Surgical treatment of MTC is usually total thyroidectomy and central lymph node dissection, with consideration of lateral cervical lymph node dissection depending on imaging studies and serum calcitonin levels. For patients with advanced, progressive MTC, tyrosine kinase inhibitors such as vandetanib (targeting RET, EGFR, VEGFR) and cabozantinib (targeting RET, c-MET, VEGFR) can be used as single-agent first-line systemic chemotherapy [1].

Sample Reports

The general category "MALIGNANT" is used whenever the cytomorphologic features are conclusive for malignancy. If an aspirate is interpreted as MALIGNANT, it is implied that the sample is adequate for evaluation (an explicit statement of adequacy is optional). Descriptive comments that follow are used to subclassify the malignancy as an MTC and summarize the results of special studies, if any. If the findings are suspicious but not conclusive for malignancy, the general category "SUSPICIOUS FOR MALIGNANCY" should be used (see Chap. 7).

Example 1
MALIGNANT.
Medullary thyroid carcinoma.

Note: A Congo red stain is positive for amyloid. Immunocytochemistry performed on cell block/cytocentrifuge/liquid-based preparations (choose one) shows that the malignant cells are immunoreactive for calcitonin, CEA, chromogranin, and TTF1 and negative for thyroglobulin.

Example 2
MALIGNANT.
Consistent with medullary thyroid carcinoma.

Note: Cytomorphologic features are characteristic of medullary thyroid carcinoma, but tissue is insufficient for confirmatory immunocytochemical studies. Serum chemistry for calcitonin and CEA and/or repeat FNA for calcitonin measurement in the washout fluid warrant clinical consideration.

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