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REVIEW ARTICLE

CANCER CYTOPATHOLOGY PRACTICE ESSENTIALS

The diagnostic challenges of medullary thyroid carcinoma: A practical guide for cytopathologists

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Abstract

Medullary thyroid carcinoma (MTC) is a rare but potentially aggressive neuroendocrine tumor arising from the thyroid C cells (parafollicular cells) that produce calcitonin, representing 1%–3% of thyroid malignancies but contributing to up to 15% of thyroid cancer-related deaths. Early detection is critical for improving survival and outcomes because its tumor origin, treatment, and prognosis differ completely from papillary thyroid carcinoma. However, the low incidence of MTC and its variable cytomorphology can pose significant diagnostic challenges for cytopathologists. Referred to as the *great mimicker*, MTC can resemble various primary and metastatic tumors, complicating its identification, particularly in fine-needle aspiration (FNA) biopsies. Reported FNA sensitivity for a specific MTC diagnosis varies widely from 12.5% to 88.2%, with a 2014 meta-analysis estimating an overall sensitivity of 56.5% when including suspicious lesions. False-negative FNA results, often caused by misinterpretation of cytologic features or inadequate specimen quality, can lead to delayed or suboptimal treatment. Pathologists must be familiar with MTC's diverse cytopathologic presentation and maintain a low threshold for additional diagnostic tests to ensure an accurate preoperative diagnosis. This review article provides practical guidance on diagnosing MTC, emphasizing cytologic features, ancillary studies, mimickers, and common diagnostic pitfalls, serving as a valuable resource for cytopathologists, general pathologists, and trainees to improve diagnostic accuracy and patient care.

KEYWORDS

calcitonin, carcinoembryonic antigen (CEA), cytology, fine-needle aspiration, medullary thyroid carcinoma, thyroid

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare but potentially aggressive neuroendocrine tumor arising from the C (parafollicular) cells of the thyroid gland that produce calcitonin. It accounts for less than 3% of all thyroid malignancies yet contributes to up to 15% of thyroid cancer deaths.[1–3] Early detection is critical because both the histologic stage and the initial treatment significantly influence survival and morbidity.[3] However, the low incidence of MTC makes a definitive diagnosis using fine-needle aspiration (FNA) particularly

challenging, requiring a high degree of clinical suspicion. In addition, the cytomorphologic features of MTC can be highly variable, further complicating accurate diagnosis. Known as the *great mimicker* or *melanoma of the thyroid*, MTC can resemble a wide range of primary and metastatic neoplasms both on cytology and on histology.[1] Reported FNA sensitivity for a specific diagnosis of MTC varies widely from 12.5% to 88.2%, with a 2014 meta-analysis estimating an overall sensitivity of 56.5% when including suspicious lesions, whereas positive predictive values range between 85% and 100%.[4] A 2020 study at a tertiary care center revealed that nearly one half of FNAs failed to definitively diagnose MTC preoperatively, and, in about one third of patients, no cytologic suspicion of MTC was even raised before to surgery.[5] This large variation in diagnostic accuracy is related to many factors, including study site and design, individual diagnostic skills of cytopathologists, and the use of ancillary studies. A lack of familiarity with the diverse cytopathologic features and inadequate/suboptimal specimen quality are the primary causes of misdiagnosing MTC. False-negative FNA results often lead to delayed or insufficient surgical intervention. Given these challenges, it is crucial for pathologists to recognize the diverse cytopathologic features of MTC and to be aware of potential diagnostic pitfalls. A low threshold for ordering additional diagnostic tests is essential to ensure an accurate preoperative diagnosis. This is particularly important to facilitate timely and appropriate management of MTC because this entity completely differs from papillary thyroid carcinoma (PTC) in cell of origin, treatment, and prognosis.

This review article provides practical guidance on diagnosing MTC, emphasizing cytologic features both common and uncommon, clinical presentations, ancillary studies, and diagnostic pitfalls, serving as a valuable resource for cytopathologists, general pathologists, cytotechnologists, and trainees to improve diagnostic accuracy and patient care.

Essential practice points

- *Obtain high-quality samples*: A specimen may be less than optimal for the definitive diagnosis of MTC because of technical issues like adequate cellularity or poor preservation of cells. High cellularity and representative sampling are critical. Rapid on-site evaluation, if available, may be extremely helpful in this setting to suggest the diagnosis and to appropriately triage the material for confirmatory ancillary testing (SCT and/or additional passes for calcitonin washout and/or FFPE cell blocks for proper IHC evaluation).[6]
- *Assess cytologic features*: Evaluate the cellular patterns, nuclear features, and cytoplasmic characteristics. Look for key features of MTC, including: high cellularity, cellular pleomorphism, plasmacytoid cells, round cells, discohesive cells, salt-and-pepper chromatin, and binucleation or multinucleation.[1,3,7,8] Occasionally, the cells exhibit unusual cytomorphologic features.[9]
- *Consider common mimickers*, especially follicular/oncocytic neoplasms, but also PTC, PDTC, ATC, and metastases (Table 1).
- *Apply ancillary studies judiciously and have a low threshold for ordering IHCs*: Most MTCs are immunoreactive for calcitonin, CEA, and neuroendocrine markers (synaptophysin, chromogranin) and are negative for thyroglobulin.
- *Final diagnosis*: Synthesize cytologic, IHC, and clinicoradiologic findings to reach a final diagnosis. A definitive diagnosis of MTC (Bethesda VI) can be made if sufficient material is available for IHC with conclusive results or if the cytologic findings are interpreted in the proper clinical context, including markedly elevated serum calcitonin/CEA levels, elevated calcitonin in the FNA washout fluid, or a positive molecular test. When none of these are possible, it is best to report as suspicious for MTC (Bethesda V) and add a note in the report to state that the patient may benefit from a repeat FNA and/or other ancillary studies to confirm the diagnosis before any surgical intervention.

OVERVIEW OF MTC

Clinicoradiologic features

MTC can occur in either a sporadic form (75%) or as part of familial syndromes (up to 25%), most commonly associated with autosomal-dominant disorders caused by pathogenic germline variants in the *RET* proto-oncogene.[1–3] Familial forms include multiple endocrine neoplasia (MEN) type 2 and type 3 (formerly MEN2B) as well as familial MTC, a variant of MEN2A.

Clinical presentation

- *Sporadic MTC* typically presents in the fourth through sixth decade with a solitary thyroid nodule and/or cervical lymphadenopathy (up to 50%) that may be the initial target for FNA.[3,10] High serum calcitonin levels in metastatic cases can cause flushing, diarrhea, or weight loss. Rarely (< 1%), tumors are nonsecretory. FNA is particularly important in the initial assessment of patients with sporadic MTC, the diagnosis of which often is not clinically suspected.
- *Hereditary MTC* often presents in younger patients with bilateral and multifocal disease.[3,10,11] Family history and associated endocrinopathies (e.g., pheochromocytoma, hyperparathyroidism) are key clues. Genetic testing now allows for earlier diagnosis and screening in at-risk individuals, with prophylactic thyroidectomy in childhood. Thus this category of patients seldom undergoes thyroid FNA for suspected MTC.

Ultrasound features

The ultrasound appearance of MTC is variable and often nonspecific. In a meta-analysis by Woliński,[12] the following characteristics were observed:

- Solid composition, 79.2%
- Hypoechogenicity, 83.4%
- Irregular margins, 38%
- Taller-than-wide shape, 14.4%
- Microcalcifications, 35.5%
- Macrocalcifications, 27%

Compared with PTC, MTC is less likely to present with irregular margins, microcalcifications, and a taller-than-wide shape[13] but more frequently demonstrates larger lesion size, hypervascularity, heterogeneous echotexture, hypoechogenicity, and macrocalcifications.

Functional imaging

Functional imaging plays a pivotal role in the staging and follow-up of MTC. Positron emission tomography/computed tomography (PET/CT) using ^{18}F-fluoro-l-dopa or ^{18}F-fluorodeoxyglucose is crucial in assessing the extent of disease, especially when ultrasound or conventional imaging is inconclusive.[3] These scans are instrumental in detecting persistent MTC, recurrent MTC, or metastatic disease and guiding treatment decisions, both at initial diagnosis and during postoperative follow-up.[13,14]

Prognosis and management of MTC

Prognosis

The prognosis of MTC is highly dependent on the stage at diagnosis.[3,13,14] Key prognostic factors include the presence of lymph node involvement and distant metastases. The 10-year survival rate is closely tied to the extent of the disease:

- *Localized disease*, 93%–100% survival rate
- *Regional disease* (with lymph node involvement), 71% survival rate
- *Distant metastases*, 21%–40% survival rate

At the time of diagnosis, approximately 10%–15% of patients present with distant metastases, whereas 50%–70% have regional cervical lymphadenopathy.[3] The aggressive nature of MTC, particularly in advanced stages, underscores the importance of early detection.

Management

Unlike other well differentiated thyroid carcinomas, MTC does not respond to radioactive iodine therapy, making early surgical intervention critical to improving patient outcomes. The standard management of MTC includes several key steps[3,13,14]:

Preoperative evaluation

- *Germline RET mutation testing*: All patients with MTC should undergo genetic testing to assess for germline RET mutations, which are associated with hereditary MTC.[3] Certain RET mutations carry a higher risk; and, in those patients, a prophylactic thyroidectomy is recommended in the first year of life.[3] RET testing also has implications for treatment, particularly with targeted therapies for advanced or metastatic disease (see below) and identifying at-risk family members.[3,14–19]
- *Screening for pheochromocytoma and primary hyperparathyroidism*: These are common in MEN2A, and screening is essential to avoid perioperative complications.[3]

Surgical intervention

- *Total thyroidectomy*
- *Prophylactic central neck dissection*: In contrast to PTC, routine removal of central lymph nodes is recommended for MTC given its propensity for early lymphatic spread, even in patients without clinically apparent nodal metastases, to reduce the risk of recurrence.[3,14,15]
- *Management of persistent or metastatic disease*: In cases of persistent or metastatic MTC, systemic therapy has advanced significantly with the development of targeted treatments, including *multikinase inhibitors* (e.g., vandetanib and cabozantinib)[16] and *targeted RET inhibitors* (e.g., selpercatinib) for patients with germline or somatic *RET* mutations.[15,17,18]

Histologic features of MTC

The histologic spectrum of MTC (Figures 1–6) is very diverse and varies between patients and within the same tumor, often mimicking other thyroid malignancies, which can complicate diagnosis. Whole-slide images of a wide variety of MTC cases can be viewed online at the new World Tumor Registry website (https://www.worldtumorregistry.org, May 8, 2025). The typical growth patterns observed in MTC include *solid*, *lobular*, *trabecular*, or *insular* architectures. The tumor cells are often dispersed but may appear in various forms, such as *round*, *polygonal*, *plasmacytoid*, or *spindle-shaped*.[1,19,20] Although the nuclei are usually round, they may vary in size, with *coarsely clumped chromatin* and small, sometimes indistinct nucleoli. *Mitotic activity* is generally low, although increased proliferation and/or the presence of necrosis are associated with a poorer prognosis (see MTC grading, below).[19,21] MTC cells commonly feature abundant cytoplasm, which may range from *eosinophilic* to *amphophilic* or it may display a *finely granular* texture. *Stromal amyloid deposits*, derived from calcitonin, are present in up to *90%* of cases and serve as a distinctive diagnostic feature. MTC can display numerous histologic patterns, such as papillary or pseudopapillary, follicular, spindle cell, giant cell, clear cell, oncocytic, melanotic, squamous, amphicrine (producing both calcitonin and mucin), paraganglioma-like, encapsulated, and small cell subtypes. Identifying these patterns is crucial to accurately

diagnose and differentiate MTC from other tumor types on both histology and cytology, although they do not have a significant impact on the prognosis of MTC.

Classic cytologic features of MTC

The cytologic appearance of MTC exhibits variability from case to case (Figures 7–28),[1,2,7,8] reflecting histologic variation and sampling, but some characteristic features include:

- *Cellular composition*: MTC typically presents with a *dispersed* or *loosely cohesive* population of cells (Figures 7 and 8). *Moderate to high cellularity* is common, but scant cellularity may be encountered in cases with extensive amyloid deposits and calcifications (Figure 3).

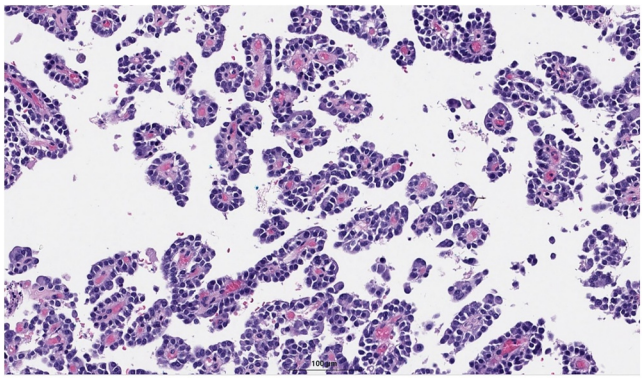

FIGURE 1 Medullary thyroid carcinoma with papillary architecture on low magnification. The malignant cells are arranged in papillary structures characterized by a central fibrovascular core. The cells appear relatively uniform with round nuclei and a scant-to-moderate amount of cytoplasm (histology; H&E stain, original magnification ×40).

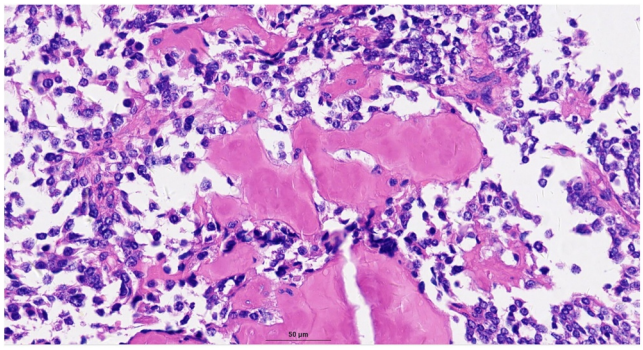

FIGURE 2 Amyloid deposits in medullary thyroid carcinoma. Medullary thyroid carcinoma may contain various amounts of amyloid deposits. Amyloid appears as waxy, pink material on H&E staining, which can be mistaken for thick colloid or *hyalinized stroma*. The malignant cells are relatively small with a high nuclear-to-cytoplasmic ratio. Note that a few malignant cells are embedded in amyloid (histology; H&E stain, original magnification ×100).

- *Cell types*: The cells are usually uniform in size and shape but *any size and shape may be present*. Cells can be *plasmacytoid*, *spindle-shaped*, round, *polygonal*, *or a combination thereof* (Figures 11, 12, and 15–20).
- *Nuclear characteristics*: The nuclei in MTC are usually *round to oval*, *often eccentrically placed*, and display a *coarse granular chromatin also known as "salt-and-pepper" pattern*, characteristic of neuroendocrine tumors (Figures 10, 14, and 19). *Nucleoli* are often inconspicuous, although they may sometimes be prominent (Figure 29). *Intranuclear cytoplasmic inclusions* can be found in 19% to 58% of cases.[1] Unlike PTC, *nuclear grooves* are not a feature of MTC.[1,2,7]
- *Cytoplasmic features*: The cytoplasm of MTC cells is often *granular* and *amphophilic*. *Intracytoplasmic azurophilic (red) granules* can be observed on *Diff-Quik/Romanowsky–stained* preparations (5%–10% of cells), in keeping with the neuroendocrine nature of the tumor.[1]
- *Amyloid*: *Amyloid deposits* are found in *34%–80%* of MTC cases on cytology (Figure 13).[1] Amyloid can be mistaken for thick colloid or *hyalinized stroma* and, on its own, is not diagnostic because it may also be present in systemic amyloidosis, plasmacytomas, amyloid goiter, or follicular lesions. Amyloid may display a *fibrillary appearance*, and tumor cells often appear embedded within its matrix. *Congo Red staining* (demonstrating apple-green birefringence under polarized light) or *calcitonin immunostaining* can confirm the presence of amyloid.

Other features

- *Binucleated and/or multinucleated giant cells* are common in MTC.
- *Colloid* is present in approximately one third of MTC cases as a contaminant (from needle penetration through normal thyroid

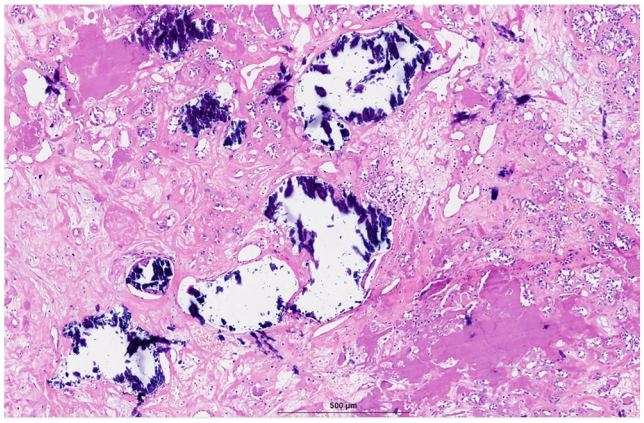

FIGURE 3 Amyloid deposits in medullary thyroid carcinoma can be associated with microcalcifications and sclerosis, which may result in paucicellular aspirates. Abundant amyloid is seen with areas of mircocalcifications and sclerosis. The malignant cells are embedded in amyloid and sclerotic areas (histology; H&E stain, original magnification ×40).

tissue), especially in small MTCs (< 1 cm), and its presence may lead to confusion with other thyroid neoplasms.
- *Necrosis* and *calcifications*, including *psammoma bodies*, may also be observed but are less frequently encountered.
- Tumor cells are predominantly single and discohesive cells or loose clusters but can also be seen as sheets, syncytia, rosettes/microfollicles (Figure 29), cords, pseudopapillae, and papillae.[1,2,7]

The prevalence of these cytomorphologic characteristics of MTC do not appear to differ significantly according to different staining methods (Papanicolaou, Romanowsky, hematoxylin and eosin).[7,8] However, with liquid-based preparations (ThinPrep [Hologic Inc.] or SurePath [Becton, Dickinson and Company]), the tumor cells are slightly reduced in size, the nuclei appear more densely stained, and the stippled chromatin pattern is more difficult to appreciate. Some representative examples of MTC cases (whole-slide images) from the Massachusetts General Hospital can be viewed online (https://learn.mghpathology.org, May 8, 2025).

MTC grading

The fifth edition (2022) of the World Health Organization classification of endocrine and neuroendocrine tumors introduced a grading system for MTC, categorizing tumors as low-grade or high-grade based on mitotic activity, the Ki-67 proliferation index, and the presence of tumor necrosis.[19,21] However, this grading is not currently recommended for FNA samples because of limitations in reliably assessing these features cytologically.[2] Nevertheless, a Ki-67 proliferation index ≥ 5% indicates low sensitivity but high specificity for predicting high-grade MTC on FNA samples.[22,23]

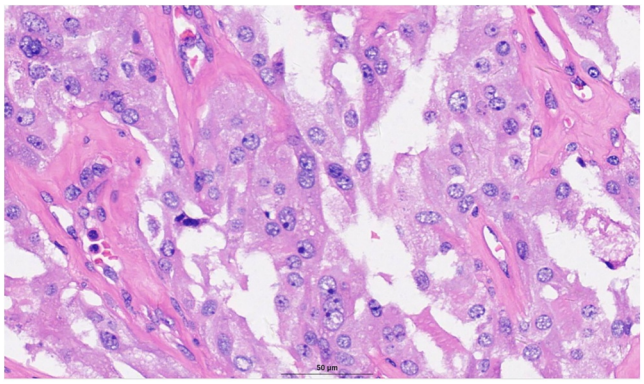

FIGURE 4 Medullary thyroid carcinoma with oncocytic features. The malignant cells are arranged in a sheet. They display oncocytic features characterized by abundant, finely vacuolated, eosinophilic cytoplasm and medium-to-large nuclei with vesicular chromatin and occasional nucleoli (histology; H&E stain, original magnification ×40).

Immunohistochemical markers

Immunohistochemistry (IHC) is essential in confirming the diagnosis of MTC and differentiating it from other thyroid lesions. IHC bridges the gap between indeterminate categories, such as *suspicious for MTC* (category V according to The Bethesda System for Reporting Thyroid Cytopathology [Bethesda V]) and a definitive diagnosis of *MTC* (Bethesda VI).[2] Whenever feasible, a small panel of stains, ideally on formalin-fixed, paraffin-embedded (FFPE) cell blocks (or another material after proper validation), is recommended to confirm the diagnosis. The American Thyroid Association 2015 guidelines state that FNA samples with findings that are inconclusive or suggestive of

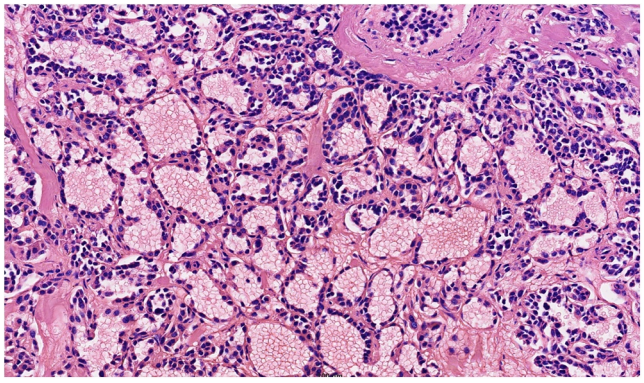

FIGURE 5 Medullary thyroid carcinoma with a microfollicular pattern. The malignant cells are arranged in small groups of cells resembling thyroid follicles. The cells are small with a high nuclear-to-cytoplasmic ratio, small hyperchromatic nuclei, and scant-to-moderate cytoplasm (histology; H&E stain, original magnification ×40). It should be differentiated from thyroid follicular neoplasms and parathyroid lesions.

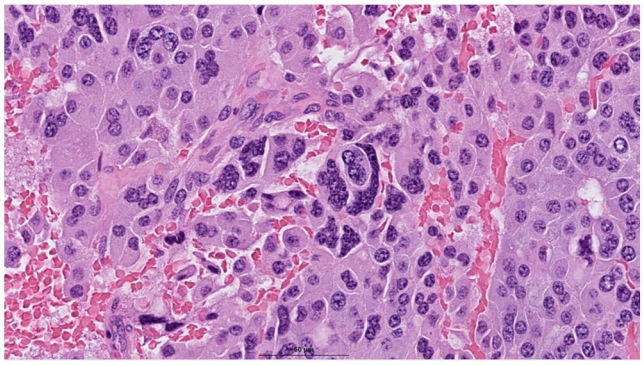

FIGURE 6 Medullary thyroid carcinoma with oncocytic features and pleomorphic/bizarre cells. Occasionally, malignant cells with oncocytic features display pleomorphic nuclei, binucleation, multinucleation, and atypical mitotic figures. The differential diagnosis includes carcinomas of follicular cell origin, such as oncocytic carcinoma and anaplastic thyroid carcinoma (histology; H&E stain, original magnification ×40).

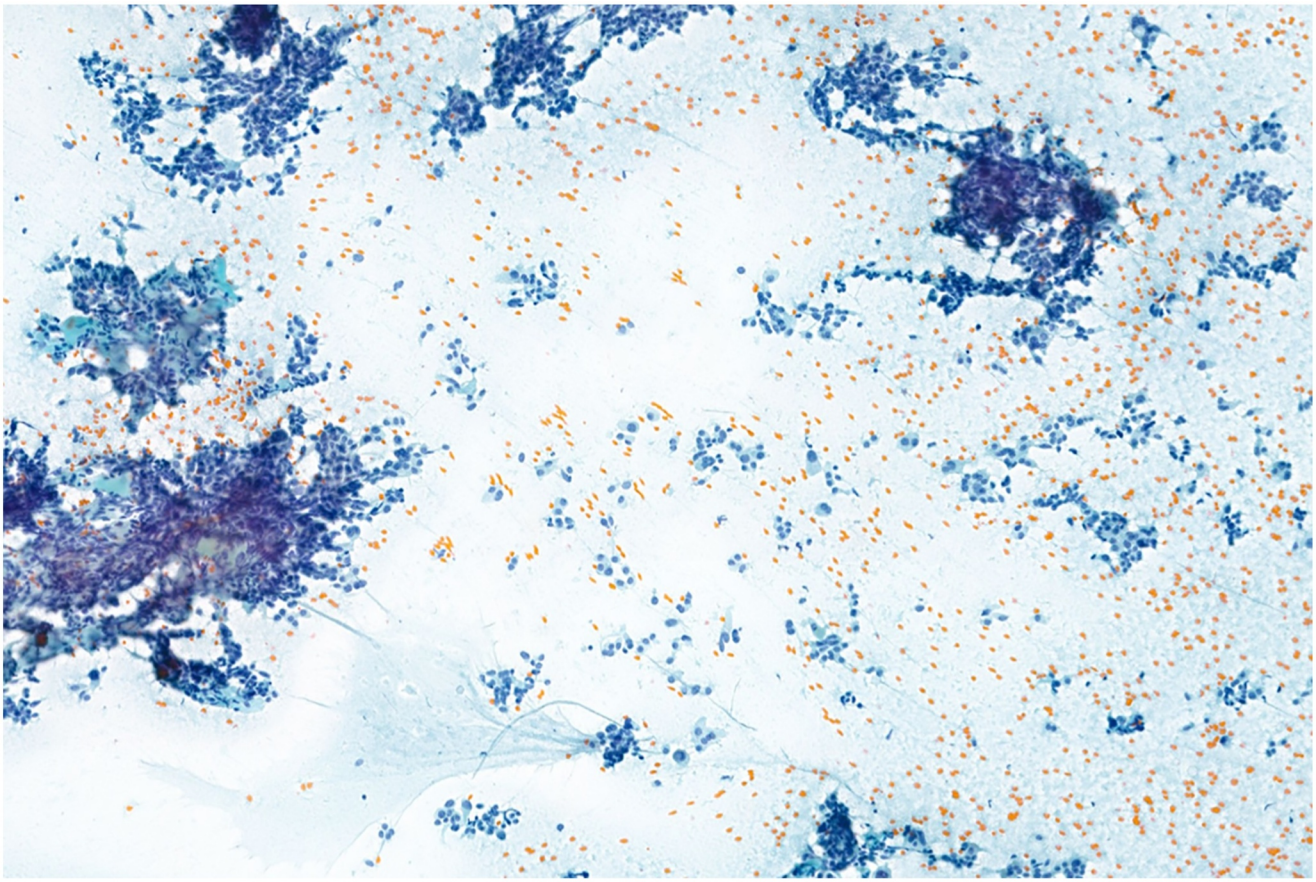

FIGURE 7 Medullary thyroid carcinoma with cohesive clusters and loosely cohesive clusters (fine-needle aspiration smear; Papanicolaou stain, original magnification ×10).

MTC should undergo IHC staining to detect the presence of markers like calcitonin, chromogranin, and carcinoembryonic antigen (CEA) and the absence of thyroglobulin.[3]

Caveat: In routine practice, cell blocks are infrequently made and/or are commonly acellular/paucicellular, and many centers rely on direct smears and ThinPrep material for the interpretation of thyroid FNAs. When MTC is suspected in such cases, additional ThinPrep slides can be prepared, and limited IHC analyses (most importantly, calcitonin) can be performed on those slides, but proper validation remains a critical issue. Very rarely, original smears may have to be destained for calcitonin IHC to be performed. Another option is the cell transfer method (or a similar method), which is performed in the following manner: (1) covering with a water-insoluble mounting medium after removal of the cover glass from the cytologic specimen, (2) peeling the material integrated with the mounting medium from the slide glass, and (3) dividing the sample into the required number of pieces and separately placing them on new glass slides.[24,25] This method can be used to produce several IHC slides using a single conventional specimen without any special equipment. However, this process is complicated, requiring skilled staff, proper validation, and several days to complete.

Key IHC markers for MTC include

- *Calcitonin*: This is the most useful and most specific marker for MTC, and the majority of cases show strong cytoplasmic positivity for calcitibub (Figure 26), although the staining may be focal.[1]

Caveat 1: *Calcitonin* can also be expressed in various *extra-thyroidal neuroendocrine neoplasms*, particularly intermediate-grade neuroendocrine tumors, especially from the *larynx*.[26]

Caveat 2: A nonspecific cytoplasmic staining can occur with oncocytic neoplasms, possibly leading to a misdiagnosis of MTC, especially if calcitonin assessment is performed in isolation. Thus applying a panel of immunostains, if feasible, is strongly recommended.

Caveat 3: Calcitonin immunoreactivity varies among MTCs.[1] Sporadic MTCs are less frequently positive for calcitonin compared with familial cases, which consistently show strong immunoreactivity. In addition, up to 7.7% of MTCs may be entirely negative for calcitonin staining (calcitonin-negative MTC)[27] or show only focal positivity. Variability in results may also arise because of differences in antibody sensitivity among commercial clones and staining protocols.

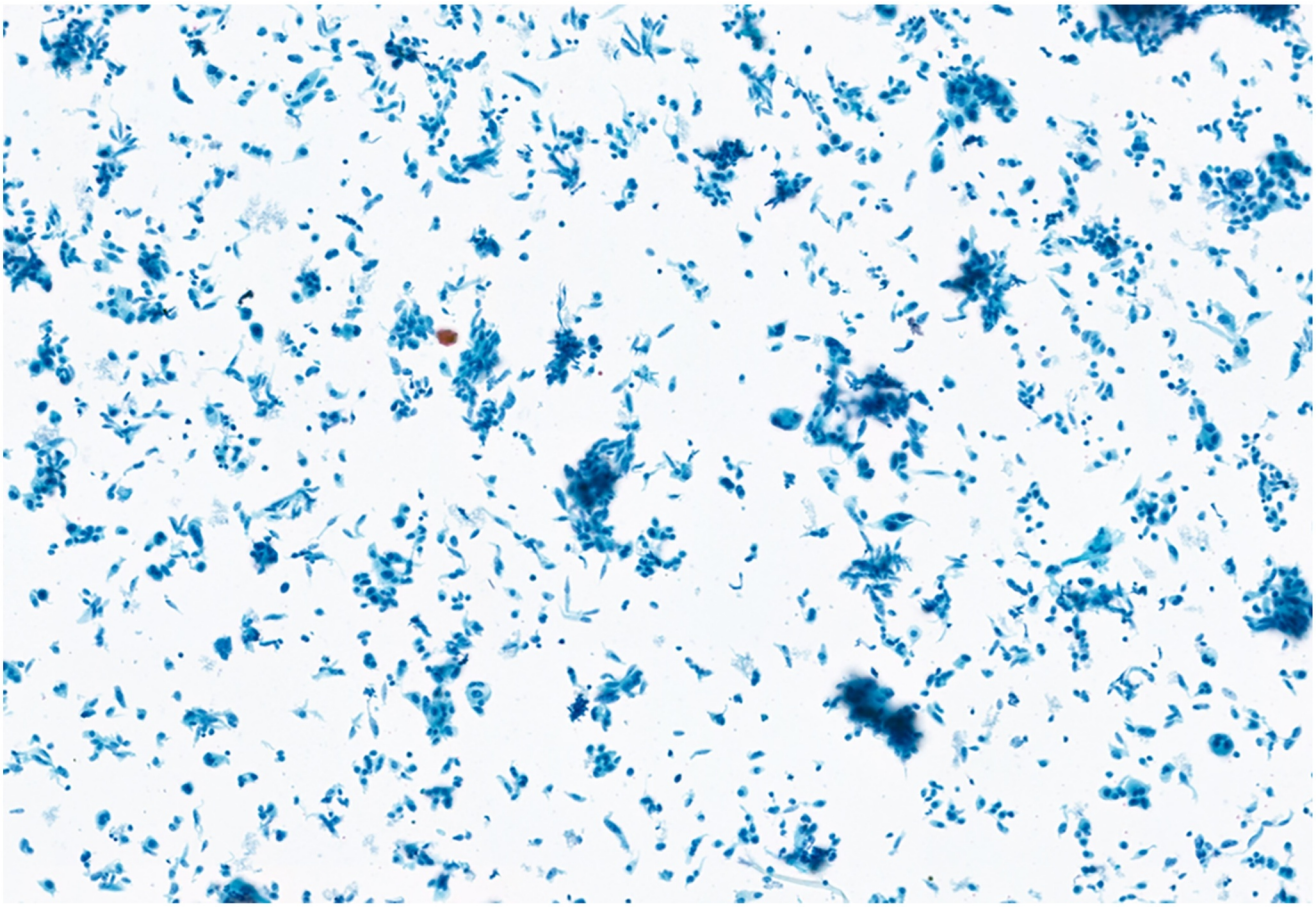

FIGURE 8 Medullary thyroid carcinoma with loosely cohesive clusters and many isolated tumor cells that have spindle morphology (fine-needle aspiration, ThinPrep preparation; Papanicolaou stain, original magnification ×10).

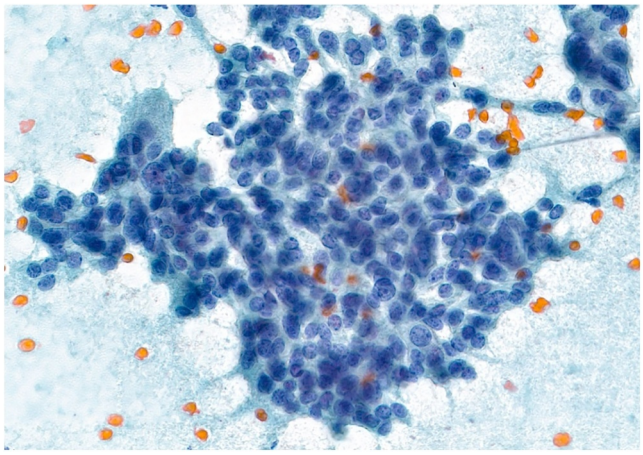

FIGURE 9 Medullary thyroid carcinoma with cohesive cluster. The malignant cells are tightly cohesive, forming a large fragment. The cells are relatively uniform and are characterized with a high nuclear-to-cytoplasmic ratio, scant cytoplasm, and round-to-oval nuclei with coarse chromatin (fine-needle aspiration smear; Papanicolaou stain, original magnification ×100).

- *CEA*: Although less specific than calcitonin, CEA is expressed in most MTCs, typically strongly and diffusely, and may be positive in rare calcitonin-negative cases, providing an additional diagnostic tool.[28]

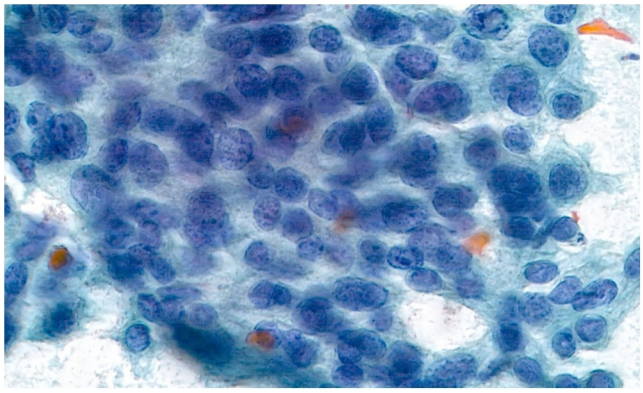

FIGURE 10 Medullary thyroid carcinoma with cohesive cluster. Higher magnification shows round-to-oval nuclei with salt-and-pepper chromatin, a feature seen predominantly in neuroendocrine cells (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

- *Neuroendocrine markers*: *Chromogranin* and *synaptophysin* are commonly positive in MTC (Figure 27). *Insulinoma-associated protein 1*, a more recent neuroendocrine marker with a nuclear staining pattern, has shown consistent positivity in MTC.[29,30]

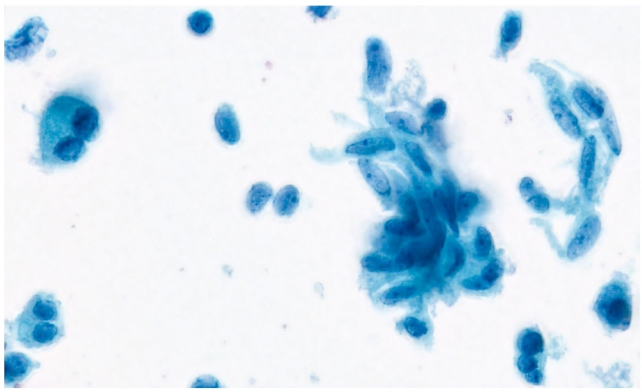

FIGURE 11 Medullary thyroid carcinoma with spindled cells and binucleated cells. The malignant cells display spindled cell features characterized by oval and elongated nuclei and scant-to-moderate, finely vacuolated cytoplasm. Binucleation is another feature that is associated with medullary thyroid carcinoma. Note the two binucleated cells on the left (fine-needle aspiration smear; Papanicolaou stain, original magnification ×200).

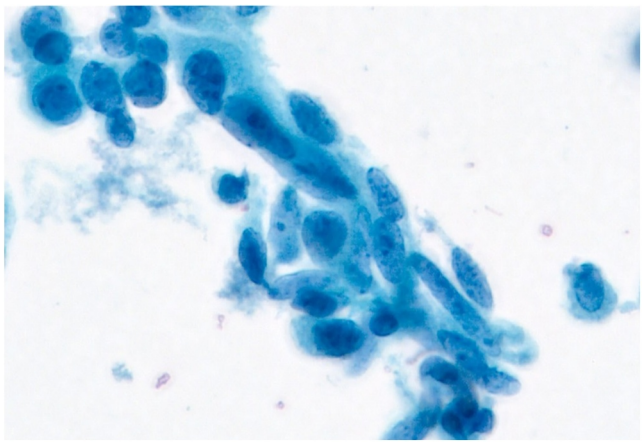

FIGURE 12 Medullary thyroid carcinoma with epithelioid/round cells and spindled cells. High magnification shows a fragment of malignant cells with epithelioid features characterized by round nuclei and scant-to-moderate cytoplasm resembling cuboidal cells. The spindled cells contain elongated nuclei with salt-and-pepper nuclei (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

- *Thyroglobulin*: Negative in MTC (other than exceptional cases in which it is mixed with follicular-cell–derived carcinoma), but nonspecific/background staining may occur.[31,32]
- *Thyroid transcription factor-1 (TTF-1)*: *TTF-1* is expressed in most MTCs, although the intensity of staining is typically less than that in normal follicular cells and their corresponding tumors.[33,34]
- *Paired box gene 8 (PAX-8)*: This is generally negative in MTC when using *monoclonal antibodies* for PAX-8.[35] Occasionally, weak positivity may be observed with *polyclonal antibodies*, but this is less common.[36] The lack of strong PAX-8 staining helps distinguish MTC from *PTC* and *follicular thyroid carcinoma*, which are positive for PAX-8.

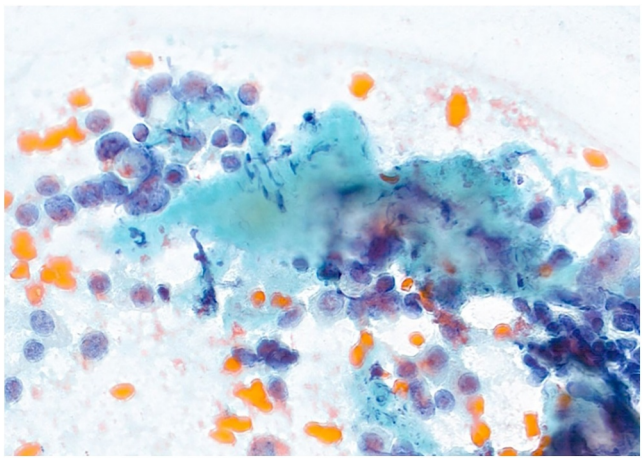

FIGURE 13 Medullary thyroid carcinoma with amyloid-like material. Medullary thyroid carcinoma with large areas of a waxy, dense matrix resembling amyloid (fine-needle aspiration smear; Papanicolaou stain, original magnification ×200).

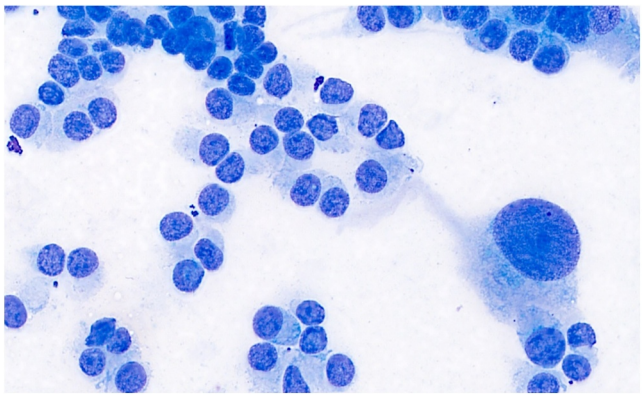

FIGURE 14 Medullary thyroid carcinoma with typical features. Typical medullary thyroid carcinoma is characterized by loosely cohesive malignant cells with eccentric nuclei or plasmacytoid features. The cells contain a moderate amount of finely granular cytoplasm and round nuclei with coarse chromatin. Occasional large nuclei can be seen (fine-needle aspiration smear; Diff-Quik stain, original magnification ×400).

Other ancillary studies for the diagnosis of MTC

Serum calcitonin testing

Serum calcitonin testing (SCT) is a valuable ancillary tool for diagnosing MTC and is generally less expensive compared with more advanced molecular testing, making it accessible in clinical practice.[37,38] SCT is widely considered a useful diagnostic adjunct, especially when FNA results are inconclusive and/or when the FNA sample is inadequate for further studies. However, routine SCT for thyroid nodules remains controversial because of the very low prevalence of MTC, variations in practice patterns, and cost considerations.[3]

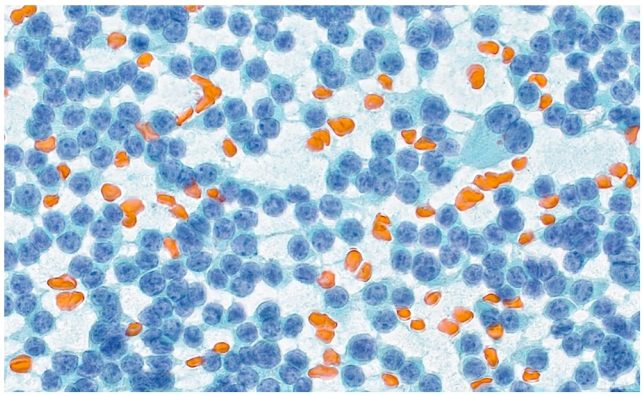

FIGURE 15 Medullary thyroid carcinoma with typical features. High magnification shows a cellular smear consisting of predominantly single cells or loosely cohesive clusters of malignant cells. The malignant cells are relatively uniform and have a high nuclear-to-cytoplasmic ratio with minimal anisonucleosis. The cells contain round nuclei with coarse chromatin and scant-to-moderate cytoplasm. The nuclei are centrally or eccentrically located. An extremely large single cell is seen with binucleation, eccentrically located nuclei (plasmacytoid), and abundant cytoplasm (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

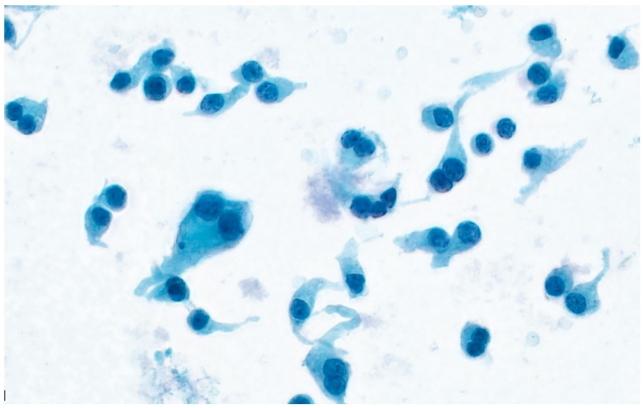

FIGURE 16 Medullary thyroid carcinoma with typical features, including plasmacytoid cells and binucleated cells. Plasmacytoid cells and binucleated cells are two cellular features commonly seen in typical medullary thyroid carcinoma. This field of a ThinPrep slide contains multiple binucleated cells with abundant cytoplasm and elongated cytoplasmic tails. The plasmacytoid cells show eccentric, round nuclei (fine-needle aspiration, ThinPrep preparation; Papanicolaou stain, original magnification ×400).

- *Sensitivity and specificity*: SCT has demonstrated higher sensitivity than FNA cytology in detecting MTC. Elevated serum calcitonin levels are typically seen in nearly all MTC cases, including small MTCs (< 1 cm).[3,37,38] However, there is lack of agreement on the calcitonin threshold to suspect MTC, with large population variations. Serum calcitonin levels may also be elevated in several other conditions (e.g., C cell hyperplasia),[3,37] resulting in a high false-positive rate (60%–90%) and a low positive predictive value (10%–40%).

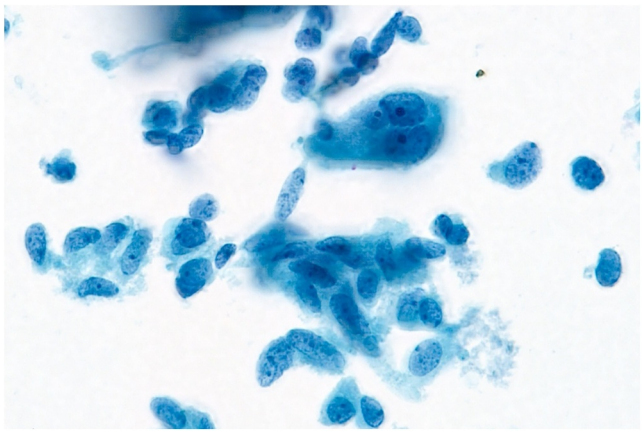

FIGURE 17 Medullary thyroid carcinoma with spindled cells and binucleated, bizarre, pleomorphic cells. Spindled cells are relatively common cell types in medullary thyroid carcinoma. However, pleomorphic spindled cells with bizarre shapes or binucleation are rare features that can be mistaken for anaplastic thyroid carcinoma. The large, elongated nuclei with coarse chromatin and occasional prominent nucleoli are striking findings (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

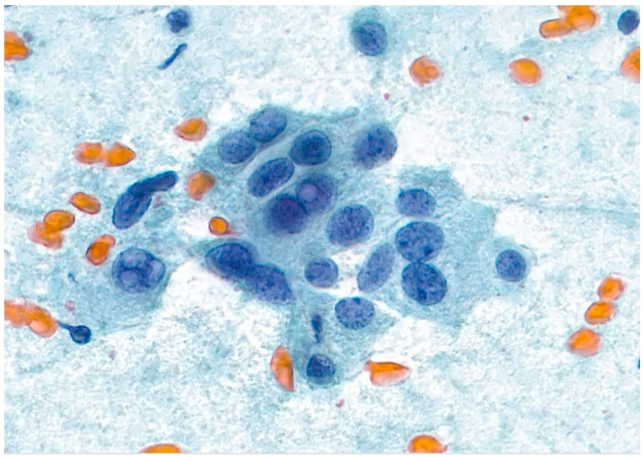

FIGURE 18 Medullary thyroid carcinoma with intranuclear pseudo-inclusions. A loosely cohesive fragment of malignant cells is seen. An intranuclear pseudo-inclusion is clearly seen in the center. The cells have nuclei with coarse chromatin and abundant cytoplasm. Intranuclear pseudo-inclusion is a feature that can be seen in 15%–20% of medullary thyroid carcinomas. The main differential diagnosis is papillary thyroid carcinoma and its different subtypes, such as oncocytic (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

- *Diagnostic threshold*: Serum calcitonin levels >500 pg/mL are strongly indicative of MTC.[3,37,38] Elevated levels correlate with tumor burden, reflecting both the size and differentiation of the tumor. Higher calcitonin levels are often seen in more advanced disease or metastatic cases.[38,39]
- *Prognostic value*: Calcitonin levels are useful not only for diagnosis but also for monitoring disease progression and recurrence.[3,39]

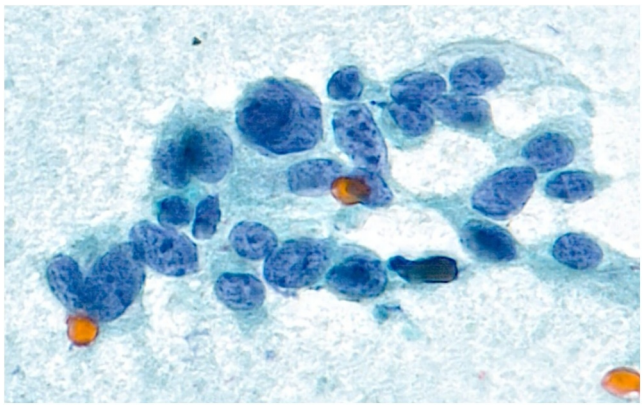

FIGURE 19 Medullary thyroid carcinoma with salt-and-pepper chromatin. Coarse chromatin also, known as salt-and-pepper chromatin, is a feature of neuroendocrine neoplasms and is best visualized in Papanicolaou stain. In this image, anisonucleosis and nuclear pleomorphism are other visible features (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

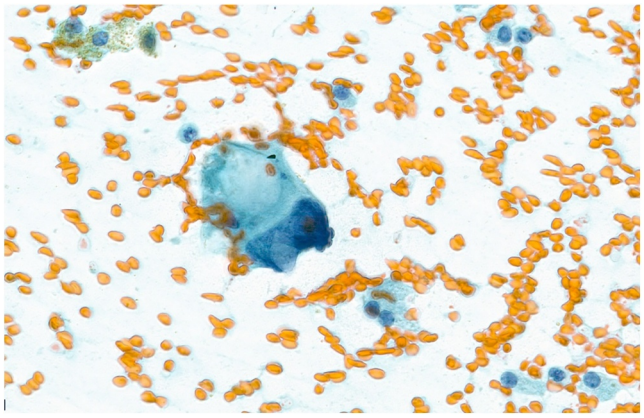

FIGURE 20 Medullary thyroid carcinoma with markedly atypical cells, mimicking anaplastic thyroid carcinoma. A large cell with plasmacytoid feature is seen characterized by a large, hyperchromatic nucleus and abundant cytoplasm, resembling an intracytoplasmic vacuole, mimicking anaplastic thyroid carcinoma. Comparing the size of the malignant cell with a few macrophages in the background indicates the large size of the malignant cell (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

Serial measurements can also help track response to therapy and detect recurrences.

Serum carcinoembryonic antigen testing

CEA is another tumor marker often elevated in MTC, particularly in advanced disease stages.[3,39] Similar to calcitonin, serum CEA levels correlate with tumor burden and can aid in both diagnosis and postoperative surveillance. CEA levels >30 ng/mL are frequently observed in MTC, and rising levels postoperatively may signal recurrence or metastasis.[39]

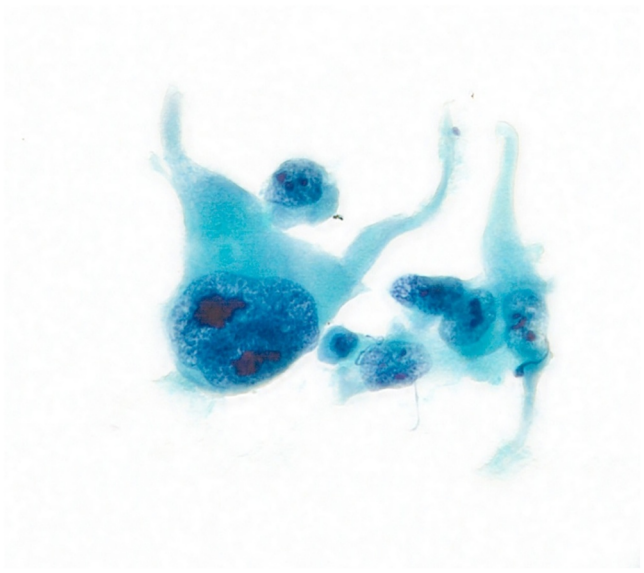

FIGURE 21 A pleomorphic cell in anaplastic thyroid carcinoma. Pleomorphic cells with bizarre shapes are frequently seen in anaplastic thyroid carcinoma. A cluster of malignant cells is seen with significant pleomorphism and size variation. There is marked anisonucleosis, with coarse chromatin and even two or more nucleoli. The cytoplasm is moderate to abundant with prominent cytoplasmic projections in two cells. These malignant cells can be misinterpreted as sarcoma or even medullary thyroid carcinoma. Microscopic examination of cells in multiple slides and clinicoradiographic correlation can be helpful in rendering a correct diagnosis (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

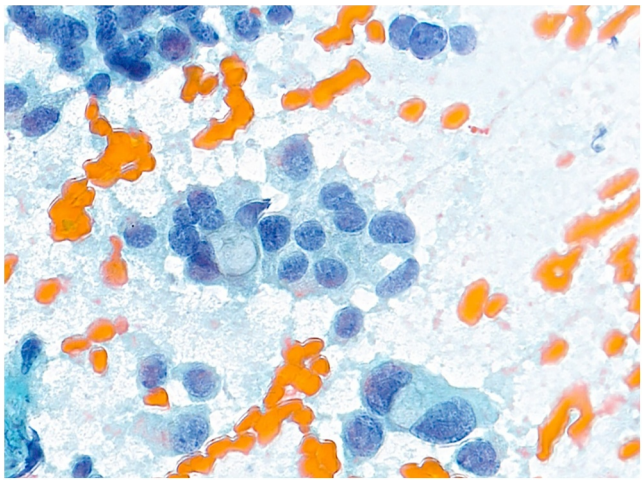

FIGURE 22 Medullary thyroid carcinoma with cytoplasmic vacuolization mimicking adenocarcinoma. Cytoplasmic vacuolization is another less common feature encountered with medullary thyroid carcinoma. This feature can simply be misinterpreted as adenocarcinoma, particularly in patients with a prior history of adenocarcinoma elsewhere. This image shows malignant cells in loosely cohesive clusters, characterized with round-to-oval nuclei and a moderate amount of cytoplasm. Large cytoplasmic vacuoles are seen in multiple cells, including several cells in the center and one in the right lower quadrant (fine-needle aspiration smear; Papanicolaou stain, original magnification ×200).

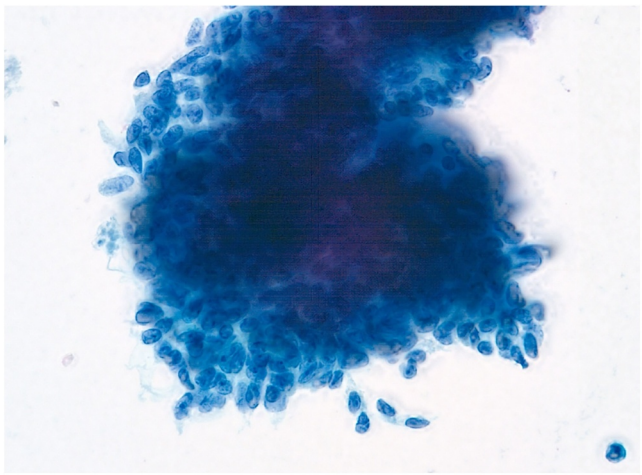

FIGURE 23 Medullary thyroid carcinoma with cohesive clusters, nuclear overlapping, and elongated nuclei with chromatin clearing, mimicking papillary thyroid carcinoma. The image is a great example of a tightly cohesive, large fragment of malignant cells in medullary thyroid carcinoma that mimics papillary thyroid carcinoma. Note the nuclear overlapping, elongated nuclei, pale chromatin, and small nucleoli in multiple cells. An intranuclear pseudo-inclusion (left lower quadrant) and longitudinal groves (lower, middle, and left upper quadrants) makes it mimic papillary thyroid carcinoma even more (fine-needle aspiration, ThinPrep preparation; Papanicolaou stain, original magnification ×200).

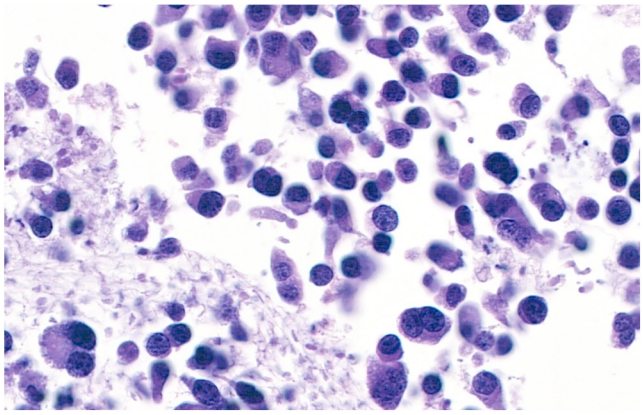

FIGURE 24 Medullary thyroid carcinoma with typical features of plasmacytoid cells and binucleated cells. Plasmacytoid cells and binucleation are common features seen in typical medullary thyroid carcinoma. The image consists of numerous, single malignant cells with plasmacytoid features and occasional binucleated cells. The plasmacytoid cells are characterized by single-cell arrangement, eccentric, round nuclei with coarse chromatin, and moderate-to-abundant cytoplasm. Although these are the typical features of medullary thyroid carcinoma, they should not be confused with malignant melanoma or plasma cell neoplasms. Cell-block preparation makes it possible to use immunostaining in challenging cases (cell-block preparation; H&E stain, original magnification ×200).

Calcitonin washout of the FNA sample

Calcitonin washout involves aspirating the thyroid nodule and/or metastatic lymph nodes and measuring the calcitonin levels in the aspirated fluid (i.e., washout fluid from the needle). Elevated calcitonin levels in the washout fluid can support the diagnosis of MTC.[1,3,40] The specificity and sensitivity of washout fluid examination are higher than those of FNA cytology.[40] When MTC was considered as a possible diagnosis, performing a calcitonin washout of the FNA sample increased sensitivity in several studies, approaching 95% or higher.[40] It is especially a valuable adjunct when cytologic features are ambiguous and/or when the FNA does not yield sufficient material for ancillary

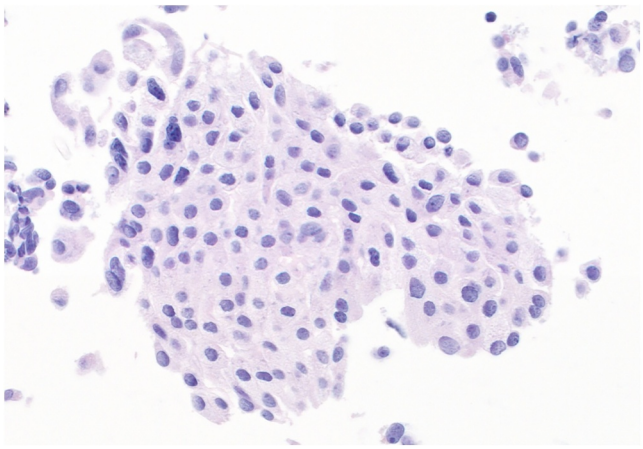

FIGURE 25 Medullary thyroid carcinoma with squamoid features. A large sheet of cohesive, malignant cells is seen that resembles squamous epithelium. The cells are characterized by low nuclear-to-cytoplasmic ratio, round-to-oval nuclei, abundant cytoplasm, and prominent cytoplasmic membrane, mimicking cytoplasmic desmosome in squamous cells. Although squamoid cells are not a feature commonly seen in medullary thyroid carcinoma, their presence in large quantity or in relatively limited material can be mistaken for squamous metaplasia of thyroid or other entities, such as developmental cysts or even squamous cell carcinoma (cell-block preparation; H&E stain, original magnification ×200).

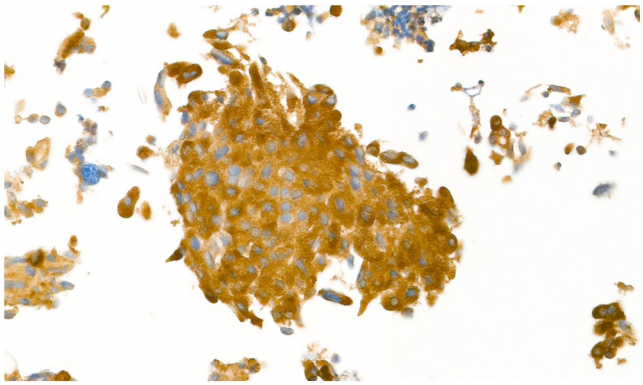

FIGURE 26 Calcitonin is a diagnostic immunostain in medullary thyroid carcinoma and is expressed in cytoplasm of the malignant cells. Cell-block preparation provides optimal material for ancillary studies like immunohistochemistry, including calcitonin (cell-block preparation; immunohistochemistry stain, original magnification ×200).

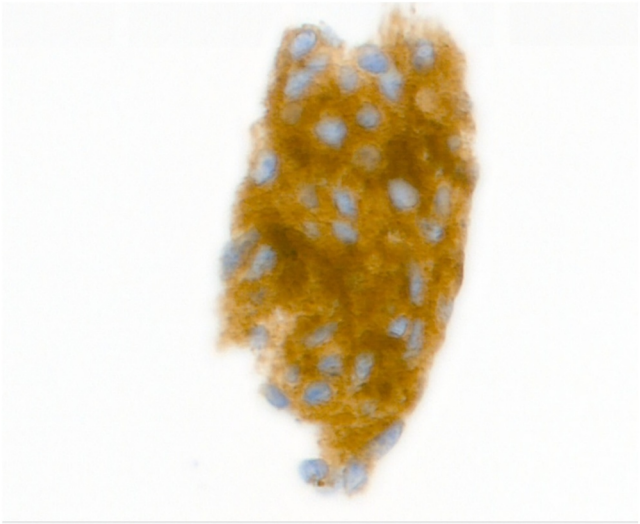

FIGURE 27 Synaptophysin immunostain in medullary thyroid carcinoma. Synaptophysin is a neuroendocrine marker expressed in cytoplasm of the malignant cells (cell-block preparation; immunohistochemistry stain, original magnification ×200).

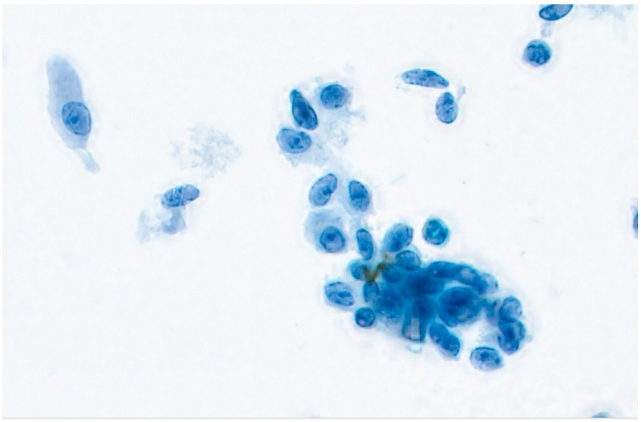

FIGURE 28 Medullary thyroid carcinoma with prominent nucleoli. In this image, malignant cells are seen arranged in single cells and as a loosely cohesive fragment. The cells range in size from small to relatively large. The nuclei are round to oval to elongated. Note the prominent, large nucleoli in several cells. Nucleoli are not a common feature of medullary thyroid carcinoma. Cells with nucleoli can resemble other malignant entities, such as carcinomas of other body sites. Of note, a prominent nuclear membrane is an additional cytomorphologic finding seen in this field (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

studies to confirm the suspicion of MTC. Indeed, the American Thyroid Association 2015 guidelines indicate that calcitonin should be measured in the FNA washout fluid if the FNA findings are inconclusive or suggestive of MTC.[3]

Limitations

- *Technical aspects*: Calcitonin washout may not be feasible in all settings or for all patients.

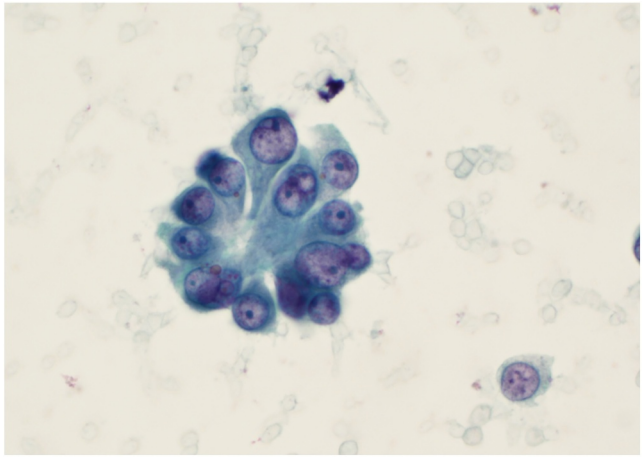

FIGURE 29 Medullary thyroid carcinoma with a rosette and with prominent nucleoli. When present, and in the absence of typical neuroendocrine features or nuclear pseudo-inclusions, these cases can be difficult to distinguish from follicular neoplasm or an oncocytic neoplasm (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

- *Procedure accuracy*: Ensure the proper technique to avoid contamination and obtain representative washout fluid. False-positive results may occur because of peripheral blood contamination in patients who have extremely high serum calcitonin levels.
- *Interpretation challenges*: Calcitonin levels in washout fluid must be compared with baseline levels and other markers for accurate interpretation.

Molecular testing

Molecular studies are increasingly playing a role in diagnosing and managing thyroid nodules including MTC, especially when standard diagnostic methods (FNA, IHC, and serum markers) are inconclusive. Furthermore, the detection of *RET* mutations is central to both sporadic and familial MTC because MTCs associated with either somatic or germline *RET* mutations are likely to respond to treatment with targeted *RET* inhibitors (as discussed above). Somatic-only *RET* mutations have been reported in 40%–60% of sporadic MTCs.[1,41,42] The M918T mutation in exon 16, which is present as a germline mutation in 98% of patients with MEN2B, is the most common mutation in sporadic tumors. Approximately 70% of tumors that are wild type for *RET* harbor *RAS* mutations (particularly *HRAS* and *KRAS*).[1,41–43] These findings can aid in the diagnosis when *RET* mutations are absent and may help clarify the tumor's biology. Less than 20% of sporadic MTCs are wild type for both *RET* and *RAS*, with no recurrent mutations found in these tumors.

Two of the most commonly used commercial molecular tests are *Afirma* (Veracyte) and *ThyroSeq* (Sonic Healthcare USA), both of which have demonstrated excellent diagnostic utility in detecting MTC and guiding treatment.[44–46] These two tests are commonly

used for indeterminate thyroid FNAs (Bethesda III and IV). Because most misdiagnosed MTCs are Bethesda III or IV, especially oncocytic-predominant MTCs (see below), these molecular tests will accurately pick up these cases. Although molecular tests like Afirma and ThyroSeq offer high diagnostic accuracy, they are more expensive than other ancillary tests, such as SCT or CEA testing, and may not be available in certain healthcare settings.

Afirma genomic sequencing classifier and Xpression Atlas

The Afirma genomic sequencing classifier (Veracyte) is a robust molecular tool that analyzes the expression of 108 differentially expressed genes to classify thyroid nodules. The Afirma Xpression Atlas, which also provides information on gene fusions and variants, complements the genomic sequencing classifier and has demonstrated high sensitivity and specificity for detecting MTC.[44,45]

ThyroSeq genomic classifier

The ThyroSeq genomic classifier (Sonic Healthcare USA) uses next-generation sequencing to assess a broad range of mutations, gene fusions, and other molecular alterations, making it highly sensitive for detecting not only MTC but also other thyroid malignancies.[46] In a retrospective analysis of 50,734 FNA samples tested using the ThyroSeq genomic classifier, including 40,622 Bethesda III and 7725 Bethesda IV samples, 124 (0.2%) were positive for MTC.[46] More than one half (74 of 124; 59.7%) of the nodules diagnosed as MTC had Bethesda III–IV cytology. Most MTCs identified (82%) had mutations in *RET* or other genes, including *HRAS*, *KRAS*, and *BRAF* (non-V600E).[46] For patients whose MTC harbored a *RET* mutation, germline genetic testing for the specific *RET* exon harboring this mutation could be considered rather than sequencing the entire *RET* gene. In contrast, the remaining patients who had MTC harboring *RAS* or *BRAF* mutations could be reassured of the sporadic nature of their disease with no need for additional germline testing or preoperative workup for pheochromocytoma.[46]

Practical ancillary tests

- *IHC*: Use specific markers to confirm the diagnosis of MTC and to rule out other entities in the differential diagnosis. For more accurate evaluation, IHC using a panel with several antibody (e.g., calcitonin, CEA, thyroglobulin, TTF-1, PAX-8, chromogranin, synaptophysin) is desirable—ideally on validated FFPE cell-block material.[47]
- *Other ancillary studies if IHC is not available or is inconclusive*: Consider SCT, calcitonin washout, molecular testing, or repeat biopsy (FNA or core biopsy).

DIFFERENTIAL DIAGNOSIS AND MIMICKERS OF MTC

The inherent cellular heterogeneity of MTC can lead to diagnostic confusion when relying solely on traditional cytologic methods. The main differential diagnosis includes follicular and oncocytic neoplasms, PTC, poorly differentiated thyroid carcinoma (PDTC), anaplastic thyroid carcinoma (ATC), parathyroid, hyalinizing trabecular tumor (HTT), paraganglioma, metastatic tumors, and lymphomas/plasmacytomas.[1,2,9,48–57] IHC plays a crucial role in distinguishing MTC from all these mimics.[52]

Follicular or oncocytic neoplasms

Significant diagnostic pitfalls may occur when MTC exhibits cytomorphologic features that closely resemble follicular-patterned lesions. MTC can occasionally demonstrate architectural arrangements, such as rosettes or true microfollicles (Figure 29), with the latter reported in up to one third of cases and, in rare instances, representing the predominant pattern. These formations can mimic follicular neoplasms, especially in the absence of overt neuroendocrine features (Table 1). Conversely, some follicular neoplasms, particularly those with oncocytic changes or degenerative atypia, may display discohesion, mild nuclear pleomorphism, and cytoplasmic granularity, potentially mimicking MTC. In such contexts, hallmark features of MTC, such as eccentrically placed nuclei with finely stippled *salt-and-pepper* chromatin, plasmacytoid morphology, and frequent multinucleation, may be subtle, focal, or entirely absent. Instead, the cytology may show bland chromatin, cohesive groups, and lack of distinctive neuroendocrine morphology, leading to misclassification as follicular neoplasm (Bethesda IV) or atypia of undetermined significance (AUS; Bethesda III).

MTC, especially its rare oncocytic subtype,[48] can be mistaken for follicular oncocytic (Hurthle cell) neoplasms because of overlapping features, such as dispersed cell patterns, prominent nucleoli, and eosinophilic granular cytoplasm (Figures 30–32).[9,48–51] Conversely, oncocytic neoplasms may exhibit nuclear pleomorphism, binucleation, and bizarre nuclear forms, which can mimic MTC. One key diagnostic pitfall arises when MTC presents as a monomorphic population of plasmacytoid cells with abundant eosinophilic cytoplasm, closely resembling oncocytic neoplasms. Accurate differentiation relies on careful assessment of nuclear and cytoplasmic features (Table 1). MTC cells typically display eccentrically placed nuclei with coarsely granular *salt-and-pepper* chromatin, whereas oncocytic cells have prominent macronucleoli and more cohesive architecture. Misclassification as follicular oncocytic neoplasm (Bethesda IV) or as AUS-oncocytic (Bethesda III) often stems from unfamiliarity with the cytologic spectrum and/or suboptimal preparations.

Given its variable morphologic presentation, MTC should be included in the differential diagnosis of thyroid FNA specimens categorized as AUS (Bethesda III) or follicular neoplasm/follicular

TABLE 1 Distinguishing and overlapping cytomorphologic features of medullary thyroid carcinoma and common mimics.

Cytologic features	Follicular neoplasm	Oncocytic follicular neoplasm	Classic medullary thyroid carcinoma	Oncocytic medullary thyroid carcinoma[a]	Oncocytic papillary thyroid carcinoma	Parathyroid lesion
Discohesiveness	Microfollicles	Variable	Present[b]	Present	Variable	Variable
Binucleation	Rare	Present	Frequent	Frequent	Rare	Rare
Multinucleation	Minimal	Frequent	Frequent	Frequent	Rare	Rare
Anisonucleosis	None	Mild	Moderate	Moderate	Moderate	None
Plasmacytoid cells	Absent	Common	Common[c]	Common	Rare	Rare
Granular cytoplasm	Absent	Dense	Variable	Loose	Dense	Variable
Azurophilic granules	Absent	Absent	Rare	Rare	Absent	Rare
Prominent nucleoli	Absent	Present	Rare	Present	Present	Rare
Intranuclear pseudo-inclusions	Absent	Absent	Common	Common	Common	Occasional
Nuclear grooves	Rare	Variable	Absent	Absent	Common	Absent
Neuroendocrine *salt-and-pepper* chromatin	Absent	Absent	Present[d]	Present[d]	Absent	Present[d]
Amyloid	Absent	Absent	Rare	Rare	Absent	Absent
Colloid	Minimal	Rare	Absent[e]	Absent[e]	Common	Absent[e]
Calcifications	Rare	Rare	Rare	Rare	Occasional	Absent

Note: Cytologic features can vary significantly according to the type of preparation and staining.

[a]Although very rare, the oncocytic variant of medullary carcinoma can exhibit prominent nucleoli.

[b]Medullary carcinoma typically exhibits hypercellular smears with single or loosely cohesive cells. Some loose clusters and rosettes are observed. Cohesive fragment, follicular, and pseudopapillary architecture can be seen and may mimic follicular neoplasm or papillary carcinoma.

[c]In oncocytic follicular neoplasms, the nuclei are predominantly eccentric and occasionally central; whereas, in plasmacytoid cells of medullary carcinoma, the nuclei are consistently located at the extreme periphery.

[d]Chromatin is coarsely stippled with a *salt-and-pepper* appearance, which may appear very similar to the granular chromatin pattern of parathyroid cells.

[e]Colloid can be seen as a contaminant in this setting.

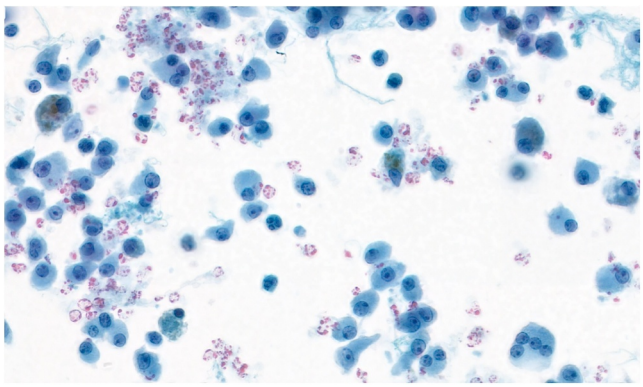

FIGURE 30 Oncocytic follicular neoplasm. It is characterized by cellular aspirates consisting of numerous individual cells with low nuclear-to-cytoplasmic ratio and round nuclei with a prominent, large nucleoli; distinct nuclear membrane; and abundant cytoplasm. Binucleation or multinucleation is seen. Oncocytic neoplasm can be mistaken for medullary thyroid carcinoma (fine-needle aspiration, ThinPrep preparation; Papanicolaou stain, original magnification ×200).

oncocytic neoplasm (Bethesda IV). These categories often encompass cases with overlapping cytologic features, in which MTC may be underrecognized. A meticulous review of the cytologic material is essential, with particular attention to subtle plasmacytoid morphology, eccentric/marginal nuclei, and cytoplasmic granularity. Romanowsky-type stains can be especially useful in highlighting neurosecretory granules that may otherwise be inconspicuous on Papanicolaou stains. In cases with ambiguous or nonclassical features, maintaining a low threshold for ancillary testing is critical to avoid misclassification and ensure appropriate clinical management.

Papillary thyroid carcinoma

When nuclear pseudo-inclusions, cohesive cell clusters and/or papillary-like structures are identified, MTC can be confused with PTC (Figure 23).[1] Amyloid may also be mistaken with the thick *bubble-gum–like* colloid of PTC. Key differences include the other architectural and nuclear features: PTC often shows sheets, cellular

whorls, papillae, and microfollicles, whereas MTC typically presents with isolated/discohesive cell patterns. Distinctive nuclear changes in PTC, such as powdery chromatin, nuclear grooves, and prominent nucleoli, can aid in differentiation. PTC may also contain psammoma bodies and multinucleated giant cells, which are typically absent in MTC. Some PTC subtypes, such as columnar cell PTC or oncocytic PTC, in which the typical nuclear features of PTC are not well developed, may also enter into the differential diagnosis.[53,54]

Poorly differentiated thyroid carcinoma

PDTCs often present with cellular smears showing insular or trabecular morphology and nuclei with granular chromatin and few or absent nuclear features of classic PTC. These features can overlap with MTC, especially when PDTC displays a single-cell pattern and plasmacytoid morphology. PDTCs usually lack the neuroendocrine *salt-and-pepper* chromatin pattern typical of MTC and often show mitotic figures and/or necrosis, which can help distinguish them. Sometimes, a more differentiated component with microfollicles and colloid or PTC will also be present in PDTC.[50]

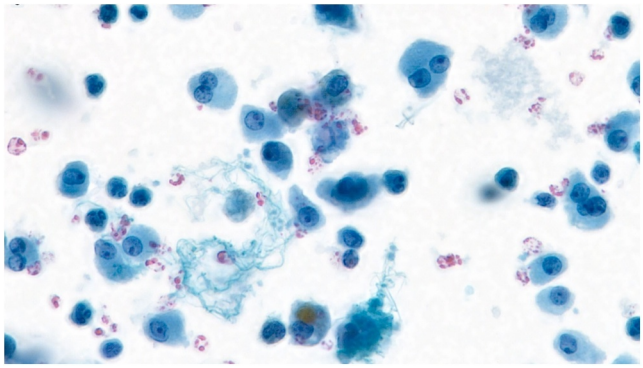

FIGURE 31 Oncocytic follicular neoplasm with binucleated cells. High magnification shows binucleation and multinucleation of oncocytic cells. Note the round, uniform nuclei with large nucleoli and prominent nuclear membrane. Oncocytic neoplasm can be mistaken for medullary thyroid carcinoma (fine-needle aspiration, ThinPrep preparation; Papanicolaou stain, original magnification ×200).

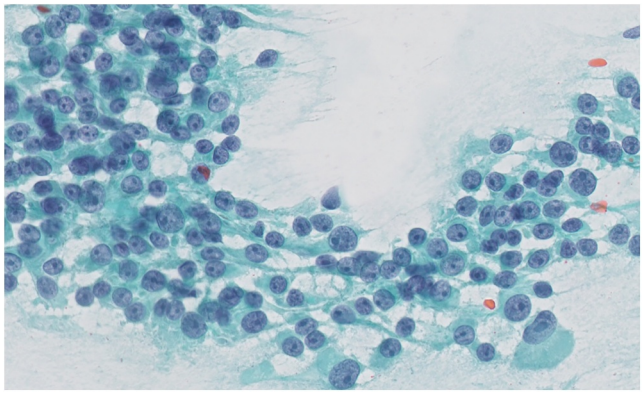

FIGURE 32 Oncocytic follicular neoplasm. In this image, oncocytic neoplasm presents as a very large, loosely cohesive sheet of cells. The neoplastic cells exhibit finely granular cytoplasm and variable sized, round-to-oval nuclei with coarse chromatin and prominent, large nucleoli. Note the single gigantic cell (lower right) with a plasmacytoid feature and very prominent nucleoli (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

Anaplastic thyroid carcinoma

MTC may exhibit extremely pleomorphic cells with large or bizarre nuclei resembling ATC (Figure 20). The spindle cell variant of MTC consists of elongate cells present singly and in loose clusters that also can be misinterpreted as ATC (or as any another spindle cell tumor).[1] Conversely, ATC can show an admixture of spindle cells, giant cells, and epithelioid cells, which can sometimes be mistaken for MTC. However, ATC cells usually have irregular nuclear membranes, coarse chromatin, and prominent nucleoli, differing from the typically round nuclei of MTC (Figure 21). Increased mitotic activity, extensive necrosis, and numerous neutrophils are also much more common in ATC than in MTC. Sometimes, a more differentiated component with microfollicles and colloid or PTC may also be present in ATC. Clinicoradiologic features and IHC can aid in differentiation. Clinically, ATC often presents as a large and rapidly enlarging neck mass with extrathyroidal extension.

Hyalinizing trabecular tumor and paraganglioma

HTT can be easily confused with MTC because of the presence of amyloid-like hyaline stroma and nuclear pseudo-inclusions (Figure 33). Differentiating between paraganglioma and MTC can

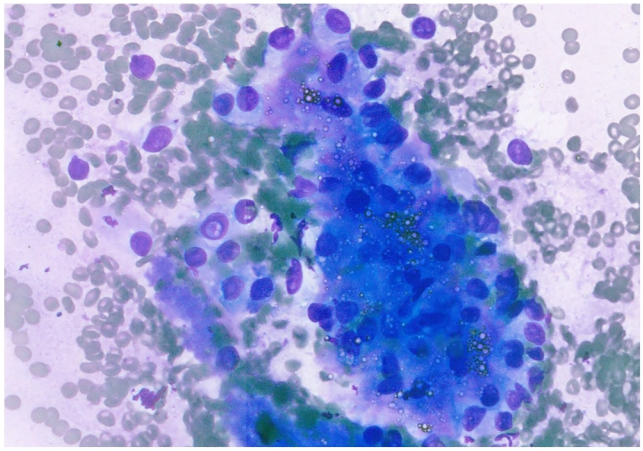

FIGURE 33 Hyalinizing trabecular tumor. In this image, the tumor cells are loosely cohesive and round to ovoid, with ovoid and sometimes eccentric nuclei. A nuclear pseudo-inclusion is present (fine-needle aspiration smear; Diff-Quik stain, original magnification ×400).

also be very challenging because both can express synaptophysin and chromogranin.[55,56] HTT also has unique IHC features with a peculiar membrane staining of MIB1 antibody tested at room temperature and is characterized by a specific *PAX8*::*GLIS1/3* fusion.[19]

Parathyroid lesions

It can be very difficult to distinguish parathyroid lesions from thyroid lesions, including MTC, because of their anatomic proximity, clinical and radiologic overlap, and similar cytomorphologic features. MTCs and parathyroid lesions can share microfollicular pattern, dispersed cell pattern, cytoplasmic granularity, neuroendocrine (stippled) nuclear chromatin features, and even intranuclear pseudo-inclusions (reported in 20% of parathyroid adenomas; Table 1 and Figure 34).[57] Both represent significant pitfalls with follicular neoplasms (Bethesda IV). Correlation with clinical findings (e.g., hypercalcemia) and a low threshold to perform ancillary studies, such as parathyroid hormone assays in the serum or in the FNA washout fluid, IHC, or molecular testing studies, can help in confirming the diagnosis Immunohistochemically, parathyroid hormone is the most specific marker for confirming parathyroid origin. Although less specific, GATA-3, with nuclear expression, can also support a parathyroid origin and help differentiate it from lesions of follicular or parafollicular cell lineage. In diagnostically challenging cases, molecular assays like Afirma and ThyroSeq have demonstrated utility in identifying a gene expression profile consistent with parathyroid tissue, thereby providing an additional layer of diagnostic confirmation for indeterminate thyroid nodules.[44–46]

Metastatic tumors

When cytologic findings do not align with features typical of primary thyroid neoplasms, the possibility of metastatic disease should always be considered. Metastatic carcinomas, most commonly from the kidney, lung, or breast, can involve the thyroid and mimic MTC on cytology.[58,59] In particular, the spindle cell variant of MTC can be

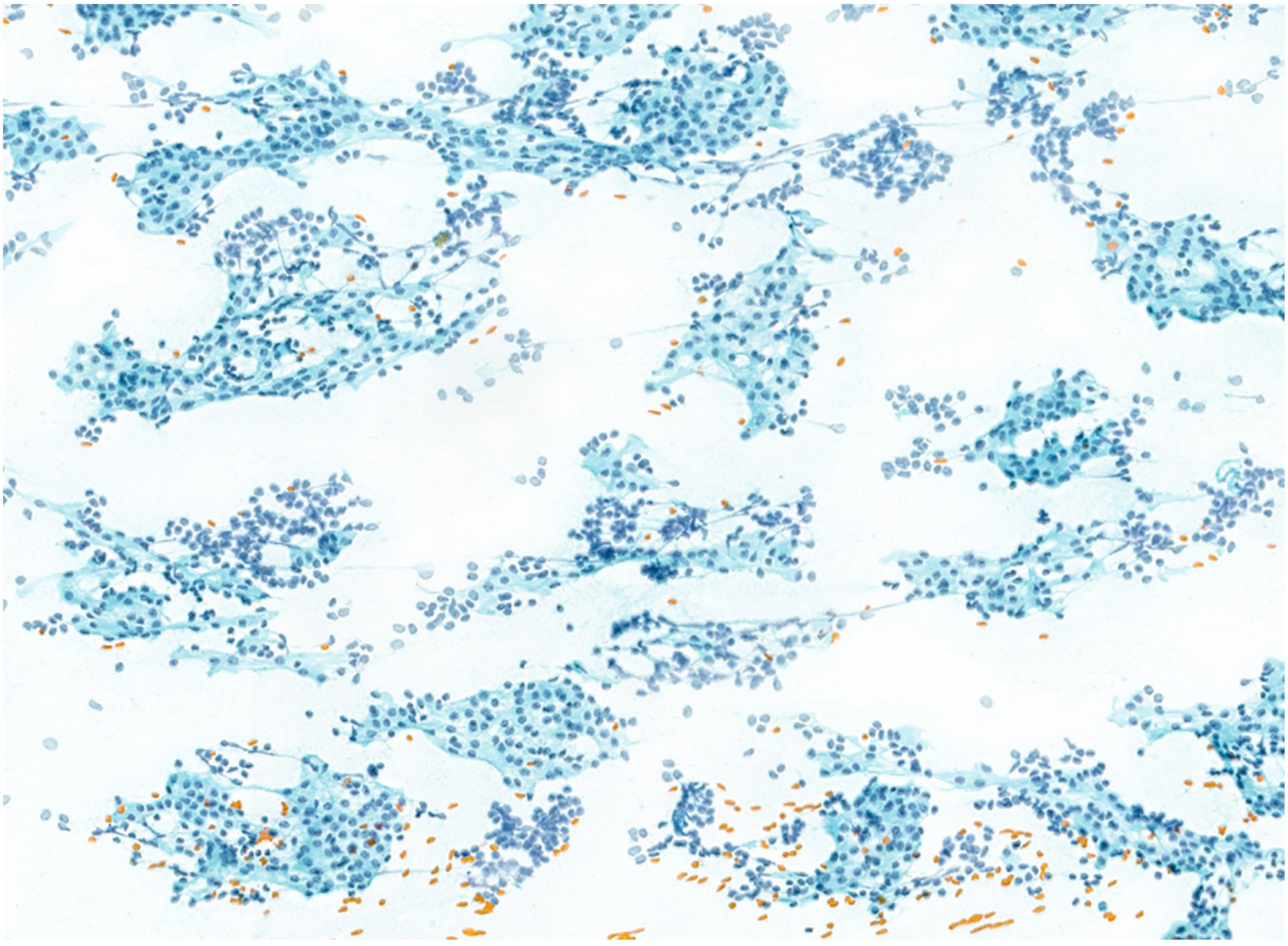

FIGURE 34 Parathyroid lesion. On low magnification, parathyroid lesions can share some of the architectural features of medullary thyroid carcinoma, including a dispersed cell pattern with or without a microfollicular pattern. However, in contrast to medullary thyroid carcinoma, the cells in parathyroid lesions are usually more monomorphic and do not show significant anisocariosis (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

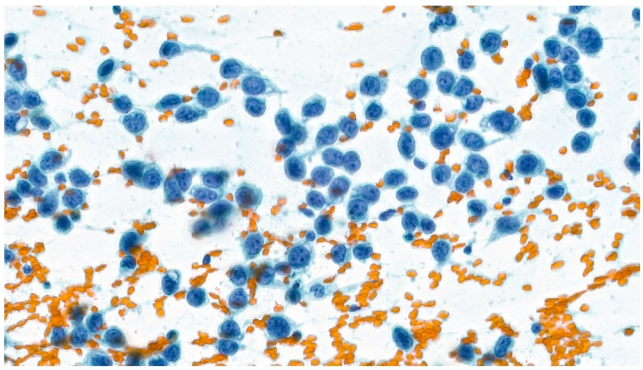

FIGURE 35 Metastatic melanoma is characterized by individual cells or loosely cohesive, small clusters. The cells exhibit high nuclear-to-cytoplasmic ratio, round-to-oval nuclei, coarse chromatin, one or more nucleoli, a slightly irregular nuclear membrane, and finely vacuolated, scant chromatin. The cells depicted in this image can be mistaken for medullary thyroid carcinoma, and ancillary studies or additional clinical information can be helpful in rendering an accurate diagnosis (fine-needle aspiration smear; Papanicolaou stain, original magnification ×200).

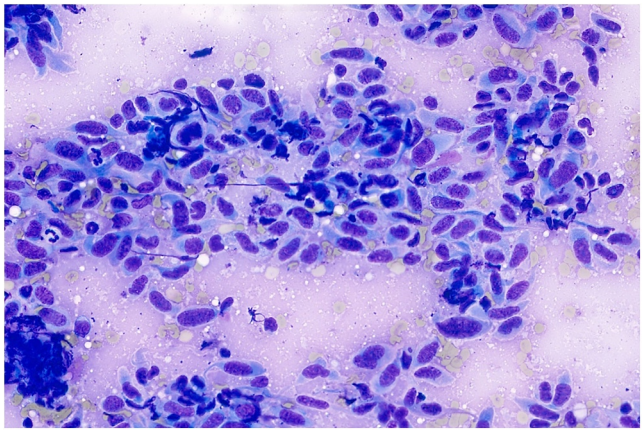

FIGURE 36 Metastatic melanoma with spindle cell morphology. In this image, the malignant cells exhibit spindle cell features with large, elongated nuclei that have coarse chromatin and a scant-to-moderate amount of cytoplasm with long cytoplasmic projections. The features seen here are overlapping with medullary thyroid carcinoma, and ancillary studies like immunohistochemistry are useful to differentiate the two entities (fine-needle aspiration smear; Diff-Quik stain, original magnification ×400).

mistaken for metastatic sarcoma or spindle cell carcinoma.[60] Distinguishing MTC from metastatic melanoma can also be especially challenging. Both entities may present as discohesive cells with a wide range of morphologies, including epithelioid, spindled, plasmacytoid, or bipolar forms (Figures 35–37). Adding to the complexity, MTC can occasionally show melanocytic differentiation and may even produce melanin pigment.[1,61] In such diagnostically difficult cases, correlation with the patient's clinical history, imaging findings, and the strategic use of IHC is essential for accurate classification.[58,59] However, it is important to recognize that, in some patients, thyroid involvement may

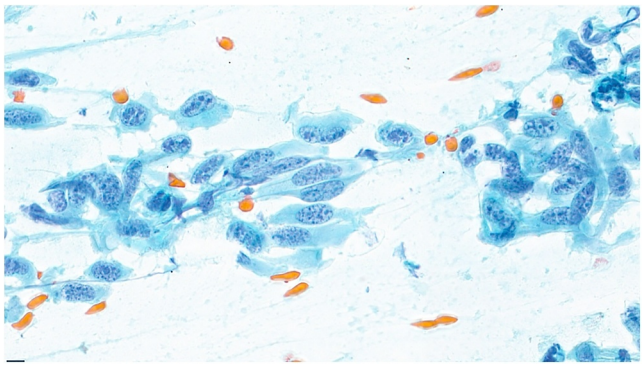

FIGURE 37 Metastatic melanoma with spindle cell morphology. High magnification shows spindle cells with elongated nuclei that have coarse chromatin and a moderate amount of cytoplasm with long cytoplasmic projections. The morphology shown here is overlapping with that in medullary thyroid carcinoma and can be misinterpreted (fine-needle aspiration smear; Papanicolaou stain, original magnification ×400).

be the initial presentation of an undiagnosed malignancy elsewhere, making a thorough diagnostic workup even more critical.

The small cell variant of MTC is a very unusual tumor that behaves more aggressively than typical MTC.[1] It may be impossible on morphologic examination to distinguish a small cell MTC from metastatic small cell carcinoma of the lung or of any another site (e.g., bladder). Other small cell tumors, such as lymphoma, Merkel cell carcinoma, neuroblastoma, and primitive neuroectodermal tumor, also enter into the differential diagnosis.[62] Moreover, amyloid may be absent, and immunoreactivity for calcitonin can be negative in this variant, which is why some authors may arguably consider it as a primary small cell carcinoma of the thyroid or as an undifferentiated form of MTC.[63] Clinical history and IHC are crucial for accurate diagnosis.

Plasmacytoma and lymphomas

In primary thyroid plasmacytoma, discohesive plasmacytoid cells and amyloid/amyloid-like materials, which are major features of MTC, all may be seen. At least two cases of thyroid plasmacytomas misdiagnosed as MTC are reported in the literature.[64,65] However, the tumor cells of MTC are generally larger than plasma cells, and the nuclear features are different. Clinical correlation and IHC are also crucial in avoiding this diagnostic pitfall. Of note, plasmacytoma may arise in a background of Hashimoto thyroiditis, and the neoplastic plasma cells may not constitute the main component of the aspirate, whereas the nonneoplastic oncocytic (Hurthle cells) cells may predominate and further confuse the interpretation.

CONCLUSIONS

Accurate preoperative diagnosis of MTC poses significant challenges because of the tumor's rarity and its wide range of cytomorphologic presentations. Although classical MTC features, such as plasmacytoid

or spindled cells with granular cytoplasm and salt-and-pepper chromatin, are typically identifiable on FNA smears, many cases exhibit noncharacteristic or overlapping features that can mimic other thyroid or neuroendocrine tumors, leading to diagnostic uncertainty and potential delays in optimal patient management. For patients in whom cytology alone is inconclusive, the use of ancillary techniques becomes crucial for confirmation. IHC markers, particularly calcitonin and CEA, are essential in distinguishing MTC from other thyroid neoplasms. In addition, the detection of elevated calcitonin levels in serum or FNA washout fluid can further support the diagnosis. Moreover, molecular testing for *RET* and other related mutations can provide valuable diagnostic and prognostic information, particularly in ambiguous cases. A thorough understanding of the cytologic spectrum of MTC, its potential mimics, and the timely integration of ancillary diagnostic tools, such as IHC, biochemical testing, and molecular assays, can substantially improve preoperative diagnostic accuracy and expedite appropriate treatment strategies for patients.

AUTHOR CONTRIBUTIONS

Marc P. Pusztaszeri: Conceptualization; writing—original draft; writing—review and editing; project administration; data curation; resources; formal analysis; visualization; investigation; methodology. **Zahra Maleki:** Methodology; writing—review and editing; resources; data curation; project administration; formal analysis; visualization; investigation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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