Medullary Thyroid Carcinoma

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Introduction to Medullary Thyroid Carcinoma

- Medullary thyroid carcinoma (MTC) represents 1–2% of thyroid carcinomas.
- MTC occurs in sporadic and familial forms; sporadic MTC accounts for 75% of cases.
- Familial cases occur in the setting of multiple endocrine neoplasia (MEN) 2A/2B and familial MTC.
- Activating point mutations in the *RET* proto-oncogene located on chromosome 10 are responsible for familial forms of MTC and can also occur in up to 80% of sporadic cases.
- Sporadic MTC usually presents as a single, solitary nodule. Patients are usually in their 5th or 6th decade
- Familial MTC tends to present in the 2nd or 3rd decade and is usually multifocal.
- Grossly, MTC nodules appear circumscribed and unencapsulated (Fig. 10.1a, b). Histologically, MTC can demonstrate various growth patterns and cytologic features; a number of variants have been described (Fig. 10.1c, d).

TBSRTC Definition of MTC

- The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) defines MTC as a malignant neuroendocrine tumor arising from C cells (parafollicular cells) of the thyroid gland.

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Cytologic Criteria for Diagnosis of MTC on Conventional Smears (CS)

- On fine needle aspiration (FNA), MTC is typically categorized as suspicious for malignancy (Bethesda V) or malignant (Bethesda VI), and rarely as Atypia of Undetermined Significance (AUS, Bethesda III) or benign (Bethesda II).
- In a study of 28 cases of FNA aspirates of MTC with surgical follow-up, Dyhdalo and Chute [5] showed one case interpreted as benign, four as AUS/FLUS, one as FN/SFN, five deemed suspicious for malignancy, and 17 as positive for malignancy. The few discordant cases tended to show air-drying artifact and lacked typical features of MTC, such as plasmacytoid appearance and dyshesion.
- In CS, the aspirates show moderate to high cellularity and are composed of groups and clusters and single tumor cells. The tumor cells show round to oval nuclei with nuclear pleomorphism and a neuroendocrine-type salt-and-pepper chromatin. The tumor cells typically show eccentrically placed nuclei and granular cytoplasm imparting a "plasmacytoid" appearance, although spindled, oncocytic, or clear cell types can be seen.
- The cells can also be arranged as trabeculae or in microfollicles (Fig. 10.2a–d). The tumor cells can frequently be binucleate or multinucleate and can exhibit intranuclear cytoplasmic pseudoinclusions (INPI) as well (Fig. 10.2e).
- Occasional bizarre neuroendocrine type atypia can be noted (Fig. 10.2f). The background can show colloid in some cases but typically shows dense, amorphous, stromal material composed of "amyloid", which is also well identified on smears and cell block sections (Fig. 10.2g, h). Among rare findings are cytoplasmic stippling, nuclear budding, and lymphoma-like cells.
- A cell block preparation is extremely helpful for ancillary confirmatory studies (Fig. 10.2h, i). Immunohistochemistry

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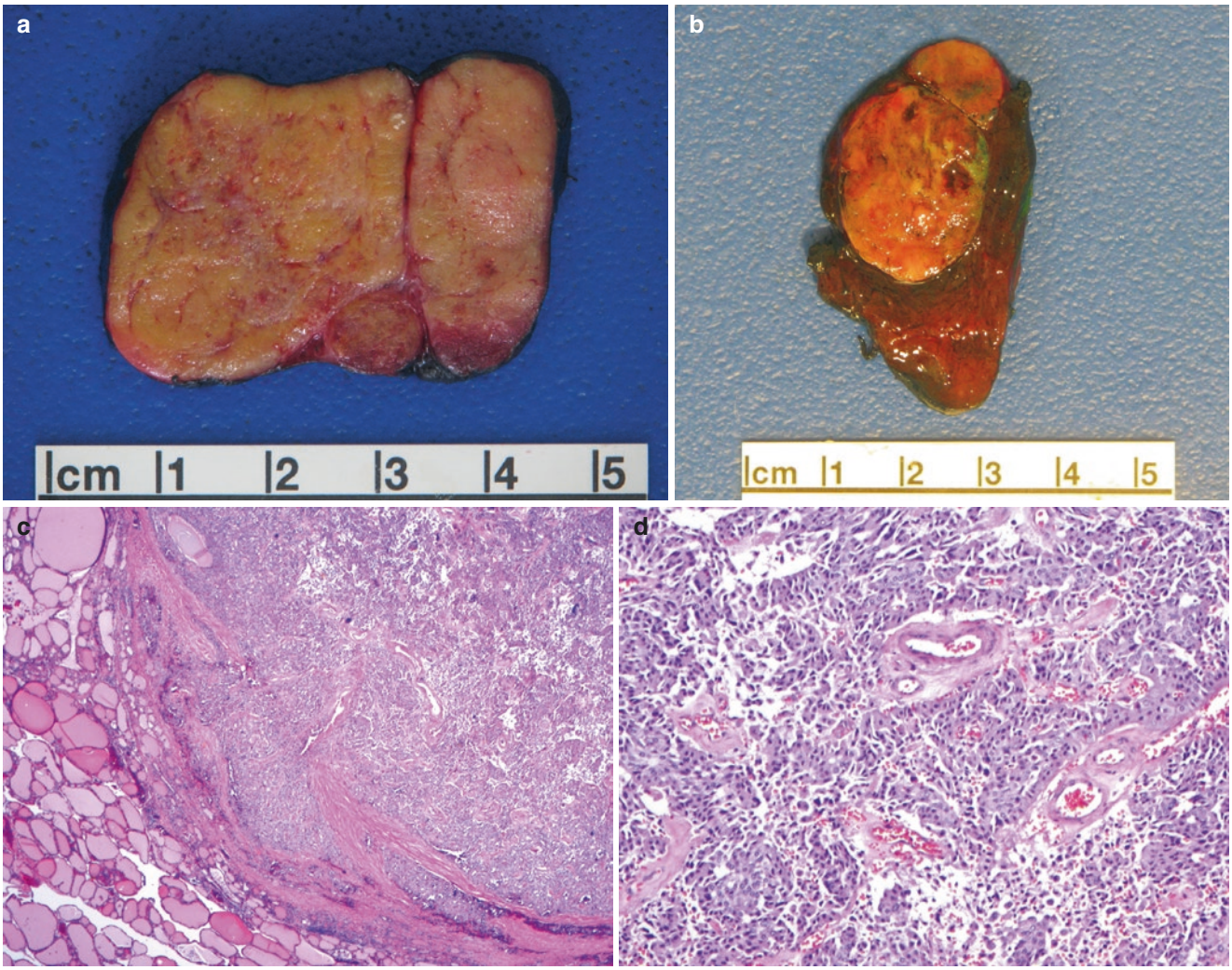


Fig. 10.1 Gross appearance of medullary thyroid carcinoma (MTC). (**a**, **b**) Grossly, two cases of MTC appear as well-circumscribed, unencapsulated nodules, which can occasionally have an infiltrative border. The cut surface is tan-white or pink to gray. Hemorrhage and necrosis are usually absent. Calcifications may be seen. (**c**, **d**) Low-power view of the histology of MTC, showing the circumscribed edge of the tumor. Higher magnification shows the spindle cell type of MTC (H&E stain)

can be strongly immunoreactive for calcitonin, CEA and other neuroendocrine markers (synaptophysin, chromogranin), and for TTF-1. Thyroglobulin is negative, and staining with PAX8 is variable (Fig. 10.2j).

Cytologic Criteria for Diagnosis of MTC on LBP

- The cytologic features of MTC are fairly similar on LBP and CS.
- A few subtle differences include the appearance of tumor cell clusters and groups that are smaller and more fragmented on LBP than on CS. Also, single tumor cells are more prominent on LBP.
- In LBP, the presence of many small, singly dispersed spindle or plasmacytoid cells should raise suspicion for MTC (Figs. 10.3 and 10.4).
- Occasionally, in LBP, the cytoplasm may appear finely vacuolated and granularity may be inconspicuous.
- The background is relatively clean on LBP. Fragments of amyloid can appear fibrillary or dense on LBP, rather than only dense, as seen in CS (*see* Fig. 10.3d, e).

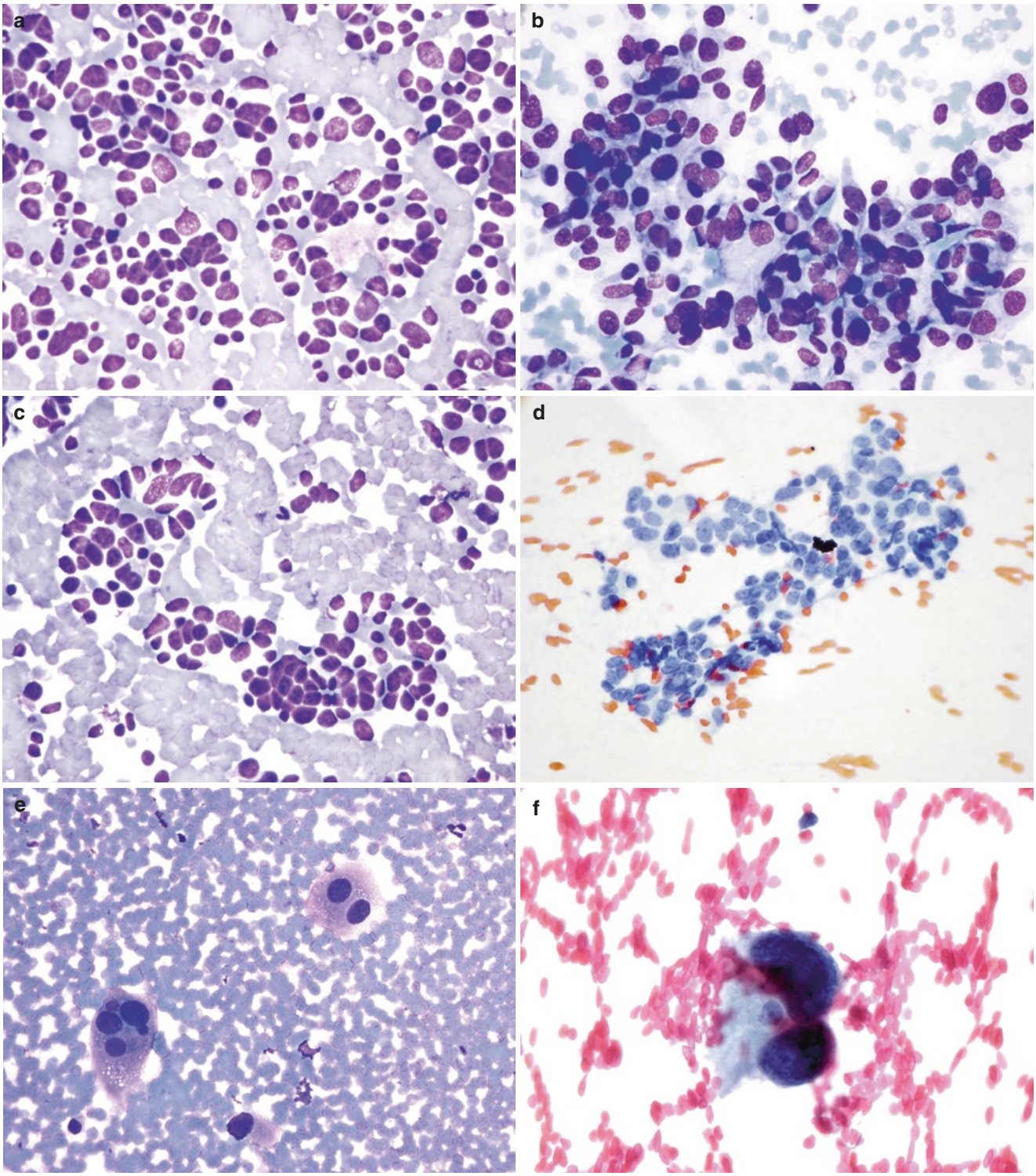


Fig. 10.2 Fine needle aspiration (FNA) of MTC on conventional smears (CS). (**a**–**c**) On CS, aspirates of MTC show moderate to high cellularity and are composed of groups, clusters, and single tumor cells. The tumor cells show round to oval to spindled nuclei, with nuclear pleomorphism arranged predominantly as single cells and as loose trabeculae (**a**–**c**, Diff Quik [DQ] stain). (**d**, **e**) Nuclei have a neuroendocrine-type, salt-and-pepper chromatin pattern. The aspirate shows binucleate and multinucleate tumor cells, which can be seen in cases of MTC. (**d**, Pap stain; **e**, Diff Quik). (**f**) MTC can show "bizarre"-type neuroendocrine atypia (Pap stain)**.** (**g**) Amyloid appears dense and acellular and mixed with abundant background blood (Pap stain)**.** (**h**, **i**) Cell block preparations of MTC shows amyloid as a cellular dense material closely associated with tumor cells. Amyloid can be identified by staining with special stain for Congo Red and using polarizing light microscopy which shows apple-green birefringence (**h**, **i**, H&E). (**j**) Immunostaining for calcitonin highlights these tumor cells by staining the cytoplasm. Almost all MTC stains positive for calcitonin. In calcitonin negative cases, the possibility of metastases and even a rare paraganglioma must be ruled out

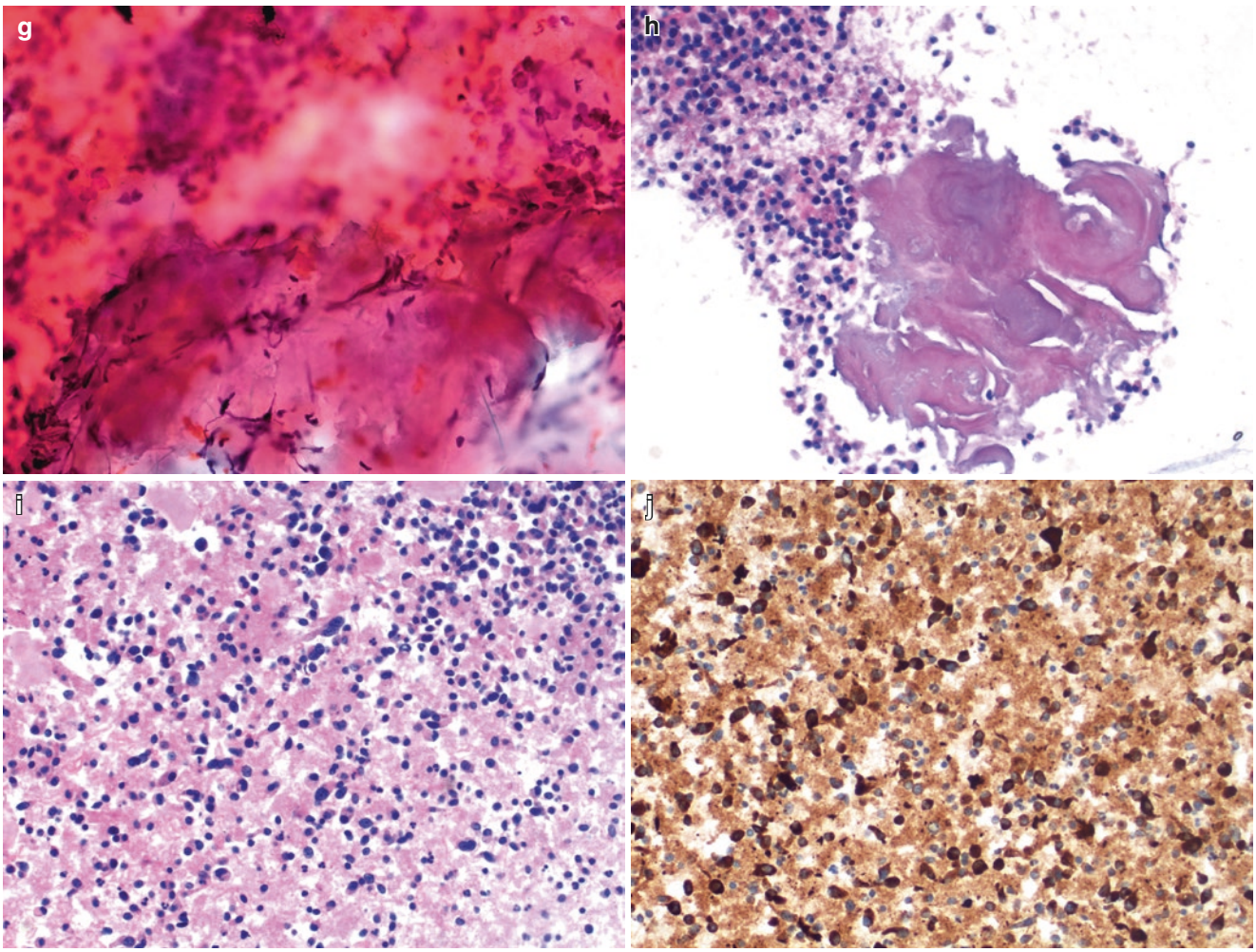


Fig. 10.2 (continued)

Variants and Differential Diagnosis of MTC

- Although most cases of MTC display a characteristic cytomorphology, MTC can demonstrate a variety of growth patterns and cytologic features.
- A number of variants have been described, as listed on Table 10.1 and illustrated in Fig. 10.5: Papillary (pseudopapillary), oncocytic, follicular, giant cell, small cell, paraganglioma-like, spindle cell, clear cell, squamous cell, melanin-producing, angiosarcoma-like, and amphicrine (mucin-producing).
- Variable tumor morphology can make the diagnosis challenging; each of these variants can mimic other primary and secondary tumors.
- Diagnostic accuracy for MTC is not as high as for papillary thyroid carcinoma (PTC) because of the diverse cytologic appearance. A large meta-analysis showed that FNA could detect only about 50% of cases of MTC.
- Diagnostic accuracy can be increased by the use of immunohistochemistry (IHC) and calcitonin assays in needle rinse.

Oncocytic Variant of MTC (MTC-OV) vs Hürthle Cell Neoplasm

- The oncocytic variant of MTC (MTC-OV) tends to show a monomorphic proliferation of tumor cells with enlarged, eccentrically placed nuclei showing salt-and-

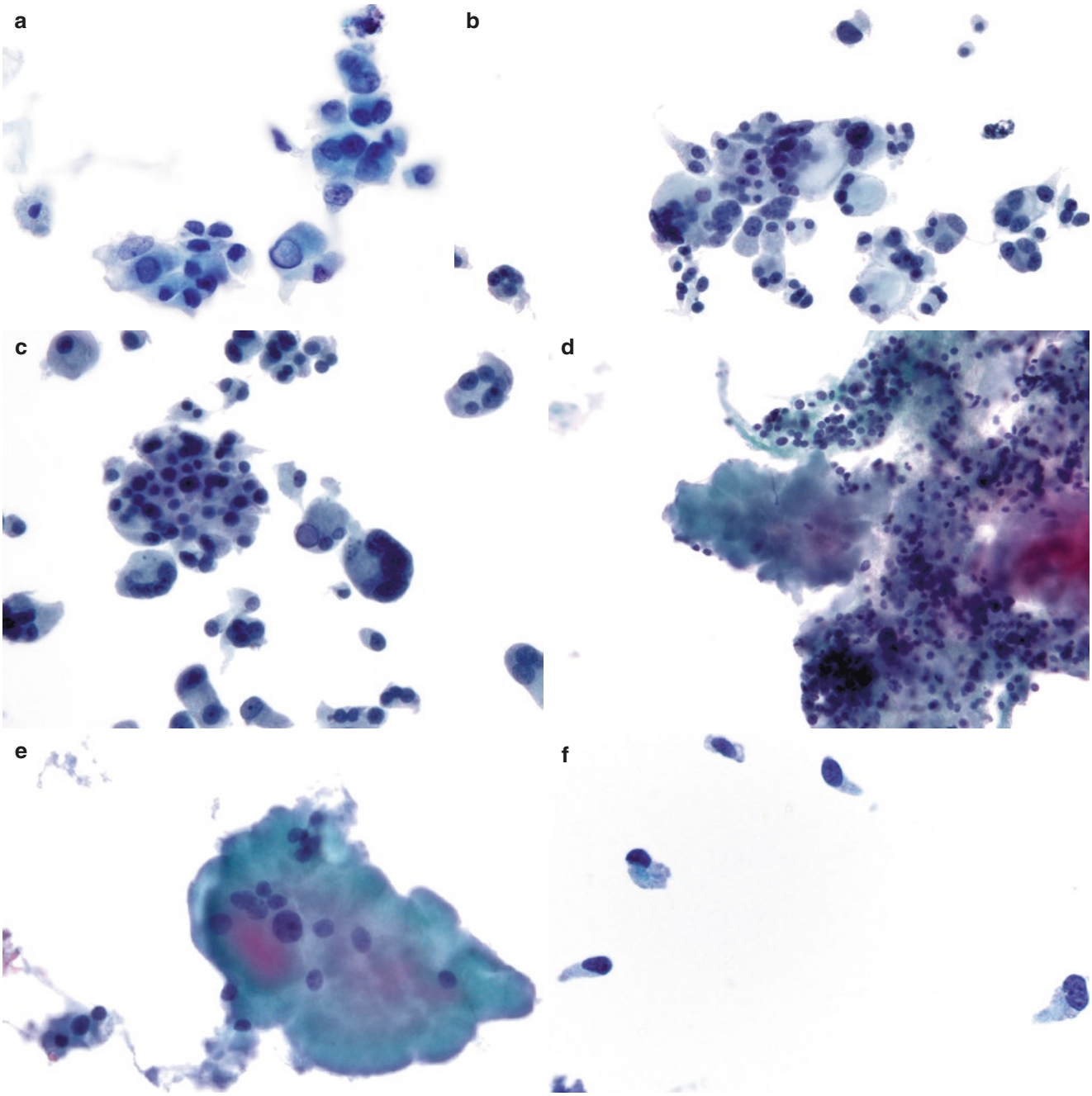
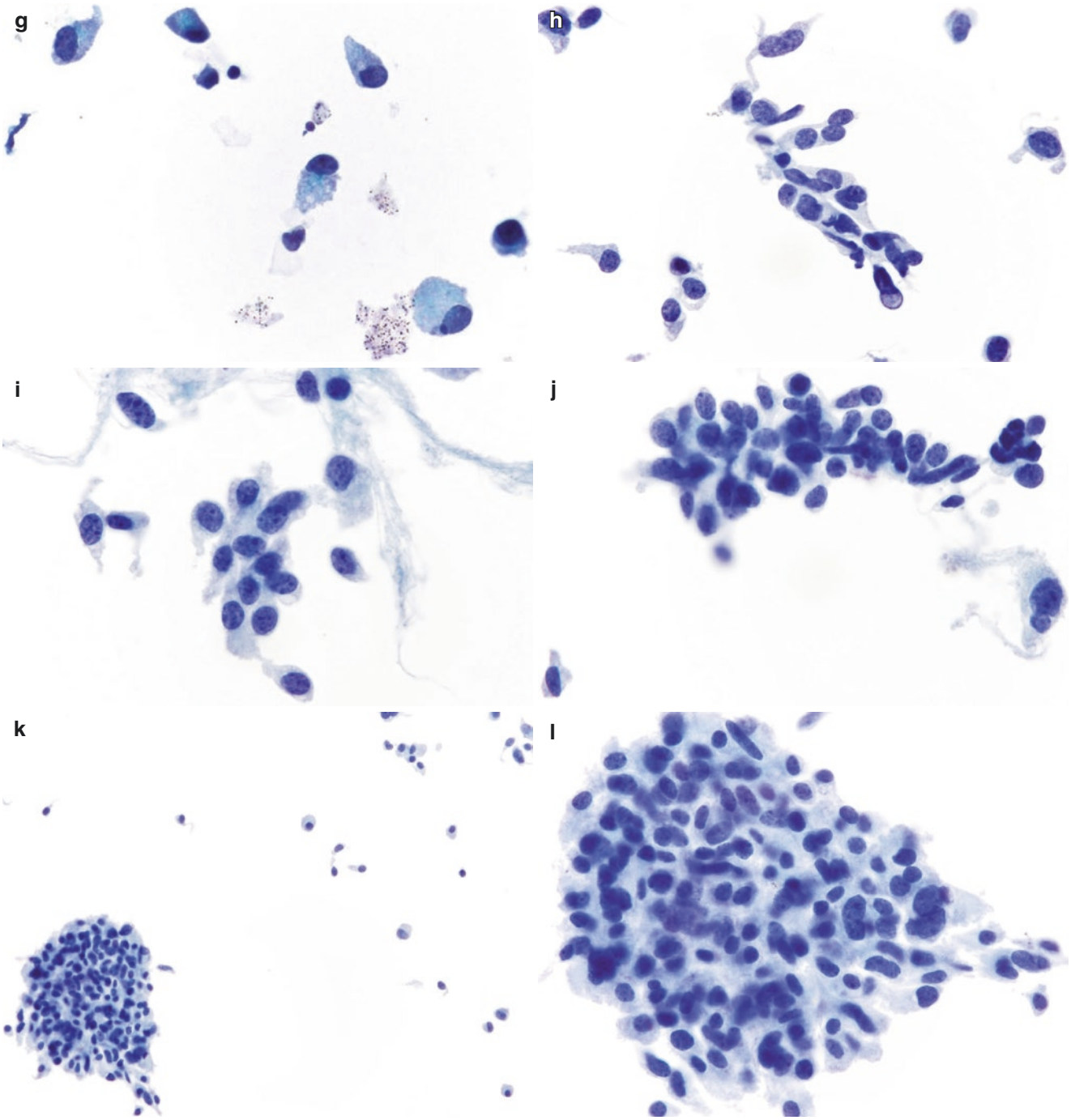


Fig. 10.3 Cytology of MTC on ThinPrep®. (**a**) Intranuclear pseudoinclusions can be seen in MTC and can be well recognized on TP as in CS. Therefore, INPI are not entirely specific for papillary thyroid carcinoma (PTC). (**b**, **c**) Just as in CS, the binucleate and multinucleate tumor cells can be prominent on TP. (**c**) One of the multinucleate cells shows an INPI and a few other tumor cells show bizarre nuclear atypia. (**d**, **e**) show appearances of "amyloid" on TP as dense amorphous stromal material appearing separate or intermixed with tumor cells. In LBP, amyloid can appear fibrillary or dense. In these examples they appear dense. Images from two different cases of MTC (**f–l** and **m–p**) processed with TP, showing tumor cells predominantly single, in trabeculae, and in clusters, similar to CS. Tumor cells are small and plasmacytoid to spindly in appearance. The cytoplasm of these cells on LBP shows microvacuolations and granularity (Pap stain, TP). When many small spindled to oval cells with spindled to oval nuclei are noted in LBP, it should raise a suspicion for MTC (Pap stain, TP)



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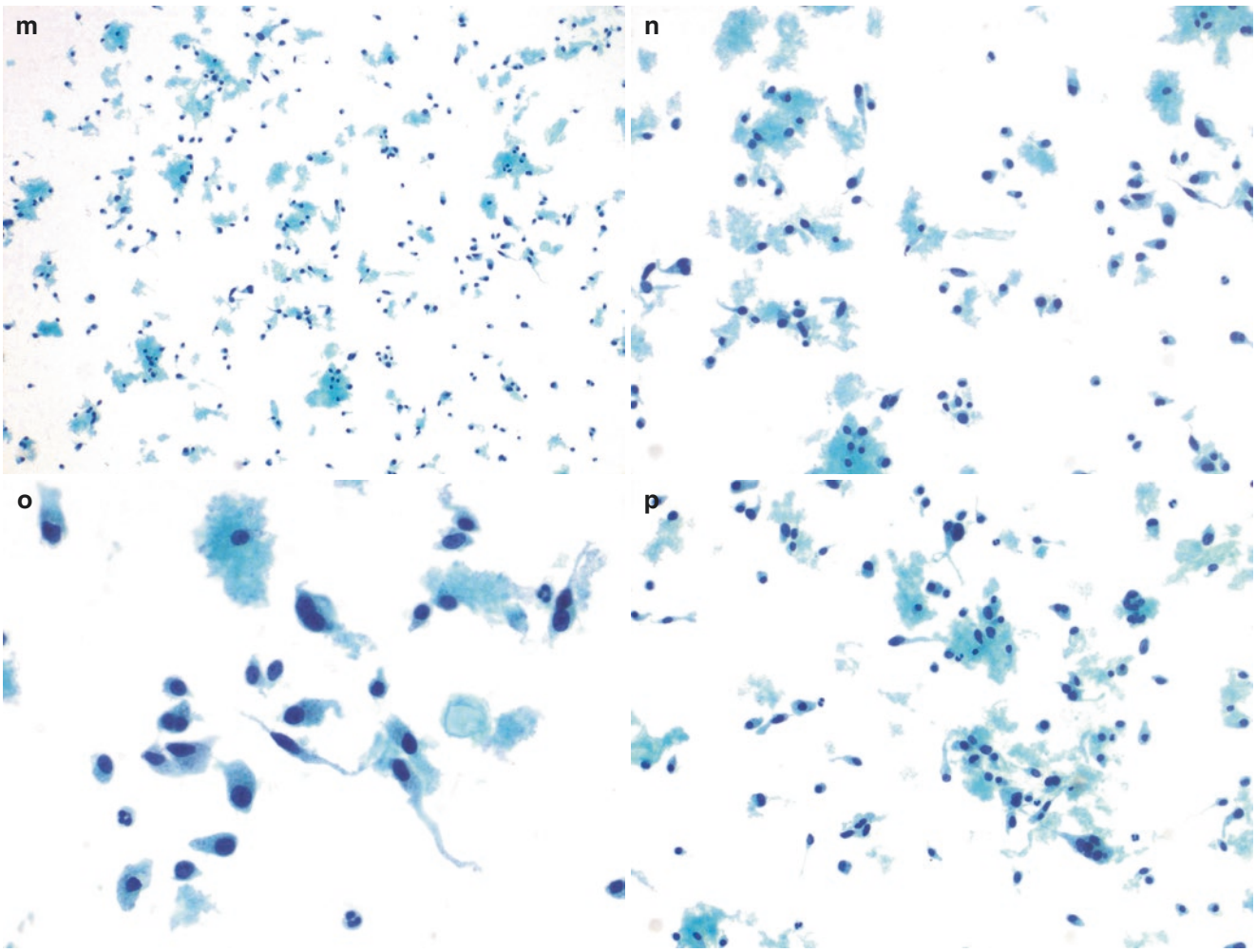

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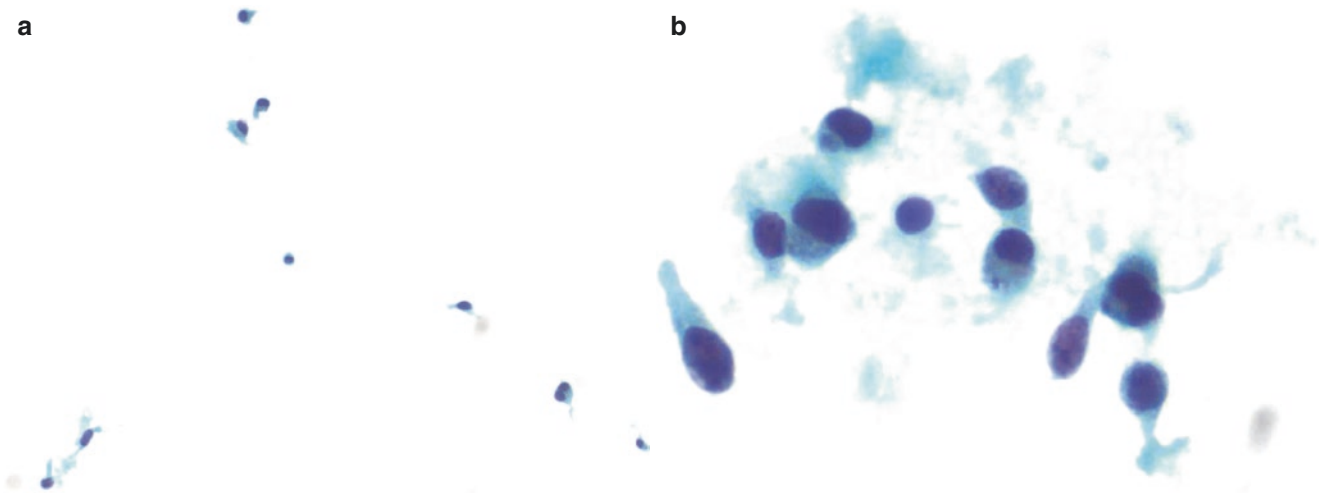


Fig. 10.4 Cytology of MTC on SurePath™ (SP). (**a**–**d**) Images from a case of MTC processed as SP show mostly single tumor cells and loosely cohesive groups. Tumor cells are spindly in appearance, with plasmacytoid to spindly nuclei. Occasional cells are binucleated. The cytoplasm is also spindled. Note that some cells appear in a different plane of focus, and nuclear morphology is less well-preserved than on TP. In both types of LBP, the presence of singly dispersed small, spindled cells should raise suspicion for MTC (Pap stain, SP)

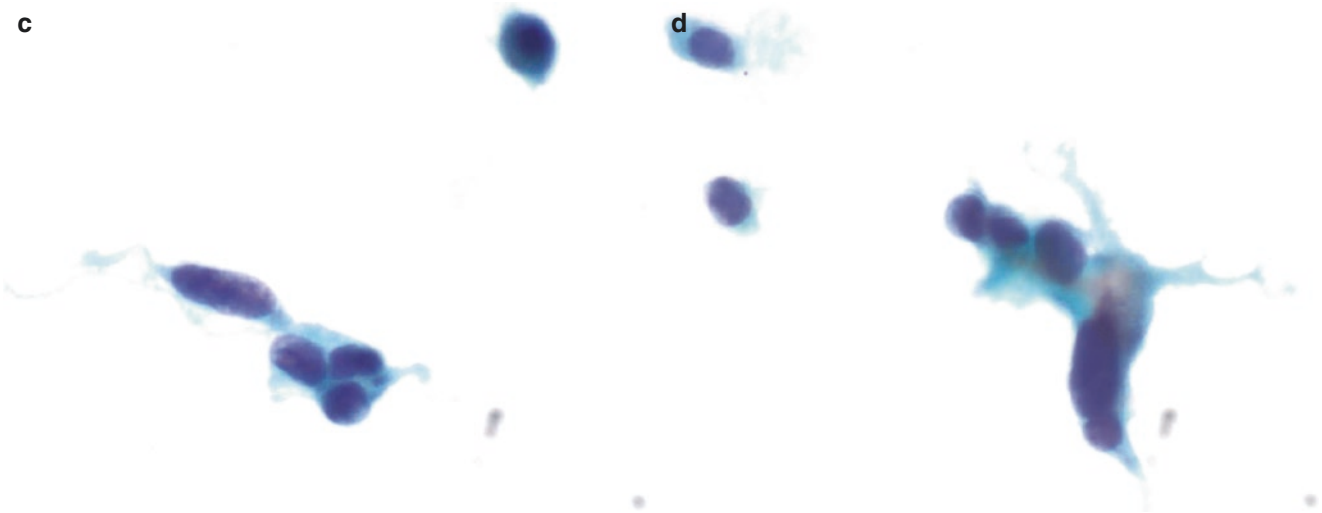


Fig. 10.4 (continued)

Table 10.1 Medullary thyroid carcinoma (MTC) variants: differential diagnosis and their immunohistochemical profile

		Immunohistochemistry (IHC)	
Variant	Differential diagnosis	Positive	Negative
Papillary/pseudopapillary	Papillary thyroid carcinoma (PTC)	TTF-1, PAX8, TG	Calcitonin, NE markers
Oncocytic	Oncocytic neoplasm PTC, oncocytic type	TTF-1, PAX8, TG	Calcitonin, NE markers
Follicular/glandular	Follicular neoplasm	TTF-1, PAX8, TG	Calcitonin, NE markers
Giant cell	Anaplastic thyroid carcinoma (ATC)	TTF-1 (variable), PAX8 (variable)	Calcitonin, TG, NE markers
Small cell	Metastatic small cell carcinoma	NE markers	Calcitonin
Paraganglioma-like	Hyalinizing trabecular tumor (HTT)	TTF-1, TG, Ki67 (membranous)	Calcitonin, NE markers
	Paraganglioma	NE markers, S100	Calcitonin, TTF-1, CK
Spindle cell	Sarcoma	Variable	Calcitonin, TTF-1, CK
Clear cell	Follicular neoplasm with clear cells	TTF-1, PAX8, TG	Calcitonin, NE markers
Squamous cell	Anaplastic thyroid carcinoma (ATC)	TTF-1 (variable), PAX8 (variable)	Calcitonin, NE markers, TG
	PTC with squamous differentiation	TTF-1, PAX8, TG	Calcitonin, NE markers
	Squamous cell carcinoma (SCC)	P63, p40	Calcitonin, NE markers
Melanin-producing/pigmented	Melanoma	S100, HMB45, A103, SOX-10	Calcitonin, TG, CK, NE markers
Angiosarcoma-like	Angiosarcoma	CD34, CD31, ERG	Calcitonin, TG, CK
Amphicrine	Metastatic adenocarcinoma	Variable depending on location	Calcitonin, TG

CK cytokeratin, *NE* neuroendocrine, *TG* thyroglobulin

pepper nuclear chromatin and oncocytic cytoplasm, with granularity and cytoplasmic vacuolization (Fig. 10.6a–f). These oncocytic variants can be misdiagnosed as Hurthle cell neoplasms (HCN), especially if they appear cohesive and lack the plasmacytoid appearance.

- MTC can be cytologically distinguished from HCN by the presence of a variable population of plasmacytoid and spindle cells, salt-and-pepper granular chromatin, and lack of prominent nucleoli.
- HCN shows round nuclei, small nucleoli, and lack the neuroendocrine type of chromatin (Fig. 10.6g–i).
- Confirmation of the diagnosis of MTC can be facilitated with positive staining for calcitonin and negative thyroglobulin staining.

Hyalinizing Trabecular Tumor/Adenoma

- Hyalinizing trabecular tumor (HTT) also known as hyalinizing trabecular adenoma (HTA) is a follicular-derived neoplasm that may resemble MTC both cytologically and histologically. (*See* Chap. 6 for more information on the hyalinizing trabecular tumor [HTT].)

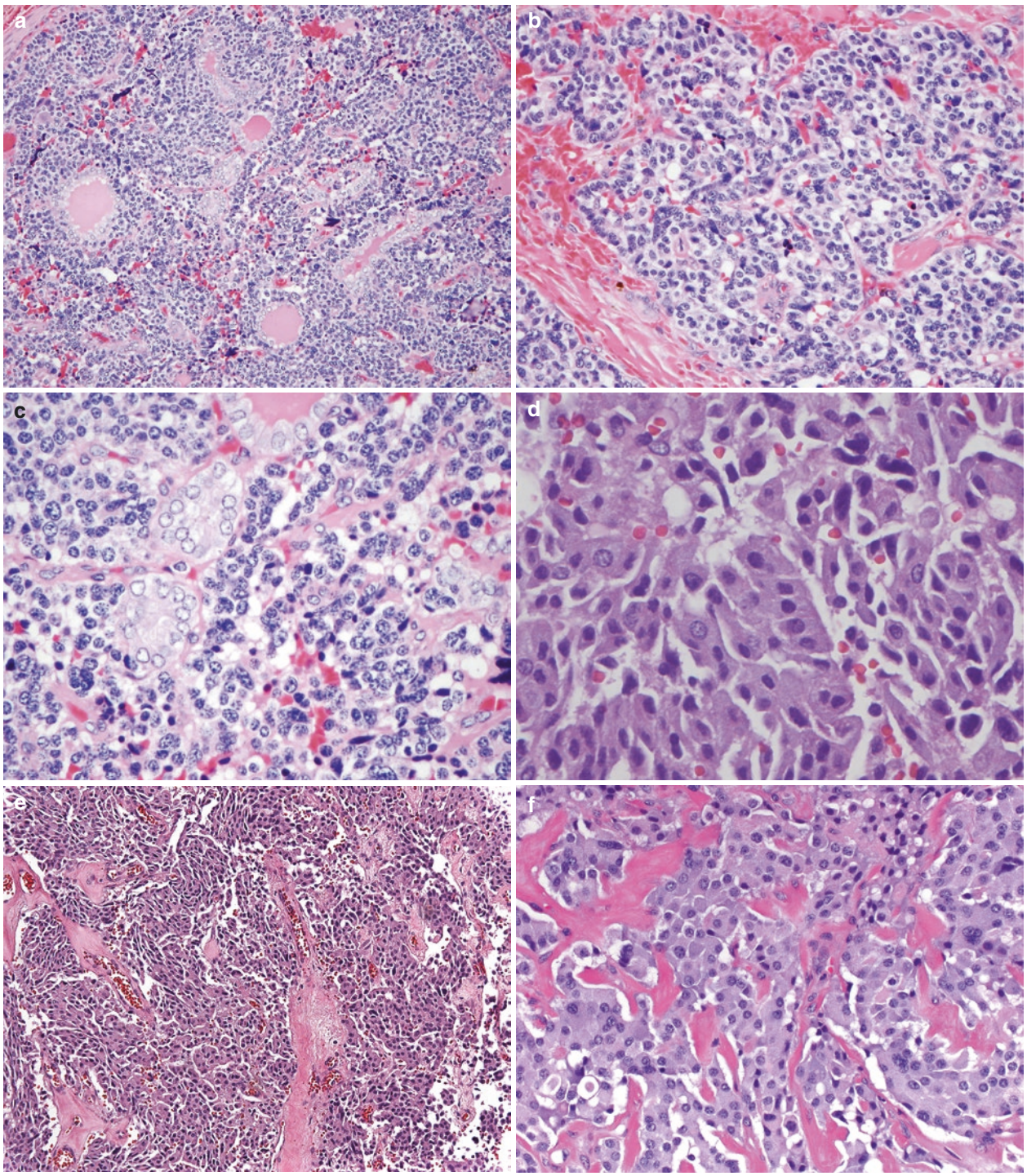


Fig. 10.5 Histology of MTC. The tumor may have a variable histologic appearance. Typical features include a combination of solid, nested, follicular, and trabecular growth pattern. The tumor cells show a combination of spindle, epithelioid, and plasmacytoid morphology. The nuclei have a salt-and-pepper chromatin pattern and may contain inclusions. (**a**–**c**) Histologic sections of a case of MTC showing syncytial and trabecular patterns of growth. Tumor cells show nuclei with "salt-and-pepper" neuroendocrine pattern and infiltrating preexisting follicles. (**d**) In this MTC, the tumor cells tend to show varying cytomorphology, with some cells having a glandular appearance and some having a plasmacytoid appearance and low nuclear-cytoplasmic (N:C) ratio. The cytoplasm appears granular. (**e**, **f**) Histologic sections of MTC with prominent plasmacytoid tumor cells. (**g**) In this histologic section of MTC, the tumor cells appear spindled and are growing in a sheet-like manner interspersed by plasmacytoid cells in nests. (**h**) The corresponding aspirate is cellular with markedly spindled cells with features very similar to that seen in the histologic section. Note the neuroendocrine chromatin pattern, which is readily appreciated on both cytology and histology. (Compare CS with the spindle cell morphology seen in TP in Fig. 10.3.) (**i**) Amyloid deposits are present in up to 80% of cases; they appear as amorphous hyaline material and strongly suggest MTC, but because they can be seen in other thyroid lesions not involving cancer cells they are not diagnostic of MTC but rather are a helpful feature in the presence of MTC cytology. (**j**) Histologic section of MTC with strong staining for calcitonin in the cytoplasm of the tumor cells. (**k**) Histologic section of MTC showing negative staining for thyroglobulin

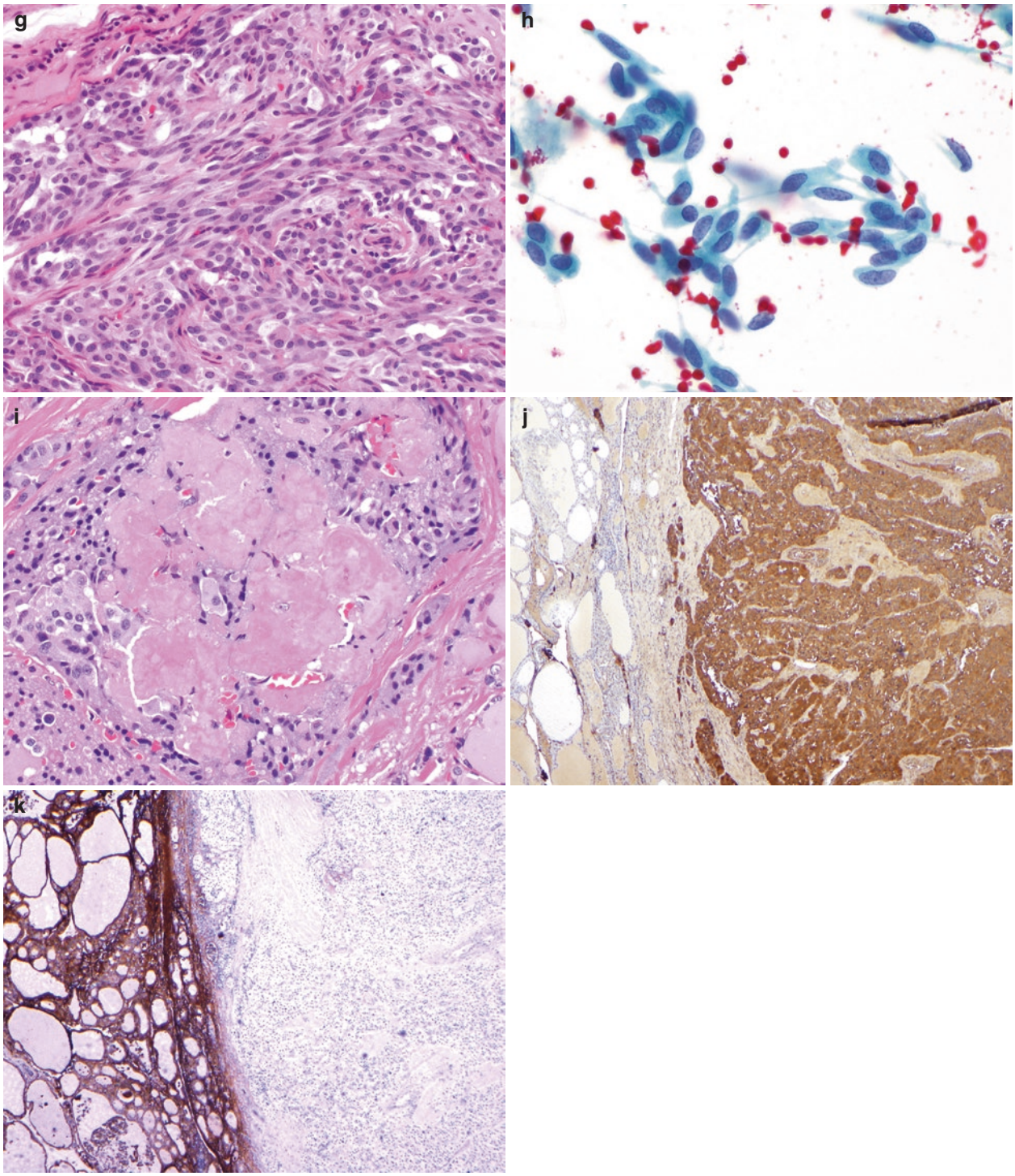


Fig. 10.5 (continued)

- Both neoplasms may show isolated cells in loose cohesive clusters, spindle-shaped cells, and acellular hyaline material. MTC can be distinguished from HTT by the presence of both plasmacytoid and spindle cells, frequent binucleation and multinucleation, and salt-and-pepper granular chromatin, as opposed to the PTC-like nuclei of HTT (Fig. 10.7; *see* Fig. 6.14).
- Immunohistochemical stains for calcitonin and thyroglobulin can aid in the distinction. MIB-1 immunostain has a distinct cytoplasmic and membranous staining in HTT unlike any other lesion/tumor.

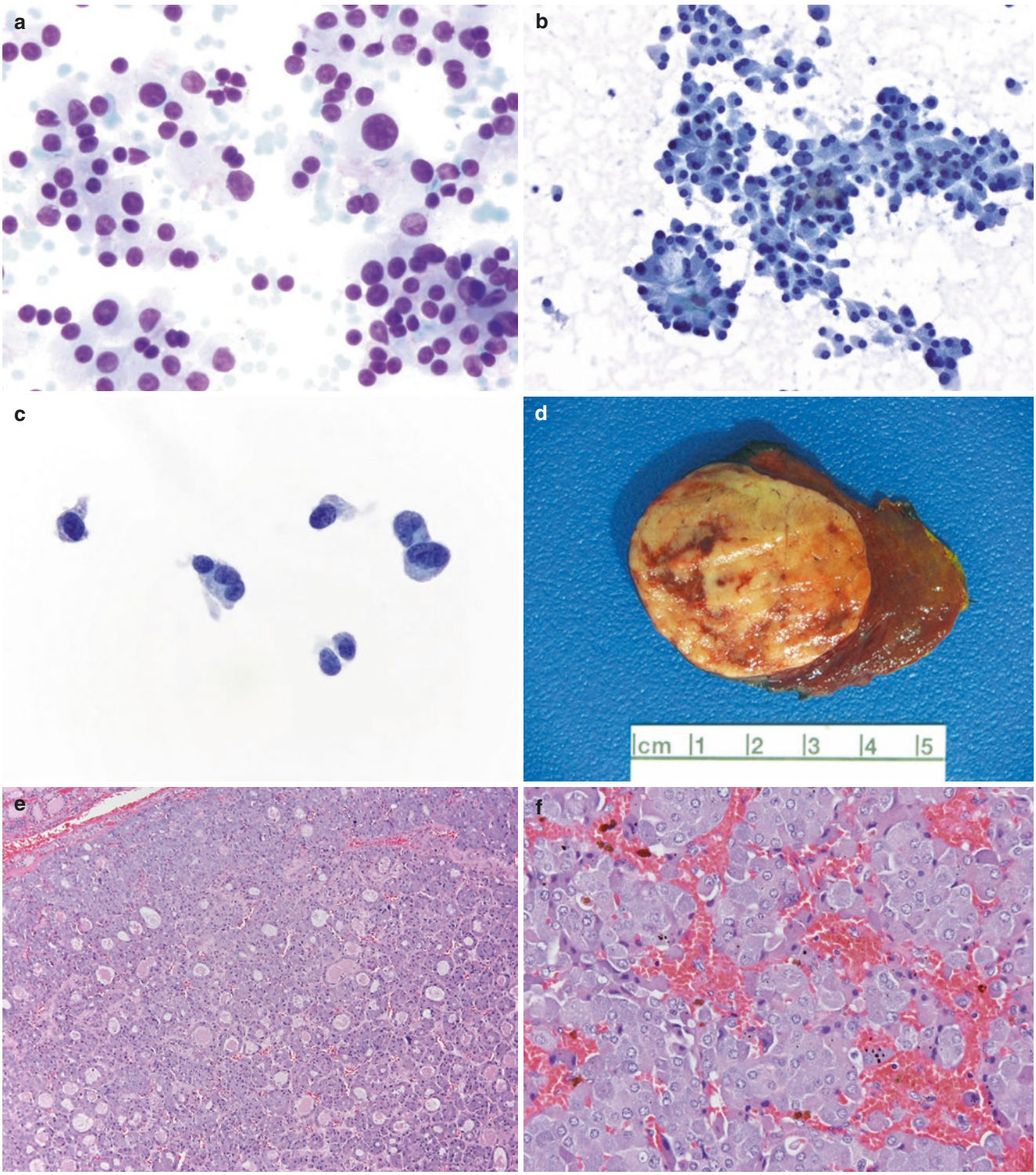
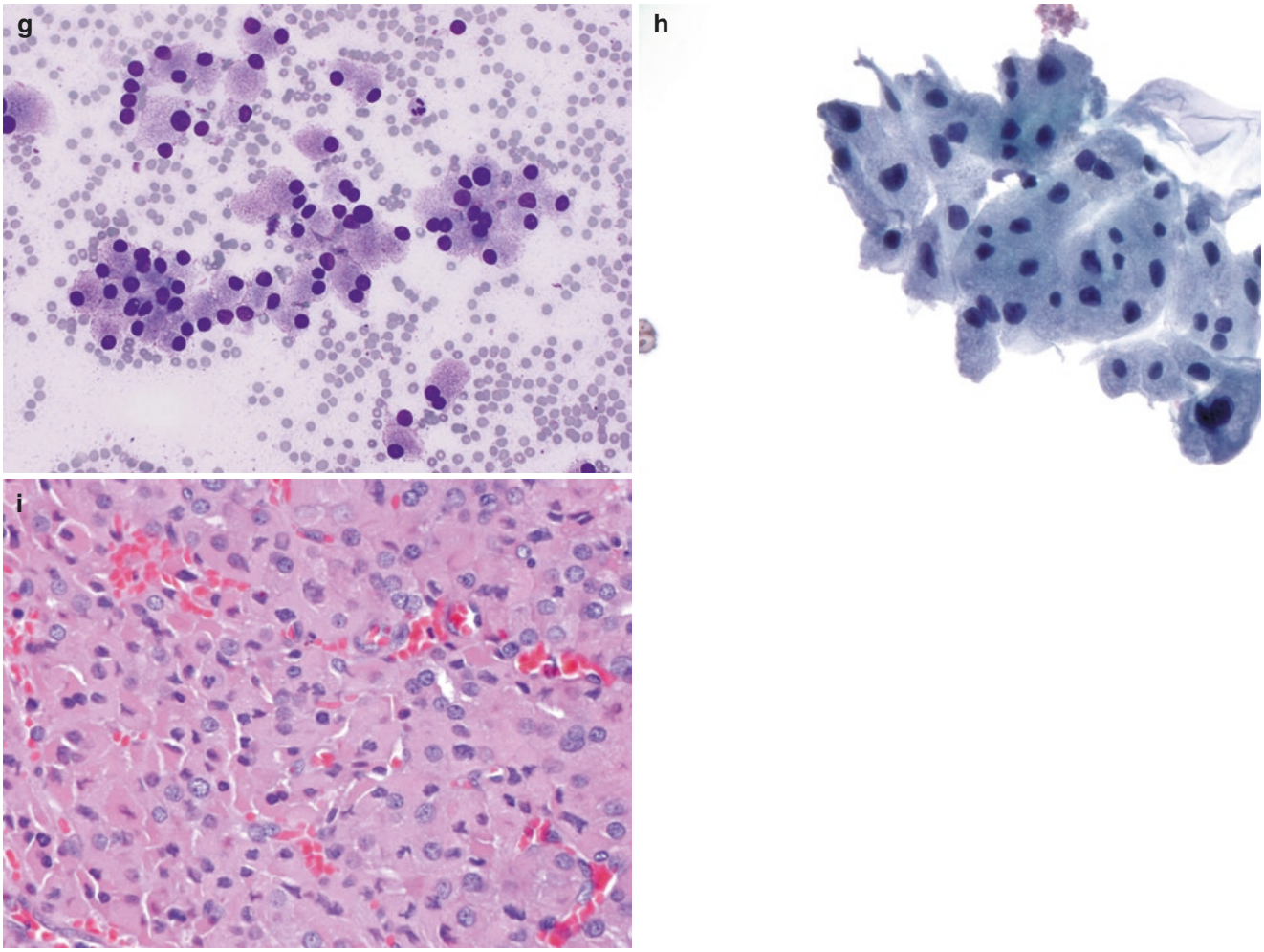


Fig. 10.6 Oncocytic variant of MTC (MTC-OV). (**a**, **b**) CS of MTC-OV show more granular cytoplasm and plasmacytoid nuclei on both DQ-stained CS (**a**) and Pap-stained CS (**b**). (**c**) Same case processed as TP shows similar features. (**d**) Gross image of MTC-OV shows a large (about 4 cm), single, circumscribed, and non-encapsulated tumor with minute areas of hemorrhage. (**e**, **f**) Histologic section of MTC-OV showing oncocytic tumor cells with granular cytoplasm and characteristic salt-and-pepper neuroendocrine chromatin; this notable feature is absent in other oncocytic tumors of the thyroid gland, such as Hürthle cell tumors (H&E stain). (**g**, **h**) This case of Hürthle cell adenoma shows follicular cells with oncocytic cytoplasm in DQ-stained CS (**g**) and Pap-stained TP (**h**). In most cases, it may be difficult to distinguish HCN from MTC-OV on DQ stain. The Pap-stained slides are more helpful in distinguishing HCN from MTC-OV because the nuclear features are well preserved. The nuclei on TP lack the characteristic neuroendocrine pattern of chromatin of MTC and also show nucleoli. Immunostaining for calcitonin and neuroendocrine markers and molecular testing, if performed, will help in rendering a definitive diagnosis. (**i**) Histologic section of Hürthle cell adenoma



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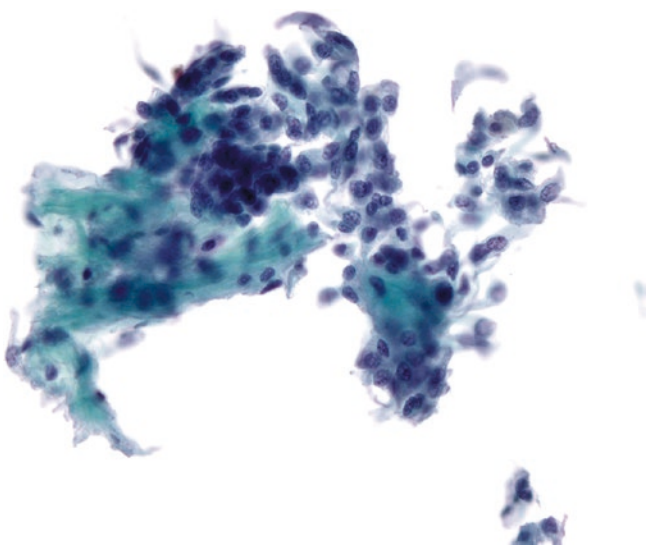

Fig. 10.7 Hyalinizing trabecular tumor (HTT) or adenoma (HTA). HTT or HTA showing loose, cohesive clusters of spindled cells with spindled to oval nuclei, few small INPI, closely associated hyaline material surrounding cells in image. This material can be mistaken for dense colloid. The nuclear pallor, grooves, INPI, and membrane irregularities mimic PTC rather than the neuroendocrine-type pattern of MTC (Pap stain, TP)

Parathyroid Adenoma

- A PTH assay performed on the FNA sample or positive staining for parathyroid hormone on smears or cell block preparations can confirm the presence of parathyroid cells. (*See* Chap. 13 on Parathyroid Gland Cytology.)

Paraganglioma

- MTC may have a paraganglioma-like pattern.
- Paragangliomas are rarely intrathyroidal.
- The salt-and-pepper chromatin and trabecular appearance resemble MTC.
- Fine, metachromatic, neurosecretory granules are noted in the cytoplasm.
- Cell block preparation is helpful for ancillary studies, for a definite distinction: S100 and neuroendocrine markers are positive; staining for calcitonin, TTF-1, and thyroglobulin are negative.
- Lesions are cytokeratin (CK)–negative, although 30% can express it.

Poorly Differentiated Thyroid Carcinoma

- The small cell variant of MTC, which consists of small uniform cells, may be difficult to distinguish from poorly differentiated thyroid carcinoma (PDTC) (Fig. 10.8). (See Chap. 11 for more information.)
- Unlike PDTC, necrosis and increased mitotic activity are usually absent in MTC aspirates.

Anaplastic (Undifferentiated) Thyroid Carcinoma

- The spindle cell pattern of MTC with pleomorphic cells may be misinterpreted as anaplastic thyroid carcinoma.
- Anaplastic thyroid carcinomas generally are more cellular and show nuclear pleomorphism and associated necrosis (Fig. 10.9).

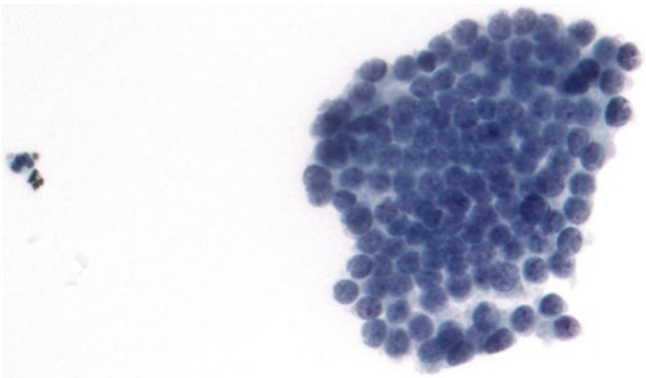

Fig. 10.8 Poorly differentiated thyroid carcinoma. LBP of a case of poorly differentiated thyroid carcinoma, showing a cellular cluster with conspicuous follicular architecture, granular chromatin and nuclei (Pap stain, TP)

- Immunostain for calcitonin may be necessary to confirm the diagnosis.

Metastatic Carcinoma Mimicking MTC

- Metastatic tumors considered in the differential diagnosis include renal cell carcinoma, melanoma, and metastatic neuroendocrine tumors.
- Immunohistochemical stains, as well as an underlying history of tumor, are useful in distinguishing MTC from its metastatic mimics.

Ultrasound features of MTC

- On ultrasonography, MTC appears as a hypoechoic, ovoid to round, solid mass with or without microcalcifications (Fig. 10.10). Lesions are read mostly as "suspicious" for malignancy.

Molecular/Genetic Alterations in MTC; the Role of Molecular Tests

- *RET* gene mutations (chromosome 10)

Management of MTC

- Total thyroidectomy and central lymph node dissection
- Lateral neck dissection may be performed, depending on imaging and calcitonin levels.

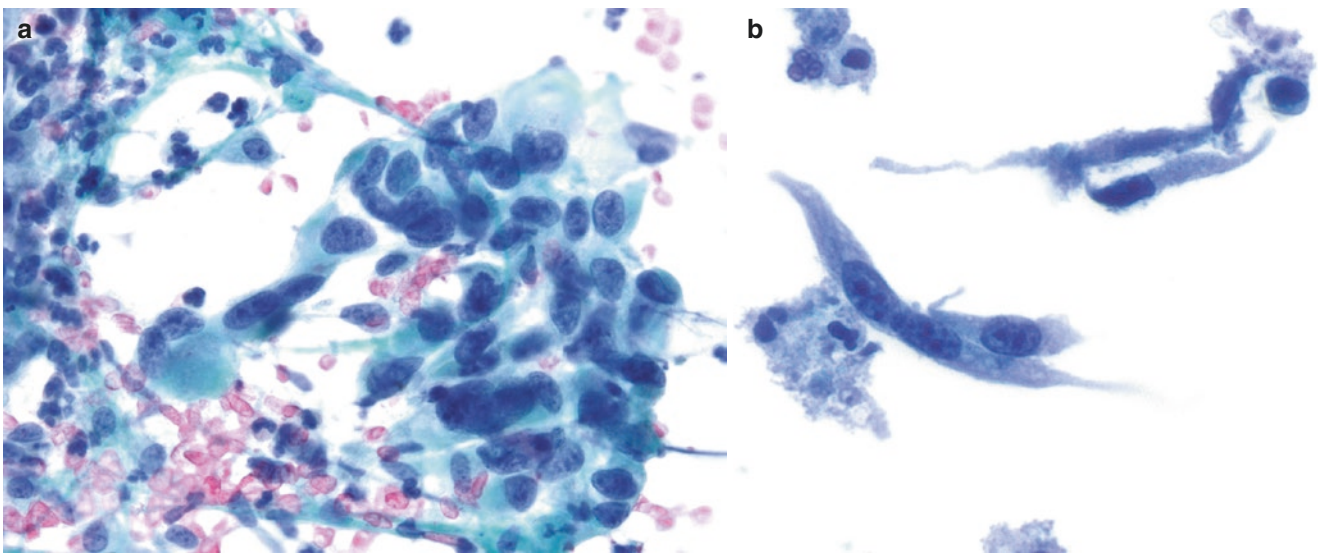

Fig. 10.9 Anaplastic thyroid carcinoma. (**a**, **b**) This case of anaplastic thyroid carcinoma shows nuclear pleomorphism and a chromatin pattern that is not the typical neuroendocrine pattern noted in MTC. Note the coarse chromatin and multiple nucleoli in the enlarged, spindled nuclei (**a**, Pap stain, CS; **b**, Pap stain, TP)

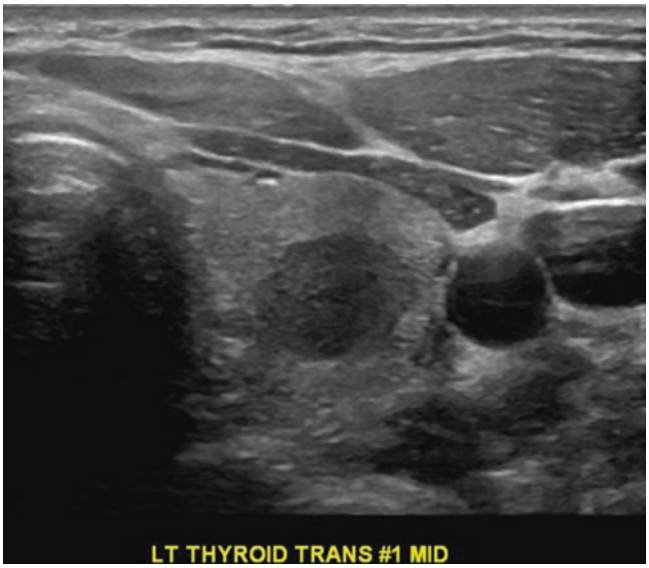

Fig. 10.10 Ultrasound features of MTC. This ultrasound image shows solid internal content, an ovoid to round shape, marked hypoechogenicity, and calcifications, findings suspicious of malignant nodules

- Genetic testing for germline *RET* mutations should be performed in patients with newly diagnosed MTC, according to the recently updated ATA management guidelines (Haugen et al.)
- Tyrosine kinase inhibitors are available for advanced disease.

Suggested Reading

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