Tumors of C Cells

11

Medullary thyroid carcinoma (MTC) comprises 5–10 % of thyroid carcinomas [1]. About 25 % of cases are familial; thus, patients are offered *RET* mutation analysis [2]. MTC occurs in multiple endocrine neoplasia 2A (MEN2A), MEN2B, and familial MTC (FMTC), autosomal dominant disorders due to *RET* mutations [3–7]. MEN2A and FMTC are associated with *RET* mutations of codons 609, 611, 618, 620, and 634 [8, 9]. In FMTC, mutations of codons 768, 790, 791, 804, 844, and 891 are associated with less aggressive disease and a later onset. Most MEN2B *RET* mutations are at codon 918 (>95 %) or 883 (2–3 %). MEN2A is associated with MTC, pheochromocytoma, and parathyroid disease. MEN2B is associated with MTC, pheochromocytoma, mucocutaneous neuromas, ganglioneuromatosis, and marfanoid habitus. MTC usually occurs before pheochromocytoma in MEN2A and MEN2B, and preoperative calcitonin levels may help identify MTC and prevent a hypertensive crisis during surgery [10, 11]. FMTC is not associated with other abnormalities. If a patient is found to have *RET* mutation, relatives are offered testing [12]. Prophylactic thyroidectomy may be performed by age 6 years for MEN2A and by 6 months for MEN2B [10, 13, 14]. Prophylactic thyroidectomy specimens are serially sectioned and immunoperoxidase studies used to evaluate for C-cell hyperplasia, medullary microcarcinomas, and carcinomas. Particular attention is given to the junction of the upper and middle lobes, as this is the area of the highest concentration of C cells. C-cell hyperplasia is not specific for syndrome-associated MTC, as it may be seen in other thyroid tumors and thyroiditis [15, 16]. Sporadic MTC often presents around age 50, whereas syndromic MTC presents earlier. MEN2B MTC may present in infancy or childhood and has been diagnosed in neonates [17]. MEN2A MTC often presents in early adulthood, and FMTC presents at an older age than other syndromic MTCs. Patients diagnosed by biochemical or molecular methods have a better prognosis than those not screened [18]. MTC is radioresistant and chemotherapy resistant, does not take up iodine, and usually is treated by thyroidectomy and node dissection [2]. Diarrhea, bone pain, and flushing often are associated with widely metastatic disease, with a 5-year survival rate of 33.3 % [18]. Patients with persistent or recurrent MTC have a life expectancy of 3.6 years [18]. Compared with less extensive surgery, total or subtotal thyroidectomy is associated with less persistent or recurrent disease and total thyroidectomy with cervical node dissection is associated with fewer reoperations for persistent or recurrent disease [18]. Negative prognostic factors are older age, male sex, clinical (vs. biochemical or molecular) presentation, TNM stage, distant metastases, sporadic (vs. hereditary) occurrence, and less extensive surgery [18].

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C-Cell Hyperplasia

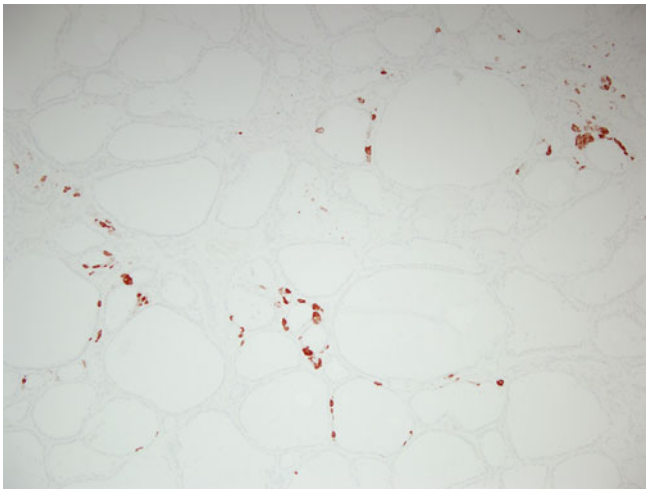

Fig. 11.1 C-cell hyperplasia. C-cell hyperplasia is highlighted with calcitonin immunostain in a prophylactic thyroidectomy. C cells are identified most readily with immunostaining for chromogranin, synaptophysin, or calcitonin. C-cell hyperplasia may be physiologic or neoplastic [15, 19, 20]. Physiologic C-cell hyperplasia may be seen in neonates and elderly people and may be associated with follicular tumors, Hashimoto thyroiditis, hypergastrinemia, or hyperparathyroidism, among other entities [20–22]. Neoplastic C-cell hyperplasia is associated with familial cases of MTC. The presence or absence of C-cell hyperplasia is not used to determine whether a patient with MTC has familial or sporadic disease. This determination is made by clinical evaluation, patient and family history, and *RET* mutation testing

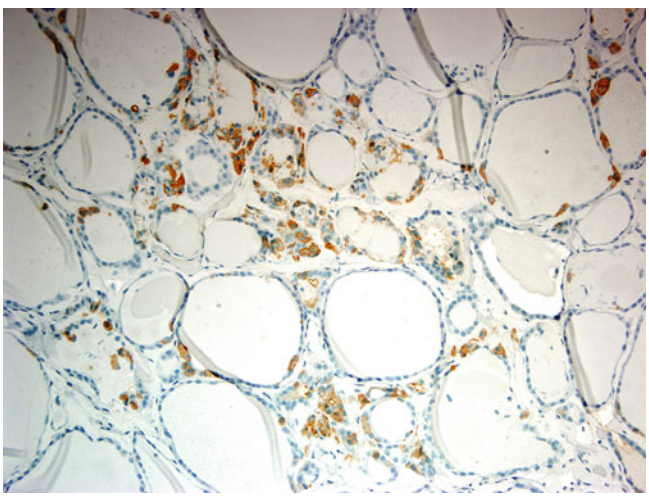

Fig. 11.2 C-cell hyperplasia. C-cell hyperplasia is highlighted with calcitonin immunostain in this prophylactic thyroidectomy specimen. Extensive sectioning, often with immunoperoxidase, with special emphasis in the middle to upper portions of the lobes is recommended to identify C-cell hyperplasia and medullary microcarcinomas. The growth pattern may be diffuse or nodular; nodular growth is more common and more prominent with neoplastic C-cell hyperplasia [15, 19–23]. The definition of C-cell hyperplasia varies, but the term generally refers to an increase in the total mass of C cells in the thyroid. One definition of diffuse hyperplasia is at least 50 C cells per low-power field bilaterally [19, 20]. Nodular C-cell hyperplasia has been described as bilateral clusters of more than six C cells in several foci [1]

Medullary Thyroid Microcarcinoma

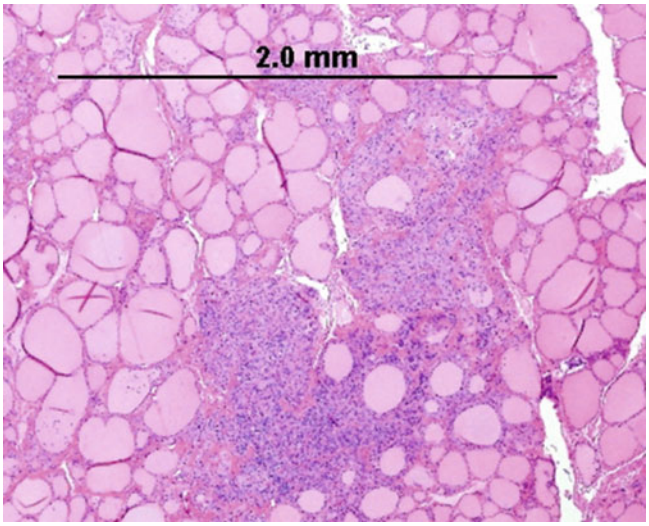

Fig. 11.3 Medullary thyroid microcarcinoma. Medullary thyroid microcarcinomas are defined as measuring 1 cm or less. In a comparison of 16 familial and 34 sporadic medullary microcarcinomas, familial tumors occurred at a younger age (mean 32 vs. 58 years) and were more often bilateral (68.8 % vs. 8.8 %), multifocal (81.3 % vs. 8.8 %), and accompanied by C-cell hyperplasia (100 % vs. 71 %) than sporadic tumors [24]. In that study, only tumors with desmoplastic stroma had lymph node metastases (8 of 50) [24]. The smallest tumor with lymph node metastasis was 3 mm [24]. From a national database of 357 sporadic medullary carcinomas larger than 1 cm, 149 familial microcarcinomas, and 80 sporadic medullary microcarcinomas, nodal metastases were more frequent with multifocal than unifocal tumors [25]. When 126 hereditary and 107 sporadic medullary microcarcinomas were stratified by tumor diameter in 2-mm increments and by biochemical cure, the incidence of nodal metastasis increased with increasing tumor size and biochemical cure rates declined [26]. The strongest predictors of a failure to achieve normal serum calcitonin were positive nodes (79 % vs. 11 % in hereditary and 79 % vs. 12 % in sporadic cases) and the number of involved nodes (6.6 vs. 0.3 in hereditary and 8.8 vs. 0.4 nodes in sporadic cases) [26]

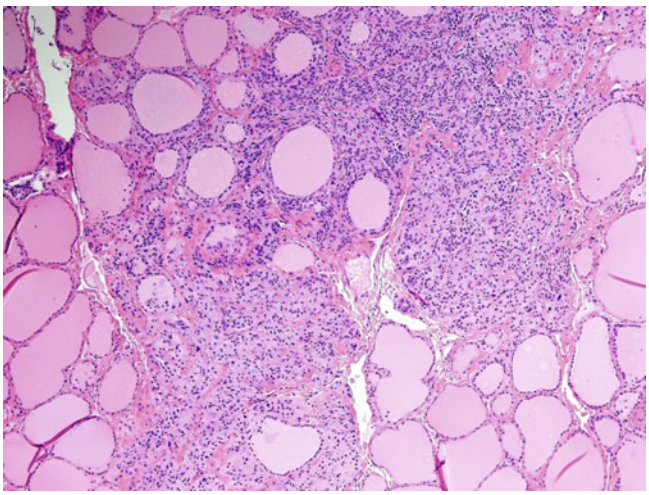

Fig. 11.4 Medullary thyroid microcarcinoma. Medullary thyroid microcarcinoma from a prophylactic thyroidectomy. In a study of 42 prophylactic thyroidectomies, C-cell hyperplasia was identified in 36 cases (multifocal in 30 and bilateral in 23), medullary microcarcinoma in 29 cases (1 had node metastasis), and medullary macrocarcinoma in 1 case [27]. Most of the microcarcinomas (83 %) had a solid growth pattern with round, polygonal, spindled, or plasmacytoid cells and desmoplastic stroma (100 %), and a subset (41 %) had focal amyloid [27]. Among 310 medullary microcarcinomas from the Surveillance, Epidemiology, and End Results database from 1988 to 2007, the mean tumor size was 5.7 mm, 31 % of tumors were multifocal, 7.8 % of tumors had extrathyroid extension, and 37 % of patients (65 of 176) with lymph nodes removed had metastases [28]. Ten-year survival rates with localized, regional, and distant disease were 96, 87, and 50 %, respectively [28]. Extrathyroid extension and tumor size were associated with lymph node metastases. The probability of lymph node metastases in tumors ≤5 mm was 23 %, increasing for tumors larger than 5 mm [28]

Medullary Thyroid Carcinoma

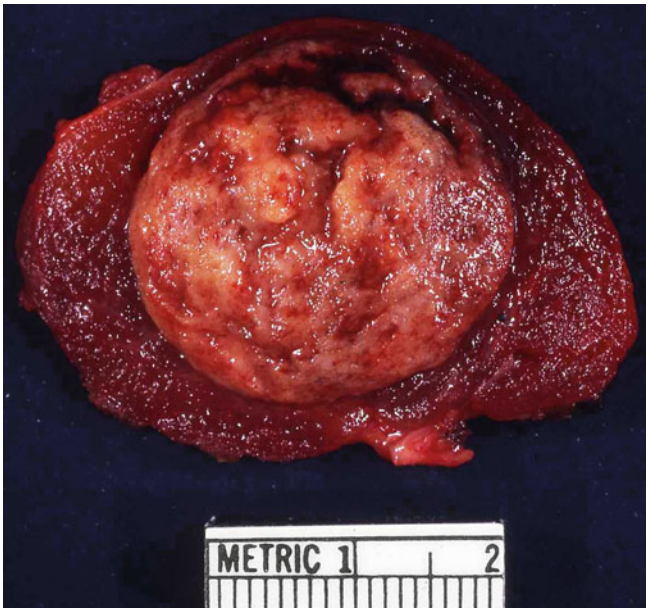

Fig. 11.5 Medullary thyroid carcinoma. This MTC forms a firm white mass in the thyroid. In sporadic cases, these tumors often are single tumors. Although MTCs in MEN2B, MEN2A, and FMTC are histologically identical to sporadic tumors, syndrome-associated tumors often are bilateral and multicentric [1, 29]. Syndromic MTCs often are associated with C-cell hyperplasia, but C-cell hyperplasia may occur with other thyroid tumors and with lymphocytic thyroiditis [15, 16]. Thus, determining whether MTC is syndrome associated is done by germline genetic testing for *RET* mutation

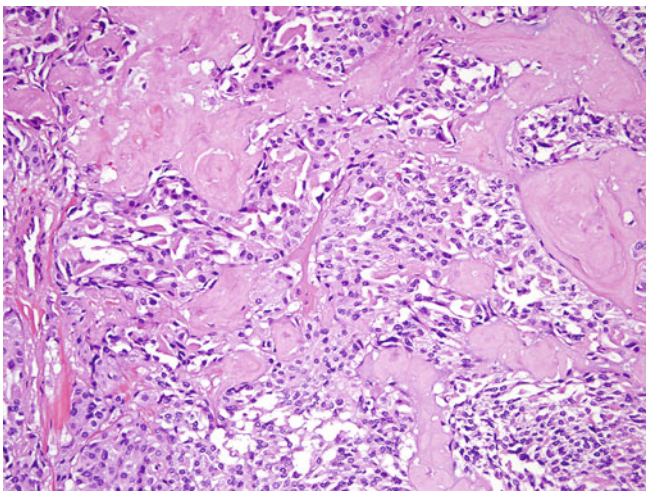

Fig. 11.6 Medullary thyroid carcinoma, amyloid. This MTC has epithelial and spindle tumor cells and prominent amyloid. Although amyloid is a helpful feature in recognizing MTC, it may be seen in the thyroid incidentally, as a secondary finding, in systemic amyloidosis, in association with lymphoproliferative and plasmacytic disorders, and in amyloid goiters. The amyloid in MTC shows apple-green birefringence with Congo red and is positive for calcitonin. The absence of colloid is helpful in identifying MTC

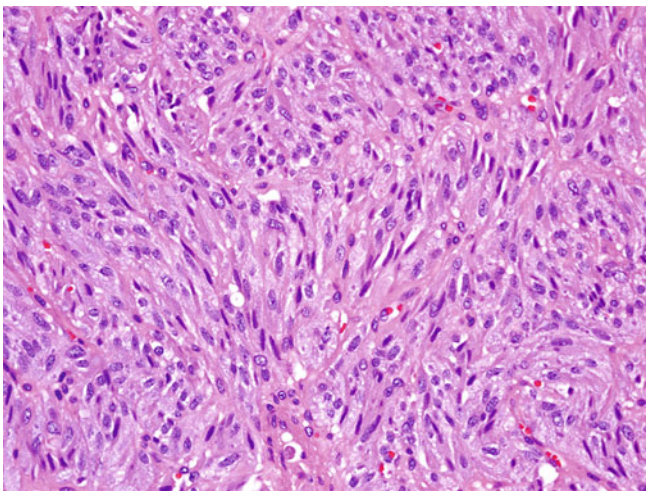

Fig. 11.7 Medullary thyroid carcinoma. Spindle cells are prominent in this MTC. MTCs may have a variety of cytomorphologies (spindle, epithelioid, oxyphilic, clear), and awareness of these possibilities enables the diagnosis. Spindle cells are particularly important. Whenever spindle cells are identified in a thyroid tumor, MTC must be ruled out. Spindle cells in the thyroid always raise the suspicion of MTC

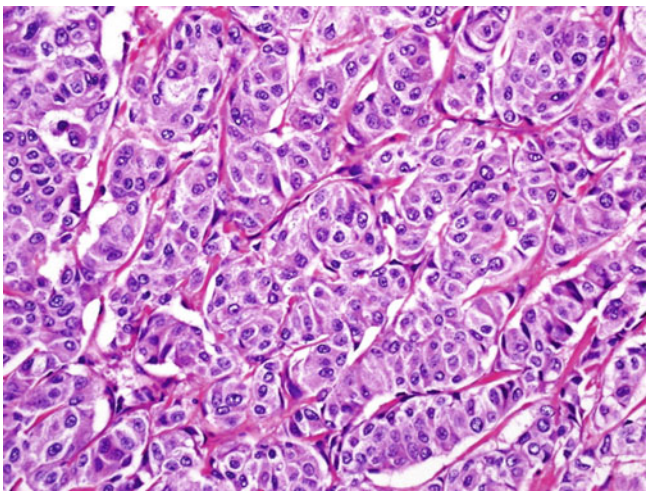

Fig. 11.9 Medullary thyroid carcinoma. A nested pattern of growth predominates in this MTC. Various growth patterns may be seen in these tumors. The lack of colloid is a clue to MTC

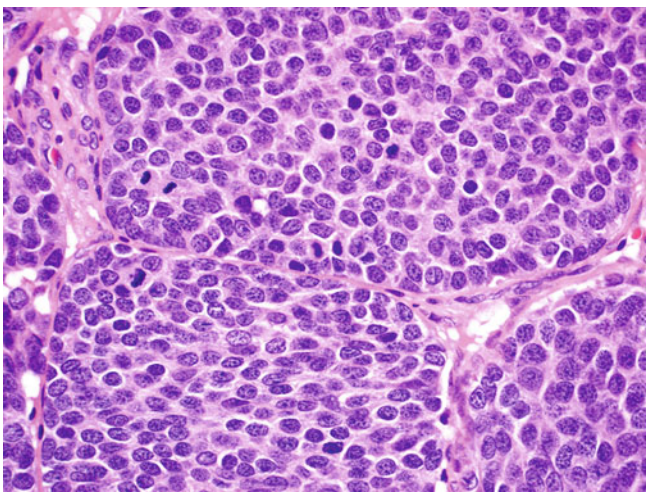

Fig. 11.8 Medullary thyroid carcinoma. Epithelioid cells predominate in this MTC. The cells have amphophilic cytoplasm and neuroendocrine nuclear features with stippled chromatin

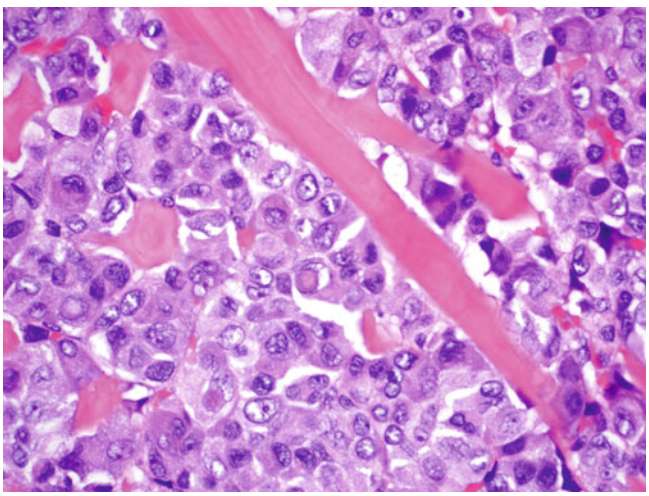

Fig. 11.10 Medullary thyroid carcinoma. Intranuclear pink holes may be seen in MTC. This feature often is emphasized in papillary thyroid carcinoma (PTC), but it is not specific. Intranuclear pink holes may be seen in MTC, PTCs, occasional Hurthle cell thyroid neoplasms, and the parathyroid

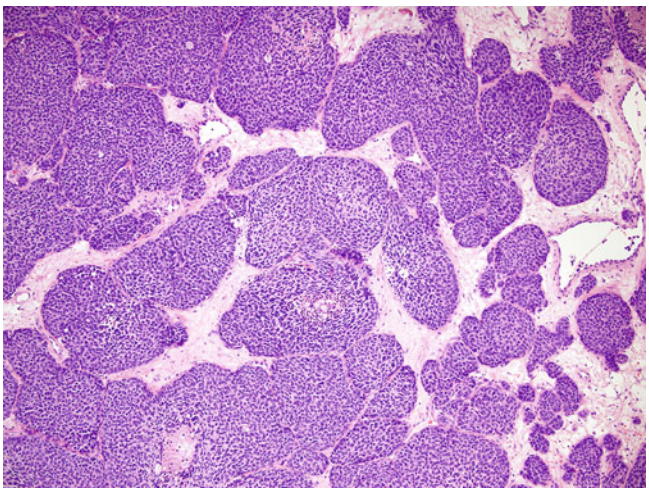

Fig. 11.11 Medullary thyroid carcinoma. A solid, nested, and somewhat insular growth pattern may be seen in MTC. Any thyroid tumor lacking colloid should raise the possibility of MTC

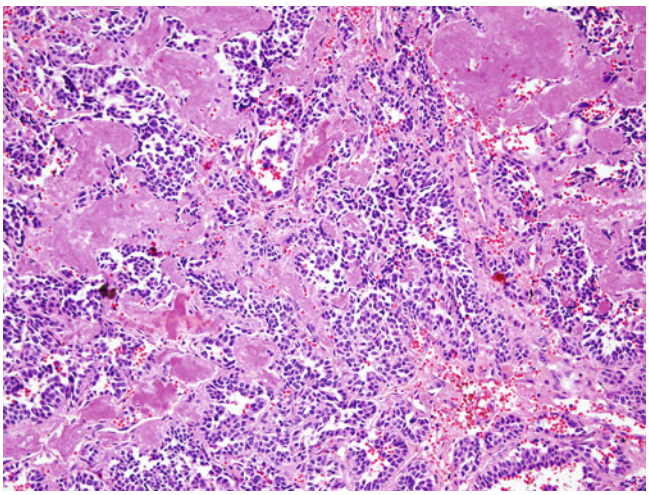

Fig. 11.13 Medullary thyroid carcinoma. This MTC is composed of epithelial cells with epithelioid and spindle morphology. Areas of amyloid deposition also are present

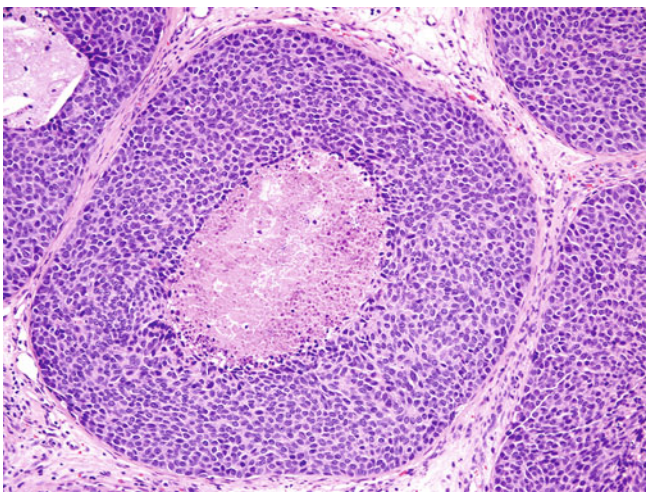

Fig. 11.12 Medullary thyroid carcinoma. Solid growth is seen in this MTC with an area of necrosis. Recognizing the neuroendocrine differentiation of the tumor is important to avoid mistaking it for a follicular thyroid carcinoma or a poorly differentiated carcinoma

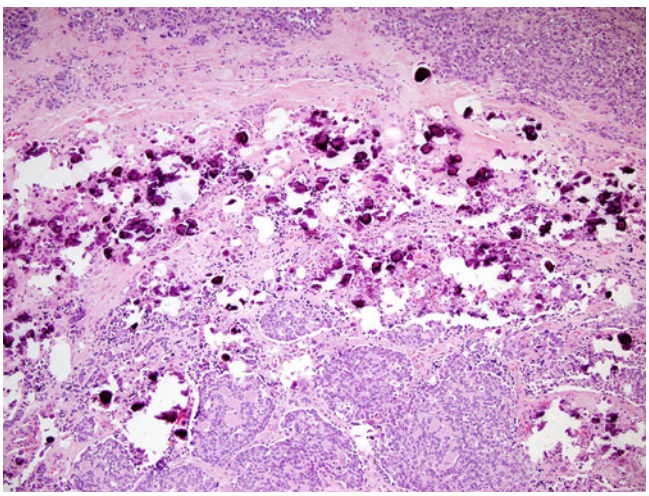

Fig. 11.14 Medullary thyroid carcinoma. Calcifications may be seen in MTC; they often are stromal and may be associated with amyloid

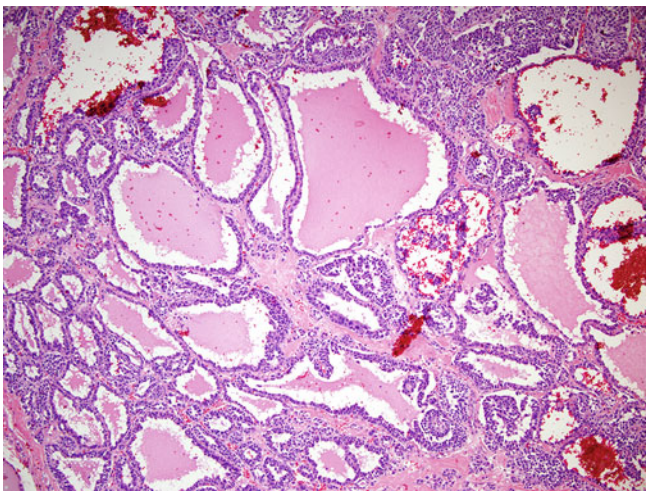

Fig. 11.15 Medullary thyroid carcinoma. Recognizing MTC with a follicular or glandular growth pattern may be very difficult. A high index of suspicion is needed, and immunostains may be helpful in difficult cases, as MTCs are positive for chromogranin, synaptophysin, and calcitonin and negative for thyroglobulin

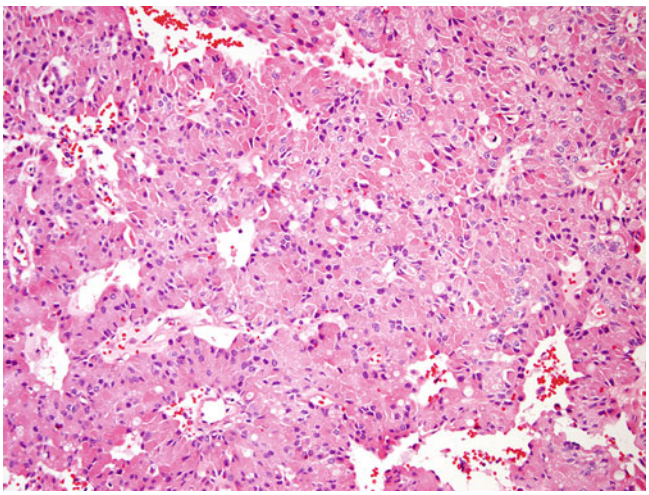

Fig. 11.17 Medullary thyroid carcinoma. Oxyphilic MTCs may be mistaken for Hurthle cell neoplasms of the thyroid. The large polygonal cells with abundant eosinophilic cytoplasm may be indistinguishable from Hurthle cells. Ultrastructural studies identified mitochondrion-rich cells containing round neurosecretory granules [30]. The lack of colloid is a clue to the diagnosis of this histologic variant of MTC

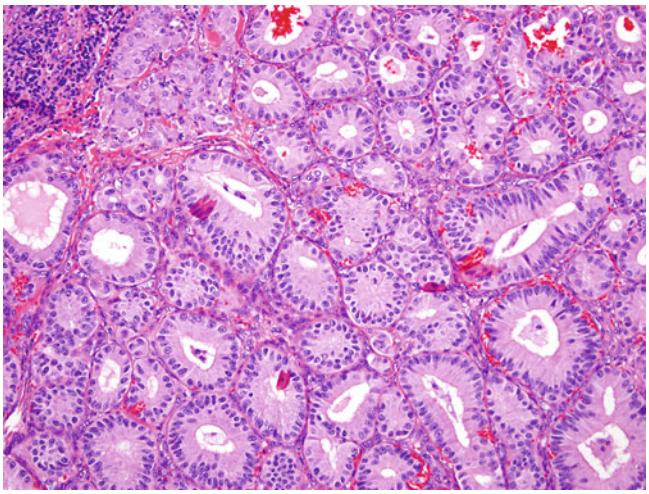

Fig. 11.16 Medullary thyroid carcinoma. This MTC has a glandular or acinar growth pattern. Recognizing the wide spectrum of histologic patterns that may be seen in MTC is important in recognizing these tumors

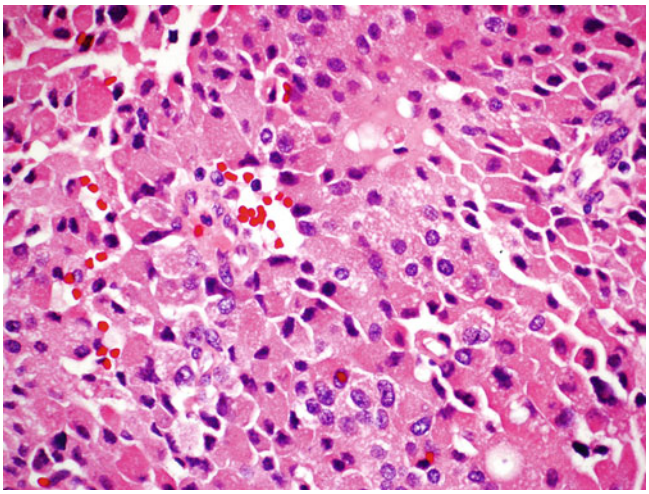

Fig. 11.18 Medullary thyroid carcinoma. The oxyphilic variant of MTC may be difficult to recognize if one is not familiar with this histologic subtype. Mistaking the oxyphilic variant of MTC for a Hurthle cell neoplasm is particularly problematic because MTC is a radioresistant tumor and is familial in 25 % of cases

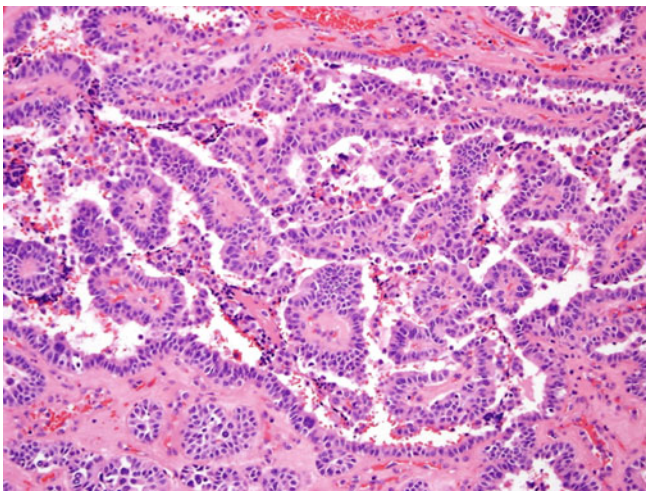

Fig. 11.19 Medullary thyroid carcinoma. The papillary architectural pattern in MTC may present a difficult diagnostic problem. Both papillary carcinomas and MTC may have intranuclear pink holes. Other than the pink holes, MTCs have nuclear features different from those of papillary carcinomas, as the nuclei of MTCs have stippled neuroendocrine chromatin and may show areas of spindling and amyloid

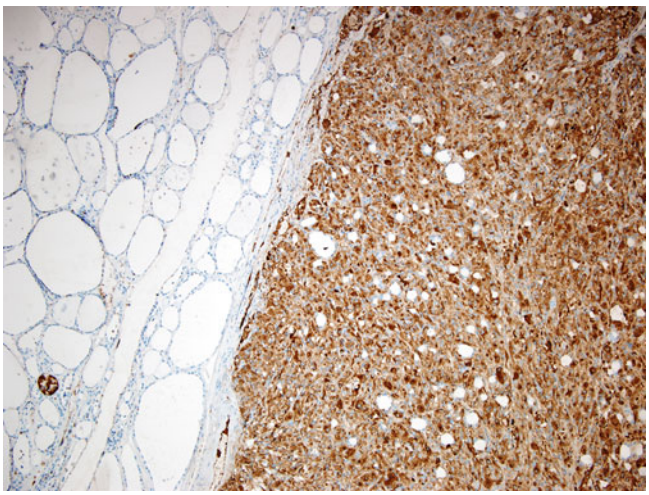

Fig. 11.21 Medullary thyroid carcinoma. Neuroendocrine markers such as chromogranin, as in this photograph, and synaptophysin are helpful in identifying neuroendocrine differentiation in a tumor. These markers are helpful in separating MTC from folliculogenic thyroid carcinomas, which do not express these markers. Of the commonly used neuroendocrine markers, chromogranin is the most specific. Parathyroid tumors are positive for neuroendocrine markers but also are positive for parathyroid hormone and negative for thyroid transcription factor 1 (TTF1). Neuroendocrine lung tumors are positive for neuroendocrine markers and TTF1 but usually are negative for calcitonin

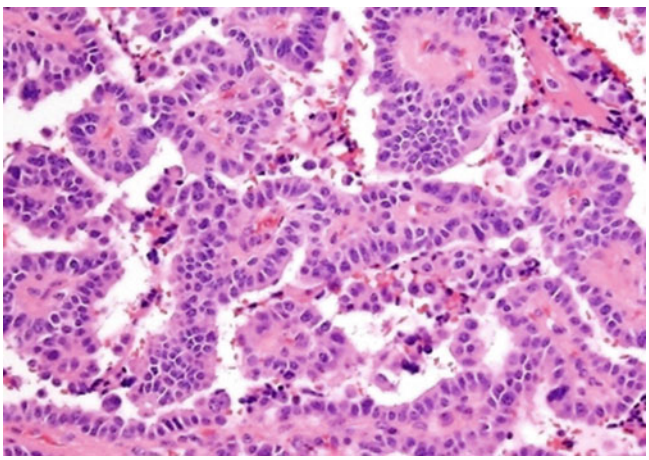

Fig. 11.20 Medullary thyroid carcinoma. Recognizing that MTCs may have papillary growth is crucial to considering it in the differential diagnosis of thyroid tumor with papillary architecture. Both MTC and PTC may have pink holes, but MTC lacks colloid and has stippled neuroendocrine chromatin. In difficult cases, immunoperoxidase studies may be helpful, as MTCs are positive for chromogranin, synaptophysin, and calcitonin and negative for thyroglobulin, whereas PTCs express thyroglobulin and are negative for chromogranin, synaptophysin, and calcitonin

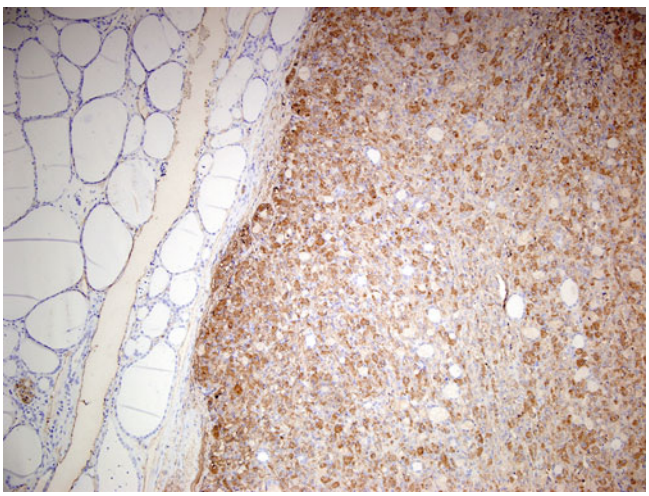

Fig. 11.22 Medullary thyroid carcinoma. Calcitonin is positive in MTC, and patients with MTC usually have elevated serum calcitonin levels. Atypical laryngeal carcinoids also express calcitonin, chromogranin, and synaptophysin, although calcitonin staining may be focal. Atypical laryngeal carcinoid is negative for TTF1. Atypical laryngeal carcinoid may be associated with elevated serum calcitonin levels, but the levels generally are lower than those in patients with MTC. Other tumors may express calcitonin aberrantly

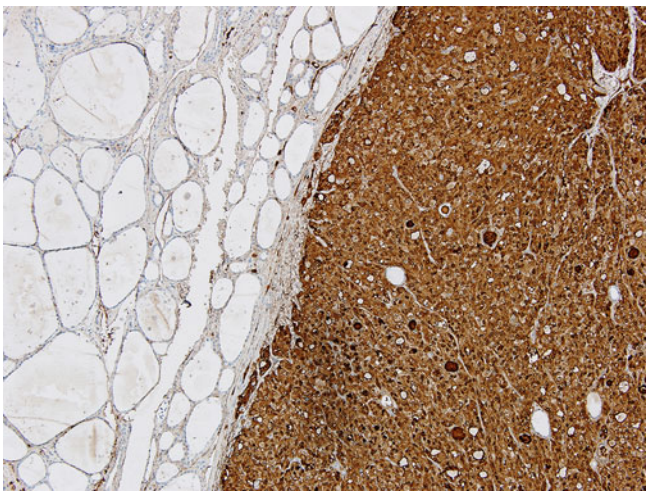

Fig. 11.23 Medullary thyroid carcinoma. Carcinoembryonic antigen (CEA) is positive in MTC. Atypical laryngeal carcinoids also are positive for CEA, chromogranin, synaptophysin, and calcitonin, but they are negative for TTF1 and calcitonin staining often is focal

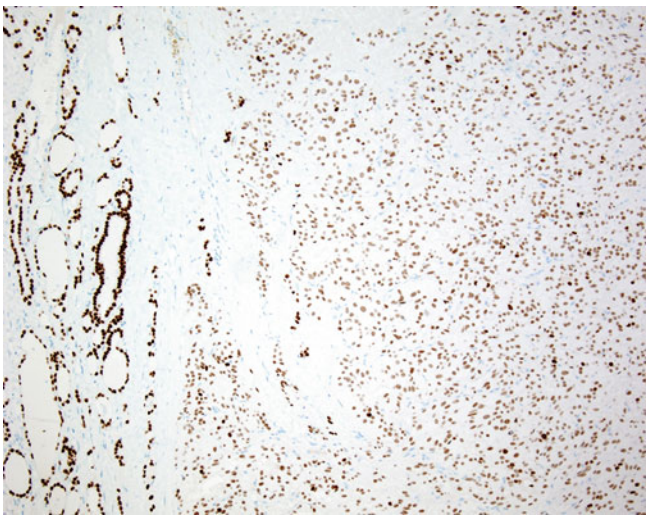

Fig. 11.24 Medullary thyroid carcinoma. MTCs are positive for TTF1, although the staining is weaker than in the subjacent thyroid parenchyma. It is unclear why medullary carcinomas are positive for TTF1, as embryologically they are distinctly different from folliculogenic tumors. The TTF1 immunopositivity, although weaker than in follicular neoplasms, is helpful in differentiating MTC from parathyroid and other neuroendocrine tumors. Neuroendocrine lung tumors usually are positive for TTF1 but generally are negative for calcitonin

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