Rare Papillary Thyroid Carcinomas

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Introduction

Papillary thyroid carcinoma (PTC) is a malignant epithelial tumour showing evidence of follicular cell differentiation and a set of distinctive nuclear features. Following the criteria of the last WHO classification, either papillae or invasion is required for a diagnosis of PTC [1]. Although the diagnosis of PTC is not usually problematic, numerous variants of PTC have been recognized,

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sometimes raising diagnostic difficulties. In the follicular-patterned tumours with PTC nuclear features, the diagnosis is based primarily on the identification of invasion signs and will not be addressed in this book [1, 2]. It is particularly important to recognize those variants of PTC that are associated with clinical aggressiveness, as is the case with tall cell variant, columnar cell variant, the recently described hobnail (micropapillary) variant of PTC and PTC displaying diffuse nuclear immunoreactivity for P53. Since the hobnail (micropapillary) variant of PTC is the rarest form of the aforementioned three morphologic variants and its diagnosis is more difficult, it will be specially addressed in this chapter, together with other (very) unusual forms of PTC.

Hobnail (Micropapillary) Variant of Papillary Thyroid Carcinoma

Hobnail (micropapillary) variant of PTC has been recently defined in the WHO classification as a rare variant requiring more than 30% of cells with hobnail features [1]. Because hobnail histology is more prevalent than micropapillary features, and the hobnail features appear to be more important for the diagnosis and prognosis of these tumours, hobnail variant (HV) of PTC is the preferred designation [3]. The prevalence of HV of PTC ranges from 0.2 to 1.2% of all PTCs [3–5].

This aggressive tumour is characterized by an advanced stage at presentation, with more than half of cases diagnosed in stages III or IV [3, 4, 6–8]. Regional lymph node metastases are present in more than 70% of cases, and distant metastases in about 30% of cases, mainly to the lung and bones [3–5, 7–10]. Extrathyroidal extension is seen in 70% and local tumour recurrence in about 25% of patients [3–8, 10]. The HV of PTC is prone to progression to undifferentiated carcinoma, thus confirming its aggressiveness [8]. For treatment, see Chap. 7.

Macroscopically, these tumours are usually large, being multifocality detected in about half of the cases [3–12]. The HV of PTC is characterized histopathologically by a combination of hobnail and micropapillary patterns [1, 4, 13] (Fig. 2.1). The hobnail cell appearance exhibits a peculiar loss of polarity in which the tumour cells lining the papillary or follicular structures display a high nuclear/cytoplasmic ratio with the nuclei located in the middle or apex of the cytoplasm. In the micropapillary areas, the neoplastic cells are loosely arranged in small clusters lacking fibrovascular cores coexisting with micropapillary structures usually lined by cuboidal, flat or hobnail cells indicating loss of polarity and cohesiveness (Fig. 2.2). HV of PTC typically shows a variable combination of papillary and follicular growth patterns and many clusters of hobnail cells that often show moderate to rarely high nuclear pleomorphism (Fig. 2.3), prominent nucleoli and

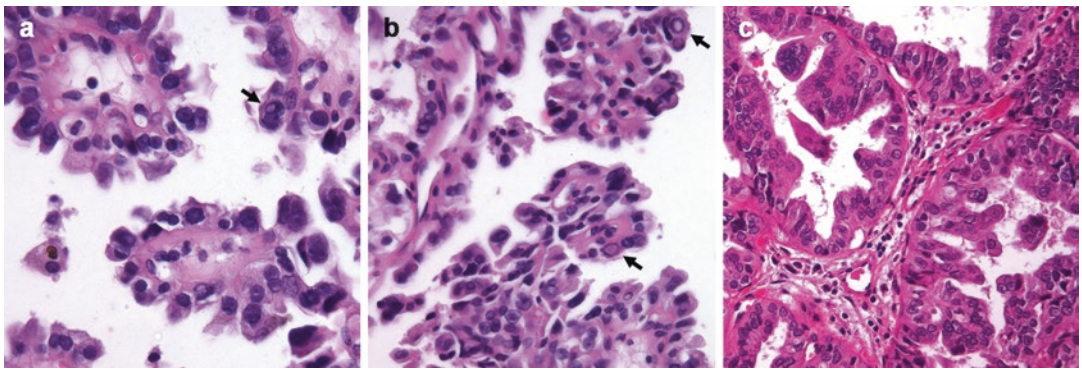


Fig. 2.1 Hobnail (micropapillary) variant of papillary thyroid carcinoma. This variant typically shows a variable combination of papillary (**a**), micropapillary (**b**) and follicular growth pattern (**c**). Both the papillae and the follicles are lined by hobnail cells with dark chromatin. Isolated nuclei with nuclear clarification and pseudoinclusions can also be seen (*arrows*). In some cases, the cytoplasm is abundant and eosinophilic (**c**)

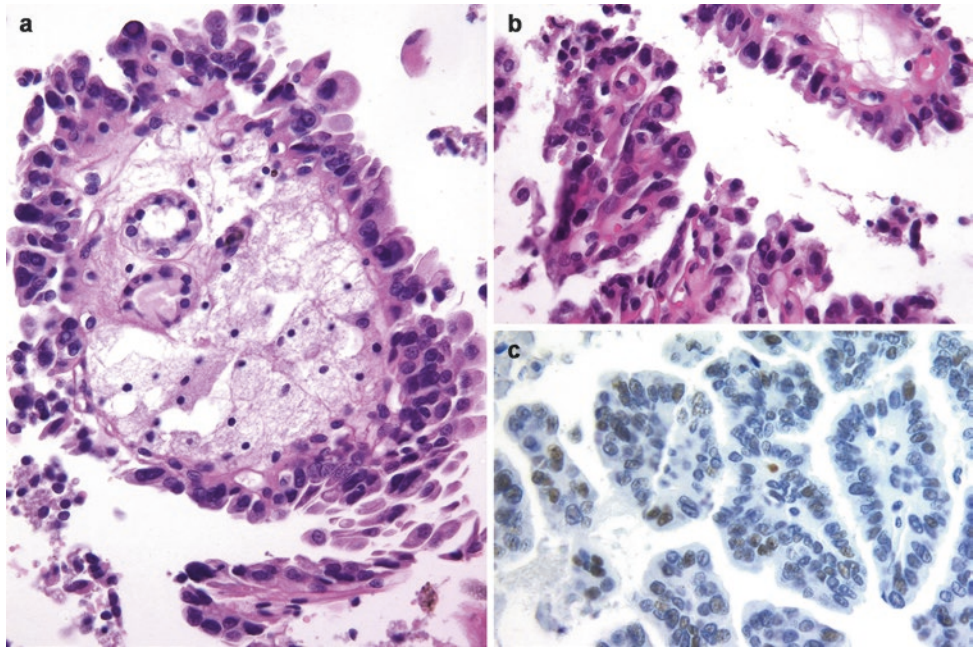


Fig. 2.2 Hobnail (micropapillary) variant of papillary thyroid carcinoma. In this variant, hobnail cells are usually associated with a micropapillary pattern of growth evidencing a loss of polarity and cohesiveness (**a**, **b**). In contrast to what occurs in classic papillary carcinoma, nuclear p53 immunoexpression is usually found in this variant (**c**)

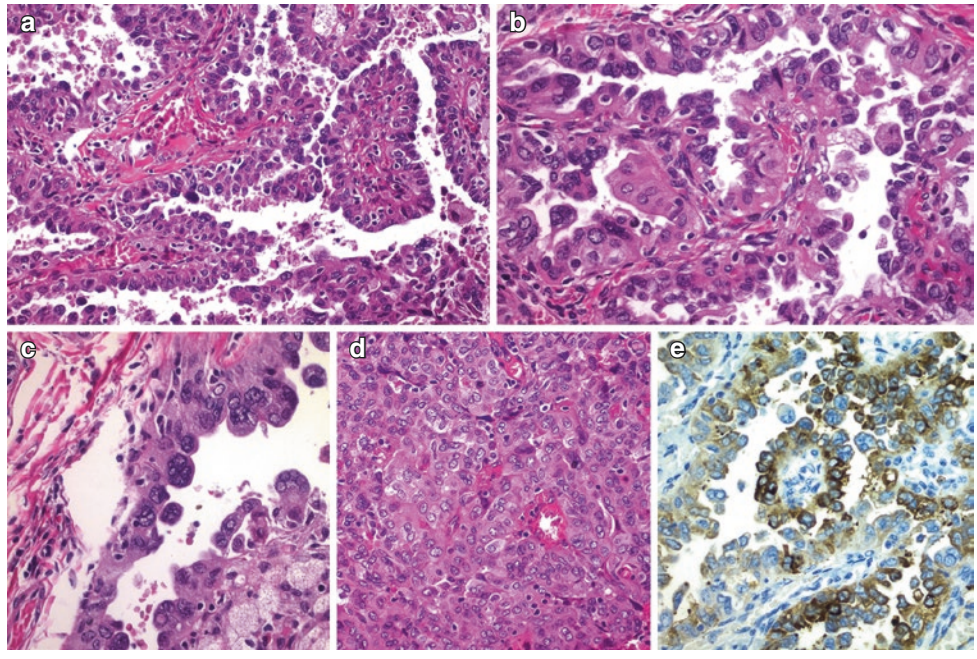


Fig. 2.3 Hobnail (micropapillary) variant of papillary thyroid carcinoma. This case showed in addition to papillary areas with typical hobnail cells (**a**, **b**), tumour cells with nuclear pleomorphism (**c**) and solid growth pattern areas (**d**). Tumour cells showed positivity for thyroglobulin (**e**) (Courtesy of Olga Prieto Gómez, Pontevedra, Spain)

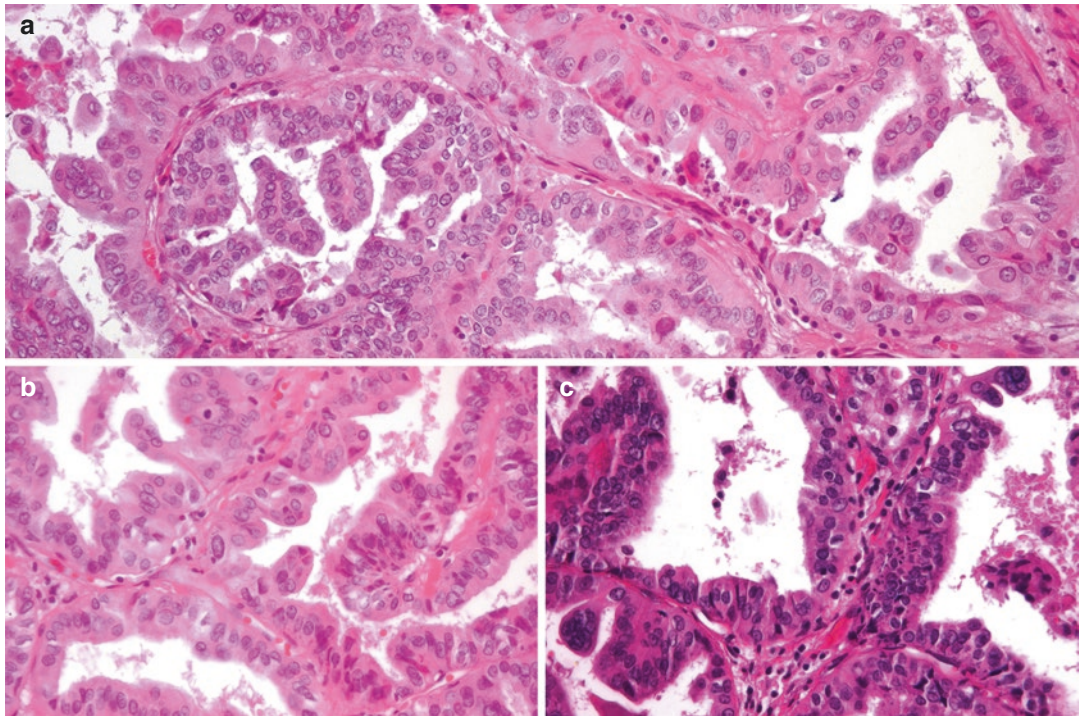


Fig. 2.4 Hobnail (micropapillary) variant of papillary thyroid carcinoma. In the three microscopic photographs of this same case of hobnail variant of PTC, micropapillary pattern of growth coexist with tall/columnar pattern, tumour cells showing tall, dense eosinophilic (oncocytic) cytoplasm with mild (tall cell like) or prominent nuclear stratification (columnar cell like) (**a**–**c**)

dark chromatin [3, 8, 9]. Typical nuclear features of PTC are present but can be focal (Fig. 2.1). The cytoplasm is usually abundant and eosinophilic; there are cases with extensive clear cell change due to accumulation of glycogen [12] or with true Hürthle (oncocytic) cells by accumulation of abnormal mitochondria [14]. The typical areas of HV of PTC can be mixed with aggressive histologic variants such as tall cell, columnar cell and/or trabecular/solid variant in varying proportions [5, 7, 8] (Figs. 2.4 and 2.5).

Mitotic figures are more frequent than in conventional PTC [3–6, 9, 10]. The Ki-67 index is about 5–10% [3, 7, 8]. Foci of necrosis were detected in about 5% of cases and lymphovascular invasion is seen in more than half of the cases. Some papillae may have stalks composed of loose myxoid stroma or may contain lymphocytes or foamy macrophages (Fig. 2.2). Psammoma bodies are rarely seen. Thyroiditis and nodular hyperplasia in the remaining thyroid tissue have been described in some cases. Coexistence of small foci of undifferentiated carcinoma has been reported in two cases, and tumour progression from HV of PTC to undifferentiated carcinoma either in the tumour recurrence or in metastases can also been seen [4] (Fig. 2.6). Although hobnail features are more commonly observed in association with

Fig. 2.6 Hobnail (micropapillary) variant of papillary thyroid carcinoma. In this case with typical morphology of hobnail variant in the primary thyroid tumour (**a**), liver metastasis showed two neoplastic components: columnar cell papillary thyroid carcinoma areas (**b**), positive for thyroglobulin (**d**), merging with solid areas composed of undifferentiated round cells (**c**) with negativity for thyroglobulin but showing positivity for thyroid transcription factor (TTF-1) (**e**). See [9] for additional details

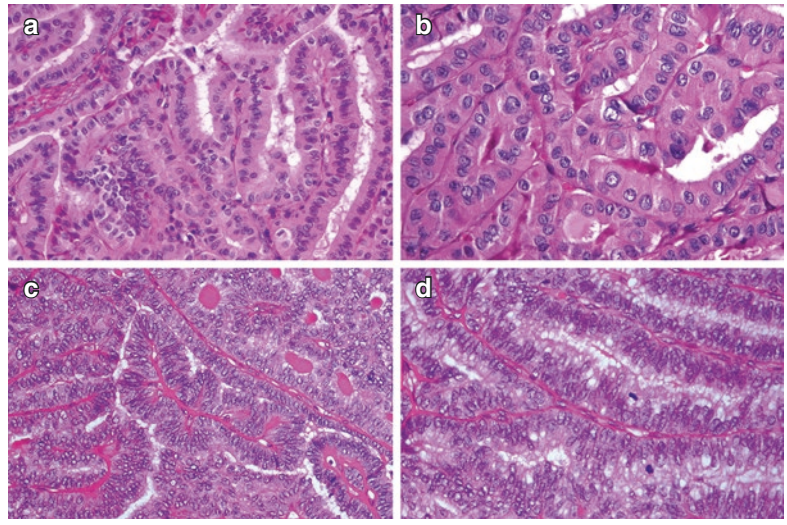
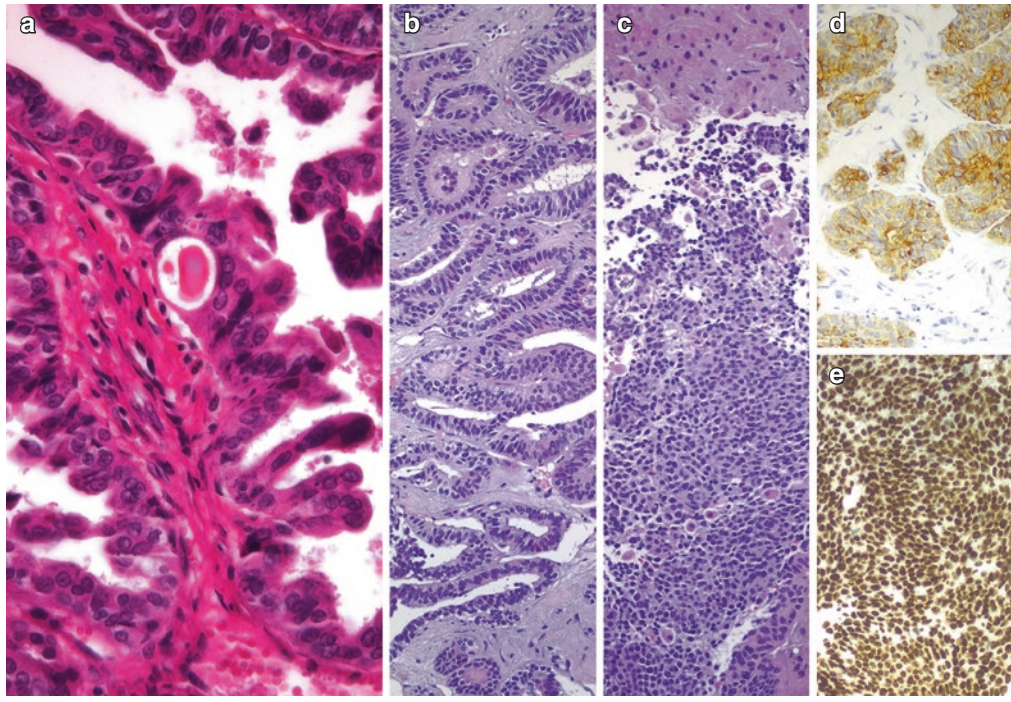


Fig. 2.5 Tall and columnar cell variants of papillary thyroid carcinoma. Hobnail variant of papillary thyroid carcinoma (PTC) can be mixed with other aggressive histologic variants such as tall cell and columnar cell variants in varying proportions. However, by definition, tall cell variant of PTC is made by cells that are two to three times taller than wide and which show abundant eosinophilic cytoplasm (oncocytic) (**a**, **b**). Typical nuclear features of papillary carcinoma are present, and nuclear pseudoinclusions are usually easily found (**b**). Since tall cell areas are frequently present in otherwise classic PTC, at least 30% of all tumour cells are reasonably required for the diagnosis of tall cell variant of PTC. Columnar cell variant of PTC is composed of columnar cells with marked pseudostratification that, at variance with the tall cell variant, lack typical nuclear features of PTC (**c**, **d**). The neoplastic cells show occasional clear cytoplasm reminiscent of an endometrioid adenocarcinoma (**d**), and coexistence of round tubular follicles with prominent nuclear pseudostratification may mimic an intestinal adenocarcinoma. Tall and columnar cell variants of PTC are both positive for thyroglobulin but lack hobnail features and micropapillary growth pattern



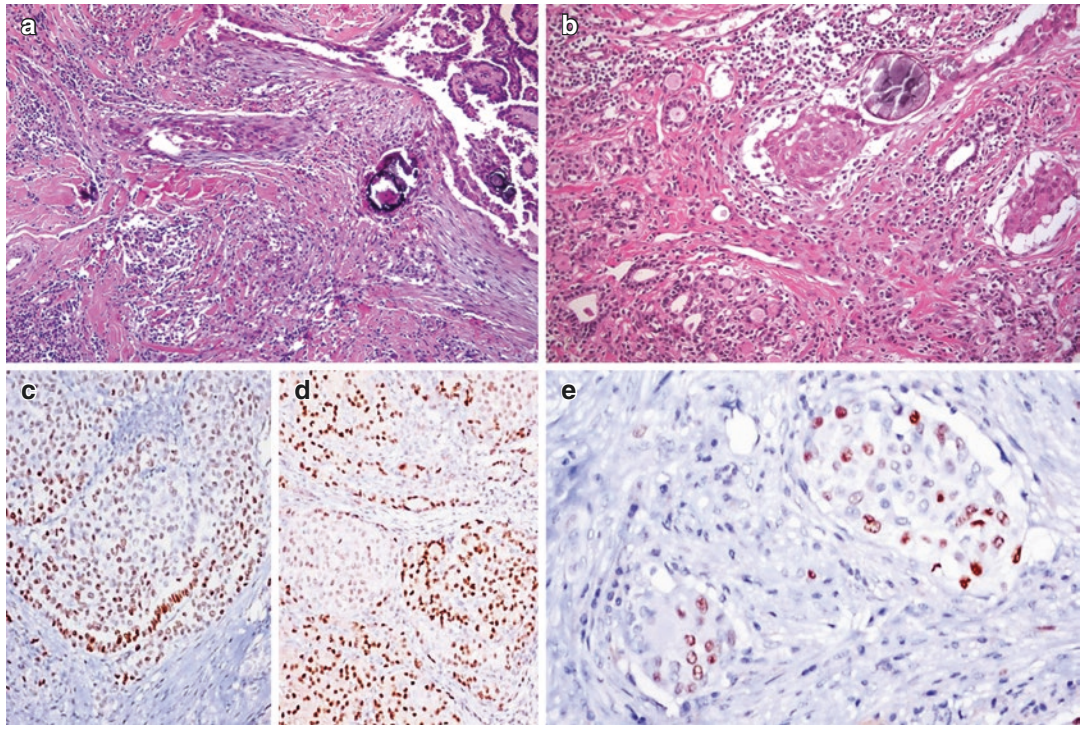


Fig. 2.7 Diffuse sclerosing variant of papillary thyroid carcinoma. In this variant there is diffuse involvement of one lobe or of the entire gland characterized by dense sclerosis, numerous psammoma bodies, papillary structures, prominent squamous metaplasia and background changes of chronic lymphocytic thyroiditis (**a**, **b**). Papillary formations partially lined by hobnail cells are typically seen (**a**). Tumour cells are positive for TTF1 (**c**), PAX8 (**d**) and p63 (**e**)

poorly differentiated thyroid carcinoma (PDTC) (22%) than with PTC [5] (1.3%), differential diagnosis between HV of PTC and PDTC should be made according to the Turin criteria [15] (see Chap. 4). Interestingly, numerous small papillary formations partially covered with hobnail cells are typically seen in the diffuse sclerosing variant of PTC, but in this variant, the papillae are located within intrathyroidal cleft-like spaces, associated with extensive squamous metaplasia, large number of psammoma bodies, lymphocytic thyroiditis and prominent fibrosis [1] (Fig. 2.7). Hobnail-like features may also occur as degenerative changes in cystic areas, but in this setting, the lesions do not display an infiltrative component and lack typical nuclear features of PTC.

Tumour cells are immunoreactive for thyroglobulin (Fig. 2.3), thyroid transcription factor-1 (TTF-1), TTF2 (FOXE1), paired box-8 (PAX8), cytokeratins (CK) (CK AE1/3, CK 7, CK 19), epithelial membrane antigen (EMA), Hector Battifora mesothelial cell-1 (HBME-1), galectin-3, cyclin D1, p27KIP1 and PTEN [3, 4, 6–10, 13]. Interestingly, in some cases, displaying positivity for thyroglobulin in the primary tumour and lymph node metastases, there may be total or partial negativity in distant metastases [3, 8, 13] (Fig. 2.6). Tumour cells are negative for CK 20, thyroperoxidase, calcitonin, chromogranin A and synaptophysin. Strikingly, intense and diffuse nuclear p53 expression is detected in most cases [3, 6–8, 10, 13, 16] (Fig. 2.2).

Fine needle aspiration biopsy (FNAB) is an effective method for diagnosing PTC, including HV cases [4, 8, 10–12]. In HV of PTC, the FNAB samples are typically highly cellular with little colloid and a bloody background. The tumour cells are organized in papillary-like, micropapillary and/or discohesive cell clusters in variable proportions. The characteristic isolated cells are of small to medium size showing eccentric nuclei teardrop cytoplasm (hobnail appearance), the so-called comet-like cells (Fig. 2.8). Syncytial cell clusters with apically placed nuclei may also

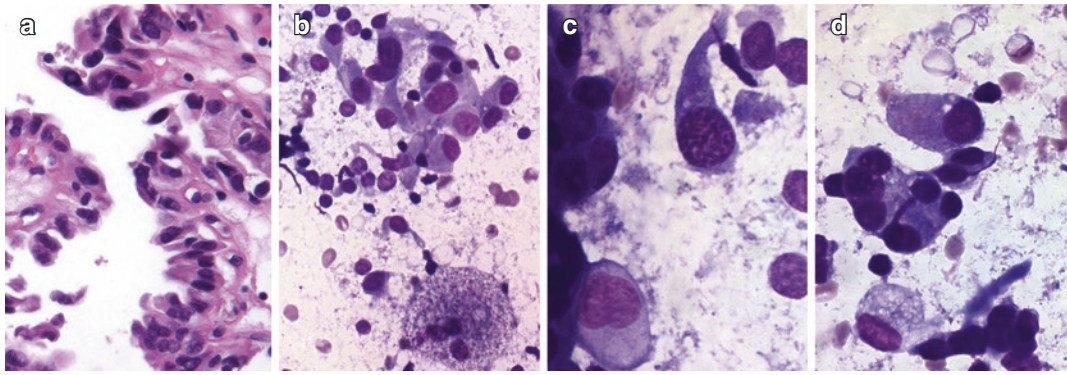


Fig. 2.8 Cytological specimens from hobnail variant of papillary thyroid carcinoma. Hobnail variant of PTC showing discohesive cells with loss of polarity and large nuclei (**a**). In this variant, samples from fine needle aspiration biopsy characteristically show isolated cells with eccentric nuclei teardrop cytoplasm (hobnail appearance), the so-called comet-like cells (**b**–**d**)

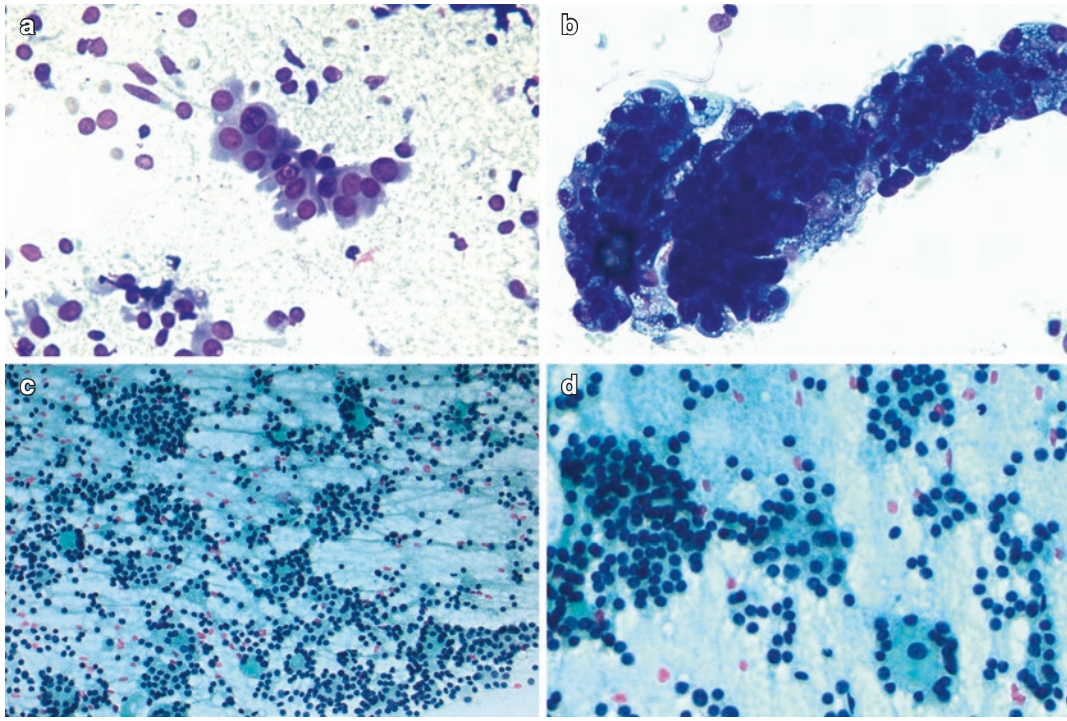


Fig. 2.9 Cytological samples from hobnail variant of papillary thyroid carcinoma. In these samples from the case showed in Fig. 2.3, columnar cells with nuclear pseudoinclusions (**a**, Diff-Quik stain) and bubbled cytoplasm (**b**, Diff-Quik stain) are seen. A poorly differentiated component, composed by aggregates of small cells with dark nuclei, is also detected ((**c**, **d**), Papanicolaou stain)

appear. Typical pseudoinclusions or multiple soap-bubble-like intranuclear inclusions are commonly detected. Variable degrees of nuclear atypia, grooves, nuclear stratification and atypical mitoses can also be seen [4, 10, 11] (Fig. 2.9). Immunohistochemical positivity for thyroglobulin, TTF-1, HBME-1, E-cadherin and p53 can be detected in cytological samples [10].

In addition to the frequent immunohistochemical positivity for p53 protein, *BRAF*^{V600E} mutation has been detected in about 70% cases of HV of PTC using both cytological or tissue samples

[4, 5, 7, 8, 10, 11, 13]. Concurrent *BRAF*^{V600E} and *TERT* promoter mutations were found in one case with undifferentiated carcinoma areas in distant metastases [8], but no *TERT* promoter mutations were identified in a series of ten cases of common HV of PTC [4]. *RET/PTC1*, but not *RET/PTC3* rearrangements, have been detected in less than 20% of HV cases [7, 8, 13].

Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma

The diffuse sclerosing variant of PTC is more frequent in female, young patients [1]. It is a PTC variant that diffusely involves one or both thyroid lobes, clinically mimicking Hashimoto thyroiditis [1, 2]. This variant is characterized by dense sclerotic stroma involving nests of solid, squamoid, spindled and papillary arranged cells (Fig. 2.7). The cells express focally thyroglobulin, TTF-1, PAX8 and p63 (Fig. 2.7). Abundant psammoma bodies, lymphocytic infiltration and extensive lymph vessel invasion are also present. Lymph node and lung metastases are frequent and may be difficult to diagnose since they may be thyroglobulin (often) and TTF-1 (more rarely) negative. The disease-free survival rate is lower than that of patients with conventional PTC.

Spindle Cell Variant of Papillary Thyroid Carcinoma

Spindle cell transformation or metaplasia has been so far demonstrated in the context of epithelial benign and malignant conditions [1, 2, 17]. Rare cases of PTC show areas of spindle cell differentiation that may represent more than 80% of the tumour [1, 17]. Microscopically, spindle tumour cells are arranged in bundles, frequently showing nuclear grooves and occasional, less frequent, pseudoinclusions (Fig. 2.10). Follicular structures are usually seen in the periphery of the

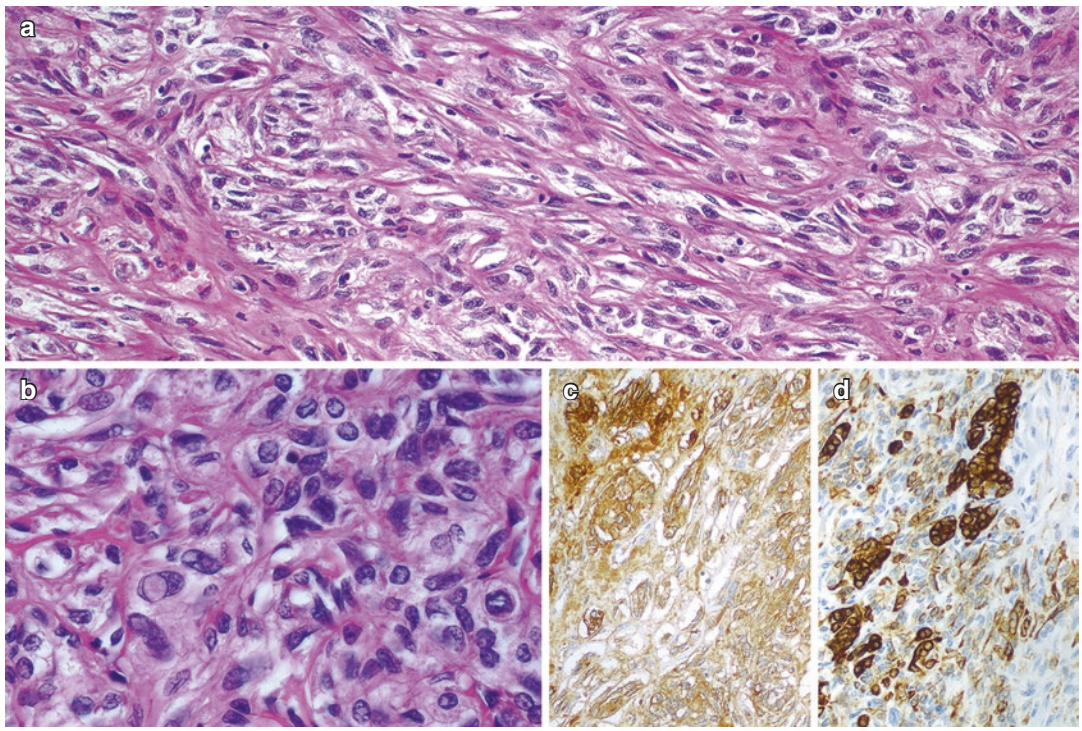


Fig. 2.10 Spindle cell variant of papillary thyroid carcinoma. This variant is mainly composed of spindle cells arranged in bundles having a mesenchymal-like appearance (**a**). The nuclei of the spindle cells are large, oval and grooved and displayed pseudoinclusions (**a**, **b**). Tumour cells are immunopositive for thyroglobulin (**c**) and keratins (clone AE1/AE3) (**d**)

tumour. The spindle cells are actually epithelial in nature and follicular cell originated, as evidenced by their positivity, sometimes focal, for pan-keratins and thyroglobulin, TTF-1 and PAX8 (Fig. 2.10). The differential diagnosis of this tumour includes reactive processes and a variety of primary thyroid tumours and metastatic neoplasms (see spindle cell tumours in Chap. 6). In contrast to reactive changes occurring post FNAB, true spindle cell foci of PTC are not associated with haemorrhage, new capillary blood vessels or hemosiderin-laden macrophages. Distinguishing features from anaplastic carcinoma include the fact that the PTC spindle cells are bland without mitotic activity, pleomorphism and necrosis. Because spindle cell variant of PTC behaves similarly to PTC lacking such features, it is important to separate this variant of PTC from aggressive spindle cell malignant neoplasms (see Chap. 6).

Spindle Cell Papillary Carcinoma with Fasciitis-Like Stroma/ Fibromatosis

In rare cases, the stroma of PTC is so abundant and cellular as to resemble nodular fasciitis, fibromatosis and other proliferative myofibroblastic processes [1, 2]. PTC with fasciitis-like stroma, also designated as PTC with fibromatosis-like stroma, is a biphasic tumour composed by a stromal benign component and PTC neoplastic foci [1]. The stromal component may predominate obscuring the presence of PTC foci. The stromal cells are spindled, bland looking and arranged in fascicles in a more or less collagen-rich background. This component, thought to be representative of a myofibroblastic population, expresses nuclear beta-catenin and cytoplasmic smooth muscle actin and does not express cytokeratins nor TTF-1 [18]. The PTC foci disclose the typical nuclear features and the respective immunohistochemical profile. The recognition of this malignant component, with the eventual aid of cytokeratins staining to highlight the epithelial cells, will allow the differential diagnosis with other stromal-rich lesions of the thyroid, namely, end-stage/fibrous variant of Hashimoto thyroiditis, IgG4-associated/Riedel thyroiditis, multifocal fibrosing thyroiditis and solitary fibrous tumour (see Chap. 6). The distinction between PTC with fasciitis-like stroma and paucicellular variant of anaplastic carcinoma is not difficult since the latter presents as (very) large tumour with atypical, often bizarre, cells throughout its extension (see Chap. 6). The overall and recurrence-free survival for patients with PTC with fasciitis-like stroma/fibromatosis may be lower than for other PTC variants.

The case illustrated in Fig. 2.11 is a PTC with fasciitis-like stroma diagnosed in a 68-year-old female patient submitted to total thyroidectomy due to nodular adenomatous goitre. The macroscopic examination disclosed a poorly circumscribed nodule in the isthmus with microscopic predominance

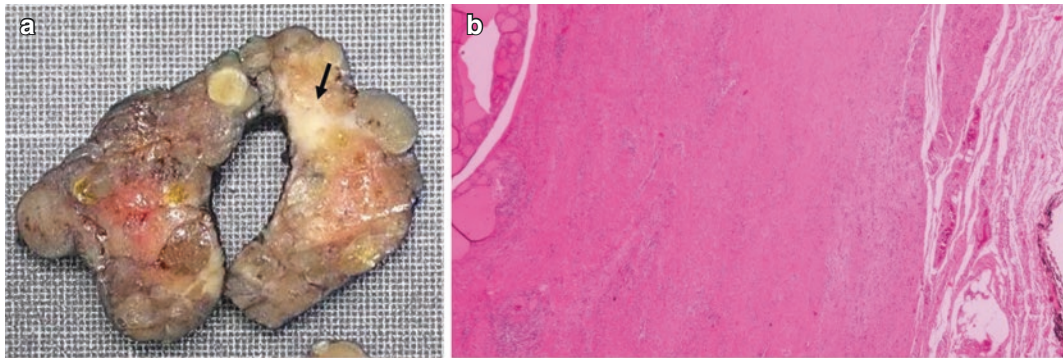


Fig. 2.11 Spindle cell papillary carcinoma with fasciitis-like stroma. Macroscopic features of the tumour (*arrow*) (**a**). There is abundant sclerotic stroma without atypical nuclei (**b**). Scattered foci of epithelial cells are arranged in trabeculae or small follicles (**c**). Papillary thyroid carcinoma nuclear features can be seen in the epithelial foci (**d**) (Courtesy of Eva Sigstad and Krystyna Kotanska-Grøholt, Oslo, Norway)

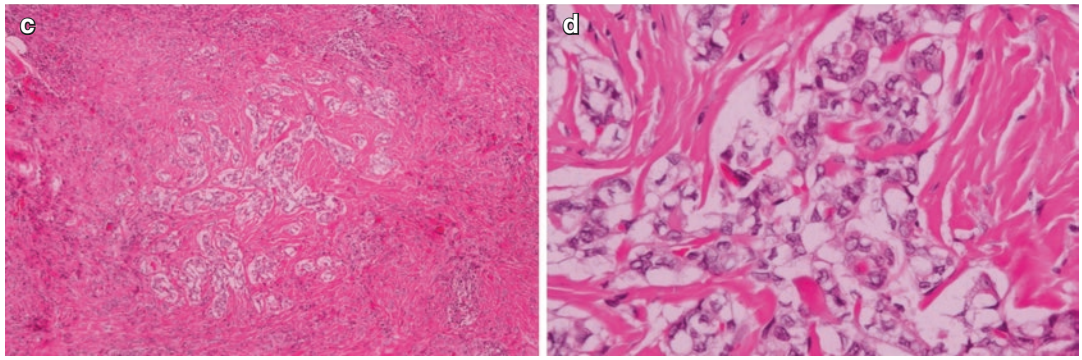


Fig. 2.11 (continued)

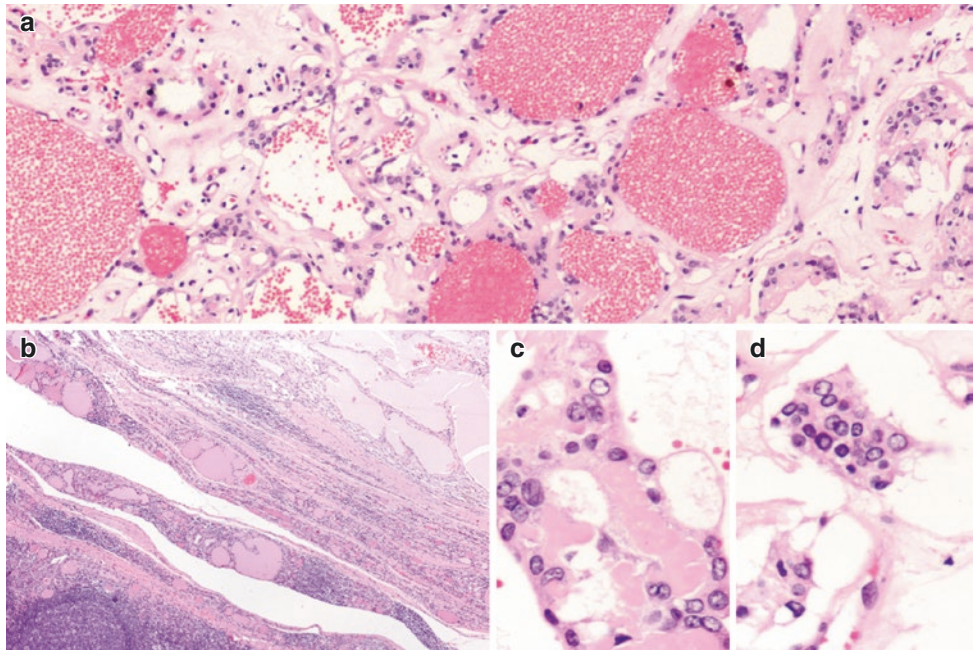


Fig. 2.12 Angiomatoid variant of papillary thyroid carcinoma. The vascular-like pattern of the tumour (**a**) in a background of Hashimoto-type thyroiditis (**b**) and the typical PTC nuclear features (**c**), including nuclear pseudoinclusions (**d**), can be seen in this angiomatous variant of PTC (Courtesy of Alexandra Betts, Malta)

of a cellular bland stroma component with occasional lymphoid aggregates and scarce PTC foci.

Angiomatoid Variant of Papillary Thyroid Carcinoma

The angiomatoid variant of PTC that develops in the context of Hashimoto thyroiditis can be confused with a vascular tumour if the characteristic nuclear features of PTC in the cells lining the vascular-like spaces are not searched at high magnification [19]. Such vascular-like spaces can display a prominent anastomosing pattern; are lined by TTF-1, PAX-8 and thyroglobulin positive; are cuboidal to flat cells; and are surrounded by a collagenous to myxoid stroma.

The case illustrated in Figs. 2.12 and 2.13 is from a 56-year-old woman with clinical and cytological diagnosis of Hashimoto thyroiditis

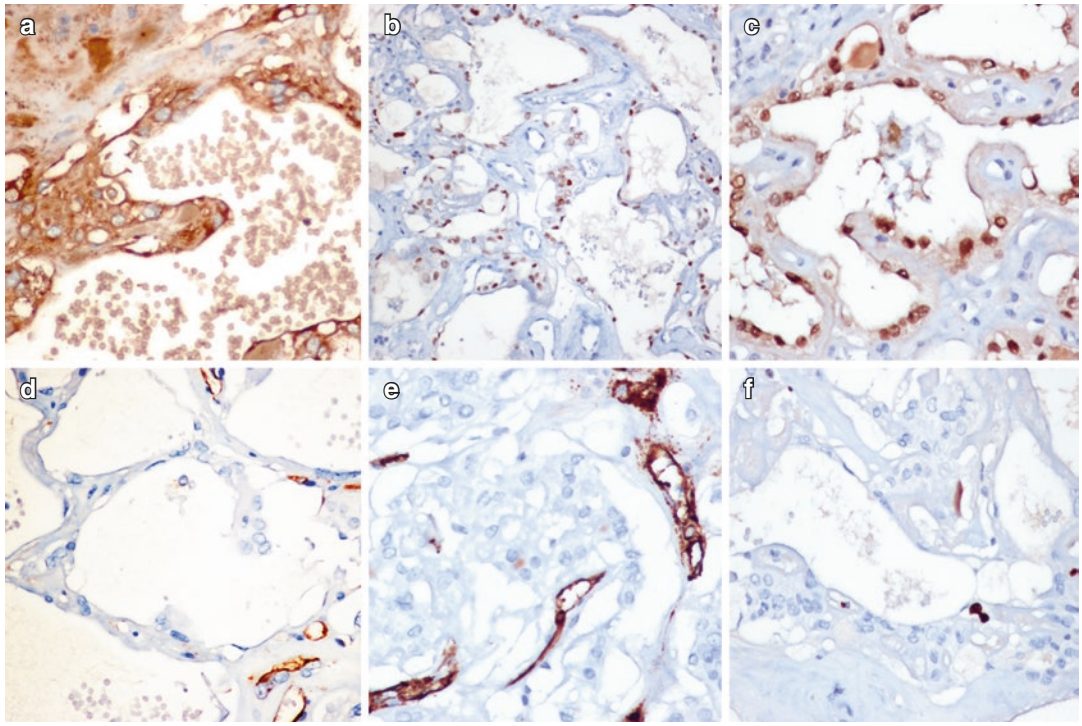


Fig. 2.13 Immunohistochemical profile of the cells that line the vascular-like spaces in the angiomatous variant of papillary carcinoma. The tumour cells express thyroglobulin (**a**), TTF-1 (**b**) and PAX8 (**c**), while the vascular markers CD31 (**d**) and CD34 (**e**) are not expressed. The Ki-67 labelling index is very low fitting with the low-grade features of the tumour (**f**)

(thyroid peroxidase antibodies >1000 IU/ml) who presented with a painless nodule in the left lobe measuring 25 mm in its largest dimension, documented in the neck ultrasound. This nodule was "cold" at scintigraphy. Macroscopically, the thyroid had a pale, vaguely nodular appearance. An encapsulated nodule measuring 25 × 25 × 17 mm was present in the upper half of the left lobe. This nodule had a solid, brownish, variegated cut surface. At histological examination, there were lesions consistent with Hashimoto-type thyroiditis and a well-circumscribed nodule surrounded by an irregular capsule (Fig. 2.12). The nodule had an angiomatoid appearance caused by irregularly shaped spaces filled with red blood cells. The lining of the spaces and some solid/trabecular areas intermingled with the spaces were composed by cells with clear and irregularly shaped nuclei, some with pseudoinclusions. There were no signs of vascular invasion. The neoplastic cells in the nodule expressed TTF-1, PAX8, thyroglobulin and cytokeratins (Fig. 2.13). Calcitonin, CD31, CD34 and D2-40 were not expressed in the neoplastic cells. CD31 and CD34 highlighted a prominent vascular network in the nodule. *BRAF* and *N-RAS* mutations were not detected.

Thyroglobulin-Negative Papillary Thyroid Carcinoma

PTC without thyroglobulin expression represents the type of tumour that is difficult to say if it is rare or if it is common but has been passed by undetected. In cases with less typical PTC cells, as occurs in the spindle cell variant, the solid variant or in the solid areas of the diffuse sclerosing variant of PTC, thyroglobulin can be expressed only focally [1, 2]. Cases of PTC that are completely negative for thyroglobulin in the setting of a normally stained remaining thyroid

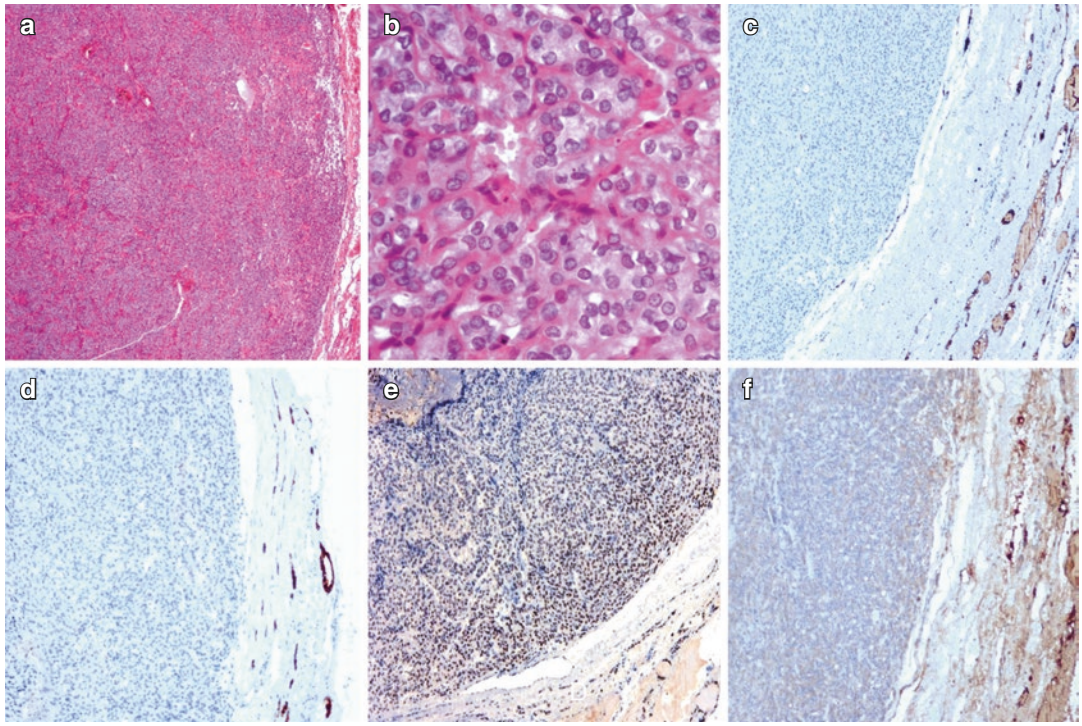


Fig. 2.14 Thyroglobulin-negative papillary thyroid carcinoma. This image shows a PTC with solid pattern (**a**) disclosing the typical nuclear features (**b**) and without reactivity for thyroglobulin (**c**) and thyroperoxidase (**d**). Tumour cells are positive for TTF-1 (**e**) and T4 (**f**)

tissue may represent situations with underlying somatic mutations of the thyroglobulin gene or other genes codifying proteins engaged in the production of thyroglobulin. The search for other products of the follicular cell metabolism, such as thyroperoxidase and T4, can help in the identification of the follicular cell differentiation, thus ruling out a C-cell differentiation. One can also search for the presence of thyroglobulin mRNA using FISH. It is very important to exclude a lack of thyroglobulin expression due to poor fixation or other pre-analytical limitations. The case of thyroglobulin-negative PTC illustrated in Fig. 2.14 is from a 2-year-old boy with a 1.5 cm nodule in the thyroid, well circumscribed, with a predominantly solid growth pattern that did not disclose infiltrative growth nor vascular invasion. The nuclei of the neoplastic cells were clear and irregularly shaped, typical of PTC. The neoplastic cells in the nodule did not express thyroglobulin nor thyroperoxidase and expressed vimentin, TTF-1 and T4 (Fig. 2.14). Calcitonin was not expressed in the neoplastic cells.

Taking into consideration that the follow-up of patients with PTC is mainly based on serum thyroglobulin measurements, this variant raises important questions from the clinical standpoint. The identification of this variant in the original pathology report should prompt physicians to perform more frequent imaging procedures, because serum thyroglobulin may not be a reliable tumour marker in this setting. On the other hand, if during the follow-up of patients with differentiated thyroid carcinomas physicians face the rare occurrence of disease persistence/recurrence with undetectable serum thyroglobulin levels, the hypothesis of a thyroglobulin-negative variant should be sought.

Papillary Thyroid Carcinomas with Unusual Immunohistochemical Reactivity

Rare cases of PTC, particularly its columnar cell variant, as well as the morular structures of the cribriform-morular variant of PTC (see Chap. 5),

can show aberrant nuclear CDX2 expression, an intestine-specific homeobox gene transcription factor [20–23]. Besides, there are rare cases of PTC with positivity for CA19.9 in the primary and/or metastatic foci, as well as cases of PTC with anaplastic transformation also reported as having CA 19.9 positivity [24, 25]. In Fig. 2.15, we illustrate a case of PTC with marked nuclear stratification (columnar cell variant) and positivity for both CDX2 and CA19.9.

Another interesting finding regards the co-expression of thyroglobulin and p53 in some cases (less than 3%) of PTC that usually display dark pseudostratified nuclei and are thought to carry a guarded prognosis [26–28]. Some aggressive forms of PTC such as tall cell, columnar cell and hobnail variant of PTC, as well as rare cases of mixed columnar cell and tall cell variant of PTC, (poorly differentiated) cribriform-morular variant of PTC and squamous cell carcinoma associated with tall cell variant of PTC, exhibit a higher rate of p53 immunopositivity than common PTC [3, 8, 13, 20, 23, 29–31]. The case illustrated in Fig. 2.16 (courtesy of Abir Al Ghuzlan, Villejuif, France) is a partially encapsulated classic PTC occurring in a 22-year-old

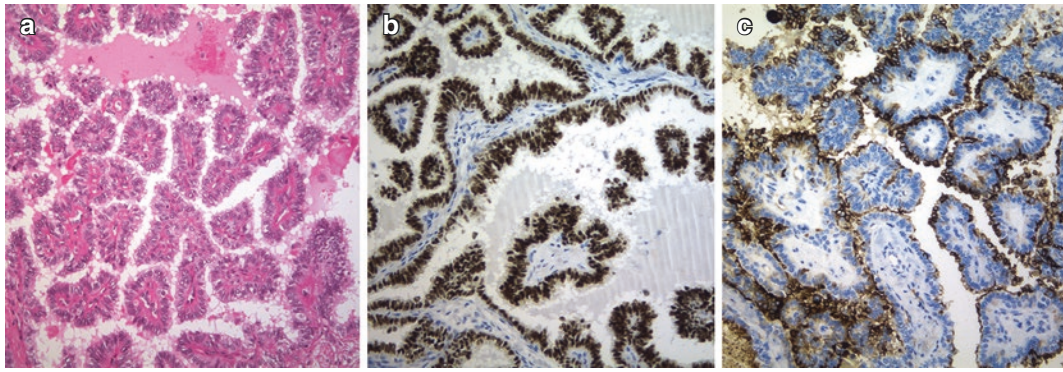


Fig. 2.15 Papillary thyroid carcinoma with unusual immunohistochemical features. This case of columnar cell variant of PTC (**a**) showed diffuse positivity for CDX2 (**b**) and CA19.9 (**c**)

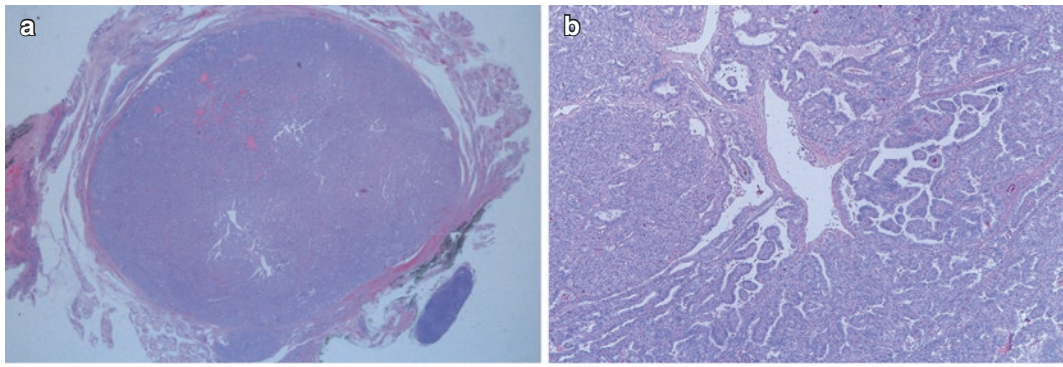


Fig. 2.16 p53 positivity in classic papillary thyroid carcinoma (PTC) with columnar cell carcinoma features**.** Partially encapsulated classic PTC (**a**) with papillary architecture (**b**, **c**) and columnar cell features (**c**). Intense, diffuse immunoexpression for p53 was encountered (**d**)

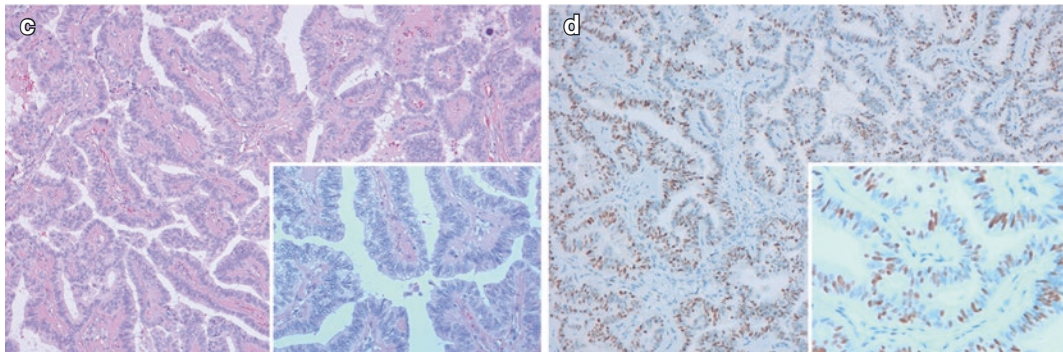


Fig. 2.16 (continued)

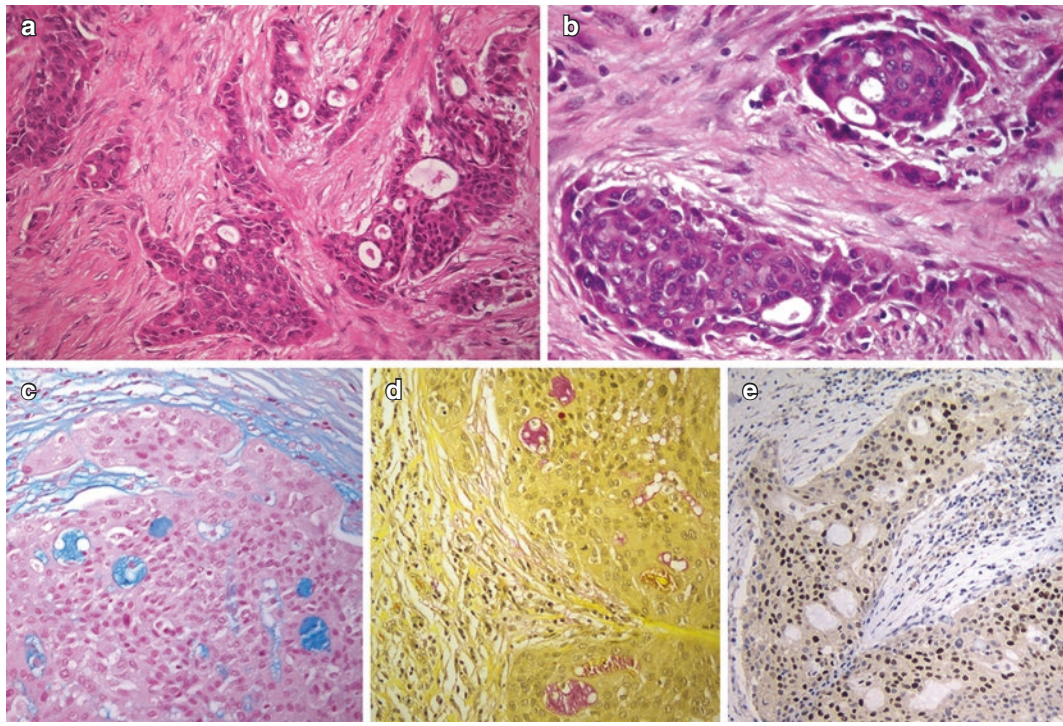


Fig. 2.17 Mucoepidermoid carcinoma of the thyroid. The tumour is composed of epithelial nests showing epidermoid and mucinous components surrounded by a fibrotic stroma (**a**, **b**). Mucinous material positive for Alcian blue stain (**c**) and Mayer's mucicarmine (**d**) can be seen in the glandular lumina. Positivity for p63 can also be seen in epidermoid and ductal cells (**e**)

woman that displayed foci with columnar cell carcinoma features (pseudostratification of the neoplastic cells and crowding of the nuclei) and intense nuclear immunoexpression for p53. Staging, including the presence of capsular and, mainly, vascular invasion, remains, nevertheless, the most important prognostic factor [16].

Mucoepidermoid Carcinoma (MEC) of the Thyroid

MEC is a malignant epithelial neoplasm characterized by a combination of squamous and mucinous components [1, 2]. Figure 2.17 shows the typical features of MEC, demonstrating inter-

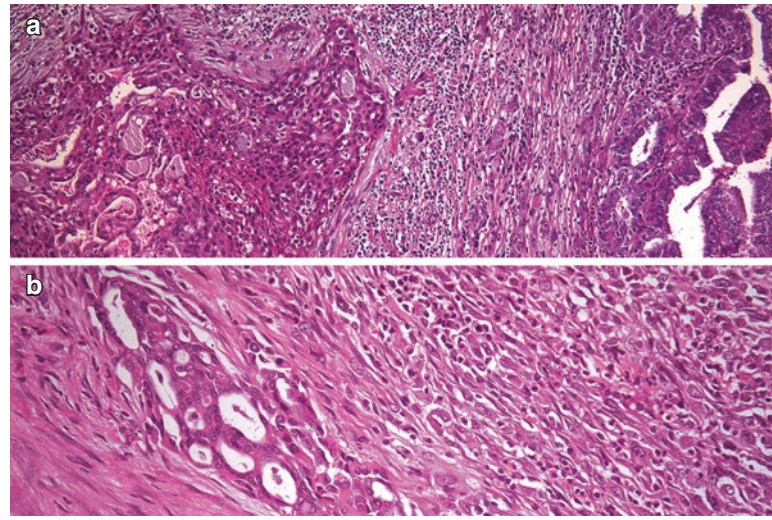


Fig. 2.18 Mucoepidermoid carcinoma of the thyroid. In this case, mucoepidermoid carcinoma (at *left*) is associated with PTC (at *right*) (**a**). In the picture below, mucoepidermoid carcinomas (at *left*) with anaplastic transformation (at *right*) is seen (**b**)

twined nests of epidermoid cells and mucinous components in a fibrotic stroma. The epidermoid component is arranged in sheets usually with keratin pearl formation, whereas the cuboidal, goblet-like mucous cells line ducts or glandular spaces. Hyaline bodies (PAS-positive droplets) resembling colloid may appear in the mucocyte cytoplasm. A cribriform-like pattern with elongated lumina containing colloid-like material and papillary infoldings can be seen. Ciliated cells are sometimes present. Mucin can be intra- and/or extracellular. The tumour cells have medium-sized nuclei with rather pale chromatin resembling PTC nuclei. Nuclear grooves and pseudoinclusions can be seen, and psammoma bodies occasionally occur. Mitotic figures are rare as are foci of necrosis. PTC (classic, follicular variant or tall cell variant) has been found associated with MEC (Fig. 2.18). In some rare cases of MEC (with or without PTC), there is merging with undifferentiated (anaplastic) areas (Fig. 2.18) or coexisting poorly differentiated (insular) transformation. Areas with follicular carcinoma or Hürthle cell carcinoma are much less common. Lymphocytic (Hashimoto) thyroiditis is frequently associated. Most MECs are focally positive for thyroglobulin, PAX8 and TTF-1, with positivity for p63 in epidermoid foci and ductal basal cells (Fig. 2.17). The main differences between MEC and sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE) are summarized in Table 2.1.

Table 2.1 Main clinical, pathological and immunohistochemical features of mucoepidermoid carcinoma (MEC) and sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE)

	MEC	SMECE
Age (years)	Median 47 (range: 10–91)	Median 55 (range: 32–89)
Gender distribution (F:M)	2:1	7:1
Extrathyroidal extension	≈25%	≈40%
Cervical lymph node metastases	≈40%	≈35%
Distant metastases	<10%	≈22%
Perineural invasion	Rare	Common
Lymphocytic thyroiditis or Hashimoto thyroiditis	≈40%	Common
Association with PTC	≈50%	Rare
Thyroglobulin positivity	Usually positive	Usually negative
TTF-1 positivity	Usually positive	≈50%

Sclerosing Mucoepidermoid Carcinoma with Eosinophilia (SMECE)

A case of SMECE from a 13-year-old female with no history of radiation exposure and a painless cervical nodule with 4 months of evolution is illustrated in Fig. 2.19. The thyroid function tests were normal and anti-thyroglobulin and anti-microsomal antibodies were detected in the serum. The ultrasound showed a solid, hypoechogenic nodule, with microcalcifications in the left lobe. The patient underwent FNAB of the nodule and a diagnosis of follicular tumour was made. The total thyroidectomy specimen disclosed a 2.5 cm well-circumscribed, whitish and firm nodule that by light microscopy was a nonencapsulated tumour composed by anastomosing clusters of squamoid cells mixed in a sclerotic background with abundant lymphocytic infiltration and eosinophils (Fig. 2.19). The tumour cells

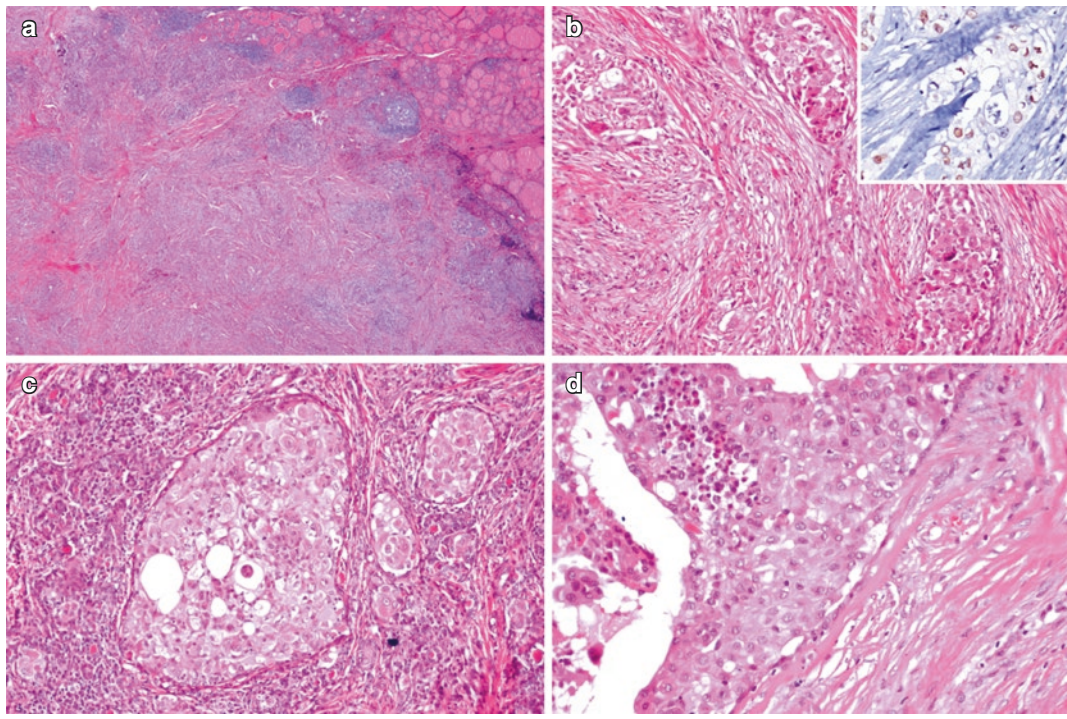


Fig. 2.19 Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE). This is a case of SMECE coexisting with exuberant lymphocytic Hashimoto-type thyroiditis (**a**). The tumour discloses nests of squamoid cells (**b**, **c**) that express p63 (**b**, *inset*) that are surrounded by a prominent collagenous stroma rich in lymphocytes and eosinophils (**d**)

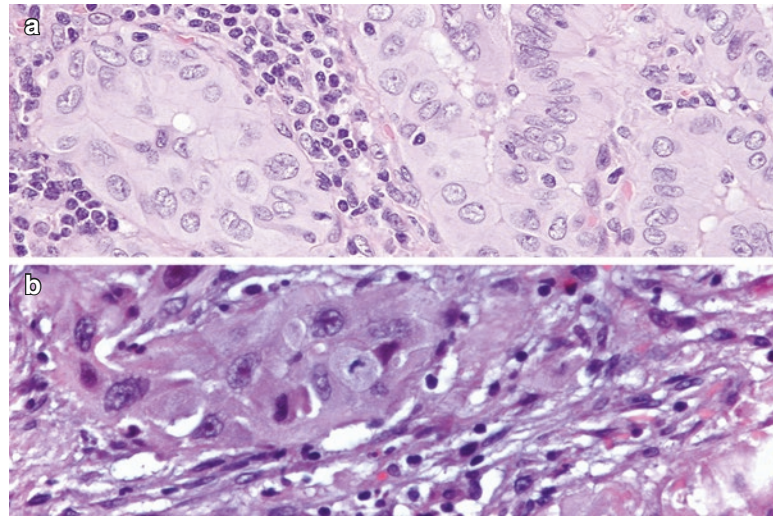


Fig. 2.20 Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE). SMECE is a low-grade tumour that may coexist with PTC and must be distinguished from both PTC with squamous cell metaplasia (**a**) and from the highly aggressive primary or metastatic squamous cell carcinoma (**b**)

showed squamoid differentiation and occasional intracellular accumulation of mucin. Thyroglobulin was not detected in the neoplastic cells as it often occurs (see Table 2.1). Vascular invasion and foci of necrosis were present. No mutations were detected in *BRAF* or (*K*-, *N*-, *H*-) *RAS* genes nor *RET/PTC* or *PAX8/PPAR*gamma rearrangements. SMECE is a low-grade tumour that may coexist with PTC and must be distinguished from PTC with squamous cell metaplasia [1, 2, 32] (Fig. 2.20).

Tumour-in-Tumour of the Thyroid with Neoplastic Solid Cell Nest Features

Tumour-in-tumour phenomena can occur in the thyroid mainly reflecting the occurrence of metastases into follicular adenoma and/or into follicular variant of PTC [33]. In other situations, the different components of the tumour that assumes a biphasic or multiphasic growth pattern originate from the thyroid [34]. This is the case of a singular tumour-in-tumour of the thyroid with neoplastic solid cell nest features illustrated in Figs. 2.21 and 2.22. It is a tumour in a 70-year-old male submitted to surgery due to non-toxic nodular goitre and normal thyroid function tests. Extensive investigation of primary tumours located in other organs was performed and nothing was found. The surgical specimen presented an encapsulated nodule in the upper pole of the right lobe with a tumour-in-tumour features and without signs of capsular or vascular invasion. There was an adenoma at the periphery of the tumour beneath the capsule. The second layer had the appearance of follicular variant of PTC and the central lesion, which constituted the core of the nodule, presented a solid pattern of growth (Fig. 2.19). This central lesion was composed of monotonous epithelioid cells with oval nuclei and eosinophilic cytoplasm that exhibited a palisade organization at the periphery, as it is frequently observed in solid cell nest component (Fig. 2.21). The central lesion did not express TTF-1, calcitonin or thyroglobulin and expressed p63, as also did the main cells of the solid cell nests (Fig. 2.22). Mutations of *BRAF* and *N-RAS* were searched, and a Q61R *N-RAS* mutation in exon 2 was detected both in the follicular variant of PTC and in the central lesion, supporting the assumption that both represent the same clonal proliferation. No mutations were identified in the *BRAF* gene.

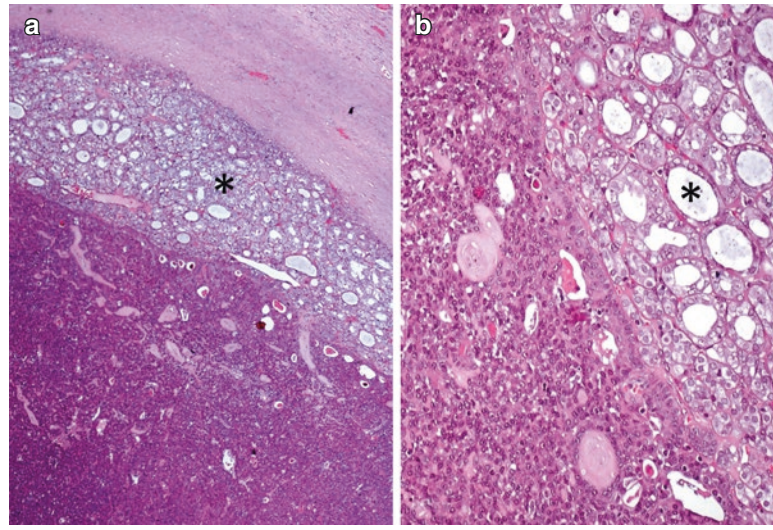


Fig. 2.21 Tumour-in-tumour of the thyroid with neoplastic solid cell nest features. The biphasic pattern of growth of a tumour-in-tumour composed by an external layer beneath the capsule with features of follicular variant of PTC (*asterisk*) and an inner core with basaloid features resembling a solid cell nest: tumour-in-tumour of the thyroid with neoplastic solid cell nest features (**a**, **b**) (See the text for details)

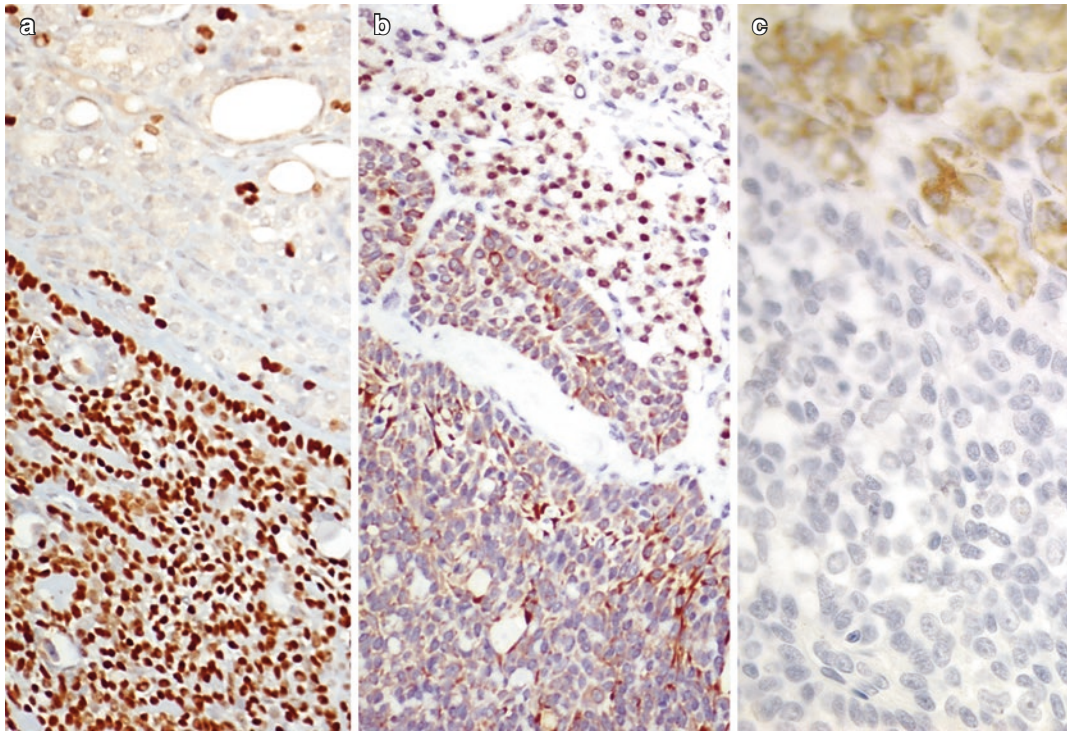


Fig. 2.22 Tumour-in-tumour of the thyroid with neoplastic solid cell nest features. This is the same case as Fig. 2.21. The nuclei of the basaloid cells of the inner core component expressed p63 (**a**) and did not express TTF-1 (**b**), at variance with the PTC external component. Thyroglobulin was not detected in the basaloid cells of the inner core component even using an in situ hybridization technique (**c**) (See the text for details)

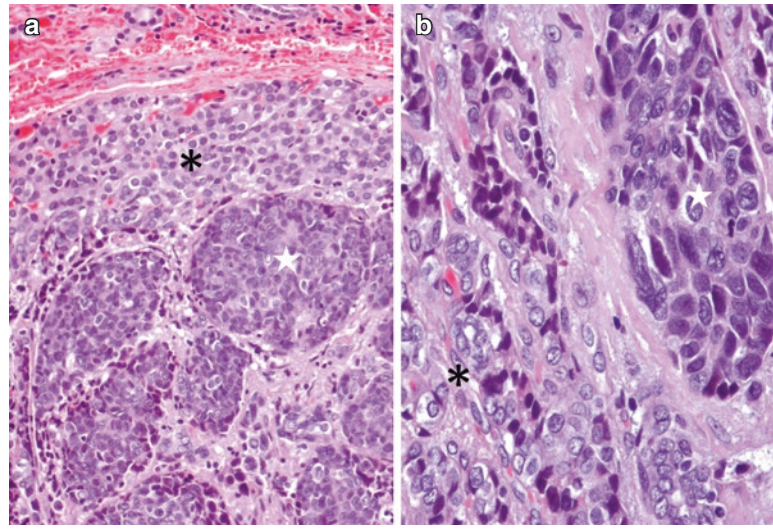


Fig. 2.23 Tumour-in-tumour phenomenon due to metastatic disease. Metastasis of invasive breast carcinoma (*white star*) into a follicular variant of PTC (*black asterisk*) (**a**, **b**)

Tumour-in-Tumour Phenomenon Due to Metastatic Disease

To illustrate the tumour-in-tumour phenomenon due to metastatic disease, we selected the case of a 51-year-old female with the diagnosis of invasive breast carcinoma with no special type, diagnosed 3 years before. The present thyroidectomy was due to a thyroid nodule (Fig. 2.23). A diagnosis of metastasis of invasive breast carcinoma into a follicular variant of PTC was made. The identification of the breast carcinoma metastatic area was not difficult as the metastatic nests were clearly demarcated from the pre-existing tumour and the clinical context was known. In other cases, the metastasis may be interpreted just as a peculiar clone of the pre-existent tumour/lesion and pass by unnoticed. In cases of biphasic or multiphasic thyroid nodules occurring in patients with previous history of cancer elsewhere, immunohistochemical testing for thyroglobulin is mandatory [33].

Mixed Medullary-Papillary Carcinoma

Figure 2.24 illustrates a case of mixed medullary-papillary carcinoma. Mixed medullary and follicular cell carcinoma is a primary malignant epithelial neoplasm of the thyroid showing morphological and immunophenotypical evidence of the coexistence of follicular and parafollicular cell-derived tumour populations within the same lesion [1, 2]. Immunohistochemistry is mandatory to prove the dual parafollicular (calcitonin positive) and follicular (thyroglobulin positive) cell differentiation. Thyroglobulin staining should be interpreted with caution due to the easy local diffusion and/or potential adsorption by medullary carcinoma cells.

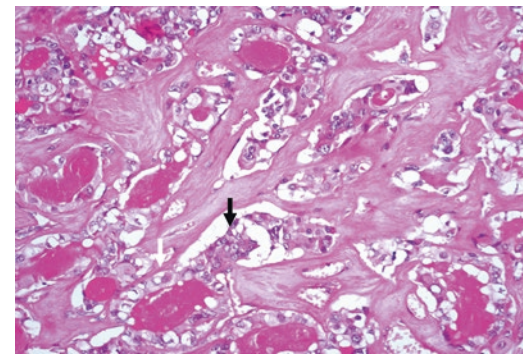


Fig. 2.24 Mixed medullary-papillary carcinoma. This tumour disclosed follicular structures that expressed thyroglobulin (*white arrow*) contiguous to solid nests of cells that expressed calcitonin (*black arrow*)

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