Chapter 17
Thyroid, Parathyroid, and Adrenal Glands

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Abstract This chapter provides a practical overview of frequently used markers in the diagnosis and differential diagnosis of both common and rare neoplasms of the thyroid, parathyroid and adrenal glands, with a specific focus on papillary thyroid carcinoma and its mimickers. The chapter contains 30+ questions; each question is addressed with a table, concise note and representative pictures if applicable. In addition to the literature review, the authors have included their own experience and tested numerous antibodies reported in the literature. The most effective diagnostic panels of antibodies have been recommended for many entities, such as CK19, HBME-1, and galectin-3 being suggested as the best diagnostic panel for identifying papillary thyroid carcinoma. New markers, such as TROP-2, are discussed. Furthermore, immunophenotypes of normal thyroid tissue have been described, which tends to be neglected in literature.

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Table 17.1 Summary of applications and limitations of useful markers

Antibodies	Staining pattern	Function	Key applications and pitfalls
Beta-catenin	C/N	A 94-kDa protein, as part of a membrane-bound cell growth-signaling complex, plays a role in cell adhesion, as well as in promotion of growth through activation of the Wnt signaling pathway	Malignant thyroid tumors: C/N staining pattern with loss of M staining. Aberrant nuclear localization in cribriform-morular variant of PTC: frequently associated with familial adenomatous polyposis
BRAF V600E	C	95-kDa synthetic peptide representing the BRAF V600E-mutated amino acid sequence from amino acid 596 to 606	BRAF V600E mutation has been reported in ~50% of PTCs; higher frequency in tall cell variant (~70%) and oncocytic variant of PTCs; lower frequency in follicular variant of PTC (~20%)
Calcitonin	C	A secreted protein produced by parafollicular C cells	Rare cases of MC are negative for calcitonin
CD10	C+M	A 90–100 kDa neutral, transmembrane metalloendopeptidase; also known as common acute lymphoblastic leukemia antigen	No expression of CD10 in normal follicular cells and MCs; focally positive in adenomatous goiter and FA in 12–22% of cases with oncocytic changes or squamous differentiation; diffuse and strong expression in 100% of ATCs
CD44v6	M	A member of immunologically related integral membrane glycoproteins mediating cell-cell and cell-matrix interactions through its affinity for hyaluronic acid	Intense membranous stain had been detected in benign (~40%) and malignant thyroid tumors, with highest in well-differentiated PTC (75–90%) and FC (90–100%)
CDX-2	N	Intestine-specific transcription factor directing intestinal development, differentiation, proliferation, and maintenance of the intestinal phenotype	Rarely positive in PTCs. A recent single study of three cases of columnar cell variant PTC shows diffuse nuclear stain for CDX-2
CGRP	C	Calcitonin gene-related peptide. A widely distributed vasodilatory peptide encoded by calcitonin gene (CALCA)	Useful marker for the diagnosis of MCs
CK7	M+C	Epithelial marker	Thyroid tumors are positive
CK19	M+C	Cytokeratin expressed by simple and glandular epithelium	Usually strong and diffuse stain in PTC; less intense and more focal stain in FA and FC; negative in normal thyroid follicles
CK20	M+C	Epithelial marker	Differentiated thyroid CAs are nonreactive
Claudin-1	M	A multipass membrane protein, as an important structural and functional component of tight junction mediated in paracellular transport	Increased claudin-1 mRNA levels have been observed in PTC. IHC studies claim expression in PTC, FC, and FA
COX-2	C	Important enzymes involved in the arachidonic acid pathway and synthesis of prostaglandins	Higher expression in PTCs and FCs than in normal follicular epithelium and FAs
DPP4 (CD26)	M	An exopeptidase involved in T-cell activation	Absent from normal thyroid tissue but highly expressed in malignant thyroid cells

Table 17.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
E-cadherin	M	An adhesion molecule of the integrin and cadherin family, involving the induction and maintenance of a functional organization of polarized epithelia	Reduced or lost expression in differentiated thyroid CAs; lost expression in PDTCs and ATCs
EZH2	N	Enhance of zeste homolog 2 (EZH2), a histone modifier protein, is important for transcriptional regulation	Overexpressed in various malignancies; in thyroid CAs, high expression in ATCs and PDTCs; no or low expression in differentiated thyroid CAs
FN-1	C, M	Multifunctional adhesive glycoproteins found in the extracellular matrix and body fluids	Oncofetal FNs are highly expressed in fetal and neoplastic tissues, including thyroid follicular-cell-derived tumors
*FOXA*1	N	A mammalian endodermal transcription factor, belonging to the winged helix/foxhead box family, plays important role during multiple phases of mammalian life	Amplified in lung, esophageal, ER+ breast, and metastatic prostate CAs. In thyroid, FOXA1 expression was reported in ATC, MC, C cells, C-cell hyperplasia and SCN
Galectin-3	C, N	A member of the non-integrin beta-galactoside-binding lectin family that plays an important role in cell-cell adhesion and in cell-matrix interaction	Overexpressed in thyroid malignant tumors. Also expressed in macrophages, neutrophils, mast cells, and Langerhans cells
HBME-1	C	A monoclonal antibody generated against the microvillous surface of mesothelial cells	A useful marker of malignancy in thyroid nodules
HMGA2	N	A member of nonhistone nuclear proteins that orchestrate the assembly of nucleoprotein complexes	Upregulated in several malignant neoplasms including thyroid tumors
IMP3	C	A member of the insulin-like growth factor II mRNA-binding protein (IMP) family	Reported high expression in thyroid follicular cell-derived CAs, correlating with the differentiation of the tumor
mCEA	C, M	Carcinoembryonic antigens	Very sensitive marker for MC and hyperplastic or neoplastic C cells
NIS	M, C	An integral plasma membrane glycoprotein that mediates active iodine transport	Reduced expression in general in thyroid CAs; not detected in ATCs by IHC
p63	N	A transcription factor belonging to the p53 gene family	Diffusely positive in SCN, CASTLE, MEC, SMEC, and nearly half of ATC
PAX8	N	A member of the paired box (PAX) family of transcription factors expressed during organogenesis of the thyroid gland, Müllerian tract, and kidney	Similar to TTF1 as a sensitive marker for thyroid tumors; ATCs are frequently positive as well
Rb (retinoblastoma)	N	A 110–114 kDa nuclear protein playing a major role in the regulation of cell growth arrest	Loss of Rb expression was observed in majority of differentiated to poorly differentiated thyroid CAs; intact expression noted in ATC and 50% (3/6) of MC
RET/PTC	C	A somatic rearrangement of RET proto-oncogene; plays a key role in the pathogenesis of PTC	Molecular testing appears superior to IHC methods in detecting those rearrangements currently
SNAI2 (SLUG)	N	One of the epithelial-mesenchymal transition inducers and the E-cadherin (CDH1) repressor	Positive in majority of ATCs; normal thyroid tissue, FAs, PTCs, and FCs are negative
Thyroglobulin	C	The primary product of the thyroid, representing the macromolecular precursor of iodinated thyroid hormones thyroxine (T4) and triiodothyroxine (T3)	A follicular cell-specific marker, but ATCs are nonreactive False positive: due to the tendency to diffuse through adjacent tissue
Thyroperoxidase	C	A thyroid-specific enzyme expressed by differentiated thyroid cells	Studies of thyroperoxidase expression by ISH and IHC show reduced or loss of expression in malignant tissue compared with normal and benign neoplastic tissue
TROP-2	M	Also known as tumor-associated calcium signal transducer 2 (TAC-STD2). A transmembrane glycoprotein associated with tumor development and progression in a variety of epithelial CAs	TROP-2 expression is low or none in normal tissues; overexpression is observed in malignancy. In thyroid neoplasms, TROP-2 exhibits a distinct membranous staining pattern in PTC, only occasional focal cytoplasmic staining in follicular neoplasms

(continued)

Table 17.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
TTF1	N	Also named NKX2 homeobox 1 (NKX2.1), a nuclear transcription factor	Both follicular cells and C cells are positive ATCs are usually nonreactive
TTF2	N	Also named forkhead box E1 (FOXE1). A thyroid-specific, forkhead-domain-containing nuclear protein, one of the three thyroid transcription factors	Few studies reported TTF2 expression exclusively in normal thyroid follicular cells, a few C cells in thyroid C-cell hyperplasia, and thyroid neoplasm
TWIST1	N	The basic helix-loop-helix transcription factor	Positive in 50–100% of ATCs; normal thyroid tissue, FAs, PTCs, and FCs are mostly negative
ZEB1	N	Zinc finger E-box binding homeobox 1, a transcription factor, plays important role in epithelial-mesenchymal transition during embryonic development and in CAs	ZEB1 has been reported to be associated with mesenchymal phenotypes in advanced pancreatic and other CAs; in thyroid CAs, high expression of ZEB1 is associated with loss of E-cadherin expression

Note: *C* cytoplasmic staining; *M* membranous staining; *N* nuclear staining; *PTC* papillary thyroid carcinoma; *MC* medullary carcinoma; *FC* follicular carcinoma; *FA* follicular adenoma; *CA* carcinoma; *mRNA* messenger RNA; *IHC* immunohistochemical; *PDTC* poorly differentiated thyroid carcinoma; *ATC* anaplastic thyroid carcinoma; *FN* fibronectin; *SCN* solid cell nests; *CASTLE* carcinomas showing thymus-like differentiation of the thyroid; *MEC* primary mucoepidermoid carcinoma; *SMEC* primary sclerosing mucoepidermoid carcinoma with eosinophilia; *ISH* in situ hybridization

TTF1 expression by immunohistochemical analysis was initially exclusively identified in thyroid and lung epithelial tissues, including normal, benign, and malignant tissues. In normal thyroid tissue, TTF1 expression is identified in both follicular epithelial cells and C cells; however, the staining intensity is stronger in follicular cells than that in C cells. In thyroid neoplasms, TTF1 expression was reported in nearly 100% of papillary thyroid carcinomas (PTCs), follicular carcinomas (FCs), and follicular adenomas (FAs), ~90% of poorly differentiated thyroid carcinomas (PDTCs) and medullary carcinomas (MCs), and zero to less than 25% of anaplastic thyroid carcinomas (ATCs). PTCs and FCs often exhibit strong positivity as compared with that of MCs, which tend to be weakly or focally positive. Many FCs demonstrate weak reactivity to TTF1 as well. In our study, 16 of 36 cases of FC showed only weak positivity for TTF1. In general, PDTCs are less intensely positive than differentiated CAs. ATC is usually negative for TTF1. Examples of expression of TTF1 in normal thyroid tissue and various thyroid tumors are shown in Fig. 17.1a–d

PAX8 expression (strong nuclear staining) in normal tissues was observed in follicular cells of the thyroid; Müllerian epithelial cells including endometrium, endocervix, and secretory cells of the fallopian tube; renal tubular epithelium; epithelial lining of the vas deferens; as well as islet cells of the pancreas. Diffuse weak to moderate nuclear staining was observed in some cases of parathyroid tissue and non-neoplastic thymic epithelial cells. Several studies investigated PAX8 expression in thyroid neoplasms, reporting a positive rate of nearly 100% in PTCs and FAs, 91–100% in FCs, 75–100% in PDTCs, and 50–80% in ATCs. MCs were reported to be PAX8-nonreactive by a majority of investigators, with rare exceptions noting PAX8 positivity in 75% (6/8, majority 1+) and 41% (13/32) of cases of MCs. Our study revealed PAX8 expression in 96%, 93%, and 80% of FAs, PTCs, and FCs, respectively. The staining intensity of PAX8 tends to be weaker in FCs than that in PTCs and FAs. A small number of MCs (n = 10) were included in our study; these showed no reactivity to PAX8; 5 cases of ATC were evaluated as well, with only 2 of the 5 showing focal reactivity to PAX8. Examples of the expression of PAX8 in various tumors are shown in Fig. 17.2a–d

TTF2 expression is restricted to the thyroid, anterior pituitary, exocrine cells of the seminiferous tubules of the testis, epidermis, hair follicles, and epithelia of the oropharynx, trachea, and esophagus. TTF2, along with TTF1 and PAX8, are thyroid-specific transcription factors that play critical roles in thyroid organogenesis and differentiation. There are only few studies in literature investigating TTF2 expression by immunohistochemical analysis in human tumors and normal tissues; these found that TTF2 was expressed exclusively in normal thyroid follicular cells, a few C cells in thyroid C-cell hyperplasia and thyroid neoplasms, including 100% cases of PTC, FA, FC, and PDTC; 75% cases of MC in a focal staining pattern; and only 7% cases of ATC with focal 1+ reactivity. No other neoplastic or non-neoplastic tissues showed reactivity. Further studies are deemed necessary to assess the diagnostic utility of TTF2 in routine surgical pathology practice

Thyroglobulin, a thyroid hormone precursor, is a glycoprotein synthesized by thyrocytes, transported to the apical surface and secreted into the follicles, constituting the major component of colloid. Normal thyroid follicular epithelial cells show diffuse reactivity to thyroglobulin. In primary thyroid CAs, the expression of thyroglobulin showed a certain degree of correlation with tumor differentiation. Studies reported 100% expression of thyroglobulin in PTC, 75–96% in FC, 57–92% in PDTC, and near lack of expression in ATC and MC. Metastatic thyroid CAs were reported to show staining patterns similar to those of the primary tumors. The staining pattern in lesions with Hurthle cell morphology was reported to be weak or focal. In our previous study, thyroglobulin expression was demonstrated in 14/14 (100%) cases of normal thyroid tissue, 45/45 (100%) cases of PTC, 36/36 (100%) cases of FC, and 0/10 (0%) cases of MC

FN-1 was reported to be upregulated in thyroid carcinoma compared with normal and benign thyroid tissue. An immunohistochemical panel consisting of FN-1, galectin-3, and Hector Battifora mesothelial-1 (HBME-1) has been reported to be effective in the diagnosis of follicular-cell-derived thyroid tumors. Fibroblasts containing a high number of copies of oncofetal FN messenger RNA (mRNA) were detected, which may cause false-positive results in molecular-based diagnosis of thyroid carcinomas in FNA biopsy specimens

Thyroid CA in general has reduced expression of NIS as compared to normal thyroid tissue. Normal thyroid tissue shows more of the basolateral membranous staining. Apical staining was not noted in normal thyroid tissue, which has been documented in a proportion of thyroid CAs. NIS protein redistribution (cytoplasmic instead of basolateral membranous staining by immunostain) has been reported in several studies

Immunohistochemical studies for CD26/DPPIV showed strong positivity in all PTCs and the majority of FCs, rare reactivity in FA and ATC, and no reactivity in MC, normal thyroid, and goiters

References: [1–301]

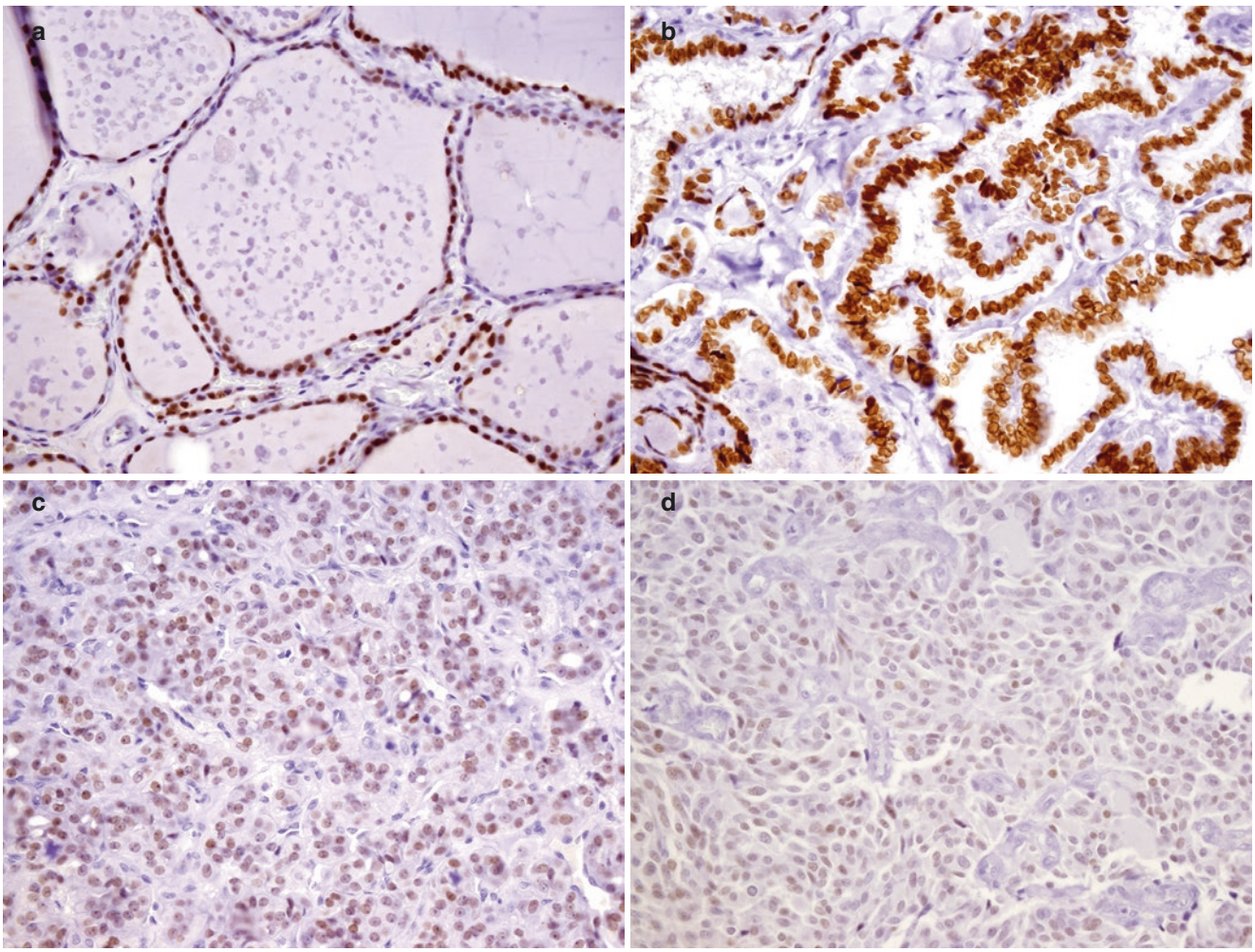

Fig. 17.1 TTF1 expression pattern in normal and various neoplasm of thyroid; (**a**) TTF1 expression in normal thyroid tissue; (**b**) TTF1 expression in papillary thyroid carcinoma, strong and diffuse; (**c**) TTF1 expression in follicular thyroid carcinoma, weaker in intensity; (**d**) TTF1 expression in medullary carcinoma, weaker in intensity

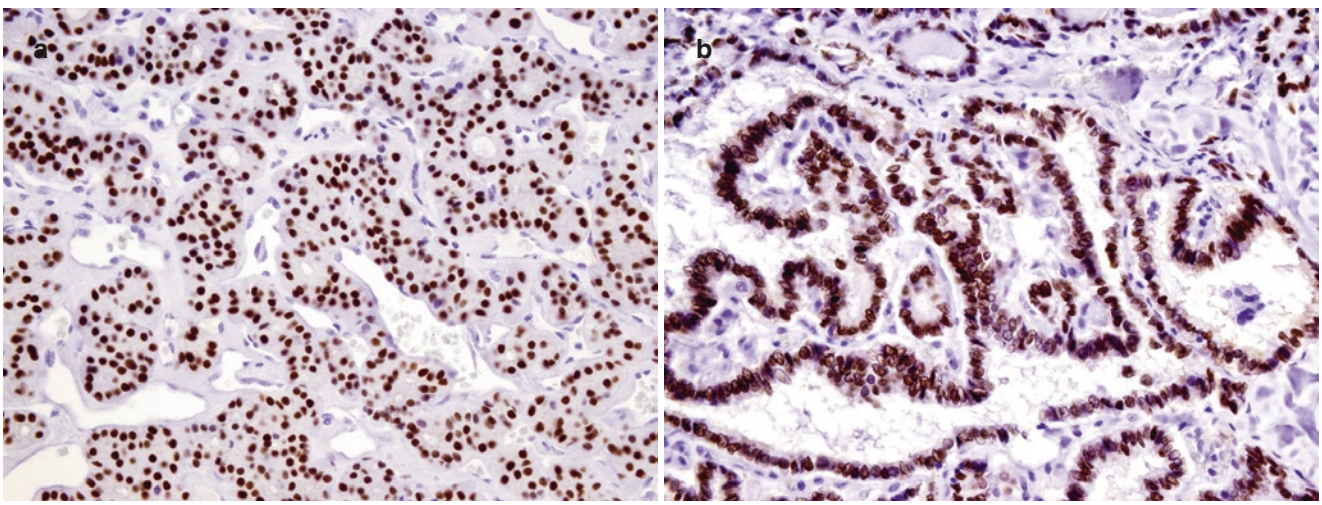

Fig. 17.2 PAX8 expression in various neoplasms of thyroid; (**a**) PAX8 expression in follicular adenoma; (**b**) PAX8 expression in papillary thyroid carcinoma; (**c**) PAX8 expression in follicular thyroid carcinoma, weak; (**d**) Lack of expression of PAX8 in medullary carcinoma

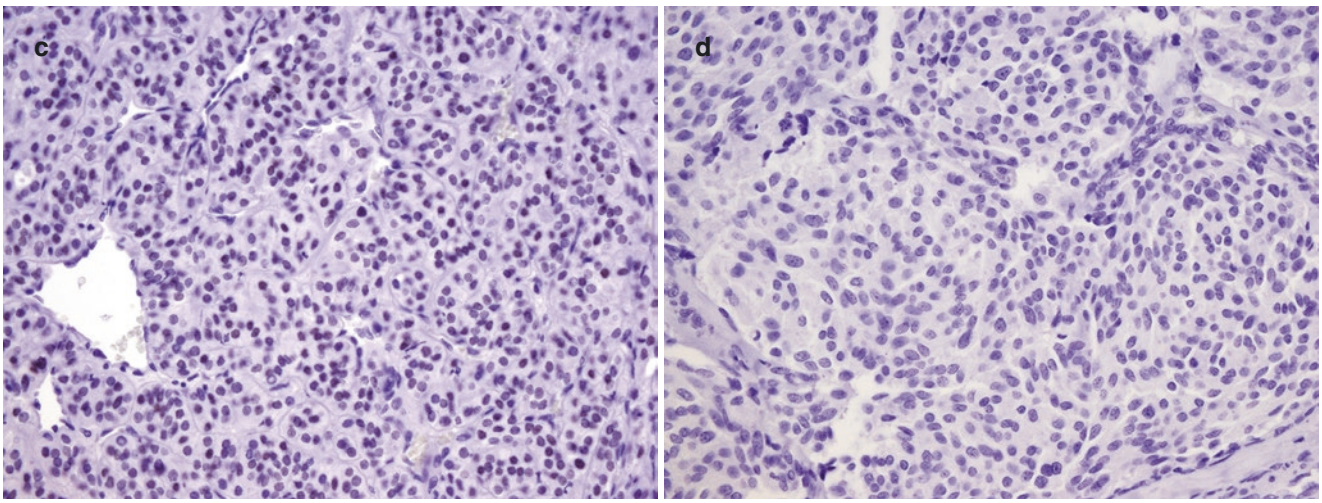

Fig. 17.2 (continued)

Table 17.2 Markers for normal thyroid follicles

	Follicular cells	
Antibodies	Literature	GML data (n = 14)
Thyroglobulin	+	100%
TTF1	+	100%
PAX8	–	100%
Calcitonin	–	0
PTH	–	0
CEA	–	0
CK19	–	0
TROP-2	ND	0
TTF2	+	ND
HBME-1	–	14%
Galectin-3	–	14%
FN-1	–	ND
AE1/AE3	+	100%
CK7	+	100%
EMA	+	0
Chromogranin	–	0
Synaptophysin	–	0
Rb	+	ND
IMP3	–	ND
CD10	–	ND
SNAI2	–	ND
TWIST1	–	ND
EZH2	–	ND
FOXA1	–	ND

References: [1–31, 101, 205, 285, 291–301]

Table 17.3 Summary of useful markers in common tumors of the thyroid gland

Antibodies	PTC	FC	MC	PDTC	ATC
TTF1	+	+	+	+ or –	–
TROP-2	+, M	–	ND	ND	ND
PAX8	+	+ or –	–	+	+ or –
Thyroglobulin	+	+	–	+ or –	–
Calcitonin	–	–	+	–	–
CEA	–	–	+	ND	–
TTF2	+	+	+	+	–
CK19	+	– or +	– or +	– or +	–
HBME-1	+	– or +	– or +	– or +	– or +
Galectin-3	+	– or +	– or +	–	+ or –
CK7	+	+	+	+ or –	+ or –
CK20	–	–	–	–	–
Synaptophysin	+ or –	+ or –	+	ND	–
Chromogranin	–	–	+	ND	–
EZH2	– or +	– or +	ND	– or +	+
E-cadherin	+	+	ND	– or +	–
FOXA1	–	–	+	–	+
Rb	–	–	– or +	–	+
TWIST	–	–	ND	+ or –	+
SNAIL	–	–	ND	– or +	+
Bcl-2	+	+	+	+ or –	–
P53	–	–	– or rare +	+ or –	+
Cyclin D1	+ or –	+ or –	ND	+	+
P21 and p27	+ or –	+ or –	ND	– or +	–

Note: *PTC* papillary thyroid carcinoma; *FC* follicular carcinoma; *MC* medullary thyroid carcinoma; *PDTC* poorly differentiated thyroid carcinoma; *ATC* anaplastic thyroid carcinoma; *M* membranous staining

Table 17.3 (continued)

The application of immunohistochemical biomarkers aids in the accurate classification of histomorphologically equivocal lesions of thyroid. Among the variety of biomarkers reported in the literature, HBME-1, galectin-3, cytokeratin 19 (CK19), Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain, 1 (CITED1), and thyroperoxidase are most promising and are recommended for use in a panel of combined immunomarkers. The combination of HBME-1, galectin-3, and CK19 was by far the most common panel evaluated by investigators, and their diffuse expression has not been reported in benign lesions

HBME-1 is an unelucidated membrane antigen found in the microvilli of mesothelial cells, normal tracheal epithelium, and adenocarcinoma of the lung, pancreas, and breast. Normal thyroid tissue showed virtually no expression of HBME-1. Overexpression of HBME-1 was demonstrated in malignant thyroid neoplasms, especially PTCs. The overall sensitivity of HBME-1 was 78.8% for thyroid malignancy, 87.3% for PTC, and 65.2% for FC. The specificity was 82.1%. HBME-1 expression was also noted in benign thyroid lesions such as FA, nodular goiter (NG), and lymphocytic thyroiditis, usually in a focal staining fashion, with a reported overall positive rate of 26%, 12%, and 19%, respectively. However, several investigators reported reduced or lack of expression of HBME-1 in HCCs or thyroid neoplasms with Hurthle cell features

CK19 is a low-molecular-weight cytokeratin found in variety of simple or glandular epithelia, both normal and their neoplastic counterparts. Normal thyroid follicular epithelium usually lacks expression of CK19, although a few reports noted a focal CK19 staining pattern in benign thyroid tissue, especially in inflamed tissue. In contrast, many investigators documented a strong and diffuse staining pattern of CK19 in PTC and claimed it was a good indicator for PTC. However, its expression in follicular cells of lymphocytic thyroiditis and follicular neoplasms (FA or FC) was also demonstrated; therefore, positive CK19 stain lacks specificity for PTC or malignancy. The overall sensitivity of CK19 was 79.3% for malignancy, 82.2% for PTC, and 44.3% for FC. The specificity was 63.1%. CK19 may have added value as part of a panel of immunomarkers in the diagnosis of PTC

Galectin-3 is a member of a family of β-galactoside-binding animal lectins shown to be involved in tumor progression and metastasis. Overexpression of galectin-3 has been reported in various human CAs, most noticeably in well-differentiated follicular-derived thyroid CAs. Galectin-3 has been found to be useful in differentiating malignant thyroid lesions (such as PTC and the follicular variant of PTC [FVPTC]) from benign lesions. The overall sensitivity of galectin-3 was 84.6% for malignancy, 87.5% for PTC, and 72.6% for FC. The specificity was 83.6%. Variable expression of galectin-3 was identified in MC, HCC, and PDTC. In general, galectin-3 expression in benign lesions is often focal, in contrast to diffuse reactivity in malignant lesions. Normal thyroid tissue is generally negative for galectin-3.

TROP-2, a 35 kDa type 1 transmembranous glycoprotein, was found in our recent study to show a distinct membranous staining pattern in PTCs; in contrast, it was nonreactive or showed only rare focal, weak cytoplasmic staining in follicular neoplasms (FAs and FTCs). We propose that TROP-2 is a potential novel immunomarker for the identification of PTC and can be used in a panel to increase diagnostic accuracy when encountering a difficult follicular-cell-derived lesion.

CK19, HBME-1, and galectin-3 are the best panel of markers to confirm a diagnosis of PTC, with over 90% sensitivity; however, the percentage tends to be lower in follicular variant PTC.

The intensity of PAX8 and TTF1 is stronger in PTC than in FC. TTF1 tends to be weakly expressed in MC and negative in ATC. PAX8 is negative in MC. CEA is a more sensitive marker for MC than calcitonin; up to 5% of MCs can be negative for calcitonin, and nearly all cases are positive for CEA.

References: [1–127, 283].

Table 17.4 Recommended nomenclature for encapsulated follicular-patterned tumors on the bases of the presence or absence of nuclear features of papillary thyroid carcinoma (PTC) and capsular or vascular invasion, 2017 WHO Classification

		Capsular or vascular invasion		
		Present	Questionable	Absent
Nuclear features of PTC	*Present*	Invasive encapsulated FVPTC	WDTUMP	NIFTP
	Questionable	WDCA, NOS		
	Absent	FC	FTUMP	FA

FC follicular carcinoma; *FA* follicular adenoma; *FVPTC* follicular variant of papillary thyroid carcinoma; *WDCA* well-differentiated carcinoma; *WDTUMP* well-differentiated tumor of uncertain malignant potential; *FTUMP* follicular tumor of uncertain malignant potential; *NIFTP* noninvasive follicular thyroid neoplasm with papillary-like nuclear features

The immunophenotype of FA, FC, and FVPTC is referred to in Tables 17.9, 17.10, 17.22, and 17.24. The immunophenotype of FTUMP is similar to that of FA, while the immunophenotype of WDTUMP is similar to that of FVPTC

Reference: [283]

Table 17.5 Markers for solid cell nests

Antibodies	Literature
p63, p40	+
mCEA	+
Thyroglobulin	–
GATA-3	+ (weaker usually)
TTF1	– or W+
Calcitonin	–
FOXA1	+
CGRP	–
Chromogranin	–
Galectin-3	+
AE1/AE3	+
HBME-1	–
PAX-8	–
PTH	–

Note: *W* weak

Solid cell nests demonstrate diffuse p63 staining. p63-positive foci are often present in PTC and Hashimoto's thyroiditis but usually absent in normal, nodular goiter, oncocytic FA, and FC. The typical immunophenotype of solid cell nests is positive for CAM 5.2, AE1/AE3, 34betaE12, CK7, and mCEA and negative for CK20 and PAX-8. GATA-3 is often positive but weaker compared to that in parathyroid gland cells

Recently, FOXA1 expression was noted in solid cell nests, with strong and diffuse nuclear staining; in addition, C cells, C-cell hyperplasia, MC, and ATC also overexpressed FOXA1, but none of the normal follicular cells, nodular goiter, Graves' disease, lymphocytic thyroiditis, and differentiated or poorly differentiated thyroid carcinomas did. There is no expression of FOXA1 in parathyroid glands and paragangliomas

References: [1–3, 128–140, 291, 292, 300, 301]

Table 17.6 Markers for hyalinizing trabecular tumor

Antibodies	Literature
MIB-1, monoclonal	M and C+
Thyroglobulin	+
TTF1	+
Calcitonin	–
HBME-1	–
CK7	+
p63	–
Galectin-3	– or +
RET/PTC	– or +
CK19	– or +
CK20	–

Note: *M* membranous staining; *C* cytoplasmic staining

Distinct membranous and cytoplasmic staining for monoclonal antibody to MIB-1 is shown in Fig. 17.3a, b. Type IV collagen and periodic acid-Schiff (PAS) demonstrate reactivity around tumor cells and nuclear pseudoinclusions

References: [1–3, 141–157]

Table 17.7 Markers for paraganglioma

Antibodies	Literature
Cytokeratins	–
Chromogranin	+
Synaptophysin	+
GATA-3	+
S100 protein	–
Thyroglobulin	–
Calcitonin	–
CEA	–
EMA	–
Vimentin	–
FOXA1	–

GATA-3, a member of the zinc finger transcription factor family, has recently been reported to be overexpressed in breast and urothelial carcinomas; in addition, few studies also documented GATA-3 expression in 49% (81/164) of salivary gland tumors, 95% (20/21) of pheochromocytomas, 89% (31/35) of paragangliomas, and 100% of parathyroid tumors

Immunostain for S100 protein is negative in paraganglioma, except in the sustentacular cells, which are positive for S100 protein

Immunohistochemical studies for CEA, calcitonin, thyroglobulin, EMA, and vimentin are usually negative

References: [1–3, 31, 158–169]

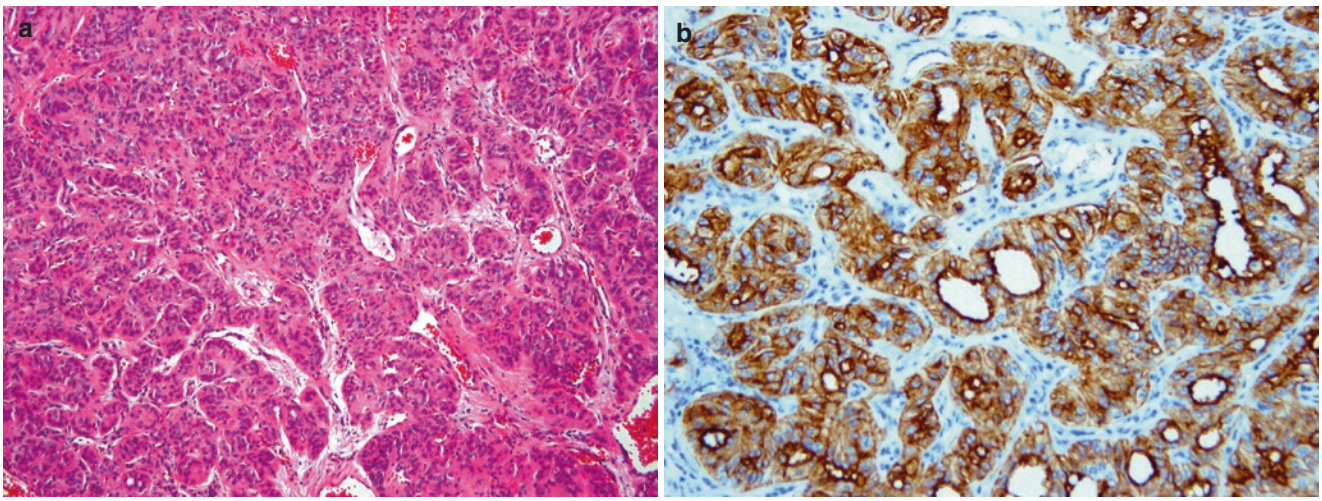

Fig. 17.3 (**a**) Hyalinizing trabecular adenoma, hematoxylin and eosin (H&E); (**b**) hyalinizing trabecular adenoma shows membranous and cytoplasmic staining pattern for MIB-1

Table 17.8 Markers for Hurthle (oncocytic) cell tumor

Antibodies	Literature
TTF1	+
Thyroglobulin	+
AE1/AE3	+
CK7	+
S100A1 and S100A6	+
FOXA1	–

References: [1–3, 32, 170–175]

Table 17.9 Markers for follicular thyroid carcinoma

Antibodies	Literature	GML data (n=36)
Thyroglobulin	+	100%
TTF1	+	94%
HBME-1	+	38%
Galectin-3	– or +	25%
CK17	–	0
TROP-2	ND	0
CK19	– or +	17%
FN-1	+	ND
AE1/AE3	+	81%
IMP3	+ or –	ND
CD10	+ or –	ND
CK7	+	97%
Vimentin	+	100%
Cyclin D1	+	94%
S100A1	+	94%
Chromogranin	–	0
COX-2	– or +	ND
CD56	– or +	44%
p53	– or +	44%
Calcitonin	Usually –	0
mCEA	–	0
E-cadherin	+	ND
Rb	–	ND
FOXA1	–	ND
SNAI2	–	ND
TWIST1	–	ND
TTF2 (FoxE1)	+	ND

Table 17.9 (continued)

Our data (unpublished) reveal that approximately 20% of FCs are nonreactive to AE1/AE3, but nearly all are positive for CK7 (97%). Renal cell carcinoma marker (RCCMa) is frequently expressed in FC and FA and less frequently in PTC (27%). The staining signal of cyclin D1 is weaker in FC than in PTC. CEA and chromogranin are usually negative, but CD56 was detected in 44% of cases in our study. An example of FC negative for AE1/AE3 and positive for RCCMa is shown in Fig. 17.4a, b

IMP3 expression was not detected in benign thyroid tissue, including normal thyroid tissue, nodular goiter, lymphocytic thyroiditis, Graves' disease, and benign thyroid neoplastic tissue (FA and Hurthle cell adenoma). In FCs, 69% (22/32) were IMP3-positive. In Hurthle cell CAs, 21% (4/19) of cases expressed IMP3. In addition, 38% (23/60) of follicular variant PTCs expressed IMP3. Therefore, IMP3 may potentially be diagnostically useful in differentiating malignant and benign follicular patterned thyroid lesions

CD10 was reported negative or focally positive in normal thyroid tissue, nodular goiter, and follicular adenoma with squamous metaplasia or oncocytic changes. Classic PTCs and MCs were reported to be negative for CD10. Tomoda et al. reported a positive rate of 80% (8/10) and 77% (7/9), in FCs and follicular variant PTCs, respectively. However, Nakazawa et al. observed CD10 expression in 27% (3/11) of FCs and 47% (27/57) of PTCs, although the authors did not specify the subtype of the PTC group. Strong and diffuse positivity was detected in 100% (47/47) of ATCs

References: [1–3, 23, 24, 31–49, 101, 205, 284–309, 293, 294]

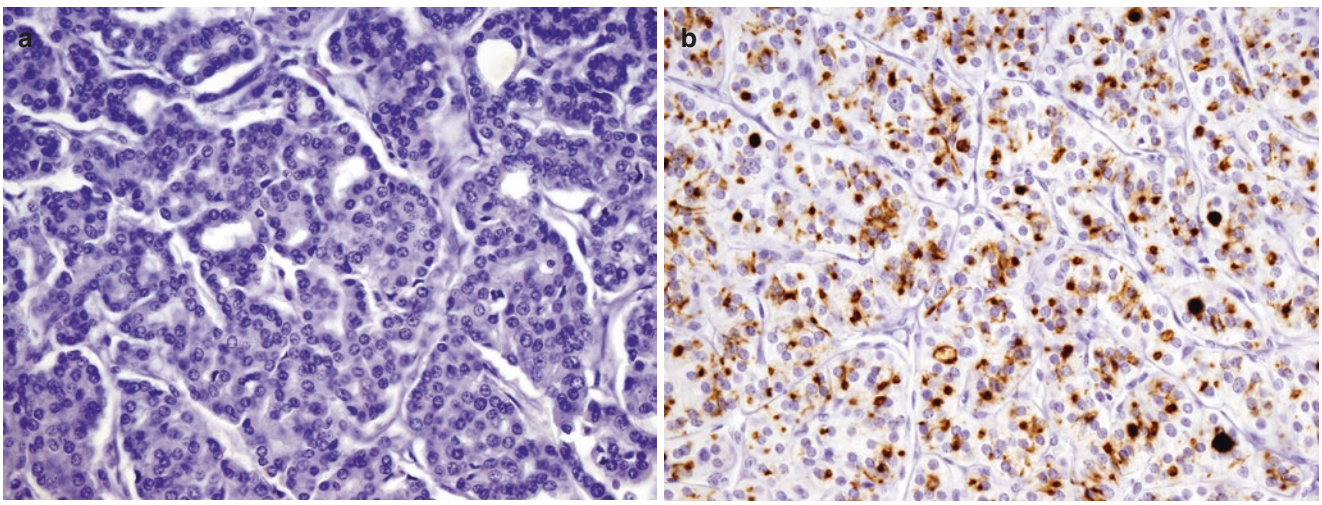

Fig. 17.4 (**a**) Follicular thyroid carcinoma, negative for AE1/3; (**b**) follicular thyroid carcinoma, positive for RCCMa

Table 17.10 Markers for papillary thyroid carcinoma

Antibodies	Literature	GML Data (n=45)
TTF1	+	100%
Thyroglobulin	+	100%
TROP-2	ND	90%, M
Galectin-3	+	93%
CK 19	+	91%
HBME-1	+	93%
RET/PTC	+	ND
PAX8	+	100%
Calcitonin	–	0
Chromogranin	–	0
FN-1	+	ND
CITED1	+	ND
mCEA	–	9% Focal +
S100A1	+	100%
S100A6	+	100%
RCCMa	ND	27%
CDX-2	ND	2%
Beta-catenin	– or +	100%
CK7	+	100%
Rb	–	ND
IMP3	– or +	ND
AE1/AE3	+	100%
E-cadherin	+	ND
Vimentin	+	100%
p53	– or +	9%
CD56	– or +	27%
CD57	+	ND
FOXA1	–	ND
SNAI2	–	ND
TWIST1	–	ND
TTF2 (FoxE1)	+	ND

TROP-2 has been reported to be overexpressed in various human CAs. Recently, we immunohistochemically evaluated the expression of TROP-2 in tissue microarray (TMA) sections of 1234 cases of neoplasms from various organs and found differential staining patterns in thyroid neoplasms. Ninety percent (43/48) of papillary thyroid carcinomas (PTCs) exhibited a strong membranous staining pattern, the majority being diffuse, while follicular adenomas (FAs) or carcinomas (FCs) were nonreactive, except 3% (3/88) which showed rare focal membranous staining as illustrated in Fig. 17.5a–d. Further study of TROP-2 expression in normal thyroid tissue ($n = 20$), benign thyroid lesions (10 surgical cases of each of nodular hyperplasia and chronic lymphocytic thyroiditis), and atypical follicular lesions ($n = 61$, including 33 cases of PTC, 17 cases of atypical follicular neoplasm and 11 cases of adenomatoid nodules with focal nuclear atypia) revealed lack of staining in normal, benign, atypical follicular neoplasm, and adenomatoid nodules with focal nuclear atypia, except rare weak to moderate membranous staining in the lining cells of a degenerative cyst in one of the ten cases of chronic lymphocytic thyroiditis, as illustrated in Fig. 17.5e–f, while 70% (23/33) of PTCs showed distinct membranous reactivity for TROP-2

Galectin-3 is overexpressed in malignant tumors of thyroid gland and usually absent in hyperplastic nodules, NG, and normal follicular epithelium. PTC characteristically demonstrates intense and diffuse cytoplasmic staining for CK19, HBME-1, galectin-3, cyclin D1, S100A1, and vimentin as shown in Fig. 17.6a–h. Rare cases may express CDX-2 (especially the columnar cell variant) in addition to TTF1 and thyroglobulin as shown in Fig. 17.7a–d. PTC of the cribriform-morular variant, poorly differentiated, and anaplastic carcinomas show aberrant nuclear stain for beta-catenin in contrast to the membranous staining pattern in other thyroid CAs. TTF1 and thyroglobulin are usually negative in areas of squamous differentiation

Although galectin-3, HBME-1, and CK19 are not entirely sensitive and specific for the diagnosis of PTC, at the present time it is considered the most effective panel of markers for confirming a diagnosis of PTC, including papillary microcarcinomas

Both S100A1 and S100A6 are usually positive in PTCs; however, normal thyroid follicles are positive as well. Our experience is that S100 is usually negative in both normal thyroid follicles and PTC

RT/PTC and NIS have been tested in the Dako system with various antigen retrieval methods and yielded suboptimal results. Based on our experience, their use as routine diagnostic markers is not recommended

In classic PTC, IMP3 expression was very limited, with focal weak-moderate positivity in 10.8% (4/37) of cases; however, the follicular variant PTCs were reported to express IMP3 in 38% (23/60) of cases

References: [1–3, 23, 24, 31, 50–80, 205]

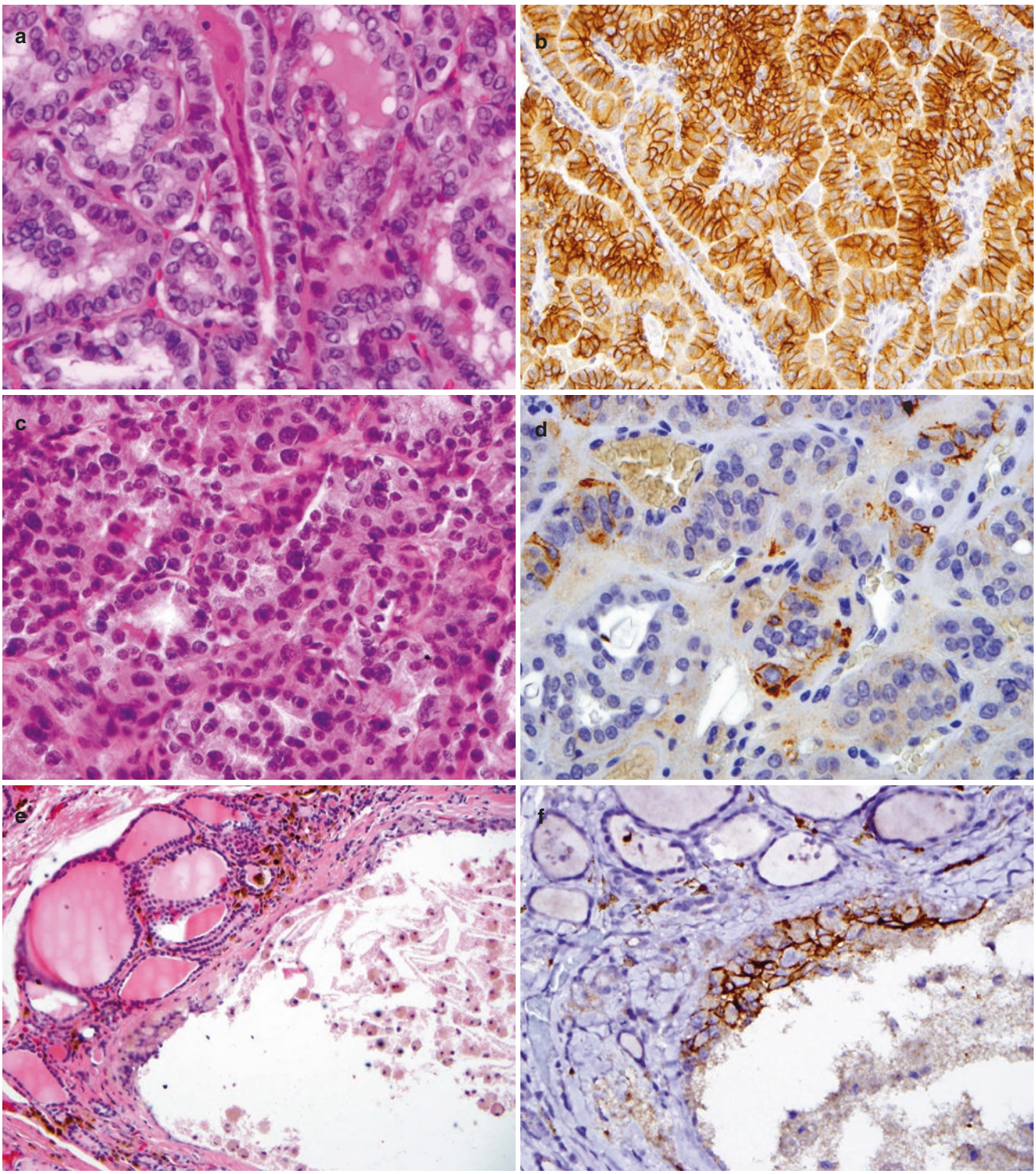

Fig. 17.5 TROP-2 staining pattern in thyroid neoplasm and lesions; (**a**) Papillary thyroid carcinoma (PTC), follicular variant, hematoxylin and eosin (H&E); (**b**) PTC, follicular variant, diffuse (4+) TROP-2 staining, membranous pattern. 90% of PTCs on TMA sections showed TROP-2 expression in a membranous staining pattern; (**c**) follicular carcinoma (FC), H&E; (**d**) FC, focal (1+) strong cytoplasmic staining for TROP-2. Follicular neoplasms (FC and follicular adenoma [FA]) showed no TROP-2 expression; only 2/51 FAs and 4/37 FCs showed focal (1+) cytoplasmic staining without membranous pattern; (**e**) H&E, focal cystic degeneration in a case of lymphocytic thyroiditis; (**f**) Focal membranous staining for TROP-2 in the lining cells of the cyst. All 20 cases of benign thyroid lesions (10 lymphocytic thyroiditis, 10 nodular goiter) were negative for TROP-2

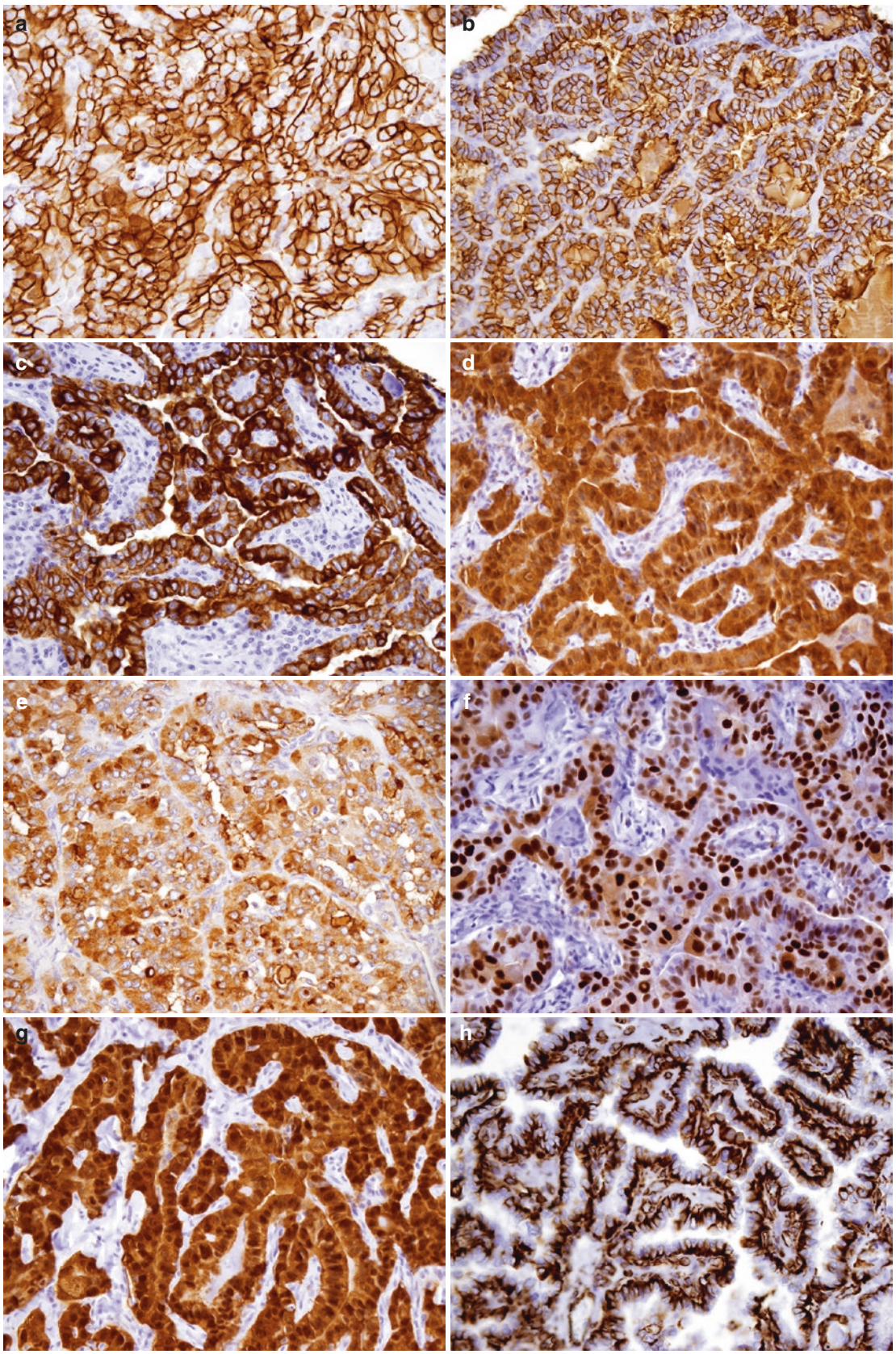

Fig. 17.6 Typical staining pattern of papillary thyroid carcinoma (PTC); (**a**) PTC, membranous staining pattern for TROP2; (**b**) PTC, cytoplasmic, and membranous staining for HBME-1; (**c**) PTC, cytoplasmic, and membranous staining for CK19; (**d**) PTC, cytoplasmic staining for galectin-3; (**e**) PTC, cytoplasmic staining for thyroglobulin; (**f**) PTC, nuclear staining for cyclin D1; (**g**) PTC, cytoplasmic staining for S100A1; (**h**) PTC, cytoplasmic staining for vimentin

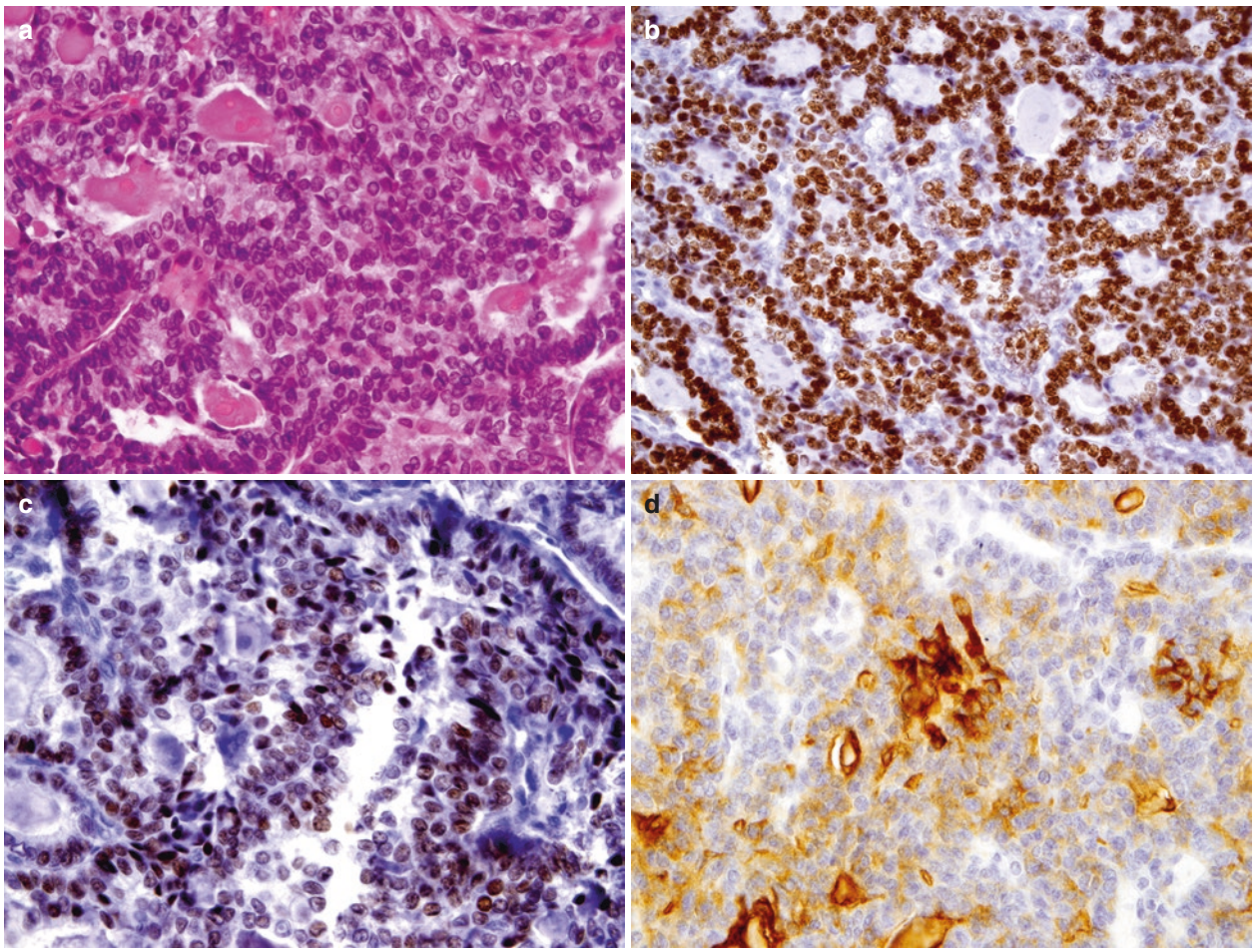

Fig. 17.7 A rare case of papillary thyroid carcinoma (PTC) showing CDX-2 reactivity; (**a**) PTC, hematoxylin and eosin (H&E); (**b**) PTC, CDX-2 positive; (**c**) PTC, TTF1 positive; (**d**) PTC, thyroglobulin positive

Table 17.11 Markers for medullary thyroid carcinoma

Antibodies	Literature	GML data (n=10)
Calcitonin	+	100%
Thyroglobulin	–	0
TTF1	+	100%, w+
CEA	+	100%
Chromogranin	+	100%
Synaptophysin	+	100%
FOXA1	+	ND
CGRP	+	ND
Neurofilament protein	+	ND
PAX8	–	0
AE1/AE3	+	100%
CK7	+	100%
CK20	–	0
CK5/6	–	0
Vimentin	+ or –	100%
COX-2	+	ND
Galectin-3	– or +	0
S100A1	ND	10%
S100A6	ND	100%
CD10	–	ND
Rb	+ or –	ND
TTF2	+	ND

Table 17.11 (continued)

The typical phenotype of MC is positive for calcitonin, CGRP, TTF1, mCEA, and neuroendocrine markers and negative for thyroglobulin (with focal stain in entrapped follicles or deposits). Rare cases of MC are negative for calcitonin (reported in up to 5% of cases), and the calcitonin-negative MC cases are usually positive for mCEA. It has been reported that 85% of cases of MC are positive for neurofilament protein, whereas normal C cells are usually negative

Our data also showed MC is usually positive for Ber-EP4 and S100A6 but negative for TAG 72 and S100A1. An example of MC positive for calcitonin, CEA, chromogranin, and S100A6 and negative for S100A1 is shown in Fig. 17.8a–f

Nonaka reported that strong diffuse nuclear expression of FOXA1 was identified in 100% of MCs (67/67), C-cell hyperplasias (5/5), solid cell nests (5/5), and normal C cells; 55% (33/60) of ATCs expressed FOXA1 with variable intensity and extent. Other tumors and tissues, including PTC ($n = 21$), FC/A ($n = 27$), HCC/A ($n = 15$), PDC ($n = 13$), NG ($n = 10$), Hashimoto's thyroiditis ($n = 10$), Graves' disease ($n = 10$), parathyroid glands/hyperplasia/adenoma/carcinoma ($n = 25$), and paragangliomas ($n = 23$) lacked FOXA1 expression. Nucera et al. studied FOXA1 mRNA and protein expression on TMA sections comprising 15 normal thyroid tissues, 30 FAs, 58 NGs, 8 cases of lymphocytic thyroiditis, 6 of Graves' disease, 48 PTCs, and 12 FCs, and on tissue sections of 3 PDCs and 20 ATCs, to reveal FOXA1 expression in 90% (18/20) of ATCs and none of the others, except foci of squamous metaplasia in 2 cases of PTC. MC was not included in this study

References: [1–3, 31, 81–100, 291, 292]

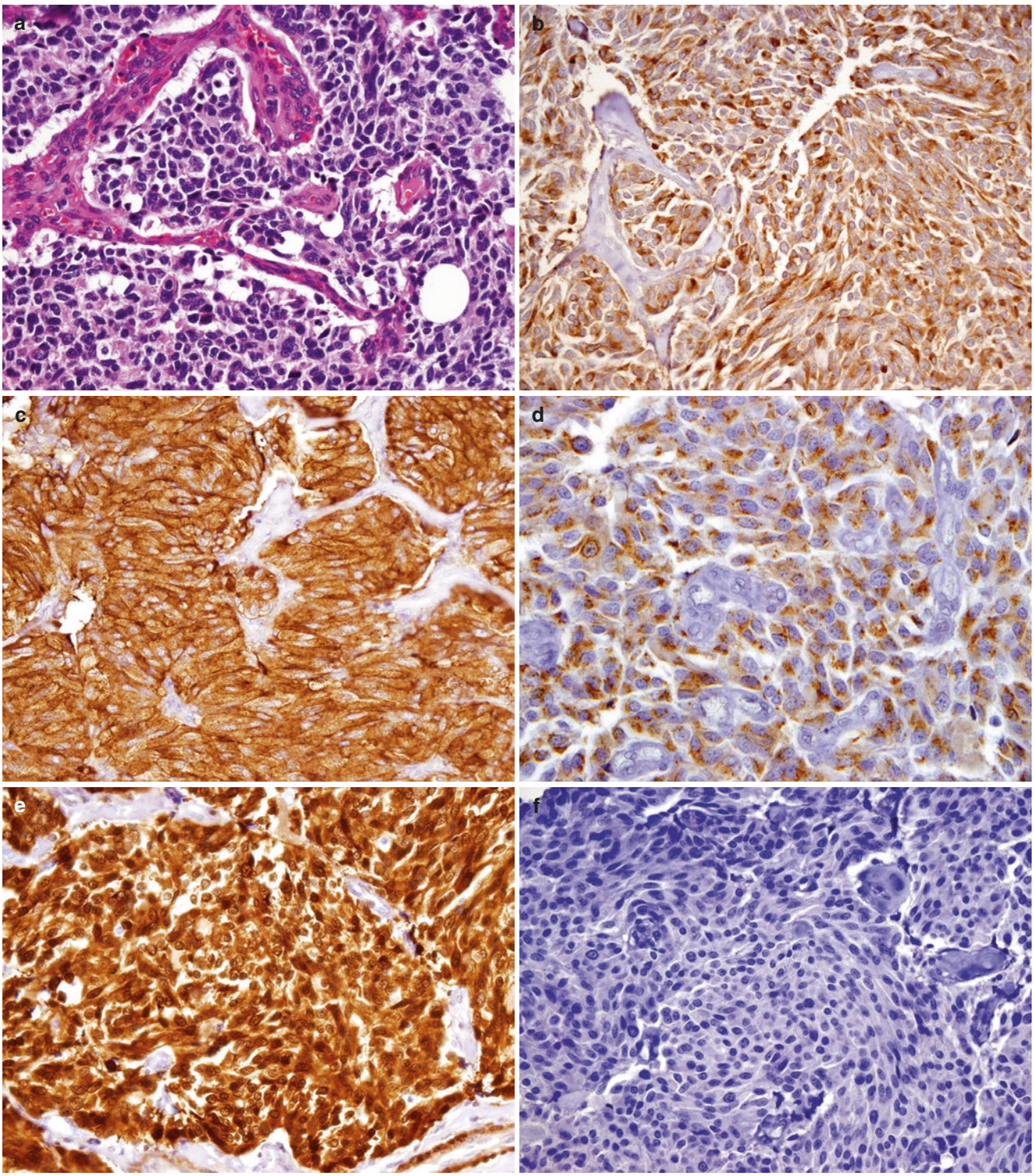

Fig. 17.8 Typical phenotype of medullary carcinoma (MC); (**a**) MC, hematoxylin and eosin (H&E); (**b**) MC, positive for calcitonin; (**c**) MC, positive for CEA; (**d**) MC, positive for chromogranin; (**e**) MC, positive for S100A6; (**f**) MC, negative for S100A1

Table 17.12 Markers for poorly differentiated thyroid carcinoma

Antibodies	Literature
Thyroglobulin	+
TTF1	+
CEA	–
AE1/AE3	+
Cyclin D1	+, N
HBME-1	+ or –
CK19	+ or –
RET/PTC	+ or –
Galectin-3	–
PAX2	–
p53	+ or –
TTF2	+
PAX8	+
IMP3	+ or –
EZH2	– or +
TWIST	+ or –
SNAIL	– or +
E-cadherin	– or +
FOXA1	–
ZEB1	–
Rb	–

Thyroglobulin stain is often weak and focal, showing a peculiar dot-like paranuclear staining pattern which is not specific and may be observed in other benign or malignant lesions with a predominantly solid/trabecular pattern of growth

In PDTCs, 59% (61/103) of cases were positive for IMP3 (semi-quantitative scoring of >2), which is also an indicator of poor prognosis

References: [1–3, 31, 101–113, 205, 288–292]

Table 17.13 Markers for anaplastic thyroid carcinoma

Antibodies	Literature
AE1/AE3	+
Pan-CK	+
Vimentin	+
PAX8	+ or –
Thyroglobulin	–
TTF1	–
Galectin-3	+
IMP3	+
p53	+
FOXA1	+
SNAI2	+
TWIST1	+
EZH2	+
E-cadherin	– (loss of membranous staining)
ZEB1	+ or –
Rb	+
mCEA	–
Calcitonin	–
HBME-1	– or +
CK19	– or +
EMA/MUC1	– or +
CD10	+
CD56	–

Table 17.13 (continued)

The most useful epithelial markers for ATC are cytokeratins, with a reported positivity rate of 50–100%. By using AE1/AE3 or Pan-CK, about 80% of cases demonstrate cytokeratin expression. Thyroglobulin is negative in ATC. When present, it is most likely the result of diffusion from entrapped or adjacent non-neoplastic thyroid tissue or from residual well-differentiated neoplastic components. TTF1 is usually nonreactive in ATC. Few studies show rare cases of ATC demonstrating isolated TTF1-reactive tumor cells, which may be due to the presence of a differentiated thyroid carcinoma component. ATCs typically show strong reactivity to p53. PAX8 is positive in about 79% of ATCs and negative in normal and neoplastic lung tissue. Therefore, PAX8 can be a useful marker in the differential diagnosis of ATC from poorly differentiated pulmonary adenocarcinoma. In our study, only 2 of 5 cases of ATC were positive for PAX8

IMP3 expression was reported highest in undifferentiated CAs (95%), and not detected in benign thyroid tissue

Nakazawa et al. reported strong and diffuse CD10 expression in 100% (47/47) of ATCs

Studies reported that nuclear expression for SNAI2 was identified in >80% (8/10; 5/6) of ATCs and for TWIST1 in 50–100% (5/10; 6/6) of ATCs. In addition, loss of E-cadherin membranous staining was observed in 70–100% (7/10; 6/6) of ATCs. In the study conducted by Montemayor-Garcia et al., the ATCs demonstrated loss of E-cadherin expression in 70% (7/10) of cases, while intact membranous staining for E-cadherin was observed in 100% of normal thyroid tissues ($n = 10$), FAs ($n = 32$), FCs ($n = 28$), and PTCs ($n = 57$). Nuclear expression for ZEB1 was reported in 60% (6/10) of ATCs in that study but none of the others

Overexpression of enhancer of zeste homolog 2 (EZH2) has been reported in various malignancies. In thyroid glands, Masudo et al. observed that no EZH2 expression was detected in normal thyroid tissue or differentiated thyroid carcinomas, while 87.5% (42/48) of ATCs and ~20% (23/116) of PDCs exhibited EZH2 overexpression

References: [1–3, 31, 101, 112, 114–127, 205, 284–297]

Table 17.14 Markers for mucoepidermoid carcinoma of the thyroid

Antibody	Pattern
CKs (AE1/AE3, CAM 5.2)	+
Thyroglobulin	+
PAX8	+
TTF1	+
Calcitonin	–
Neuron-specific enolase	+
Vimentin	+
P-cadherin	+
P63	+
CGRP	–
Chromogranin, Synaptophysin	–
CEA	+ or –

There are few case reports in the literature. Immunohistochemically, most of these cases are reported positive for cytokeratin (AE1/AE3, CAM 5.2), thyroglobulin (at least focally), and neuron-specific enolase and negative for calcitonin and neuroendocrine markers (chromogranin and synaptophysin). The immunoprofile for CEA (polyclonal or monoclonal) is variable

References: [1–3, 176–190, 283]

Table 17.15 Markers for sclerosing mucoepidermoid carcinoma with eosinophilia of thyroid

Antibody	Literature
CKs (AE1/AE3, CAM 5.2)	+
CK19	+
P63	+
CD10	+
Galectin-3	+
Thyroglobulin	–
Calcitonin	–
S100	–
TTF1	+ or –
CEA	+ or –

There are only few cases reported in the literature. Immunohistochemically, most of these cases are reported positive for cytokeratin (AE1/AE3, CAM 5.2), CK19, p63, CD10, and galectin-3 and negative for thyroglobulin, calcitonin, and S100. TTF1 was reported positive in about 50% of cases

References: [1–3, 176–190, 283]

Table 17.16 Markers for spindle epithelial tumor with thymus-like differentiation

Antibody	Literature
HMWCK (CK903, CK5/6, CK14)	+
CK7	+
LMWCK (CAM5.2)	– or +
P63	– or +
CD10	– or +
CEA	–
Thyroglobulin	–
Calcitonin	–
S100	–
TTF1	+ or –
CD5	–

Both spindled and glandular cells express HMWCK diffusely, and that can be useful in distinguishing them from their histological mimics, such as synovial sarcoma. The spindled cells may express myoepithelial differentiation, such as p63 and CD10

References: [1–3, 176–190, 283, 301]

What Is the Utility of BRAF Mutation-Specific Antibody in Diagnosing Papillary Thyroid Carcinoma?

The BRAF oncogene has been demonstrated to be mutated in several types of tumors, such as colorectal adenocarcinoma, PTC, glioma, gastrointestinal adenocarcinoma, melanoma, and pulmonary adenocarcinoma. The most common mutation in BRAF is due to a T to A switch at position 1796, which results in an alteration from valine to glutamate at V600E. The BRAF V600E point mutation has been reported in 30–90% of PTCs of all histotypes, with a higher frequency in tall cell variant (60–95%) and oncocytic variant and a much lower frequency (5–25%) in follicular variant. The BRAF V600E mutation is generally negative in benign follicular lesions, normal thyroid tissue, MC, and FC. A meta-analysis of 5655 patients suggested PTC with the BRAF mutation is associated with a higher risk of recurrent persistent disease, lymph node metastasis, and extrathyroidal extension. Many molecular techniques have been employed to detect the BRAF V600E point mutation, including single-strand conformation polymorphism, mutation-specific polymerase chain reaction (PCR), direct gene sequencing, and colorimetric mutation analysis. These methods tend to be expensive, time-consuming, labor-intensive, and difficult to validate and implement in some clinical settings.

There are two commercially available, mutation-specific antibodies against BRAF V600E; one is VE1 clone (Spring Bioscience, Pleasanton, CA) and the other is anti-B-Raf mouse monoclonal antibody (New East Bioscience, Malvern, PA). Most studies used the VE1 clone, and only rare studies used anti-B-Raf mouse monoclonal antibody. In general, BRAF mutation-specific antibody has been shown to be useful in detection of the BRAF V600 mutation, with a sensitivity and specificity of over 95% when compared to other molecular methods. In fact, some studies suggested that anti-BRAF mutation-specific antibody may be more sensitive than molecular testing in detecting the BRAF mutation. An example of the BRAF mutation in a papillary thyroid microcarcinoma detected by IHC using the VE1 clone is shown in Fig. 17.9a, b.

References: [191–197].

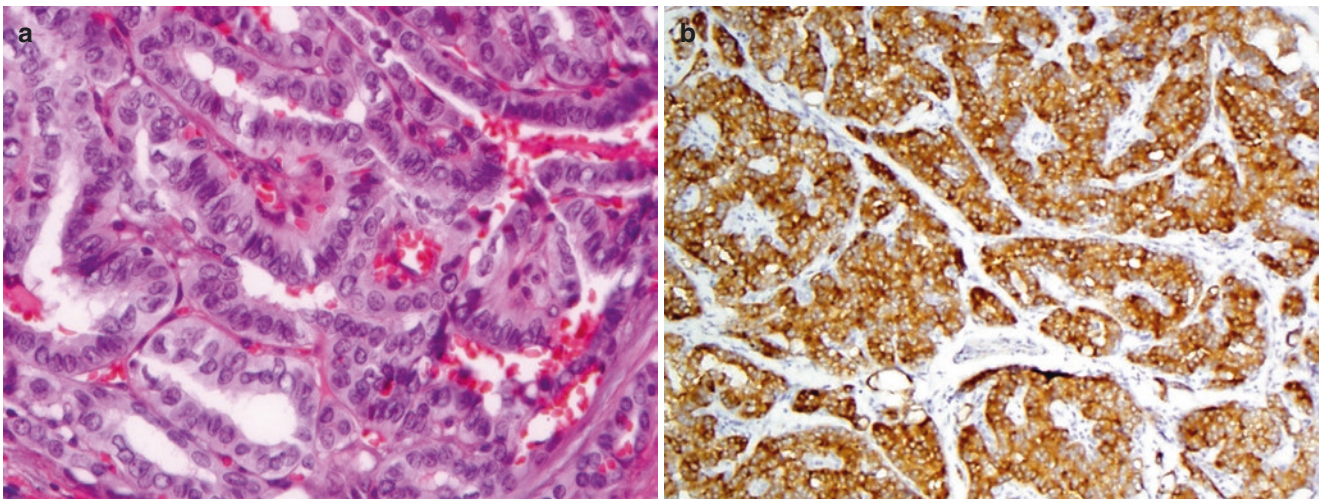

Fig. 17.9 (**a**) Papillary thyroid carcinoma (PTC), hematoxylin and eosin (H&E); (**b**) PTC, positive for BRAF

Differential Diagnosis

Table 17.17 Solid cell nests versus nodular C-cell hyperplasia

Antibody	Solid cell nests	Nodular C–cell hyperplasia
p63	+	–
Calcitonin	–	+
Galectin-3	+	–
Chromogranin	–	+
Synaptophysin	–	+
TTF1	–	+, focal
Thyroglobulin	–	–
AE1/AE3	+	+
CEA	+	+
FOXA1	+	+

References: [1–3, 128–140, 191–195, 291, 292]

Table 17.18 Solid cell nests versus papillary microcarcinoma

Antibody	Solid cell nests	Papillary microcarcinoma
CEA	+	–
Thyroglobulin	–	+
p63	+, diffuse	– or +, focal, variable
TTF1	– or focal w+	+, diffuse and strong
HBME-1	–	+
TROP-2	ND	+, M
CGRP	–	–
FOXA1	+	–
AE1/AE3	+	+
CK19	+	+
Galectin-3	+	+
Chromogranin	–	– or +
Synaptophysin	–	– or +
Calcitonin	–	–

References: [1–3, 23, 24, 31, 50–80, 128–140, 291, 292]

Table 17.19 Hyalinizing trabecular tumor versus paraganglioma

Antibody	Hyalinizing trabecular tumor	Paraganglioma
Thyroglobulin	+	–
TTF1	+	–
CK7	+	–
AE1/AE3	+	–
MIB-1 (Ki-67)	+, M, C	–
GATA-3	–	+
Chromogranin	– or +	+
S100	–	Scattered SC +
Vimentin	+	–
Calcitonin	–	–
FOXA1	ND	–

Note: *M* membranous staining; *C* cytoplasmic staining; *SC* sustentacular cell

References: [1–3, 31, 141–169]

Table 17.20 Hyalinizing trabecular tumor versus papillary carcinoma

Antibody	Hyalinizing trabecular tumor	Papillary carcinoma
MIB-1	+, M, C	+, N
HBME-1	– or +	+
34betaE12	–	+
CK19	– or +	+
Galectin-3	– or +	+
TROP-2	ND	+, M
Thyroglobulin	+	+
TTF1	+	+
Calcitonin	–	–
CK7	+	+
Rb	ND	–

Note: *M* membranous staining; *C* cytoplasmic staining; *N* nuclear staining

MIB-1 is a marker-labeling nuclei in general but demonstrating membranous and cytoplasmic staining in hyalinizing trabecular tumor

References: [1–3, 23, 24, 31, 50–80, 141–157]

Table 17.21 Hyalinizing trabecular tumor versus medullary carcinoma

Antibody	Hyalinizing trabecular tumor	Medullary carcinoma
Calcitonin	–	+
MIB-1 (Ki-67)	+, M, C	+, N
TGB	+	–
Mcea	ND	+
Chromogranin	– or focal +	+
TTF1	+	Weakly +
FOXA1	ND	+
CK7	+	+
Rb	ND	+ or –

Note: *M* membranous staining; *C* cytoplasmic staining; *N* nuclear staining

References: [1–3, 31, 81–100, 141–157]

Table 17.22 Follicular adenoma versus follicular carcinoma

Antibody	Follicular adenoma	Follicular carcinoma
FN-1	– or +	+
HBME-1	– or +	+ or –
CITED1	– or +	+ or –
Galectin-3	– or +	+ or –
IMP3	–	+ or –
Rb	+	–
CK19	– or +	– or +
CD10	–	+ or –
RET/PTC	–	+ or –
CD44v6	– or +	+

Retinoblastoma (Rb), a 110–114 kDa nuclear protein, plays a key role in the regulation of cell growth arrest. Rb expression is present in all cells. Anwar et al. studied Rb expression in a series of benign and malignant thyroid lesions, including 19 NGs, 34 FAs, 7 HAs, 9 FCs, 23 PTCs (including FVPTC), 5 HCs, 4 PDCs, 4 ATCs, and 6 MCs. Loss of Rb expression was observed in a majority of the differentiated to poorly differentiated thyroid carcinomas, including 100% of PTCs and PDCs; 89% of FCs; 80% of HCs; and 50% of MCs; in contrast, intact Rb expression was noted in benign thyroid lesions, including 100% of FAs and 89% of NGs, with the exception of HA, which showed 100% of cases with loss of expression for Rb

References: [1–3, 31–49, 203–215, 293]

Table 17.23 Differentiation of follicular adenoma with clear cell changes

Antibody	Follicular adenoma with clear cell changes	Metastatic renal cell carcinoma	Parathyroid adenoma
Chromogranin	–	–	+
TTF1, TTF2	+	–	–
Thyroglobulin	+	–	–
PTH	–	–	+
GATA-3	–	–	+
KIM-1	–	+	–
VHL	–	+	–
RCCMa	– or +	+	+
PAX-8	+	+	–
CD10	–	+	ND
CK7	+	– or +	ND
Vimentin	+	+	ND

Our experience shows that von Hippel-Lindau gene product (VHL) and KIM-1 (kidney injury molecule-1) are usually positive in metastatic renal cell carcinoma and negative in follicular adenoma and parathyroid adenoma or carcinoma. RCCMa is not very useful, since the positive staining is frequently observed in normal thyroid follicular epithelium and neoplasms

References: [1–3, 31, 216–218]

Table 17.24 Follicular variant of papillary thyroid carcinoma versus follicular neoplasm

Antibody	FVPTC	Follicular neoplasm
TROP-2	+, M	–
CK19	+	– or +
FN-1	+	–
HBME-1	+	– or +
Galectin-3	+	– or +
CD57	+	– or +

Note: *FVPTC* follicular variant of papillary thyroid carcinoma; *M* membranous staining

References: [1–3, 23, 24, 31, 50–80, 219–222]

Table 17.25 Differential diagnosis of anaplastic carcinoma

Antibody	Anaplastic carcinoma	Rhabdomyosarcoma	Leiomyosarcoma	Angiosarcoma	Malignant melanoma
PAX8	+	–	–	–	–
AE1/AE3	+	–	–	– or +	–
FOXA1	+	ND	ND	ND	ND
MSA	–	+	+	– or +	–
Desmin	–	+	+	–	–
Myogenin	–	+	–	–	–
MyoD1	–	+	–	–	–
ERG	ND	–	–	+	–
Factor VIII	–	–	–	+	–
CD31	– or +	–	–	+	–
CD34	– or +	– or +	– or +	+	–
S100	– or +	–	–	–	+
HMB-45	ND	–	– or +	–	+
MART-1	–	–	–	–	+
Vimentin	+	+	+	+	+

References: [1–3, 31, 112, 114–127, 223–243]

Table 17.26 Metastatic cystic papillary carcinoma versus metastatic cystic squamous cell carcinoma

Antibody	Metastatic cystic papillary carcinoma	Metastatic cystic squamous cell carcinoma
CD57	+	–
CK5/6	–	+
GLUT-1	– or +	+
Rb	–	+
TTF1	+	–
PAX-8	+	–
TGB	+	–
CK7	+	– or +
CK14	– or +	+
Vimentin	+	– or +
p63, p40	– or +	+
CK19	+	+

References: [1–3, 31, 50–80, 244–247]

Table 17.27 Proliferative, prognostic, and cell cycling markers in normal follicular epithelium and thyroid carcinomas

Antibody	NL	WDTC	PDTC	UDTC
MIB-1 (Ki-67)	Very low (<5%)	Low (<10%)	Intermediate (10–30%)	High (>30%)
Bcl-2	+	+	Usually +	–
Cyclin D1	–	Low	Intermediate	High
p27	+	High	Intermediate	Low

Note: *NL* normal; *WDTC* well-differentiated thyroid carcinoma; *PDTC* poorly differentiated thyroid carcinoma; *UDTC* undifferentiated thyroid carcinoma

Bcl-2 has been reported a prognostic marker for worse survival. Some groups found low levels of expression of p27 in PTCs. Studies show variably reduced E-cadherin expression in well-differentiated thyroid carcinomas, and it is frequently absent in poorly differentiated and anaplastic carcinomas. Loss of E-cadherin expression is an adverse prognostic factor in differentiated thyroid carcinomas. Studies reveal that loss of membranous beta-catenin immunostaining is an indicator of loss of differentiation and adverse prognosis. Aberrant nuclear immunoreactivity for beta-catenin is associated with stabilizing CTNNB1 exon 3 mutations that are found almost exclusively in PDTCs and ATCs. The cribriform-morular variant of PTC has been reported to demonstrate cytoplasmic and nuclear accumulation of beta-catenin and CTNNB1 exon 3 mutation

References: [1–3, 31, 101–113, 248–254]

Table 17.28 Summary of useful markers in the evaluation of the parathyroid gland

Antibodies	Staining pattern	Function	Key applications and pitfalls
PTH	C	An 84-amino-acid peptide secreted by parathyroid chief cells, regulating calcium metabolism	Parathyroid gland specific; staining is more intense in normal than in hyperplastic or neoplastic tissue
Chromogranin A	C	A member of a family of acidic glycoproteins that localize within secretory granules of endocrine, neuroendocrine, and neuronal tissue.	Positive in normal, hyperplastic, and neoplastic parathyroid tissue, more intense in normal than other tissue
Gcm2	N	Glial cells missing homolog 2, also known as chorion-specific transcription factor GCMb: the key transcription factor that acts as an essential regulator of parathyroid gland development	Highly specific for parathyroid tissue
CK8/18	C	Members of the keratin family, expressed in simple epithelia, not in stratified epithelial cells	Positive in adenomatous and normal parathyroid tissue
CK19	C	A member of the keratin family of intermediate filament proteins	Positive in adenomatous and normal parathyroid tissue
Parafibromin (HRPT2)	N, C	The 531-amino-acid protein product of HRPT2 gene responsible for hyperthyroidism-jaw tumor syndrome	Loss of expression has been suggested to be of value in making the diagnosis of parathyroid carcinoma
GATA-3	N	A 50-kDa nuclear protein, member of the GATA family of transcription factors	GATA-3 expression was reported in normal and neoplastic parathyroid tissue

Note: *C* cytoplasmic staining; *N* nuclear staining
References: [1–3, 167–169, 255–283]

Parathyroid Gland

Table 17.29 Markers for normal parathyroid gland

Antibodies	Chief cells
Parathyroid hormone (PTH)	+, C
Gcm2	+, N
Chromogranin A	+, C
GATA-3	+
p53	–
CK19, CK8/18	+

Note: *C* cytoplasmic staining; *N* nuclear staining
References: [1–3, 167–169, 255–258, 273–279]

Table 17.30 Markers for parathyroid neoplasms

Antibodies	Parathyroid adenoma	Parathyroid carcinoma
Parathyroid hormone (PTH)	+	+
Chromogranin A	+	+
Parafibromin (HRPT2)	+	–
Galectin-3	–	+
MIB-1 (Ki-67)	Low (≤4%)	High (6–8.4%)
p27, Bcl-2, MDM2	+	– or +
PGP9.5	–	+
Synaptophysin	+	+
Thyroglobulin	–	–
TTF1	–	–
CK8, 18, 19, CAM5.2	+	+
GATA-3	+	+
Rb	+	– or +
RCCMa	+	+ or –
APC	+	–

APC adenomatous polyposis coli; *PGP9.5* protein gene product 9.5

Immunohistochemical studies may be helpful in supporting a diagnosis of carcinoma or adenoma, but none is discriminant. Many studies (molecular and/or immunohistochemical analyses) reveal that overexpression of p27, Bcl-2, and MDM2 is a more frequent finding among parathyroid adenoma than carcinoma, but this finding is not consistent among studies. High Ki-67 proliferative index is more often seen in parathyroid carcinoma

An example of expression of parafibromin in parathyroid adenoma and carcinoma is shown in Fig. 17.10a, b
References: [1–3, 167–169, 255–282]

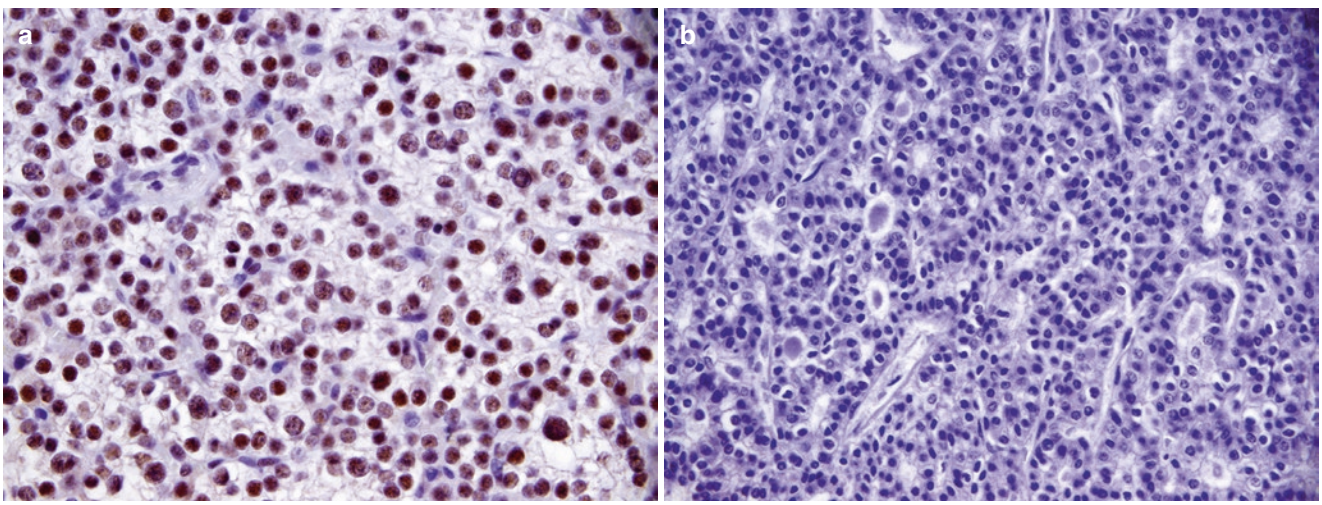

Fig. 17.10 (**a**) Expression of parafibromin is more frequent in parathyroid adenoma; (**b**) loss expression of parafibromin in parathyroid carcinoma

Adrenal Glands

Table 17.31 Summary of useful markers for evaluation of adrenal glands

Antibodies	Staining pattern	Function	Key applications and Pitfalls
Bcl2	C	B-cell lymphoma 2 protein in the adrenal is expressed in a steroid-dependent fashion and inhibits steroid-induced apoptosis	Suggested to be of help in the differential between adrenal cortical (reactive) and medullary tumors (unreactive)
Calretinin	N; C	Calcium-binding protein detected in over two-thirds of adrenal cortical neoplasms	Used in identifying adrenal cortical neoplasms and distinguishing them from adrenal medullary neoplasms
CD56	C; M	Neuron adhesion molecules	Pheochromocytomas are typically strongly positive. Focal positivity noted in adrenal cortical carcinomas. Positive in neuroendocrine tumor including small cell carcinoma and a subset of non-small cell carcinoma with neuroendocrine differentiation
Chromogranin A	C	Present in neurotransmitter dense-core secretory vesicles	Found in most pheochromocytomas, neuroblastomas, paragangliomas; usually negative in cortical neoplasms
D2-40	C; M	Oncofetal transmembrane mucoprotein	Expressed in neoplastic and non-neoeplastic adrenal cortex. Also expressed in germ cell tumors, lymphatic endothelium, and mesothelium
EMA	M	Epithelial marker	Typically negative in pheochromocytomas and adrenal cortical neoplasms
ENT1	C; M	Equalibrative nucleoside transporter 1 plays a role in adenosine signaling and cellular uptake of nucleoside for DNA and RNA synthesis. It is a target of adenosine reuptake inhibitors like gemcitabine	
Inhibin A	C	Dimeric glycoprotein produced by the gonads that inhibits FSH secretion by the pituitary	More sensitive but less specific than MART-1 in identifying adrenal cortical tumors
MART-1	C	Melanoma marker, cross reacts with an epitope present in steroid producing cells	Used in identifying adrenal cortical neoplasms and distinguishing them from adrenal medullary and metastatic neoplasms; also commonly referred to as A103 and Melan-A in literature
Vimentin	C	Intermediate filament	Frequently positive in both adrenal cortical neoplasms and pheochromocytomas
S100	N; C	Belongs to the family of S100 calcium-binding proteins	Identifies sustentacular cells in the adrenal medulla
SF-1	N	Nuclear hormone receptor, regulates endocrine development and function of adrenal glands and gonads	Expressed in steroidogenic tissues
SRC1	C	Steroid receptor coactivator 1 is an inner nuclear membrane protein that plays a role in transcription across many signaling pathways with a major role in mediating hormone receptor responsiveness	
Synaptophysin	C	Present in neurotransmitter dense-core secretory vesicles	Found in all pheochromocytomas and paragangliomas

References: [302–322]

Table 17.32 Expression of markers in normal adrenal gland

	Cortex	Medulla
INHA	+[a]	–
D2-40	+	–
Bcl-2	+	–
SF-1	+	ND
Calretinin	+	–
Melan-A	+	–
AE1/AE3	+	–
INHB/activin	–	+
P504s	–	–
S100	–	–[b]
PAX8	–	–
CA IX	–	ND

Notes:

[a]Strong staining seen in zona reticularis; weak staining in zona fasciculata; no staining in zona glomerulosa

[b]Chief cells are negative; positive staining occurs in sustentacular cells

References: [302, 305, 308, 314, 317, 322–328]

Table 17.33 Markers for sustentacular cells versus chief cells in the medulla

	Sustentacular	Chief
Vimentin	+	
S100	+	–
CD56	+	
GFAP	+ or –	–
Neuron-specific enolase	–	+
Chromogranin	–	+
Synaptophysin	–	+

References: [326, 329–332]

Table 17.34 Cortical neoplasms versus pheochromocytoma

	CAD	CAC	Pheo
Calretinin	+	+ or –	–
SF-1	+[a]	+	–
D2-40	+	+	–
GATA-3	–	–	+
Chromogranin	–	–	+
S100	–	–	+ or –[b]
Vimentin	+	+	–
Bcl-2	– or +	– or +	– or +
c-kit	–	– or +	– or +
INHA	+ or –[c,d]	+ or –[c,e]	– or +
Synaptophysin	+ or –	+	+[f]
MART-1	+	+	– or +
Melan-A	+	+ or –	–
CAM5.2	+ or –	– or +	–
AE1/AE3	–	–	–
SRC1	ND	+	–
PAX8	–	–	–
CA IX	– or +	+ or –	– or +
EMA	–	–	–

Abbreviations: *CAD* Cortical adenoma, *CAC* Cortical adenocarcinoma, *Pheo* Pheochromocytoma

Notes:

[a]positive in nonfunctioning adenomas, as well as aldosterone and cortisol producing adenomas; SF-1 decorates steroid-producing cells in adrenal cortex, showing a nuclear staining pattern, as illustrated in Fig. 17.11; calretinin highlights adrenal cortical cells in a cytoplasmic staining pattern, as illustrated in Fig. 17.12

[b]stains sustentacular cells only; it should be noted that sustentacular cells are absent in 50% of malignant pheochromocytomas

[c]overall, 27% of adrenocortical neoplasms are negative for INHA, so caution should be used if stain is negative

[d]75% of sex steroid producing (virilizing) adenomas are positive; 30% of cortisol producing adenomas are strongly positive; fewer aldosterone-producing or nonfunctioning adenomas stain and they tend to only stain weakly

[e]aldosterone and cortisone-producing carcinomas usually stain; aldosterone-producing or nonfunctional carcinomas are frequently negative, or they stain only 20–20% of cells and are weakly positive

[f]shows granular cytoplasmic staining; Synaptophysin stains chief cells, as illustrated in Fig. 17.13; S100 decorated the sustentacular cells, as illustrated in Fig. 17.14

References: [302–305, 310–313, 316–319, 322, 324, 325, 327, 328, 331–349]

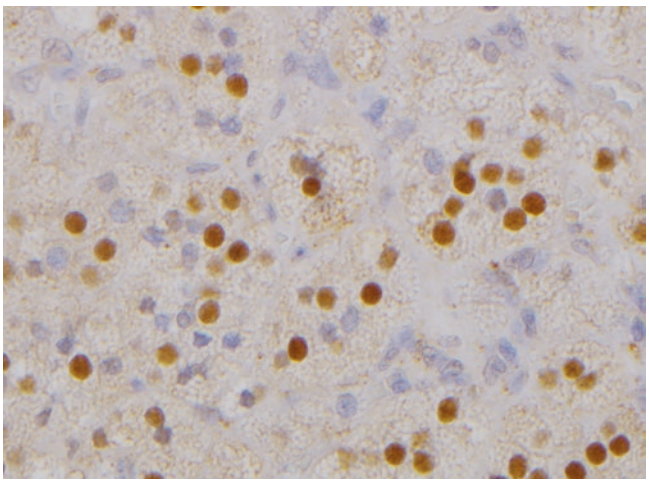

Fig. 17.11 SF-1 is a newer antibody for marking steroid producing cells. Here steroid producing cells in the adrenal cortex demonstrate nuclear staining for SF-1 protein

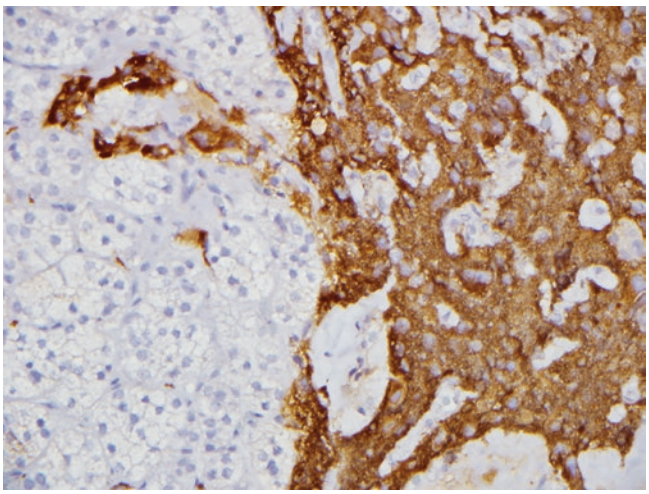

Fig. 17.13 Synaptophysin stains the chief cells in a pheochromocytoma (right half of photo), but does not stain the adrenal cortical cells (left half of photo)

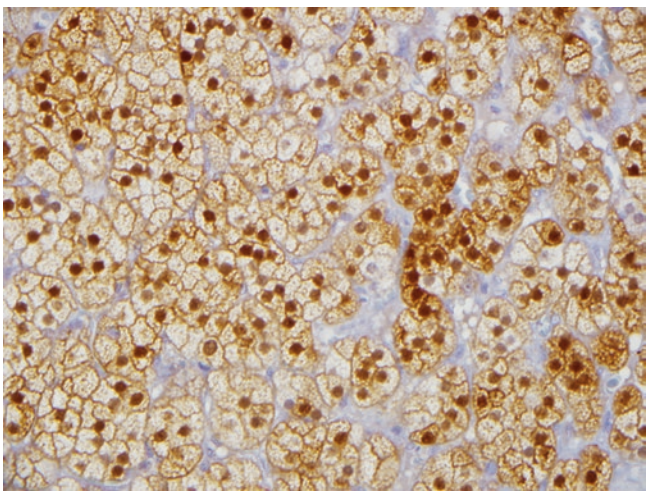

Fig. 17.12 Calretinin is a useful marker to identify adrenocortical cells; here it nicely demonstrates the bubbly appearance of the steroid product in the cytoplasm

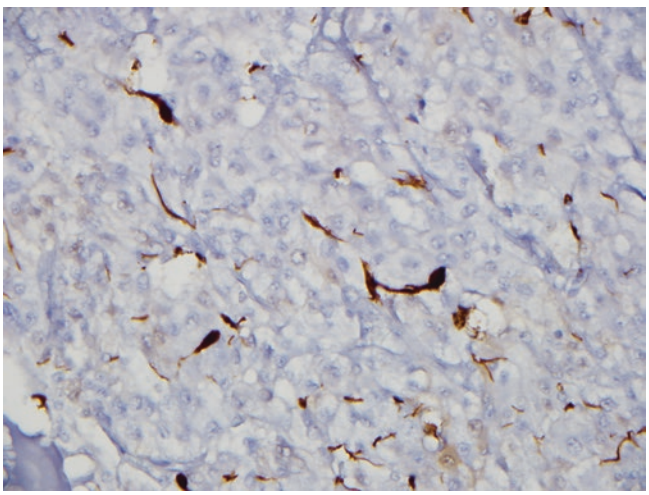

Fig. 17.14 S100 stains the sustentacular cells in this pheochromocytoma, but not the chief cells

Table 17.35 Differential of tumors with abundant clear to granular cytoplasm, round nuclei, and nucleoli

	ACN	CCRCC	HCC	PRCA
SF-1	+	–	–	–
PAX8	–	+	–	–
RCCMa	–	+	–	–
CD10	–	+[a]	– or +	+ or –
Hep-Par1	– or +	–	+	–
P504s	–	+	+	+
CA IX	– or +	+	ND	–
Calretinin	+	–	–	–
Chromogranin	– or +	– or +	–	+ or –
INHA	+[b]	–	–	ND
MART-1	+	– or +	–	–
Synapaptophysin	+ or –	–	–	+ or –
AE1/AE3	–	+ or –	– or +	
CAM5.2	+ or –	+ or –	+	
EMA	–	+ or –	– or +	+
Vimentin	+	+	– or +	–
SRC1	+	–	–	ND
KIM-1	–	+	ND	ND

Abbreviations: *ACN* Adrenocortical neoplasm, *CCRCC* Clear cell renal cell carcinoma, *HCC* Hepatocellular carcinoma, *PRCA* Prostatic adenocarcinoma

Notes:

[a]predominantly membranous staining pattern, may also see nuclear staining

[b]strongest expression is in zona reticularis

References: [302, 304, 310–312, 314, 319, 322–323, 328, 337–342, 345, 346, 350–360]

Table 17.36 Differential of normal and neoplastic oncocytic cells

	NAC	ACAd	ACCA	AON	MetRCC
Calretinin	+	+	+	+	–
Melan-A	+	+	+ or –	+	–
INH	+	+ or –	+ or –	+	–
RCC	ND	–	–	ND	+
PAX8	–	–	–	ND	+
CAIX	–	– or +	ND	ND	+
Synaptophysin	ND	+ or –	+	+	–
SF-1	+	+	+	ND	–
KIM-1	ND	–	–	ND	+
ENT1	+	+	+	+	ND
SRC1	+	+	+	ND	– or +
CAM5.2	ND	+ or –	– or +	ND	+ or –
S100	–	–	–	–	–
Vimentin	ND	+	+	+	+
Chromogranin	ND	– or +	–	ND	– or +
AE1/AE3	+	+ or –	+ or –	ND	– or +

Abbreviations: *NAC* Normal adrenal cortex, *ACAd* Adrenocortical adenoma, *ACCA* Adrenocortical carcinoma, *AON* Adrenal oncocytic neoplasm, *MetRCC* Metastatic renal cell carcinoma

References: [302–305, 307, 301–314, 316–319, 322, 325, 327, 328, 335, 337–342, 344–347, 350, 351, 360–362]

Table 17.37 Markers useful in the differential of tumors most frequently metastatic to adrenal gland

	Lung	Breast	Ovary	MMel	HCC	CCRCC
AE1/AE3	+	+	+	– or +	– or +	+ or –
CD10	ND	–	–	ND	– or +	+[a]
GATA-3	– or +	+	–	–	–	–
Hep-Par1	– or +	–	–[b]	– or +	+	–
Glypican-3	– or +	– or +	– or +	– or +	+	–
INHA	–	–	–	–	–	–
MART-1	–	–	–	+	–	– or +
PAX8	–[c]	–[d]	+	–	–	+
RCCMa	ND	ND	–	ND	ND	+
S100	–	–	ND	+	–	–
SF-1	–	–	–	ND	–	–
TTF1	+	–	–	ND	–	–

Abbreviations: Lung = Primary adenocarcinoma, Breast = Ductal carcinoma, Ovary = Serous adenocarcinoma, *MMel* Malignant melanoma, *HCC* Hepatocellular carcinoma, *CCRCC* Clear cell renal cell carcinoma

Notes:

[a]Predominantly membranous staining with some cytoplasmic staining

[b]May see weak, focal staining in mucinous or clear cell carcinoma, but not in serous carcinoma

[c](−/+) in squamous cell carcinoma

[d]also (−) in lobular carcinoma

References: [304, 310, 311, 314, 319, 326-328, 333-335, 338, 339, 341, 342, 345, 346, 350, 352-357, 363-367]

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