Chapter 13
Breast

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Abstract Immunohistochemistry plays a crucial role in the routine practice of breast pathology. This chapter answers questions about immunohistochemistry many applications to topics including stromal invasion, columnar cell lesions, intraductal proliferations, papillary lesions, sclerosing lesions, spindle cell lesions, nipple neoplasia and Paget's disease, fibroepithelial lesions, prognostic and predictive factors and genomic phenotypes (luminal A, B, basal and Her-2). The application of GATA-3 in breast pathology is discussed and illustrated. Photomicrographs demonstrate the characteristic staining patterns of common stains such as nuclear and cytoplasmic myoepithelial markers, membranous E-cadherin and p120 catenin proteins in lobular neoplasia and D2-40 in lymphatic invasion. Images also show novel dual color staining techniques such as p63 and c-kit staining of adenoid cystic carcinoma.

Keywords Calponin • CK5/6 • CK7 • CK8/18 • CK14 • CK17 • CK19 • D2-40 • E-cadherin • ER • GATA-3 • GCDFP-15 • Her-2/neu • Mammaglobin • Maspin • NY-BR-1 • P120 catenin • p53 • p63 • P-cadherin • PR • S100 • SMA • Smooth muscle myosin heavy chain (SMM-HC) • TFF1 • TFF3 • TTF1 • Columnar cell lesions • Flat epithelial atypia • Stromal invasion • Ductal carcinoma • Lobular carcinoma • Medullary carcinoma • Metaplastic carcinoma • Tubulolobular carcinoma • Micropapillary carcinoma • Mucinous (colloid) carcinoma • Apocrine carcinoma • Secretory carcinoma • Adenoid cystic carcinoma • Basal-like carcinoma • Papillary neoplasm • Fibroepithelial neoplasm • Fibroadenoma • Phyllodes tumor • Myoepithelial neoplasm • Hyperplasia • Tubular carcinoma

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Differential Diagnosis

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Table 13.1 Summary of frequently used antibodies

Markers	Localization (N, M, C)	Function	Application and pitfalls
AE1/AE3	M	Pankeratin peptides	Both epithelia and myoepithelia are reactive; useful used in combination with p63 to confirm small foci of CA
ARP	N	A nuclear protein belonging to the steroid receptor family	Positive for apocrine lesions, both benign and malignant
CA-125	C	A high molecular weight glycoprotein	Gynecologic CAs and mesotheliomas are positive. Breast CAs are non-reactive
CAM 5.2	M, C	LMWCK, simple keratin peptide, recognize CK8 and CK18	Positive in epithelia; perinuclear cytoplasmic staining pattern for lobular CA; cytoplasmic and membranous staining pattern with molding of the neighboring cells in ductal CA; as part of the broad spectrum of CKs in the workup of spindle cell lesions (may be positive for sarcomatoid CA - carcinosarcoma, spindle cell CA, metaplastic CA)
Calponin	C	A 34kD, smooth muscle-restricted regulatory protein	Positive in myoepithelium; a good marker for MECs, with lesser degree of cross-reaction with stromal myofibroblasts
CD10	M, C	A type II integral membrane glycoprotein	MEC marker, less sensitive than others; also labels luminal cells of the terminal duct lobular unit and tumor cells
CD31	M	A 130kD integral membrane protein mediating cell-to-cell adhesion	Expressed on the surface of endothelial cells, weakly on peripheral leukocytes and platelets. Used to identify vascular invasion or vascular neoplasm
CD34	M	A single-chain trans-membrane glycoprotein	Expressed on immature hematopoietic precursor cells, also capillary endothelial cells
CD56	C	Neural cell adhesion molecule	The prototypic natural killer cell marker, also found in subsets of CD4- and CD8-positive T cells. A broad-spectrum NE marker
CEA	C	A 180kD glycoprotein	Breast CAs are often CEA positive
Chromogranin	C	Main protein extract of NE granules of NE cells	A NE marker, more specific than synaptophysin
CK5/6	M	HMWCK	Both epithelia and myoepithelia are reactive; similar utilities as CK903, used as a basal marker
CK7	M	A 54 kD type II simple keratin	Both epithelia and myoepithelia are reactive; may be used in the workup of metastatic disease. Majority of breast CAs (over 95 %) are positive
CK8/18	M, C	LMWCK, same as CAM 5.2	Positive in epithelia; luminal type CAs are reactive. Same utilities as CAM 5.2
CK14	M	HMWCK	Both epithelia and myoepithelia are reactive; used as a basal marker
CK17	M	HMWCK	Both epithelia and myoepithelia are reactive; used as a basal marker
CK19	M, C	A 43 kD simple keratin	Positive in epithelia; luminal type CAs are reactive
CK903	M, C	HMWCK	Both epithelia and myoepithelia are reactive; used as a basal marker to identify basal-like CA; useful in the differentiation of UDH (diffuse mosaic staining pattern) vs ADH/DCIS (negative); limited utility in the evaluation of stromal invasion due to low sensitivity to MECs and its reactivity in epithelium; useful in the workup of spindle cell lesions
c-kit	M	Transmembrane type 3 receptor tyrosine kinase	Expressed in 90–100 % of GISTs; a marker for adenoid cystic CA, decorating the luminal cells; high level of c-kit expression is also seen in malignant phyllodes tumor. Recently added to the panel to define basal-like CA

(continued)

Table 13.1 (continued)

Markers	Localization (N, M, C)	Function	Application and pitfalls
D2-40	C	A 40-kD sialoglycoprotein against an oncofetal antigen—M2A	A marker labeling lymphatic endothelia and mesothelia, recently noted to label MECs in breast; used to identify lymphatic invasion. Pitfall: Weakly reactive to MECs; may mistake small duct for lymphatic space
E-cadherin	M	A calcium-dependent transmembrane adhesion protein	A negative marker for lobular neoplasia. M pattern in ductal lesions
EGFR (Her1)	M	Receptor tyrosine kinases	Frequently overexpressed in variety of CAs. A marker to identify basal-like CA
EMA	M	T transmembrane glycoprotein	A general epithelial marker (M); normal breast demonstrates an apical M pattern while breast CA demonstrates a circumferential M pattern
ER	N	A nuclear protein belonging to the steroid receptor family	A favorable prognostic marker for breast CA. Also used in metastatic disease as a marker for breast and gynecologic primary
GATA-3	N	A 50 kDa nuclear protein, member of the GATA family of transcription factors, regulates breast luminal epithelial cell differentiation and commitment	Highly sensitive (100 % for lobular CA, 91 % for ductal CA, 69 % for ER-negative CA) and relatively specific for breast CAs. Other reported GATA-3-positive tumors include urothelial CA (86 %), salivary gland tumors (100 % for salivary duct CA, mammary analogue secretory CA and oncocytoma), autonomic nervous system tumors (89 % for paraganglioma, 95 % for pheochromocytoma and 100 % for neuroblastic tumors), and parathyroid tumors (100 %)
GCDFP-15	C	Androgen and prolactin responsive protein	Expressed in benign and malignant human breast, salivary gland and skin adnexal tumors. Lower sensitivity but higher specificity for breast primary compared with mammaglobin
Her-2/neu	M	Transmembrane tyrosine kinase belongs to the ErbB receptor family	An unfavorable prognostic marker for breast CA, usually overexpressed in high-grade tumor
HHF-35	C	Anti-muscle specific actin	Positive in myoepithelium
Mammaglobin	C	A glycoprotein of the secreto-globin family	Positive in breast and gynecologic tumors. Higher sensitivity but lower specificity for breast primary compared with GCDFP-15
Maspin	N	A member of the serpin family of serine proteases	Positive in myoepithelium; MEC marker, also labels luminal cells of the terminal duct lobular unit and tumor cells
MIB-1	N	A nuclear antigen associated with cell proliferation	Expressed in all proliferating cells which are in the active phases of the cell cycle (late G1, S, G2 and mitosis); used as a prognostic marker, associated with worse prognosis
MNF116	C	Pan-CK	Positive in myoepithelium and epithelium
MUC1	C	A high molecular weight glycoprotein	Normal ductal/lobular epithelium and majority of breast CAs (over 95 %) are positive
MUC2	C	A high molecular weight glycoprotein	Normal ductal/lobular epithelium and breast CAs are negative
MUC4	C	A high molecular weight glycoprotein	Normal ductal/lobular epithelium and majority of breast CAs (over 95 %) are negative
MUC5AC	C	A high molecular weight glycoprotein	Normal ductal/lobular epithelium and majority of breast CAs (over 95 %) are negative
MUC6	C	A high molecular weight glycoprotein	Normal ductal/lobular epithelium and majority of breast CAs (over 90 %) are negative
NSE	C	Enolase enzyme	Expressed in a variety of normal and neoplastic NE cells, with poor specificity
NY-BR-1	C, N	A differentiation antigen of mammary gland	NY-BR-1 mRNA expression was restricted to normal breast and testis tissues (at a much lower level); at protein level, NY-BR-1 is expressed in 84 % (21/25) of breast CAs but no other normal or tumor tissues; later studies revealed its expression in 46.6–70 % of breast CAs, 75–81 % of Paget's disease, and rare others
p120 catenin	C or M	A member of the transmembrane E-cadherin proteins	A positive marker for lobular neoplasia. M pattern for ductal neoplasia and C pattern for lobular neoplasia
p53	N	A tumor-suppressor and transcription factor	p53 is frequently mutated or inactivated in CAs; used as a prognostic marker, associated with high-grade tumor and worse prognosis. High immunoreactivity was reported in apocrine CAs, especially in-situ CA
p63	N	A homologue of the tumor suppressor protein p53	Positive in myoepithelium; the most specific marker for MECs, useful in the evaluation of stromal invasion and spindle cell lesions. Reported in 5-12 % of invasive CAs (esp. high grade) and UDH showing scattered staining
Pan-CK	M	Pankeratin peptides	Both epithelia and myoepithelia are reactive; similar utility as AE1/AE3. Frequently expressed in metaplastic CAs of the spindle cell component

(continued)

Table 13.1 (continued)

Markers	Localization (N, M, C)	Function	Application and pitfalls
P-cadherin	M, C	A calcium dependent cellular adhesion molecule	Reported positive in myoepithelium; normal breast luminal cells are non-reactive. Frequently expressed in high-grade breast CA
PR	N	A nuclear protein belonging to the steroid receptor family	A favorable prognostic marker for breast CA
S100	N, C	A calcium flux regulator	One of the earliest MEC markers, also labels normal and neoplastic luminal epithelial cells; no longer used for the purpose of detecting breast MECs
SMA	C	Micro-filamentous contractile polypeptide	Positive in myoepithelium; with cross-reaction to stromal myofibroblasts, making it difficult to identify the myoepithelium in cases of DCIS with periductal desmoplasia
SMM-HC	C	A 200 kD, unique structural component of myosin	Positive in myoepithelium; an excellent marker for MECs, no or few cross-reactions with myofibroblasts, useful for the evaluation of stromal invasion
SOX10	N	Neural crest transcription factor	SOX10 expression supports the diagnosis of melanoma, also nerve sheath tumors. In breast tissues, SOX10 expression has been documented in benign breast MECs, triple-negative and metaplastic breast CAs
Synaptophysin	C	A glycoprotein in NE secretory granule	A broad-spectrum NE marker
TFF1	C	A small cysteine rich acidic secretory protein belongs to trefoil factor family, expressed in stomach and colon mainly	TFF1 is overexpressed in a variety of human malignancies. In mammary CAs, TFF1 expression was reported in 72 % of breast ductal CAs and 87 % of breast lobular CAs. A useful marker to add to the differential panel to distinguish lung adenocarcinoma (5 % positive) from breast CA
TFF3	C	A member of the TFF family, mainly expressed in small intestine	Increased expression in breast CAs, which is reported in 84 % of ductal CAs and 94 % of lobular CAs. A useful marker to add to the differential panel to distinguish lung adenocarcinoma (22 % positive) from breast CA however less specific than TFF1
TTF1	N	A transcription factor	Expressed in thyroid, diencephalon and lung. Breast CAs are non-reactive
Vimentin	C	A 57-kD protein, member of the intermediate filament family	Not a cell type-specific marker, useful to serve as a "control marker" to ensure tissue proper handling. Often coexpressed in metaplastic CA
WT1	N	Antibody to the carboxy-terminal (C-terminal) region of WT gene	Positive in myoepithelium; an earlier basal marker labeling MECs

N nuclear staining, *M* membranous staining, *C* cytoplasmic staining, *LMWCK* low molecular weight cytokeratin, *CA* carcinoma, *CK* cytokeratin, *MEC* myoepithelial cells, *NE* neuroendocrine, *HMWCK* high molecular weight cytokeratin, *UDH* usual ductal hyperplasia, *ADH* atypical ductal hyperplasia, *DCIS* ductal carcinoma in situ, *GIST* gastrointestinal stromal tumor, *mRNA* messenger RNA, *TFF* trefoil factor

References: [1–330]

Table 13.2 Epithelial markers of breast tissue/neoplasm

Marker	Pattern	Target	Comment
AE1/AE3	M, C	Luminal epithelium; myoepithelium	Breast CAs are positive
Pan-CK	M, C	Luminal epithelium; myoepithelium	Breast CAs are positive. Often expressed in metaplastic CAs
CK7	M	Luminal epithelium; myoepithelium	Majority of breast CAs (over 95 %) are positive
CAM 5.2	M	Luminal epithelium	Positive for luminal type CA
CK8/18	M	Luminal epithelium	Positive for luminal type CA
CK19	M	Luminal epithelium	Positive for luminal type CA
CK5/6	M	Myoepithelium; benign hyperplastic luminal epithelium	Basal-type CK, positive for basal-like CA. High frequency of expression in metaplastic CAs
CK14	M, C	Myoepithelium; benign hyperplastic luminal epithelium	Basal-type CK, positive for basal-like CA. High frequency of expression in metaplastic CAs
CK17	M, C	Myoepithelium	Basal-type CK, positive for basal-like CA. High frequency of expression in metaplastic CAs
CK903	M, C	Myoepithelium; basal-like CA	Positive for basal-like CA and lobular CAs. High frequency of expression in metaplastic CAs

High molecular weight cytokeratins (HMWCKs) or basal cytokeratins (CK903, CK5/6, CK14 and CK17) along with p63 are among the most sensitive immunomarkers to detect cytokeratin expression in the spindle cell area of metaplastic carcinomas (CAs). Pan-CK is positive for breast CA, often labeling metaplastic CAs. In contrast, AE1/3, CAM 5.2, CK8/18 and CK7 show lower sensitivity in this setting

References: [1, 5–14, 20, 58, 186, 187, 218, 229–236]

Table 13.3 Myoepithelial/basal cell markers of breast tissue/neoplasm

Marker	Pattern	Component	Comment
p63	N	Myoepithelium; rare tumor cells	One of the most sensitive and specific MEC markers, showing continuous "dot-like" pattern in normal ducts; focally discontinuous "dotted" line in in-situ CAs; non-reactive or attenuated in invasive or papillary CAs
SMM-HC	C	Myoepithelium; blood vessel; occasional myofibroblasts	Very sensitive MEC marker, but slightly less specific than p63, showing cross-reactivity with stromal myofibroblasts and vascular smooth muscle cells, although in less frequency compared with calponin; non-reactive in invasive CAs; positive with gap in in situ CAs; positive and intact in normal ducts
Calponin	C	Myoepithelium; myofibroblast; blood vessel; rare tumor cells	A good MEC marker demonstrating continuous cytoplasmic linear pattern; high frequency of cross-reactivity with stromal myofibroblasts and vascular smooth muscle cells; cross-reactivity with tumor epithelial cells in 18 % of cases
SMA	C	Myoepithelium; myofibroblast; blood vessels; rare epithelium	Sensitive but not specific MEC marker, with marked cross-reaction to stromal myofibroblasts and vascular smooth muscle cells
CK14	C, M	Myoepithelium; hyperplastic luminal epithelium; rare myofibroblasts	A HMWCK used as a MEC or basal marker; mosaic pattern in hyperplastic luminal epithelium. Non-reactive in majority of invasive CAs and DCIS, except basaloid phenotype or high-grade DCIS (frequent co-expression of luminal and basal markers)
CK5/6	C, M	Myoepithelium; hyperplastic luminal epithelium	Similar to CK14
CK17	C, M	Myoepithelium/basal cells	Similar to CK14
CD10	C, M	Myoepithelium; fibroblasts; epithelium	Negative or attenuated in invasive CA or papillary CA. Positive in normal ducts and in-situ CAs
S100 protein	C, N	Epithelium, myoepithelium	Invasive breast CAs: reported 48 % positive
Maspin	N	Myoepithelium, tumor cells	Sensitive MEC marker; no cross-reaction with stromal myofibroblasts and vascular smooth muscle cells but limited utility due to the staining of tumor cells
P-cadherin	C	Myoepithelium; Epithelial proliferation	MEC marker; also stains some tumor cells
D2-40	C	Lymphatic endothelia, myoepithelium	Weak, patchy staining for MECs compared with lymphatics; may misinterpret DCIS and LCIS for intralymphatic invasion
P75NTR	M, + or − C	A transmembrane glycoprotein member of the TNF-receptor superfamily	Reported consistently positive for MECs in breast, comparable to that of p63 and SMM-HC; often positive in metaplastic CAs
SOX10	N	Neural crest transcription factor	Reported labeling MECs in breast, salivary gland and bronchial glands; preferentially expressed in triple-negative and metaplastic CAs

LCIS lobular carcinoma in situ, *TNF* tumor necrosis factor

Although considered one of the best myoepithelial cell (MEC) markers, p63 also labels the following breast CAs in a diffuse fashion: adenoid cystic CAs and metaplastic CAs of the squamous component. A small subset of ductal CAs of the not otherwise specified (NOS) type and papillary CAs demonstrates p63 reactivity in a minor fraction of tumor cells, up to 33.3 % of cases

The combination of p63 and SMM-HC or p63 and calponin has been recommended in the literature for the evaluation of invasion, especially in cases of sclerosing lesions and papillary lesions. p63 alone with its "dot-like," discontinuous pattern, may make interpretation difficult. The combination of nuclear (p63) and cytoplasmic (SMM-HC and calponin) biomarkers enhances the detection of MECs. Examples of p63 and calponin immunostains in normal tissue are illustrated in Fig. 13.1

Maspin is a sensitive MEC marker with both a nuclear and cytoplasmic staining pattern and clean background without cross-reactivity to stromal myofibroblasts or vascular smooth muscle cells. However, its utility as a diagnostic MEC marker is limited due to its expression in some invasive breast CAs and ductal carcinomas in situ (DCIS); in our study, 29 % (75/259) of invasive breast CAs showed a partial to diffuse staining pattern. Figure 13.2 illustrates maspin staining patterns in benign breast tissue, DCIS, and invasive breast CAs

SOX10, a marker for melanoma, tumors with Schwann cell differentiation and some salivary gland neoplasms, especially those with myoepithelial differentiation, was noted to be expressed in MECs in breast, salivary glands and bronchial glands. Cimino-Methews reported that SOX10 is primarily expressed in basal-like, unclassified triple-negative, and metaplastic CAs with a positive rate of 66 % (38/58), as compared with 5 % (2/42) of the luminal A, B, and Her-2 CAs

References: [1–6, 9, 11, 14–25, 40–43, 218, 237–254]

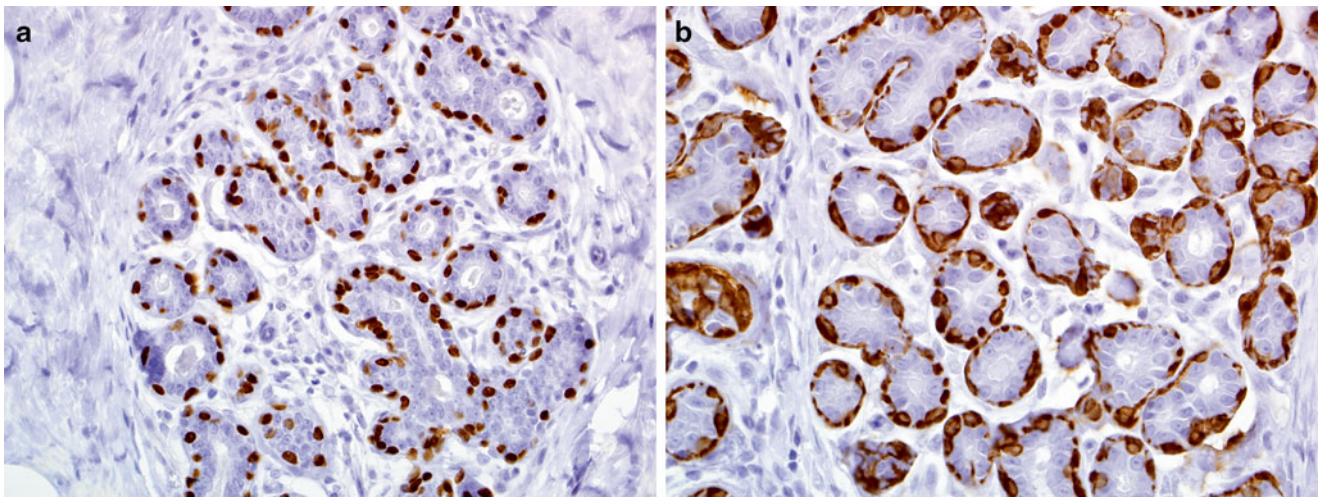

Fig. 13.1 (**a**) p63 nuclear staining for myoepithelial cells in normal breast tissue, continuous "*dot*-like" pattern. (**b**) Calponin cytoplasmic staining for myoepithelial cells in normal breast tissue, continuous linear pattern

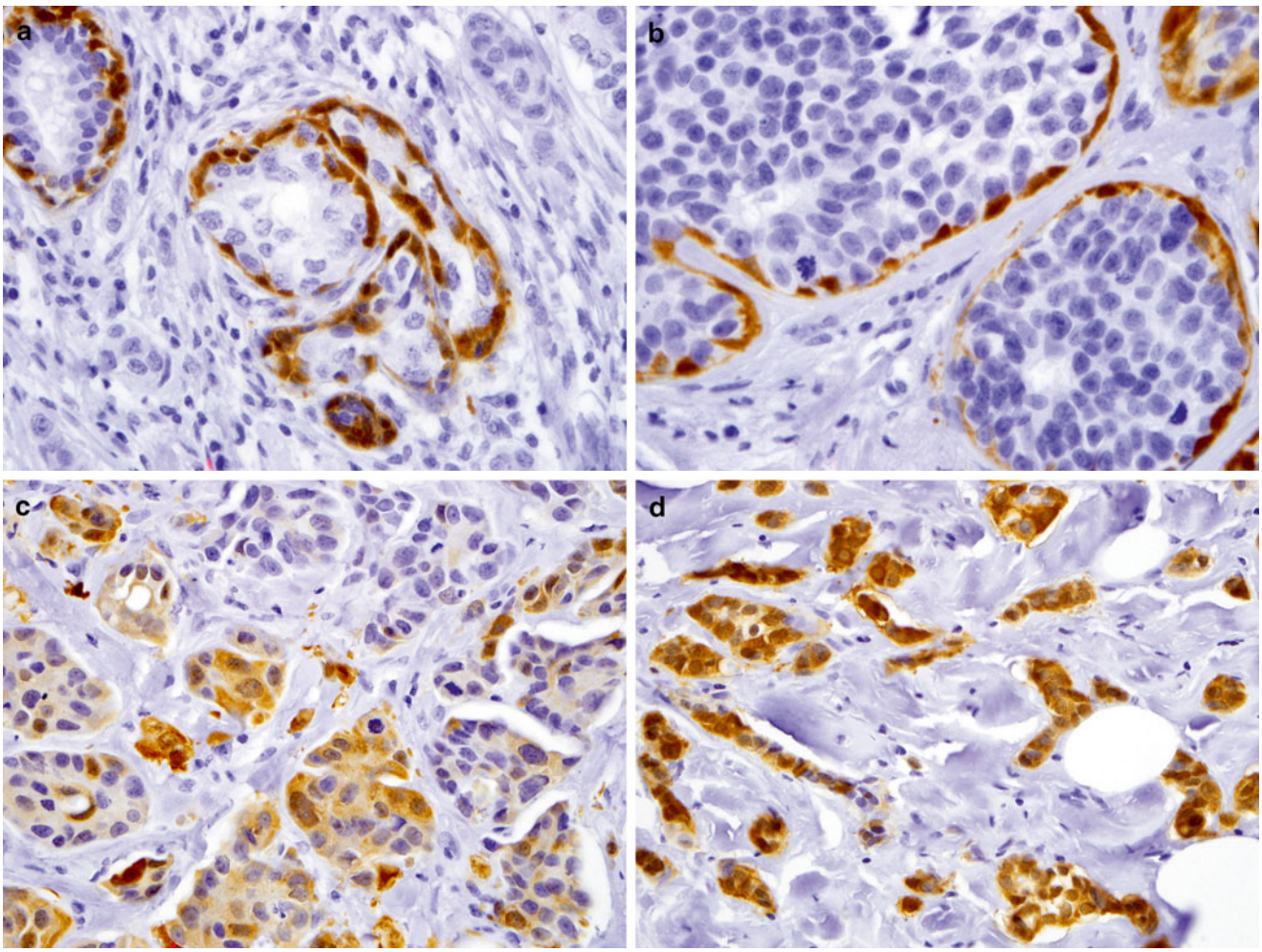

Fig. 13.2 (**a**) Maspin decorates myoeithelial cells of the two normal ducts and a cluster of ducts involved by ductal carcinoma cells, both nuclear and cytoplasmic staining pattern; Note small nests of invasive ductal carcinoma cells lacking peripheral myoepithelial cells; there are no reactivities to stromal myofibroblasts or vascular smooth muscle cells. (**b**) Maspin staining pattern in nests of DCIS, rare focal discontinuous pattern. (**c**) 29 % of invasive breast carcinomas (IDC) showed maspin reactivity; an example of IDC showing partial staining. (**d**) An example of IDC showing diffuse staining pattern for maspin

Table 13.4 Phenotype of normal breast ductal/lobular epithelium

Marker	Pattern
AE1/AE3	+, M, C
CK7, CK8/18, CK19	+, M
CK5/6, CK14, CK17, CK903	–
E-cadherin	+, M
P^{120} catenin	+, M
ER, PR	+, N, scattered
Her-2/neu	–
GATA-3	+, N, focal
MUC1	+, apical M and secretion
MUC2, MUC5AC, MUC6	–
NY-BR-1	+, C, N (focal N)

Normal breast epithelium (ductal and lobular) demonstrates an intense linear membranous staining pattern for E-cadherin and p^{120} catenin. In lobular neoplasia, mutation of the E-cadherin gene leads to a complete absence of E-cadherin protein or abnormal localization (apical or perinuclear). Immunohistochemically, lobular neoplasia is negative for E-cadherin and cytoplasmic staining, with loss of membranous staining for p^{120} catenin

Table 13.4 (continued)

We evaluated GATA-3 expression in normal breast tissue (N = 10) by immunohistochemistry and found that 50 % of the cases showed nuclear labeling in the luminal epithelial cells in a patchy fashion; none of the myoepithelial cells was reactive. The evaluation of MUC1, 2, 5 AC and 6 in 24 normal breast tissues demonstrated MUC1 expression in the luminal epithelial cells at the apical membrane and intraluminal secretion; no immunoreactivities were identified for MUC2, MUC5AC and MUC6; the myoepithelial cells were non-reactive to all four markers

Examples of E-cadherin, p^{120} catenin, GATA-3 and MUC1 in normal breast tissue are illustrated in Fig 13.3

References: [1, 5–9, 14, 15, 20, 26–29, 216, 218, 255]

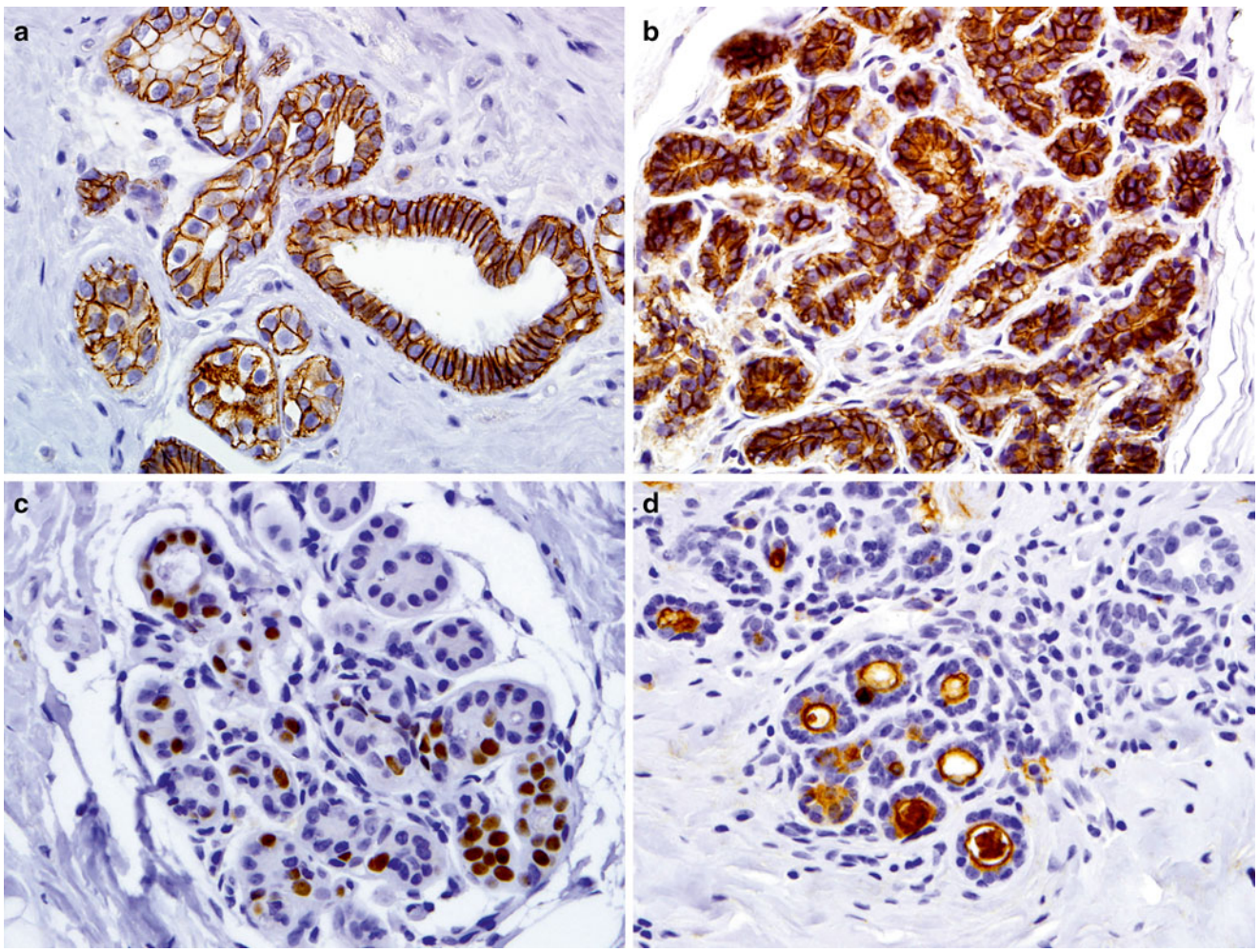

Fig. 13.3 (**a**) E-cadherin membranous staining pattern in normal ductal and lobular epithelium. (**b**) p120 catenin membranous staining pattern in normal ductal and lobular epithelium. (**c**) GATA-3 labels luminal epithelial cells in a patchy fashion in 50 % of the normal mammary gland tissue tested. (**d**) MUC1 is expressed in luminal epithelial cells at the apical membrane and intraluminal secretions. Note negative staining in myoepithelial cells

Table 13.5 Phenotype of columnar cell lesions (columnar cell changes/hyperplasia)

Marker	Pattern
LMWCK (CK8/18, CK19)	+
HMWCK (CK5/6, CK903, CK14)	–
ER, PR	+, N, Strong and diffuse
E-cadherin	+, M
Her-2/neu	–
p53	–
MIB-1	Low

HMWCKs are non-reactive in columnar cell lesions, except in lesions with hyperplasia, which usually show a central luminal position—the residual luminal cells

HMWCK and ER/PR immunostains are used to distinguish usual ductal hyperplasia (UDH) from atypical ductal hyperplasia (ADH) or DCIS however are not helpful in the differentiation of atypical vs non-atypical columnar cell lesions

References: [1–7, 9, 14, 28, 30–34]

Table 13.6 Phenotype of flat epithelial atypia

Marker	Pattern
LMWCK (CK8/18, CK19)	+, M
HMWCK (CK903, CK5/6)	–
ER, PR	+, N, strong and diffuse
Bcl-2	+, C, strong and diffuse
Cyclin D1	+, V
MIB-1	Low

Flat epithelial atypia (FEA) commonly coexists with ADH, low-grade DCIS, lobular neoplasia and tubular CAs, and is considered a possible precursor to or the earliest morphologic manifestation of DCIS. The immunophenotype of FEA is similar to low-grade DCIS

HMWCKs may show intense staining in the residual luminal epithelial cells adherent along the luminal surface

References: [3, 4, 9, 30, 35–39]

Table 13.7 The evaluation of stromal invasion

Marker	Pattern	Comment
p63	N	Negative in invasive CA. "Dotted" line surrounding normal ducts and in-situ CAs
SMM-HC	C	Negative in invasive CA. Present in normal ducts and in-situ CAs
Calponin	C	Negative in invasive CA. Present in normal ducts and in-situ CAs
SMA	C	Negative in invasive CA. Present in normal ducts and in-situ CAs

The presence of an intact peripheral myoepithelial cell layer characterizes normal, benign and in-situ lesions. Loss of the myoepithelial cell layer is the hallmark of invasive CA. Several myoepithelial markers have been used to assess invasion. p63, SMM-HC, calponin and SMA are most commonly used for this purpose. Studies report using a combination of p63 and SMM-HC or p63 and calponin is helpful

(continued)

Table 13.7 (continued)

Other MEC markers, such as SMA, P-cadherin, WT1, S100, and HMWCKs or basal-type cytokeratins (CKs: CK5/6, CK14, CK17, CK903), are less commonly used currently for evaluating invasion due to marked cross-reactivity with myofibroblasts and vascular smooth muscle cells (such as SMA), frequent reactivity in tumor cells (such as HMWCKs or basal-type CKs, maspin, S100, P-cadherin), or low sensitivity (WT1 and S100)

References: [1–6, 9, 11, 14–25, 40, 218, 237–244]

Table 13.8 The evaluation of angiolymphatic invasion

Marker	Pattern	Comment
CD31	C	Positive for endothelial cells of vascular channels
CD34	C	Positive for endothelial cells of vascular channels
D2-40	N	Positive for endothelial cells of lymphatics

D2-40 is a selective lymphatic endothelial marker that usually stains very intensely. A pitfall is weak to occasionally moderate staining of ducts, which may be mistaken for lymphatic invasion. An example of tumor lymphatic invasion with D2-40 immunostain is illustrated in Fig. 13.4

References: [1–6, 9, 14, 41–43, 218, 245–247]

Table 13.9 Phenotype of ductal carcinoma of breast

Marker	Literature	GHL data (%), n=176
GATA-3	+, N	94.0 %
E-cadherin	+, M	ND
CK7	+	91.7 %
ER	+ or –	59.1 %[a]
Mammaglobin	– or +	42.2 %
GCDFP-15	– or +	31.4 %
NY-BR-1	+	ND
P120 catenin	+, M	94.6 %, M
CK8	+, peripheral-predominant membranous pattern	98.8 %
CK903	–	ND
TFF1	+, C	72 %
TFF3	+, C	84 %
MUC1	+, C	97 %
MUC2	– or +, C	3 %
MUC4, MUC5AC	–	0
MUC6	– or +, C	8.4 %

[a]The data was collected before 2010, using Monoclonal Mouse Anti-Human Estrogen Receptor α, Clone 1D5. Current ER positive rate in our laboratory is approximately 85 %, using Anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody

The majority of breast ductal CAs are non-reactive to CK903, except basal-like phenotype. CK8/18 demonstrates a peripheral-predominant membranous staining pattern in ductal CA, as illustrated in Fig. 13.5a; in contrast, a perinuclear,

(continued)

Table 13.9 (continued)
ring-like, cytoplasmic staining pattern is seen in lobular CA, as illustrated in Fig. 13.5b

E-cadherin, a negative marker for lobular neoplasia of breast, decorates ductal CAs in a membranous pattern, as illustrated in Fig. 13.5c, d. p^{120} catenin, a positive marker for lobular neoplasia of the breast showing a perinuclear cytoplasmic staining pattern, decorates ductal CAs in a membranous pattern, as illustrated in Fig. 13.5e, f

GATA-3, also known as GATA-binding protein 3, is a member of the family of six zinc-finger transcription factors. It regulates the specification and differentiation of tissues, such as breast, kidney, nervous system, parathyroid gland, hair follicle, and T cells. Higgins' study and our previous studies of GATA-3 expression in various tumors and normal tissues found that GATA-3 is highly expressed in urothelial CAs (67 % and 86 %) and breast CAs (100 % and 94 %), as well as 2 % (2/96) of endometrial adenocarcinomas in our study; all other tumors tested lacked GATA-3 expression, including lung adenocarcinoma, gastrointestinal and biliary-pancreatic adenocarcinomas (except a small fraction of pancreatic adenocarcinomas, usually focal and weakly positive), the majority of gynecologic carcinomas, clear cell renal cell carcinomas, and germ cell tumors (seminomas, embryonal CAs and yolk sac tumors). However, more studies were conducted by several investigators who reported GATA-3 expression in breast CAs (69–100 %), urothelial CAs (73-91 %), salivary gland tumors (49 %), parathyroid tumors (100 %), pheochromocytomas (95 %), paragangliomas (89 %), and benign Brenner tumors of the

Table 13.9 (continued)
ovary (2/2 positive). A minor fraction of squamous cell CAs of lung (0–23 %), pancreatic adenocarcinomas (~10 %) and renal oncocytomas (11 %) were also reported to express GATA-3. We further studied GATA-3 expression in ER-negative primary breast CAs and found that 69 % (66/99) of ER-negative breast CAs expressed GATA-3, as illustrated in Fig. 13.6; in contrast, only 15 % (14/96) and 35 % (34/96) expressed GCDFP-15 and mammaglobin, respectively. Cimino-Mathews reported that GATA-3 was expressed in 67 % (66/99) of ER-negative breast CAs, including 43 % of triple-negative and 54 % of metaplastic CAs. Overall, GATA-3 is a sensitive and reasonably specific immunomarker for breast CAs, superior to other available breast-specific immunomarkers such as ER, mammaglobin and GCDFP-15

TFF1 and TFF3 expression is not specific for breast CAs; it has been reported in various other tumors. We studied TFF1 and TFF3 expression in more than 1,000 tumors from various organs and found that 72 % (68/95) and 84 % (81/96) of invasive ductal CAs expressed TFF1 and TFF3, respectively; in contrast, only 5 % (5/111) and 22 % (24/111) of lung adenocarcinomas expressed TFF1 and TFF3, respectively. Our findings suggest that TFF1 may have diagnostic utility as part of a panel to differentiate breast from lung primary when working on tumors with only these two primary sites being considered. Representative photos are illustrated in Fig. 13.7

References: [1–6, 9, 13, 14, 26, 27, 45, 175–182, 216–228, 256–278]

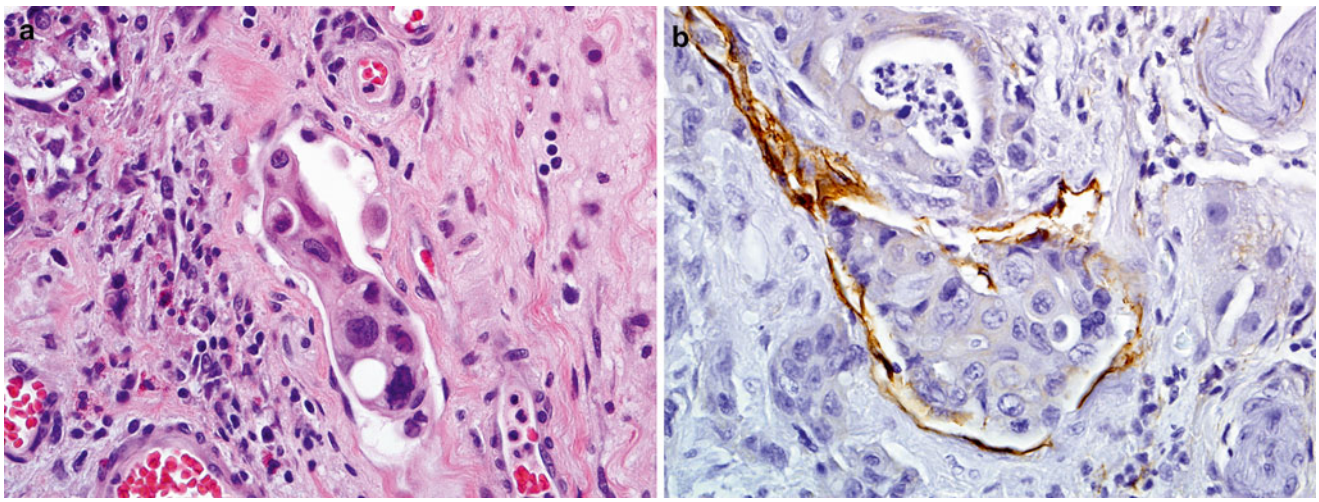

Fig. 13.4 (**a**) Lymphatic invasion, H&E stain. (**b**) Immunostain for D2-40 highlights the endothelial cells of the lymphatic channel

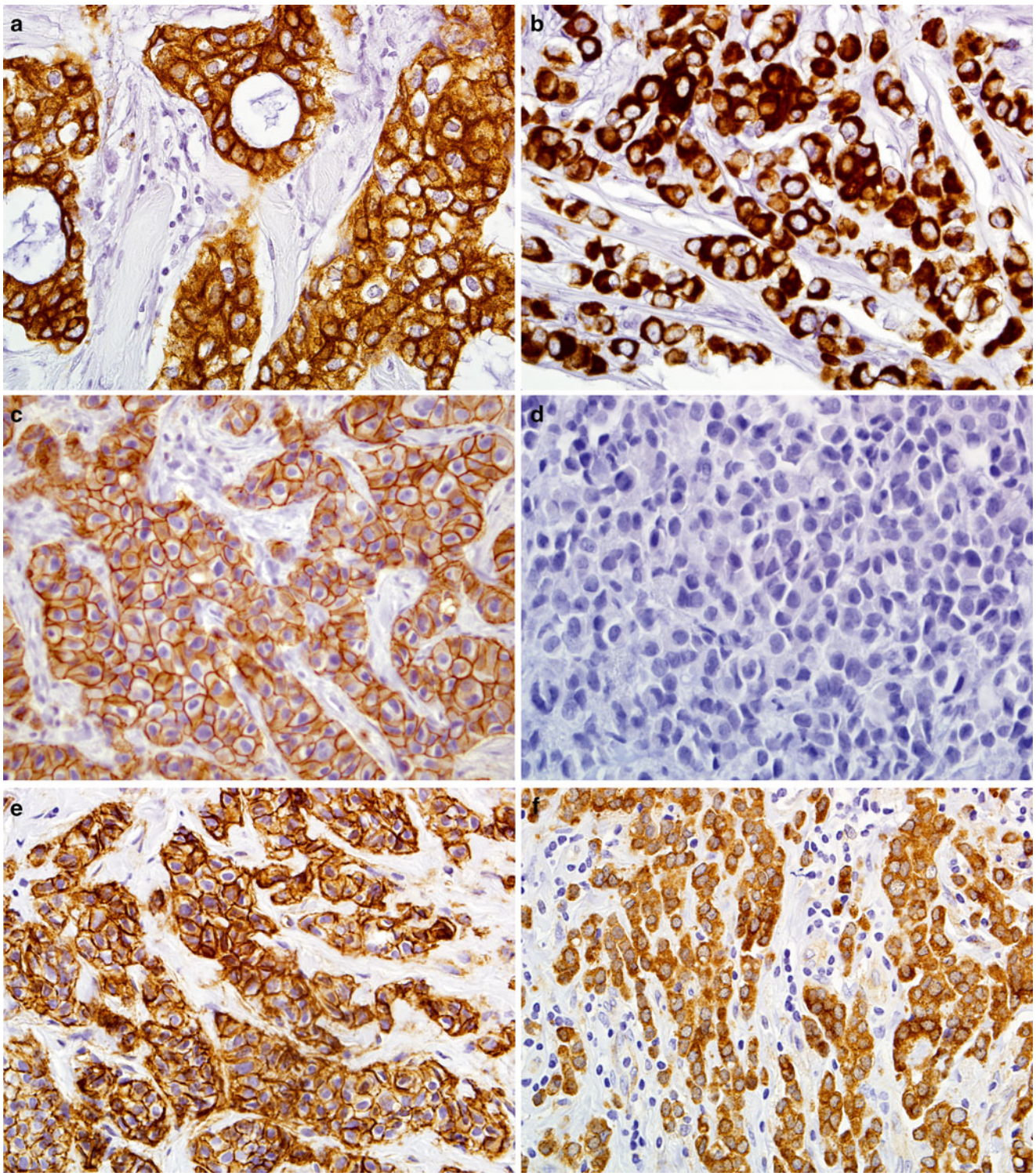

Fig. 13.5 (**a**) Immunostain for CK8/18 in ductal carcinoma, demonstrating peripheral-predominant membranous staining pattern. (**b**) Immunostain for CK8/18 in lobular carcinoma, demonstrating perinuclear, ring-like, cytoplasmic staining pattern. (**c**) E-cadherin membranous staining pattern in ductal carcinoma. (**d**) E-cadherin, loss of expression in lobular carcinoma. (**e**) p120 catenin membranous staining pattern in ductal carcinoma. (**f**) p120 catenin perinuclear, cytoplasmic staining pattern in lobular carcinoma

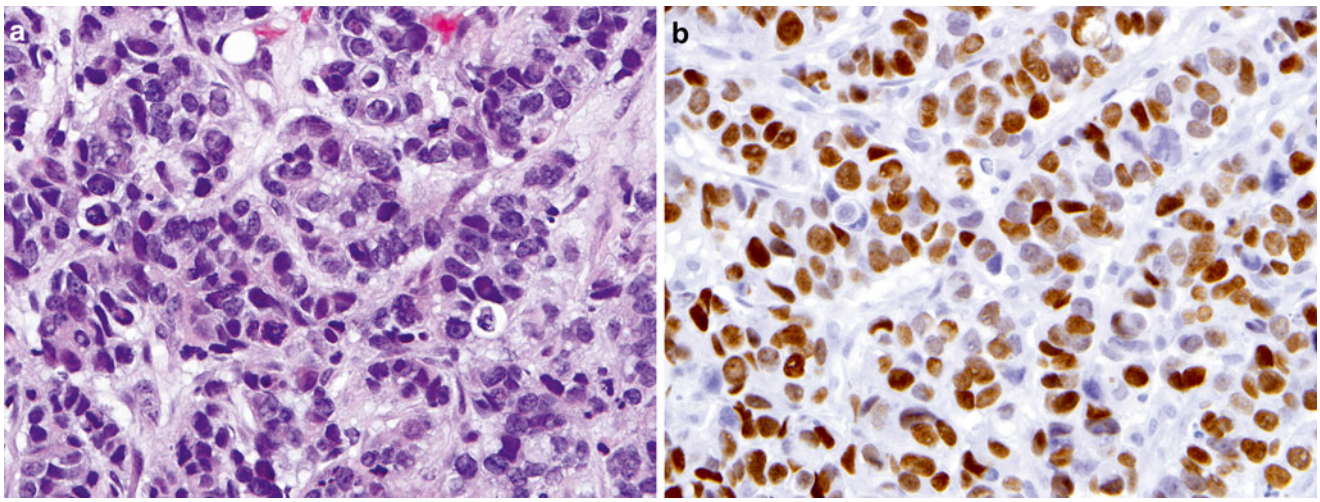

Fig. 13.6 (**a**) High grade, ER-negative invasive ductal CA, H&E stain. (**b**) High grade, ER-negative invasive ductal CA shows strong, diffuse nuclear staining for GATA-3. GATA-3 expression was identified in 69 % (66/99) of the ER-negative breast CAs

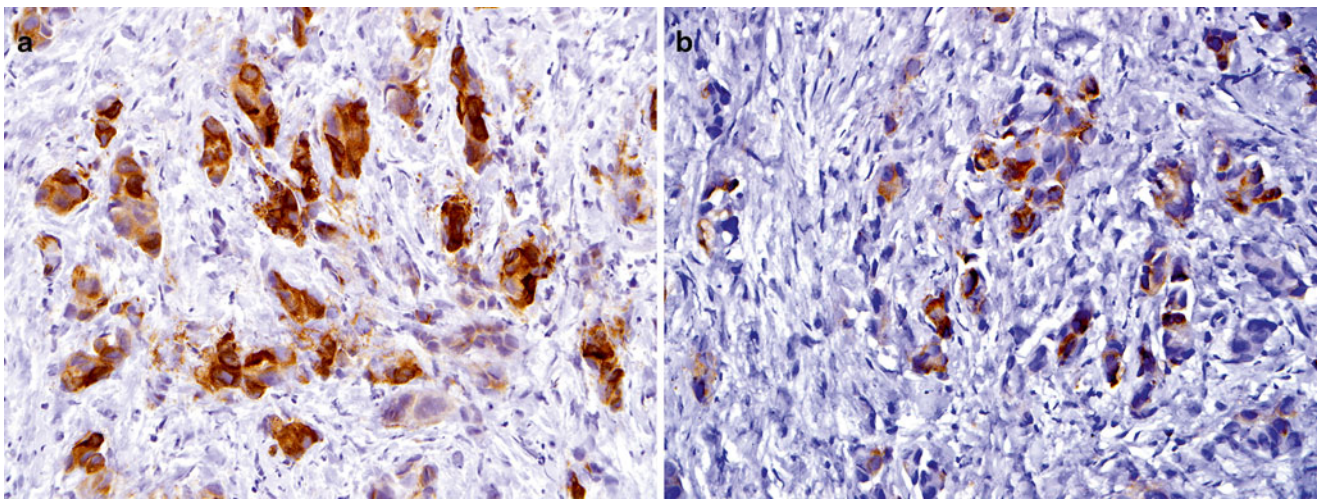

Fig. 13.7 (**a**) 72 % (68/95) invasive ductal CA express TFF1. (**b**) 84 % (81/96) invasive ductal CA express TFF3

Table 13.10 Phenotype of lobular carcinoma of breast

Marker	Literature	GHL data (N=76)
CK903	+	96.3 %
E-cadherin	–	0
P^{120} catenin	+, C	100 %
GATA-3	+, N	100 %
CK7	+	90 %
TFF1	+, C	87 %
TFF3	+, C	94 %
ER	+	83.7 %
NY-BR-1	+	ND
CK8	+, perinuclear, ring-like, cytoplasmic pattern	100 %
GCDFP-15	– or +	28.3 %
Mammaglobin	+ or –	69.5 %
MUC1	+	100 %
MUC2, MUC4, MUC5AC	–	0
MUC6	– or +	16.2 %

CK8/18 demonstrates a perinuclear, ring-like, cytoplasmic staining pattern in lobular CA, as illustrated in Fig. 13.5b. E-cadherin is a negative membranous marker for lobular neoplasia of the breast. The majority of lobular CAs demonstrate loss of E-cadherin expression (negative staining for E-cadherin), as illustrated in Fig. 13.5d. p^{120} catenin is a useful positive marker for lobular neoplasia of the breast, with a cytoplasmic staining pattern as illustrated in Fig. 13.5f

(continued)

Table 13.10 (continued)

Aberrant E-cadherin expression was identified in occasional lobular CAs, with a reported range of 2-16 % of cases. The definition of aberrant E-cadherin expression was described as E-cadherin immunophenotype that did not correspond to the apparent histologic classification of the lesion. Several authors suggested that the expression of E-cadherin in tumors showing characteristic features of lobular CA should not preclude the diagnosis of lobular CA

GATA-3 expression in lobular CAs was reported as nearly 100 %. The vast majority of lobular CAs are also ER-positive. In contrast, gastric signet ring cell carcinomas lack expression of both markers (GATA-3 and ER). This differential phenotype is very helpful when working on a tumor with high-grade, single-cell histomorphology, raising the differential diagnosis of gastric signet ring cell carcinoma and metastatic lobular CA of the breast. Figure 13.8 illustrates the typical immunophenotype of a metastatic lobular CA of the breast to the stomach

Our study found that 87 % (41/47) and 94 % (45/48) of invasive lobular CAs expressed TFF1 and TFF3, respectively

References: [1–6, 9, 13, 14, 26, 27, 45, 175–182, 216–228, 256–278]

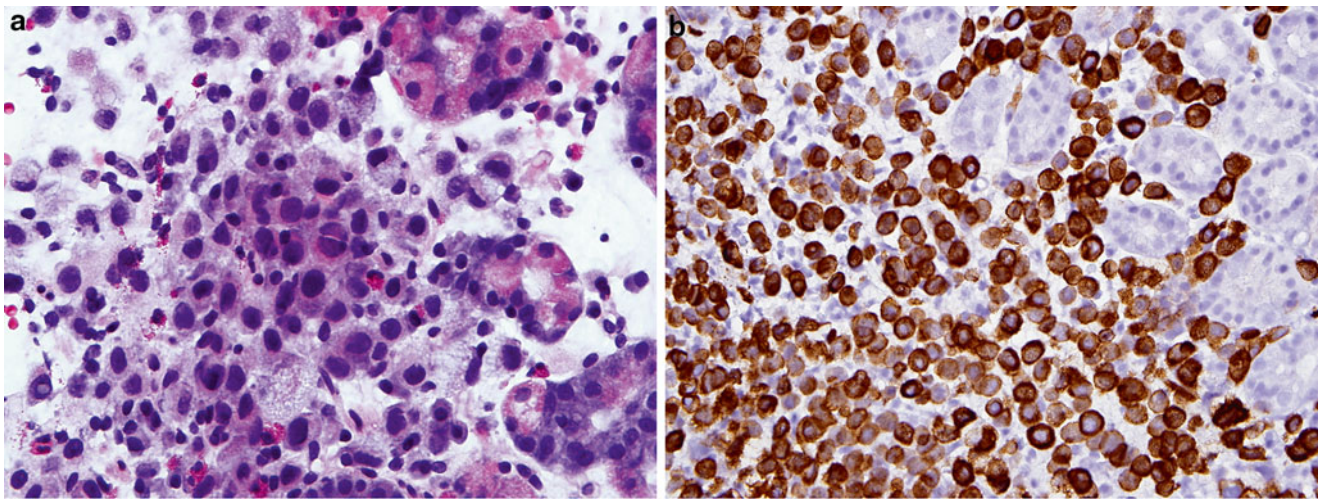

Fig. 13.8 (**a**) Metastatic lobular CA to stomach, H&E stain. (**b**) Metastatic lobular CA shows diffuse CK7 positivity. (**c**) Metastatic lobular CA shows strong nuclear staining for GATA-3. (**d**) Metastatic lobular CA shows strong nuclear staining for ER

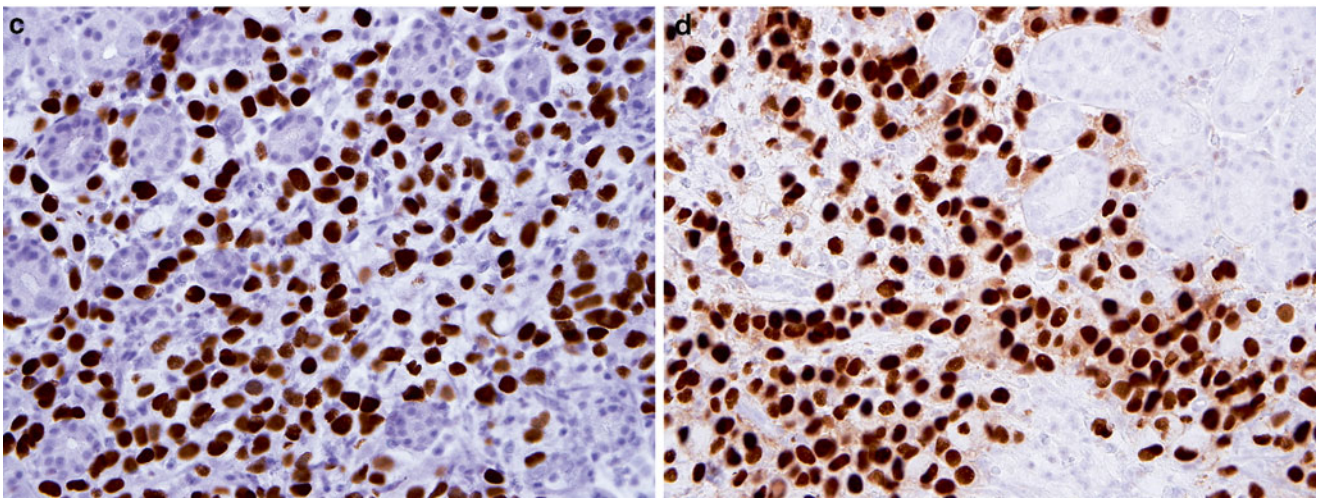

Fig. 13.8 (continued)

Table 13.11 Phenotype of medullary carcinoma of breast

Marker	Pattern
ER, PR, Her-2/neu	–
p53	+ or –
MIB-1	High
CK5/6, CK14, CK903	+ or –
P-cadherin	+ or –
EMA	+
AE1/AE3, CAM5.2	+
Mammaglobin	–
S100 protein	+
CK7	+ or –
E-cadherin	+
Vimentin	+ or –
GATA-3	– or +

Medullary CAs are usually ER-, PR-, Her-2- tumors exhibiting basal-like phenotype, high proliferative activity, p53 overexpression and frequent BRCA1 mutation or protein deficiency. Medullary CAs usually lack mammaglobin expression. In contrast, atypical medullary CAs express mammaglobin, and also overexpress Her-2/neu in nearly half of the cases

Table 13.11 (continued)

GATA-3 expression in medullary CA has not been well documented. In our previously published study, in which only three cases were medullary CAs, partial weak GATA-3 reactivity was noted in one of the three (33 %) cases; the other two were non-reactive. However, more data is needed to characterize GATA-3 expression in medullary CAs. An example of medullary CA is illustrated in Fig. 13.9

References: [1–6, 9, 14, 44, 46–57, 216, 218, 219]

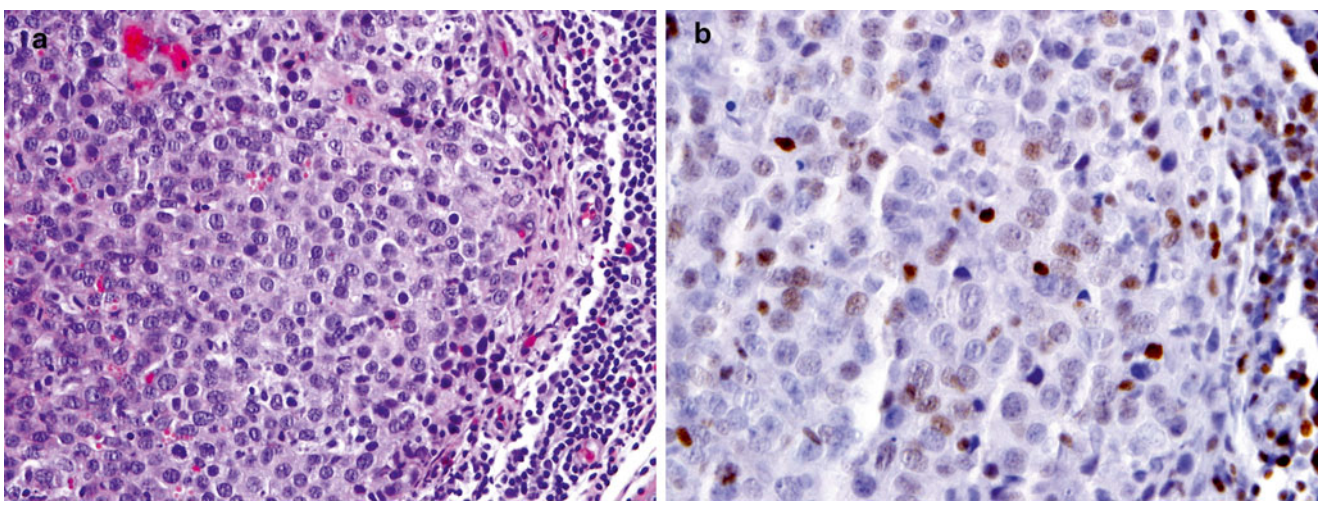

Fig. 13.9 (**a**) Medullary CA, H&E stain. (**b**) One of the three cases of medullary CAs showed weak, 2+ nuclear staining for GATA-3. Other two were non-reactive

Table 13.12 Phenotype of metaplastic carcinoma

Marker	Literature
Pan-CK (MNF-116)	+
HMWCK (CK5/6, CK14, CK17, CK903)	+
MEC markers (p63, CD10, Calponin, SMA)	+
ER, PR, Her-2/neu	–
AE1/AE3, CAM 5.2	+ or –
EGFR	+
CK7	+
Vimentin	+
GATA-3	– or +
CD34	–
SOX10	+ or –

Reported CK immunoreactivity ranges widely in metaplastic CA, both epithelial and spindle cell elements; it is usually focal in an unpredictable fashion. Therefore, a broad panel of low molecular weight cytokeratin (LMWCK) (CAM 5.2, CK19), HMWCK (CK5/6, CK14, CK17, CK903) and pan-CK (MNF116) should be applied when encountering a spindle cell lesion of the breast. CK7 was reported in the epithelial element only. HMWCKs and pan-CK are among the most sensitive markers to detect CK expression in this setting. MEC markers (p63, calponin, CD10, SMA) are often

Table 13.12 (continued)

expressed in metaplastic CA in the spindle cell element and should be included in the panel.

In our limited experience with GATA-3 expression in metaplastic CAs, one of the six metaplastic CAs showed focal weak reactivity. However, in Cimino-Mathews' study, 54 % (7/13) of metaplastic CAs were observed expressing GATA-3. The characterization of GATA-3 expression in metaplastic CAs requires further additional studies

SOX10 expression has been observed in benign breast myoepithelial cells; in breast CAs, 66 % (38/58) of basal-like, unclassified triple-negative, and metaplastic CAs expressed SOX10. In contrast, SOX10 was expressed in only 5 % (2/42) of luminal A, B and Her-2-type breast CAs

Immunohistochemical and molecular studies of metaplastic CA reveal that the majority of metaplastic CAs exhibit EGFR overexpression (57–87 %) associated with EGFR gene amplification (about one-third of those cases)

An example of metaplastic CA of the breast is illustrated in Fig. 13.10

References: [1–6, 9, 14, 20, 24, 40, 58–68, 186, 187, 216, 218, 219, 229–236, 250–254]

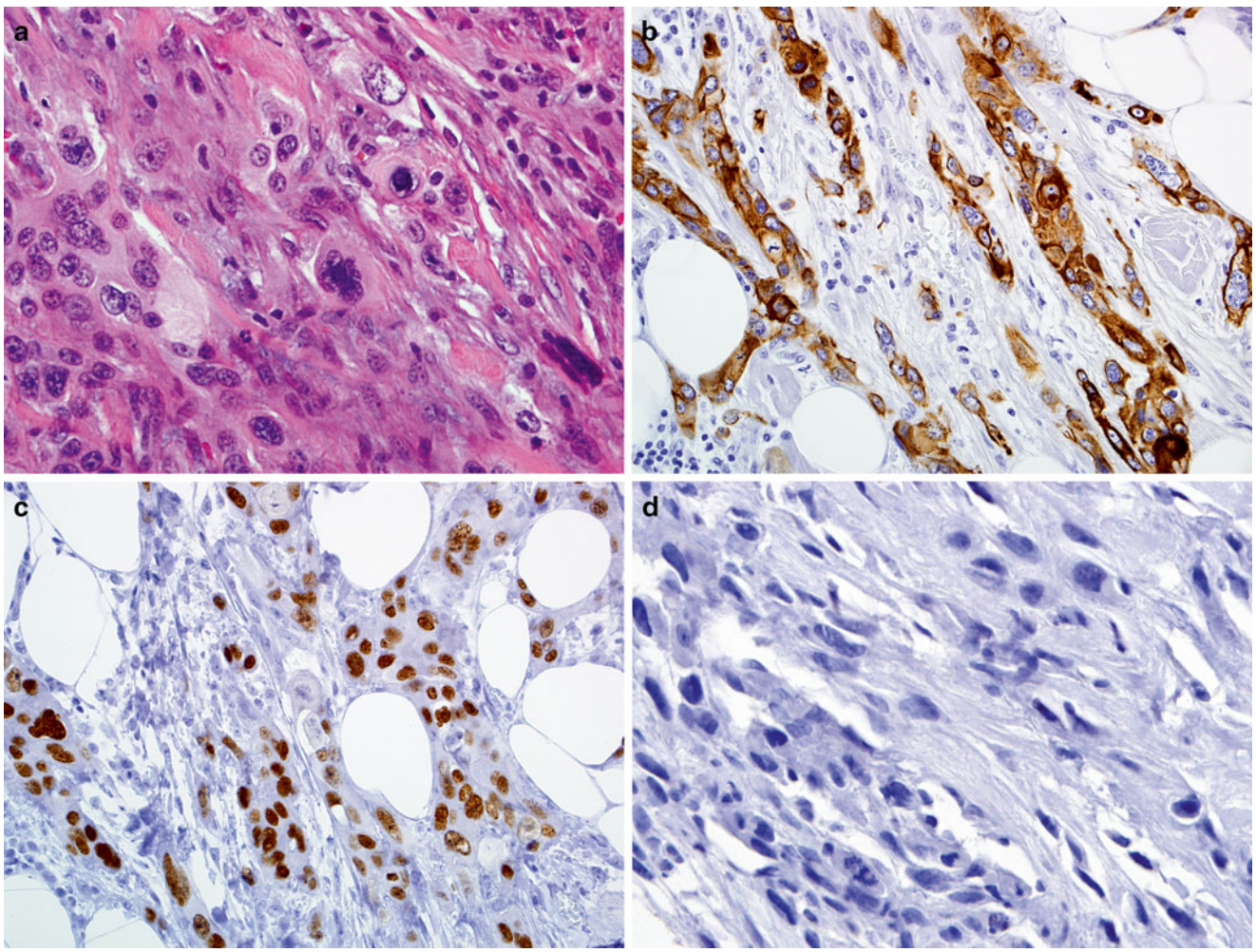

Fig 13.10 (**a**) Metaplastic carcinoma of breast, H&E stain. (**b**) Metaplastic carcinoma of breast demonstrates cytoplasmic staining for CK903. (**c**) Metaplastic carcinoma of breast demonstrates nuclear staining for p63. (**d**) Metaplastic carcinoma of breast shows no GATA-3 reactivity. Only one of the six cases of metaplastic CAs in our study showed focal, weak reactivity to GATA-3

Table 13.13 Phenotype of tubulolobular carcinoma of breast

Marker	Pattern
ER, PR	+
Her-2/neu	–
E-cadherin	+
CK903	+
GATA-3	+
Beta-catenin	+ or –
Alpha-catenin	– or +

Tubulolobular CA of the breast is a tumor with a hybrid morphology and immunoprofile, exhibiting features of both ductal and lobular differentiation. This tumor is usually ER+, PR+, Her-2/neu–, but rare cases may be Her-2/neu+

References: [1, 2, 4–6, 9, 14, 69–73, 216–228]

Table 13.14 Phenotype of micropapillary carcinoma of breast

Marker	Pattern
EMA	+, M, "inside-out" pattern
MUC1	+, External surface adjacent to stroma
E-cadherin	+, M, mainly between tumor cells
GATA-3	+
N-cadherin	+ or –
CK7	+
CK5/6	–
ER, PR, Her-2/neu	– or +
p53	– or +
EGFR, c-kit	–

Micropapillary CA is considered to behave aggressively; it is frequently associated with vascular invasion and axillary lymph node metastases but not associated with poorer survival rates

Studies reported that micropapillary CAs have a higher level of p53 expression, a higher Her-2/neu overexpression rate and a lower frequency of ER expression compared with invasive ductal CA, NOS type. The CK expression profile shows no difference from ductal CA of the NOS type. The differentiation of invasive ductal CA with retraction artifact vs. micropapillary CA may be achieved by immunohistochemical study using EMA or MUC1. Invasive ductal CAs demonstrate an apical or cytoplasmic staining for EMA or MUC1, while micropapillary CAs show an "inside-out" staining pattern: accentuation of the basal surface (stromal facing or periphery) of the tumor cells. The E-cadherin stain shows accentuation between CA cells but not the contiguous surfaces. However, this "inside-out" staining pattern is not specific for micropapillary CAs. Pure mucinous type of ductal CAs show a similar staining pattern

Study reported GATA-3 expression in 100 % (12/12) cases of micropapillary CAs

The immunostaining patterns of micropapillary CAs are illustrated in Fig. 13.11

References: [1–4, 9, 74–82, 218, 279–281]

Table 13.15 Phenotype of mucinous (colloid) carcinoma of breast

Marker	Pattern
CK7	+
ER, PR	+
Her-2/neu	–
MUC2	+
MUC6	+ or –
CK20	–
WT1	+ or –, N
CEA	+ or –
EGFR	–

Mucinous CA of the breast is usually ER+, PR+, Her-2/neu–. By gene profiling, mucinous CA is of luminal subtype. Its CK expression profile is similar to ductal CA, NOS type. Studies revealed an increased expression of MUC1, MUC6 and WT1 in mucinous CA of breast

Our data (invasive ductal CA, NOS, N = 175; mucinous CA, N = 2) showed that MUC2 is positive in 2.3 % (4/175) of invasive ductal CAs NOS, and both cases of mucinous CA, as illustrated in Fig. 13.12

References: [1–6, 9, 14, 83–89]

Table 13.16 Phenotype of apocrine carcinoma of breast

Marker	Pattern
GCDFP-15	+, C
ARP	+, N
ER, PR	–
p53	+ or –, N
Her-2/neu	– or +
EGFR	+ or –, M
E-cadherin	+, M
AE1/AE3, CK7	+, M, C
CEA	+, M, C
S100 protein	–
GATA-3	+ or –, N
MIB-1	High

Apocrine CAs are usually ARP+ and triple negative (ER–, PR–, Her-2/neu–) or Her-2/neu overexpressed (ER–, PR–, Her-2/neu+) tumors. A higher rate of EGFR expression is reported in apocrine CA than in conventional ductal CA. Nearly all of the apocrine lesions are positive for GCDFP-15, however, which also decorates non-apocrine breast epithelial cells. In breast CAs, our study revealed GCDFP-15 expression in 30 % (71/237) of invasive breast CAs (including invasive ductal and lobular CAs of all grades and types) and only 15 % (14/96) of ER-negative breast CAs; among the 14 cases of ER-negative breast CAs expressing GDCFP-15, all six cases of apocrine CAs were included

Apocrine CA is frequently positive for p53, especially in in-situ CA. Benign apocrine lesions are usually non-reactive to p53

(continued)

Table 13.16 (continued)

GATA-3 expression in apocrine CAs, in our experience, is variable, showing a heterogeneous staining pattern. Among the six apocrine CAs included in our study, two showed strong diffuse positivity, one weak diffuse, two weak focal, and one negative

Positive membranous staining for E-cadherin has been reported to distinguish apocrine CA from pleomorphic lobular CA

Table 13.16 (continued)

Special stains for periodic acid-Schiff-diastase (PAS-D), toluidine blue and trichrome reveal cytoplasmic, granular staining in apocrine neoplasms. The cytoplasmic secretion is occasionally positive for mucicarmine

An example of apocrine CA is illustrated in Fig. 13.13

References: [1–6, 9, 14, 90–98, 216, 218, 219]

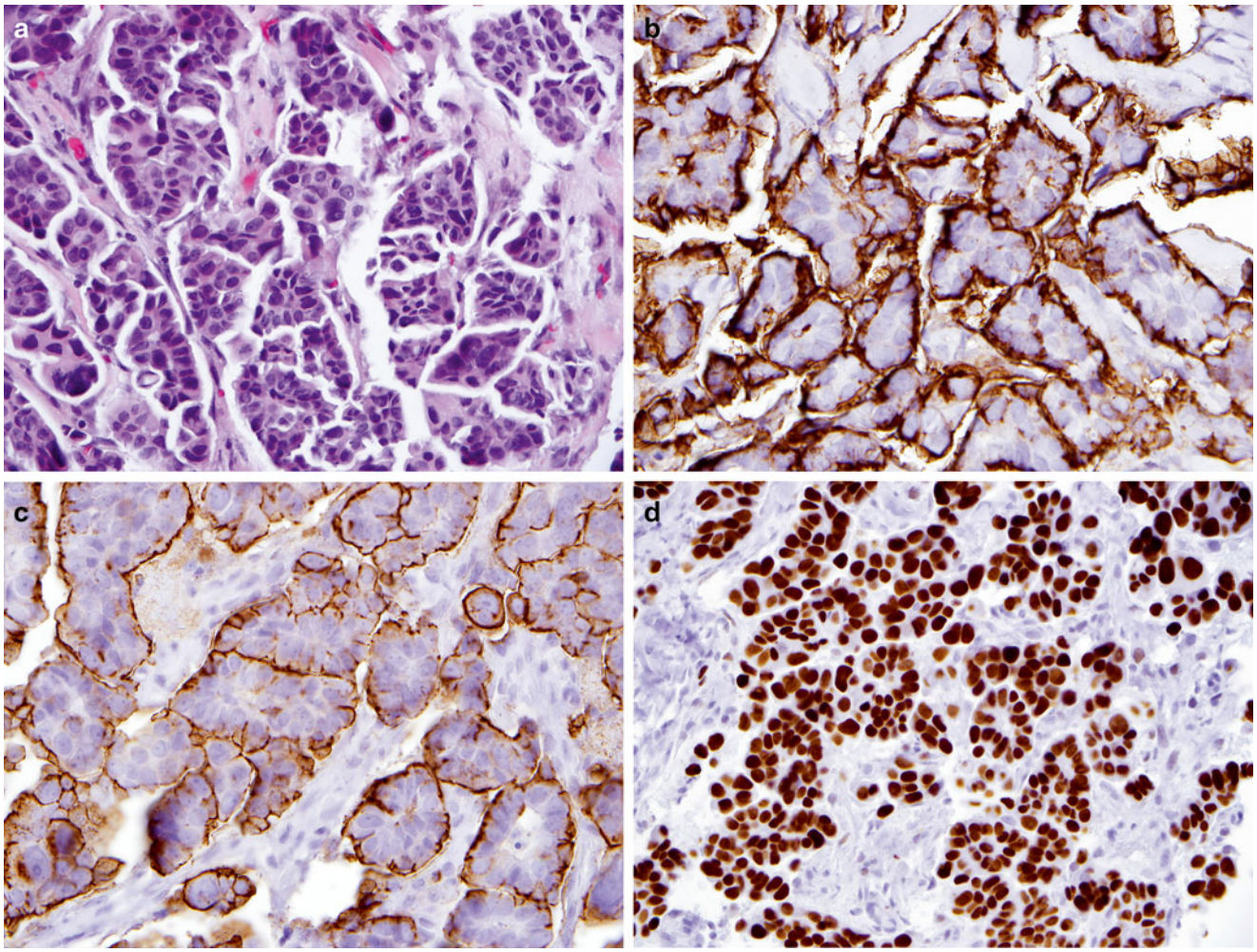

Fig. 13.11 (**a**) Micropapillary CA of breast, H&E stain. (**b**) Micropapillary CA of breast, EMA staining pattern shows accentuation of the basal surface of the tumor cells, an "inside-out" pattern. (**c**) Micropapillary CA of breast, an "inside-out" staining pattern for MUC1. (**d**) Micropapillary CA of breast shows diffuse nuclear staining for GATA-3

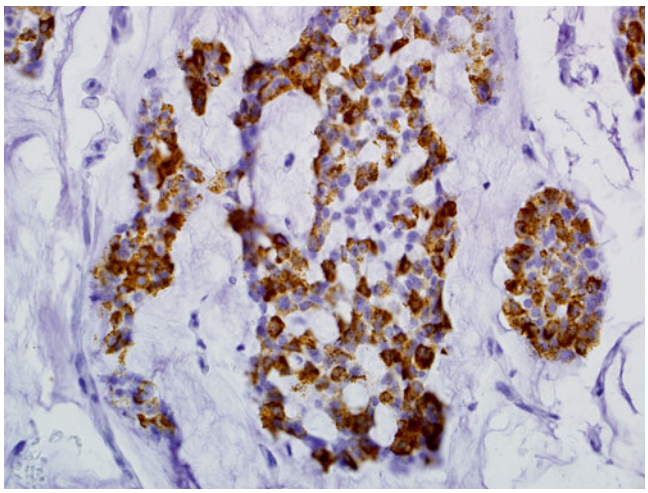

Fig. 13.12 Mucinous carcinoma of breast demonstrates positive stain for MUC2

Table 13.17 Phenotype of secretory carcinoma of breast

Marker	Pattern
ER, PR, Her-2/neu	–
S100 protein	+
CK5/6	+, diffuse or focal
E-cadherin	+
CK8/18	+
Vim	+
GCDFP-15	–
p63	–

A typical finding in secretory CA is the presence of intracellular or extracellular secretory material which is positive for PAS-D and Alcian blue and negative for mucicarmine

Secretory CAs are typically triple negative (ER–, PR–, Her-2/neu–) and basal-like CAs, which express basal cytokeratins (CK5/6, CK14, CK17). In contrast to triple-negative conventional breast CAs with an aggressive course, secretory CAs behave in a low-grade fashion.

References: [1–7, 14, 99–102]

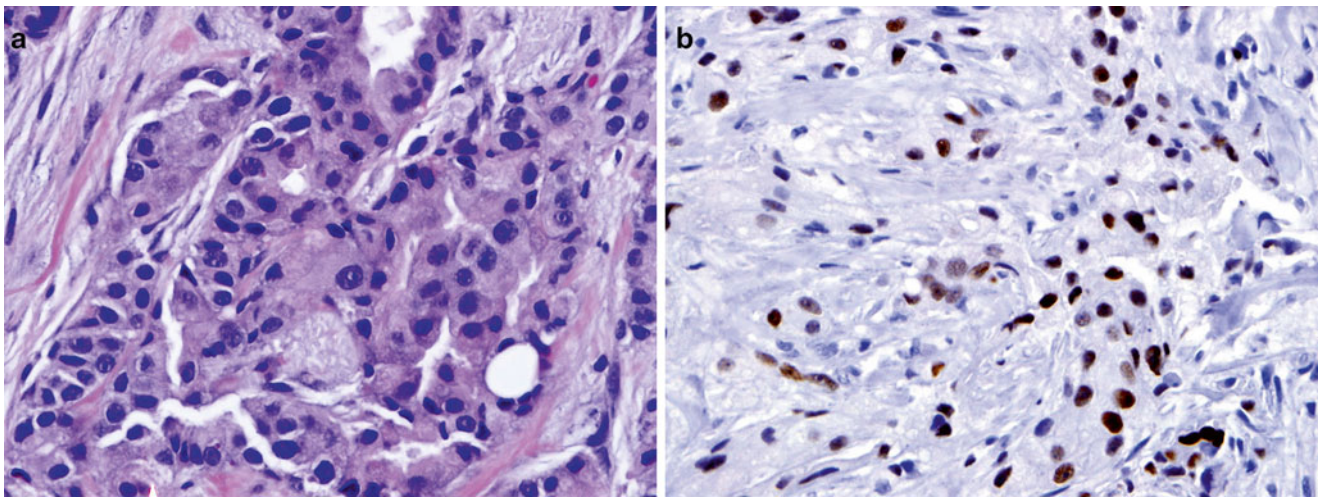

Fig. 13.13 (**a**) Apocrine CA of breast, H&E stain. (**b**) Apocrine CA of breast, 3+ strong nuclear staining for GATA-3

Table 13.18 Phenotype of adenoid cystic carcinoma of breast

Marker	Pattern
ER, PR, Her-2/neu	–
c-kit	+, LC
P63	+, MEC
CK7	+, LC
S100, maspin, calponin	+, MEC
CK8/18	+, LC
E-cadherin	+, M
Beta-catenin	+, M
CK903, CK5/6, CK14, CK17	+, MEC
p53	–
ARP	–
IMP3	+

LC luminal cells

Mammary adenoid cystic CA, a salivary gland-type tumor of the breast, is typically a triple- negative (ER−, PR−, and Her-2/neu−) and basal-like CA. In contrast to triple-negative conventional breast CAs with an aggressive clinical course, adenoid cystic CAs behave in a low-grade fashion. Histologically, adenoid cystic CA is composed of a dual-cell population of epithelial (luminal) and myoepithelial (basaloid) cells forming tubular, cribriform and solid patterns

The dual-cell population can be demonstrated by immunohistochemical analysis. p63 and c-kit are useful adjuncts in the differentiation of adenoid cystic CA from other types of ductal CAs. p63 is a specific myoepithelial marker, labeling the myoepithelial (basaloid) cells at the periphery or in the solid area. c-kit labels the epithelial (luminal) cells, not the myoepithelial cells; therefore, the solid area (which is composed of myoepithelial cells) is non-reactive. In addition, the hormonal status (triple negative) is a valuable aid in the differential diagnosis between classic adenoid cystic CA and invasive cribriform CA, which is a low-grade ductal CA and usually ER+, PR+

EGFR protein has been reported to be overexpressed in adenoid cystic CAs without underlying EGFR gene mutation. However, lack of overexpression of EGFR in adenoid cystic CAs has also been reported. p53 protein expression is low in adenoid cystic CAs. ARP expression is infrequent

IMP3, a recently proposed basal phenotype marker, has been described as overexpressed in 81.3 % (13/16) of primary adenoid cystic CAs, with a predominantly membranous staining pattern and mean percentage of positive cells of 50 %

The eosinophilic hyaline material in the pseudolumens is periodic acid-Schiff (PAS)-positive, diastase (D)-resistant and immunohistochemically reactive to collagen IV and laminin; the lightly basophilic myxoid substance in glandular spaces is Alcian blue positive. Ultrastructurally, these materials have been demonstrated to represent duplicated basal lamina and glycosaminoglycans, respectively

Figure 13.14 demonstrate the immunostaining pattern of adenoid cystic CA with double stain for p63 and c-kit

References: [1–6, 9, 14, 103–108, 218, 282–294]

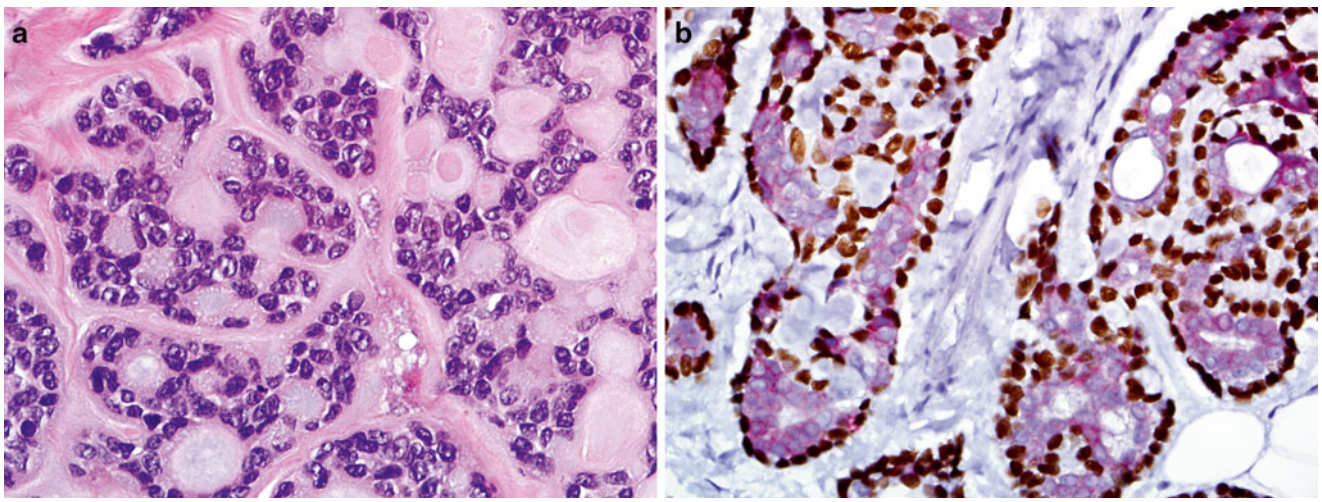

Fig. 13.14 (**a**) Adenoid cystic carcinoma of breast, H&E stain. (**b**) Adenoid cystic carcinoma of breast demonstrates double stain for p63 (*brown* nuclear stain, peripheral myoepithelial cells) and c-kit (*pink* cytoplasmic stain, luminal ductal cells)

Table 13.19 Phenotype of small cell carcinoma of breast

Marker	Pattern
CK7	+
CK20	–
NSE	+
Bcl-2	+
E-cadherin	+
AE1/AE3, CAM 5.2	+
CD56, synaptophysin, chromogranin	+ or –
TTF1	– or few +
ER, PR	+ or –
Her-2/neu	–

The diagnosis of primary small cell CA of the breast can only be made with confidence if a non-mammary primary is excluded or if an in-situ component can be demonstrated

More than half of the reported mammary small cell CAs are ER + and PR+; all cases reported are Her-2/neu–

The CK7 and CK20 immunostaining pattern aids in the differentiation of pulmonary vs breast primary. Neuroendocrine markers showed a variable staining pattern in mammary small cell CA, except NSE, which is positive in all reported cases

The majority of primary small cell CAs of the breast are positive for E-cadherin, suggesting a form of ductal CA. However, rare E-cadherin-negative mammary small cell CA has been reported

References: [1–4, 9, 14, 109–113, 295–301]

Table 13.20 Phenotype of basal-like carcinoma of breast

Marker	Pattern
Basal keratins (CK5/6, CK14, CK17, CK903)	+ or –
ER, PR, Her-2/neu	–
EGFR	+
c-kit	+
p53	+ or –
MIB-1	High
p63	+ or –
P-cadherin, nestin, SMA, S100	+ or –
Vimentin	+
Luminal CK (CK8/18, CK7, CK19)	+

Basal-like breast CAs are identified by gene expression profiling. Immunohistochemical surrogates have been developed, including basal CK and EGFR. Currently, there is no international consensus on biomarkers to identify tumors as basal-like subtype. The most widely used immunohistochemical surrogate to define a tumor as basal-like is that proposed by Nielsen and colleagues, in which basal-like CAs were defined as ER–, Her-2/neu– and CK 5/6 and/or Her-1 (EGFR) + phenotype. This panel has a sensitivity of 76 % and specificity of

Table 13.20 (continued)

100 % in identifying breast CAs with a basal-like phenotype as defined by expression profiling analysis. Recently, some authors proposed adding c-kit to the panel, defining basal-like breast CAs as ER–, PR–, Her-2/neu–, one basal CK+, Her 1+, and/or c-kit+. Approximately 80 % of BRCA1-associated breast CAs have a basal-like profile

Basal-like CAs are usually ER–, PR–, Her-2/neu– (triple-negative), expressing basal CKs (CK5, 5/6; CK14, CK17, CK903), EGFR, vimentin, p53, and some markers with myxoid differentiation (such as p63, P-cadherin, nestin, CD10, SMA and S100). However, basal-like breast CAs do not express all basal CKs; they may express one or more instead. EGFR and c-kit are highly expressed in basal-like breast CAs and rarely expressed in non-basal-like breast CAs

References: [1–6, 9, 14, 114–124, 154, 158, 302–305]

Table 13.21 The evaluation of papillary neoplasm

Marker	Benign papillary neoplasm	Malignant papillary neoplasm
p63	+	– or scattered +
CK5/6, CK14, CK903	+, diffuse or mosaic pattern	–
ER	– (only scattered +)	+ (usually diffuse)
SMM-HC	+	– or scattered +
Calponin	+	– or scattered +
CD10	+	– or scattered +

Benign papillary neoplasms include papilloma and papilloma with florid epithelial hyperplasia. Malignant papillary neoplasms include invasive papillary CA, papillary CA in-situ (intracystic papillary CA) and DCIS involving papilloma

HMWCKs (CK5/6, CK14, CK903) decorate luminal cells (especially hyperplastic) and myoepithelial cells, in a diffuse or mosaic pattern in benign papillary neoplasms and are non-reactive in malignant papillary neoplasms. Myoepithelial markers (p63, SMM-HC, calponin, CD10, myosin, S100, SMA) highlight myoepithelial cells at the basement membrane in benign papillary neoplasm but not in malignant papillary neoplasm. Scattered tumor cells may stain for p63

Hormonal receptors, such as ER, may have additional value; in general, benign lesions show only scattered staining, while atypical papillary lesions are usually diffusely positive. Studies also reported expression of neuroendocrine markers, such as synaptophysin and chromogranin, in the majority of solid papillary CAs however no expression in benign and atypical papillary lesions

References: [1–6, 9, 11, 14, 20, 31, 40, 125–130, 218, 309–314]

Table 13.22 The evaluation of fibroepithelial neoplasm (fibroadenoma vs. phyllodes tumor)

Marker	Fibroadenoma	Benign PT	Borderline PT	Malignant PT
Mitosis	Unusual	<2/10 HPF	2-5/10 HPF	>5/10 HPF
p53	Few	Few	Increased	High
MIB-1	Very low	Few	Increased	High
CD117, EGFR, CD10	+, Scattered	+, Scattered	Increased	High
IMP3	–	–	–	+
PR	+, Stromal cells	+, Stromal cells	+, Stromal cells	+, Stromal cells
CK5/6, CK903	–	–	–	–

PT phyllodes tumor, *HPF* high-power field

No definitive consensus exists on the number of mitoses required for classification of phyllodes tumors (PTs) into three subgroups. The numeric figures listed in the table above are recommendations by some authors. The World Health Organization classification of PT requires more than 10 mitoses per 10 high-power field (HPF) for malignant PT but provides no numeric figure for benign and borderline PTs

Studies using a variety of immunohistochemical markers demonstrated a good correlation between MIB-1 index and histologic category or grade of phyllodes tumors, as did p53 expression. However, there are no nummeric criteria to define subgroups; those markers are not independent predictors of outcome, such as local recurrence or metastases

CD117, EGFR and CD10 have been reported with higher expression in malignant than in benign PT; however, there are no significant differences to distinguish between borderline and malignant PT

Recently, Yang et al. observed that IMP3 is preferentially expressed in all malignant PTs but not in borderline or benign tumors or benign surrounding breast tissues

References: [1–4, 9, 14, 131–144, 218, 312–314]

Table 13.23 The evaluation of myoepithelial neoplasms

Marker	Adenomyoepithelioma, benign	Myoepithelioma	Myoepithelial CA
Myoepithelial markers	–, glandular cells +, myoepithelial cells	+	+
CK7, EMA	+, glandular cells –, myoepithelial cells	–	–
ER	+, glandular cells; –, myoepithelial cells	–	–
MIB-1	Low (<or=2/HPF)	Low (<or=2/HPF)	High
AE1/AE3, CAM 5.2	+	+	+

Myoepithelial markers include p63, SMA, calponin, caldesmon, SMM-HC, CD10, S100, maspin and HMWCKs (CK5/6 and CK14)

Adenomyoepithelioma is composed of both glandular and myoepithelial elements. There are PAS or mucicarmine-positive secretions within the glands, which are also positive for CEA

Myoepithelial neoplasms are non-reactive to desmin and CD34. Myoepithelial carcinoma is usually ER–, PR– and Her-2/neu– and positive for EGFR and vimentin

References: [1–6, 9, 14, 145–153, 218, 315, 316]

Table 13.24 Genomic phenotype (luminal A, B, basal, and Her-2) of breast carcinoma

Marker	Luminal A	Luminal B	Basal-like	Her-2
ER	+	+	–	–
PR	+	+	–	–
Her-2/neu	–	+	– or +	+
CK5/6	–	–	+	–
EGFR	–	–	+	–
Ki-67	< or = 14 %	> or = 14 % (if Her-2–)	High	High

DNA microarray profiling studies categorize breast carcinomas into ER+/luminal, normal breast-like, Her-2/neu overexpressing and basal-like subtypes. Basal-like and Her-2/neu overexpressing subtypes frequently have *Tp53* mutation and worse prognoses. An association with BRCA-1-associated CAs in basal-like subtype of breast CA has been described

Recently, a novel claudin-low subtype of breast CA has been described by gene expression analyses. Studies discovered that the majority of claudin-low subtype breast CAs were triple-negative (ER-, PR,/Her-2/neu-), basal-like tumors with a high frequency of metaplastic and medullary differentiation

References: [1–6, 9, 14, 114, 116–122, 154–158, 218, 304, 305, 317–320]

Table 13.25 Prognostic and predictive markers if breast carcinoma

Marker	Pattern	Comment
ER, PR	+, N	Good prognostic factor
Her-2/neu	+, M	Worse prognostic factor
p53	+, N	High expression associated with high-grade tumor and worse prognosis
MIB-1	+, N	High Ki67 relates to poor outcome. Post therapy Ki67 is a strong predictor of outcome for patients not achieving a pathological complete response
ARP	+, N	Studies suggest ER and ARP are coexpressed in the majority of breast tumor cells. A low level of ARP in ER-positive breast CA is a worse prognostic factor

References: [1–6, 9, 14, 159–167]

Table 13.26 The differentiation of columnar cell lesions (including flat epithelial atypia) vs normal/usual ductal hyperplasia

Marker	CCL (including FEA)	NL or UDH
CK5/6, CK14, CK903	–	+, Mosaic or diffuse
ER, PR	+, N, diffuse	– or +, N, scattered
ARP	+	– or +, Rare
CK19	+	+
E-cadherin	+	+
Her-2/neu	–	–
MIB-1, cyclin D1	Higher	Lower
Bcl-2	Decreased	High

FEA flat epithelial atypia, *CCL* columnar cell lesions, *NL* normal, *UDH* usual ductal hyperplasia

Normal/UDH demonstrates a mixed staining pattern for HMWCKs (CK903, CK14 and CK5/6), and usually scattered nuclear staining for ER/PR

References: [1–6, 9, 14, 28, 130–139, 171–174, 218]

Table 13.27 The differentiation of usual duct hyperplasia vs atypical duct hyperplasia or ductal carcinoma in-situ

Marker	UDH	ADH or DCIS
CK5/6, CK903	+, Diffuse	– or Focally weakly +
ER, PR	Scattered +	+, Diffuse
CK8/18/19	+	+

UDH usual duct hyperplasia, *ADH* atypical duct hyperplasia, *DCIS* ductal carcinoma in situ

The HMWCKs CK5/6 and CK903 are reported to be useful in the differentiation of UDH vs ADH or DCIS, demonstrating diffuse reactivity in UDH (a mosaic staining pattern) vs non-reactive in ADH or DCIS (except rare residual luminal epithelial cells in ADH and basal layer in DCIS or basaloid DCIS). The immunophenotypes reflect growing evidence that UDH is a hyperplastic process, while ADH/DCIS is neoplastic, with clonal proliferation of luminal epithelial cells. Basaloid DCIS (positive for HMWCK with a reported incidence of 3.7 %) is often a high-grade, triple-negative tumor with necrosis, easily recognized by morphology

ER and PR often show diffuse nuclear staining in ADH and DCIS, especially in low-grade lesions, and only scattered nuclear staining in UDH

References: [1–6, 9, 10, 13, 30, 35–38, 168–174, 218]

Table 13.28 The differentiation of lobular carcinoma vs ductal carcinoma

Marker	Ductal CA	Lobular CA
E-cadherin	+	–
P^{120} catenin	+, M	+, C
CK903	–[a]	+
CK8	+, Peripheral-predominant membranous pattern	+, Perinuclear, ring-like, cytoplasmic pattern

*Ductal CA is negative for CK903, except basaloid type

The vast majority of lobular CAs showed a complete loss of E-cadherin expression; in contrast, diffuse membranous staining for E-cadherin was seen in ductal CAs. However, aberrant E-cadherin expression was identified in 2–16 % of lobular CA cases. Several authors suggested that the expression of E-cadherin in tumors showing characteristic features of lobular CA should not preclude the diagnosis of lobular CA

p^{120} catenin stains both lobular and ductal CAs with different staining patterns: membranous stain for ductal CA and cytoplasmic stain for lobular CA

CK8 decorates ductal and lobular CAs in different patterns, which have been described as tumor cells "molding" to each other in ductal CA and a "bag of marbles" appearance in lobular CA

References: [1–6, 9, 13, 27, 45, 175–182, 218, 270, 271]

Table 13.29 The differentiation of tubular carcinoma vs. sclerosing adenosis and microglandular adenosis

Marker	TC	SA	MA
Markers of MEC	–	+	–
Markers of BM	–	+	+
S100	–	–	+
ER	+	Scattered	–

TC tubular carcinoma, *SA* sclerosing adenosis, *MA* microglandular adenosis, *MEC* myoepithelial cells, *BM* basement membrane

Markers of MEC: p63, SMM-HC, calponin, CD10, maspin, SMA

(continued)

Table 13.29 (continued)

Markers of basement membrane (BM): laminin, type IV collagen, reticulin, and PAS

Both tubular CA and microglandular adenosis lack myoepithelium. Laminin, type IV collagen, reticulin and PAS decorate the basement membrane, which is present in microglandular adenosis and absent in tubular CA

Myoepithelial cells are usually proliferating in sclerosing adenosis, demonstrating more intense staining for myoepithelial markers

The epithelial cells of microglandular adenosis show strong immunoreactivity for S100; while the epithelial cells of tubular CAs and sclerosing adenosis lack S100 expression. Immunohistochemical evaluation for ER may aid in differential diagnosis as well; tubular CAs are usually ER + in a diffuse fashion; benign lesions, such as sclerosing adenosis, often show patchy positivity; microglandular adenosis is reported ER negative

References: [1–6, 9, 14, 22–24, 29, 183–185, 218, 325–330]

Table 13.30 The differentiation of classic adenoid cystic carcinoma vs tubular or cribriform carcinoma, and collagenous spherulosis

Markers	ACC, classic	TC or CC	CS
c-kit	+	–	–
p63	+	–	+
ER, PR	–	+	+ or –
Calponin, CD10	–	–	+
SMM-HC, HHF-35	–	–	+
Her-2/neu	–	–	–
E-cadherin	+	+	+

ACC adenoid cystic carcinoma, *TC* tubular carcinoma, *CC* cribriform carcinoma, *CS* collagenous spherulosis

In general, adenoid cystic carcinomas (ACCs) are triple-negative (ER-, PR-, Her-2/neu-) tumors, but tubular carcinoma (TC) and cribriform carcinoma (CC) are low-grade ductal CAs, often positive for ER and PR, and negative for Her-2/neu (ER+, PR+, Her-2/neu–). A reported 15 % of ACCs are ER+, PR+, and 15 % of TCs and CCs show weak, incomplete membranous staining for Her-2/neu

References: [1–6, 9, 14, 22–24, 103–108, 218, 282–294, 321]

Table 13.31 The differentiation of spindle cell tumors of breast

Marker	ME	MFB	SpCC	MPT	MM
Pan-CK (MNF-116)	+	–	+	–	–
CK5/6, CK14, CK903	+	–	+	–	–
AE1/AE3	–	–	– or +	–	–
CAM 5.2	–	–	– or +	–	–
p63	+	–	+ or –	–	–
Calponin	+	+ or –	– or +	–	–
SMA	–	+	+ or –	+ or –	–
CD34	–	+	–	– or +	–
Desmin	–	+	–	+ or –	–
S100	+	– or +	–	–	+
HMB-45	–	–	–	–	+

ME myoepithelioma, *MFB* myofibroblastoma, *SpCC* spindle cell carcinoma, *MPT* malignant phyllodes tumor, *PS* primary sarcoma, *MM* malignant melanoma

Primary breast sarcomas with spindle cell morphology (other than high-grade angiosarcoma) are exceedingly rare and therefore not included in this table

When encountering a spindle cell neoplasm of the breast, a battery of CKs, including pan-CK, HMWCKs (CK5/6, CK14, CK17, CK903) and LMWCKs (CAM 5.2, CK19) should be applied to detect spindle cell CA, which is far more common than primary spindle cell sarcoma. Many studies showed myoepithelial differentiation in spindle cell CA of breast. p63, a specific and sensitive myoepithelial marker, was proposed to include in the workup panel for spindle cell neoplasm. PTs (benign or malignant) are negative for p63, except the normal myoepithelial cells surrounding ductal structures

Myofibroblastoma is reported positive for CD34, desmin, SMA, Bcl2, vimentin and steroid receptors. An example of myofibroblastoma is illustrated in Fig. 13.15

References: [1–6, 9, 14, 58–63, 65–68, 186–193, 218]

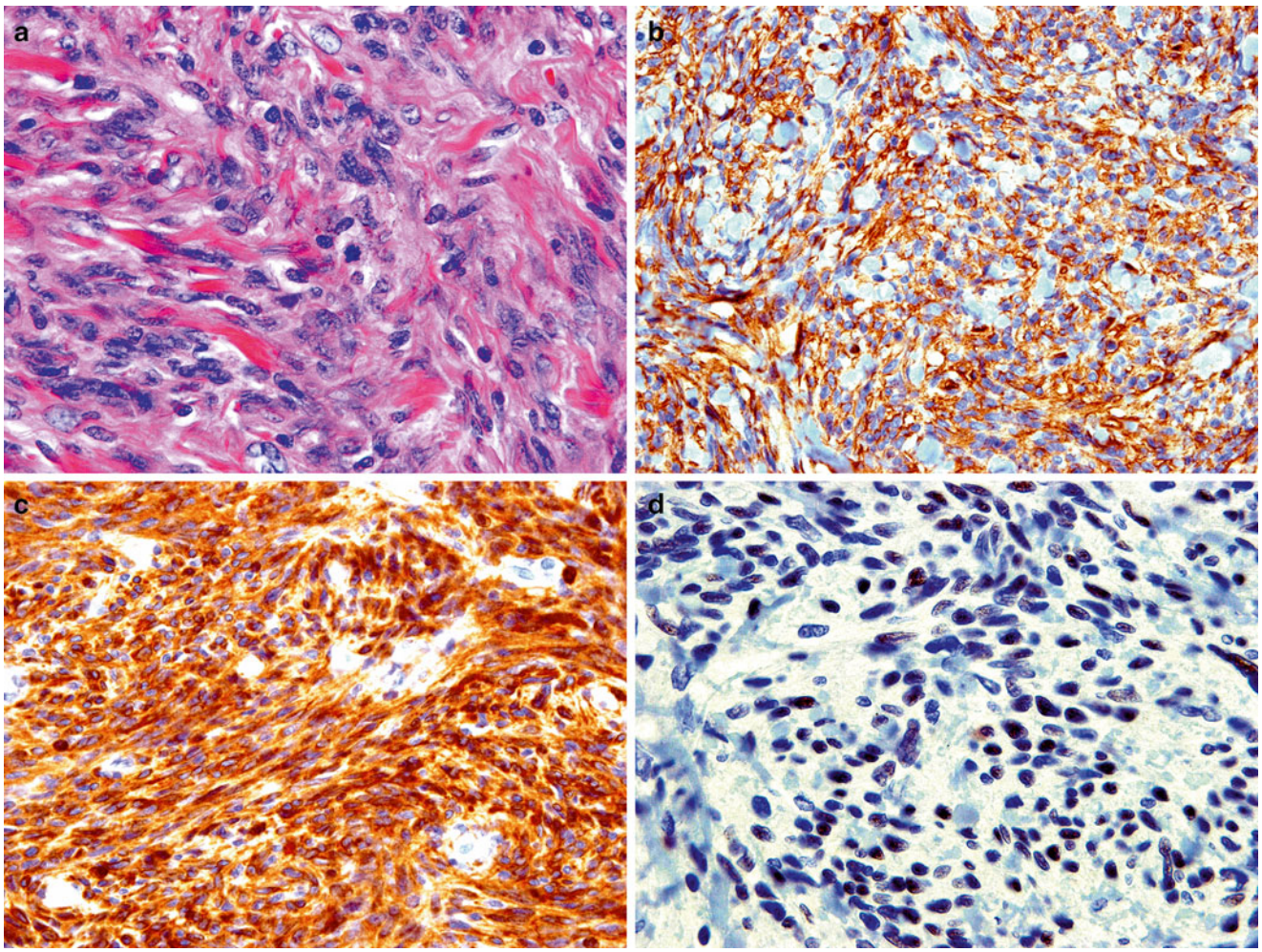

Fig. 13.15 (**a**) Myofibroblastoma, H&E stain. (**b**) Myofibroblastoma, demonstrating positive staining for CD34. (**c**) Myofibroblastoma, demonstrating positive staining for Bcl2. (**d**) Myofibroblastoma, demonstrating positive nuclear staining for ARP

Table 13.32 The differentiation of micropapillary patterned carcinoma (ovarian vs breast)

Marker	Ovarian serous CA	Micropapillary CA of the breast
PAX8	+	–
GATA-3	–	+
WT1	+	–
CA-125	+	–
GCDFP-15	–	+ or –

Diffuse nuclear stain for WT1 and cytoplasmic stain for CA-125 (>90 %) favor a metastatic papillary ovarian CA. A small percentage of micropapillary CAs of the breast are reactive to WT1 (3–26 %) and CA-125 (21 %)

References: [1–4, 9, 14, 74–82, 194–198, 216, 218, 226, 279–281]

Table 13.33 Markers used in the evaluation of metastatic breast carcinoma

Marker	Pattern
GATA-3	+
Mammaglobin	+ or –
GCDFP-15	– or +
CK7	+
ER, PR	+ or –
NY-BR-1	+
Her-2/neu	– or +
P120-catenin	+
CK20	–

The majority of breast CAs show a CK7+ and CK20– phenotype. In addition to ER, GCDFP-15 and mammaglobin are used as markers of breast differentiation. The sensitivities for breast CA were reported as 35–74 % for GCDFP-15 and 50-84 % for mammaglobin. Our data (invasive ductal and lobular CA, N = 252) reveals a sensitivity of 30.6 % for GCDFP-15 and 50.6 % for mammaglobin, although GCDFP-15 is reported in the literature to be more specific than mammaglobin. However, the utility of GCDFP-15 and mammaglobin in the workup of tumors of unknown primary is often limited due to their low sensitivities. Our recent study of the expression of GCDFP-15 and mammaglobin in 96 cases of ER-negative breast CAs revealed their expression in only 15 % and 35 %, respectively. GATA-3 has been emerging as a promising breast-specific marker; however, be aware of its expression in urothelial CA, salivary gland tumors, autonomic nervous system tumors (paragangliomas/pheochromocytomas and neuroblastic tumors) and parathyroid tumors

NY-BR-1, a differentiation antigen of the mammary gland, was first described in 2001 by Jager et al. using SEREX (serological analysis of recombinant tumor complementary deoxyribonucleic acid [cDNA] expression libraries) in a breast cancer patient. They reported that NY-BR-1 messenger ribonucleic acid (mRNA) expression was restricted to normal breast and testis tissues (although at a much lower level), and to 84 % (21/25) of breast CAs, whereas a variety of other normal and a majority of other tumor tissues showed lack of expression. Subsequent studies reported NY-BR-1 expression in 46.6-70 % of invasive breast CAs, showing a strong association with ER-positive and lower-grade tumors. In other tumors studied, NY-BR-1 expression was noted in 27 % (3/11) of sweat gland CAs; 75 % (18/24) of mammary Paget's disease, 80.8 % (21/26) of extramammary Paget's disease; 5.6 % (8/142) of müllerian carcinomas and 7 % (1/15) of pancreatic tumors

p^{120} catenin, a positive marker of lobular neoplasia, may be helpful in the panel for the workup of a metastatic lobular CA

References: [1–6, 9, 14, 194–198, 216–228, 255–263]

Table 13.34 The evaluation of mammary Paget's disease

Marker	Pattern
CK7	+
ARP	+
ER, PR	–
Her-2/neu	+
LMWCK (CAM 5.2)	+
HMFG	+
Mucicarmine, Alcian blue-PAS stains	+
EMA	+
CK20	–
HMWCK	–
MUC1	+
MUC2	–
MUC5AC	–

HMFG human milk-fat globule membrane antigen

The majority of mammary Paget's diseases are ARP+, ER–, Her-2+. The CK7 and CK20 profile is different from that of extramammary Paget's disease, which is positive for both

References: [1–6, 9, 14, 199–215, 322–324]

Table 13.35 The evaluation of nipple adenoma (syringomatous adenoma of nipple), large duct papilloma and low-grade ductal/tubular carcinoma

Marker	Nipple (syringomatous) adenoma	Large duct papilloma	Low-grade ductal/tubular carcinoma
p63	+	+	–
Calponin	+	+	–
SMM-HC	+	+	–
SMA	+	+	–
ER	–	+ or –	+
PR	–	+ or –	+

Both nipple adenoma and papilloma are benign lesions with an intact myoepithelial cell layer. p63 is an excellent marker of myoepithelial cells but is also reactive to cells of squamous differentiation

References: [1–6, 9, 11, 14, 22–24, 29]

Table 13.36 The differentiation of Paget's disease vs. Bowen's disease vs. malignant melanoma

Marker	Paget's disease	Bowen's disease	Malignant melanoma
CK7	+	−	−
HMB-45	−	−	+
S100 protein	−	−	+
HMFG	+	−	−
ARP	+ or −[a]	−	−
Her-2/neu	+	− or +	−
HMWCK	−	+	−
CAM 5.2	+	−	−
EMA	+	−	−
ER	− or +	−	−
GCDFP-15	+	−	−
CEA	− or +	−	−
Mucicarmine	+	−	−

HMFG human milk fat globule membrane antigen

[a]The majority of Paget's disease is reported positive for ARP (88 %) and Her-2/neu (68-97 %). Intraepidermal CK 7 expression is not restricted to Paget's disease. It is also reported in Toker cells and Merkel cells, which are Her-2/neu negative

References: [1–5, 9, 14, 199–214]

Note for All Tables

Note: "+", usually greater than 70 % of cases are positive; "−", less than 5 % of cases are positive; "+ or −", usually more than 50 % of cases are positive; "− or +", less than 50 % of cases are positive. *ND* no data available, *V* variable.

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