Breast

5

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Summary of Pearls and Pitfalls

- Fine needle aspiration (FNA) cytology and core needle biopsy (CNB) of breast lesions are the key components of the triple test for detecting breast malignancies.
- The advantages of FNA cytology are its rapid, cost-effective and, in experienced hands, highly sensitive and specific as well.
- The major limitations of FNA of breast lesions are the need for expertise in cytology for the interpretation of FNA material, inability to differentiate atypical ductal hyperplasia (ADH) from ductal carcinoma in situ (DCIS), limited ability to diagnose invasion, and often inadequate sample (and/or inadequate preparation of the material) for hormonal analyses in cases of carcinomas.
- For nonpalpable breast lesions, CNB has become the standard procedure for pathologic diagnosis.
- For palpable lesions, FNA is still utilized but has rapidly declined in popularity in recent years.
- At the current time, the common indications for FNA of breast lesions are as follows: (a) an expected benign cyst by ultrasound; (b) a sonographic lesion in a pregnant or postpartum patient or a patient with contraindications for CNB; (c) a sonographic lesion in a location unsuitable for CNB, such as behind the nipple or close to the chest wall; (d) to confirm an inoperable and locally advanced malignancy; (e) a suspected recurrence or metastasis; and (f) preoperative staging of axillary lymph nodes.
- Complications are rare, with the most common being bleeding.

Normal Cytology of Breast

- The female mammary gland is composed of 15–20 (or 25) lobes or segments that converge on the nipple in a radial pattern.
- Each lobe consists of a lactiferous duct, lactiferous sinus, segmental collecting duct, subsegmental duct, ductule (terminal duct), and acini (terminal ductules).
- The terminal duct lobular units (TDLUs) are comprised of ductile and acini, as shown in Fig. 5.1a, b, which is the most hormone-sensitive, therefore, the major site of origin of breast pathology.
- The smears of benign non-neoplastic glandular tissue are usually low cellularity, arranged in tight small, large or branching clusters, as well as monolayer sheets.
- The cells are cohesive; uniform; with small, round-to-oval, hyperchromatic nuclei; inconspicuous or very small nucleoli, and scant cytoplasm without distinct cell borders.
- The nuclei are irregularly distributed within the clusters to impart a crowded, overlapping appearance, as shown in Fig. 5.2a.
- Myoepithelial cells or stromal cells are appreciated at the periphery or admixed within the clusters.
- Naked bipolar nuclei (myoepithelial cells) may be seen in the background.
- Figure 5.2b illustrates a sample of benign glandular epithelial cells in a monolayer sheet.

Nipple Discharge Cytology

A spontaneous nipple discharge in a non-lactating or pregnant woman is abnormal and may suggest an underlying breast lesion (such as papilloma/papillomatosis or carcinoma) or

F. Lin et al., *Handbook of Practical Fine Needle Aspiration and Small Tissue Biopsies*, DOI 10.1007/978-3-319-57386-1_5

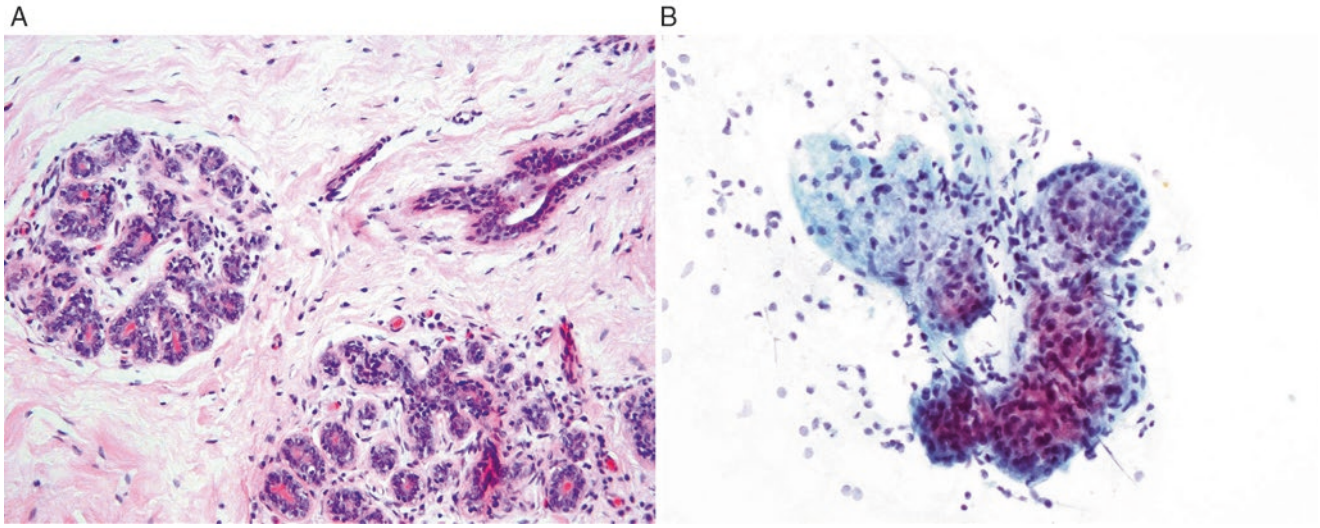

Fig. 5.1 (**a**, **b**) Normal terminal duct lobular unit (TDLU). (**a**) Histology, H&E; (**b**) cytology, Pap stain

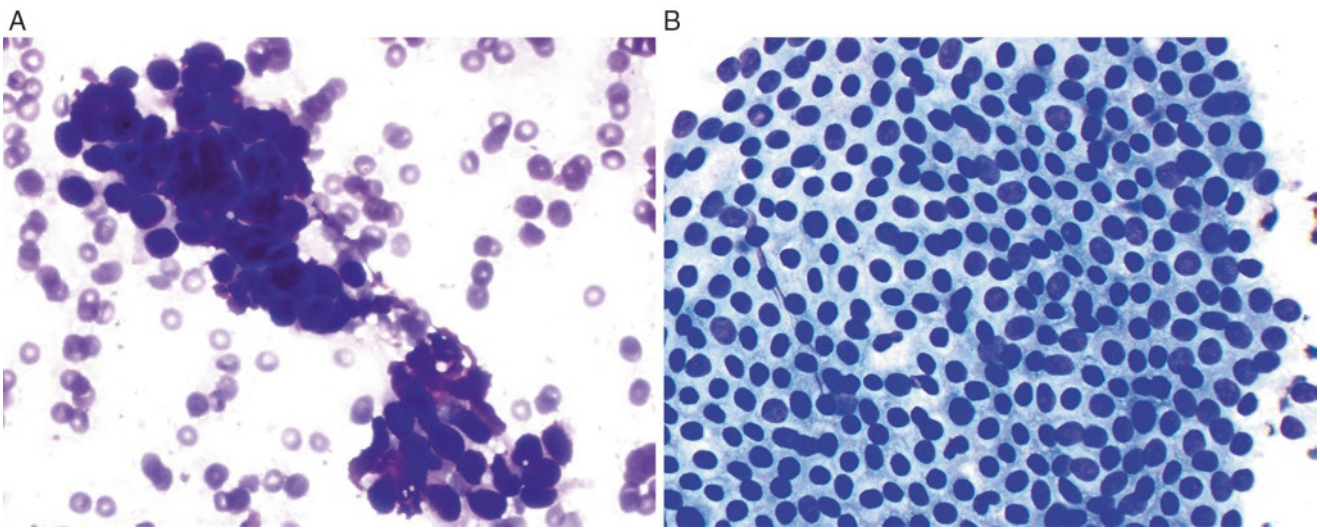

Fig. 5.2 (**a**, **b**) Benign ductal and lobular epithelial cells. (**a**) Benign ductal cells in crowded cluster, Diff-Quik; (**b**) benign ductal cells in monolayer sheet, Pap stain

hormonal abnormalities. However, nipple discharge cytology has a low sensitivity for detecting an underlying malignancy. Cases with unilateral, serous, bloody nipple discharge from a single duct are pathological and frequently associated with papillary lesions. In addition, the probability of detecting an underlying malignancy is increased in those specimens.

Cytological Features

Benign Nipple Discharge

- Usually sparsely cellular.
- Scattered foamy histiocytes.
- Rare benign ductal cells in small clusters.
- Inflammatory cells may be present.
- Proteinaceous debris in background.
- Figure 5.3a, b.

Atypical or Malignant Nipple Discharge

- Significant increase of cellularity.
- Clusters or isolated ductal cells with enlarged and pleomorphic nuclei displaying nucleoli.
- Stripped nuclei.
- Papillary groups may be seen.
- Necrosis may present.

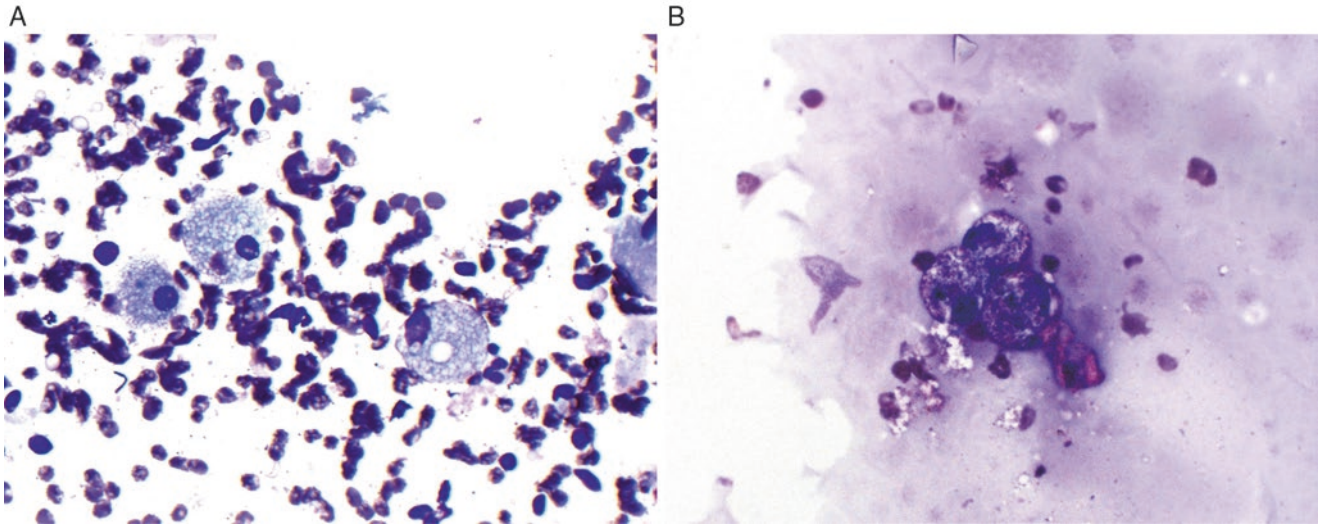

Fig. 5.3 (**a**, **b**) Contents of benign nipple discharge. Sparsely cellular smear contains few foam histiocytes and proteinaceous debris. (**a**) histiocytes, Diff-Quik; (**b**) degenerated histiocytes and rare crystals in a background of proteinaceous debris, Diff-Quik

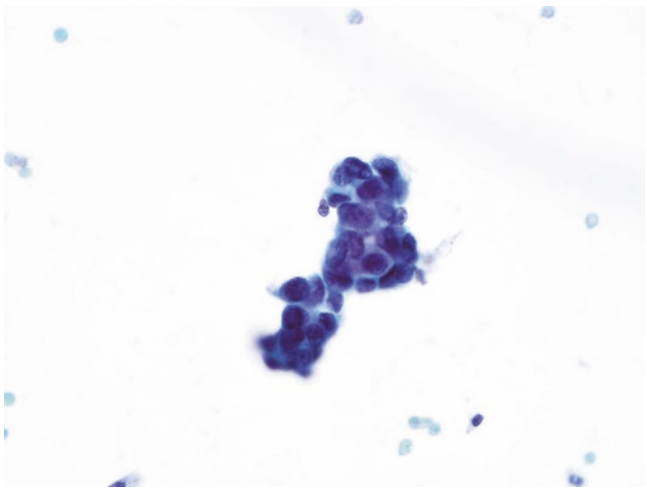

Fig. 5.4 Contents of atypical nipple discharge, showing a tight cluster of atypical ductal epithelial cells with enlarged nuclei, hyperchromatic chromatin, and moderate nuclear pleomorphism, Pap stain

- Acute inflammation and bloody background.
- Figure 5.4.

Fat Necrosis

Key Clinical Features

- The result of various injuries, such as trauma, previous procedure, chemoradiation therapy, and rupture of cyst
- Mimics breast carcinoma clinically, such as a firm mass, skin retraction, or thickening

Key Radiological Features

- Variable, may mimic breast carcinomas radiographically

Cytological Features

- Degenerated adipose tissue, giant cells, and foamy histiocytes
- Dirty background with amorphous or granular debris, fat droplets, and normal or degenerating adipose tissue
- Reactive stromal cells and occasional inflammatory cells
- Paucity of epithelial cells
- Figure 5.5a, b

Differential Diagnosis

- Infectious panniculitis
- Invasive lobular carcinoma

Histology

- Usually a well-demarcated area of vacuolated fat admixed with infiltrates of foamy histiocytes, multinucleated giant cells, lymphocytes, and plasma cells.
- Hemosiderin-laden macrophages and occasional cholesterol clefts are present.
- Granulation tissue with fibrosis and reactive ductal epithelial cells are occasionally identified.
- Representative image is illustrated in Fig. 5.5c, d.

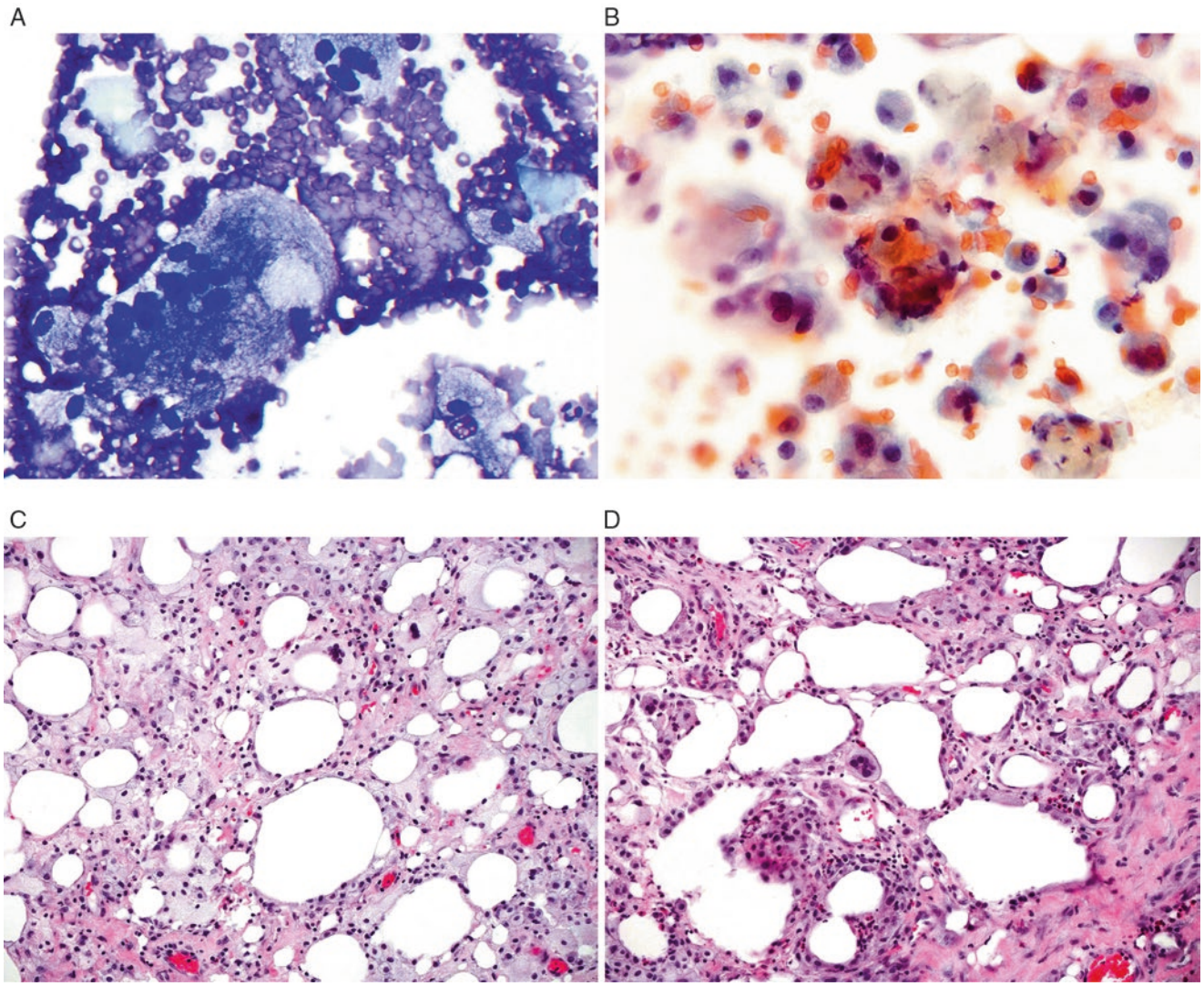

Fig. 5.5 (**a**–**d**) Fat necrosis. (**a**, **b**) Cytology, showing foamy histiocytes including multinucleated forms and debris (**a**, Diff-Quik; **b**, Papanicolaou [Pap] stain); (**c**, **d**) histology, abundant foam histiocytes including multinucleated forms, fat and fibrous tissue, hematoxylin, and eosin (H&E)

Immunohistochemistry

- Fat necrosis is mainly a histological diagnosis.
- Immunohistochemistry (IHC) is rarely applied on post-procedural specimens from breast carcinoma patients when the histiocytes show significant atypia; cluster of differentiation 68 (CD68) decorates histiocytes, while cytokeratin (CK) AE1/3 is nonreactive.

Subareolar Abscess

Key Clinical Features

- Also called "recurrent subareolar abscess"
- In the subareolar region, starts as a localized inflammation to form abscess, with subsequent healing and squamous metaplasia of the lactiferous ducts, then keratin plugging, dilatation and rupture of the ducts, as well as sinus tract formation

Cytological Features

- Abundant anucleated squames and neutrophils (Fig. 5.6a–d).
- Keratin debris, cholesterol crystals, and strips of squamous epithelial cells may be present.
- Rare ductal cells.
- Reactive stromal cells and giant cells.

Differential Diagnosis

- Epidermal inclusion cyst: peripheral and periareolar location

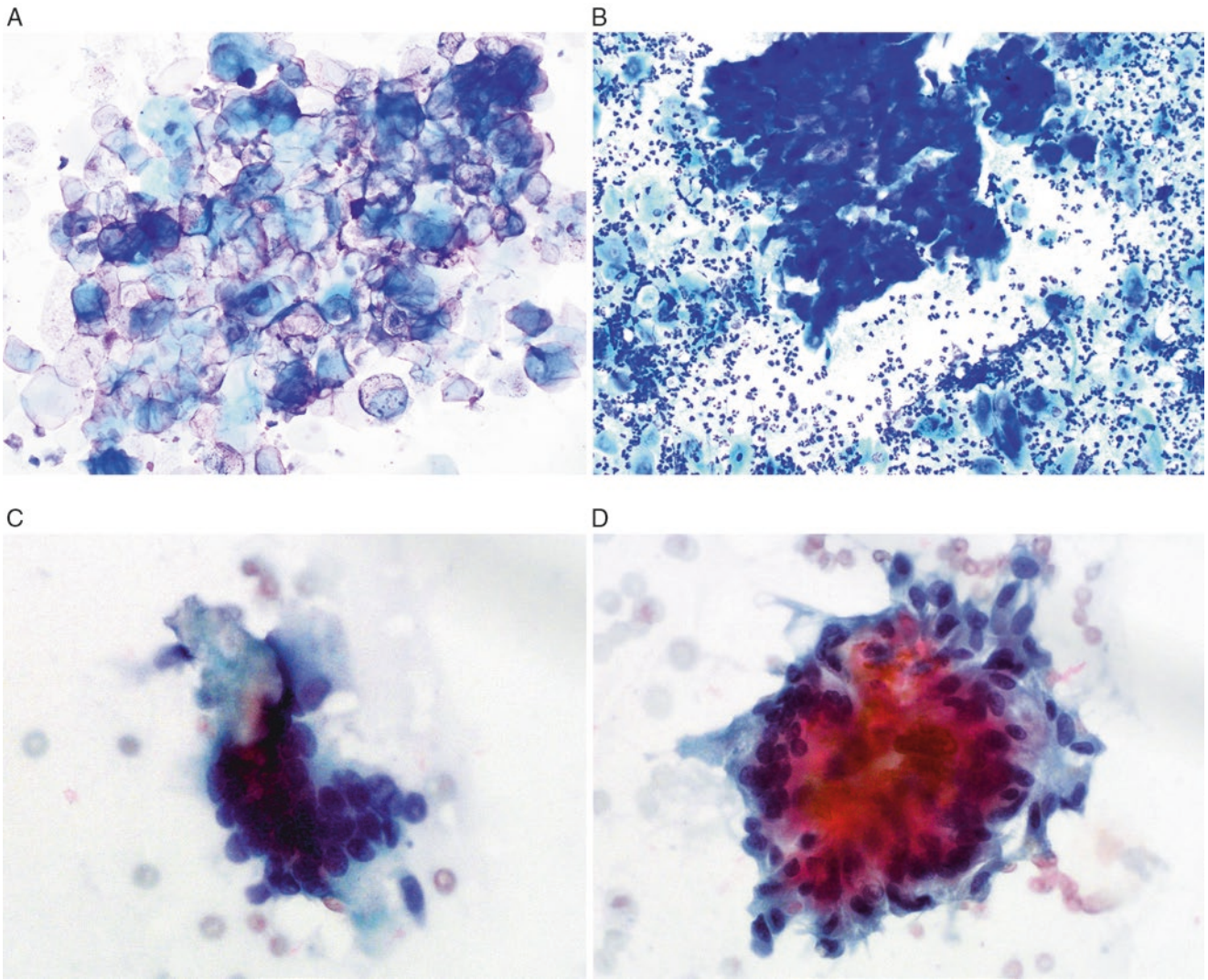

Fig. 5.6 (**a**–**d**) Subareolar abscess, cytology. There are abundant anucleated squamous epithelial cells, neutrophils, and dirty debris (**a**, **b**, Diff-Quik). Occasional multinucleated giant cells with adjacent keratin debris are seen (**c**, Pap stain), may form granulomatous aggregate (**d**, Pap stain)

Histology

- Breast tissue is displaced by chronic active inflammation with numerous neutrophils and a scant mixture of plasma cells and histiocytes.
- In recurrent cases, dilated duct with inflamed wall, granulation tissue, and intraluminal debris is present; may form a fistula.
- Representative images are shown in Fig. 5.7a, b.

Immunohistochemistry

- Immunohistochemistry is usually not applied for the diagnosis of subareolar abscess.

Fibrocystic Change

Fibrocystic change is the most common breast disorder, characterized by any combination of small/large cysts, apocrine metaplasia, fibrosis, adenosis, and duct hyperplasia.

Key Clinical Features

- Usually palpable nodularity in women of 20–50 years of age.
- The nodules are not well-defined, usually tender or even painful, changing with menstrual cycle.
- Generally multifocal, may be bilateral.

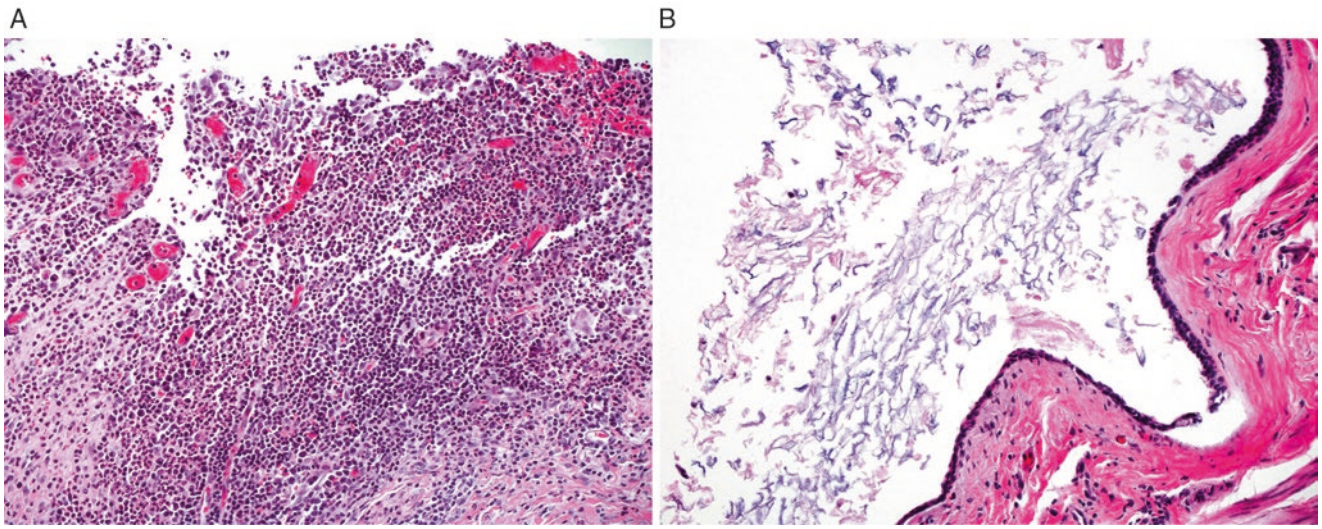

Fig. 5.7 (**a**, **b**) Subareolar abscess, histology. (**a**) Breast tissue with chronic active inflammation with numerous neutrophils and a scant mixture of plasma cells and histiocytes, H&E; (**b**) dilated duct with inflamed wall, granulation tissue, and intraluminal debris, including abundant anucleated squamous epithelial cells, H&E

- May be more localized to produce a palpable mass: the most common mass-producing lesion in women older than 30 years.
- May come to attention due to calcifications on mammogram.

Radiological Features

- Nodular densities or solitary, round or ovoid, and/or well-circumscribed masses of low-to-intermediate density on mammogram; may have microcalcifications.
- Simple cysts show lack of internal echoes and increased echogenicity of the posterior tissue on ultrasound.

Cytological Features

Nonproliferative Fibrocystic Changes

- Low-to-moderate cellularity
- A mixture of cellular components: cohesive groups or sheets of bland ductal cells, myoepithelial cells, apocrine cells, and histiocytes
- Scattered naked bipolar nuclei, fat, stromal tissue, and proteinaceous fluid in the background
- Figure 5.8a–d

Proliferative Fibrocystic Change

Ductal Proliferative Lesion Without Atypia

- Sheets and tight clusters of cells without significant nuclear overlap
- Finely granular chromatin pattern
- Inconspicuous to small nucleoli

Ductal Proliferative Lesion with Atypia

- Sheets and tight clusters of cells with significant nuclear overlap, loss of polarity, punched-out spaces, and mitosis
- Finely to coarsely granular chromatin
- Prominent to multiple nucleoli
- Figure 5.9a, b

Differential Diagnosis

Ductal Proliferative Lesion Without Atypia

- Intraductal papilloma
- Fibroadenoma

Ductal Proliferative Lesion with Atypia

- ADH and/or DCIS
- Ductal carcinoma

Histology

- Fibrocystic change refers to a complex of lesions, including dilated ducts/cysts, stromal fibrosis, apocrine metaplasia, blunt duct adenosis, mild sclerosing adenosis, and usual ductal hyperplasia (UDH).
- Atypical ductal proliferative lesions show ADH or DCIS.

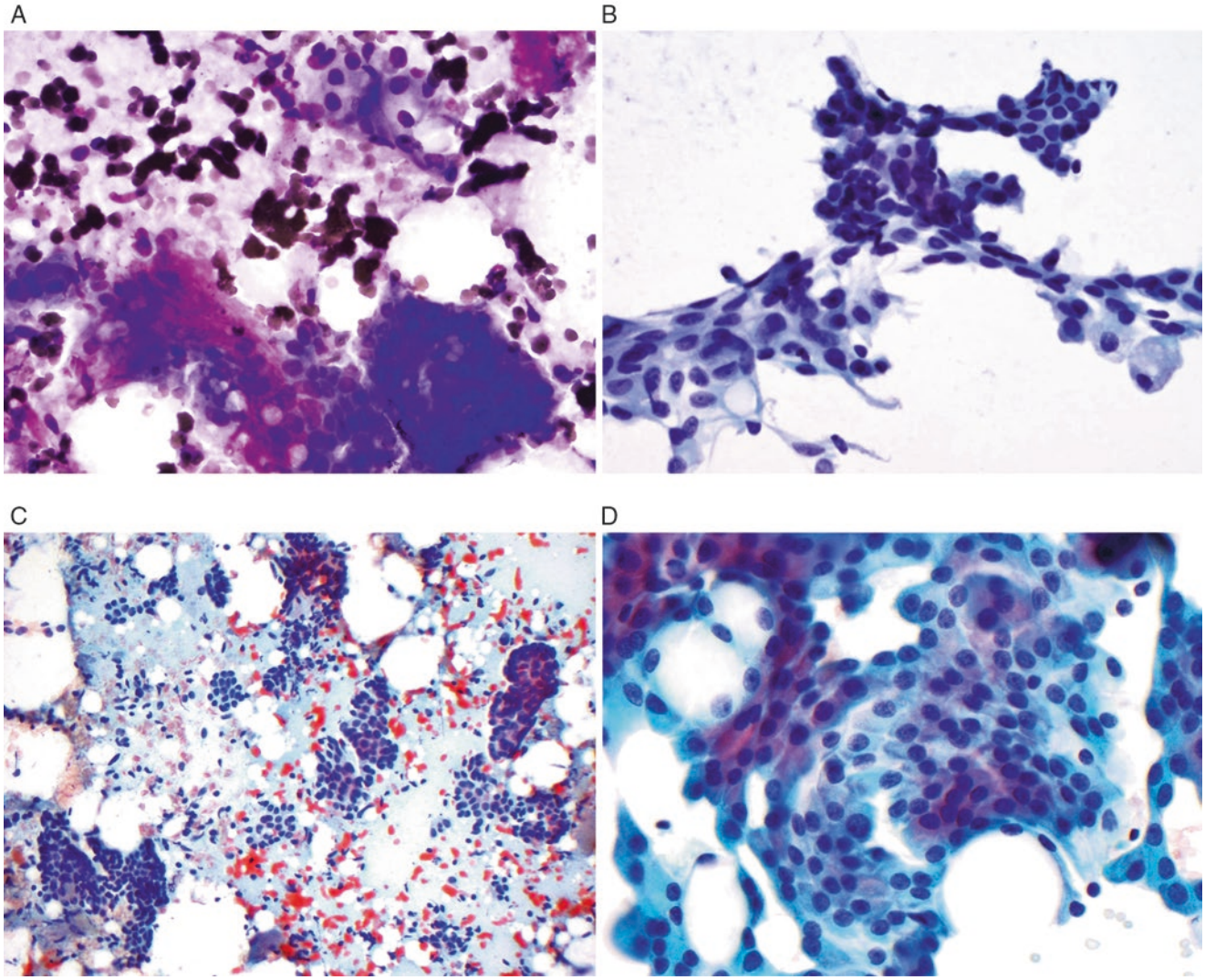

Fig. 5.8 (**a**–**d**) Nonproliferative fibrocystic changes. (**a**) Benign ductal cells in cohesive cluster with appreciable myoepithelial cells and stromal fragment, Diff-Quik; (**b**) myoepithelial cells are easily identified, in addition, few macrophages are seen, Pap stain; (**c**) Cohesive groups and sheet of benign ductal epithelial cells in a background of many bipolar naked stromal nuclei, Pap stain; (**d**) cluster of bland-looking ductal epithelial cells admixed with adipocytes and myoepithelial cells, Pap stain

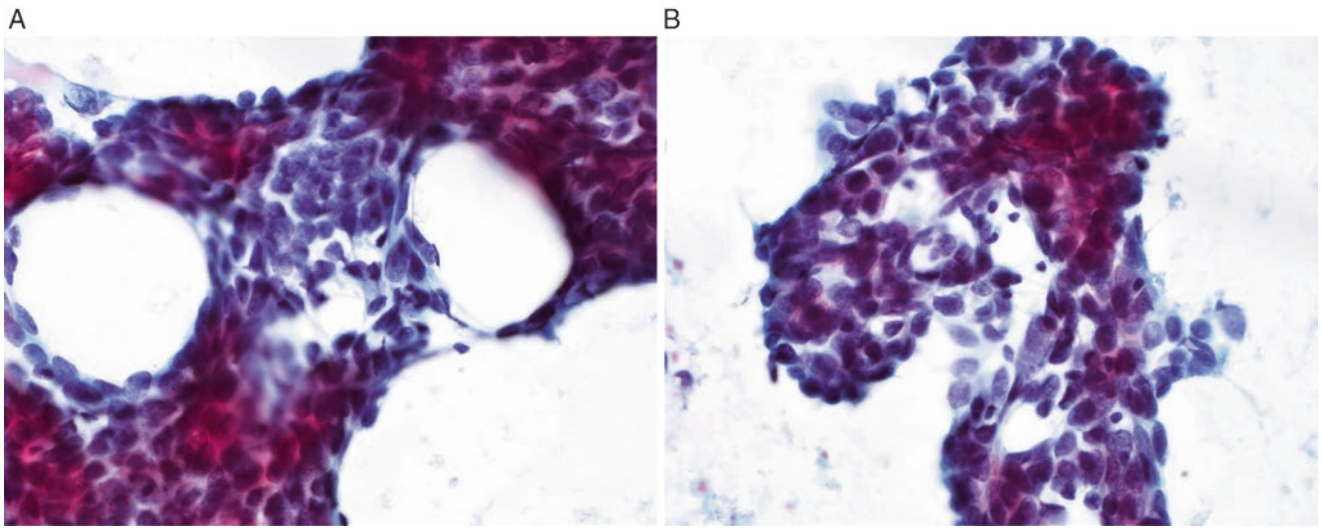

Fig. 5.9 (**a**, **b**) Ductal proliferative lesion with atypia. (**a**) Cluster of atypical ductal epithelial cells with monotonous enlarged nuclei, coarsely granular chromatin pattern, nucleoli, and punched-out spaces, suggesting ductal carcinoma in situ. Myoepithelial cells are identified at the periphery, Pap stain; (**b**) group of atypical ductal cells with appreciable punched-out spaces, myoepithelial cells identified focally, Pap stain

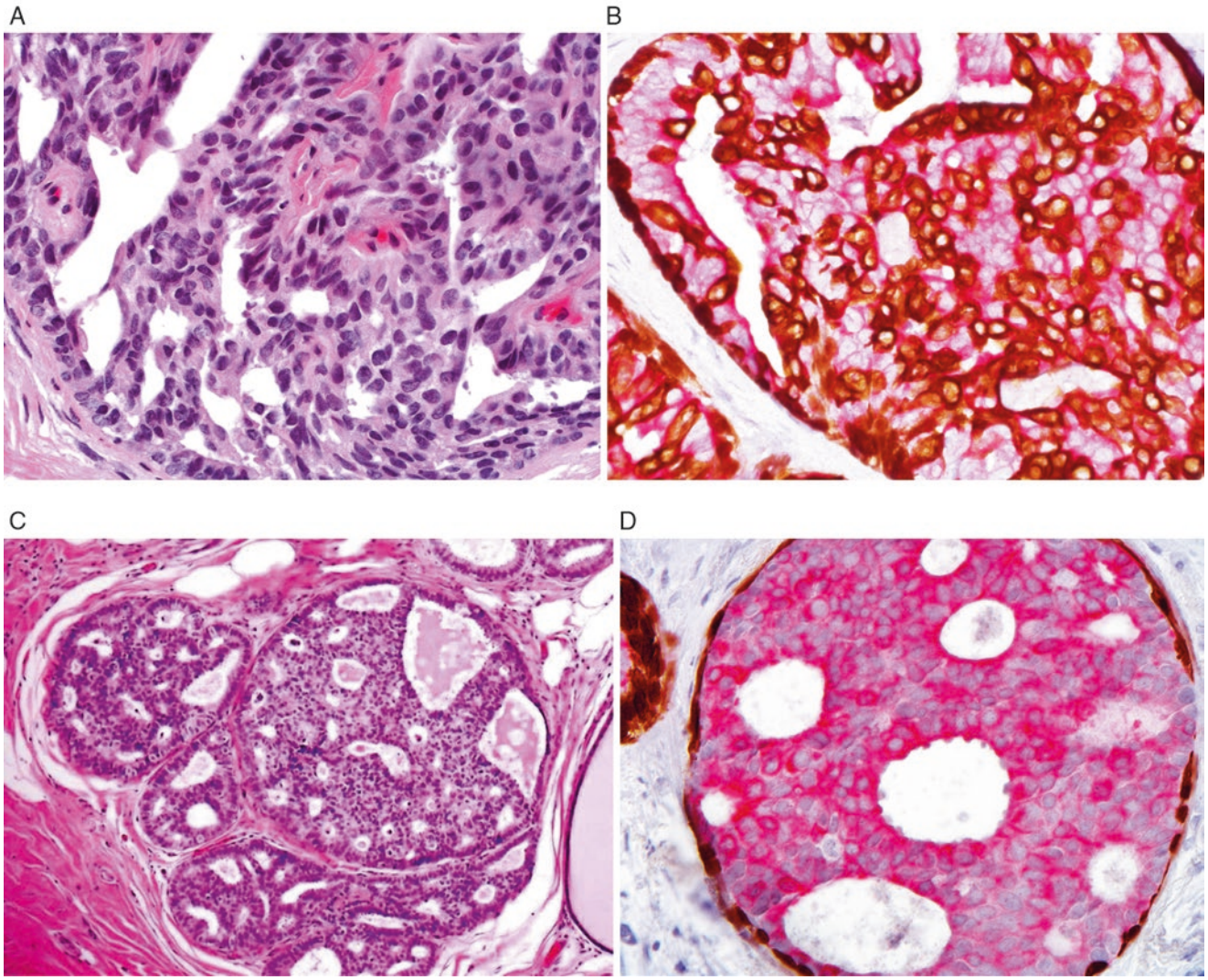

Fig. 5.10 (**a**–**d**) Differential immunophenotype of atypical ductal hyperplasia (ADH)/ductal carcinoma in situ (DCIS) vs usual ductal hyperplasia (UDH). (**a**) UDH, H&E; (**b**) UDH, ADH5 shows a mosaic pattern, both CK903 and luminal cytokeratin staining pattern, IHC; (**c**) ADH, H&E; (**d**) ADH, loss of expression for HMWCK, CK903, ADH5 staining, IHC

Immunohistochemistry

- Nonproliferative fibrocystic change is mainly a histomorphological diagnosis.
- IHC comes to play a role only when a ductal hyperplasia is present and the morphological features border on UDH and ADH.
- UDH is a hyperplastic process, with high expression of basal cell-type keratin or high molecular weight cytokeratin (HMWCK) and scattered ER expression.
- ADH/DCIS is neoplastic with a clonal proliferation of luminal epithelial cells, showing loss or focal weak expression of basal cell-type keratin or HMWCK and diffuse ER positivity.
- By application of ADH5, a breast marker cocktail consisting of CK5, CK14, p63, CK7, and CK18, UDH exhibits a mosaic staining pattern, and ADH/DCIS shows a clonal proliferation of luminal epithelial cells with negative HMWCK (basal cell type) staining, as shown in Fig. 5.10a–d, respectively.

Tumors of the Breast

The World Health Organization (WHO) classifications of tumors of the breast are summarized in Table 5.1.

Table 5.1 WHO Classification of Tumors of the Breast, 2012

Epithelial tumors
Microinvasive carcinoma
Invasive breast carcinoma
Invasive carcinoma of no special type (NST)
Pleomorphic carcinoma
Carcinoma with osteoclast-like stromal giant cells
Carcinoma with choriocarcinomatous features
Carcinoma with melanotic features
Invasive lobular carcinoma
Classic, solid, alveolar, pleomorphic, tubulolobular, mixed lobular carcinomas
Tubular carcinoma
Cribriform carcinoma
Mucinous carcinoma
Carcinoma with medullary features
Medullary carcinoma
Atypical medullary carcinoma
Invasive carcinoma NST with medullary features
Carcinoma with apocrine differentiation
Carcinoma with signet-ring-cell differentiation
Invasive micropapillary carcinoma
Metaplastic carcinoma NST
Low-grade adenosquamous carcinoma
Fibromatosis-like metaplastic carcinoma
Squamous cell carcinoma
Spindle cell carcinoma
Metaplastic carcinoma with mesenchymal differentiation
Chondroid, osseous, other types of mesenchymal differentiations
Mixed metaplastic carcinoma
Myoepithelial carcinoma
Rare types
Carcinoma with neuroendocrine features
Neuroendocrine tumor, well-differentiated
Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)
Carcinoma with neuroendocrine differentiation
Secretory carcinoma
Invasive papillary carcinoma
Acinic cell carcinoma
Mucoepidermoid carcinoma
Polymorphous carcinoma
Oncocytic carcinoma
Lipid-rich carcinoma
Glycogen-rich clear cell carcinoma
Sebaceous carcinoma
Salivary gland/skin adnexal-type tumors
Cylindroma, clear cell hidradenoma
Epithelial-myoepithelial tumors
Pleomorphic adenoma
Adenomyoepithelioma
Adenomyoepithelioma with carcinoma
Adenoid cystic carcinoma
Precursor lesions
DCIS
Lobular neoplasia
Lobular carcinoma in situ
Classic or pleomorphic lobular carcinoma in situ
Atypical lobular hyperplasia
Intraductal proliferative lesions
UDH
Columnar cell lesions, including flat epithelial atypia
ADH
Papillary lesions
Intraductal papilloma
Intraductal papillomas with ADH, or DCIS, or LCIS
Intraductal papillary carcinoma
Encapsulated papillary carcinoma
Encapsulated papillary carcinoma with invasion
Solid papillary carcinoma
In situ, invasive
Benign epithelial proliferations
Sclerosing adenosis
Apocrine adenosis
Microglandular adenosis
Radial scar/complex sclerosing lesion
Adenomas
Tubular, lactating, apocrine, ductal adenomas
Mesenchymal tumors
Nodular fasciitis
Myofibroblastoma
Desmoid-type fibromatosis
Inflammatory myofibroblastic tumor
Benign vascular lesions
Haemangioma, angiomatosis, atypical vascular lesions
Pseudoangiomatous stromal hyperplasia
Granular cell tumor
Benign peripheral nerve sheath tumors
Neurofibroma, schwannoma
Lipoma
Angiolipoma
Liposarcoma
Angiosarcoma
Rhabdomyosarcoma
Osteosarcoma
Leiomyoma
Leiomyosarcoma
Fibroepithelial tumors
Fibroadenoma
Phyllodes tumor
Benign, borderline, malignant, periductal stromal sarcoma, low grade
Hamartoma
Tumors of the nipple
Nipple adenoma
Syringomatous tumor
Paget disease of the nipple

(continued)

(continued)

Table 5.1 (continued)

Malignant lymphoma
Diffuse large B-cell lymphoma
Burkitt lymphoma
T-cell lymphoma
Anaplastic large cell lymphoma, anaplastic lymphoma kinase (ALK) negative
Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type
Follicular lymphoma
Metastatic tumors
Tumors of the male breast
Gynecomastia
Carcinoma
Invasive carcinoma, in situ carcinoma
Clinical patterns
Inflammatory carcinoma
Bilateral breast carcinoma

Used with permission from WHO Classification of Tumours of the Breast. Edited by Lakhani SR et al. Lyon: IARC Press; 2012

Fibroepithelial Tumors

Fibroadenoma

Key Clinical Features

- Most common benign tumor
- Asymptomatic or a mobile, painless, well-defined breast nodule/mass
- In premenopausal women, usually in their second or third decades
- Usually solitary
- Occasionally multifocal and bilateral, reported in Afro-Caribbean women

Key Radiological Features

- Well-defined mass, with or without microcalcifications
- Homogeneous, hypoechoic, and well-circumscribed mass on ultrasound

Cytological Features

- Cohesive benign ductal epithelial cells arranged in a branching antler-horn configuration in a background of many naked bipolar or spindled nuclei
- Myoepithelial cells at periphery
- Hypocellular myxoid stroma
- Focal ductal cells with apocrine changes
- Figure 5.11a–d

Differential Diagnosis

- Benign proliferative fibrocystic changes
- Phyllodes tumor
- Mammary hamartoma
- Tubular adenoma

Histology

- Fibroadenomas are composed of both epithelium and stroma with a well-demarcated, lobulated, or smooth border.
- The epithelium shows two growth patterns: pericanalicular and intracanalicular, as illustrated in Fig. 5.11e, f.
- The stroma is variable in morphology and cellularity, however homogeneous throughout in individual cases.

Immunohistochemistry

- Immunohistochemistry is usually not applied for the diagnosis of fibroadenoma.

Phyllodes Tumor

Key Clinical Features

- 0.3–1% of all breast neoplasms
- In peri- and postmenopausal women, usually their fifth decade
- Presents with a palpable breast mass, usually painless, mobile, multinodular and firm, or presents with an abnormal mammography

Key Radiological Features

- Well-circumscribed, lobulated mass on mammography
- Solid, hypoechoic, well-circumscribed mass on ultrasound

Cytological Features

- Cellular specimen
- Mixed epithelial and stromal fragments
- Hypercellular stromal fragments, comprised of spindle-shaped cells singly or enmeshed in stroma; significant atypia of the spindle cells with mitotic activity suggesting malignant phyllodes tumor
- Many naked bipolar or spindle nuclei in the background
- Occasional ductal hyperplasia with or without atypia
- Figure 5.12a–c

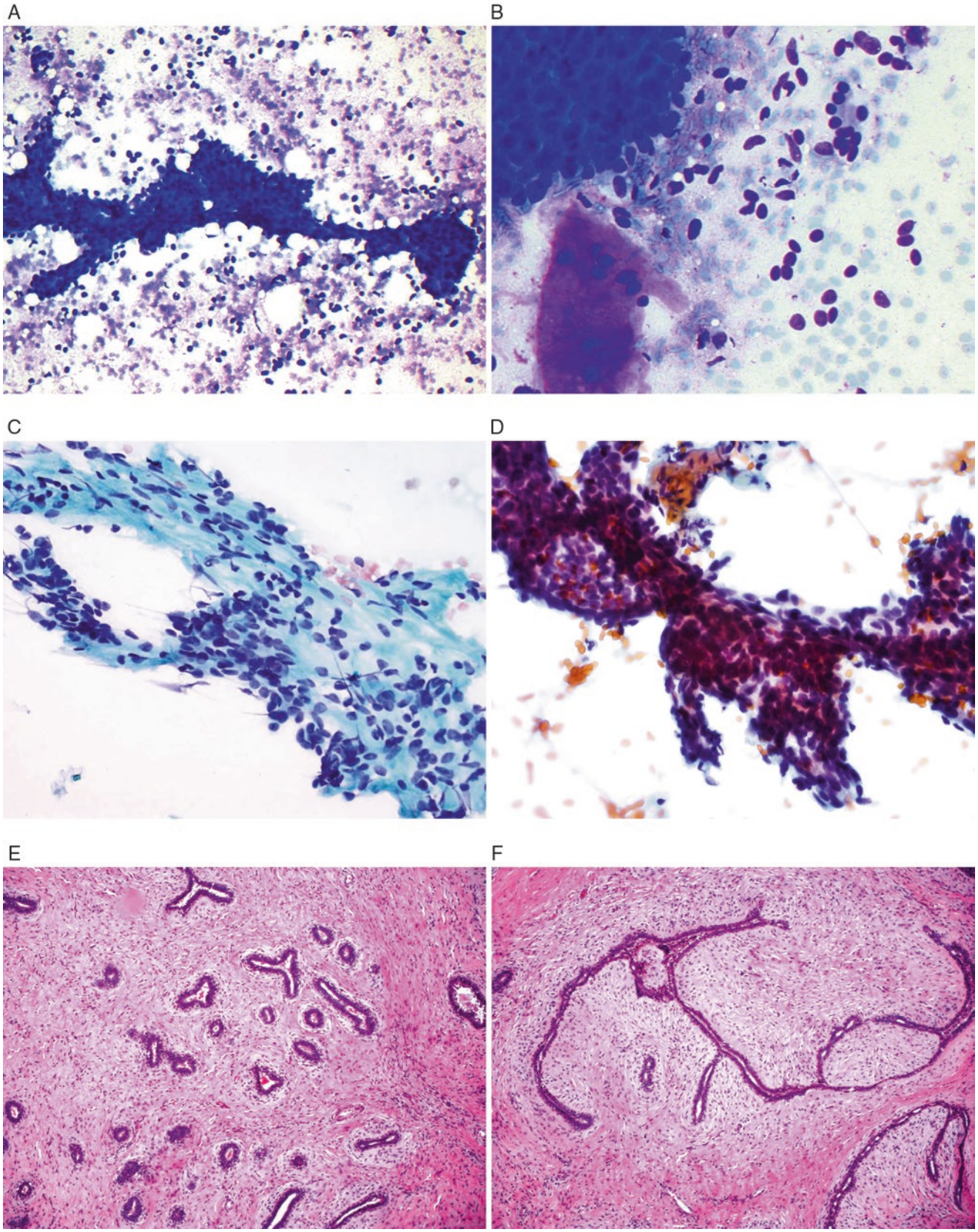

Fig. 5.11 (**a**–**f**) Fibroadenoma, cytology and histology. (**a**, **b**) Branching antler-horn benign ductal cells in a background of many bipolar or spindled naked nuclei and rare stromal tissue, Diff-Quik; (**c**) benign ductal epithelial cells and stromal tissue, Pap stain; (**d**) Antler-horn fragment of benign ductal epithelial cells and scant stroma. Myoepithelial cells are present, Pap stain; (**e**) pericanalicular pattern, H&E; (**f**) Intracanalicular pattern, H&E

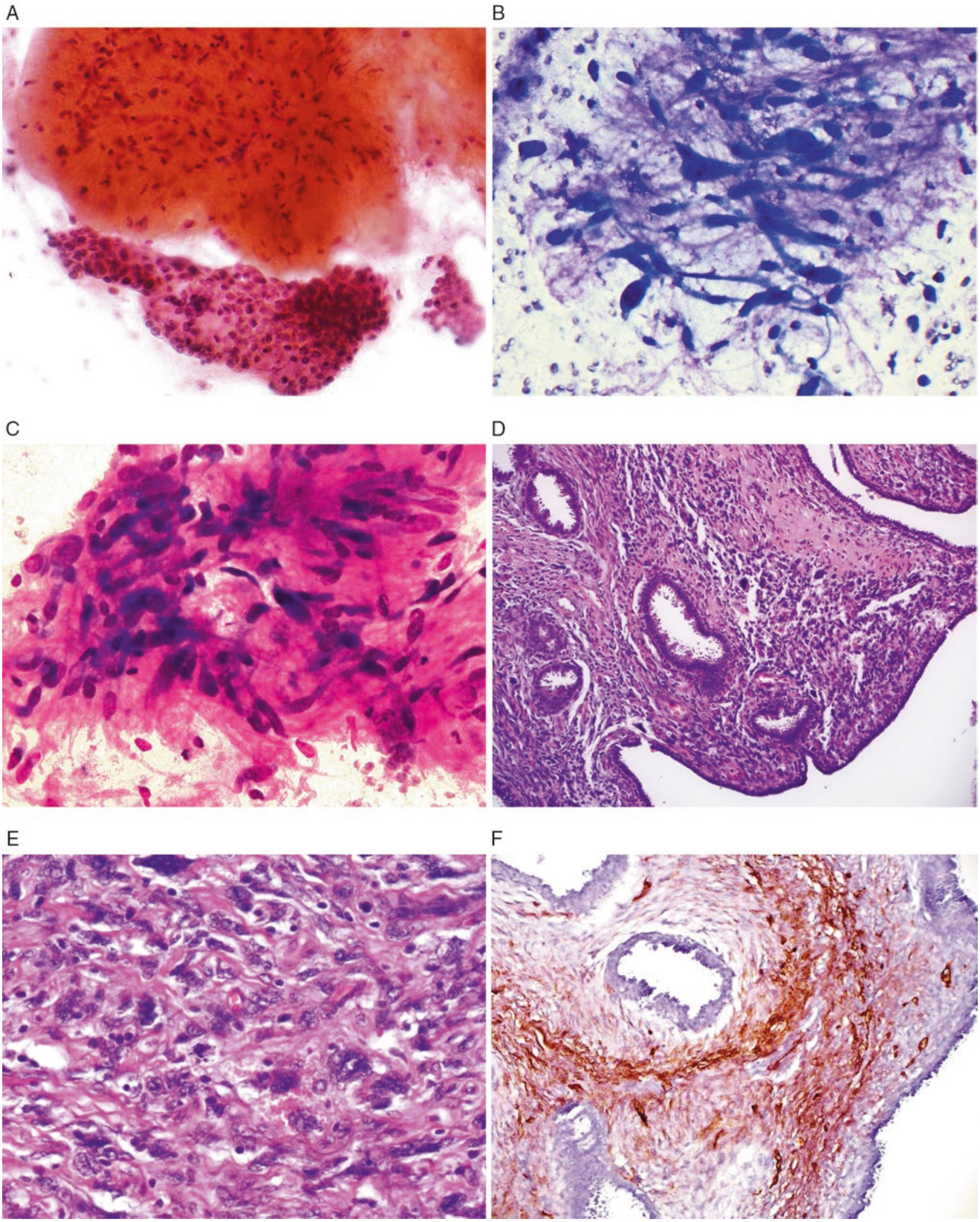

Fig. 5.12 (**a**–**h**) Phyllodes tumor, cytology, histology, and immunophenotype. (**a**) Cohesive cluster of ductal epithelial cells with mild atypia and fragment of stroma, Pap stain; (**b**) the stromal cells are spindled with atypia and a rare mitotic figure, Diff-Quik; (**c**) stroma with increased cellularity and atypia, Pap stain; (**d**, **e**) leaflike pattern, highly cellular and atypical stroma with mitotic figures, H&E; (**f**) positive CD34 staining, IHC; (**g**) high expression of p53, IHC; (**h**) high proliferative index (MIB-1), IHC

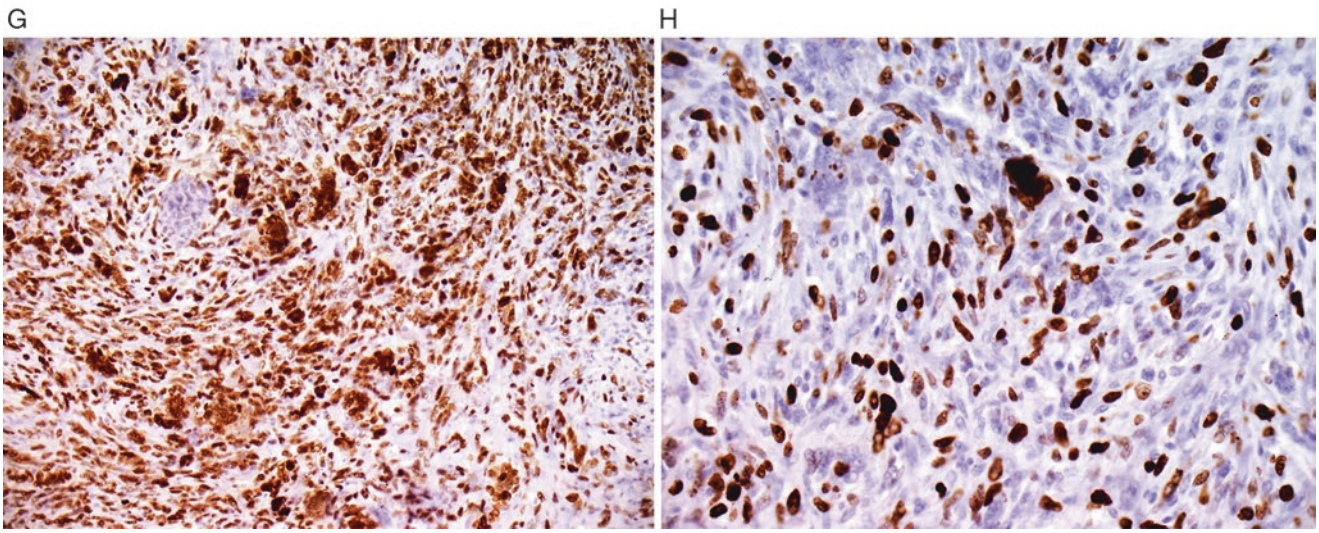

Fig. 5.12 (continued)

Differential Diagnosis

- Fibroadenoma
- Metaplastic carcinoma
- Primary sarcoma
- Sclerosing adenosis

Histology

- A biphasic tumor contains epithelial and stromal components, usually with a prominent intracanalicular growth pattern to form leaf-like structures.
- The stroma is usually heterogeneous in cellularity with mitotic activity.
- Representative images are illustrated in Fig. 5.12d, e.

Immunohistochemistry

- Immunohistochemistry does not usually contribute to the diagnosis of phyllodes tumor. However, the expression of Ki-67 and p53 correlates with tumor grade.
- CD34 and B-cell CLL/lymphoma-2 (Bcl2) were reported to be positive and can be used to differentiate a malignant phyllodes tumor from metaplastic (spindle cell) carcinoma.
- Representative images are illustrated in Fig. 5.12e–h.

Hamartomas

Key Clinical Features

- Less than 1% of benign breast masses
- Common in pre- and perimenopausal women
- Presents as a mobile, painless, soft-to-firm, well-defined palpable mass

Key Radiological Features

- Well-circumscribed, round-to-oval inhomogeneous mass on mammogram; characteristically, the mass is centrally dense with a radiolucent rim.
- Sonographic features are variable; difficult to delineate the margins due to the resemblance to normal breast tissue; and may appear as a well-defined, solid lesion with mixed internal echotextures and without any lesional microcalcifications.

Cytological Features

- Low-to-moderate cellularity specimen
- Scattered sheets of benign ductal epithelial cells, some showing irregular branching
- Lobular cells forming acini, presenting as an intact lobular units
- Minimal-to-absent cellular discohesion or atypia
- Adipose tissue in various amounts and occasional stromal fragments, may have attached epithelial cells
- Frequent bipolar stromal nuclei, occasional apocrine cells, foam cells, and myoepithelial cells

Differential Diagnosis

- Fibrocystic changes
- Fibroadenoma

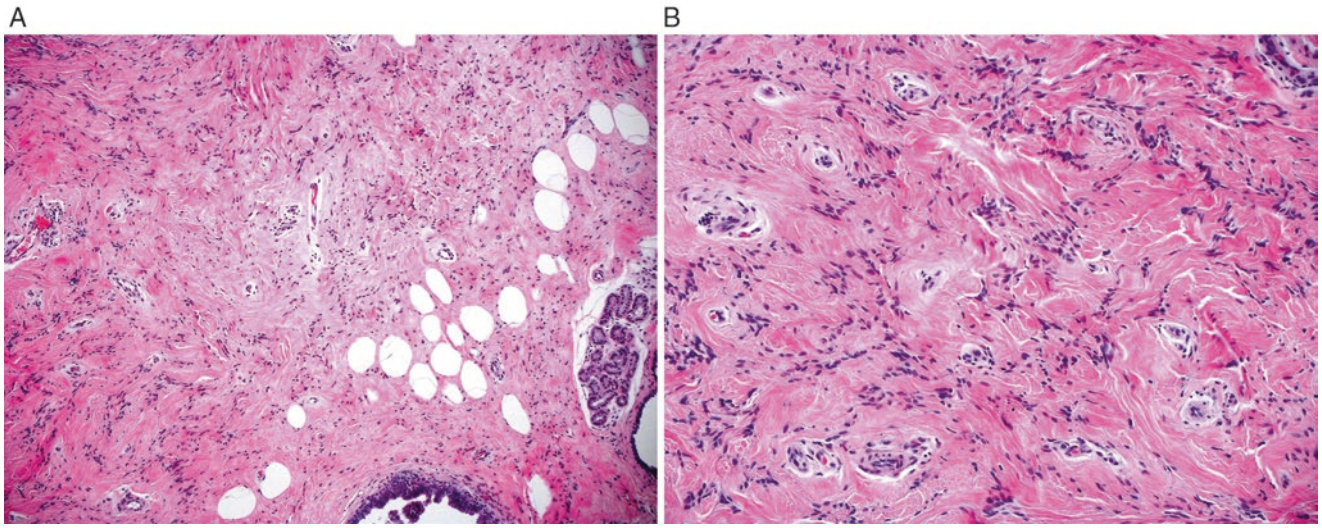

Fig. 5.13 (**a**, **b**) Mammary hamartoma, histology. (**a**) Disorganized growth of fat, fibrous connective tissue forming nodule, H&E; (**b**) disorganized growth of fibrous connective tissue, H&E

Histology

- A disproportionate and disorganized growth of mature mammary tissues, including ducts, lobules, fat, fibrous connective tissue, and smooth muscle, forming well-defined nodules.
- The presence of fibrous tissue within the lobules (interlobular fibrosis) or fibrous tissue and fat in the stroma should alert the pathologist to the possibility of a hamartoma.
- Representative images are shown in Fig. 5.13a, b.

Immunohistochemistry

- Immunohistochemistry plays no role in the diagnosis of a mammary hamartoma.

Epithelial Tumors

Benign Epithelial Proliferation

Lactating Adenoma

Lactating adenoma is a term used for a fibroadenoma with superimposed changes of lactation.

Key Clinical Features

- Typically a breast mass in a young pregnant or postpartum woman
- Occasionally can be large and painful

Key Radiological Features

- Similar to fibroadenoma; occasionally shows atypical features on ultrasound, such as irregular margins, heterogeneous echogenicity, and posterior shadowing

Cytological Features

- Cellular specimen with a milky or lipid background
- Ductal epithelial cells with nuclear enlargement and conspicuous nucleoli
- Ductal cells with smooth nuclear contour and evenly distributed chromatin
- Many naked nuclei with small-to-prominent nucleoli
- Figure 5.14a, b

Differential Diagnosis

- Carcinoma, ductal, or lobular
- Non-Hodgkin's lymphoma

Histology

- Lactating adenoma is composed of a compact aggregate of lobules exhibiting secretory hyperplasia during pregnancy or postpartum.
- The glandular elements are diffusely distributed in a sparsely cellular stroma; the glandular cells show vacuolated cytoplasm.
- A representative image is shown in Fig. 5.14c, d.

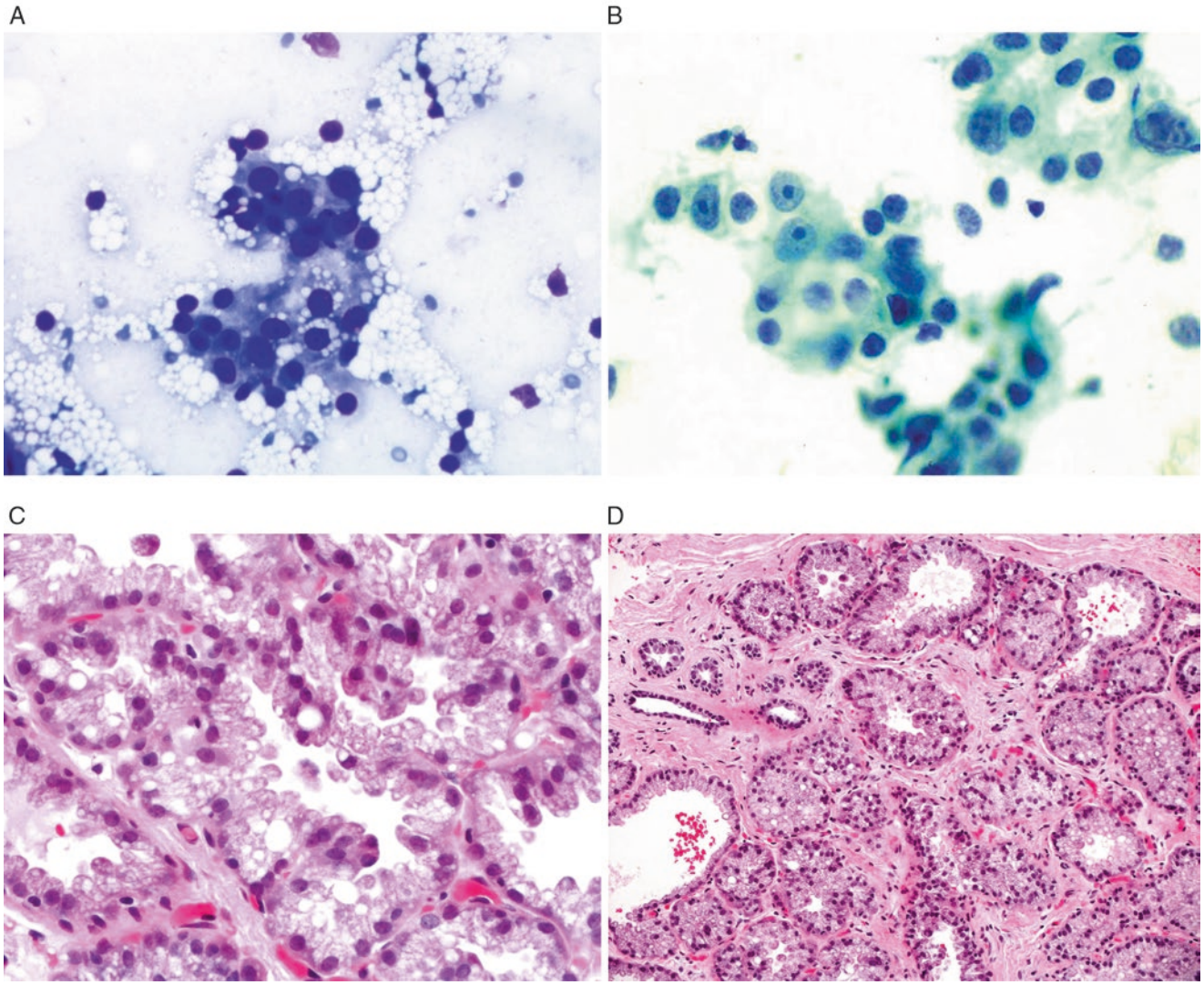

Fig. 5.14 (**a–d**) Lactating adenoma. (**a, b**) Cellular smear contains loosely cohesive clusters of ductal epithelial cells with enlarged nuclei, small to prominent nucleoli, and vacuolated cytoplasm in a milky or lipid background with naked nuclei, (**a**) Diff-Quik; (**b**) Pap stain; (**c, d**) Hiatology, H&E; well-circumscribed, compact aggregate of lobules exhibiting secretory hyperplasia (**d**); the glandular cells show vacuolated cytoplasm, diffusely distributed in a sparsely cellular stroma (**c**)

Immunohistochemistry

- Immunohistochemistry is usually not applied for the diagnosis of lactating adenoma.

Papillary Lesions

Key Clinical Features

- Intraductal papilloma: solitary, usually centrally located tumor in peri- and postmenopausal women, often presents as bloody nipple discharge; can be peripheral and multiple, may present as mass lesions
- Papillary carcinoma: 1–2% of breast cancers; usually in postmenopausal women; can present as a mass; one-third of patients present with bloody nipple discharge; favorable prognosis.

Key Radiological Features

- Central papillary lesions may present as a circumscribed subareolar mass with well-defined borders, without stromal distortion on mammography; an intraductal mass with associated dilated duct or a complex cystic lesion on ultrasonography. Peripheral papillary lesions present as mammographic abnormalities or may be radiographically occult.

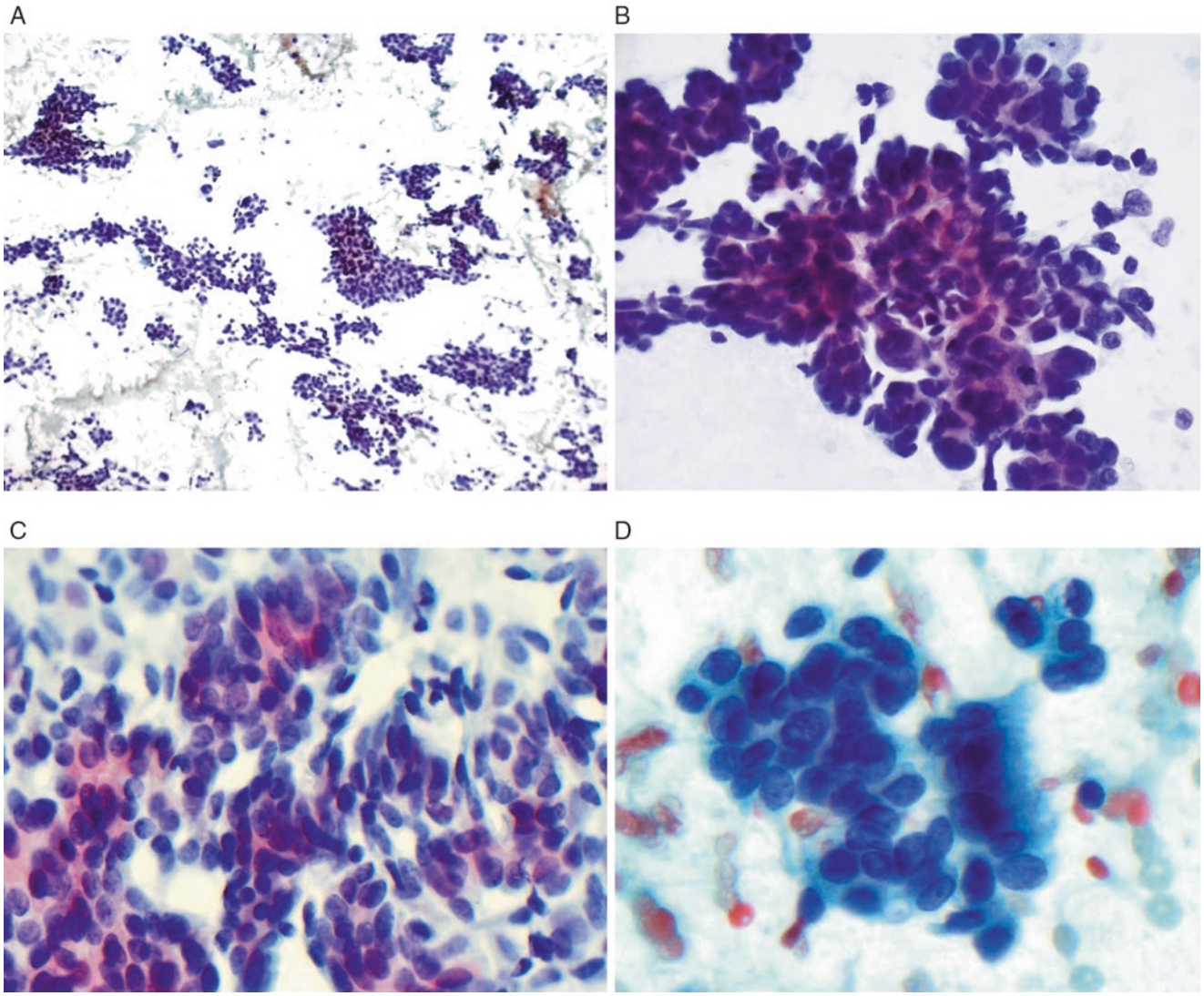

Fig. 5.15 (**a**–**d**) Papillary lesions, cytology, histology, and immunophenotype. (**a**) numerous papillary groups, Pap stain; (**b**) Papillary groups with the overlying epithelial cells showing columnar morphology; (**c**, **d**) loosely cohesive and single columnar cells with intact cytoplasm in background, Diff-Quik and Pap stain

Cytological Features

- Highly cellular sample
- Many groups and sheets of ductal cells with papillary fronds (Fig. 5.15a, b)
- Cells usually columnar shaped with many single or loosely cohesive cells with tall columnar-shaped and intact cytoplasm (Fig. 5.15c, d)
- Nuclear atypia and mitosis indicating atypical hyperplasia or more severe lesion
- A mixture of cellular components such as ductal cells, apocrine cells, and histiocytes indicating a papilloma

Differential Diagnosis

- Intraductal hyperplasia
- Fibroadenoma
- Ductal carcinoma

Histology

- Papillary lesions include a heterogeneous group of epithelial proliferations ranging from benign to malignant.
- Benign intraductal papilloma is composed of a few broad fronds with well-defined fibrovascular cores lined by two

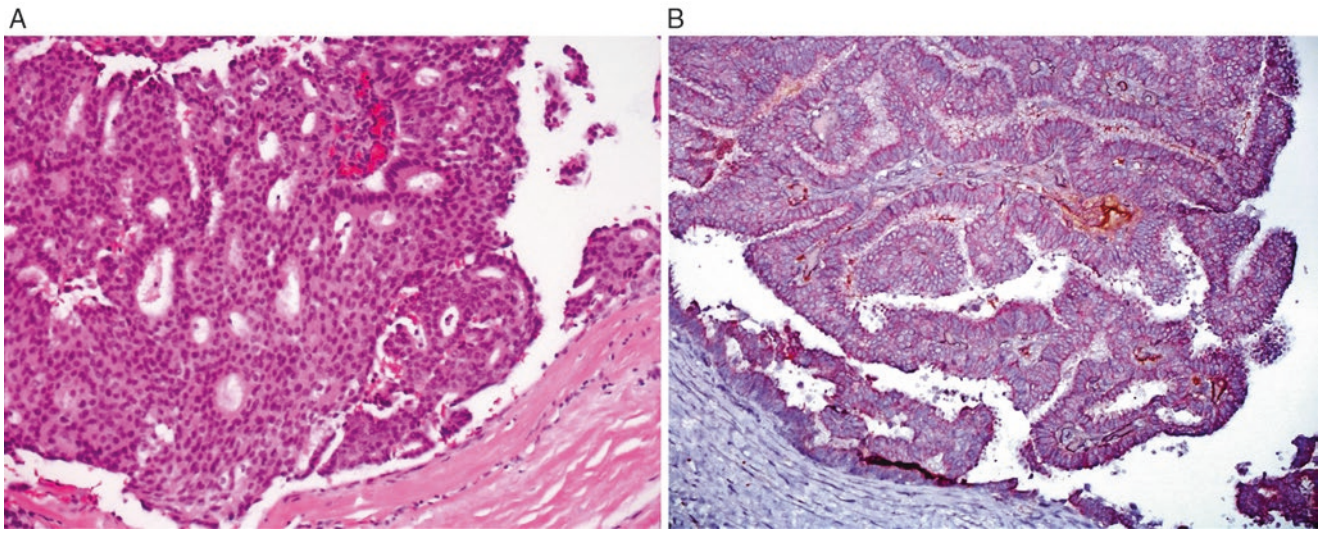

Fig. 5.16 (**a**, **b**) Intracystic papillary carcinoma, histology, and immunophenotype. (**a**) Cystically dilated duct with a fibrotic wall encircling an arborizing, complex papillary network lined by one or more layers of uniform epithelial cells, H&E; (**b**) ADH5 staining reveals loss of basal cells at periphery and over fibrous vascular core, with loss of CK903 staining, IHC

layers of cells: the ductal epithelial cells and myoepithelial cells. The ductal epithelial cells may undergo hyperplasia, atypical hyperplasia, or metaplasia. There may be sclerosis in the stroma.

- Papillary DCIS is a DCIS with a papillary growth pattern. The papillary stalks are usually thin and inconspicuous with frequent epithelial hyperplasia and atypia without myoepithelial cells, except at the periphery. The epithelial cells are monotonous.
- Encapsulated (intracystic) papillary carcinoma is traditionally considered a variant of DCIS, although this has been challenged recently. Histologically, the tumor is composed of a cystically dilated duct with a fibrotic wall encircling an arborizing, complex papillary network lined by one or more layers of uniform epithelial cells. Myoepithelial cells are absent within and at the periphery of the tumor.
- Representative images are shown in Fig. 5.16a, b.

Immunohistochemistry

- IHC plays an important role in the diagnosis of papillary lesions, especially in small biopsy specimens.
- Myoepithelial cell (MEC) markers (p63, calponin, smooth muscle myosin heavy chain [SM-MHC]), in conjunction with HMWCK (CK903, CK5/6, CK14) and ER, are most useful in the differential diagnosis of papillary lesions.
- The loss of myoepithelial cells (at the periphery and over the fibrovascular core) classifies a papillary lesion as malignant (encapsulated papillary carcinoma or solid papillary carcinoma).
- When a papillary lesion with intact myoepithelial cells (at the periphery, may or may not be over the fibrovascular core), immunoassays for HMWCK (CK903, CK5/6, CK14) and ER should be utilized; benign papilloma expresses HMWCK with a mosaic staining pattern and ER with focal weak staining pattern in the area of proliferation, while atypical papilloma or papillary DCIS shows loss of expression for HMWCK and strong diffuse reactivity to ER. However, caution should be exercised when interpreting ER results because papilloma is usually diffusely reactive to ER.
- In addition, neuroendocrine markers (synaptophysin and chromogranin) are positive in the majority of solid papillary carcinomas but negative in benign and atypical papillary lesions.
- Representative images are illustrated in Fig. 5.17a–d.

Invasive Ductal Carcinoma (NST)

Key Clinical Features

- Accounts for about 55–80% of invasive breast carcinomas.
- Symptomatic, presents as a breast lump with or without pain; asymptomatic, with mammographic abnormalities.
- Nipple abnormalities or skin dimpling/changes may present.

Key Radiological Features

- Mammography: variable, including well-defined, ill-defined, and spiculated masses, parenchymal deformity, and calcifications with or without mass lesions.

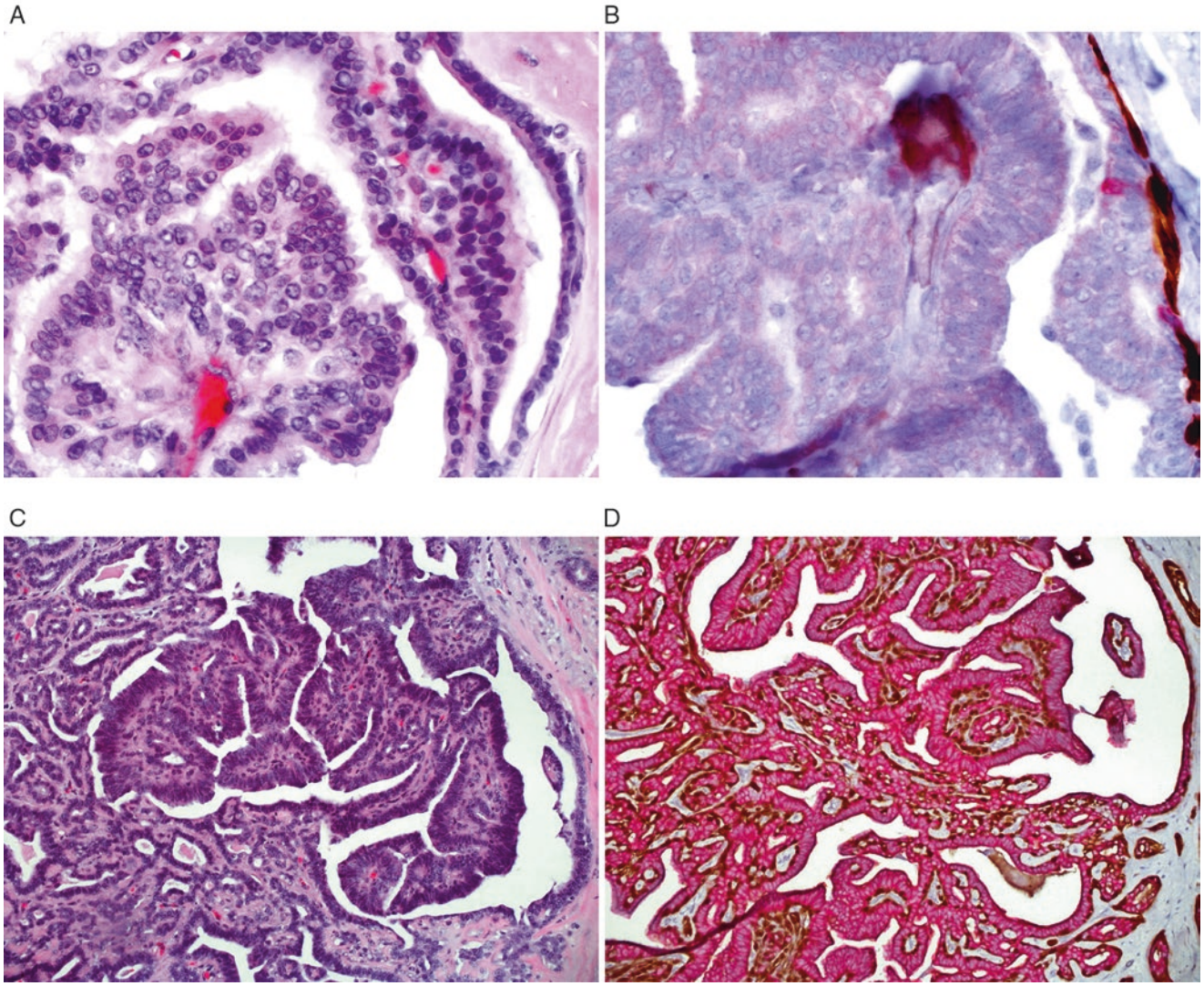

Fig. 5.17 (**a**–**d**) Differential immunophenotypes of papillary ductal carcinoma in situ and papilloma. (**a**) Papillary DCIS, H&E; (**b**) papillary DCIS, ADH5 showing intact basal cells at the periphery (nuclear decoration by p63 and cytoplasmic brown staining for CK903) and loss of expression for CK903 with luminal cytokeratin decoration, IHC; (**c**) benign papilloma, H&E; (**d**) papilloma, ADH5 showing intact basal cells at the periphery and in the stalks (nuclear decoration by p63 and cytoplasmic brown staining for CK903) and mosaic staining pattern for CK903 (brown; pink staining for luminal cytokeratins)

- Sonography: an irregular mass with ill-defined margins and an inhomogeneous echo texture with acoustic shadowing. The anteroposterior diameter is greater than the transverse diameter.

Cytological Features

- Moderate-to-high cellularity specimen
- Many loosely cohesive groups and singles
- Nuclear enlargement >2–3 times the size of a red blood cell (RBC)
- Single cells with intact cytoplasm
- Hyperchromasia, prominent nucleoli, nuclear membrane irregularity, and nuclear pleomorphism
- Mitosis and tumor necrosis
- Intracytoplasmic lumina
- Apocrine changes and cytoplasmic vacuoles
- Figure 5.18a–e

Differential Diagnosis

- DCIS
- Cytological atypia in benign lesions, such as fibroadenoma, papillary neoplasm, or epithelial hyperplasia
- Gynecomastia (male breast)
- Metastases

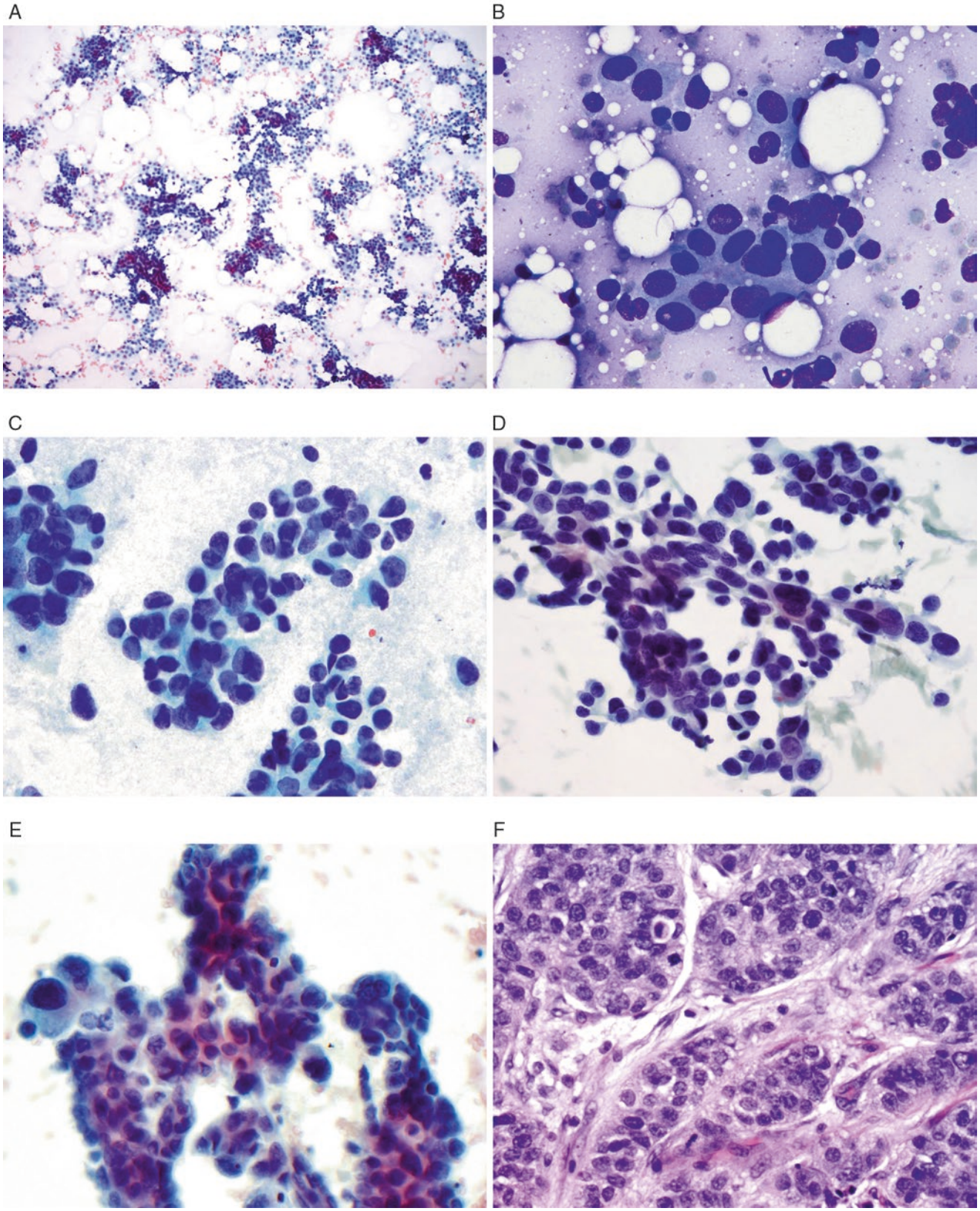

Fig. 5.18 (**a**–**f**) Invasive ductal carcinoma, NST. (**a**) Moderately to highly cellular smear comprised of loosely cohesive clusters and many single cells with intact cytoplasm, Pap stain; (**b**) Diff-Quik showing individual cells with pleomorphic nuclei, prominent nucleoli and intact cytoplasm; (**c**, **d**) Pap stain reveals the tumor cells with enlarged nuclei (at least 2–3× RBC), irregular nuclear membrane, nucleoli and coarse chromatin pattern; (**e**) Carcinoma cells show apocrine changes, Pap stain; (**f**) histology, H&E

Histology

- A non-specialized pattern comprises at least 50% of the tumor.
- Malignant cells arranged in cords, trabeculae, poorly formed tubular structures, or sheets infiltrate a desmoplastic or collagenous stroma.
- A representative image is shown in Fig. 5.18f.

Immunohistochemistry

- The loss of myoepithelial cells confirms its malignant nature.
- Intact membranous staining pattern for E-cadherin and p120 catenin.
- GATA3 positive in 94% of cases.
- 70–80% of invasive ductal carcinomas are ER positive.
- 15–25% of tumors overexpress human epidermal growth factor receptor-2 (Her-2/neu).

Invasive Lobular Carcinoma

Key Clinical Features

- Represents 5–15% of all invasive breast carcinomas.
- Usually presents as a palpable mass with irregular borders; may present as a poorly defined thickening or fine diffuse nodularity.
- Multifocal and bilateral lesions are more frequent, often in the central area.

Key Radiological Features

- Asymmetrical, ill-defined, or irregular masses or densities on mammography
- Usually presents as a hypoechoic mass with irregular or indistinct margins and posterior acoustic shadowing on sonography; about 10% invisible on ultrasonography

Cytological Features

- Low-to-moderate cellularity specimen
- Small loosely clusters and single lobular carcinoma cells, some lining up as a row
- The lobular carcinoma cells with mildly enlarged nuclei (1.5–2 times the size of an RBC), intact cytoplasm, and high nuclear-to-cytoplasmic ratio
- Hyperchromasia and nuclear membrane irregularity
- Intracytoplasmic lumina often seen
- Single atypical cells within adipose tissue
- Figure 5.19a–e

Differential Diagnosis

- Low-grade ductal carcinoma
- Neuroendocrine tumors
- Melanoma
- Lymphoma

Histology

- Invasive carcinomas showing lobular morphology in greater than 90% of the tumor are classified as invasive lobular carcinomas.
- For those with a 50–90% lobular morphology in addition to NST pattern, a mixed ductal and lobular carcinoma should be classified.
- The invasive lobular carcinoma cells are usually uniform, dyshesive, and round or oval cells with eccentrically placed nuclei containing small nucleoli and a scant amount of cytoplasm, classically in a single-file pattern. Intracytoplasmic lumina may be appreciated.
- There are subtypes, such as tubulolobular, solid, alveolar, and mixed patterns.
- Representative images are shown in Fig. 5.19f, g.

Immunohistochemistry

- A complete loss of expression of E-cadherin or aberrant localization of E-cadherin protein (cytoplasmic, as apical or perinuclear): due to loss of E-cadherin function or a dysfunctional cadherin-catenin complex or both caused by *cadherin 1 (CDH1)* gene aberrations at molecular genetic level. See Fig. 5.19h.
- Cytoplasmic staining pattern for p120 catenin, with loss of membranous staining.
- In morphologically challenging cases, E-cadherin and p120 catenin can be used to accurately classify a tumor as ductal or lobular type. Differential patterns of staining are illustrated in Fig. 5.20a–f.
- GATA3 positive in 100% of cases.
- 67–92% of lobular carcinomas are ER positive.
- Her-2/neu overexpression is uncommon.
- When lobular carcinoma metastasizes, especially to the gastrointestinal (GI) tract (e.g., stomach), a panel of immunomarkers consisting of ER, GATA binding protein 3 (GATA3), CK7, and caudal-type homeobox (CDX2) is most helpful in reaching a differential diagnosis.

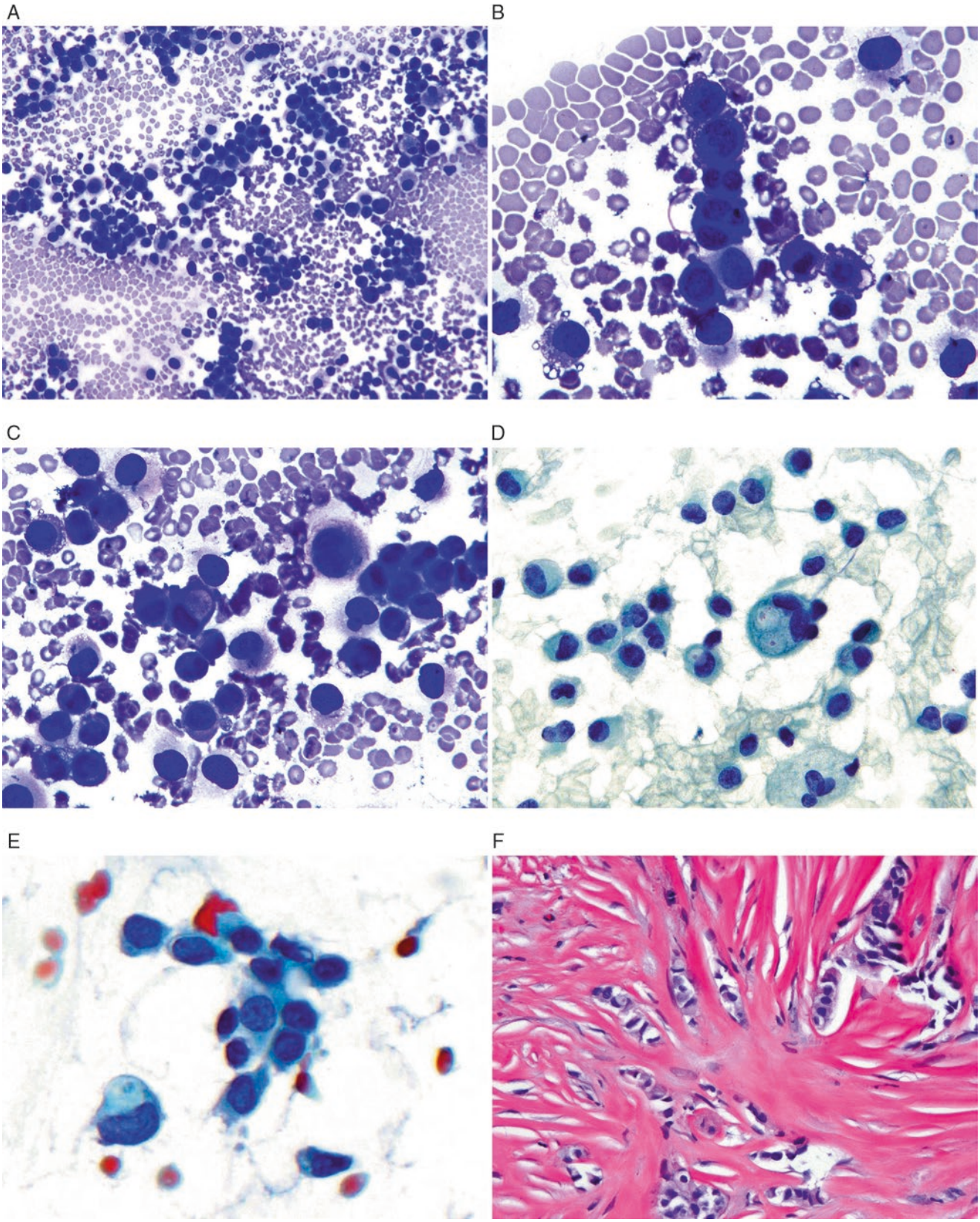

Fig. 5.19 (**a**–**h**) Invasive lobular carcinoma. (**a**, **b**) Low-to-moderate cellularity specimen contains small loose clusters and many single lobular carcinoma cells, some lining up as a row, Diff-Quik; (**c**) the lobular carcinoma cells are single, with mildly enlarged nuclei of 1.5–2 × RBC, some containing intracytoplasmic lumen, Diff-Quik; (**d**, **e**) intracytoplasmic lumen containing targetoid mucin noted, Pap stain; (**f**) classic lobular carcinoma, H&E; (**g**) pleomorphic lobular carcinoma, H&E; (**h**) pleomorphic lobular carcinoma, loss of E-cadherin expression

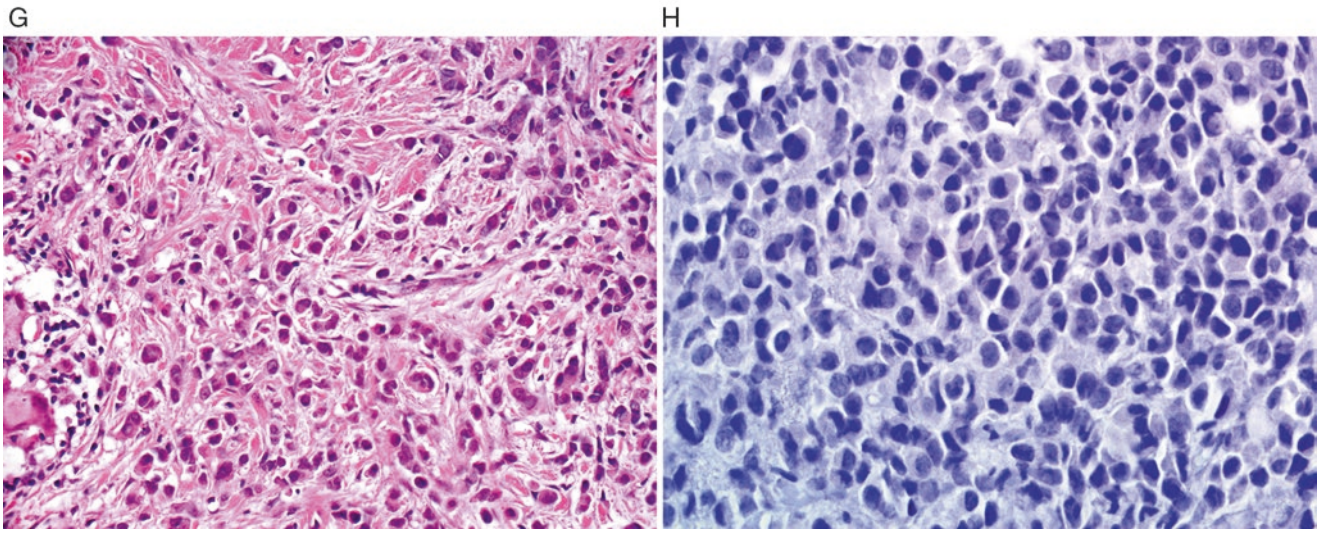

Fig. 5.19 (continued)

Tubular Carcinoma

Key Clinical Features

- Less than 2% of all invasive breast carcinomas
- More common in women in their late 50s and early 60s, rare in men
- Majority present with a palpable mass in the past; nonpalpable mammographic abnormalities at current time
- Excellent prognosis

Key Radiological Features

- A mass lesion, oval or round or lobulated, with irregular or spiculated margins, central density, and occasional microcalcifications on mammography
- Ill-defined hypoechoic masses with posterior acoustic shadowing on ultrasonography

Cytological Features

- Relatively low-cellularity specimen
- Angulated, pointed tubular/glandular structures
- Little or no nuclear atypia
- Few single cells with intact cytoplasm
- Lack of myoepithelial cells
- Bipolar naked stromal nuclei generally absent
- Figure 5.21a, b

Differential Diagnosis

- Sclerosing adenosis, tubular adenosis, and radial scars
- Fibroadenoma
- Invasive lobular carcinoma
- Invasive ductal carcinoma, not otherwise specified (NOS)

Histology

- Characterized by a haphazard proliferation of infiltrative tubules distributed in a stellate configuration.
- The tubules are angulated with a single layer of monotonous cuboidal to low columnar ductal epithelial cells, often showing apical "snouts" and open lumina.
- The stroma is desmoplastic, often with elastosis.
- Mitoses are rare.

Immunohistochemistry

- IHC is often applied in small biopsy specimens.
- The lack of myoepithelial cells confirms the diagnosis of tubular carcinoma, as illustrated in Fig. 5.21c, d.
- GATA3 positive.

Medullary Carcinoma

Key Clinical Features

- 1–10% of all invasive breast carcinomas
- Affects younger women, in their 30s and 40s, with a predominantly early-onset age distribution in which the incidence increases until age 50, then plateaus or decreases

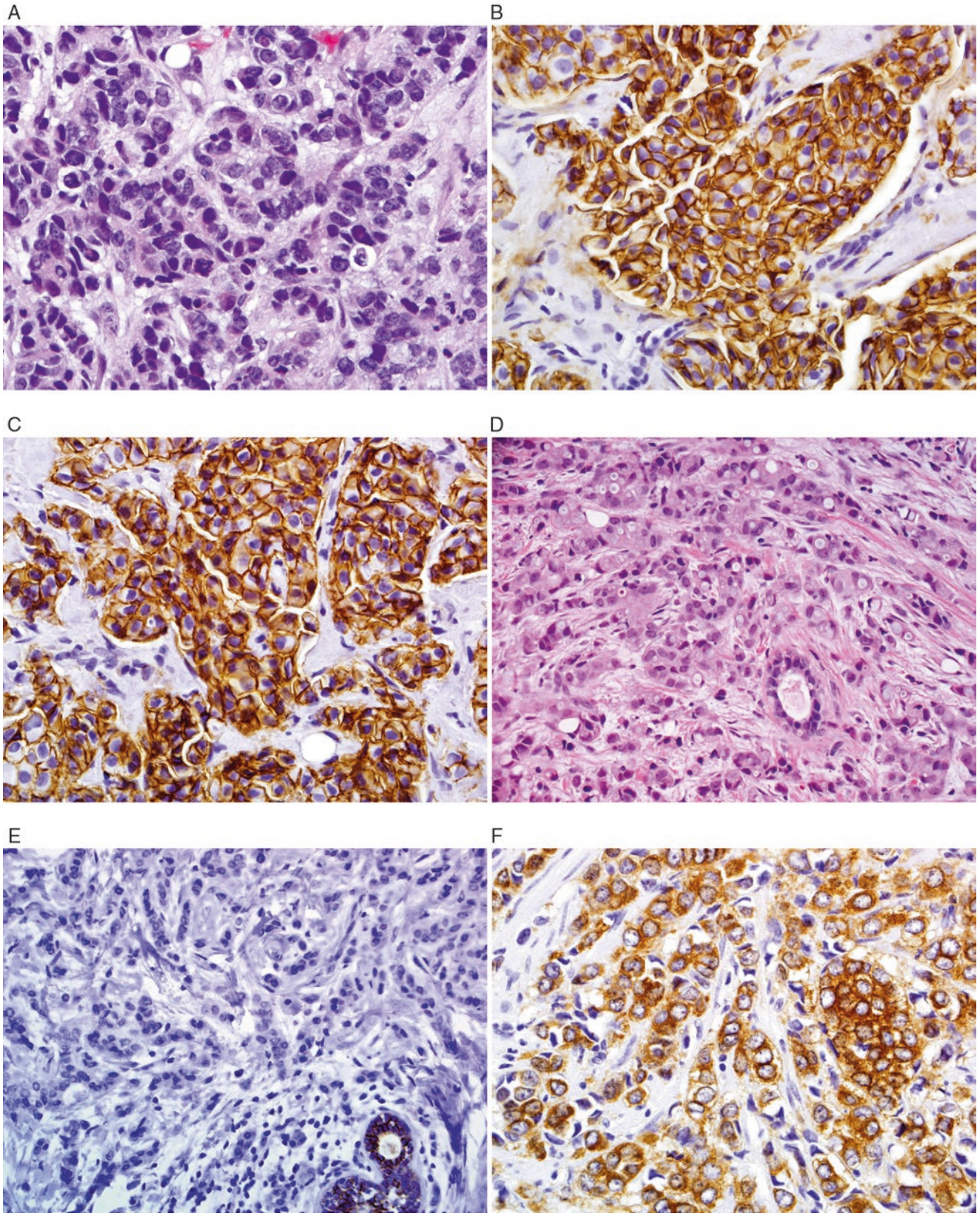

Fig. 5.20 (**a**–**f**) Differential immunophenotype for invasive ductal (IDC) and lobular carcinomas (ILC). (**a**) IDC, H&E; (**b**) IDC, membranous staining for E-Cadherin; (**c**) IDC, membranous staining for p120; (**d**) ILC, H&E; (**e**) ILC, loss E-Cadherin staining; (**f**) ILC, cytoplasmic staining for p120

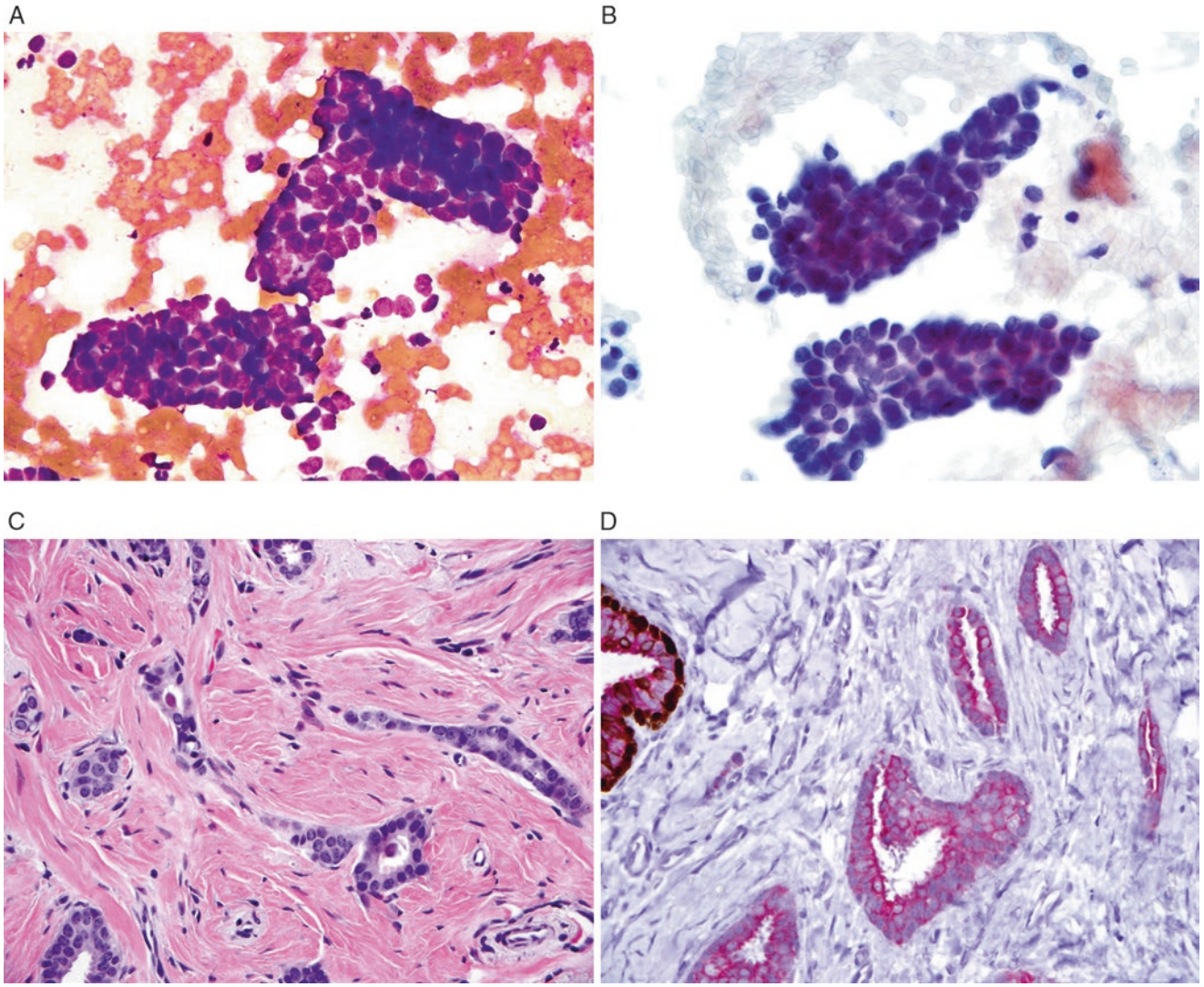

Fig. 5.21 (**a**–**d**) Invasive tubular carcinoma. (**a**) Angulated, pointed atypical ductal epithelial cells with low-grade morphology, Diff-Quik; (**b**) PAP; (**c**) tubular carcinoma, H&E; (**d**) ADH5 staining reveal loss of basal cells

- Usually a palpable soft mass, often in the upper outer quadrant
- Favorable prognosis
- Higher frequency in harboring *breast cancer 1* (*BRCA1)* mutations

Key Radiological Features

- A round, oval, lobulated noncalcified mass with well-defined borders on mammography
- A well-circumscribed, hypoechoic, round or oval, or lobulated mass on ultrasonography

Cytological Features

- Cohesive groups or sheets of ductal cells with marked nuclear atypia
- Many lymphoid cells including plasma cells in the background
- Fig. 5.22a–e

Differential Diagnosis

- Invasive ductal carcinoma, high grade
- High-grade DCIS (comedocarcinoma)
- Metastasis

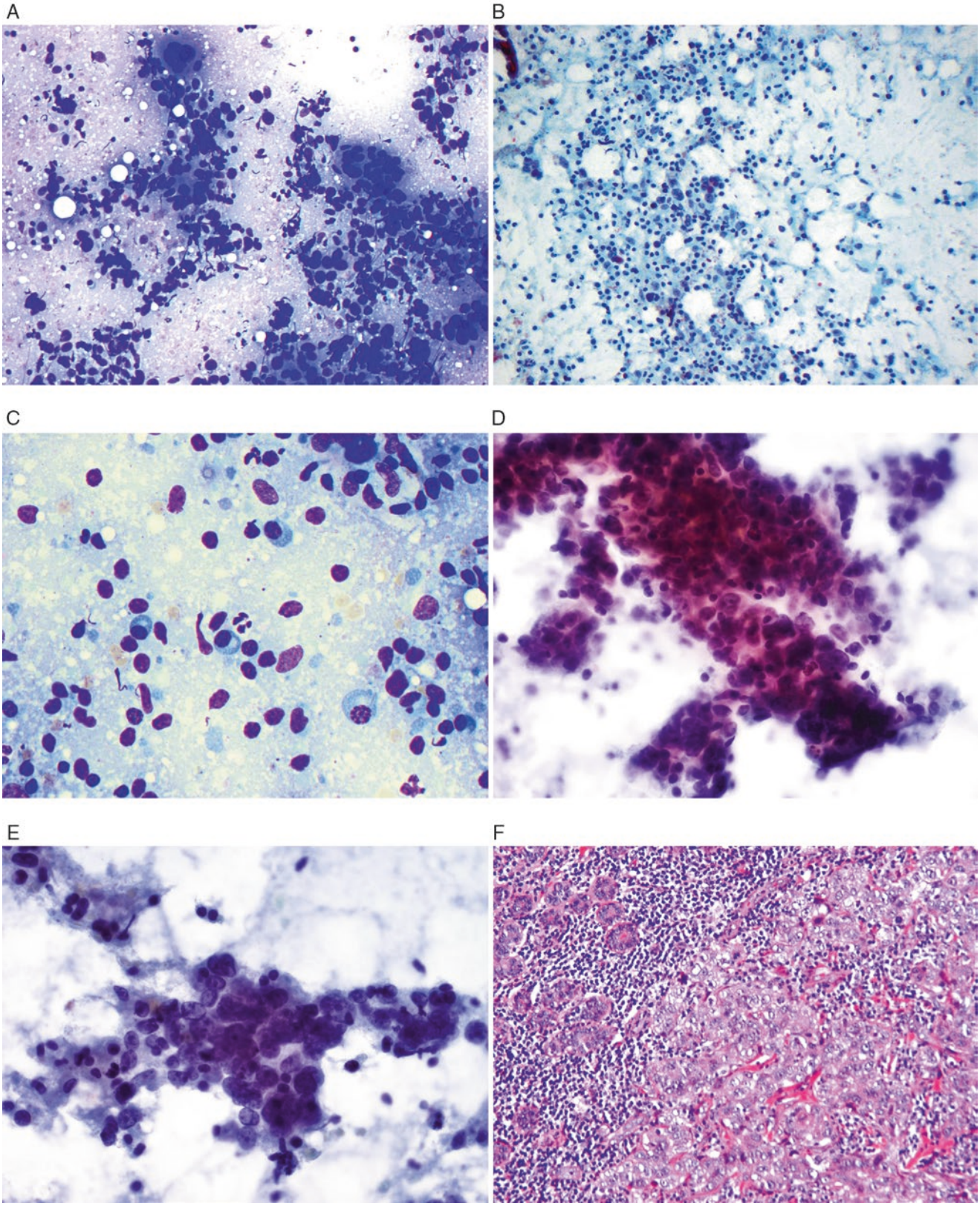

Fig. 5.22 (**a**–**h**) Medullary carcinoma. (**a**) Cellular smear contains clusters of atypical ductal cells in a background of lymphoid cells, Diff-Quik; (**b**) the same, Pap stain; (**c**) Background lymphocytes and plasma cells, Diff-Quik; (**d**) cohesive cluster of highly atypical ductal epithelial cells with prominent nucleoli admixed with lymphocytes, Diff-Quik; (**e**) the same, Pap stain; (**f**, **g**) histology, medullary carcinoma with syncytial growth pattern and lymphocytes, H&E; (**h**) CK5/6 decorates tumor cells, IHC

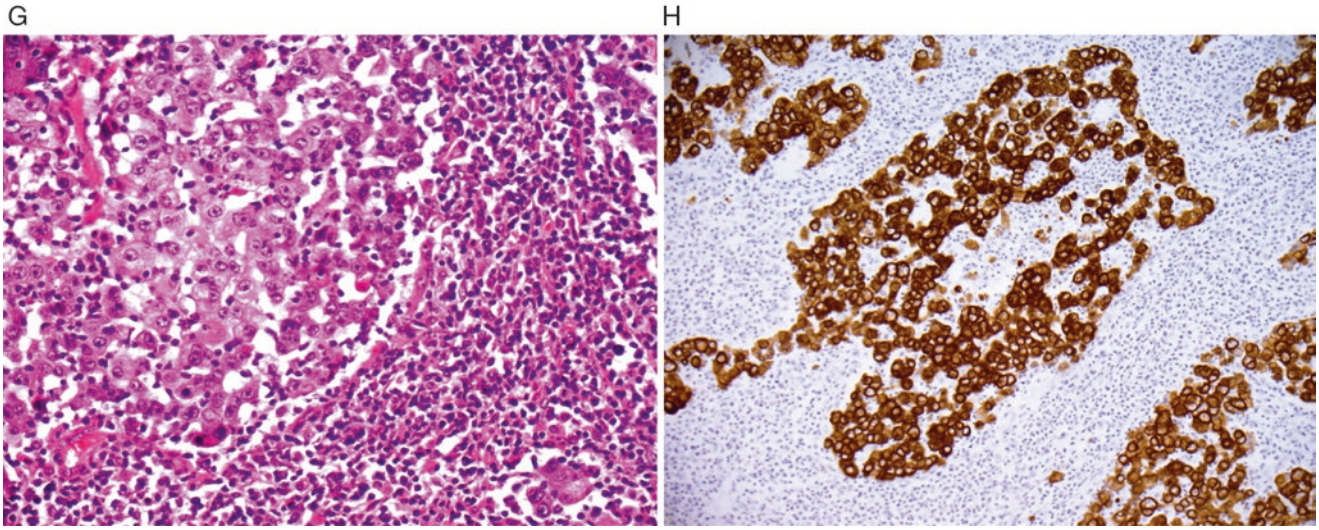

Fig. 5.22 (continued)

Histology

- The diagnostic criteria for medullary carcinoma include a predominantly syncytial growth pattern (>75%), absence of glandular differentiation, a diffuse moderate to marked lymphoplasmacytic infiltrate, high nuclear grade (grade 3), and microscopic circumscription.
- The tumor cells are usually poorly differentiated with high mitotic activity, showing pleomorphic nuclei, coarse chromatin pattern, and prominent nucleoli.
- Representative images are shown in Fig. 5.22f, g.

Immunohistochemistry

- Medullary carcinomas show a basal-like phenotype, expressing epithelial growth factor receptor (EGFR), HMWCK, and CD117 (Fig. 5.22h, CK5/6 staining).
- p53 is positive in a majority of medullary carcinomas.
- GATA3 positive in approximately 50% of cases, usually weak expression
- Typically triple negative (ER-, progesterone [PR]-, Her-2/neu-)

Mucinous Carcinoma

Key Clinical Features

- 1–2% of all invasive breast carcinomas
- More common in older women, with median age of 71 years
- Often presents as a palpable soft mass in the past; nonpalpable mammographic abnormalities at the current time
- Favorable prognosis

Key Radiological Features

- An oval or lobulated mass, well circumscribed, rarely associated with microcalcifications on mammography
- Ultrasonography: a mass with well-defined borders and isoechoic echo texture or hypoechoic with microlobulated margins

Cytological Features

- Cohesive groups or balls of mildly atypical ductal cells without myoepithelial cells
- Single cells with intact cytoplasm
- Mucinous background, which is more easily identifiable on Diff-Quik stain
- Figure 5.23a–d

Differential Diagnosis

- Benign or atypical mucocele-like lesions
- Micropapillary carcinoma

Histology

- The diagnosis of invasive mucinous carcinoma is reserved for tumors with at least a 90% mucinous component.
- The characteristic feature of invasive mucinous carcinoma is the presence of pools of extracellular mucin with nests, trabeculae, acini, or sheets of neoplastic cells.
- Representative images are shown in Fig. 5.23e, f.

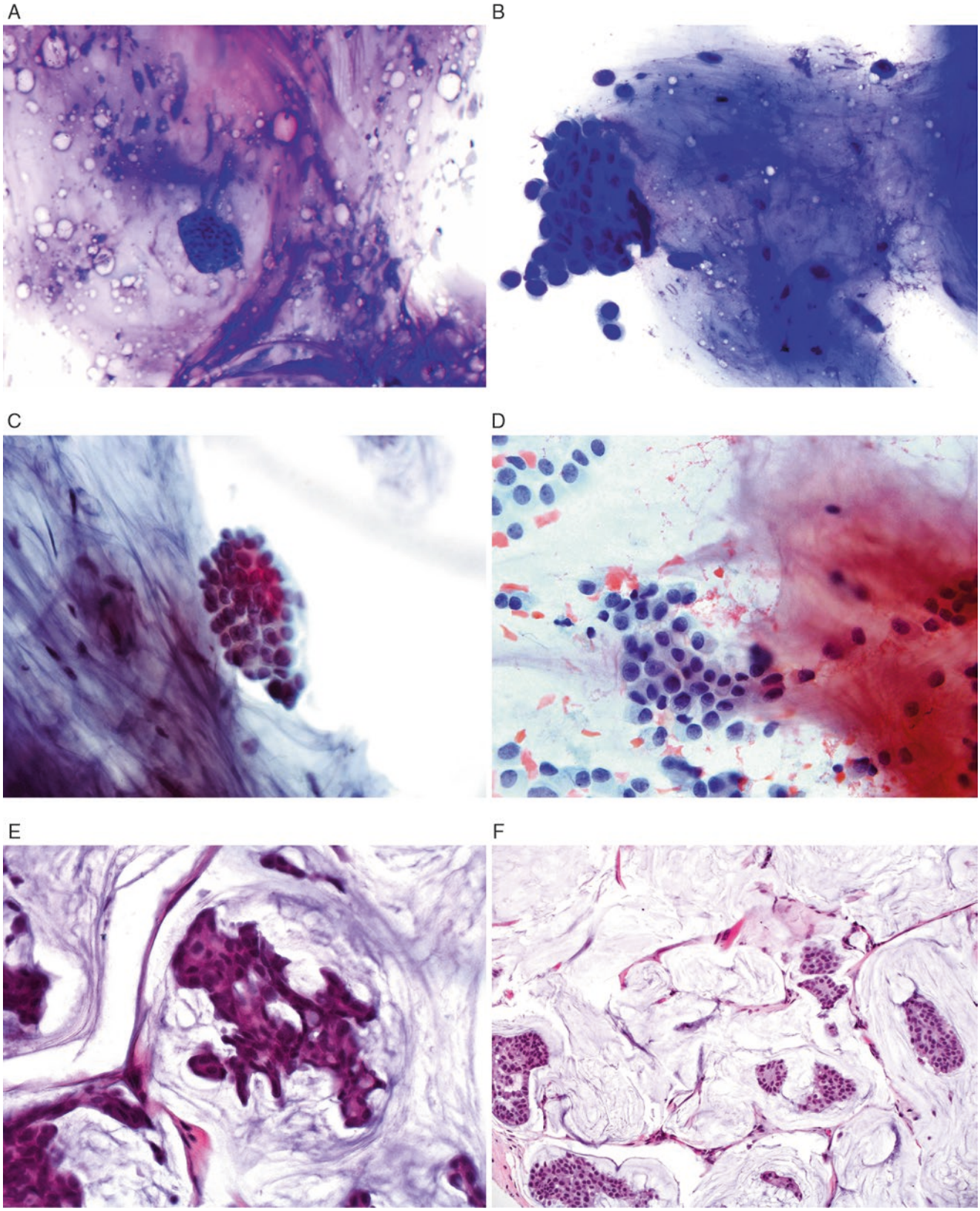

Fig. 5.23 (**a**–**h**) Mucinous carcinoma. (**a**) Cohesive cluster of mildly atypical ductal epithelial cells in a background of thick mucin, Diff-Quik; (**b**) high-power view shows low-grade morphology, Diff-Quik; (**c**, **d**) the same, Pap stain; (**e**, **f**) Small clusters of mildly atypical ductal epithelial cells with a cribriform pattern floating in a pool of mucin, H&E; (**g**) tumor cell strongly positive for ER, IHC; (**h**) MUC2 decorates tumor cells

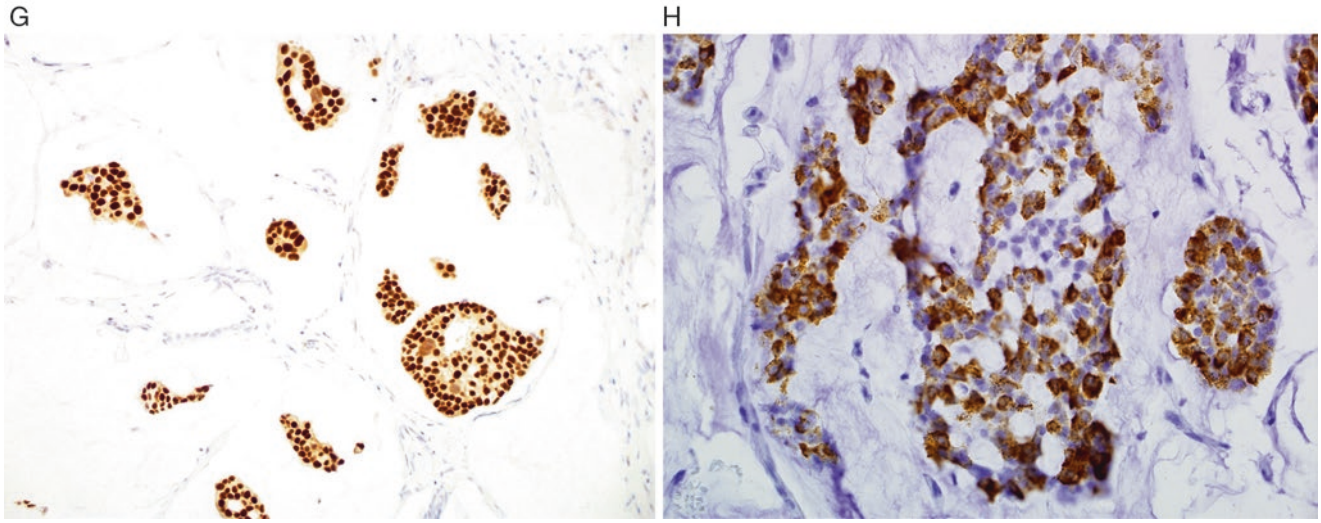

Fig. 5.23 (continued)

Immunohistochemistry

- MEC markers (p63, calponin and SMM-HC) are occasionally utilized to document the lack of myoepithelial cells in neoplastic clusters.
- Neuroendocrine differentiation in mammary mucinous carcinoma has been reported.
- GATA3 positive.
- Mucinous carcinomas are usually positive for ER and PR, negative for Her-2/neu.
- Representative images shown in Fig. 5.23g, h.

Carcinoma with Apocrine Differentiation

Key Clinical Features

- Less than 5% of all invasive breast carcinomas.
- Clinical presentation is no different from that of invasive ductal carcinoma, NOS.

Key Radiological Features

- No distinct imaging features, similar to that of invasive ductal carcinoma, NOS

Cytological Features

- Cellular specimen
- Syncytial fragments or individual atypical cells with large, pleomorphic nuclei, macronucleoli, and abundant basophilic to eosinophilic granular cytoplasm
- Figure 5.24a–c

Differential Diagnosis

- Lipid-rich carcinoma
- Secretory carcinoma
- Granular cell tumor
- Alveolar soft part sarcoma
- Carcinoma with squamous differentiation

Histology

- The overall growth pattern of apocrine carcinoma is no different from invasive ductal carcinoma, NST.
- The neoplastic cells with apocrine differentiation in >90% of the tumor (Rosen's strict definition is the entire tumor.).
- The cytological features of apocrine differentiation include abundant eosinophilic granular cytoplasm or foamy vacuolated cytoplasm and enlarged round vesicular nuclei with prominent eosinophilic (occasionally basophilic) nucleoli.
- Representative images are shown in Fig. 5.24d.

Immunohistochemistry

- Usually androgen receptor (AR) + 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 carcinoma than in conventional ductal carcinoma.
- Nearly all of the apocrine lesions are positive for gross cystic disease fluid protein-15 (GCDFP-15), however, which also decorates non-apocrine breast epithelial cells.
- Apocrine carcinoma is frequently positive for p53, especially in in situ carcinoma.

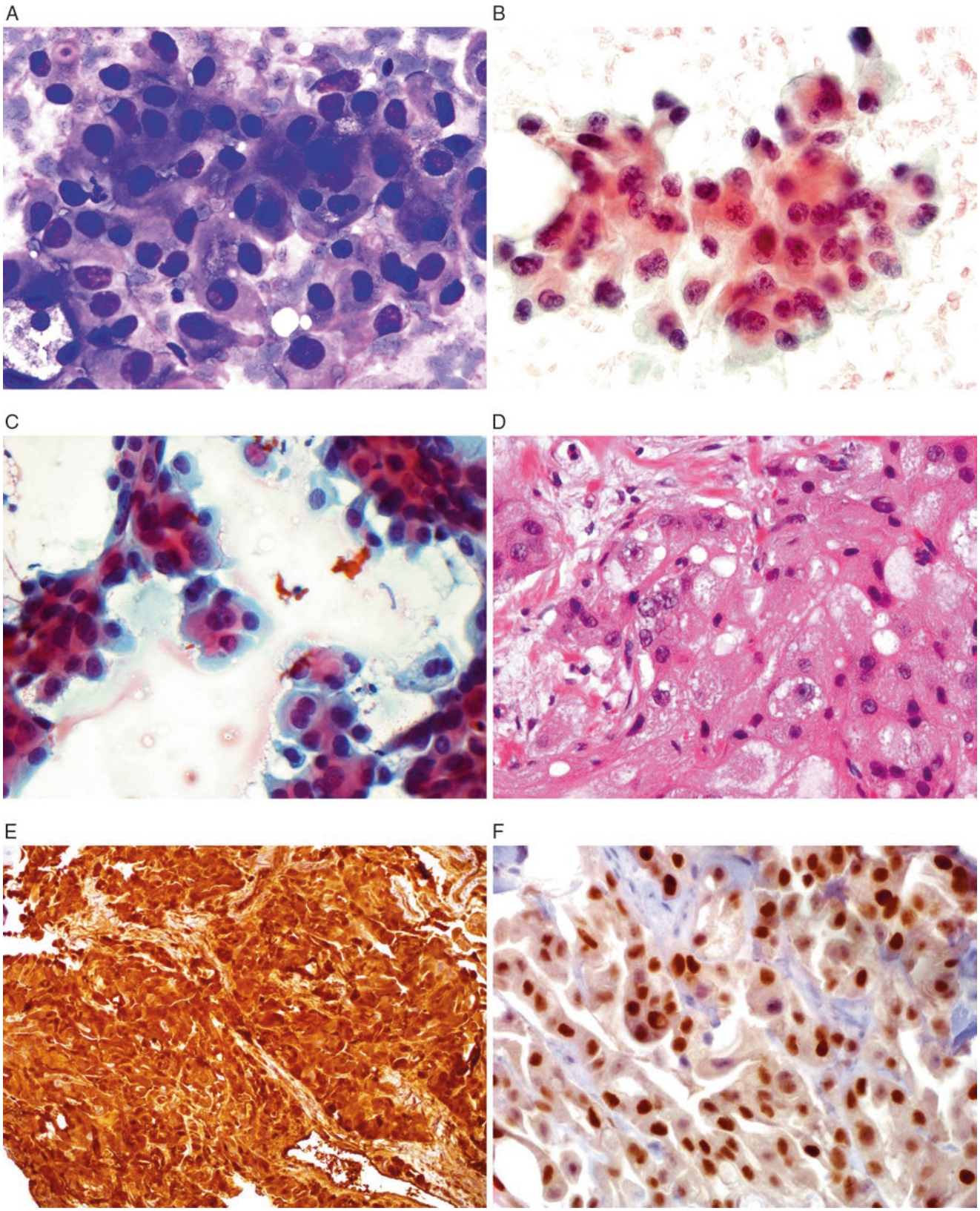

Fig. 5.24 (**a**–**f**) Apocrine carcinoma. (**a**) Apocrine carcinoma cells with large nuclei, prominent nucleoli and abundant granular cytoplasm, Diff-Quik; (**b**, **c**) the same, PAP; (**d**) histology, tumor cells contain enlarged, round, vesicular nuclei with prominent nucleoli, and abundant eosinophilic granular or foamy vacuolated cytoplasm, H&E; (**e**) strong GCDFP15 staining, IHC; (**f**) nuclear staining for AR, IHC

- GATA3 expression in apocrine carcinomas, in our experience, is variable, showing a heterogeneous staining pattern. Among the six apocrine carcinomas included in our study, two showed strong diffuse positivity, one weak diffuse, two weak focal, and one negative.
- Representative images are illustrated in Fig. 5.24e, f.

Metaplastic Carcinoma

Key Clinical Features

- Less than 1% of all invasive breast carcinomas
- Most common in older women, with a mean age of 68 years
- Presentation similar to that of invasive ductal carcinoma, NOS

Key Radiological Features

- Well-defined mass or densities on mammography or ultrasonography; may reveal microcalcifications or ossifications

Cytological Features

- Heterogeneous, with a mixture of atypical spindle cells and epithelial cells with a variety of differentiations
- Spindle cells and epithelial cells with squamous features
- Inflammatory cells and amorphous debris in the background
- Figure 5.25a–c

Differential Diagnosis

- Adenomyoepithelioma
- Myofibroblastoma
- High-grade ductal carcinoma
- High-grade sarcoma or malignant phyllodes tumor
- Metastasis

Histology

In 2012, WHO defined metaplastic carcinoma as "a group of neoplasms characterized by differentiation of the neoplastic epithelium into squamous cells and/or mesenchymal-looking elements, including but not restricted to spindle, chondroid, osseous, and rhabdomyoid cells." These neoplasms may be composed of either entirely metaplastic elements or a complex admixture of carcinoma and metaplastic areas. Histologically, metaplastic carcinoma has been further subclassified as the following types:

- Low-grade adenosquamous carcinoma (Fig. 5.25d)
- Fibromatosis-like metaplastic carcinoma (Fig. 5.25e)
- Squamous cell carcinoma (Fig. 5.25f)
- Spindle cell carcinoma (Fig. 5.25g)
- Metaplastic carcinoma with mesenchymal differentiation: chondroid differentiation, osseous differentiation, other types of mesenchymal differentiation
- Mixed metaplastic carcinoma (Fig. 5.25h)
- Myoepithelial carcinoma

Immunohistochemistry

- Typically triple-negative tumors (ER-, PR-, Her-2/neu-).
- A broad panel of low molecular weight cytokeratins (LMWCKs) (CAM 5.2, CK19), HMWCKs (CK5/6, CK14, CK17, and CK903), and pan-CK (MNF116) should be applied.
- 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, smooth muscle actin [SMA]) are often expressed in metaplastic carcinoma in the spindle cell element.
- The HMWCKs and p63 are most likely to be positive, as shown in Fig. 5.25i, j.

Adenoid Cystic Carcinoma

Key Clinical Features

- Only 0.1% of all invasive breast carcinomas.
- Usually in postmenopausal women, with a mean age of 66 years.
- Clinical presentation is no different from that of invasive ductal carcinoma, NOS.
- Better prognosis.

Key Radiological Features

- No distinct imaging features, similar to that of invasive ductal carcinoma, NOS

Cytological Features

- Hypercellular specimen.
- Cohesive groups of uniform, small basaloid cells with hyperchromatic, angulated nuclei with coarse chromatin pattern, small nucleolus and scant cytoplasm.
- Hyaline globules of basement membrane material are present, eosinophilic on Diff-Quik and pale green on Papanicolaou stain.
- Figure 5.26a–d.

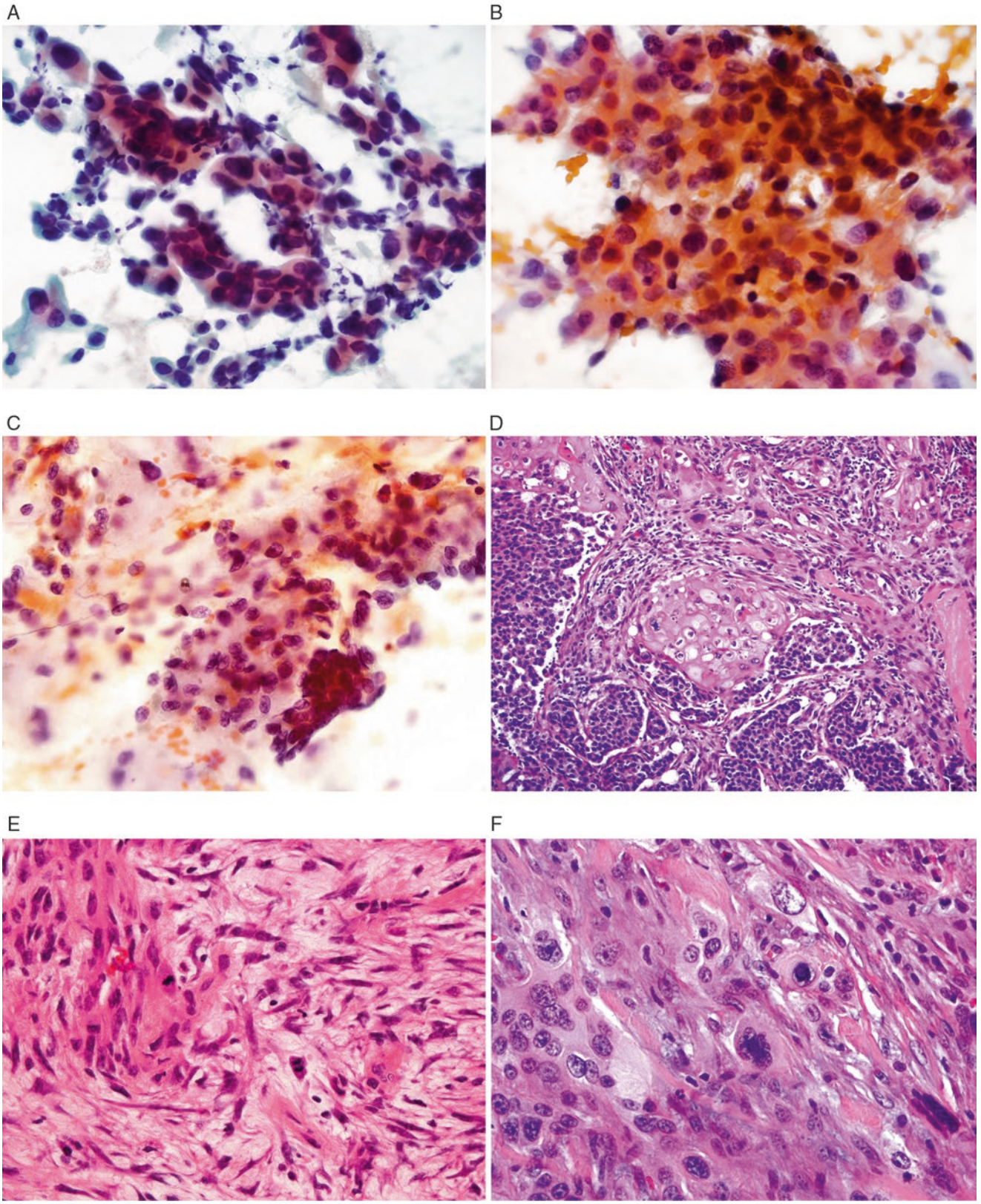

Fig. 5.25 (**a**–**j**) Metaplastic carcinoma, cytology and histology. (**a**, **b**) Spindle cells and epithelial cells with squamous features, Pap stain; (**c**) inflammatory cells and amorphous debris in the background, Pap stain; (**d**) low-grade adenosquamous carcinoma, H&E; (**e**) Fibromatosis-like metaplastic carcinoma, H&E; (**f**) squamous cell carcinoma, H&E; (**g**) spindle cell carcinoma, H&E; (**h**) mixed metaplastic carcinoma, H&E; (**i**) positive CK903 staining in area with squamoid morphology, IHC; (**j**) positive p63 staining in area with squamoid morphology, IHC

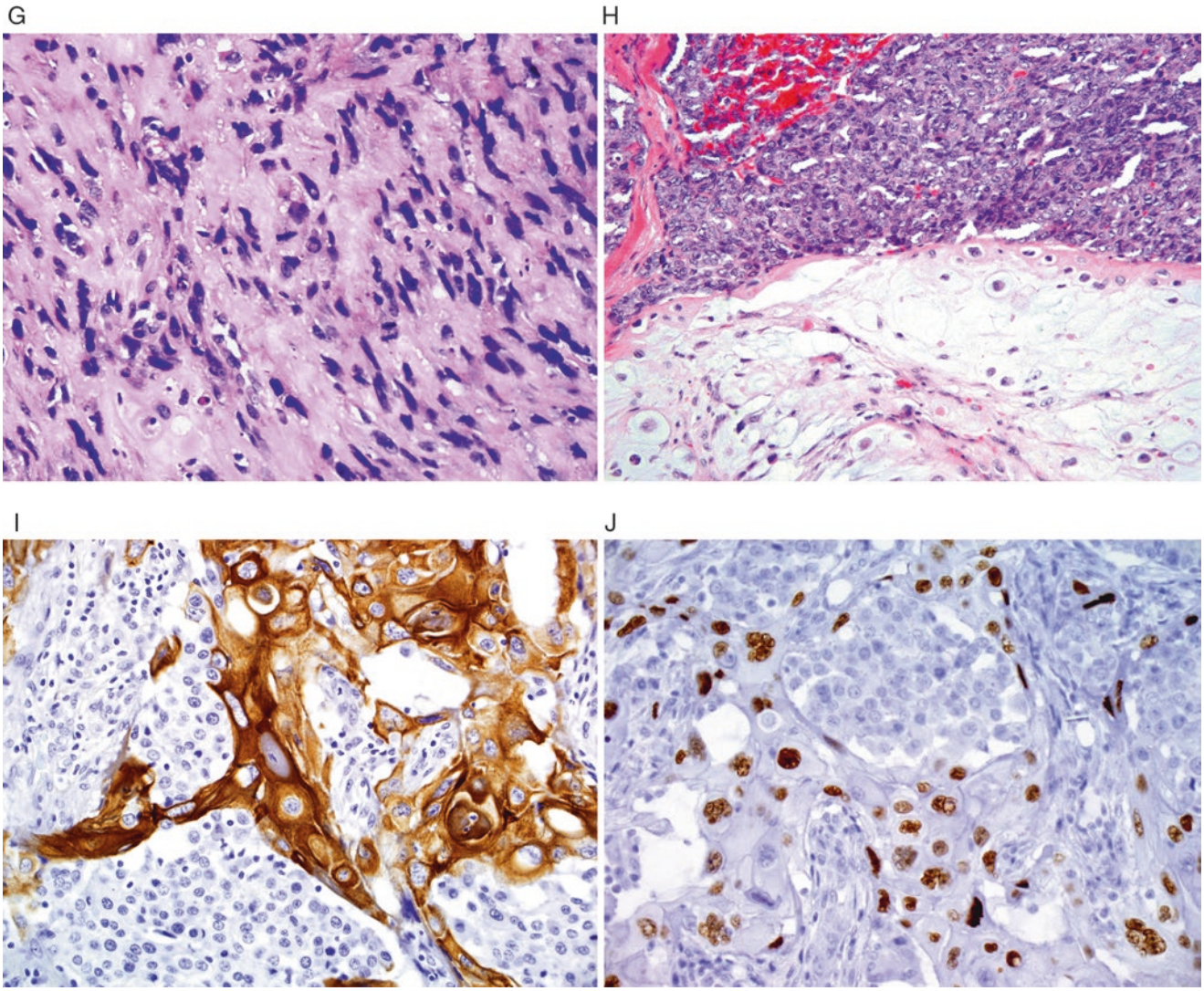

Fig. 5.25 (continued)

Differential Diagnosis

- Collagenous spherulosis
- Invasive cribriform carcinoma

Histology

- Composed of a dual-cell population of epithelial (luminal) and myoepithelial (basaloid) cells forming tubular, cribriform, and solid patterns.
- The neoplastic cells are polarized around glandular spaces or pseudolumina.
- The majority of tumor cells are small and hyperchromatic with scant cytoplasm.
- The glandular spaces are lined by epithelial cells, while the pseudolumina are surrounded by myoepithelial cells containing eosinophilic spherules or cylinders of hyaline material.
- Representative images are shown in Fig. 5.26e–g.

Immunohistochemistry

- Typically a triple-negative (ER-, PR-, and Her-2/neu-) and basal-like carcinoma.
- p63 is a specific myoepithelial marker labeling the myoepithelial (basaloid) cells at the periphery or in the solid area.
- c-kit (CD117) labels the epithelial (luminal) cells, not the myoepithelial cells; therefore, the solid area (which is composed of myoepithelial cells) is nonreactive.
- The eosinophilic hyaline material in the pseudolumens is periodic acid-Schiff (PAS) positive, diastase (D) resistant,

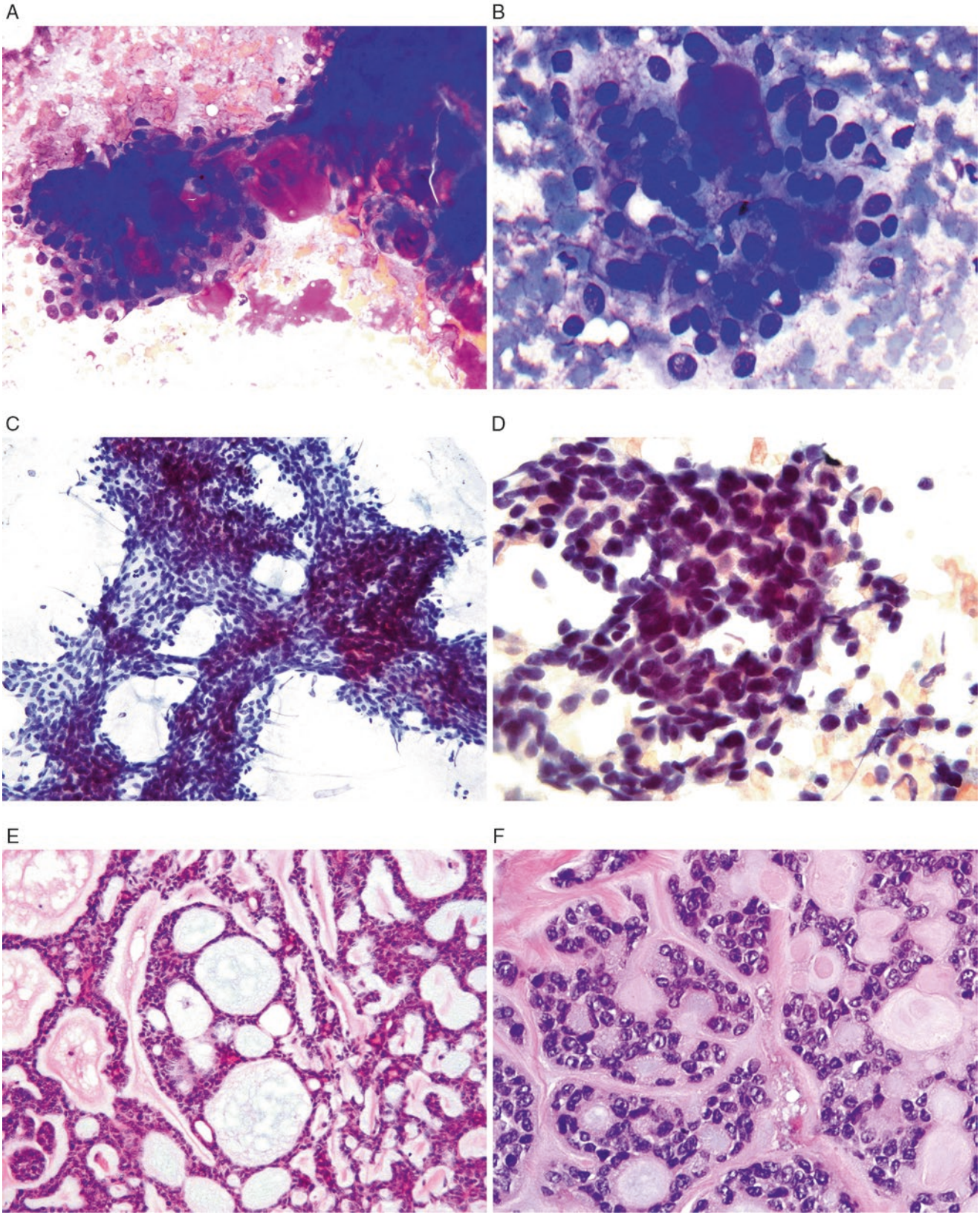

Fig. 5.26 (**a**–**h**) Adenoid cystic carcinoma, cytology, histology, and immunophenotype. (**a**, **b**) Cohesive groups of uniform, small basaloid cells surrounding eosinophilic hyaline globules, Diff-Quik; (**c**, **d**) the hyaline globules appear pale on Pap stain; the tumor cells are hyperchromatic with an angulated appearance, Pap stain; (**e**) cribriform pattern, H&E; (**f**) pseudolumina containing eosinophilic hyaline material, H&E; (**g**) solid pattern with hyperchromatic, basaloid cells, H&E; (**h**) cocktail p63 and CD117 staining, p63 decorating basal cells (brown, nuclei), while CD117 highlighting luminal cells (pink, cytoplasm), IHC

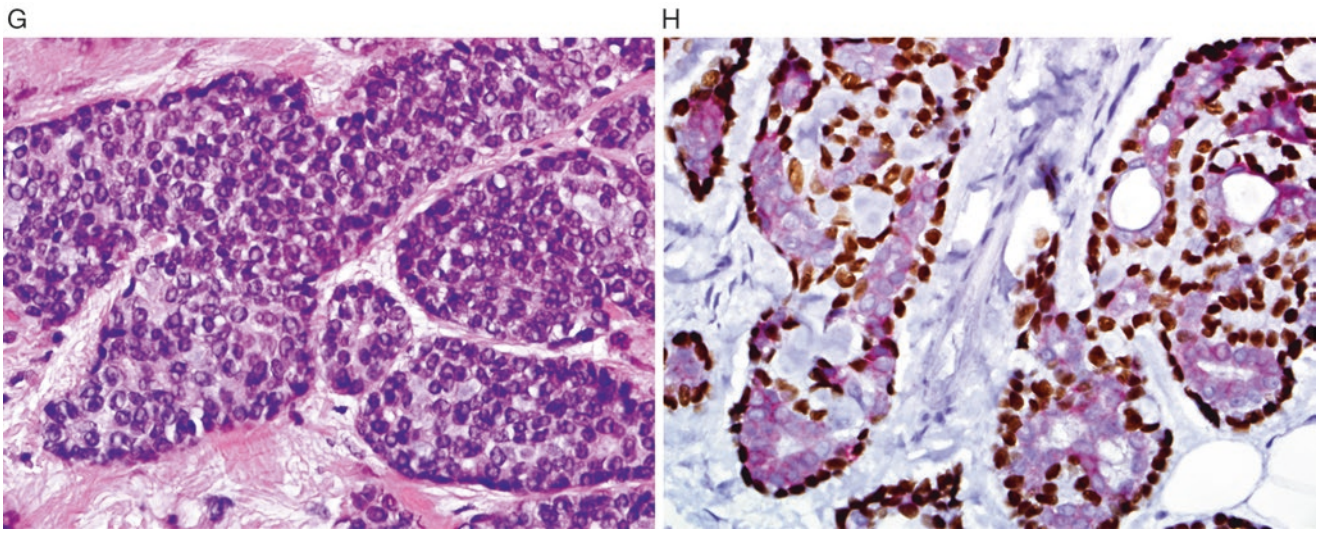

Fig. 5.26 (continued)

and immunohistochemically reactive to collagen IV and laminin; the lightly basophilic myxoid substance in glandular spaces is Alcian blue positive.
- Representative image is illustrated in Fig. 5.26h.

Mesenchymal Tumors

Myofibroblastoma

Key Clinical Features

- Most common in elderly men and women, occasionally associated with gynecomastia
- Usually presents as a slowgrowing, solitary nodule/mass, rarely bilateral and multifocal

Key Radiological Features

- Usually a well-circumscribed, homogeneous solid mass devoid of microcalcifications

Cytological Features

- Cellular smears containing single and clusters of mesenchymal cells with elongated or oval nuclei, a finely granular chromatin pattern, inconspicuous nucleoli, nuclear grooves, occasional intranuclear inclusions, and scant cytoplasm

Differential Diagnosis

- Nodular fasciitis
- Fibromatosis
- Spindle cell metaplastic carcinoma
- Leiomyoma
- Invasive lobular carcinoma: to differentiate from epithelioid cell myofibroblastoma

Histology

- Usually composed of uniform spindle to oval cells arranged in short, haphazardly intersecting fascicles interrupted by thick bands of brightly eosinophilic collagen.
- Adipocytes are present in variable amounts.
- Smooth muscle, cartilaginous, or osseous metaplasia occasionally may be observed.
- No necrosis and rare mitoses are evident.
- There is usually no entrapment of mammary ducts or lobules within the tumor.
- Representative images are shown in Fig. 5.27a–c.

Immunohistochemistry

- The neoplastic cells are positive for desmin, CD34, SMA, Bcl2, CD99, CD10, and hormone receptors (ER, PR, AR).
- H-caldesmon expression is reported in 2–10% of myofibroblastoma cells.
- Representative images are illustrated in Fig. 5.27d–f.

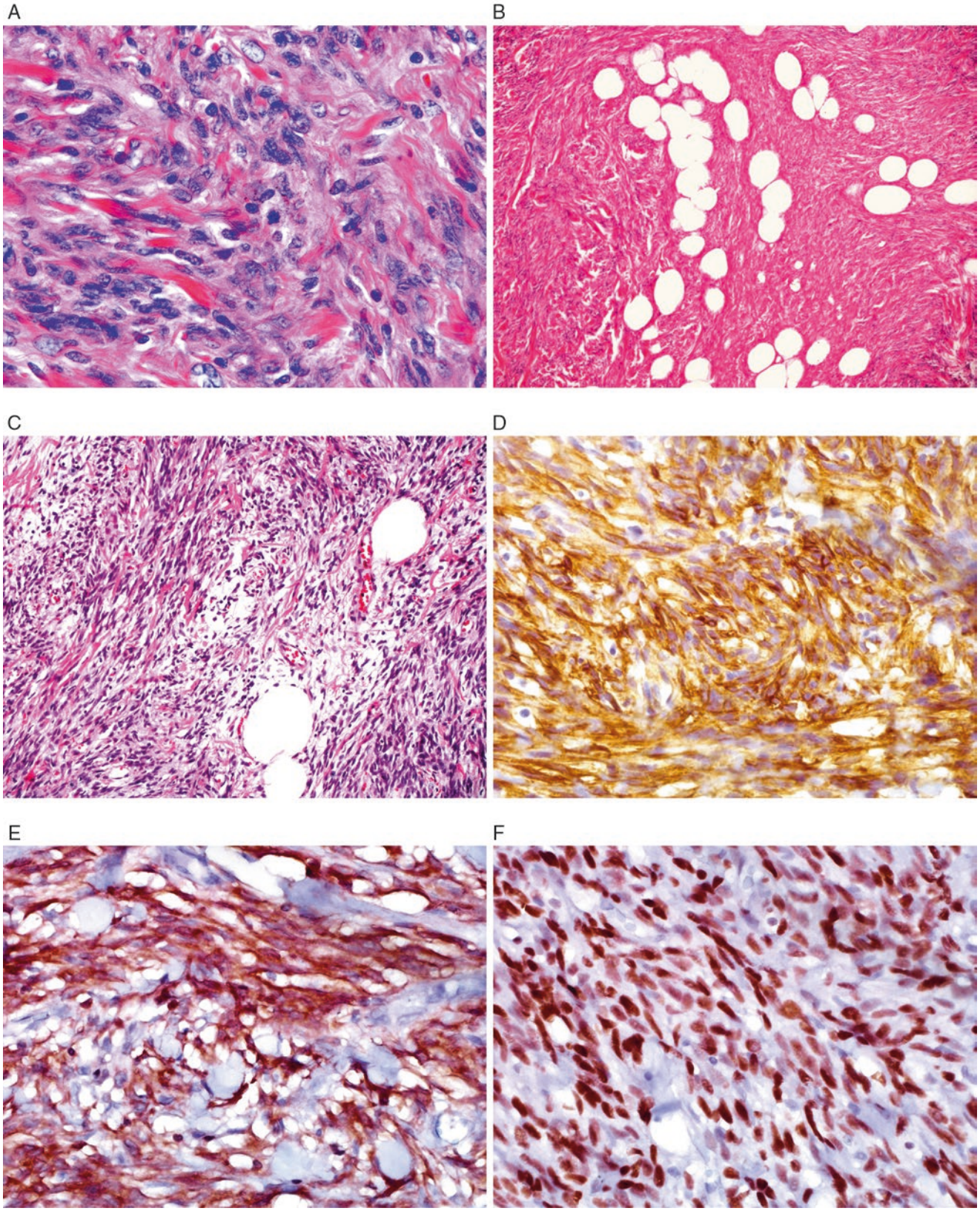

Fig. 5.27 (**a**–**f**) Myofibroblastoma, histology, and immunophenotype. (**a**) Uniform spindled to oval cells arranged in short, haphazardly intersecting fascicles interrupted by thick bands of brightly eosinophilic collagen, H&E; (**b**, **c**) adipocytes are present in variable amounts, H&E; (**d**) rumor cells are positive for CD34; (**e**) Bcl2 decorating tumor cells; (**f**) nuclear staining for AR

Desmoid-Type Fibromatosis

Key Clinical Features

- Most common in women in their second to fourth decades.
- Presents as a firm palpable mass; may be associated with dimpled skin.
- May be sporadic or associated with FAP.
- The sporadic cases may be associated with trauma or history of breast surgery, including implant surgery.

Key Radiological Features

- Mammography: a spiculated mass that simulates carcinoma
- Ultrasonography: a hypoechoic mass

Cytological Features

- Usually sparsely cellular, contains fibrohistiocytic cells, singly or in tissue fragments.
- The cells are spindled and bland; occasional small groups of benign ductal cells may be present.

Differential Diagnosis

- Spindle cell carcinoma
- Lipomatous myofibroblastoma
- Nodular fasciitis

Histology

- Cytologically bland spindle cells arranged in long, sweeping and intersecting fascicles in a collagenous or myxoid background.
- The margins are ill-defined and infiltrative, blending into adjacent normal breast stroma or deep skeletal muscle.
- There are often lymphoid aggregates at the edge.
- Representative images are shown in Fig. 5.28a, b.

Immunohistochemistry

- Aberrant nuclear expression of beta-catenin is reported in 67–100% of cases.
- Keratin, epithelial membrane antigen (EMA), CD31, Bcl-2, and CD34 are negative.
- Actin, desmin, and S100 may be expressed in occasional cases.
- Representative images shown in Fig. 5.28c, d.

Primary Sarcoma

Key Clinical Features

- A heterogeneous group of neoplasms, account for <1% of all breast neoplasms
- Any age of adults, women or men, average age in the sixth decade
- Presenting as a progressively enlarging, typically solitary breast mass, may be associated with pain or skin changes
- Coexisting lymphadenopathy in up to one-third of patients, however reactive by histology.

Key Radiological Features

- Mass lesion, usually lobulated

Cytological Features

- Smears usually contain fragments of cellular mesenchymal tissue and dispersed spindle cells with variable degree of nuclear atypia.
- Primary high-grade sarcomas of the breast are highly cellular, comprised of pleomorphic spindled to plump cells with hyperchromatic nuclei, a coarse chromatin pattern and prominent nucleoli; necrosis is common.
- High-grade angiosarcomas are moderately cellular, composed of clusters and single of atypical plump, spindled and oval cells with a moderate amount of cytoplasm in background of hemorrhage.
- The presence of a few single pleomorphic cells with intracytoplasmic hemosiderin deposits in a hemorrhagic background should raise the diagnostic possibility of angiosarcoma.
- The presence of small clusters of cells or vasoformative features, such as microacini, fragments of arborizing microtissue, and intracytoplasmic lumen in a bloody background, suggests vascular differentiation.

Differential Diagnosis

- Spindle cell carcinoma
- Malignant phyllodes tumor
- Fibromatosis
- Nodular fasciitis
- Spindle cell melanoma

Histology

- Depending on the specific tumor type, primary mammary sarcomas show histologic features similar to those arising from soft tissue.

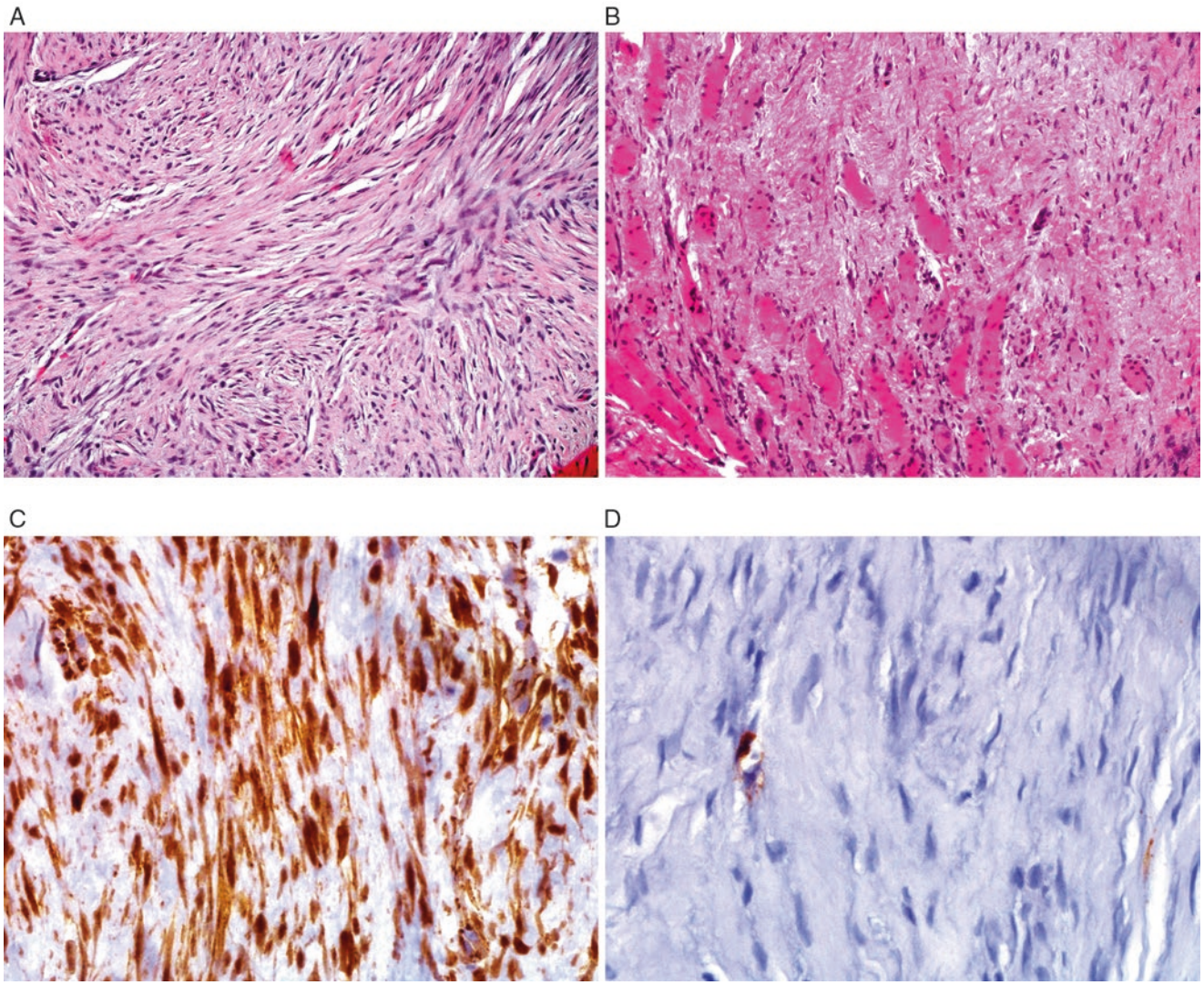

Fig. 5.28 (**a**–**d**) Desmoid-type fibromatosis, histology, and immunophenotype. (**a**, **b**) Cytologically bland spindle cells arranged in long, sweeping, and intersecting fascicles in a collagenous or myxoid background, focally infiltrating underlying skeletal muscle, H&E; (**c**) nuclear staining for β-catenin; (**d**) negative for CD34, rare capillary highlighted

- Angiosarcoma: the most common, composed of a broad spectrum of growth patterns (vasoformative, solid, papillary endothelial, and capillary-type patterns) and variable nuclear atypia; the neoplastic cells may be flat, plump, spindled, or epithelioid in shapes; can be classified as low (type I), intermediate (type II), and high (type III) grade based on histomorphology on resection specimens.
- Liposarcoma: includes well-differentiated, myxoid, pleomorphic, and dedifferentiated.
- Leiomyosarcoma is composed of fascicles of smooth muscle cells with nuclear atypia, mitosis, and necrosis; epithelioid morphology and heterogeneous elements have been reported.
- Representative images of angiosarcoma are shown in Fig. 5.29a–d.

Immunohistochemistry

- For liposarcoma, IHC or fluorescence in situ hybridization (FISH) for mouse double minute 2 homolog (MDM2) and cyclin-dependent kinase 4 (CDK4) may help to confirm the diagnosis and exclude other types of sarcoma or benign fatty tumors.
- Leiomyosarcoma is immunohistochemically positive for actin and desmin.
- Angiosarcoma is positive for vascular markers (CD31, CD34, Factor VIII) and ETS-related gene (ERG) and negative for cytokeratin and EMA; ER and PR are negative in the majority of angiosarcomas.
- An example of angiosarcoma is illustrated in Fig. 5.29e, f.

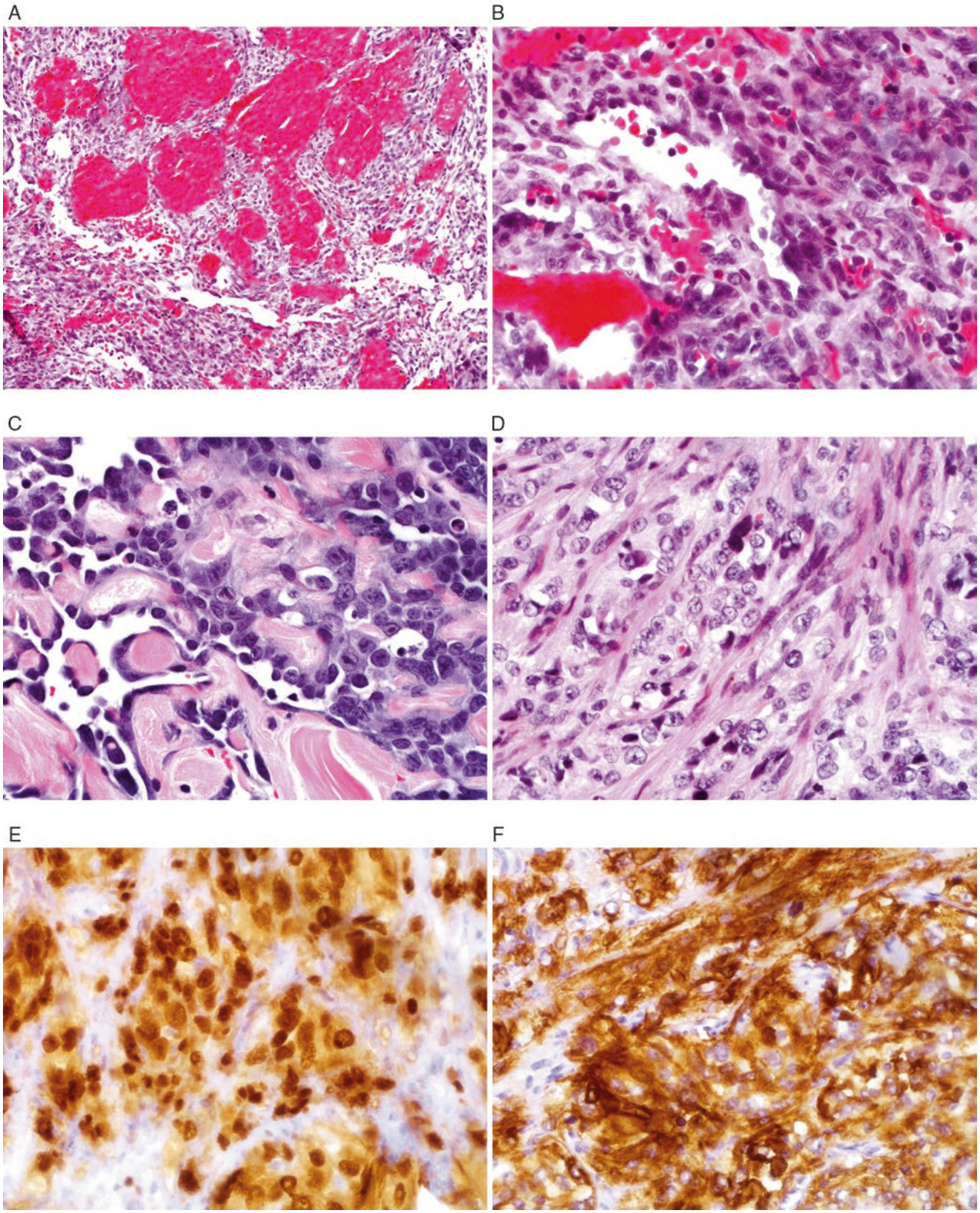

Fig. 5.29 (**a**–**f**) Angiosarcoma of the breast, histology and immunophenotype. (**a**–**d**) Vasoformative growth, with production of highly infiltrative, irregularly configured vascular channels, with intraluminal papillary projections, and variety of growth patterns that varies from sieve-like to solid, H&E; (**e**) ERG decorates tumor cells, nuclear staining pattern; (**f**) tumor cells are positive for CD31

Lymphoma

Clinical Features

- Rare, <0.5% of all breast malignancies.
- Often seen in postmenopausal women.
- The majority are non-Hodgkin's lymphomas, most common diffuse large B-cell lymphoma.
- Usually presents with a palpable, painless breast mass lesion.

Radiological Features

- Radiographic features are variable, indistinguishable from invasive carcinomas.

Cytological Features

- Hypercellular smears consist of a population of monomorphic atypical lymphocytes in a background of round basophilic cytoplasmic fragments (lymphoglandular bodies).
- Cytological features of the tumor cells are identical to those of lymphomas arising from lymph nodes, based on the type of lymphoma.
- Figure 5.30a, b.

Differential Diagnosis

- Poorly differentiated carcinomas
- Neuroendocrine tumors
- Granulocytic sarcoma
- Chronic mastitis

Histology

- The diagnosis of lymphomas of the breast requires integration of clinical, morphologic, immunophenotypic, genetic, and flow cytometric information.
- Lymphomas of the breast are commonly well-circumscribed tumors of varying size; however, histologically, the borders are infiltrative, with tumor cells permeating around lobules and ducts.
- The histomorphology is similar to those seen at other anatomic sites, depending on the tumor type. Diffuse large B-cell lymphoma is composed of sheets of large atypical lymphoid cells with irregular nuclear contours, a vesicular chromatin pattern, and prominent nucleoli. The tumor cells infiltrate and replace the underlying normal breast lobular structures.
- Representative image of a cell block section is shown in Fig. 5.30c.

Immunohistochemistry and Flow Cytometry Studies

- Depending on the tumor type, mammary lymphomas show identical phenotypes by IHC, flow cytometry studies, and/or cytogenetic evaluations.
- Diffuse large B-cell lymphomas express CD20, CD79a, and paired box gene 5 (PAX5) and variably express germinal center-associated and other B-cell subset markers, including CD10 (−/+), CD5 (−/+), Bcl6 (+/−), and interferon regulatory factor 4 protein/multiple myeloma 1 [IRF4/MUM-1] (+/−). Immunostains for CD3, cyclin D1, and cytokeratins are negative. Representative images shown in Fig. 5.30d–f.

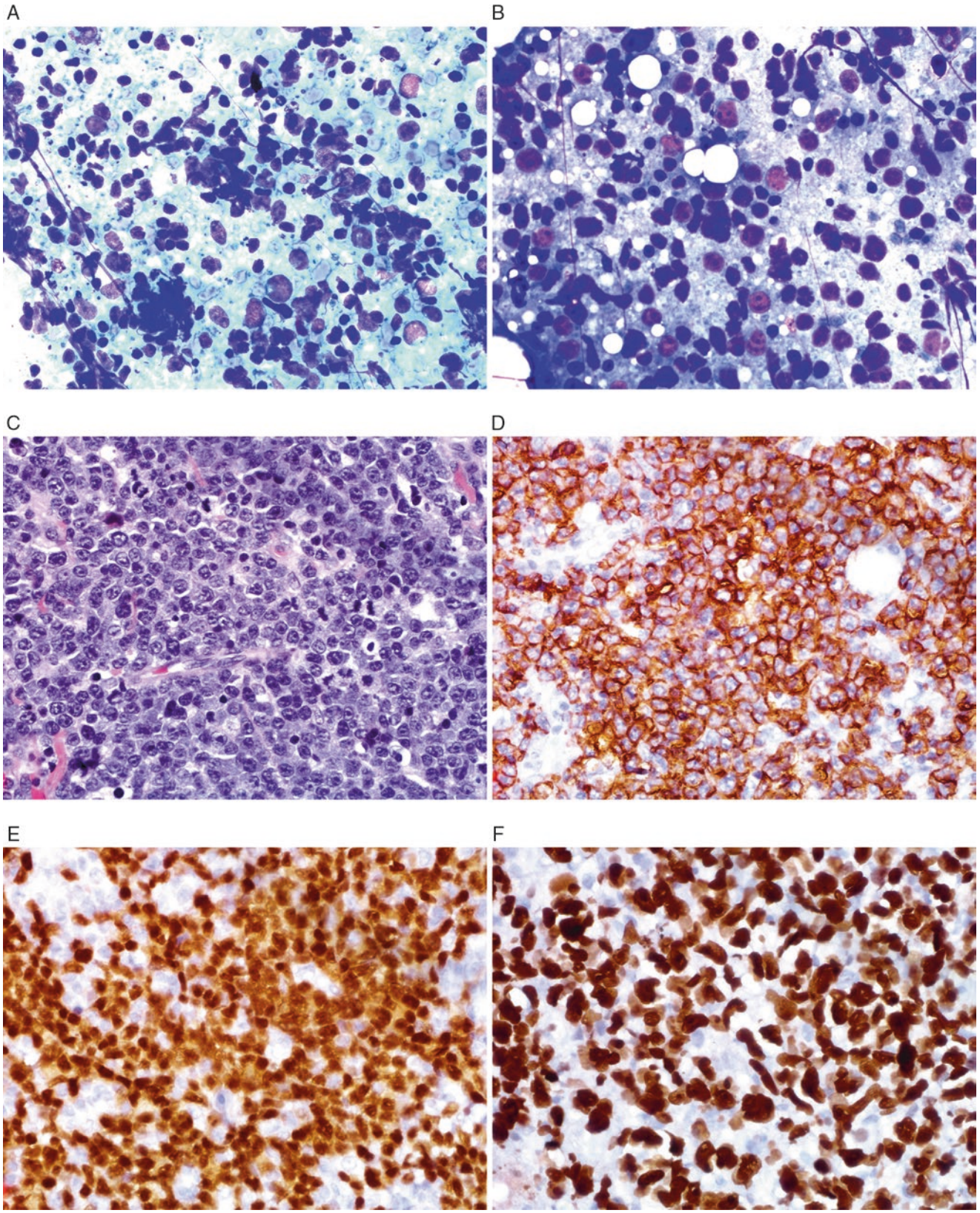

Fig. 5.30 (**a**–**f**) Diffuse large B-cell lymphoma of the breast. (**a**) Highly cellular smear comprised of individual blue cells, Diff-Quik; (**b**) tumor cells with large, vesicular nuclei, prominent nucleoli in background of lymphoglandular bodies, Diff-Quik; (**c**) core biopsy shows monotonous atypical lymphocytes with large nuclei, prominent nucleoli, and abundant mitotic activity, H&E; (**d**) positive for CD20, IHC; (**e**) nuclear decoration with PAX5, IHC; (**f**) high MIB-1 labeling, estimated at over 90%, IHC

Case Presentations

The following are three cases that are commonly encountered in daily practice. Case Scenario 1 is a case of intracystic (encapsulated) papillary carcinoma of the breast. The objective of this case presentation is to demonstrate an algorithmic approach for the workup of papillary lesions. Case Scenario 2 is a mammary spindle cell carcinoma. The objective is to illustrate the crucial role of IHC in the diagnosis of spindle cell lesions. Case Scenario 3 is a gastric metastasis of mammary lobular carcinoma. The objective is to illustrate the utility and pitfalls of breast organ-specific immunomarkers.

Case Scenario 1

Learning Objectives

1. To exercise histo- and cytomorphological diagnosis of papillary lesions
2. To illustrate an algorithmic approach for the diagnostic workup of papillary lesions
3. To suggest the effective panel of immunomarkers for the diagnosis of papillary lesions

Case

The diagnosis of papillary lesions of the breast is often challenging, especially in small biopsy specimens. IHC is commonly applied in this setting, using the algorithmic approach as provided in the previous section. The role of IHC workup on cytology cell block material is limited in the setting of papillary lesions.

A 69-year-old female presented with nipple discharge and a slow growing nodule/mass for a year. Mammogram revealed a multinodular increased density in upper right quadrant toward central region. An ultrasound-guided FNA and CNB were performed. The smears were cellular, comprised of papillary fragments and abundant single cells with a columnar or elongated appearance, as illustrated in Fig. 5.31a–e. The CNB revealed multiple cores of tissue comprised of vaguely papillary fragments containing a delicate fibrovascular stalk with overlying proliferation of monotonous neoplastic epithelial cells showing low-to-intermediate-grade nuclei. The neoplastic cells were focally arranged in solid or cribriform patterns. Focal surrounding thick fibrous capsule and cystic spaces were appreciated. No discernible myoepithelial cells were identified in the stalks and at periphery. Immunohistochemical studies including ADH5 and ER were performed and illustrated in Fig. 5.31f–h.

Papillary lesions encompass a spectrum of tumors from benign papilloma to invasive papillary carcinoma. The first step in the workup of a papillary lesion is to determine its benign vs malignant nature; this can be achieved by morphological assessment and, more accurately, the application of basal/myoepithelial markers, especially p63, calponin and HMWCKs (CK903, CK5/6, and CK14). The lack of basal/myoepithelial cells (both at the periphery and over fibrovascular stalks) identifies a malignancy, either intracystic (encapsulated) papillary carcinoma or invasive papillary carcinoma. The presence of basal/myoepithelial cells classifies the papillary lesion as benign or atypical. The latter includes ADH or DCIS involving papilloma and papillary carcinoma in situ. The next step is to separate benign from atypical, which is often achieved by the application of HMWCK (commonly CK903 or CK5/6) and ER. Studies well documented that ADH/DCIS is a neoplastic process with a clonal proliferation of luminal epithelial cells; by immunohistochemistry, these lesions show lack of or focal weak expression for HMWCK. In contrast, UDH is a hyperplastic process, exhibiting a mosaic staining pattern for ADH5, a cocktail consisting CK7, CK AE1/3, p63, CK903, and CK14. In addition, ER expression is scattered in UDH and diffuse in ADH/DCIS. However, papilloma itself is usually ER positive in a diffuse and strong fashion; therefore, caution should be exercised when interpreting the ER result. The loss of expression for HMWCK in conjunction with diffuse strong expression of ER in an area of proliferation suggests an atypical papillary lesion (ADH/DCIS involving papilloma or papillary DCIS), while a mosaic pattern of staining for HMWCK in conjunction with patchy weak expression for ER is in favor of a benign papilloma.

The current case reveals loss of myoepithelial cells (p63-, both at the periphery and over the stalks), loss of expression for HMWCK, and diffuse strong nuclear staining for ER; the phenotype supports the diagnosis of an encapsulated papillary carcinoma.

Case Scenario 2

Learning Objectives

1. To exercise histo- and cytomorphological diagnosis of spindle cell lesions
2. To illustrate the diagnostic workup of spindle cell lesions, especially metaplastic carcinoma
3. To suggest the effective panel of immunomarkers for the diagnosis of metaplastic carcinoma

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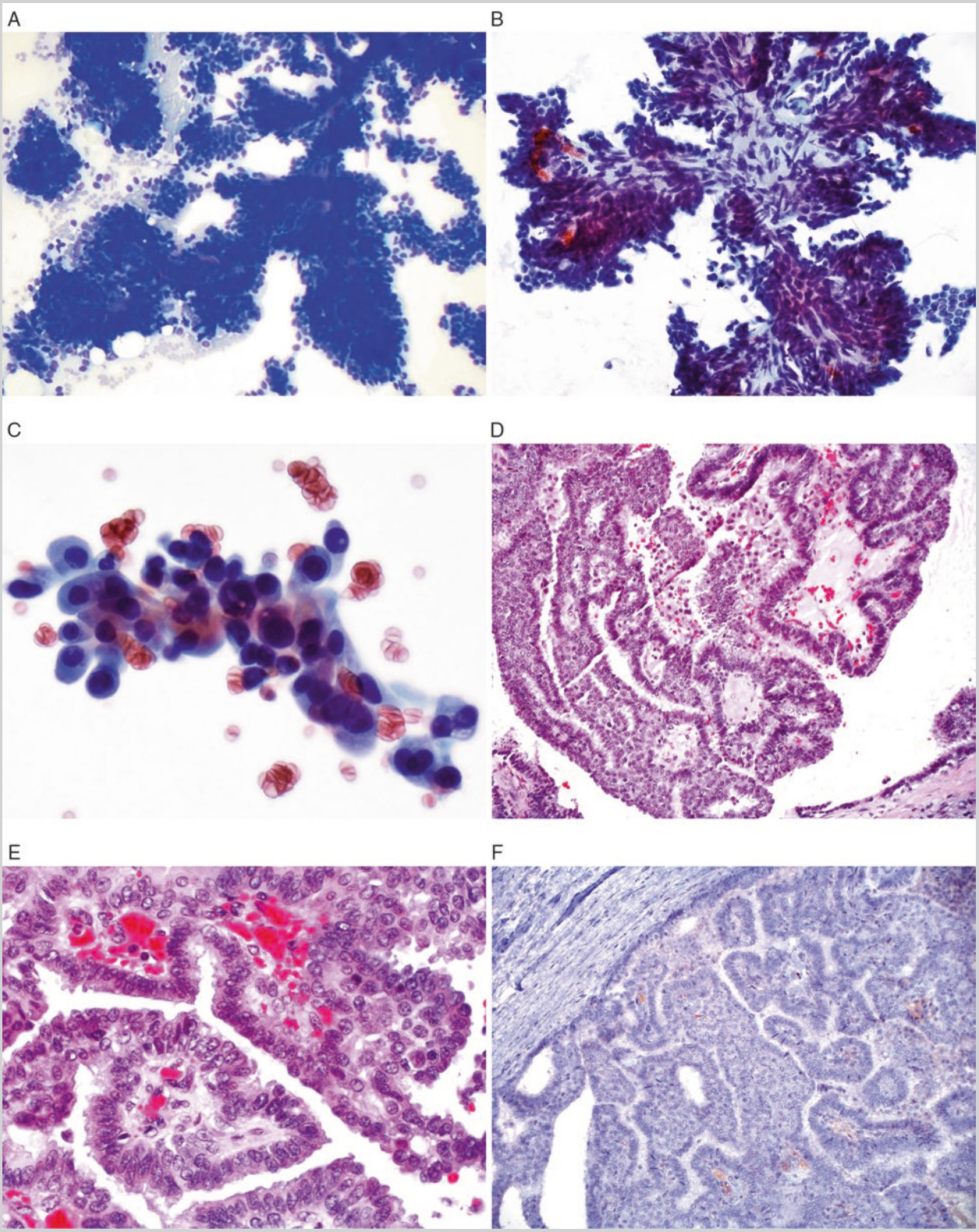

Fig. 5.31 (**a**–**h**) Encapsulated papillary carcinoma, cytology, histology, and immunophenotype. (**a**) Many papillary fragments of atypical ductal cells, Diff-Quik; (**b**) fibrovascular core with overlying monomorphic tumor cells, some with columnar morphology, Pap stain; (**c**) focally mild pleomorphic, with columnar morphology, Pap stain; (**d**) histology, papillary proliferation within cystic space, H&E; (**e**) high-power view of fibrovascular cores with overlying single or focally stratified ductal cells with columnar morphology, H&E; (**f**) p63 stain reveals lack of basal cells at the periphery and over vascular cores, IHC; (**g**) tumor cells show loss of expression for CK903, BNC5, IHC; (**h**) diffuse ER expression, IHC

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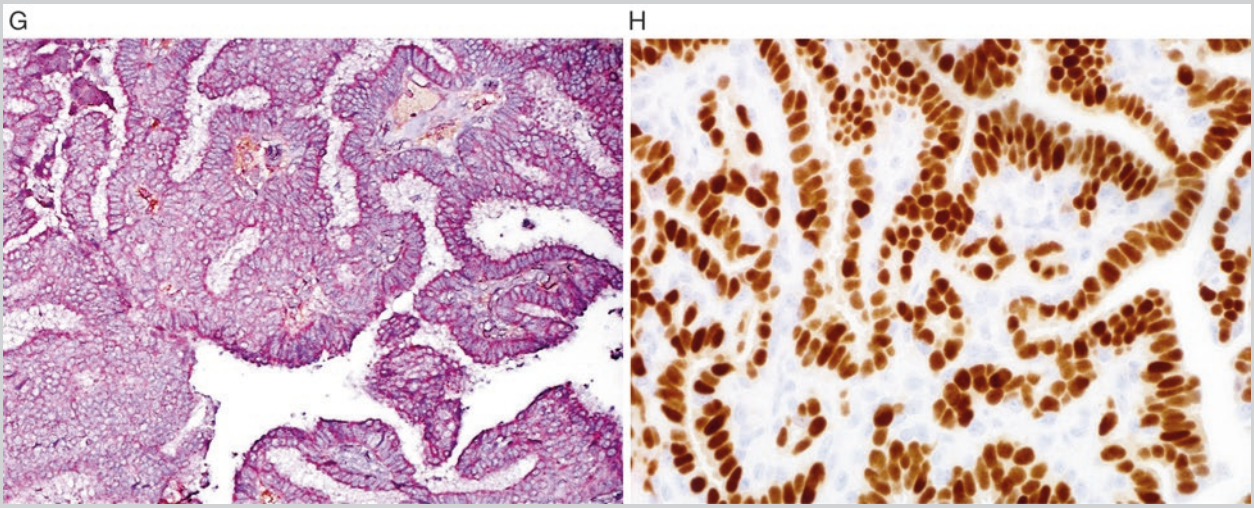

Fig. 5.31 (continued)

Case

The diagnostic approach for spindle cell lesion of the breast should focus on the exclusion of spindle cell carcinoma, due to the fact that primary spindle cell lesions of other types are rare. Therefore, is this a spindle cell carcinoma? That is always the first question to ask when encountering a spindle cell lesion of the breast. If the answer is yes, the case is done. If the answer is no, the next question is: is this a benign or malignant lesion? If it is malignant, the next question is: primary or secondary? Is it low grade or high grade? What is the lineage of the tumor? To answer those questions, IHC analysis plays an essential role. Here we propose an effective small panel of immunomarkers in the workup of a spindle cell lesion, particularly the metaplastic carcinoma of the mammary gland.

A 52-year-old female presented with a palpable breast mass of 2 cm. An ultrasound-guided FNA was performed, followed by CNB. The smears were moderately cellular, comprised of a mixture of mildly atypical spindle cells singly or in clusters, and occasional atypical epithelial cells with squamoid features. Neutrophils and amorphous debris were seen in the background, as illustrated in Fig. 5.32a, b. The CNB specimen revealed cores of tissue composed of a proliferation of mildly atypical spindle cells, rare multinucleated giant cells, and focal nests of epithelial cells with squamous differentiation. Focal necrosis and neutrophilic infiltrates were noted. Immunoassays were performed. Representative images are illustrated in Fig. 5.32c–h.

The World Health Organization Classification of Tumors of the Breast (2012) defines the metaplastic carcinoma of the mammary gland as "a group of neoplasms characterized by differentiation of the neoplastic epithelium into squamous cells and/or mesenchymal-looking elements, including but not restricted to spindle, chondroid, osseous, and rhabdomyoid cells." Histologically, there is a wide range of appearances. In 2012, WHO further classified metaplastic carcinoma into the following subtypes: (1) low-grade adenosquamous carcinoma, (2) fibromatosis-like metaplastic carcinoma, (3) squamous cell carcinoma, (4) spindle cell carcinoma, (5) metaplastic carcinoma with mesenchymal differentiation, and (6) mixed metaplastic carcinomas. The diagnosis of metaplastic carcinoma is challenging and often requires IHC studies with multiple immunomarkers, especially in small biopsy tissues. For tumors with spindled, low-grade morphology, the differential diagnosis usually includes malignant phyllodes tumor, fibromatosis, or even nodular fasciitis. For tumors with high-grade morphology,

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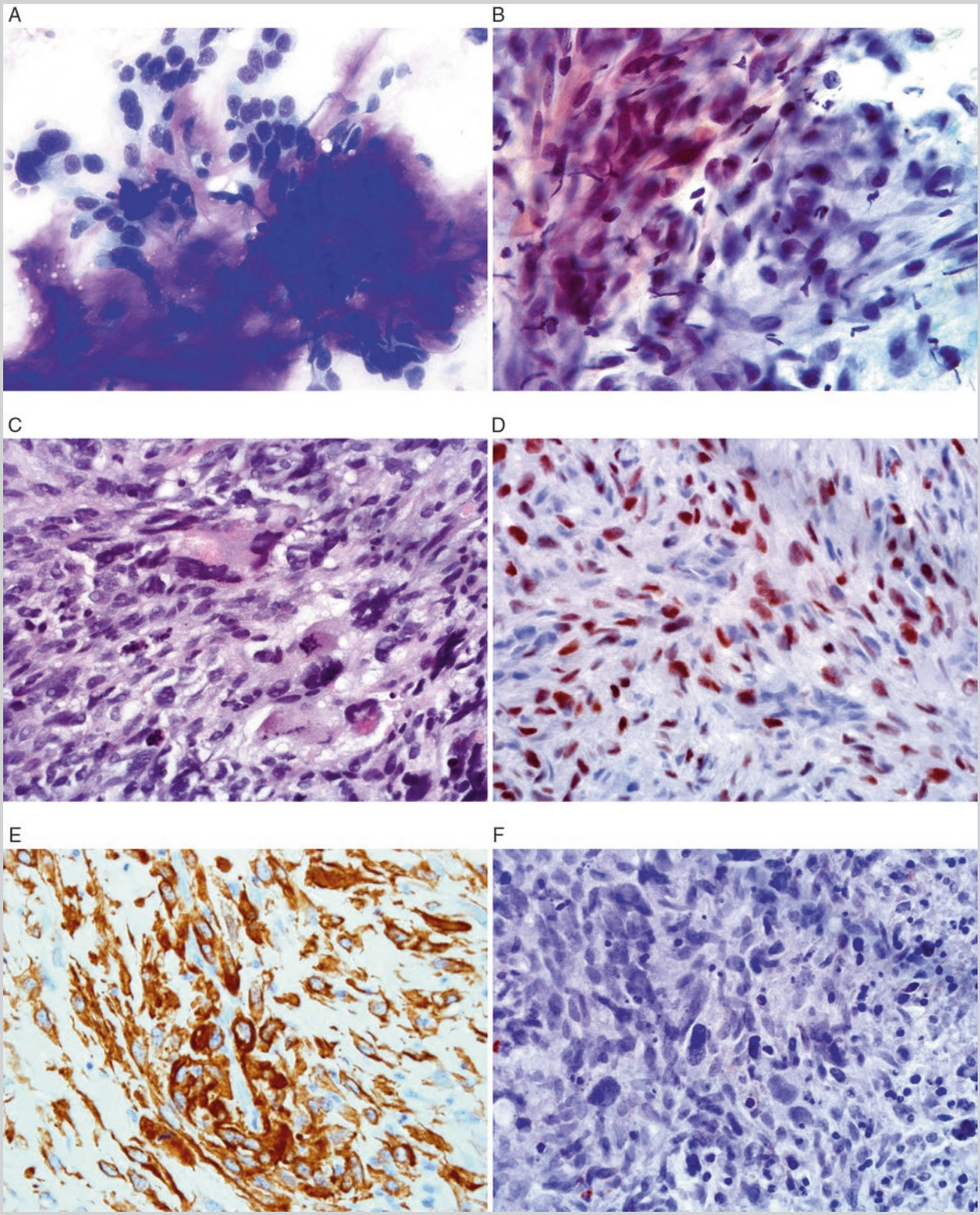

Fig. 5.32 (**a**–**h**) Metaplastic carcinoma. (**a**) Cluster of plump to spindled cells embedded in stromal tissue, Diff-Quik; (**b**) a typical spindled cells with scattered neutrophils, Pap stain; (**c**) H&E section revealing a metaplastic carcinoma comprised of highly atypical spindle cells with few multinucleated forms. Nests of malignant epithelial cells with squamoid features are noted but not shown in the photo; (**d**) p63 decorating scattered nuclei in spindle cell component as well as the epithelial nests (not shown); (**e**) CK903 decorating the epithelial cells and the spindle cell component; (**f**) CD34 is negative; (**g**) β-catenin stain shows a cytoplasmic granular pattern, no nuclear positivity; (**h**) EMA positive in spindle cell component

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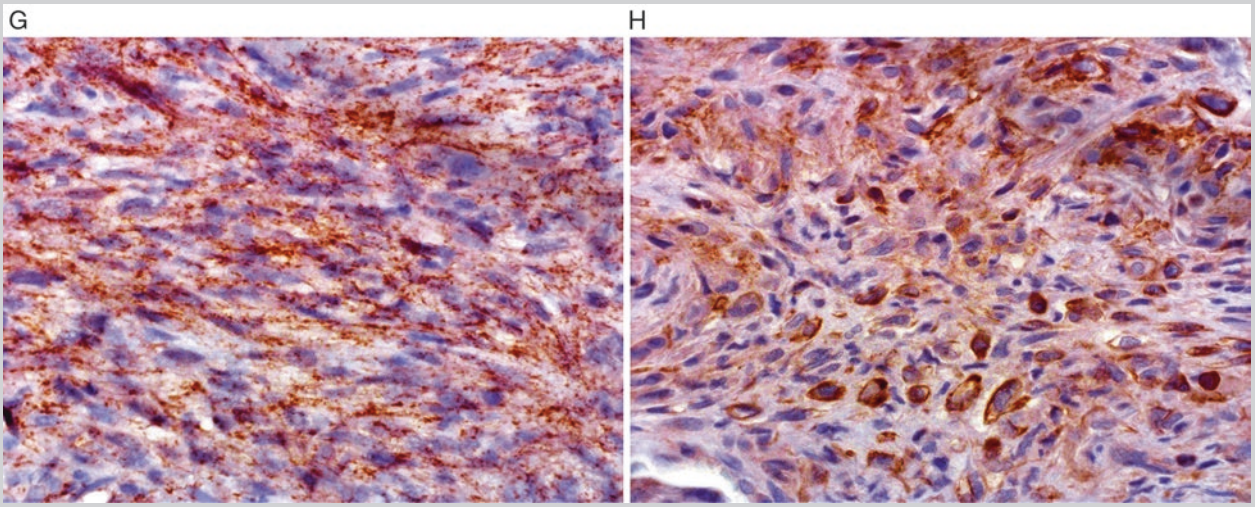

Fig. 5.32 (continued)

primary mammary sarcoma and metastasis should be considered in the differential diagnosis. The first step in establishing a diagnosis of metaplastic carcinoma is to confirm its epithelial differentiation; therefore, a broad panel of cytokeratins, especially HMWCK (CK903, CK5/6, and CK14) and pan-cytokeratin, such as AE1/AE3, is often applied. The majority of metaplastic carcinomas express cytokeratins in the spindle cell components, usually focally. Luminal cytokeratins, such as CK7 and CAM5.2, are commonly negative. No single cytokeratin is expressed in all metaplastic carcinomas; therefore, a panel of a variety of cytokeratins, including both basal and luminal types, is essential. However, not all spindle cell lesions with cytokeratin expression are metaplastic carcinomas. Metastatic spindle cell melanomas and leiomyosarcomas may express cytokeratin, usually CAM5.2. Therefore, one should interpret IHC results on the basis of histomorphology. In addition to the frequent expression of cytokeratins, especially basal keratins, metaplastic carcinomas often express other basal or myoepithelial markers. p63 is positive in >90% of cases and carries a higher specificity. p63 has not been reported in the entities in the differential diagnosis of metaplastic carcinomas, such as phyllodes tumors and fibromatosis. Therefore, the best panel of immunomarkers consists of CK903 or CK5/6, AE1/AE3, and p63. In addition, CD34 and Bcl2 should be included in the panel to differentiate metaplastic carcinoma from phyllodes tumor. When fibromatosis is in the differential consideration, the addition of β-catenin may be helpful. The differential IHC phenotypes are summarized in Table 5.2.

Table 5.2. Differential immunophenotypes of metaplastic carcinoma, phyllodes tumor, and fibromatosis

Tumor/marker	CK903	AE1/AE3	p63	β-catenin	CD34	Bcl2
MCA	+, focal	+, focal	+	−/+, N	−	−
PT	−	−	−	+, N	+	+
Fibromatosis	−	−	−	+, N	−	−

NOTE: The differential phenotype applies to the spindle cell component of the tumors
MCA metaplastic carcinoma, *N* nuclear, *PT* phyllodes tumor, + positive, − negative

Metaplastic carcinomas are often triple-negative tumors with the expression of CK5/6 and/or EGFR, belonging to the basal-like tumor group.

The current case revealed patchy positivity for AE1/AE3, CK903, and p63, while negative for CD34 and Bcl2, supporting the diagnosis of a metaplastic

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carcinoma. Hormonal analyses reveal the tumor to be triple negative (ER-, PR-, Her-2/neu-).

Case Scenario 3

Learning Objectives

1. To illustrate the diagnostic workup for metastatic breast carcinomas
2. To suggest the effective panel of immunomarkers for the identification of breast primary
3. To discuss the applications and pitfalls of commonly used immunomarkers in breast pathology

Case

Gastric metastases are rare events. Breast carcinoma has been reported as the most common tumor to metastasize to the stomach. The histomorphology may suggest a possible primary site; however, IHC assays are essential for an accurate diagnosis in this context.

A 60-year-old female with no known past medical history of malignancy presented with dyspepsia and heartburn not responsive to medical treatment. An upper GI endoscopy was performed, revealing erythematous gastric mucosa with thickening of the folds. Biopsies were taken and consisted of fragments of gastric mucosa in which an abnormal population of cells is present in the lamina propria and submucosa, singly as well as focally, in a single-file pattern. The abnormal cells are plasmacytoid in appearance, relatively uniform, with small to prominent nucleoli. Occasional intracytoplasmic lumina are noted. Representative images are shown in Fig. 5.33a, b.

The histomorphology raises the differential diagnosis of metastatic lobular carcinoma of the breast, gastric signet-ring cell carcinoma, and, less likely, a metastatic urothelial carcinoma of plasmacytoid morphology. A panel of IHC markers was performed, including CK7, CK20, GATA3, ER, E-cadherin, and uroplakin II. Representative images are illustrated in Fig. 5.33c–f.

The relatively low-grade morphology of the tumor cells is in favor of a metastasis. Primary gastric carcinoma with signet-ring cell features tends to show a higher nuclear grade. CK7 expression is common for all three tumors included in the differential considerations. However, a positive CK7 stain can rule out other tumors with plasmacytoid morphology, such as plasmacytic neoplasia or malignant melanoma. CK20 can be positive in urothelial carcinoma and occasionally gastric carcinoma. Negative CK20 reaction in this case does not rule in or rule out a diagnosis. E-cadherin decorates epithelial cells in a membranous pattern; however, this pattern of expression for E-cadherin is characteristically lost in lobular carcinomas. A positive GATA3 stain suggests a breast or urothelial primary. However, ER expression favors the breast in this setting.

The vast majority of the breast carcinomas express CK7, of course. When working on a CK7-positive metastatic tumor with unknown primary, especially in a female patient, breast carcinoma should always be included in the differential considerations. The immunomarkers may serve as breast organ-specific, including GATA3, ER, mammaglobin (MGB), and GCDFP-15. In metastatic breast carcinomas, the ER-positive rate is about 50%. Both GCDFP-15 and MGB suffer low sensitivities, reported in the ranges of 35–55% and 65–70%, respectively. Our data on tissue microarrays (TMAs) of 250 cases of invasive breast carcinomas, including ductal, lobular, and other special types, is even lower: 30% for GCDFP-15 and 50% for MGB. GATA3, at the current time, is the most optimal breast organ-specific immunomarker. The expression of GATA3 in CK7+ tumors was reported mainly in breast carcinoma, urothelial carcinoma, benign Brunner tumor of the ovary, and salivary gland tumors. Our published data reveal that GATA3 is expressed in 94% (138/147) of breast carcinomas overall and 69% (66/96) of ER-negative breast carcinomas. When working up a metastatic tumor, if a breast primary is considered, a panel of immunomarkers including CK7,

(continued)

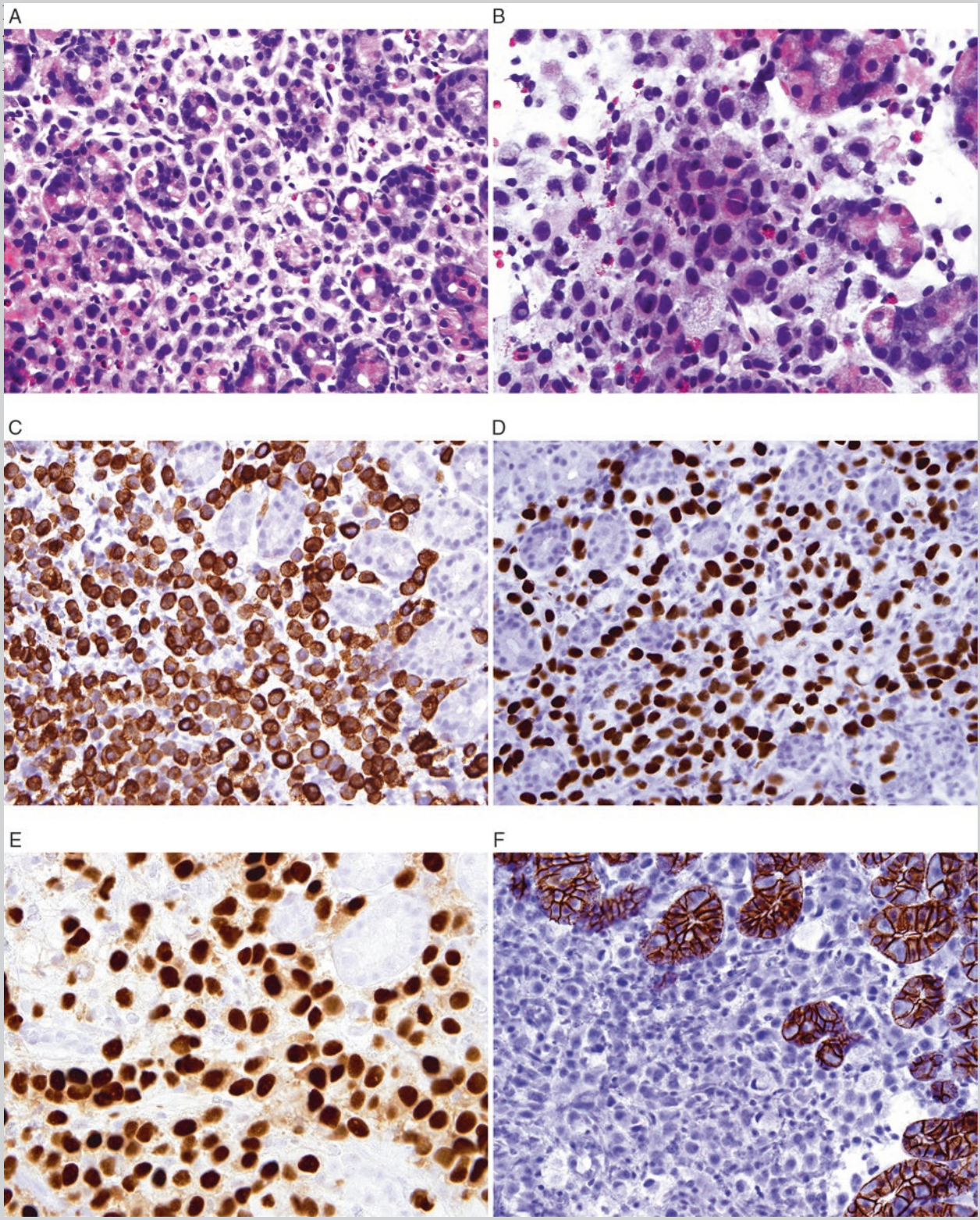

Fig. 5.33 (**a**–**f**) Metastatic lobular carcinoma of the breast to stomach. (**a**). An abnormal population of cells is present in the lamina propria and submucosa, singly as well as focally, in a single-file pattern, H&E; (**b**) the abnormal cells are plasmacytoid in appearance, relatively uniform, with small to prominent nucleoli. Occasional intracytoplasmic lumina are noted, H&E; (**c**) the tumor cells are positive for CK7; (**d**). Nuclear staining for GATA3; (**e**) positive for ER; (**f**) lack of membranous staining pattern for E-cadherin; note the gastric submucosal glands showing membranous staining for E-cadherin

Abbreviations List

Abbreviation	Full Text
ADH	Atypical ductal hyperplasia
ADH5	Breast marker cocktail consisting of CK5, CK14, p63, CK7, and CK18
ALK	Anaplastic lymphoma kinase
AR	Androgen receptor
Bcl (Bcl2, Bcl6)	B-cell CLL/lymphoma (2, 6)
Bcl2	B-cell CLL/lymphoma-2
BRCA1	Breast cancer 1
CDH1	Cadherin 1
CDK4	Cyclin-dependent kinase 4
CDX2	Caudal type homeobox 2
CK	Cytokeratin
c-kit	CD117
CNB	Core needle biopsy
D	Diastase
DCIS	Ductal carcinoma in situ
EGFR	Epithelial growth factor receptor
EMA	Epithelial membrane antigen
ER	Estrogen receptor
ERG	ETS-related gene
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
GATA3	GATA binding protein 3
GCDFP-15	Gross cystic disease fluid protein-15
GI	Gastrointestinal
Her-2/neu	Human epidermal growth factor receptor 2
HMWCK	High molecular weight cytokeratin
IHC	Immunohistochemistry
ILC	Invasive lobular carcinoma
IRF4/MUM1	Interferon regulatory factor 4/myeloma oncogene 1
IVD	Invasive ductal carcinoma
LMWCK	Low molecular weight cytokeratin
MALT	Mucosa-associated lymphoid tissue
MCA	Metaplastic carcinoma
MDM2	Mouse double minute 2 homolog
MEC	Myoepithelial cell
MGB	Mammaglobin
NOS	Not otherwise specified
NST	No special type
Pap	Papanicolaou stain
PAS	Periodic acid-Schiff
PAX	Paired box gene
PR	Progesterone receptor
PT	Phyllodes tumor
SMA	Smooth muscle actin
SMM-HC	Smooth muscle myosin heavy chain
TDLU	Terminal duct lobular unit
TMA	Tissue microarray
UDH	Usual ductal hyperplasia
WHO	World Health Organization

Suggested Reading

Cytology/Fine Needle Aspiration

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