Invasive Carcinoma of the Breast: Special Types

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List of Frequently Asked Questions

1. **What is invasive cribriform carcinoma and what are its key diagnostic features?**

Invasive cribriform carcinoma is characterized histologically by the cribriform growth pattern of the invasive carcinoma [1, 2]. The glands are morphologically similar to those of cribriform-type ductal carcinoma in situ (DCIS), manifested as fenestrated, rounded, or angulate infiltrating glands. The tumor cells are usually low to intermediate nuclear grade. Mucinous secretion is sometimes present within the lumens, as well as microcalcifications. The surrounding stroma is often fibroblastic, sometimes associated with osteoclast-like giant cells [3]. Pure invasive cribriform carcinoma has >90% of the tumor with this cribriform morphology. Areas of tubular growth pattern are commonly seen, and those with minor tubular component (<50%) are also included in this category. If the minor component is of another morphological type other than tubular pattern, they are regarded as being "mixed type" [1, 2].

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2. **What is the most common tumor profile status of invasive cribriform carcinoma?**

As a well-differentiated carcinoma, invasive cribriform carcinoma is usually estrogen receptor (ER) positive, progesterone receptor (PR) positive, and human epidermal growth factor receptor 2 (HER2) negative. See Fig. 3.1a–g.

3. **Does invasive cribriform carcinoma have a better prognosis compared to other types of breast cancer?**

Compared to invasive ductal carcinoma of no special type, invasive cribriform carcinoma has a better and favorable prognosis [1, 2].

4. **What is tubular carcinoma and what are its key diagnostic features?**

Tubular carcinoma is characterized by haphazardly arranged small tubules that closely resemble normal ductules. The tubules are angulated, oval or round in shape, lined by a single layer of epithelial cells with low-grade nuclear atypia and enclosed in an open lumen. There is no consensus for required proportion (75–100%) of tubule formation for the diagnosis of tubular carcinoma. But practically, ≥90% is needed to render a diagnosis of pure tubular carcinoma. When the tubular component involves <90% of the tumor, it is referred to as a "mixed" tubular carcinoma or invasive ductal carcinoma of no special type with tubular features. Complex architecture, marked nuclear pleomorphism, and high mitotic activity are contradictions for the diagnosis of tubular carcinoma [4].

Most tubular carcinomas are 2 cm or less in size. Under low-power examination, the stroma admixed with tubular carcinoma is usually desmoplastic or fibroelastotic, different

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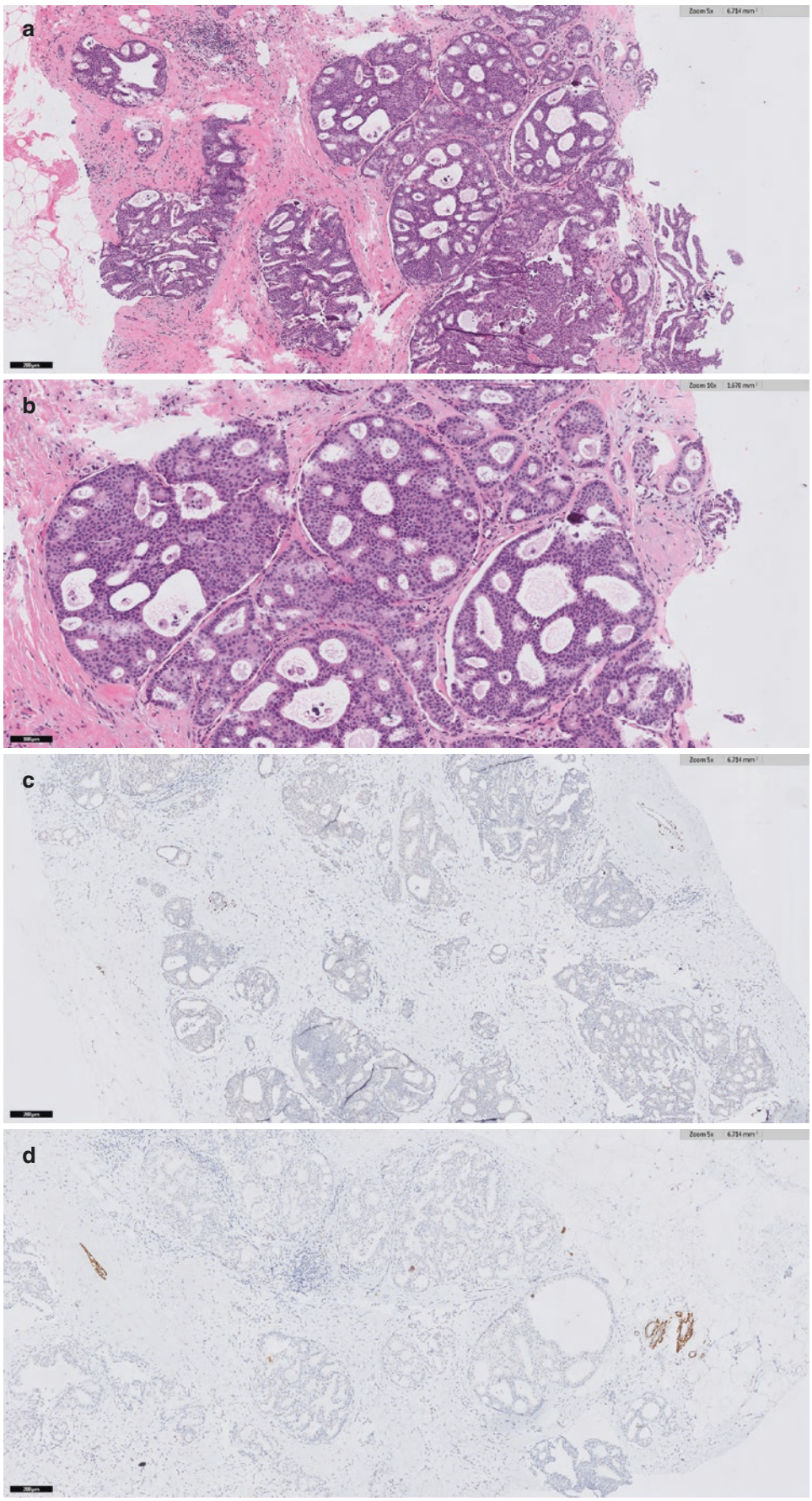


Fig. 3.1 Invasive cribriform carcinoma. Carcinoma cells grow in cribriform pattern with microcalcification (**a**). Carcinoma cells show low-grade nuclei at high magnification (**b**). p40 (**c**), SMMS (**d**), and CK5 (**e**) immunostains show the absence of myoepithelial cell layers around carcinoma cells. Carcinoma cells are strongly and diffusely positive for ER (**f**) and PR (**g**)

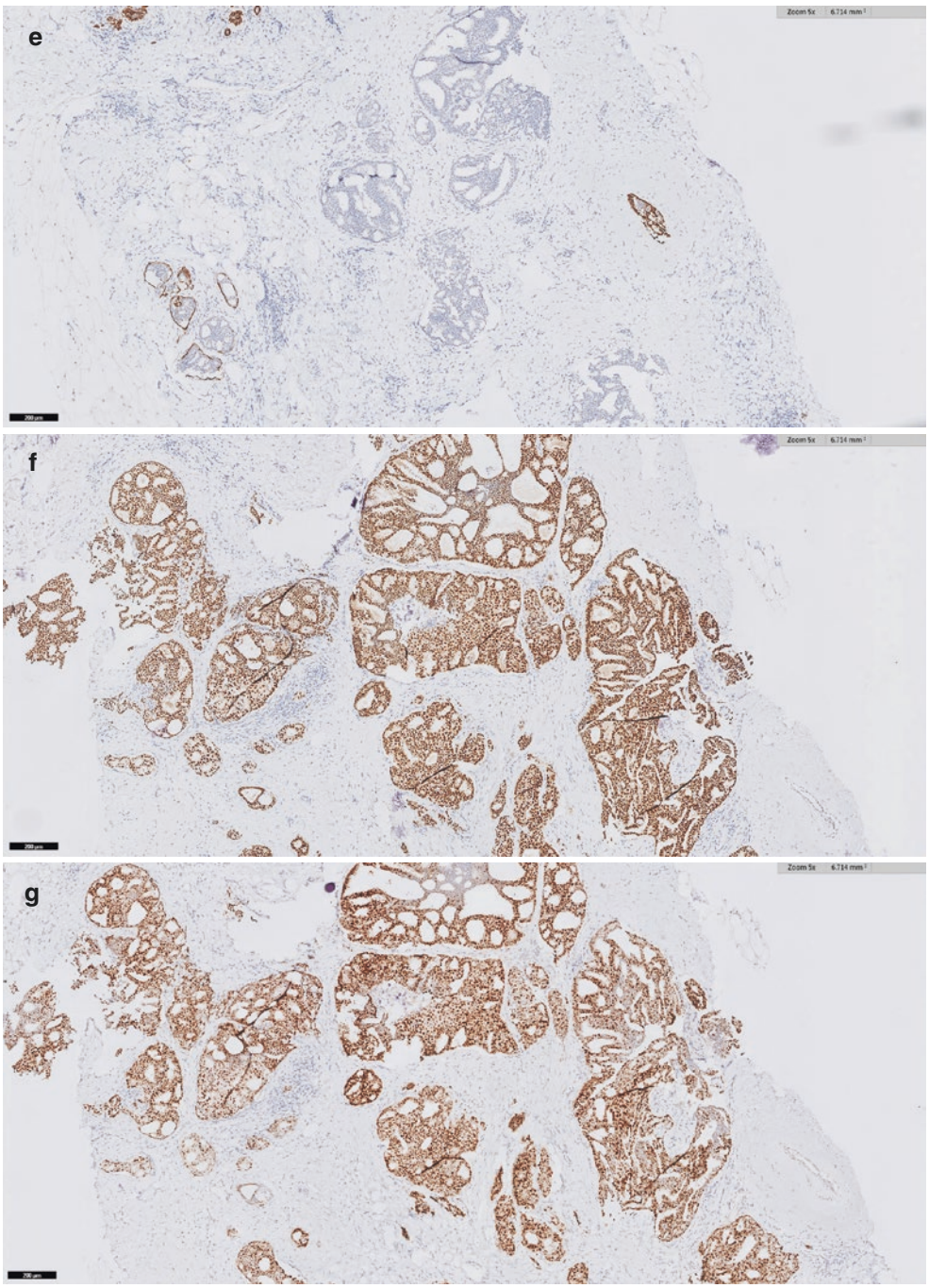


Fig. 3.1 (continued)

from the surrounding benign breast stroma, providing a useful clue for the diagnosis.

Tubular carcinoma is frequently associated with columnar cell lesions, ranging from columnar cell change (CCC), columnar cell hyperplasia (CCH), to CCC or CCH with atypia. DCIS and LCIS are also seen. DCIS arising in the background of CCC often has a low nuclear grade and cribriform or micropapillary architecture. The commonly associated CCC, LCIS (classic type), and invasive tubular carcinoma have been referred to as the "Rosen triad" [5].

5. **What is the most common tumor profile status of tubular carcinoma?**

Tubular carcinoma is usually ER positive, PR positive, and HER2 negative. See Fig. 3.2a–d.

6. **Does tubular carcinoma have the best prognosis among all types of breast cancer?**

Tubular carcinoma has an excellent prognosis. Most studies suggest that patients with tubular carcinoma have a longer disease-free survival than patients with invasive ductal carcinoma of no specific type. In some studies, it is comparable to that of age-matched set of women without breast cancer or the general population [4, 6].

7. **What is mucinous carcinoma and what are its key diagnostic features?**

Mucinous carcinoma is characterized by clusters of tumor cells floating in a pool of extracellular mucin. The relative proportion of mucin and tumor cells is variable. The diagnosis of pure mucinous carcinoma is reserved for at least 90% of the tumor showing mucinous component. Those in which the mucinous component comprising 50–90% of the lesions are regarded as "mixed" mucinous carcinoma. Invasive ductal carcinomas with less than 50% of the mucinous component are best referred to as having focal mucinous differentiation.

Pure mucinous carcinoma is uncommon and accounts for about 2% of invasive breast carcinomas [4]. The mean age of patients with invasive mucinous carcinoma is in general older (mean age is 71 years) than those with breast cancer of no special type [7].

Pure mucinous carcinoma grossly has a characteristic gelatinous and glistening appearance on the cut surface due to the presence of abundant extracellular mucin. Microscopically, the tumor cells form small clusters, large sheets, or with papillary or cribriform configurations floating in the pool of mucin. The tumor cells are usually low to intermediate nuclear grade. High nuclear grade is rare and should be emphasized in the diagnostic pathology report because the clinical course may be worse than usual pure mucinous carcinoma. The periphery of most tumors is characterized by a pushing border due to their slow growth. When assessing the margin status, the presence of extracellular mucin without tumor cells at the margin is considered positive.

Based on the morphology, mucinous carcinoma has been subclassified as type A and type B [8]. Overall, mucin is more abundant in type A than in type B tumors, which show hypercellularity. Type B tumors also show frequent neuroendocrine differentiation. Currently, no clinical implications have been noted in separating these subtypes, and the subtyping is barely mentioned in routine diagnosis.

A micropapillary variant of pure mucinous carcinoma has been reported [9, 10]. The tumor cells form micropapillae. Epithelial membrane antigen (EMA) immunostain is positive in the outer surface of the micropapillae, indicating the reversed polarity of the epithelium, similar to that in invasive micropapillary carcinoma of the breast. The variant seems to have a more aggressive behavior than conventional pure mucinous carcinoma and has a higher frequency of lymph node metastasis.

Radiographically, mucinous carcinoma usually mimics fibroadenoma, a common benign breast tumor.

8. **What is the most common tumor profile status of mucinous carcinoma?**

The majority of pure mucinous carcinomas are ER positive, PR positive, and HER2 negative. Mucinous carcinomas predominantly express MUC2 and MUC6 [11]. See Fig. 3.3a, b.

9. **Does mucinous carcinoma have a better prognosis compared to other types of breast cancer?**

Invasive mucinous carcinoma has a favorable prognosis compared to breast cancer of no special type. The accumulation of extracellular mucin serves as a barrier to the spread of tumor cells. Major prognostic factors are similar to most types of breast carcinoma. Nodal status is the most significant prognostic factor; others include age at diagnosis, tumor size, status of PR expression, and nuclear grade.

10. **What is invasive micropapillary carcinoma and what are its key diagnostic features?**

Invasive micropapillary carcinoma is characterized by tumor cells forming micropapillae and tubuloalveolar or morule-like clusters without fibrovascular cores, surrounded by clear stromal space. There is no universal criterion to distinguish mixed and pure invasive micropapillary carcinoma. In practice, pure invasive micropapillary carcinoma refers to those with at least 75% of the tumor showing micropapillary configuration. The cell clusters display reversed polarity with the luminal aspect of the cells present on the outer surface of the clusters close to the stroma. This can be well demonstrated by epithelial membrane antigen (EMA) immunostaining the cell membrane facing toward the stroma. MUC1, like EMA, also stains the similar pattern. The nuclear grade of invasive micropapillary carcinoma is usually intermediate to high. The clear spaces around the tumor cells mimic lymphovascular invasion, but they are not lined by endothelial cells. They are usually attributed to artifacts during tissue processing. However, invasive micropapillary carcinomas do have a higher frequency of lymphovascular invasion [12], and the tumor emboli in the lymphovascular spaces show similar micropapillary morphology.

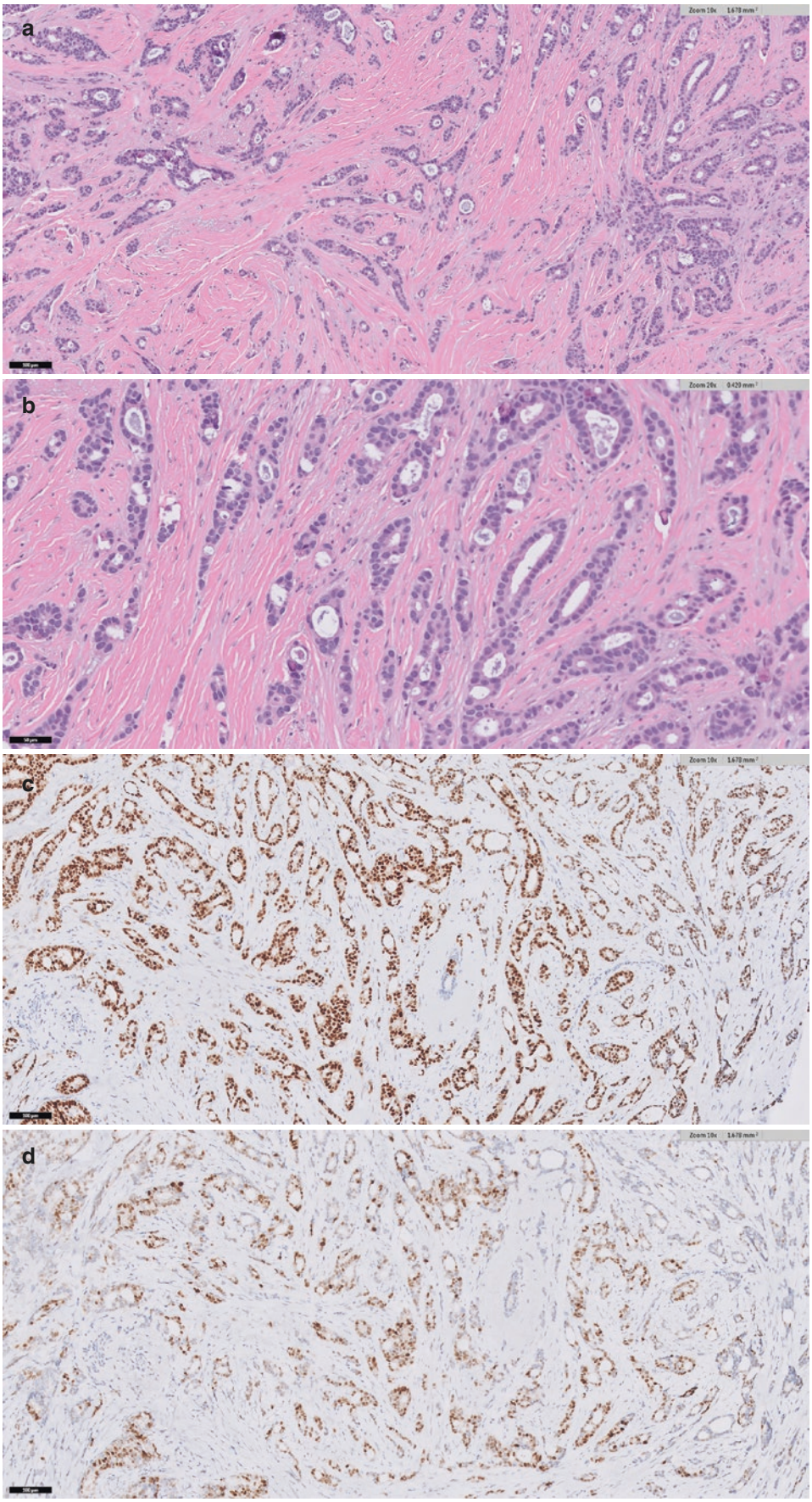


Fig. 3.2 Invasive tubular carcinoma. (**a**) The majority of carcinoma cells grow in tubules, which are angulated, irregular, and infiltrating into the surrounding stroma. (**b**) Carcinoma cells show low-grade nuclei at high magnification. (**c**) Positive for ER (strong and diffuse). (**d**) Positive for PR (variable)

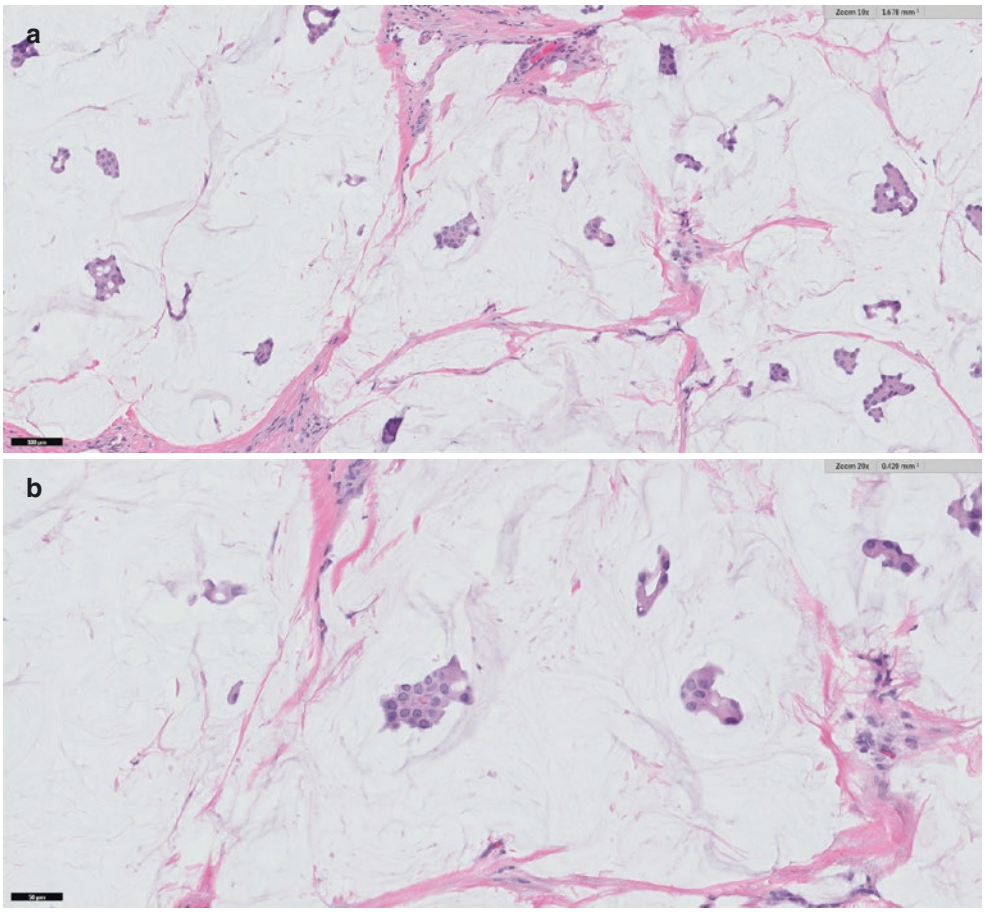


Fig. 3.3 Invasive mucinous carcinoma. (**a**) Small clusters of carcinoma cells are floating in a mucinous pool. (**b**) Carcinoma cells show low-grade nuclei at high magnification

11. **What is the most common tumor profile status of invasive micropapillary carcinoma?**

Most invasive micropapillary carcinomas are positive for ER and PR. HER2 protein is variably overexpressed in a fraction of tumors. See Fig. 3.4a, b.

12. **Does invasive micropapillary carcinoma have an increased risk for nodal metastasis and a worse prognosis compared to other types of breast cancer?**

When compared with invasive ductal carcinoma of no special type, invasive micropapillary carcinoma has a higher frequency of lymphovascular invasion and lymph node metastasis, and more lymph nodes are involved [13]. Patients usually have a significantly shorter disease-free survival (DFS) and overall survival (OS) [14]. But when stratified for the number of involved lymph nodes and other prognostic factors, patients seem to have similar survival rates to those with non-micropapillary invasive ductal carcinoma [15]. Unlike other special-type breast carcinomas, the poor prognosis associated with this entity appears to be the same whether the micropapillary component is present focally or diffusely within a tumor [15].

13. **What is invasive apocrine carcinoma and what are its key diagnostic features?**

Invasive apocrine carcinoma is composed of tumor cells with apocrine differentiation of tumor cells, characterized with abundant densely eosinophilic, granular, or vacuolated cytoplasm, large nuclei, and often prominent nucleoli. Compared to benign apocrine cells, apocrine tumor cells demonstrate an increase in nuclear size, significant nuclear pleomorphism, irregular nuclear membrane, hyperchromatic nuclei, and one or more macronucleoli. Features of cytoplasm are similar to those in the benign apocrine cells. Pure apocrine carcinoma is reserved for a tumor consisting of almost all malignant apocrine cells. If only a portion (>10%) of the tumor consists of malignant apocrine cells, then it can be considered as invasive carcinoma with apocrine differentiation. Apocrine differentiation can be seen in up to 30% of all breast cancers [16].

It has been reported that some benign cystic and papillary apocrine lesions show little or no detectable surrounding myoepithelial cells [17]. Without cytological atypia, the absence of immunoreactive myoepithelial layer is not an absolute criterion for the diagnosis of invasive apocrine carcinoma.

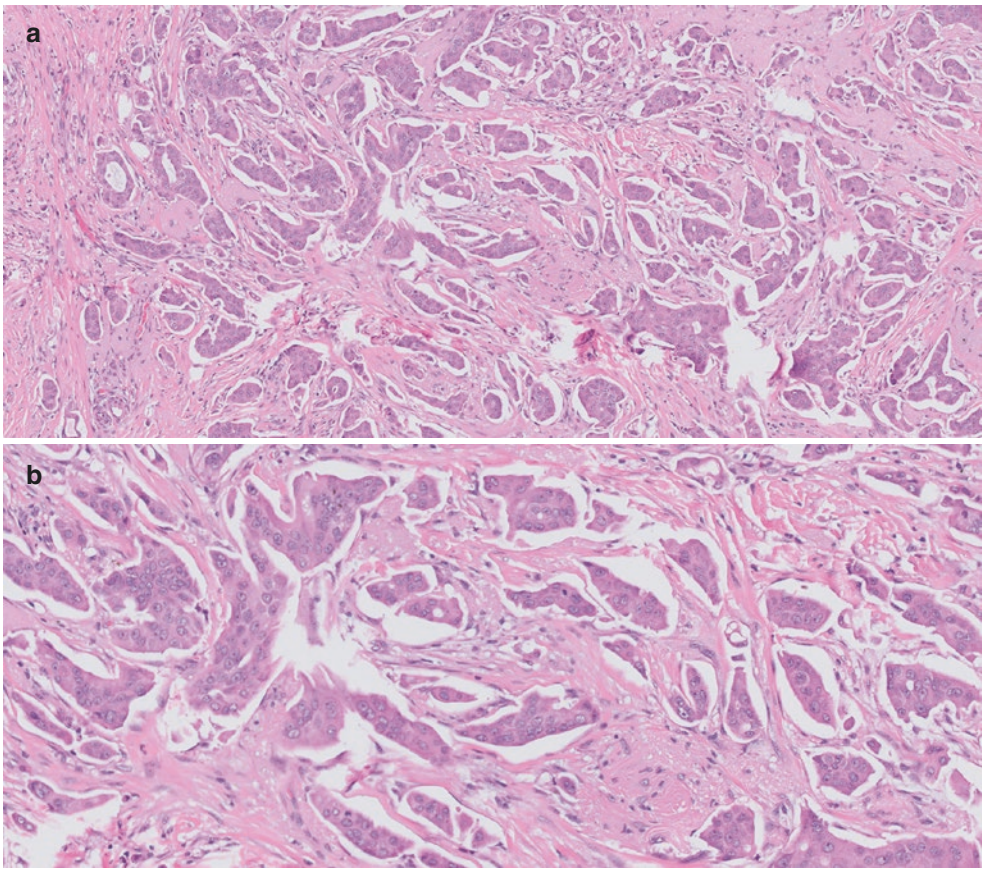


Fig. 3.4 Invasive micropapillary carcinoma. (**a**) Carcinoma cells grow in a micropapillary pattern without fibrovascular cores. There are empty spaces around the clusters of carcinoma cells. (**b**) Carcinoma cells show variable grade nuclei at high magnification

14. **Is there any difference on the tumor profile in apocrine carcinoma compared to other types of breast cancer?**

Most invasive apocrine carcinomas are negative for ER and PR, but positive for androgen receptor (AR). Some studies have regarded only tumors with apocrine morphology and ER-negative, PR-negative, and AR-positive immunoprofile as pure apocrine carcinoma. About half of pure apocrine carcinomas are HER2 negative and the remaining HER2 positive [18]. Immunohistochemical studies may be used to confirm the diagnostic impression of apocrine differentiation but are not essential to establish the morphological diagnosis of apocrine carcinoma. See Fig. 3.5a, b.

GCDFP-15 (BRST-2) immunostain is positive in a high percentage of invasive apocrine carcinoma [16].

15. **Does invasive apocrine carcinoma carry a worse prognosis than other types of breast cancer?**

The prognosis of invasive apocrine carcinoma is related to tumor grade, size, lymph node status, and tumor stage, similar pathologic parameters as those of non-apocrine breast carcinomas.

16. **What is mammary carcinoma with osteoclast-like giant cells and what are its key diagnostic features?**

Carcinomas with osteoclast-like giant cells are characterized by the presence of multinucleated osteoclast-like giant cells in the stroma. These cells are non-neoplastic, while the carcinomatous components can be a variety of histological types. Frequently, the carcinomatous components are invasive ductal carcinoma of no special type with a cribriform growth pattern, but other histological types such as lobular, squamous, papillary, mucinous, and metaplastic carcinoma have also been reported [19–22]. Grossly, the tumors display red-brown to dark-brown color, which is due to the presence of hemorrhage and hemosiderin-laden macrophages in the tumors. Microscopically, the giant cells are variable in size as well as the number of nuclei. They are cytologically bland with no mitotic activity. Hemorrhage in the stroma is commonly seen in the tumor, which may be a clue for the presence of osteoclast-giant cells under low-power examination. These giant cells may also be present in metastatic and recurrent tumors.

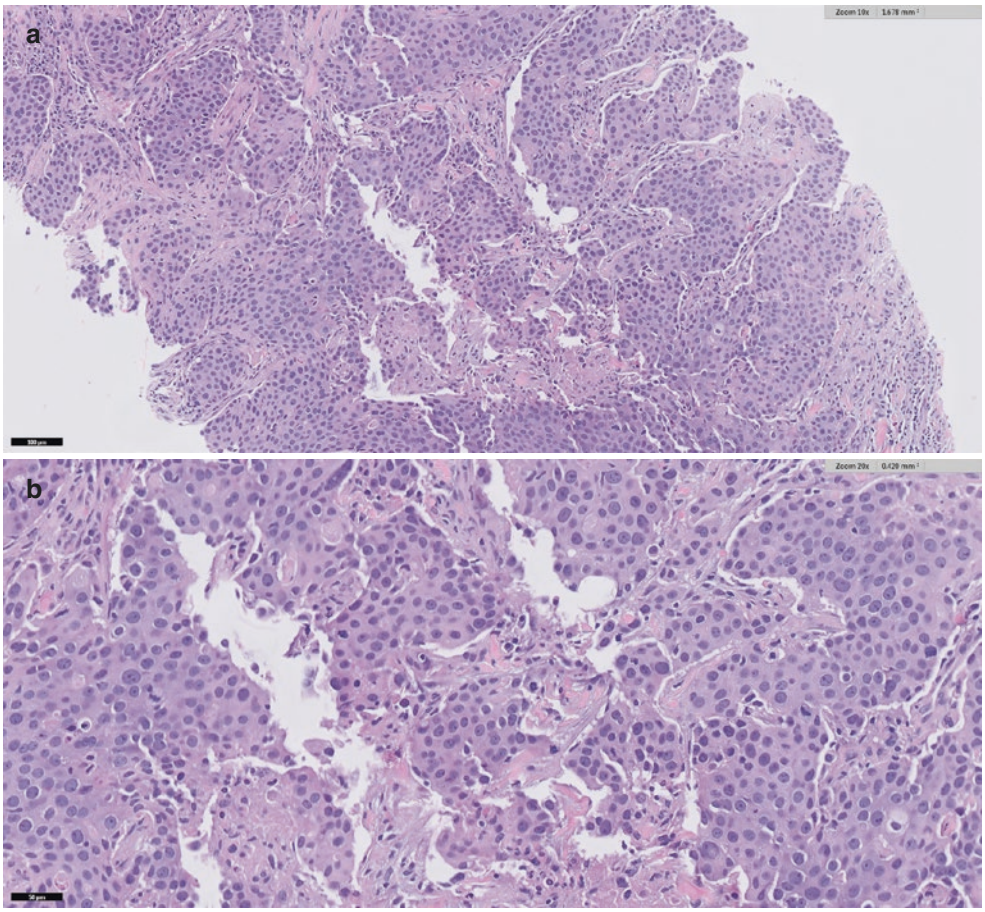


Fig. 3.5 Invasive apocrine carcinoma. (**a**) Carcinoma cells grow in solid nests with minimal intervening stroma. (**b**) Carcinoma cells show intermediate to high nuclear pleomorphism with abundant eosinophilic cytoplasm at high magnification

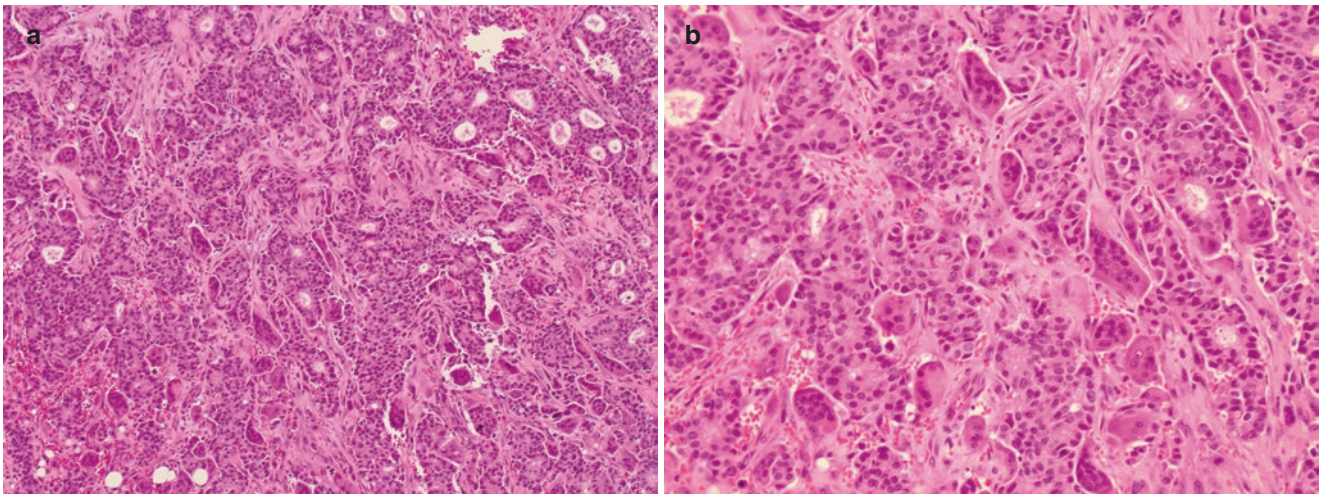


Fig. 3.6 Invasive mammary carcinoma with osteoclast-like giant cells. (**a**) Carcinoma cells grow in solid nests intermixed with osteoclast-like giant cells. (**b**) Osteoclast-like giant cells are large with abundant cytoplasm, multiple nuclei, and prominent nucleoli

17. **What is the tumor profile status of mammary carcinoma with osteoclast-like giant cells?**

The osteoclast-like giant cells in the carcinoma are of histiocytic lineage, which express CD68, acid phosphatase, nonspecific esterase, and lysozyme, and are negative for S100, actin, and keratin [23, 24]. See Fig. 3.6a, b. However, the mechanism by which they are formed is still unknown.

The tumor profile status of the carcinoma depends on the histological type of its carcinomatous component.

18. **What is the prognosis of mammary carcinoma with osteoclast-like giant cells?**

Lymph node metastases are seen in about one third of the cases, and the 5-year survival rate is around 70% [24]. The presence of osteoclast-like giant cells does not carry any specific prognostic implications. Prognosis is related to the histologic and immunophenotypic features of the associated carcinoma.

19. **What is invasive ductal carcinoma with medullary features and what are its key diagnostic features?**

In the 2003 World Health Organization (WHO) Classification of Tumors of the Breast, medullary carcinoma was defined as a "well circumscribed carcinoma composed of poorly differentiated cells with scant stroma and prominent lymphoid infiltration" [25]. The classical morphologic features include a well-circumscribed smooth rounded pushing border, a syncytial growth pattern greater than 75% of the tumor (broad anastomosing sheets of tumor cells with indistinct cell borders), diffuse lymphoplasmacytic infiltrates within the tumor, and, at greater than 75% of the tumor periphery, a high degree of nuclear pleomorphism, prominent nucleoli, and a brisk mitotic activity. Breast fibroglandular tissue should not be present within the invasive carcinoma [26]. In the most recent 2012 edition of the WHO classification, the term of this entity was revised to invasive ductal carcinoma with medullary features (see Fig. 3.7a, b), which also includes "atypical medullary carcinoma" referring to tumors that do not fulfill all the diagnostic criteria [27].

20. **What is the most common tumor profile and genomic abnormality of invasive ductal carcinoma with medullary features?**

Invasive ductal carcinomas with medullary features are often triple-negative breast cancers with a basal-like phenotype expressing CK5/6, CK14, and EGFR [28–31]. These tumors are often associated with *BRCA1* mutations (in up to 60% of tumors), whereas less frequently associated with *BRCA2* mutations [27]. About 11% of patients showed *BRCA1*germline mutations. In addition, invasive ductal carcinoma with medullary features shows more frequent genomic instabilities, aneuploid or polyploid, and *p53* mutations than invasive ductal carcinoma NOS [27].

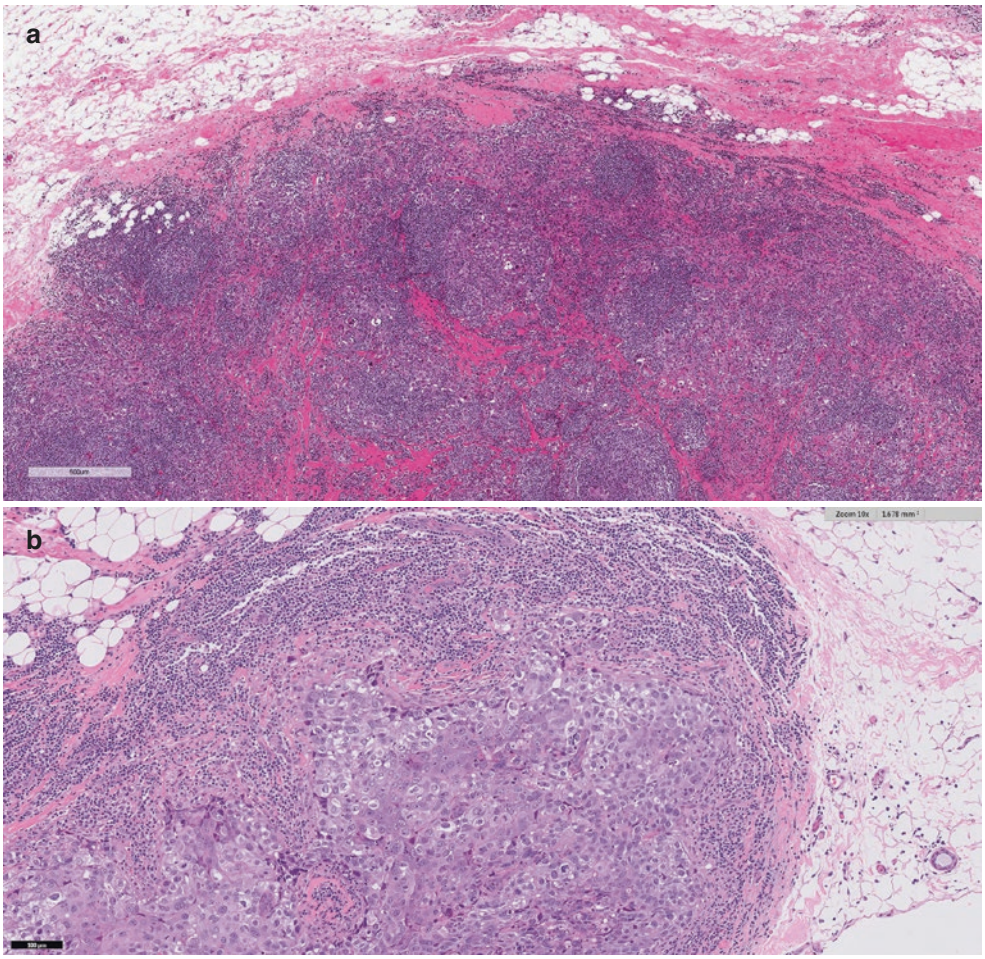


Fig. 3.7 Invasive ductal carcinoma with medullary features. (**a**) Carcinoma with well-circumscribed border and prominent lymphocytic infiltrates at the periphery. (**b**) Syncytial growth pattern of anaplastic tumor cells admixed with lymphoplasmacytic cells

21. Does invasive ductal carcinoma with medullary features carry a better prognosis?

Invasive ductal carcinoma with medullary features has been considered a distinctive subgroup of triple-negative carcinomas with a favorable prognosis despite its high-grade morphology. However, it is necessary to adhere to strict morphologic criteria for the diagnosis of this tumor in order to predict its better prognosis [31–36].

Recently, it has been reported that breast invasive carcinomas with prominent lymphocytic infiltrates (also called tumor infiltrating lymphocytes, or TILs) have better prognosis and response to neoadjuvant chemotherapy, especially in high-grade HER2-positive and triple-negative breast carcinoma [37–39]. The relatively good outcome seen in patients with this tumor may result from prominent lymphocytic infiltrates rather than an inherently better prognosis. Therefore, most breast pathologists prefer to diagnose invasive ductal carcinoma with medullary features as a basal-like triple-negative carcinoma with prominent lymphocytic infiltrates.

22. What is invasive carcinoma with neuroendocrine features and what are its key diagnostic features?

In the 2003 WHO classification, neuroendocrine carcinomas of the breast were divided into solid neuroendocrine carcinoma, small cell/oat cell carcinoma, and large cell neuroendocrine carcinoma [25]. In the 2012 WHO classification, the term of the tumor was revised to carcinomas with neuroendocrine features, which was defined as carcinomas with neuroendocrine differentiation exhibiting morphology similar to that of neuroendocrine tumors of the lung and gastrointestinal tract. No definitive threshold for neuroendocrine marker positivity was required [27].

Histologically, these tumors can be classified into three categories: well-differentiated neuroendocrine tumor (WD-NET), poorly differentiated neuroendocrine carcinoma/small cell carcinoma (PD-NEC/SCC), and invasive breast carcinoma with neuroendocrine differentiation (IBC-NED). Morphologically, WD-NET consists of cellular solid expansile nests and trabeculae separated by delicate fibrovascular stroma, similar to NET from other sites. The tumor cells are usually spindled, plasmacytoid, or polygonal with abundant granular or clear vacuolated cytoplasm [40–42]. The nuclear features include classic smooth nuclear borders and salt-and-pepper chromatin seen in carcinoids of other sites. PD-NEC/SCC is morphologically identical to its counterpart in other sites, consisting of densely packed hyperchromatic cells with scant cytoplasm and crushing artifact. Mitotic activity and necrosis are common [43–47]. IBC-NED can show variable morphology with only subtle cytologic/nuclear features of neuroendocrine differentiation. Neuroendocrine differentiation has been demonstrated in up to 30% of invasive ductal carcinomas, most commonly in mucinous carcinoma or solid papillary carcinoma [46]. Neuroendocrine differentiation can also be seen in invasive lobular carcinoma, especially alveolar variant [43]. See Figs. 3.8a–h and 3.9a–f.

23. What is the most common immunoprofile of invasive carcinoma with neuroendocrine features?

The diagnosis of neuroendocrine tumor usually requires demonstrating the expression of neuroendocrine markers. Synaptophysin and chromogranin A are the most commonly used neuroendocrine markers, with synaptophysin as the most sensitive and chromogranin A as the most specific immunohistochemical marker. Other neuroendocrine markers such as neuron-specific enolase (NSE) and CD56 may also be used, with less sensitivity and specificity. Neuroendocrine markers are usually diffusely positive in WD-NET and PD-NEC/SCC, while patchy and focal in IBC-NED. There is only limited information available regarding the expression of biomarkers (tumor profile) in invasive carcinomas with neuroendocrine features. Available data suggest that these tumors are most commonly ER positive, PR positive, and HER2 negative [27]. ER and PR are positive in the majority of WD-NETs and in greater than 50% of PD-NECs, but variable in IBC-NEDs [43–47]. Similar to SCCs of other sites, primary SCCs of the breast can show expression of thyroid transcription factor −1 (TTF-1) [47].

24. Do the neuroendocrine features of invasive carcinoma play a role in prognosis and treatment decision?

No specific guidelines exist for grading breast carcinomas with neuroendocrine features, and the 2012 WHO classification states that grading is unlikely to be clinically significant [27]. Currently carcinomas with neuroendocrine features of the breast are staged, histologically graded, and treated similarly to invasive carcinomas of no special type. The use of endocrine therapy or HER2 targeted therapy depends on the status of the tumor's ER, PR, and HER2 expressions [27]. No consensus has been reached on the prognosis for this group of tumors. Although many studies demonstrate a poor prognosis for breast carcinomas with neuroendocrine features, the results are conflicting, likely due to varying inclusion criteria [44, 47–50].

25. What is secretory carcinoma of the breast and what are its key diagnostic features?

Secretory carcinoma is a rare, special type of invasive carcinoma with a solid, microcystic, and tubular architecture and large amounts of extracellular and intracellular secretions. Historically, secretory carcinoma was known as "juvenile breast carcinoma" as it was originally identified

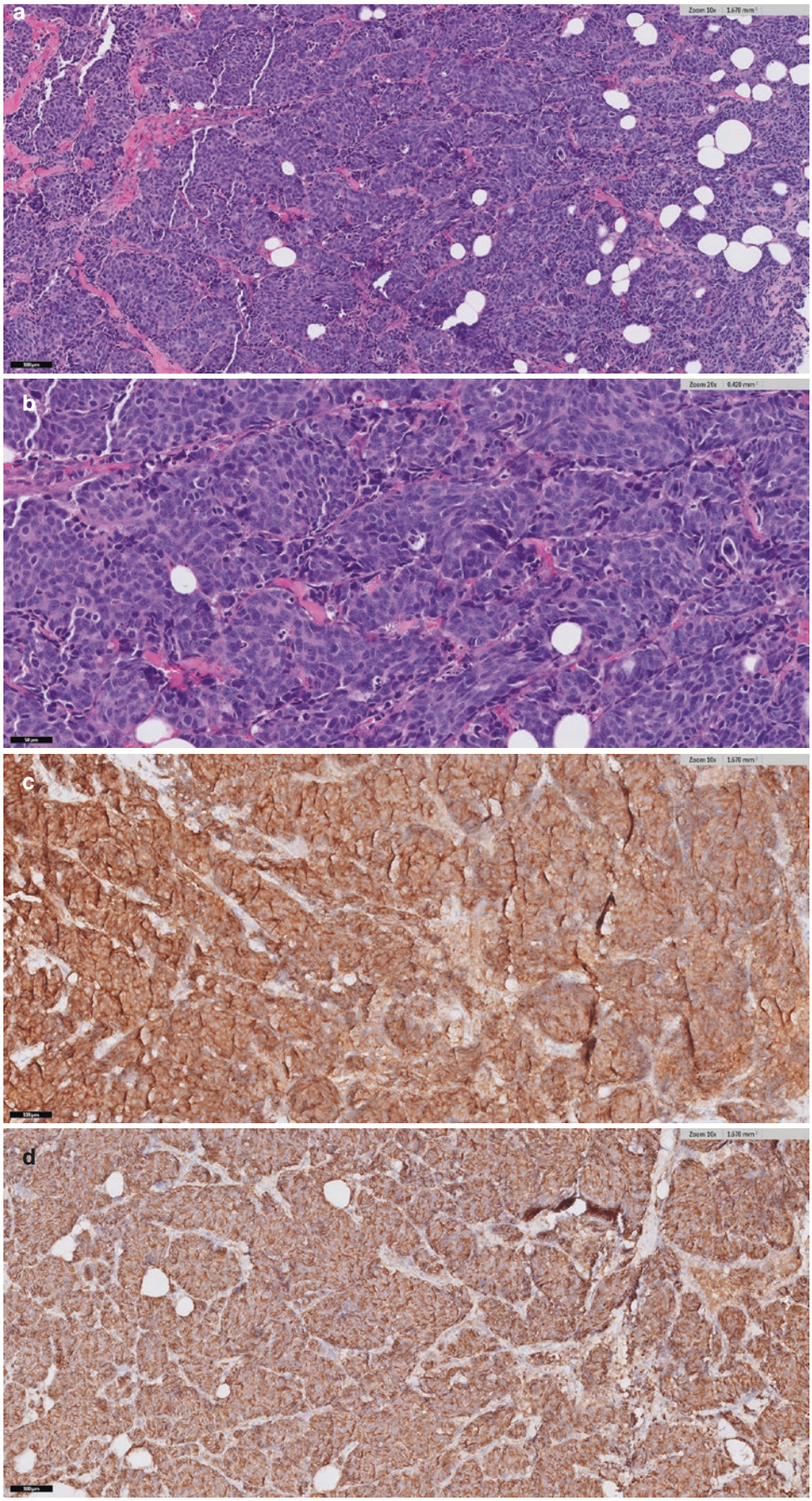
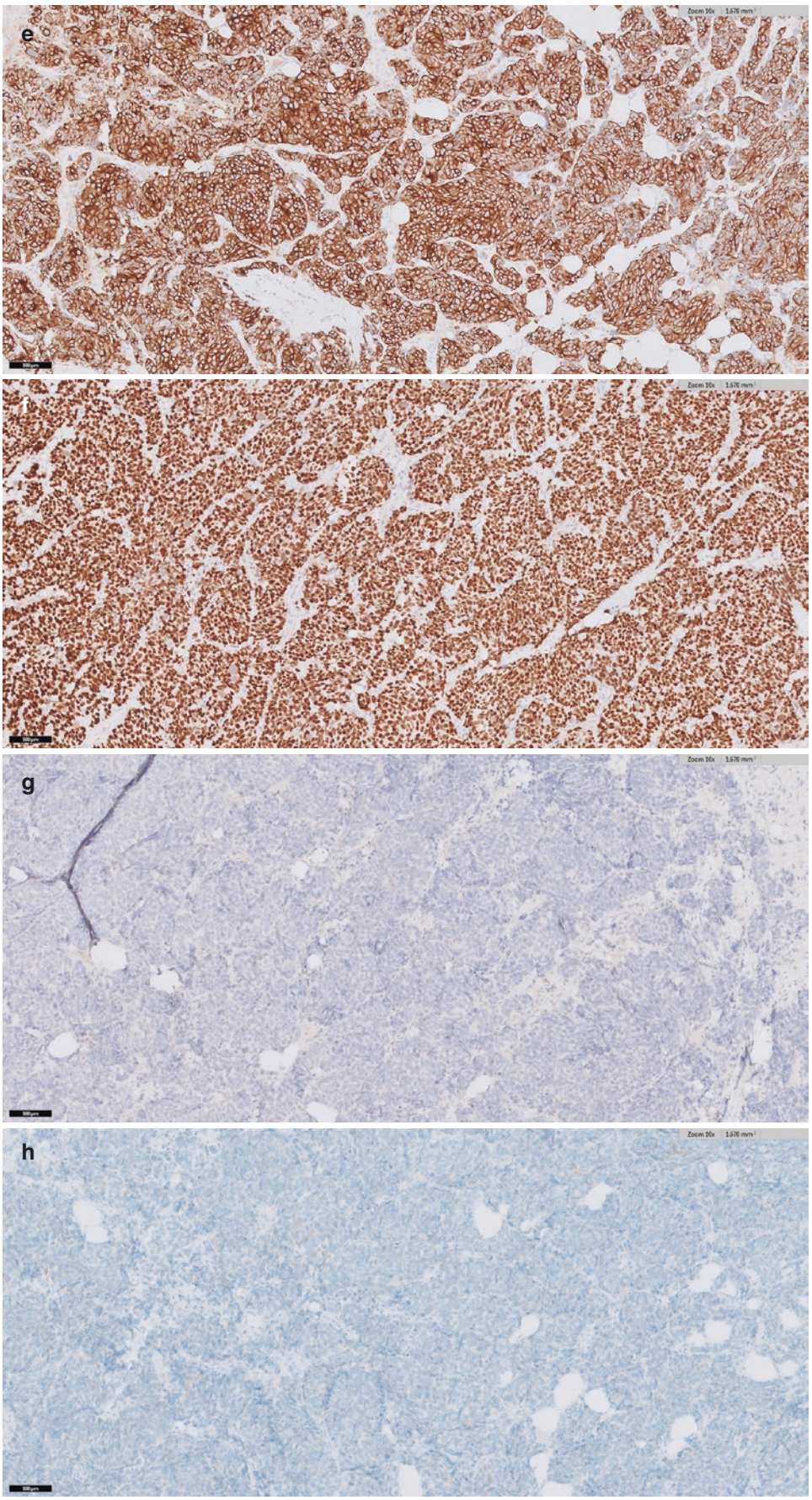


Fig. 3.8 Invasive ductal carcinoma with neuroendocrine features. The tumor is composed of epithelial cells in trabecular growth pattern (**a**). Neuroendocrine nuclear features are appreciated at high magnification (**b**). The tumor cells are positive for synaptophysin (**c**), chromogranin A (**d**), CK7 (**e**), and ER (**f**). The tumor cells are negative for PR (**g**) and HER2 (0-1+) (**h**)



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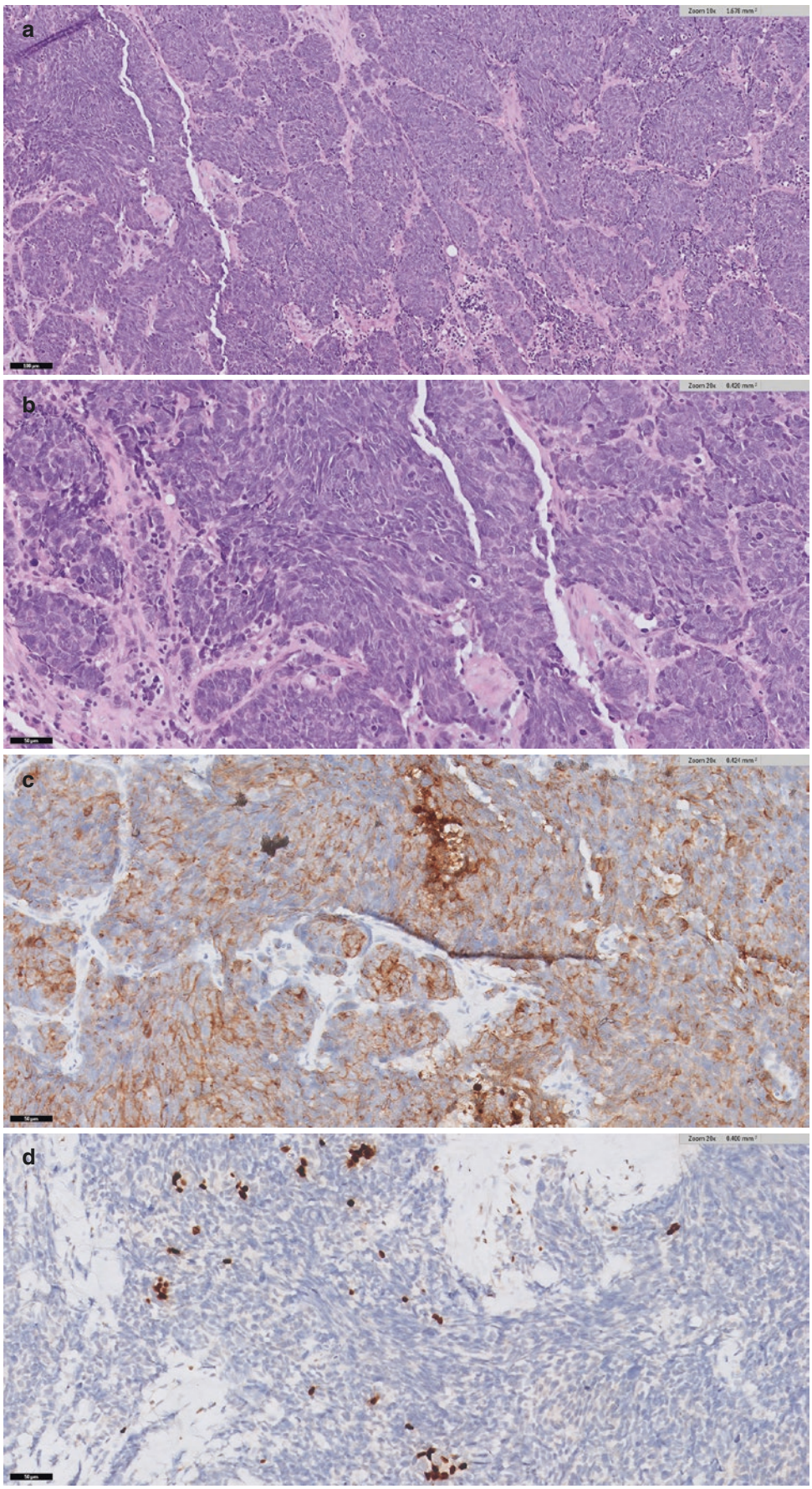
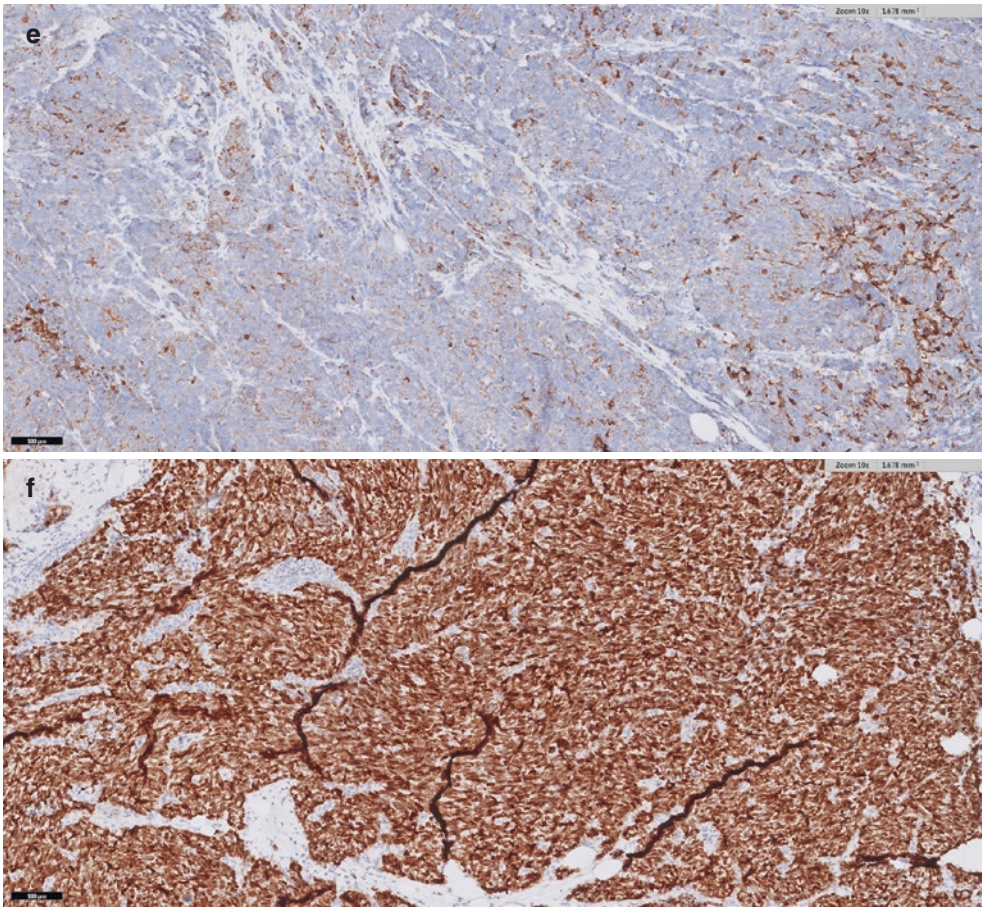


Fig. 3.9 Small cell carcinoma of the breast. The tumor is composed of nests of malignant epithelial cells with high nuclear to cytoplasmic ratio and hyperchromatic nuclei (**a**). Neuroendocrine nuclear features and nuclear molding (**b**). The tumor cells are positive for chromogranin A (**c**), GATA3 (very focal) (**d**), CK7 (patchy) (**e**), and TTF-1 (diffuse) (**f**)

Fig. 3.9 (continued)



in young patients. However, it has been reported in patients in a wide range of age (3–87 years) and a median age of 25 [27, 51].

Secretory carcinomas are composed of well-circumscribed nodules with tumor cells growing in three patterns: solid, microcystic, and tubular patterns. The microcystic pattern shows multiple small cysts resembling thyroid follicles. The tubular pattern shows tubules with lumen containing secretions. Most tumors contain all three patterns with various combinations. Tumor cells are usually uniform with round or angulated contour, mild nuclear atypia, and finely granular or vacuolated cytoplasm containing dense eosinophilic secretions. Signet ring cells can be present. Extracellular eosinophilic secretions are present within the lumens of tubules or microcysts. The eosinophilic secretions are positive for Periodic acid–Schiff (PAS), PAS diastase, and Alcian blue. Ductal carcinoma in situ with similar secretory features can be seen together with invasive secretory carcinoma [51–53]. See Fig. 3.10a, b.

26. What is the most common tumor profile status of secretory carcinoma?

Secretory carcinoma is significantly more common in females and usually presents as a mobile, palpable lesion in the subareolar region. Radiological breast imaging shows a well-circumscribed mass with regular margins, which can be easily mistaken as a fibroadenoma in young patients.

Like adenoid cystic carcinoma, secretory carcinoma is typically a low-grade triple-negative carcinoma with a basallike phenotype with expression of high-molecular-weight cytokeratins (CK5/6, 34E12, CK14, CK17), EGFR, and c-kit. Ki67 proliferative index is low (<15%). The carcinoma cells are also positive for S100 (strong and

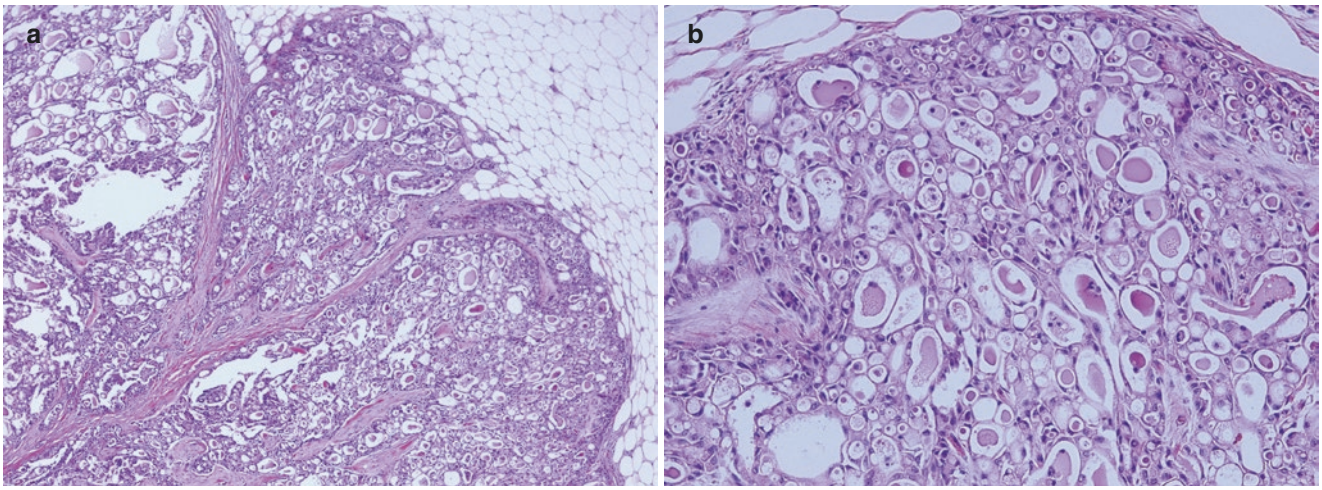


Fig. 3.10 Secretory carcinoma of the breast. (**a**) The tumor is composed of irregular lobules of eosinophilic cells separated by band-like fibroconnective tissue. (**b**) Dense eosinophilic secretion is intermixed with cytologically bland tumor cells. (Courtesy of Dr. Shi Wei, University of Alabama at Birmingham)

diffuse) and mammaglobin but negative for GCDFP-15 [54, 55].

27. **Is secretory carcinoma associated with a better prognosis?**

Secretory carcinoma usually manifests as an indolent, well-circumscribed mobile lump with excellent prognosis. Axillary lymph node metastases may occur but rarely involve more than three lymph nodes. Secretory carcinoma should not be confused with invasive ductal carcinoma with apocrine features, which is more common and has a more aggressive behavior [54].

28. **What is genetic abnormality in secretory carcinoma?**

Secretory carcinoma is characterized with chromosomal translocation t(12:15), resulting in the *ETV6NTRK3* fusion gene. The *ETV6* (*TEL) oncogene* encodes a transcription factor involved in development. The same translocation t(12:15) leading to *ETV6NTRK3* fusion gene also occurs in congenital fibrosarcoma and mesoblastic nephroma. FISH for the *ETV6* break apart probe or RT-PCR for the *ETV6NTRK6* fusion gene is a diagnostic tool for these tumors [56].

29. **What is adenoid cystic carcinoma of the breast and what are its key diagnostic features? How does one differentiate this entity from its counterpart in the head and neck?**

Adenoid cystic carcinoma (ACC) of the breast, an analogue to its counterpart in the salivary gland, accounts for only about 0.1% of all breast carcinomas. ACC predominantly affects postmenopausal women with a median age of 60 years in contrast to triple-negative invasive ductal carcinoma of no special type, which usually affects younger patients (<50 years) [27, 57, 58].

Similar to ACC of the salivary gland, mammary ACC is also composed of two populations of cells: glandular luminal cells and basaloid cells, with three growth patterns: tubular, cribriform, and solid. The basaloid cells have myoepithelial features. Eosinophilic hyaline or mucoid material may be seen in the lumen of cribriform structures and tubules. Carcinoma cells are usually small with scant cytoplasm and vesicular nuclei without prominent nucleoli. The mitotic activity is low [59]. Nottingham histologic grading system is also used for ACC of the breast. The solid variant of ACC is a high-grade variant with a more aggressive behavior. Tumor cells in this variant are larger with moderate to marked nuclear pleomorphism and increased mitotic activity [60]. Mammary ACC is a triple-negative breast cancer with a basallike phenotype. However, unlike most basal-like breast cancers that are high grade with an aggressive clinical course, mammary ACC except solid variant is usually low grade with an indolent clinical course.

ACC of the breast is morphologically similar to ACC of the salivary gland. Recent studies reveal that both mammary and salivary gland ACCs share a recurrent translocation t(6:9) which leads to the chimeric fusion gene *MYBNFIB* and may explain the phenotypic similarity [61, 62]. Clinical history is important to make a diagnosis of ACC of the breast instead of a metastasis from head/neck ACC.

ACCs should be graded using the standard Nottingham grading system with most exhibiting mild to moderate nuclear pleomorphism and low to moderate mitotic activity. As a result, most are classified as histologic grade one or two depending on the proportion of solid areas. See Fig. 3.11a–h.

30. **What is the immunohistochemical profile of adenoid cystic carcinoma of the breast?**

Mammary ACC cells are typically negative for ER, PR, and HER2 expressions; however, rarely they may exhibit weak ER or PR staining. Similar to ACC of the salivary gland, the basaloid cells of ACC of the breast are typically positive for myoepithelial markers (p40, p63, smooth muscle myosin, calponin, and S-100), basal cytokeratins (CK5 or CK5/6, CK14, and CK17), and epidermal growth factor receptor

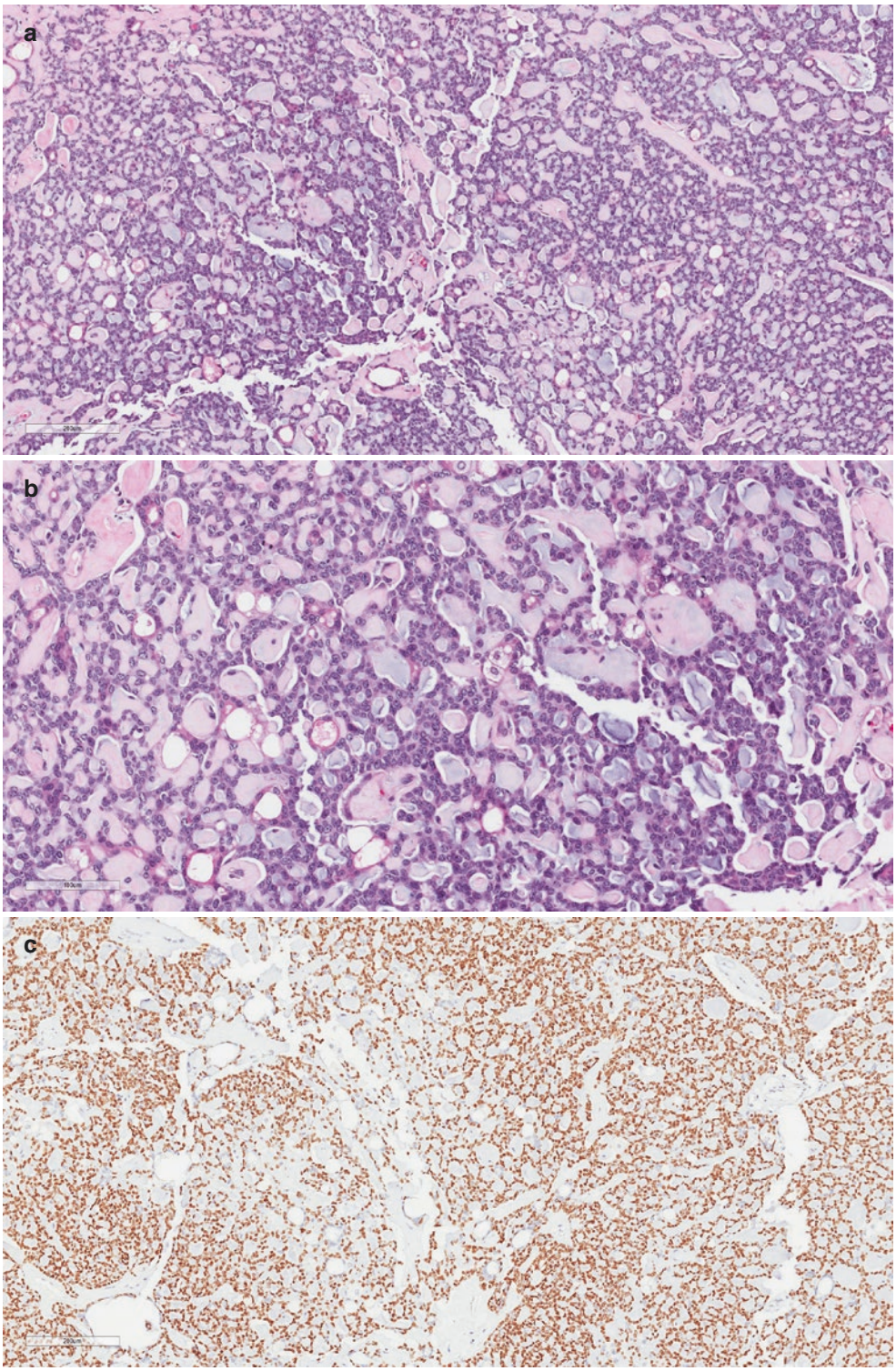
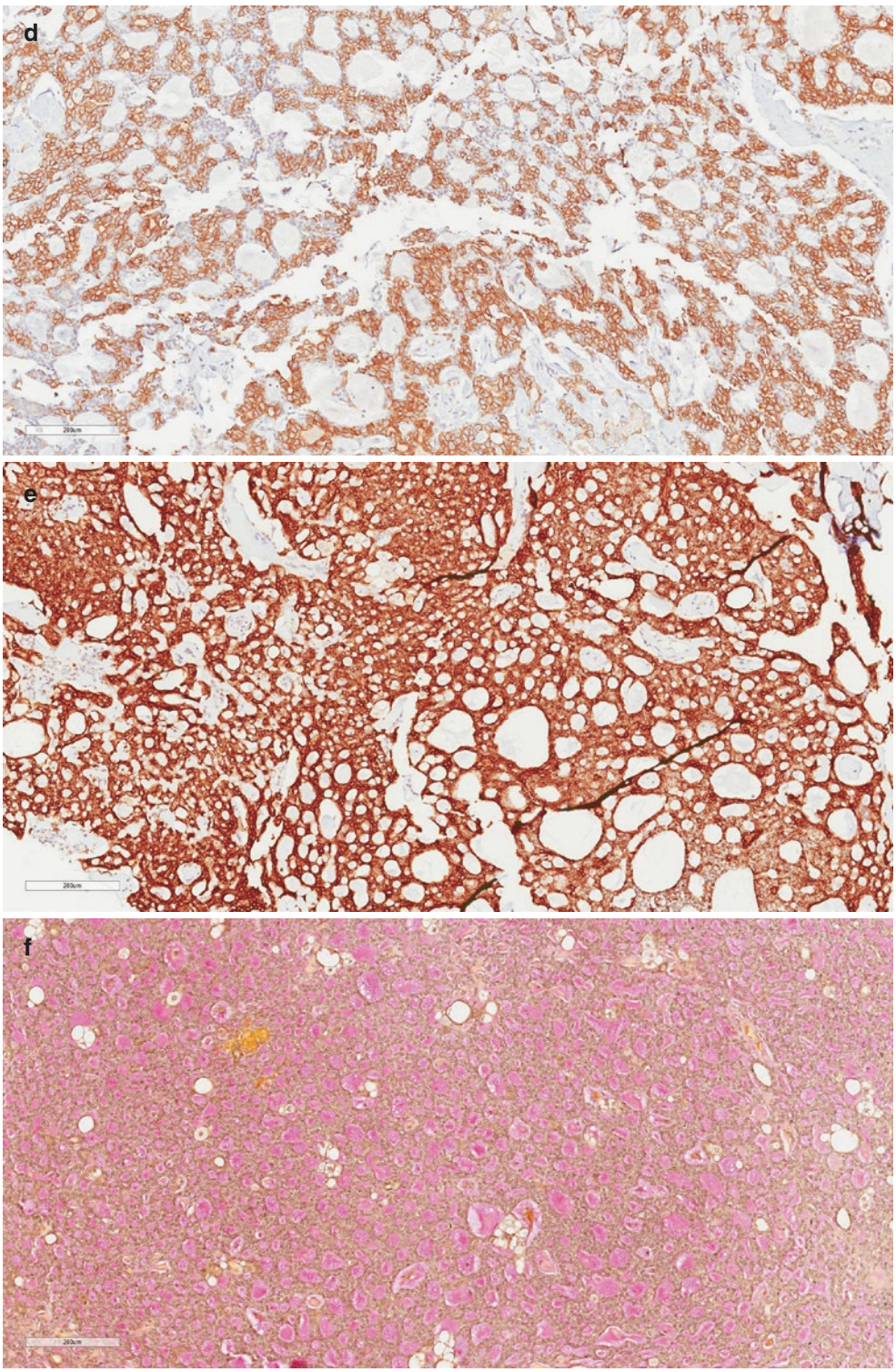


Fig. 3.11 Adenoid cystic carcinoma of the breast. Invasive cribriform nests of carcinoma cells surrounded by desmoplastic stroma (**a**). Cribriform nests with eosinophilic globular material (**b**). P63 stains basaloid cells of the tumor (**c**). Glandular luminal cells of the tumor are diffusely positive for c-Kit (CD117) protein (**d**) and CK5 (**e**). Mucicarmine stains the eosinophilic globular material (**f**). The tumor cells are negative for ER (**g**) and PR (**h**)



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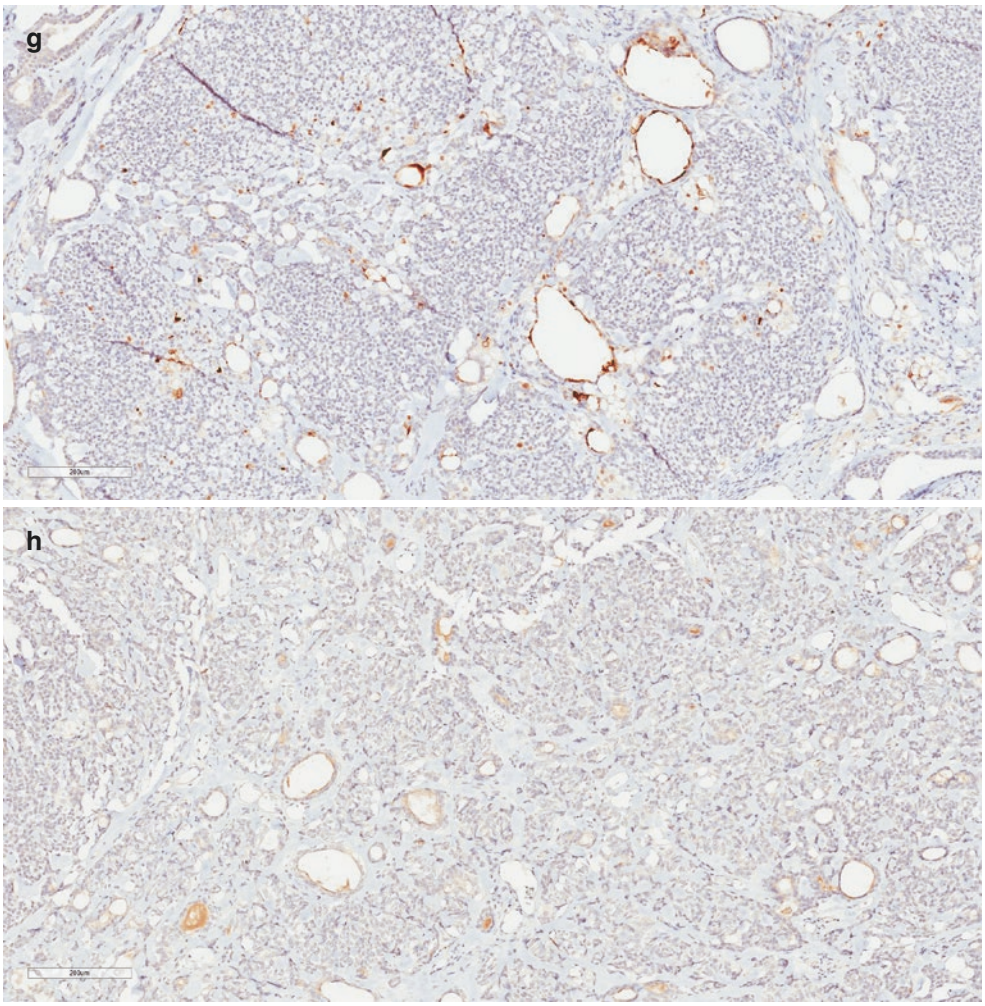


(EGFR) [63]. The glandular luminal cells are usually positive for CK7, CK8/18, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), and c-Kit (CD117) [64]. Interestingly, the CK5 or CK5/6 can be diffusely positive in the glandular luminal cells as well [27]. The proliferative index labeled with Ki-67 is usually low but can be variable depending on the variants or grading of the tumors. The immunohistochemical profile of the mammary ACC is very similar to that of the basal-like triple-negative breast carcinoma (TNBC); however, prognosis of mammary ACC is better than that of basal-like TNBC [65–67]. Androgen receptor (AR) is negative in ACCs, but positive in around 30% of basal-like TNBCs [68].

31. What are the molecular features of adenoid cystic carcinoma of the breast?

Similar to ACCs of the salivary gland, ACCs of the breast also demonstrate recurrent t(6;9)(q22-23;p23-24) translocation with a *MYB-NFIB* gene fusion, resulting in an oncogenic fusion protein with transcription factor function [61, 69, 70]. This finding is confirmed with MYB RNA overexpression, which can be demonstrated by in situ hybridization. Besides MYB translocation, other genomic alterations in ACC of the breast include gains of 1p36.12-p35.3, 11p15.5, 12p13.31, 16p13.3, and 19p13 and losses of 6p25.3-q26 and 9p11.1-q21.11 [69].

32. Is adenoid cystic carcinoma associated with a better prognosis?

ACC of the breast is usually indolent as a localized disease with a low frequency of axillary lymph node metastasis (<8%) [71]. However, the solid variant of mammary ACCs has relatively higher incidence of the nodal metastases than classical ACCs, which may indicate a more aggressive behavior [72]. Distant metastases may occasionally occur in patients with ACC of the breast (<20%), most commonly to the lung or the bone [71, 73].

A breast-conserving surgical approach with or without radiotherapy is usually recommended for the treatment of ACC. Most studies have demonstrated an excellent clinical outcome with 10-year survival exceeding 90% after the treatment. Patients with mammary ACC have a prolonged and

indolent clinical course even when they present with local recurrence or distant metastasis [74, 75].

In ACCs of the salivary glands, MYB expression has been associated with a better survival compared with MYB-negative ACCs [76]. However, the association of MYB expression with survival remains unknown in patients with ACC of the breast.

33. What are the differential diagnoses for adenoid cystic carcinoma of the breast?

The differential diagnosis of ACC includes other types of invasive breast carcinomas and intraductal lesions that have a cribriform growth pattern and collagenous spherulosis. Invasive cribriform carcinoma can be confused with ACC, but the cribriform carcinoma has only one cell type and has glandular lumina without the mucinous or basement membrane material. In addition, most other types of breast carcinomas with a cribriform growth pattern are ER and PR positive and do not express p63 or c-kit. Collagenous spherulosis, a benign breast lesion, can also be confused with ACC, especially as the p63 is expressed in both lesions. However, ckit should not be expressed in collagenous spherulosis and can be helpful in the differential diagnosis. Another potential pitfall is with ACCs that have a predominantly nonclassical growth pattern, such as the solid variant, which can be confused with a higher-grade breast carcinoma. p63, EGFR, and c-kit may not be useful as these markers can be positive in high-grade invasive ductal carcinoma. In such cases, the FISH split-apart or fusion probes to detect the t(6;9) rearrangement and/or RTPCR for the *MYBNFIB* fusion gene may be needed to establish the diagnosis of ACC.

34. What are the current classification and subtypes of metaplastic breast carcinoma?

Metaplastic carcinoma (MC) of the breast represents 0.25–1% of all breast cancers diagnosed annually [27]. Based on the 2012 World Health Organization classification of Tumors of the Breast, MC is classified based on the histological features of tumor cells: (1) purely epithelial components (low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, and spindle cell carcinoma) and (2) mixed epithelial and mesenchymal components (metaplastic carcinoma with mesenchymal differentiation and mixed metaplastic carcinoma) [27].

35. What is low-grade adenosquamous carcinoma of the breast and what are its key diagnostic features?

Low-grade adenosquamous carcinoma is an uncommon variant of metaplastic carcinoma with a good prognosis [77, 78]. Morphologically, round or comma-shaped infiltrating ducts are admixed with foci of squamous differentiation. The lumens of the ducts are usually compressed. Eosinophilic material or keratin may be present in the lumens. The tumor cells show low-grade nuclear features. The tumor stroma can be edematous or sclerotic and have variable spindle cells, but the cellularity of the stroma around the epithelial nests is often increased [79, 80]. See Fig. 3.12a–g.

36. What are the differential diagnoses for low-grade adenosquamous carcinoma of the breast?

The differential diagnosis of low-grade adenosquamous carcinoma includes benign breast lesions, such as sclerosing adenosis, squamous metaplasia or syringomatous adenoma of the nipple, and malignant lesions such as invasive tubular carcinoma. The absence of myoepithelial cells demonstrated by immunostains (SMMS, p40 or p63) will help to exclude benign lesions [78]. The intramammary parenchymal location of low-grade adenosquamous carcinoma is important to differentiate it from syringomatous adenoma of the nipple. Demonstrating squamous differentiation in low-grade adenosquamous carcinoma by careful sampling and histologic examination is important to differentiate it from the invasive tubular carcinoma [80].

37. What is fibromatosis-like metaplastic carcinoma and what are its key diagnostic features?

Fibromatosis-like spindle cell carcinoma (FLSCC) is a recently described low-grade variant of metaplastic carcinoma with a favorable prognosis [81, 82]. FLSCC grossly presents as a firm and white mass, and the cut surface shows a fibrous, gray-white nodular parenchyma. Microscopically, FLSCC shows the proliferation of cytologically bland, low-grade, spindled, fibroblast-like cells and stellate myofibroblast-like cells, resembling fibromatosis. The cellularity of proliferation of neoplastic cells is variable among FLSCCs. The neoplastic spindle cells show minimal nuclear atypia and pale eosinophilic cytoplasm; the nuclei vary from thin, slender, spindled nuclei with tapered ends to more plump, round to oval nuclei with discrete nucleoli. The tumor border is usually infiltrative with broad, finger-like projections into the surrounding tissue. Neoplastic squamous or glandular epithelial elements may be present but should be less than 5% of the total tumor volume. FLSCC may also show collagenous stroma, similar to fibromatosis. The presence of small, cohesive clusters of fusiform to polygonal epithelioid cells scattered among the spindle cells is a defining and characteristic histologic feature for FLSCC [83, 84]. See Fig. 3.13a–i.

A panel of immunohistochemical stains is generally needed to demonstrate the epithelial origin of the spindle cells in FLSCCs in order to differentiate it from other spin-

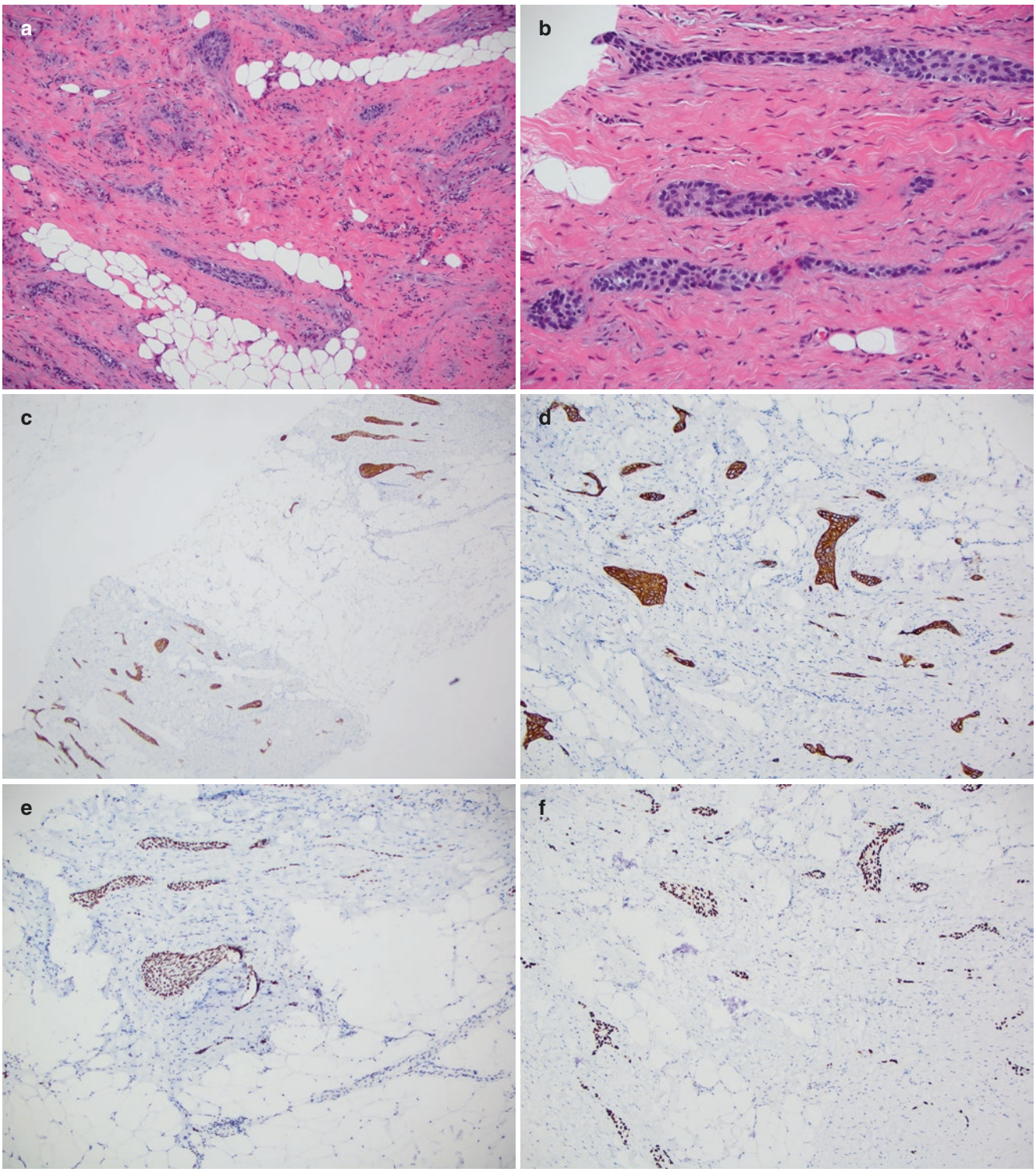


Fig. 3.12 Low-grade adenosquamous carcinoma of the breast. Infiltrating solid glandular structures of carcinoma cells into surrounding stroma (**a**). The tumor cells are low grade, bland looking with both squamous and glandular differentiation (**b**). The tumor cells are diffusely positive for BerEP4 (**c**), CK5 (**d**), GATA3 (**e**), and p63 (**f**). SMMS stain shows loss of myoepithelial cells around the tumor (**g**)

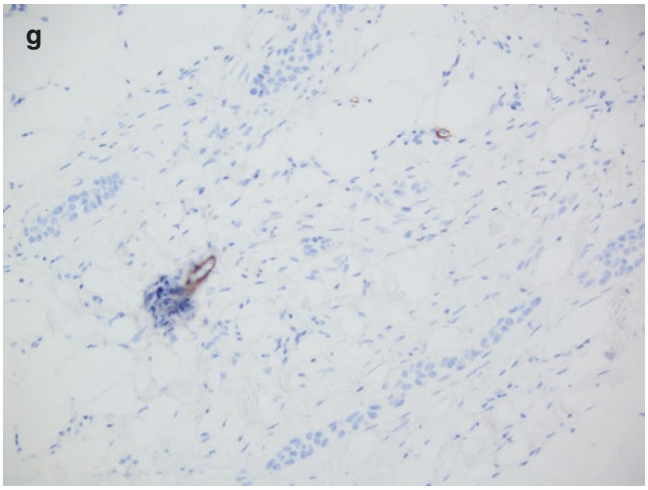


Fig. 3.12 (continued)

dle cell lesions of the breast. The cytokeratin immunohistochemical stains can include antibodies against broad-spectrum cytokeratins (AE1/AE3 and pankeratin), basal cytokeratins (CK5, 34βE12, and CK14), and luminal cytokeratins (CK7, CK19, and CAM 5.2). The spindle cell component and small clusters of epithelioid cells usually exhibit immunoreactivity for basal cytokeratins, but no to focal immunoreactivity for luminal cytokeratins. It has been suggested that the neoplastic spindle cells actually demonstrate an immunoprofile more compatible with myoepithelial differentiation with immunoreactivity of basal cytokeratins (34βE12, CK14, and CK5) and myoepithelial markers (smooth muscle actin, S100, p63 and p40). A study has demonstrated that p63 was strongly positive in 87% of metaplastic carcinomas and was positive in all metaplastic carcinomas with spindle cell and/or squamous differentiation [85]. The neoplastic spindle cells of FLSCCs are negative for smooth muscle myosin heavy chain (SMMHC) and epithelial membrane antigen (EMA); the proliferation index of FLSCC is typically low with less than 5% of Ki-67 staining [84, 86].

38. What are the differential diagnoses for fibromatosis-like metaplastic carcinoma?

The main differential diagnoses for FLSCC include nodular fasciitis and fibromatosis. Nodular fasciitis is a benign proliferative lesion containing fibroblasts and myofibroblasts in myxoid stroma with prominent vasculature. The lesion is very rarely seen in the breast and should be diagnosed only after extensive sectioning and with negative cytokeratin staining. Fibromatosis is a clonal proliferation of benign-appearing fibroblasts and myofibroblasts with an infiltrative growth pattern. The spindle cells in fibromatosis are negative for cytokeratins but show positive staining of beta-catenin in the nuclei. Other differential diagnoses include myofibroblastoma and pseudoangiomatous stromal hyperplasia (PASH). Myofibroblastoma is a rare benign proliferation of myofibroblasts. Myofibroblastomas were originally reported to occur more frequently in males, but recent data suggest they are equally frequent between males and females [87]. Histologically, myofibroblastomas are composed of bland-appearing spindle cells in short haphazard fascicles separated by collagen bands. Patchy perivascular chronic inflammatory infiltrates are characteristic findings. The myofibroblast cells are positive for vimentin and variably positive for desmin, CD34, smooth muscle actin, estrogen receptor, progesterone receptor, and Bcl-2, but negative for cytokeratins [88, 89]. PASH is a benign lesion with anastomosing empty, slit-like pseudovascular spaces lined by myofibroblasts (not endothelial cells) in a dense collagenous stroma. Similar to those in the myofibroblastoma, the spindle cells in the PASH are positive for vimentin and variably positive for desmin, CD34, and smooth muscle actin, but negative for cytokeratins [90].

39. What is squamous cell carcinoma of the breast and what are its key diagnostic features?

Metaplastic squamous cell carcinomas can be pure or mixed with other forms of invasive carcinoma. Pure squamous cell carcinomas in the breast are rare. More commonly, squamous differentiation is identified coexisting with invasive ductal carcinomas and carcinomas with medullary features. Squamous cell carcinomas usually present as cystic lesions with squamous lining cells showing variable atypia and nuclear pleomorphism. The tumor cells can show sheets, cords, or nests of proliferation infiltrating into the stroma with a prominent stromal reaction and lymphocytic response [27]. See Fig. 3.14a–f.

40. What are the differential diagnoses for squamous cell carcinoma of the breast?

If the tumor is composed entirely of malignant squamous cells, a metastasis from another site, especially skin, lung, or head/neck region, must be ruled out before making the diagnosis of mammary squamous cell carcinoma. The other differential diagnosis is mucoepidermoid car-

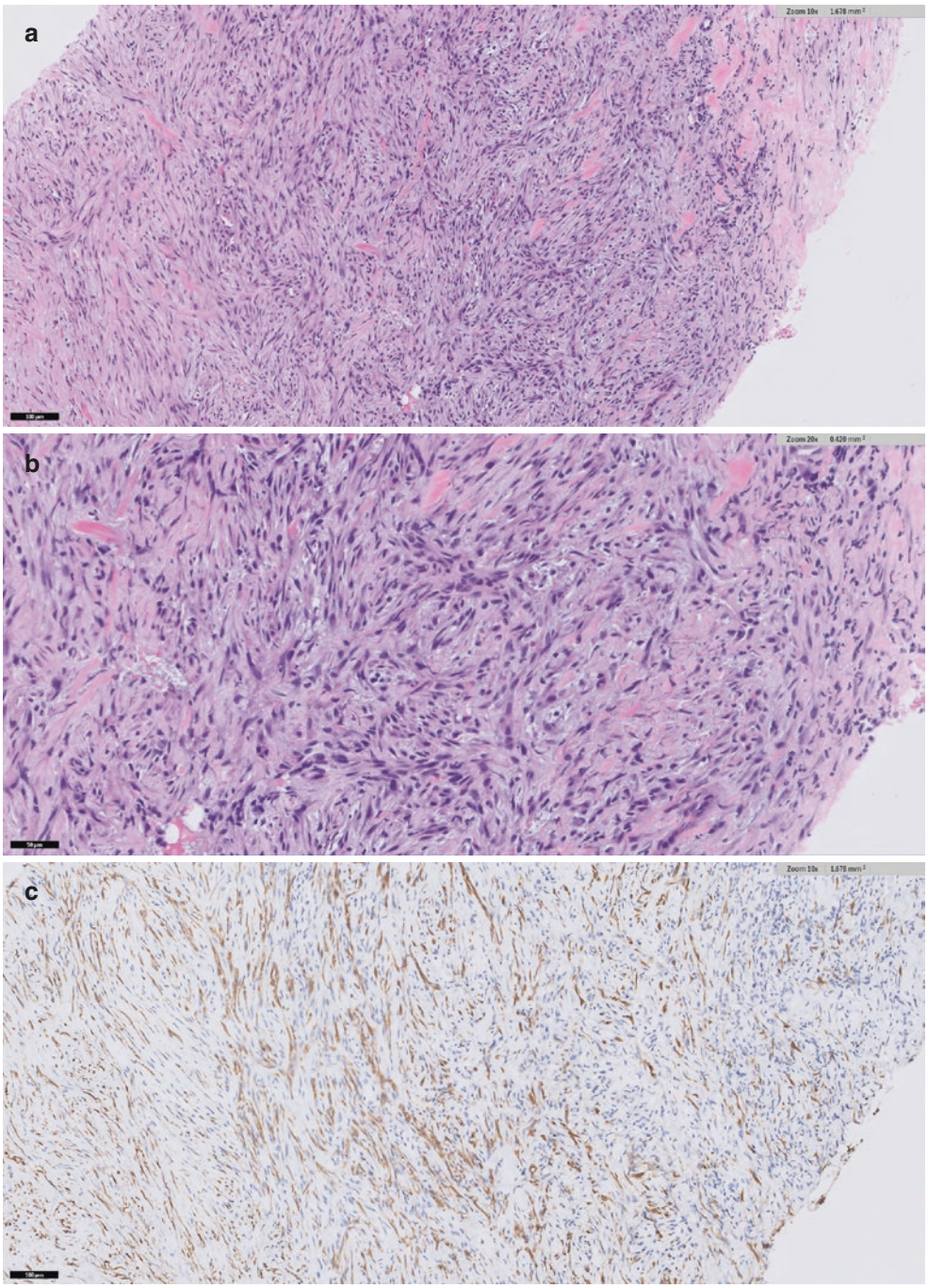
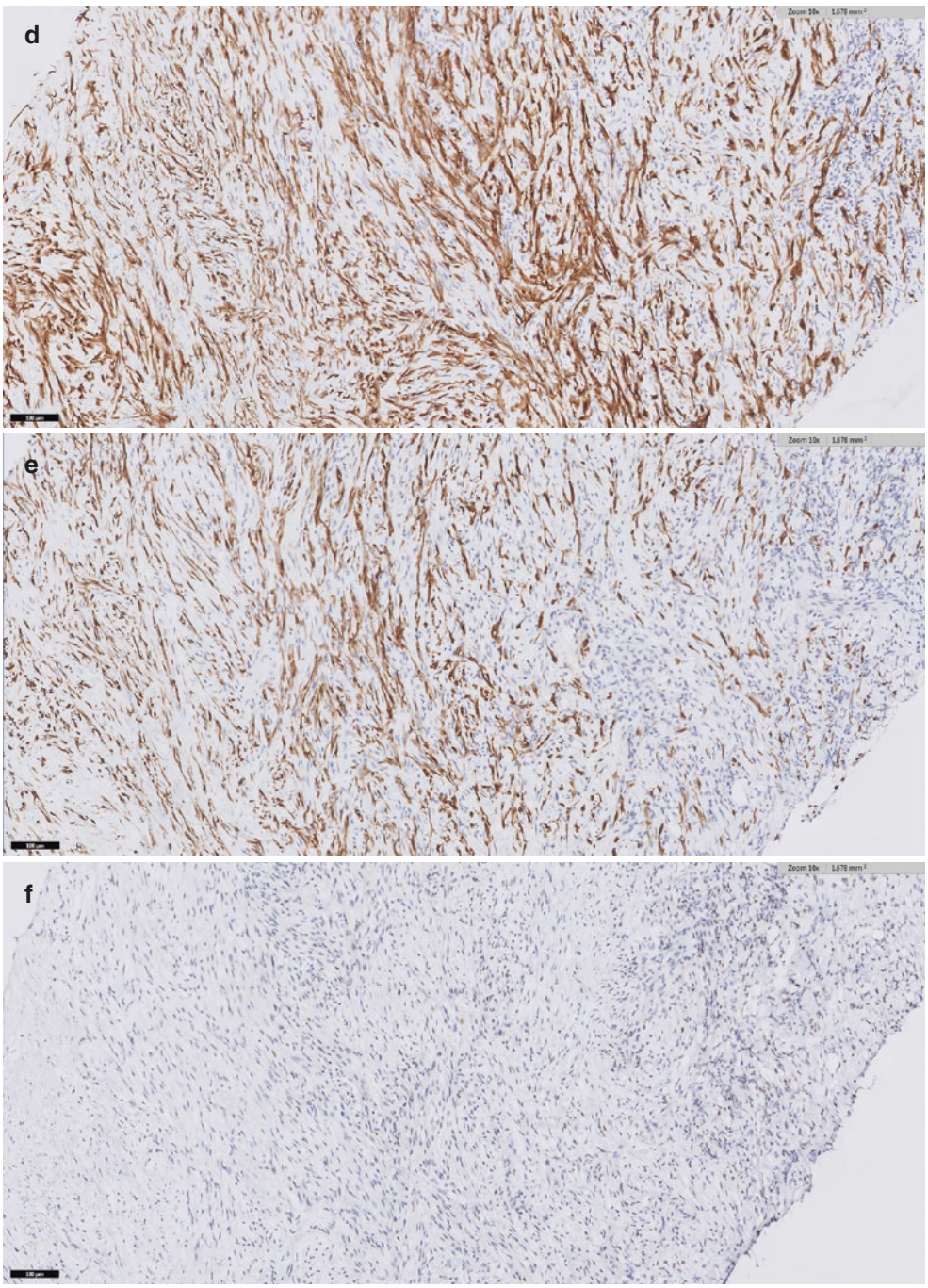


Fig. 3.13 Low-grade fibromatosis-like spindle cell carcinoma (FLSCC). Broad infiltrative projections of the tumor extending into the surrounding soft tissue (**a**). The tumor is composed of cytologically bland cells with thin and spindled to round or oval nuclei (**b**). The tumor cells are positive for cytokeratin AE1/AE3 (**c**), MNF116 (**d**), and CK5 (**e**) and positive for CK7 (**f**). The tumor cells are focally positive for GATA3 (**g**) and negative for desmin (**h**) and ER (**i**)



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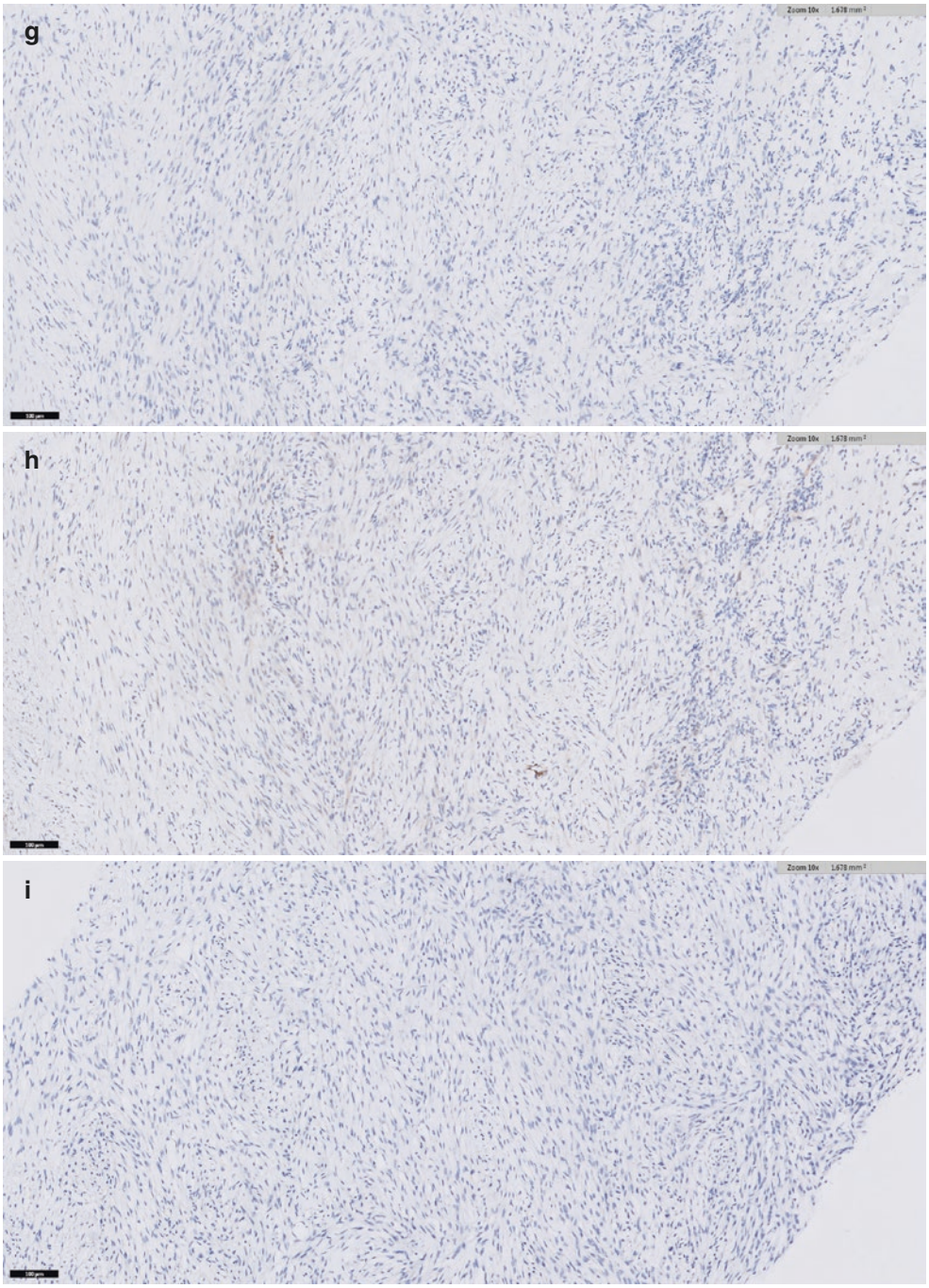


cinoma (both low- and high-grade types), which usually shows extracellular or intracellular mucin [91, 92]. Squamous metaplasia in the breast varies from syringoma-like differentiation to inconspicuous foci in largely glandular lesions. Keratinizing cysts are uncommon, but small osteocartilaginous foci can be seen [77]. Some benign squamous lesions in the breast may also get into the differential diagnosis of squamous cell carcinoma of the breast, including posttraumatic lobular squamous metaplasia [93], mixed squamous–mucous cysts [94], squamous metaplasia in gynecomastia [95], Zuska's disease (squamous metaplasia of lactiferous ducts), and infarction with squamous metaplasia of intraductal papilloma [96, 97].

41. **What is spindle cell carcinoma (sarcomatoid carcinoma) of the breast and what are its key diagnostic features?**

Spindle cell carcinomas of the breast can be pure or mixed with other components, such as glandular, heterologous, or squamous elements [98, 99]. These tumors are composed of atypical spindle cells in a growth pattern of long fascicles (herringbone or interwoven pattern) or short fascicles (storiform). The atypical spindle cells can range from bland appearing to highly pleomorphic. The cytoplasm can range from elongated to plump spindle and the nuclei can range from bland-looking to apparently pleomorphic. Mitotic rate can be variable among spindle cell carcinomas of the breast. The spindle cells infiltrate into the surrounding stroma with entrapped benign ducts and lobules [100]. Nottingham grading is not applicable to metaplastic spindle cell carcinomas [27].

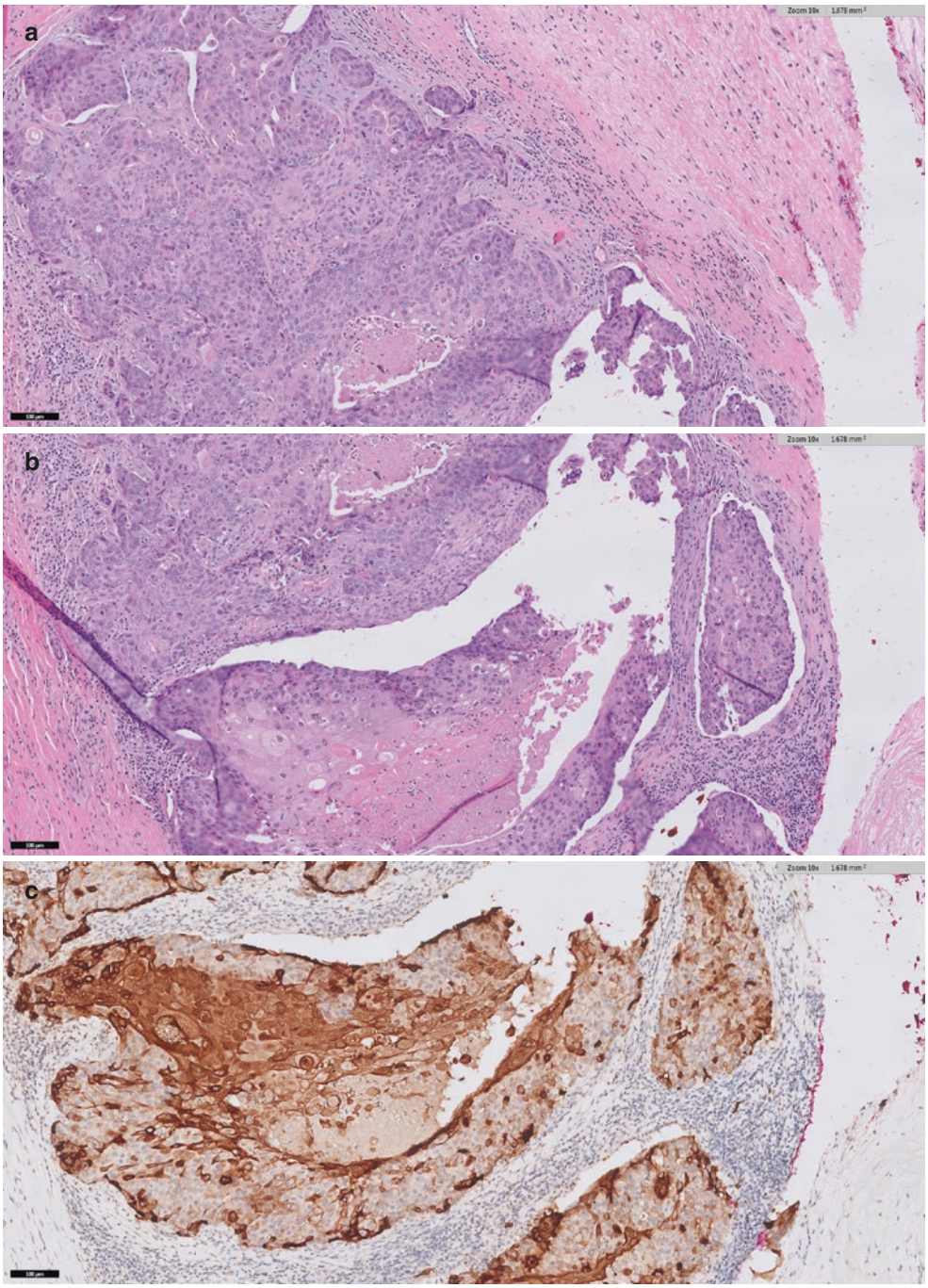
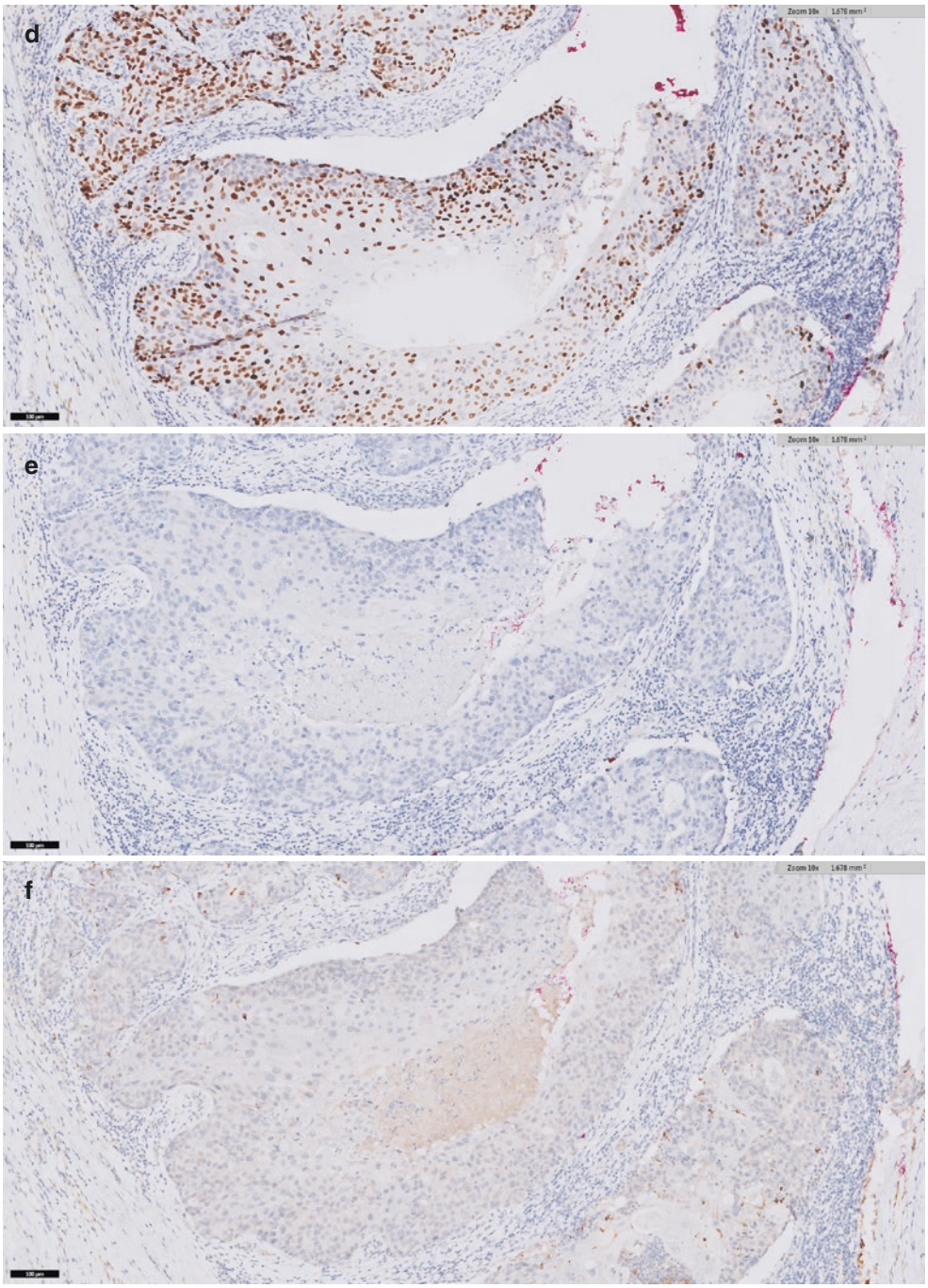


Fig. 3.14 Metaplastic squamous cell carcinoma of the breast. Invasive carcinoma with both squamous differentiation and ductal differentiation with focal necrosis and lymphocytic response (**a**). Squamous carcinoma cells show nuclear pleomorphism and keratinization (**b**). The tumor cells are diffusely positive for CK5 (**c**) and p40 (**d**) and negative for ER (**e**) and PR (**f**)

Fig. 3.14 (continued)



Spindle cell carcinomas of the breast can coexist with an epithelial component of invasive ductal carcinoma or ductal carcinoma in situ. For any lesion with pure spindle cells, a suspicion for metaplastic spindle cell carcinoma must be high so that immunostains for epithelial differentiation should be performed. A panel of cytokeratins is often necessary with a broad spectrum of cytokeratins, including high-molecular-weight cytokeratins (CK5/6 and 34βE12) and low-molecular-weight cytokeratins. The neoplastic spindle cells usually express myoepithelial markers such as p63, p40, smooth muscle actin, and muscle specific actin. Similar to other subtypes of metaplastic carcinoma, spindle cell carcinomas are generally negative for ER, PR, and HER2 [27, 100]. See Fig. 3.15a–i.

42. What are the differential diagnoses for spindle cell carcinomas of the breast?

For spindle cell carcinomas of the breast, the main differential diagnoses include malignant phyllodes tumor with prominent spindle cell overgrowth, sarcomas (angiosarcoma, fibrosar-

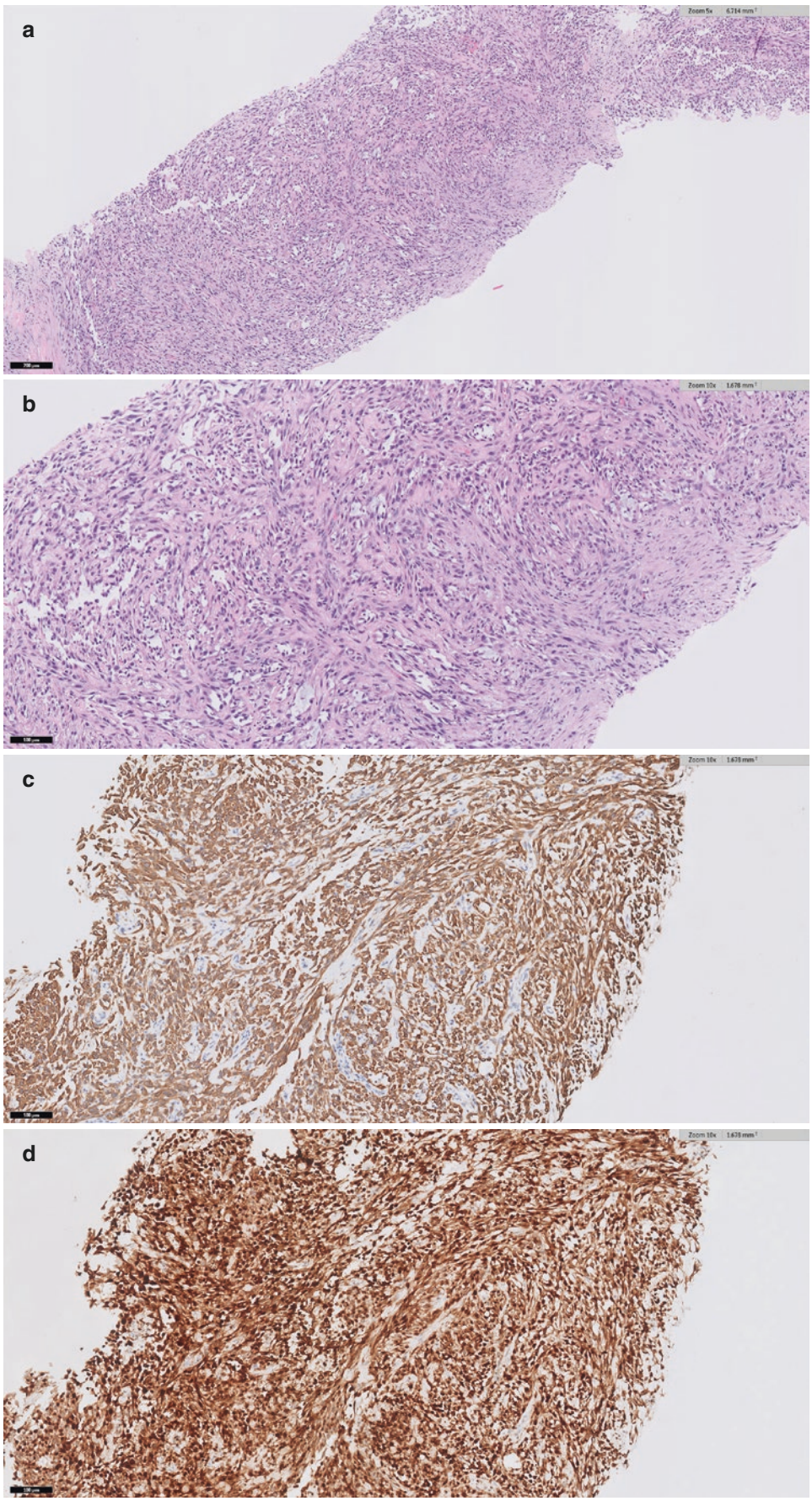
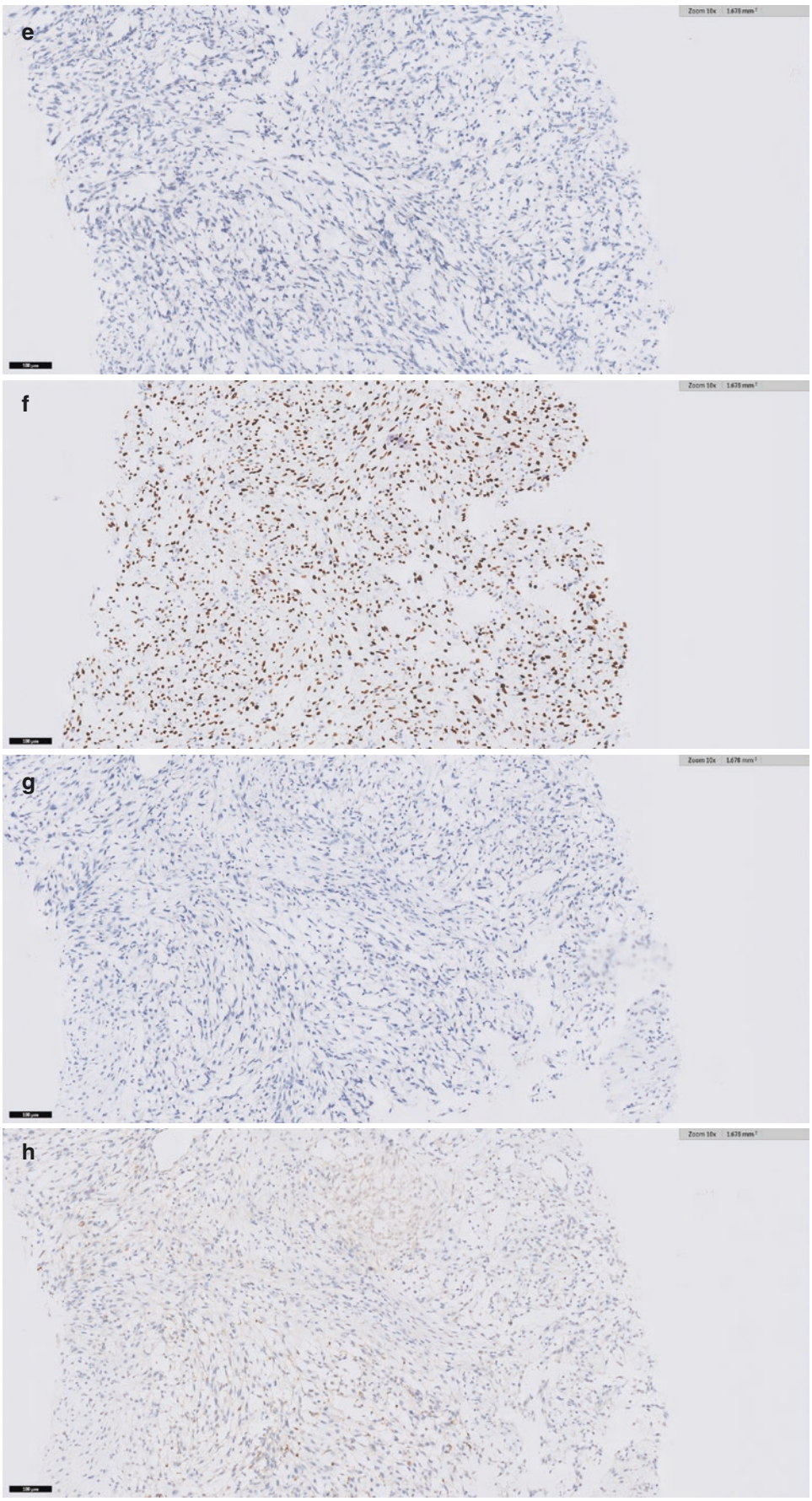


Fig. 3.15 Spindle cell carcinoma of the breast. The tumor is composed of atypical spindle cells in a growth pattern of long fascicles with desmoplastic stromal reaction (**a**). The atypical spindle cells are mildly to moderately pleomorphic and the cytoplasm is mostly elongated to plump spindly (**b**). The tumor cells are diffusely positive for cytokeratin AE1/AE3 (**c**) and CAM5.2 (**d**) and negative for CK7 (**e**). The tumor cells are also diffusely positive for p40 (**f**) and negative for ER (**g**), PR (**h**), and HER2 (**i**)



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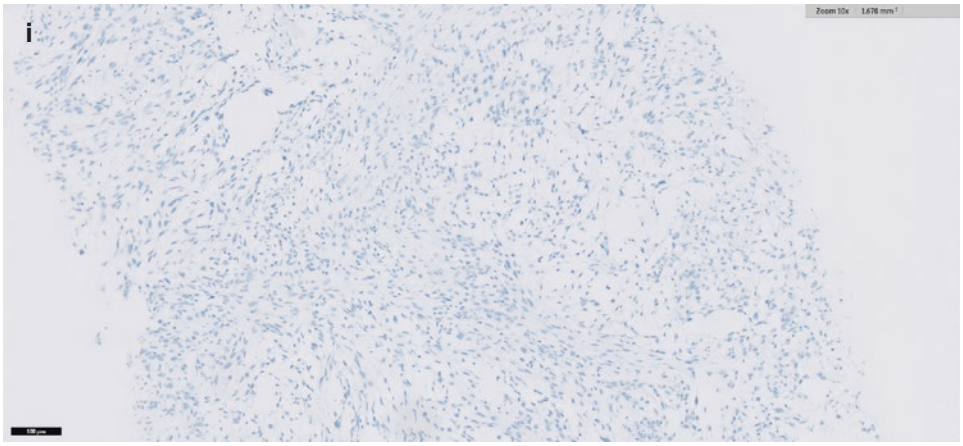

coma, etc.), and benign spindle cell lesions, such as fibromatosis and PASH. Extensive sampling to identify malignant epithelial component is important, and epithelial immunohistochemical markers such as cytokeratins and p63/p40 are almost always necessary to make the diagnosis. The leaf-like architecture is characteristic of phyllodes tumor. The stromal spindle cell proliferation in the phyllodes tumor is generally negative for cytokeratins and positive for CD34. The spindle cells of fibromatosis usually show nuclear staining for beta-catenin but negative staining for cytokeratins [27, 100].

43. What is metaplastic carcinomas with mesenchymal differentiation and what are its key diagnostic features?

Metaplastic carcinomas with mesenchymal differentiation contain mesenchymal elements (cartilage, bone, rhabdoid, or a chondromyxoid matrix) admixed with carcinomatous components [101]. The osseous and chondroid elements can appear histologically benign or frankly malignant with an appearance of chondrosarcoma or osteosarcoma [101]. Extensive sampling may be necessary to identify epithelial components. At the same time, a broad panel of cytokeratins may also be necessary to reveal the epithelial component when no apparent glandular component is present. Metaplastic breast carcinomas with mesenchymal differentiation originate from carcinomas that undergo sarcomatous transitions as a result of further genetic instability or mutations, and the identical clonality of the carcinomatous and mesenchymal components has been confirmed. The term "matrix-producing carcinoma" was historically used for a subtype of metaplastic carcinomas with mesenchymal differentiation, which usually contains chondroid differentiation or chondromyxoid matrix [102]. See Fig. 3.16a–c. Similar to other subtypes of metaplastic carcinomas, metaplastic carcinomas with mesenchymal differentiation are also negative for ER, PR, and HER2 [27].

44. What are the differential diagnoses for metaplastic carcinomas with mesenchymal differentiation?

The main differential diagnoses of metaplastic carcinoma with mesenchymal differentiation are sarcomas. Primary breast sarcomas are exceedingly rare and most frequently arise in association with a phyllodes tumor. To make a distinction between these two entities, extensive sampling is usually necessary to identify either malignant epithelial component for diagnosis of metaplastic carcinoma with mesenchymal differentiation or benign-appearing epithelial component and/or leaf-like architecture for phyllodes tumor in cases with predominantly sarcomatous proliferation [27].

45. What is the prognosis of most metaplastic carcinomas? Do all metaplastic carcinomas carry a bad prognosis?

Due to the heterogeneity of metaplastic carcinoma, the prognosis largely depends upon the histologic features. Some low-grade subtypes of metaplastic carcinomas such as low-grade adenosquamous carcinoma or fibromatosis-like metaplastic carcinoma usually have a favorable prognosis with only local recurrence and rare distant metastases, while others (high-grade spindle cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, or squamous cell carcinoma) have an aggressive clinical course with poor outcomes.

In general, patients with metaplastic carcinoma have larger tumors with negative hormone receptor status and less involvement of the regional lymph nodes [103]. However, even in the absence of lymph node metastasis, distant metastasis to the brain and lungs can occur [104, 105]. The prognosis of fibromatosis-like metaplastic carcinoma parallels that of fibromatosis, suggesting that wide excision with clear margins or simple mastectomy without axillary lymph node dissections should be sufficient for

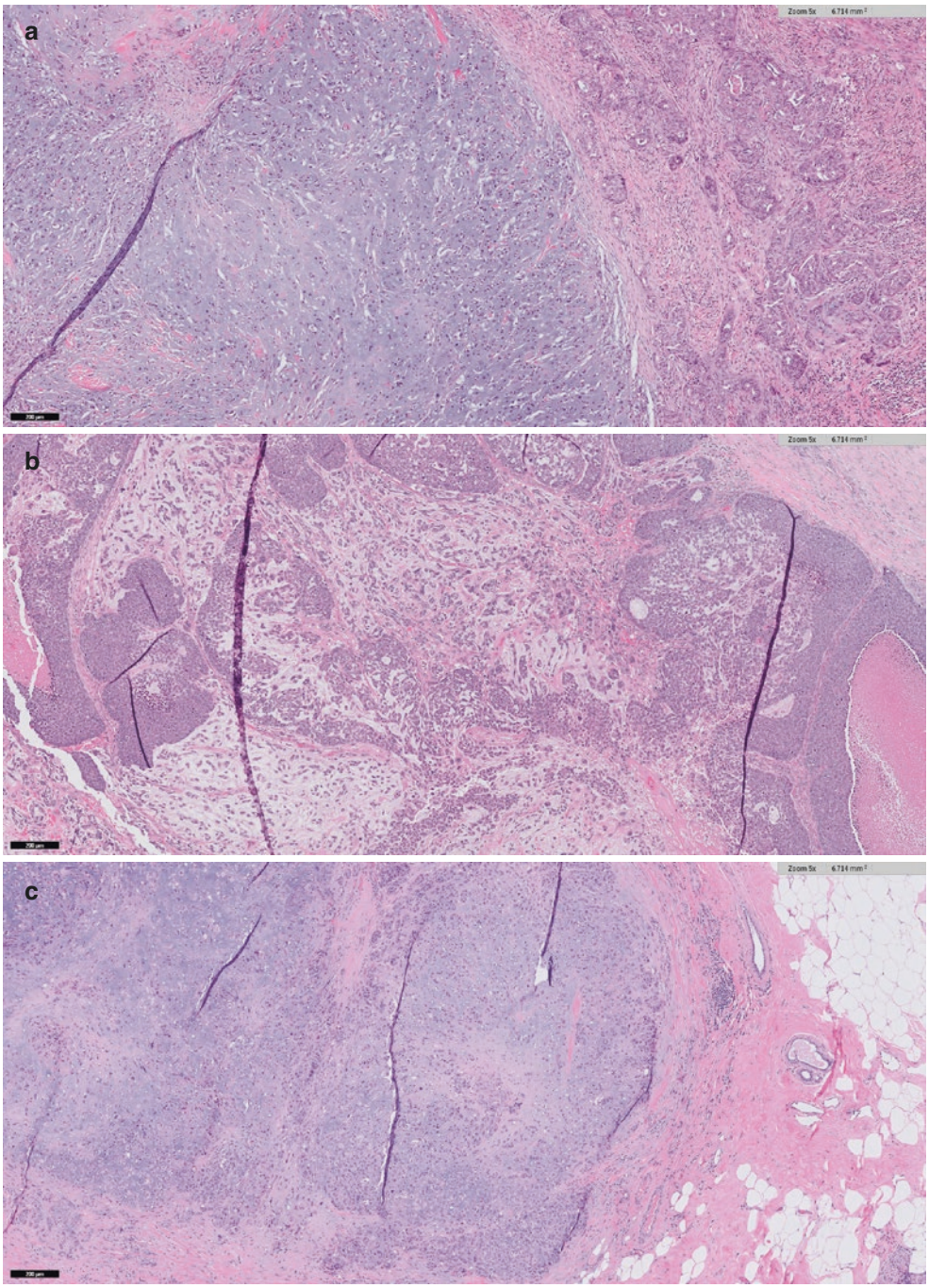

Fig. 3.16 Metaplastic carcinoma with mesenchymal differentiation. Metaplastic carcinoma with chondromyxoid matrix (**a**). Metaplastic carcinoma with chondromyxoid matrix intermixed with malignant epithelial cells (**b**). Metaplastic carcinoma with chondromyxoid matrix intermixed with malignant mesenchymal cells (**c**)

initial treatment of FLSCC; chemotherapy and radiation therapy may not be needed. However, the data are limited and more studies are warranted. On the other hand, patients with high-grade metaplastic carcinomas usually have a relatively poor prognosis and should be treated like Nottingham grade 3 invasive ductal carcinoma of the breast [106–108].

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