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Special Histologic Types and Special Morphologic Patterns of Invasive Ductal Carcinoma of No Special Type: Mucinous, Micropapillary, Mucinous Cystadenocarcinoma, Neuroendocrine Neoplasm, Cystic Hypersecretory, Glycogen-Rich Clear Cell, Carcinoma with Osteoclast-Like Giant Cells

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Mucinous Carcinoma

Overview

Mucinous carcinoma, also known as "colloid carcinoma," is a special histologic type of breast cancer, which accounts for approximately 2% of all breast cancers [1]. By definition, greater than 90% of tumor cells must be present within mucinous stroma. Many other types of breast carcinoma can show focal mucin production, and those tumors where <90% of the tumor is mucinous should be classified as "mixed tumors with a mucinous carcinoma component" or as "invasive carcinomas with focal mucinous features."

Pure mucinous carcinoma typically occurs in older patients [2, 3] with a median age at diagnosis of 71 years (mean: 68 years, range: 25–85 years) as compared to those with invasive ductal carcinoma of no special type (NST) (median and mean age: 61 years) [2, 3]. Approximately one-third of patients with mucinous carcinoma present with a palpable breast mass, while the remaining two-thirds are detected by screening mammography or sonography.

Pure mucinous carcinoma is associated with a favorable clinical outcome, as well as favorable pathologic features, including smaller tumor size, lower frequency of regional lymph node involvement, and high probability of hormone receptor positivity [2, 3].

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Invasive mucinous micropapillary carcinoma is a variant that has distinct histomorphology and clinical behavior apart from pure invasive mucinous carcinoma. While it should still be classified fundamentally as a mucinous carcinoma, this variant is important to recognize as it has been found to be biologically more aggressive than pure mucinous carcinoma. Since it was first described in 2002, there have been increasing reports of this variant in the literature [4–12].

Invasive mucinous micropapillary carcinoma tends to occur in younger patients with a median age range of 44–55 years [4, 7–12]. These tumors typically show higher tumor grade and Ki-67 proliferation rate and more frequent human epidermal growth factor 2 (HER2) overexpression and are associated with higher incidences of lymphovascular invasion and axillary lymph node metastasis. Consequently, affected patients experience a more aggressive clinical course and adverse outcome as compared to those with conventional mucinous carcinomas [8–12].

Gross and Radiologic Features

Grossly, the tumors are typically lobulated and well circumscribed with soft gelatinous/glistening cut surfaces. More than 95% of tumors are less than 5 cm with a mean size of 1.5–2.0 cm [2, 3].

Mammography often shows a well-circumscribed lesion [13, 14], and by sonography, these lesions are hypoechoic or isoechoic [14]. Due to their innocuous appearing features by imaging, a significant number are misinterpreted as benign, resulting in delayed diagnosis [15].

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Microscopic Features

Microscopically, mucinous carcinoma is characterized by islands of tumor cells suspended in extracellular mucin pools. The tumor cells are arranged in nested, trabecular, tubular, papillary, or micropapillary configurations and exhibit low-to-intermediate nuclear grade. Delicate fibrous septa with vascular proliferation are identified within mucin pools.

As previously mentioned, pure mucinous carcinoma is defined as a tumor where >90% of the neoplastic cells are immersed in mucin pools, and consequently, such a diagnosis cannot be rendered in core needle biopsy (CNB) material since the tumor has only been representatively sampled. A diagnosis of "invasive mammary (or ductal) carcinoma with prominent mucinous features" with a note stating that final classification would be performed after the evaluation of the entire tumor in the forthcoming surgical excision specimen would be appropriate to state in the core biopsy report. When examining the excisional biopsy specimen, if the non-mucinous component is present in >10% of the tumor, the tumor should be classified as "mixed mucinous carcinoma."

Traditionally, mucinous carcinomas have been further categorized into two types: type A, hypocellular, and type B, hypercellular (Figs. 13.1 and 13.2) [1]. Type A tumors often have mucin content of 60–90%, with predominantly trabecu-

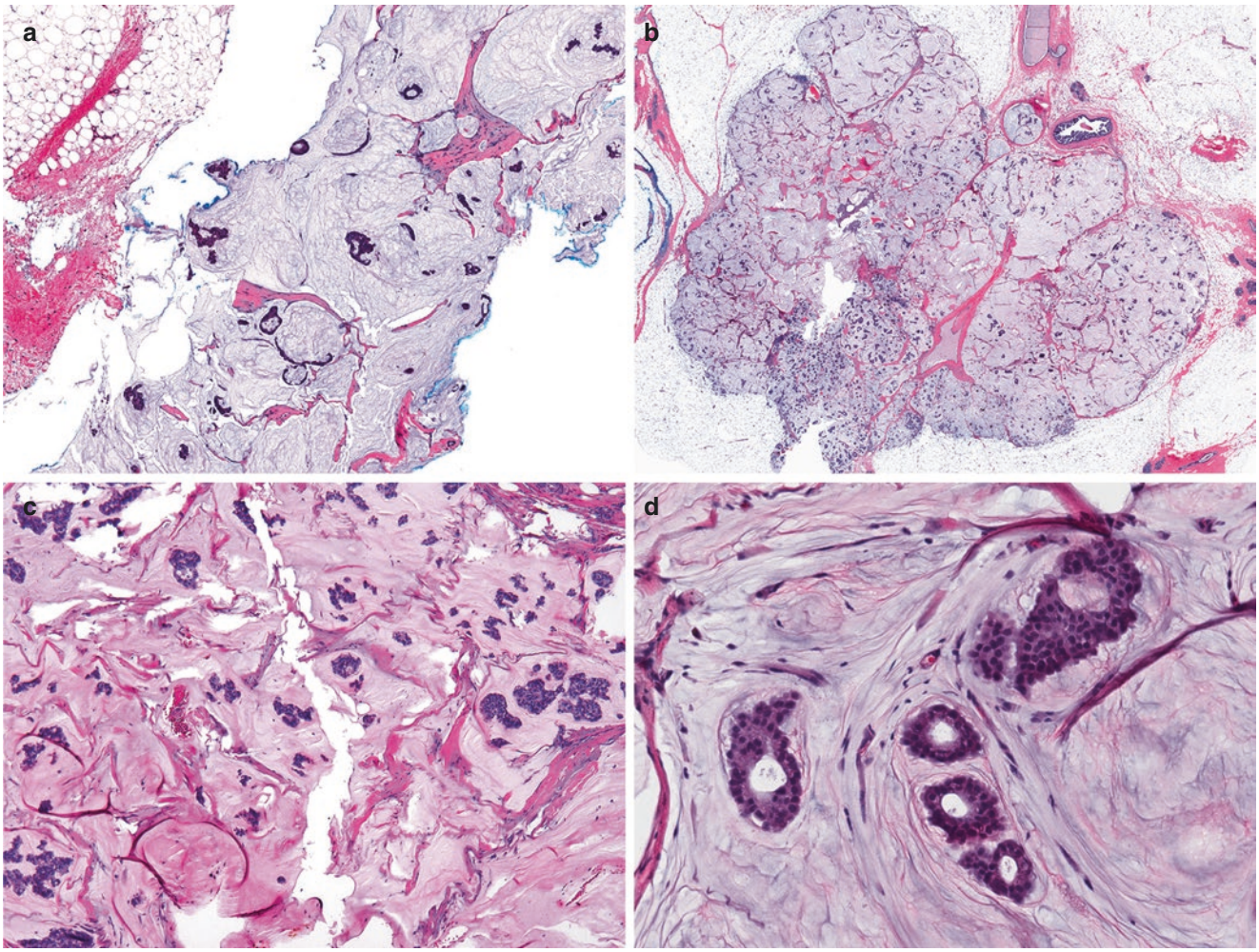


Fig. 13.1 Type A, hypocellular mucinous carcinoma. (**a**) CNB shows cords, glands, and small nests of tumor cells suspended in a pool of mucin. (**b**) Specimen from surgical resection demonstrates that >90% of the tumor cells are confined within a pool of mucin. (**c**) Medium-power view demonstrates that the mucin pool is supported by fibrous septa with vascular proliferation. (**d**) The neoplastic cells are uniform and low grade

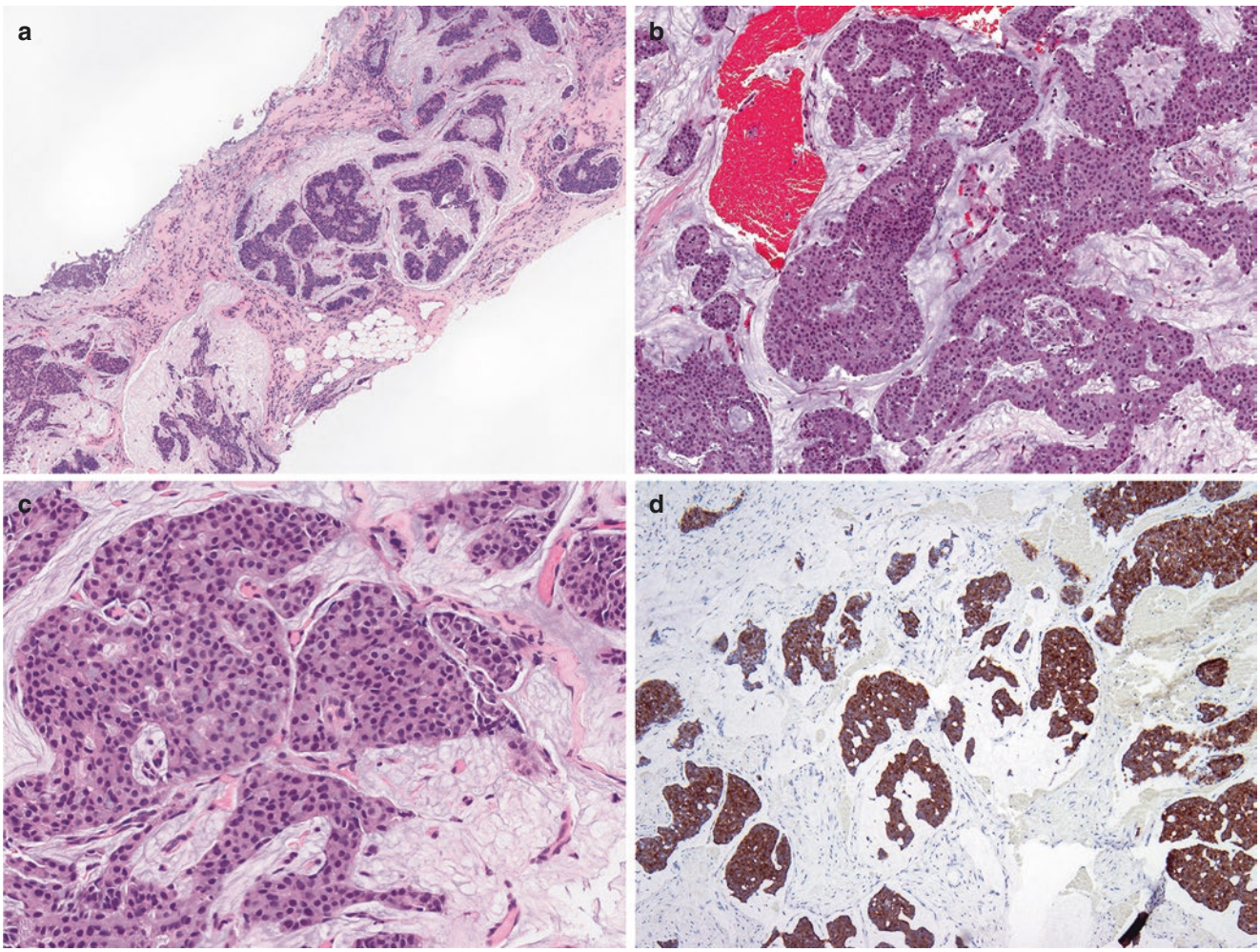


Fig. 13.2 Type B, hypercellular mucinous carcinoma. (**a**) CNB shows large nests and cores of tumor cells suspended in a mucin pool. (**b**) The tumor cells are uniform and low grade. (**c**) Another case of hypercellular mucinous carcinoma shows solid papillary configuration (**d**) with diffuse neuroendocrine differentiation, demonstrated by positive immunoreactivity for synaptophysin

lar and glandular cellular arrangement, while type B tumors often have mucin content <50%, and tumor cells often form nests or sheets. Type B tumors can sometimes show focal solid papillary architecture and may be associated with neuroendocrine differentiation (Fig. 13.2d). In routine practice, further classification as type A or type B mucinous carcinoma is not included in pathology reports. But a recent molecular study showed that these two types of tumor have distinct molecular profiles [16]. The clinicopathologic differences between these two types of tumor have not yet been investigated; additional studies are warranted.

Even in core biopsy samples, it is important to recognize whether the tumor may represent the invasive mucinous micropapillary carcinoma variant (Fig. 13.3). Like its conventional counterpart, >90% of the mucinous micropapillary carcinoma is mucinous, but tumor cells suspended in mucin pools additionally show a predominantly micropapillary configuration with pseudoacinar formation. The solid sheets, cribriform, trabecular, or ribbonlike arrangements that are frequently seen in conventional type are not formations seen in mucinous micropapillary carcinoma and, if identified, should exclude the possibility of this variant.

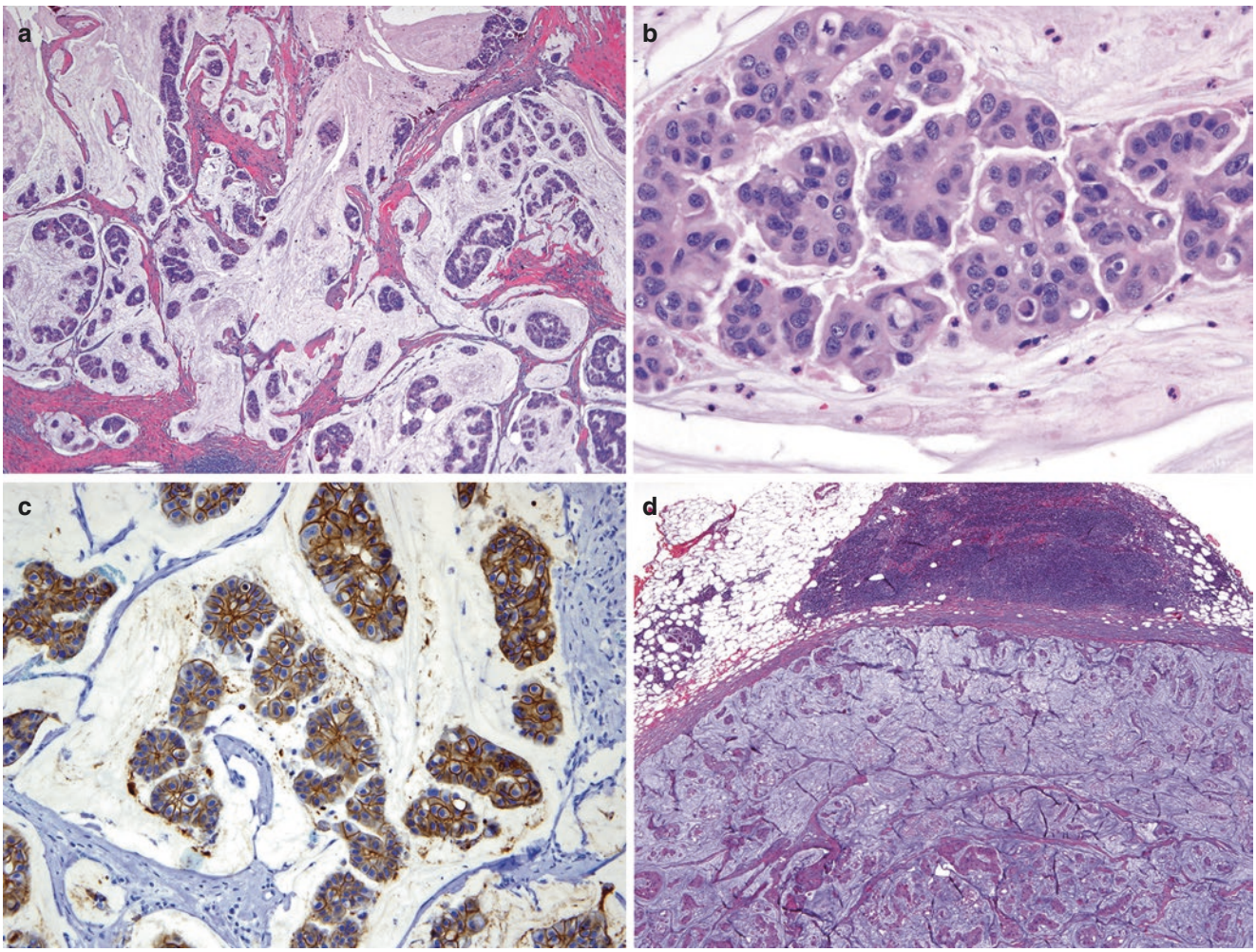


Fig. 13.3 Invasive mucinous micropapillary carcinoma. (**a**, **b**) The neoplastic cells in the mucin pool demonstrate micropapillary configuration, and the neoplastic cells are intermediate to high grade. (**c**) Twenty percent of mucinous micropapillary carcinomas are positive for HER2/neu overexpression as shown in this case. (**d**) Up to one-third of these cases have regional lymph node metastasis as shown in this case

Differential Diagnosis

The most important considerations in the differential diagnosis for mucinous carcinoma are other mucinous lesions of the breast and metastatic mucinous tumors from extramammary sites. Among the former group, mucocele-like lesion (MLL) is the most frequently encountered mucinous lesion in CNBs. MLLs are mucin-filled dilated ducts with or without concomitant rupture and mucin extravasation into the surrounding stroma. MLLs are usually small in size (0.1–0.6 cm) [17]. More than 90% of cases are the target of CNB due to their association with mammographically evident microcalcifications. The remainder of cases form a mass lesion that can be detected by sonogram [17]. Depending on the type of epithelial cells lining the dilated ducts, MLLs can be benign or contain atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS). A recent study showed that more than half of MLLs are benign (57%), 33% are associated with ADH and the remaining 10% with DCIS [18].

Benign MLLs are comprised of dilated ducts lined by uniform cuboidal or columnar cells with or without concomitant extravasated acellular mucin. Occasionally, usual ductal hyperplasia may be present. A diagnostic pitfall is the occasional instance of benign epithelium detaching and shedding into luminal mucin, and thus mimicking invasive mucinous carcinoma (Fig. 13.4a). In these cases, it is important to see that the contour of the mucin pool is usually rounded and similarly shaped to the adjacent intact dilated ducts. Also, despite being detached from the duct wall, benign epithelium remains as strips with myoepithe-

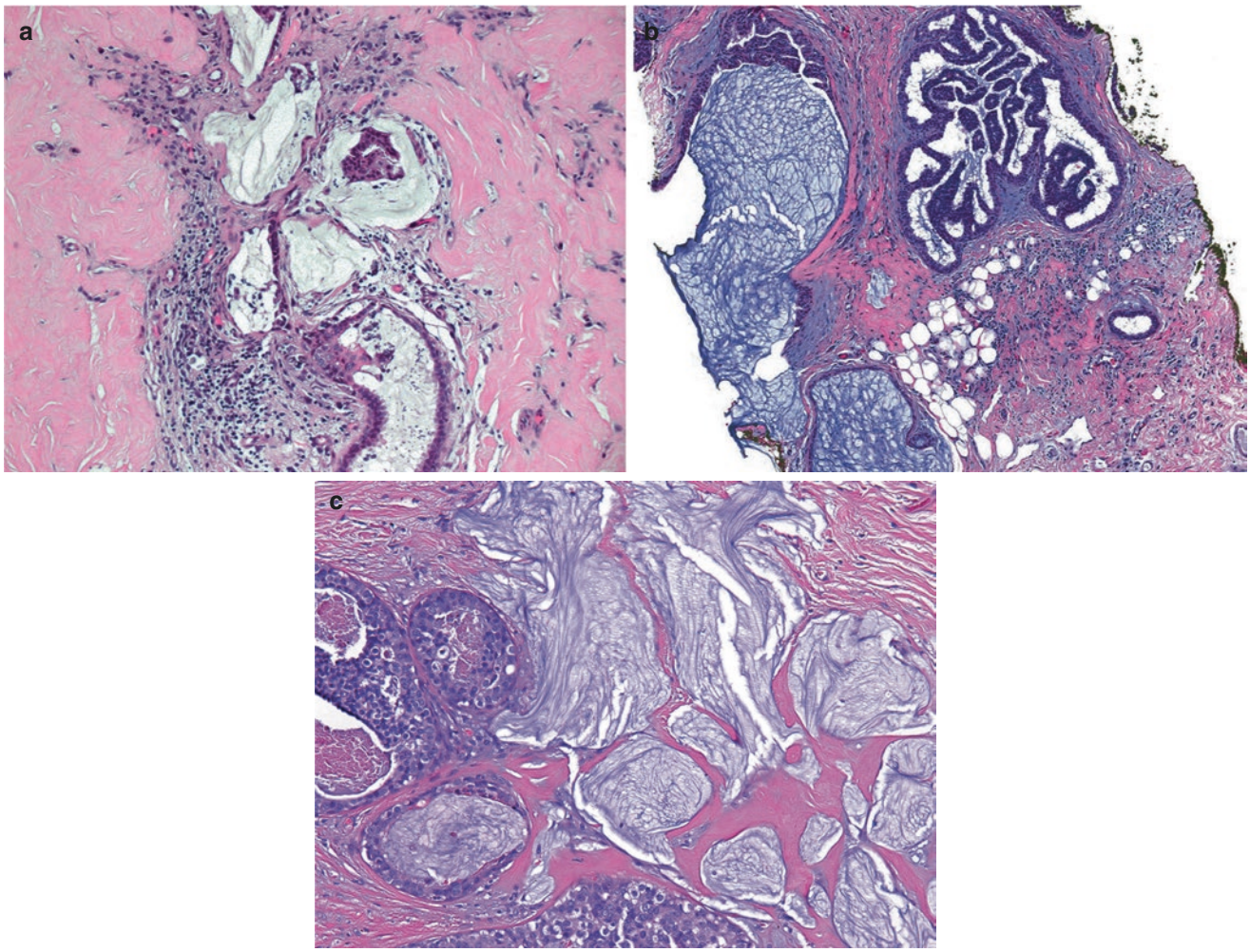


Fig. 13.4 Mucocele-like lesions. (**a**) A cluster of detached epithelial cells floated in the extravasated mucin, mimicking invasive mucinous carcinoma. However, the cell cluster contains mixed epithelial and myoepithelial cells (highlighted by myoepithelial staining, not shown). MLL may also be associated with (**b**) ADH and (**c**) DCIS. Both lesions have extravasated mucin into adjacent stroma. Deeper levels are warranted in these cases to rule out the presence of invasive carcinoma

lial cells as seen in normal duct-lining epithelium. In challenging cases, the presence of myoepithelial cells can be demonstrated using myoepithelial immunostains. In contrast, floating tumor cells of invasive mucinous carcinoma form clusters and lack myoepithelial cells. Additionally, vascular proliferations within the delicate septa of the mucin pools are usually prominent in mucinous carcinoma and not present in MLLs, as angiogenesis is the hallmark of cancer. When MLL is associated with ADH or DCIS, the epithelial lining contains monotonous cells with regular spacing and distinct cell borders, forming cribriform or micropapillary architecture (Fig. 13.4b, c).

Mucinous carcinomas of other organs, such as colorectum, lung, or gynecologic tract, metastatic to breast have been rarely encountered (Fig. 13.5). A good clinical history is helpful in the differentiation of metastatic mucinous carcinoma from primary mucinous carcinoma. Histologically, primary mucinous carcinoma of the breast has relatively low histologic grade. Immunohistochemical stains are positive for hormone receptors in most primary breast tumors as compared to metastatic mucinous carcinomas. Tissue-specific markers such as GATA3, TTF1, CDX2, and PAX8 are useful for identifying tumor origin. WT1 staining is not useful in the differential diagnosis, as it can be positive in mucinous carcinoma of the breast.

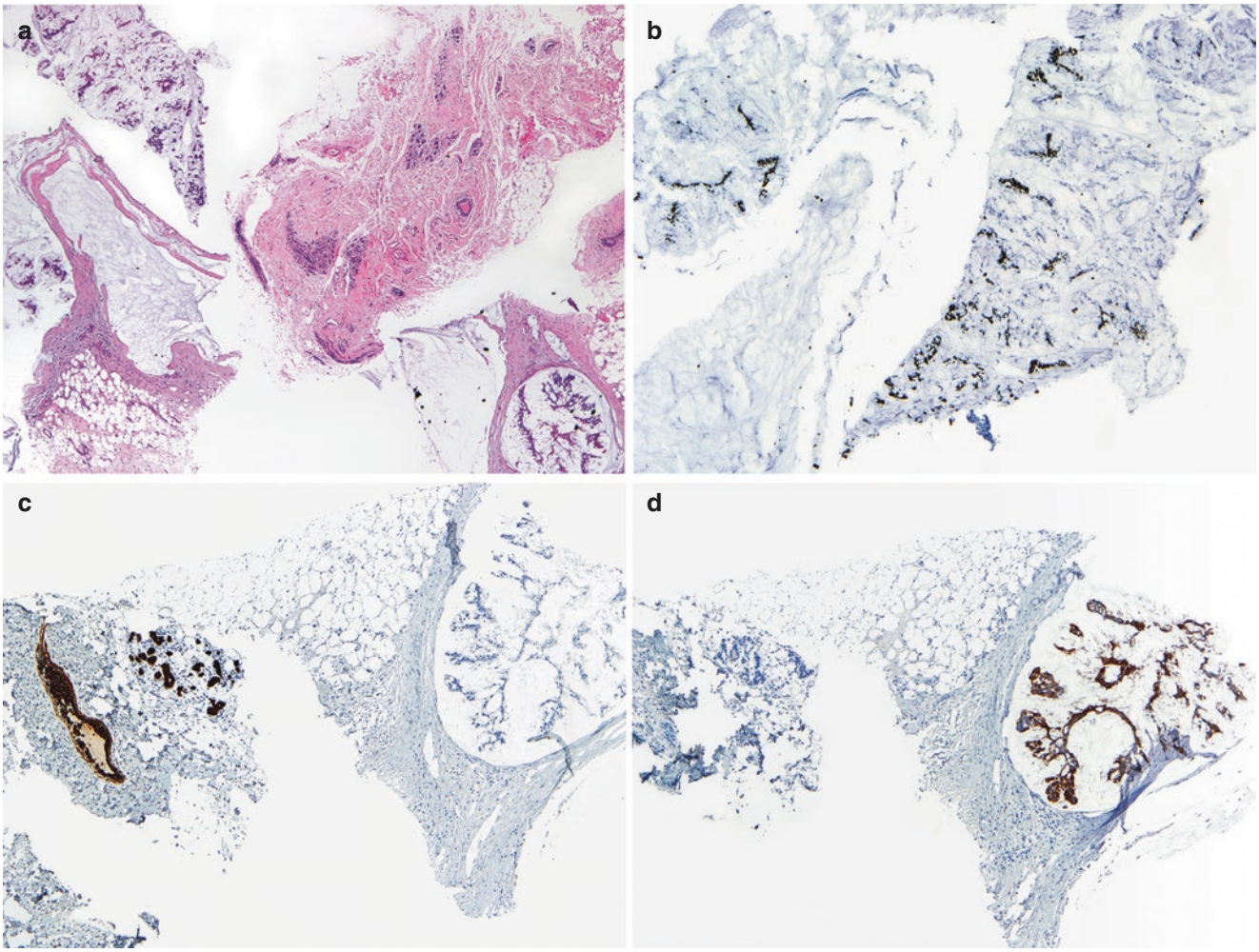


Fig. 13.5 Mucinous carcinoma from colorectal origin metastatic to the breast. (**a**) CNB demonstrates mixed mucinous carcinoma and normal breast tissue. The tumor cells are negative for hormone receptors, raising suspicion for metastatic carcinoma. Further workup demonstrates that the tumor cells are positive for (**b**) CDX2 and (**d**) CK20 and negative for (**c**) CK7; in contrast, the normal breast tissue is positive for CK7 and negative for CK20. The history of rectal mucinous carcinoma also supports the above diagnosis

Immunohistochemical Workup

More than 90% of mucinous carcinomas are estrogen receptor (ER) positive, and about 70–80% of them are progesterone receptor (PR) positive [2, 3]. HER2 overexpression or amplification is uncommon in conventional mucinous carcinoma but can be seen in 20–33% of mucinous micropapillary carcinoma [8, 9].

Pathogenesis

The pathogenesis of mucinous carcinoma is still under investigation. Available data show that mucinous carcinoma has a different molecular pathogenesis than invasive ductal carcinoma NST [16, 19]. A low level of genetic instability is identified in these tumors [16]. The gene profile of hypocellular mucinous carcinoma is different from that of the hypercellular type. The genetic profile of hypercellular mucinous carcinoma is similar to that of neuroendocrine carcinoma (NEC), which is consistent with the clinicopathologic finding that some hypercellular mucinous carcinomas show neuroendocrine differentiation [16].

Prognosis

Conventional pure mucinous carcinoma in general is associated with an excellent prognosis [2, 3]. The largest series with more than 11,000 patients showed disease-specific survival of 94% (5 years), 89% (10 years), 85% (15 years), and 81% (20 years) as compared to 82% (5 years), 72% (10 years), 66% (15 years), and 72% (20 years) in patients with invasive ductal carcinoma NST [3]. An earlier study

showed that the 5-year overall survival of patients with mucinous carcinoma was similar to that of the age-matched general population [2]; however, late distant recurrence may occur after 25 years [2]. While rates of regional nodal involvement are low (12–14%) [3, 20], nodal status is the most significant prognostic factor followed by age, tumor size, hormonal receptor status, and nuclear grade [3]. The prognostic significance of neuroendocrine differentiation in mucinous carcinoma remains unclear.

As mentioned previously, mucinous micropapillary carcinoma appears to be a distinct clinicopathologic entity with a more aggressive clinical course [8–12]. Early local recurrence has been reported in affected patients. A recent study with 10-year follow-up showed that patients with invasive mucinous micropapillary carcinoma experienced worse recurrence-free and overall survival than those with stage (II–III)-matched conventional mucinous carcinoma [10]. However, the prognosis of patients with invasive mucinous micropapillary carcinoma is still better than that of patients with invasive micropapillary carcinoma in all stage I–III-matched cases [10]. Therefore, it appears that the prognosis of patients with invasive mucinous micropapillary carcinoma is in between that of those with conventional mucinous carcinoma and invasive micropapillary carcinoma.

Invasive Micropapillary Carcinoma

Overview

Invasive micropapillary carcinoma was first described by Fisher et al. in 1980 [21] and further defined by Petersen [22] and Siriaunkgul and Tavassoli in 1993 [23]. Pure invasive micropapillary carcinoma accounts for <2% of all invasive breast carcinomas. However, about 7% of invasive ductal carcinomas of NST contain a focal micropapillary component [24]. Pure micropapillary carcinoma and mixed micropapillary carcinoma have higher frequencies of lymphovascular invasion and axillary nodal metastasis as compared to invasive mammary carcinoma NST [24].

About half of the patients with invasive micropapillary carcinoma present with a palpable mass. The age at diagnosis is similar to that of patients with invasive mammary carcinoma NST.

Gross and Radiologic Features

Invasive micropapillary carcinomas do not have specific gross or radiographic features. Similar to invasive carcinoma NST, it often presents as an irregular mass with white/tan firm cut surfaces on gross examination. Radiographically, both mammogram and ultrasound display imaging findings that are highly suspicious for malignancy [25, 26]. Mammogram often shows a high-density irregular mass with infiltrating margins and associated microcalcifications. Sonogram similarly shows an irregular hypoechoic mass.

Microscopic Features

Characteristically, the tumor cells are arranged in small nests or glands surrounded by clear stromal spaces. In contrast to true papillary structures, fibrovascular cores are absent within tumor cell nests (Figs. 13.6 and 13.7). The tumor cells have reverse polarity, with the apical aspect of cytoplasmic membrane facing the empty stromal space instead of the luminal space. This histologic feature can be confirmed by

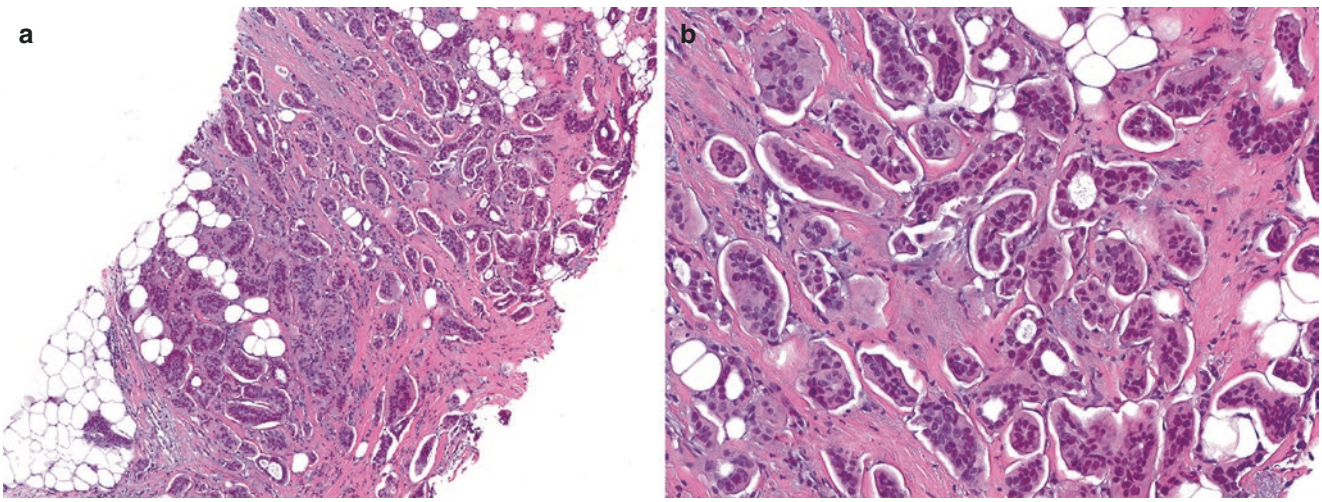


Fig. 13.6 Invasive micropapillary carcinoma. (**a**) CNB reveals small nests and glands of tumor cells with clear spaces around them. (**b**) The tumor cells are low grade in this case

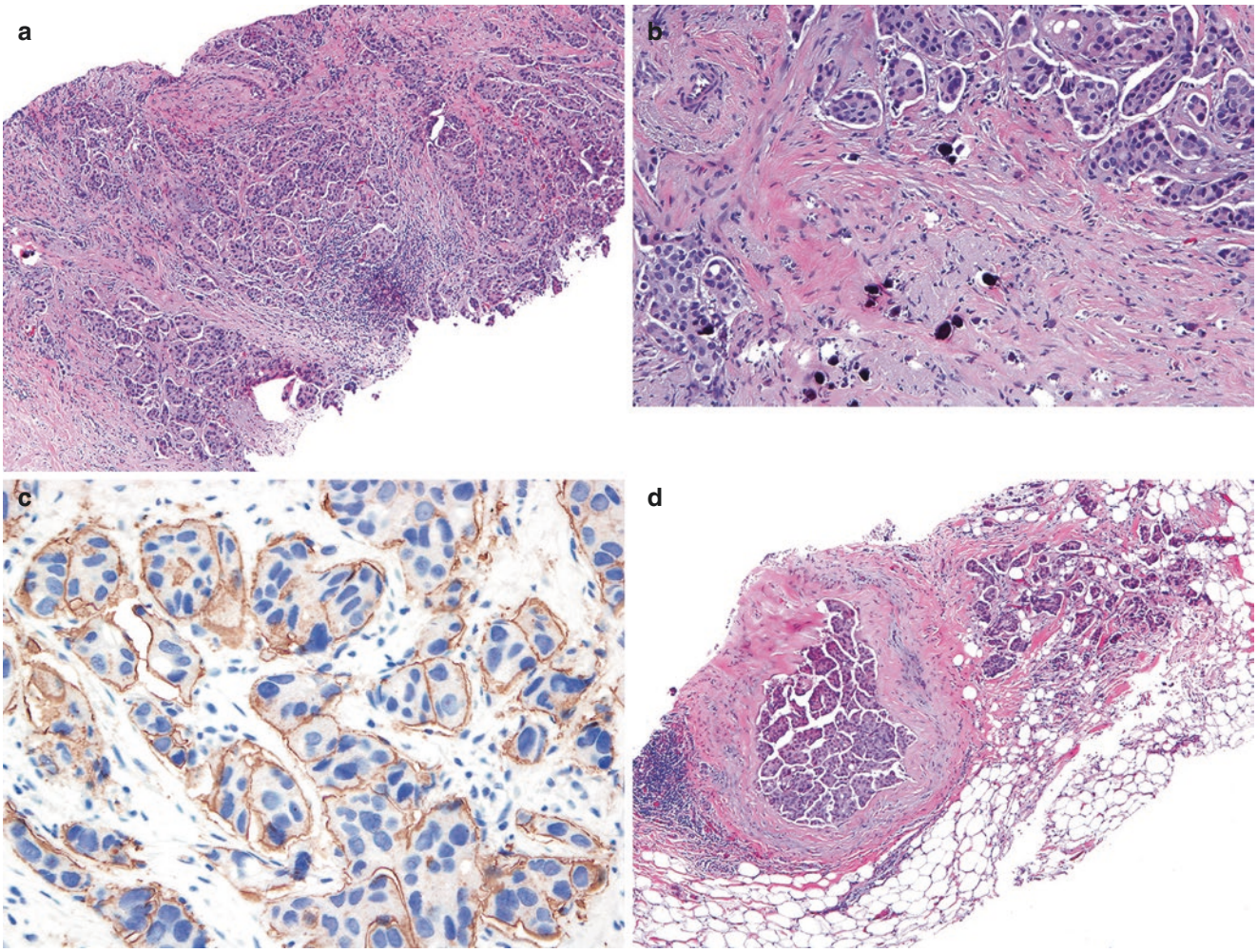


Fig. 13.7 Invasive micropapillary carcinoma with associated psammoma bodies. (**a**, **b**) CNB shows small nests of tumor cells with clear spaces around them. Psammoma bodies are readily identified in the tumor stroma. The tumor cells in this case are moderately differentiated. (**c**) Immunohistochemical staining of EMA highlights the outside cellular membranes of the tumor cell nests, indicating the "inside-out" reverse polarity of the tumor cells. (**d**) Vascular invasion is also identified in the adjacent tissue

MUC1 or epithelial membrane antigen (EMA) immunohistochemical staining (Fig. 13.7c) [27, 28]. The MUC1 and EMA staining highlight the cellular membrane facing the stromal surface in micropapillary carcinoma, while inner/luminal cell surfaces are highlighted in non-micropapillary carcinoma. Only a minority (7%) of invasive ductal carcinomas with no clear-cut micropapillary pattern show the staining pattern seen in micropapillary carcinoma [29]. Psammomatous calcifications are occasionally present (Fig. 13.7a). Invasive micropapillary carcinoma is often of low to intermediate grade, and overt nuclear pleomorphism is rare. Occasionally, invasive micropapillary carcinoma with apocrine features is seen.

The characteristic presence of a clear space around individual tumor cell nests can be difficult to distinguish from true lymphovascular invasion. However, true lymphovascular invasion is more easily identified in the peri-tumoral lymphovascular bundles (Fig. 13.7d).

Differential Diagnosis

Invasive micropapillary carcinoma needs to be distinguished from invasive carcinoma with retraction artifact. Tumor cells with retraction artifact lack the typical reverse polarity of the glands of invasive micropapillary carcinoma, and this can be confirmed by immunohistochemical staining with MUC1 or EMA.

Another important consideration is the possibility of metastatic carcinoma with micropapillary features from other organs, such as the gynecologic tract or lung. Serous carcinoma of the gynecologic tract is one of the most common

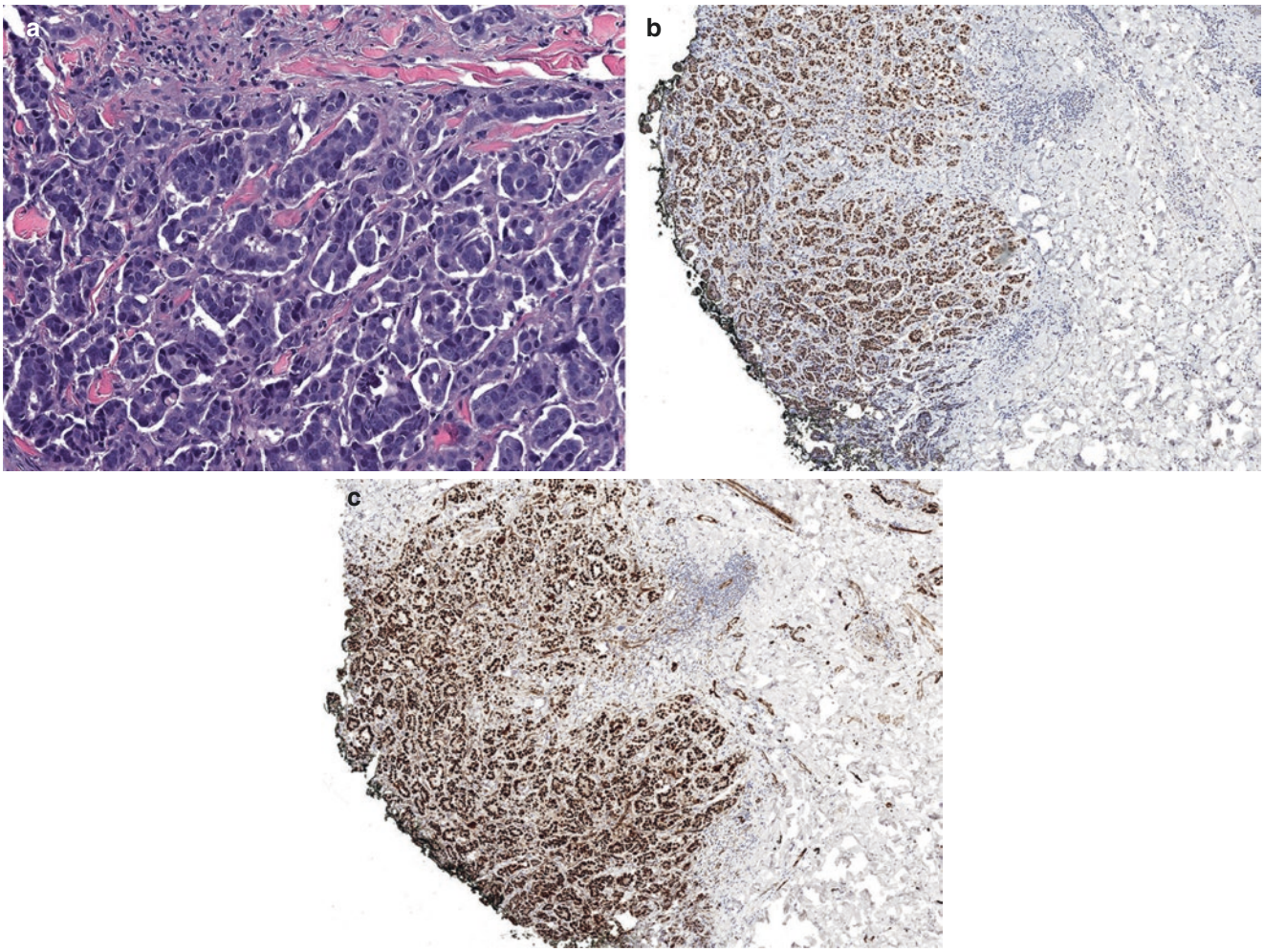


Fig. 13.8 Papillary serous carcinoma metastatic to the breast mimics primary invasive micropapillary carcinoma. (**a**) In this case, patient presented clinically as inflammatory breast cancer with diffuse erythematous skin change. CNB shows the tumor with micropapillary configuration within clear spaces. Prominent lymphovascular invasion is present. Due to prior history of serous carcinoma, immunohistochemical staining of tissue-specific markers was performed, and it revealed that the tumor cells were (**b**) PAX8 positive, (**c**) WT1 positive, and GATA3 negative (not shown), supporting the diagnosis metastatic serous carcinoma

carcinomas metastatic to the breast [30]. Metastatic micropapillary carcinomas from other organs are histologically similar or identical to mammary micropapillary carcinoma, and occasionally they can present clinically as inflammatory breast cancer with extensive dermal lymphatic invasion [31]. Tissue-specific immunohistochemical stains (e.g., TTF1, PAX8, GATA3) and clinical history can be helpful in excluding this possibility (Fig. 13.8).

Immunohistochemical Workup

Most invasive micropapillary carcinomas are ER positive (61–100%) and PR positive (46–83%) [24]. HER2 overexpression is variable and is present in approximately one-third of cases.

MUC-1 or EMA can be used to differentiate true invasive micropapillary carcinoma from retraction artifact, and tissue-specific markers such as GATA3 (breast), TTF1 (lung), PAX8, and WT1 (GYN tract) can be used to differentiate primary versus metastatic carcinoma.

Pathogenesis

The pathogenesis of micropapillary carcinoma is still under investigation. Recent studies show that compared to invasive carcinoma NST, invasive micropapillary carcinoma has a distinct molecular profile including recurrent amplification of the oncogenes *c-MYC*, *CCND1*, and *FGFR1* [32]. In addition, somatic mutations of genes involved in cellular polarity and shape have been identified in pure invasive micropapil-

lary carcinoma, which may contribute to the morphological features of these tumors [33].

Prognosis

Due to the high rate of lymphovascular invasion and regional nodal metastasis, patients with invasive micropapillary carcinoma often present with higher clinical and pathologic stages, and therefore have a relatively poor prognosis [34–36]. The reported 5-year overall survival rate ranges from 59 to 85% [36–38]. The 5-year disease-specific survival rate ranges from 70 to 92% [38, 39]. Nevertheless, when adjusted for stage, patients with micropapillary carcinoma experience similar overall survival as compared to those with invasive mammary carcinoma NST [37].

Similar prognostic factors have been identified in association with invasive micropapillary carcinoma as in invasive mammary carcinoma NST. Age less than 50 years at diagnosis, large tumor size (>2 cm), and negative hormonal receptor status are adverse prognostic factors [38]. Patients with four or more positive regional lymph nodes have a worse prognosis than node-negative patients. However, patients with 1–3 positive lymph nodes have similar disease-specific and overall survival as compared to node-negative patients [38]. It is unclear whether the survival benefits of contemporary chemoradiation therapy in breast cancer patients with low-volume regional nodal disease as seen in the ACOSOG Z0011 trial are also seen in this group of patients [40].

Mucinous Cystadenocarcinoma

Overview

Mucinous cystadenocarcinoma is an exceedingly rare form of breast carcinoma, which was first described in 1998 by Koenig and Tavassoli in their series of four patients [41]. Subsequently, there have been fewer than 30 cases reported in the literature, largely as case reports or small series. Patients are usually postmenopausal and slightly older than those women who develop invasive carcinoma NST [42, 43]. Most recently, the 2019 edition of the WHO Classification of Tumours added this as a special type of breast carcinoma [44].

Gross and Radiologic Features

The typical presentation is that of a solitary breast mass. Grossly, these tumors are described as well-delineated, occasionally lobulated, tumor masses ranging from 0.8 to 19 cm in size [41, 43]. The cut surface is gray-white or tan in color with a cystic and/or mucinous, gelatinous appearance [41, 42]. On mammogram, these tumors are of medium to high density, by ultrasound show mixed hypoechogenicity, or by magnetic resonance imaging show enhancement [45, 46].

Microscopic Features

Histologically, mucinous cystadenocarcinoma consists of closely approximated variably sized cystic spaces lined by neoplastic mucinous epithelial cells, which collectively demonstrate a pushing tumor border. The single layer of epithelium also forms tufts and branching papillae. These cells are cytologically bland with basally located nuclei and abundant intracellular mucin (Fig. 13.9). In some instances, the cells show increasing cytologic atypia and mucin depletion and may rarely demonstrate squamoid features [41, 42]. Luminal mucin has been found extravasated in the adjacent stroma in about one-third of reported cases, however, without floating neoplastic cells [45]. Coexisting invasive carcinomas of NST or mucinous type or with metaplastic features (squamoid, sarcomatous) have been reported [41, 45, 47]. Moreover, concurrent conventional DCIS with intermediate or high nuclear grade or with mucinous features has been reported [45, 47, 48].

Differential Diagnosis

Among other mammary entities, mucinous cystadenocarcinoma should be distinguished from other more common malignancies such as mucinous carcinoma, solid papillary carcinoma with invasion (mucinous carcinoma), and cystic hypersecretory carcinoma. Lobular carcinoma in situ with signet ring cell morphology is a lower priority consideration.

More importantly, exclusion of metastatic carcinoma from the pancreas, appendix, or ovary is paramount. The presence of in situ carcinoma is helpful in excluding metastasis in the differential diagnosis; however, a thorough clinical evaluation and imaging workup should be performed. Immunohistochemical workup is particularly helpful in this regard (see below).

Morphologically, invasive mucinous carcinoma consists of neoplastic epithelial cells floating in pools of extravasated mucin. An important distinction from mucinous cystadenoma is that neoplastic epithelial cells in mucinous carcinoma do not contain abundant intracytoplasmic mucin. A more obvious distinction is that mucinous carcinomas lack a multicystic appearance. In fact, mucinous cystadenocarcinoma is more likely to be mistaken for in situ carcinoma that can accompany invasive mucinous carcinoma exhibiting both intracytoplasmic and luminal, extracellular mucin, however, still lacking a multicystic appearance. Although mucinous cystadenocarcinoma and cystic hypersecretory

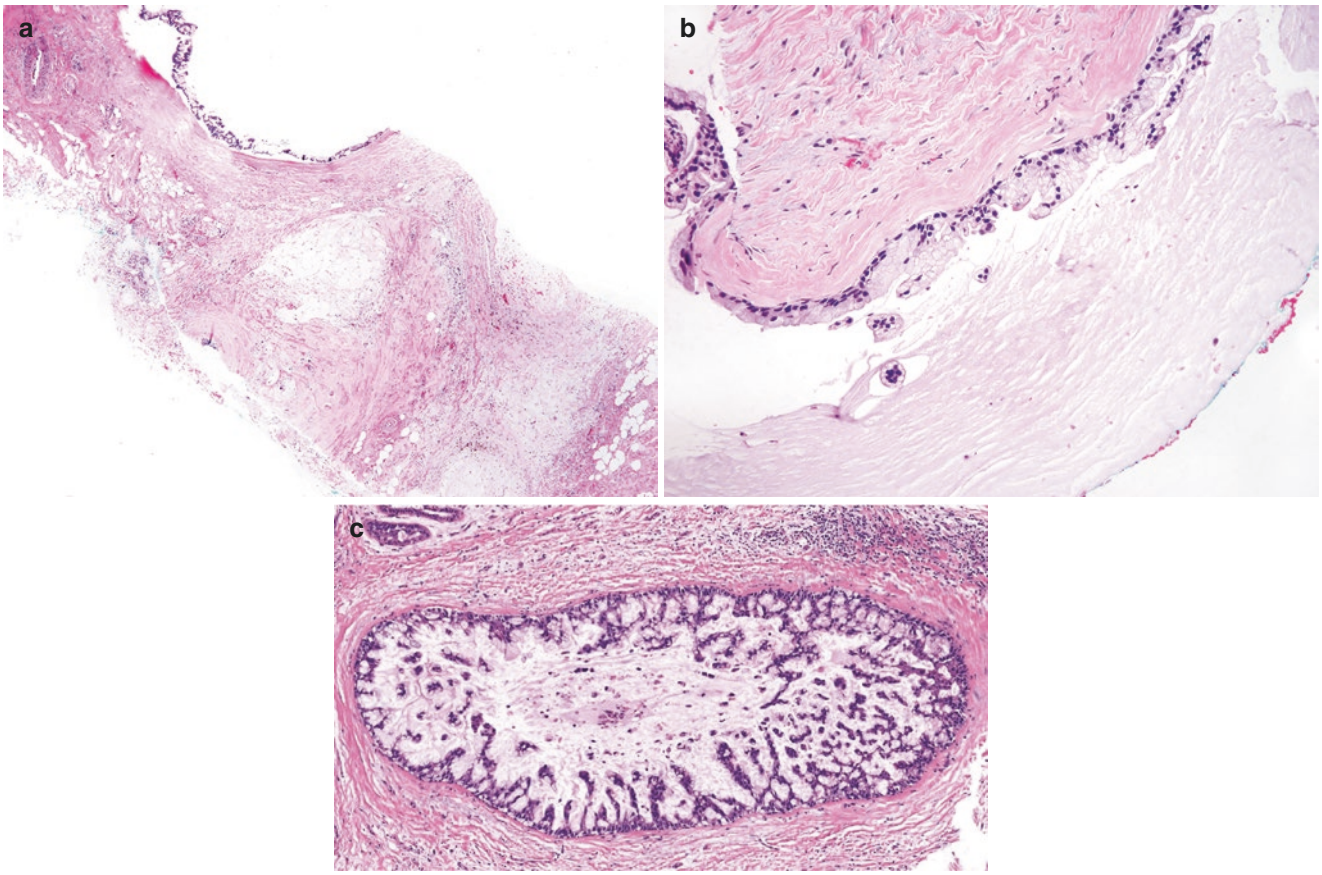


Fig. 13.9 Mucinous cystadenocarcinoma of the breast. (**a**) Low-power magnification of CNB showing a transected cystic space lined by neoplastic mucinous columnar epithelium. (**b**) Higher magnification highlighting neoplastic epithelium with abundant intracellular mucin and basally located nuclei, and abundant luminal mucin. (**c**) Another example of mucinous cystadenocarcinoma with prominent papillae, *courtesy of Dr. Chengqin Wang, Qingdao University Medical College,* with permission

carcinoma share a multicystic appearance at low magnification, the presence of eosinophilic colloid-like luminal secretions and absence of intracellular mucin in the latter are discerning features. Some examples of solid papillary carcinomas produce intracytoplasmic mucin, which can become extracellular and lead to evidence of invasion (mucinous carcinoma). Morphologically, these should be easily distinguishable from mucinous cystadenocarcinoma. See Chap. 6 regarding more information on solid papillary carcinoma with invasion. While there is similarity on the epithelial cellular level, lobular carcinoma in situ with signet ring cell features characteristically obscures the lumens of the terminal duct lobular units in which they occupy.

Immunohistochemical Workup

Mucinous cystadenocarcinomas are triple-negative (ER−/PR−/HER2−) breast carcinomas and typical of invasive carcinomas lack investment by myoepithelial cells as evidenced by absence of staining for myoepithelial markers [41, 45]. Rare HER2+ examples have been reported [49]. Interestingly, Ki-67 proliferation index is notably high in these tumors (20.5–90% in reported cases) despite its characteristically favorable prognosis [45, 49]. Like other breast carcinomas, mucinous cystadenocarcinomas show an immunoprofile of CK7+/CK20−/CDX2−, whereas metastatic mucinous adenocarcinomas from the ovary/pancreas or colon show different immunoprofiles of CK7+/CK20+/CDX2+ and CK7−/CK20+/CDX2+, respectively. It is important to note that markers considered to be breast specific (GATA3, GCDFP-15, mammaglobin) can be negative. In contrast to mucinous cystadenocarcinomas, invasive mucinous carcinomas are typically ER+/PR+ and exhibit a low Ki-67 proliferation index. More recently, investigators have found that these tumors exhibit a MUC5+/MUC2− immunoprofile, which appears to distinguish them from other mucinous-type carcinomas both primary and metastatic to the breast [43, 50]. More studies are needed to validate this potentially unique characteristic of mucinous cystadenocarcinoma.

Pathogenesis

The pathogenesis is currently uncertain, largely due to the inability to study this rare tumor in sufficient numbers. With that said, Nayak et al. surmised that due to the presence of "focal abrupt squamous differentiation" in several cases including their own, as well as other reports of sarcomatous transformation, mucinous cystadenocarcinomas are a result of metaplastic differentiation in the breast [45]. Chen W-Y et al. separately described a transition from conventional DCIS to "mucinous cystadenocarcinoma in situ," suggesting a process of metaplasia [47].

Prognosis

Patients experience a favorable prognosis, and recurrence is infrequent. Most reported patients are alive without evidence of disease; three cases have reportedly died of disease in 14 months to 9 years [48].

Neuroendocrine Neoplasm

Overview

Neuroendocrine neoplasm (NEN) of the breast is an evolving and controversial entity. Its prevalence is reported to be <1% of all breast carcinomas [51]. Nevertheless, the true prevalence is hard to assess as neuroendocrine markers are not routinely evaluated on breast cancers. It was first recognized in 1963 by Feyrter and Hartmann who reported two invasive breast cancers with carcinoid growth pattern [52]. Later, it was described by Cubilla and Woodruff as "carcinoid tumor of the breast" due to its morphological similarity to carcinoid tumors of other organs [53].

In the distant past, a modified silver (Grimelius) stain and electron microscopy were utilized to identify neurosecretory granules [54]. Currently, however, neuroendocrine differentiation is demonstrated by immunohistochemical staining for neuroendocrine-specific markers, such as synaptophysin and chromogranin.

Limited numbers of case reports and case series have been published in the literature using various cutoffs for neuroendocrine differentiation [55–74]. Mammary NEN was first officially adopted into the World Health Organization (WHO) Classification of Tumours in 2003 as "neuroendocrine carcinoma," a subtype of invasive mammary carcinoma bearing histologic features similar to NEN of the lung and gastrointestinal tract, with expression of neuroendocrine markers in >50% of the tumor cells [75].

In the 2012 edition of the WHO Classification of Tumours, the spectrum of mammary NEN was broadened into a category of "carcinoma with neuroendocrine features," which included well-differentiated neuroendocrine tumor, poorly differentiated neuroendocrine carcinoma, and invasive carcinoma with neuroendocrine differentiation [51]. The requirement for >50% tumor cells expressing neuroendocrine markers was not present in the 2012 WHO edition.

Most recently, the 2019 edition of the WHO Classification of Tumours lists "neuroendocrine neoplasm" as a separately defined entity with regard to invasive breast carcinoma NST [76]. This change is based on a recommendation from the expert panel of the International Agency for Research on Cancer that a uniform classification for neuroendocrine neoplasms should be applied to all organ systems, including breast [77]. As a result, the WHO currently defines breast NEN as tumors with >90% neuroendocrine histologic pattern and diffuse (>50%), uniform immunoreactivity for synaptophysin and/or chromogranin. NEN is further subclassified as well-differentiated neuroendocrine tumor (NET) or NEC based on diagnostic criteria similar to those used in the gastrointestinal tract and lung. Special entities including mucinous carcinoma with neuroendocrine differentiation and solid papillary carcinoma are no longer classified as NEN of the breast [76].

A large database study showed that the age of patients with mammary NEN ranged from 26 to 99 years (mean: 64 years), which is slightly older than patients with invasive carcinoma NST (mean: 61 years) [71]. More than 50% of patients presented with palpable masses; however, approximately 25% were asymptomatic and had tumors detected by screening mammography.

Gross and Radiologic Features

Most tumors are lobulated, with white-to-tan cut surfaces similar to invasive carcinoma NST. Some show red-to-brown and slightly soft cut surfaces due to high intratumoral vascularity. Tumor sizes range from <1 to 11 cm (median: 2.5 cm) [71]. Lobulated mass lesions are the most common radiographic findings by mammography and sonography [78].

Microscopic Features

Neuroendocrine neoplasm of the breast shows morphologic features similar to its counterparts in the lung or gastrointestinal tract. Well-differentiated NET often exhibits a nested histologic pattern, which can be dispersed or packed to form large tumor nodules, with sinusoid-like vasculature. The tumor cells can be round, ovoid, plasmacytoid, or spindled. The cytoplasm is typically eosinophilic, granular, or clear [79]. Examples are shown in Figs. 13.10, 13.11, and 13.12. Whereas well-differentiated NETs in the gastrointestinal tract are classified as grades 1, 2, or 3 based on mitotic rate

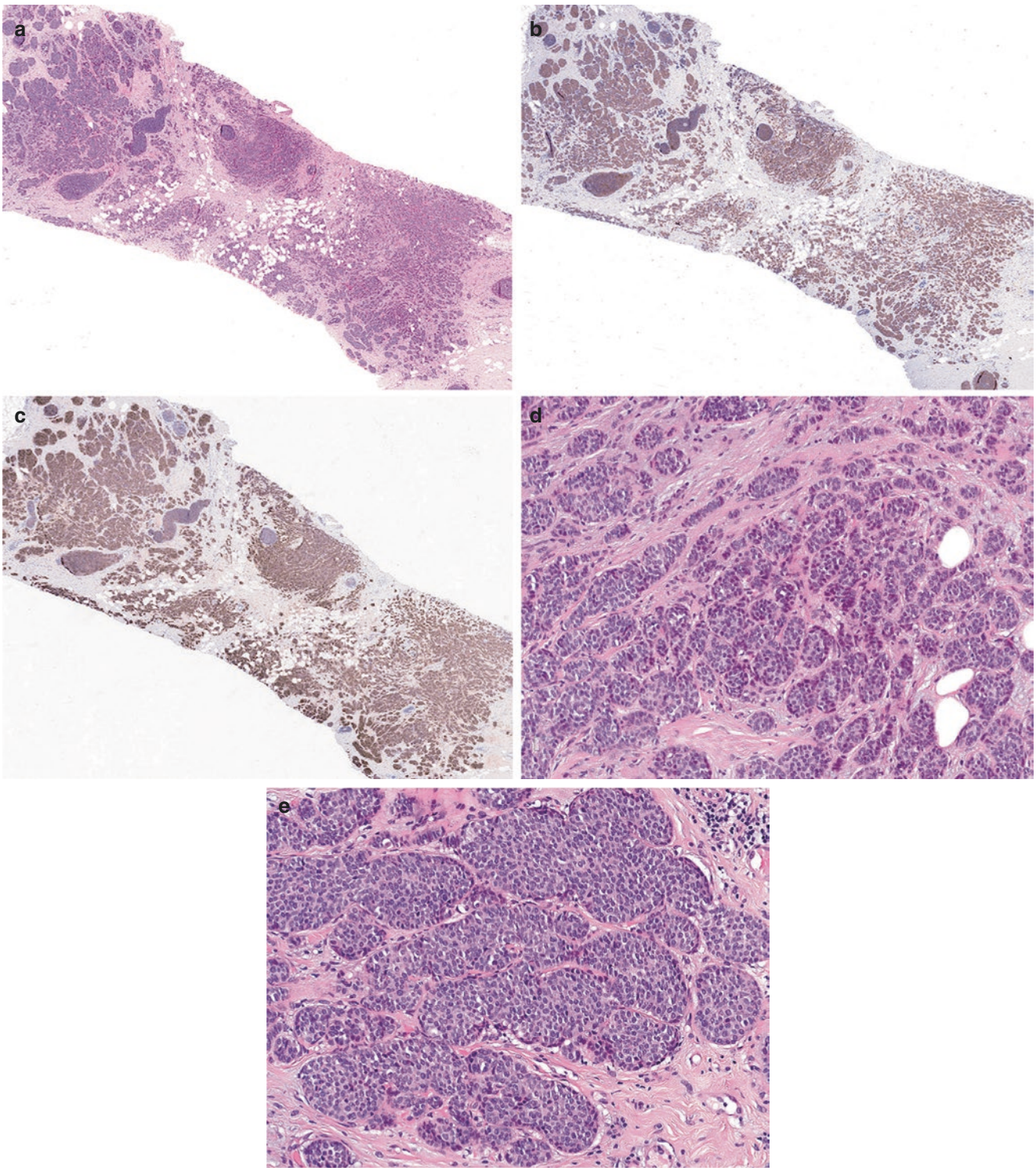


Fig. 13.10 Neuroendocrine tumor with a nested growth pattern. (**a**) Low-power view shows an invasive component with associated carcinoma in situ. Both invasive and in situ tumor cells are diffusely positive for (**b**) synaptophysin and (**c**) chromogranin. (**d**, **e**) Medium- and high-power views show that the tumor cells are uniformly low grade

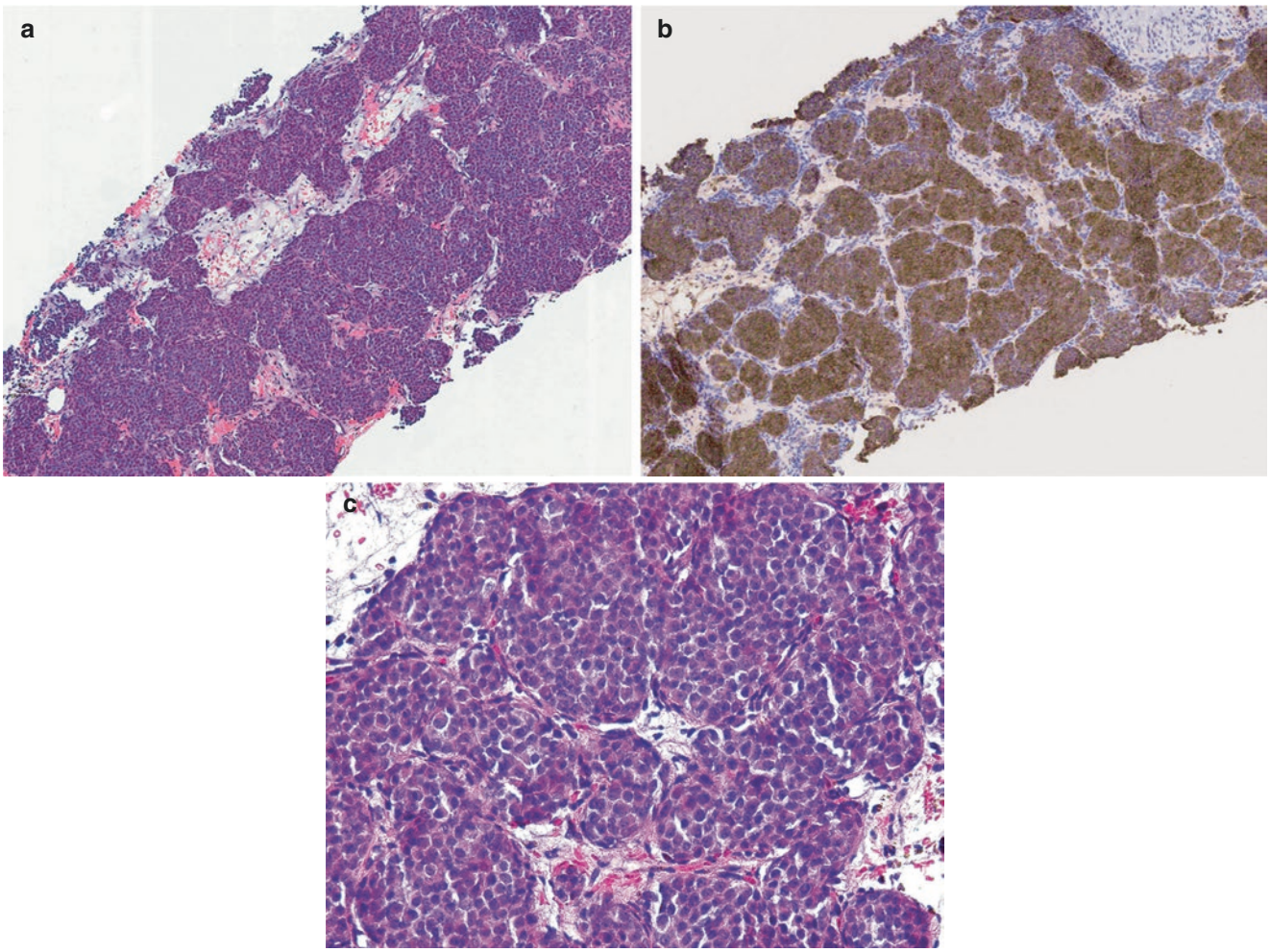


Fig. 13.11 Neuroendocrine tumor with an alveolar growth pattern. (**a**) Low-power view shows tumor cells arranged in organoid nests with intervening sinusoidal vasculature. (**b**) Tumor cells are diffusely positive for synaptophysin. (**c**) Medium-power view shows that the tumor cells are low to intermediate grade

and Ki-67 proliferation index, the WHO still recommends Nottingham histologic grading for breast neuroendocrine neoplasms. Nevertheless, both grading schemes are highly concordant as mitotic count constitutes one of the main parameters in both systems.

Poorly differentiated NECs are subdivided into large-cell neuroendocrine carcinoma and small-cell carcinoma. Small-cell carcinoma of the breast is histologically identical to its counterparts in other organs. It is composed of densely packed tumor cells with hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm. Nuclear molding, brisk mitoses, and tumor necrosis are frequent (Fig. 13.13). Most mammary small-cell carcinomas are associated with an in situ carcinoma. Half are associated with invasive ductal carcinoma NST or invasive lobular carcinoma [80].

Large-cell NEC is composed of nests of large tumor cells with abundant granular or clear cytoplasm, vesicular nuclei, and prominent nucleoli. Tumor nodules are often supported by fibrovascular septa with rich vasculature. Brisk mitotic activity and tumor necrosis are frequently present (Fig. 13.14). Differentiating large-cell NEC from grade 3 well-differentiated NET can sometimes be challenging. Compared to grade 3 NET, large-cell NEC shows significantly more cytologic atypia and lacks the classic architectural pattern of NET. Table 13.1 lists a few additional features that can help to differentiate the two.

Differential Diagnosis

The main differential diagnosis for primary mammary NEN is metastatic NEN from other organs to the breast. Due to their overlapping or identical histologic features, clinical history in conjunction with tissue-specific markers such as GATA3 (breast), TRPS1 (breast), TTF1 (lung), and CDX2 (gastrointestinal tract) is essential for correct diagnosis [82, 81]. The presence of DCIS supports mammary primary; however, it is important to bear in mind that metastatic NEN

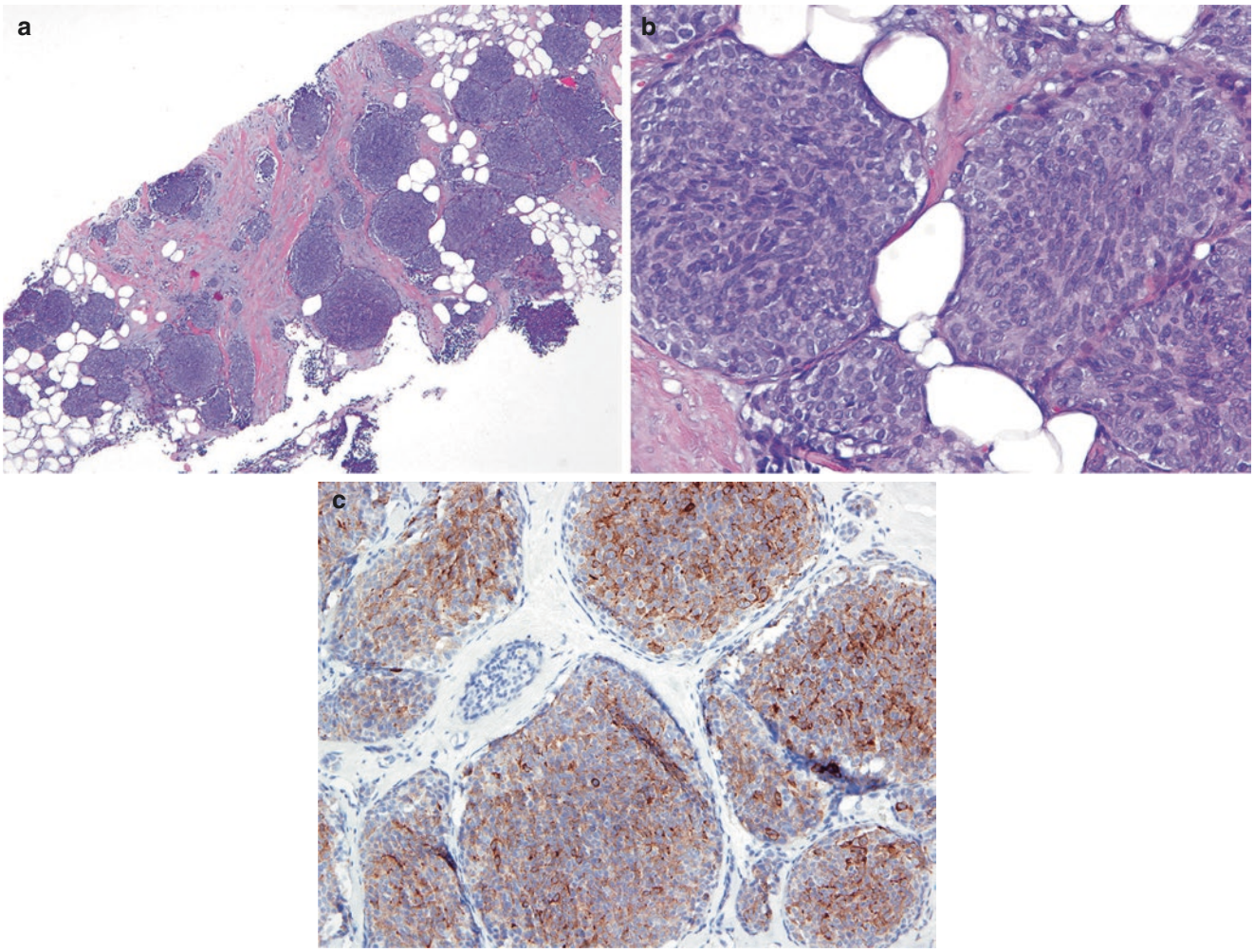


Fig. 13.12 Neuroendocrine tumor with prominent spindled cells. (**a**) The tumor cells are arranged in variably sized nests infiltrating fibroadipose tissue. (**b**, **c**) High-power views demonstrate that the tumor cells are predominantly spindled and are diffusely positive for synaptophysin

can morphologically mimic in situ carcinoma (Fig. 13.15). Histologically and immunohistochemically, primary mammary small-cell carcinoma is indistinguishable from metastatic small-cell carcinoma. Therefore, the presence of DCIS or an invasive carcinoma NST component and clinical history are key in distinguishing between the two.

Immunohistochemical Workup

By definition, >50% of the tumor cells should express neuroendocrine markers. Synaptophysin and chromogranin are considered to be the most specific markers for neuroendocrine differentiation [83]. Other markers such as neuron-specific enolase (NSE) and CD56 are sensitive, but not specific, for NEN [83]. INSM1, a potential novel neuroendocrine marker, is currently under investigation.

Most mammary NETs express estrogen receptor (77–95%) and progesterone receptor (40–70%) and are negative for HER2 overexpression or amplification. Breast NENs also express GATA3 and TRPS1, which can be used to differentiate primary mammary tumors from metastases. Of note, TTF1 is not helpful for differentiating primary mammary small-cell carcinoma from metastatic small-cell carcinoma as both mammary and non-mammary small-cell carcinomas can express TTF1.

Pathogenesis

The pathogenesis of mammary NEN is still under investigation. Unlike the lung and gastrointestinal tract, endogenous endocrine cells do not reside in normal breast tissue. One hypothesis is that mammary NENs are derived from argyrophilic cells of neural crest origin, which migrate to the breast. Recently, two studies showed the presence of isolated and hyperplastic benign-appearing neuroendocrine cells in breast parenchyma containing NEN, suggesting that neuroendo-

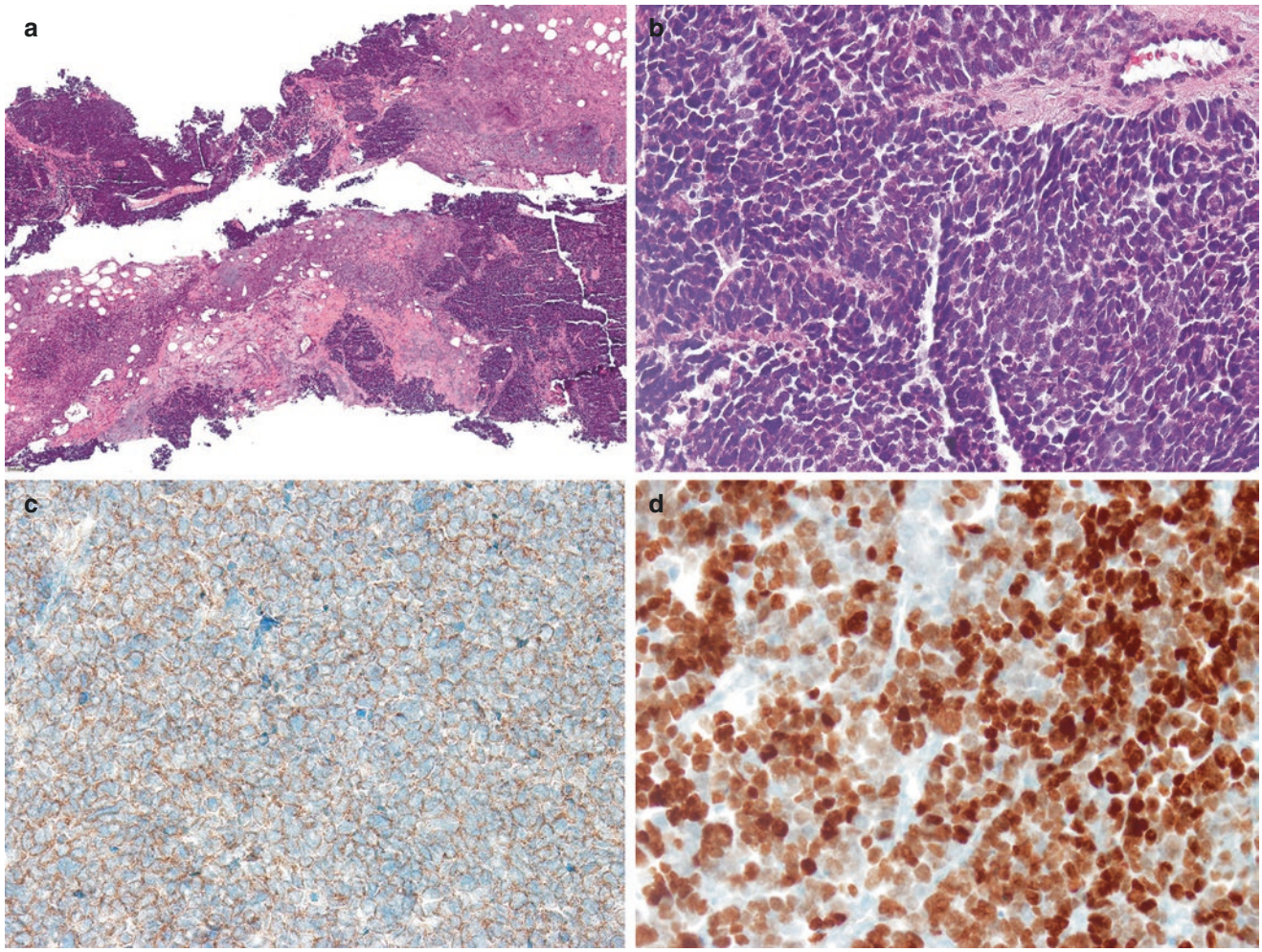


Fig. 13.13 Small-cell carcinoma. (**a**) CNB shows a friable tumor with a large area of necrosis. (**b**) Medium-power view shows densely packed tumor cells with scant cytoplasm, hyperchromatic nuclei, and absence of nucleoli. Nuclear molding is prominent. Mitoses are also readily identified. The tumor cells are diffusely positive for (**c**) synaptophysin and (**d**) TTF1

crine cell hyperplasia might be a precursor lesion to NEN in the breast [84, 85].

Another hypothesis is that mammary NEN originates from cancer stem cells with divergent luminal epithelial and neuroendocrine differentiation. A recent study showed that most mammary NENs fell into the luminal B molecular subtype of breast cancer [86]. Consistent with the wide morphological spectrum of NEN, limited cytogenetic studies have revealed various genetic changes with low-grade mammary NET sharing some cytogenetic abnormalities seen in low-grade NETs of the lung and gastrointestinal tract, while poorly differentiated mammary NECs demonstrate considerably more complex genetic abnormalities, suggesting that different molecular alterations underlie various types of NEN in the breast [87].

Next-generation sequencing (NGS) analysis has revealed the presence of mutations in *FGFR1*, *FGFR2*, *VEGFR2*, and *HRAS* genes, which are extremely rare in invasive mammary carcinoma NST. These findings suggest the potential for targeted therapy against specific tyrosine kinase receptors for breast NENs [88].

Prognosis

The clinical outcome varies and depends on the type of NEN. Poorly differentiated NEC, whether small or large cell, carries a very poor prognosis.

There are conflicting results concerning the clinical outcomes of the vast majority of mammary NEN, namely, the well-differentiated NETs [57, 60, 61, 63, 64, 66–75]. Some of these conflicting results are secondary to differing diagnostic criteria for neuroendocrine differentiation used in previous years. However, most of the recent large series studies indicate that mammary NET has a worse clinical outcome as compared with invasive carcinoma NST [68–70, 72–74, 89].

The most recent surveillance, epidemiology, and end result database study showed that both NET and NEC have

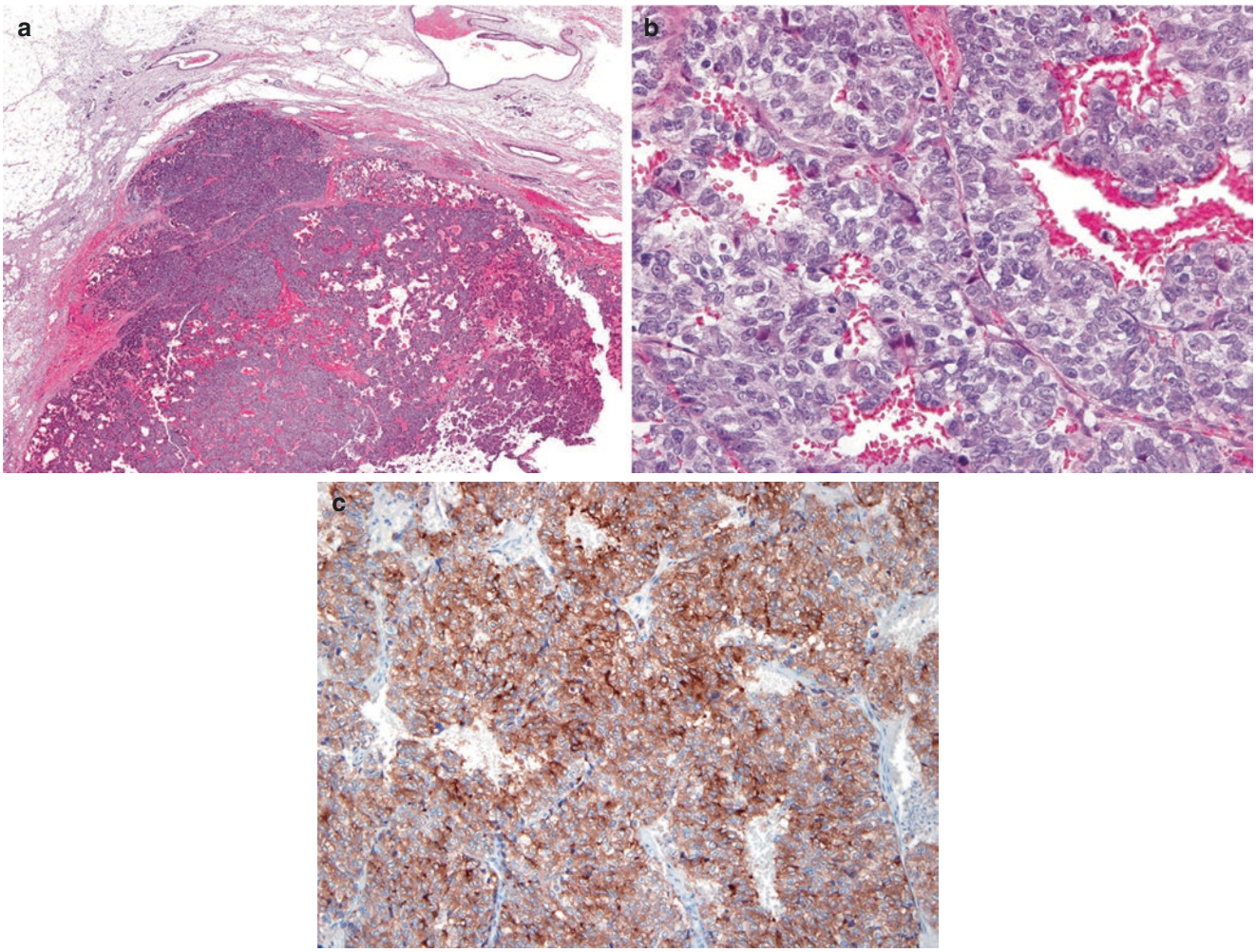


Fig. 13.14 Large-cell neuroendocrine carcinoma. (**a**) The tumor is relatively well circumscribed. (**b**) Tumor cells are large with clear to granular cytoplasm, vesicular nuclei, and prominent nucleoli and show brisk mitosis. Prominent vasculature is present. (**c**) Tumor cells are diffusely positive for synaptophysin

Table 13.1 Differentiating grade 3 neuroendocrine tumor from large-cell neuroendocrine carcinoma

	Mitoses (per 10 HPF)	Ki-67 index (%)	Loss of RB protein/ p53 mutation
Grade 3 NET	Often >20	>20, usually <55	–
Large-cell NEC	Usually >20	Usually >55	+

worse overall survival (OS) and disease-specific survival (DSS) than invasive ductal carcinoma NST [89]. The 5-year OS rates for NET, NEC, and invasive ductal carcinoma NST are 56%, 39%, and 83%, respectively. The 5-year DSS rates for NET, NEC, and invasive ductal carcinoma NST are 63%, 46%, and 89%, respectively. While NEN tends to present with more advanced disease (36% with regional nodal metastasis and 20% with systemic metastasis), even within the same stage or grade, NET and NEC have worse OS and DSS than corresponding stage or grade invasive ductal carcinoma NST [89]. Several case-control studies that matched clinical and pathologic parameters, including age, stage, hormone receptor status, and surgical procedure, further confirm the adverse outcome of patients with NEN compared to those with invasive carcinoma NST [67, 72, 74].

Of note, invasive carcinoma with neuroendocrine differentiation (<50% of the tumor cells expressing neuroendocrine markers) is no longer classified as NEN of the breast. It may constitute up to 30% of invasive breast cancer NST. Early studies indicated that invasive carcinoma with focal neuroendocrine differentiation does not differ prognostically from invasive carcinoma NST [60, 61].

Multivariate analyses show that positive regional nodal status, negative PR status, and lack of surgery are adverse independent prognostic factors for DSS [71] and that posi-

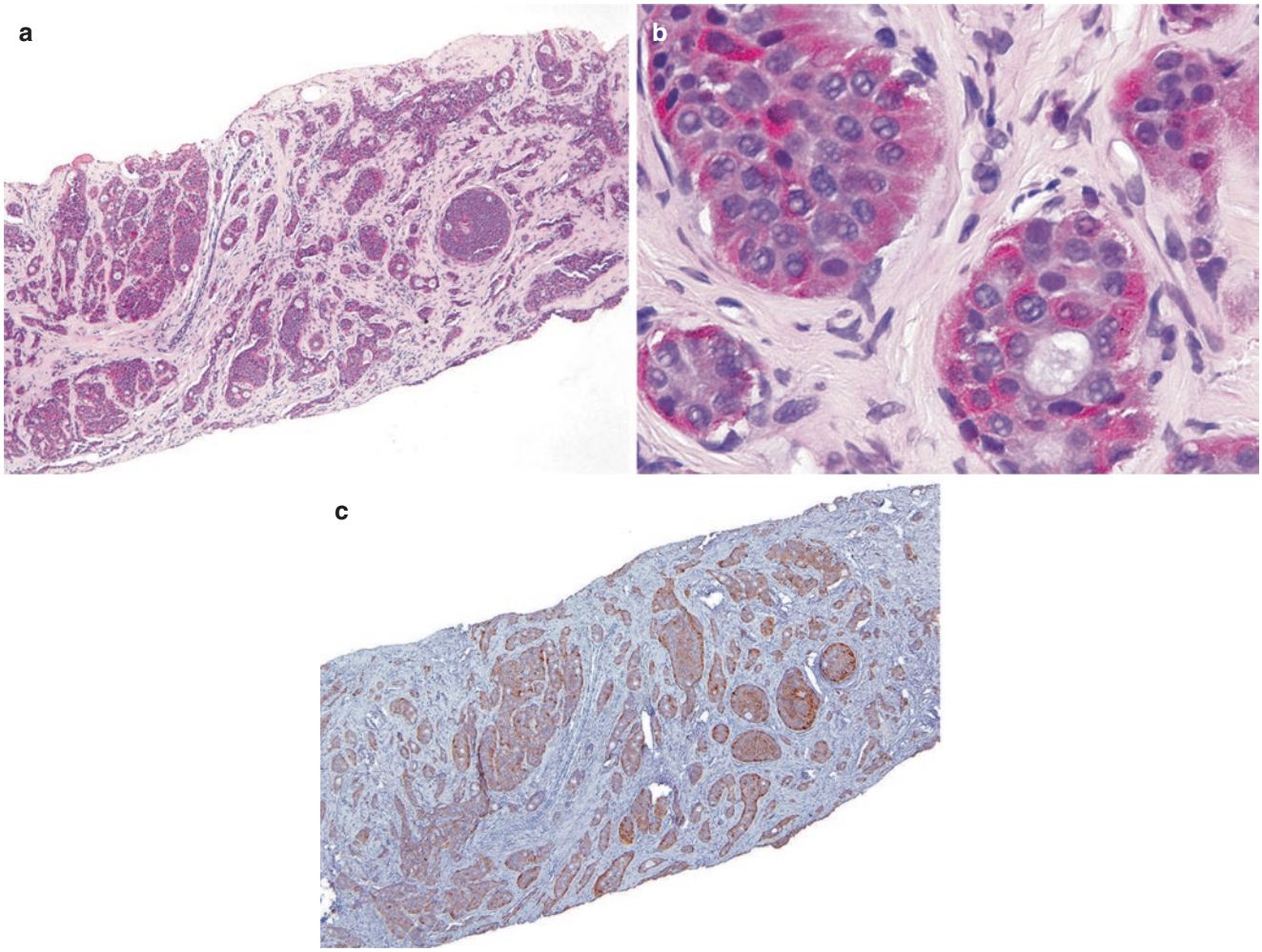


Fig. 13.15 Metastatic neuroendocrine tumor from ileum mimicking primary neuroendocrine tumor of the breast. (**a**) Low-power view of the CNB shows tumor cells arranged in solid nests, cords, and glands, mimicking invasive ductal carcinoma with DCIS. (**b**) High-power view demonstrates prominent eosinophilic neuroendocrine granules. (**c**) Neuroendocrine differentiation is confirmed by immunohistochemical staining with synaptophysin

tive regional nodal status, advanced age (>60 years), and high Ki-67 proliferation rate are independent adverse prognostic factors for OS in mammary NEN [71, 89, 90].

Cystic Hypersecretory Lesions Including Cystic Hypersecretory Carcinoma

Overview

Cystic hypersecretory lesions (CHLs) include cystic hypersecretory hyperplasia (CHH), CHH with atypia, and cystic hypersecretory (in situ) carcinoma (CHC), all of which share a common histologic characteristic of closely arranged cysts of varying sizes. CHLs come to medical attention due to their tendency to form a breast mass or cause nipple discharge and more recently present as a radiographic abnormality including mammographically detected calcifications [91]. The epithelial lining of these cysts varies from benign to atypical to carcinomatous, which in turn determines their classification as CHH, CHH with atypia, and CHC, respectively.

Cystic hypersecretory carcinoma is a distinct histologic type of in situ carcinoma that is associated with an indolent clinical course. Rarely, invasive carcinoma can arise in a CHL (invariably also containing areas of CHC), and a subset of these patients are also found to have metastatic involvement of axillary lymph nodes.

Gross and Radiologic Features

CHLs commonly form a grossly evident mass, which can attain a large size (up to 10 cm) but typically average about 5 cm in greatest diameter [91–100]. They are firm, and the cut surface is gray-brown with multiple cysts. The cysts vary in size and are filled with viscous gelatinous or mucoid material. Areas that are histologically found to be CHC versus CHH are indistinguishable by gross examination.

The mammographic appearance of mass-forming CHLs is varied and ranges from unremarkable to a focal asymmetry or a mass without calcifications [91, 98, 101, 102]. More recently, some examples have been identified mammographically by their association with calcifications [91]. By sonography, mass-forming CHLs have been described as an anechoic heterogeneous mass containing multiple small cysts and dilated ducts [97, 101, 103].

Microscopic Features and Differential Diagnosis

The fundamental structure of CHLs should be obvious on low-power magnification where a localized arrangement of closely approximated and rounded cysts filled with eosinophilic luminal secretions is appreciated (Figs. 13.16 and 13.17). Not uncommonly, scattered lymphoid infiltrates and histiocytes are seen in the adjacent stroma, likely secondary to the rupture of some lesional cysts (Fig. 13.18).

Luminal secretions in CHLs are a diagnostic requirement and typically abundant in CHH and CHH with atypia. In contrast, luminal secretions are notably diminished in CHC, which may serve as a helpful clue in some cases.

The appearance of luminal secretions can vary from case to case. Luminal secretions of CHLs are best known

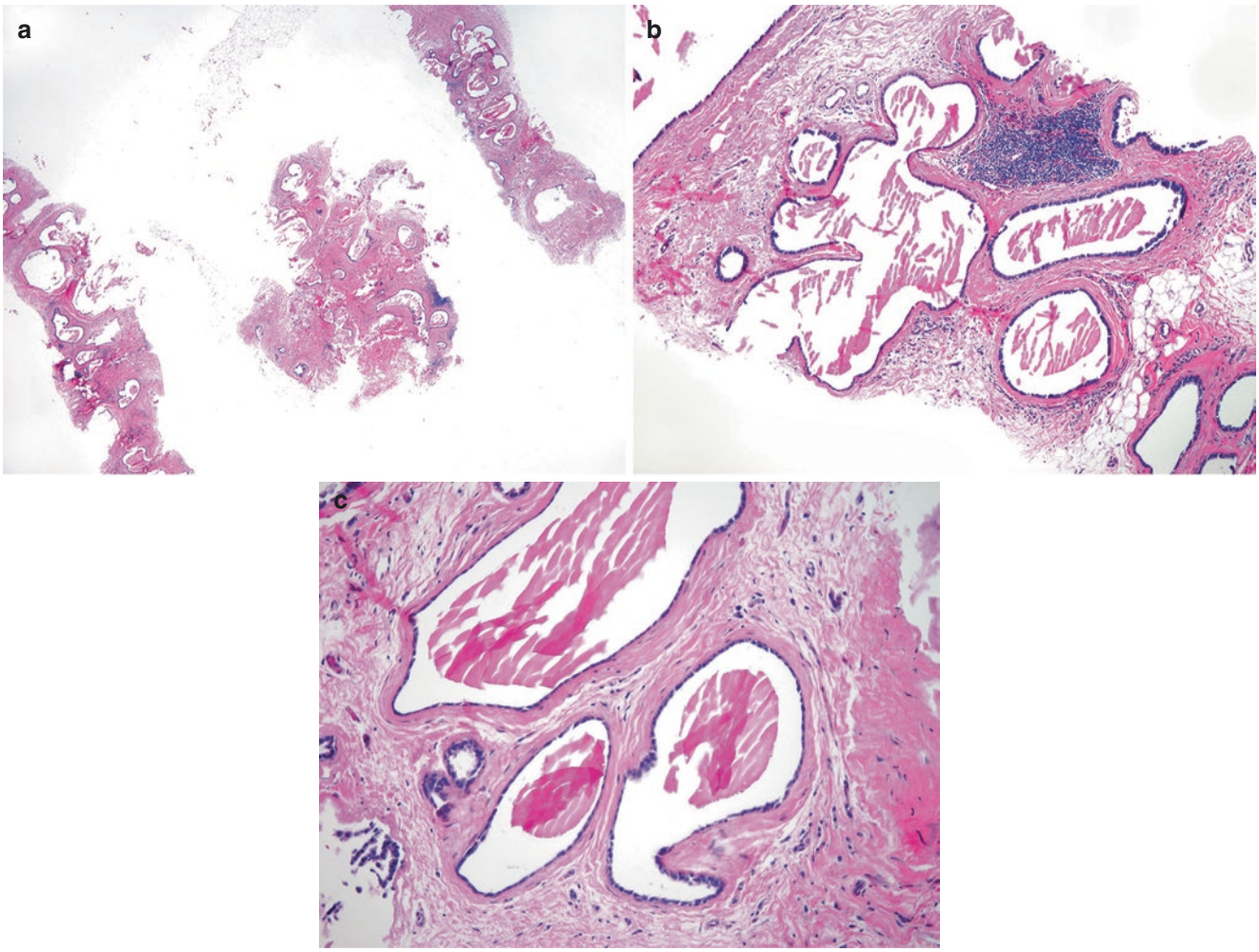


Fig. 13.16 Cystic hypersecretory hyperplasia. (**a**–**c**) CNB samples showing multiple closely approximated cysts with characteristic pink luminal secretions

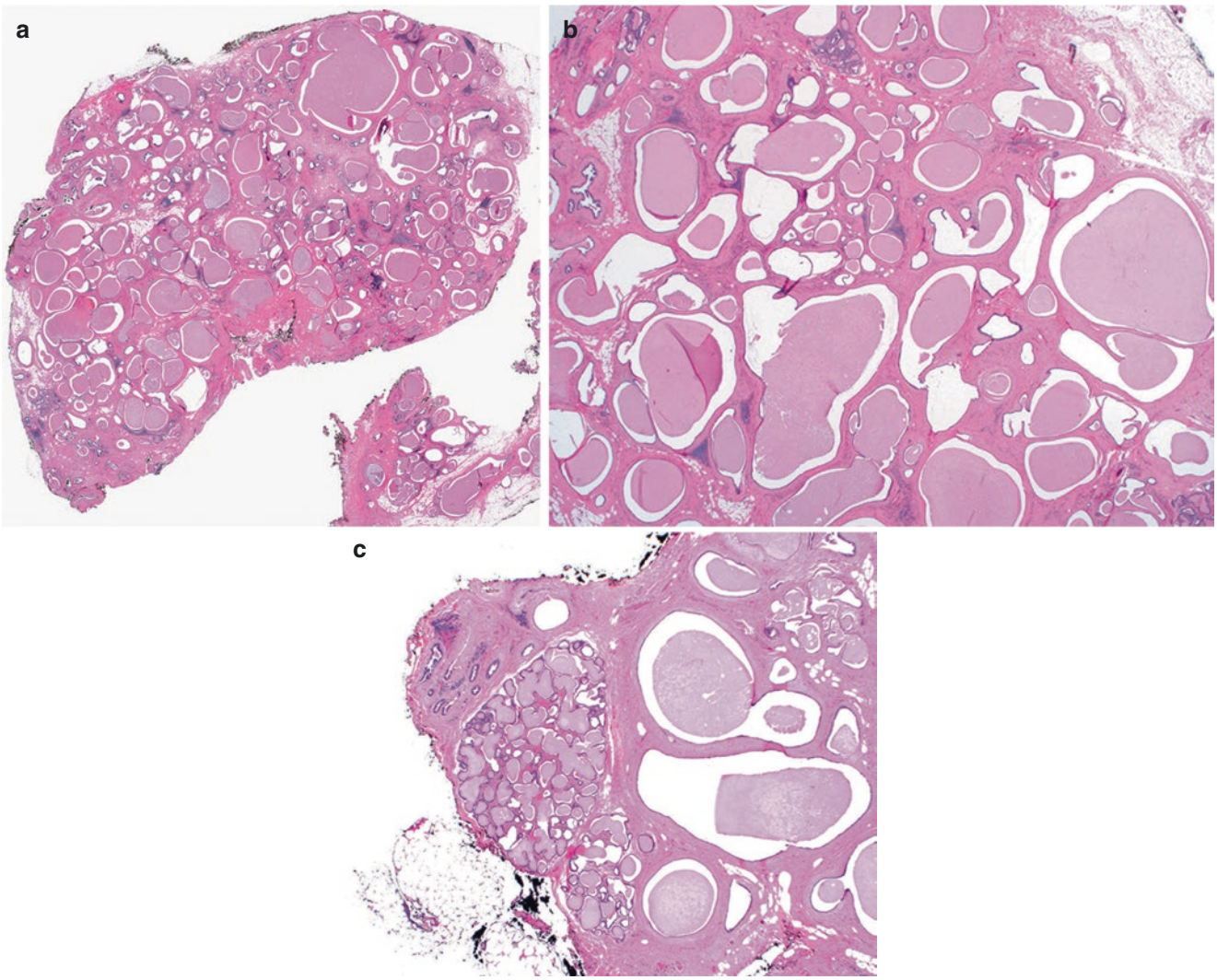


Fig. 13.17 Cystic hypersecretory hyperplasia. (**a**) Scanning view of an excisional biopsy performed for a breast mass showing a nodular mass of variably sized cysts. (**b**) Another example on medium-power view showing abundant opaque pink secretions in many of the cysts. (**c**) Cystic hypersecretory hyperplasia is seen here extending into a terminal duct lobular unit

to be dense and brightly eosinophilic, resemble thyroidal colloid, and also show prominent retraction with or without scalloped edges from the cyst wall (Fig. 13.19). Less commonly, secretions can assume a lighter shade of pink, appear less dense, and contain "pock" marks (Fig. 13.20). In other instances, the secretions can appear textured (Fig. 13.21). The presence of parallel cracks in the secretions reminiscent of venetian blinds is also a trait of CHLs, and in some instances, fragmented secretions can fall away from the lumen and dislodge into the surrounding breast parenchyma (Fig. 13.22). In addition, luminal histiocytes can be seen admixed with pink secretions in certain examples (Fig. 13.23).

CHH represents the benign end of the cystic hypersecretory proliferative spectrum and, in its simplest form, is characterized by cysts lined by a single layer of bland cuboidal or minimally columnar shaped epithelium. The epithelial lining can appear flattened and sometimes be extremely attenuated and difficult to evaluate histologically (Fig. 13.24).

The main entities to consider in the differential diagnosis are benign cysts as part of the spectrum of fibrocystic dis-

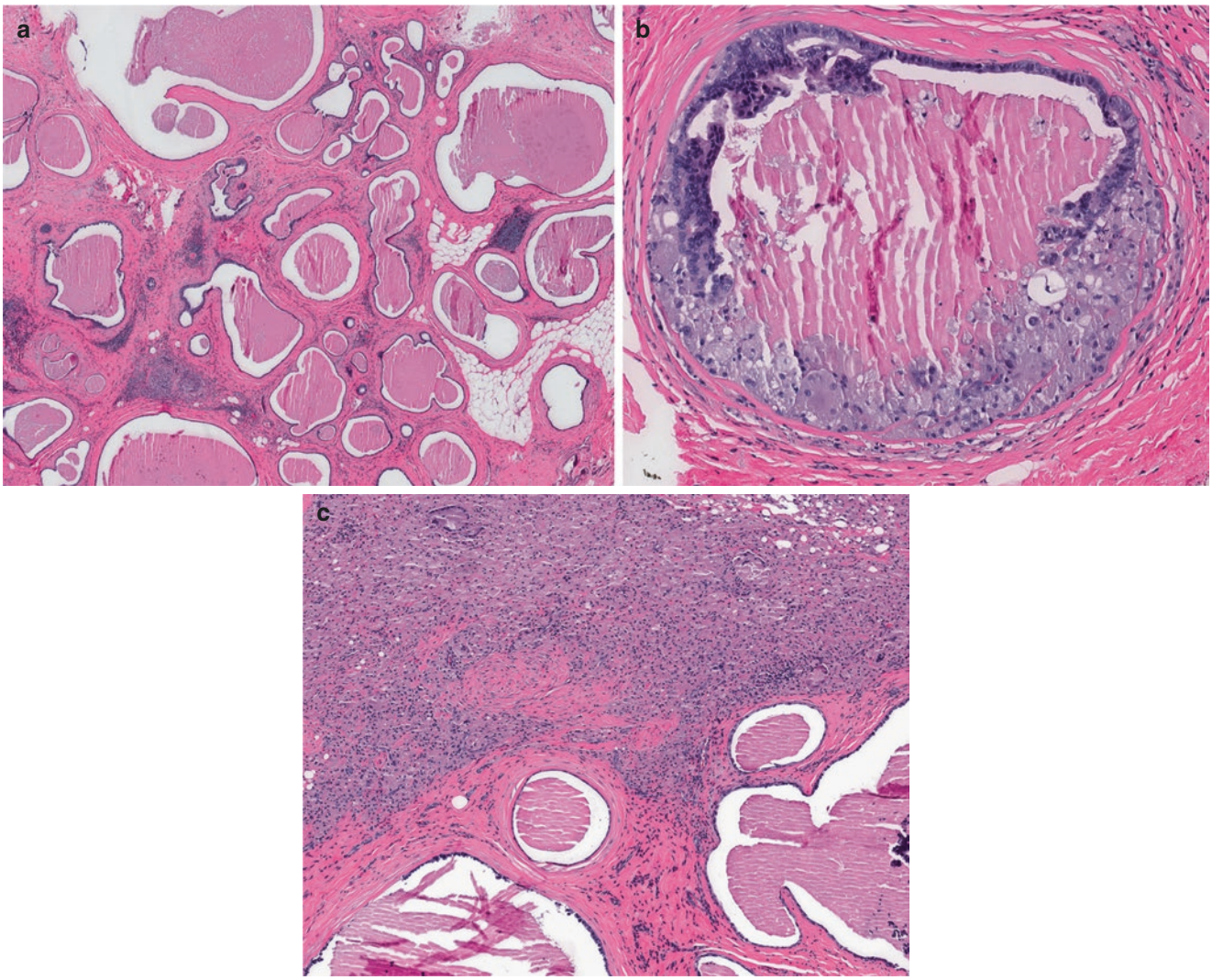


Fig. 13.18 Stromal changes seen in cystic hypersecretory lesions. (**a**) Low-power magnification shows scattered lymphoid aggregates and infiltrates between cysts. (**b**) Some cysts undergo rupture eliciting a histiocytic reaction in the stroma. (**c**) The stromal histiocytes are particularly abundant in this cystic hypersecretory lesion

ease, CHH with atypia, and CHC. Low-power scanning of multiple cysts lined by simple epithelium and containing pink luminal secretions can be easily mistaken for evidence of fibrocystic disease; however, the localized highly concentrated number of cysts should alert one to consider other entities. At this junction, juvenile papillomatosis could be considered as it is also characterized by a localized arrangement of cysts. However, unlike CHLs, juvenile papillomatosis will also contain proliferative elements such as ductal hyperplasia, apocrine metaplasia, and papillomas. Once the presence of these coexisting entities is excluded, the possibility of juvenile papillomatosis can be excluded. The more ominous pitfall is the failure to recognize CHH with atypia or CHC, which can manifest as a single layer of cytologically atypical or frankly carcinomatous epithelium, respectively, in lesional cysts (Fig. 13.25). This underscores the importance of high-magnification evaluation of all CHLs. It is also essential to know that the epithelial changes seen in one cyst can be markedly different from adjacent cysts, and not uncommonly, a spectrum of epithelial changes ranging

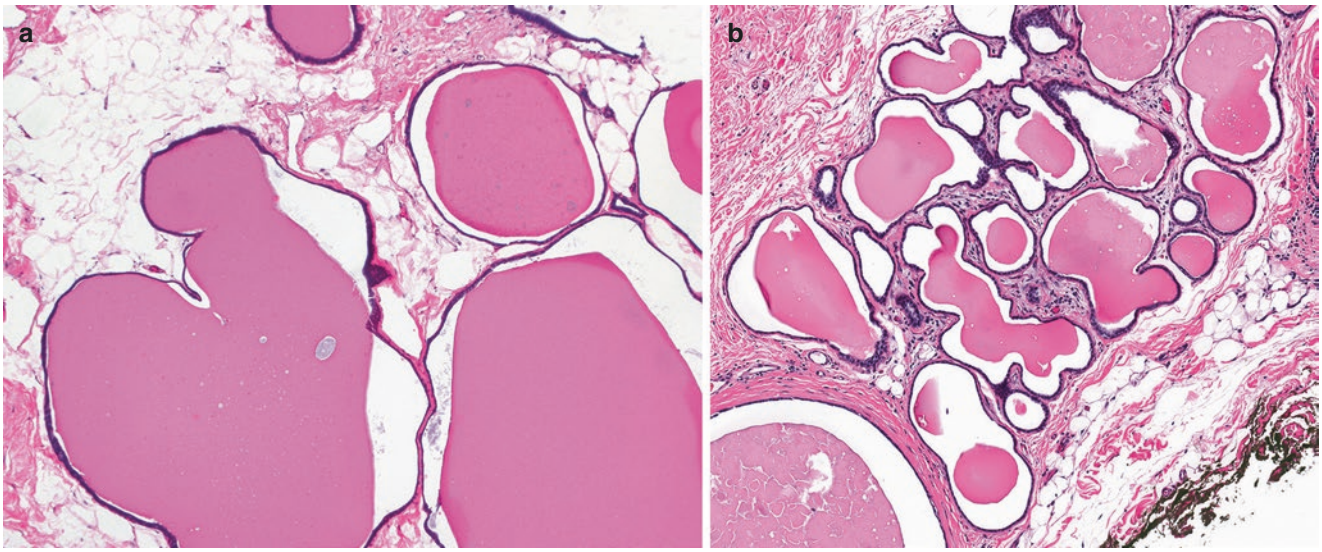


Fig. 13.19 Secretions in cystic hypersecretory lesions. (**a**) Luminal secretions in this entity are typically pink but sometimes can have a reddish hue. Characteristically, the pink secretions can be dense, thyroidal colloid-like, and glassy appearing with prominent retraction from the cyst wall. (**b**) Another example of dark pink, glassy secretions involving a lobule

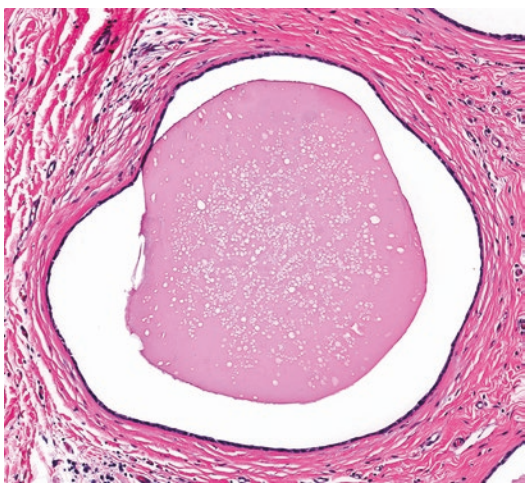


Fig. 13.20 Other characteristics of cystic hypersecretory secretions. This image shows typical "pock" marks seen in some secretions. Note the lighter shade of pink and greater translucency seen in this example containing pockmarks in contrast to the typical thyroidal colloid-like secretions seen in Fig. 13.19

from benign to carcinoma can be seen within a single cyst with or without morphologic transition (Figs. 13.26 and 13.27).

CHH can also be mildly proliferative where the epithelial cells are piled up but maintain cytologic and architectural benignity. The growth pattern is largely seen as abortive papillary tufts (Fig. 13.24c–e). It is necessary to scrutinize these proliferative examples of CHH on higher magnification to exclude the possibility of atypia in which case a diagnosis of CHH with atypia would be more appropriate. The diagnostic criteria used for conventional ADH are similarly applied to hyperplasia in this setting, and the degree of atypia would fall short of that necessary for a diagnosis of in situ carcinoma.

When the epithelial lining of a CHL is frankly malignant, then the diagnosis of cystic hypersecretory carcinoma is made. In the majority of cases, the in situ carcinoma demonstrates micropapillary (usual or flat/clinging) or papillary architecture with intermediate or high nuclear grade. Solid growth pattern can be seen in a minority of cases. Mitoses are readily identified. Some but not all examples contain luminal necrosis and/or calcifications [95]. Luminal secretions are diminished as previously mentioned. CHC can also involve neighboring terminal duct lobular units (Figs. 13.28, 13.29, 13.30, and 13.31).

CHC invariably arises in a clinically evident CHL, but CHC, itself, may not constitute the bulk of the lesion. CHC arising within a CHL is typically multifocal, making the assessment of tumor burden difficult. In one report, CHC comprised at most 50% of the gross tumor mass (CHL) while the remainder represented CHH or CHH with atypia [102]. Clearly communicating the distribution and extent of CHC in the pathology report will avoid having clinicians misconstrue gross tumor size as representing the extent of the in situ carcinoma in these cases. Concurrent conventional DCIS is not found. Associated Paget's disease has been reported in one case [102].

Invasive ductal carcinoma has been found in approximately 20% of reported CHC cases [96, 97, 103]. These examples are typically poorly and sometimes moderately differentiated without cystic hypersecretory features (Fig. 13.32).

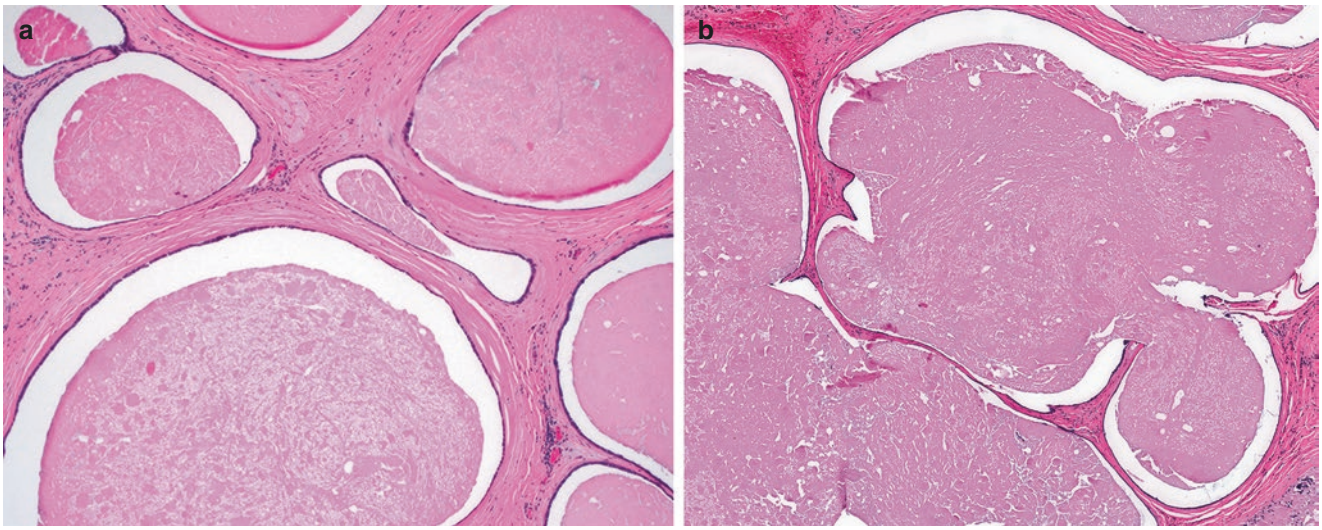


Fig. 13.21 Cystic hypersecretory secretions. (**a**, **b**) Occasionally, luminal secretions demonstrate a textured appearance that has a woven or fabric-like quality

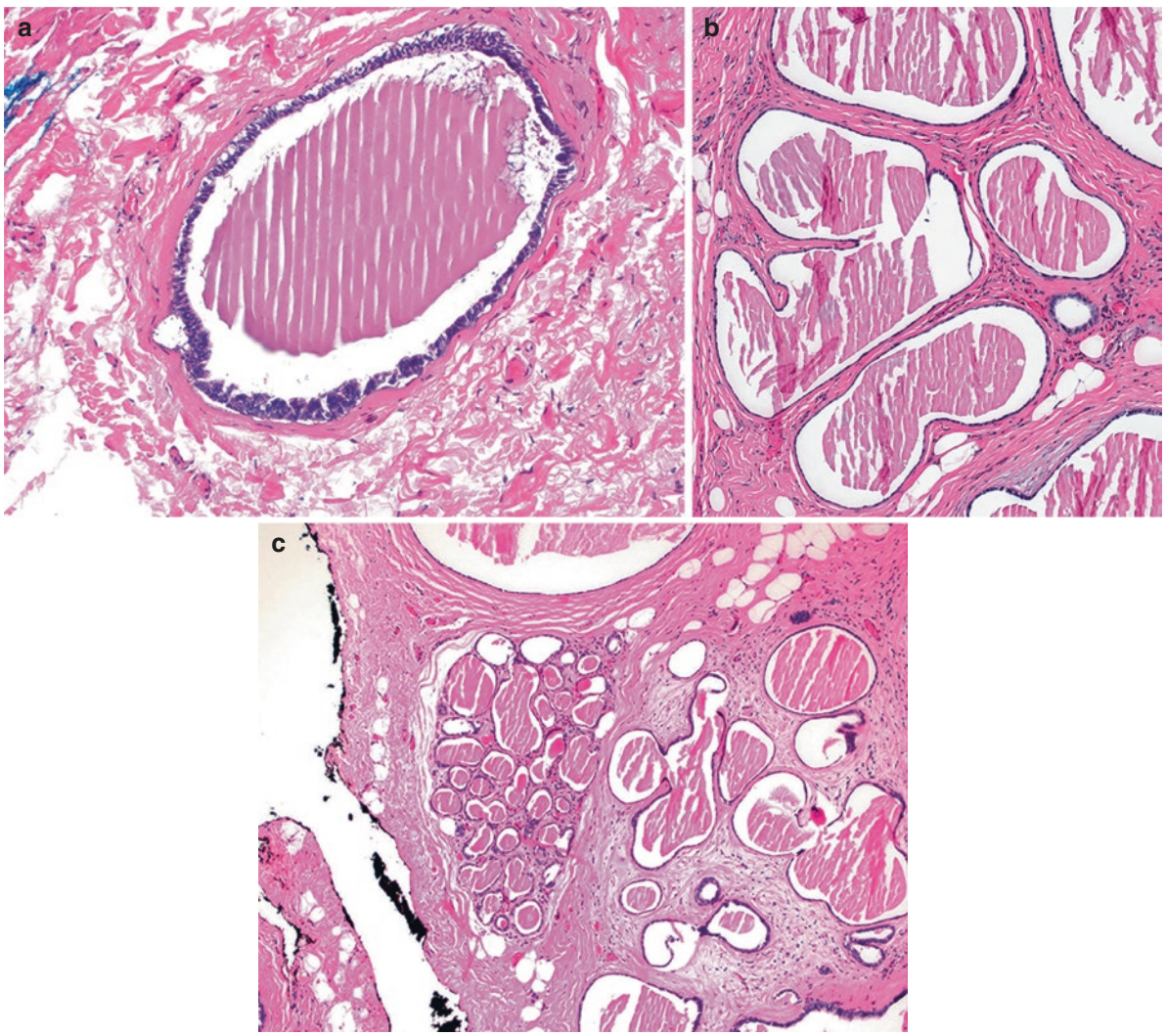


Fig. 13.22 Luminal secretions with a "venetian blind" appearance. (**a**, **b**) These parallel cracks throughout the span of the secretions can become dislodged in some areas. (**c**) This appearance can even be appreciated in a terminal duct lobular unit

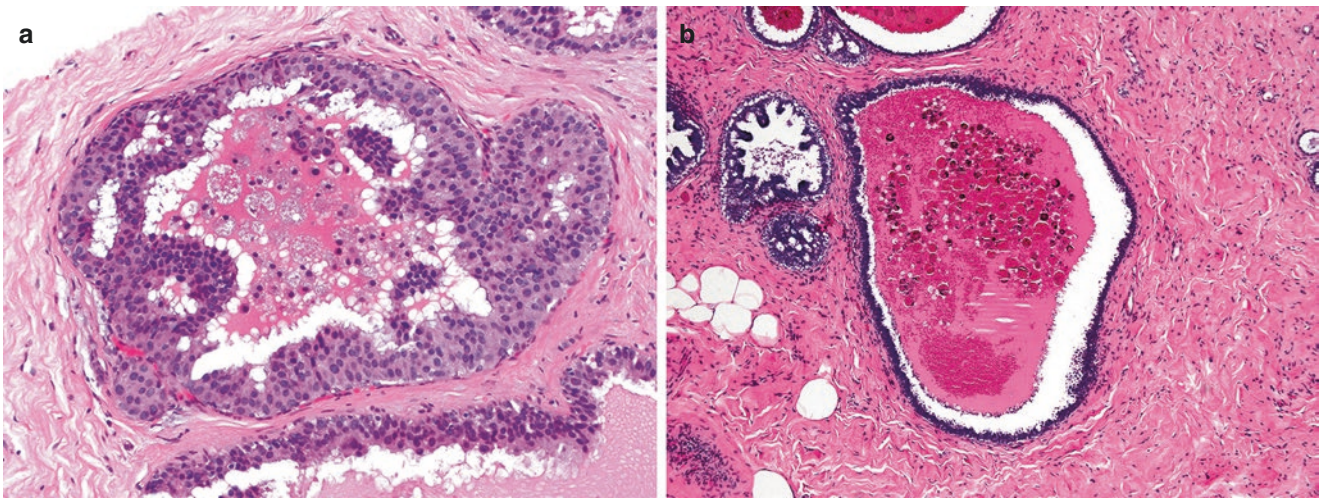


Fig. 13.23 Luminal histiocytes in cystic hypersecretory lesions. (**a**, **b**) Luminal histiocyte examples

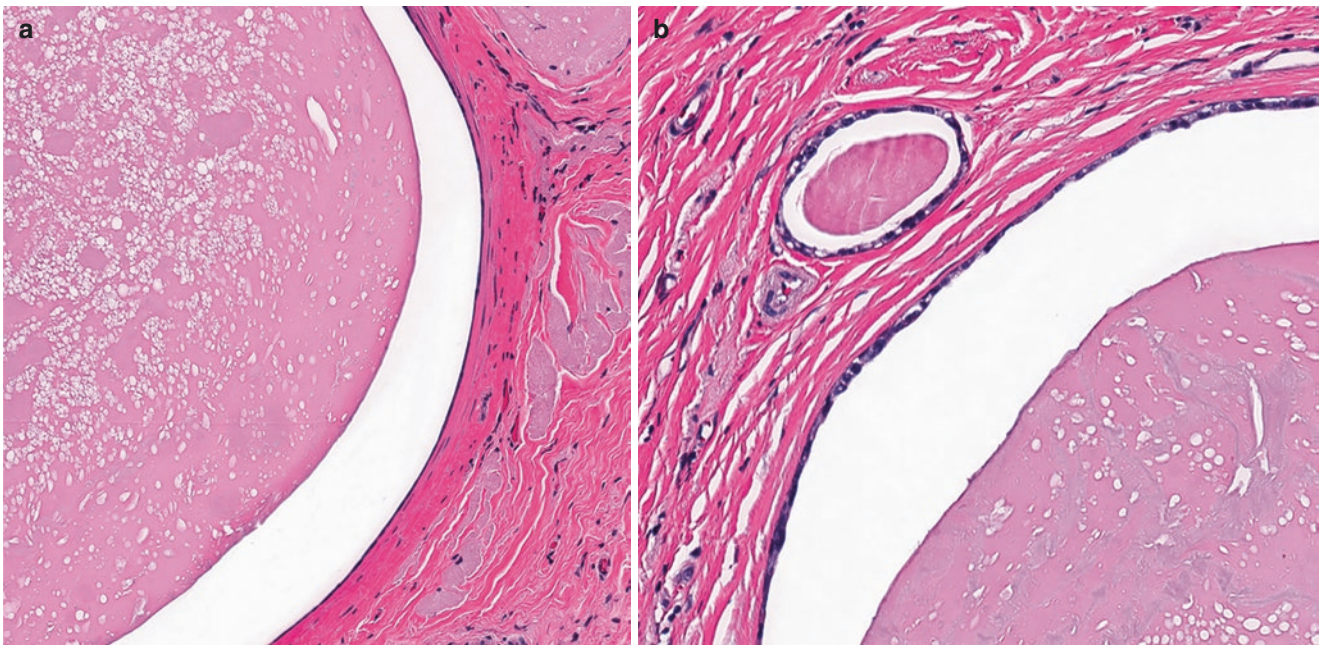


Fig. 13.24 Cystic hypersecretory hyperplasia. (**a**, **b**) The lining of cysts can be very inconspicuous consisting of a single layer of bland flattened cuboidal epithelium. (**c**, **d**) Another example of cystic hypersecretory hyperplasia which is mildly proliferative. (**e**) Cystic hypersecretory hyperplasia containing individual cysts that are non-proliferative and proliferative

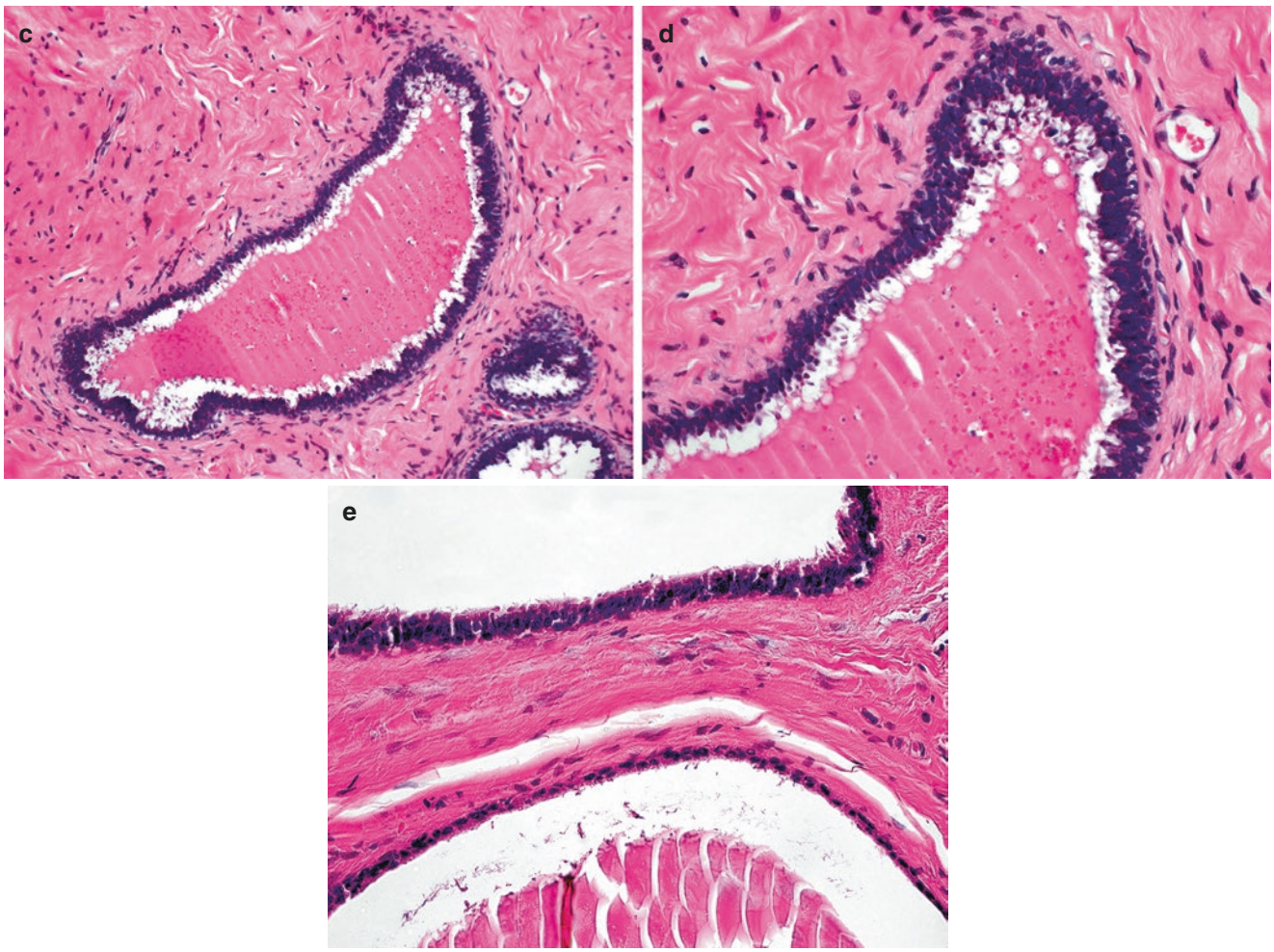


Fig. 13.24 (continued)

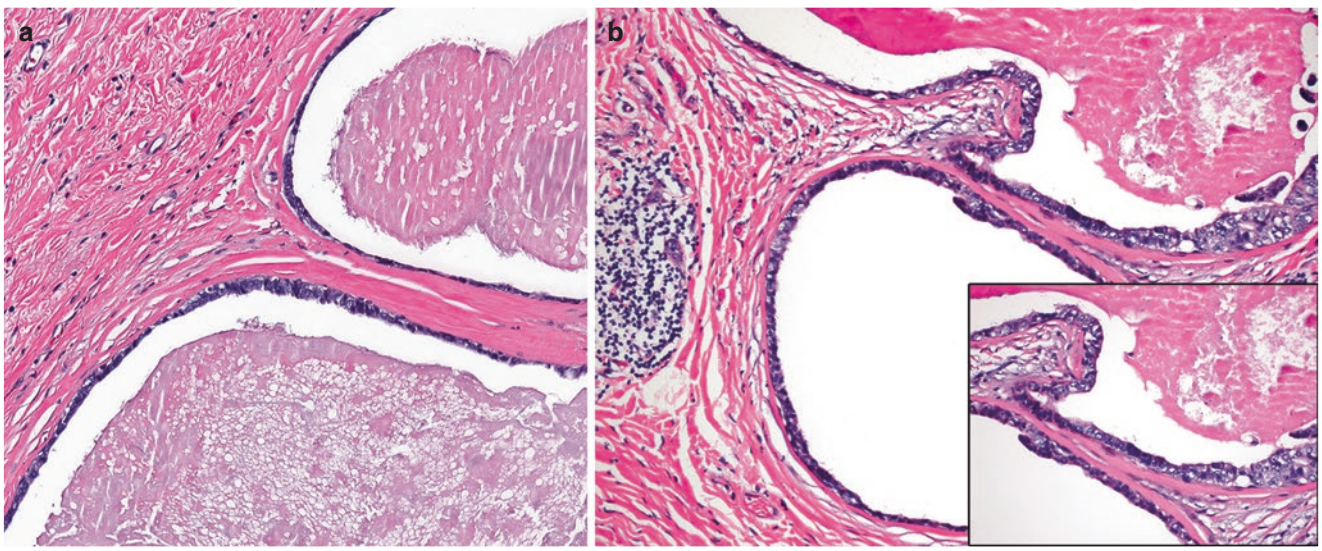
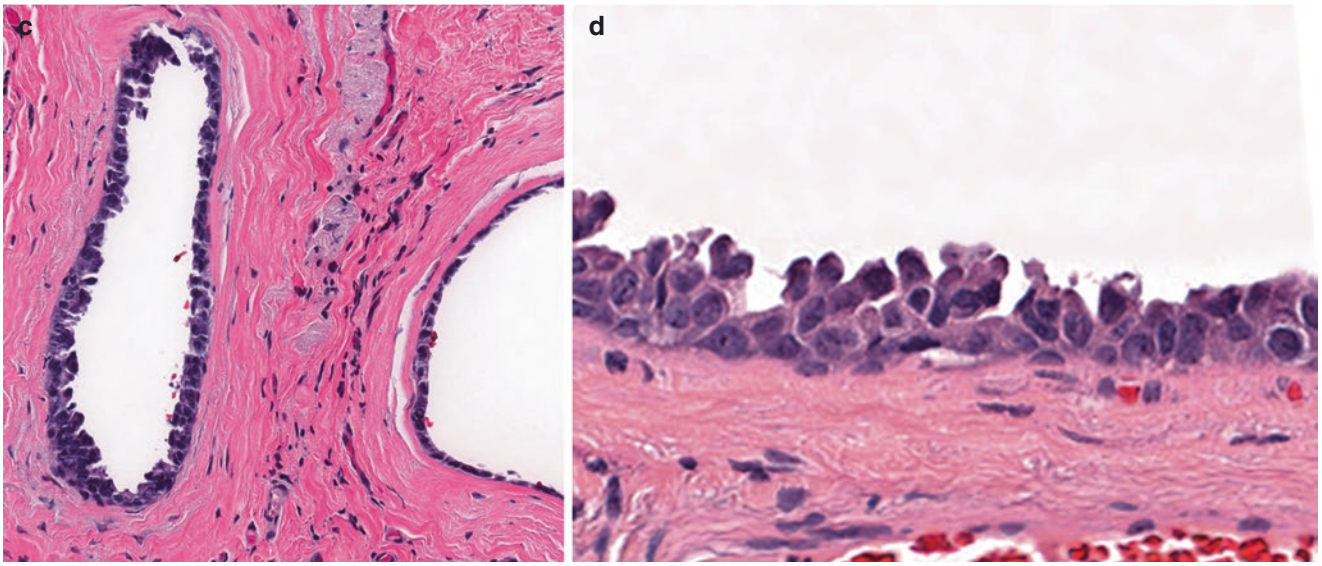


Fig. 13.25 Atypical cystic hypersecretory hyperplasia misconstrued as cystic hypersecretory hyperplasia. (**a**, **b**) Similar to columnar cell change with atypia (i.e., flat epithelial atypia), atypia in these lesions can be easily missed if scanning on low magnification. (**c**) In some cases, nuclear hyperchromasia can be detected at low magnification, which is helpful but still requires a high index of suspicion. (**d**) Malignant epithelium is confirmed on high-magnification examination in this case of minimally proliferative cystic hypersecretory in situ carcinoma



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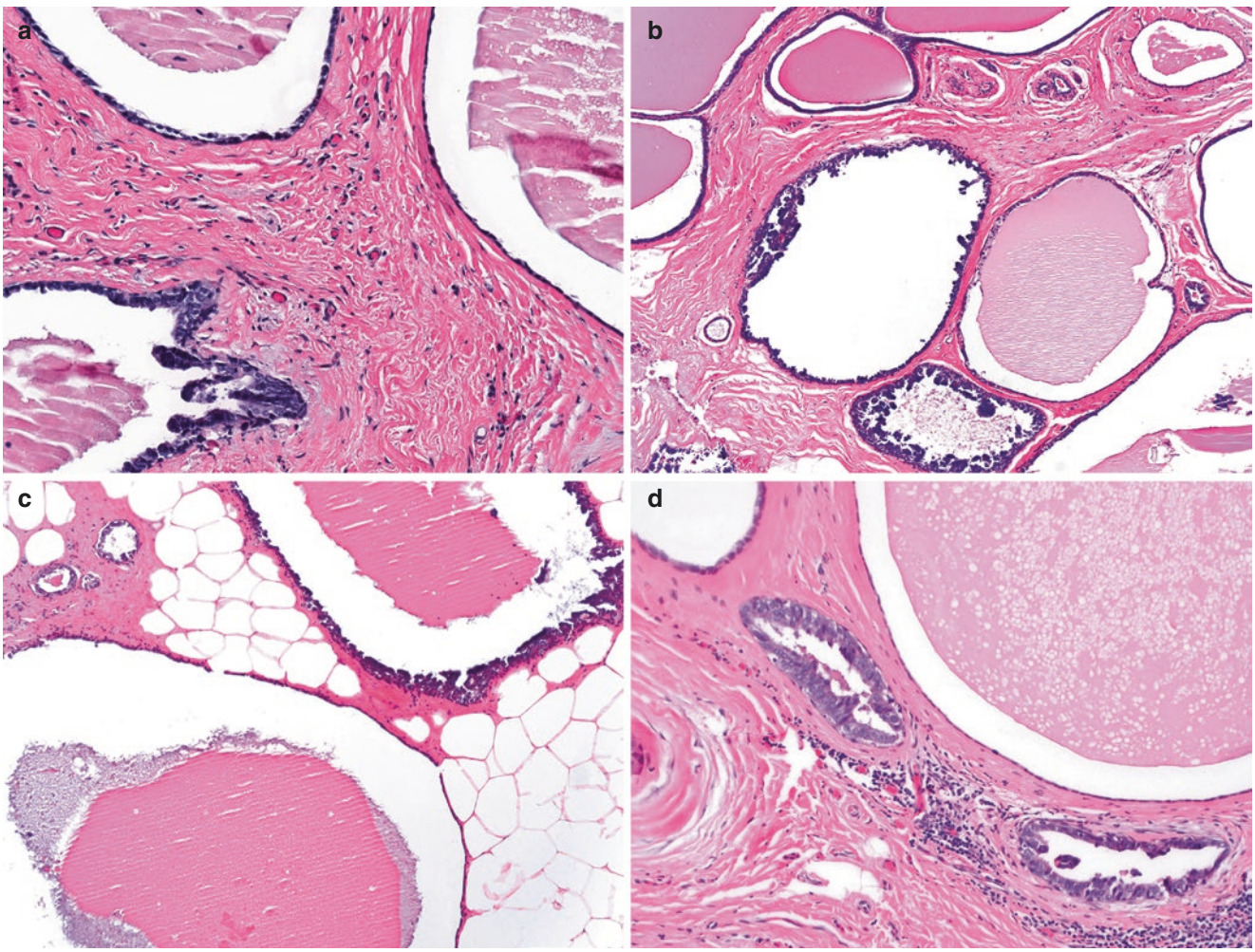

Fig. 13.26 Benign, atypical, and carcinomatous cystic hypersecretory lesions. (**a**–**d**) These are typically juxtaposed to one another

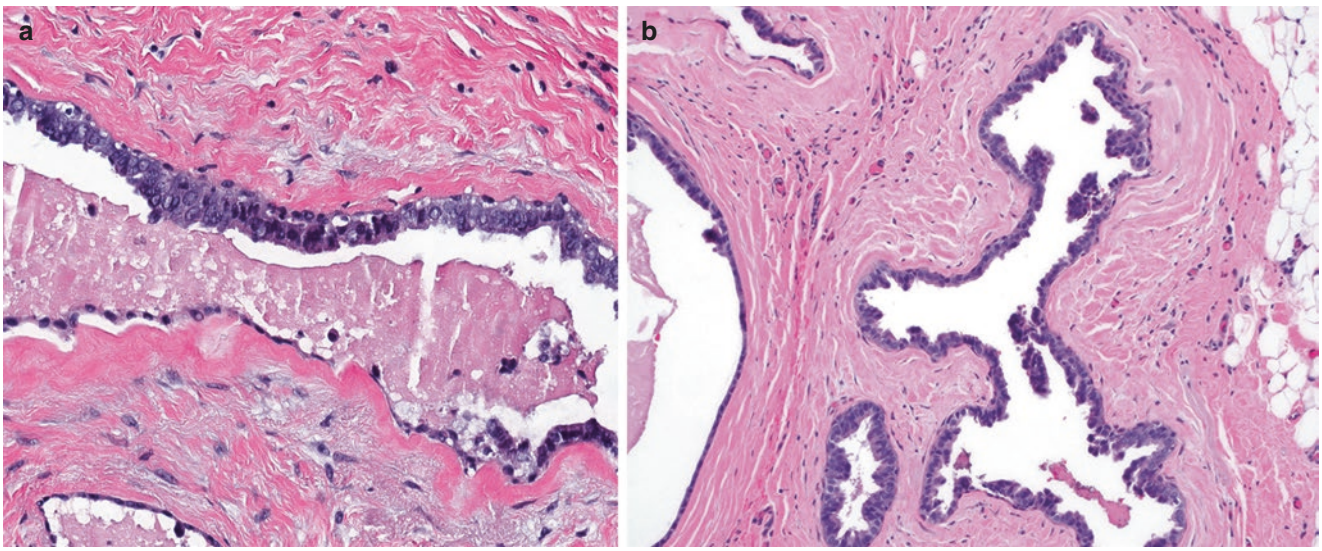

Fig. 13.27 Cystic hypersecretory lesions. (**a**) The epithelial lining of a single cyst can show cytologic transition from benign to carcinoma. (**b**) This phenomenon can be appreciated in the cyst on the left, while the one in the center is completely involved by atypical epithelium

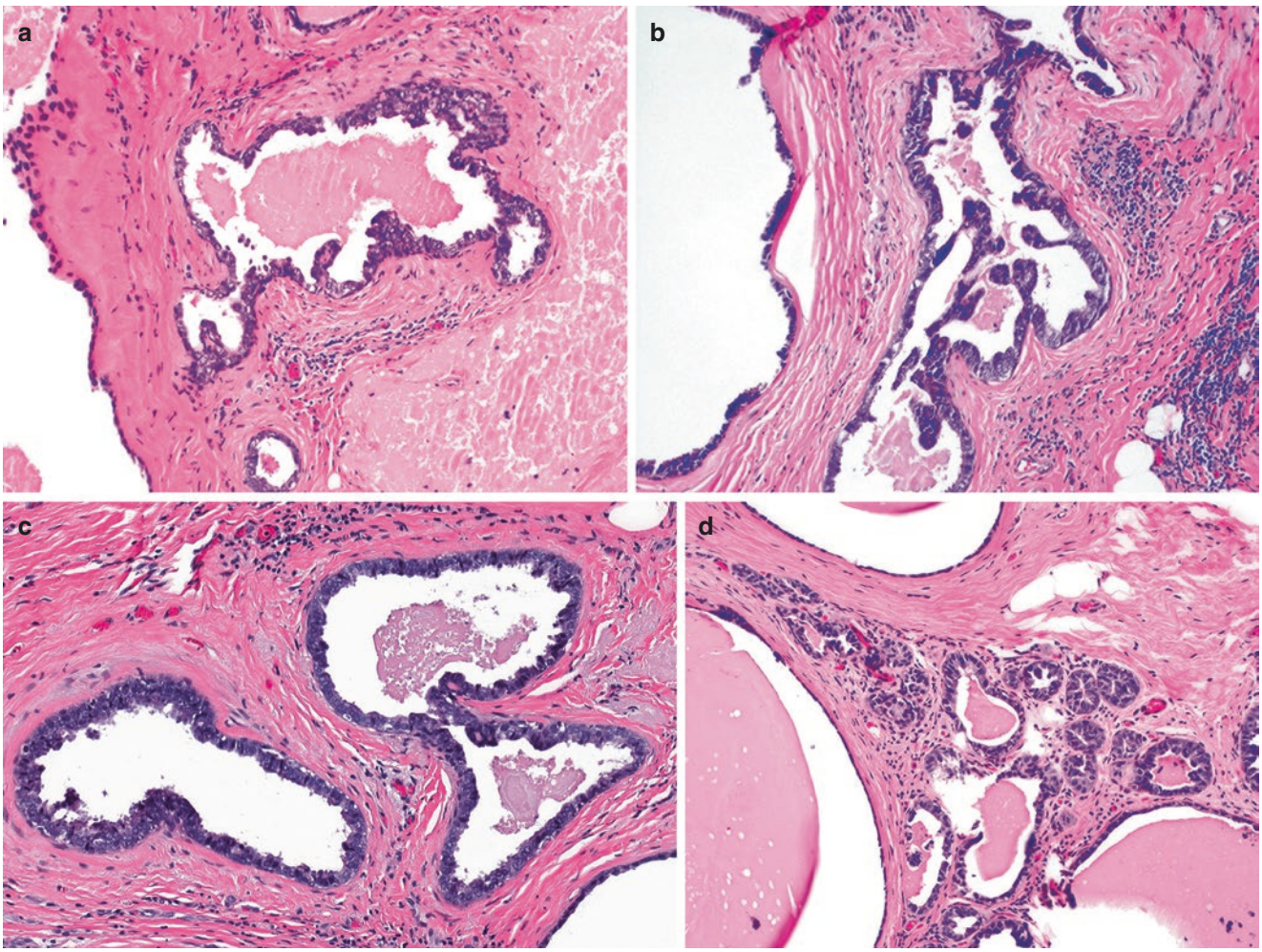

Fig. 13.28 Cystic hypersecretory carcinoma. (**a**–**c**) The most common architectural growth pattern in this type of in situ carcinoma is micropapillary. Both usual and flat (clinging) types can be seen. (**d**) CHC can involve lobules. (**e**) This focus of cystic hypersecretory carcinoma shows focal weak immunoreactivity for ER. Note in figures (**a**–**c**) that the luminal secretions are noticeably diminished in these malignant cases

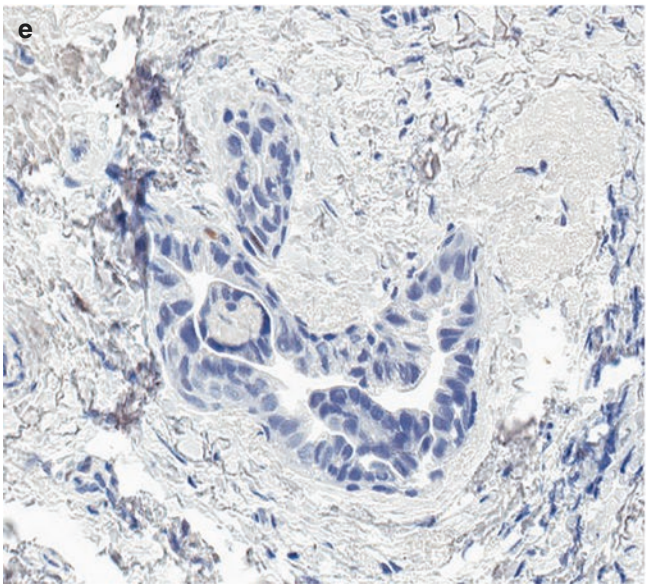

Fig. 13.28 (continued)

Rarely, metastatic disease has been reported in these patients, all of which manifested as axillary lymph node involvement with the exception of one case of bone metastasis [92].

Immunohistochemical Workup

Myoepithelium investing CHLs can be demonstrated using immunostains routinely used for this purpose [p63, smooth muscle myosin heavy chain (SMM), calponin]; however, rarely these stains can be negative similar to that seen in some papillary carcinomas [91, 104].

CHCs are typically negative for basal-like carcinoma markers such as epidermal growth factor receptor (EGFR), CK14, and CK5 [91]. These in situ carcinomas are variably positive for ER and PR, but the majority of studies have found CHC to be ER positive [91, 93, 96–98, 102, 103, 105–107]. One study also studied androgen receptor (AR) expression, which was

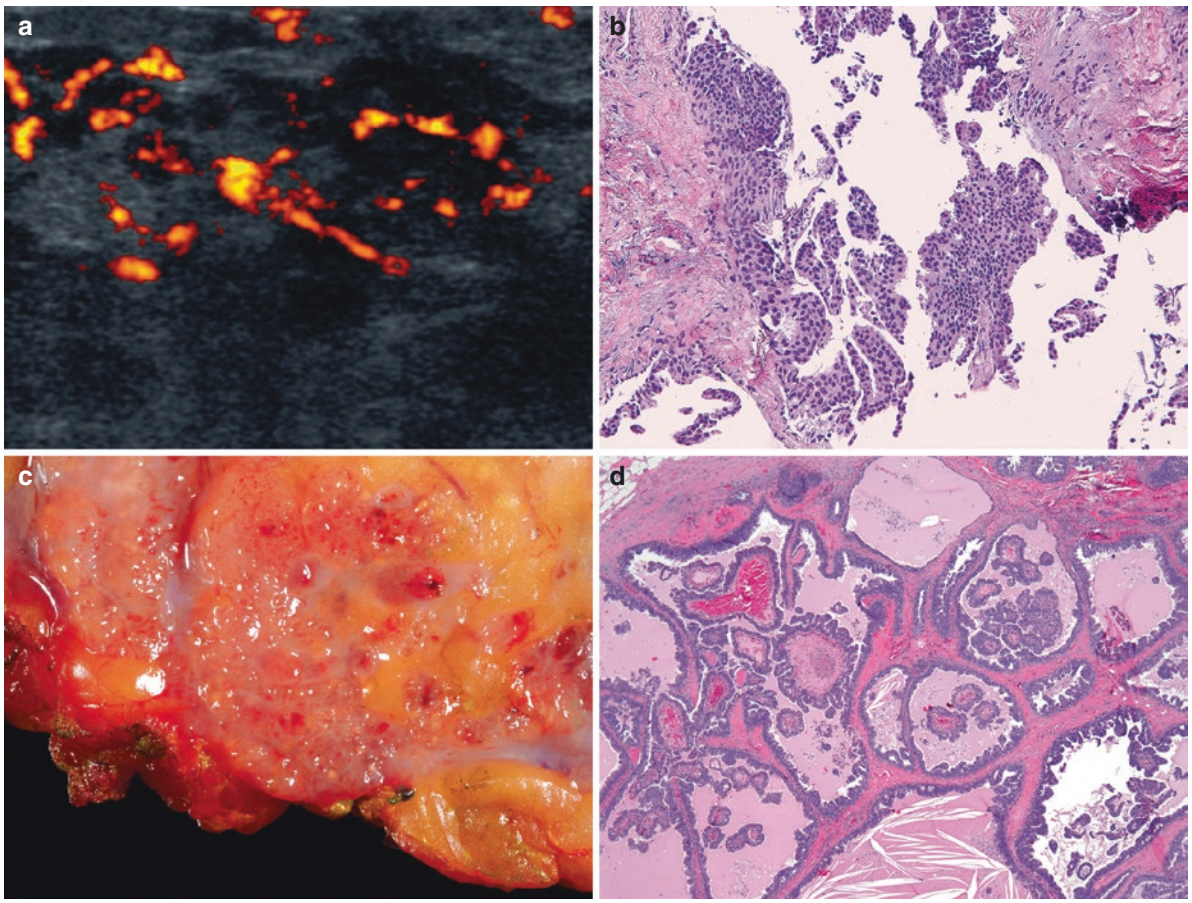

Fig. 13.29 Cystic hypersecretory carcinoma. (**a**) A large ill-defined lesion was examined under sonography, which showed numerous small anechoic cysts and dilated ducts, with substantially increased vascularity. Ultrasound-guided CNB was performed and yielded small tissue fragments. (**b**) Focal area showed collapsed ducts with focal micropapillary atypical proliferation. Due to discordant clinical, pathologic, and radiographic findings, segmental mastectomy was performed. (**c**) Fresh resection specimen shows numerous cysts and dilated ducts filled with viscous translucent material. (**d**) Histologic examination revealed many cysts and dilated ducts filled with dense and eosinophilic secretions and lined by carcinomatous epithelium with papillary and micropapillary growth patterns

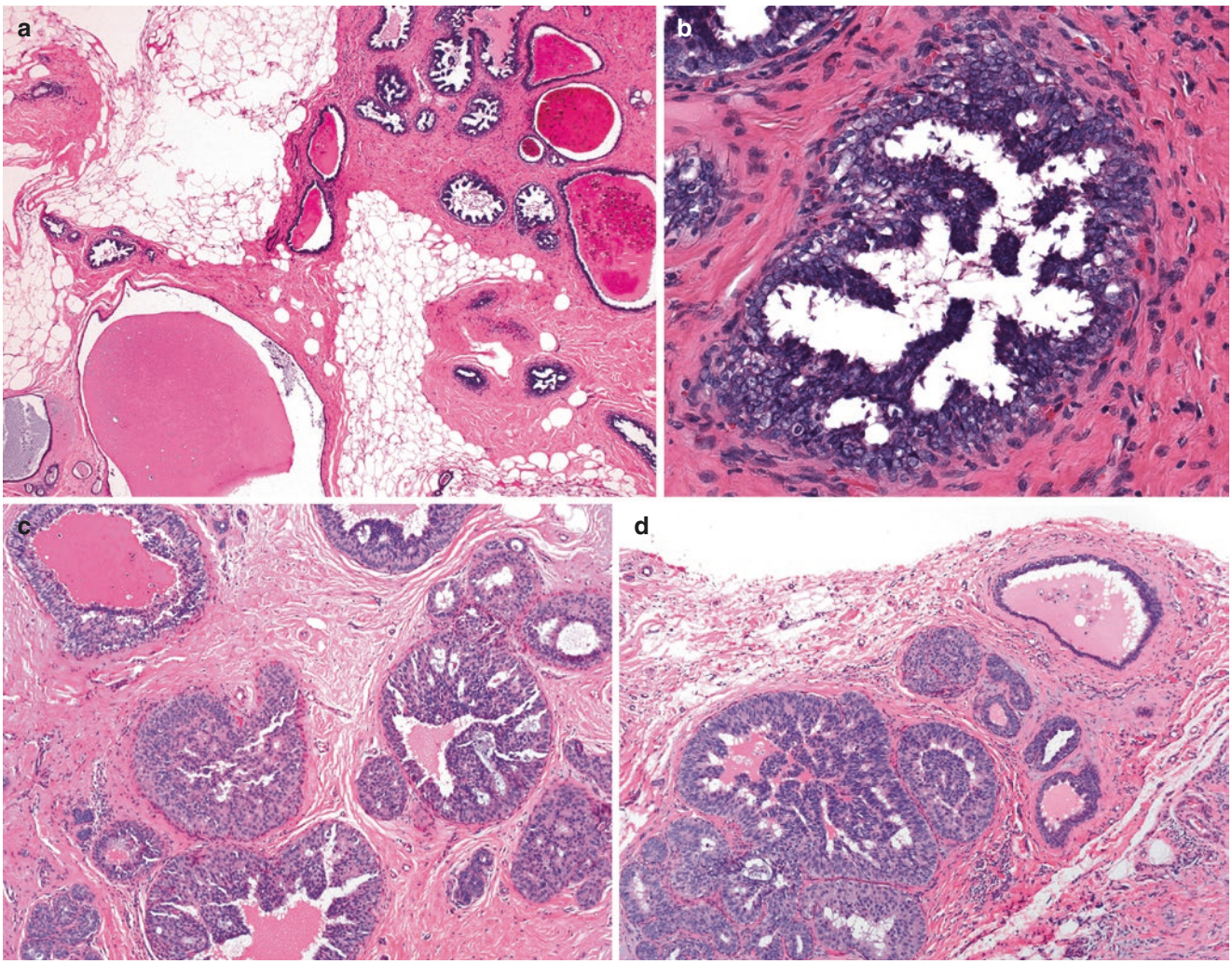

Fig. 13.30 Cystic hypersecretory carcinoma. (**a**) At low-power magnification, lesional cysts are lined by noticeably darker staining epithelium (flat or micropapillary) in contrast to cystic hypersecretory hyperplasia, which is also seen in the same field (*lower left*). (**b**) High-power view confirms the overtly malignant features of the micropapillary epithelial lining of cystic hypersecretory carcinoma. (**c**, **d**) A second example of CHC exhibiting more proliferative micropapillary growth pattern

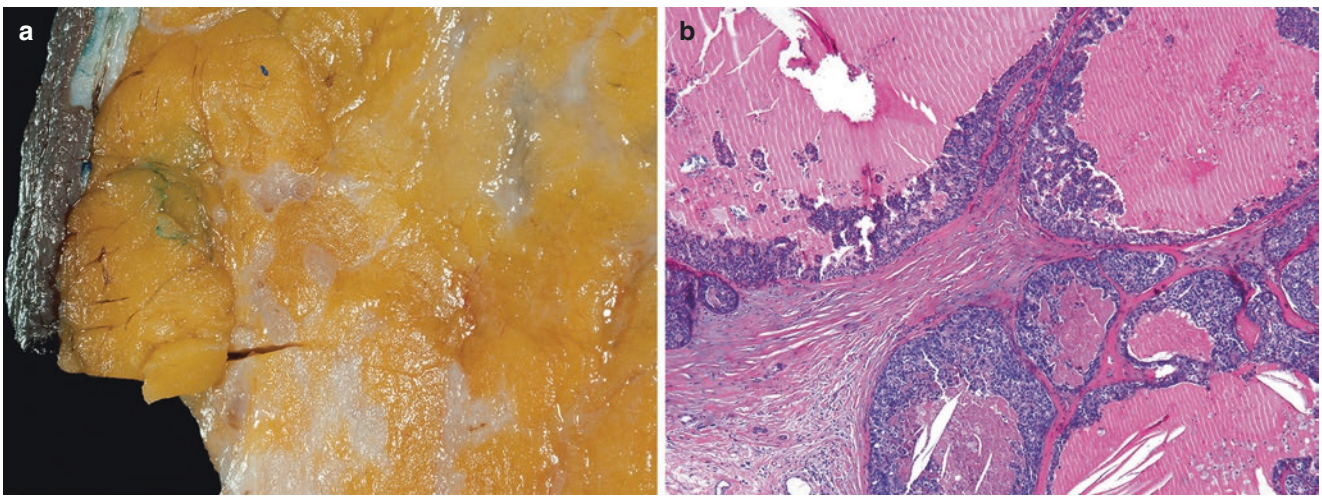

Fig. 13.31 Cystic hypersecretory carcinoma. (**a**) Another example of cystic hypersecretory carcinoma from a fixed gross specimen. Multiple cysts can be appreciated within fibrous areas. (**b**) Histologic examination shows dilated ducts and cysts filled with dense, eosinophilic secretions with cracks. Cystic hypersecretory carcinoma shows micropapillary and flat micropapillary (clinging) growth patterns

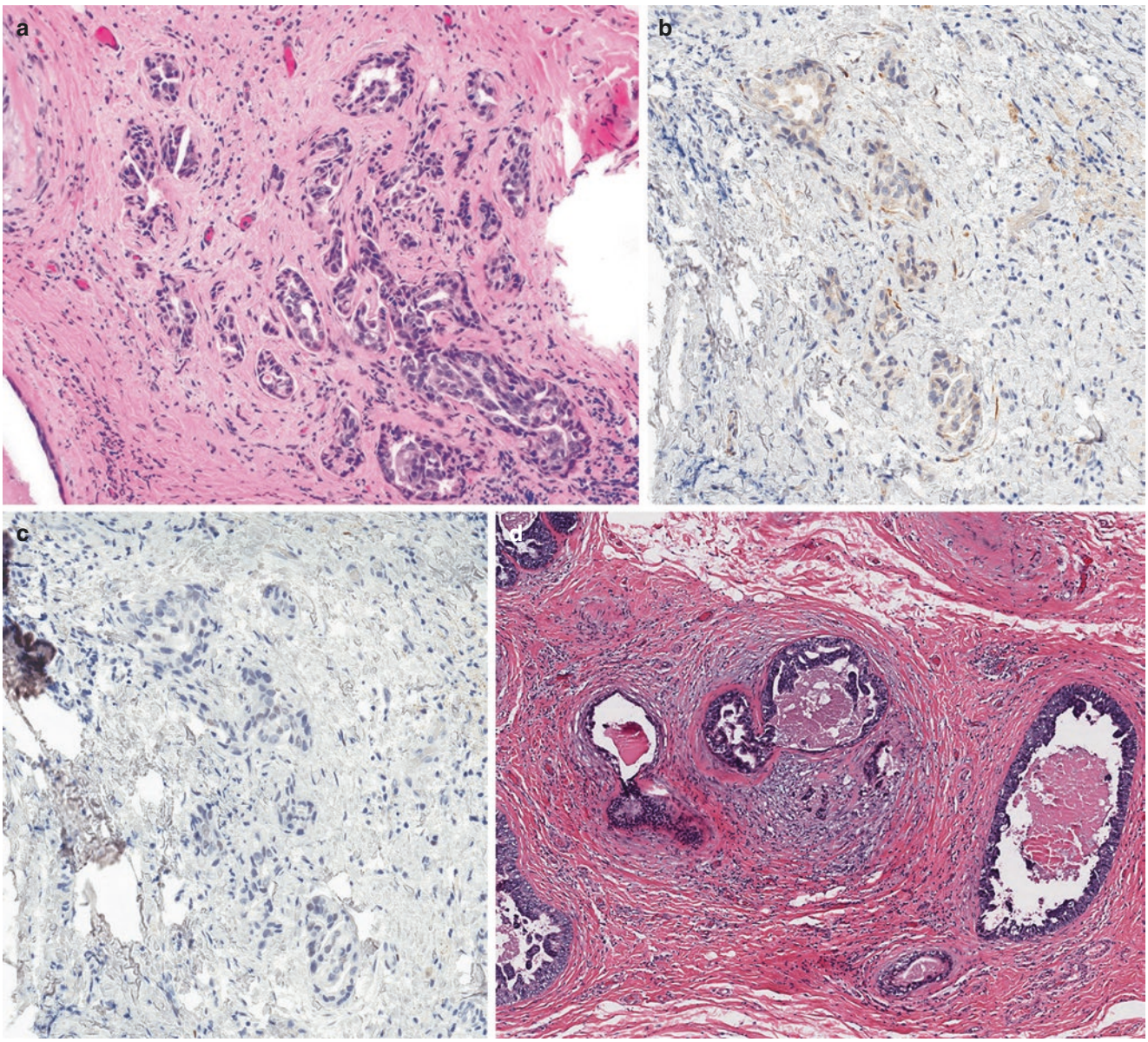

Fig. 13.32 Invasive ductal carcinoma arising in cystic hypersecretory carcinoma. (**a**) The invasive carcinoma is moderately differentiated and measured 3 mm in size. (**b**) Calponin immunostain demonstrates lack of myoepithelium in the invasive carcinoma. Neighboring blood vessels are positive (not shown). (**c**) The invasive carcinoma is focally and very weakly positive for ER. (**d**) Another example of invasive ductal carcinoma directly arising adjacent to cystic hypersecretory carcinoma. This focus is microinvasive in size and shows high nuclear grade. Note that cystic hypersecretory traits are not apparent in the invasive components of either example

also found to be variably positive [91]. The HER2 status of CHC has not been well studied but was not found to be overexpressed (3+ staining) in one study [91]. Invasive carcinoma arising in this setting shows similar biomarker expression as CHC, and when studied, similar immunoexpression has been observed in both in situ and invasive components [91].

Pathogenesis

The variable biomarker expression in CHC suggests that this entity is a heterogeneous preinvasive carcinoma much like that of conventional DCIS. This may in part explain why (most) examples are associated with an indolent clinical

course while a minor subset progress to invasive carcinoma and even metastasize. Much more investigation is needed to elucidate the biologic underpinnings of this special type of in situ carcinoma, which has been largely limited by the scarcity of this distinctive carcinoma.

Prognosis and Management in the Core Biopsy Setting

Patients diagnosed with CHH in excisional biopsies experience a benign course. Obtaining negative surgical margins is not indicated. However, in the CNB setting, cystic hypersecretory proliferations of any type should be further investigated by surgical excision due to the multifocal, scattered distribution by which CCH with atypia and CHC arise in CHLs and therefore can easily go unsampled at the time of initial biopsy.

In some instances, cystic hypersecretory changes can be seen in concert with pregnancy-like (pseudolactational) proliferations at the time of initial CNB [108], and moreover, in situ or invasive carcinoma (some cystic hypersecretory in type) has been found to arise in this morphologic background [109]. These two seemingly unrelated lesions can be found together (coexisting or histologically merging) in CNB samples targeted for calcifications associated with pregnancy-like change/hyperplasia, and not infrequently, atypia of one or both components is seen in the subsequent excisional biopsy [108] (Fig. 13.33). These observations have led to the recommendation of excisional biopsy in such instances even if both components are benign in the CNB sample [108].

If CHH with atypia is found in a CNB sample, excisional biopsy is recommended to further evaluate the area and to exclude a clinically more significant lesion (i.e., CHC, invasive carcinoma). However, it is not clear at this time how to clinically manage a patient with CHH with atypia as the highest order diagnosis (in an excisional biopsy).

Patients with CHC are treated similarly to those affected by conventional forms of in situ ductal carcinoma (surgery ± radiotherapy, hormonal therapy). The clinical course has been reported to be indolent with the most recent reported series showing no evidence of disease in four patients with long-term follow-up (mean: 5.5 years) including one who also harbored microinvasive disease.

Despite the nonaggressive course associated with CHC, the invasive carcinomas that arise in this setting are typically poorly or moderately differentiated. Cystic hypersecretory traits are not appreciated in invasive or metastatic counterparts of CHC [92]. So-called invasive cystic hypersecretory carcinomas described in the literature are in fact cases of CHLs from which only a portion of the tumor represents invasive carcinoma [91, 99, 109, 110]. It is imperative to clearly state in the pathology report the size of only the invasive carcinoma for proper staging as the gross tumor size of the CHL is invariably much larger.

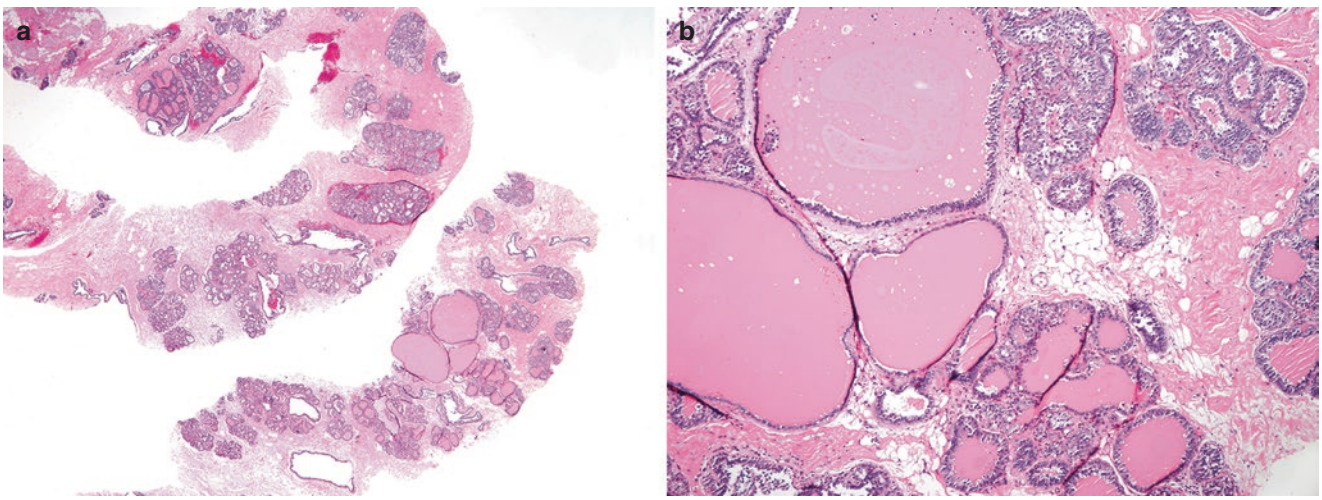

Fig. 13.33 Cystic hypersecretory hyperplasia merged with pregnancy-like hyperplasia. (**a**, **b**) CNB samples show ectatic lobular glands showing pregnancy-like hyperplasia, which in areas are merged with large cysts filled with eosinophilic secretions typical of cystic hypersecretory hyperplasia

Glycogen-Rich Clear-Cell Carcinoma

Overview

Glycogen-rich clear-cell carcinoma (GRCCC) is an uncommon breast carcinoma, which constitutes approximately 1–3% of breast carcinomas [111]. The first case was reported by Hull et al. in 1981 [112]. Since then, fewer than 100 cases have been reported in the literature [113–124]. The median age at presentation is 51 years (range, 31–81 years) [124]. The clinical presentation of patients with this tumor is no different from those with invasive carcinoma NST [111]. Most patients present with a breast mass, while others additionally experience nipple discharge. A rare case manifesting as inflammatory breast cancer has also been reported [124]. This tumor is now considered to be a special histologic pattern under the invasive breast carcinoma of no special type in the most current WHO classification [125].

Gross and Radiologic Features

No specific gross features are associated with GRCCC. The tumor size ranges from 1 to 8 cm, and most of them are 2–5 cm.

Radiographically, a high-density mass with intratumoral calcifications is the most common mammographic finding, while sonography often shows a hypoechoic mass with or without calcifications [124].

Microscopic Features

By definition, GRCCC is an invasive carcinoma where >90% of the tumor cells have abundant cytoplasm containing glycogen (Fig. 13.34). The tumor cells are usually intermediate to high nuclear grade. The tumor cells are arranged in cords, solid nests, or papillary configurations

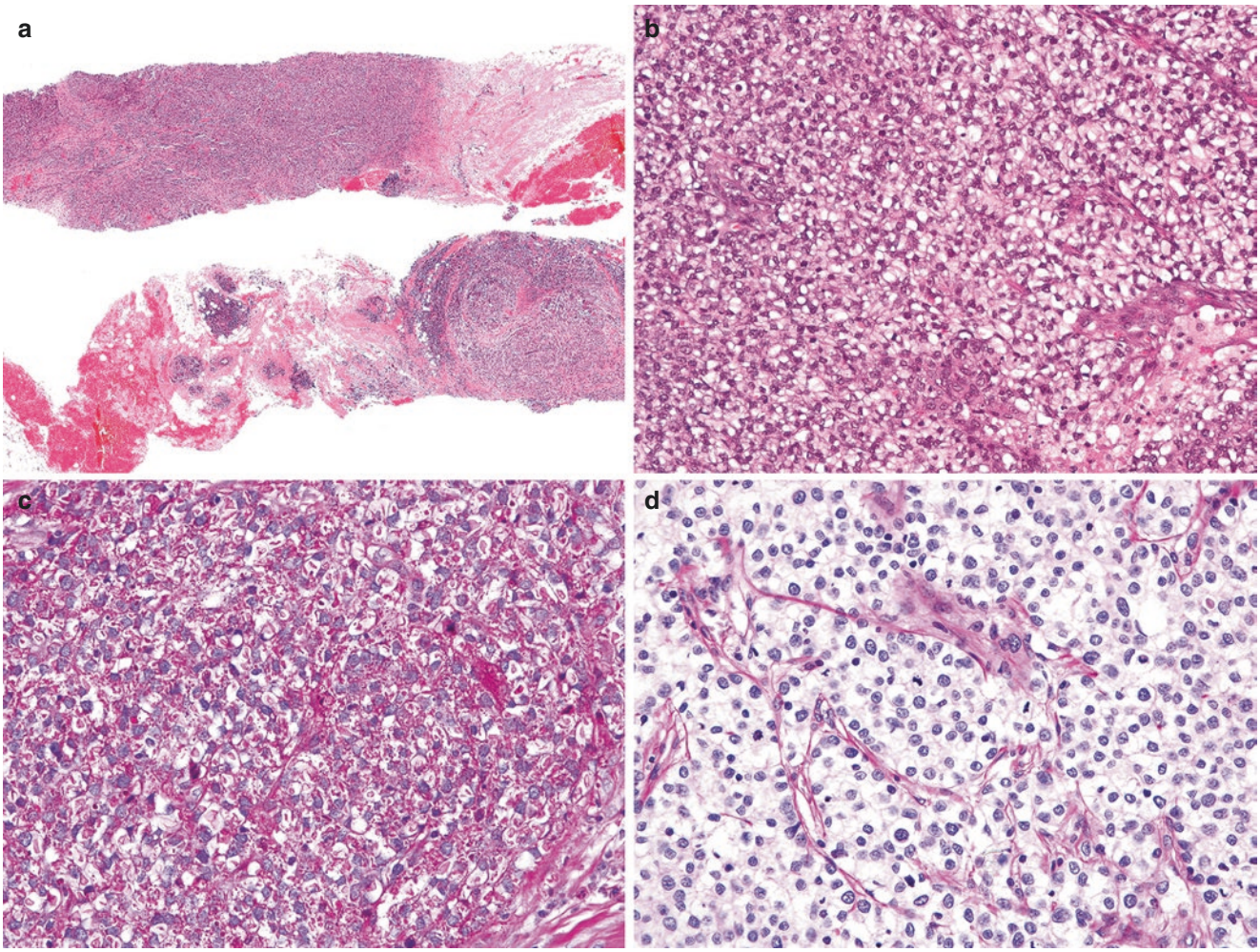

Fig. 13.34 Glycogen-rich carcinoma. (**a**) Low-power magnification of a biopsy core of glycogen-rich carcinoma. The tumor cells with clear cytoplasm and sharp cytoplasmic membrane form a well-circumscribed tumor nodule. (**b**) Cytoplasmic glycogens are highlighted by (**c**) PAS staining, and (**d**) digested by diastase

and, individually, are polygonal with sharp cytoplasmic borders. The cytoplasm is clear or granular, containing PAS-positive diastase-labile glycogen (Fig. 13.34c, d). Associated in situ carcinoma shows similar histologic features. Glycogen-rich clear-cell DCIS as a primary diagnosis has also been reported [126].

As CNB only representatively samples the tumor, the diagnosis of GRCCC cannot be rendered on this material as it requires microscopic examination of the entire tumor. The diagnosis of GRCCC can be suspected on CNB ("invasive carcinoma with glycogen-rich or clear-cell features") and confirmed on final resection specimen.

Differential Diagnosis

GRCCC is not a distinct clinicopathologic entity. But due to its peculiar histologic features, it should be differentiated from other carcinomas with clear-cell features, including lipid-rich carcinoma, myoepithelial carcinoma, primary NEC with clear-cell features, and metastatic clear-cell renal cell carcinoma.

Lipid-rich carcinoma also has clear and vacuolated cytoplasm in >90% of the tumor cells. However, the cytoplasm contains lipids instead of glycogen, which are positive for oil red O or Sudan Black.

Pure spindle cell myoepithelial carcinoma is histologically and immunophenotypically indistinguishable from spindle cell metaplastic carcinoma and is considered as a type of metaplastic carcinoma by most pathologists [127]. However, rare myoepithelial carcinomas are composed of epithelioid polygonal cells with clear cytoplasm, resembling clear-cell myoepithelial tumors of the salivary glands [128, 129], and should be differentiated from GRCCC. Myoepithelial carcinoma is negative for glycogen and positive for myoepithelial markers S100 protein and smooth muscle actin. Anecdotal glycogen-rich clear-cell myoepithelial carcinoma has been reported [130].

In some examples, NEC of the breast may have clear-cell cytoplasm and should be distinguished from GRCCC. With that said, a rare case of GRCCC with neuroendocrine differentiation has been reported, wherein, in addition to having the diagnostic features of GRCCC, the tumor cells were also found to be diffusely positive for neuroendocrine markers synaptophysin and chromogranin-A [131].

Metastatic clear-cell renal cell carcinoma is another entity which can be morphologically mistaken for GRCCC. The presence of rich vasculature, lack of in situ carcinoma, and previous clinical history can often lead to the correct diagnosis.

Immunohistochemical Workup

Special stains periodic acid–Schiff (PAS) and PAS-D (with diastase) are used to confirm the diagnosis of GRCCC as cytoplasmic glycogen stains positively for PAS but negatively for PAS-D. GRCCC has variable expression of hormonal receptors and has no specific immunophenotypic profile. A recent study reported that GRCCC showed a similar biomarker profile as invasive ductal carcinoma NST with 64% of them being ER positive, 60% being PR positive, and HER2 overexpression or amplification seen in 12% of the cases [124].

To differentiate GRCCC from other neoplasms with clear cytoplasm particularly clear-cell renal cell carcinoma, tissue-specific markers CD10, PAX8, and PAX2 (kidney) and GATA3 (breast) are helpful for the correct diagnosis.

Pathogenesis

The pathogenesis of GRCCC is unclear.

Prognosis

Conflicting data regarding the prognosis for GRCCC are reported in the literature. Some studies show a good prognosis [112, 113], while others show aggressive clinical course [124, 126, 130]. However, the prognosis of GRCCC is no different from invasive carcinoma NST when the tumors are matched by size, grade, and lymph node status [117, 124].

Invasive Mammary Carcinoma with Osteoclast-like Giant Cells

Overview

Invasive breast carcinoma with osteoclast-like multinucleated giant cells is a rare variant of primary breast carcinoma. Osteoclast-like multinucleated giant cells can occur in many different tumor types including carcinomas and sarcomas of various organs such as lung, liver, gallbladder, thyroid, pancreas, kidney, and urinary tract [132–137]. Factor et al. first described two cases of invasive mammary carcinoma with osteoclast-like giant cells in the English literature in 1977 [138], which was followed by a small series of eight cases reported by Angnantis and Rosen in 1979 [139]. Identification of osteoclast-like multinucleated giant in association with invasive breast carcinoma is described in less than 2% of breast cancer patients. Only about 250 cases have been published in the literature thus far [140–146]. Due to its distinctive

histologic appearance, this tumor type is recognized as invasive breast carcinoma NST with special morphological patterns by the most recent WHO classification [147]. Since osteoclast-like multinucleated giant cells can be associated with almost all histologic types of breast cancer, it is viewed as a histologic finding rather than a distinct histologic subtype.

Gross and Radiologic Features

Clinical features of breast cancer with osteoclast-like multinucleated giant cells are similar to those of invasive carcinoma NST. It can occur in a wide range of ages (range: 28–88 years) [142]. The tumor size ranges from 0.5 to 10 cm [139, 142]. The most described cases are reported to be round well-circumscribed masses with microcalcifications. A red-brown gross appearance usually due to hemorrhage and associated hemosiderin deposition is commonly described as a characteristic of this tumor.

Microscopic Features

The defining histologic feature is the presence of varying amounts of osteoclast-like multinucleated giant cells in the stroma of invasive carcinoma (Fig. 13.35). Osteoclast-like multinucleated giant cells have been reported in various histological types of invasive breast cancer, including invasive

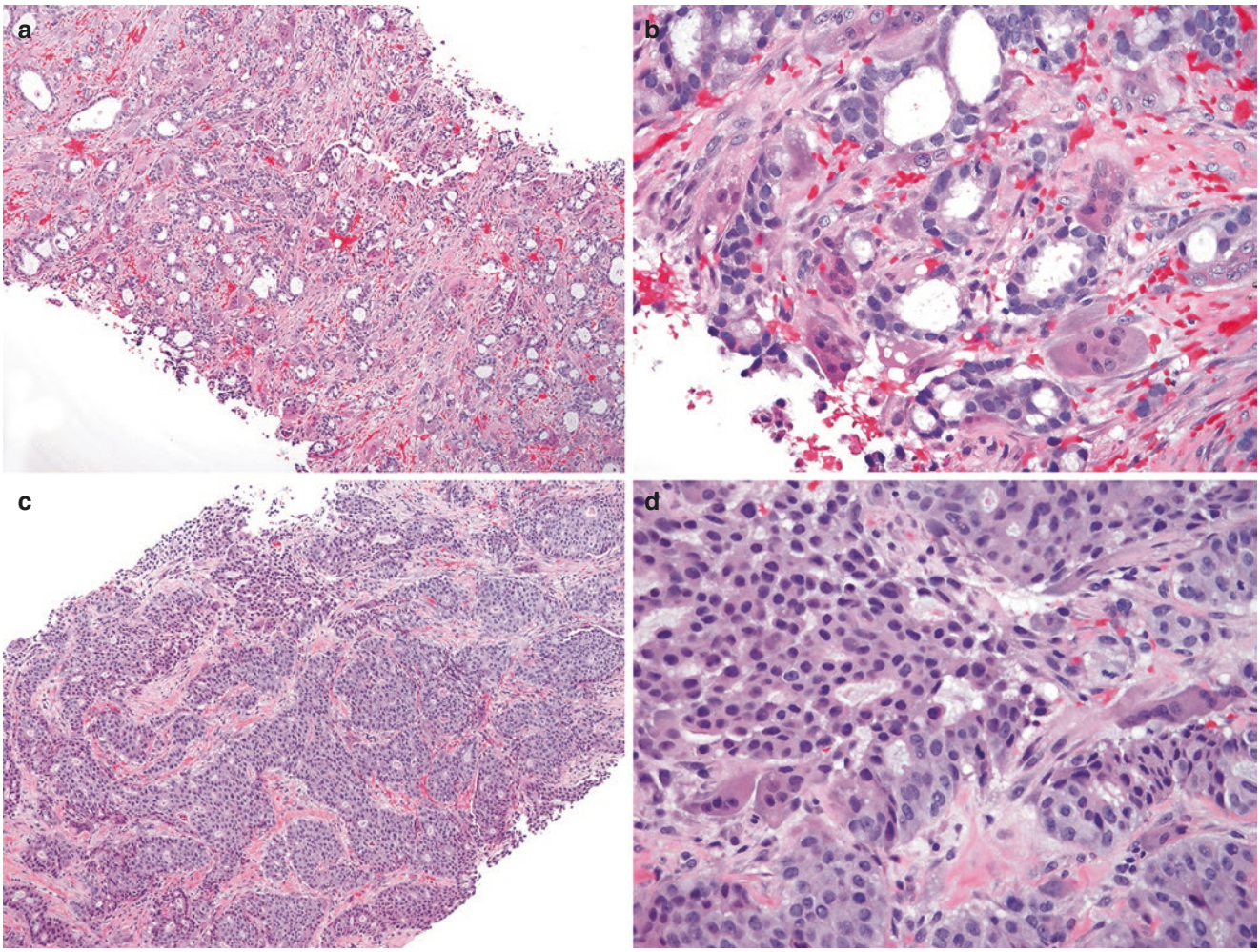

Fig. 13.35 Invasive ductal carcinoma with osteoclast-like giant cells. (**a**, **b**) CNB of a well-differentiated invasive ductal carcinoma shows associated multinucleated osteoclast-like giant cells. (**c**, **d**) Another example of moderately differentiated invasive ductal carcinoma with rare, scattered osteoclast-like giant cells

ductal carcinoma, invasive cribriform carcinoma, tubular carcinoma, mucinous carcinoma, papillary carcinoma, lobular carcinoma, and pleomorphic and metaplastic carcinoma [139, 143, 148, 149]. Osteoclast-like multinucleated giant cells have also been reported in association with both ductal and lobular carcinoma in situ [150]. The number of osteoclast-like multinucleated giant cells present in stroma may be quite variable from case to case and even in different areas of a tumor. Osteoclast-like multinucleated giant cells show bland cytologic features without atypia and most importantly without mitotic activity. Hemorrhage and hemosiderin deposition are common in the tumoral stroma.

Differential Diagnosis

The diagnosis of invasive carcinoma with osteoclast-like giant cells is straightforward when both multinucleated osteoclast-like giant cell and invasive carcinoma are readily identified. It can become diagnostically challenging when the carcinoma component is not readily identified, particularly in limited CNB material.

The differential diagnosis includes a benign reactive process with a giant cell component or malignant neoplasms of epithelial and/or mesenchymal origin. In a benign reactive process, atypical cells are not identified. However, when atypical cells, e.g., spindle cells or pleomorphic cells, are present together with osteoclast-like giant cells, the differential diagnosis includes pleomorphic carcinoma, metaplastic/sarcomatoid carcinoma with osteoclast-like giant cells, and sarcoma (Fig. 13.36). Definitive diagnosis can be deferred to the resection specimen in uncertain cases.

Immunohistochemical Workup

The associated multinucleated giant cells are of histiocytic origin, and they are CD68 positive and S100 protein negative. The carcinoma associated with osteoclast-like giant cells will be positive for cytokeratin and additionally may be associated with in situ carcinoma. In contrast, sarcomas will not be immunoreactive for cytokeratins and will lack an in situ carcinoma component.

Invasive carcinomas with osteoclast-like giant cells are frequently positive for hormonal receptors (ER and/or PR) and negative for HER2, although high-grade tumors including metaplastic carcinoma can be triple negative (ER−/PR−/HER−).

Pathogenesis

The mechanism for formation of osteoclast-like giant cells is still unknown. Immunohistochemical studies have confirmed histiocytic lineage of osteoclast-like multinucleated giant cells since they are positive for CD68 and negative for S100 protein. Secretion of specific cytokines, such as vascular endothelial growth factor and matrix metallopeptidase 12, has been described, and it has been hypothesized that the characteristic inflammatory and hypervascular stroma, which is commonly observed in breast carcinoma with osteoclast-like multinucleated giant cells, may be associated with the activation of these cytokines [151, 152].

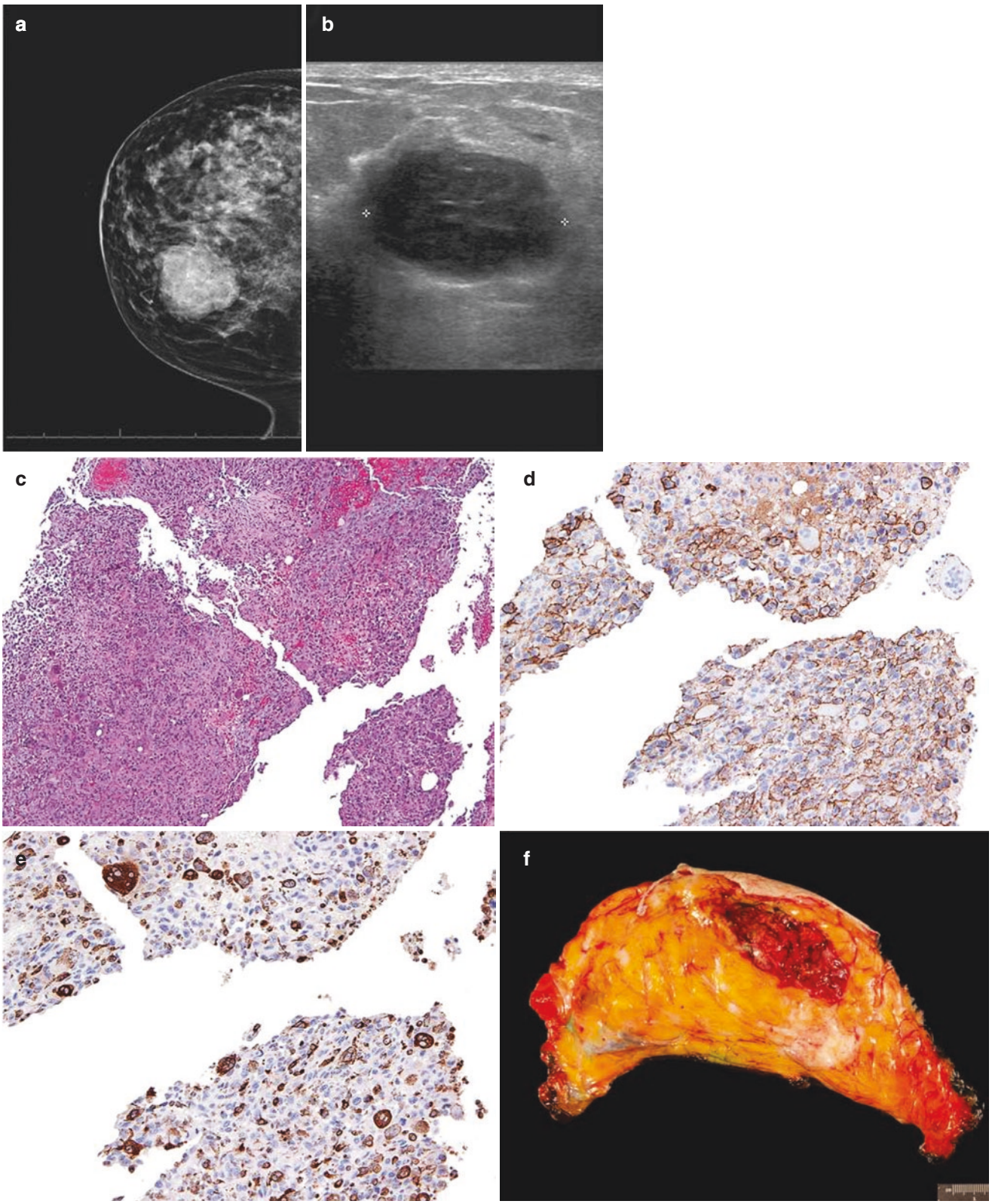

Fig. 13.36 Metaplastic/sarcomatoid carcinoma with osteoclast-like giant cells. (**a**) A 52-year-old women presented with a large palpable mass in her right breast. Diagnostic mammogram revealed a 4 cm lobulated, partially circumscribed, partially obscured mass, which was further confirmed by (**b**) sonogram. (**c**) Core needle biopsy was performed and showed a cellular high-grade neoplasm with mixed spindle, pleomorphic cells and osteoclast-like giant cells. The differential diagnosis includes metaplastic/sarcomatoid carcinoma versus sarcoma. (**d**, **e**) Further work-up showed the pleomorphic and spindle cells were positive for EMA (**d**) and multinuclear giant cells were positive for CD68 (**e**). Metaplastic/sarcomatoid carcinoma was favored. Patient underwent total mastectomy. (**f**) Gross evaluation revealed a well-demarcated large mass with brown hemorrhagic soft cut surface. (**g**, **h**) Histologic examination showed sheets of pleomorphic and spindle cells with admixed multinucleated giant cells; (**i**) focal area of high grade ductal carcinoma in situ was also present

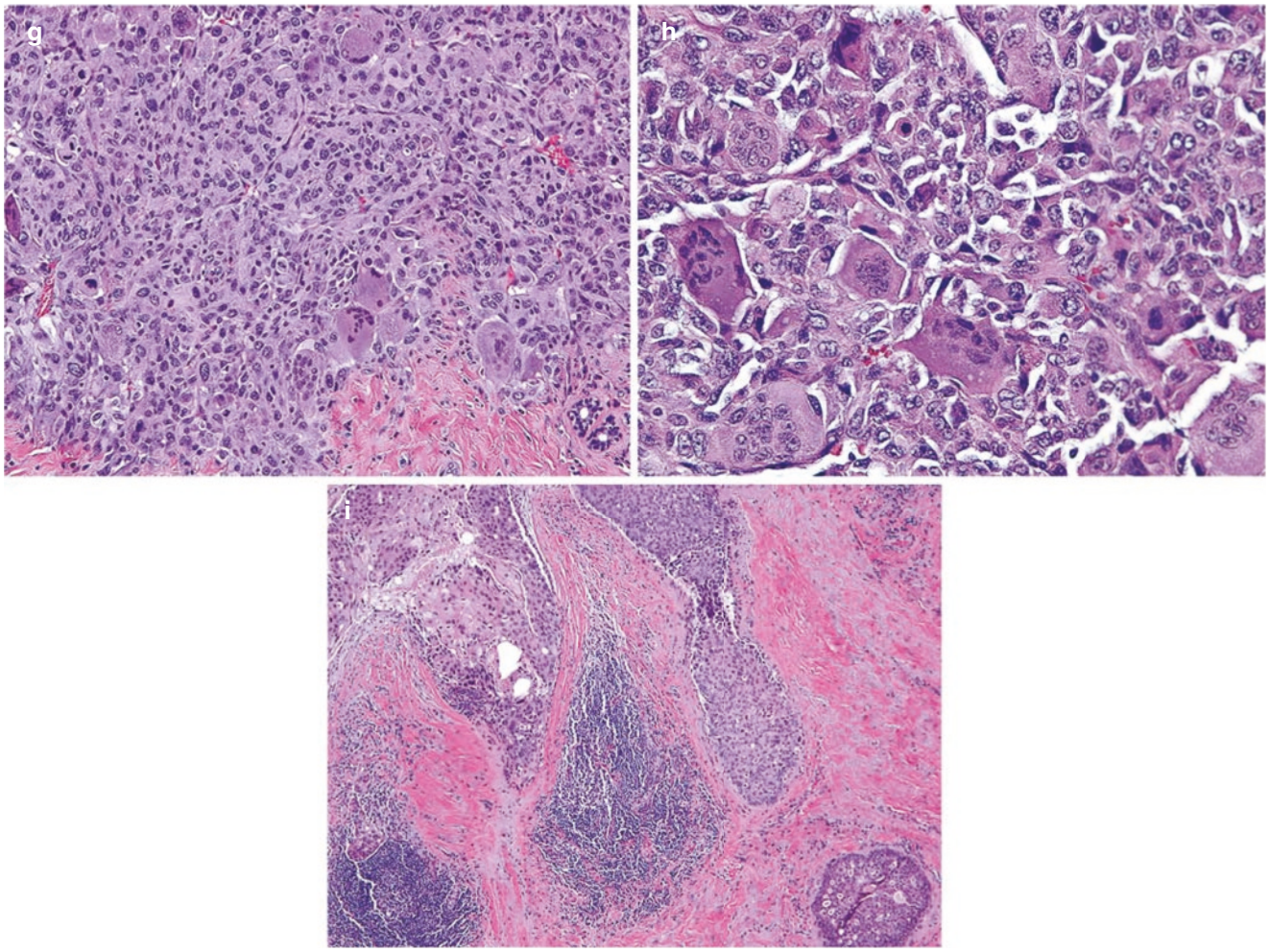

Fig. 13.36 (continued)

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