Special Types of Invasive Breast Carcinoma

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Javier A. Arias-Stella III, Isabel Alvarado-Cabrero, and Fresia Pareja

Breast carcinoma is a vastly heterogeneous disease encompassing a wide array of entities with different morphology, biology, clinical behavior, and prognosis. Special types of breast carcinoma include tumors with morphologies that deviate from invasive carcinoma of no special type (NST). As a group, special types comprise up to 25% of all breast cancers, and encompass entities ranging from low to high-grade, and with different hormone receptor and HER2 status. The recognition of the different special types of breast cancer is of paramount importance, as their proper classification is relevant not only for taxonomic purposes, but has also therapeutic implications.

15.1 Invasive Lobular Carcinoma

Invasive lobular carcinoma (ILC) is the most common special type of breast cancer and accounts for approximately 15% of breast invasive carcinomas [1]. While the incidence of invasive carcinoma of no special type (NST) has been stable, incidence of ILC appears to have increased [2].

Patients with ILC usually present with an ill-defined palpable mass or diffuse breast nodularity, at an older age, and with larger tumors than patients with invasive carcinoma, NST [3]. ILC has a tendency to occur bilaterally and multicentrically [4]. The most frequent mammographic finding of ILC is a mass with irregular borders, while microcalcifications are rarely seen [5–7]. However, mammography has a relatively low sensitivity for the detection of ILC, with up to 30% of false negative cases [7]. On ultrasonogram, ILC is commonly detected as an irregular hypoechoic mass with spiculated borders; posterior acoustic shadowing is observed more frequently than in invasive carcinoma, NST [5]. While the tumor size of ILC is frequently underestimated by mammography and ultrasonogram [8], magnetic resonance imaging (MRI) findings correlate better with the histologic size of the tumor [9].

Classic ILC is composed of discohesive tumor cells arranged in a linear pattern or as single cells. Classic ILC is associated with negligible desmoplasia or host lymphocytic reaction and does not disrupt the normal breast architecture (Fig. 15.1), displaying a targetoid concentric distribution around ducts and lobules (Fig. 15.2). The tumor cells resemble those of lobular carcinoma in situ (LCIS), and are small and uniform with occasional intracellular lumina, round and uniform nuclei, inconspicuous nucleoli, and infrequent mitotic figures (Fig.15.3).

A wide array of ILC variants can be recognized, which differ from classical ILC in their morphology and behavior, including the solid, alveolar, trabecular, tubulolobular, signet ring cell, and pleomorphic variants. ILC histologic variants are found occasionally admixed with classic ILC or with other ILC variants. The solid variant of ILC is characterized by discohesive tumor cells growing in solid nests, and may show pleomorphism or increased mitotic activity (Fig. 15.4) [10]. The alveolar variant of ILC is composed of tumor cells arranged in discrete clusters or aggregates of 20 or more cells, separated by thin fibrous septa (Fig. 15.5) [11]. The trabecular variant of ILC is characterized by tumor cells growing in bands thicker than two cells. The tubulolobular variant of ILC is composed of small cords and tubules of tumor cells arranged in a linear fashion, with a hybrid tubular and lobular morphology [12]. Pleomorphic ILC has the same growth pattern as classic ILC, but the tumor cells show greater cytological atypia and pleomorphism and display a higher mitotic rate (Figs. 15.6 and 15.7) [13].

Cytologic smears of ILC show small tumor cells in poorly cohesive clusters or as isolated cells, with occasional

J. A. Arias-Stella III, MD · F. Pareja, MD, PhD (✉)
Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: ariasstj@mskcc.org; parejaf@mskcc.org

I. Alvarado-Cabrero, MD, PhD
Department of Pathology, Hospital de Oncologia, Centro Medico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico

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single-cell linear alignments (Fig. 15.8) [14]. Despite the challenges associated with the diagnosis ILC on cytology, fine-needle aspiration (FNA) remains a useful diagnostic tool. Nonetheless, caution should be exerted to distinguish ILC from its mimickers, such as inflammatory cells in mastitis, which may result in a false positive interpretation.

The differential diagnosis of ILC includes lymphoma, metastatic carcinoma, tubulolobular carcinoma, and invasive carcinoma NST with lobular features. Classic ILC, and in particular its histologic variants, must sometimes be distinguished from invasive carcinoma NST, and E-cadherin is widely used for this purpose. *CDH1* mutations cause loss of expression of E-cadherin, a molecule involved in cell-to-cell adhesion, which results in the facilitation of epithelial to mesenchymal transition and tumorigenesis [15]. The expression of E-cadherin is reduced or completely absent in ILC (Fig. 15.9) [16], although some cases may express E-cadherin aberrantly [17]. Notably, the cadherin-catenin complex appears to be non-functional in ILC with aberrant E-cadherin expression, and the latter should not preclude the diagnosis of ILC in cases with a typical lobular morphology [17]. Immunohistochemical stains for β-catenin, which is reduced in ILC, and p120, which shows a diffuse cytoplasmic expression, are also helpful to define a lobular phenotype. ILCs are generally positive for estrogen receptor (ER) and progesterone receptor (PR), while negative for the human epidermal growth factor receptor 2 (HER2), although ILC variants, such as pleomorphic ILC, may more frequently display a HER2-positive or triple negative phenotype [18]. ILCs are enriched for mutations in *CDH1*, *PTEN*, *TBX3*, and *FOXA1* [19], and the majority of them are of luminal A molecular subtype [20].

ILC has a favorable clinical outcome and has a significantly better 5-year disease-free survival than invasive carcinoma NST. Nonetheless, ILC is associated with late recurrences and metastasis in atypical locations [21], and with a higher frequency of positive or close surgical margins than invasive carcinoma NST [22]. Moreover, some histologic variants of ILC, such as pleomorphic ILC, have more aggressive clinicopathologic features. Older age and triple negative phenotype have been shown to significantly correlate with a worse clinical outcome in pleomorphic ILC [23].

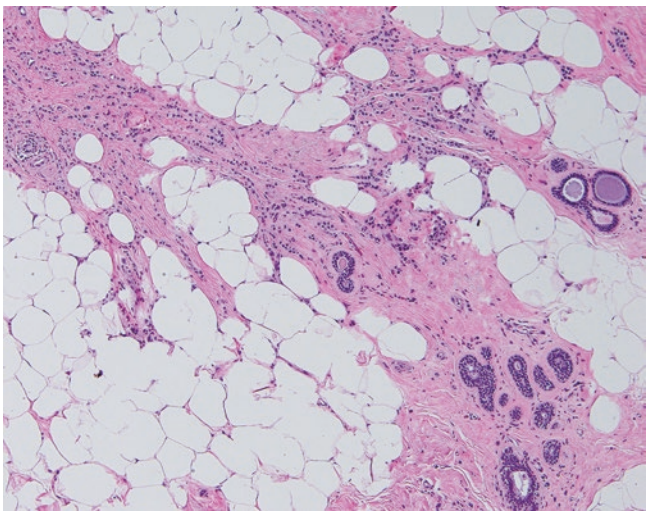

Fig. 15.1 Classic invasive lobular carcinoma: the carcinoma is composed of discohesive cells growing in a linear pattern without disrupting the normal breast architecture

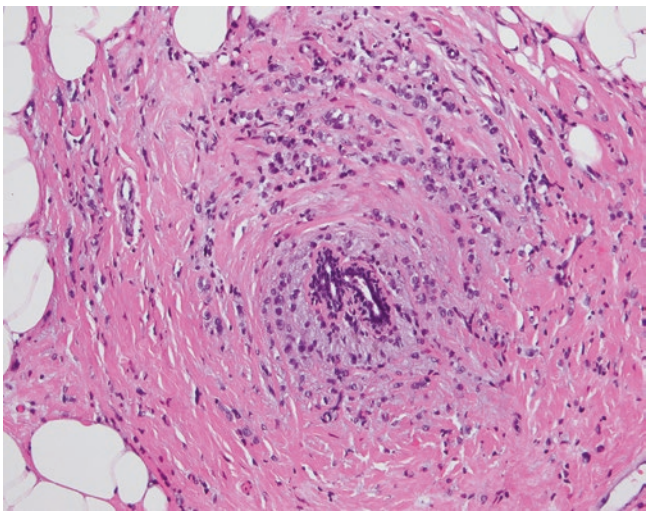

Fig. 15.2 Classic invasive lobular carcinoma: the tumor cells show a targetoid growth around normal ducts

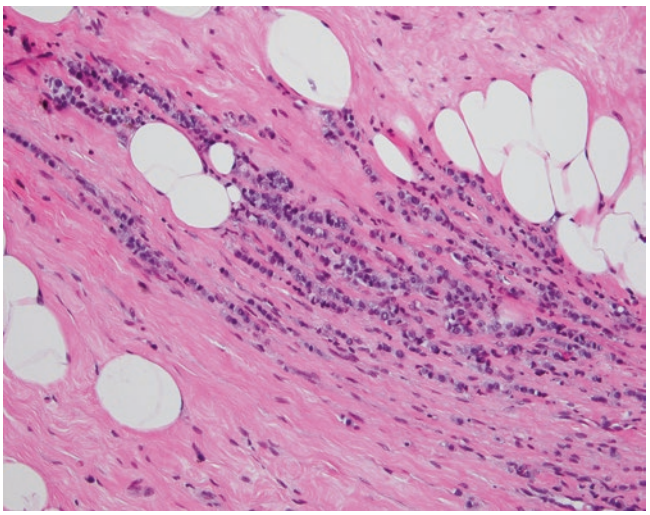

Fig. 15.3 Classic invasive lobular carcinoma: the carcinoma is composed of small monotonous bland cells

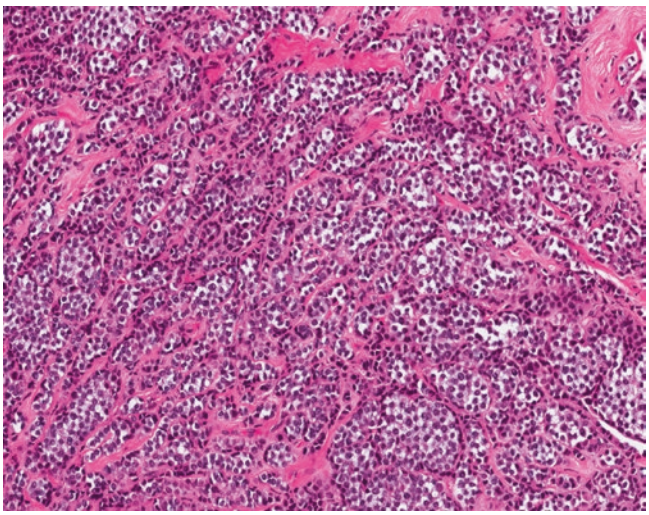

Fig. 15.5 Alveolar variant of invasive lobular carcinoma: the carcinoma cells are arranged in small clusters of cells separated by fibrous septae

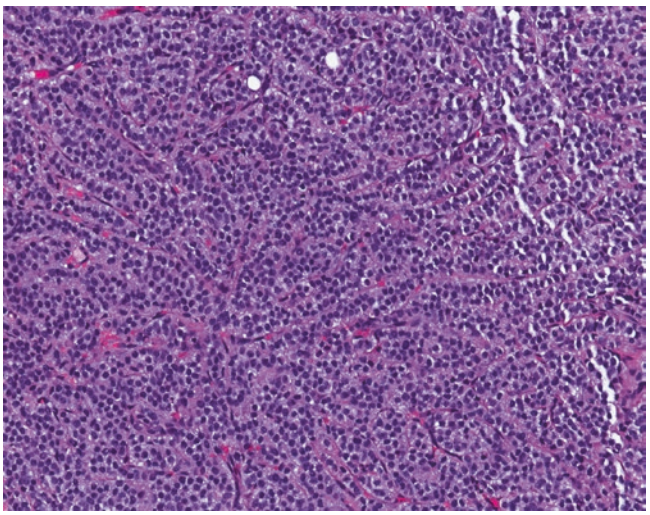

Fig. 15.4 Solid variant of invasive lobular carcinoma: the carcinoma cells are arranged in sheets

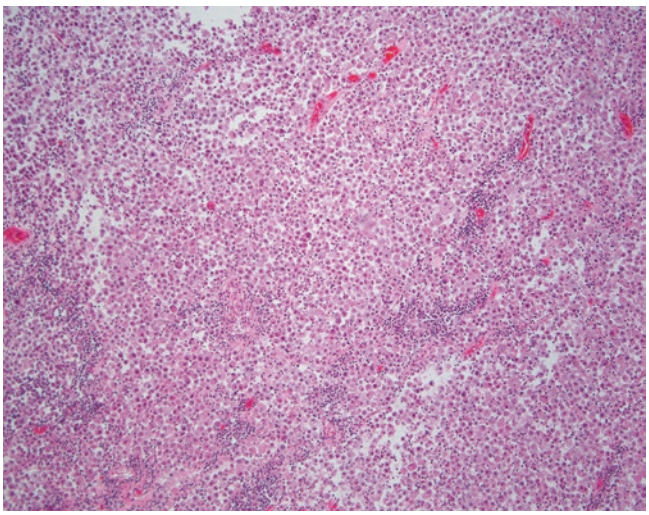

Fig. 15.6 Pleomorphic lobular carcinoma: the carcinoma is arranged in solid sheets and is composed of discohesive large atypical cells with marked pleomorphism

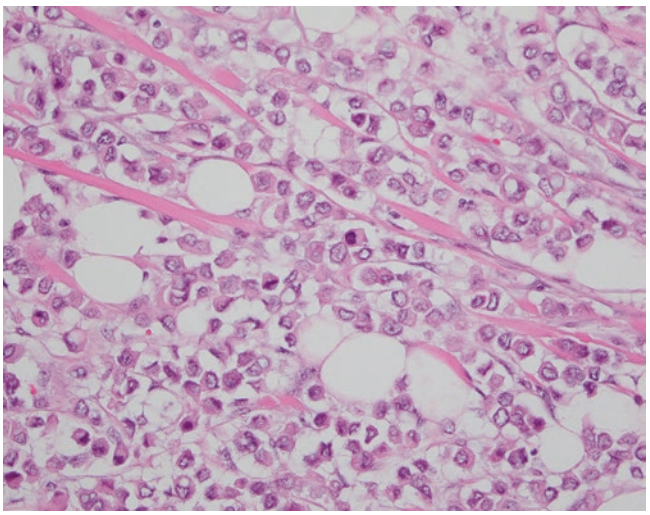

Fig. 15.7 Pleomorphic lobular carcinoma: the tumor cells show a high nuclear/cytoplasmic ratio and frequent mitoses

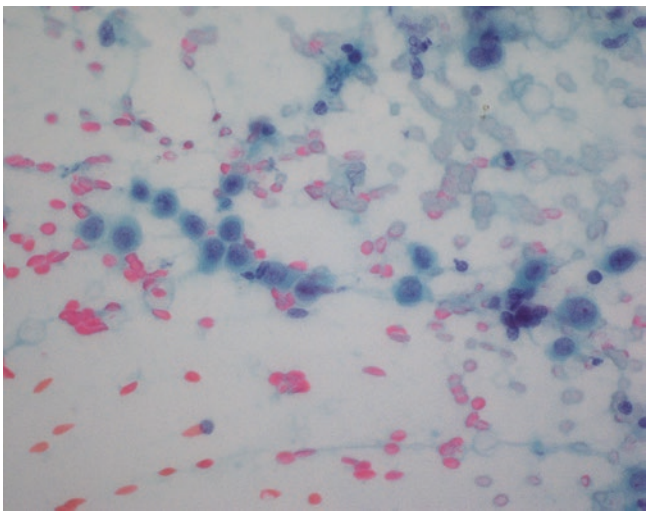

Fig. 15.8 Invasive lobular carcinoma, cytology: FNA smear shows discohesive tumor cells arranged in a linear pattern

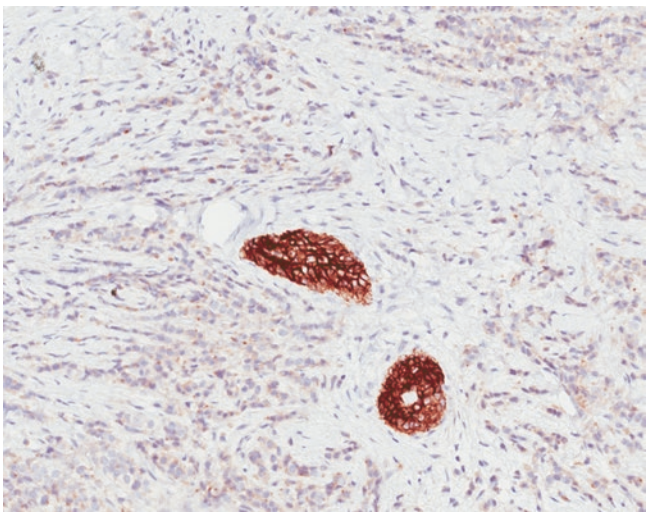

Fig. 15.9 Invasive lobular carcinoma, immunohistochemical stain for E-cadherin: the carcinoma cells show markedly decreased E-cadherin expression compared to the normal breast epithelium which exhibits strong E-cadherin membranous expression

15.2 Tubular Carcinoma

Tubular carcinoma is an uncommon histologic subtype, accounting for approximately 1–4% of breast invasive carcinomas [24]. Tubular carcinoma is not commonly associated with a palpable mass and is usually detected as an incidental finding on screening mammography [25]. On mammogram, tubular carcinomas appear as irregularly shaped masses with central densities and spiculated margins, and as hypoechoic masses with irregular margins and posterior acoustic shadowing on ultrasonogram [26].

Tubular carcinomas are composed of tubules with open lumina and oval or angulated contours in a haphazard arrangement. The tubules are lined by a single layer of epithelium with cuboidal or columnar cells with minimal pleomorphism and basally located round-to-oval nuclei (Fig. 15.10) [27]. More than 90% of the tumor should have the aforementioned morphologic features for it to be classified as a pure tubular carcinoma, whereas tumors with >50–75% of tubular component are best categorized as mixed tubular carcinomas.

The diagnosis of tubular carcinoma on FNA smears is challenging. Cytologic features of tubular carcinoma include moderate-to-high cellularity, angular epithelial clusters of oval cells, and dispersed single epithelial cells with minimal atypia in the background [28].

Tubular carcinomas are classically ER-positive and HER2-negative, and have a luminal A phenotype (Fig. 15.11) [29]. Tubular carcinomas belong to the "low-grade breast neoplasia family" and are frequently seen in association with columnar cell lesions, atypical ductal hyperplasia, low-grade ductal carcinoma in situ, and lobular neoplasia [20]. In a way akin to low-grade IDC-NST, ILC, cribriform, and tubulolobular carcinomas, tubular carcinomas are characterized by 16q losses coupled to 1q gains [20].

Benign sclerosing lesions, such as radial scars or sclerosing adenosis, may show a pseudoinvasive morphology and mimic tubular carcinoma, and myoepithelial markers such as p63 and CD10 have been proven useful to discriminate between these lesions [30]. Microglandular adenosis is another mimicker of tubular carcinoma. However, tubular carcinoma lacks the characteristic eosinophilic secretions and strong S100 positivity characteristic of microglandular adenosis [31].

Tubular carcinoma of the breast is associated with a low rate of nodal metastasis and recurrences, and a life expectancy that is close to normal [24].

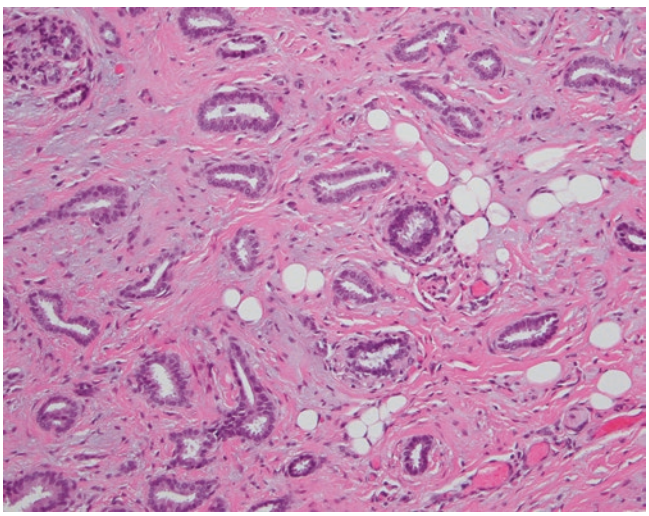

Fig. 15.10 Tubular carcinoma: neoplastic oval and angular glands with open lumens invading fibroadipose tissue

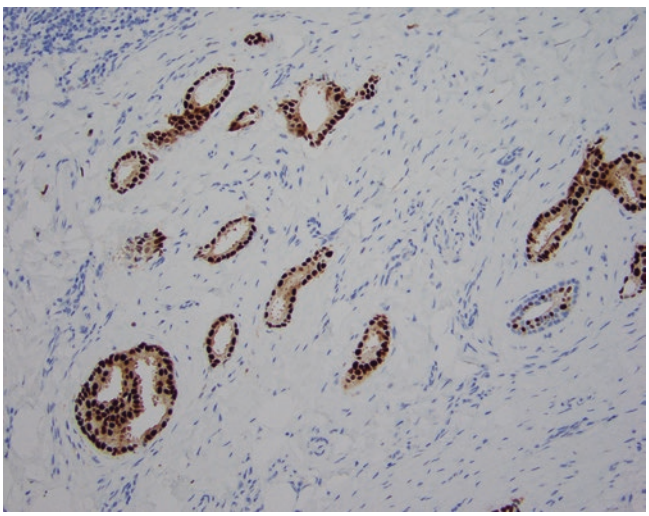

Fig. 15.11 Tubular carcinoma: the tumor cells display strong and diffuse expression of estrogen receptor

15.3 Mucinous Carcinoma

Mucinous carcinomas represent approximately 1.5% of all breast carcinomas [32]. Patients present at a significantly older age than those with IDC-NST [33]. The diagnosis of pure mucinous carcinoma requires >90% of tumor to be admixed with mucin, whereas tumors in which the mucinous component is less than 90% should be classified as mixed mucinous carcinomas (Figs. 15.12 and 15.13) [34].

On mammography, pure mucinous carcinomas appear as well-circumscribed oval masses, whereas mixed mucinous carcinomas show more aggressive imaging features [35]. On ultrasound, pure and mixed mucinous carcinomas are isoechogenic and hypoechogenic to subcutaneous fat, respectively [35, 36]. Pure mucinous carcinomas show MRI features which may be observed in benign lesions, such as a circumscribed shape, and a very high signal intensity of fat-saturated T2-weighted images, whereas mixed lesions display more suspicious imaging findings [35, 37].

Mucinous carcinoma is characterized by an invasive component admixed with varying amounts of extracellular mucin. The tumor cells are arranged in architectural patterns, such as nests, trabeculae, sheets, and cell clusters with glandular lumen formation. According to criteria put forward by Capella et al., two morphologic subtypes may be distinguished: type A and B [38]. Type A mucinous carcinomas are characterized by abundant extracellular mucin, whereas type B tumors have less extracellular mucin and show neuroendocrine differentiation (Figs. 15.14 and 15.15). Tumors with an intermediate morphology are classified as of type AB [38].

Typically, mucinous carcinomas display strong and diffuse positivity for ER and PR (Fig. 15.16), have a low Ki67 index, and express WT1 more frequently than ER-matched invasive carcinoma NST [39]. Expression of neuroendocrine markers is more frequent in type B mucinous carcinomas [39].

The features of breast mucinous carcinomas in FNA smears include a mucinous background, branching capillaries, and tumor cells in clusters or as single cells (Figs. 15.17 and 15.18) Nevertheless, these findings may be present in other malignant or benign breast lesions, making the identification of mucinous carcinoma on cytology specimens challenging [40].

The main differential diagnoses of stromal mucin in a core-needle biopsy specimen are mucinous carcinomas and mucocele-like lesions, which may be associated with benign, atypical, or malignant epithelium [41, 42].

Pure mucinous carcinomas show more favorable clinicopathologic features than invasive carcinoma NST, such as smaller tumor sizes, lower rates of lymph node positivity, and higher rates of ER and PR positivity [43]. Patients with pure breast mucinous carcinomas have better relapse-free survival than those with invasive carcinoma NST [43]. Even though type A mucinous carcinomas occur in older patients, have a lower nuclear grade, and lower rates of HER2 positivity and nodal involvement than type B tumors [44], the prognostic significance of this morphologic classification is uncertain and warrants further study.

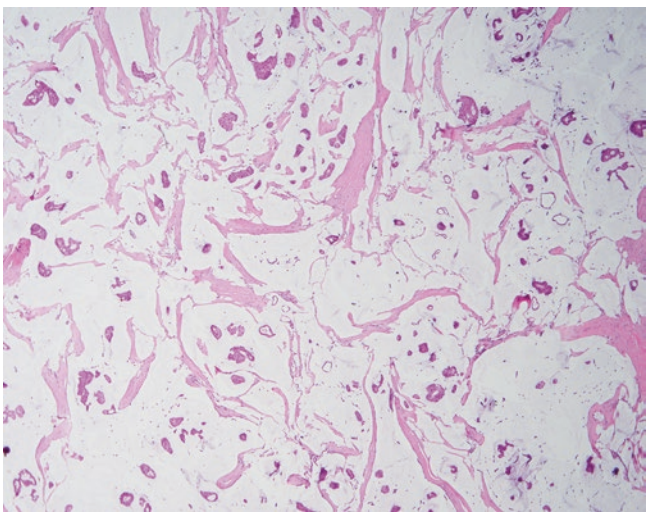

Fig. 15.12 Pure mucinous carcinoma: the tumor is entirely composed of nests of carcinoma cells floating in pools of mucin

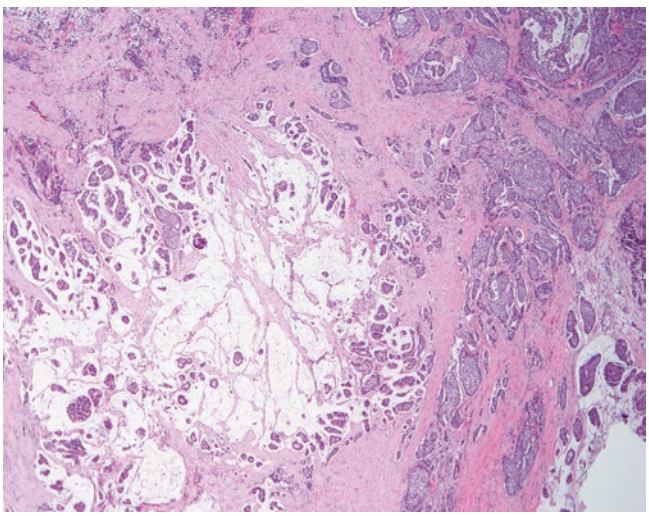

Fig. 15.13 Mixed mucinous carcinoma: the tumor has a predominant mucinous component admixed with a ductal component

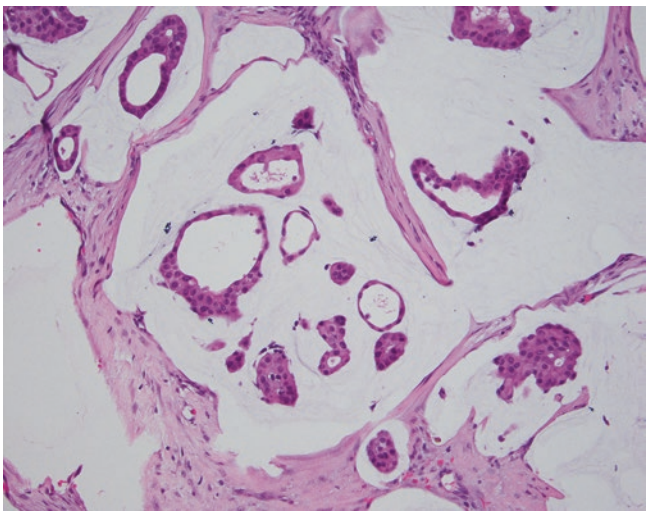

Fig. 15.14 Mucinous carcinoma, type A: the tumor is hypocellular and has abundant extracellular mucin

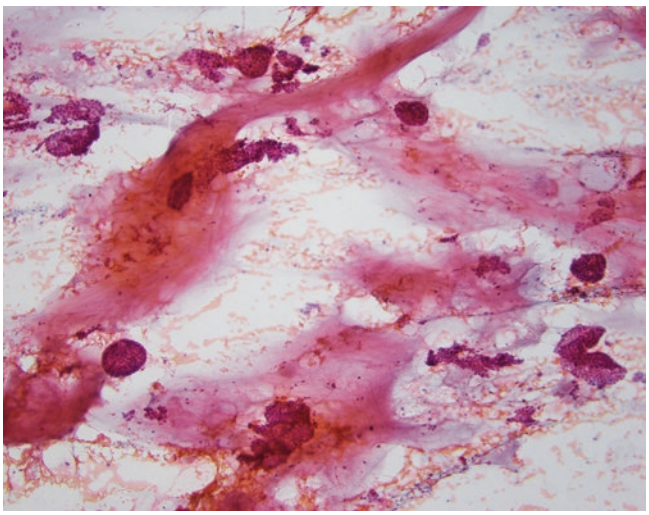

Fig. 15.17 Mucinous carcinoma, cytology: FNA smear showing cohesive clusters of carcinoma cells in a background of abundant mucin

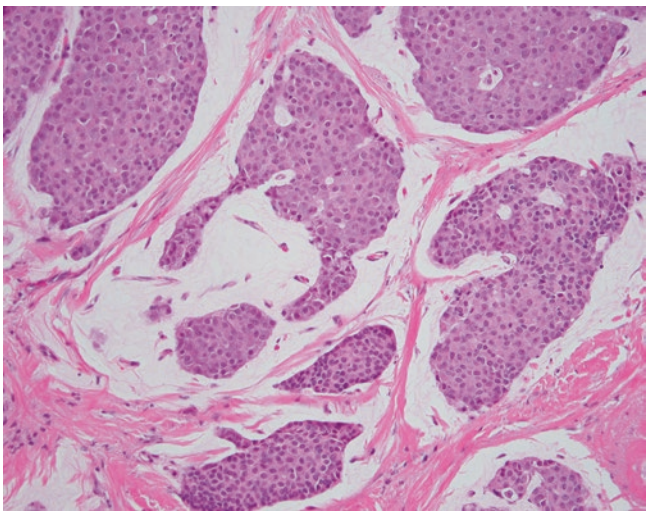

Fig. 15.15 Mucinous carcinoma, type B: the carcinoma is hypercellular

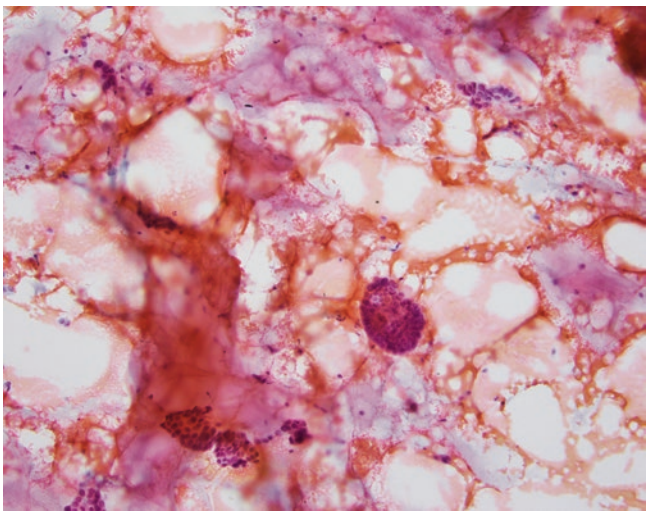

Fig. 15.18 Mucinous carcinoma, cytology: FNA smear shows tumor cells with a bland appearance admixed with mucin

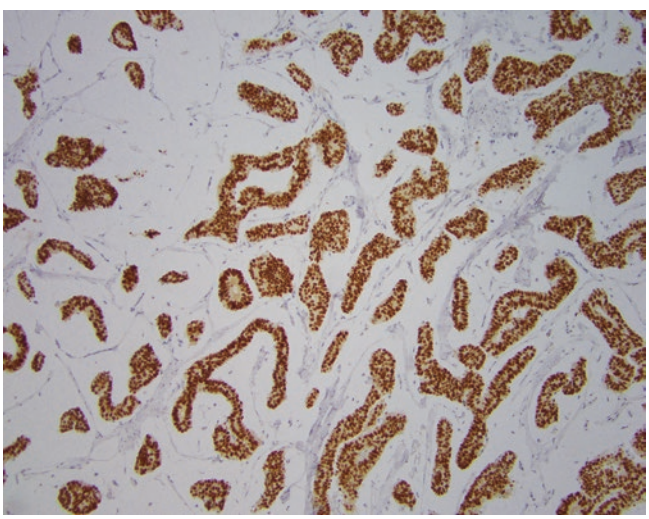

Fig. 15.16 Mucinous carcinoma: the carcinoma cells are strongly and diffusely positive for estrogen receptor

15.4 Micropapillary Carcinoma

Micropapillary carcinoma is rare and accounts for <2% of breast carcinomas [45]. Patients usually present with a palpable mass.

On mammogram, micropapillary carcinomas appear as masses with irregular shape and spiculated margins, frequently associated with microcalcifications [46]. Sonographically, these masses are hypoechoic and lack posterior acoustic enhancement or shadowing [46, 47]. MRI demonstrates masses with irregular or spiculated margins, with initial rapid enhancement and washout [46, 47].

Histologically, breast micropapillary carcinomas are composed of small morule-like clusters of tumor cells lacking fibrovascular cores within empty spaces, which may resemble lymphovascular invasion (Fig. 15.19) [48]. The tumor clusters show reverse polarity (inside-out growth pattern), with the apical aspect of the cells facing the stroma [48]. Pleomorphism and atypia are usually moderate, and mitotic activity is variable. Associated psammomatous calcifications are not infrequent (Fig. 15.20) [49, 50]. Invasive carcinoma NST and other histologic subtypes of breast cancer may be associated with a minor micropapillary component [49].

FNA smears of micropapillary carcinomas have a moderate-to-high cellularity and show tightly cohesive angular cell clusters of mildly to moderately pleomorphic tumor cells with high nuclear/cytoplasmic ratio and an inside-out pattern, admixed with single discohesive cells [51].

Micropapillary carcinomas are usually positive for ER and PR, and have variable rates of HER2 expression [52]. Expression of HER2 is restricted to the basolateral membranes of the tumor cells, as it is absent in the membrane aspect facing the stroma [53], posing challenges to its accurate interpretation. Notably, almost half of micropapillary carcinomas with a HER2 score of 1+ by immunohistochemistry (IHC) were found to be HER2 amplified by FISH [54]. Indeed, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines recommend the use of an alternative method for evaluation of HER2 expression in micropapillary carcinomas that show intense but incomplete HER2 expression by IHC [55].

The reverse polarization of the tumor cells in micropapillary carcinomas can be highlighted by MUC1 and EMA, which are positive in the apical, stroma-facing aspect of the tumor cell membranes [56, 57], and by E-cadherin and p120, which have a "cup-shaped" staining pattern, present in the lateral cell borders, and absent in the apical membrane facing the stroma [57, 58]. Vascular markers such as CD31, CD34, factor VIII, and D2-40 may be useful for the discrimination of true lymphovascular invasion from the clear stromal spaces of micropapillary carcinoma [59]. Micropapillary carcinomas are mostly of luminal B molecular subtype [60], and harbor recurrent mutations in *NBPF10* and in genes of the mitogen-activated protein kinase (MAPK) family [61].

Micropapillary carcinoma should be distinguished from invasive carcinoma NST with marked retraction artifact, which lacks inside-out morphology. Importantly, in the absence of clear *in situ* carcinoma, or in the metastatic setting, a panel of immunohistochemical stains including uroplakin, CK20, TTF-1, ER, WT1, PAX8, and mammaglobin might be useful to discriminate breast micropapillary carcinoma from micropapillary carcinoma of other anatomic origins, such as ovary, bladder, lung, salivary glands, and the gastrointestinal tract [62].

Micropapillary carcinoma is associated with more aggressive clinicopathologic features than invasive carcinoma NST, such as larger tumor size, increased incidence of lymphovascular invasion, and a higher rate of lymph node metastasis [63, 64]. Indeed, the majority of patients present with nodal metastasis at diagnosis, and nodal positivity is the most important independent prognostic predictor of recurrence-free survival [64]. Nonetheless, the disease-specific and overall survival of patients with micropapillary carcinoma does not appear to differ from that of patients with invasive carcinoma NST of similar stage [65].

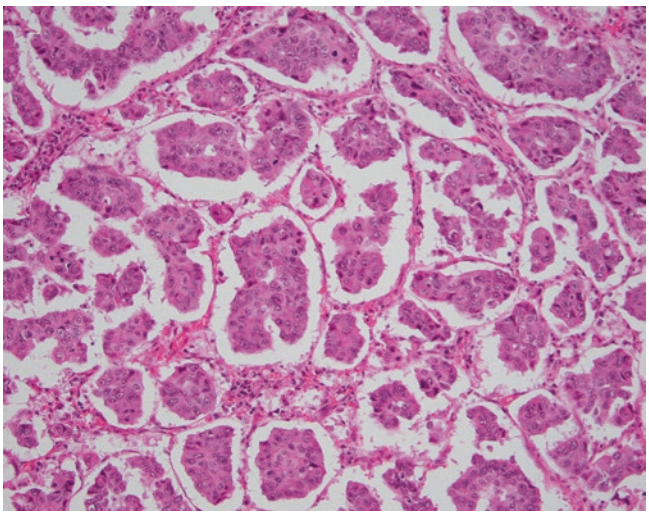

Fig. 15.19 Micropapillary carcinoma: the tumor is arranged in morule-like clusters, with no fibrovascular cores, in empty spaces separating them from the stroma

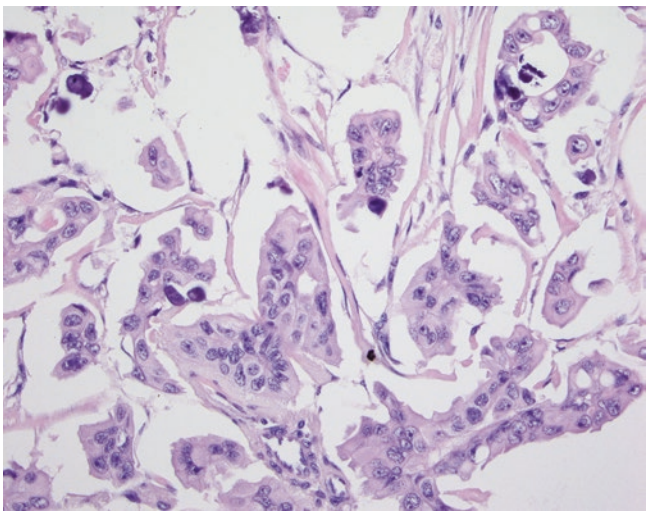

Fig. 15.20 Micropapillary carcinoma: the carcinoma cells have high nuclear grade. Psammomatous calcifications are seen

15.5 Mucinous Micropapillary Carcinoma

Mucinous micropapillary carcinoma, also known as micropapillary variant of mucinous carcinoma, is an unusual form of invasive breast cancer that exhibits dual mucinous and micropapillary morphology [66].

Mucinous micropapillary carcinomas display a hybrid histology, characterized by floret-like or pseudoacinar structures of hobnail cells in stromal spaces filled with mucin (Figs. 15.21 and 15.22) [67]. Psammomatous calcifications can be readily identified.

Akin to micropapillary carcinomas and pure mucinous carcinomas, mucinous micropapillary carcinomas display reverse polarity, which may be highlighted by IHC stains for EMA and MUC1 [67]. These tumors are diffusely positive for ER and PR [67], and show a higher rate of HER2 overexpression/amplification than mucinous carcinomas, which ranges between 10% and 20% [44, 66].

Cytologic preparations have a moderate cellularity, and show micropapillary clusters of tumor cells with nuclear hobnailing in pools of mucin. Single cells in the background are present to a lesser degree than in micropapillary carcinoma, and psammomatous calcifications are not uncommon [68, 69].

Mucinous micropapillary carcinoma displays clinicopathologic features intermediate between mucinous and micropapillary carcinoma, such as an intermediate rate of lymphovascular invasion, nodal metastasis, and HER2 overexpression/amplification. The rate of regional recurrence and distant metastasis of mucinous micropapillary carcinoma is also intermediate, between the rates of recurrence and distant metastasis of mucinous and micropapillary carcinomas [44, 66, 67].

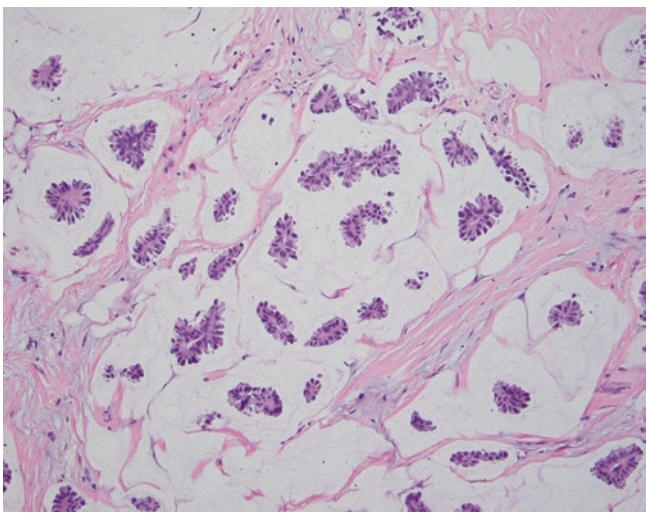

Fig. 15.21 Mucinous micropapillary carcinoma: tumor cells are arranged in morule-like clusters with hobnail cells floating in pools of mucin

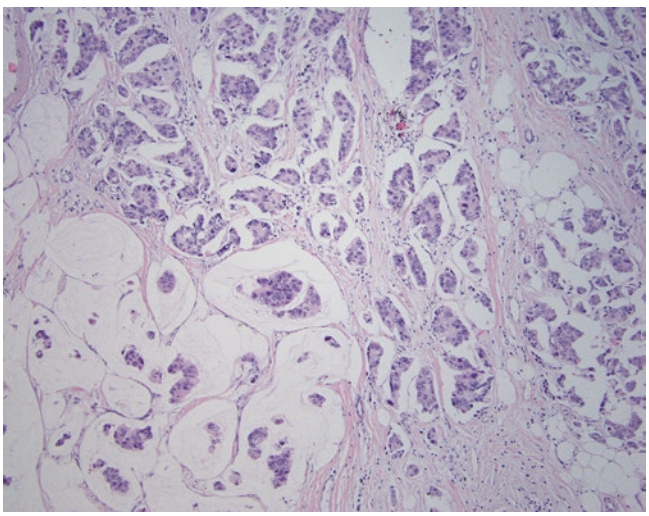

Fig. 15.22 Mucinous micropapillary carcinoma: mucinous micropapillary carcinoma (left) with tumor clusters floating in mucin transitions to an area with micropapillary morphology in which the carcinoma cells are present in empty spaces (right)

15.6 Carcinoma with Medullary Features

Carcinoma with medullary features is a category encompassing tumors previously designated as medullary carcinoma and atypical medullary carcinoma. Grouping of these entities under this category is recommended due to their overlapping morphology associated with diagnostic challenges and a poor inter-observer reproducibility. Carcinomas with medullary features are rare, and represent <5% of breast invasive carcinomas [70]. Patients with carcinomas with medullary features present at a younger age than those with invasive carcinoma NST [71].

Carcinomas with medullary features present as well-circumscribed masses on mammography and ultrasound. Posterior acoustic enhancement on sonogram is more frequent in typical than in atypical medullary carcinomas [72]. On MRI, carcinomas with medullary features show an oval shape, well-circumscribed borders, and frequent rim enhancement with or without enhancing internal septations [73].

The classic morphologic criteria used to define typical medullary carcinomas include predominant syncytial growth (>75% of the tumor), circumscribed and pushing borders, lack of tubule formation, diffuse prominent stromal lymphoplasmacytic infiltrate, and high nuclear grade (Figs. 15.23 and 15.24) [74]. Tumors that don't display all these features were called atypical medullary carcinomas.

On FNA specimens, carcinomas with medullary features are highly cellular and show distinctive characteristics, such as syncytial sheets of cells with bizarre nuclei and prominent nucleoli, and marked chronic lymphoplasmacytic infiltrate [75].

Carcinomas with medullary features are usually triple negative [76], and display a basal immunophenotype (ER−, PR−, HER2−, CK5/6+ and/or EGFR+) more frequently than does high-grade invasive carcinoma NST [77].

Despite their aggressive morphologic features, carcinomas with medullary features are associated with a favorable prognosis [78], and the outcome of typical and atypical medullary carcinomas does not seem to differ [79]. Notably, the prognosis of carcinoma with medullary features is similar to the one of high-grade ductal carcinoma with prominent inflammatory infiltrate [80], and the excellent outcome of these tumors appears to be related to their associated host inflammatory response, a favorable prognostic and predictive marker of triple negative breast cancer (TNBC) treated with chemotherapy [81].

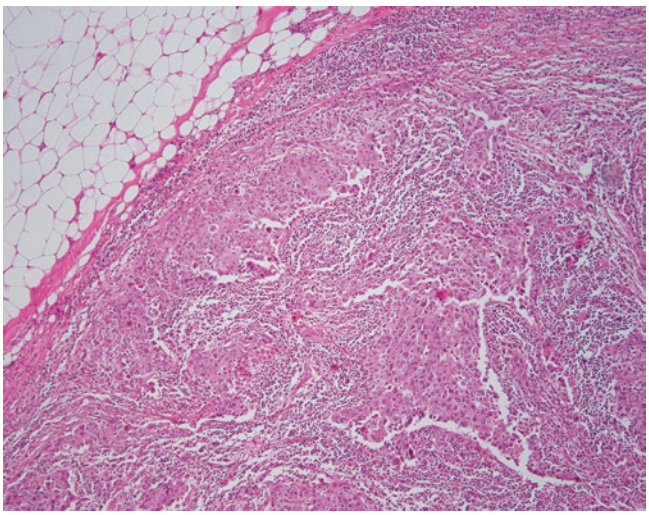

Fig. 15.23 Carcinoma with medullary features: the tumor has a circumscribed pushing border. The tumor cells grow in a syncytial pattern and are intermixed with marked host lymphoplasmacytic infiltrate

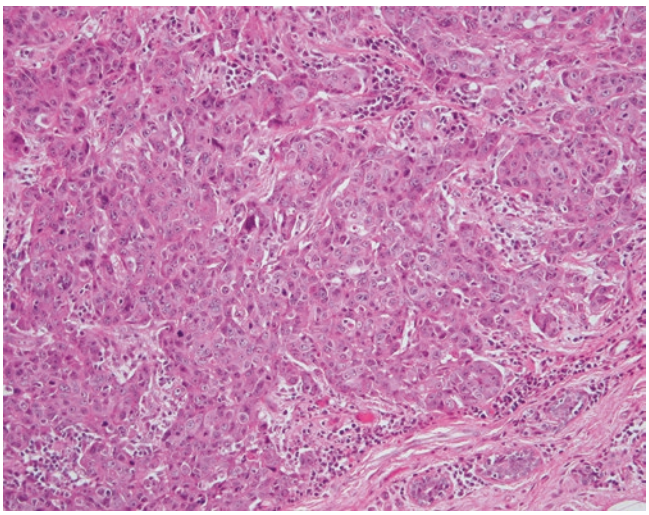

Fig. 15.24 Carcinoma with medullary features: the tumor cells show marked atypia and frequent mitoses

15.7 Apocrine Carcinoma

Apocrine carcinomas are composed of tumor cells with abundant densely eosinophilic cytoplasm with large nuclei and prominent nucleoli, and represent up to 4% of all breast carcinomas [82, 83]. Apocrine morphology may be present in different breast cancer histologic subtypes, and there is currently a lack of uniformity in the diagnostic criteria for apocrine carcinoma. Some authors advocate to restrict this diagnosis to tumors composed of more than 90% of apocrine cells [84].

A large SEER database study showed that patients present with apocrine carcinoma at an older age and with larger tumors than patients with invasive carcinoma NST [85]. Sonographic, mammographic, and MRI findings of apocrine carcinomas do not differ from those of invasive carcinoma NST [86–88].

Apocrine carcinomas may be composed of type A cells, which have an abundant eosinophilic granular cytoplasm, type B cells, which have a foamy and vacuolated cytoplasm, or a combination of both. The tumor cells exhibit large centrally to eccentrically located nuclei, prominent nucleoli, and distinctive cell borders (Figs. 15.25, 15.26, and 15.27).

Apocrine carcinomas are mostly negative for ER and PR [83, 84], although it has been shown that they frequently express ER-α36, an isoform of ER [89]. Approximately half of apocrine carcinomas display HER2 overexpression/amplification [90], and most of them are positive for androgen receptor (AR) [90]. Indeed, some authors consider tumors that display apocrine morphology, are negative for ER and PR, and positive for AR as "pure apocrine" carcinomas, while those that exhibit ER or PR positivity, and are negative for AR are considered "apocrine-like carcinomas" [91]. Apocrine carcinomas belong to the luminal androgen receptor transcriptomic subtype of TNBC [92], and harbor a higher rate of mutations in *PIK3CA* and other genes of the Phosphoinositide 3-kinase (PI3K) pathway, and a lower frequency of *TP53* mutations and *MYC* gains compared to other TNBCs [93, 94].

The diagnosis of apocrine carcinoma in cytology specimens is challenging due to their morphologic overlap with benign apocrine lesions [95, 96]. FNA smears of apocrine carcinomas are usually highly cellular and show tumor cells arranged in sheets, clusters, and singly scattered. The tumor cells show moderate-to-marked pleomorphism, a dense granular cytoplasm, large nuclei with coarse chromatin, prominent nucleoli, and occasional intranuclear inclusions (Fig. 15.28) [95, 96].

The recurrence-free survival of patients with apocrine carcinomas appears to be similar to that of patients with non-apocrine ductal carcinomas when matched for stage [97]. Nonetheless, a study indicated that patients with "pure apocrine" carcinoma have a worse outcome that those with invasive carcinoma NST [91].

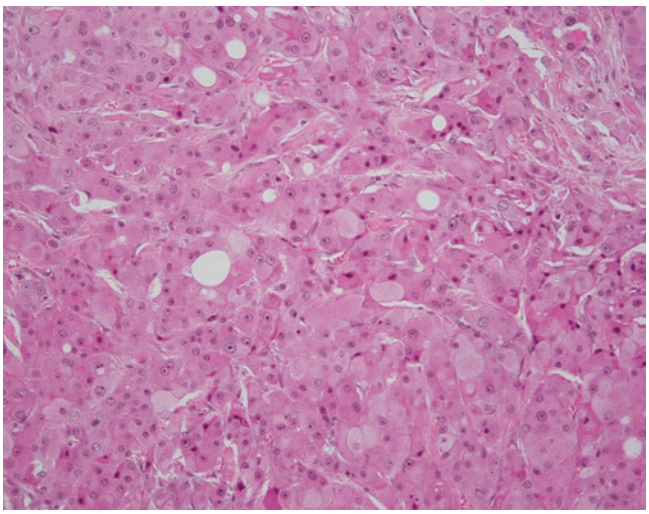

Fig. 15.25 Apocrine carcinoma: the tumor is composed of cells with abundant eosinophilic cytoplasm and cells with foamy cytoplasm. Scattered intracytoplasmic vacuoles can be seen

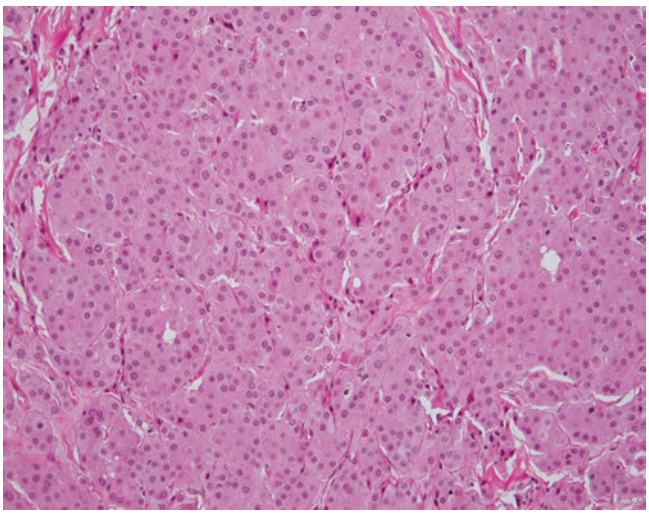

Fig. 15.26 Apocrine carcinoma: the tumor has a nested architecture with focal glandular formation. The tumor cells have an intermediate nuclear grade

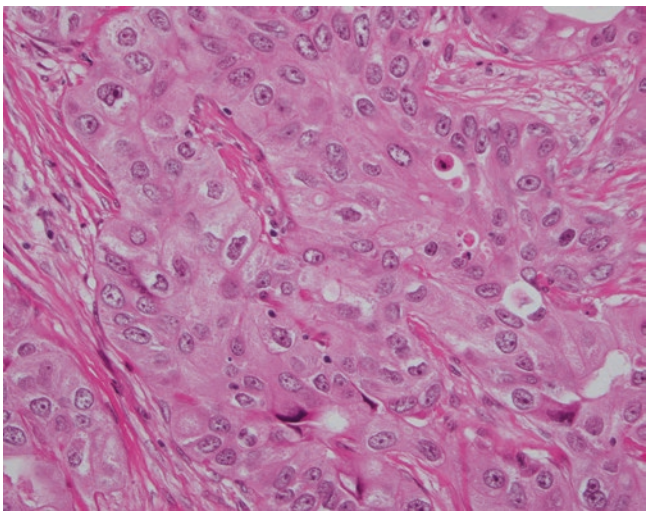

Fig. 15.27 Apocrine carcinoma: the tumor cells show marked pleomorphism and prominent nucleoli

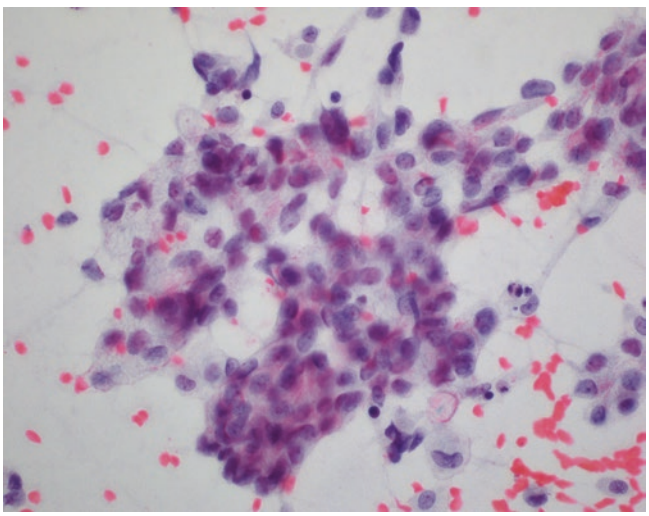

Fig. 15.28 Apocrine carcinoma: FNA smear shows tumor cells with moderate pleomorphism, dense granular cytoplasm and large nuclei with prominent nucleoli

15.8 Metaplastic Breast Carcinoma

Metaplastic carcinomas encompass a heterogenous group of carcinomas characterized by non-glandular morphology, including squamous or mesenchymal differentiation, such as spindle, chondroid, and osseous features [98]. There is currently no consensus regarding the extent of metaplastic elements required for the diagnosis of metaplastic carcinoma, and a wide range of cutoffs have been used [99, 100]. Although most metaplastic carcinomas are high-grade tumors, low-grade variants are also recognized. Metaplastic carcinomas are rare and account for 0.2–5% of breast carcinomas [98].

Patients with metaplastic carcinoma present usually with a palpable mass, and at an older age and with larger tumors than patients with invasive carcinoma NST [101, 102]. Most metaplastic carcinomas are identified as masses on mammogram and ultrasound, and show enhancing, and not uncommonly central necrosis on MRI [103]. Areas of calcification in metaplastic carcinomas with osseous or chondroid differentiation are occasionally detected by imaging [104]. Although the imaging features of metaplastic carcinomas show overlap with those of invasive carcinoma NST [105, 106], features of malignancy, such as irregular shape, spiculated margins, pleomorphic calcifications in a segmental distribution, and posterior acoustic shadowing have been reported to be less frequent in metaplastic carcinomas than in invasive carcinomas NST [107].

Morphologically, metaplastic carcinomas are a heterogeneous group of tumors with marked inter- and intra-tumor heterogeneity. Several subtypes are recognized, including squamous cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, spindle cell carcinoma, including intermediate- and high-grade spindle cell carcinomas, as well as the low-grade fibromatosis-like spindle cell carcinoma and low-grade adenosquamous carcinoma.

Confirmation of epithelial differentiation, such as focal epithelial morphology, presence of ductal carcinoma in situ (DCIS), or positivity for epithelial or myoepithelial markers is required for the diagnosis of metaplastic carcinoma.

The diagnosis of squamous cell carcinoma is reserved for tumors composed of least 90% of squamous elements. Squamous cell carcinomas are frequently associated with cysts (Fig. 15.29) and are composed of polygonal cells with abundant eosinophilic and occasionally clear cytoplasm infiltrating the stroma, frequently associated with marked host lymphocytic reaction (Figs. 15.30 and 15.31). A spindle cell component may be present. Breast squamous cell carcinomas are morphologically similar to squamous cell carcinomas arising in other locations [108, 109].

Metaplastic carcinomas with mesenchymal differentiation are tumors with an overt carcinoma component asso-

ciated with a mesenchymal component with chondroid or osseous differentiation (Figs. 15.32 and 15.33), or less frequently with rhabdomyosarcomatous, liposarcomatous, or angiosarcomatous differentiation. Matrix-producing carcinomas were classically defined as those in which the carcinoma component directly transitions to chondroid or osseous matrix, without the presence of intervening spindle cells or osteoclastic giant cells (Fig.15.34). The matrix-producing component may occasionally display a mucoid appearance and mimic mucinous carcinoma (Fig. 15.35) [110].

Metaplastic spindle cell carcinomas may arise in association with fibrosclerotic lesions of the breast, like papillomas, complex sclerosing lesions and nipple adenomas [111]. Metaplastic spindle cell carcinomas have infiltrative margins and are composed of spindle cells with moderate-to-marked atypia, arranged haphazardly, or in fascicular, herringbone, and storiform architectural patterns, and frequently show associated inflammatory infiltrate (Fig. 15.36) [112]. Necrosis and numerous mitoses and are common (Fig. 15.37). Focal clusters of cells with more epithelioid morphology or squamous differentiation or focal areas of conventional invasive carcinoma, usually poorly differentiated, and ductal carcinoma in situ (DCIS) may be present (Figs. 15.38 and 15.39) [112].

Low-grade fibromatosis-like metaplastic spindle cell carcinoma (LG-FLMC) is a low-grade form of spindle cell carcinoma with morphologic resemblance to fibromatosis. LG-FLMCs have irregular infiltrative margins with finger-like projections (Figs. 15.40 and 15.41), and are composed of bland spindle cells with absent-to-minimal atypia, arranged in wavy fascicles in more than 95% of the tumor (Fig. 15.42). LG-FLMCs range from hypocellular to hypercellular and are intermixed with collagenous areas [113]. The spindle cells are frequently admixed with few clusters of glandular or squamous epithelial cells [113].

Low-grade adenosquamous carcinomas (LGASC) have a stellate configuration with poorly defined borders, and are composed of elongated or ovoid infiltrating glands with tumor cells of low nuclear grade and various degrees of squamous differentiation (Fig. 15.43). The LGASC glands appear to blend with the surrounding stroma, which ranges from hyalinized to cellular (Fig. 15.44). Lymphocytic aggregates are frequently seen in the periphery of the lesions [114, 115].

FNA smears of metaplastic carcinomas are usually highly cellular and frequently show necrosis. Clues for the diagnosis of metaplastic carcinoma on cytology material include squamous carcinoma cells, atypical spindle cells, and heterologous elements fragments (Fig. 15.45) [116–118]. Nonetheless, identification of both epithelial and heterologous elements in cytology specimens is uncommon, and the diagnosis of metaplastic carcinoma on cytology material is challenging (Fig. 15.46).

Metaplastic carcinomas are usually triple negative, have a basal immunophenotype [119, 120], and are of basal-like molecular subtype [112, 121, 122]. The identification of epithelial differentiation in metaplastic carcinomas requires a broad panel of epithelial and myoepithelial markers, as the immunoreactivity of metaplastic carcinomas to cytokeratins or myoepithelial markers is highly variable and may be focal, and no individual marker has been found to be uniformly positive. The majority (70–80%) of metaplastic carcinomas are positive for broad spectrum cytokeratins (AE1/AE3 and MNF116) and for high molecular weight cytokeratins (34βE12, CK5/6, CK14 and CK17), whereas low molecular weight cytokeratins (CK8/18, CK7 and CK19) are less frequently positive in metaplastic carcinomas (30–60%) (Fig. 15.47) [120]. Myoepithelial markers, such as p63, are frequently positive [112]. Metaplastic breast carcinomas share the complex genetic abnormalities and high frequency of *TP53* mutations with conventional TNBCs, and are associated with mutations in *PIK3CA*, *PIK3R1*, *PTEN*, *FAT1* and *AXIN1* resulting in an increased activation of the PI3K and Wnt pathways [123, 124].

The differential diagnosis of metaplastic carcinoma is broad. Therefore, metastatic squamous cell carcinoma from a distant anatomical site or direct extension from a squamous cell carcinoma arising in the overlying skin should be excluded before rendering the diagnosis of breast squamous cell carcinoma. Phyllodes tumor with stromal overgrowth should be considered in the differential diagnosis of spindle cell metaplastic carcinomas, and cytokeratins and p63 are useful IHC markers in this scenario. Nevertheless, caution should be exerted, as a subset of phyllodes tumors may be focally positive for p63 and cytokeratins [125]. CD34 is consistently negative in metaplastic carcinomas and may help differentiate metaplastic carcinomas from phyllodes tumors [120]. Discrimination of LG-FLMC from fibromatosis might be particularly challenging due to their marked morphologic overlap. While fibromatosis is negative for cytokeratins and shows nuclear β-catenin expression [126], β-catenin may also be expressed in metaplastic carcinomas, and should not be used as the sole marker for the distinction between these entities [123]. LGASCs may show morphologic overlap with tubular carcinoma, adenomyoepithelioma, and syringomatous tumor of the nipple [127]. A study using lineage-tracing analysis suggested that LGASCs and syringomatous tumors of the nipple are identical or nearly identical lesions [127].

Metaplastic carcinomas show a lower rate of nodal metastasis than invasive carcinoma NST [101, 102, 128]. Like other TNBCs, metaplastic carcinomas may develop distant metastasis in the absence of nodal metastasis [106]. These tumors

show a lower response rate to neoadjuvant and adjuvant chemotherapy [129–131]. Several studies indicate that metaplastic carcinomas have a worse prognosis than invasive carcinoma NST [122, 129, 132–134], although a multi-institutional study that included over 400 cases showed that when matched for grade, nodal status, and ER/HER2 receptor status, metaplastic carcinomas have an outcome similar to invasive carcinoma NST. In the aforementioned study, spindle cell carcinoma had a worse outcome than other subtypes of metaplastic carcinoma [119]. Unlike other types of metaplastic carcinomas, LGASCs and LG-FLMCs have an indolent clinical behavior and a good prognosis [135, 136].

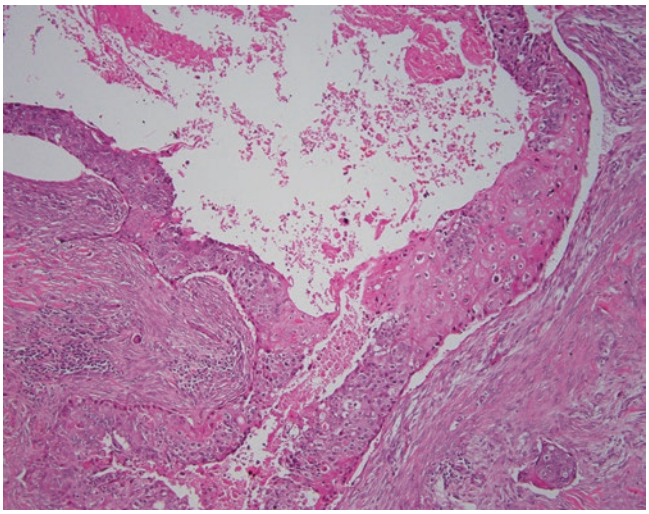

Fig. 15.29 Squamous cell carcinoma: the carcinoma is associated with cystic areas

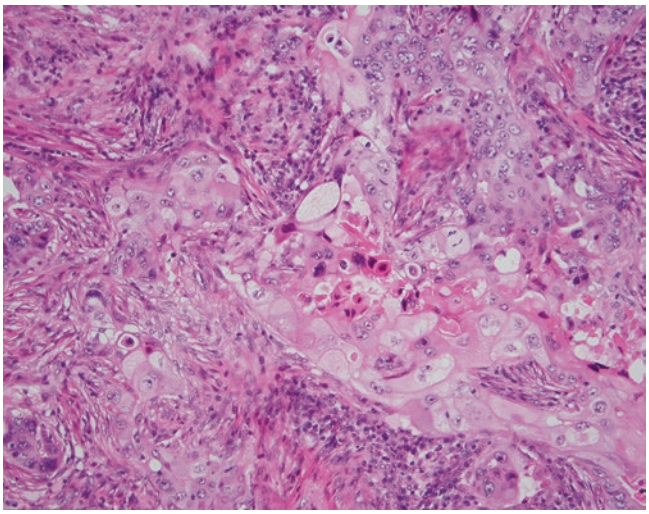

Fig. 15.31 Squamous cell carcinoma: tumor cells show abundant eosinophilic cytoplasm, focal clearing, and marked pleomorphism

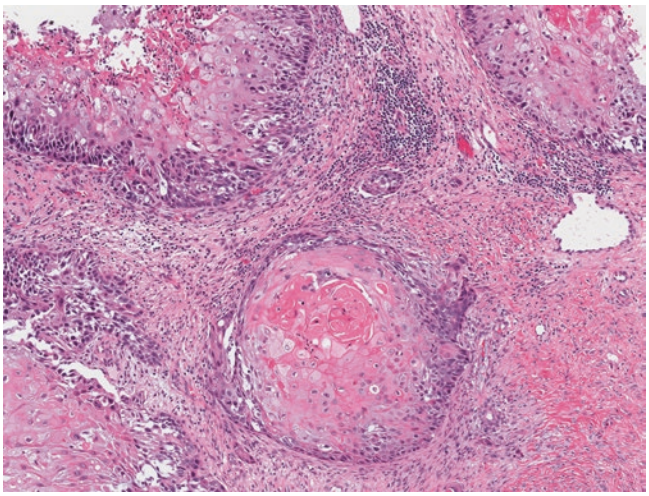

Fig. 15.30 Squamous cell carcinoma: nests of tumor cells with marked keratinization associated with host inflammatory infiltrate

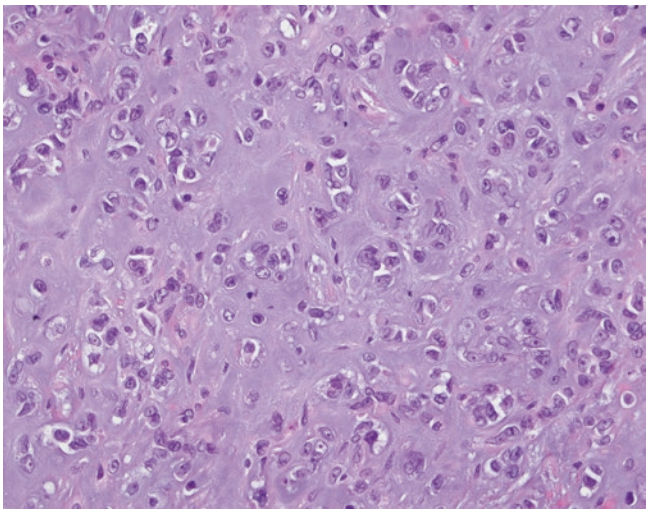

Fig. 15.32 Metaplastic carcinoma with chondroid differentiation: the carcinoma shows chondroid morphology

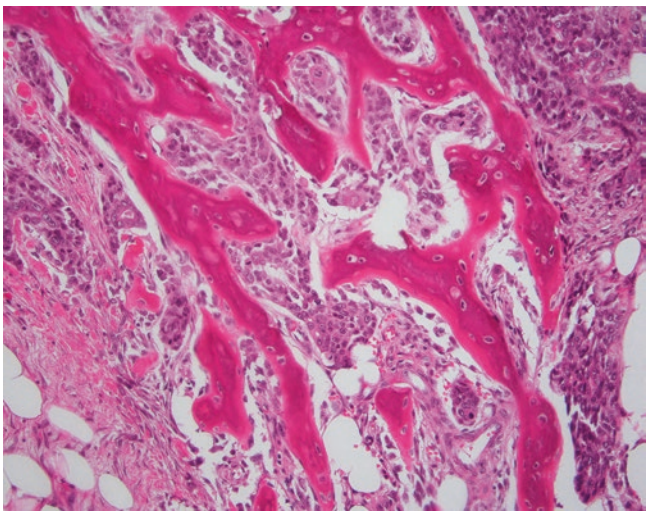

Fig. 15.33 Metaplastic carcinoma with osseous differentiation: the carcinoma shows osteoid production

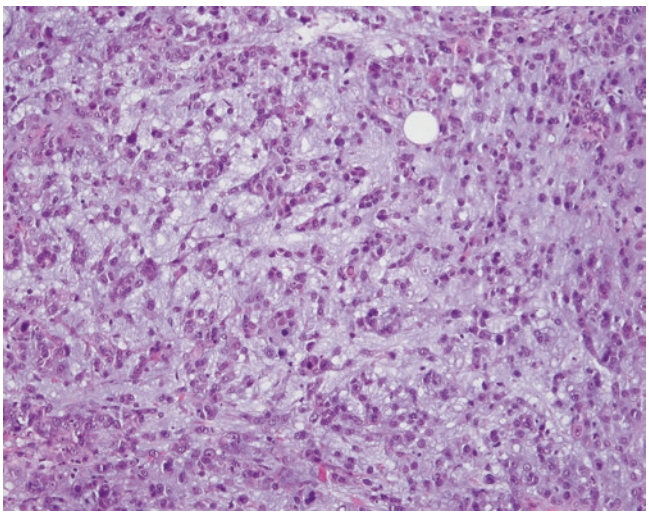

Fig. 15.35 Metaplastic carcinoma, matrix-producing: poorly differentiated carcinoma admixed with matrix material with a mucin-like morphology

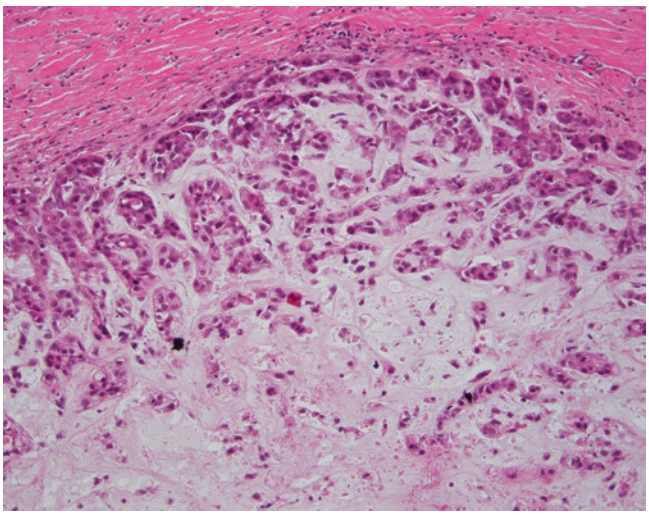

Fig. 15.34 Metaplastic carcinoma, matrix-producing: poorly differentiated carcinoma transitioning to a hypocellular matrix area with focal necrosis

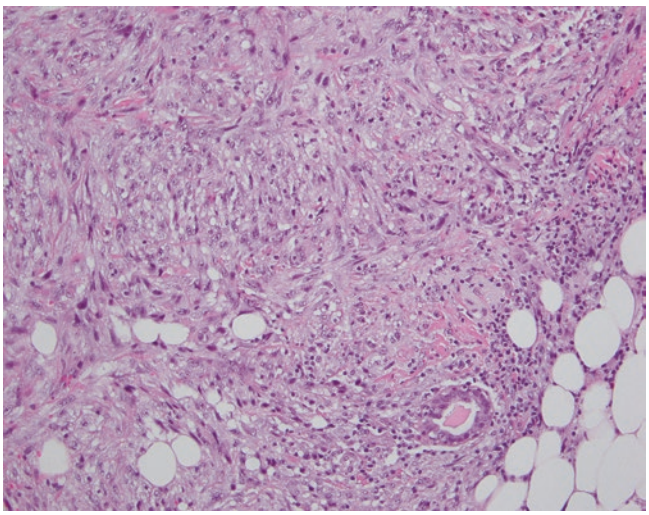

Fig. 15.36 Metaplastic carcinoma, spindle cell: the spindle cells are arranged haphazardly and are associated with peritumoral lymphocytic infiltrate

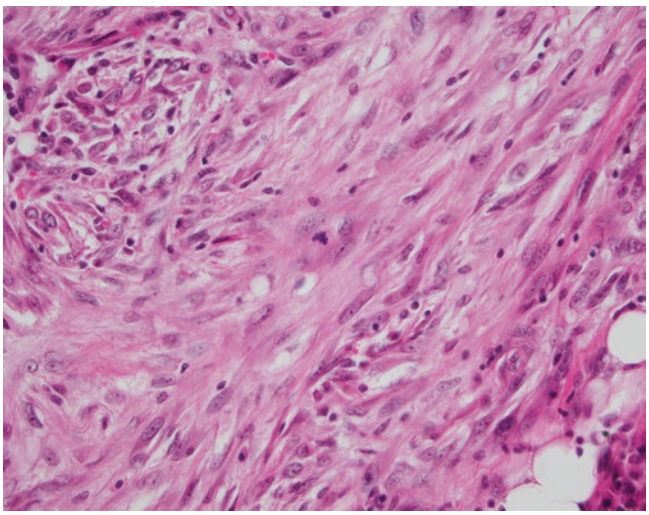

Fig. 15.37 Metaplastic carcinoma, spindle cell: the tumor cells display marked atypia and frequent mitoses

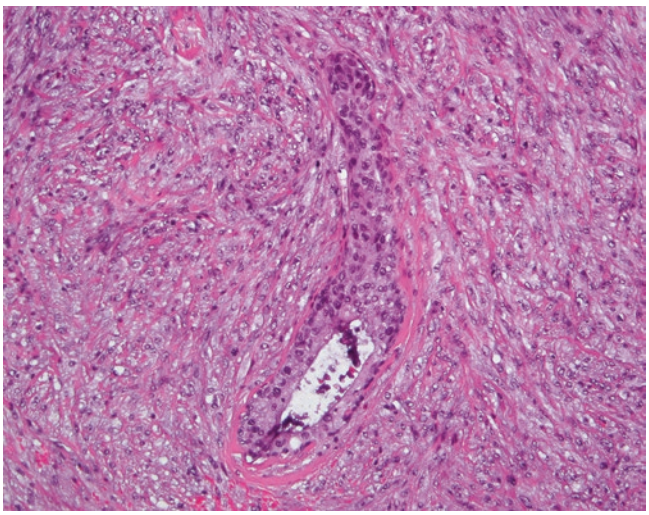

Fig. 15.39 Metaplastic carcinoma, spindle cell: focal high-grade DCIS is identified admixed with the spindle cell carcinoma

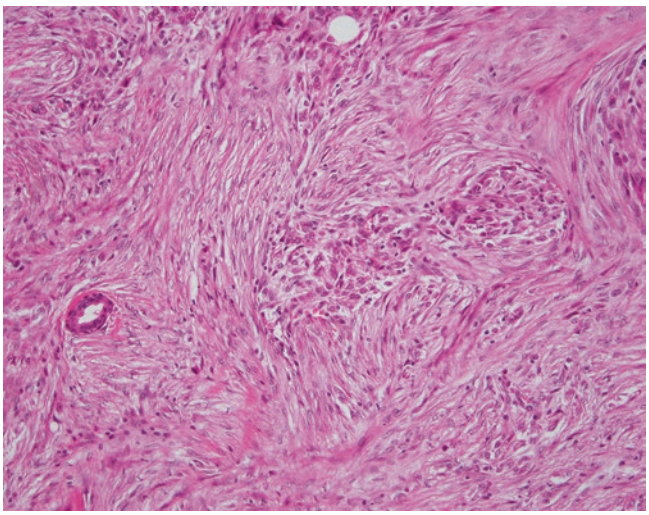

Fig. 15.38 Metaplastic carcinoma, spindle cell: the spindle carcinoma cells are admixed with clusters of cells with epithelioid morphology

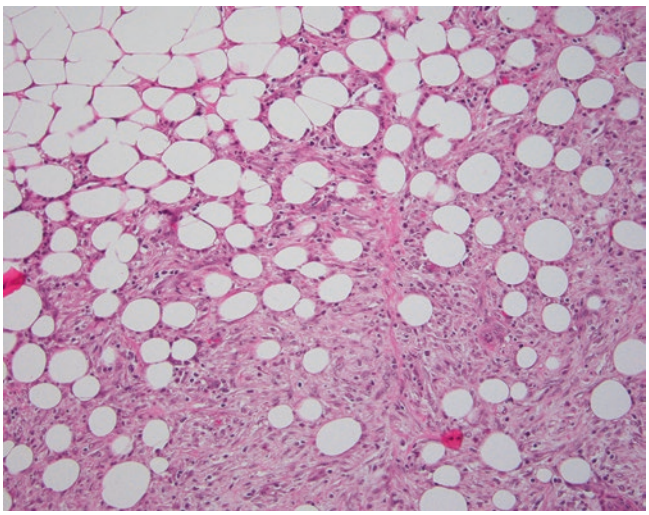

Fig. 15.40 Low-grade fibromatosis-like metaplastic spindle cell carcinoma: bland-appearing spindle cells infiltrate adipose tissue

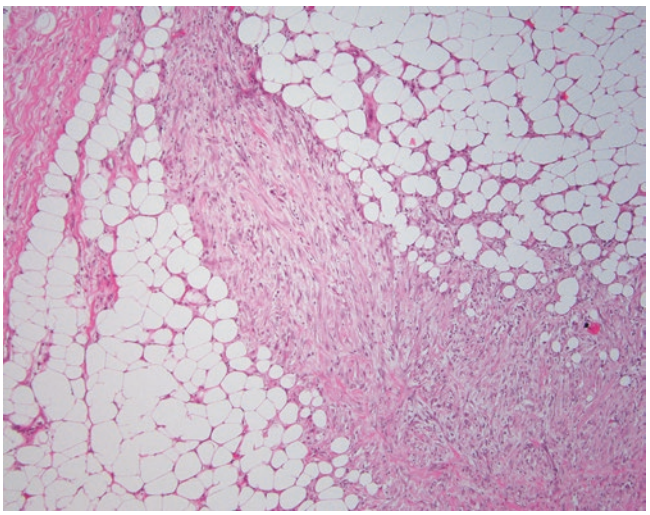

Fig. 15.41 Low-grade fibromatosis-like metaplastic spindle cell carcinoma: the carcinoma has an infiltrative growth with finger-like projections

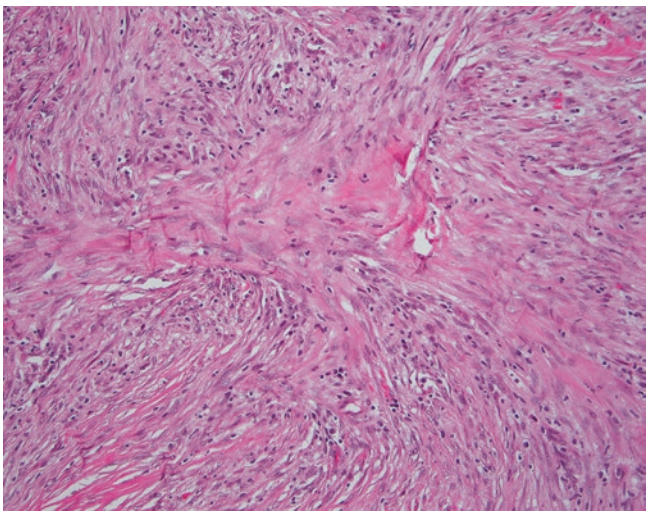

Fig. 15.42 Low-grade fibromatosis-like metaplastic spindle cell carcinoma: the tumor cells are arranged in wavy fascicles surrounded by collagenous stroma

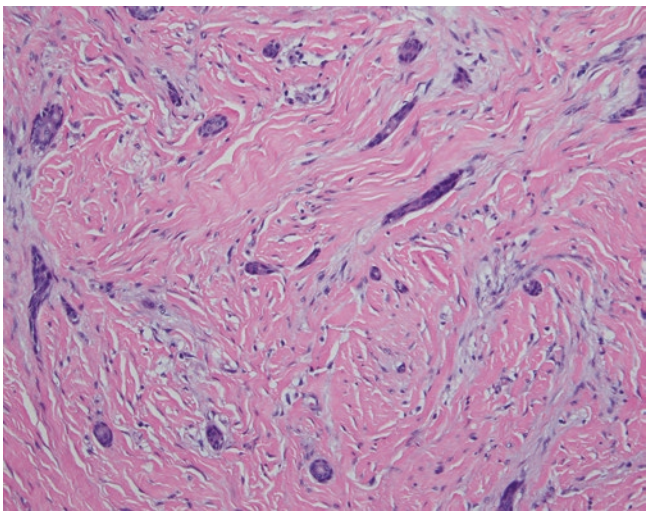

Fig. 15.43 Low-grade adenosquamous carcinoma: neoplastic cells are arranged in nests and glands with an infiltrative pattern

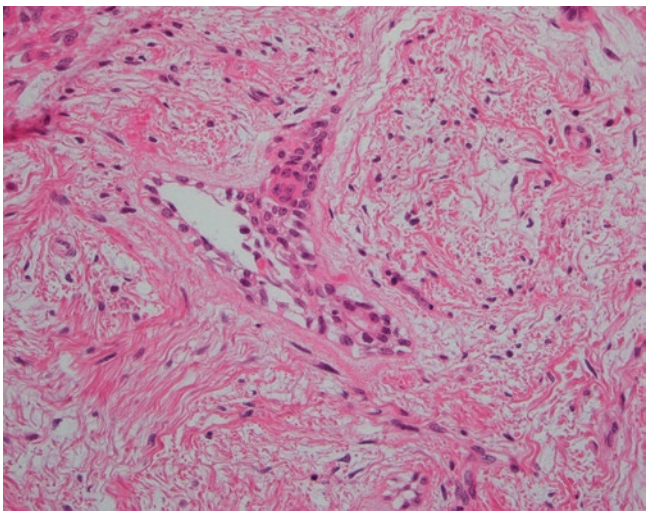

Fig. 15.44 Low-grade adenosquamous carcinoma: angulated gland with tumor cells with low nuclear grade and squamous differentiation, surrounded by a hypocellular stroma

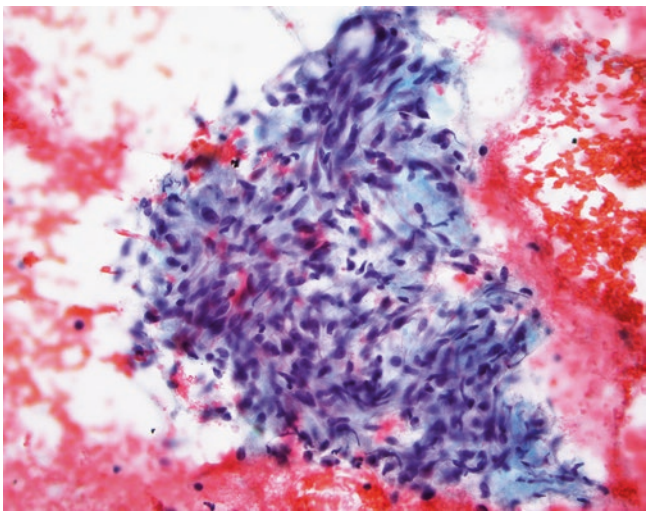

Fig. 15.45 Metaplastic carcinoma, spindle cell, cytology: FNA smear shows large clusters of spindle tumor cells in a background of red blood cells

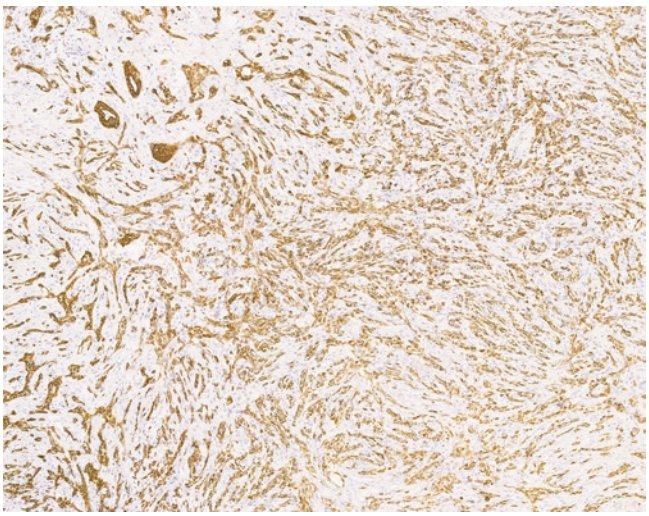

Fig. 15.47 Metaplastic carcinoma, spindle cell: the spindle cell metaplastic carcinoma shows diffuse positivity for 34βE12

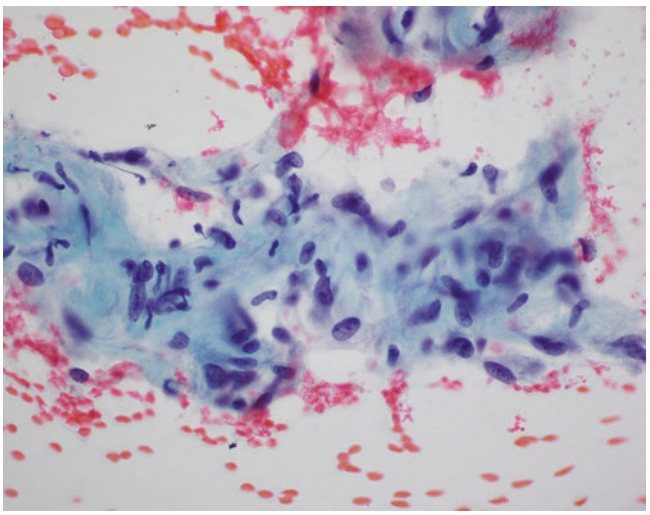

Fig. 15.46 Metaplastic carcinoma, matrix-producing, cytology: FNA smear shows tumor cells admixed with matrix

15.9 Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (AdCC) typically arises in the salivary glands, but may also originate at other anatomic locations, such as the respiratory and gastrointestinal tracts, skin, and breast [137]. Breast AdCCs account for approximately 0.1% of breast carcinomas [138]. The usual clinical presentation of AdCC is a palpable mass, frequently located in the subareolar region.

On mammography, AdCCs appear as irregular or lobulated masses [139], and are usually heterogenous or hypoechoic on sonogram [140]. On MRI they display suspicious enhancement kinetics [140].

AdCCs are biphasic tumors, composed of epithelial and myoepithelial cells arranged in different patterns, histologically indistinguishable from their counterparts arising in other anatomic locations [141]. The most characteristic growth pattern of AdCC is the cribriform one. Cribriform AdCCs are composed of islands of tumor cells with smooth contours and a sieve-like appearance with pseudolumina formed by the invagination of the stroma, containing eosinophilic PAS-positive hyaline and/or alcian blue-positive myxoid material, and less frequent true glandular spaces surrounded by epithelial cells (Figs. 15.48 and 15.49) [142]. Other AdCC morphologies include the tubular/glandular, trabecular/reticular, and solid patterns (Fig. 15.50 and 15.51) [141]. A solid variant of AdCC with basaloid features has been described, and is characterized by large infiltrative solid nests of basaloid cells with marked nuclear atypia within hyalinized, myxoid, or desmoplastic stroma [143].

The luminal epithelial component of AdCC is positive for low molecular weight cytokeratins, such as CK7, CK8/18, and for EMA and CD117, whereas the myoepithelial cells are positive for basal cytokeratins, like CK5/6, CK14, and for myoepithelial markers such as smooth muscle actin and p63 [144–146]. Breast AdCCs generally have a triple negative phenotype and are of basal-like molecular subtype [20, 147]. Akin to their salivary gland counterparts, breast AdCCs are underpinned by the t(6;9)(q22–23;p23–24) translocation, which results in the *MYB-NFIB* fusion gene and subsequent overexpression of the MYB oncogene [148], a sensitive and specific finding for AdCC [149]. Recently, breast *MYB-NFIB* fusion gene-negative AdCCs have been shown to be driven by alternative genetic alterations, such as *MYBL1* rearrangements and *MYB* amplification [150].

Cytologic preparations of breast AdCCs show cellular smears with three-dimensional clusters of basaloid and epithelial cells surrounding extracellular metachromatic spherules (Figs. 15.52 and 15.53) [151, 152].

The differential diagnosis of breast AdCC includes invasive cribriform carcinoma, cribriform DCIS, and collagenous spherulosis. The distinction of AdCC from collagenous spherulosis might be particularly challenging in core-needle biopsies. CD117, which is positive in AdCC and negative in collagenous spherulosis, and calponin and smooth muscle myosin heavy chain, which is negative in AdCC but strongly positive in collagenous spherulosis, may be useful for such diagnostic distinction [153].

Breast AdCCs show a low rate of nodal metastasis [154], and unlike their salivary gland counterparts and conventional TNBC, they have a favorable clinical course [155]. Nevertheless, transformation to high-grade TNBC has been described [156].

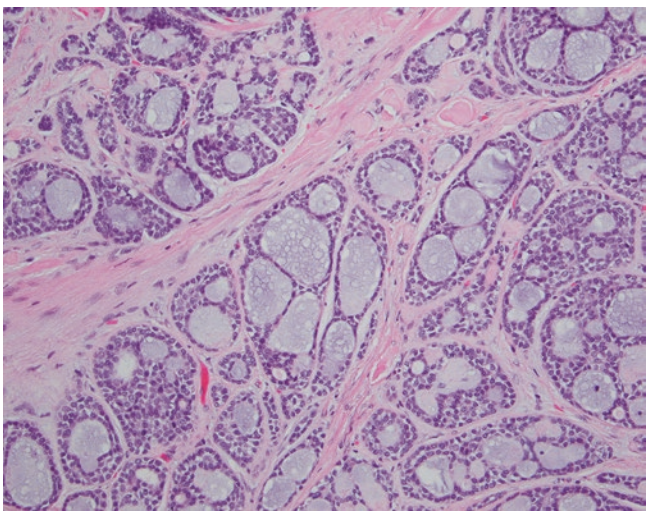

Fig. 15.48 Adenoid cystic carcinoma: the carcinoma shows a cribriform growth pattern with basophilic secretions within pseudolumina

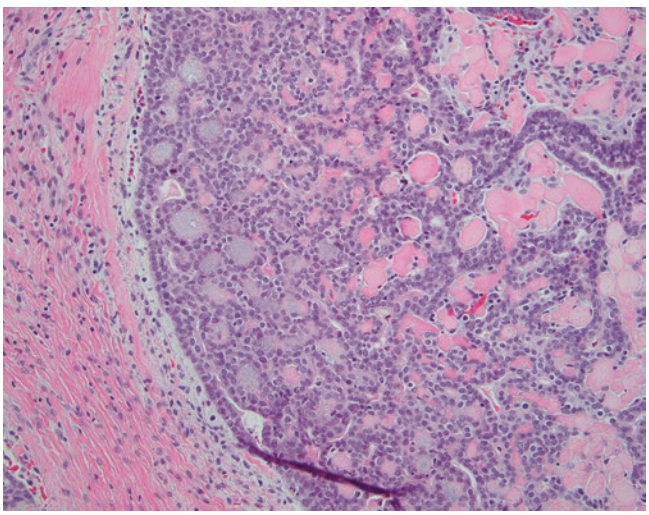

Fig. 15.49 Adenoid cystic carcinoma: the pseudolumina contained myxoid material or invaginated collagenous stroma

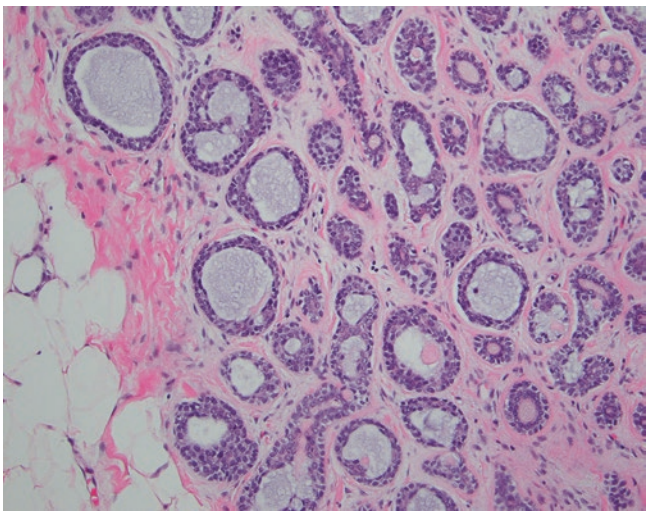

Fig. 15.50 Adenoid cystic carcinoma: the tumor shows a tubular/glandular growth pattern

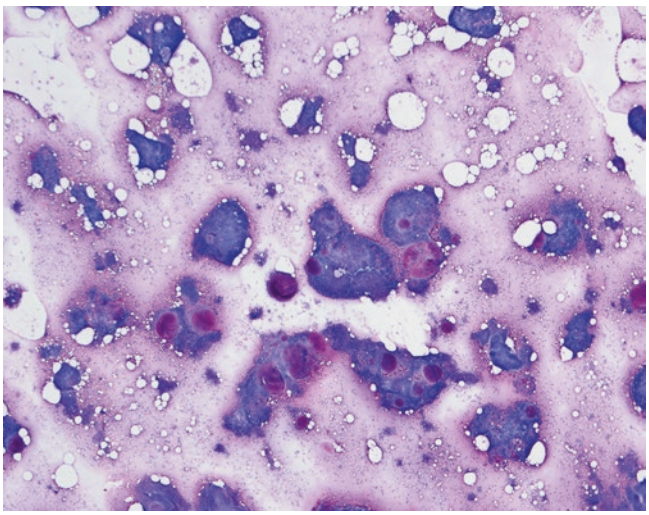

Fig. 15.52 Adenoid cystic carcinoma, cytology: FNA smear shows cohesive clusters of basaloid cells surrounding spheres of basement metachromatic material. Numerous bare nuclei are present in the background

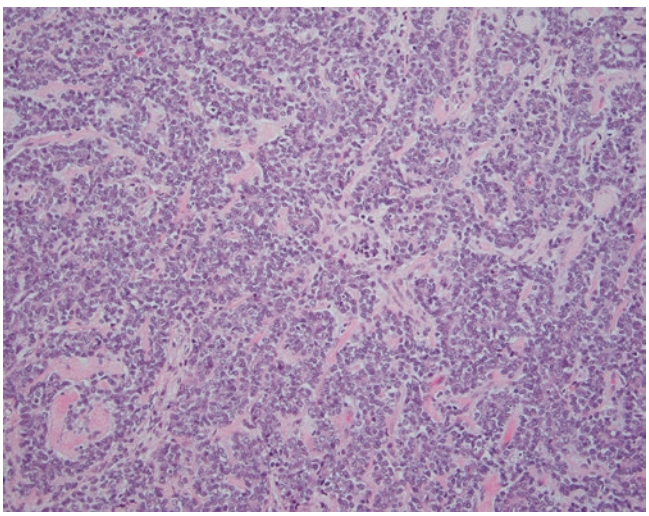

Fig. 15.51 Adenoid cystic carcinoma: the carcinoma displays a trabecular growth pattern

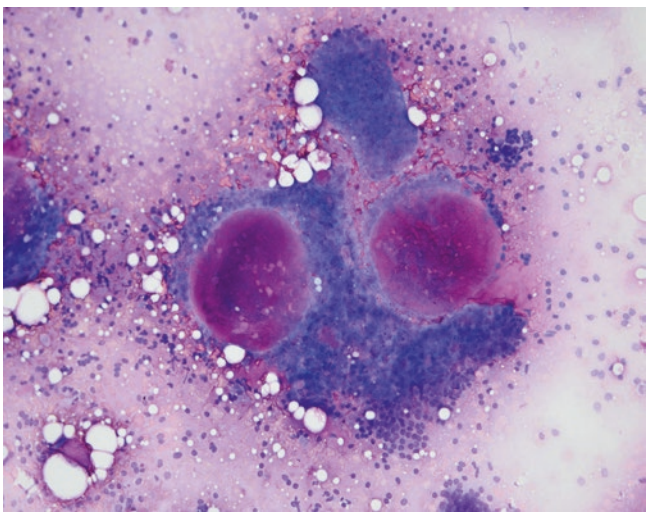

Fig. 15.53 Adenoid cystic carcinoma, cytology: FNA smear show small uniform cells with scant cytoplasm and round-to-oval nuclei surrounding amorphous acellular material

15.10 Secretory Carcinoma

Secretory carcinoma was originally described in children and initially named juvenile carcinoma [157]. However, it occurs at a later age than initially recognized, with the median age at diagnosis of 53 years [158]. Secretory carcinomas are extremely rare and represent less than 0.1% of breast carcinomas [158].

The imaging features of secretory carcinomas are variable and nonspecific. Mammographic findings range from well-circumscribed isodense masses to suspicious lesions with spiculated margins [159]. On sonography, they appear as well-circumscribed or partially microlobulated iso- or hypoechoic nodules [159, 160].

Secretory carcinomas grow in different architectural patterns (microcystic, tubular, solid, and papillary), which often coexist (Figs. 15.54 and 15.55) [161, 162]. Tumor cells have a granular eosinophilic-to-clear cytoplasm with low-grade nuclei, inconspicuous nucleoli, and minimal mitotic activity. The hallmark of secretory carcinomas is abundant intra- and extracellular dense PAS-positive eosinophilic secretions, which may resemble thyroid colloid when found in association with microcystic regions (Fig. 15.56) [162].

Although few cases have been reported to weakly express hormone receptors, most secretory carcinomas are triple negative and show a basal-like immunoprofile [161]. Secretory carcinomas are positive for S-100, mammaglobin, alpha-lactalbumin, EMA, MUC4, and SOX10 [162–165].

Akin to mammary analog secretory carcinomas (MASCs) in salivary glands or skin, breast secretory carcinomas are underpinned by the t(12;15)(p13;q25) translocation, which results in the *ETV6-NTRK3* fusion gene [165]. In contrast to high-grade TNBC, secretory carcinomas show a low mutational burden, no pathogenic mutations in genes frequently altered in breast cancer, and few copy number alterations [165].

Cytologic preparations of breast secretory carcinomas are of low cellularity and show bland tumor cells with cytoplasmic vacuoles admixed with colloid material [166, 167].

The differential diagnosis of secretory carcinoma includes entities with cystic architecture and prominent secretions, such as acinic cell carcinoma and cystic hypersecretory carcinoma [168]. Cystic hypersecretory carcinomas are mostly *in situ* lesions, composed by large cysts and abundant secretions, and are generally ER-positive, whereas secretory carcinomas frequently display a microcystic pattern and are triple negative [169]. Unlike secretory carcinomas, acinic cell carcinomas are positive for amylase, lysozyme and α1-antytripsin [170]. Importantly, the *ETV6-NTRK3* fusion gene is pathognomonic for secretory carcinoma in a breast-specific context [171].

Secretory carcinomas have an excellent outcome, even in the presence of nodal involvement [158].

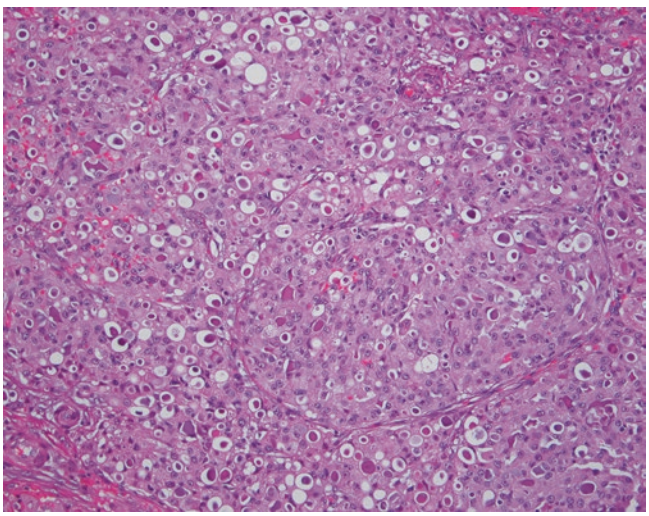

Fig. 15.54 Secretory carcinoma: the carcinoma shows a microcystic growth pattern.

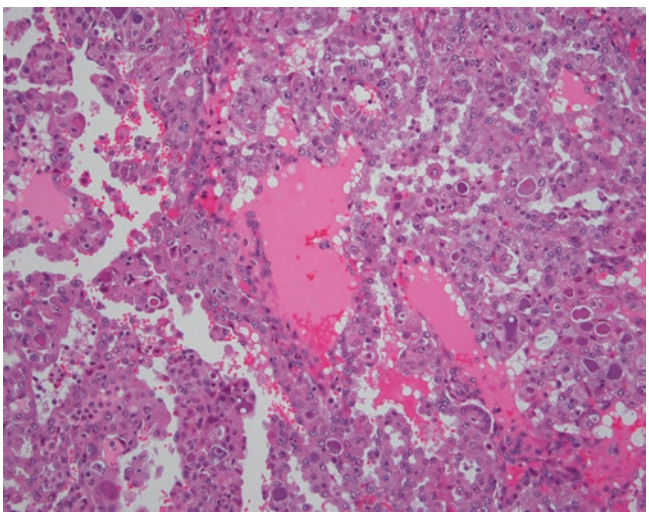

Fig. 15.55 Secretory carcinoma: the carcinoma shows a papillary growth pattern with a focal microcystic component

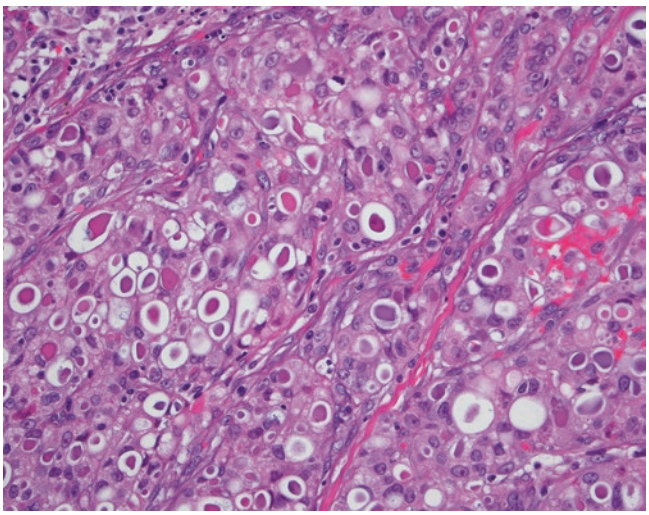

Fig. 15.56 Secretory carcinoma: the carcinoma displays abundant intra and extracellular secretions

15.11 Solid Papillary Breast Carcinoma Resembling the Tall Cell Variant of Papillary Thyroid Neoplasms/Solid Papillary Carcinoma with Reverse Polarity

These tumors have been described by different names, including solid papillary carcinoma resembling the tall cell variant of papillary thyroid neoplasms (BPTC), and solid papillary carcinoma with reverse polarity (SPCRP). They constitute a vanishingly rare histologic type of breast carcinoma, with less than 50 cases reported in the literature to date [172–177]. They have a benign appearance with regular margins on mammography or ultrasound [177].

BPTCs/SPCRPs have a very distinctive morphology, reminiscent of the morphology of the tall cell variant of papillary thyroid carcinoma. They are composed of circumscribed tumor nodules with solid, papillary, and follicular architectural patterns, and often coexist in the same case. The follicular structures contain a colloid-like eosinophilic material (Fig. 15.57). The tumor cells are cuboidal-to-columnar with eosinophilic granular cytoplasm and apically polarized nuclei, simulating reverse polarization (Fig. 15.58), although MUC1 is expressed in the apical cellular border [175]. Akin to papillary thyroid carcinomas, SPCRPs have nuclei with clear chromatin, grooves, and pseudoinclusions (Fig. 15.59 and 15.60) [172].

Despite their resemblance to papillary thyroid neoplasms, BPTCs/SPCRPs are negative for thyroid markers, such as thyroglobulin and TTF-1 [172, 175, 178], and show focal positivity for GCDFP-15 and GATA-3 [172, 177]. These tumors are HER2-negative, and two-thirds of cases are also negative for ER and PR [172, 175, 177].

BPTCs/SPCRPs are underpinned by highly recurrent *IDH2* R172 hotspot mutations or *TET2* mutations, with frequent concurrent mutations targeting genes of the PI3K pathway [175, 176]. Despite their morphological overlap with the tall cell variant of papillary thyroid carcinoma, no *RET*/*PTC* and *BRAF* genetic alterations have been described in these tumors [172, 173, 179].

Due to their remarkably similar morphology, metastasis from a tall cell variant of papillary thyroid carcinoma should be considered in the differential diagnosis of BPTCs/SPCRPs. IHC stains for thyroglobulin and TTF-1 are useful for this distinction. BPTCs/SPCRPs may show morphologic overlap with secretory carcinomas, another low-grade TNBC, and assessment of the *IDH2* mutational status and of the presence of *ETV6-NTRK3* fusion gene might be useful in this scenario.

BTPCs/SPCRPs have an indolent behavior and a favorable course, and there have been only occasional reports of regional or distant metastasis [173, 175, 177, 178, 180].

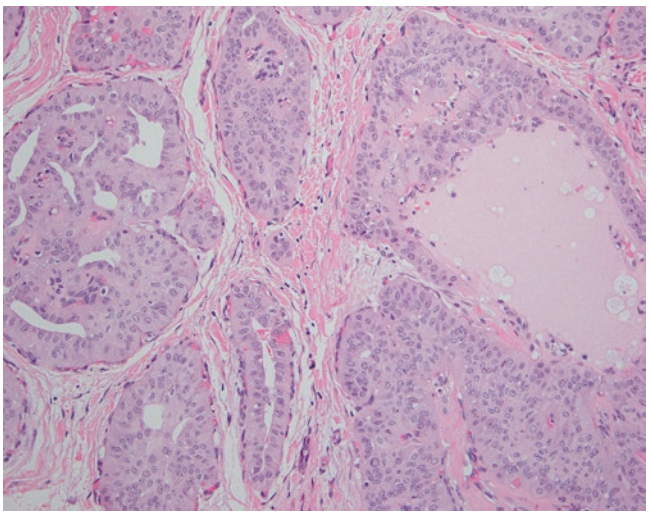

Fig. 15.57 Solid papillary breast carcinoma resembling the tall cell variant of papillary thyroid neoplasms/solid papillary carcinoma with reverse polarity: tumor nodules with solid papillary and follicular patterns. Thick eosinophilic material is identified within the follicles

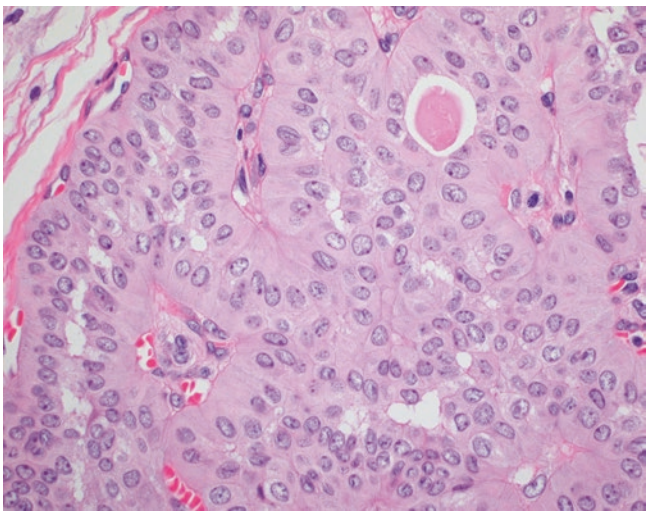

Fig. 15.59 Solid papillary breast carcinoma resembling the tall cell variant of papillary thyroid neoplasms/solid papillary carcinoma with reverse polarity: the carcinoma cells show nuclear clearing and nuclear grooves

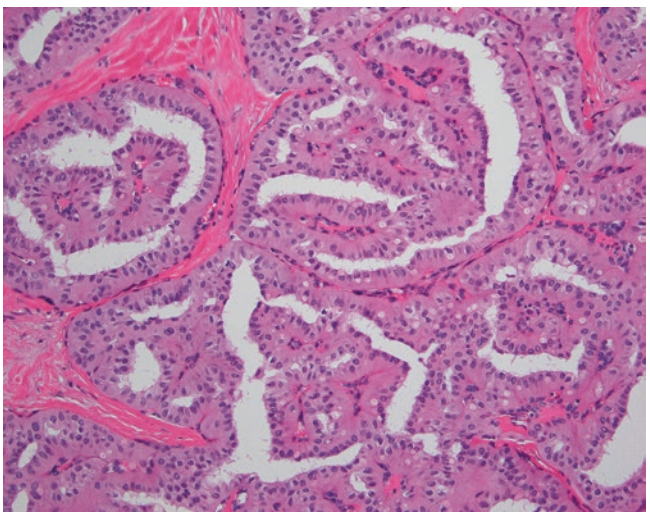

Fig. 15.58 Solid papillary breast carcinoma resembling the tall cell variant of papillary thyroid neoplasms/solid papillary carcinoma with reverse polarity: the tumor cells appear to have a reverse polarization with nuclei located in the apical aspect of the cells

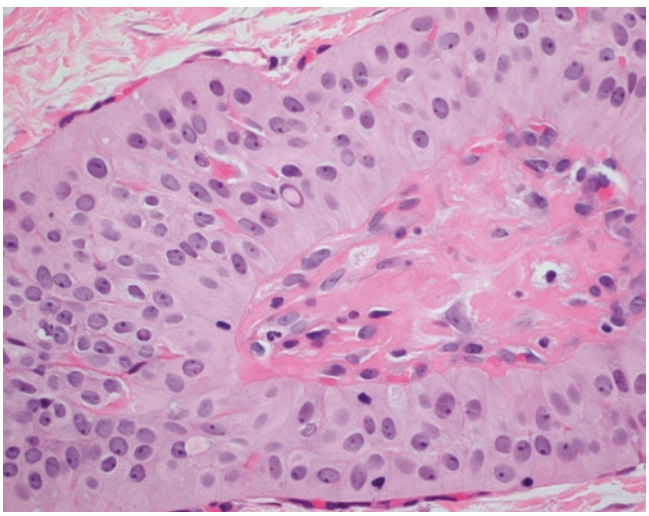

Fig. 15.60 Solid papillary breast carcinoma resembling the tall cell variant of papillary thyroid neoplasms/solid papillary carcinoma with reverse polarity: the carcinoma cells show occasional nuclear pseudoinclusions

15.12 Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer. This phenotype is characterized clinically by acute inflammatory changes of the breast presenting, within ≤3 months, diffuse erythema and edema, with or without palpable mass.

IBC accounts for 1–2% of all invasive breast cancer [181]. It is characterized by a higher risk of early recurrence, distant metastases, and metastases to the central nervous system compared with non-inflammatory locally advanced cancer.

The classic histologic finding in IBC on biopsy of affected skin is dermal lymphatic invasion by tumor cells (Fig. 15.61). These malignant cells form tumor emboli which are responsible for both the local signs and symptoms and for the development of metastatic disease [182].

Inflammatory breast cancer includes basal (20–40%), HER2 (20–40%) and luminal A and B subtypes. Loss of heterozygosity is detected in approximately one-half of IBC, and the most frequently loss alleles are at 3p, 6p, 8p, 11q, 13q, and 17q [183].

The differential diagnosis includes:

- Infection (mastitis, cellulitis, abscess). Mammary infection should be distinguished from IBC clinically. Mastitis typically develops rapidly over a few days; erythema is associated with tenderness and typically occupies a wedge-shaped quadrant of breast. However, symptomatic women improvement should occur within 24–48 h of initiation of antibiotics.
- Locally advanced carcinoma with skin invasion. Large carcinomas may directly invade into skin and cause skin ulceration. Focal dermal lymph vascular invasion may be present adjacent to the area of skin invasion. This type of cancer should not be classified as IBC.

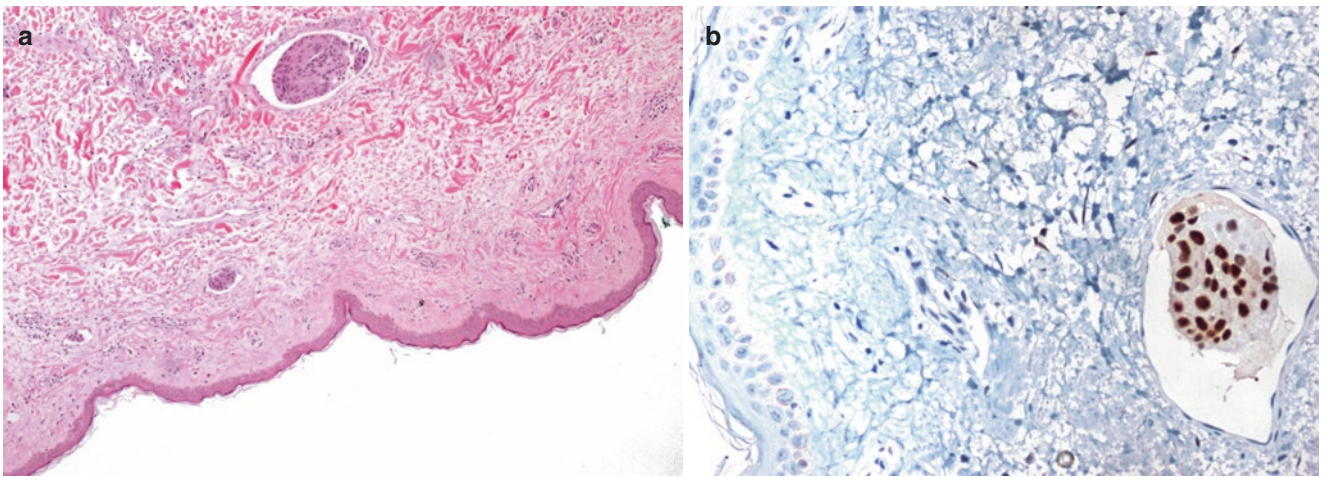

Fig. 15.61 Inflammatory breast carcinoma. (**a**) Dermal lymphovascular invasion is present. (**b**) Tumor cells showing staining with estrogen receptor

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