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REVIEW

Breast carcinomas of low malignant potential

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Abstract
Some breast carcinomas have a very low likelihood of metastasis to regional lymph nodes and distant sites and may be considered carcinomas of low malignant potential. In this article, we review the clinical, pathologic, immunophenotypic, and molecular features of selected breast carcinomas of low malignant potential including low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, encapsulated papillary carcinoma, solid papillary carcinoma, and tall cell carcinoma with reversed polarity.

Keywords Breast cancer · Low malignant potential · Low-grade adenosquamous carcinoma · Fibromatosis-like metaplastic carcinoma · Encapsulated papillary carcinoma · Solid papillary carcinoma · Tall cell carcinoma with reversed polarity

Most lesions in the breast are fairly common, readily categorized by pathologists as benign or malignant, and associated with relatively predictable clinical outcomes. However, there are some breast lesions currently categorized as carcinomas that have been repeatedly shown to have a very low risk of metastasizing to regional lymph nodes and distant sites. Included among this group are low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, encapsulated papillary carcinoma, solid papillary carcinoma, and tall cell carcinoma with reversed polarity. In this article, we will review the clinical and pathologic features and, where relevant, the molecular features of these breast carcinomas of low malignant potential. Not included in this review are more common breast carcinomas with a low risk of metastatic spread (e.g., tubular carcinomas) or salivary gland-type carcinomas arising in the breast, many of which also show indolent behavior.

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Low-grade adenosquamous carcinoma

Low-grade adenosquamous carcinoma (LGASC) is a rare subtype of metaplastic breast carcinoma with 155 cases published to date [1–4]. These tumors most often occur in women older than 50 years of age (Supplementary Table 1). LGASC may arise de novo, but frequently occur in association with other breast lesions including sclerosing papillomas, complex sclerosing lesions, and adenomyoepitheliomas [3, 5].

Macroscopically, LGASCs are firm, poorly defined lesions with a white or pale yellow cut surface. The average size of reported cases is 20 mm with a wide range (0.5–86 mm) (Supplementary Table 1).

Microscopically, LGASCs show a variable admixture of well-formed tubular glands and solid clusters and cords of cells with squamous differentiation, arranged in a haphazard pattern and typically surrounded by a pale, cuff-like, mildly edematous desmoplastic stroma containing bland spindle cells (Fig. 1). The remainder of the stroma is often cellular but may sometimes be collagenous or even hyalinized. The spindle cell component often focally expresses cytokeratins (Fig. 2) and myoepithelial markers. Furthermore, a variable layer of myoepithelial cells is seen around the tubules, a feature usually associated with benign lesions. Even within a given case, the myoepithelial layer around the tubules can vary from complete to partial to absent [3, 6] (Fig. 3). Both the glandular and the solid components, as well as the spindle cell component, show only mild cytologic atypia,

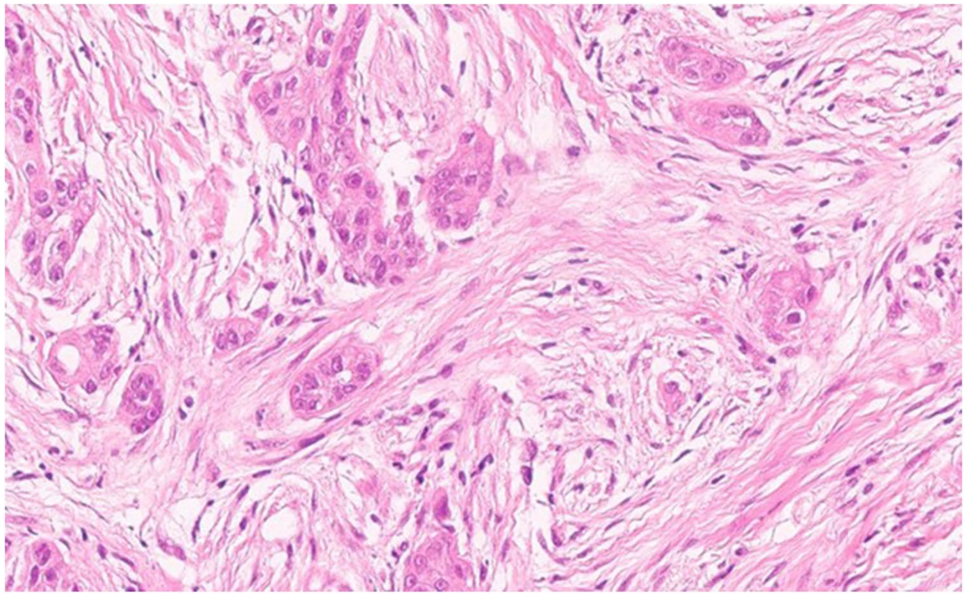

Fig. 1 Hematoxylin and eosin–stained section of a low-grade adenosquamous carcinoma with glandular, squamous, and spindle components

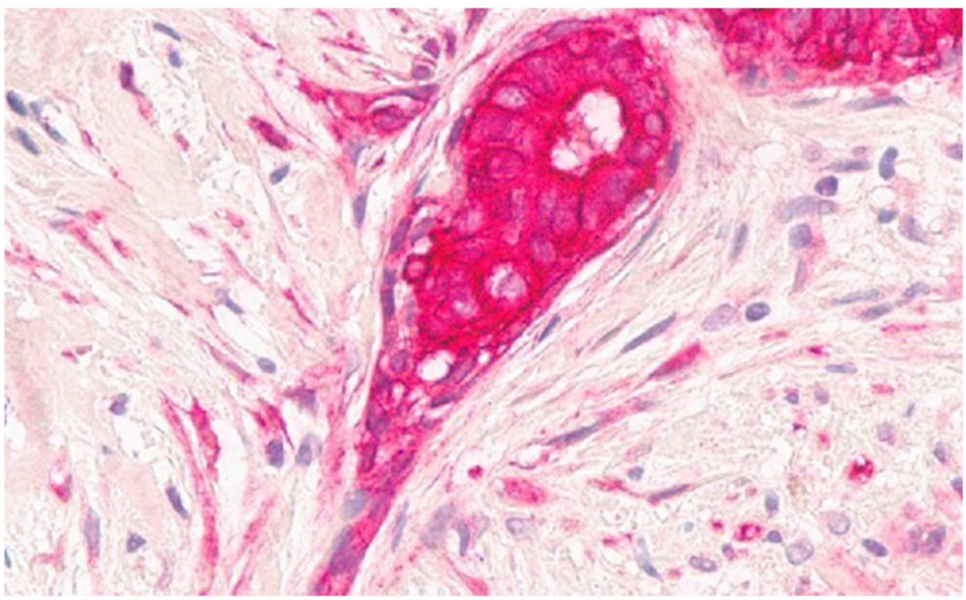

Fig. 2 Cytokeratin AE1/AE3 immunostain demonstrating focal expression of cytokeratins by the spindle cells surrounding a tubule in low-grade adenosquamous carcinoma

few mitoses, and a low Ki67 proliferation rate. In addition, small aggregates of stromal lymphocytes are typically present. Rarely focal chondroid and/or osseous metaplasia has been reported [2, 7].

The relationship between benign LGASC and benign sclerosing lesions of the breast is of particular interest. The benign lesions with which LGASC are associated are characterized by the presence of the common element of adenosquamous proliferation (ASP). ASP shares a nearly identical histological and immunohistochemical profile with LGASC [6] ASP in sclerosing lesions has been characterized as a clonal proliferation and has been postulated to be a non-obligate precursor of LGASC [6, 8].

LGASCs are typically ER, PR, and HER2 negative (triple negative). The absence of staining for hormone receptors [[1, 3, 8, 9] in combination with expression of CK5/6, CK7 and CK14, E-cadherin, p63, and SMA [21] is considered a typical immunophenotype for LGASC.

Gene expression profiling studies showed a basal-like phenotype for LGASC, confirming the immunohistochemical impression [9]. The same genetic aberrations have been found in the lesional epithelial cells as well as in part of the spindle cells confirming the metaplastic nature of LGASC with typical epithelial-mesenchymal transition.

LGASCs show a high rate of PIK3CA mutations and absence of TP53 mutations [9, 10] [11, 21]. Baitallion et al.

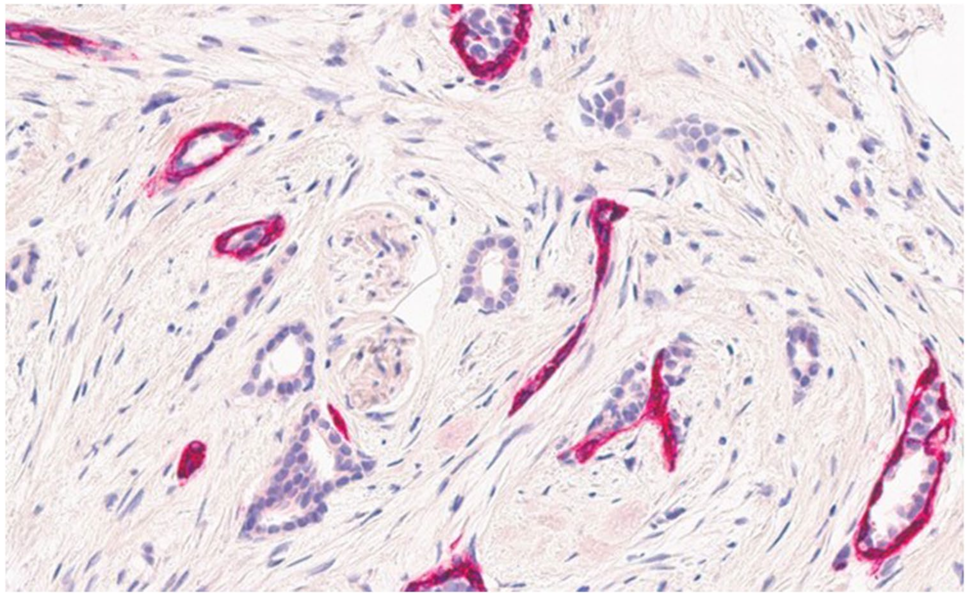

Fig. 3 At least some of the tubules of the glandular component of this low-grade adenosquamous carcinoma are more or less continuously surrounded by myoepithelial cells in this CK5/6 immunostain. However, other histologically similar tubules show no surrounding myoepithelial cell layer

state that these findings, combined with the triple-negative phenotype and androgen receptor negativity, confirm LGASC as a distinct genetic entity among metaplastic carcinomas [10].

LGASC must be distinguished from a variety of benign and malignant breast lesions.

Due to the infiltrative pattern composed of a variable mixture of well-formed glands and solid cell strands with squamous differentiation and with typically minimal cytologic atypia, radial scar/complex sclerosing lesion may be in the differential diagnosis in some circumstances (especially in core needle biopsies). The more cell-rich spindle cell desmoplastic background, but especially the triple-negative phenotype, supports the diagnosis of LGASC [10]. Adenomyoepithelioma (AME) may also enter the differential diagnosis. Whereas classic AME is composed of glandular structures surrounded by a double cell layer, AME of spindle cell subtype is characterized by a prominent growth of spindle myoepithelial cells surrounding and compressing glandular structures lined by epithelial cells, which can sometimes be difficult to visualize. There are no strict criterion-based boundaries here. Accordingly, cases in which an association between AME and LGASC is observed seem to be more than coincidental [3, 5]. A major differential diagnostic consideration is a syringomatous tumor of the nipple (ST). LGASC and ST have a similar histological appearance and immunophenotype, differing only in their location [11]. However, it was proposed early on that ST arises from the pluripotent adnexal epidermal keratinocytes with dual follicular and sweat gland differentiation, whereas LGASC arises primarily from the myoepithelium [12]. Accordingly, LGASCs are also found within the mammary parenchyma without reference to the overlying skin or nipple epidermis, while STs are restricted to the dermis of the nipple [4, 13]. Both lesions appear to have similar variable myoepithelial staining patterns, although the luminal and peripheral myoepithelial cytokeratin staining patterns mentioned above are usually absent in ST [6]. Both lesions are locally aggressive with a propensity for local recurrence. LGASC should be distinguished from other triple-negative/basal-like carcinomas that are associated with aggressive behavior. In high-grade adenosquamous carcinoma, there is always a mixture of an atypical squamous component and an NST type adenocarcinoma component whose architecture and cytology are not compatible with the LGASC-type glandular components described above [14]. Any sarcomatous spindle cell or heterologous (chondroid, osseous, rhabdomyoid) component in a metaplastic carcinoma excludes LGASC by definition and a high-grade spindle cell or high-grade metaplastic carcinoma with heterologous mesenchymal differentiation is present [14]

The prognosis of LGASC is excellent. Among the 155 published cases, follow-up data from a total of 102 patients (with 103 lesions) are available to confirm this: LGASCs show a low rate of local recurrence (10/103, 10%) and an extremely low rate of regional lymph node metastases (1/103 cases, 1%) and distant metastases (1/103 cases, 1%). Only one patient died from metastatic tumor [2, 3, 7, 15] (Supplemental Table 1).

Fibromatosis-like metaplastic carcinoma

Fibromatosis-like metaplastic carcinoma (FLMC) is a very rare subtype of metaplastic breast carcinoma with a total of 70 published cases to date [16–28] (Supplementary Table 2).

FLMC usually affects women over the age of 50; only one case under the age of 40 has been reported [26]. The published cases were almost exclusively detected as solitary palpable masses; however, it must be considered that FLMCs are today increasingly detected by imaging studies [16–28].

On macroscopic examination, FLMCs are compact whitish tumors and typically 2–3 cm in size (reported range, 1.9–7.0 cm) (Supplementary Table 2). They are sometimes well circumscribed but may have irregular borders. They are very rarely cystic and never encapsulated [16, 17] (Fig. 4).

On histologic examination, FLMC is characterized by a proliferation of spindle-shaped, fibroblast-like, and myofibroblast-like cells, which account for more than 95% of the tumor [14, 16]. These cells are arranged in interlacing fascicles, often infiltrating the adjacent breast tissue, and histologically resembling desmoid-type fibromatosis (Fig. 5). Focally, bands of hyalinized collagen may dominate the interspersed spindle cells. Normal pre-existing ducts and lobules may be entrapped within the tumor. Patchy round cell inflammatory infiltrates may be seen inside the tumor, but are more often present at the periphery [16, 17] (Fig. 6).

The neoplastic cells are cytologically bland with no or minimal nuclear atypia and pale eosinophilic cytoplasm. Within the same tumor, the neoplastic nuclei may vary from thin, slender, and spindled with tapered ends to more plump, round to oval nuclei with discrete nucleoli within finely distributed chromatin. There may be a gradual transition from the slender spindle cells to the plump cell component (Fig. 7). The more plump spindle cells may assume an epithelioid appearance when cut in cross-section and tend to be arranged in a perivascular pattern [16, 17, 29]. High nuclear grade is not seen [14, 16, 17]. Mitotic figures are either completely absent or rare [16, 17]. Necrosis is not identified.

Neoplastic squamous or glandular epithelial elements may be admixed among the spindle cells. By definition, however, these should represent less than 5% of the total tumor area and FLMC should not contain any otherwise differentiated component [14].

Expression of epithelial markers by tumor spindle cells is the characteristic immunophenotypic feature of FLMC. However, FLMC may occasionally show only focal cytokeratin expression (Fig. 8). Therefore, the epithelial origin should preferably be verified by immunohistochemistry with a broad panel of cytokeratin antibodies that includes antibodies to both low and high molecular weight cytokeratins such as AE1/AE3, pan-keratin MNF116, CK5/6, CK14, and 34βE12 [16–18, 22, 29, 30]. Additionally, nuclear expression of p63 in the spindle cell component has proven to be a sensitive and specific diagnostic feature [30]; thus, p63 should also be included in the panel of immunostains. Myoepithelial markers, such as CD10, calponin, and α-SMA, may be also expressed [17, 30]. These tumors are typically ER, PR, and HER2 negative (triple negative) [30].

FLMCs show a claudin-low phenotype, with low expression of claudin 1–4 and E-cadherin, evidence of epithelial-mesenchymal transition and tumor-infiltrating immune cells. Activating EGFR mutations have not been found [31].

The diagnosis of FLMC requires, on the one hand, the exclusion of benign and other low-grade spindle cell lesions of the breast and, on the other hand, the exclusion of higher-grade spindle cell metaplastic carcinoma. Benign and low-grade neoplastic spindle cell lesions of the breast may cause differential diagnostic problems, particularly in core needle biopsies. FLMC may occasionally show

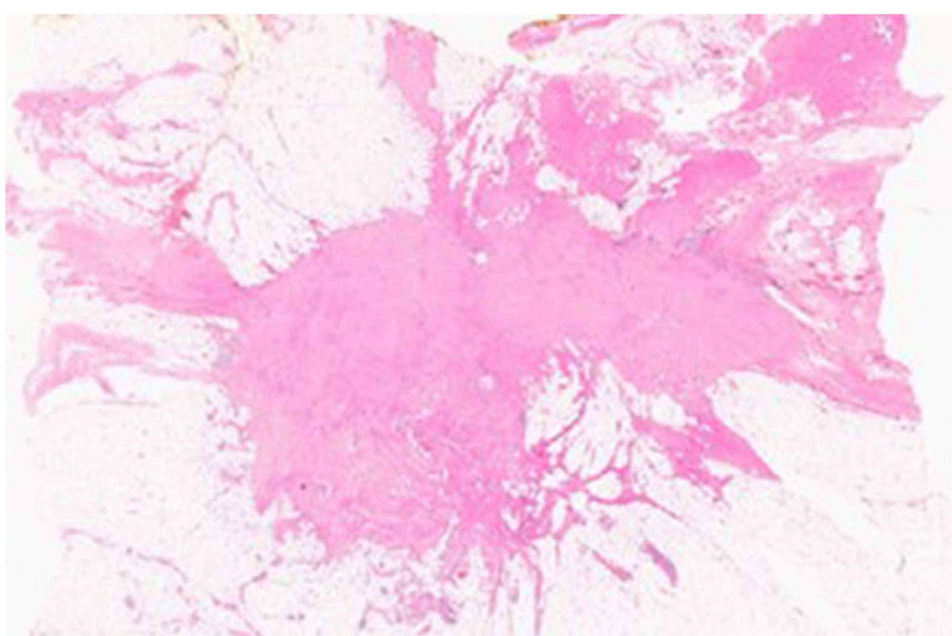

Fig. 4 Scanning magnification of a large format section of a 32-mm fibromatosis-like metaplastic carcinoma with irregular, radiating infiltration of surrounding tissue

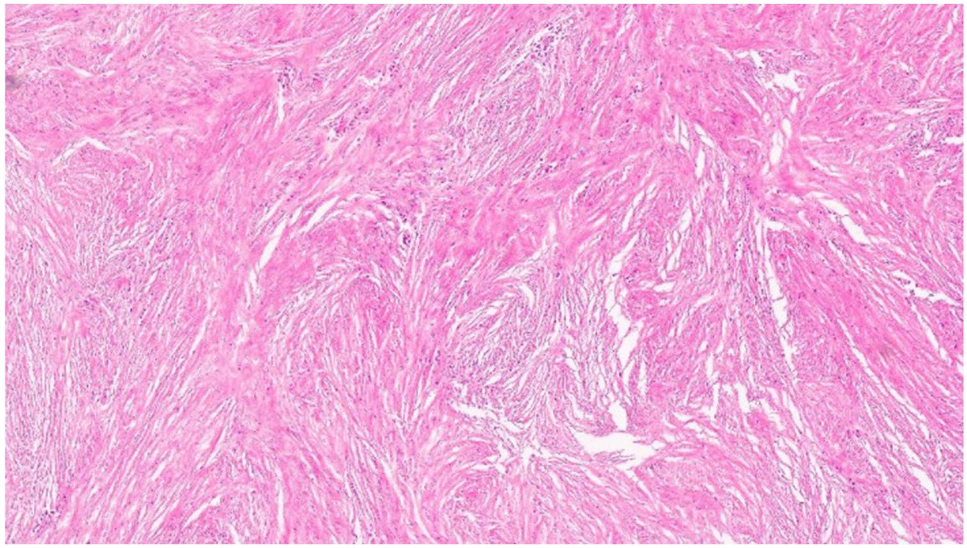

Fig. 5 Low-power view of a fibromatosis-like metaplastic carcinoma showing interlacing fascicles of cytologically bland spindle cells with absent to minimal nuclear atypia and pale eosinophilic cytoplasm

a storiform pattern, fibromyxoid or pseudoangiomatoid areas, or collagen-rich foci with hyalinized collagen bands and a scattered inflammatory infiltrate of lymphocytes and plasma cells. The resulting spectrum of differential diagnoses, therefore, includes exaggerated scar tissue, benign fibrous histiocytoma, pseudoangiomatous stromal hyperplasia, nodular fasciitis, myofibroblastoma, inflammatory myofibroblastic tumor (IMT), solitary fibrous tumor (SFT), phyllodes tumor, and dermatofibrosarcoma protuberans. In addition to morphology, clinical history, and imaging, immunohistochemistry can help in making the diagnosis: the expression of epithelial markers by tumor spindle cells of FLMC and negative results for ALK, ER, CD34, and STAT6 helps to rule out these other entities. Desmoid fibromatosis also typically shows nuclear β-catenin expression, which is detectable due to the mutation in the CTNNB1 gene and is present in over 80% of cases [19, 32]. The high-grade or malignant spindle cell lesions that enter into the differential diagnoses of FLMCs include in particular other types of metaplastic carcinoma as well as rarer spindle cell malignancies such as leiomyosarcomas, fibrosarcomas, and spindle cell melanomas.

Because of the favorable prognosis of FLMCs, these tumors should be distinguished from the more common high-grade spindle cell metaplastic carcinomas. In these cases, conspicuous mitoses and a predominance of plump cells with unequivocal nuclear atypia strongly argue against an FLMC (Fig. 6). A proportion of the spindle cell component of less than 95% or a metaplastic carcinoma with a heterologous component also speaks against an FLMC (see above). An NST component in the tumor also rules out a FLMC by definition [14, 30]. Spindle cell sarcomas such as leiomyosarcomas and high-grade pleomorphic sarcomas, which may express not only SMA but also cytokeratin,

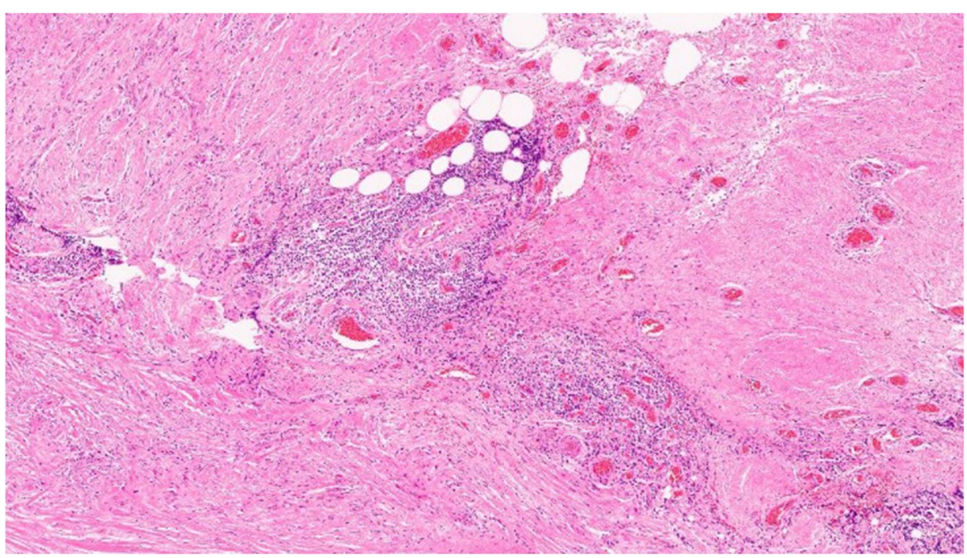

Fig. 6 Cloudy lymphocytic infiltrate at the periphery of the lesion in a fibromatosis-like metaplastic carcinoma

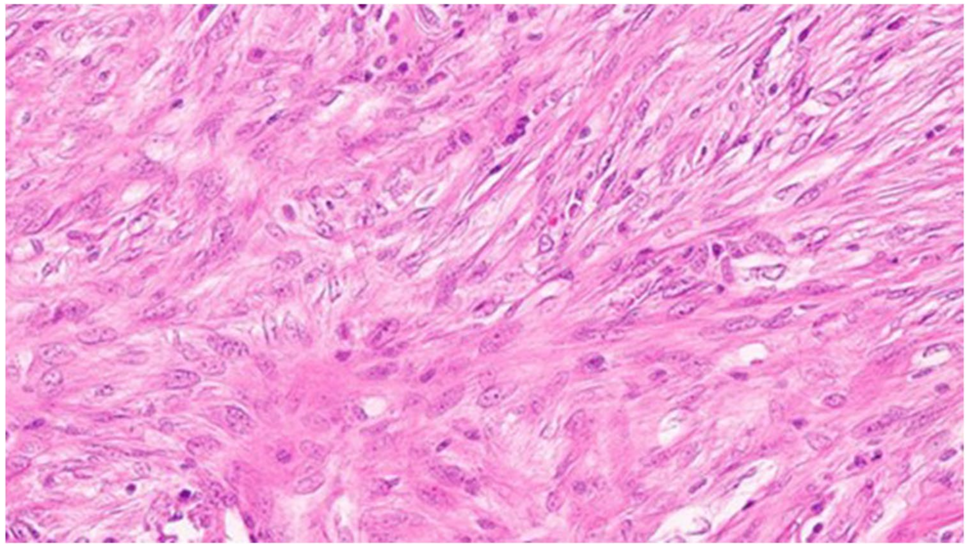

Fig. 7 Gradual transition from bland spindle cells to more plump cells with round to oval nuclei with discrete nucleoli within finely distributed chromatin

should be clearly distinguished from FLMC. Leiomyosarcomas usually show strong and diffuse staining for muscle-specific actin, desmin, and caldesmon, compared to the weak and focal staining observed in FLMC. High-grade pleomorphic sarcoma can be discriminated from FLMC on the basis of a more pronounced nuclear atypia and an elevated number of mitoses [16, 17]. The rare fibrosarcoma is more cellular and has a characteristic "herringbone" growth pattern of impressively atypical spindle cells. Spindle cell melanoma may be negative for HMB-45 and melan A; thus, the strong, diffuse expression of S100 protein distinguishes it from FLMC, in which the expression of S100 protein is a more focal feature [33, 34].

Among the 70 cases of FLMC reported to date in the English-language literature, follow-up data are available for 41 patients. While these tumors have a high rate of local recurrence (14/41 cases, 34%), the low frequency of regional lymph node metastases (3/41 cases, 2%) and distant metastases (5/41 cases, 12%) indicates clinically indolent behavior [16–28] (Supplementary Table 2).

An association between tumor size and the risk of distant metastasis suggested by some authors is not confirmed by a literature review [16–28] (Supplementary Table 2). Although FLMCs often are of considerable size when detected, they are usually detected at an early stage, unlike other subtypes of metaplastic carcinoma [19, 33]. The literature review suggests that the risk of local recurrence is at least partly related to inadequate local resection [16, 17, 21]. Histologic risk factors associated with local recurrence or distant metastasis have not been identified [14, 16–30, 32].

There are no evidence-based treatment guidelines for FLMC. In terms of local therapy, wide excision appears to be adequate to prevent local recurrence [16, 17, 23]. From the available data, there is no evidence for a beneficial effect of

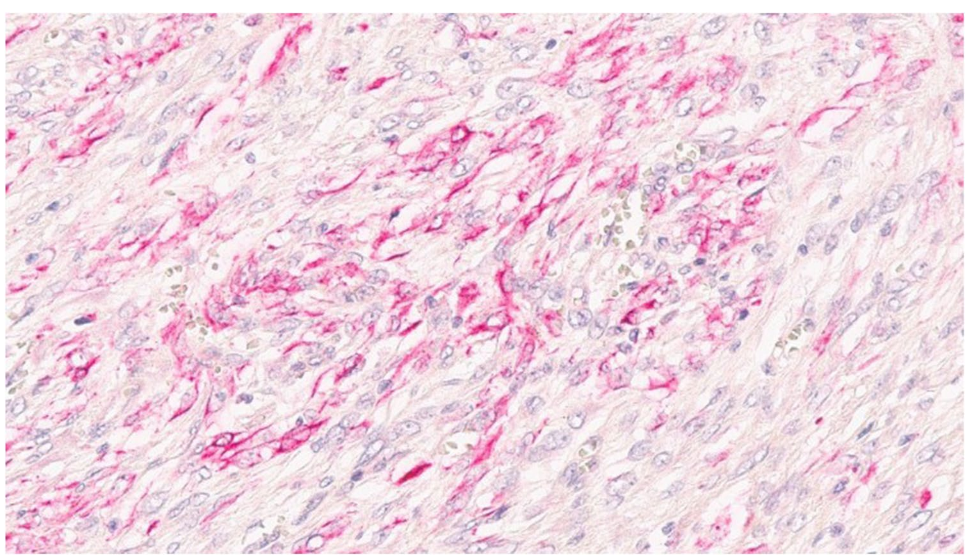

Fig. 8 Fibromatosis-like metaplastic carcinoma. AE1/AE3 stain showing that cytokeratin staining may be only focal and weak

adjuvant radiotherapy or chemotherapy in reducing the risk of local recurrence or distant metastasis [16–28]] (Table 1). However, some authors advocate adjuvant radiotherapy for larger lesions [2]. Due to the very low risk of regional lymph node metastases, several authors have argued against axillary lymph node evaluation[16, 30].

Encapsulated papillary carcinoma

Encapsulated papillary carcinoma (EPC), previously known as intracystic papillary carcinoma and encysted papillary carcinoma, is an expansile, well-circumscribed neoplasm characterized by delicate fibrovascular papillae covered by neoplastic epithelium of low to intermediate nuclear grade and typically lacking myoepithelial cells around the periphery of the lesion and within the fibrovascular cores [35–40]. It is an uncommon tumor comprising 1% of breast cancer cases and is primarily seen in women, mainly in the seventh and eighth decades [41]. Rare cases have been described in men [42].

The majority of EPCs are centrally located. Historically, these lesions came to attention as a palpable mass with or without nipple discharge but EPC now commonly present as mammographically detected masses. Macroscopically, the tumors are circumscribed, soft, friable masses, often within an apparent cystic space, sometimes with associated hemorrhage, especially after fine-needle aspiration or biopsy [39, 43].

Histologically, these tumors are well-circumscribed nodules that may appear to be within a cystic space and surrounded by a fibrous capsule. Some tumors consist of an aggregate of nodules with variable intervening fibrous stroma, especially following core needle biopsy. EPCs are characterized by branched, mostly slender, but occasionally broad fibrovascular stalks covered by one to several layers of monomorphic epithelial cells with low- to intermediate-grade nuclear atypia (Fig. 9). In rare cases, the epithelium has apocrine features [44].

In most cases, no myoepithelial cells are present within the fibrovascular stalks or around the periphery of the lesion. The absence of myoepithelial cells both within fibrovascular stalks and at the periphery is a feature that distinguishes EPC from benign papillary lesions and is a useful feature in core needle biopsies. Areas of cribriform or solid growth may be present. The surrounding fibrous capsule may contain entrapped epithelial structures. This needs to be distinguished from frank invasion transgressing the capsule, which usually takes the form of invasive carcinoma of no special type [45]. Therefore, a diagnosis of invasion in a core needle biopsy with a low- to intermediate-grade papillary carcinoma should only be made with clear evidence of infiltrating glands. EPC usually exhibits strong positivity for estrogen receptors.

EPC is characterized by low genomic complexity with a common loss of 16q and gains of 1q and 16p and a high frequency of *PIK3CA* mutations, similar to the genomic profile of low grade, hormone receptor–positive invasive carcinomas [46, 47]. EPCs usually belong to the luminal A group by gene expression profiling.

The differential diagnosis of EPC encompasses a broad range of lesions with papillary features and diverse biological behavior [39]. Differentiation from benign papillary lesions is easy in most cases by virtue of the monotonous appearance of lesional epithelial cells and lack of myoepithelial cells; the latter can be confirmed, if necessary, by staining for myoepithelial markers. Papillary ductal carcinoma in situ (DCIS), which may be present in breast issues adjacent to EPC, shows the presence of myoepithelial cells at the periphery of the involved ducts. Rare cases of EPC show high-grade cytology and these may be ER negative [48]. While it has been recommended to stage high-grade EPC as conventional invasive carcinoma, there are no strong data to support this since only one of ten patients reported developed a recurrence and died of disease [48]. An invasive component accompanying EPC should only be diagnosed, when clearly neoplastic aggregates are found beyond the fibrous capsule. Despite the characteristic absence of myoepithelial cells, EPC has a prognosis similar to that of ductal carcinoma in situ. In order to prevent overtreatment, in the absence of frankly invasive carcinoma that extends beyond the fibrous capsule, EPC should be assigned a nuclear grade and staged as pTis (DCIS) [40]. When there is an accompanying frankly invasive carcinoma, it is the invasive component that should be used for grading (using the Nottingham system) and determining the T stage.

EPC is adequately treated with local therapy. The risk of local recurrence appears to be related to the presence of ductal carcinoma in situ in the adjacent breast tissue [40] Rare cases of lymph node metastases have been reported [49] but the possibility that this was related to undetected invasive carcinoma in these cases cannot be excluded.

Solid papillary carcinoma

Solid papillary carcinomas (SPCs) are defined by the WHO as tumors characterized by a solid growth pattern with delicate fibrovascular cores that frequently show neuroendocrine differentiation and are biologically indolent. These lesions are most often seen in post-menopausal women, typically during the 7th decade or later and may be in situ or invasive [50]. These lesions may present as a palpable or mammographic mass, mammographic microcalcifications, or bloody nipple discharge.

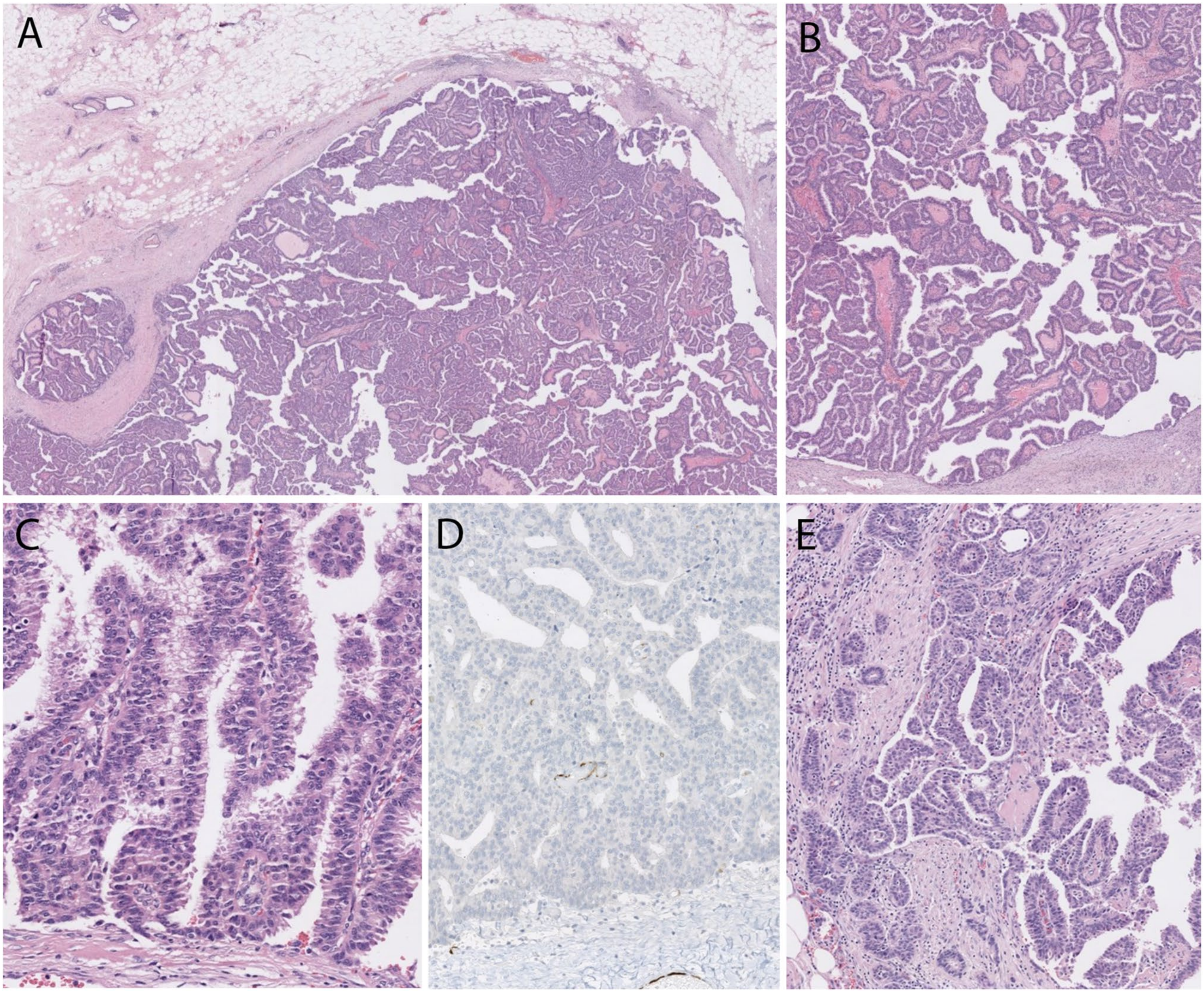

Fig. 9 Encapsulated papillary carcinoma. **A** Scanning magnification shows an encapsulated papillary lesion. **B** Branched papillae of variable thickness are covered by a monotonous epithelial proliferation. **C** At high power, one to several layers of columnar epithelial cells with increased nuclear to cytoplasmic ratio, loss of nuclear polarity, and mild atypia are evident. **D** Immunostaining for smooth muscle myosin heavy chain demonstrates complete absence of myoepithelial cells both on the papillae, as well as in the inner lining of the cyst. **E** Early invasion in encapsulated papillary carcinoma. Isolated glandular and papillary structures start to infiltrate beyond the fibrous capsule. Entrapped epithelia in the fibrous capsule alone would not qualify for invasion

Histologically, SPC consists of one or more solid, well-circumscribed expansile nodules of monotonous neoplastic epithelial cells of low to intermediate nuclear grade with a round to spindled nuclei reminiscent of DCIS with solid growth pattern [51, 52]. However, the nodules of SPC contain slender fibrovascular cores which separate SPC from solid pattern ductal carcinoma in situ. Palisading of tumor cells around the fibrovascular cores is a characteristic feature. Signet ring cell morphology, mucin accumulation, a microcystic pattern, and calcifications can be observed. Occasionally, a streaming appearance similar to usual ductal hyperplasia can occur. Myoepithelial cells are usually absent or sparse both within, as well as at the periphery of individual nodules. [53] As long as the expansile and rounded character of the nodules is preserved, SPC is regarded as in situ lesion irrespective of the presence or absence of surrounding myoepithelial cells (Fig. 10). The assessment of invasion in SPC can be difficult, especially in cases which show a jigsaw puzzle-like appearance with irregularly shaped solid tumor nodules (Fig. 11). Invasive SPC is frequently associated with extracellular mucin pools and must clearly be distinguished from frank mucinous carcinoma or invasive carcinoma NST [54, 55]. SPCs are usually ER and PR positive and HER2 negative.

Neuroendocrine differentiation with expression of neuroendocrine markers such as synaptophysin or chromogranin

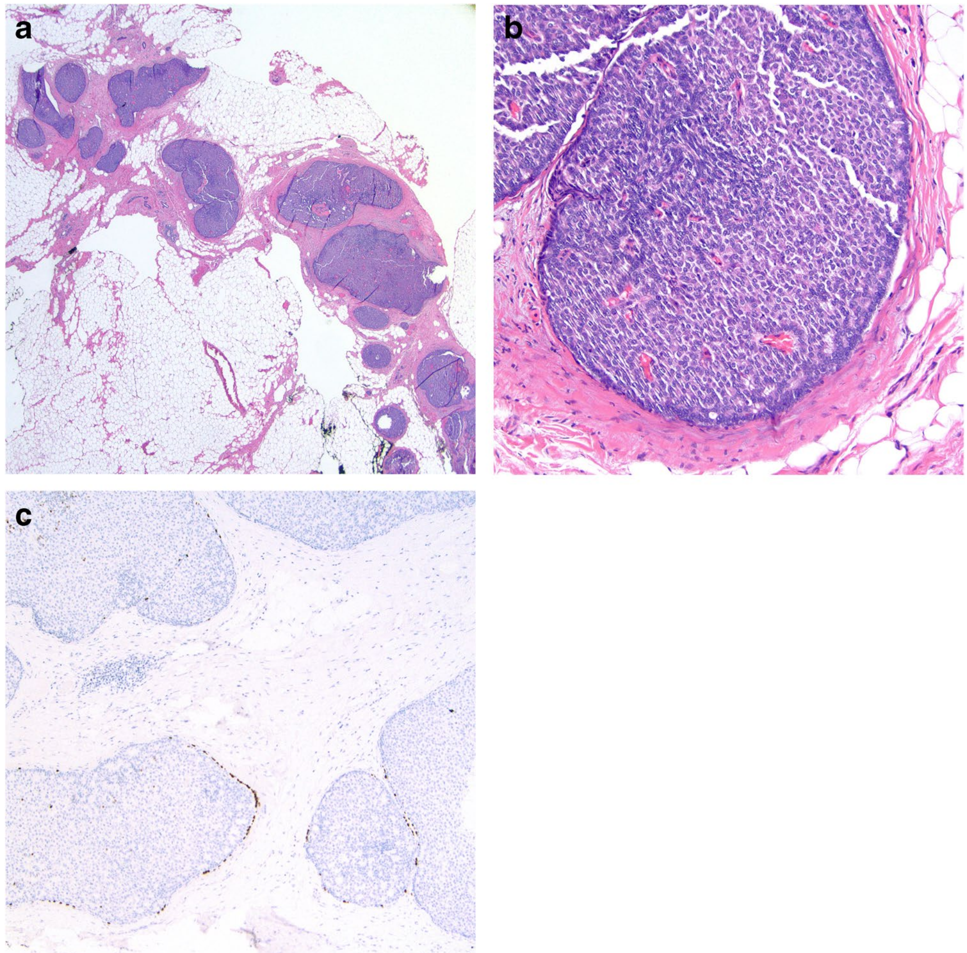

Fig. 10 Solid papillary carcinoma in situ. **A** At scanning magnification, the lesion consists of multiple circumscribed nodules. **B** At higher power, the tumor cells are uniform in appearance and grow in a solid pattern; delicate fibrovascular cores are evident. **C** An immunostain for p63 demonstrates variable numbers of myoepithelial cells around the periphery of the nodules. The nodule on the upper right has no surrounding myoepithelial cells

A has been described in at least half of the cases of SPC and is commonly present also in the invasive part [54–56].

SPCs, like EPC, share low genomic complexity with a common loss of 16q and gains of 1q and 16p and a high frequency of *PIK3CA* mutations with hormone receptor-positive carcinomas of low grade [46, 47]. SPCs more frequently than EPC are of luminal B molecular type. HER2 amplification and *TP53* mutations are distinctly infrequent.

The differential diagnosis of SPC includes florid, usual ductal hyperplasia (UDH) with solid growth pattern, solid pattern DCIS, and neuroendocrine tumors of the breast. The distinction from UDH should be easily made with immunostains for high molecular weight cytokeratins (variably positive in UDH and negative in SPC), ER (variably positive in UDH and strongly and diffusely positive in SPC), and neuroendocrine markers (negative in UDH and positive in many cases of SPC) [57, 58]. The presence of rare fibrovascular cores should prompt the inclusion of SPC in the differential diagnosis of solid pattern DCIS and staining for neuroendocrine and myoepithelial markers should be performed. SPC shares many features with the hypercellular or type B mucinous carcinoma, supporting their close relationship. The distinction from tall cell carcinoma with reversed polarity is discussed below [59–65].

The prognosis of SPC is excellent, with a rare occurrence of lymph node (2–3%) or distant metastasis [38]. Among 265 published cases, Guo et al. reported 11 local recurrences in their meta-analysis (2 for in situ; 9 for invasive SPC). In SPC in situ, neither lymph node nor distant metastases were seen in 265 published cases (even in cases without peripheral myoepithelial confinement). Lymph node or distant metastases occurred exclusively in 5 and 7 cases, respectively, of the 135 invasive SPCs, while all 129 in situ SPCs were metastasis-free [66]. The WHO currently recommends that, in the absence of an obvious invasive component, SPC should be staged as pTis (DCIS) regardless of whether or not a myoepithelial cell layer is identified at the periphery of the nodules whereas SPC with invasion is staged according to the size of the invasive component only [50].

The key features of EPC and SPC are summarized in Supplementary Table 3.

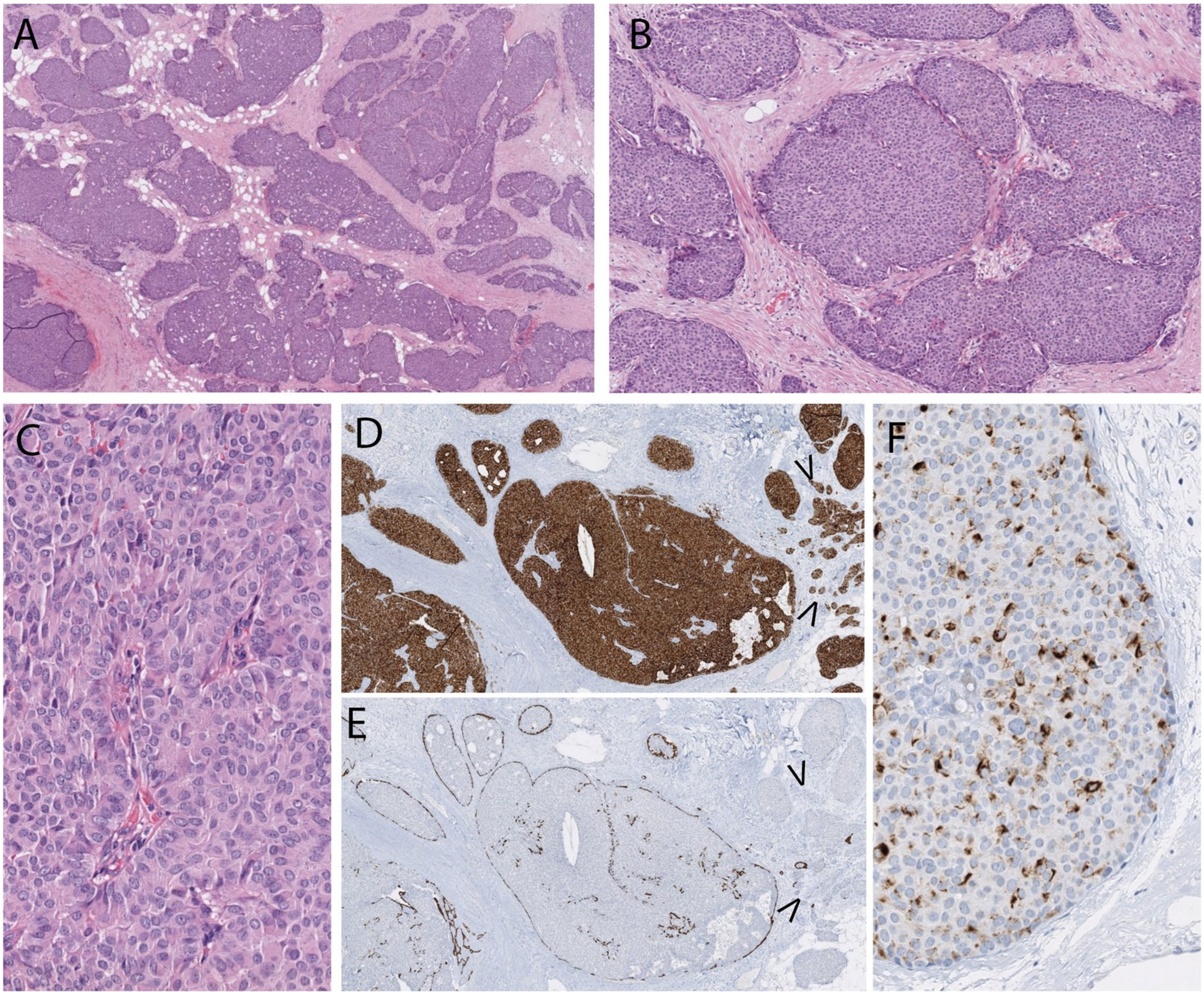

Fig. 11 Solid papillary carcinoma with focal invasion. **A** Scanning magnification shows solid nests of tumor with mostly smooth, rounded contours. **B** This area with round nodules does not fulfill the criteria for invasion. **C** The high-power view shows a solid proliferation of epithelial cells with round to oval low-grade nuclei with palisading around delicate fibrovascular cores. **D** Synaptophysin is strongly and homogenously expressed and highlights an area of invasion with irregular small tumor islands (arrowheads). **E** The immunostain for cytokeratin CK5/14 of the same area shows tumor nodules with complete, incomplete, and absent basal cell layers. However, only the same area as above between the arrowheads would be considered true invasion. **F** Variable staining for chromogranin A

Tall cell carcinoma with reversed polarity

Tall cell carcinoma with reversed polarity (TCCRP) was recently recognized by the WHO as a rare subtype of invasive breast carcinoma [67]. This tumor was first reported by Eusebi et al. as “breast tumor resembling tall cell variant of papillary thyroid carcinoma” [68] and subsequently reported as “solid papillary carcinoma with reverse polarity” [59] and “solid papillary carcinoma resembling tall cell variant of papillary thyroid carcinoma” [69]. To date, approximately 80 cases of this tumor have been reported.

TCCRP primarily occurs in post-menopausal women in their 6th to 7th decades and present most often as relatively small mammographic abnormalities (typically T1 lesions). Histologically, these tumors are composed of solid, circumscribed nodules consisting of tall columnar epithelial cells. The nodules often have relatively inconspicuous fibrovascular cores imparting a solid papillary appearance, and these cores may contain foamy histiocytes (Fig. 12). Infrequently, true papillae are formed. The nodules are haphazardly distributed in the breast stroma, are present around and between normal ducts and lobule, and may extend into adipose tissue. The stroma is typically collagenous with little or no desmoplasia. In some cases, cystic or follicular structures containing colloid-like secretions are present. The columnar cells comprising the nodules have eosinophilic

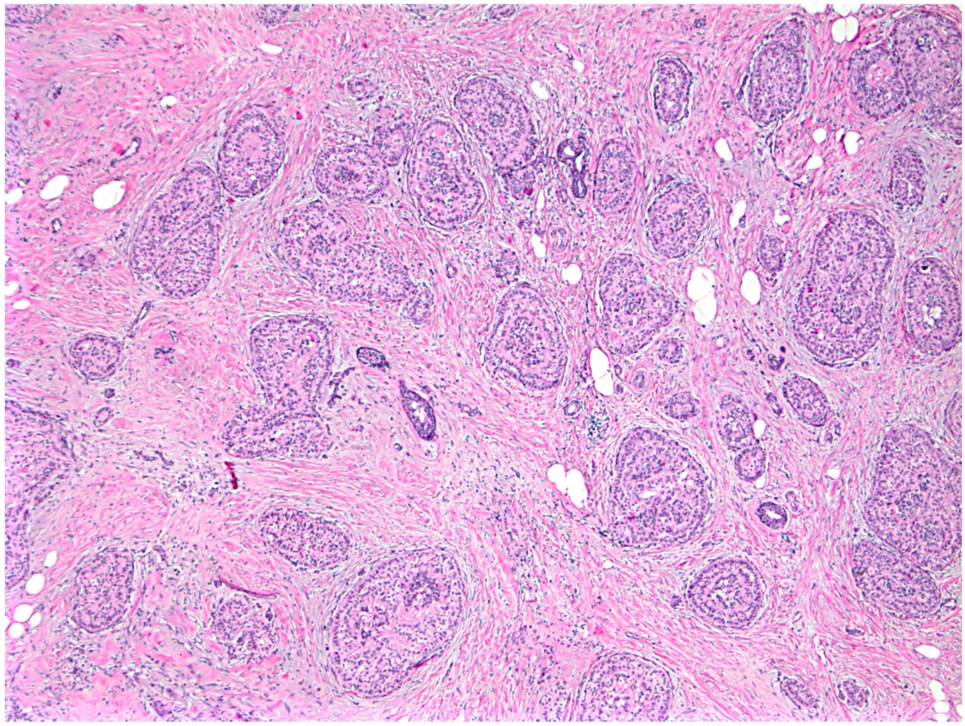

Fig. 12 Low-power view of a tall cell carcinoma with reversed polarity showing haphazard distribution of relatively rounded tumor cells nests, many of which contain fibrovascular cores imparting a solid papillary appearance

cytoplasm and usually intermediate-grade nuclear atypia. In some nodules, the cells are present in a double layer with a back-to-back appearance. Nuclear grooves and cytoplasmic pseudo-inclusions may be seen. However, the most distinctive feature of these cells is the presence of the nuclei at the apical rather than the basal pole, creating the impression of reversed polarity (Fig. 13)[59].

The tumor nodules lack a surrounding myoepithelial cell layer supporting the invasive nature of these lesions (Fig. 14). The nodules are surrounded by a rich vascular

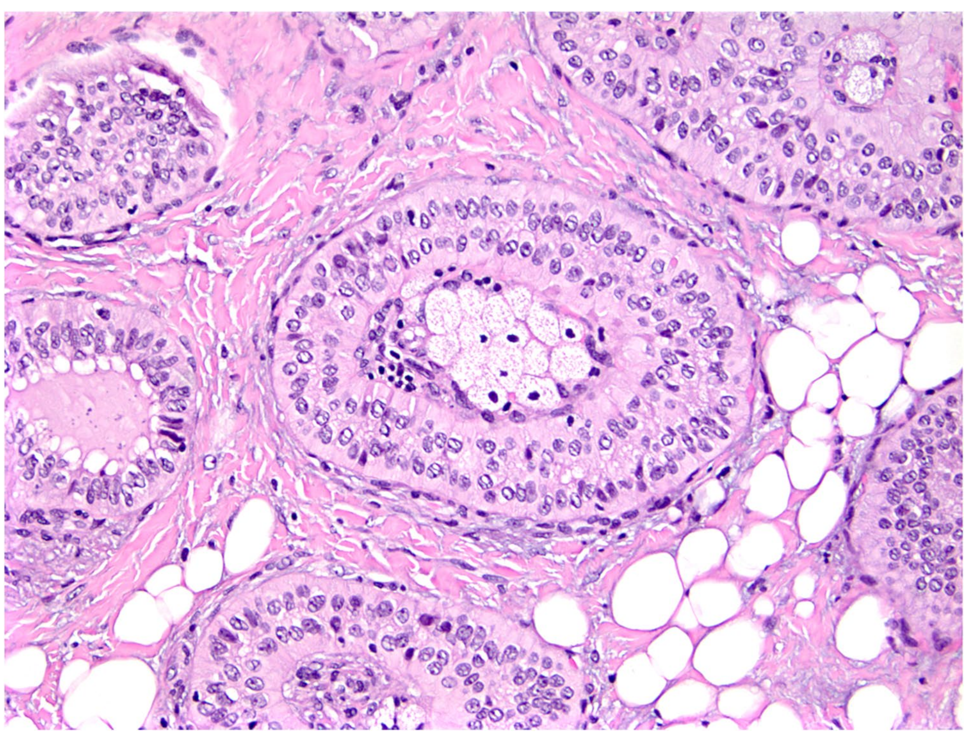

Fig. 13 In this high-power view of a tall cell carcinoma with reversed polarity the nuclei are clearly evident at the apical rather than the basal pole of the columnar epithelial cells. The nest in the center of the field contains foamy histiocytes within the fibrovascular core

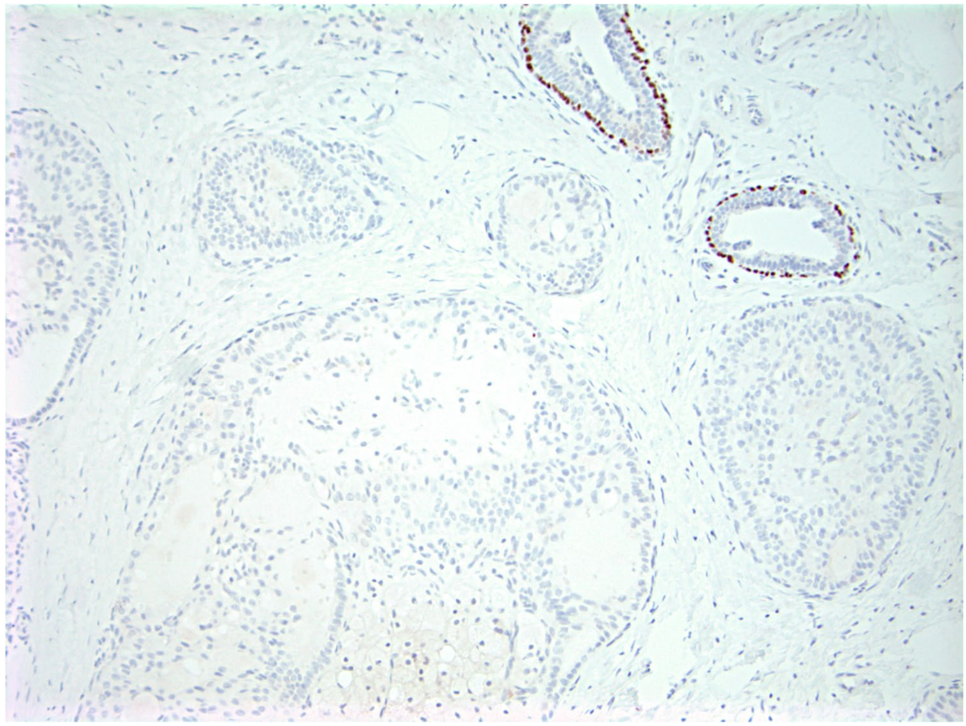

Fig. 14 p63 immunostain of a tall cell carcinoma with reversed polarity demonstrates absence of myoepithelial cells around the tumor cell nests (note the presence of myoepithelial cells around the normal ducts)

network on immunostains for endothelial markers such as CD31 and CD34. The epithelial cells comprising these lesions typically show strong staining for both low molecular weight (luminal) and high molecular weight (basal) cytokeratins and may show staining for GATA3, gross cystic disease fluid protein, and mammaglobin [59–63, 65, 68, 69]. These cells typically show staining for calretinin [62, 65] as well as a basal pattern of staining for mitochondrial antigen [69]. The cells comprising TCCRP are typically negative for estrogen receptor (ER), progesterone receptor (PR), and HER2 (triple negative), but some tumors show low levels of ER and or PR expression [59, 63]. MUC1 staining, which highlights the apical poles of columnar epithelial cells, is present at the end of the cells closest to the nuclei confirming the abnormal nuclear location [59]. The tumor cells have a low Ki67 proliferation rate (< 5%) [69]. Despite the superficial resemblance to the tall cell variant of papillary thyroid carcinoma, these lesions are uniformly negative for thyroglobulin and TTF-1 [59, 65, 68, 69].

Chiang et al. were the first to describe the genomic alterations in TCCRP. Among 13 cases studied, 10 (77%) showed *IDH2* R172 hot spot mutations and 8 concurrently displayed mutations in the PI3 kinase pathway (in either *PIK3CA* or *PIK3R1*) [59]. In addition, in that series one *IDH2* wild-type tumor displayed a *TET2* Q548 truncating mutation coupled with a *PIK3CA* mutation. Of note, *IDH2* mutations had not been previously reported in any breast carcinomas. Functional studies demonstrated that *IDH2* and *PIK3CA* hot spot mutations are likely drivers resulting in the reverse polarity phenotype. Subsequent studies by other groups have confirmed the presence of *IDH2* R172 hot spot mutations in these tumors and to date this mutation has been found in 34 of 40 TCCRP studied (85%) [59–65] Pareja et al. have reported that demonstration of the *IDH2* R172 protein by immunohistochemistry is a sensitive and specific marker for TCCRP and provides a rapid and inexpensive alternative to sequencing [70]. Of note, no *BRAF* mutations or *RET/PTC* rearrangements have been reported in TCCRP providing further evidence of a lack of a relationship to thyroid tumors [59, 61–65]

The differential diagnosis of TCCRP includes several entities. The circumscribed nature of the nodules often gives the impression of DCIS, but the lack of surrounding myoepithelial cells, the haphazard distribution of the nodules in the stroma, and the tall columnar cells with nuclei at the apical poles of the cells distinguish TCCRP from DCIS. The presence of fibrovascular cores in the nodules may raise concern for a SPC (in situ or invasive). However, solid papillary carcinomas do not have tall columnar epithelial cells with reversed polarity. The similarity of some features of TCCRP to some thyroid neoplasms may raise the question of a metastatic lesion of thyroid origin. However, the presence of reversed polarity, lack of expression of thyroid markers, and the characteristic immunophenotype and genotype distinguish TCCRP from tumors of thyroid origin.

TCCRP generally pursue an indolent clinical course. There are four reported cases with axillary lymph node metastases and a single reported case of distant metastases to bone [67]. However, it is unclear if the tumor that metastasized to bone is a *bona fide* example of TCCRP since this tumor at presentation was large (4.1 cm), had associated DCIS with comedo necrosis, demonstrated lymphovascular invasion and lymph node metastases, was ER positive, and had a high Ki67 proliferation rate, all unusual features for TCCRP [71].

In summary, TCCRP is a histologically low-grade invasive breast carcinoma with distinctive morphologic, immunophenotypic, and genotypic features. These tumors typically pursue an indolent clinical course despite a triple-negative phenotype and expression of high molecular weight (basal) cytokeratins and add to the list of low-grade triple-negative neoplasms that includes adenoid cystic carcinomas, secretory carcinomas, and acinic cell carcinomas.

Conclusion

Some breast carcinomas, including low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, encapsulated papillary carcinoma, solid papillary carcinoma, and tall cell carcinoma with reversed polarity have a very low likelihood of aggressive behavior, particularly distant metastases, and are best categorized as carcinomas of low malignant potential. Recognition and appropriate classification are important so that patients with these tumors can avoid overtreatment.

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This manuscript complies with the ethical standards of the authors' institutions.

Declarations

Conflict of interest The authors declare no competing interests.

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