Journal of Clinical and Translational Pathology **2022** vol. 2(2) | 37–47
DOI: 10.14218/JCTP.2022.00010

Review Article

Low-Grade Invasive Triple Negative Breast Carcinoma

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Received: April 20, 2022 | **Revised:** May 15, 2022 | **Accepted:** May 19, 2022 | **Published:** June 2, 2022

Abstract

Triple-negative breast carcinomas (TNBCs) are defined as estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor receptor 2-negative breast carcinomas and are composed of a heterogeneous group of breast carcinomas with most of them having aggressive behavior and poor prognosis. However, some TNBC cases are low grade with indolent clinical outcome and low risk of metastasis to other organs or regional lymph nodes. Low-grade TNBCs include low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, low-grade invasive (ductal or lobular) carcinoma with apocrine differentiation, classic adenoid cystic carcinoma, secretory carcinoma, tall cell carcinoma with reversed polarity, acinic cell carcinoma, and low-grade mucoepidermoid carcinoma. This review aims to summarize the clinicopathological correlation and the molecular features of low-grade special TNBC subtypes.

Citation of this article: Shaker N, Ding Q, Wang Y, Li Z. Low-Grade Invasive Triple Negative Breast Carcinoma. J Clin Transl Pathol 2022;2(2):37–47. doi: 10.14218/JCTP.2022.00010.

Introduction

Triple negative breast carcinomas (TNBCs) are defined as breast carcinomas with triple negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBCs usually follow an aggressive behavior and have unfavorable prognosis. However, some TNBCs cases are low grade with favorable prognosis. Low-grade TNBCs may not need adjuvant chemotherapy or neoadjuvant chemotherapy, therefore, recognizing such cases is essential to avoid unnecessary treatment.

This review summarizes the clinicopathological correlation and the characteristic histological presentation and molecular features of each entity of low-grade TNBC. The distinct entities that are included in this study are low-grade adenosquamous carcinoma (LGASC), fibromatosis-like metaplastic carcinoma (FLMC), low-grade invasive (ductal or lobular) carcinoma with apocrine differentiation, classic adenoid cystic carcinoma (AdCC), secretory carcinoma, tall cell carcinoma with reversed polarity (TCCRP), acinic cell carcinoma (ACC), and low-grade mucoepidermoid carcinoma (MEC).

Low-grade adenosquamous carcinoma

Low-grade adenosquamous carcinoma (LGASC) is a rare distinct entity of metaplastic carcinoma that usually follows an indolent clinical course and has a good prognosis.[1,2] It occurs in patients with a wide age range (19–88 years old) and frequently presents as a firm palpable mass.[3] Histologically, LGASC demonstrates round or comma-shaped glandular ducts with variable degrees of squamous differentiation infiltrating into the fibrotic stoma. Tumor cells are composed of a mixture of two types of glandular and squamous cells with low grade nuclei. An increased cellularity in the stroma surrounding the tumors cells is often encountered.[4,5] The lumens of the ducts are usually compressed and may contain keratin debris or eosinophilic material. The tumor nests lack myoepithelial cells as demonstrated by smooth muscle myosin heavy chain (SMMS) immunohistochemistry (IHC), while tumor cells are usually positive for p63/p40 and cytokeratins (CK) 5/6. As the name implies, tumor cells are usually negative for ER, PR, and HER2 (Fig. 1).

This entity should be distinguished from benign breast lesions such as squamous metaplasia and sclerosing adenosis. Invasive tubular carcinomas should also be considered high in the differential diagnosis. Distinguishing malignant breast neoplasms from benign breast lesions is feasible with the addition of IHC staining. The absence of myoepithelial cell markers in IHC staining is essential in excluding benign lesions.[2] A careful identification of squamous differentiation is important in differentiating this entity from other invasive tubular carcinoma.[4] Syringomatous adenoma of the nipple reveals similar histological morphology to LGASC, but the

Keywords: Triple negative breast carcinoma; Low-grade adenosquamous carcinoma; Fibromatosis-like metaplastic carcinoma; Adenoid cystic carcinoma; Secretory carcinoma; Tall cell carcinoma with reverse polarity.

Abbreviations: ACC, acinic cell carcinoma; AdCC, adenoid cystic carcinoma; AR, androgen receptor; CCH, clear cell hidradenoma; CEA, carcinoembryonic antigen; CK, cytokeratin; DCIS, ductal carcinoma *in situ*; EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen; ER, estrogen receptor; FISH, fluorescence *in situ* hybridization; FLMC, fibromatosis-like metaplastic carcinoma; HER2, human epidermal growth factor receptor 2; IBC-NST, invasive breast carcinoma-no specific type; IDC-NOS, invasive ductal carcinoma of no special type; IHC, immunohistochemistry; LGASC, low-grade adenosquamous carcinoma; MEC, mucoepidermoid carcinoma; MGA, micro-glandular adenosis; PAS, periodic acid Schiff; PASH, pseudoangiomatous stromal hyperplasia; PR, progesterone receptor; RT-PCR, reverse transcriptase-polymerase chain reaction; SMMS, smooth muscle myosin heavy chain; SPC, solid papillary carcinoma; TCCRP, tall cell carcinoma with reversed polarity; TNBC, triple negative breast carcinoma; WHO, World Health Organization.

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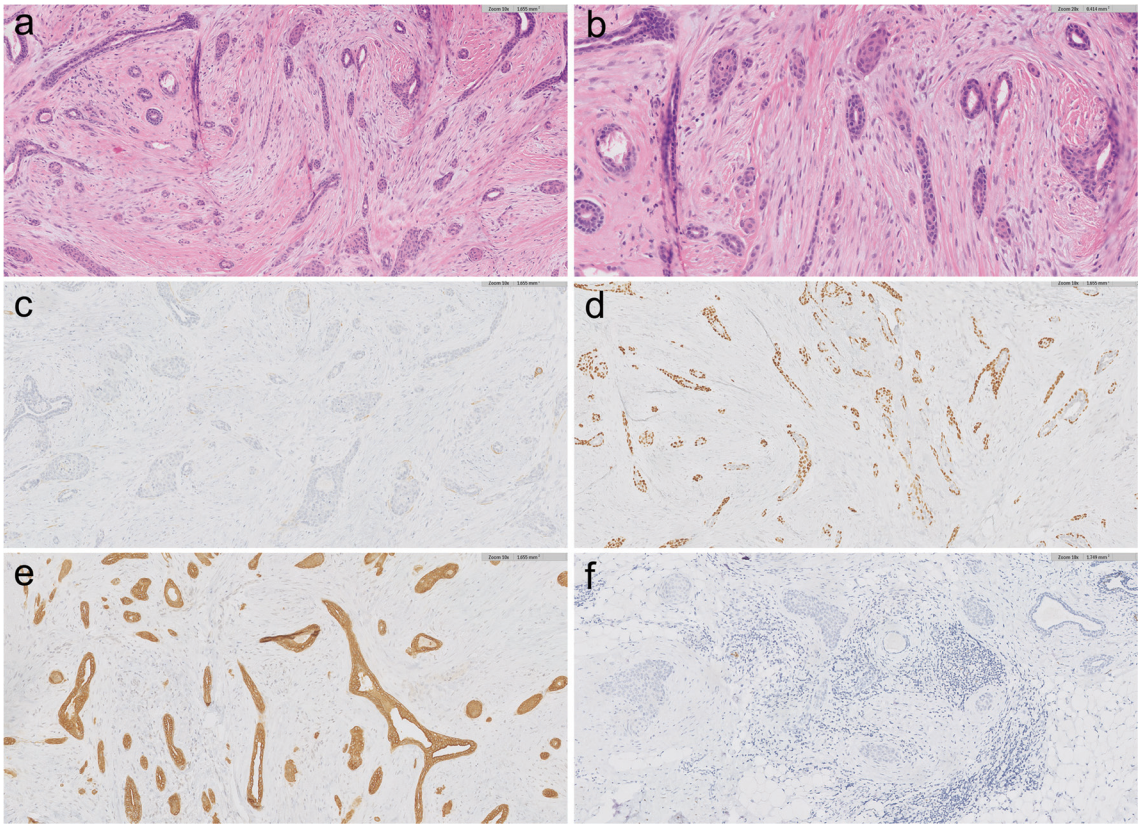

Fig. 1. Low-grade adenosquamous carcinoma of the breast shows infiltrative solid glandular ducts into surrounding stroma (a), which are composed of low-grade, bland looking cells with squamous and glandular components (b). Myoepithelial cells are absent around the tumor in smooth muscle myosin heavy chain (SMMS) staining (c). The tumor cells are diffusely positive for p40 (d) and cytokeratin 5 (CK5) (e), but negative for estrogen receptor (ER) (f). b, ×20; others, ×10.

nipple area site will aid in separating these two entities. The intramammary parenchymal location of LGASC is important to differentiate it from syringomatous adenoma of the nipple.

Although LGASC has a favorable clinical behavior, local recurrence can occur if not completely excised. Currently, LGASC is treated with complete surgical excision followed by adjuvant radiation therapy for conservative surgery. LGASC seldom responds to chemotherapy. Therefore, additional neoadjuvant or adjuvant chemotherapy is not warranted.

Fibromatosis-like metaplastic carcinoma

Fibromatosis-like metaplastic carcinoma (FLMC) was first reported in the literature in 1999. FLMC is a low-grade subtype of metaplastic carcinoma with a favorable prognosis.[6,7] FLMC usually occurs in women between 40 and 80 years old. Grossly, FLMC often appears as a white firm mass with fibrous, grey-white nodular parenchyma on the cut surface. Histologically, FLMC is composed of short interlacing bundles or long fascicles of bland spindle shaped cells or stellate cells, which can show mild nuclear atypia and discrete nucleoli. Mitotic activity is rare. FLMC is characterized by small clusters of polygonal epithelioid cells dispersed within spindle cells.[8–10] The tumor border is usually infiltrative with broad, finger-like projections into the surrounding breast parenchyma. Rare neoplastic squamous or glandular epithelial elements may be present. FLMC may also show collagenous stroma (Fig. 2).

A panel of CK markers pancytokeratins (AE1/3, MNF116) and high molecular weight markers (CK5/6, CK14, and 34βE12) is necessary to demonstrate the epithelial origin of the spindle cells in FLMCs. However, low molecular weight markers such as CK7, CK19, and CAM 5.2 are often negative. Spindle tumor cells demonstrate positive expression for p63 and p40 and negative expression for SMMS and epithelial membrane antigen (EMA).[11] The proliferation index with Ki-67 staining is usually low with 5% expression (Fig. 2).[9,12]

The main differential diagnosis for FLMC includes fibromatosis and nodular fasciitis. Fibromatosis is a benign proliferative lesion of fibroblasts and myofibroblasts that demonstrates an infiltrative growth pattern. Negative staining for CKs accompanied by positive nuclear staining for beta-catenin aids in separating this entity from FLMC which demonstrates a reverse staining pattern. Nodular fasciitis is a rarely encountered diagnosis in the breast. A thorough and extensive sectioning accompanied with the exclusion of other entities is mandatory to establish a final diagnosis. Nodular fasciitis demonstrates proliferative benign fibroblasts and myofibroblasts in a myxoid stroma with prominent vasculature and negative CK staining. Myofibroblastoma and pseudoangiomatous stromal hyperplasia (PASH), may be in the differential diagnosis as well. Of note, myofibroblastomas can occur in both male and female patients.[13] Morphologically, myofibroblastomas show short haphazard fascicles composed of bland-appearing spindle cells. Dense collagen bands are present between fascicles and patchy perivascular chronic inflammatory infiltrates may be present. Myofibroblastoma cells are usually positive for desmin, CD34, smooth muscle actin, ER, PR, and

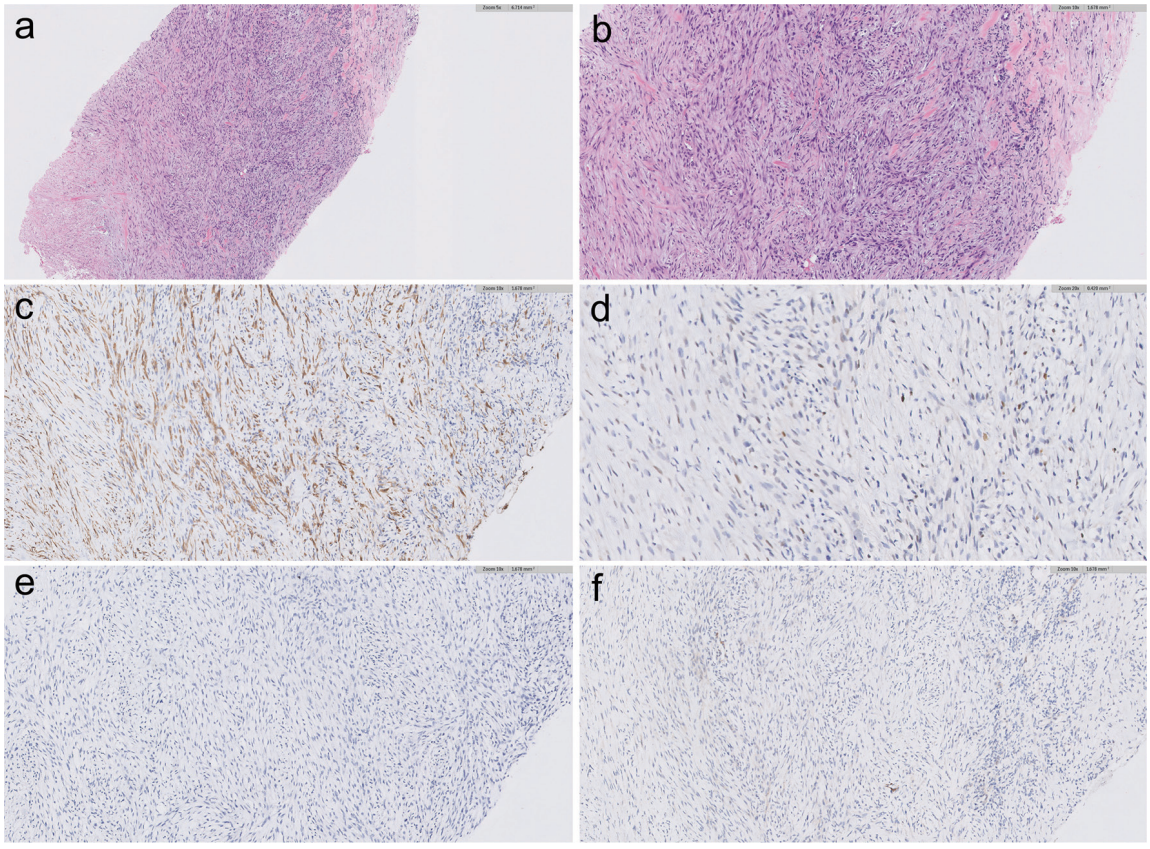

Fig. 2. Fibromatosis-like spindle cell carcinoma shows the tumor infiltrates into the surrounding breast parenchyma (a). The tumor is composed of cytologically bland spindle shaped cells with small round to oval nuclei. Also note the lack of mitotic figures (b). The tumor cells are positive for AE1/AE3 (c), focally positive for GATA binding protein 3 (GATA3) (d), and negative for ER (f) and desmin (f). a, ×5; b–c, e–f, ×10; d, ×20.

B cell lymphoma-2, but negative for CKs.[14,15] PASH shows anastomosing empty, slit-like pseudovascular spaces lined by myofibroblasts (not endothelial cells) in a dense collagenous stroma, and the myofibroblast cells are positive for desmin, CD34, and smooth muscle actin but negative for CKs.[9,11,12,16–19] FLMC is mostly negative for GATA binding protein 3 (GATA3) and Trichorhinophalangeal syndrome type 1 (TRPS1), a newly identified breast marker.[20–22]

FLMC lesions usually have an indolent clinical process with a favorable prognosis. Minimal local recurrence, lymph node involvement, or distant metastasis is usually expected in these tumors.[9,23,24] A radical surgical approach is curative in most cases. Neoadjuvant or adjuvant chemotherapy is usually not necessary.

Low grade invasive (ductal or lobular) carcinoma with apocrine differentiation

Per World Health Organization (WHO) classification, carcinoma with apocrine differentiation is a distinct category, characterized by more than 90% of tumor cells with apocrine features. Low-grade invasive (ductal or lobular) carcinoma with apocrine differentiation is usually intermediate to high-grade and could be triple negative. The prognosis remains contradictory. Focal apocrine differentiation can be seen in up to 30% of invasive breast carcinomas.[25] Invasive carcinoma with apocrine differentiation is classified as invasive breast carcinomas of no special type (IBC-NST) with mixed apocrine and non-apocrine carcinoma cells. These tumors are treated like IBC-NST. Compared to benign apocrine cells, apocrine tumor cells demonstrate increased nuclear size and nuclear membrane irregularity, nuclear pleomorphism, and nuclear hyperchromasia.

However, rare invasive pure apocrine carcinomas demonstrate predominantly tubule formation and relatively low cytologic atypia, resulting in an overall low histologic grade (Fig. 3). These low-grade invasive apocrine carcinomas have the same apocrine differentiation of ductal cells with abundant granular dense eosinophilic, or vacuolated cytoplasm with increased nuclear size.

Immunohistochemically, low-grade invasive apocrine carcinoma is negative for ER and PR. Androgen receptor (AR) is usually positive. HER2 is variable with up to 20% being positive.[26] In addition, gross cystic disease fluid protein (GCDFP)-15 (BRST-2) is positive in most cases of invasive apocrine carcinomas.[25] GATA3 is usually positive in apocrine component of breast carcinomas while TRPS1 is usually negative.[20]

Similar to non-apocrine breast carcinomas, the prognosis of invasive apocrine carcinoma is associated with the tumor grade, tumor size, clinical stage, and the presence or absence of lymph node metastasis.

Classic adenoid cystic carcinoma

Adenoid cystic carcinoma (AdCC) rarely occurs in the breast, accounting for less than 0.1% of all breast carcinomas. AdCC predominantly affects older women in their

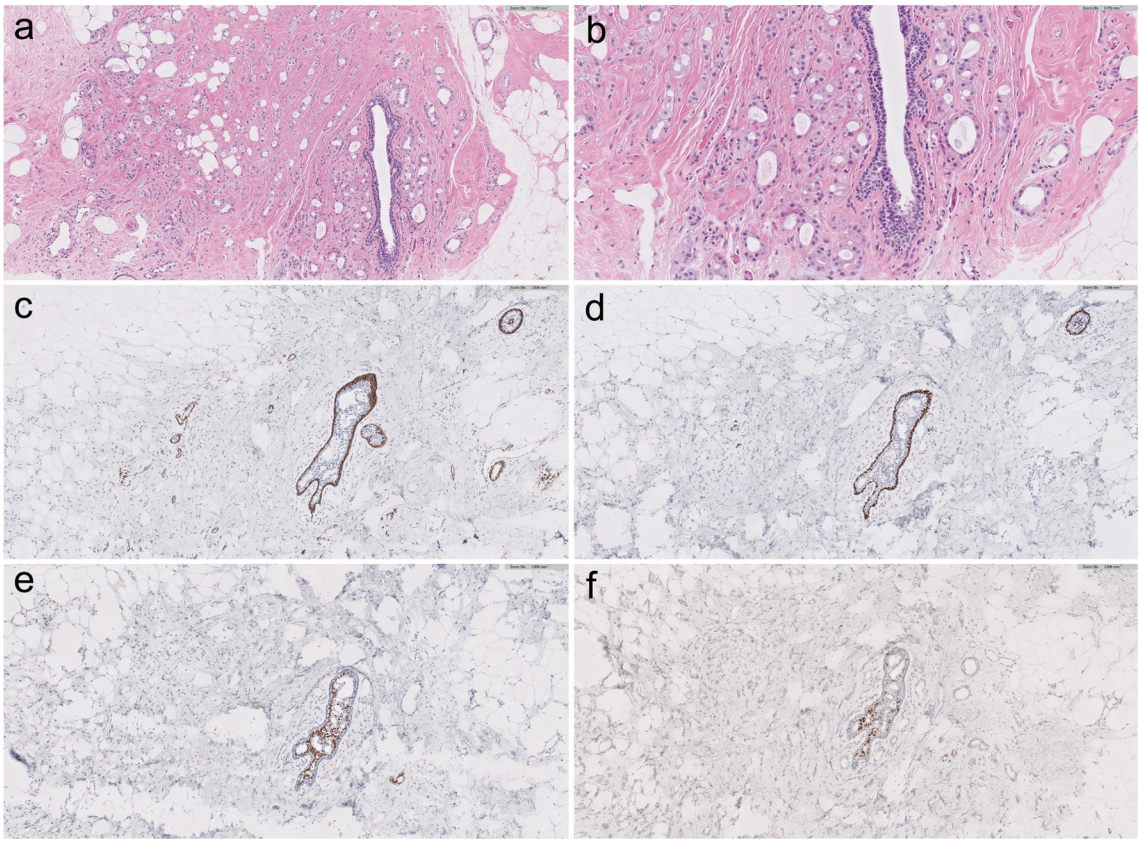

Fig. 3. Low grade invasive apocrine carcinoma shows solid growth pattern with minimal stroma (a, b). The carcinoma cells show mild to intermediate nuclear pleomorphism with abundant eosinophilic cytoplasm. SMMS (c) and p40 (d) show a lack of myoepithelial cells around invasive carcinoma. Tumor cells are negative for ER (e) and progesterone receptor (PR) (f). b, ×20; others, ×10.

sixties, while triple negative invasive ductal carcinoma of no special type (IDC-NOS) usually affects relatively younger patients aged less than 50 years.[27,28]

AdCC of the breast shows similar morphology to AdCC of the salivary gland, consisting of two distinct cells populations (glandular luminal cells and basaloid cells) arranged in three various growth patterns (cribriform, tubular, and solid). Based on the growth pattern, AdCC can be classified into classic AdCC or the solid variant of AdCC. Classic AdCC is predominantly composed of tubules and/or cribriform structures. Eosinophilic hyaline or mucoid material may be seen in the lumen of cribriform structures. In classic AdCC, tumor cells are usually small with scant cytoplasm and vesicular nuclei without prominent nucleoli, and the mitotic activity is low.[29] In contrast, the solid variant of AdCC is a high-grade variant with solid growth pattern and a more aggressive behavior. Tumor cells in the solid variant of AdCC are larger with moderate to marked nuclear pleomorphism and increased mitotic activity.[30]

Basaloid cells of AdCC of the breast are characteristically positive for myoepithelial markers such as p63, p40, SMMS, and calponin, basal CKs such as CK5/6, CK14, and CK17, as well as epidermal growth factor receptor (EGFR).[31] The glandular luminal cells are usually positive for CK7, CK8/18, EMA, carcinoembryonic antigen (CEA), and c-Kit (CD117).[32] Ki-67 proliferation index is usually low in classic AdCC of the breast. AdCC of the breast is typically triple negative for ER, PR, and HER2. Weak expression of ER and PR is encountered in rare cases. AdCCs show variable positivity for breast markers GATA3 and TRPS1 (Fig. 4).[20]

AdCCs of the breast demonstrate genetic translocation of t (6;9) (q22–23; p23–24), resulting in avian myeloblastosis virus oncogene homolog (MYB) - nuclear factor 1/B (*NFIB*) gene fusion (*MYB-NF1*). *In situ* hybridization results in an identifiable oncogenic fusion protein with transcription factor function.[33–36] Other genomic alterations in AdCC of the breast include losses of 6p25.3–q26 and 9p11.1–q21.11 and gains of 1p36.12–p35.3, 11p15.5, 12p13.31, 16p13.3, and 19p13.[34,35]

The differential diagnosis of AdCC of the breast includes other types of invasive and *in situ* carcinomas such as invasive cribriform carcinoma and cribriform ductal carcinoma *in situ* (DCIS) with a cribriform growth pattern and benign lesions such as collagenous spherulosis. Invasive cribriform carcinoma shows a cribriform growth pattern without surrounding myoepithelial cells. However, it has only one cell type (glandular luminal cells) and lacks mucinous or basement membrane materials in lumens. Another differential diagnosis is cribriform DCIS, which also shows a cribriform growth pattern, but contains myoepithelial cells around the cribriform structures. More importantly, invasive cribriform carcinoma and cribriform DCIS usually show strong positivity for ER and PR, but tumor cells are negative for p63/p40 or c-kit. A benign breast lesion, collagenous spherulosis, can be included in the differential diagnosis of AdCC. Ckit can be helpful in the differential diagnosis since it is not expressed in collagenous spherulosis. Additionally, fluorescence *in situ* hybridization (FISH) split-apart or fusion probes to detect the t (6;9) rearrangement and/or reverse transcriptase-polymerase chain reaction (RTPCR) for the *MYBNFIB* fusion gene can provide supportive evidence for diagnosing AdCC. Of note, AdCCs

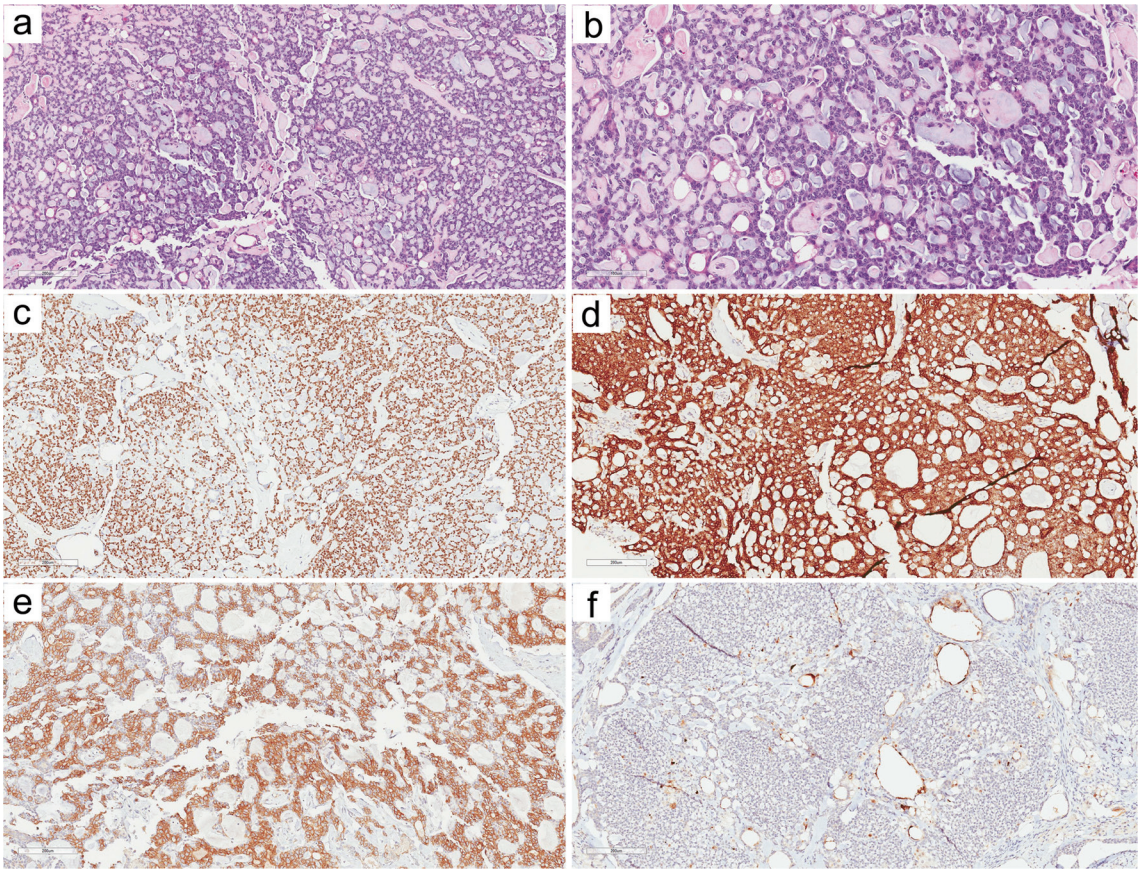

Fig. 4. Classic adenoid cystic carcinoma of the breast shows cribriform growth pattern (a). Eosinophilic globular material is present in the lumen of cribriform structures, which are composed of low-grade basaloid tumor cells (b). P63 is positive in the basaloid cells (c). Luminal epithelial cells are diffusely positive for CK5 (d) and c-Kit (CD117) (e). The tumor cells are negative for ER (f), GATA3 (g) and Trichorhinophalangeal syndrome type 1 (TRPS1) (h). b, ×20; others, ×10.

of salivary gland origin should always be considered in the differential diagnosis. Although GATA3 and TRPS1 can be used to identify primary breast tumors, our recent study demonstrated both are variable in AdCC of the breast and cannot be used to differentiate breast AdCC from salivary gland.[20] Instead, clinical and radiologic information is always necessary in this scenario.

AdCC of the breast is graded using the standard Nottingham grading system as histologic grade one or two due to mild to moderate nuclear pleomorphism and low to moderate mitotic activity. Classic AdCC of the breast demonstrates an indolent clinical course presenting as a localized disease with a low frequency of axillary lymph node involvement (<8%).[37] These tumors have a more favorable prognosis than triple negative IDC-NOS.[38–40] However, the solid variant of AdCC of the breast has higher incidence of nodal metastases than classic AdCCs, indicating a more aggressive behavior and adverse clinical outcome.[41] Distant metastases to the lung and bone are the most frequently encountered solid organ involvments.[37,42]

The treatment of choice for classic AdCCs is usually conservative surgery with/without radiation therapy. This approach results in an excellent outcome in more than 90% of patients with 10-year survival. Local recurrence and distant metastasis occur rarely but seem not to alter the prognosis in most patients.[43,44] In AdCCs of the salivary gland, MYB expression has shown a favorable association with a better survival,[45] however, such an association has not been established in patients with AdCC of the breast.

Secretory carcinoma

Secretory carcinoma is an exceedingly rare subtype of invasive breast carcinoma. Secretory carcinoma was originally identified in young patients, and was known as "juvenile breast carcinoma."[46] However, the literature shows a wide range of ages from 3 to 87 years.[47] Secretory carcinoma usually presents as a mobile, palpable mass in the subareolar region. Imaging shows a well-circumscribed mass with smooth borders that can be easily mistaken as a fibroadenoma in young patients.

Grossly, secretory carcinoma shows a tan to yellow well-circumscribed mass. Histologically, secretory carcinoma shows well-circumscribed nodules with three growth patterns: microcystic, tubular, and solid. In the microcystic pattern, small cysts are present, which resemble thyroid follicles. Tubules in the tubular pattern may show secretions in the lumens. Most secretory carcinomas contain various combinations of all three patterns. Secretory carcinoma cells are round or angulated in shape with vacuolated or finely granular cytoplasm. Eosinophilic secretions may be present intracellularly or extracellularly in small cysts or the lumens of tubules (Fig. 5).[47–49]

Secretory carcinoma cells are of basallike phenotype expressing high molecular weight CKs (CK5/6, 34E12, CK14, CK17), EGFR, and c-kit. Tumor cells are positive for S100 (strong and diffuse) and mammaglobin, but negative for GCDFP-15.[50,51] Secretory carcinoma is diffusely positive for

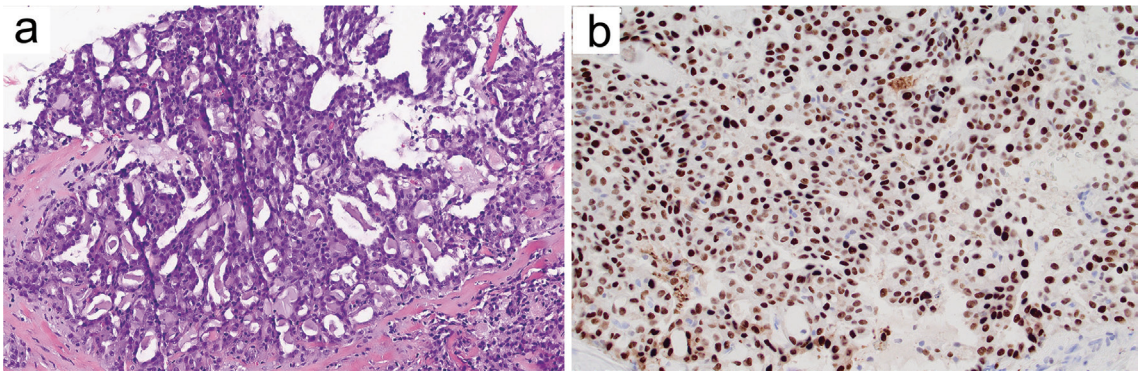

Fig. 5. Secretory carcinoma of the breast. (a) Irregular lobules of eosinophilic tumor cells separated by band-like fibroconnective tissue. Low grade tumor cells with abundant dense luminal eosinophilic secretion. (b) Tumor cells are diffusely positive for TRPS1. a–b, ×20.

GATA3 and TRPS1 (Fig. 5).[20] The eosinophilic secretions are positive for periodic acid-Schiff (PAS), diastase-PAS, and Alcian blue. Secretory carcinomas are triple negative for ER, PR, and HER2 with a low Ki67 proliferative index. Chromosomal translocation t(12:15) is present in secretory carcinoma, resulting in the ETS-variant transcription factor 6 (*ETV6)* neurotrophic receptor tyrosine kinase 3 (*NTRK3*) fusion gene (*ETV6-NTRK3*). This translocation can be confirmed by either FISH with *ETV6* break-apart probe or RT-PCR.[52]

Secretory carcinomas are low-grade triple negative breast carcinomas with an excellent prognosis, especially in younger patients. Secretory carcinoma is usually treated with conservative surgery with/without radiation therapy. Lymph node metastases may be present, but usually within a limited numbers of lymph nodes (≤ 3).

Tall cell carcinoma with reversed polarity

Tall cell carcinoma with reversed polarity (TCCRP) is a rare subtype of invasive breast carcinoma. This entity was first described by Eusebi *et al*.[53] in 2003 and was originally called a breast tumor resembling tall cell variant of papillary thyroid carcinoma. The newest edition of the WHO classification of breast carcinomas described this tumor as a distinct entity.[54] It usually affects women of postmenopausal age (median age 64).[55]

Histologically, TCCRP is composed of tall columnar mitochondrion-rich to oxyphilic cells arranged in nests with a predominant follicle-like/solid papillary pattern. The nuclei are located at the apical rather than the basal pole of the cells, evidencing the reverse polarization. An essential diagnostic criterion for diagnosis is the absence of myoepithelial cells at the periphery of the tumor nests. The various nuclear histological appearance was observed in some cases, including nuclear grooves and pseudo-inclusion, resembling the tall cell variant of thyroid papillary carcinomas.[56] The stroma between tumor cell nests is generally collagenous and dense with little or no desmoplasia. The neoplastic nests are often surrounded by a delicate rim of capillaries (Fig. 6).[56]

TCCRPs are usually triple negative for ER, PR, and HER2.[55] Some cases may demonstrate weak hormone receptor positivity and expression of ARs. Co-expression of high and low-molecular-weight CKs is recognized as a desirable diagnostic criterion in the WHO classification. However, the mosaic-like pattern staining of CK5 should not be mistaken for the diagnosis of benign or hyperplastic lesions of the breast.[57] Breast specific markers such as GATA3, GCDFP-15, and mammaglobin are well expressed in TCCRP. TCCRP cells are often positive for mucin 1 at the apical poles of columnar epithelial cells (Fig. 6). Due to the presence of mitochondria-rich neoplastic cells, anti-mitochondrial antibody immunostaining shows strong positivity, especially at the basal pole of the tumor cells, demonstrating the reversed polarity.[58]

This entity shows a distinct isocitrate dehydrogenase 2 (IDH2) R172 hotspot mutation unique to this entity and very uncommon in other subtypes of breast carcinomas.[59–61] Recently, IHC using the specific antibody against IDH2 R172 protein has been demonstrated to be a sensitive and specific marker for TCCRP.[62]

The differential diagnosis of TCCRP includes solid papillary carcinoma (SPC), papillary DCIS, and metastatic thyroid carcinoma. Although SPC harbors papillary architecture with fibrovascular cores, SPC cells do not have tall columnar epithelial cells with reversed polarity. In addition, SPC cells are usually strongly positive for ER and PR. Papillary DCIS also shows a papillary growth pattern; however, papillary DCIS has surrounding myoepithelial cells that can be highlighted by myoepithelial markers and DCIS cells are usually positive for ER. TCCRP may show similar features to some thyroid neoplasms, raising concerns of a metastatic thyroid carcinoma to the breast in patients with a history of thyroid carcinoma. However, the lack of thyroid marker expression (transcription termination factor 1, paired-box 8, etc.), the presence of breast marker expression (GATA3, etc.), and the presence of reverse polarity can distinguish TCCRP from metastatic thyroid carcinoma.

TCCRP is a low grade triple negative breast carcinoma with an indolent clinical course and a favorable prognosis.[55] Axillary lymph node metastases and/or distant metastases rarely occur.[63] Conservative surgery is the first line treatment for TCCRP. The benefit of chemotherapy and/or radiation therapy is still controversial.

Low-Grade acinic cell carcinoma of the breast

Acinic cell carcinoma (ACC) of the breast is composed of tumor cells with serous acinar differentiation. It is extremely rare and mainly affects adult women.[64] Similar to its salivary gland counterpart, ACC of the breast shows a wide spectrum of structures composed of a diffuse infiltrative proliferation of monotonous small round glands with a micro-glandular pattern, which are lined by a single layer of cuboidal to columnar epithelial cells with clear vacuolated cytoplasm or finely granular eosinophilic or basophilic cytoplasm.[65,66] Dark eosinophilic zymogen-type coarse granules may be prominent, resembling intestinal Paneth cells. Central round nuclei and prominent nucleoli are also present. Cytologically, tumor cells usually show low or inter-

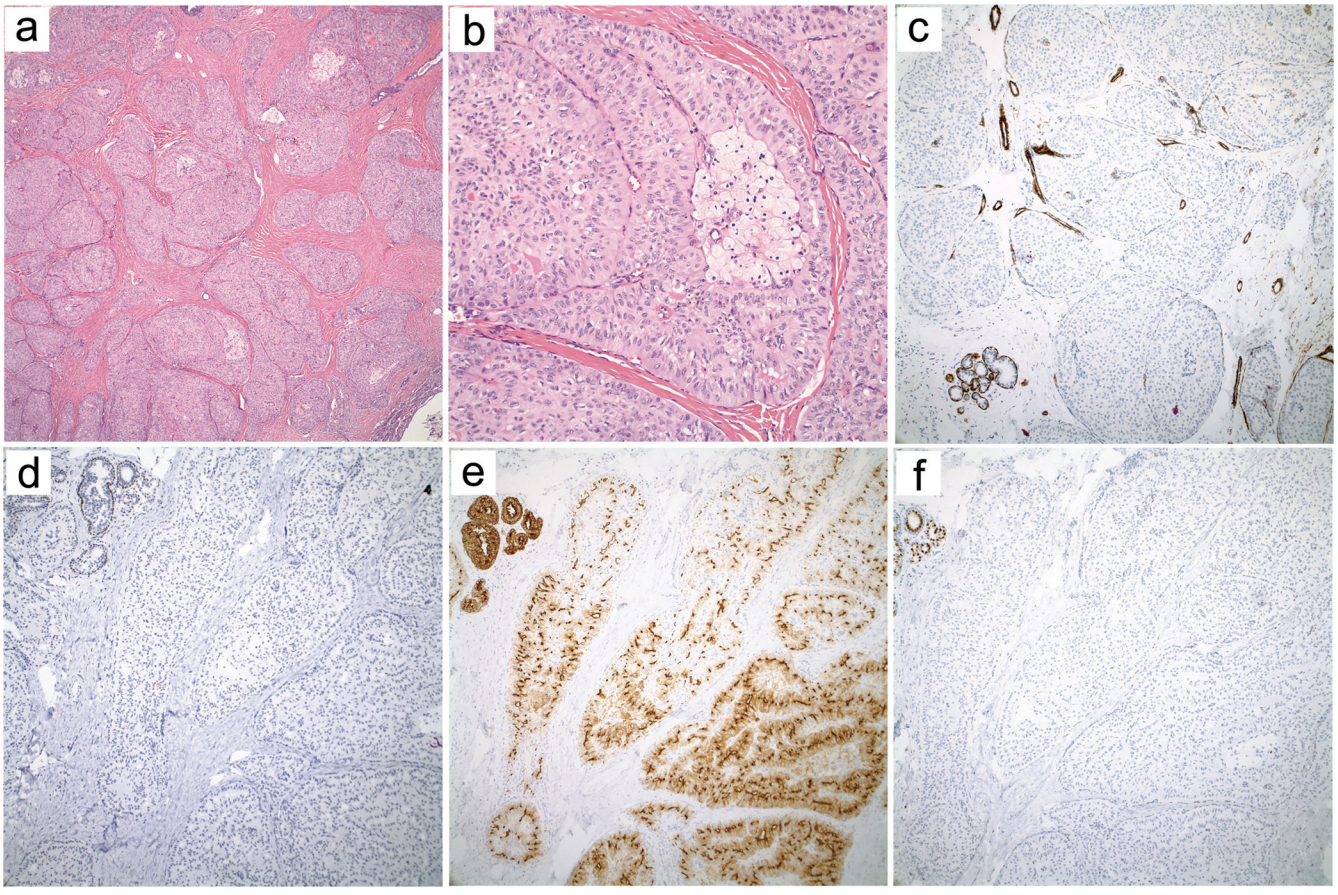

Fig. 6. Tall cell carcinoma with reversed polarity. (a, b) Tall cell carcinoma with reversed polarity of the nuclei. i.e., the nuclei are located on the apical rather than the basal aspect of the cells. Note the haphazard distribution of columnar tumor cells nests, many of which contain fibrovascular cores. SMMS (c) and p63 (d) immunostaining demonstrates the absence of myoepithelial cells around the columnar tumor cell nests. Tumor cells are positive for mucin 1 (e), but negative for ER (f). b, ×20; others, ×10.

mediate nuclear pleomorphism with rare mitoses. However, the high-grade tumor component may present with a solid tumor nest, prominent nuclear pleomorphism and numerous mitoses.

ACC of the breast shows serous differentiation with a positive immunohistochemical staining for amylase, lysozyme, and α-1 antichymotrypsin. EMA, myoepithelial markers (including S-100), and low molecular weight CKs are usually positive. CK7 may be focal or weak. Granules are PAS+ diastase resistant. GCDFP-15 may be positive.

Differential diagnosis includes ACCs of salivary gland origin and lactating lobule. Lactating lobule demonstrates benign morphology and positive staining for lysozyme. The presence of intact basal lamina in micro glandular adenosis helps differentiate this entity from ACC of the breast. ACC is usually negative for GATA3 and TRPS1 (Fig. 7).[20]

The genomic alterations in this tumor are similar to those seen in the conventional TNBCs of no specific types. The most common encountered alterations include mutations in tumor protein 53 (*TP53*), phosphatidyl-inositol 3 kinase CA *(PIK3CA),* lysine(K)-specific methyltransferase 2D (*KMT2D*), erb-B2 receptor tyrosine kinase B4 (*ERBB4/ERBB3*), nebulin (*NEB*), breast cancer gene 1 (*BRCA1*), mammalian target of rapamycin (*MTOR*), catenin beta 1 (*CTNNB1*), inositol polyphosphate-4-phosphatase type IIB (*INPP4B*), and fibroblast growth factor receptor 2 (*FGFR2*).[67,68] Recently, it has been suggested that ACC of the breast may be related to microglandular adenosis (MGA). Both lesions consistently express S-100 protein and are negative for ER/PR. More importantly, ACC frequently shows an MGA-like growth pattern. Indeed, molecular studies revealed that *TP53* was the sole highly recurrently mutated gene in both MGA and ACC. Both tumors were genetically distinct from hormone receptor-positive or HER2-positive breast carcinomas.[67]

The differential diagnosis of ACC includes secretory carcinoma and granular cell tumor. All tumors show some degree of similar morphologic features and are positive for S-100 protein. As discussed before, secretory carcinoma is also a low-grade TNBC. However, it is often composed of microcysts, tubules, acini and/or solid islands with characteristic abundant eosinophilic materials intracellularly and/or extracellularly. A granular cell tumor is a benign tumor and occasionally occurs in the breast. Morphologically, it is composed of large, polygonal cells with central small bland nuclei and abundant, eosinophilic, and granular cytoplasm. Granular cell tumor cells are also positive for CD68 and express nuclear staining of transcription factor E3 and melanocyte-inducing transcription factor, but are negative for CKs.

The prognosis of ACC remains questionable due to limited available literature reviews on the follow-up of this tumor. According to WHO classification, ACC is classified as TNBC with intermediate aggressive potential. Although ACCs of the breast are generally triple negative, most reported ACCs of the breast are low histologic grade and demonstrate a favorable outcome. However, recent studies have suggested that a subgroup of ACCs of the breast with high-grade tu-

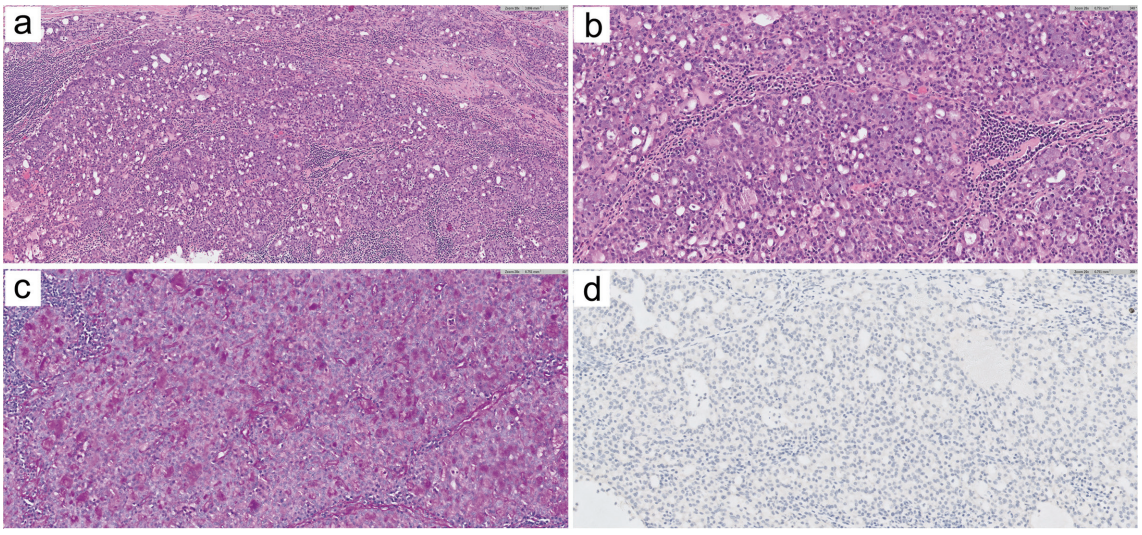

Fig. 7. Acinic cell carcinoma of the breast. (a) Tumor nests with acinar or glandular structures growing in diffuse infiltrative patterns. (b) Tumor cells are characterized by monotonous round cells with a finely granular, weakly eosinophilic, or clearly vacuolated cytoplasm resembling acinic cells of the salivary glands. Tumor cells show diffuse periodic acid-Schiff (c) positivity, but negative for ER (d). a, ×10; others, ×20.

mor components (solid tumor nest, prominent nuclear pleomorphism and numerous mitoses) have poor outcome.[69,70]

Low-grade mucoepidermoid carcinoma of the breast

MEC of the breast is an invasive carcinoma composed of mixed components of mucoid, epidermoid (squamoid), and intermediate cells similar to its resemblant counterpart in the salivary glands.[71] MEC of the breast is exceedingly rare and often affects middle-aged to elderly women.[72] Imaging studies may reveal a unilateral benign-looking nodule with a cystic component.

Histologically, MEC of the breast may show various patterns ranging from low to high grade. The majority of MECs of the breast are low grade, which usually present as cystic lesions and are composed of mucoid, epidermoid, and basaloid cells. Mucoid cells usually line the cystic spaces but may be dispersed within the epidermoid or intermediate cells. High-grade MEC is predominantly composed of solid sheets of epidermoid cells with minimal mucocytes. High-grade MEC shows highly atypical cells in both glandular and epidermoid components with nuclear atypia, high mitotic figures, and the presence of necrosis. The intermediate grade has been rarely reported. True keratinization is not present in MEC. When present, other diagnoses such as adenosquamous carcinoma should be considered (Fig. 8).

MEC of the breast is usually triple negative for ER, PR, and HER2. Each cell type component can be highlighted by immunostains. Mucoid cells are positive for low molecular weight CKs such as CK7, while high molecular weight CKs such as CK5, CK14, and p63 can highlight the epidermoid and basaloid cells.[73] Similar to its analogue in the salivary glands, low-grade MEC of the breast harbors a t(11;19)(q21;p13) translocation resulting in genetic fusion of mas-

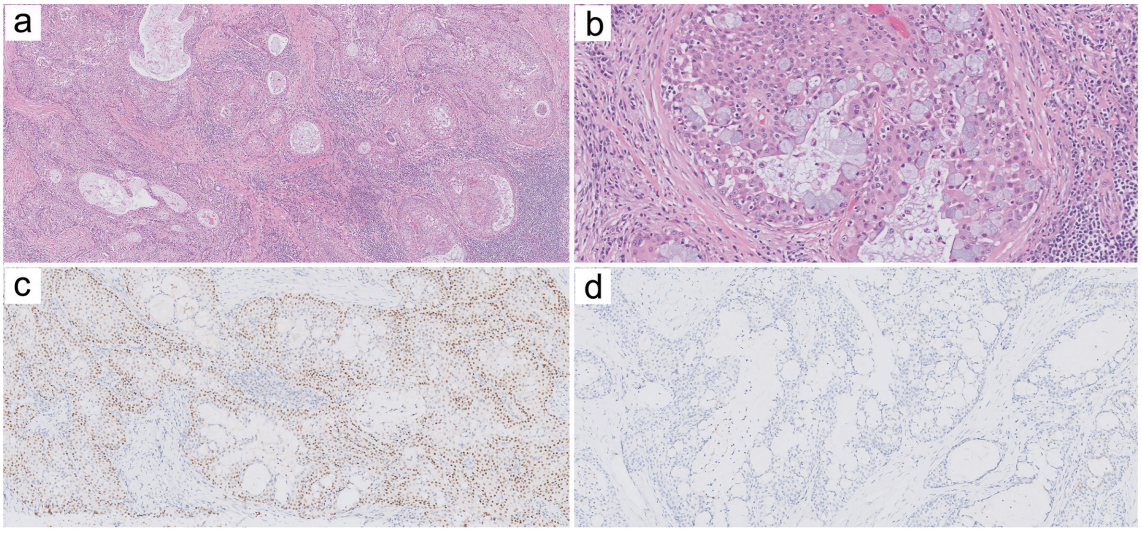

Fig. 8. Low grade mucoepidermoid carcinoma. (a, b) Tumor nests with glandular structures growing in diffuse infiltrative patterns. Tumor nests are composed of mixed squamoid, mucocytes and intermediate cells. Tumor cells are positive for p63 (c), but negative for ER (d). b, ×20; others, ×10.

termind-like transcriptional coactivator 2 (*MAML2*) and creb-regulated transcriptional coactivator 1 (*CRTC1*).[74] In addition, partial deletion of 11q21 (*MAML2*) has been found in MEC of the breast.[75]

Low-grade MECs may need to be differentiated from their counterparts of salivary gland origin, intraductal papilloma of the breast, adenomyoepithelioma, low-grade adenosquamous cell carcinoma, and clear cell hidradenoma (CCH). Both intraductal papilloma and adenomyoepithelioma may show similar morphologic features to low-grade MEC; however, both should demonstrate surrounding myoepithelial cells. The preservation of myoepithelial cell markers can help in diagnosing intraductal papilloma and adenomyoepithelioma. True keratinization with squamous pearls is not seen in low-grade MEC but can be present in low-grade adenosquamous cell carcinoma. In addition, low-grade adenosquamous cell carcinoma lacks mucoid cells, usually present in low-grade MEC. CCH is not a true breast parenchyma tumor rather it is a benign adnexal tumor with eccrine gland differentiation. However, it can be included in the differential diagnosis of low-grade MEC, when occurring near the skin. In addition, although CCH usually occurs in the nipple or subareolar region, it may arise in the deep breast tissue.[76] CCH is usually composed of predominantly clear cells, although it may occasionally show squamoid, mucinous, oncocytic, and epidermoid cells. Duct-like cystic spaces and glandular structures can be seen in CCH. *MAML2* gene rearrangement has been reported in some CCH cases,[77] thus should not be used to differentiate these two entities.

The prognosis of MEC of the breast is dependent on the histological grading. High-grade MECs are associated with unfavorable prognosis, distant metastasis and poor clinical outcomes, while low-grade MECs have a good prognosis. Adjuvant chemotherapy is usually not indicated in low-grade MEC patients.

Conclusions

TNBCs are a heterogeneous group of breast carcinomas with diverse clinicopathologic characteristics, histological types, genetic alterations, and clinical outcomes. TNBCs are often considered aggressive breast carcinomas with high histological grade, poor prognosis, and requirement for systemic chemotherapy. Low-grade TNBCs are uncommon but represent a distinct group of TNBCs with favorable prognosis and indolent clinical course. These tumors are usually managed with unique treatment modalities different from TNBCs of no special type. We have reviewed these low-grade TNBCs, emphasizing the morphological features, diagnostic criteria, molecular alterations, and differential diagnosis. It is essential to recognize these low-grade special types of TNBCs to guide therapeutic modalities.

Acknowledgments

None.

Funding

None.

Conflict of interest

Dr. Zaibo Li and Dr. Yihong Wang are editorial board members of *Journal of Clinical and Translational Pathology*. Dr. Zaibo Li is a consultant for PathAI and served as Chinese American Pathologists Association Treasurer. The other authors have no conflicts of interest related to this publication.

Author contributions

NS, QD, YW and ZL contribute to manuscript writing and critical revision. All authors have made a significant contribution to this study and have approved the final manuscript.

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