Metaplastic Breast Carcinoma Revisited; Subtypes Determine Outcomes

Comprehensive Pathologic, Clinical, and Molecular Review

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KEYWORDS

• Metaplastic carcinoma • Triple-negative breast cancer • Histologic subtype
• Spindle cell lesion • Immunohistochemistry • Immunotherapy • Molecular subtypes
• Diagnostic algorithm

KEY POINTS

- Metaplastic breast carcinoma (MpBC) is a heterogeneous group of tumors that clinically could be divided into low risk and high risk.
- It is important to recognize the different types of MpBC, as the high-risk subtypes have worse clinical outcomes than triple-negative breast cancer.
- Spindle cell lesion of the breast has a wide range of differential diagnoses. It is important for the pathologist to be aware of the MpBC entities and use the herein proposed algorithms to assist in the diagnosis.
- Metaplastic breast carcinoma has less response rate to the traditional chemotherapy (adjuvant or neoadjuvant) than the other types of breast cancer.
- Few options of target therapies and immunotherapy are available for the patients with MpBC.

OVERVIEW

The name origin of metaplasia is from the Greek verb *metaplasein*, which means "change in form." It is the transformation from one differentiated cell type to another differentiated cell type. Metaplastic breast carcinoma (MpBC) is a heterogeneous group of tumors that have only one thing in common. The tumor cells transformed

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from the benign mammary cell (epithelial or myoepithelial) to a cell type with malignant properties such as squamous cell, chondroid cells, and so forth. These tumors have more differences than similarities, including the morphology, the biology, and more importantly the prognosis and therefore the management.

The World Health Organization (WHO) classified these tumors into 5 subtypes: low-grade adenosquamous carcinoma (LGASC), fibromatosis-like metaplastic carcinoma (FLMC), squamous cell carcinoma (SqCC), spindle cell carcinoma (SpCC), and metaplastic carcinoma with heterologous mesenchymal differentiation (MCHMD). When a tumor has mixed components, it is designated as mixed metaplastic carcinoma (MMC).[1] In this review, the following subjects are going to be discussed: the histomorphologic features of each subtype, a proposed approach to spindle cell lesions detected in a core needle biopsy (CNB) with the differential diagnosis and the immunohistochemistry (IHC) workup, the molecular alterations, tumor microenvironment, and up-to-date target therapy and immunotherapy.

PATHOLOGY

Histologic Subtypes

Low-Grade Adenosquamous Carcinoma

The LGASC is an ill-defined tumor with infiltrating borders, composed of a mixture of infiltrating neoplastic glandular and squamous structures, all present in the background of sclerotic or desmoplastic stroma with bland nuclear morphology.[2] The glandular component usually reveals well-developed glandular and tubular formations with minimal, if any, angulation, unlike tubular carcinoma. The squamous component varies from extensive epidermoid growth, syringoma-like differentiation, and isolated small clusters and solid nests.[3] The overall nuclear grade is low with minimal, if any, mitotic figures. Aggregates of lymphocytes located within or at the periphery of the tumor having "Cannonball"-like configuration can also be encountered[1] (**Fig. 1**A, B). These tumors are usually negative for myoepithelial markers.[4] However, p63 stains the squamous component with nonmyoepithelial-like diffuse staining pattern. Therefore, other myoepithelial markers are required to confirm the invasive nature of the tumor (**Fig. 1**C–E). The radiologic imaging (mammography or ultrasound) of LGASC is nonspecific with the mammography usually demonstrating ill-defined infiltrating lesion (**Fig. 1**F).

Fibromatosis-Like Metaplastic Carcinoma

The FLMC, as the name implies, has similar histologic morphology to breast fibromatosis. FLMC may show epithelioid or squamous cell differentiation and may have ductal carcinoma in situ (DCIS). When these histologic features are absent, IHC staining with epithelial markers (cytokeratin [CK] and p63) can be helpful to differentiate between these 2 lesions (**Fig. 2**).[5,6] The tumor cells are spindle and bland with rare, if any, mitotic figures, arranged in a wavy, interlacing fascicle or long fascicle with fingerlike extensions infiltrating the adjacent breast tissue. The tumor has infiltrating borders with a background of varying degrees of collagenization.[1] FLMC and SpCC are spectrum of the spindle cell neoplasm with substantial difference in the outcomes and treatment. Some cases could pose a challenge for the pathologist to classify. The degree of nuclear atypia, the mitotic count, and percentage of spindle cell component seem to help subclassify these tumors.[7–10] In the author's opinion, when in doubt, the case should be discussed in a multidisciplinary approach.

Squamous Cell Carcinoma

Primary breast SqCC could be pure, mixed with invasive carcinoma of no special type (NST) (high-grade adenosquamous carcinoma) or metaplastic carcinoma with

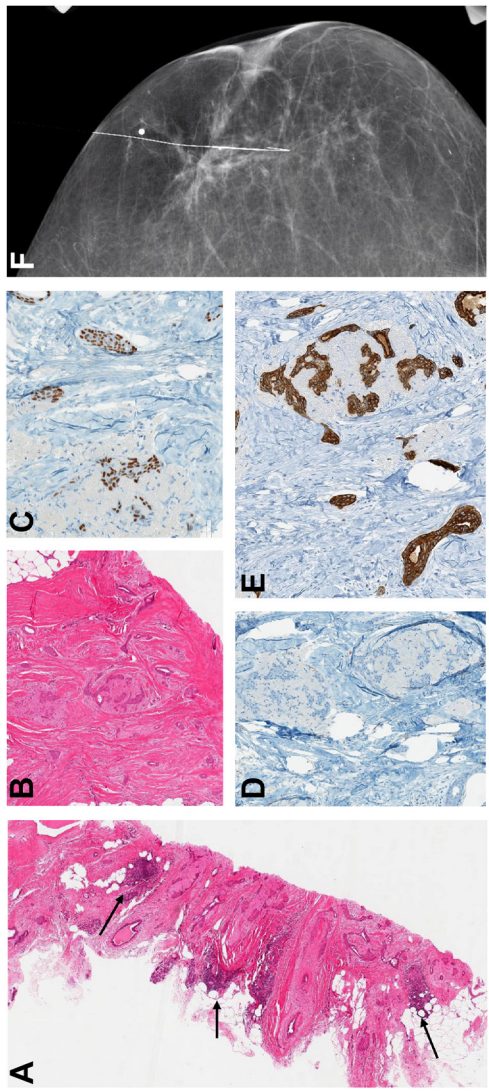

Fig. 1. Low-grade adenosquamous carcinoma. (*A*) Scanning magnification of core biopsy showing infiltrating epithelial neoplasm within a background of dense stroma; note the aggregates of lymphocytes at the periphery of the tumor (*arrows*) (H&E); (*B*) higher magnification image showing both components of infiltrating glandular and squamous clusters of cells in a background of sclerotic and desmoplastic stroma (H&E, 4x); (*C*) p63 staining showing diffuse nonmyoepithelial-like staining pattern (10x); (*D*) smooth muscle myosin image showing lack of myoepithelial cell layer in both squamous and glandular components, confirming invasion (5x); (*E*) cytokeratin 5/6 image showing diffuse staining in both the squamous and glandular components (10x); (*F*) mammography image showing ill-defined infiltrating tumor in the upper part of the breast.

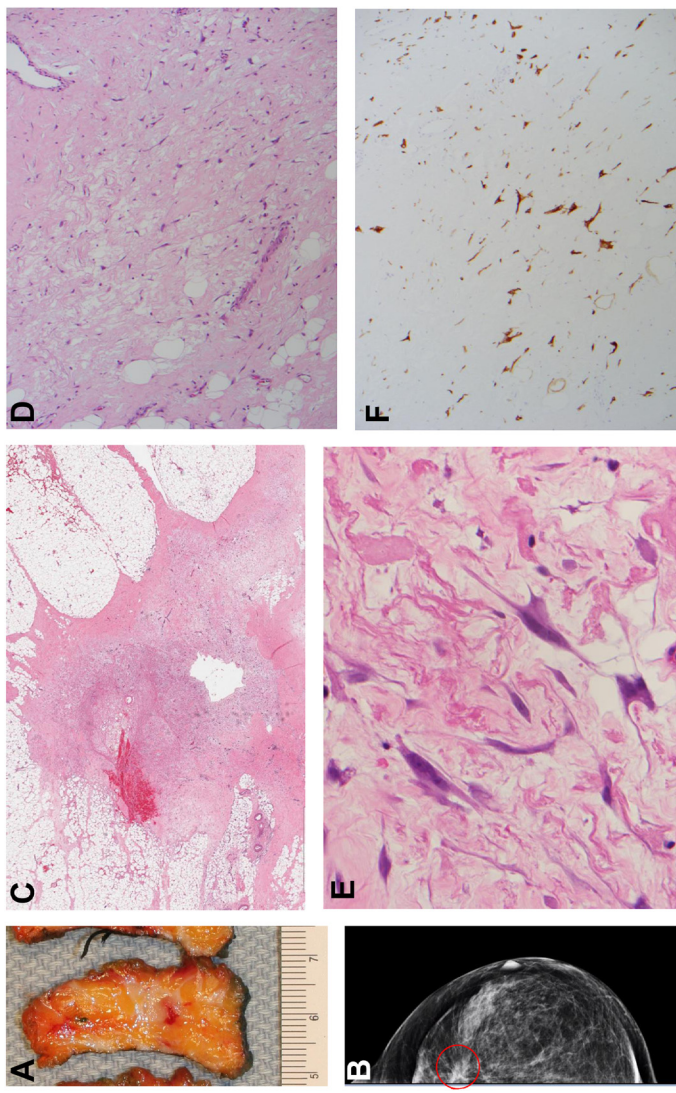

Fig. 2. Fibromatosis-like metaplastic carcinoma. (*A*) Gross image showing white fibrotic infiltrating lesion; (*B*) mammography showing irregular deeply seated lesion in the upper half of the breast; (*C*) scanning magnification of the tumor showing infiltrating fingerlike projections into the surrounding adipose tissue, corresponding to the gross image (H&E); (*D*) high power magnification showing infiltrating bland spindle cells with background of collage fibers (20x, H&E); (*E*) occasional intermediate to high atypical nuclei (60x, H&E); (*F*) pancytokeratin (AE1/3) IHC stain decorating the tumor cells (20x).

pseudoangiomatous acantholytic pattern. Moreover, SpCC could have a component of squamous differentiation. Pure SqCC usually presents as cystic mass lined up with squamous cells with varying degrees of differentiation. The periphery of the tumor shows infiltration into the surrounding stroma in forms of sheets, cords, or nests (Fig. 3). Some investigators classify this tumor separately from MpBC.[11] It is important to correlate with the clinical presentation, in order to rule out skin-based SqCC, or more importantly metastatic SqCC, from other organs such as lung. High-grade adenosquamous carcinoma is composed of 2 components, adenocarcinoma (ductal) and carcinoma with squamous differentiation. They are usually intermingled and difficult to appreciate the morphologic difference. Therefore, this entity is underrecognized (Fig. 4). The squamous component varies in proportion with a spectrum of differentiation ranging from mature keratinizing epithelium to spindle cell or with pseudoangiomatous growth pattern. Metaplastic carcinoma with pseudoangiomatous acantholytic pattern has distinctive histologic architecture with closed or interconnected irregular spaces lined with atypical malignant squamous cells (Fig. 5). Some investigators classify this entity under SpCC.[3] It is important to recognize this entity, as the differential diagnosis includes angiosarcoma.[12] IHC staining can be helpful, as the tumor is usually positive for one of the CK stains (high-molecular-weight or CK5) and negative for CD34.[13]

Spindle Cell Carcinoma

The SpCC or carcinosarcoma is a spectrum of spindle neoplastic disease with varying degrees of nuclear atypia, growth patterns, and differentiation. As the name implies, the tumor has spindle cell morphology with epithelioid differentiation (Fig. 6A). The tumor could be pure spindle cell (Fig. 6B) or mixed with ductal (Fig. 6C), or squamous differentiation/metaplasia (Fig. 6D). To differentiate this tumor from the less aggressive tumor FLMC, the tumor must have intermediate or highly atypical nuclei, easily identifiable or brisk mitotic figures. The other differential diagnosis is primary or metastatic sarcoma (fibrosarcoma) when the tumor has a fascicular growth pattern (see Fig. 6B).[14,15] Sarcoma (primary or metastatic) is treated differently from SpCC, making the distinction clinically essential. SpCC also could have variable growth pattern in which the fascicles are long, herringbone, or interwoven (see Fig. 6B), to short and storiform (Fig. 6E).[10,14,16] Presence of DCIS (Fig. 6F),[10] epithelioid cells (see Fig. 6A), and/or expression of one of the epithelial markers favors SpCC (see

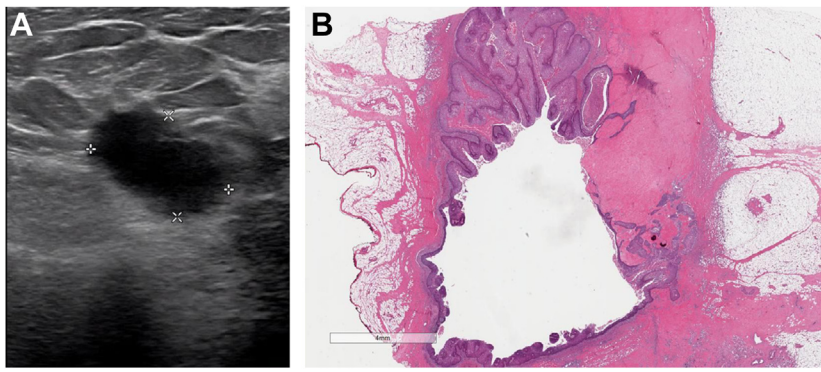

Fig. 3. Pure SqCC. (*A*) Ultrasound showing hypoechoic complex cystic and solid mass with irregular margins and some thick internal septations; (*B*) scanning magnification showing cystic formation lined up with well-differentiated SCC (H&E).

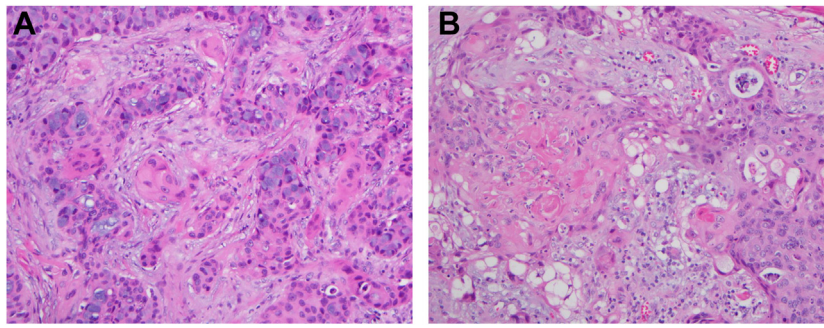

Fig. 4. Adenosquamous carcinoma. (*A*) Adenocarcinoma with intracellular mucin production intermingled with SCC (H&E, 10x); (*B*) SCC component with better differentiation (H&E, 10x).

Fig. 6E, inset). When spindle cell lesion of the breast is encountered in a CNB, MpBC diagnosis should be on the top of the differential diagnosis (see later discussion).

Metaplastic Carcinoma with Heterologous Mesenchymal Differentiation

The MCHMD, also known as heterologous metaplastic carcinoma,[3] are mixed epithelial/mesenchymal variants of metaplastic carcinoma with chondroid or osseous

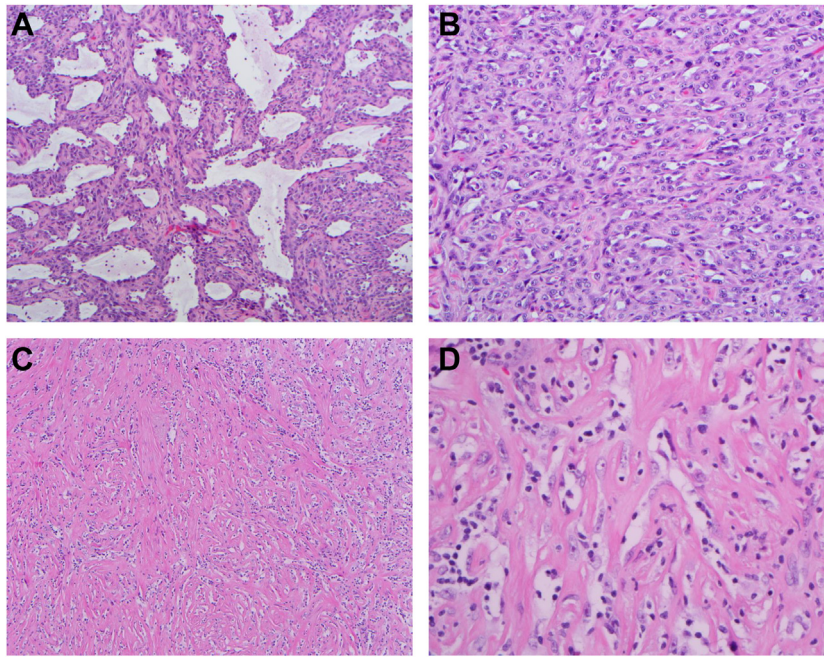

Fig. 5. SqCC acantholytic pseudoangiomatous pattern. (*A*) Dilated partially interconnected staghorn-like spaces and pseudoangiomatous growth pattern (H&E, 10x); (*B*) other areas may show only pseudoangiomatous growth pattern mimicking high-grade angiosarcoma (H&E, 20x); (*C*) another case showing collagenous background mimicking pseudoangiomatous stromal hyperplasia (H&E, 10x); (*D*) with intermediate-grade nuclear atypia (H&E, 40x).

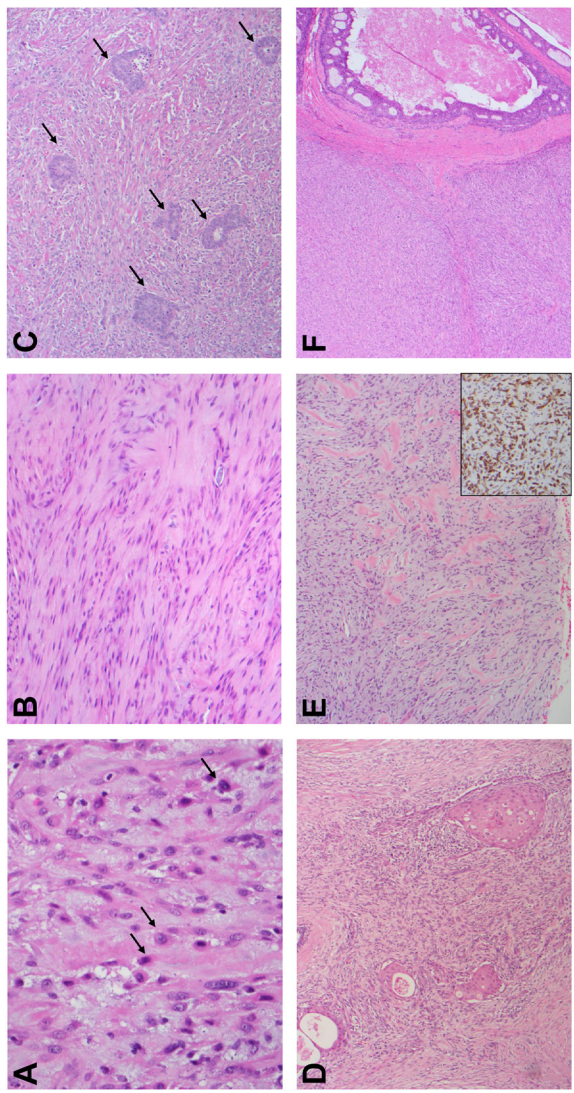

Fig. 6. SpCC. (*A*) Spindle cells with epithelioid morphology (*arrows* indicate epithelioid cells, H&E, 40x); (*B*) pure spindle cell with long sweeping fascicles (H&E, 20x); (*C*) mixed with ductal carcinoma of no special type, resembling malignant adenomyoepithelioma but lacks myoepithelial staining (*arrows* indicate ductal component, H&E, 10x); (*D*) mixed with SqCC (H&E, 10x); (*E*) pure spindle cell with short storiform fascicles (H&E, 10x; inset pancytokeratin AE1/3 staining 10x); (*F*) SpCC with DCIS (H&E, 4x).

differentiation.[17] The hallmark of these tumors is having heterologous elements, including chondroid, osseous, rhabdoid, or neurologic differentiation (Fig. 7A, B).[1] The other component of the tumor could be glandular, tubular, or squamous (Fig. 7C, D).[14,18,19] These components (heterologous elements and conventional breast carcinoma) could have either an abrupt transition or intervening zones of spindle cell metaplasia (Fig. 7C–E). In some cases, the tumor is completely composed of the heterologous elements with no epithelial differentiation. These tumors pose a challenge differentiating it from primary or metastatic sarcoma (osteosarcoma, chondrosarcoma, rhabdomyosarcoma). The only way of making the diagnosis is the positive staining of epithelial markers favoring carcinoma. In some instances, however, the definitive diagnosis might not be possible.

Mixed Metaplastic Breast Carcinoma

The MMC is defined as a carcinoma with a mixture of different histologic elements including various metaplastic components (SqSS, SpCC, MCHMD) or any of these elements and conventional breast carcinoma such as NST and lobular, among others (see Fig. 4A, B, 6C, D, 7D, Fig. 8). Because MpBCs have worse clinical outcomes than conventional breast carcinoma (see later discussion), it is recommended to report it as metaplastic carcinoma and mention the distinct conventional carcinoma components.[1] In the author's opinion, a percentage of each component should be mentioned when possible.

Some investigators classify carcinoma with multinucleated giant cells resembling osteoclasts and carcinoma with choriocarcinomatous morphology as MpBC.[3] However, these tumors are currently reclassified by the WHO under invasive breast carcinoma NST with special morphologic patterns.[1]

Unusual Clinical and Pathologic Presentation

Metaplastic Carcinoma Arising Within Complex Sclerosing Lesions

There are a few reports of complex sclerosing lesions (sclerosing papilloma and nipple adenoma) associated with metaplastic carcinoma.[20–23] In the largest series of 33 cases reported by Gobbi and colleagues, most of the cases had dominant spindle cell component with various degrees of atypia, with the majority having fibromatosis-like or low-grade morphology. Squamous metaplasia and low-grade glandular elements are common features (Fig. 9). DCIS and invasive mammary carcinoma could be seen but less common. Ten cases stained with IHC markers, all showing expression of at least one of the CK markers (HMW-CK, AE1/3, or CK7).[23] This entity is very important to recognize, as it can easily be overlooked when evaluating complex sclerosing lesions.

Approach to Spindle Cell Lesions of the Breast Detected in a Core Biopsy

Because MpBC is a major differential diagnosis for spindle cell lesions detected in a CNB, the author herein presents a short summary of the differential diagnosis and pitfalls and recommends histologic and IHC algorithmic approaches.

For histomorphology, first look for specific morphology such as epithelium (intimately admixed or separately coexisted) or vascular spaces. If the tumor is composed of pure spindle cells, evaluate the nuclear atypia. In this situation, clinical history of trauma or prior malignancy could be helpful. For imagining the borders of the tumor, well-defined versus infiltrative could narrow down the diagnosis (Fig. 10).

The IHC staining should be used in the context of the clinical and histologic findings; otherwise, they could be misleading. Identifying the cell lineage is the key in the IHC approach (epithelial, vascular vs other). First and foremost, MpBC should be at the

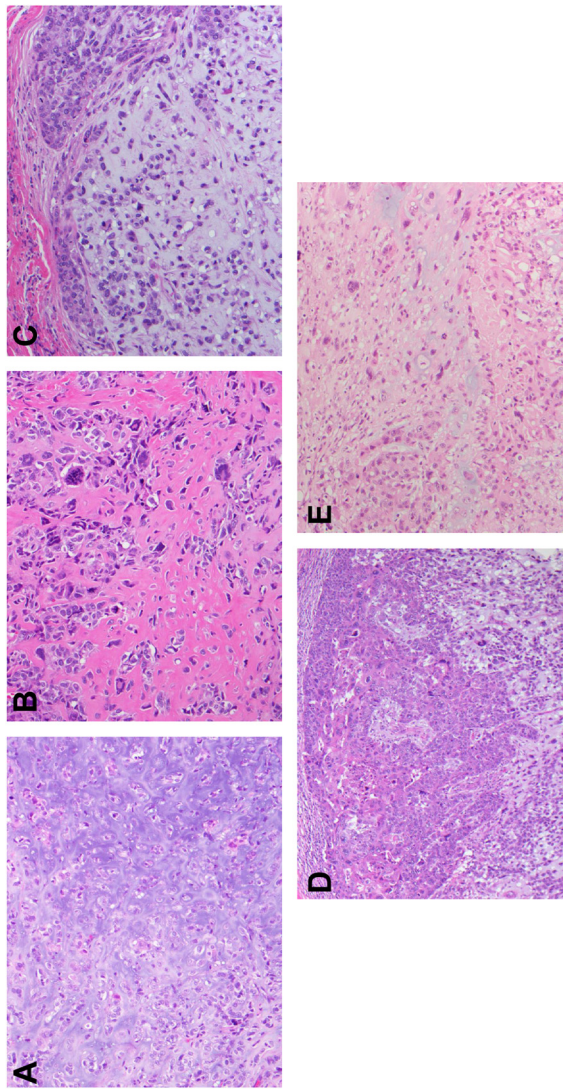

Fig. 7. MCHMD. (*A*) Matrix producing (chondroid) (H&E, 20x); (*B*) matrix producing (osteoid) (H&E, 20x); (*C*) carcinomatous (no special type) area at the periphery, note abrupt transition (H&E, 20x); (*D*) carcinomatous (squamous) area at the periphery, note abrupt transition (H&E, 20x); (*E*) zones of spindle cell metaplasia intervening between the carcinomatous and chondroid component (H&E, 20x).

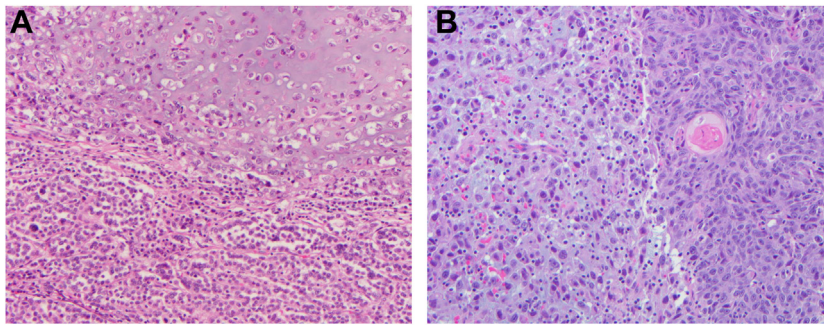

Fig. 8. Mixed metaplastic carcinoma. (*A*) MCHMD-chondroid (upper half) and lobular carcinoma (lower half) (H&E, 20x); (*B*) mixed MCHMD-chondroid (left) and SqCC (right), note the squamous pearl (H&E, 20x).

top of the differential diagnosis, and the stains should aim to rule it in or out. The most commonly used epithelial stains are AE1/3, MNF-116, HMW-CK, CK5/6, and p63.[10,24] Diffuse and strong staining patterns are usually encountered in MpBC (**Fig. 11**).

Pitfalls

- Atypical cells may be seen in benign entities such as nodular fasciitis and biopsy site, whereas some malignant entities could have bland cells such as FLMC.[1]
- It has been reported and it is in the author's experience that focal staining for keratin and p63 markers could occur in MpBC and non-MpBC tumors such as sarcoma and phyllodes tumor (PT).[25,26]
- β-catenin in PT and MpBC: Lacroix-Triki reported that all fibromatosis cases, 23% of MpBC, and 57% of PT (benign and malignant) expressed nuclear beta-catenin. However, β-catenin is usually focal when stains MpBC.[27] The author came across a case of a woman whose breast CNB had MpBC but mistakenly diagnosed as fibromatosis based on the expression of β-catenin and misinterpretation of CK stain. She presented 6 months later with double the size of the tumor. Therefore, β-catenin should be interpreted with caution in the context of the rest of the clinical and histologic findings.

MOLECULAR ALTERATIONS AND TARGET THERAPY

MpBC is usually triple-negative (estrogen receptor [ER] negative/progesterone receptor [PR] negative/HER-2/neu negative).[1,28–31] Intrinsic gene profiling classified these tumors under basal-like or claudin-low.[32,33] Further subclassification of these tumors grouped them under mesenchymal-like molecular subtype of triple-negative breast cancer (TNBC) as proposed by Lehmann and colleagues.[34] There have been many studies performed to elucidate the molecular alterations of these tumors in order to identify actionable genetic changes for potential targeted therapeutic intervention. The gene mutations are detailed in a review by González-Martínez and colleagues.[35] They reviewed 14 series with a total of 539 molecularly characterized tumors.[36–49] *TP53* was the most common mutation, followed by *PIK3CA*. *MYC* was the most amplified gene followed by *EGFR*. The most common gene loss was *CDKN2A/CDKN2B* locus (**Table 1**). There are limited data on MpBC in proper with regard to the effect of the target therapy on the actionable genes. Often, they are combined with TNBC clinical trials. However, in breast cancer in general, these monoclonal antibodies could be classified into tiers I to V and X based on the strength of the clinical evidence as

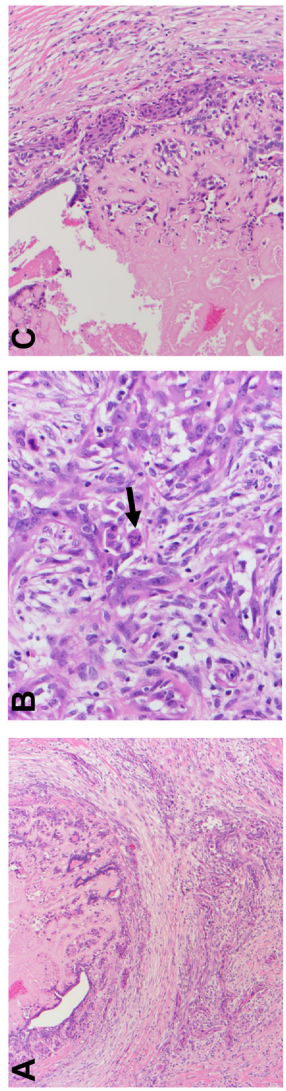

Fig. 9. Metaplastic carcinoma arising within complex sclerosing lesion. (*A*) Sclerosing lesion with infiltrative epithelioid cells (H&E, 4x); (*B*) plump fusiform and polygonal atypical tumor cells with rounded nuclei and prominent nucleoli (*arrow* indicates atypical mitotic figure) (H&E 40x); (*C*) squamous metaplasia at the periphery of the papilloma (H&E, 10x).

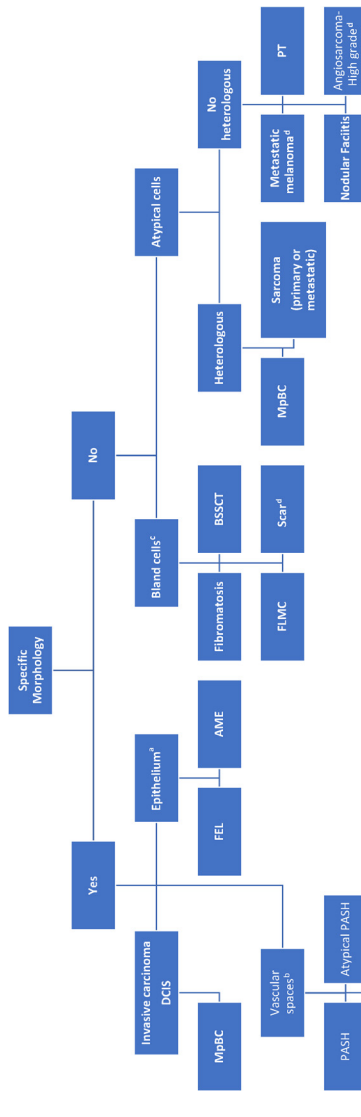

Fig. 10. Suggested algorithm of spindle cell lesion detected in core needle biopsy. [a]FEL and AME: both epithelium and stromal growths separately coexist with different proportions (AME: the spindle cells are predominantly myoepithelial). [b]IHC: CD31 positive in angiosarcoma and negative in PASH. [c]BSSCT: well-defined borders by imaging, whereas fibromatosis, FLMB, and scar: ill-defined infiltrative. [d]Scar: history of recent trauma; metastatic melanoma and metastatic sarcoma: history of the diseases; angiosarcoma: history of radiation therapy. AME, adenomamyoepithelioma; BSSCT, benign stromal spindle cell tumor (includes myofibroblastoma, spindle cell lipoma, solitary fibrous tumor); FEL, fibroepithelial lesion; FLMC, fibromatosis-like metaplastic carcinoma; MpBC, metaplastic breast carcinoma; PASH, pseudoangiomatous stromal hyperplasia; PT, phyllodes tumor.

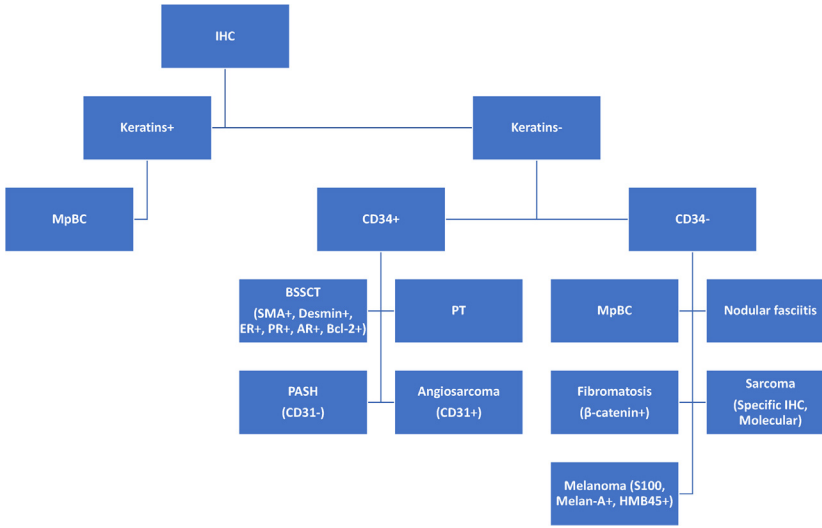

Fig. 11. Suggested IHC algorithm of spindle cell lesions detected in core needle biopsy. Keratin stains and CD34 are the major markers that can narrow down the diagnosis. Additional stains such as CD31 could be helpful. The rest of IHC should be used based on the histologic and clinical suspicion (eg, β-catenin for fibromatosis, melanoma markers, and so forth). BSSCT, benign stromal spindle cell tumor; IHC, immunohistochemistry; MpBC, metaplastic breast carcinoma; PASH, pseudoangiomatous stromal hyperplasia; PT, phyllodes tumor.

explained by Condorelli and colleagues.[50] Sporadic case reports and small clinical trials have been published illustrating variety of therapeutic approaches. The author and his colleagues reported a case of a metastatic MpBC with osseous differentiation and *BRCA1* mutation who had a marked response to liposomal doxorubicin.[51] A phase I trial on 59 patients with metastatic MpBC treated with liposomal doxorubicin, bevacizumab, with either temsirolimus or everolimus, revealed an objective response rate of 21%. All 4 patients who achieved a complete response had a mutation in the *PI3K* pathway.[52] Another observation is that MpBC patients should be tested for *BRCA* germline mutations. In addition to the benefit from adding platinum agents, they are more susceptible to Poly (ADP-ribose) polymerase inhibitors.[53]

This diverse molecular profile reflects, in part, the diversity of the histologic subtypes of MpBC. However, when dissecting through the studies, variation could be appreciated among the MpBC subtypes (SpCC, SqCC, MCHMD). SqCC and MCHMD had more frequent *TP53* mutation, whereas *PIK3CA* alterations were more frequent in SpCC.[36,46] *TERT* alteration was seen in SpCC and SqCC but not in MCHMD.[42] When MpBC was compared with non-MpBC-TNBC, the former had more *PIK3CA* alteration and less *TP53* alteration. It is worth noting that these studies focused on high-grade tumors excluding FLMC and LGASC.

TUMOR MICROENVIRONMENT AND IMMUNOTHERAPY

With the advancement of immunotherapy, few studies investigated the immune microenvironment of MpBC. Two monoclonal antibodies have been approved by the Food and Drug Administration to treat locally advanced and metastatic TNBC expressing PD-L1 with TECENTRIQ (atezolizumab) or KEYTRUDA (pembrolizumab). The corresponding IHC assays are clone SP142 and 22C3, respectively.[54,55]

Table 1
Molecular alteration in metaplastic carcinoma

Mutation	
Gene	**Frequency (%)**
TP53	58.7 (26–70)[a]
PIK3CA	32.8 (12–48)[a]
TERT	25
PI3K/AKT Pathway	
PTEN	12.7
PIK3R1	11.2
NF1	9.8
HRAS	8.5
AKT1	—
WNT Pathway	
APC	5
FAT1	11
DNA Repair	
BRCA1	3–15
BRCA2	2–6
ATM	2–12
Chromatin Remodeling	
KMT2D	17
ARID1A	6
Copy Number Variation (CNV)	
Amplification	
MYC	17.3
EGFR	17.2
CCND1	8.4
CCNE1	5.9
CDK4	4
CCND3	15
CCND2	5
FGFR1	5
ERBB2	4.8
RAS	5
NF1	5
PIK3CA	5
SOX2	5
AKT3	5
Gene Loss	
CDKN2A/CDKN2B	19
PTEN	14.9
RB1	6.5

[a] Median (range).

Adapted from González-Martínez S, Pérez-Mies B, Carretero-Barrio I, et al. Molecular Features of Metaplastic Breast Carcinoma: An Infrequent Subtype of Triple Negative Breast Carcinoma. Cancers (Basel). 2020;12(7):1832. Published 2020 Jul 8. https://doi.org/10.3390/cancers12071832

Tumor infiltrating lymphocytes (TILs) and PD-L1 have been extensively studied in TNBC. However, only a few focused on MpBC. Lien and colleagues scored TILs in 82 MpBC and found that 34.1% had intermediate (>10% to 60%) or high TILs (>60%) (SqCC [50%], MMC [34.1%], SpCC [30.8%], and MCHMD [14.3%]). Multivariate analysis showed that high/intermediate TILs correlated with better survival.[56] Chao and colleagues also found high TILs density in SqCC compared with other subtypes. Interestingly, in mixed MpBC/NST, TILs were denser in MpBC component than in INST component. Overall, TILs, high CD4, and high CD8 had borderline significance in correlating with clinical outcomes. In SqCC, TILs had stronger correlation with outcomes.[57]

Lien and colleagues investigated the expression of PD-L1 (SP142) in MpBC and found that it is expressed in 72% of 82 cases. When different metaplastic components were compared, the rate of expression was highest in SqCC (61.1%) and MMC (52.9%) and lowest in the chondroid component (14.3% in both the MCHMD and MMC). PD-L1 positivity did not correlate with the outcomes.[56] Other studies included MpBC as part of TNBC or breast carcinomas of all types.[44,58]

It would be clinically relevant to investigate the role of TILs in the response to neoadjuvant chemotherapy, particularly with the recent call of deescalating the therapy in patients with TNBC.

TREATMENT

Adjuvant Therapy

Classic therapeutic approaches including adjuvant chemotherapy, surgery, and radiation therapy have been previously discussed, and it is beyond the scope of this review.[59,60]

It is worth noting here in this brief review of the adjuvant treatment that as the variation in the subtypes in terms of the histopathology and the prognosis, the treatment also varies. Although high-risk MpBC is treated with surgical removal and chemotherapy, low-risk tumors (eg, LGASC and FLMC) are treated with surgical removal alone unless presented with positive lymph node.[61] Tumors that have intermediate morphology between SpCC and FLMC must be managed in a multidisciplinary approach as mentioned earlier.

Neoadjuvant Therapy

There is also a dearth of studies examining the role of neoadjuvant chemotherapy in MpBC. It is long thought that MpBC do not respond well due to the epithelial mesenchymal transformation that is commonly seen in these tumors.[62,63] Three studies with 1, 12, and 21 cases, respectively, reported low rate of pathology complete response (pCR).[64–66] In the author's experience 2 of 6 patients achieved pCR. However, in a recent study by Han and colleagues who studied 29 patients, 5 (17%) achieved pCR, most of whom were MCHMD type.[67] Overall, the rate of response is lower than the nonmetaplastic TNBC.[68] However, all these studies are retrospective and have small number of cases, making it difficult to draw any conclusions.

PROGNOSIS

There are many limitations to the published studies that investigated the clinical behavior of MpBC. MpBC is heterogeneous in terms of its clinical behavior. More specifically, these tumors can be grouped into 2 categories: low risk that includes LGASC and high risk that includes SqCC, SpCC, and MCHMD. FLMC is a unique entity, as it has intermediate risk and is considered as part of the SpCC spectrum (see later

Table 2
Studies comparing the clinical outcome between metaplastic breast carcinoma and nonmetaplastic breast carcinoma (mostly triple-negative breast cancer)

Ref	Cases (No.)	Institution	Histologic Subtypes (%)	• Matching Criteria • No. Case-to-Case	DFS	OS	Multivariate Analysis	DFS (HR)	OS (HR)
Lester et al,[8] 2012	47	Single	SpCC (100)	• Age, stage, therapy (CT, RT) • One-to-one	MpBC > TNBC	Not calculated	Not calculated	Not available	Not available
Downs-Kelly et al,[18] 2009	32	Single	MCHMD (100)	• Age, stage, grade • One-to-two	MpBC > BC[a]	Not calculated	Not calculated	Not available	Not available
Jung et al,[77] 2010	35	Single	SqCC (60) MCHMD (11.4) SpCC (11.4) Mixed (14.3) LGASC (2.9)	• Grade • One-to-one	MpBC > TNBC	MpBC > TNBC	Yes	3.99	3.14
Luini et al,[78] 2007	37	Single	MCHMD (51.4) SpCC (8.1) Carcinosarcoma (24.3) SqCC (18.9) With osteoclastic giant cell (2.7)	• Grade, year of surgery, T-stage, N-stage • One-to-two	Not significant	MpBC > TNBC HR = 5.0	Not calculated	Not calculated	Not calculated
Lee et al,[79] 2012	67	Single	SqCC (52.2) SpCC (13.4) MCHMD (23.9) Mixed (7.5)[b]	• Stage • All cases	MpBC > TNBC	MpBC > TNBC	Yes	2.53	2.56
El Zein et al,[69] 2017	46	Single	MCHMD (37) SqCC (26.1) SpCC (30.4) Mixed (6.5)	• Age, stage, Nottingham grade, therapy (CT, RT) • One-to-one	MpBC > TNBC	MpBC > TNBC	Yes	1.99	Not significant
Beatty et al,[48] 2006	24	Single	SqCC (50) MCHMD (12.5)	• Date of diagnosis, age, tumor size,	Not significant	Not significant	No	Not calculated	Not calculated

			SpCC (25) Not stated (16.5)[c]	node status, ER, PR, and HER2 (all cases TNBC) • Three-to-one				
Rakha et al,[81] 2015	405	Multiinstitutional	SpCC (31.9)[d] SqCC (21.1) Mixed SpCC/SqCC (13.5) MCHMD (28.6) FLMC (4.9)	• Age, Nottingham grade, N-stage, ER and HER2 • 405–285	Not significant[e]	Not recorded	No	Not calculated	Not calculated
Li et al,[70] 2019	586	SEER	Not recorded	• Age, race, grade, AJCC stage, therapy (CT, RT) • One-to-three	MpBC > TNBC	MpBC > TNBC	Yes	1.42	1.36
Polamraju et al,[71] 2020	5142	NCDB (2004–2013)	Not recorded	• Age, race, insurance status, T-stage, N-stage, grade, Charlson Deyo Score, year of diagnosis, income, therapy (CT, HT, RT) • All cases	Not performed	MpBC > TNBC	Yes	Not calculated	1.48
Tadros et al,[80] 2021	132	Single	SpCC (19.7) SqCC (19.7) Mixed SpCC/SqCC (22.7) MCHMD (34.1)	• Age, year of surgery, type of surgery, T-stage, N-stage, • All cases	MpBC > TNBC	MpBC > TNBC	Yes	2.3	1.9

Abbreviations: DFS, disease-free survival; MpBC, metaplastic breast carcinoma; NCDB, National Cancer Data Base, OS, overall survival; SEER, Surveillance Epidemiology End Result; TNBC, triple-negative breast carcinoma.

[a] DFS (regional and distant).

[b] Two cases were not subtyped (see **Table 2**, Lee et al[79]).

[c] Cases do not add up to 100% (Beatty et al[48]).

[d] Only 364 cases had reported subtypes.

[e] Breast cancer–specific survival was calculated.

discussion). All published studies are retrospective. In the author's experience, defining MpBC is not always straightforward. For instance, in the author's published study, 28 of 81 (34.6%) reported MpBC were reclassified on review to carcinoma of NST.[69] Therefore, there is doubt about the studies that included large number of cases without pathologic review and verification.[66,70–72] On the other hand, studies with small number of cases lack statistical powers.

LGASC is largely indolent but locally aggressive. Rarely, the tumor develops lymph node or distant metastasis. In the largest series of 32 cases, the clinical outcome correlated with the tumor size.[73] FLMC is locally aggressive tumor and has the potential of distant metastasis. The risk of local recurrence could reach up to 44%.[74] Few studies reported the tumor could have potential to metastasize to other organ such as the lung,[10,75,76] although this tumor seems less aggressive than the SpCC. However, the histologic distinction between the 2 entities could be challenging. More studies are required to better define this entity, in order to better manage the patient and minimize the incidence of local or distant recurrence.

Overall, MpBC is an aggressive disease that presents as advanced disease more often than the other types of breast carcinomas. About 20% present with positive lymph node and about 25% with stage III or IV.[66,72] Often SqCC, SpCC, and MCHMD are combined in one category and compared with other tumors such as nonmetaplastic TNBC,[69–71,77–80] or NST, although matched for ER and HER2.[48,81] There are sporadic studies that investigated a single diagnosis such as SpCC[8] or MCHMD.[18] Other studies investigated if these 3 subtypes differ in the outcomes.[69,80,81] Most of these studies revealed that MpBC has worse clinical outcomes than TNBC, including 2 studies with large number of cases; the hazard ratio ranged from 1.36 and 3.99.[8,69–71,77–79] Only a single study with relatively large number of cases revealed no statistical significance between MpBC versus matching NST when only stages 1 and 2 cases were included in the analysis[81] (**Table 2**). Some studies attempted to compare the clinical outcomes between the different MpBC subtypes but limited by the small sample size.[69,82] However, Tadros and colleagues found that MCHMD had the best outcome and SqCC had the worst.[80] Rakha and colleagues revealed that SpCC, pure or mixed with SqCC, had worse clinical outcomes than SqCC or MCHMD.[81] Downs-Kelly and colleagues found that less matrix (<40%) in MCHMD signified worse clinical outcome.[18]

Comments

MpBCs are diverse group of tumors with 2 extremes, the very low risk and the very high risk. Therefore, the author recommends revising the WHO classification by proceeding the diagnoses of the least malignant tumors LGASC and FLMC with the term "low risk" and the most malignant tumors SqCC, SpCC, and MCHMD with "high risk." The high-risk tumors have the worst clinical outcomes, with some suggesting that MCHMD has better outcomes. The novel discoveries of tumor microenvironment and molecular alterations have led to the advancement in immunotherapies and target therapy. However, with few successful and promising therapies presented in the literature in the form of case reports and small clinical trials, unfortunately most of the patients succumb to this disease. Therefore, further discoveries are urgently needed.

CLINICS CARE POINTS

- High-risk MpBC has worse clinical outcomes than TNBC.
- Combining various histologic subtypes under one entity designated as MpBC is misleading.

- Some of the subtypes have the worst clinical outcomes among all breast carcinomas, whereas the other group has indolent clinical behavior.
- SpCC associated with complex sclerosing lesions could be challenging to diagnose, and the pathologists should be aware of this entity.
- Proper histomorphology interpretation and wise choices of immunohistochemistry staining could assist in rendering the correct diagnosis of spindle cell lesion of the breast.
- Target therapy and immunotherapy are promising ways to combat high-risk MpBC of various molecular alterations and up-to-date target therapy and immunotherapy.

DISCLOSURE

Breast Pathology Faculty Advisor for AstraZeneca on HER2 assay.

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