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*Original Article*

# Fibromatosis-like metaplastic carcinoma of breast: a challenge for clinicopathologic diagnosis

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**Abstract:** Fibromatosis-like metaplastic carcinoma of breast (FLMC) is a newly described metaplastic tumor in the (4th) edition of the WHO classification of breast tumors in 2012. It is a low-grade tumor formed by spindle cells with mild or absent nuclear atypia, embedded in collagenized stroma, and it has only <5% tumor cells showing epithelial traits. Because its biological behavior is better than that of general spindle cell metaplastic cancer, this cancer type is added to the new WHO classification. Due to their mild morphology, breast FLMCs are often misdiagnosed as benign interstitial proliferative lesions or benign mesenchymal tumors. Accurate diagnosis is a challenging task particularly in needle core biopsies. We systematically reviewed 23 cases of metaplastic breast carcinoma (MBC), 8 cases of metaplastic carcinoma with squamous cell component, 12 cases of spindle cell/sarcomatoid metaplastic carcinoma, and 3 cases of FLMC. Also, we performed CK, CK high molecular weight (34βE12), CK7, CK5/6, P63, CD10, ER, PR, HER-2, SMA, Desmin, CD34, CD117, and S-100 immunohistochemistry, using Envision staining. This study was focused on clinical and pathological features of 3 FLMC cases and assessed the immunoprofile of MBC subtypes in a large series to improve the understanding of these diseases.

**Keywords:** Breast, fibromatosis-like metaplastic carcinoma, diagnosis, immunohistochemistry

## Introduction

MBC is a rare and aggressive histologic subtype comprising approximately 0.5% to 5.0% of all invasive breast cancers [1]. It includes a heterogeneous group and is characterized by differentiation of the malignant epithelial cells into squamous and/or mesenchymal cells [2]. The 2012 WHO classification distinguishes five subtypes: low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and carcinoma with mesenchymal differentiation (chondroid differentiation, osseous differentiation, and other types of mesenchymal differentiation) [3]. When an invasive lesion of the breast showing mesenchymal or squamous differentiation is associated with conventional mammary invasive or in-situ carcinoma, the diagnosis of MBC is usually straightforward. But if there is absence of the above features or histological diversity, the diagnosis in routine practice is sometimes challenging [4]. At this time, diagnosis of MBC is based on the demonstration of epithelial differentiation typically using immunohistochemistry. FLMC is a newly described MBC because of their resemblance to pure fibromatosis, their propensity for local recurrence and their favorable prognosis among the MBC [5]. The diagnosis is potentially challenging because of the morphologic overlap with other low-grade spindle cell lesions. Recognition of a proliferation of cytologically bland spindle cells with areas of epithelial differentiation in combination with immunohistochemistry using antibodies against cytokeratins and myoepithelial markers should aid in producing a definitive diagnosis [6]. We performed histological observation on 23 cases of MBC and studied by immunohistochemical method and focused on 3 cases of FLMC. We focus on their diagnosis and differential diagnosis to raise our awareness of such lesions.

## Materials and methods

We collected 23 cases of breast MBCs in the First Affiliated Hospital of Bengbu Medical Col-

**Table 1.** Sources of the antibodies used in the immunohistochemical analysis

| Source | Antibody |
|---|---|
| CK | MonoclonalAE1/AE3 |
| CKH (34βE12) | Monoclonal, clone34βE12 |
| CK7 | Monoclonal, cloneOV-TL12/30 |
| CK5/6 | Monoclonal, clone D5/16B4 |
| p63 | Monoclonal, clone 4A4 |
| CD10 | Monoclonal, clone 56C6 |
| SMA | Monoclonal, clone 1A4 |
| calponin | Monoclonal, clone CALP |
| P53 | Monoclonal, cloneDO-7 |
| EMA | Monoclonal, cloneE29 |
| Vimentin | Monoclonal, cloneSP20 |
| β-catenin | Monoclonal, cloneCAT-5H10 |
| Desmin | Monoclonal, cloneD33 |
| CD34 | Monoclonal, cloneQBEnd/10 |
| S100 | Monoclonal, clone4C4.9 |
| CD117 | Monoclonal, cloneYR145 |
| ER | Monoclonal, clone SP1 |
| PR | Monoclonal, clone1A6 |
| HER-2 | Monoclonal, cloneCB11 |

lege from January 2010 to July 2017 including 8 cases of metaplastic carcinoma with squamous cell component, 12 cases of spindle cell/sarcomatoid metaplastic carcinoma, and 3 cases of FLMC. H and E-stained sections (4 um thickness) were reexamined to evaluate the tumor's histological features and immunohistochemistry was performed with Elivision technique. Antibody details are given in **Table 1**. Clinical demographics and follow-up data were obtained from medical records and referring physicians.

All antibodies were obtained from Maixin Biotech, Inc. (Fuzhou, China), and were ready to use.

This study was approved by the Ethics Committees of the First Affiliated Hospital of Bengbu Medical College and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

## Results

*Clinical features*

*Case 1:* A 65-year-old woman presented with a 3.5×3.0 cm mass with irregular margins in the upper and outer quadrant of left breast. The patient discovered the nodule 2 months previously by self-palpation. Nipple secretion was not observed. No lymph node swelling was observed at the ipsilateral axillary. Mammography and ultrasonography confirmed the presence of a 35-mm nodular lesion with a multilobular shape.

*Case 2:* A 55-year-old woman presented with the complaints of a left-sided breast lump of one month duration. On clinical examination a 4.0×4.0 cm firm, mobile, nontender lump was identified in the outer quadrant of her left breast. There was no significant axillary or cervical lymphadenopathy. Six months ago, B-ultrasound had suggested that the left breast had a hypoechoic nodule 1.0 cm in diameter. The patient had undergone a previous surgical operation of the left breast one year ago at other hospital. The pathology suggested a benign lesion. A lumpectomy was performed and sent for frozen section, which revealed presence of spindle cells showing mild atypia in a sclerotic stroma. The tumor cells revealed prominent infiltration into the adjacent fat.

*Case 3:* A 51-year-old woman who was diagnosed with right breast cancer after routine staging assessment underwent lumpectomy and the specimen was sent for frozen section. On gross examination, the tumor was a well-circumscribed, hard mass of 3.0×2.5 cm with a gray-white, gritty cut surface. On frozen section the lesion showed a proliferation of bland spindle cells of fibroblastic/myofibroblastic morphology arranged in intersecting and storiform fascicles.

*Gross and histological features*

The three breast tumors' diameter were 3.5 cm, 4.0 cm and 3.0 cm. Grossly, the masses were firm and gray, nodular, irregular, infiltrative. The cut surface revealed unencapsulated gritty, fibrous, grey-white nodular parenchyma. Histological features were characterized by the proliferation of low-grade, cytologically bland spindle cells, which composed at least 95% of the total tumor area and histologically resembled pure fibromatosis. These tumors exhibited irregular infiltrative peripheral margins with broad, fingerlike projections of neoplastic cells into the surrounding mammary structures and soft tissue (**Figure 1A**). In case 1, the neoplastic spindle cells were cytologically bland with absent to minimal nuclear atypia and pale

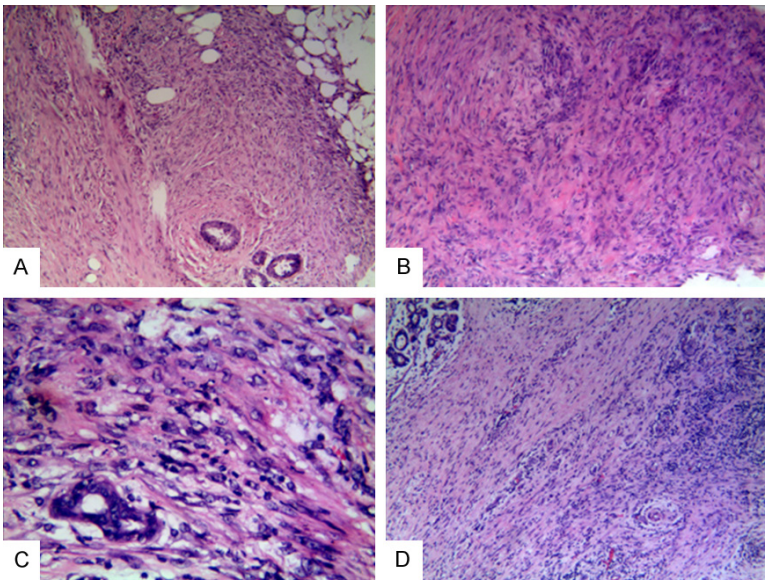


**Figure 1.** A. Low-grade fibromatosis-like spindle cells entrap normal breast glandular structures and surrounding fat tissue. (magnification, ×100). B. The cells are mainly arranged in fascicles and displayed tapering nuclei with mild anisonucleosis. (magnification, ×100). C. Some areas show cells with nuclei ranging from spindled to round or oval with discrete nucleoli. (magnification, ×400). D. Interstitial scattered lymphocytes, plasma cells, and other inflammatory cell infiltration. (magnification, ×100) (Hematoxylin and Eosin).

eosinophilic cytoplasm (**Figure 1B**). The stroma was sclerotic with elastofibrosis. In case 2, the neoplastic nuclei ranged from thin, slender, and spindled to round and oval (**Figure 1C**). Neoplastic glandular epithelial elements were admixed with the neoplastic spindle cells but these accounted for less than 5% of the total tumor area. In case 3, we can see the presence of small, cohesive clusters of fusiform to polygonal epithelioid cells with rounded nuclei and prominent nucleoli scattered among the spindle cells. There are interstitial scattered lymphocytes, plasma cells, and other inflammatory cells(**Figure 1D**).

*Immunohistochemical features*

In the three cases, neoplastic spindle cells expressed epithelial markers CK (**Figure 2A**), CK7 (**Figure 2B**), 34βE12, and myoepithelial markers p63 (**Figure 2C**), CK5/6, and CD10. Spindle cells were diffusely positive, epithelioid cells were weakly positive, and the typical epithelial component was negative for mesenchymal marker vimentin. SMA was partially positive and ER, PR, HER-2, S-100 protein, CD34, and CD117 were negative. Ki-67 positive index was 15% to 20%; the index of local areas may be higher (**Figure 2D**).

## Discussion

Accurate diagnosis of breast FLMC is potentially challenging because the differential diagnosis is broad and includes many lesions that are considered rare in the breast. The differential diagnosis includes fibromatosis, reactive spindle cell nodules, nodular fasciitis, phyllodes tumor, inflammatory myofibroblastic tumor and other low-grade spindle cell tumors [7].

*Fibromatosis*

In the breast, this lesion presents as a painless, slow-growing mass. Histologically, it is locally aggressive within filtrative margins and is composed of a proliferation of uniform, cytologically bland fibroblasts and myofibroblasts. No small clusters of epithelioid cells should be observed and if present these should suggest the diagnosis of FLMC [8]. The spindle cells of fibromatosis express SMA and β-catenin and lack cytokeratin and p63 expression.

*Reactive spindle cell nodules*

This is a recently described entity reported in breast tissue that has undergone fine-needle aspiration or core needle biopsy [9]. These lesions are localized, nodular collections of spindle cells with mild to moderate nuclear atypia admixed with a delicate network of thin-walled blood vessels. The presence of hemosiderin, fat necrosis, chronic inflammatory cells and other reactive features favors this lesion [10]. These nodules are frequently associated with papillomas and complex sclerosing lesions. The spindle cells in these reactive nodules express vimentin and SMA but lack cytokeratin expression [11].

*Nodular fasciitis*

This is more commonly found in the subcutaneous tissues of the upper extremities and trunk but rarely occur in the breast [12]. This lesion typically presents as a tender, well-circumscribed lesion with a rapid onset in young

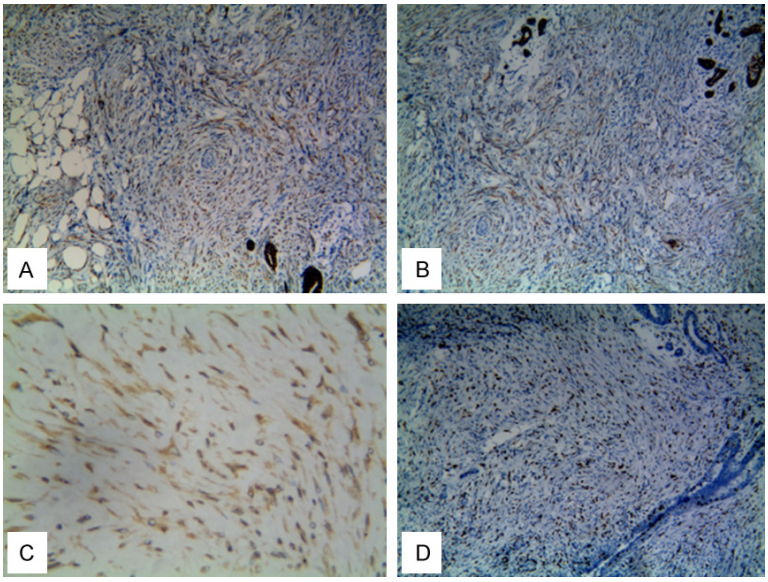


**Figure 2.** A. The neoplastic spindle cells are positive for CK protein. (magnification, ×100). B. The neoplastic spindle cells are positive for CK7 protein. (magnification, ×100). C. The neoplastic spindle cells are positive for P63 protein. (magnification, ×400). D. Ki-67 positive index was 15% to 20%; the index focally may be higher.

adults. Histologically, it is composed of proliferation of plump fibroblasts and myofibroblasts arranged in short fascicles and whorls set in a feathery, myxoid stroma rich in delicate blood vessels, wisps of collagen fibers, and focal extravasated red blood cells. The spindle cells have uniform prominent nucleoli and frequent mitotic figures. Inflammatory cells can be seen admixed within and at the periphery of these lesions [13]. The spindle cells express vimentinand SMA, but lack cytokeratin expression.

*Inflammatory myofibroblastic tumor*

This commonly presents in the soft tissue and viscera but rarely occurs in the breast. These lesions are composed of variably cellular proliferation of fibroblasts and myofibroblasts admixed with acute and chronic inflammatory cells in myxoid to collagenized stroma [14]. The spindle cells characteristically express vimentin, SMA, and factor XIIIa and some cases demonstrate desmin, cytokeratin or anaplastic lymphoma kinase expression [15].

*Phyllodes tumors*

Compared with fibroadenoma, phyllodes tumors are uncommon fibroepithelial proliferations in the breast. This is composed of varying degrees of stromal proliferation that create leaflike clefts that are lined by benign mammary glandular epithelium [16]. Depending on the degree of atypical proliferative changes in the stromal component, phyllodes tumors are classified as benign, borderline, or malignant. Stromal cells with increased cellularity, nuclear crowding, atypia, and mitotic activity imply malignant behavior [17]. Phyllodes tumors with prominently expanded stromal proliferation may not have a readily identifiable benign epithelial lining and therefore may resemble other spindle cell neoplasms of the breast, including metaplastic carcinomas and sarcomas [18]. The spindled stromal cells of phyllodes tumors express vimentin, CD34, β-catenin, actin and desmin, but lack expression of cytokeratin.

*Other low-grade spindle cell tumors*

Most of these tumors are negative for CK and other epithelial markers and combined with their respective immunohistochemical markers can be identified.

Overall clinical history and immunohistochemistry can help in making a correct diagnosis in morphologically challenging cases. To make an accurate diagnosis, it is important to maintain a wide differential diagnosis and be familiar with the diverse morphological appearances of these different entities [19].

The results of immunohistochemistry for 23 cases of MBC suggest that the antibodies cytokeratin (AE1/AE3) is most frequently positive in MBC (approximately 95.6%). CKH (34βE12) and CK5/6 are positive in approximately 86.9% and 69.6%. CK7 is positive in approximately 56.5%. Myoepithelial markers are also frequently positive, particularly p63 (approximately 91.3%). ER, PR and HER-2 are usually all negative. CD34 (a marker often positive in phyllodes tumors) is consistently negative in MBC.

In our three cases, 2 patients received modified radical mastectomy; in 1 case the patients received segmental mastectomy and sentinel lymph node detection. Lymph nodes were all

negative. 3 cases all had received chemotherapy, 1 case had received radiotherapy. Follow-up to July 2017, had a follow-up time of 12 to 49 months. Chest wall mass appeared in 1 case at 13 months after operation. The pathology was confirmed as tumor recurrence but no distant metastasis.

Until now, no definitive conclusions regarding the biologic behavior of FLMC have been made because most case series are limited by small sample size, variable clinical follow-up intervals, and differences in treatment regimens [20]. Despite mild histological appearance, FLMC still has the potential of local recurrence and distant metastasis. The propensity for recurrence of FLMC cannot be ignored and remind us in the pathological diagnosis of breast disease, especially spindle cell lesions, it is important to maintain a wide differential diagnosis and to get enough clinical data to ensure the correctness of diagnosis.

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## Disclosure of conflict of interest

None.

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