Low-Grade Fibromatosis-like Spindle Cell Carcinoma of the Breast

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- Low-grade fibromatosis-like spindle cell carcinoma is a rare tumor in the breast, and represents a variant of the very heterogeneous group of metaplastic carcinomas of the breast. These tumors warrant distinction because of their resemblance to pure fibromatosis, their propensity for local recurrence, and their favorable prognosis among the metaplastic carcinomas of the breast. The diagnosis is potentially challenging, particularly on core needle biopsies, 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. These tumors can be locally aggressive with an increased incidence of local recurrence, but the potential for lymph node or distant metastasis is low. Complete excision with adequate margins is considered curative in the majority of cases.


Spindle cell carcinoma represents one subclassification of metaplastic carcinomas in the breast, which are generally regarded as extremely rare malignancies, usually less than 1% of invasive malignancies in the breast.1 The majority of malignant neoplasms in the breast arise from mammmary glandular epithelium, but metaplastic carcinomas are entirely or partially composed of neoplastic epithelial cells that have undergone the process of metaplasia to exhibit a nonglandular growth pattern.2 The term metaplastic carcinoma was first described in 1973 by Huvos et al.3 The type and degree of metaplastic change is quite variable among these tumors; this unfortunately has resulted in multiple classification schemes and designations. According to the World Health Organization, metaplastic carcinomas of the breast should be classified into 2 broad categories: purely epithelial or mixed epithelial and mesenchymal.1 Purely epithelial tumors are further subclassified into squamous cell carcinoma, adenocarcinoma with spindle cell differentiation, or adenosquamous carcinomas. Mixed epithelial and mesenchymal tumors are further subclassified into carcinoma with chondroid metaplasia, carcinoma with osseous metaplasia, or carcinosarcoma.2 A separate classification system proposed by Wargotz and Norris4–7 and Wargotz et al8 differentiates metaplastic carcinoma of the breast into 5 subtypes: spindle cell, squamous cell, carcinosarcoma, matrix-producing, and metaplastic carcinoma with osteoclast giant cells. In their classification, Wargotz et al9 define spindle cell carcinomas as metaplastic carcinomas composed of spindle cells that are contiguous or merged with an invasive squamous or glandular component. Several subsequent case series of metaplastic carcinoma in the breast have determined that the majority of these tumors are actually spindle cell carcinomas, with spindle cell atypia ranging from low-grade fibromatosis-like tumors to tumors resembling high-grade sarcomas.8–10 Low-grade fibromatosis-like spindle cell carcinoma (FLSCC) is a recently described variant of spindle cell carcinoma that warrants distinction because of its unique resemblance to pure fibromatosis, its propensity for local recurrence, and its favorable prognosis among the metaplastic carcinomas in the breast.9 It also poses a diagnostic challenge because of the broad differential diagnosis for low-grade spindle cell lesions in the breast, which includes many other benign and malignant entities with strikingly similar histologic features.

CLINICAL FEATURES

Fibromatosis-like spindle cell carcinoma has been reported only in women, and is usually seen in older, postmenopausal women. In 2 of the original case series of FLSCC, the average age at initial diagnosis was 63.4 years9 and 66 years.11 Patients typically present with a unilateral, rapidly enlarging, and palpable breast mass. In some case series, more women presented with a mass in the left breast.8,9,11,12 Complaints of swelling, tenderness, and nipple inversion have also been reported at diagnosis.8,9 Fibromatosis-like spindle cell carcinoma tumors do not have a predilection for any specific anatomic location in the breast.

Metaplastic carcinomas of the breast have variable appearances on mammography and ultrasound imaging modalities. These masses have been described as round, oval, lobular, or irregularly shaped with densely solid, heterogeneous, or cystic parenchyma and well-circum-
scribed, irregular, partially nodular, or circumscribed with partially spiculated margins.9,13 Günhan-Bilgen et al14 and Patterson et al15 note that, in general, metaplastic carcinomas of the breast are more likely to have circumscribed margins, especially if the mass is composed of spindle cells. More specifically, the metaplastic component of these tumors typically demonstrates circumscribed or lobular margins, whereas the invasive epithelial component, if present, demonstrates infiltrative margins.15 Calcifications within these masses are uncommon.13 As of the present, to our knowledge, a case series specifically assessing the radiologic findings of FLSCC masses has not been performed.

**GROSS PATHOLOGIC FEATURES**

Average FLSCC tumor sizes are reported as approximately 3 cm, with a range of 1 to 7 cm.9,11 Grossly, the masses are firm and white, and have been described as well-circumscribed, nodular, irregular, infiltrative, or cystic.9,11,12,16 The cut surface typically reveals unencapsulated gritty, fibrous, grey-white nodular parenchyma. Necrosis, hemorrhage, and calcifications are not typical for these tumors.9,11,12,16

**MICROSCOPIC PATHOLOGY AND IMMUNOHISTOCHEMISTRY**

As mentioned previously, FLSCC is a subset of spindle cell carcinoma characterized by the proliferation of low-grade, cytologically bland spindle cells, which compose at least 95% of the total tumor area and histologically resemble pure fibromatosis.9 Despite its rather benign clinical and radiologic presentation, it is the infiltrative peripheral margins of FLSCC tumors that bear the most resemblance to pure fibromatosis. More specifically, the majority of FLSCC tumors exhibit irregular infiltrative peripheral margins with broad, fingerlike projections of neoplastic cells into the surrounding mammary structures and soft tissue.9,11 (Figure 1, A). However, there are reported cases of FLSCC with nodular, pushing margins or partially nodular margins with focal fingerlike extensions.9 Another notable similarity between FLSCC and pure fibromatosis is the proliferation of low-grade spindled fibroblast-like cells and stellate myofibroblast-like cells.11 Among FLSCC tumors, the proliferation of neoplastic cells is variably cellular. On high magnification, the neoplastic spindle cells are cytologically bland with absent to minimal nuclear atypia and pale eosinophilic cytoplasm (Figure 1, B). Within the same tumor, the neoplastic nuclei may vary from thin, slender spindled nuclei with tapered ends to more plump, round to oval nuclei with discrete nucleoli (Figure 1, C). Neoplastic squamous or glandular epithelial elements may be admixed with the neoplastic spindle cells, histologically emphasizing the metaplastic nature of these tumors, but these should account for less than 5% of the total tumor area. This minority of squamous or glandular epithelial elements contrasts with low-grade adenosquamous carcinoma, a variant of metaplastic carcinoma in which bland glandular and squamous elements account for the majority of the neoplasm, and may have a background of spindle cells.

A defining and characteristic histologic feature of FLSCC is the presence of small, cohesive clusters of fusiform to polygonal epithelioid cells with rounded nuclei and prominent nucleoli scattered among the spindle cells.9,11 (Figure 1, D). In the original case series by Gobbi et al,9 the 33% of FLSCC tumors that did not have recognizable squamous or glandular elements had the small clusters of epithelioid cells, a finding supported by other case series and reports.11,12,16,17 On closer examination, these small clusters were frequently seen in a gradual histologic transition to the neoplastic spindle cells.9 It was concluded that their presence may represent evidence of epithelial differentiation in FLSCC tumors, especially those that do not have readily identifiable neoplastic epithelial elements.

Finally, an additional overlapping morphologic feature between FLSCC tumors and pure fibromatosis is variably collagenous stroma. In FLSCC, an abundance of collagen may be noted within the center of the tumor, the neoplastic spindle cells may be scattered within a densely sclerotic stroma reminiscent of keloid formation, or they may be dispersed between thick bands of hyaline collagen.9

The architectural arrangements of the neoplastic spindle cells in FLSCC tumors are also variable, ranging from intersecting fascicles to vaguely storiform patterns, haphazard sheetlike growth, individually infiltrating cells, or vascular-akantholytic growth patterns characterized by vessellike gaping spaces lined by spindle cells.9,11 Mitotic figures are generally rare, with usually no more than 3 mitotic figures per 10 high-power fields.9 Lymphatic, perineural, and blood vessel invasion is not typical for the spindle cell component in these tumors. If definitive lymphovascular invasion is identified in an FLSCC tumor, the malignant epithelial component of the tumor is usually identified within the lymphatic or vascular spaces as opposed to the spindle cell component.12 Scattered collections of acute and chronic inflammatory cells may be seen within and at the periphery of FLSCC tumors. Other reported morphologic features include focal fibromyxoid stroma, pseudoangiomatoid stroma, and entrapment of normal breast glandular structures and ducts by the neoplastic spindle cells (Figure 2, A). The pathologic findings reported in breast parenchyma adjacent to these tumors include benign ductal epithelial hyperplasia, ductal carcinoma in situ, lobular carcinoma in situ, and squamous metaplasia.9,13 Recently published studies have also reported an increased incidence of metastatic spindle cell carcinomas, including FLSCC, in association with papillomas, radial scars, complex sclerosing lesions, nipple adenomas, and squamous metaplasia in the breast.16,18 The nature of the interaction between these epithelial lesions of the breast and FLSCC remains uncertain.

The diagnosis of metaplastic spindle cell carcinoma, including FLSCC, may not be obvious in tumors composed exclusively of spindle cells. In these instances, a panel of immunohistochemical stains is generally needed to distinguish metaplastic spindle cell carcinoma from other spindle cell lesions of the breast. In all cases of metastatic spindle cell carcinoma, the epithelial origin of the spindle cells should be demonstrable with the use of cytokeratin immunohistochemical stains. Unfortunately, there is no consensus as to which cytokeratin stains are the most reliable for identifying these tumors. In fact, the results of immunohistochemical staining among studies of metaplastic spindle cell carcinomas are not easily comparable, even when the same panel of immunohistochemical stains is used.9,12 Regardless, all studies agree that a panel of cytokeratin immunohistochemical stains is necessary for the accurate diagnosis of metastatic spindle cell carcinoma.9,12,19,20 The cytokeratin immunohistochemical stains used most frequently in the studies of these tumors include antibodies against broad-spectrum cytokeratins (AE1/AE3,
pankeratin), basal cytokeratins (cytokeratin 5 [CK5], 34βE12, CK14), and luminal cytokeratins (CK7, CK19, CAM 5.2). Some studies conclude that a panel of stains specifically against broad-spectrum cytokeratins or high-molecular-weight cytokeratins provides the most sensitive marker for metaplastic carcinomas of the breast. In general, the spindle cell component and small clusters of epithelioid cells exhibit immunoreactivity for the basal cytokeratins and no to focal immunoreactivity for luminal cytokeratins, suggesting a tumor phenotype similar to squamous epithelium. Figures 2, B). The spindle cell component and small clusters of epithelioid cells have also been shown to coexpress vimentin (Figure 2, C), lending further support to the metaplastic nature of these cells. In contrast, the epithelial components typically demonstrate diffuse staining with all of the cytokeratin stains and are negative for vimentin.

More recent publications have suggested that the metaplastic components in spindle cell carcinomas actually demonstrate an immunostaining pattern more compatible with myoepithelial differentiation, specifically immunoreactivity with myoepithelial and basal cytokeratins 34βE12, CK14, and CK5, in addition to other myoepithelial markers such as smooth muscle actin, S100, maspin, and p63. Most notably, consistent nuclear immunoreactivity for the myoepithelial marker p63 in the metaplastic components of metaplastic carcinomas is proving to be a more sensitive and specific diagnostic marker (Figure 2, D). Koker et al noted that p63 was strongly expressed in approximately 87% of metaplastic carcinomas and was positive in all metaplastic carcinomas with spindle cell or squamous differentiation. When compared with other neoplastic breast lesions, the sensitivity and specificity of p63 staining in metaplastic carcinomas were 86.7% and 99.4%, respective.

The demonstration of immunoreactivity with myoepithelial markers in the metaplastic components of metaplastic carcinoma of the breast may suggest that these tumors are actually of myoepithelial origin, but this has never been proven. The process by which these tumors arise in the breast has been long debated in the literature, but molecular and genetic studies of these tumors have demonstrated monoclonal origin of the epithelial and metaplastic components. Koker et al suggest that metaplastic carcinomas may arise from a single stem cell, a group of different cells, or a common progenitor cell with the capability of differentiating into other cell types. Dunne
et al. suggest that the myoepithelial phenotype may actually represent a transitional phenotype between epithelial and sarcomatous lines of differentiation.

The spindle cells in FLSCC are typically negative for smooth muscle myosin heavy chain and epithelial membrane antigen, but epithelial membrane antigen positivity may be seen in the epithelial components. The proliferation indices of FLSCC with Ki-67 are usually less than 5%. Fibromatosis-like spindle cell carcinoma, and the majority of metaplastic carcinomas of the breast for that matter, are classically negative for estrogen receptor, progesterone receptor, and HER2/neu by immunohistochemistry.

**DIFFERENTIAL DIAGNOSIS**

Accurate diagnosis of low-grade spindle cell lesions in the breast is potentially challenging because the differential diagnosis is broad and includes many lesions that are considered rare in the breast. In general, the differential diagnosis for any metaplastic carcinoma is dependent on the degree of atypia in the tumor. As mentioned previously, FLSCC represents a low-grade variant of spindle cell carcinoma, and is essentially a neoplasm composed almost exclusively of cytologically bland spindle cells. The differential diagnosis includes pure fibromatosis, exuberant scars, reactive spindle cell nodules, nodular fasciitis, inflammatory myofibroblastic tumor, myofibroblastoma, pseudoangiomatous stromal hyperplasia, phyllodes tumor, dermatofibrosarcoma protuberas, and spindle cell sarcomas.

The most important lesion to distinguish from FLSCC is pure fibromatosis. Pure fibromatosis in the breast typically presents as a painless, slow-growing mass. On microscopic examination, fibromatosis lesions are locally aggressive with infiltrative margins and are composed of a proliferation of uniform, cytologically bland fibroblasts and myofibroblasts. Some morphologic clues to the diagnosis of fibromatosis include long, sweeping fascicles of neoplastic spindle cells with entrapped benign breast glandular epithelial elements and peripheral lymphocytic infiltrates. No small clusters of epithelioid cells should be observed, and if present, these should suggest the diagnosis of FLSCC. The spindle cells of fibromatosis lesions express smooth muscle actin and muscle-specific actin and show nuclear expression of β-catenin, but lack cytokeratin expression.

Exuberant, extensive scars, reactive spindle cell nodules, and nodular fasciitis are reactive entities that may mimic FLSCC. The presence of hemosiderin, fat necrosis, and foreign body multinucleated giant cells favors scar formation. Reactive spindle cell nodules are a recently described entity reported in breast tissue that has undergone fine-needle aspiration or core needle biopsy. These lesions are localized, nodular collections of spindle cells with mild to moderate nuclear pleomorphism admixed with a delicate network of thin-walled blood vessels, hemosiderin, chronic inflammatory cells, and other reactive features. These nodules are frequently associated with papillomas and complex sclerosing lesions. The spindle cells in these reactive nodules express vimentin, smooth muscle actin, and muscle-specific actin, but lack cytokeratin expression. The myofibroblastic expression profile of the spindle cells suggests that these lesions represent an exuberant reactive process following needle biopsy of various fibrosclerotic breast lesions that regularly contain myofibroblasts. Nodular fasciitis is more commonly found in the subcutaneous tissues of the upper extremities and trunk, but rarely may occur in the breast. These lesions typically present as a
tender, well-circumscribed lesion with a rapid onset in young adults. On microscopic examination, the lesions are composed of a 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 and multinucleated giant cells can be seen admixed within and at the periphery of these lesions. The spindle cells express vimentin, smooth muscle actin, and muscle-specific actin, but lack cytokeratin expression. In addition, entrapment of benign breast glandular elements by the spindle cells is not typical for nodular fasciitis.

Inflammatory myofibroblastic tumor, also referred to as inflammatory pseudotumor, more commonly presents in the soft tissue and viscera, but may rarely occur in the breast. These lesions are composed of a variably cellular proliferation of fibroblasts and myofibroblasts admixed with acute and chronic inflammatory cells in a myxoid to collagenized stroma. The spindle cells characteristically express vimentin, smooth muscle actin, and factor XIIIa, but some cases may demonstrate desmin, cytokeratin, or anaplastic lymphoma kinase expression. The nature of these lesions continues to be debated in the literature. Although the lesions were once considered reactive, several recent molecular studies have demonstrated a clonal origin in the spindle cells, indicating a potentially neoplastic lesion.

Myofibroblastoma is a benign myofibroblastic neoplasm that may rarely occur in the breast. These lesions typically present as lobular, well-circumscribed, slow-growing masses in adults, usually in the sixth to eighth decade. Myofibroblastomas were originally reported to occur more frequently in the male breast, but recent data indicate they may actually occur with equal frequency in men and women. On microscopic examination, these lesions are composed of a proliferation of uniform, cytologically bland spindle cells arranged in short, haphazard fascicles separated by bands of collagen. Variable amounts of fat, mast cells, and patchy, perivascular chronic inflammatory infiltrates are also characteristic findings in these lesions. Mitotic figures should be rare. The spindle cells express vimentin and variably express desmin, CD34, muscle-specific actin, smooth muscle actin, estrogen receptor, progesterone receptor, and BCL2. They lack expression of CD31, smooth muscle myosin heavy chain, S100, and cytokeratin.

Pseudoangiomatous stromal hyperplasia is a benign proliferative lesion composed of anastomosing empty, slitlike pseudovascular spaces lined by myofibroblasts that resemble endothelial cells set in a dense collagenous stroma. These lesions may also harbor foci of increased cellularity with myofibroblasts arranged in fascicles, mimicking FLSCC. Pseudoangiomatous stromal hyperplasia has been described in association with many benign and malignant breast lesions, including carcinoma, hamartoma, fibroadenoma, and phyllodes tumors, but it has also been described in a nodular form that was not associated with other breast lesions. The spindle cells have the immunohistochemical profile of myofibroblasts, including expression of vimentin and variable expression of desmin, CD34, smooth muscle actin, muscle-specific actin, etc, but lack cytokeratin expression.

Phyllodes tumors are uncommon fibroepithelial proliferations in the breast, especially when compared with the more frequent fibroadenoma. Phyllodes tumors are composed of varying degrees of stromal proliferation that create leaflike clefs that are lined by benign mammary glandular epithelium. 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, whereas the lack of these features indicates that the lesion is benign. Phyllodes tumors with prominent, expanded stromal proliferation may not have readily identifiable benign epithelial lining and therefore may resemble other spindle cell neoplasms of the breast, including metaplastic carcinomas and sarcomas. The spindle stromal cells of phyllodes tumors express vimentin, CD34, b-catenin, actin, and desmin, but lack expression of cytokeratin. Expression of p63 can be seen in the normal myoepithelial cells associated with the benign epithelial element of phyllodes tumors, but in the spindled stromal cells lack expression of p63.

Dermatofibrosarcoma protuberans is an uncommon cutaneous tumor that rarely presents in the breast. These tumors have a predilection for the deep dermal to subcutaneous tissue plane superficial to the breast parenchyma, and present as well-circumscribed masses. On microscopic examination, they are composed of a proliferation of cytologically bland spindle cells arranged in a storiform architectural pattern. Few mitotic figures, rare necrosis, and multinucleated giant cells may also be seen. The spindle cells express vimentin and CD34, but lack expression of factor XIIIa and cytokeratin.

Finally, primary sarcomas in the breast are also rare but represent an extremely important entity to distinguish from FLSCC. Primary sarcomas usually require extensive sampling in order to distinguish them from metaplastic spindle cell carcinomas. The types of primary mammary sarcomas that more often present as a tumor composed of spindle cells exclusively are fibrosarcomas, liposarcomas, and pleomorphic undifferentiated sarcomas (previously malignant fibrous histiocytoma). In general, primary sarcomas can usually be distinguished from FLSCC by the increased nuclear atypia, brisk mitotic rate, and occasional distinct architectural patterns observed in primary sarcomas.

**TREATMENT AND PROGNOSIS**

When compared with other infiltrating mammary carcinomas, metaplastic carcinomas of the breast tend to present with larger, more aggressive tumors at higher disease stages, have a higher incidence of local recurrence, have poor response to traditional chemoradiation therapies, and are overall associated with worse outcomes. The exception to this generalization is FLSCC. On the spectrum of metaplastic spindle cell carcinomas of the breast, FLSCC represents a low-grade variant with clinically indolent behavior that is similar to pure fibromatosis. According to Gobbi et al, FLSCC tumors have an increased incidence of local recurrence, but have low potential for regional lymph node or distant metastasis. In their case series, 8 of 18 FLSCC cases with clinical follow-up developed local recurrence within 5 to 72 months after diagnosis. Seven of these patients were treated with excisional biopsy alone. None statistically significant clinicopathologic differences were identified in the recurrent tumors when compared with the nonrecurrent tumors. Therefore, it was concluded that recurrences were likely directly related to inadequate local excision. No axillary lymph node or distant metastases were observed.
identified in any of their FLSCC cases. Similarly, in the case series study by Sneige et al,11 2 of their 7 FLSCC cases treated by local excision developed recurrence within 2 years of diagnosis, 1 of which had confirmed negative surgical resection margins. In addition, they noted that 2 of their cases demonstrated distant metastases. Analysis of these 2 cases revealed that both tumors were composed of low-grade spindle cells with focal acantholytic growth pattern, and these features were also seen in the metastases. Grossly, both cases had larger than average tumor sizes, suggesting that increased tumor size may be a negative prognostic factor for recurrence, but this could not be shown to be statistically significant because of the small sample size.

No definitive conclusions regarding the biologic behavior of FLSCC tumors have been made because most case series are limited by small sample sizes, variable clinical follow-up intervals, and differences in treatment regimens. Regardless, Gobbi et al12 suggest that the behavior and prognosis of these tumors parallel that of pure fibromatosis, and that wide excision with clear margins or simple mastectomy should be sufficient for initial treatment of FLSCC. Axillary lymph node dissections, radiation, and chemotherapy are not necessary.11-13 The data are limited, but there may be a small risk for distant metastasis in patients with FLSCC, necessitating close clinical monitoring following excision. However, the overall risk of distant metastasis in these tumors appears to be lower than that for other carcinomas of the breast.11

### SUMMARY

Fibromatosis-like spindle cell carcinoma is a recently described, rare low-grade variant of metaplastic spindle cell carcinomas of the breast, which in turn represents a subclassification of metaplastic carcinoma in the breast. Fibromatosis-like spindle cell carcinoma warrants distinction from other metaplastic carcinomas in the breast because of its unique resemblance to pure fibromatosis, its propensity for local recurrence, and its favorable prognosis. Fibromatosis-like spindle cell carcinoma is a potentially challenging diagnosis, particularly on core needle biopsy, because of its morphologic similarity to many other low-grade spindle cell lesions in the breast. A definitive diagnosis of FLSCC is aided by identifying areas of epithelial differentiation in the tumor and by using a panel of immunohistochemical stains with antibodies against cytokeratins and myoepithelial markers. However, lack of cytokeratin immunohistochemical staining in a core needle biopsy demonstrating a spindle cell proliferation does not completely exclude a diagnosis of FLSCC until the entire lesion is removed and examined microscopically. Therefore, suspicion or diagnosis of FLSCC from a core needle biopsy should merit complete excision of the lesion.

Fibromatosis-like spindle cell carcinoma tumors have a clinically indolent course, similar to that of pure fibromatosis. The tumors are locally aggressive with an increased risk of recurrence, but the potential for axillary and distant metastases is low. Complete excision with adequate margins is curative in the majority of cases. No definitive conclusions can be made about the clinical behavior of FLSCC. Continued studies of FLSCC in addition to close clinical monitoring of patients following removal of these tumors will hopefully shed new light on specifications regarding the biologic behavior and appropriate management of these unusual breast tumors.

### References