Metaplastic Carcinomas of the Breast: Diagnostic Challenges and New Translational Insights

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• Comprising less than 1% of invasive carcinomas of the breast, metaplastic carcinomas are a heterogeneous group of malignant tumors in which part or all of the carcinomatous epithelium is transformed into a nonglandular (metaplastic) growth process. Metaplastic carcinomas with a low-grade spindle cell component resembling fibromatosis, as in our present case, are worthy of particular note because they are infrequent, difficult to recognize, and have a high risk of local recurrence. The differential diagnosis of metaplastic carcinomas depends on the degree of atypia observed in the tumor and includes exuberant scars, fibromatosis, nodular fasciitis, myofibroblastomas, pseudoangiomatous stromal hyperplasia, acute and chronic abscess with fat necrosis, malignant phyllodes tumor, and primary or metastatic sarcoma. Limited studies done on the molecular pathology of metaplastic carcinomas show that activation of the Wnt signaling pathway is common in these tumors and that approximately 70% of metaplastic carcinomas show EGFR gene amplification and overexpression. This may have treatment implications because they may lead to targeted treatment for patients with metaplastic carcinomas.


This case presentation reviews a challenging case of metaplastic carcinoma of the breast with spindle cell features and metastasis in an intramammary lymph node arising within a complex, sclerosing lesion. It also discusses the morphologic mimics and how to avoid misdiagnosis. Spindle cell lesions of the breast are a heterogeneous group of reactive and neoplastic entities that commonly present as diagnostic challenges. Among differential diagnoses, recognition of spindle cell carcinoma is critical because, being uncommon, many surgical pathologists, even those with vast experience, find them diagnostically challenging.

REPORT OF A CASE

This case was received as a consult for opinion from an outside institution. The patient was a 55-year-old woman whose routine mammogram showed bilateral, diffuse densities with associated pleomorphic calcifications. No discrete lesion was identified. Histologic sections from the left breast wire-localization biopsy contained a radial sclerosing lesion with a background of extensive proliferative, fibrocystic changes and a focus of low nuclear grade ductal carcinoma in situ (Figure 1, a and b). Adjacent to the radial sclerosing lesion, we noted highly cellular areas of spindle cell proliferation with mild atypia resembling a low-grade, fibromatosis-like lesion, infiltrating the fat and breast parenchyma, which raised concern for a metaplastic carcinoma (Figure 1, c). No clear squamous differentiation was observed in the tumor. However, one of the sections contained an intramammary lymph node with a focus of metastatic carcinoma exhibiting clear-cut, keratinizing squamous cells (Figure 1, d). To support the diagnosis of metaplastic carcinoma, we performed an immunohistochemical stain panel, which showed that the spindle cell results were positive for CK903, MNF116, and p63 and negative for a cytokeratin cocktail (CK AE1/AE3 and CAM 5.2) (Figure 2, a through e). Taken together with the pathologic features described above, this immunohistochemical profile supports the diagnosis of metaplastic carcinoma with spindle cell differentiation and intramammary lymph node metastasis. The opposite breast biopsy showed a radial sclerosing lesion in a background of extensive, proliferative, fibrocystic changes including florid sclerosing adenosis and the usual ductal hyperplasia with micocalcifications.

COMMENT

Comprising less than 1% of invasive carcinomas of the breast, metaplastic carcinomas are a heterogeneous group of malignant tumors in which part or all of the carcinomatous epithelium is transformed into a nonglandular (metaplastic) growth process. Metaplastic carcinomas are often clinically palpable and large. Grossly, they appear well circumscribed. Metaplastic carcinomas are almost invariably negative for estrogen and progesterone receptors and for HER2/neu overexpression. Attesting to the heterogeneity within the diagnosis of metaplastic carcinomas is the difficulty in a precise, histologic categorization. The Table shows how the World Health Organization classifies metaplastic carcinomas. Histologically, the tumor cells in metaplastic carcinomas vary from cytologically bland to highly pleomorphic, and they may range from no mitosis, as seen in low-grade fibromatosis-like tumors, to high mitotic rates.

Metaplastic carcinomas with a low-grade spindle cell component resembling fibromatosis, as in our present case,
are infrequent, difficult to recognize, and have a high risk of local recurrence. They may arise de novo or, as observed in the present case, in association with papillomas and/or complex, sclerosing lesions. Although this type of metaplastic carcinoma mimics fibromatosis, it exhibits cytokeratin immunoreactivity and may show foci of epithelial or squamous differentiation. When present, foci of ductal carcinoma in situ alert to the diagnosis. The key morphologic features in diagnosing metaplastic carcinomas with low-grade spindle cells are irregular infiltration of fat, adjacent ductal carcinoma in situ alert to the diagnosis. The key morphologic features in diagnosing metaplastic carcinomas with low-grade spindle cells are irregular infiltration of fat, adjacent ductal carcinoma in situ (often not present), entrapped ducts with variable atypia, and plump, atypical spindle cell nuclei. Pure spindle cell lesions are diagnostically challenging, and the use of immunohistochemistry may be required for a correct diagnosis. Although there is no consensus on the minimal antibody panel, several antibodies are useful in supporting the diagnosis of metaplastic carcinoma. Studies have shown that the spindle cells in metaplastic carcinomas are positive for high–molecular-weight/basal cytokeratin, such as 34βE12 and CK5/6 with high sensitivity. Broad-spectrum cytokeratin antibodies, such as MNF116, are positive as well. CAM 5.2 and AE1/AE3 antibodies are often negative or focally positive. Cytokeratin expression in metaplastic carcinomas may be focal and patchy, which underscores the need for staining several sections and carefully assessing cytokeratin expression in all fields. Additionally, the neoplastic cells frequently express smooth muscle actin, muscle-specific actin, and p63, supporting the hypothesis that metaplastic carcinomas may derive from myoepithelial cells. p63 expression may be observed in both epithelial and spindle cell components.

The differential diagnosis of metaplastic carcinomas depends on the degree of atypia observed in the tumor. Metaplastic carcinomas with bland spindle cell need to be distinguished from exuberant scars, fibromatosis, and nodular fasciitis and, more infrequently, from myofibroblastomas, pseudoangiomatous stromal hyperplasia, and acute and chronic abscess with fat necrosis. Metaplastic carcinomas with evident atypia must be distinguished from malignant phyllodes tumor and primary or metastatic sarcoma. Below, we summarize the most useful pathologic and immunohistochemical features in the differential diagnosis of metaplastic carcinomas.

Figure 1. Hematoxylin-eosin–stained sections of our case. 

a. Low-power magnification of a radial, sclerosing lesion. 
b. Adjacent focus of low nuclear grade ductal carcinoma in situ with a solid growth pattern. 
c. Low-power view of the cellular, haphazardly infiltrating spindle cells. 
d. Keratinizing squamous nest in an intramammary lymph node (original magnifications ×4 [a and c] and ×20 [b and d]).
Figure 2. a, Atypical spindle cells infiltrating breast parenchyma and adipose tissue. Although there is dense cellularity and hyperchromasia, pleomorphism is not a salient feature (hematoxylin-eosin stain, intermediate power, ×20). b, The spindle cell results are negative for a cytokeratin cocktail (CK AE1/AE3 and CAM 5.2). An entrapped lobule serves as positive internal control. c, High–molecular-weight cytokeratin stain (K903) highlights the spindle cells. d, MNF116 stain is also positive in the spindle cell component. e, p63 immunostain is positive in the nuclei of the malignant spindle cells (original magnifications ×20).
mas can mimic scars. However, the presence of hemosiderin deposition, fat necrosis, and foreign body–type giant cells favor a diagnosis of scar. A prior history of trauma, including surgery, can be a helpful clue. Mammary fibromatosis presents as a painless, slowly growing mass. On histology, it exhibits an infiltrative, locally aggressive proliferation of fibroblasts and myofibroblasts. Mammary fibromatosis may be associated with familial adenomatous polyposis, hereditary desmoid syndrome, or Gardner syndrome.8 Entrapment of benign breast parenchyma, peripheral lymphocytic infiltrate, and a long fascicular growth pattern are the best histologic clues for a diagnosis of fibromatosis rather than metaplastic carcinoma with spindle cells. The spindle cells of fibromatosis show immunoreactivity with actin, and nuclear expression of β-catenin is observed in about three-fourths of these cases.9 Myofibroblastomas are rare, benign tumors of the breast presenting as slow-growing, circumscribed, mobile masses, clinically mimicking fibroadenomas. Myofibroblastomas are composed of bland spindle cells arranged as short fascicles intermixed with variable amounts of fat, mast cells, and patchy, perivascular lymphoplasmacytic infiltrate. The cells of myofibroblastomas show expression of CD34, desmin, estrogen and progesterone receptors, and BCL2.10 Similarly, pseudoangiomatous stromal hyperplasia (PASH), which represents the other end of the spectrum of the myofibroblastic lesions, also exhibits foci of increased cellularity with a fascicular arrangement of myofibroblasts resembling the bland spindle cell malignant fibromatosis.

Nodular fasciitis is another uncommon lesion occurring usually in young adults with a short history. These lesions can be tender; however, local recurrence is rare, unlike mammary fibromatosis. Histologically, these lesions are composed of plump fibroblasts and myofibroblasts arranged in short fascicles and whorls with prominent but uniform nuclei and readily identifiable mitotic figures. Similar to fibromatosis, peripheral lymphoid aggregates may be present, but entrapped mammary ducts and lobules are not present within these lesions. Nodular fasciitis lacks the nuclear atypia of sarcomas and most spindle cell carcinomas and does not have the long, sweeping fascicles and infiltrative edge of fibromatosis. Unlike metaplastic spindle cell carcinomas, it lacks cytokeratin expression and typically expresses actin.

The distinction between metaplastic carcinoma and malignant phyllodes tumors11–12 of the breast is critical because the treatment and prognosis differ significantly. Leaflike architecture and lack of cytokeratin expression can be helpful hints favoring a diagnosis of phyllodes tumor. The possibility of a prominent stromal component of a malignant phyllodes tumor is more likely than it is with a pure sarcoma,13 and a careful evaluation for the presence of a benign, epithelial component should be attempted. Immunohistochemistry using a broad panel of cytokeratin antibodies and p63 can help exclude spindle cell carcinoma14; CD34 is often expressed by the stroma of phyllodes tumors but does not appear to be expressed by spindle cell carcinoma or fibromatosis.

The diagnosis of metaplastic carcinomas in core biopsy samples can be achieved when key diagnostic features are present. For example, an atypical and mitotically active spindle cell tumor, which is positive for cytokeratin, presents no difficulties. However, there are instances in which the diagnosis is not as straightforward. In particular, the distinction between metaplastic carcinoma with spindle areas from fibromatosis and phyllodes tumors, especially when cytokeratin stains are negative, may not be possible in core biopsies and needs to await resection of the tumor. Cytokeratin positivity may be focal in metaplastic carcinomas and may not be represented in the core-biopsy sample. We propose prudence and reserve a definitive diagnosis of metaplastic carcinoma in core biopsies to times when diagnostic features are evident. If faced with an atypical spindle cell proliferation, a simplified approach has been proposed by Tse et al15 to evaluate 2 principle components of the lesions, namely, spindle cells and epithelial cells. The spindle cell proliferation can have banal morphology, or it can be pleomorphic, and it may be mixed with an epithelial component, which may be benign or malignant. Based on these criteria, Tse et al15 divided the spindle cell lesions into 4 groups:

1. Biphasic lesions with a predominant spindle cell component and a benign epithelial (ductal) component, such as fibroadenomas, phyllodes tumors, pseudoangiomatous stromal hyperplasia, and adenomyoepithelioma.
2. Biphasic lesions with a predominant spindle cell component and a malignant epithelial (ductal) component, such as biphasic metaplastic carcinoma with a ductal component.
3. Monophasic lesions with pure, pleomorphic spindle cells only, such as monophasic metaplastic carcinoma, sarcomalike angiosarcoma, and malignant fibrous histiocytoma.
4. Monophasic lesions with pure, bland spindle cells only, such as fibromatosis-like metaplastic carcinoma, fibromatosis, and other unusual conditions like dermatofibrosarcoma protuberance.

**NEW DIRECTIONS: INSIGHTS FROM RECENT TRANSLATIONAL STUDIES**

There are limited studies on the molecular pathology of metaplastic carcinomas. A recent study by Hayes et al16 concluded that activation of the Wnt signaling pathway is common in this subtype of breast carcinoma. CTNNB1 (β-catenin), APC, and WISP3 gene mutations were seen in 11 of 27 of metaplastic carcinomas (41%) analyzed. A significant portion, approximately 70% of metaplastic carcinomas, show EGFR gene amplification and overexpression, an observation reported by Leibl et al.17 Other studies propose that metaplastic carcinomas are basallike tumors exhibiting EGFR mutation.17,18 Collectively, these studies may have treatment implications because they may lead to targeted treatment for patients with metaplastic carcinomas.
Another study proposed that the nonglandular component of metaplastic carcinomas expressed biologic markers of an epithelial to mesenchymal transition. The spindle cell component of metaplastic carcinomas exhibited overexpression of ZEB1 and downregulation of E-cadherin and was associated with acquisition of breast cancer stem-cell markers ALDH-1 and CD44(high)/CD24(low). These data shed light into the pathogenesis of metaplastic carcinomas and lead to the hypothesis that blockade of the epithelial to mesenchymal transition and/or tumor stem cells may improve patient outcome.

CONCLUSION

Metaplastic carcinomas need to be in the differential diagnosis of spindle cell lesions in the breast. A definitive diagnosis can be reached in core biopsies. However, given the notorious heterogeneity and focal cytokeratin positivity of metaplastic carcinomas, a diagnosis may not be achievable on needle biopsies. Metaplastic carcinomas with low-grade spindle cell component are deceptively bland and may resemble fibromatosis. Immunohistochemistry is helpful in the diagnosis of metaplastic carcinomas but because cytokeratin expression may be focal, a panel of anti-cytokeratin antibodies should be performed, including broad-spectrum cytokeratins and high–molecular-weight/basal cytokeratins, such as 34βE12 and cytokeratin 5/6, which are the most sensitive and specific in this setting. Basic and translational research is providing a better understanding of the pathobiology and heterogeneity of metaplastic carcinomas. A novel link has recently been established between the spindle cell component and the presence of breast cancer stem-cell features. Furthermore, new mutations have been reported in these tumors. These new data may provide novel therapeutic targets and diagnostic tools for metaplastic carcinomas in the near future.

References

17. Leibl S, Moinfar F. Metaplastic breast carcinomas are negative for Her-2 but frequently express EGFR (Her-1): potential relevance to adjuvant treatment with EGFR tyrosine kinase inhibitors? J Clin Oncol. 2005;23(7):700-704.