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Metaplastic carcinomas of the breast: Diagnostic challenges and new translational insights

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Metaplastic carcinoma; spindle cell carcinoma; K903; p63; MNF-116

INTRODUCTION

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. Amongst the differential diagnosis the recognition of spindle cell carcinoma is critical as being uncommon many surgical pathologists, even with vast experience often find them diagnostically challenging.

REPORT OF A CASE

This case was received as a consult case for opinion from an outside institution. The patient is a 55 year old female 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 in a background of extensive proliferative fibrocystic changes and a focus of low nuclear grade ductal carcinoma in-situ (Figure 1A 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 1C). 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 1D). To support the diagnosis of metaplastic carcinoma, we performed an immunohistochemical stain panel which showed that the spindle cells were positive for CK-903, MNF-116 and p63 and that they were negative for a cytokeratin cocktail (CK AE1/AE3 and CAM 5.2) (Figure 2A–E). Taken together with the pathological 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 usual ductal hyperplasia with microcalcifications.

DISCUSSION

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 non-glandular (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 (ER and PR), and for HER-2/neu overexpression. Attesting to the heterogeneity within the diagnosis of metaplastic carcinomas is the difficulty in a precise histological categorization. Table 1 shows how the World Health Organization (WHO) classifies metaplastic carcinomas. Histologically, the tumor cells in metaplastic carcinomas vary in appearance from cytologically bland to highly pleomorphic; and they may have virtually 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 our present case are worthy of particular note because they are infrequent, difficult to recognize and have a high risk of local recurrence³. They may arise de novo or, as observed in the present case in association with papillomas and/or complex sclerosing lesions². Although this type of metaplastic carcinoma mimics fibromatosis, they exhibit 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 DCIS (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 to come to a correct diagnosis. Although there is no consensus on the minimal antibody panel, several antibodies are useful in supporting the diagnosis of metaplastic carcinoma. Studies⁴⁻⁵ have shown that the spindle cells in metaplastic carcinomas are positive for high molecular weight /basal cytokeratin such as 34 β E12 and CK 5/6 with high sensitivity. Broad spectrum cytokeratin antibodies such as MNF116 are positive as well. CAM5.2 and AE1/AE3 antibodies are often negative or focally positive. We need to keep in mind that cytokeratin expression in metaplastic carcinomas may be focal and patchy, which underscores the need of 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 cells⁶. P63 expression may be observed in both epithelial and spindle cell components.⁶

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, 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 pathological and immunohistochemical features in the differential diagnosis of metaplastic carcinomas. Metaplastic carcinomas 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 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 syndrome¹⁴. Entrapment of benign breast parenchyma, peripheral lymphocytic infiltrate and a long fascicular growth pattern are the best histologic clues for a diagnosis of fibromatosis over metaplastic carcinoma with spindle cells. The spindle cells of fibromatosis show immunoreactivity with actin and nuclear expression of B-catenin is observed in about three quarters of these cases¹¹. 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 amount of fat, mast cells and patchy perivascular lymphoplasmacytic infiltrate. The cells of myofibroblastomas show expression of CD34, desmin, estrogen and progesterone receptors and bcl2¹². Similarly, pseudoangiomatous stromal hyperplasia (PASH) which represents the other end of the spectrum of the myofibroblastic lesions also exhibit foci of increased cellularity with a fascicular arrangement of myofibroblasts resembling the bland spindle cell metaplastic carcinoma.

Nodular fasciitis is another uncommon lesion occurring usually in young adults with a short history. These lesions can be tender however; the 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 nucleoli 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 also does not have the long, sweeping fascicles and infiltrative edge of fibromatosis. Unlike metaplastic spindle cell carcinomas, they lack cytokeratin expression and typically express actin.

The distinction between metaplastic carcinoma and malignant Phyllodes tumors of the breast is critical because the treatment and prognosis differ significantly. Leaf-like architecture and lack of cytokeratin expression can be helpful hints favoring a diagnosis of Phyllodes tumor. One should also keep in mind that the possibility of prominent stromal component of a malignant Phyllodes tumor is more than a pure sarcoma 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 carcinoma¹⁸; CD34 is often expressed by the stroma of Phyllodes tumors, but does not appear to be expressed by spindle cell carcinoma or fibromatosis¹⁵.

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 cytokeratin positive, 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. It is important to remember that cytokeratin positivity may be focal in metaplastic carcinomas and not be represented in the core biopsy sample. We propose to be prudent and reserve a definitive diagnosis of metaplastic carcinoma in core biopsies when diagnostic features are evident. If faced with an atypical spindle cell proliferation, a simplified approach has been proposed by Tse et al¹⁷; to evaluate two principle components of the lesions, namely spindle cells and epithelial cells. The spindle cell proliferation can have banal morphology or can be pleomorphic, and they may be mixed with an epithelial component, which may be benign or may be malignant. Based on this criterion, they divided the spindle cell lesions into four groups:

1. Biphasic lesions with predominant spindle cell component with benign epithelial (ductal) component e.g., fibroadenomas, Phyllodes tumors, pseudoangiomatous stromal hyperplasia (PASH), adenomyoepithelioma.

2. Biphasic lesions with predominant spindle cell component with malignant epithelial (ductal) component e.g., biphasic metaplastic carcinoma with a ductal component.
3. Monophasic lesions with pure pleomorphic spindle cells only e.g., monophasic metaplastic carcinoma, sarcomas like angiosarcoma, malignant fibrous histiocytoma.
4. Monophasic lesions with pure bland spindle cell only e.g., fibromatosis like metaplastic carcinoma, fibromatosis and other unusual conditions like dermatofibrosarcoma protuberance (DFSP).

NEW DIRECTIONS: INSIGHTS FROM RECENT TRANSLATIONAL STUDIES

There are limited studies on the molecular pathology of metaplastic carcinomas. A recent study by Hayes et al¹³ concluded that activation of the Wnt signaling pathway is common in this subtype of breast carcinoma. *CTNNB1* (B-catenin), *APC* and *WISP3* gene mutations were seen in 11 of 27 (41%) of metaplastic carcinomas analyzed. A significant portion, approximately 70% of metaplastic carcinomas show *EGFR* gene amplification and over-expression, an observation reported by Leibl et al²¹. Other studies propose that metaplastic carcinomas are basal-like tumors exhibiting *EGFR* mutation^{19, 20}. Collectively, these studies may have treatment implications as they may lead to targeted treatment for patients with metaplastic carcinomas.

Another study¹⁶ proposed that the non-glandular component of metaplastic carcinomas expressed biological 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⁺/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 since 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 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.

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FIGURE 1.

Hematoxylin and eosin stained sections of our case. **a.** Low power magnification of a radial sclerosing lesion (4×); **b.** Adjacent focus of low nuclear grade ductal carcinoma in situ with a solid growth pattern (20×); **c.** Low power view of the cellular, haphazardly infiltrating spindle cells (4×); **d.** Keratinizing squamous nest in an intramammary lymph node (20×).

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; **b.** The spindle cells 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.** MNF-116 stain is also positive in the spindle cell component; **e.** P63 immunostain is positive in the nuclei of the malignant spindle cells.

TABLE 1Classification of metaplastic carcinoma proposed by the World Health Organization¹.

Purely epithelial
Squamous
Large cell keratinizing
Spindle cell
Acantholytic
Adenocarcinoma with spindle cell proliferation
Adenosquamous, including mucoepidermoid
Mixed epithelial and Mesenchymal
Carcinoma with chondroid metaplasia
Carcinoma with osseous metaplasia
Carcinosarcoma