Case Report

Mammary epithelioid myofibroblastoma mimicking invasive carcinoma: case report and literature review

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Abstract: Myofibroblastoma (MFB) of the breast is a rare benign neoplasm, which exhibits several morphologic variants and presents diagnostic dilemmas for pathologists. Here, we describe a case of a 42-year-old female patient diagnosed as epithelioid MFB. This painless tumor was well-circumscribed and found in the left breast for three months. Histologically, this tumor was predominantly composed of epithelioid cells, which arranged as single cells or small clusters, and formed a cellular nodule. Tumor stroma was collagenized, with scattered myxoid areas. This case was misinterpreted as invasive lobular carcinoma in the original diagnosis. Immunohistochemical profile demonstrated positivity for desmin, SMA, calponin, CD34 and hormone receptors, whereas pan-CK, CK7, CK8, CK34bE12, CK5/6, EMA, p63 and S-100 were negative, confirming the diagnosis of epithelioid MFB. Awareness of this unusual variant and careful integration of clinicopathologic findings would be critical to diagnosis this challenging lesion and avoid potential diagnostic pitfalls.

Keywords: Breast, epithelioid myofibroblastoma, differential diagnosis, immunohistochemistry

Background

Mesenchymal lesions of the breast are uncommon lesions which present diagnostic problem for even the most experienced pathologists. Myofibroblastoma (MFB) of the breast is a rare benign mesenchymal tumor. The clinical presentation is characterized by a mobile, well defined and solid palpable tumor. Histologically, classic-type MFB is well-circumscribed and composed of spindle cells structured collagen bundles [1]. Based on histological, immunohistochemical and ultrastructural observations, tumor cells have mesenchymal origin and show myofibroblastic differentiation. This tumor causes differential diagnostic problems as it appears in several different variations. We report this case which can be confused with invasive lobular carcinoma, metaplastic carcinoma and metastatic carcinoma.

Case presentation

Clinical summary

A 42-year-old woman had a physical examination that found a painless lump in the left mammary region three months ago. There was family history of breast cancer. On physical examination, the mass was located in the region of the left breast at 3 o’clock, about 2.5 cm from the nipple. It could be palpable and measuring 2.0 cm x 1.5 cm. It had clear boundary, good activity and no adhesion with skin. Nipple discharge, abnormal skin findings and axillary adenopathy were not found. Ultrasound scan revealed a 1.5 cm x 1.0 cm oval, well-circumscribed, hypoechoic nodule in the upper external quarter. There was no obvious blood flow signal for this nodule (Figure 1). Clinically, a diagnosis of benign tumor was suspected. A complete surgical excision of the nodule was performed (Figure 2). The patient is well after a 20-month follow-up period.

Pathological findings

Grossly, the mass was well-circumscribed, ovoid, rubbery and measuring 1.5 cm x 1.2 cm x 1.0 cm, reminiscent of a fibroadenoma. The cut surface of the mass was pearly white showing whorled intersecting fascicles, without necrosis or hemorrhage.
Histological examination revealed a well-defined tumor surrounded by a thin fibrous pseudocapsule (Figure 3). A few atrophic mammary lobules were present at the periphery of the lesion. This tumor was predominantly (>70%) composed of medium-sized polygonal epithelioid cells, which had variable pale to eosinophilic cytoplasm with stellate processes, and round to oval, central or eccentric nuclei with inconspicuous or prominent basophilic nucleoli. The epithelioid cells were variously arranged as single cells, single files or in small clusters (Figure 4). In one area of the lesion, the densely packed epithelioid cells grew in alveolar groups to form a cellular nodule (Figure 5). A second population of tumor cells consisted of medium-sized spindle cells with fusiform nuclei. The spindle cells adopted a fascicular or storiform arrangement and closely intermingled with the epithelioid cells. Abundant eosinophilic collagen bundles of varying size were interspersed among single neoplastic cells or surrounding tumor nests (Figure 6A). Binucleated and multinucleated neoplastic cells were easily identified within the tumor (Figure 6B). Both cell populations may exhibit a mild-moderate nuclear pleomorphism. Scattered myxoid stromal...
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Changes and vascularization of small blood vessels were noted within the tumor. In addition, a minority of mature adipocytes were dispersed throughout the lesion. No mitotic activity, necrosis or haemorrhage was observed.

Immunohistochemical stains demonstrated that the tumor cells (Figure 7A) were diffusely immunoreactive for vimentin, desmin (Figure 7B), α-smooth muscle actin (SMA) (Figure 7C), calponin (Figure 7D), estrogen receptor (ER) (Figure 7E), progesterone receptor (PR) (Figure 7F) and multifocally positive for CD34 (Figure 7G). No immunoreactivity was obtained with pan-CK (Figure 7H), CK34bE12, CK5/6, CK7, CK8, epithelial membrane antigen (EMA), E-cadherin, p120, GCDFP-15, CD99, bcl-2, CD10, p63 (Figure 7I), S-100 and CD68. The proliferative fraction of tumor cells, detected with Ki-67, was 1-3%. The immunohistochemical findings were consistent with a diagnosis of MFB.

Discussion

MFB was originally described as a typical tumor occurring in the breast of adult males. Currently, it is believed that MFB can occur in both sexes [1-5]. The patients range in age at presentation from 25 to 87 years [3, 4]. Tumor size ranges from a few millimeters to 11 cm [4]. Macroscopically, MFB is generally a well-delineated, round to oval, firm or rubbery, unencapsulated mass [1-5]. The cut surface is usually gray-white to tan, lobulated, and bulging. In some cases, the cut surface may have focal to extensive lipomatous or mucoid appearance. Necrosis, cystic degeneration, and hemorrhage have not been reported. Microscopically, the MFB is generally a well-circumscribed mass with pushing borders, and devoid of breast ducts and lobules. The classical MFB composed of bland-looking spindle cells with infrequently nuclear grooves or pseudoinclusions, one-to-two inconspicuous nucleoli, relatively abundant eosinophilic cytoplasm, and indistinct cell borders [1-5]. The spindle cells are arranged in short intersecting fascicles and are frequently interrupted by varying degrees of hyalinized collagen and/or myxoid stroma. Scattered epithelioid cells, multinucleated giant cells and fat cells may be noted. Immunohistochemically, the MFBs are usually reactive for vimentin, desmin, actin, ER, PR and CD34 [1-6]. Immunoreactivity is obtained for bcl-2, CD10, CD99, CD68, factor XIIIa in some cases [5]. A focal expression of h-caldesmon can be encountered [5, 7]. Cytokeratins, EMA, HMB-45, S-100 and c-Kit (CD117) are consistently negative [5].

Several variants of MFB have been recognized based on histologic features, including cellular, epithelioid, lipomatous, collagenized/fibrous, myxoid, infiltrative, and deciduoid-like variants. The recognition of the wide morphologic spectrum exhibited by MFB is crucial to avoid confusion with other benign or malignant breast lesions. Among these variants, the epithelioid MFB may represent a diagnostic pitfall, and can be a significant source of diagnostic error [5, 8, 9].

Mammary epithelioid MFB is rare with less than 15 cases have been reported in the English literature (Table 1). This variant is composed mostly of epithelioid cells comprising at least 50% of the tumor [9]. The epithelioid cells are medium-sized, oval to polygonal, with abundant eosinophilic cytoplasm and round to oval, eccentrically placed nuclei containing small evi-
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Mitoses are rarely encountered within epithelioid variant (mitotic rate of 0-2/10 HPFs), and atypical mitoses are generally not seen [5, 9]. A variable number of binucleated or multinucleated neoplastic cells can be observed. The epithelioid cells are variously arranged in nests, cords, alveolar groups or even in single cells. A single cell file arrangement, as seen in invasive lobular carcinoma, can be noted. The tumor cells are variably embedded in a fibrous or myxoid stroma. Hyalinized collagen bundles of varying size are detected among tumor cells. The immunohistochemical profile of epithelioid variant resembles that of classic MFB. Epithelioid MFB may show cytologic atypia and arrange in a multinodular growth pattern [10]. If there is no mitoses, necrosis and infiltrative borders, the diagnosis of atypical MFB would be an appropriate choice. All patients reported in literature showed no recurrence or metastasis during the follow-up time.

The challenge faced when dealing with epithelioid MFB is to differentiate it from invasive mammary carcinomas [5, 9, 11]. The admixture of epithelioid cells with fibro-fatty stroma imparts a pseudo-infiltrative growth pattern, reminiscent of invasive carcinoma. Literature review show that >40% epithelioid MFB cases were initially misinterpreted as invasive carcinoma, especially for invasive lobular carcinoma (Table 1). In our case, the epithelioid cells with mild-moderate pleomorphism arranged in small clusters, cords or individually, and closely intermingled with collagen fibers, resulting in a pseudo-infiltrative appearance simulating invasive pleomorphic lobular carcinoma. This case was misinterpreted as a lobular carcinoma in the original diagnosis. Immunoreactivity with hormone receptors and negative staining for E-cadherin reinforced the mistaken impression of invasive lobular carcinoma. However, the well-circumscribed borders and smooth external surface of the mass, and the absence of

Figure 7. Epithelioid cell population. H&E-stained (A), Immunohistochemical staining showed the tumor cells to be positive for desmin (B), SMA (C), calponin (D), ER (E), PR (F), and CD34 (G). No immunoreactivity was obtained with pan-CK (H), and p63 (I).
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Table 1. Mammary epithelioid MFB reported in previous studies

<table>
<thead>
<tr>
<th>Cases</th>
<th>Studies</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Size (cm)</th>
<th>Cell types</th>
<th>Growth pattern</th>
<th>Mitoses</th>
<th>Cell atypia</th>
<th>Initial diagnosis</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reis-Filho et al. [4]</td>
<td>25</td>
<td>M</td>
<td>5</td>
<td>E+P</td>
<td>Nests, chords and alveolar</td>
<td>None</td>
<td>None</td>
<td>Epithelioid MFB</td>
<td>Lumpectomy</td>
<td>NA</td>
</tr>
<tr>
<td>2-5</td>
<td>Magro et al. [9]</td>
<td>49/57</td>
<td>F/M</td>
<td>1.5/2</td>
<td>R+E</td>
<td>Solid</td>
<td>None</td>
<td>Focal, mild</td>
<td>Epithelioid MFB</td>
<td>Lumpectomy</td>
<td>No recurrence (23 mo)</td>
</tr>
<tr>
<td>6</td>
<td>Magro et al. [10]</td>
<td>66</td>
<td>F</td>
<td>1</td>
<td>E+S</td>
<td>Multinodular</td>
<td>&lt;1/50 HPFs</td>
<td>Mild to moderate</td>
<td>Atypical epithelioid MFB</td>
<td>Lumpectomy</td>
<td>No recurrence (48 mo)</td>
</tr>
<tr>
<td>7</td>
<td>Arafah et al. [11]</td>
<td>53</td>
<td>F</td>
<td>1.6</td>
<td>E+S</td>
<td>Linear, curvilinear arrays</td>
<td>None</td>
<td>None</td>
<td>Invasive lobular carcinoma</td>
<td>Lumpectomy, SLND</td>
<td>No recurrence (56 mo)</td>
</tr>
<tr>
<td>8, 9</td>
<td>Alizadeh et al. [14]</td>
<td>67/50</td>
<td>F/M</td>
<td>1/3</td>
<td>E+S+P</td>
<td>Nests and nodules</td>
<td>None</td>
<td>Moderate</td>
<td>Metaplastic carcinoma</td>
<td>Lumpectomy</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Yildiz et al. [15]</td>
<td>80</td>
<td>M</td>
<td>3</td>
<td>E+R</td>
<td>Single file and small clusters</td>
<td>NA</td>
<td>None</td>
<td>Epithelioid MFB</td>
<td>Lumpectomy</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>Magro G. [16]</td>
<td>40</td>
<td>F</td>
<td>NA</td>
<td>E</td>
<td>NA</td>
<td>NA</td>
<td>Local control</td>
<td>Epithelioid MFB</td>
<td>Lumpectomy</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>Zalewska et al. [17]</td>
<td>65</td>
<td>F</td>
<td>1.2</td>
<td>E+S</td>
<td>Strands and rows</td>
<td>None</td>
<td>Slight to moderate</td>
<td>Invasive lobular carcinoma</td>
<td>Mastectomy and ALND</td>
<td>NA</td>
</tr>
</tbody>
</table>

E, epithelioid-shaped cells; F, polygonal-shaped cells; R, rounded shaped cells; S, spindle shaped cells. y, year; NA, not available; ALND, axillary lymph nodes dissection; SLND, sentinel lymph node dissection; F, female; M, male; MFB, myofibroblastoma.
mitoses were features against malignancy. This specimen was received in West China Hospital for a second opinion. Additional immunohistochemical studies supported a diagnosis of epithelioid MFB.

The second differential diagnosis is metaplastic carcinoma. Several subtype of metaplastic carcinoma contain epithelial and spindle cell component, including fibromatosis-like metaplastic carcinoma and spindle cell carcinoma. In our case, the epithelioid cells intimately admixed with spindle neoplastic cells in some areas, which made it necessary to differentiate this lesion from metaplastic carcinoma. The absence of infiltration of surrounding tissue, marked cytologic atypia, and high mitotic activity, along with insidious onset, are helpful features to exclude spindle cell carcinoma. Most importantly, immunohistochemistry can assist in correctly classifying these challenging lesions and avoiding diagnostic pitfalls. The spindle cells in metaplastic carcinoma will be variably positive for cytokeratins, particularly high molecular weight cytokeratins. Furthermore, p63 has been reported to be a highly sensitive and specific marker of metaplastic carcinoma [12]. Whereas epithelioid MFB cells are always negative for cytokeratins and p63. Additionally, combination of clinical history and immunohistochemistry is helpful to rule out the metastatic carcinoma from other sites.

Cytogenetic studies found that most of the mammary MFB showed FOXO1/13q14 deletion, which suggested a histogenetic link between MFB, spindle cell lipoma and cellular angiofibroma [13]. The absence of this genetic change in mammary epithelioid MFB may be associated with it’s epithelioid morphology.

Conclusion

As an unusual morphological variant, the epithelioid MFB may represent a potential diagnostic pitfall, especially when interpreting needle core biopsy. Pathologists should keep this tumor in mind for differential diagnosis when encountering an epithelial or epithelioid lesion with a low mitotic rate, mild-moderate nuclear pleomorphism, and pushing borders. Careful integration of clinical information, and close examination of the gross, histopathologic, and immunohistochemical findings can assist in establishing the correct diagnosis and avoiding a misdiagnosis of malignancy.

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Disclosure of conflict of interest

None.

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