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Characterization of the leiomyomatous variant of myofibroblastoma: a rare subset distinct from other smooth muscle tumors of the breast

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Running head: Leiomyomatous myofibroblastoma of the breast

Conflicts of interest: None
ABSTRACT

Mammary myofibroblastoma is a benign spindle cell tumor that can show variable morphologic patterns and lines of differentiation. Myofibroblastoma belongs to a family of CD34-positive tumors with similar morphology that show a deletion of 13q14, which includes \( RB1 \) and \( FOXL1A \) genes. A subset of these tumors demonstrates distinct smooth muscle differentiation which can be confused with other smooth muscle tumors of the breast, itself constituting a rarified morphological subgroup. We aimed to characterize 4 cases of the leiomyomatous variant of myofibroblastoma arising in the breast by clinicopathological, immunohistochemical, and molecular means. All 4 examples arose in women aged 41-62 years (median, 46.5 years). Tumors ranged in size from 1.7 to 2.5 cm (median, 2.2 cm). Morphologically, all tumors were characterized by bundles of smooth muscle cells with elongated cigar-shaped nuclei and eosinophilic cytoplasm. All four tumors showed diffuse positive staining with desmin, caldesmon, smooth muscle actin (SMA), estrogen receptor (ER), and Bcl-2. \( CD34 \) staining was diffusely positive in two cases, weak and patchy in one case, and was negative in one case. Two of four (50%) tumors showed deletion of \( RB1 \) by fluorescence in situ hybridization (FISH). Loss of Rb staining was seen in one tumor with \( RB1 \) deletion by FISH, while intact Rb staining was observed in one non-deleted case studied. In conclusion, this rare variant of myofibroblastoma is a distinct subgroup of tumors among an already uncommon category of (smooth muscle) breast tumors. Some reported examples of “parenchymal leiomyoma” may represent the leiomyomatous variant of myofibroblastoma.

Key words: myofibroblastoma, leiomyomatous, RB1, 13q14

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INTRODUCTION

Tumors of smooth muscle derivation are exceedingly rare in the breast, largely in part due to the absence of indigenous smooth muscle in this anatomic site, with the exception of the nipple. Still, reports of benign smooth muscle dominant tumors such as leiomyomas and myoid (or “muscular”) hamartomas have been described in the literature [1-11]. In addition, other benign mammary entities are known to occasionally demonstrate smooth muscle differentiation to varying degrees such as fibroadenomas, phyllodes tumors, and myofibroblastomas. Due to the rarity of these tumors, a critical review of benign mammary smooth muscle tumors has not been performed. This invariably perpetuates not only the ambiguity of classifying them in practice but also understanding them as part of distinct subgroup possessing specific clinical, morphologic, immunohistochemical and/or molecular features.

Mammary myofibroblastoma is a benign stromal tumor characterized by bland spindle cells growing in fascicles with intervening bands of collagen and variable amounts of fat. Various morphologic variants have been described, including cellular, infiltrating, epithelioid, and myxoid, among others, and some show heterologous differentiation in the form of mature chondroid, osseous, or leiomyomatous components[12,13]. In recent years, myofibroblastoma and morphologically similar non-mammary CD34-positive tumors including (extra) mammary-type myofibroblastoma, spindle cell lipoma, and cellular angiofibroma of vulva have been found to share a deletion of 13q14, which includes \(RB1\) and \(FOX01A\) genes[14-18]. In reported cases of mammary myofibroblastomas specifically, deletion of 13q14 has been found in 78.5% (11/14) examples studied [14,16,18-21]. Identifying this common deletion in CD34-positive tumors motivated us to better characterize a rare variant of myofibroblastoma which can be non-immunoreactive for CD34 – considered a hallmark of mammary myofibroblastomas, which in its absence, may pose a diagnostic pitfall. Moreover, we aimed to better understand how the leiomyomatos variant of myofibroblastomas fits in the overall context of benign smooth muscle tumors in the breast.
MATERIALS AND METHODS

Case selection

This study was conducted under an institutional review board (IRB) - approved protocol. Four cases of mammary myofibroblastoma with leiomyomatous differentiation were identified from our surgical pathology and breast consultation files. Slides were reviewed by two breast pathologists (TD, SS). Clinical data were obtained from electronic patient records and from submitting pathologists and clinicians.

Immunohistochemistry

Immunohistochemical staining was accomplished using the Bond III Autostainer (Leica Microsystems, Illinois, USA) (Table 1). Formalin-fixed paraffin-embedded (FFPE) whole tissue sections were first baked and deparaffinized. For antigen retrieval, slides were heated on the Bond III Autostainer at 99-100°C. Sections were then subjected to sequential incubation with the endogenous peroxidase block, primary antibody, post-primary (equivalent to secondary antibody), polymer (equivalent to tertiary antibody), diaminobenzidine (DAB) and hematoxylin. Finally the sections were dehydrated in 100% ethanol, and mounted in Cytoseal™ XYL (Richard-Allan Scientific, Kalamazoo, MI). Appropriate positive and negative controls were included.

Florescence in situ hybridization (FISH) Analysis

Dual-color interphase FISH was performed on 5 µm–thick paraffin whole-tissue sections from selected blocks using the following probes: RB1 (red) and a control probe on 10q (green). The RB1 probe was made from BAC RP11-305D15 DNA and the control probe was made from BAC RP11-431P18 [BACPAC Resource Center (BPRC), Children's Hospital Oakland Research Institute (CHORI), Oakland, California, USA] as per standard methods. Cutoff value for RB1 deletion was determined by analyzing five normal FFPE tonsil samples. The cutoff values were calculated using the using the beta inverse function formula

\[ = \text{BETAINV(CONFIDENCE LEVEL,} \#\text{FALSE POSITIVE+1,} \#\text{CELLS SCORED}) \] on an Excel spread sheet. A sample was considered to demonstrate RB1 deletion if \( \geq 18.5\% \) cells showed allelic deletion of RB1 gene. A minimum of 100 non-overlapped intact (uniform DAPI staining with intact nuclear contours) interphase nuclei of consecutive cells in at least two different areas of the section was scored. An H&E-stained section was used to verify the presence of tumor. Spindle cell lipomas of soft tissue served as positive controls for RB1 deletion.
RESULTS

A summary of the clinicopathologic, immunohistochemical, and cytogenetic features of studied cases is outlined in Table 2.

Clinical Characteristics

Patients included four women aged 41-62 years (median, 46.5 years) (Table 2). All patients presented with a unifocal mass (right breast: 1 case; left breast: 3 cases). Tumors ranged in size from 1.7 to 2.5 cm (median, 2.2 cm). Two cases were evaluated in the form of needle core biopsy samples, 1 was evaluated from an excisional biopsy specimen, and in the remaining case, needle core biopsy and excisional biopsy material were available. Of the cases in needle core biopsy material, 1 case was subsequently excised and showed morphologically-similar myofibroblastoma. Follow-up surgical information was not available for the remaining patient.

Pathologic features

Morphologic and immunohistochemical features

All tumors were circumscribed with rounded borders and showed smooth muscle (leiomyomatous) differentiation by morphology and immunohistochemistry. These tumors were composed of bundles of smooth muscle cells with elongated cigar-shaped nuclei and eosinophilic cytoplasm (Figures 1-2). Interspersed fat and scattered mast cells were present in 3 tumors while one tumor lacked fat and mast cells. Neither cytologic atypia nor mitotic figures were identified. Necrosis was absent in all cases. Two cases showed intratumoral benign breast glandular tissue. In both, scattered isolated glands were present that collectively constituted a minor component (<10%) of the tumors (Figure 1). All four tumors showed diffuse strong positive staining with desmin, caldesmon, smooth muscle actin (SMA), estrogen receptor (ER), and Bcl-2. Two tumors showed diffuse positive staining with CD34 (Figure 2B). One tumor showed complete absence of CD34 staining. The remaining tumor showed patchy weak staining in approximately 10% to 20% of tumor cells (Figure 1D).

Assessment of RB1 loss by FISH and Rb immunohistochemistry
Two of four (50%) tumors showed deletion of *RB1* by FISH (Figure 1F). Deletion of *RB1* was seen in 50% of tumor cells in one case and 30% of tumor cells in the other. The remaining cases showed a normal signal pattern for *RB1*. Immunohistochemical staining for Rb was performed on 2 cases, including one case that showed *RB1* deletion by FISH. Lesional cells in the tumor showing deletion by FISH showed loss or markedly diminished nuclear Rb staining compared with normal endothelial cell nuclei (Figure 1G) in the majority (>80%) of cells. The remaining (non-deleted) tumor showed intact Rb nuclear staining.

**DISCUSSION**

After its initial characterization nearly 3 decades ago by Wargotz et al.[13], several morphologic variants of mammary myofibroblastoma have been described [12,13]. A relatively less common variant of mammary myofibroblastoma is one that demonstrates smooth muscle differentiation. The differential diagnosis of leiomyomatous myofibroblastoma includes other benign tumors such as leiomyoma, myoid hamartoma, and fibroepithelial tumors with prominent stromal myoid metaplasia. The list of diagnostic possibilities expands in a small core biopsy sample due to the fact that morphologic features of smooth muscle differentiation may not be entirely obvious. Therefore, the differential diagnosis of such tumors with a spindle cell pattern includes additional entities, some of which are biologically more aggressive such as fibromatosis and spindle cell metaplastic carcinoma.

In our study, we found that leiomyomatous myofibroblastomas can be non-reactive for CD34, an observation that has not been sufficiently emphasized in the literature. Only four examples of this variant have been described in the literature, and CD34 expression in all reported cases was absent or focal [21-24]. Thomas et al. reported a case of myofibroblastoma with smooth muscle differentiation occurring at the periphery of the tumor[24]. The conventional spindle cell component of the tumor was CD34-positive with scattered cells showing desmin staining, while the peripheral smooth muscle component was negative for CD34 and showed strong staining with desmin. Similarly, Mnif et al. reported a myofibroblastoma with smooth muscle differentiation occurring in a man in which smooth muscle areas showed staining with actin, desmin, and
caldesmon, while CD34 staining was present in the conventional spindle cell areas of the tumor[22]. Fukunaga and Ushigome described a myofibroblastoma with smooth muscle differentiation with pleomorphic atypical cells, akin to a symplastic leiomyoma of the uterus[23]. They describe CD34 staining in “some cells” without further detail, while diffuse strong positivity was seen with desmin, smooth muscle actin, and HHF-35 (muscle specific actin). The morphologic and immunohistochemical features of our 4 studied cases are similar to these previously reported, including half demonstrating weak absent or weak patchy immunoreactivity for CD34.

There is some debate regarding the true nature of the neoplastic cells of myofibroblastoma. Evidence from ultrastructural studies shows that myofibroblastoma cells appear to have properties more indicative of smooth muscle, rather than myofibroblasts [25-27]. However, regardless of the cell of origin, myofibroblastoma cells have features of undifferentiated CD34-positive mesenchymal cells that can undergo differentiation to specific cell types, such as smooth muscle or cartilage. During differentiation, CD34 expression may be lost while expression of other markers such as actins and caldesmon are gained. In some tumors, there may be distinct less-differentiated and more-differentiated components that may or may not be recognizable on H&E examination and correspond to CD34-positive and negative areas, respectively. One of the four cases in this study demonstrated patchy immunoreactivity for CD34 which is in line with these aforementioned observations.

In such CD34-poor cases, well-informed pathologists can further investigate the possibility of myofibroblastoma by performing additional immunohistochemical stains such as ER, desmin, smooth muscle actin, and bcl-2[28-30]. It is important to note here that ER should be utilized with caution in this diagnostic scenario for several reasons. In limited material, the infiltrative and epitheloid variants of myofibroblastoma can be deceptively similar in appearance to invasive carcinoma, particular the lobular type, and furthermore, both are strongly and diffusely immunoreactive for ER. In such situations, as a priority above other stains, a cytokeratin immunostain should be performed to confirm the cell lineage. ER may also be immunoreactive in smooth muscle tumors of the breast. In cases where lesional cells show smooth muscle differentiation, confirmation of leiomyomatous change (versus myofibroblastic) can be performed by immunohistochemical staining for h-caldesmon [31,32]. In the appropriate clinical setting of a well-circumscribed breast mass,
positive h-caldesmon and ER staining with or without concurrent CD34 expression can strongly suggest a smooth muscle tumor including the leiomyomatous variant of myofibroblastoma, and effectively exclude other possibilities such as fibromatosis and spindle cell metaplastic carcinoma.

The finding of “deficient” staining with Rb is theoretically limited by the frequency in which leiomyomatous myofibroblastomas harbor the 13q14 deletion containing the \textit{RB1} gene. In a recent study of 143 mammary-type myofibroblastomas, 10 of which originated in the breast, 92% of studied cases lacked Rb protein expression\cite{28}. While the exact number of mammary myofibroblastomas devoid of Rb expression was not specified, it is highly probable that some were negative. However, it is important to recognize that the presence of 13q14 deletion was not confirmed in these cases, therefore, the correlation between 13q14 deletion and loss of Rb protein expression is not known for mammary myofibroblastomas. Among the reported cases of the leiomyomatous variant arising in the breast\cite{21-24}, only one case has been by FISH and was found to harbor this deletion, however, immunohistochemical staining for Rb was not performed \cite{21}.

The current report is the largest series of leiomyomatous mammary myofibroblastomas to be studied and moreover, the first to report the presence of the 13q14 deletion and Rb loss by immunohistochemistry in studied cases. Two of four cases (50%) were found to harbor this deletion. One of these two cases showed absent and weak staining for Rb (Figure 1G), and immunohistochemical staining for Rb was not performed on the other. One additional case showed strong positive staining for Rb and no deletion was found by FISH. Rb staining was not performed in the remaining case. These findings raise the possibility that the presence of 13q14 deletion in the leiomyomatous variant of myofibroblastoma may not always lead to complete absence of Rb staining by immunohistochemistry. However, more cases need to be studied to validate such preliminary observations. The significance of relatively weaker Rb staining intensity in cases where the deletion is identified (as compared to non-deleted cases) also needs to be further investigated but may prove to be confirmatory of the underlying cytogenetic aberration.
Theoretically, the use of Rb protein expression is only of value if it demonstrates absence in a given case, as this further supports a diagnosis of leiomyomatous myofibroblastoma over other benign smooth muscle tumors of the breast. Conversely, while yet to be confirmed by additional independent studies, the retention of Rb expression may not help to further narrow the differential diagnosis. As for CD34 expression, we were unable to find a correlation between staining (or lack thereof) and the presence of the 13q14 deletion due to the small number of tumors studied, as is true in other studies [16-18,21]. CD34-negativity is likely related to the smooth muscle differentiation in these tumors since this has been routinely reported in mammary leiomyomas as well [3,4,6,8,33].

Our aim to better characterize this rare variant of an already uncommon entity of myofibroblastoma led us to ponder how this variant fits in the overall context of benign smooth muscle dominant tumors in the breast. Historically, benign smooth muscle tumors arising in the breast are rare and include only a few entities: leiomyoma, myoid hamartoma, and leiomyomatous variant of myofibroblastoma. Leiomyomas that are referred to as “superficial” or “cutaneous” in type most commonly arise in the nipple or subareola where native smooth muscle is abundant (Figure 3). However, the origin of deep seated examples known as “parenchymal” leiomyomas is uncertain. Various possibilities of histogenesis have been proposed, including the muscular wall of arterial vessels, myoepithelium of mammary glands, pluripotent mesenchymal cells, or migrated cells from the areolar region into the deeper breast tissue during embryonic development[3,34].

To date, about forty cases of parenchymal leiomyomas of the breast have been reported with the largest series published by Jones et al. in 1994[1,3-8,10,33-35]. After perusal of these reports, it became obvious that many of them lacked thorough microscopic descriptions and/or informative histologic images. Many show a high magnification of lesional cells but the incorporation of adipocytes or normal breast glandular tissue within these tumors is not clearly addressed in almost all reports reviewed. One report of parenchymal leiomyoma included a low magnification image of the tumor with incorporated adipose and breast glandular tissue [33]. We surmised that at least some reported parenchymal leiomyomas would be better classified as
myofibroblastomas with leiomyomatous differentiation or myoid hamartomas. Needless to say, none of these were tested for the 13q14 deletion or stained for Rb protein by immunohistochemistry.

Myoid hamartomas (Figure 4) can be difficult to identify on limited material such as core biopsy samples, but once the tumor is excised, the admixture of smooth muscle, benign adipose and breast glandular tissue becomes evident. It should be emphasized that both adipose tissue and the presence of sclerosing adenosis are critically important for the diagnosis of myoid hamartoma as the smooth muscle component of these tumors is believed to originate from myoid metaplasia of its investing myoepithelium. Leiomyomatous myofibroblastomas by definition should not contain sclerosing adenosis. In myoid hamartomas, breast glandular tissue is characteristically more abundant than what is seen in leiomyomatous myofibroblastomas. Also, the components of smooth muscle, adipose tissue, and breast glandular tissue typically occupy regions of a given tumor of myoid hamartomas, unlike leiomyomatous myofibroblastomas where smooth muscle represents the main composition of the tumor and adipocytes and breast lobules are scattered within the tumors, if present.

In summary, tumors demonstrating a predominant smooth muscle phenotype constitute a very small subset of entities native to the breast. In routine practice, it is important to recognize the presence of smooth muscle differentiation in a given case since the differential diagnosis of a mass-forming smooth muscle dominant tumor in the breast proper is limited to myoid hamartoma, parenchymal leiomyoma, and leiomyomatous myofibroblastoma. If smooth muscle features are not evident morphologically, particularly in small samplings, a negative CD34 result could lead to the erroneous exclusion of myofibroblastoma from the differential diagnosis. When smooth muscle features are histologically obvious, then it may be useful to include Rb as part of an initial immunohistochemical workup which if confirmed by other independent studies, an absent (or weak) staining result would favor a diagnosis of leiomyomatous myofibroblastoma over other smooth muscle tumors. In this study, the characterization of the leiomyomatous variant of myofibroblastoma led us to re-assess benign smooth muscle tumors known to arise in the breast. Our investigations led us to surmise that at least a subset of the reported cases of parenchymal leiomyomas may in fact represent leiomyomatous myofibroblastomas.
REFERENCES


FIGURE LEGENDS

Figure 1. Myofibroblastoma with leiomyomatous differentiation that showed deletion of RB1 by FISH.

(A) Bundles of elongated spindle cells with pink cytoplasm, characteristic of smooth muscle differentiation, are present in the tumor (H&E, 200X). (B) Cells show cigar shaped-nuclei without atypia. Scattered mast cells are present (H&E, 400X). (C) Benign inactive breast glandular tissue was present within the tumor as rare scattered foci (H&E, 200X). (D) Weak patchy staining with CD34 is seen (CD34, 200X). (E) Caldesmon shows strong and diffuse staining (caldesmon, 200X). (F) Interphase FISH hybridized with RB1 (red) and a control probe on 10q (green) demonstrates monoallelic loss of RB1 (13q14), indicated by the presence of a single red signal in the majority of nuclei. (G) Lesional cells showed loss or decreased nuclear expression of Rb protein compared with endothelial cell nuclei and inflammatory cells (Rb, 200X).

Figure 2. Myofibroblastoma with leiomyomatous differentiation – needle core biopsy and subsequent excisional biopsy

(A-D, needle core biopsy) (A) The tumor is composed of bundles of smooth muscle cells (H&E, 200X). Inset: tumor cells have cigar-shaped nuclei with eosinophilic cytoplasm (H&E, 400X). Diffuse immunohistochemical staining in the tumor is observed with (B) CD34, (C) smooth muscle myosin, and (D) estrogen receptor. (B-D, 200X) (E, F, excisional biopsy) (E) Low and (F) high power images show a circumscribed tumor in the breast containing scattered adipocytes within the tumor. (E, H&E, 20X), (F, H&E, 200X).
Figure 3: Leiomyoma of the nipple  (A) Incisional biopsy of the nipple shows smooth muscle bundles arising in thick collagen bundles characteristic of the dermis (H&E, 40X). (B) Closer inspection of this proliferation demonstrates its confluent growth, not characteristic of native smooth muscle in this area (H&E, 100X). (C) Low power magnification of an excised nipple containing a leiomyoma (H&E, 20X).

Figure 4: Myoid hamartoma  (A) Similar to leiomyomatous myofibroblastomas, myoid hamartomas are composed of smooth muscle, adipose tissue, and breast glandular tissue. However, adipose tissue in these tumors tend to aggregate and constitute large areas of a given tumor (H&E, 20X). (B) The smooth muscle component of these tumors is intimately associated with sclerosing adenosis and is thought to arise from myoid metaplasia of its investing myoepithelium. (H&E, 40X). (C) Another area of this tumor where smooth muscle is admixed with adipose tissue is seen (H&E, 40X).
Table 1. Antibodies, retrieval methods, dilutions, and sources of immunohistochemical stains employed in this study.

<table>
<thead>
<tr>
<th>Antibody</th>
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<th>Dilution</th>
<th>Source</th>
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<td>H2 - 20 min</td>
<td>RTU</td>
<td>Leica</td>
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<tr>
<td>Desmin</td>
<td>D33</td>
<td>H1 - 10 min</td>
<td>1:30</td>
<td>Dako</td>
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<tr>
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<td>NT</td>
<td>1:200</td>
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<tr>
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<td>1:100</td>
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<td>Rb</td>
<td>4H1</td>
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<td>1:100</td>
<td>Cell Signaling</td>
</tr>
</tbody>
</table>

Abbreviations: H2, heated in Bond Epitope Retrieval 2; RTU, ready to use; H1, heated in Bond Epitope Retrieval 1; ER, estrogen receptor; SMA, smooth muscle actin; NT, no treatment
Table 2. Clinical, morphologic, immunohistochemical, and cytogenetic features of myofibroblastomas with leiomyomatous differentiation

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Spec. type</th>
<th>Size (cm)</th>
<th>Tumor border</th>
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<th>Breast glands in tumor</th>
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<th>Rb</th>
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Abbreviations: yrs, years; cm, centimeter; spec, specimen; ER, estrogen receptor; SMA, smooth muscle actin; Rb, retinoblastoma protein; FISH, fluorescence in situ hybridization; circ, circumscribed; NCB, needle core biopsy; EX, excisional biopsy; NP, not performed