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Lipomatous myofibroblastoma: a potential diagnostic pitfall in the spectrum of the spindle cell lesions of the breast

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Abstract We report on two cases of myofibroblastoma (MFB) of the breast comprised predominantly of a mature fatty component, representing approximately three quarters of the entire tumour area. Both tumours consisted of a well-circumscribed lipomatous tumour mass containing dispersed nodular or irregularly shaped spindled cellular areas. The fatty component was represented exclusively by mature adipocytes, uniform in size and shape, lacking nuclear pleomorphism. The cellular areas contained spindly to oval cells with morphological and immunophenotypical features typical of MFB. The two components were so intimately admixed that a finger-like infiltrating growth pattern was apparent.

The cases reported here as "lipomatous MFB" aim to clarify further the morphological spectrum of MFB of the breast. Lipomatous MFB may potentially mimic other benign or aggressive tumour-like lesions or even bland-looking malignant spindle cell tumours such as fibromatosis, nodular fasciitis, spindle cell lipoma, spindle cell liposarcoma, spindle cell variant of metaplastic carcinoma, spindle cell malignant myoepithelioma, and low-grade fibrosarcoma/malignant fibrous histiocytoma. The histogenesis of the present bimorphic mesenchymal tumours could be explained as the result of a dual, myofibroblastic and lipomatous, differentiation from a common pluripotential mesenchymal precursor cell, probably represented by the vimentin$^+$/CD34$^+$ fibroblast of the mammary stroma.

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Introduction

Myofibroblastoma (MFB) of the breast is a relatively rare benign spindle cell tumour first described by Wargotz et al. [33]. However, it is likely that examples of this tumour have been previously recorded in the literature as "benign spindle cell tumours" [29]. The name "MFB" indicates that most basic cells of the tumour are myofibroblastic in nature as shown by immunohistochemistry and electron microscopy [2, 22, 33]. It has become clear that MFB of the breast may exhibit microscopically a greater variety of morphological features than originally described. This may represent a potential diagnostic pitfall [9, 12, 16, 22]. Although foci of fat may be found in MFB of the breast [2, 22], to our knowledge, a tumour composed predominantly of a mature lipomatous component has not been reported.

We report two cases of MFB of the breast with a prominent (approximately 75% of the tumour area) mature fatty component and for which the term "lipomatous MFB" is proposed.

Clinical history

Case 1

A 45-year-old woman presented with a painless, free-movable, solitary, 3-cm lump in her left breast. Mammography showed a round, dense, sharply demarcated nodule. There was no evidence of calcifications. Diagnosis of fibroadenoma was suspected. A complete surgical excision of the nodule was performed. The patient is well after a 1-year follow-up period.

Case 2

A 69-year-old man presented with a painless, solitary, 2-cm lump in his right breast that appeared firm and well circumscribed on physical examination. Preoperative ultrasonography and mam-

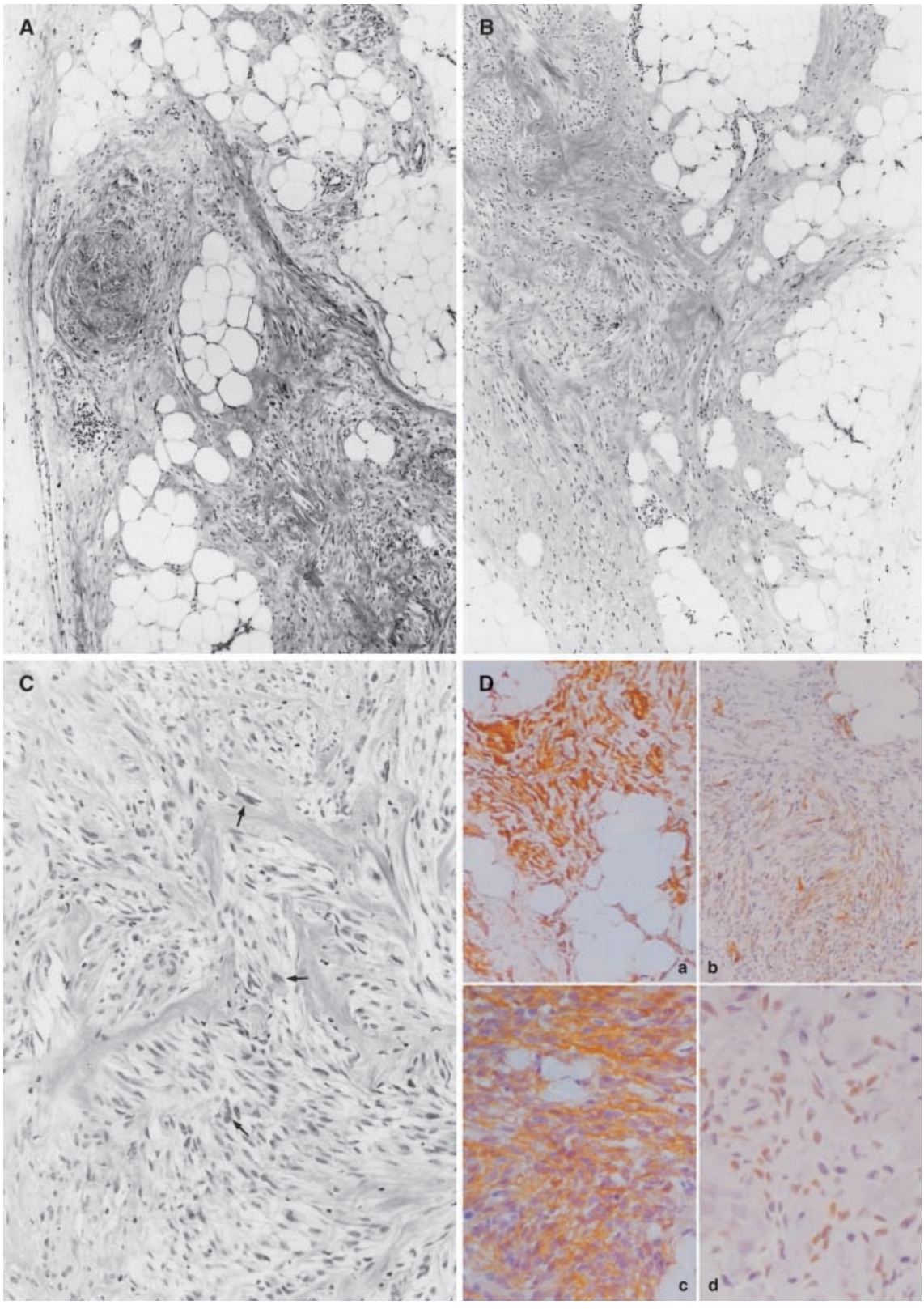

Fig. 1 **A** Well circumscribed lipomatous tumour containing nodular and irregularly shaped fibrous spindled cellular areas. Haematoxylin-eosin, ×80. **B** Tumour area showing an infiltrating fibromatosis-like growth pattern toward fatty component. Haematoxylkin-eosin, ×80. **C** Short fascicles of spindle cells separated by thick collagen bands are typical of myofibroblastoma. Mild to moderate nuclear pleomorphism is seen (arrows). Haematoxylkin-eosin, ×100. **D** Neoplastic cells are stained with α-smooth muscle actin (*a*), bcl-2 protein (*b*), CD34 (*c*), and ER (*d*). Streptavidin-biotin peroxidase

mography confirmed a circumscribed, solid tumour mass in the breast parenchyma. A complete surgical excision of the mass, including a rim of adjacent grossly normal parenchyma, was performed. No recurrence or other complaints have been experienced 2 years following surgery.

Materials and methods

The excised tumours were fixed in 4% formalin followed by conventional processing and embedding in paraffin wax. Sections were stained with haematoxylin and eosin. Immunohistochemical studies were performed on formalin, paraffin-embedded tissues, using the standard labelled streptavidin-biotin technique and commercially available reagents (LSAB kit, Dako, Glostrup, Denmark). Tissue sections were incubated with primary antibodies to vimentin (monoclonal, Immunotech, Marseille, France; prediluted), desmin (monoclonal, Dakopatts, Glostrup, Denmark; diluted 1:500), α-smooth muscle actin (monoclonal, Dakopatts, Glostrup, Denmark; dilution 1:300), CD34 (monoclonal, Immunotech, Marseille, France; prediluted), S-100 protein (polyclonal, Dakopatts, Glostrup, Denmark; dilution 1:800), pan-cytokeratins (monoclonal; Immunotech, Marseille, France; prediluted), oestrogen receptors (ER) (monoclonal, Biogenex, San Ramon, Calif.; dilution 1:50), progesterone receptors (PR) (monoclonal, Biogenex, San Ramon, Calif.; dilution 1:50), androgen receptors (AR) (monoclonal, Biogenex, San Ramon, Calif. dilution 1:50), and bcl-2 protein (monoclonal, Dako, Glostrup, Denmark; dilution 1:100). Tissue sections for steroid hormone receptors, and bcl-2 determinations were pre-treated by microwaving in citrate buffer (pH 6.0) for antigen retrieval [17]. Bound peroxidase was visualized using 0.05% 3,3-diaminobenzidine tetrahydrochloride (Sigma Chemical Co., St. Louis, Mo. USA) as a chromogenic substrate for 10 min at room temperature. Slides were counterstained with haematoxylin, dehydrated, and mounted. Positive controls for ER, PR, bcl-2 protein and AR, included previously tested positive breast and prostatic cancers. Negative controls included omission of the primary antibodies from the staining sequence.

Pathological findings

Gross pathology showed both tumours to consist of a well-circumscribed, incompletely encapsulated lipomatous mass, 3 cm (case 1) and 2 cm (case 2) in diameter. On cut sections a yellow tumour mass with some interspersed whitish areas was evident. Calcifications, haemorrhage, and necrosis were not identified. In both cases, histological examination revealed a well-circumscribed neoplasm composed predominantly of mature adipose tissue containing dispersed nodular and irregularly shaped spindled cellular areas (Fig. 1A). The nodular areas clearly butted onto fat, whilst the irregularly shaped areas seemed to infiltrate the fat in finger-like extensions (Fig. 1B). The mature fatty component occupied approximately 75% of the tumour area in both cases. Adipocytes were uniform in size and shape and lacked nuclear pleomorphism. Lipoblasts were not seen. The cellular areas consisted of spindly to oval cells arranged in short, haphazardly intersecting fascicles interrupted by broad bands of brightly eosinophilic collagen that focally formed whorls closely resembling the amianthoid fibres (Fig. 1C). The cells showed an eosinophilic cytoplasm with ill defined borders and an oval nucleus with one or two small distinct nucleoli. A mild to moderate nuclear pleomorphism (Fig. 1C) and rare mitoses were observed. Mammary ducts or lobules were not trapped within the tumour. Immunocytochemically, the spindly to oval cells were diffusely positive for vimentin and α-smooth muscle actin, while a heterogeneous immunoreactivity was obtained with desmin, CD34 and Bcl-2 protein (Fig. 1D). Interestingly, immunoreactivity for ER, PR and AR was observed in about 70% and 10–20% of spindle to oval cells in case 1 and case 2, respectively (Fig. 1D). No staining was obtained with any other antibodies.

Discussion

Myofibroblastoma of the breast is basically a bland-looking spindle to oval cell neoplasm characterized by a distinct growth pattern and consisting of short, straight, haphazardly intersecting fascicles with interspersed thick collagen bands [22, 33]. However, uncommon variations on this basic theme, such as atypical mono- or multinucleated cells [12, 16, 22], pleomorphic lipoma-like and myxoid liposarcoma-like areas [16], may confound the diagnosis. The purpose of this paper is to broaden the morphological range of MFB of the breast. It focuses attention on a lipomatous variant characterized by the close juxtaposition of spindle to oval cells with mature adipocytes, resulting in a finger-like infiltrative growth pattern of the former towards the latter. Thus, lipomatous MFB needs to be distinguished from several other benign and even bland-looking malignant spindle cell lesions of the breast. Lipomatous tumours with a significant spindle cell component, such as spindle cell lipoma and spindle cell liposarcoma, may closely mimic lipomatous MFB, owing to their bland cytology and low mitotic activity [20]. Neoplasms with overlapping features of spindle cell lipoma of soft tissues have been reported rarely in the breast as “spindle cell lipoma” [21, 25] or “benign spindle cell tumour” [15, 29]. These tumours are composed of mature adipocytes blended with well-aligned and unevenly distributed vimentin$^+$/CD34$^+$ spindly cells [15, 21] that are lacking the typical architectural arrangement and the immunoreactivity for myogenic markers (α-smooth muscle actin and/or desmin) usually observed in MFB. Spindle cell liposarcoma is a distinctive clinico-pathological entity occurring in soft tissues [20]. Unlike our cases, the adipocytic component of spindle cell liposarcoma shows quite a striking variation in cell size and shape, as well as hyperchromatic and atypical nuclei, dispersed lipoblasts and even atypical stromal cells [20]. As far as the tumour-like lesions of the breast are concerned, mainly fibromatosis and nodular fasciitis are likely to be confused with lipomatous MFB. Fibromatosis is a relatively rare primary tumour-like lesion of the breast. It may occur sporadically or in the context of genetic syndromes [14, 2, 34], exhibiting infiltrating borders and entrapping fat and glandular tissue of the breast parenchyma [14, 22, 34]. It is composed of long, sweeping cellular fascicles embedded in a vari-

able amount of fibrous stroma rather than of short fascicles separated by thick collagen bands as MFB. Fibromatosis, which is usually immunoreactive for α-smooth muscle actin, does not express CD34 molecule, a marker generally detectable in MFB, albeit at a variable degree from case to case [17]. Recently, we also observed that bcl-2 protein and ER, PR, and AR are expressed by MFB (including the present cases), whilst they are lacking in fibromatosis of the breast [17]. Similar results, showing no immunoreactivity for sex steroid hormone receptors, were recently obtained in a large series of primary breast fibromatosis [7]. Nodular fasciitis has rarely been observed in the breast [30]. Although the cell population is reactive with α-smooth muscle actin, in keeping with its myofibroblastic nature, it is characterised by spindly to round plump cells with frequent mitoses. It is variably embedded in a myxoid (tissue-culture-like appearance) to fibrous stroma containing an inflammatory lymphocytic component, extravasation of red blood cells and microcystic degeneration [30].

Difficulty may also arise in distinguishing lipomatous MFB from bland-looking malignant spindle cell tumours of the breast, mainly monophasic spindle cell metaplastic carcinoma (sarcomatoid carcinoma), spindle cell malignant myoepithelioma, and low-grade fibrosarcoma/malignant fibrous histiocytoma. However, all these tumours usually have infiltrating margins, entraped fat, mammary ducts and lobules rather than an expansile growth pattern pushing them aside, as in MFB. As to metaplastic carcinoma, the "pure" spindle cell variant is rare; this spindly component is generally associated with an in situ or infiltrating carcinomatous component [1,35]. This entity may closely mimic lipomatous MFB, owing to the bland appearance of the spindle cells which show only a mild to moderate pleomorphism, low mitotic activity and a wavy fascicular growth pattern [1]. However, a correct diagnosis of this malignant tumour is easily achieved by immunocytochemistry. This demonstrates cytokeratin expression, in addition to a variable vimentin, α-smooth muscle actin and S-100 protein immunoreactivity [1, 35]. The spindle cell malignant myoepithelioma is a term that should be applied to neoplasms composed exclusively of spindly myoepithelial cells arranged in haphazardly interlacing bundles sometimes with a focal storiform pattern. This tumour usually displays cytological atypia and a low to high mitotic activity. Immunocytochemistry, demonstrating the myoepithelial nature of the cells (variable coexpression of cytokeratins, vimentin, α-smooth muscle actin, and S-100 protein), is an important ancillary diagnostic tool [6, 27]. The category of low-grade fibrosarcoma/malignant fibrous histiocytoma covers a continuous morphological spectrum of lesions sharing features of both fibrosarcoma and malignant fibrous histiocytoma [10]. They are composed of highly spindly cellular areas with mild to moderate cytological atypia, an evident herringbone and/or storiform pattern with possible detection of histiocytes and/or multinucleated giant cells with hyperchromatic nuclei [10]. Immunocytochemistry reveals a diffuse vimentin, while α-smooth muscle actin and CD34 may only be focally detected [9, and personal observations].

The detection of a prominent fatty component as an integral part of MFB of the breast raises some intriguing histogenetic considerations. It is known that MFB, solitary fibrous tumour and spindle cell lipoma are lesions sharing morphological and immunophenotypical features (common expression of vimentin, CD34 and bcl-2) [4, 5, 15–17, 22, 26]. This fact supports the view that these three tumours are histogenetically-related lesions probably arising from a common mesenchymal cell lineage [4, 15, 17, 26]. Some authors have suggested that both solitary fibrous tumour and spindle cell lipoma of soft tissues may arise from the vimentin$^+$/CD34$^+$ fibroblast that is ubiquitously distributed in the connective tissues [4, 26]. The existence of a similar vimentin$^+$/CD34$^+$ fibroblast in mammary stroma (both intralobar and interlobular) ([24, 31] and personal observation) lead us to speculate that this may be the putative precursor cell of spindle cell lipoma [15, 21], solitary fibrous tumour [18, 23] and even of MFB occurring in the breast. The myofibroblastic differentiation observed in MFB is explained if we assume that the mammary stromal cell is capable of altering its phenotype along different mesenchymal lines of differentiation. This is demonstrated by the variable coexistence of fibroblasts, myofibroblasts, mature smooth muscle cells, adipocytes and even occasional foci of mature cartilaginous and osseous tissues in the same case of MFB of breast [2, 8, 9, 11, 22, 28, 29, 33]. Moreover, a similar multipotential differentiation of the mammary stroma is a well known occurrence in several breast pathologic conditions such as fibroadenoma with myofibroblastic [24] or leiomyomatous component [22], phyllodes tumour, hamartoma and so-called benign mesenchymoma [22].

According to this histogenetic hypothesis, the lipomatous MFB of the breast should be tentatively regarded as the morphological result of an unbalanced bidirectional differentiation of the precursor mammary stromal cell, with the adipocytic component overwhelming the myofibroblastic portion. The etiopathogenesis of MFB of the breast is still unclear. However, the detection of ER, PR, AR, in many cases (including the present ones) points to a potential pathogenetic role via sex steroid hormones [17, 19]. This is consistent with the evidence that MFB and the so-called pseudo-angiomatous stromal hyperplasia of the mammary stroma, a lesion morphologically and immunohistochemically related to MFB [22], may coexist with gynecomastia [3, 13, 32]. This is a pathological condition with a well known hormonal pathogenesis.

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