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Original Contributions

Lipophyllodes of the breast. A reappraisal of fat-rich tumors of the breast based on 22 cases integrated by immunohistochemical study, molecular pathology insights, and clinical follow-up

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ABSTRACT

We have studied 22 cases of mammary lipophyllodes tumors (LPT), analyzing their clinicopathologic features along with available follow-up. All cases were tested for cytokeratins, S100 protein, and *MDM2*, and in selected cases for estrogen receptor, smooth muscle actin, bcl2, desmin, and myogenin. Patients were women aged 21 to 69 years (average, 45 years), and LPT size ranged from 1.6 to 30 cm (average, 9.7 cm). Microscopically, LPT segregated as follows: atypical lipoma-like tumor/well-differentiated liposarcoma (ALT/WDL), 8 cases; myxoid, 6; and pleomorphic/poorly differentiated/round cell, 8, including a case of dedifferentiated liposarcoma. Immunohistochemistry studies showed focal positive staining for S100 and CD34 in most ALT/WDL, and desmin and myogenin in 2 cases with evidence of rhabdomyoblastic differentiation. *MDM2* positivity was focally seen in 1 case. Follow-up was available in 8 cases. Multiple recurrent tumors were seen in 2 patients, and metastatic disease to the lung was seen in 2 patients. In 4 patients with a follow-up between 2 and 15 years there was no evidence of recurrent or metastatic disease. Patients with ALT/WDL (2/2) were alive with no evidence of disease; 2 of 4 patients with myxoid liposarcoma component experienced tumor recurrence, whereas pleomorphic liposarcoma LPT pursued a less favorable course although only 1 patient died of the condition. Absence of *MDM2* reactivity in most cases seems not as meaningful as in fatty tumors of somatic soft parts.

1. Introduction

A number of tumors and tumor-like conditions of the breast may be microscopically characterized by a variable amount of mature adipose tissue [1]; these lesions include mammary hamartoma, lipomatous adenosis, myofibroblastoma [2,3], and tumors reflecting an adipocytic line of differentiation such as lipoma and liposarcoma (LS) [1]. In biphasic stromal-epithelial tumors, a preponderant fatty component may occasionally be seen, hence the designation *lipophyllodes*, introduced more than 20 years ago by Powell and Rosen [4] and Rosen et al [5]. In their seminal articles published in the *Archives of Pathology*, the lipophyllodes tumor (LPT) was described as a special variant of "cystosarcoma" of the breast, in which well-differentiated adipose tissue was consistently seen. The origin of this tumor is not clear, although LPT may have a parental relationship to the specialized mammary stroma undergoing adipocytic metaplasia. The prognosis of these breast lesions remains difficult to assess by histopathology alone. Based on available follow-up data, resection with clear margins proved to be the appropriate treatment in most cases. Although the histologic features and clinical outcome in a few cases of LPT have been reported, specific studies based on larger series have not been available. Therefore, the present study was performed to describe the clinicopathologic features of 22 cases of LPT, detailing its histopathologic spectrum and integrating morphologic features with molecular study for the *MDM2* amplification oncogene and providing follow-up when available.

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2. Materials and methods

Cases of breast tumors from departmental or consultation files accessioned between 1980 and 2013 and diagnosed as "phyllodes tumor with liposarcoma" or descriptively as "phyllodes tumor with atypical lipomatous component" were retrieved. Only cases with available paraffin-embedded tissue were considered. Patients with a history of LS of somatic soft parts at other sites were also ruled out. Finally, phyllodes tumors with focal mature adipose tissue, likely representing mere fatty metaplasia, were not included in the series. Gross findings—including tumor size, quality of margins (infiltrating vs expansile), necrosis, and hemorrhage—were recorded. Microscopic features such as mitotic activity, cellularity, stromal overgrowth, and heterologous components (smooth or skeletal muscular, bony or chondroid) were considered as well. The adipocytic component was classified along the lines set forth by the World Health Organization, namely, atypical lipoma-like tumor or well-differentiated LS (ALT/WDL), myxoid LS, or high-grade/pleomorphic LS. Atypical lipoma-like tumor or well-differentiated LS features mature fat admixed with lipoblasts (ie, atypical cells displaying nuclear hyperchromasia and one or more cytoplasmic vacuoles scalloping the nuclei), as opposed to myxoid LS, which is characterized by a loose mucinous substance rich in finely branching small vessels, or a "chicken-wire pattern," comprising lipoblasts. For practical purposes, round cell and dedifferentiated forms were grouped within the pleomorphic LS category. Follow-up was available for patients with departmental accession or retrieved from caring physicians in cases submitted for outside consultation.

A panel of antibodies was applied on paraffin sections using commercially available antibodies and reagents (Table 1). All cases had been tested for cytokeratins, S100 protein, MDM2, and CD34; in selected cases, desmin, estrogen receptor, smooth muscle actin, bcl2, and myogenin were evaluated as well.

Fluorescence in situ hybridization (FISH) analysis for *MDM2* amplification status was performed in 14 cases with a commercially available probe (ZytoLight SPEC MDM2/CEN 12 Dual Color Probe; Zytovysion, Bremerhaven, Germany). Fluorescence in situ hybridization analysis was performed on 3-μm sections of formalin-fixed, paraffin-embedded tissue. After deparaffinization with xylene and dehydration with ethanol, all tissue sections were pretreated with NaSCN solution at 80°C for 30 minutes and then digested with protease solution at 37°C for 25 minutes. Denaturation was carried out at 85°C for 5 minutes followed by 18 hours of hybridization at 35°C. After stringent washing with 2× SSC/0.3% NP-40 at 75°C for 5 minutes, the sections were counterstained with DAPI II in mounting medium (Abbott, Wiesbaden, Germany) and visualized under a Zeiss Axioplan 2 microscope.

At least 20 cells were analyzed from each tumor. Only nuclei with at least 2 *CEP12* signals were evaluated to minimize nuclear truncation artifact that can occur in paraffin-embedded sections. The average number of *MDM2* and *CEP12* signals was then determined, and an *MDM2*/*CEP12* ratio was calculated for each case. A ratio 2.0 or greater was considered amplified for the *MDM2* gene, whereas a ratio less than 2.0 was considered nonamplified.

3. Results

3.1. Clinical findings

In all, 22 phyllodes tumors with features of adipocytic differentiation were available (Table 2). The patients' ages at the time of diagnosis ranged from 21 to 69 years (median, 45 years). Patients were referred for a progressively growing nontender unilateral breast tumor.

Treatment consisted in wide tumor resection or mastectomy. The latter was done in 4 cases as a primary choice or with recurrent lesions. Radiation therapy was delivered to metastatic tumors in 2 cases.

3.2. Salient gross and microscopic features

The tumor ranged in size from 1.6 to 30 cm (median, 4 cm); they were multilobulated and firm, with a discernible leaf-like outline. A yellow discoloration was common in tumors harboring a mature adipose component (Fig. 1). A glistening, sometimes lucent/gelatinous surface or fleshy, necrotic appearance could be observed in tumors with a myxoid LS and pleomorphic LS component, respectively. Margins were mostly expansile; poorly defined tumors displayed an infiltrative border. Microscopically, the tumors displayed a fibroepithelial pattern that was more pronounced in LPT segregating within the ALT/WDL category (8 cases) (Fig. 2) but retained a discernible epithelial component even when the stromal component was preponderant in less differentiated tumors (Fig. 3); a variable amount of lipoblasts could be recognized (Fig. 4). In addition to the ALT/WDL rubric, the adipose component segregated within the myxoid (Fig. 5) and pleomorphic LS (Figs. 6 and 7) categories in 6 and 8 cases, respectively. Pleomorphic LS also included 1 tumor featuring a round cell component (Fig. 8) or dedifferentiated areas (Fig. 9). Pleomorphic LS exhibiting divergent rhabdomyoblastic differentiation was noted in 2 cases as well (Fig. 10).

3.3. Results of immunohistochemical and molecular studies

Tumor cell immunoreactivity is summarized in Table 1. In all cases, cytokeratin antibodies highlighted the epithelial ductal component; in ALT/WDL, the adipose tissue was immunoreactive for S100 protein and CD34 (Fig. 11A). The rhabdomyoblastic component was strongly positive for antibodies directed against desmin and myogenin (Fig. 11B). Immunohistochemical evaluation of the MDM2 reactivity was carried out in 22 cases, documenting focal nuclear positivity in 1 case of pleomorphic LS (Fig. 11C). In 14 cases tested by using of FISH analysis, no amplification for the MDM2 locus was observed.

Table 1
Immunohistochemical findings in 22 cases of lipophyllodes of breast

Antibody information	Positive cases/total tested cases	Notes
Cytokeratins (MNF 116)	0/22	Positive in the epithelial component
CD34 (QBEND 10)	8/22	Focally positive in all WDL/ALT
S100 protein (polyclonal)	12/22	Focally positive in WDL/ALT in myxoid LS
ER	0/3	Positive in scattered epithelial cells
Desmin (DE-R-11)	2/15	Positive in rhabdomyoblastic elements of pleomorphic LS
Smooth muscle actin (1A4)	0/14	
MDM2[a]	1/22	Focally reactive in 1 case of pleomorphic LS
Bcl2	0/3	
Myogenin	2/2	Tested only in cases of pleomorphic LS with rhabdomyoblastic features

Positive reactivity is referred to the stromal component.
Abbreviation: ER, estrogen receptor.
[a] FISH for *MDMD2* performed in 7 cases.