CASE REPORT

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A malignant phyllodes tumor with liposarcomatous differentiation case with 3-year follow-up

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Abstract

Phyllodes tumors (PTs) are a group of rarely breast tumors of fibro-epithelial origin, counting for about 1% of the breast malignancies divided, based on histological features, in benign, borderline and malignant neoplasms, arising most of them in women in their 40's. Among this complex group of tumors, the liposarcomatous differentiation is an even more rare lesion, counting for about 0.3% of all primary sarcomas of the breast. This article presents a case of a 48-year-old woman with a breast malignant PT with liposarcomatous differentiation, diagnosed by guided core biopsy, treated by excision and subsequent simple mastectomy followed by radiotherapy, with a 3-year follow-up.

Keywords: breast cancer, phyllodes tumor, liposarcomas, immunohistochemistry, mastectomy.

Introduction

Phyllodes tumors (PTs) are a group of rare breast tumors of fibro-epithelial origin (biphasic tumors), usually divided in benign, borderline and malignant categories, based on histopathological features, such as atypia, mitotic activity or overgrowth in the stroma, according to the *World Health Organization* (WHO) *Classification of tumors of the breast* [1] and *WHO Classification of soft tissue tumors and bone* [2]. Rare, malignant PT may exhibit heterologous differentiation; when this occurs, most often is a liposarcomatous differentiation [3–5] resembling the well-differentiated or pleomorphic subtypes of extramammary situated liposarcomas [2]. Other differentiations include fibrosarcoma, chondrosarcoma, osteosarcoma or even rhabdomyosarcoma [2, 6–9].

Malignant PTs of the breast are rare, counting for only 0.3–0.5% of malignant breast neoplasms [10, 11]. Usually, malignant PT of the breast arises in woman in their 40's, with the big majority of cases between 35 to 55 years old [12, 13].

We present the case of a 48-year-old woman with a breast malignant PT with liposarcomatous differentiation.

Case presentation

A 48-year-old woman (C.G.) from a Romanian village, with no family history of cancers (nor breast neither other localizations) presents in our Service ("Prof. Dr. Ion Chiricuţă" Oncological Institute, Cluj-Napoca, Romania), in September 2016, with multiple bilateral breast tumors. Prior to the presentation in our Service, she presented to her family doctor who referred her to our Service. She had no personal history of any malignancy, no important associated illness, minor surgical antecedents, with no prior breast surgery.

Clinical examination in our Service revealed a patient in good shape, a little anxious for the masses she found a month ago in her breasts, one of which, in left breast, presented a quick grow-up. Local exam found a 50 mm diameter, relatively well-delimited, high consistency, polylobate tumor of the upper-internal quadrant of the left breast, with incomplete skin adhesion, with no bilateral axillary or supraclavicular adenopathy, considered suspicious for a PT. Also, two well-delimited, mobile, high-consistency, round-oval tumors were also found in each breast.

The diagnostic work-up in our Service primary consisted in bilateral digital mammography and ultrasound (US) examination.

Bilateral mammography showed multiple dense, round and oval masses, some of them with partially obscured margins. The biggest mass was reported in the left upper inner quadrant, with dystrophic calcifications included (Figure 1, a and b).

US examination showed a large, circumscribed, oval, isoechoic left breast mass, heterogeneous, with eccentric cystic spaces and vascular flow in the periphery, corresponding to the palpable abnormality – a breast imaging-reporting and data system (BI-RADS) 4a lesion. In the right breast, the US exam reported a well-defined hypoechoic oval mass, heterogeneous, with some marginal vessels; three other similar masses in the right breast and four in the left breast were also present (Figure 2, a and b).

An US-guided core biopsy of the palpable mass from the

left upper inner quadrant was performed. The biggest nodule of the right breast was also biopsied. The pathological report stated fibroadenoma with no malignancy signs for the right breast lesion. For the left breast lesion, the six tissue fragments (1 to 1.5 cm each) showed the microscopic appearance of a PT with the stromal component replaced by atypical lipomatous proliferation that posed the problem of the differential diagnosis between a well-differentiated liposarcoma (lipoma-like) and a lipoma (Figures 3 and 4).

The pathological report concluded that the histological appearance was compatible with a PT with atypical lipomatous stromal proliferation requiring the excision of the entire tumor for a certain final diagnosis (liposarcoma or lipoma).

Next, the excision of the tumor was performed (not wide excision because the patient, during the discussion of the alternatives of treatment, asked for mastectomy if malignancy will be certain established, refusing the idea of a local large excision, which anyway would conduct to a poor cosmetic result).

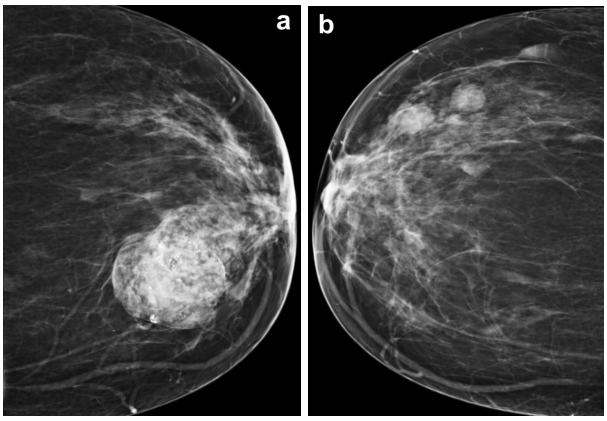

Figure 1 – ***(a and b) Bilateral mammography showing multiple dense, round and oval masses, some circumscribed, some with partially obscured margins: (a) Left CC; (b) Right CC. The biggest mass is located in the left upper inner quadrant (a), with dystrophic calcifications included. CC: Craniocaudal.***

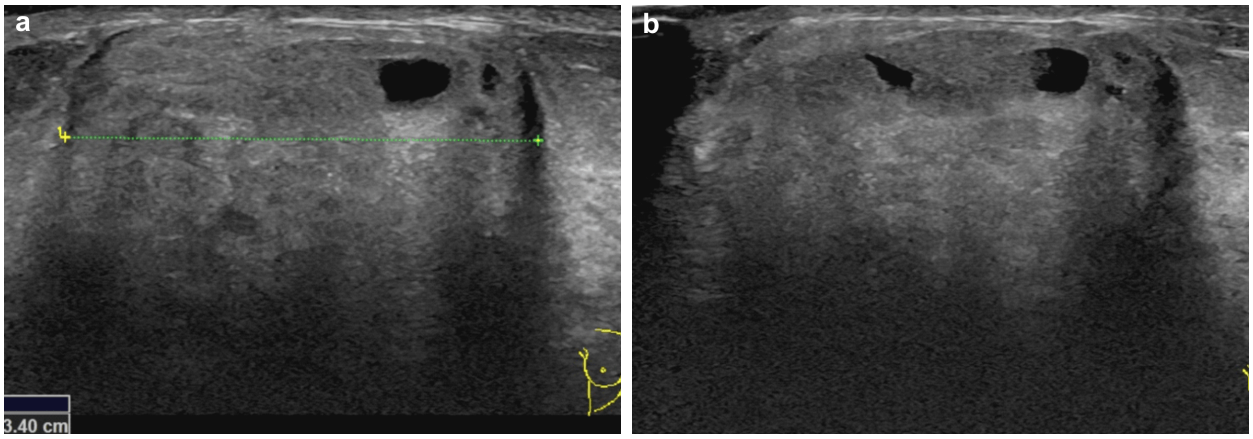

Figure 2 – ***(a and b) Ultrasound examination of the left breast showing a large, well-defined, isoechoic mass, heterogeneous, with eccentric cystic spaces (BI-RADS 4a). BI-RADS: Breast imaging-reporting and data system.***

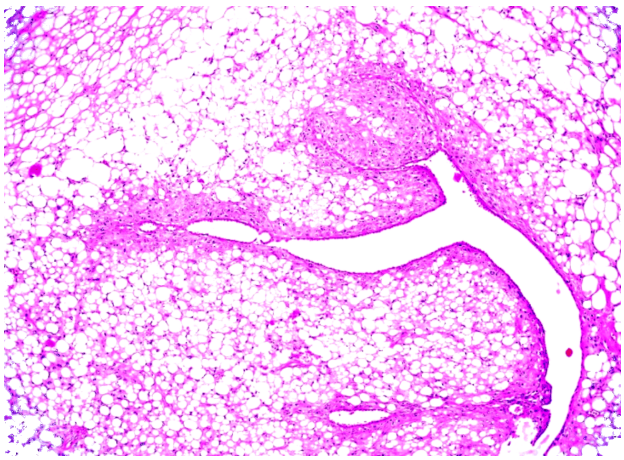

Figure 3 – ***Typical appearance of phyllodes tumor, with a benign epithelial component lining narrow lumen and an unusual-looking, lipomatous stroma. HE staining, ×100.***

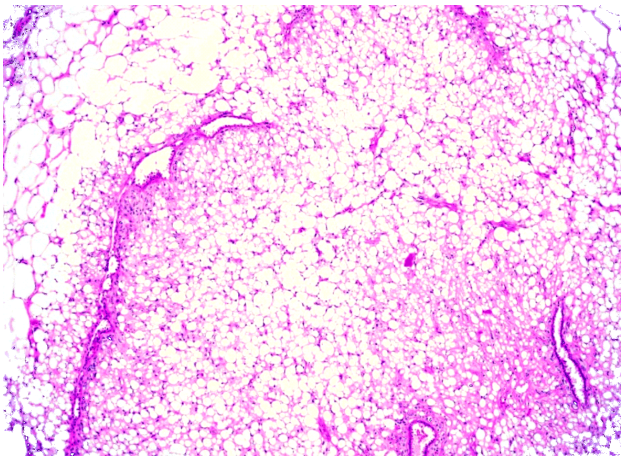

Figure 4 – ***Tumor of mixed appearance with a duct in the form of cleft covered with a benign epithelium and stroma with malignant appearance of liposarcoma. HE staining, ×100.***

Excised tissue was fixed in 10% formalin solution and included in histological paraffin. At the microtome were made sections with a thickness of 4 μm, which were stained with Hematoxylin–Eosin (HE). The pathological report showed a biphasic tumoral proliferation of a malignant phyllodes-type tumor with well-differentiated liposarcoma differentiation of the stromal component, lipoma-like. Periductal stromal component presented fusocellular zones, with moderate and marked nuclear pleomorphism, with a mitotic index of 10 mitoses/10 high power fields (HPFs), with the presence of atypical mitosis. Distant from the ductal component, the stromal component presented

adipose differentiation, with lipoblasts and adipocytes in different maturation stages (Figures 5 and 6).

Zones of stromal condensation and periductal hypercellularity, zones of stromal expansion and small zones of necrosis with calcifications were observed.

The epithelial component presented typical ductal hyperplasia, with no clear malignancy images in HE staining.

Entire tumor was focal delimited by a fibrous capsule but there were areas of invasive appearance and satellite tumoral nodules to the medial aspect of the specimen.

There was no perineural or angiolymphatic invasion, no skin invasion.

All resection margins were clear, with close margins posterior (1 mm) and inferior (6 mm). Also, there were two fibroadenomas found on the resection specimen, one of 5 mm with periductal pattern and the second 10 mm large predominant intraductal.

For differential diagnosis, we considered it necessary to perform some immunohistochemical (IHC) examinations. Thus, we used the following IHC markers: cytokeratin 7 (CK7) (monoclonal mouse anti-human CK7, clone OV-TL 12/30, 1:50 dilution, Dako), S100 (polyclonal rabbit S100, 1:500 dilution, Dako), p16 [anti-p16^{INK4a} antibody (1D7D2), clone MA5-17054, 1:100 dilution, Invitrogen], cyclin D1 (monoclonal mouse anti-human cyclin D1, clone dcs-6, 1:100 dilution, Dako), cluster of differentiation 34 (CD34) (monoclonal mouse anti-human CD34 Class II, clone QBEnd 10, 1:50 dilution, Dako), Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1:50 dilution, Dako), and mouse double minute 2 homolog (MDM2) (monoclonal mouse anti-MDM2, clone D-7, Santa Cruz Biotechnology).

Anti-CK7 antibody immunostainig showed the epithelial component with no malignancy signs (Figure 7). Anti-S100 antibody positivity was predominant on the component with adipose differentiation and isolated, punctuated on the component with fusocellular adipose morphology (Figure 8). The Ki67 proliferation index had a variable expression higher in the fusocellular areas, with a maximum of 25% (Figure 9). Cyclin D1 was negative on both stromal compartments. p16 was positive on the adipose and fusocellular areas. CD34 focal positivity predominates on fusocellular areas. Reaction of anti-MDM2 antibody was negative (Figure 10).

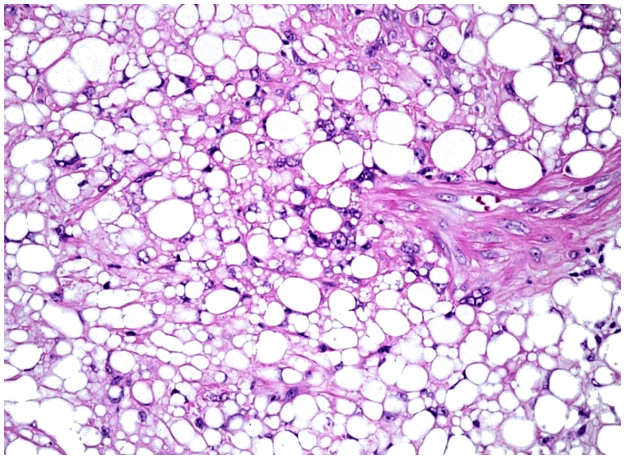

Figure 5 – ***A lipoblasts nest seen at high magnification in the middle of lipomatous stroma of the tumor. HE staining, ×200.***

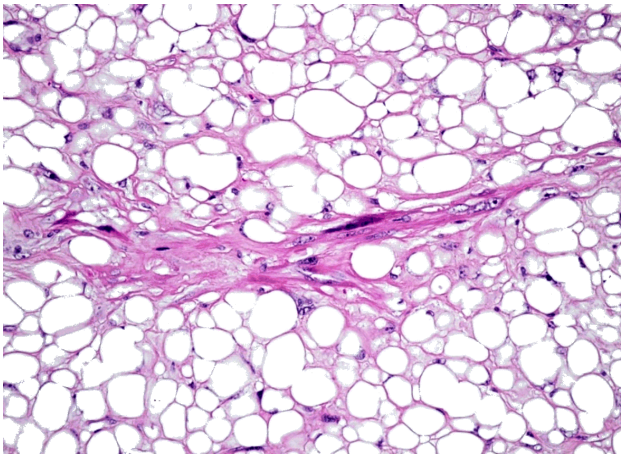

Figure 6 – ***Inside the lipomatous stroma, in the center of the image, a fibrous septum with atypical cells is observed. Fat cells have variable sizes and nuclei with mild atypia. HE staining, ×400.***

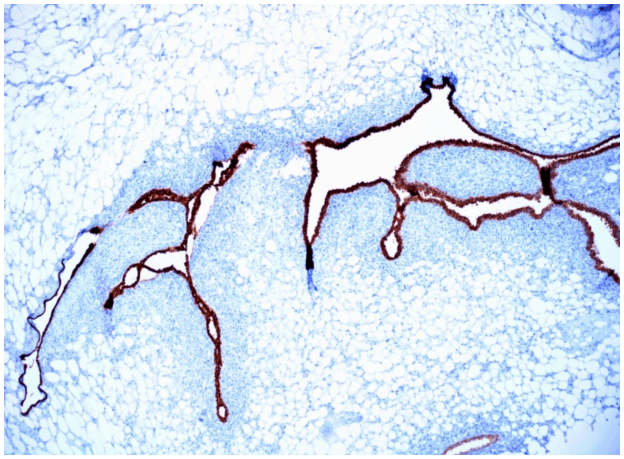

Figure 7 – ***Typical appearance of phyllodes tumor, with epithelial component highlighted in CK7 immunostaining. Immunostaining with anti-CK7 antibody, ×40. CK7: Cytokeratin 7.***

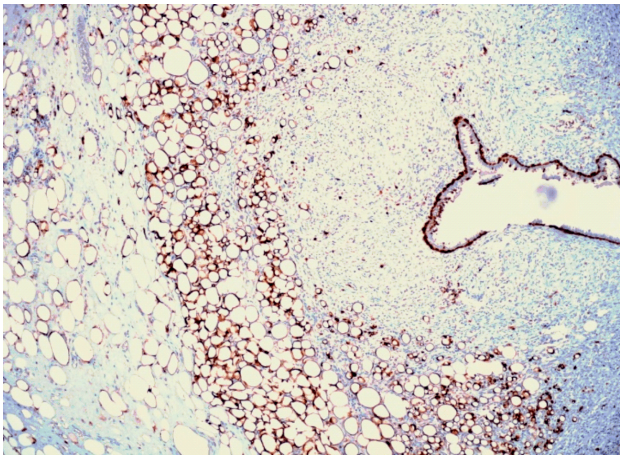

Figure 8 – ***S100 immunostaining was positive in the adipose stroma, more intense on lipoblastic cells than on mature adipocytes, as well as on myoepithelial cells lining the ducts. Immunostaining with anti-S100 antibody, ×100.***

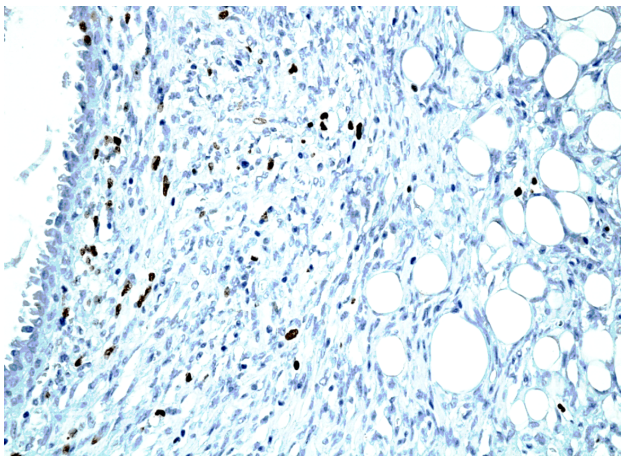

Figure 9 – ***Proliferation index of stromal cells was higher near the ducts (with a value of 25%). Immunostaining with anti-Ki67 antibody, ×200.***

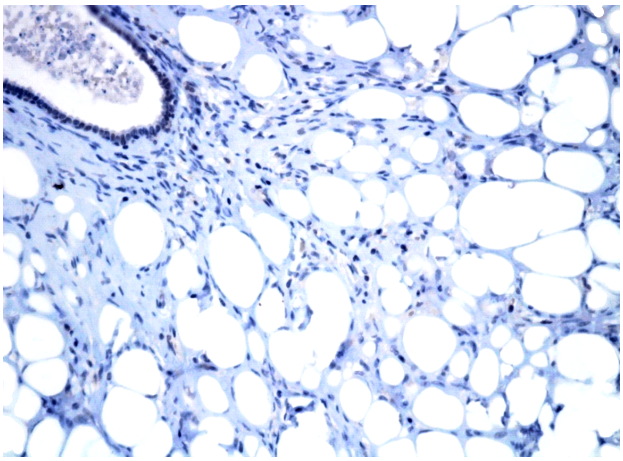

Figure 10 – ***Reaction of tumor cell nuclei was negative for anti-MDM2 antibody. Immunostaining with anti-MDM2 antibody, ×200. MDM2: Mouse double minute 2 homolog.***

Pathological report concluded for a malignant PT with sarcomatized stromal component, with well-differentiated liposarcoma morphology (lipoma-like).

Computed tomography (CT) scan showed no distant metastasis and the simple left mastectomy was performed showing no residual tumor, only fibroadenomas.

Soft tissue tumors board indicated radiotherapy and the patient underwent conformational radiation therapy at total dose (TD) of 50 Gy/25 fractions in another Service, closer to her home.

She presented for each follow-up visit, all clinical, CT scans, mammographic and breast US exams were with no evidence of local or distant recurrence during the first 36 months of follow-up. Figures show the mammographic and US clear appearance of the remaining breast during the follow-up, at 12 months and 36 months respectively.

Discussions

A few studies have been published about the malignant PT with lipomatous differentiation and most of them are case reports or small series with or without reviewing the literature. This is certainly due to the rarity of these cases. Despite the rarity of differentiation of malignant PTs, when this occurs, most often is liposarcomatous [3–5]. Although in the past decades the pathological diagnosis and classification of such tumors has evolved very much, with clear criteria for both diagnostic and classification [1, 2, 14], there is no prospective trial regarding the treatment of malignant PTs.

Clarifications of the pathological diagnosis and classification of this complex tumor group have helped to an accurate classification of these tumors by distinguishing them for other (even more rare) tumors of the breast, like spindle cell metaplastic carcinoma or primary breast liposarcoma, two of the most difficult differential diagnosis [2, 8, 14, 15].

Although a more common extra-mammary type of sarcoma, the breast primary liposarcomas are exceptionally rare [2, 14, 16]. Leaf-like architecture of the malignant PTs helps separating them from the liposarcomas. More recent studies stated that IHC testing for MDM2 and cyclin-dependent kinase 4 (CDK4) can help distinguishing between the two entities, both MDM2 and CDK4 showing no amplification for malignant PT with liposarcomatous differentiation and amplification for primary breast liposarcomas [8, 16]. Our case also was negative for MDM2 immunostaining.

Main therapeutic approach in the management of malignant PT remains the surgical treatment either wide local excision or total mastectomy, with an increasing number of breast conservative surgery cases in last years [12, 13, 17]. Surgical margins have been found on several studies as very important for predicting recurrence most of the authors opting for a 10 mm clear margin [12, 18–20]. Sometimes, this renders the cosmetic result very poor and the total mastectomy remains the option to choose [14]. Even in our case, the patient opted for mastectomy from the very beginning of the discussion about the therapeutic alternatives, the excision being performed only for a proper diagnosis.

Axillary lymph nodes dissection is not required given the very low rate of lymph nodes involvement [13, 14, 21].

Most of the articles and reviews of the literature propose that the treatment of malignant PT with liposarcomatous differentiation should include surgery and in case of breast conservative surgery, for clear margins <10 mm radiotherapy should be added [12–14]. A clear attitude regarding the utility of adjuvant radiotherapy is not available yet [12, 14]. Our soft tissue tumors board indicated radiotherapy consult and the patient underwent radiotherapy to a TD of 50 Gy/25 fractions.

Studies have showed no benefit from adjuvant chemotherapy in the treatment of non-metastatic malignant PT with liposarcomatous differentiation [13, 14, 17], meanwhile the metastatic disease seems to benefit most from Doxorubicin–Ifosfamide chemotherapy regimen [18, 22] but, unfortunately, mean survival period from diagnostic of metastases to death being of seven months [14].

Conclusions

We present a rare case of malignant PT with liposarcomatous differentiation of the stromal component diagnosed and surgically treated in our Institute, with no recurrence in 36 months of follow-up from diagnostic.

Informed consent

An explicit written informed consent for publication as case report, using patient's clinical file and surgical specimen for histopathological studies was obtained from the patient and a copy is available at the Editor.

Approval of Ethical Committee from "Prof. Dr. Ion Chiricuţă" Oncological Institute, Cluj-Napoca, Romania, was asked and obtained for using data from patient's file and publication as scientific article.

Conflict of interests

All authors declare no conflict of interests.

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