Rom J Morphol Embryol 2021, 62(4):1035–1044 ISSN (print) 1220–0522, ISSN (online) 2066–8279 doi: 10.47162/RJME.62.4.16

CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Diagnostic difficulties in giant benign phyllodes tumor

RAMONA-ANDREEA MATEI[1)], MIHAI MEHEDINŢU-IONESCU[2)], ŞTEFAN PAITICI[3,4)], EUGEN FLORIN GEORGESCU[3,5)], ANDREAS DONOIU[4)], ADINA MARIANA GHEMIGIAN[6)], MIHAELA POPESCU[7)], BOGDAN DAN TOTOLICI[8)], CARMEN NEAMŢU[8)], STELIAN ŞTEFĂNIŢĂ MOGOANTĂ[3,4)]

[1)]*PhD Student, Doctoral School, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Clinic of Plastic Surgery and Reconstructive Microsurgery, Prof. Dr. Agrippa Ionescu Emergency Hospital, Bucharest, Romania*

[3)]*Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania*

[4)]*3rd General Surgery Clinic, Emergency County Hospital, Craiova, Romania*

[5)]*1st General Surgery Clinic, Emergency County Hospital, Craiova, Romania*

[6)]*Department of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[7)]*Department of Endocrinology, University of Medicine and Pharmacy of Craiova, Romania*

[8)]*Department of Surgery, Faculty of Medicine, Vasile Goldiş Western University of Arad, Romania*

Abstract

Phyllodes tumors (PTs) are rare tumors of the breast, which encompass both stromal and epithelial components. The maximum incidence is in the fourth decade of life. Most of these tumors are benign, but about one third can be malignant acting as sarcomas. Due to their rarity and atypical clinical behavior (especially for the giant ones), the management of these tumors is usually difficult. We report a case of a 24-year-old woman who presented in the Department of Oncology for rapid increase in volume of the left breast. She had no personal pathological or family history. Initial clinical exam showed a large irregular mass in the left breast of approximately 30 cm and palpable lymph nodes in the ipsilateral axilla. A core needle biopsy for the tumor was performed with histopathological (HP) result that revealed an aspect suggesting fibroadenoma/PT. Contrast-enhanced computed tomography (CT) scan identified lymph node enlargement in the left axilla and a peripheral nodule in the lung about 5.5/3.4 mm with no specific features. The patient was then transferred to the Department of Surgery, where left mastectomy and axillary lymph node sampling were performed. HP result of the surgical specimens confirmed the presence of both fibroadenoma and PT, with clear margins above 1 cm, but recommended immunohistochemistry (IHC) to clearly specify benign *versus* borderline type. Five lymph nodes out of six resected presented microscopic reactive changes. We performed a search of literature using the keywords "giant", "benign" and "phyllodes". The results were used to summarize and discuss some of the main features of this type of tumors as well as diagnostic and therapeutic difficulties.

Keywords: phyllodes tumor, fibroadenoma, breast cancer, benign tumor, surgical treatment.

Introduction

Phyllodes tumors (PTs) are rare breast tumors, accounting for less than 1% of breast tumors [1, 2], which develop later than fibroadenoma and earlier then invasive lobular or ductal breast cancer, the average age being reported around 40 years [3]. In most cases, phyllodes are benign tumors, but in 8–29% [4] they are malignant acting as sarcomas and generating hematogenous distant metastasis. The common places for the metastasis are usually represented by the bones and lungs but rarely also in other organs [5]. Pathophysiologically, they are characterized as being biphasic – stromal and epithelial –, with a microscopic appearance of a leaflike pattern that arises from the intensified intracanalicular extension pattern, cleft-like spaces covered by epithelium, and hypercellular stroma [6]. By clinical behavior, histopathological (HP) features regarding presence or absence of stromal overgrowth, stromal cellularity and cellular atypia, mitotic activity, and the nature of tumor margins there are three subtypes of PTs: benign (60–75%), borderline (15–26%) and malignant (8–29%) [2, 3, 7]. Surgical treatment remains the main therapeutic resource for all types, but for the proper surgical planning, the pathology plays a very important role in the preoperative diagnosis. About 10–16.1% of patients have local recurrence, while 6.3–31% of patients with malignant PT may develop distant metastases [8]. A few studies have demonstrated that immunohistochemical markers like Ki67 and p53 protein correlates with HP classification, helping to distinguish between malignant and benign PTs [9]. About 20% of all PTs are larger than 10 cm in diameter and they are considered giant PTs [10].

Aim

Management of giant breast tumors rise numerous diagnostic and therapeutic challenges. Those aspects were highlighted by our clinical case, where the patient presented with a large breast tumor that was measuring about 30 cm (29/27/18 cm), with a rapid growth during the last eight months. To have a better understanding regarding giant benign PTs proper diagnostic and treatment, we selected and analyzed 16 cases including our own.

Case presentation

A 24-year-old female without significant familial or personal history, referred to the Department of Oncology, Emergency County Hospital, Craiova, Romania, in October 2020, accusing a tumoral growth in the left mammary gland that was detected eight months before presentation. According to the patient, the growth rhythm was accelerated in the last three months.

The initial physical examination revealed a large painless mass in the left breast exceeding 30 cm in diameter. The skin covering the mass was thin and had small erosions due to containment attempts. Intertrigo was present in the submammary sulcus and on the sternum and tortuous dilated veins were obvious under the distended skin (Figures 1 and 2). Palpation identified a polylobate tumor extended to the whole breast, with a hard consistency, mobile on the deep planes but adherent in certain areas of the skin. In the ipsilateral axilla, we found palpable enlarged but mobile lymph nodes with a firm consistency. Right breast and axilla were found clinically normal.

Ultrasound (US) of the left breast revealed multiple hypoechoic structures, with sizes between 5 mm to 85/61 mm. The tumors were imprecisely delineated, with complex echostructure and tortuous blood vessels disposed at the periphery of each nodule but also inside, especially in the largest ones. Mammography showed an enlarged left breast through the presence of multiple non-homogeneous opacities spread over the entire glandular area, with irregular and macro-bosselated outline. Microcalcifications were present, and BI-RADS score 5 was established (Breast Imaging-Reporting and Data System score – *American College of Radiology*) (Figure 3, A and B). Right breast and axilla were found normal.

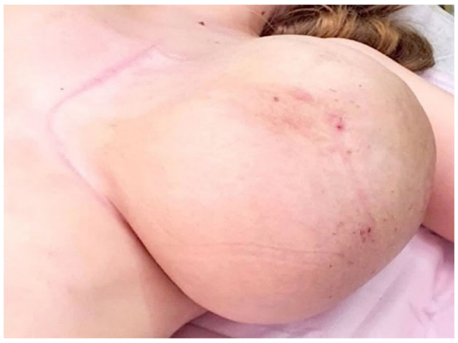

Figure 1 – ***Preoperative image of the patient left breast with giant bosselated tumoral growth. Intertrigo was present in the sternal area and submammary sulcus. Small erosions of the skin.***

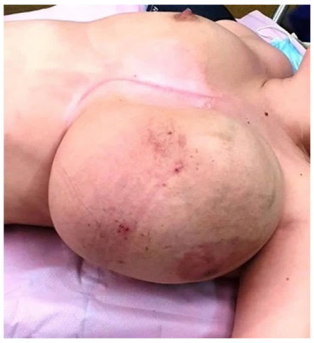

Figure 2 – ***Preoperative lateral image of the thoracal area. The left breast is at least five times enlarged compared to the right one. Areola is laterally displaced by inhomogeneous tumoral growth. The left nipple seems retracted. Tortuous superficial veins with abnormal dilated caliber were present.***

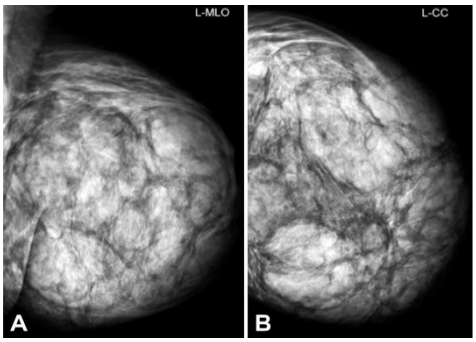

Figure 3 – ***Mammographic aspect of the left breast in middle to lateral oblique (L-MLO) (A) and cranio-caudal incidence (L-CC) (B). Numerous bossellated opacities with various intensity and unclear margins.***

US-guided core needle biopsy was performed and classical Hematoxylin–Eosin (HE) staining of six specimens described lesions compatible with fibroadenoma and benign/borderline PT but failed to overrule malignancy.

Concurrent computed tomography (CT) scan of the chest, abdomen and pelvis revealed tumoral enlargement of the left breast through the presence of multiple formations with tissue densities, which distorted the entire glandular and interstitial breast tissue, with infiltration of subcutaneous tissue over a distance of about 68/13 mm (Figure 4, A–D). Left axillary and retrosternocleidomastoid lymphadenopathy (Figure 5, A and B) were present.

Based on clinical and paraclinical elements, the Tumor Board established the diagnosis of giant PT with unknown features – possible malignant with immediate indication for surgical removal with adequate oncological margins. Breast reconstruction was considered hazardous in the same procedure, remaining to be scheduled at distance depending on the follow-up. Conservative surgery was excluded due to local extent and unclear histology on the core needle biopsy. Left mastectomy with level I axillary lymph-adenectomy was performed. The left mammary gland containing the giant tumor was resected with the fascia of the *pectoralis major*. Following the tumor excision, the left axillary region was surgically evaluated and five enlarged lymph nodes of 1.5 cm to 2.1 cm with elastic consistency, all situated in the lower part of the axilla, were resected.

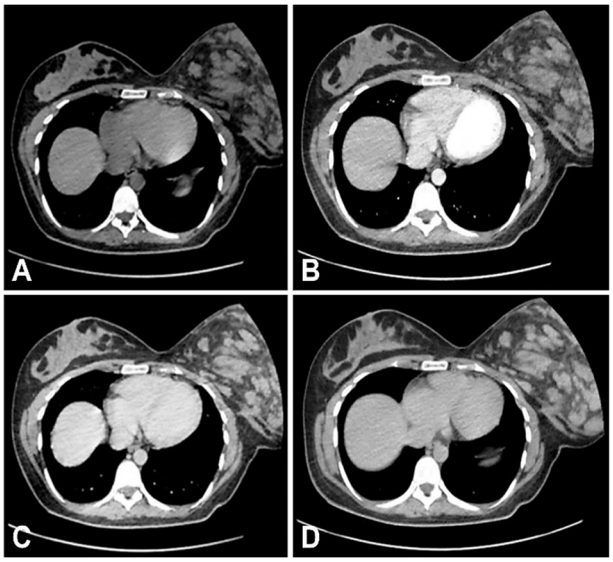

Figure 4 – ***Chest computed tomography (CT) showing enlarged left breast exceeding the acquiring possibilities of the imaging equipment. The normal mammary parenchyma was undetectable, being replaced by multiple images with different inhomogeneous densities. Different level images suggesting insular infiltration of the subcutaneous tissue and prethoracic plane. (CT is not adequate for proper breast disorders evaluation).***

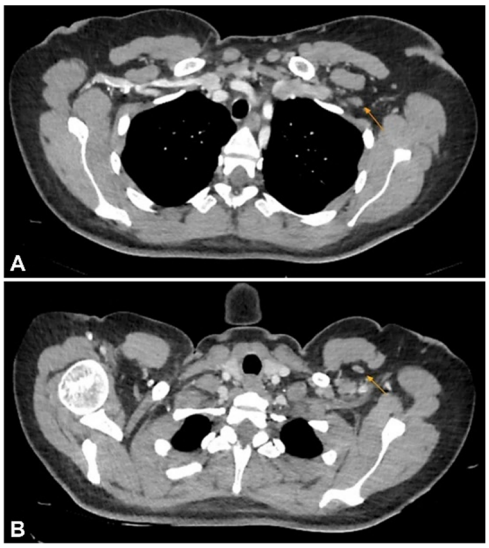

Figure 5 – ***CT coronal sections showing axillary (A) and retrosternocleidomastoid (B) lymphadenopathy, respectively.***

The excised tumor together and the axillary lymph nodes were labeled, then fixed in 10% neutral buffered formalin solution and sent to the Laboratory of Pathology for HP examination. Fragments of about 2/1.5 cm were taken from the tumor, which were embedded in paraffin, using the usual HP protocol. Due to the high tumoral volume, the margins were evaluated in 36 points. After microtome sectioning, the sections were stained with HE and examined under a Nikon 55i microscope (Nikon GmbH, Wien, Austria) equipped with a 5 MP color charge-coupled device (CCD) camera and analyzed using Image-Pro® Plus Advanced Microscopy Suite (AMS) software package (Media Cybernetics, Bethesda, MA, USA).

Microscopic examination showed that the tumor was composed of canalicular structures as narrow as slits, branched like a "fern leaf", lined by a cubic double-layer epithelium, with rare nuclear atypia and rare mitotic cells. The stromal component was abundant, consisting of dense connective tissue with a relatively small number of fibroblast-like cells, without nuclear atypia, collagen fibers, and blood vessels (Figures 6–8). In some areas, intracanalicular stromal proliferations have been observed, compressing and deforming the epithelial ductal structures. Thus, classical HP exam using HE staining confirmed PT together with phyllodes-like fibroadenoma, with clear resection margins over 1 cm, but also failed to exclude borderline lesions and recommended immunohistochemistry (IHC). Five of six axillary lymph nodes that were analyzed had reactive changes. For the IHC study, we used a large spectrum of antibodies to reveal multiple characteristics of the tumor, both in the epithelial structures and in the stromal component: anti-MNF116 [monoclonal mouse anti-human cytokeratin (CK), clone MNF116, 1/100 dilution, Dako]; anti-CK7 (monoclonal mouse anti-human CK7, clone OV-TL 12/30, 1/50 dilution, Dako); anti-CK20 (monoclonal mouse anti-human CK20, clone Ks20.8, 1/40 dilution, Dako); anti-alpha-smooth muscle actin (α-SMA) (monoclonal mouse anti-human SMA, clone 1A4, 1/100 dilution, Dako); anti-p63 (monoclonal mouse anti-human p63 protein, clone 4A4, 1/50 dilution, Dako); anti-cluster of differentiation (CD)117 [polyclonal rabbit anti-human CD117 (c-Kit), 1/400 dilution, Dako]; anti-epidermal growth factor receptor (EGFR) (monoclonal mouse anti-human EGFR, clone H11, 1/40 dilution, Dako); anti-p16 [anti-$p16^{INK4a}$ antibody (1D7D2), clone MA5-17054, 1/100 dilution, Invitrogen]; anti-p53 (monoclonal mouse anti-human p53 protein, clone DO-7, 1/50 dilution, Dako); anti-CD34 (monoclonal mouse anti-human CD34 Class II, clone QBEnd 10, 1/50 dilution, Dako); anti-Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1/50 dilution, Dako).

Ductal epithelial cells were intensely positive for anti-pan-CK MNF116 antibodies (Figure 9), anti-CK7 antibody (Figure 10) and negative for anti-CK20 antibody (Figure 11). Both ductal and stromal cells were moderately positive for α-SMA (Figure 12), p63 (Figure 13), CD117 (Figure 14), and EGFR (Figure 15), and negative for p16 and p53 (Figures 16 and 17) immunomarkers. The CD34 immunomarker marked intensely the stromal cells and the vascular endothelial cells, but not the ductal cells (Figure 18). Regarding the Ki67 cell proliferation marker, it had a weak reaction, marking 4–6 cells, stromal or epithelial, on a microscopic field with medium power objective (×20) (Figure 19). However, Ki67 labeling index in stromal cells, calculated on high-power field was less than 1%.

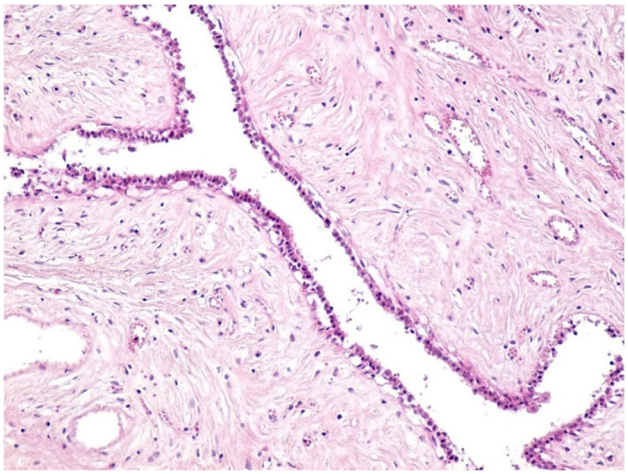

Figure 6 – ***Microscopic image of the phyllodes tumor with the epithelial component represented by leaf-shaped branched duct, lined by a bilayered epithelium and surrounded by an abundant stromal component, consisting of connective cells, collagen fibers and blood vessels. Hematoxylin–Eosin (HE) staining, ×100.***

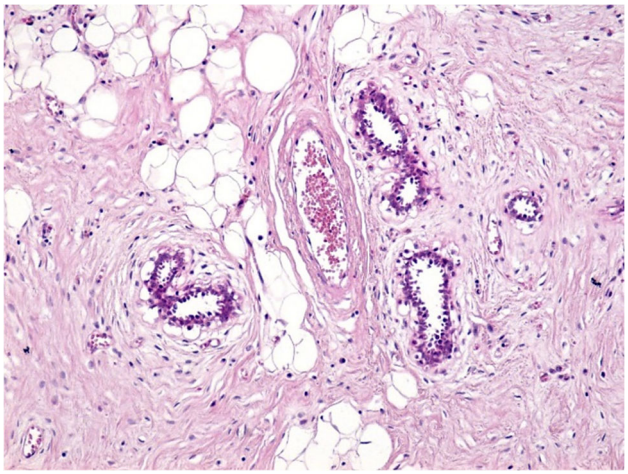

Figure 7 – ***Tumoral area with abundant connective stroma, consisting of fibrous connective tissue dissociating adipose tissue, with a large amount of collagen fibers, but with a small number of stromal cells. HE staining, ×100.***

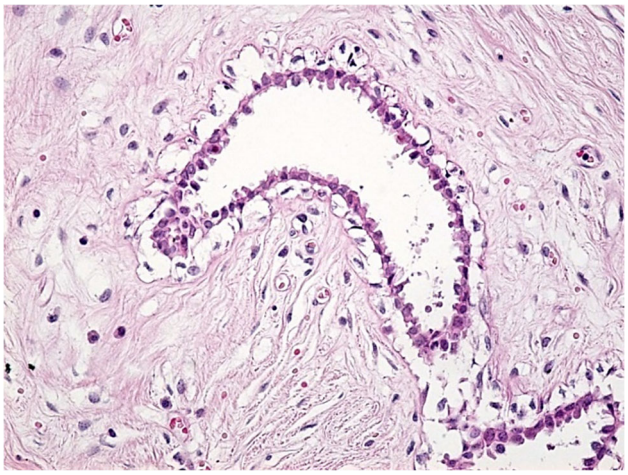

Figure 8 – ***Detailed image showing the ductal double layered epithelium with vacuolization of the cells: extensive cytoplasmatic clearing in the external layer. HE staining, ×200.***

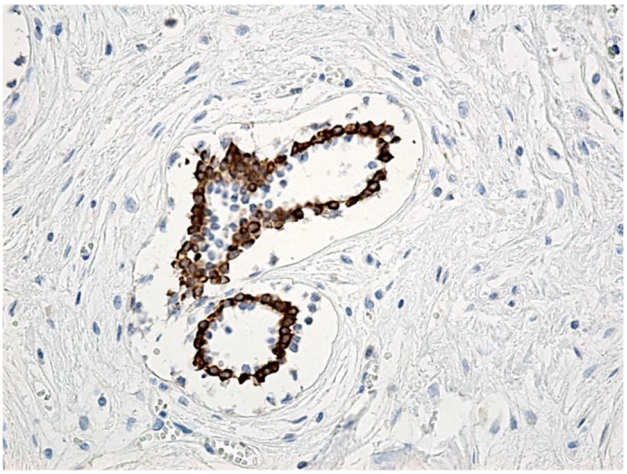

Figure 9 – ***Ducts with intense pan-cytokeratin MNF116 immunoreaction in the internal layer. Immunolabeling with anti-MNF116 antibody, ×200.***

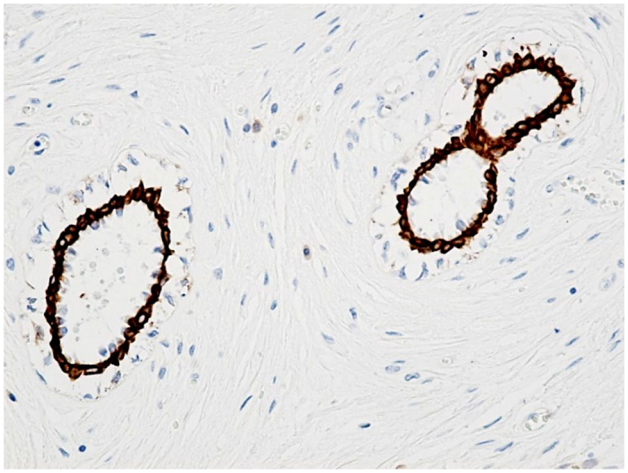

Figure 10 – ***Ductal epithelial cells with intense immuno-reaction to cytokeratin 7 (CK7). Immunolabeling with anti-CK7 antibody, ×200.***

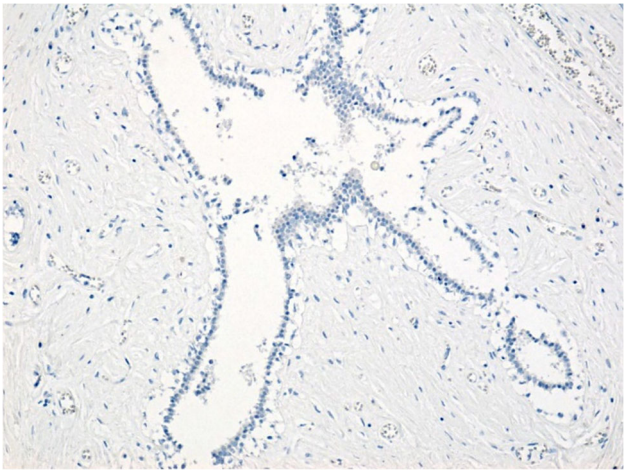

Figure 11 – ***Ductal cells with a negative reaction to cytokeratin 20 (CK20). Immunolabeling with anti-CK20 antibody, ×100.***

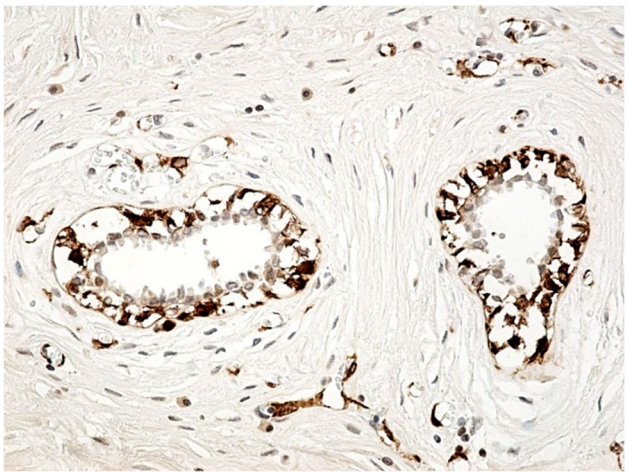

Figure 12 – ***Positive, moderate reaction of ductal basal cells (myoepithelial) and stromal cells (myofibroblasts) to the alpha-smooth muscle actin (α-SMA) immunomarker. Immunolabeling with anti-α-SMA antibody, ×200.***

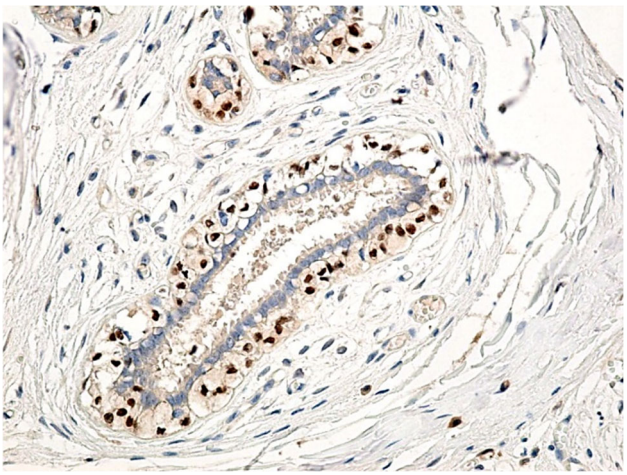

Figure 13 – ***Positive, intense reaction of basal cell nuclei (myoepithelial cells) to the p63 immunomarker with just a few positive cells in the stroma. Immunolabeling with anti-p63 antibody, ×200.***

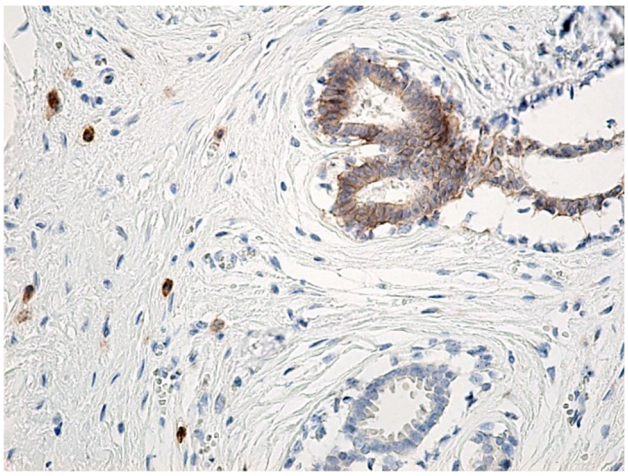

Figure 14 – *Ductal epithelial and stromal cells both with inconsistent reaction (positive/negative) to the cluster of differentiation 177 (CD117) immunomarker. Immunolabeling with anti-CD117 antibody, ×200.*

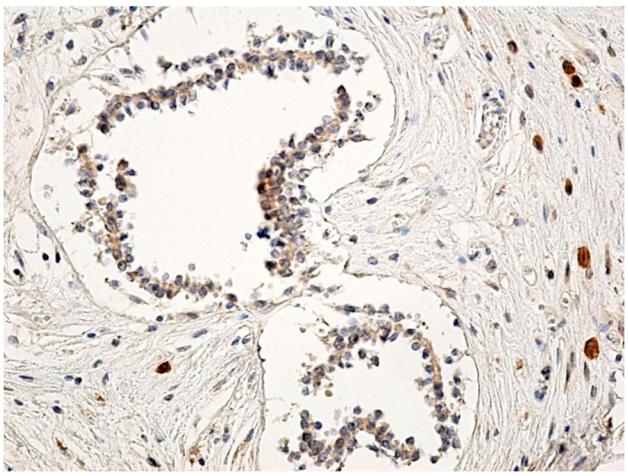

Figure 15 – *Moderately positive reaction to the epidermal growth factor receptor (EGFR) immunomarker in both ductal epithelial cells and stromal cells. Immunolabeling with anti-EGFR antibody, ×200.*

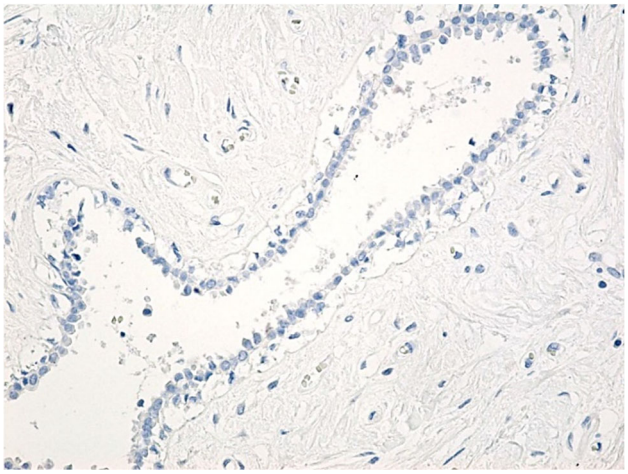

Figure 16 – *Negative reaction of ductal and stromal cells to the p16 immunomarker. Immunolabeling with anti-p16 antibody, ×200.*

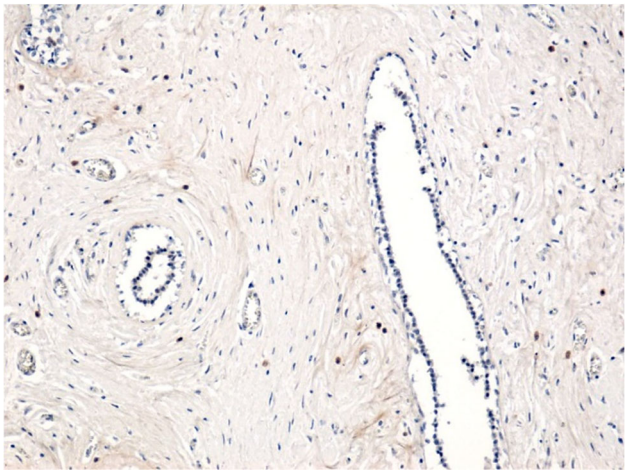

Figure 17 – *Negative reaction of canalicular and stromal cells to the p53 immunomarker. Immunolabeling with anti-p53 antibody, ×100.*

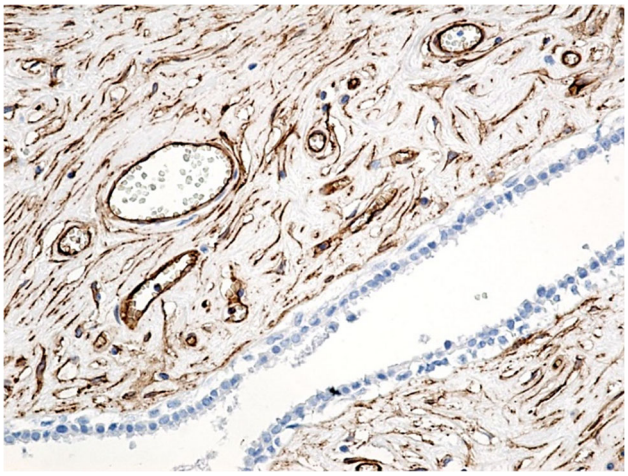

Figure 18 – *Stromal tumor cells with an intense reaction to the cluster of differentiation 34 (CD34) immunomarker, while ductal cells remained negative to the same. Immunolabeling with anti-CD34 antibody, ×200.*

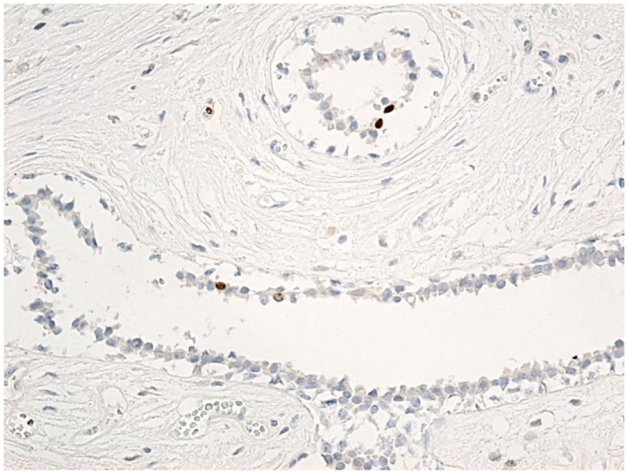

Figure 19 – *Reduced proliferative reaction of tumor cells (4–6 positive cells to the Ki67 immunomarker). Immunolabeling with anti-Ki67 antibody, ×200.*

At one year evaluation, the patient had no signs of recurrence. In November 2021, the Tumor Board decided that reconstruction was safe, but the procedure was postponed for six months due to coronavirus disease 2019 (COVID-19) reasons.

Discussions

For a comprehensive view on giant benign PT, we performed a search of the literature using, *PubMed*, *Web of Science* and *Google Scholar* from 2000 to 2021 using the terms "giant", "phyllodes" and "benign" as keywords. We've extracted 16 cases of giant PTs, which were larger than 10 cm. These cases have been described in Tables 1 and 2 and discussed further together.

From clinical point of view, PT appears as a palpable, painless tumor, mobile on the superficial and deep planes. They are usually fast-growing with dimensions of 10 cm or larger, the average being 5 cm [10, 11]. When a PT has a diameter above 10 cm, it can be classified as a giant PT [12]. Most of the cases in our review presented local signs of inflammation, venous congestion [13, 14], bleeding [10, 15, 16], "peau d'orange" [17, 18] or even necrosis or skin ulcers [7, 10, 14–16, 19–21] while others had no other clinical manifestation than the enlargement of the affected breast [22–25]. Local complications are attributed to the increased pressure that the rapid tumoral growth exerts on the skin but can be difficult to interpret since they are encountered also in malignancy [26]. In our case, superficial small erosion of the skin was secondary to patient's attempts to contain the tumor. We've also noticed skin thinning, areolar diversion, and a slight nipple retraction due to the eccentric tumoral growth. Ipsilateral axillary lymph nodes were palpable, mobile, but firm, 1–2 cm in diameter. Lymphadenopathy is reported in about 20% of PTs [10] but in most cases is probably reactive to local inflammation.

Table 1 – ***Principal characteristics across the literature reported cases of giant PTs between 2000 and 2021***

Study [Ref.]	Age [years]	Disease duration	Size [cm]	Clinical characteristics	Axillary lymph node surgery	Margins status	Recurrence	Reconstructive breast surgery
Likhitmaskul *et al.* [7]	36	5–6 months	20	Cutaneous necrosis, intermittent local pain	Yes, level 1	Free surgical margins	–	Immediate, musculocutaneous flap
Islam *et al.* [8]	44	1 year	50	Ulceration, fungating, anemia, malnourished	Yes	Free surgical margins	Malignant pleural effusion after several months from surgery	–
Fernández-Ferreira *et al.* [10]	40	3 years	25	Blisters on the nipple; erythema; venous network; foul smell; skin ulceration; bleeding; rapid growth in the last year	No	Free surgical margins	None	–
Câmara *et al.* [13]	58	Unknown	13	Local pain and inflammatory characteristics	No	Free surgical margins	Yes, after 4 years and 7 months	Immediate breast reconstruction with *latissimus dorsi* muscle flap (and breast expander)
Kolia *et al.* [14]	38	>2 years	24	Skin ulcer in the lower outer quadrant, dilatations of superficial veins on the breast	No	Free surgical margins	Is not specified	Reconstruction with tissue expander
Zhang *et al.* [15]	42	1 year	30	Ulceration, bleeding, fever, infection, lung adenocarcinoma	No	Free surgical margins	None for 12 months	Refused by the patient
Yap *et al.* [16]	43	13 months	28	Engorgement of superficial veins, ulceration with necrosis, spontaneous bleed, pale and tachycardic, hemoglobin 4.3 g/dL, serum albumin 2.2 g/dL	No	Free surgical margins	None for 6 months	–
Tee & Valayatham [17]	46	6 months	20	Three ulcerated lesions and "peau d'orange" skin changes, confusion, seizure and hypokalemia and hypoglycemia	No	Free surgical margins	None at 4 months	–
Sarvanandan *et al.* [18]	36	3 years	40	Inferomedially deviated and retracted nipple with "peau d'orange" skin changes	Yes	Free surgical margins	None at 12 months	*Latissimus dorsi* pedicle flap reconstruction
Bhattacharjee *et al.* [19]	13	8 months	13	Both breasts, dilated veins, nipples retraction, ulcer, mild serous discharge	Yes	Free surgical margins	None at 2 months	–

Study [Ref.]	Age [years]	Disease duration	Size [cm]	Clinical characteristics	Axillary lymph node surgery	Margins status	Recurrence	Reconstructive breast surgery
Ur Rab *et al.* [20]	23	18 months	22×16	Bloody discharge from the nipple, non-tender swelling, bosselated, hard in consistency, ulceration of skin overlying the tumor	No	Does not say	Does not say	–
Bhasin *et al.* [21]	16	3 years	56 52	Bilateral, mild pallor, five lumps in the right breast, multiple ulcers in right breast	Unclear	Does not say	None at 18 months for the right breast and none at 6 months for the left breast	No
Baldiwala & Vaidya [22]	14	2 months	Unclear	Enlargement of left breast five times as compared to right breast	No	Does not say	None at 7 months	–
Liang *et al.* [23]	70	Unknown	12	No	Yes	Free surgical margins	None for 6 years	–
Okamoto *et al.* [24]	45	5 months	14	Post-lumpectomy status	No	Free surgical margins	None for 7 years	NSM and immediate reconstruction of the breast
Paryani [25]	50	6 months	61	Weakness, anorexia, dull aching pain, pallor	No	Free surgical margins	None for 8 months	–
Our case	24	8 months	30	Grating injuries on the skin covering the mass, painless, venous congestion	Yes	Free surgical margins	None at 12 months	Awaiting reconstruction

NSM: Nipple sparing mastectomy; PT: Phyllodes tumor.

Table 2 – ***Comparison between pre-op diagnosis and post-op histopathological results across reported cases of giant benign PTs between 2000 and 2021***

Study [Ref.]	Pre-op diagnosis/ core needle biopsy	Post-op histopathology	IHC
[7]	Likely benign PT	Benign PT with lactating changes	–
[8]	Fibroadenoma/benign PT	Benign PT	–
[10]	Fibroadenoma	Areas of fibroadenoma and benign PT	Ki67 PI 2%
[13]	Fibroepithelial tumor	Borderline PT	–
[14]	Fibroepithelial lesion	Borderline PT	–
[15]	Malignancy not excluded/benign PT	Benign PT	Ki67 PI 1% p53 index – focally positive
[16]	Fibroadenoma	Benign PT	–
[17]	Spindle cell neoplasm	Benign PT	–
[18]	PT	Borderline PT	–
[19]	Borderline PT	Benign PT	–
[20]	"Benign proliferative breast disease" either phyllodes or fibroadenoma	Benign PT	–
[21]	Bilateral benign PT with fibroepithelial hyperplasia, without any atypia	Benign PT	–
[22]	Fibroadenoma	Benign PT	–
[23]	Cellular fibroadenoma or PT	Benign PT	Ki67 PI 4%
[24]	Benign PT	Borderline PT	–
[25]	Fascicular pseudo-angiomatous stromal hyperplasia/PT	Benign PT	–
Our case	Benign fibroepithelial lesion (fibroadenoma/ phyllodes)	Benign PT	Ki67 PI 4%

IHC: Immunohistochemistry; PI: Proliferation index; Post-op: Post-operative; Pre-op: Preoperative; PT: Phyllodes tumor.

Time since onset of symptoms and patients' presentation varied between two months and three years. In our case, we observed a biphasic growth pattern with a slower phase for five months then an accelerated one for three months in which the tumor doubled its volume according to the patient. Same pattern was observed and reported in other cases [10] and somehow can be misleading, because it raises the suspicion of a malignant transformation appeared in a previously benign tumor, or a fibroadenoma turning in a PT [6, 27].

A particular aspect of our case is related to patient's age at the time of diagnosis. The patient was diagnosed at a much younger age (24 years old) compared to the average age of diagnosis for this type of tumor. Personal and familial history were negative for Li Fraumeni syndrome, breast cancer, trauma, pregnancy or other factors that were cited in relation with the development of PT [27]. Endocrinological consult and hormone tests showed a normal endocrine profile.

Preoperative imagistic methods, such as mammography, US and nuclear magnetic resonance imaging (MRI) could assist the clinician in creating the differential diagnosis between PT and fibroadenomas and other breast neoplasm. These aspects were demonstrated in a retrospective study that included 72 patients with fibroadenomas and 70 patients with PTs. The important elements found in patients with PT were size greater than 3 cm, irregular shape, irregular macrobosselated margins, and hypervascularization [28]. In our case, BI-RADS scores of 5 and 4, respectively, established by two different examinators on US and mammography, raised a serios suspicion of malignancy. Unfortunately, MRI which better correlates to PT HP grade than US and mammography (95.8% *vs* 62.5% *vs* 70% accuracy) [29] was not available for our case. CT of the cervix, thorax, abdomen, and pelvis confirmed cervical and axillary lymphadenopathy and was useful in excluding

distant metastases or other tumoral pathology, but not for characterization of primary lesions since it lacks specificity for breast tissue. The presence of a pulmonary nodule can mimic a metastasis as Zhang *et al.* reported [15]. In our case, the nodule was small, without tumoral features, but determined us to perform a follow-up CT at six months.

For a correct treatment planning, a core needle biopsy is usually indicated to exclude other pathological entities and confirm clinical suspicion, but it cannot always differentiate between fibroadenoma and phyllodes [1]. HP examination in classical HE staining performed on eight samples obtained in our case, detected areas of fibroadenoma coexisting with benign phyllodes in a myxoid stroma. HP report mentioned "probably benign lesion but cannot overrule malignancy". Since fibroadenoma and different types of phyllodes (benign, borderline, and malignant) usually coexist in the same tumor [6] a HP result of benignity in a multifocal giant tumor can become deceptive.

PT treatment is individualized on a case-by-case basis, with the main element being complete excision of the tumor with a 1 cm margin or mastectomy, depending on the size of the tumor in relation to the breast [1]. Radiotherapy remains a controversial topic but can be applied in local recurrences. Chemotherapy is reserved for malignant phyllodes with distant metastases that should be treated as a soft tissue sarcoma [3, 30]. Mastectomy, performed in various fashions (simple, radical, radical extended, etc.) did not show superior results compared to local excision [31]. However, local excision is not feasible for giant phyllodes especially when the lesion is multifocal and extended to the whole mammary parenchyma, as in our case. Axillary lymphadenectomy is not recommended in PT since less than 1% cases reported in the whole literature had positive lymph nodes [3, 32]. Six of the patients including our own underwent axillary lymphadenectomy [7, 8, 19, 20, 23]. In a larger retrospective study in USA published in 2009, Gullett *et al.* reports axillary lymph node dissection, performed in various extents, in more than 25% of all cases of phyllodes, but only in nine cases positive lymph nodes were found [33]. It seems that, despite recommendation, the clinical or imagistic detection of enlarged lymph nodes in the axilla of a patient with a large breast tumor and unclear histopathology, becomes a subliminal indication for the surgeon to resect at least some nodes.

Breast reconstruction after mastectomy can be performed in the same procedure after resection or at some distance in time [23]. In three of the revised cases, breast reconstruction was immediate [7, 13, 24]. In our case, the Tumor Board decided to perform the reconstruction in a second operation since the diagnostic of benignity was doubtful.

Rare tumors like the phyllodes and fibroadenoma are both fibroepithelial tumors which include stromal and epithelial components. The differential diagnosis between these two entities is challenging due to many common features [34, 35]. One of the elements that emphasize the difficulty of differential diagnosis is related to the possibility of their common origin. This aspect is suggested by the presence of a common somatic mutation – *MDM12* – identified by genomic sequencing tests [6].

Given the fact that fibroadenomas have a low risk of local recurrence while PTs have an increased risk and potential for metastasis, an accurate HP diagnosis is important in choosing the right therapeutic attitude. This fact has been reported in a study which aimed to differentiate between fibroadenomas and PTs based on HP features. The study included 61 patients on whom eight HP features (among which stromal mitosis, stromal fragmentation and overgrowth, fat entrapment) were analyzed on initial core biopsy and on the surgical specimens. The conclusions of the study highlighted two important findings: ≥3 mitoses and/or ≥3 HP features are the main criteria in specifying the existence of PT on subsequent excision [36].

It is also important to distinguish between the three HP subtypes of the PT. Even though it is known that most of them are benign, there is a need for precaution in diagnosing malignant PTs, because about 22% of them have distant metastasis. Lung and bones are the most frequent sites of distant metastasis, but there are also three cases of pancreatic metastasis described in the literature [5].

Only HP features are sometimes insufficient in distinguishing the subtype of the PT or might not be always predictive for their clinical behavior [37–39]. Thus, there is a need for further characteristics which can help in achieving an accurate diagnosis. This fact has been reported in a retrospective study which analyzed the link between the expression of three immunomarkers (Ki67, p53 and CD10) and the HP grade of the PTs. The expression of these markers was evaluated both in the stroma and in the epithelium [40]. There was a statistically significant difference of the immunomarkers' expression in the stroma between the three types of PTs, but not in the epithelium. Stromal Ki67 labeling index were at least double in malignant phyllodes compared with benign phyllodes. The immunohistochemical evaluation might play an important role in differentiation benign form malignant PTs, thus Ki67 and p53 could be prognostic biomarkers [40, 41]. In only four of the revised cases, including our own, immunohistochemical examination was performed on the postoperative specimen and none on the core needle biopsies. In all cases, Ki67 proliferation index was found less than 4%. Of the selected cases, four of which were considered benign PTs before surgery turned out to be borderline at postoperative HP examination.

Our immunohistochemical tests sought to highlight the exact type of PT, as some clinical features raised the suspicion of a malignant tumor (appearance in a young woman, rapid development, large size). CKs were positive in ductal epithelium but negative in stroma and together with p63 immunomarker that was found weakly positive in the stroma and intense positive in the myoepithelial cells' nuclei, excluded a sarcomatous carcinoma. p63 was previously reported as focal positive in a subset of malignant PTs but negative in fibroadenoma and benign phyllodes [42]. In the same manner, CD34 and CD117 were reported to have an inverse relation in PT types in the sense that CD34 is expressed in most benign phyllodes, lower in borderline, and lowest or absent in malignant ones, while CD117 seems to be expressed in large proportion of malignant phyllodes, lesser of borderline ones, and only in one third of benign phyllodes [43]. In our case, CD34 stromal reaction was strong, while CD117 was weak and inconstant, advocating for a benign PT. Thus, Ki67

low stromal positivity, CD34 intense expression and CD117 weak reaction in stromal cells, concurrently with negative p53 and moderate positive at α-SMA and EGFR [41, 44], allowed us to formulate the final diagnostic of benign PT.

Conclusions

Given the rarity of the PTs, diagnosis and therapeutic decisions remain difficult. The initial HP result on the core needle biopsy does not differentiate between fibroadenomas and PTs. Considering the unfavorable prognosis of malignant PTs due to their metastatic potential, differentiation of the PT subtype remains essential, influencing the therapeutical decision and impacting patients' prognostic. Where there are difficulties in establishing the subtype of PT based on HP characteristics, immunohistochemical markers, such as Ki67, p53, CD34 and CD117, might be useful in this direction. The standard of treatment in PTs remains the surgical approach. Based on clinical data (young age, rapid growth), imaging examinations and initial HP examinations, which did not allow us to rule out a borderline or malignant PT, we performed left mastectomy with axillary sampling lymphadenectomy, the clinical evolution of the patient being favorable, without local recurrence or metastases at 18 months after surgery.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Ramona-Andreea Matei and Mihai Mehedinţu-Ionescu equally contributed to the research and manuscript thus sharing first authorship.

References

[1] Telli ML, Horst KC, Guardino AE, Dirbas FM, Carlson RW. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. J Natl Compr Canc Netw, 2007, 5(3):324–330. https://doi.org/10.6004/jnccn.2007.0027 PMID: 17439760

[2] Rosen PP. Fibroepithelial neoplasms. In: Weinberg RW, Donnellan K, Palumbo R (eds). Rosen's breast pathology. 2nd edition, Lippincott Williams & Wilkins, Philadelphia, USA, 2001, 176–200. https://www.worldcat.org/title/rosens-breast-pathology/oclc/836897818?referer=di&ht=edition

[3] National Comprehensive Cancer Network. NCCN Guidelines for breast cancer version 8.2021 (phyllodes tumors of the breast). https://www.nccn.org/guidelines/category_1

[4] World Health Organization (WHO) Classification of Tumours Editorial Board. Breast tumours. 5th edition, vol. 2, International Agency for Research on Cancer (IARC) Press, Lyon, France, 2019. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Breast-Tumours-2019

[5] Amir RA, Rabah RS, Sheikh SS. Malignant phyllodes tumor of the breast with metastasis to the pancreas: a case report and review of literature. Case Rep Oncol Med, 2018, 2018:6491675. https://doi.org/10.1155/2018/6491675 PMID: 30050709 PMCID: PMC6040289

[6] Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. Arch Pathol Lab Med, 2016, 140(7):665–671. https://doi.org/10.5858/arpa.2016-0042-RA PMID: 27362571

[7] Likhitmaskul T, Asanprakit W, Charoenthammaraksa S, Lohsiriwat V, Supaporn S, Vassanasiri W, Sattaporn S. Giant benign phyllodes tumor with lactating changes in pregnancy: a case report. Gland Surg, 2015, 4(4):339–343. https://doi.org/10.3978/j.issn.2227-684X.2015.01.09 PMID: 26312220 PMCID: PMC4523627

[8] Islam S, Shah J, Harnarayan P, Naraynsingh V. The largest and neglected giant phyllodes tumor of the breast – a case report and literature review. Int J Surg Case Rep, 2016, 26:96–100. https://doi.org/10.1016/j.ijscr.2016.07.022 PMID: 27475116 PMCID: PMC5010640

[9] Kleer CG, Giordano TJ, Braun T, Oberman HA. Pathologic, immunohistochemical, and molecular features of benign and malignant phyllodes tumors of the breast. Mod Pathol, 2001, 14(3):185–190. https://doi.org/10.1038/modpathol.3880282 PMID: 11266524

[10] Fernández-Ferreira R, Arroyave-Ramírez A, Motola-Kuba D, Alvarado-Luna G, Mackinney-Novelo I, Segura-Rivera R. Giant benign mammary phyllodes tumor: report of a case and review of the literature. Case Rep Oncol, 2021, 14(1):123–133. https://doi.org/10.1159/000510741 PMID: 33776693 PMCID: PMC7983586

[11] Venter AC, Roşca E, Daina LG, Muţiu G, Pirte AN, Rahotă D. Phyllodes tumor: diagnostic imaging and histopathology findings. Rom J Morphol Embryol, 2015, 56(4):1397–1402. PMID: 26743286

[12] Mishra SP, Tiwary SK, Mishra M, Khanna AK. Phyllodes tumor of breast: a review article. ISRN Surg, 2013, 2013:361469. https://doi.org/10.1155/2013/361469 PMID: 23577269 PMCID: PMC3615633

[13] Câmara S, Gonzàlez-Farré X, Vargas-Moniz J. Giant phyllodes tumour – case report, oncoplastic treatment and literature controversies [Tumor phyllodes gigante – caso clínico, cirurgía oncoplástica y controversias en la literatura]. Rev Senol Patol Mamar (J Breast Sci), 2017, 30(2):79–84. https://doi.org/10.1016/j.senol.2017.03.001 https://www.sciencedirect.com/science/article/abs/pii/S0214158217300208?via%3Dihub

[14] Kolia AK, Kalles V, Zografos CG, Chamzin A, Michalopoulos NV. Giant phyllodes tumor occupying the whole breast in a young female: feasibility of mastectomy and immediate reconstruction. J Surg Case Rep, 2020, 2020(4):rjz410. https://doi.org/10.1093/jscr/rjz410 PMID: 32280449 PMCID: PMC7135843

[15] Zhang T, Feng L, Lian J, Ren WL. Giant benign phyllodes breast tumour with pulmonary nodule mimicking malignancy: a case report. World J Clin Cases, 2020, 8(16):3591–3600. https://doi.org/10.12998/wjcc.v8.i16.3591 PMID: 32913869 PMCID: PMC7457108

[16] Yap RV, De La Serna FM, Cala-Or MA, Castillon AG. Pre-operative embolization of a giant benign phyllodes tumor: a case report and review of literature. Int J Surg Case Rep, 2021, 89:106602. https://doi.org/10.1016/j.ijscr.2021.106602 PMID: 34784531 PMCID: PMC8599164

[17] Tee HC, Valayatham VM. Recurrent severe hypoglycemia secondary to benign phyllodes tumor of the breast: a rare case of non-islet cell tumor-induced hypoglycemia (NICTH). J ASEAN Fed Endocr Soc, 2021, 36(2):223–226. https://doi.org/10.15605/jafes.036.02.16 PMID: 34966211 PMCID: PMC8666494

[18] Sarvanandan R, Thangaratnam R, Leong AC. Immediate *latissimus dorsi* pedicle flap reconstruction following the removal of an eight kilogram giant phyllodes tumour of the breast: a case report. J Med Case Rep, 2011, 5:44. https://doi.org/10.1186/1752-1947-5-44 PMID: 21276231 PMCID: PMC3037889

[19] Bhattacharjee SS, Suresh G, Arun BR. A rare case of synchronous bilateral phyllodes tumor in a 13-year-old female. Indian J Surg, 2021, 83(2 Suppl):560–562. https://doi.org/10.1007/s12262-020-02702-0 https://link.springer.com/article/10.1007/s12262-020-02702-0

[20] Ur Rab AZ, Alim AA, Ali WM. Giant phyllodes tumor of breast post fibroadenoma excision: a rare case report and review of literature. Int J Surg Sci, 2020, 4(1 Pt D):188–190. https://doi.org/10.33545/surgery.2020.v4.i1d.331 http://www.surgeryscience.com/archives/2020.v4.i1.d.331

[21] Bhasin SK, Kumari S, Kumar V, Saini P, Sharma G, Akram M. Bilateral benign giant phyllodes tumor in an adolescent female: a rare case report. Int Surg J, 2014, 1(3):177–180. https://doi.org/10.5455/2349-2902.isj20141115 https://www.ijsurgery.com/index.php/isj/article/view/467

[22] Baldiwala AS, Vaidya HP. Phyllodes tumor in an adolescent female. Int Surg J, 2021, 8(11):3460–3462. https://doi.org/10.18203/2349-2902.isj20214393 https://www.ijsurgery.com/index.php/isj/article/view/8177

[23] Liang MI, Ramaswamy B, Patterson CC, McKelvey MT, Gordillo G, Nuovo GJ, Carson WE 3rd. Giant breast tumors: surgical management of phyllodes tumors, potential for reconstructive surgery and a review of literature. World J

Surg Oncol, 2008, 6:117. https://doi.org/10.1186/1477-7819-6-117 PMID: 19014438 PMCID: PMC2648962
[24] Okamoto A, Goto T, Omori M, Miyashita M. Nipple sparing mastectomy for a giant phyllodes tumor; a case report. Int J Surg Case Rep, 2021, 88:106470. https://doi.org/10.1016/j.ijscr.2021.106470 PMID: 34655975 PMCID: PMC8521126
[25] Paryani J. A huge benign phyllodes tumour of the breast: a rare entity. Indian J Surg Oncol, 2019, 10(2):389–391. https://doi.org/10.1007/s13193-019-00911-y PMID: 31168269 PMCID: PMC6527716
[26] Banno A, Shimada A, Aga K, Harada H, Kaburagi T, Seki H, Yasui N, Matsumoto H. Total mastectomy and chest reconstruction for a rapidly progressing giant phyllodes tumor with skin necrosis: a case report. Surg Case Rep, 2015, 1:82. https://doi.org/10.1186/s40792-015-0082-9 PMID: 26389024 PMCID: PMC4569663
[27] Faridi SH, Siddiqui B, Ahmad SS, Aslam M. Progression of fibroadenoma to malignant phyllodes tumour in a 14-year female. J Coll Physicians Surg Pak, 2018, 28(1):69–71. https://doi.org/10.29271/jcpsp.2018.01.69 PMID: 29290198
[28] Duman L, Gezer NS, Balcı P, Altay C, Başara I, Durak MG, Sevinç AI. Differentiation between phyllodes tumors and fibroadenomas based on mammographic sonographic and MRI features. Breast Care (Basel), 2016, 11(2):123–127. https://doi.org/10.1159/000444377 PMID: 27239174 PMCID: PMC4881274
[29] Tan H, Zhang S, Liu H, Peng W, Li R, Gu Y, Wang X, Mao J, Shen X. Imaging findings in phyllodes tumors of the breast. Eur J Radiol, 2012, 81(1):e62–e69. https://doi.org/10.1016/j.ejrad.2011.01.085 PMID: 21353414
[30] Kyriazoglou A, Zagouri F, Dimopoulos MA. Olaratumab administered in two cases of phyllodes tumour of the breast: end of the beginning? ESMO Open, 2019, 4(3):e000479. https://doi.org/10.1136/esmoopen-2018-000479 PMID: 31321082 PMCID: PMC6598554
[31] Reinfuss M, Mituś J, Smolak K, Stelmach A. Malignant phyllodes tumours of the breast. A clinical and pathological analysis of 55 cases. Eur J Cancer, 1993, 29A(9):1252–1256. https://doi.org/10.1016/0959-8049(93)90067-p PMID: 8393684
[32] Shafi AA, AlHarthi B, Riaz MM, AlBagir A. Giant phyllodes tumour with axillary & interpectoral lymph node metastasis; a rare presentation. Int J Surg Case Rep, 2020, 66:350–355. https://doi.org/10.1016/j.ijscr.2019.12.026 PMID: 31927226 PMCID: PMC6953703
[33] Gullett NP, Rizzo M, Johnstone PAS. National surgical patterns of care for primary surgery and axillary staging of phyllodes tumors. Breast J, 2009, 15(1):41–44. https://doi.org/10.1111/j.1524-4741.2008.00669.x PMID: 19141133
[34] Bode MK, Rissanen T, Apaja-Sarkkinen M. Ultrasonography and core needle biopsy in the differential diagnosis of fibroadenoma and tumor phyllodes. Acta Radiol, 2007, 48(7): 708–713. https://doi.org/10.1080/02841850701367911 PMID: 17728999
[35] Krings G, Bean GR, Chen YY. Fibroepithelial lesions; the WHO spectrum. Semin Diagn Pathol, 2017, 34(5):438–452. https://doi.org/10.1053/j.semdp.2017.05.006 PMID: 28688536
[36] Yasir S, Gamez R, Jenkins S, Visscher DW, Nassar A. Significant histologic features differentiating cellular fibroadenoma from phyllodes tumor on core needle biopsy specimens. Am J Clin Pathol, 2014, 142(3):362–369. https://doi.org/10.1309/AJCPZUZ96RESGPUP PMID: 25125627 PMCID: PMC4361036
[37] Lenhard MS, Kahlert S, Himsl I, Ditsch N, Untch M, Bauerfeind I. Phyllodes tumour of the breast: clinical follow-up of 33 cases of this rare disease. Eur J Obstet Gynecol Reprod Biol, 2008, 138(2):217–221. https://doi.org/10.1016/j.ejogrb.2007.08.002 PMID: 17868973
[38] Karim RZ, Gerega SK, Yang YH, Spillane A, Carmalt H, Scolyer RA, Lee CS. Phyllodes tumours of the breast: a clinicopathological analysis of 65 cases from a single institution. Breast, 2009, 18(3):165–170. https://doi.org/10.1016/j.breast.2009.03.001 PMID: 19329316
[39] Tan PH, Thike AA, Tan WJ, Thu MMM, Busmanis I, Li H, Chay WY, Tan MH; Phyllodes Tumour Network Singapore. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. J Clin Pathol, 2012, 65(1):69–76. https://doi.org/10.1136/jclinpath-2011-200368. Erratum in: J Clin Pathol, 2013, 66(5):455–456. PMID: 22049216
[40] Shubham S, Ahuja A, Bhardwaj M. Immunohistochemical expression of Ki-67, p53, and CD10 in phyllodes tumor and their correlation with its histological grade. J Lab Physicians, 2019, 11(4):330–334. https://doi.org/10.4103/JLP.JLP_106_19 PMID: 31929699 PMCID: PMC6943865
[41] Singh Y, Hatano T, Uemura Y, Shikata N, Senzaki H, Hioki K, Tsubura A. Immunohistochemical profile of phyllodes tumors of the breast. Oncol Rep, 1996, 3(4):677–681. PMID: 21594434
[42] Cimino-Mathews A, Sharma R, Illei PB, Vang R, Argani P. A subset of malignant phyllodes tumors express p63 and p40: a diagnostic pitfall in breast core needle biopsies. Am J Surg Pathol, 2014, 38(12):1689–1696. https://doi.org/10.1097/PAS.0000000000000301 PMID: 25046342 PMCID: PMC4373607
[43] Noronha Y, Raza A, Hutchins B, Chase D, Garberoglio C, Chu P, Weiss L, Wang J. CD34, CD117, and Ki-67 expression in phyllodes tumor of the breast: an immunohistochemical study of 33 cases. Int J Surg Pathol, 2011, 19(2):152–158. https://doi.org/10.1177/1066896910382009 PMID: 21087983
[44] Tse GMK, Lui PCW, Vong JSL, Lau KM, Putti TC, Karim R, Scolyer RA, Lee CS, Yu AMC, Ng DCH, Tse AKY, Tan PH. Increased epidermal growth factor receptor (EGFR) expression in malignant mammary phyllodes tumors. Breast Cancer Res Treat, 2009, 114(3):441–448. https://doi.org/10.1007/s10549-008-0030-5 PMID: 18443904

Corresponding authors

Stelian Ştefăniţă Mogoantă, Professor, MD, PhD, Department of Surgery, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania; Phone +40726–323 242, e-mail: ssmogo@yahoo.com

Ştefan Paitici, Assistant, MD, Department of Surgery, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania; Phone +40764–655 015, e-mail: stefanppaitici@gmail.com

Received: January 10, 2022

Accepted: May 17, 2022