Case Report

High grade phyllodes tumor with osteosarcomatous differentiation: Case report and review of the literature ☆,☆☆

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ABSTRACT

Phyllodes tumors (PTs) are rare fibroepithelial malignancies of the breast, accounting for less than 1% of malignant breast tumors. PTs are usually solitary tumors but can be associated with other malignancies, such as DCIS or invasive carcinomas and sarcomas. Osteosarcomatous differentiation of a malignant phyllodes tumor is rare, and differentiation of this rare breast tumor from other entities is of vital importance to clinicians due for appropriate treatment and prognosis. We present a case of rare high-grade phyllodes tumor with osteosarcomatous differentiation presenting on mammogram as a calcified lobulated mass; ultrasound revealed a 1.5 cm irregularly calcified mass, suggestive of bone. An ultrasound-guided core biopsy and subsequent lumpectomy revealed a cellular stroma with osteoid stromal matrix and cytologic atypia with bone formation. At 18 months postprocedure, a recurrence was identified at the previous surgical site, and the patient underwent a mastectomy. Here we present a single case of high-grade PT with osteosarcomatous differentiation and a comprehensive literature review, highlighting the mammographic and histologic characteristics of this rare presentation.

Introduction

Phyllodes tumors (PTs) are rare biphasic breast tumors (composed of both epithelial and stromal components) arising from the peri-ductal stroma and account for only 0.3%-1% of all primary breast malignancies [1–3]. PTs can be classified histopathologically into benign, borderline, and malignant based on stromal cellularity, cellular atypia, high mitotic index, and stromal overgrowth [4]. Benign PTs (60%-75%
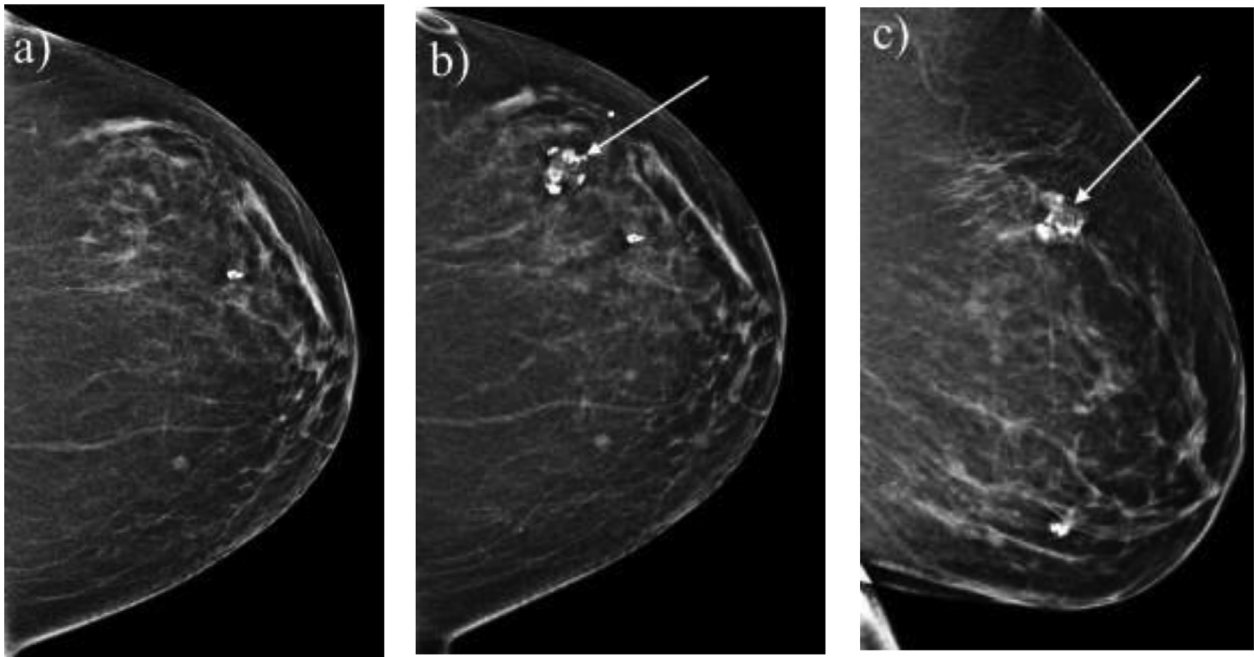
Fig. 1 – Mammogram. (A) Screening examination, left craniocaudal (CC) view, 1 year prior demonstrating no abnormality. Left CC (B) and mediolateral oblique (MLO) views (C) demonstrating a new calcified, palpable mass in the upper outer left breast, suggesting bone (white arrow).

of PTs) typically show a slight increase in stromal cellularity, while malignant PTs (10%-20% of PTs) show increased cellular atypia, with significant mitotic activity, and markedly elevated stromal cellularity, often with stromal overgrowth [1–3,5]. Borderline classification (15%-20% of PTs) is an intermediate stage between these two.

In some cases, the stromal component can have heterologous elements (2%) such as liposarcomatous, chondrosarcomatous, or osteosarcomatous differentiation, or a combination of these, the presence of which automatically classifies the tumor as malignant [3,6]. The etiology of these rare subtypes is unknown, although postirradiation transformation or mechanical injury have been suggested [7].

One of the rarest subtypes of PT is osteosarcomatous differentiation [8]. The cells seen within osteosarcomatous components can have fibroblastic, osteoblastic, or osteoclastic cell predominance [8,9]. Conflicts regarding prognosis have noted better survival rates due to associated smaller tumor sizes [8]; however, higher proliferation rates and aggressivity have also been noted [10]. Thus, while most PTs are treated with surgical excision, the prognosis can be vastly different. Thus, differentiation between PTs with osteosarcomatous differentiation from several other breast tumor types is of vital importance to clinicians. Following IRB approval and patient consent, we present the following case report and review of the literature.

Case report

A 63-year-old white female with a history of hypertension, diabetes, and obstructive sleep apnea presented to her commu-
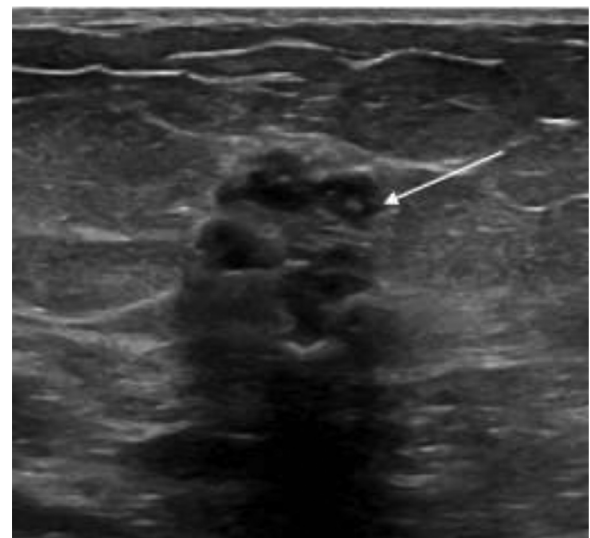
Fig. 2 – Ultrasound examination demonstrating a lobulated, hypoechoic mass containing calcifications measuring 1.5 cm in the 1-o'clock position of the left breast, 7 cm from the nipple (white arrow).

nity OB/GYN with a lump in her left breast 3 months after a normal OB/GYN exam; past medical history included menarche at age 12, 2 uncomplicated pregnancies (first at 26 years old), a hysterectomy at 43 and menopause at age 55 with no history of breast, colon, or ovarian cancer. Physical exam revealed no rash, tenderness, or lymph node enlargement, but was significant for a rubbery firmness in the upper, outer
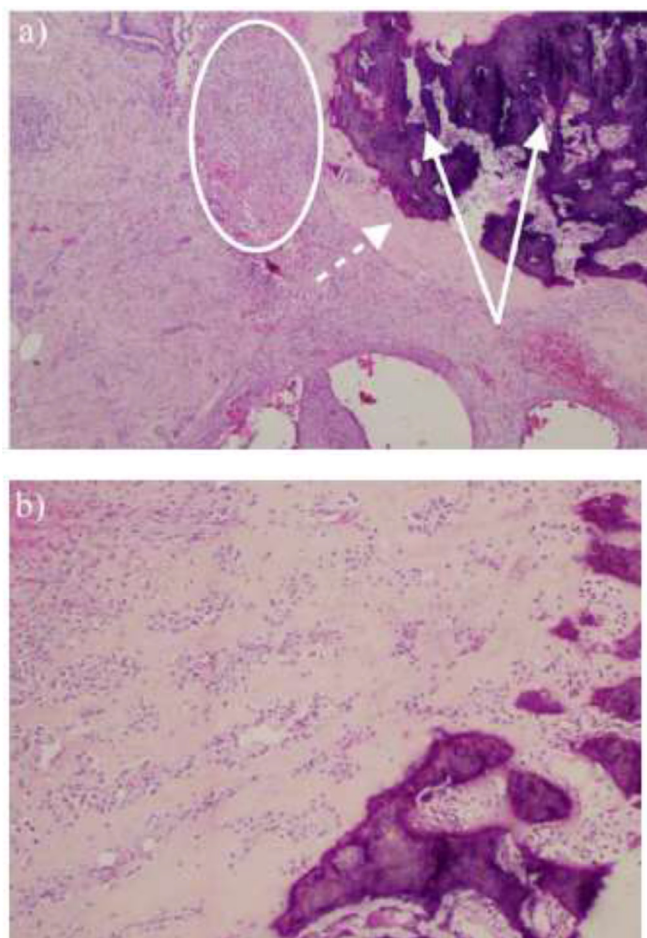
Fig. 3 – Original histology. (A) lower power image (40x) demonstrating cellular spindled stroma (circled) and areas of osteoid matrix (dashed arrow) and bone (solid arrow). (B) Higher powered image (100x) noting the malignant osteoid matrix.

quadrant of the left breast; no discharge, nipple inversion, or skin discoloration were noted. The previous year's normal mammogram (Fig. 1A) was compared to the bilateral diagnostic 3D mammogram, which noted calcified benign-appearing masses in both breasts; however, the area of palpable concern corresponded to a calcified lobulated mass in the left upper outer quadrant (Figs. 1B and C). A targeted ultrasound of the left breast revealed a 1.5 cm irregularly calcified mass, suggestive of bone (Fig. 2). An ultrasound-guided core biopsy was subsequently obtained and indicated an atypical biphasic lesion with metaplastic bone formation. Differentials included periductal stromal sarcoma and phyllodes tumor. A surgical consult and MRI were recommended. Due to the patient's body habitus, MRI was not completed. A lumpectomy was completed, due to the short onset of the abnormal lesion. Histologic analysis revealed a cellular stroma with osteoid stromal matrix and cytologic atypia with bone formation (Figs. 3A and B). The mitotic rate was noted to be 5 per 10 high power fields, with no necrosis and no lymphovascular invasion found. P53 and Ki-67 markers were both increased, and the specimen stained negative for pankeratin, CK5/6, SMA, and desmin. Genetic factor testing revealed EGFR and VEGFA amplification along with PIK3CA, MTAP, and CDK2NA/B loss. The final diag-

nosis was high-grade phyllodes tumor with osteosarcomatous differentiation, excised with clear margins (pT1pNX).

Due to the wide clear margins but noting the rare nature of this malignancy, particularly that phyllodes tumors tend to be locally aggressive and have an increased risk of lung metastasis given the ostial sarcomatous differentiation, a 3-month chest and abdominal CT interval imaging surveillance was initiated. All interval imaging was negative. A diagnostic bilateral mammogram at 1-year postlumpectomy noted stable postoperative changes with no mammographic evidence of malignancy (Figs. 4A and B).

At 18 months postprocedure, the patient reported a lump at the surgical site. A mammogram (Figs. 5A and B) and a targeted ultrasound (Figs. 5C and D) noted a 4.9-5.5 cm mass adjacent to the surgical clips in the upper outer quadrant of the left breast; pleomorphic calcifications similar to the original lesion with stranding and linear extension towards the nipple were also noted. The total extent with the anterior extension is 9.8 cm. An ultrasound-guided core biopsy identified atypical ductal hyperplasia with the involvement of a mildly cellular biphasic lesion, which, in the setting of a prior phyllodes tumor, suggested a recurrence. A simple mastectomy was completed; a phyllodes tumor with osteosarcomatous differenti-
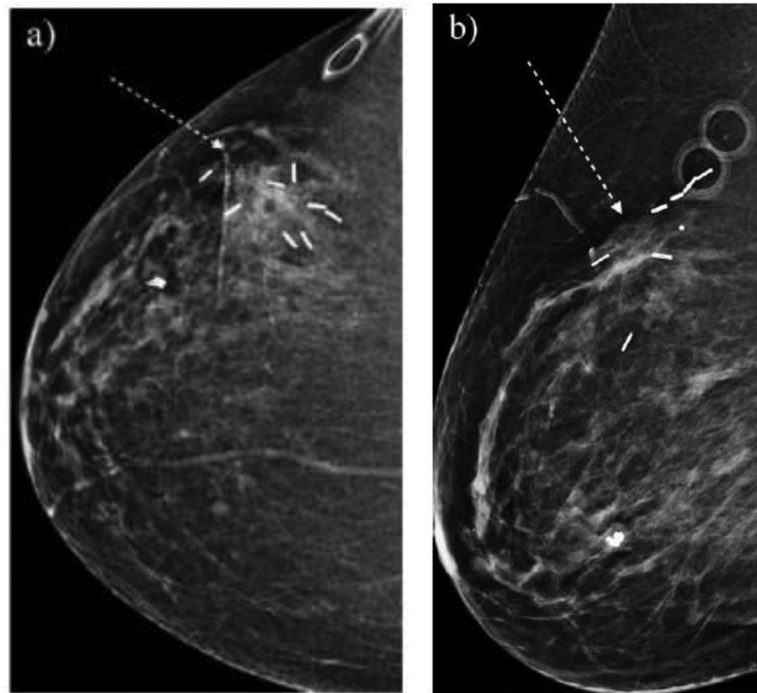
Fig. 4 – Postprocedural mammogram. (A) Screening examination, left CC view and (B) left ML views demonstrate postoperative changes in the upper outer quadrant (broken arrow) but no other abnormality.

ation was identified (Figs. 6A and B). No lymph nodes were submitted. The patient recovered without incident, and the 3-month postmastectomy interval mammogram was clear.

Discussion

High-grade PT with osteosarcomatous differentiation is an extremely rare and aggressive PT variant that portends a poor prognosis [8,11]. The pathogenesis of these tumors is thought to be due to the stromal-epithelial interaction, with the stromal component acting as the primary source of neoplastic transformation [12], and is reminiscent of characteristics typically associated with mesenchymal stem cells and their ability to differentiate into adipocytes, chondrocytes, or osteocytes [13]; the metaplastic change in the stromal cells exhibited by focal markers positive for actin and myoD1 has also been suggested [10].

A comprehensive review of the literature (Table 1) revealed a total of 28 cases reported between 1958 and 2022. The mean age of the cohort was 54.7 years old; all patients were female. While typically unilateral (Left =13; Right =9), 2 presented bilaterally. The most common symptom was a painless, enlarging mass in the breast. Of the 28 cases, 12 (43%) reported imaging findings; 9 reported calcifications, and 3 cases reported no calcifications evident on imaging. Mitotic indices were reported in 12 (43%) cases, 8 of which demonstrated 10/10 HPF or higher (high grade); 9 reports commented on the presence of necrosis. Further differentiation of the osteosarcomatous component included osteoblastic cell type (n = 4), osteoclastic cell type (n = 6), and both cell types (n = 6). Mixed tumor types

with osteosarcomatous differentiation primarily, but sometimes including chondrocytes or lipoblasts, were also noted (n = 7). Metastasis was noted in 21 reports, with 10 (47%) indicating no metastases. Lung metastases were reported in 8 cases (38%). Death was reported in 8 cases, with an average of 19 months from diagnosis until death. Of those that died, only 2 reported using adjuvant chemotherapy along with surgery, and 2 reported radiotherapy.

As the imaging profile of PT overlaps with fibroadenomas, an understanding of the characteristics of PT is essential for a definitive diagnosis. The mammographic appearance of all PT is a circumscribed round or oval mass [14]. Calcifications are typically not present; however, when calcifications are present coarse and amorphous findings suggest a benign process, while fine, linear, and branched calcifications typically suggest a malignant lesion [14]. The mammographic findings of our patient noted neither descriptor but rather unusual irregular calcifications, suggestive of bone formation nor a rarer pathology. On ultrasound, PTs are solid circumscribed masses with heterogeneous echogenicity; malignant PTs are more likely to display an irregular shape, as was noted in our patient [14,15]. MRI notes PTs as circumscribed round or oval masses with homogeneous T2 hyperintensity; rapid contrast enhancement and washout kinetics are also indicative of these lesions and have been associated with higher histologic grade [14]. Due to the patient's body habitus, an MRI was unable to be obtained, so these characteristics of the lesion were not identified. But, the findings on the mammogram and the US, along with the quick onset of a new mass, substantiated a confirmatory biopsy.

As the PT becomes more malignant with heterologous component growth, the biphasic features start to disappear,
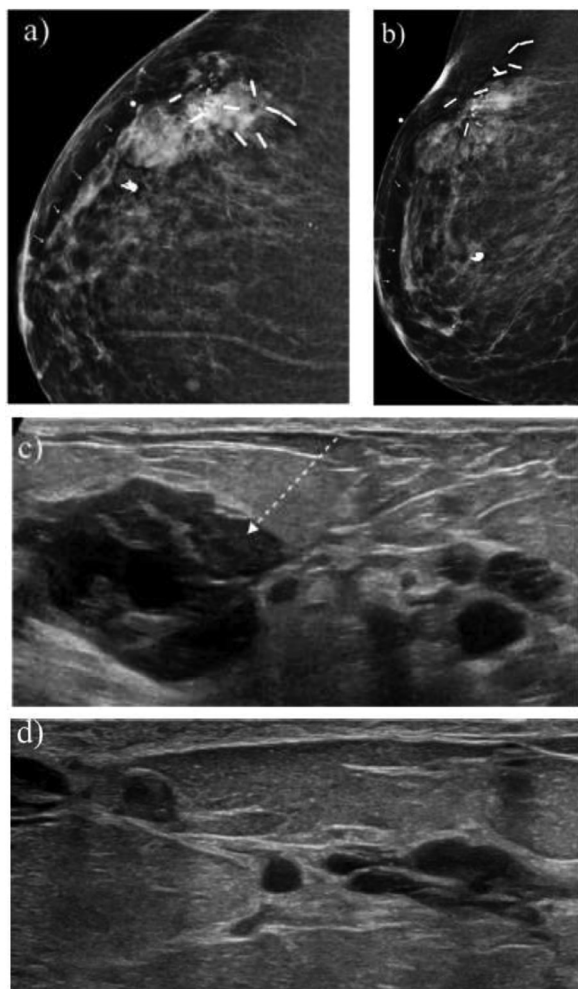
Fig. 5 – Recurrence imaging. Eight months after the normal postprocedural mammogram (A) a diagnostic examination, left CC view, noted a 5.5 cm lobulated mass with pleomorphic calcifications, (B) with stranding and linear extension towards the nipple (yellow arrows). (C) Ultrasound of the upper outer quadrant mass demonstrates a lobulated, partially solid, partially cystic mass (broken arrow) with (D) linear extension towards the nipple.

Fig. 6 – Mastectomy Histology. (A) Low-power image (40x) malignant cellular stroma (black arrow) and with low-power leaf-like space (circled). (B) Higher powered image (200x) showing spindled malignant stroma (black arrow) and open leaf-like space (dashed arrow).

and sarcomatous features begin to arise [16], making it necessary to delineate the tumor as a PT versus osteosarcoma of the breast [3,8]. Continued neoplastic transformation in the setting of osteosarcomatous differentiation produces histologically identifiable osteoclasts and/or osteoblasts. The presence of metaplastic bone formation, as was noted in our patient, immediately narrows the differential diagnosis for the tumor; however, despite the characteristic leaf-like pattern of epithelial cells surrounding cellular stroma, differentiation of PTs from fibroadenomas or metaplastic carcinoma or primary breast sarcomas is essential. Diagnosis by core biopsies alone is typically insufficient due to the biphasic nature of these tumors (variable cytokeratin and vimentin staining) and the possibility of sampling errors [10] Thus, as in our case, a definitive diagnosis was dependent on a lumpectomy.

Pathologically, PTs have varying degrees of increased stromal cellularity with leaf-like processes, periductal stromal condensation and increased mitotic activity, as seen in our case [5,17] However, differentiation of malignant PTs from metaplastic carcinoma, is essential [5,17] and relies on cytokeratin staining of the epithelial cells or by immunohistochemistry for other epithelial markers [5,8,18]. Differentiation of PTs from primary breast sarcomas is also essential, as, although uncommon (1.25%-1.65% of all soft tissue sarcomas), these malignant neoplasms can produce bone in tissue such as the breast [5,7]. Pathologically, the presence of the epithelial components, as determined by staining, is diagnostic for PTs [5,9].

Due to the potential for metastasis and recurrence [19], treatment for phyllodes tumors is always surgical excision, especially in the case of malignant PTs. Wide surgical excision with negative surgical margins ≥1 cm without axillary lymph node dissection is considered standard of care, reducing the risk of local recurrence up to 65% [15]. There is limited data on the role of adjuvant chemotherapy for malig-

Table 1 – Comprehensive literature review.

Author, Year	Age	Side	Presentation	Calcs	Mitoses	Necrosis	Heterologous Component	Chemo/Radio	Mets	Mortality
		Physical Exam		**Imaging**		**Pathology**		**Treatment**	**Prognosis**	
Robb, 1958	67	L	painless				osteoid, cartilage, also a carcinoma present	radiation	Ovaries, adrenal	
Jernstrom, 1963	69	L	painful, enlarging, red, mass	yes			chondroid < osteoid, osteoblasts and osteoclasts		none	death, "several years"
Kay, 1971	62	R	enlarging mass				osteoid w/ osteoclasts, some cartilage			
Anani, 1972	38	L	painful mass	yes			osteoblasts and osteoclasts	radiation	recurrence, lungs	death, 11 months
Argawal, 1978	68	L	enlarging mass ulceration and bleeding			yes	osteoid with osteoblasts			
Pietruszka, 1978	50				14/ 10 hpf		osteogenic sarcoma			alive, 8 months
Chan, 1982	50	R	painful mass w/o increase in size				osteoid		none	alive, 2.5 years
Farringer, 1985	64		painful, enlarging mass	yes			osteosarcoma w/o carcinoma + PTs (osteoblasts)	radiation	lungs	death, 15 years after mastectomy (2 years after dx)
Pandit, 1985	32	bilateral	mass with ulceration			yes	osteosarcomatous with osteoclasts			
Ward, 1986	46				> 20 / 10 hpf	yes	osteosarcoma		none	alive, 269 months
Graadt van Roggen, 1998	50	R	enlarging painless mass	no	~1/HPF		telangiectatic extraskeletal osteosarcoma	chemo	lungs	
Matsuo, 2001	64	L	painless , enlarging mass	yes			neoplastic osteoblasts and some osteoclastic giant cells	none	none	alive, 6 months
McKenzie, 2002	63		mass		5 mitoses per 10 HPFs	yes	osteosarcoma with osteoclasts		lungs	
Tsubochi, 2004	54	L	painless mass	no		yes	osteosarcomatous component not seen	none	lungs	Alive, 3 years
Mukherjee, 2004	51	R	painful, enlarging, mass	yes			osteosarcoma, osteoblastic and clastic with vascular spaces	chemo	none	
Bhartia, 2005	45	L		yes			osteoid	Both	lung	death, 19 months
Ribeiro-Silva, 2006	49	R	enlarging painless mass			yes	osteoid with osteoblastic and numerous osteoclast		recurrence in breast, liver, brain, lungs, skin of right forearm	death, 1 year
Tomas, 2007	71	R	painless mass		5 of 10		osteoid w/ osteoblasts and osteoclasts> lipomatous w/ lipoblasts and mesenchymal cells, and a center chondromatous matrix w/ cartilaginous tissue	chemo	none	alive, 1 year
Uner, 2008	44	Bilateral					osteoblastic osteoid	Both	none	alive, 28 months
Reisenbichler, 2009	55	L	mass		10 of 10	yes	osteosarcoma	radiation	none	alive, 6 months
Saeed, 2009	36	R	enlarging, painful mass	no	19 of 10		osteosarcomatous with some chondroid	none	none	alive, 6 months
Phalak, 2013	63	L	painless enlarging mass	yes	22 of 10		osteosarcomatous	Both	lungs	
Mačák, 2014	74	R			5 of 10		osteosarcomatous with atypical osteoblasts		heart	death, 3 years
Patil Okaly, 2015	40	L	hard, painless mass		10 of 10		osteoclastic cells > chondrosarcoma	none	none	alive, 1 year
Tokoyoda, 2018	52	L	enlarging mass	yes			osteoclastic cells and some cartilaginous			
Berkesoglu, 2020	55	R	painless enlarging mass		12 of 10	yes	osteosarcomatous	chemo	Yes, unknown location	death, 40 months
Laforga, 2020	56	L	enlarging mass			yes	osteoid, osteoclasts, vascular as well	chemo	lungs	death, 31 months
Hall, 2022	63	L	painless enlarging mass	yes	5 of 10		osteosarcomatous	none	none	alive, 8 months

Grayed boxes indicate that the information was not noted in the report.

nant PT [14,18], and a clear benefit in reducing local recurrence, distant metastases and increasing overall survival has not been shown [14]. Several different therapy options have been reported, including adjuvant chemotherapy, adjuvant radiotherapy, and surgery alone (Table 1). As there are no established guidelines for optimal treatment of PTs [14], let alone PTs with osteosarcomatous differentiation, our patient initially opted for surgical excision followed by imaging surveillance [14]; however, after 18 months, a local recurrence was noted, prompting a simple mastectomy.

Further studies of molecular predictors of outcome, including TP53, chromosome imbalance, or 1q gains could also be utilized for prognosis consideration for these lesions [5]. The stromal component differentiates to develop the osteosarcomatous features, and therefore is the neoplastic portion that has the ability to metastasize [9], promoting hematogenous spread primarily to the lungs [1]. While other studies have reported PTs with osteosarcomatous features reporting a local recurrence or metastatic rate of 43% [8]. Interestingly, our review indicated 11 (52%; Table 1) of the reports noting metastatic spread, and, of those, 8 (73%) exhibited lung metastases. To date, our patient has not reported any metastatic spread.

Although rare, phyllodes tumors with osteosarcomatous differentiation are malignant breast pathology with the propensity to metastasize without early detection and intervention. Identification of unusual calcifications by mammographic or US imaging is the first step to achieve a definitive diagnosis, with certainty produced from the trained eye of a pathologist able to recognize distinct differences in this tumor type from other similar malignancies.

Data availability

Data not available for sharing unless there is a agreement with the institution.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of Health Sciences SC; Prisma Health (NO:1958835-1) and individual consent was obtained by universal consent; other required consent for this retrospective analysis was waived. A copy of the written consent is available for review by the editorial office of this journal.

Patient consent

Written informed consent for the publication of this case report has been obtained.

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