CASE REPORT

Giant malignant phyllodes tumor with distant metastases: a case report and review of the literature

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Abstract

Background: Phyllodes tumors (PTs) represent a rare type of breast tumor and are classified into benign, borderline, and malignant. Giant PTs, meaning those sized more than ten cm, are even rarer, most commonly malignant, and usually have a dismal prognosis due to the high metastatic potential.

Case report: We report the case of a 55-year-old woman who underwent modified radical mastectomy and left axillary lymphadenectomy for a rapidly growing, giant, ulcerated mass of the left breast. Histopathologic examination revealed a malignant phyllodes tumor (MPT). Over one year after the initial surgery, the patient was found to have extensive thoracic and retroperitoneal metastases.

Conclusion: Although giant PTs are uncommon, clinical suspicion should be high in rapidly growing breast mass patients. A comprehensive review of all metastatic giant MPT cases reported in the English literature emphasizes the lack of consensus regarding appropriate treatment. In the case of metastatic foci, pathologists need to be aware of the previous history to make a definitive diagnosis. Also, a comparative histopathologic study of the primary and metastatic tumors is sometimes necessary. HIPPOKRATIA 2022, 26 (1):41-45.

Keywords: Biphasic breast tumor, breast tumors, giant phyllodes tumor, malignant fibroepithelial tumor, metastatic breast tumor, metastatic phyllodes tumor

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Introduction

Phyllodes tumors (PTs) account for 0.3-1 % of all primary breast neoplasms[1]. Classification of PTs into benign, borderline, and malignant is based on specific histological features[1]. Their size may vary from smaller than five cm to larger than ten cm; in the latter case, they are considered giant. A minority of the reported giant PTs are benign or borderline, whereas most are malignant. Giant MPTs are exceedingly rare and often present with metastases shortly after complete surgical excision. In fact, to date, only 26 cases of metastatic giant MPTs have been reported in the English literature.

We describe an unusual case of a giant MPT with extensive thoracic and retroperitoneal metastases over one year post-mastectomy, along with a review of similar cases in the literature.

Case report

A 55-year-old woman with an insignificant personal and family history presented to the surgical department with a large mass of her left breast, rapidly growing over the preceding two months. Physical examination showed a giant ulcerating mass of the left breast, measuring approximately 45 cm in greatest diameter, prominent skin ulceration, dilated superficial veins (Figure 1), and enlarged lymph nodes in the left axillary region. There were no additional lesions on the computed tomography (CT) scan of the chest, upper and lower abdomen, and brain. The patient underwent a modified radical mastectomy (MRM) and left axillary lymphadenectomy. One month

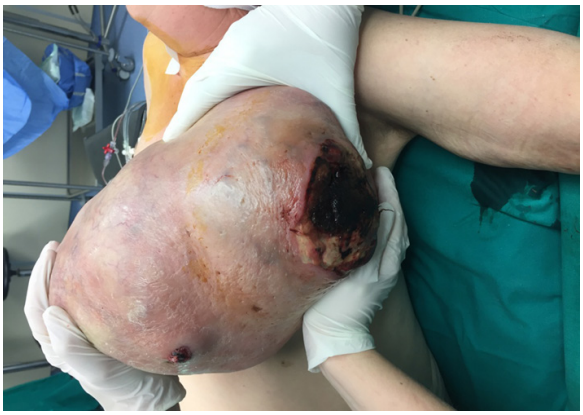

Figure 1: Perioperative image showing a huge ulcerated left breast tumor.

later, postoperative chest, upper and lower abdomen, brain CT, and bone scintigraphy showed no evidence of metastatic disease. Subsequently, the patient received adjuvant radiation therapy using a linear accelerator, with a total dose of 60 Gray (Gy) in ten fractions. Two months after the completion of radiation treatment, the patient declined to attend the scheduled follow-up appointment.

One year and four months after the initial surgery, the patient presented with low back pain and edema of lower extremeties. On the CT scan of the chest, upper and lower abdomen a large mass was found occupying the left hemithorax, causing the mediastinum to shift to the right. The mass surrounded the thoracic aorta, invading the pleura and the diaphragm, and extended downwards, reaching the lower pole of the spleen and left kidney, surrounding the left ureter, and invading the ilium as well as the gluteal muscles. Biopsy of the mass confirmed the extensive spreading of the malignancy, The patient received symptom control treatment and ultimately succumbed to the disease 17 months after the initial diagnosis.

The mastectomy specimen, consisting of the left breast and its overlying skin and nipple, was sent for pathologic examination. Also, the specimen of the left axillary dissection was sent, in which five lymph nodes were identified, measuring 0.3-3.2 cm in the greatest dimension. A tan-colored, lobulated tumor almost entirely occupied the breast grossly, with areas of hemorrhage and necrosis. The microscopic examination demonstrated a fibroepithelial neoplasm, comprised of areas with a leaf-like growth pattern, characterized by cleft-like spaces lined by a double layer of epithelial and myoepithelial cells and surrounded by an expanded stromal component (Figure 2A). Stromal cellularity ranged from mild (Figure 2B) to remarkably increased. On a low-power field (x4), areas composed exclusively of stromal elements were observed ("stromal overgrowth") (Figure 2C). A considerable proportion of the stromal cells exhibited marked nuclear pleomorphism and cellular atypia. Moreover, there were some anaplastic or bizarre multinucleated neoplastic cells. The mitotic activity was as high as 13 mitoses per 10 High Power Fields. Notably, foci with heterologous chondrosarcomatous differentiation were apparent (Figure 2D). Immunohistochemical examination revealed the following immunophenotype of the stromal cells: vimentin+, EGFR+, CD10+, CD34+ (Figure 2E), Bcl2+, AE1/AE3-, CK8/18-, CK5/6-, 34βE12-, p63-, CD117-, SMA-, ER-, PR-, HER2-. The Ki67 proliferative index showed variable percentages of positivity among stromal cells ranging from 1 to 20 %. Based on described findings, we established the diagnosis of MPT, after which adjuvant radiation therapy commenced. All five axillary lymph nodes examined were negative for metastases.

Histopathological examination of the biopsy of the gluteal mass showed a neoplastic lesion composed of short to elongated spindle cells arranged in a random pattern within a loose myxoid stroma (Figure 2F). Mild to moderate atypia and nuclear pleomorphism, as well as scant mitotic figures, were noted. Regions of tumor necrosis were also present. Upon immunohistochemical examination, tumor cells were positive for CD10 and CD34 and negative for SMA, ER, PR, and AE1/AE3 antigens. The percentage of cells with Ki67-positive nuclear immunostaining ranged from 1 to 5 %. Overall, the morpho-

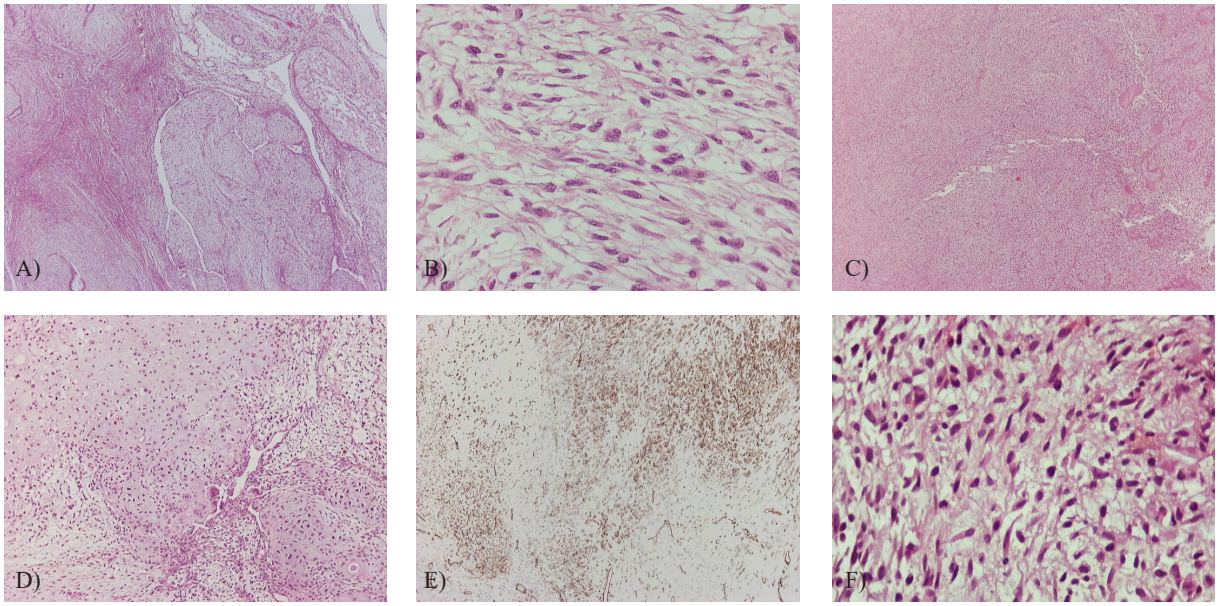

Figure 2: Histologic images of the giant malignant phyllodes breast tumor and the metastasis. Malignant phyllodes tumor is characterized by: A) areas with leaf-like pattern [hematoxylin eosin staining (H&E), x40], B) stroma of mild to high cellularity (H&E, x400), C) stromal overgrowth (H&E, x40), or D) chondrosarcomatous differentiation (H&E, x100). E) Stromal cell positivity to CD34 antibody (immunohistochemistry, x100). F) Biopsy of gluteal metastatic lesion presenting short to elongated spindle cells, randomly dispersed within loose myxoid stroma (H&E, x400).

logic and immunohistochemical findings were compatible with the less histologically aggressive areas of her prior MPT.

Discussion

PTs of the breast constitute a rare type of fibroepithelial lesions, accounting for only 0.3 to 1 % of all primary breast neoplasms and 2.5% of all mammary fibroepithelial tumors[1]. The average incidence is 2.1 per million per year in females, whereas isolated cases have been reported in males[2]. PTs predominantly affect middle-aged females in their fourth or fifth decade of life, usually before menopause, which means 15 to 20 years later than the average age of fibroadenoma's first clinical presentation[3].

Typically, the clinical manifestation of PTs is a rapidly enlarging, firm, mobile, well-defined, painless mass, usually located in the upper outer quadrant of the breast, with a median size of four to five cm[3]. Some of these tumors grow larger than ten cm and are known as giant PTs[4]. The prevalence of giant PTs has yet to be well documented in the literature, and they are usually presented in the form of case reports. However, according to Reinfuss et al, in an analysis of 170 PT cases, 21.2 % were giant[5], while Rowell et al reviewed 18 PT cases, 16.6 % of which were giant[3]. In giant PTs, the overlying skin may be stretched upon physical examination with dilated superficial veins and blue discoloration. Less often, skin ulceration and nipple retraction can be observed[6], as described in our case. In addition, the giant size of these tumors is a significant predictive factor for distant metastasis following primary surgical resection. Specifically, according to Kapiris et al[7], a tumor size larger than ten cm is associated with the development of distant metastases, with a hazard ratio of 11.1 ($p = 0.007$) translated into a 91.7 % probability of distant metastases for giant PTs.

We identified 26 cases[8-28] of giant metastatic MPTs, published in English literature, between 1982 and 2020 which we reviewed along with the present case (Table 1). The mean age of patients was 51 (range: 23-83) years. In 12 of the 20 cases (60 %) that report tumor location, the tumor involved the left breast. In 21 (21/26, 80.7 %) cases, metastases were identified within a year, six synchronous with the breast mass. Regarding the site of metastasis, 15 patients (15/23, 65.2 %) presented multiple metastatic sites, the most common being the lung (11/23, 47.8 %), followed by the brain (8/23, 34.8 %), skeleton (5/23, 21.7 %), chest wall, thoracic cavity, and mediastinum (5/23, 21.7 %). Less common sites of metastasis were the abdominal cavity and peritoneum (3/23, 13 %), gastrointestinal tract (2/23, 8.7 %), soft tissues (2/23, 8.7 %), adrenals (2/23, 8.7 %), epidural space (2/23, 8.7 %), pelvis (2/23, 8.7 %), liver (1/23, 4.3 %), and heart (1/23, 4.3 %).

Radiological investigation and histopathological findings are the keys to the diagnosis of PTs. Imaging features are not pathognomonic, making the distinction between fibroadenomas and PTs difficult and the classification of PTs into a subtype almost impossible[29]. Similarly, both fine needle aspiration cytology (FNAc) and core biopsy are frequently unable to establish a preoperative diagnosis of PTs[30]. Considering the histological heterogeneity of the reported case, exhibiting loose mesenchymal areas with mild cellularity and atypia to pleomorphic areas and stromal overgrowth, it can be concluded that even in excisional biopsies, a definite diagnosis cannot always be achieved. It is of interest that the biopsy specimen of the metastasis in this presented case showed a mesenchymal tumor characterized by low cellularity and atypia, which could have easily led to misdiagnosis if the pathologist had been unaware of the patient's previous history.

Adequate surgical excision remains the mainstay of PT management. To date, in international literature, wide local excision (WLE) with negative margins of at least one cm is generally accepted as the optimal primary treatment of PTs[31]. This approach also seems to be adopted for giant PTs, which could explain the differences observed in the conducted review (Table 1). Although palpable axillary lymph nodes are not uncommon, metastatic involvement is extremely rare[6]. In five of the giant, metastatic PT cases reported, an axillary lymphadenectomy was performed without any evidence of neoplastic involvement of the excised lymph nodes.

Regarding adjuvant or palliative treatment, six patients (6/18, 33.3 %) received chemotherapy, five patients (5/18, 27.7 %) radiotherapy, two patients (2/18, 11.1 %) a combination of chemotherapy and radiotherapy, and one patient (1/18, 5.5 %) medroxyprogesterone acetate. Four patients (4/22, 22.2 %) received no adjuvant or palliative treatment, while no information regarding adjuvant/palliative treatment was available for nine patients. Adjuvant radiotherapy of the breast/chest wall after resection of local recurrence, either in the form of breast-conserving surgery or total mastectomy, has been recommended for patients with MPTs; however, this remains controversial, since no significant difference in disease-free survival and overall survival has been proven yet[31]. In cases with systemic recurrence, adjuvant chemotherapy with doxorubicin in combination with ifosfamide has yielded promising outcomes, but further assessment with randomized clinical trials is required[2]. Taking into account our review's data, it is concluded that there are no treatment guidelines, despite the undisputable aggressive nature of these tumors. A therapeutic approach similar to that of soft tissue sarcomas should be reconsidered and established by analogy with MD Anderson Cancer Center recommendations.

Conclusion

Although giant MPT represents an uncommon clinical and surgical entity, clinicians should preserve high clinical suspicion in patients with a rapidly enlarging breast mass. Fine needle aspiration and core biopsy may be helpful, but a definitive diagnosis is usually established after *in toto* surgical excision of the mass and histopathologic examination. Pathologists should be aware

Table 1: Clinical data of all metastatic giant malignant phyllodes tumors reported to date in the English literature.

No	Author, Year	Age (y)	Site of tumor	Type of surgery	Adj/Pall treatment	Site(s) of metastasis	Time to metastasis (from diagnosis)	Follow-up
1	Gregston, 2019[8]	32	L breast	Radical mastectomy, STSG	CT	Lung, brain	2 months (lung), 6 months (brain)	Died 20 months post-surgery
2	Moon, 2019[9]	48	R breast	Mastectomy, ALND, TA Flap, STSG	CT	Lung	Synchronous	Alive 3 years post-surgery
3	Liu, 2020[10]	82	L breast	Simple mastectomy	RT	Chest wall, stomach	2 months (chest wall), 6 months (chest wall & stomach)	Died 13 months post-surgery
4	Ramakant, 2015[11]	40	R breast	Simple mastectomy, ALND	CT & RT	Brain, lung, adrenals	7 months	Died 1 month post-CT
5	Ramakant, 2015[11]	28	L breast	Simple mastectomy, ALND, LD Flap cover	CT	Lung	2 months	Died 8 months post-surgery
6	Khanal, 2018[12]	37	L breast	MRM	None	Lung, adrenals, brain	3 months	Died 20 days after diagnosis of metastasis
7	Patel, 2019[13]	45	R breast	Simple mastectomy, Flap reconstruction	CT & RT	Skull	3 years	Alive & free of disease (4 years after relapse)
8	de Foucher, 2017[14]	57	L breast	Radical mastectomy, ALND, partial pectoral muscle resection	CT	Soft tissues	Few weeks	Died 4 months after initial diagnosis
9	Morcos, 2010[15]	52	L breast	WLE, TRAM Flap	N/A	Caecum, lung, soft tissues	13 months (caecum), following months (UNS) (lung, soft tissues)	Died 18 months later
10	Collin, 2013[16]	57	L breast	Simple mastectomy	N/A	Lungs, adrenals, pelvis	5 years (lungs), 6 years (adrenals/pelvis)	Died 9 years after initial diagnosis
11	Roberts, 2014[17]	50	Rbreast	Simple mastectomy	None	Chest, brain	Synchronous (chest) 3 weeks (brain)	Died 7 weeks later
12	Sanchez, 2016[18]	60	Rbreast	Radical mastectomy	N/A	Liver	Synchronous	Alive (3 months post-surgery)
13	Jhawar, 2015[19]	63	L breast	Simple mastectomy, STSG	N/A	Brain	1 week	Alive & free of disease (6 months post-surgery)
14	Johnson, 2016[20]	66	L breast	Simple Mastectomy	RT	Bone, brain,lungs	1 year	N/A
15	Kataoka, 1998[21]	54	L breast	Simple Mastectomy	MPA	Lung	Synchronous	Alive & free of disease (16 months post-surgery)
16	Nayak, 2017[22]	29	R breast	Simple Mastectomy	RT	N/A	12 months	N/A
17	Al Saad, 2011[23]	53	R breast	Lumpectomy followed by mastectomy	RT	lungs, peritoneum	4 months	Died within weeks (UNS)
18	Lindquist, 1982[24]	45	N/A	Simple Mastectomy	N/A	N/A	Synchronous	Died after 21 months
19	Al-Zoubaidi, 2011[25]	59	L breast	Simple mastectomy, en-bloc partial pectoralis major muscle resection, fasciocutaneous advancement flap	CT	Lung, brain	Synchronous (lungs 5 weeks (brain)	Died 8 months after initial diagnosis
20	Chika, 2017[26]	38	R breast	Simple Mastectomy	None	Abdomen generalized	5 weeks	N/A
21	Hawkins, 1992[27]	44	N/A	Mastectomy	CT	N/A	22 months	Died after 25 months
22	Hawkins, 1992[27]	52	N/A	Mastectomy	None	N/A	5 months	Died after 12 months
23	Barrio, 2007[28]	60	N/A	Mastectomy	N/A	Bone, brain, epidural space	N/A	N/A
24	Barrio, 2007[28]	83	N/A	MRM	N/A	Chest wall, thoracic cavity	Several months later (UNS)	Died (UNS)
25	Barrio, 2007[28]	23	N/A	Radical mastectomy	N/A	Chest wall, sternum mediastinum	2 months	Died (UNS)
26	Barrio, 2007[28]	59	N/A	Mastectomy	N/A	Epidural space, vertebrae	Several years later (UNS)	N/A
27	Present case	55	L breast	MRM & left ALND	RT	thoracic, abdominal & pelvic cavity	1 year & 4 months	Died 17 months after initial diagnosis

Adj/Pall: Adjuvant/Palliative, y: years, N/A: not available; R: right; L: left, STSG: split-thickness skin graft; ALND: Axillary Lymph Node Dissection, TA Flap: Thoracoabdominal Flap; LD Flap: Latissimus Dorsi Flap; MRM: Modified Radical Mastectomy; WLE: Wide Local Excision; TRAM Flap: Transverse rectus abdominus myocutaneous Flap; UNS: unspecified time.

that a biopsy specimen of a metastatic PT may lead to misdiagnosis, especially if the previous clinical history of a patient is unknown; where necessary, a comparative study of the primary and metastatic tumor specimens can be of help. Their adverse biologic behavior, specifically the high probability of metastasis, justifies the previous nomenclature that clearly stated their sarcomatous nature. Guidelines are required for appropriate therapeutic management of giant MPTs, reconsidering following the same principles applied to treating soft tissue sarcomas[32].

Conflict Interests

The authors report no conflicts of interest.

Acknowledgement

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