Metastatic Malignant Phyllodes Tumor of the Breast: An Aggressive Disease—Analysis of 7 Cases

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Abstract Malignant phyllodes tumor (PT) of the breast behaves aggressively and the presentation of distant metastases is varied, ranging from synchronous or short interval commonly to a decade rarely. To assess the clinical and temporal pattern of distant metastases in malignant PTs. A retrospective analysis of patients with Phyllodes tumor of the breast from January, 2001 to November, 2014. There were a total of 167 patients with PT; 49 (29 %) were malignant PT out of which 7 developed distant metastases. Detailed analysis of these 7 patients showed that mean age was 36.71 years (range 28–53 years). Three of the seven patients had additional local recurrences post lumpectomy. The procedure performed were wide local excision with muscle reconstruction ($n=1$), lumpectomy ($n=1$) and mastectomy ($n=5$). The distant metastases were synchronous ($n=2$) and other 5 had metastases developing within 2 months to 13 years. The sites for distant metastases included lung, brain, adrenal, para-aortic nodes and bone. Six patients received palliative chemotherapy (CT) and 2 also had radiation therapy for brain metastasis. Only 1 patient is alive and receiving CT and all others succumbed to the disease. Patients with malignant PT of the breast with distant metastases behave

aggressively and have a dismal outcome with rare exceptions. They need multimodality therapy and close follow up. Newer targeted therapies may have a role to improve the outcome.

Keywords Malignant phyllodes tumor of breast · Distant metastases

Introduction

Phyllodes tumor (PT) of the breast is classified commonly into benign (58 %), borderline malignant (12 %) and malignant (30 %) sub-types [1]. Borderline malignant PTs behave more like benign PTs in having more local recurrences but very rarely distant metastases. Malignant PT behaves like a sarcoma and spreads hematogenously to distant organs in up to 22 % patients [2]. Sites for distant metastases may include lung, liver, brain, adrenal, bone and rare sites like duodenum, heart, parotid and oral cavity [3–8]. Patients develop distant metastases either synchronously or within a few months; rarely the metastasis may present after many years.

Most patients with distant metastases behave very aggressively and have a dismal outcome. Surgery in form of wide local excision or mastectomy plays a key role in reducing local recurrences. Chemotherapy and radiation therapy are used in palliative settings for distant metastases though they have a limited role to improve the survival. Hormonal therapy is usually not used for these patients. One of our patients recently presented 13 years after mastectomy with a bone lesion in the femur that intriguingly turned out to be a metastasis. So, we retrospectively analyzed our case series to study the pattern of metastatic disease presentation in patients with malignant PT of the breast.

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Methodology

Retrospective data analysis of patients with Phyllodes tumor of the breast ($n=167$) from January, 2001 to November, 2014. Consent for conducting this study was obtained from Institutional Research Board. Detailed analysis was done for all ($n=7$) patients with malignant PTs with distant metastases.

Result

Out of total 167 patients with PT, 49 (29 %) were malignant and 7 had distant metastases. The patients clinical and management details are summarized in Table 1.

Patient details:

- Patient 1** A 40 years aged lady presented with breathlessness and left sided chest pain for 1 month in 2005. She was diagnosed to have right breast malignant phyllodes tumor with lung metastases and hypercalcaemia. She received palliative chemotherapy and then had surgery and further chemotherapy. She needed repeated aspirations for pleural effusion and also management for hypercalcaemia. She developed brain metastases 2 months later and was given whole brain radiation therapy 30Gy in 10 fractions (RT). She succumbed to the disease shortly thereafter.
- Patient 2** A 36 year-old lady presented with history of having bilateral breast operations elsewhere in 2002 with a pathologic diagnosis of cystosarcoma phyllodes with heterologous differentiation and rhabdomyosarcomatous component. She did not receive any adjuvant treatment. She developed headache, vomiting and convulsions in February, 2008 and on evaluation found to have left parieto-occipital tumour and bleed. A biopsy from this site was suggestive of metastatic poorly differentiated tumor, suggestive of metastases from phyllodes tumor. She underwent decompressive surgery and radiation therapy. On further evaluation she had disseminated disease with metastatic foci in duodenum, para-aortic nodes, 10 cm heterogeneously enlarged right adrenal gland involving right kidney with renal vein thrombosis, left gluteal region and lung. The right adrenal lesion was biopsied and the histology was poorly differentiated large cell malignant tumor. She also succumbed to the disease.
- Patient 3** A 29 year-old lady presented with a lump in the right breast for 5 years duration. She had lumpectomy elsewhere in February 2008 after which the lump recurred in 2 months time and increased rapidly in size. The biopsy was malignant phyllodes

tumour. She had 15 cm large recurrent right breast lump. She underwent wide local excision with Latissimus Dorsi (LD) muscle flap reconstruction. She had lung metastases and received 4 cycles of palliative chemotherapy with Mesna, Doxorubicin, Ifosfamide and Dacarbazine (MAID regimen). She died 1 year later.

- Patient 4** A 40 year-old lady presented with right breast lump with rapid increase in size for 2 months in 2010. She had around 15×10 cm large lump in her right breast. She underwent simple mastectomy. Her biopsy was malignant PT. She was given adjuvant RT to chest wall and was on regular follow up. In 2013, evaluation with PET scan showed multiple extra axial lesions in the brain and left adrenal gland metastases (7.7 cm large, biopsy proven) (Fig. 1). She was then given 3 cycles of palliative chemotherapy with Ifosfamide and Doxorubicin. As she had disease progression, they deferred further management. She died 1 month later at home.
- Patient 5** A 28 years aged lady presented with left breast recurrent lump with rapid increase in size (15×10 cm) for 9 months duration. She had lumpectomy elsewhere 9 months back and then noticed local recurrence. She underwent simple mastectomy with axillary clearance and LD muscle flap reconstruction for closure. Her biopsy was malignant spindle cell neoplasm with osteosarcomatous and chondrosarcomatous components. On follow up, 2 months later CT thorax was done for metastatic work up and it showed lung metastasis. She received 6 cycles of Doxorubicin based chemotherapy. Three months later she presented with progressive dyspnoea. She had right sided pleural effusion and ECHO done showed a pedunculated mass ? thrombus attached to left mitral leaflet. The patient opted to be on best supportive care and shortly succumbed to the disease.
- Patient 6** A 31 year-old lady diagnosed with malignant phyllodes right breast in 2001 and had lumpectomy elsewhere. When the tumor recurred she underwent mastectomy with axillary clearance the same year. Her biopsy was malignant PT with all nodes free of disease. In 2014, 13 years after initial diagnosis she presented with pain in the left groin region for 4 months. Following evaluation, she was diagnosed with probable metastases in left proximal Femur for which she had left proximal Femur resection and reconstruction with cemented proximal Femur megaprosthesis (Fig. 2). The biopsy was reported as malignant mesenchymal tumour from proximal Femur with features similar to breast histology suggestive of metastases. PET

Table 1 Patients ($n=7$) clinic-pathological and management details

Number/year of management	Age in years	Initial diagnosis	Surgery	Adjuvant /Palliative treatment	Time period for metastasis	Sites for distant metastases	Follow up
1/2005	40	Right Malignant PT with pleural effusion Hypercalcaemia	Simple mastectomy and axillary clearance	Chemotherapy Ifosfamide and Doxorubicin Radiation therapy to brain	Synchronous in lung 2 months later brain metastases	Lung Brain	Died 2 months post treatment
2/2002	36	Bilateral malignant PT	Mastectomy	RT to brain	6 years	Brain Lung Adrenal Duodenum Para aortic nodes Lung	Died 6 years after initial diagnosis at time of metastases
3/2008	29	Right recurrent malignant PT, Previous lumpectomy Right Malignant PT	WLE+LD Flap cover	CT- Ifosfamide, Doxorubicin, Dacarbazine RT to chest wall CT- Ifosfamide Adriamycin	synchronous		Died 1 year later
4/2010	40		Simple Mastectomy and axillary clearance		7 months	Brain Lung Adrenal	Died 1 month post CT
5/2012	28	Left Malignant PT	Simple Mastectomy and axillary clearance LD Flap cover	CT Cisplatin Adriamycin	2 months	Lung Tumor thrombus left atrial leaflet	Died 8 months after surgery
6/ 2001	31	Right recurrent Malignant PT Previous WLE	Simple Mastectomy and axillary clearance	CT Adriamycin Ifosfamide	13 years	Bone -excised Mediastinal nodes	Alive and completed CT; doing well at 10 months, nodal regression on PET
7/2014	53	Left recurrent Malignant PT post lumpectomies withlung metastases	lumpectomies twice done elsewhere	Palliative care, no CT/RT	1 year	lung	Died due to distant metastases 1 year after first surgery

PET Scan showing Left Adrenal gland and Brain metastases from malignant PT of the Breast

Fig. 1 PETscan showing brain and left adrenal gland metastases from malignant Phyllodes tumor of the breast

CT scan done for metastatic work up revealed left supraclavicular nodes and mediastinal nodal metastases. She is now receiving palliative CT with Ifosfamide and Doxorubicin.

Patient 7 A 53 years old lady presented in a critical state with history of having left breast recurrent malignant PTs post lumpectomies twice done elsewhere. She had left breast lump and underwent 2 times excision in 2013 and had local recurrence within 6 months period. She again had local recurrence in 2014 and when she came to our hospital for further management of local recurrence she also had fever, cough, dyspnoea and right sided pleuritic chest pain. She was in septic shock. She had 8 cm by 7 cm ulcero-proliferative growth over the left breast scar site in axillary tail region with no axillary lymphadenopathy. Her biopsy slides were reviewed and confirmed malignant PTs. She had CT thorax done which showed pleural effusion and hilar lymphadenopathy. She had chest tube

insertion. Her rest of the metastatic workup could not be done due to her critical state and she succumbed to the disease in 3 days of the hospital stay.

Pathological Details (Figs. 3, 4)

Histopathological examination of primary tumours could be done in all patients except one (patient 2). In 4 of the 5 cases, mastectomy specimen was received for examination. One (patient 6) had only the slides of mastectomy specimen and one had slides of lumpectomy (patient 7). Size of the primary tumour (assessable in 3 pts) ranged from 10 to 11.5 cm. Mitotic rate ranged from 4/10hpf (patient1) to 35/10 hpf (patient3), 4 of 5 tumours had more than 10/10 hpf. All the tumours showed spindle cells arranged in fascicles and sheets displaying moderate to marked nuclear pleomorphism.

MRI showing PT metastasis in head of femur

Fig. 2 MRI showing metastases in proximal femur in patient with malignant Phyllodes tumor

Heterologous differentiation was seen in 3 cases (Patients 4,5, 6) Multinucleate giant cells were seen in 2 cases. Stromal overgrowth was present in all the cases. Infiltrative borders were seen at least focally in all cases.

Discussion

Malignant Phyllodes tumor constitutes 20–30 % of all PTs of the breast [9]. In our series published on data of total 150 patients with PTs, we found local recurrences more in malignant PT (53 %) compared to benign PT (20 %) [9]. We found recurrence rates in lumpectomy (39.3 %) compared to wide local excision (27.3 %) and simple mastectomy (33.9 %) (p 0.049) [9]. In this series of seven patients, 3 had local recurrences along with distant metastases. It is difficult to co-relate

Fig. 3 Histopathology picture showing Malignant Phyllodes tumor with stromal overgrowth and heterologous osseous elements

Fig. 4 Histopathology picture showing Malignant Phyllodes tumor with pleomorphic spindle cells

local recurrence directly with distant metastases as metastases are a very rare (7/167 patients overall PT, and 7/49 malignant PT) phenomenon in PTs. We did not find statistically significant association of local recurrence with distant metastases (p 0.07). However, we recommend aggressive surgical approach to minimize local recurrences.

There are scarce data available in form of case reports on the outcomes and prognosis of patients with malignant PTs with distant metastases. This subgroup of PT behaves aggressively and needs more aggressive management in form of multimodality therapy. Predisposing factors include malignant histology, large tumor size (>10 cm) and local recurrences post inadequate surgical resections. Pathologically these tumors are characterized by high mitotic rates, stromal hypercellularity, atypia and infiltrating margins as seen in our patients who had aggressive outcome and had all these features.

Local recurrences have been found in benign, borderline malignant and malignant PTs. Distant metastases have been found in both borderline malignant and malignant PTs though majority occur in malignant ones only [10]. Distant metastases have never been seen in benign phyllodes tumors. Distant metastases in borderline malignant PTs are very rare (0.57 %) and hence the outcomes of borderline malignant PTs are quite similar to benign PTs [11]. However, in our series, all patients with malignant PTs only presented with metastases and three of them also had local recurrences.

Malignant PTs have been found to have metastases in 22 % of patients [12]. The common sites for distant metastases include lung, pleura, liver and bone. Few rare sites reported include the brain, pancreas, duodenum, adrenal gland, oral cavity and parotid gland. In our review 7/49 (14 %) of patients with malignant PT had metastatic disease either synchronously or metachronously involving the brain, lung, adrenal gland, bone, para aortic nodes and possibly heart. In our series, lung was the most common site for distant metastases in patients with malignant PTs.

Diagnostic modalities for local disease include clinical examination, core tissue biopsy and ultrasound or mammogram of the breast. CT scan or MRI may be needed when there is very large tumor fixed to the chest wall. There are no guidelines to assess metastases in every case of malignant PTs. However it appears that plain radiographs, ultrasound, isotope bone scan or cross-sectional imaging of any particular region may be used based on symptoms.

Metastases may have the same morphology histologically as the primary tumor but mesenchymal components in the form of osteosarcomatous/ chondrosarcomatous or rarely liposarcomatous patterns mixed with epithelial components also have been described [13, 14]. The origin of the sarcomatous component within phyllodes tumors is due to the metaplastic potential of the myoepithelial cells in the breast and this adds to the heterogeneity in the clinical and pathological outcomes in the patients. One patient's histology in our series showed rhabdomyomatous differentiation and another had osteosarcomatous/chondromatous differentiation.

Distant metastases may present either synchronously or may present after few months/ years to as long as more than 10 years. One patient in our series presented with bone metastases 13 years after the primary tumor.

Adequate primary surgery plays key role in reducing recurrence. In our series, 3/7 patients had local recurrences post lumpectomy. The key clinical point is to suspect the disease in larger apparently benign breast tumours and use core biopsy for diagnosis when suspected. Surgical options include wide local excision or mastectomy with or without reconstruction. Radical excision of large PT mass helps to reduce local recurrences [15]. As axillary metastasis is very rare, combined lymph node dissection is usually avoided. Guidelines to manage local disease are well established; however the management of the rare distant metastasis remains challenging with poor response.

Post-operative radiation therapy is used to reduce local recurrence in cases of recurrent malignant PTs and as palliation for pain relief or brain metastases.

Chemotherapy has a limited role and is given for palliation in the metastatic setting. The stromal elements usually metastasize and hence the systemic therapy is based on management of a soft tissue sarcoma. The various chemotherapeutic agents used are Ifosfamide, Cisplatin, Etoposide or Doxorubicin [16]. There are few recent studies on role of molecular analysis and molecular targeting agents (tyrosine kinase inhibitors) and use of Taxanes for the metastatic malignant PTs [16]. TP53 and NRAS genomic changes have been correlated with malignant potential of the PTs [16].

Once metastasis develops, prognosis is dismal and very few patients survive more than a year [17, 18]. The longest duration to distant metastases has been reported to be 12 years. In our series, one patient developed metastases after 13 years and only this patient is alive till date at 10 months following

surgery, local RT and chemotherapy; all the rest succumbed to the disease.

Hypercalcemia of malignancy in setting of malignant phyllodes tumor has not been reported in the literature though it was seen in one of our patients with metastases. She had a very poor prognosis.

Conclusion

Patients with metastatic malignant Phyllodes tumor of the breast have dismal outcomes and need close follow up and multimodality therapy. Metastasis may rarely present very late and must be considered in the counseling and follow up of these patients. In the absence of effective systemic therapy, there is a need for assessing the role of newer targeted therapies in this disease.

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