Case Report

Palliative treatment of metastatic phyllodes tumors: a case series

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Abstract: Up to 20% of malignant phyllodes tumors (PT) metastasize, most frequently to the lungs, bone, and brain. Descriptions of metastatic PT are limited in the literature. In this series, we present three cases of malignant PT metastatic to various unusual sites including the peritoneum, soft tissue of the thigh, and scalp. All three patients initially received surgical resections, and two underwent adjuvant radiation. All three patients developed lung metastases first. Several palliative modalities were used including surgical resection, gamma-knife stereotactic radiosurgery, external beam radiation, and chemotherapy. All three patients died within 3 years of the initial diagnosis.

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Introduction

Phyllodes tumors (PT) are biphasic, fibroepithelial lesions, which span a morphologic spectrum from benign, resembling fibroadenomas, to malignant, which resemble sarcomas (1). Malignant PTs are rarely encountered, accounting for less than 1% of all cases of breast cancer. The metastatic potential of the tumor is determined by its stromal component, although metastases are thought to occur in less than 20% of malignant cases (2). It typically spreads hematogenously, with high frequencies of distant metastases noted to the lungs and bones (3).

Adequate surgical resection with clear margins remains the mainstay in the treatment of phyllodes (4). Endocrine treatments are not typically used, despite hormone receptors present in the epithelial component of some PT (5). One observational study observed no statistically significant differences in recurrence-free survival with adjuvant doxorubicin and dacarbazine in patients with malignant PT, and recommended consideration of the treatment in only those with high-risk malignant disease (6). The efficacy of chemotherapy regimens centered on ifosfamide and doxorubicin were investigated in early studies but is limited to palliative settings. In the palliative setting, a retrospective analysis conducted by Mituś *et al.* demonstrated improved mean survival (MS) with doxorubicin (7 months) and doxorubicin in combination with cisplatin, cyclophosphamide or ifosfamide (9 months) (7). It is recommended by the National Comprehensive Cancer Network (NCCN) that clinicians follow practice guidelines for treatment of soft tissue sarcoma (7).

This series presented three cases of malignant PT metastasizing to various distant sites, palliated with an array of modalities including surgery, radiation and chemotherapy.

Case presentation

Case 1

A 43-year-old woman underwent core biopsy for self-detected mass in the left breast and pathology revealed spindle cell sarcoma. She underwent left wedge resection for a 3.5 cm tumour which pathology indicated as malignant PT with features of high cellularity and high-grade atypia. All resection margins were negative for malignancy, with the closest margin being 3 mm posteriorly. Given this relatively close margin, the patient was given adjuvant radiation to the

breast, receiving in 50 Gray (Gy) in 25 fractions as well as a boost of 16 Gy in 8 fractions to the post-operative bed.

Post-operative imaging was scheduled for every 3 months. The patient developed a recurrence in the lungs 16 months later, detected by routine chest X-ray of the chest. She underwent thoracotomy for a 2-mm nodule in the right middle lobe and 3 cm nodule in the left lower lobe. Surgical pathology confirmed a malignant spindle cell tumor consistent with metastatic PT. Chemotherapy was initiated with doxorubicin and ifosfamide. Two months after initiation, brain metastases were detected and resected with a craniotomy. She restarted with chemotherapy.

A year after completion of chemotherapy, the patient experienced abdominal discomfort, distention and pain, anuria and obstipation, and was found to have a large abdominopelvic mass causing bilateral hydronephrosis. A CT scan of the region demonstrated peritoneal metastases. At this point, the patient's performance status was poor so she was not fit for surgical resection. She passed away due to her disease a few weeks following the onset of the abdominal symptoms, 30 months after her mastectomy and 14 months after distant recurrence.

Case 2

A 48-year-old woman noticed a mass in her left breast, for which she sought medical attention 2 months later due to fluctuation in size. Core biopsy indicated a fibroepithelial lesion suspicious of a malignant PT. She underwent a mastectomy and resection of the left pectoralis muscle for a tumour 13 cm in the maximum dimension. All margins were negative, with the closest margin measuring 1 mm posteriorly. Stromal overgrowth with extensive necrosis, marked stromal cellularity and atypia, with a mitotic index of over 22 figures per 10 high power field (HPF) were reported. The tumour was also found to have osteosarcomatous elements, and a separate 2 mm focus of high-grade ductal carcinoma *in situ*. Staging CT scans indicated evidence of an indeterminant 4 mm lung nodule, which was stable in follow-up scans every 3 months. The patient then underwent adjuvant radiation to the chest-wall at a dose of 50 Gy in 25 fractions.

Six months post-mastectomy, multiple bilateral lung metastases, including the previously noted nodules, were detected on post-treatment serial imaging. The patient was started on a doxorubicin chemotherapy regimen. Two cycles into the regimen, the patient experienced increased cough and dyspnea, and scans revealed progression of the lung nodules, malignant pleural effusion, tension hemothorax and partial collapse of the left lung. After drainage, the lung re-expanded and the patient was switched to a chemotherapy regimen of ifosfamide and etoposide. The largest lung mass prior to initiating the 2nd line of chemotherapy measured 5 cm × 5 cm.

After two cycles of chemotherapy, the patient had a seizure and left sided weakness, and a subsequent scan of the brain showed multiple brain metastases, with the largest centered in the right frontal lobe, and others in the temporal lobe, mid cingulum and left occipital lobes. A lesion of the right tempo-parietal scalp was also resected and confirmed as a site of skin metastases. The patient underwent a craniotomy for the largest brain tumour (3.3 cm) in the frontal lobe, and pathology was consistent with PT. After resection, the patient underwent gamma knife stereotactic radiosurgery to the smaller lesions. The weakness ceased and there were no reports of subsequent seizures.

A month after the craniotomy, the patient was then admitted due to post-obstructive pneumonia, dyspnea and left-sided pleuritic chest pain. Imaging showed significant involvement of the left hemithorax, and fracture of the 6th rib due to bony erosion from progression of the lung mass. The patient was planned to receive 20 Gy of external beam radiation to the left lung in 5 fractions; however, she was unable to finish the treatment due to progressive disease and poor performance status. The patient passed away 4 months after the initial diagnosis of metastases, and 11 months following her mastectomy.

Case 3

A 64-year-old woman noted a rapidly growing mass in her right breast. Core biopsy revealed a spindle cell tumor and she underwent a partial mastectomy. Final pathology showed a 10.7 cm, high-grade PT with infiltrative borders, tumor necrosis, moderate to marked stromal cellularity, marked atypia and a mitotic rate exceeding 20 figures per 10 HPF. There was no malignant heterologous component. The closest margin was located anteriorly at 1 mm. She declined adjuvant radiation, and post-surgical surveillance was initiated with repeat imaging conducted on a 3-month basis.

A lung nodule was first noted in a CT scan 11 months post-mastectomy. A soft tissue lesion was found in the posterior aspect of the right thigh and a biopsy confirmed metastatic PT. The patient was then started on a regimen consisting of doxorubicin and ifosfamide. During her

first cycle of the treatment, she developed treatment-related encephalopathy. Due to continued development of encephalopathy despite the use of prophylactic thiamine, the ifosfamide was discontinued and the patient continued treatment with single agent doxorubicin. The patient was then switched to a regimen of gemcitabine 2 months later. Although the soft tissue mass remained enlarged, the patient reported decreased pain with treatment.

The patient passed away from tumor progression 16 months following the first detection of the nodule, 6 months after local recurrence, and a little over 2 years following her mastectomy.

Discussion

This series presented the cases of three unusually aggressive malignant PTs. All three patients self-identified the breast lumps. After the initial resection, lung nodules were the first sites of recurrent disease. In cases 1 and 3, recurrent disease was identified 16 and 11 months post resection respectively. More modern modalities of treatment were employed such as gamma-knife stereotactic radiosurgery for symptomatic brain metastases. Ultimately, survival was limited to less than 3 years of initial resection for PT, and within 14 months of the start of chemotherapy.

In an earlier retrospective reviews of malignant PTs, Reinfuss *et al.* reported distant metastases to the lung as the main reason for treatment failure in their cohort of 55 cases (8). Since its publication, multidirectional differentiation towards the bones—and to lesser extents—the brain and liver have been documented. Aside from liver metastases, several cases of abdominal metastases have been documented in the literature, with sites including the stomach (9), gastrointestinal tract (10-12), kidneys (13), adrenal glands (14), and pancreas (15). Metastases to the skin are very unusual, with two cases reported in the English literature to our knowledge (16,17).

Although these diagnoses of PT occurred in the span of over a decade, the course of treatment recommended remained essentially unchanged. Complete surgical resection of the tumour is attempted, with an aim of creating a margin of at least 1 cm (18). Due to its hematogenous spread, lymph node sampling at time of surgical resection is largely unhelpful in the metastatic workup of PT (19). First developed by Tan *et al.* (20) and later validated in a cohort study (21), the Singapore nomogram "AMOS" uses the degree of stromal atypia, mitotic count, overgrowth and surgical margin status to predict the clinical behaviour of breast PT. A review of 352 cases of PT (90 malignant) at the Memorial Sloan-Kettering Cancer Center indicated that the 5 patients who developed distant disease composed 71% of patients whose pathological features were aggressive (≥7.0 cm tumor size, infiltrative borders, marked stromal overgrowth, marked stromal cellularity, high mitotic count, necrosis). Tumor necrosis was significantly associated with increased local failure (P=0.006), and was present in all 5 cases of distant disease (22).

In cases of high risk histological features (e.g., >20 mitotic figures per 10 HPF, tumor size >5 cm), previous recurrences, or suboptimal surgical margins, adjuvant radiotherapy is recommended that the magnitude of benefit in increasing is not clear given the rarity of these tumors. Adesoye *et al.* remarked upon increasing use of adjuvant radiotherapy in their analysis of patients with PT in the Surveillance, Epidemiology, and End Results Program (4). Improved local control with radiotherapy was observed in patients with malignant PTs (23). However, evidence for the role of surgery and radiation is limited in the palliative setting (7). Palliative resection of individual distant metastases in this series was done with the aim of improving local control and/or relieving associated symptoms.

In a retrospective analysis of 37 patients with metastatic PT, Mituś *et al.* observed a MS of 7 months in patients treated with single agent doxorubicin, and 9 months in patients treated with polychemotherapy using doxorubicin with cisplatin, cyclophosphamide or ifosfamide (7). The highest MS was observed in patients with bone metastases (n=5) who achieved partial remission with doxorubicin and palliative radiotherapy. Patients with brain metastases (n=4) were treated similarly; however, no remission was observed, resulting in a MS of less than 3 months. Patients with lung metastases (n=24) composed the majority of the sample in this retrospective review. Survival ranged from 2 to 11 months, with cases of complete remission and higher MS observed in patients treated with doxorubicin polychemotherapy. Completion rates in this sample are unknown.

Chemotherapeutic agents ifosfamide, cisplatin and doxorubicin have shown some efficacy in treating symptomatic, metastatic PT. Recent studies identifying biomarkers in malignant PTs may open new possibilities for adjuvant and palliative therapies of recurrent or metastatic PT going forward (2).

Conclusions

Malignant PTs should be closely surveilled post definitive

management due to the potential of the disease to rapidly progress with an unpredictable course. All patients should be considered for adjuvant radiotherapy, acknowledging the absence of high level data showing the magnitude of benefit it provides. More studies are needed to investigate the impact on local control and survival with palliative chemotherapy in this population, though should be considered on a patient to patient basis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Verbal informed consent was obtained from all the patients included in this study.

References

1. Spitaleri G, Toesca A, Botteri E, et al. Breast phyllodes tumor: A review of literature and a single center retrospective series analysis. Crit Rev Oncol Hematol 2013;88:427-36.
2. Gatalica Z, Vranic S, Ghazalpour A, et al. Multiplatform molecular profiling identifies potentially targetable biomarkers in malignant phyllodes tumors of the breast. Oncotarget 2016;7:1707-16.
3. Moffat CJ, Pinder SE, Dixon AR, et al. Phyllodes tumours of the breast: a clinicopathological review of thirty-two cases. Histopathology 1995;27:205-18.
4. Adesoye T, Neuman HB, Wilke LG, et al. Current Trends in the Management of Phyllodes Tumors of the Breast. Ann Surg Oncol 2016;23:3199-205.
5. Roberts N, Runk DM. Aggressive malignant phyllodes tumor. Int J Surg Case Rep 2015;8C:161-5.
6. Morales-Vásquez F, Gonzalez-Angulo AM, Broglio K, et al. Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. Breast J 2007;13:551-6.
7. Mituś JW, Blecharz P, Walasek T, et al. Treatment of Patients with Distant Metastases from Phyllodes Tumor of the Breast. World J Surg 2016;40:323-8.
8. Reinfuss M, Mituś J, Smolak K, et al. Malignant phyllodes tumours of the breast. A clinical and pathological analysis of 55 cases. Eur J Cancer 1993;29A:1252-6.
9. Choi DI, Chi HS, Lee SH, et al. A rare case of phyllodes tumor metastasis to the stomach presenting as anemia. Cancer Res Treat 2017;49:846-9.
10. Schechet SA, Askenasy EP, Dhamne S, et al. Anemia and jejunal intussusception: An unusual presentation for a metastatic phyllodes breast tumor. Int J Surg Case Rep 2012;3:62-4.
11. Morcos BB, Baker B, Hashem SA. Ileocaecal intussusception secondary to metastatic phyllodes tumour of the breast. Ann R Coll Surg Engl 2010;92:W29-30.
12. Kelly RJ, Barrett C, Swan N, et al. Metastatic phyllodes tumor causing small-bowel obstruction. Clin Breast Cancer 2009;9:193-5.
13. Karczmarek-Borowska B, Bukala A, Syrek-Kaplita K, et al. A Rare Case of Breast Malignant Phyllodes Tumor With Metastases to the Kidney: Case Report. Medicine (Baltimore) 2015;94:e1312.
14. Collin Y, Chagnon F, Mongeau CJ, et al. Adrenal metastasis of a phyllodes tumor of the breast: Case report and review of the literature. Int J Surg Case Rep 2013;4:687-9.
15. Yu PC, Lin YC, Chen HM, et al. Malignant phyllodes tumor of the breast metastasizing to the pancreas: case report. Chang Gung Med J 2000;23:503-7.
16. Swapp RE, Shon W, Peethambaram PP, et al. Cutaneous presentation of a distant metastasis of malignant phyllodes tumor. Int J Dermatol 2012;51:72-4.
17. Sera T, Kashiwagi S, Takashima T, et al. Multiple metastatic malignant phyllodes tumor of the breast with tonsillar metastasis: a case report. BMC Res Notes 2017;10:55.
18. National Comprehensive Cancer Network. Phyllodes Tumor (Version 1. 2016). Accessed 19 Jun 2017. Available online: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
19. Zhang Y, Kleer CG. Phyllodes Tumor of the Breast: Histopathologic Features, Differential Diagnosis, and Molecular/Genetic Updates. Arch Pathol Lab Med 2016;140:665-71.
20. Tan PH, Thike AA, Tan WJ, et al. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. J Clin Pathol

2012;65:69-76.
21. Chng TW, Lee JYH, Lee CS, et al. Validation of the Singapore nomogram for outcome prediction in breast phyllodes tumours: An Australian cohort. J Clin Pathol 2016;69:1124-6.
22. Barrio AV, Clark BD, Goldberg JI, et al. Clinicopathologic Features and Long-Term Outcomes of 293 Phyllodes Tumors of the Breast. Ann Surg Oncol 2007;14:2961-70.
23. Varghese SS, Sasidharan B, Manipadam MT, et al. Radiotherapy in phyllodes tumour. J Clin Diagn Res 2017;11:XC01-3.

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