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Distant Metastasis from Benign Phyllodes Tumor

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Objective: As there is a dearth of information on phyllodes tumors of the breast in the Philippines yet this ultimately impacts on the management and survival of Filipino patients, the authors reviewed their surgical cases of phyllodes tumors, focusing in this report, for the first time in Philippine literature, on the real risk of distant metastasis from the more common benign variety of phyllodes tumors. They therefore aim to identify case/s and do a review of literature on distant metastasis from benign phyllodes tumors.
Methods: A review of records of all surgical cases of phyllodes tumor managed at PGH from 2005 - 2014 was done. Data from patients who on follow up were found to have distant metastasis were gathered and further reviewed. A literature search on metastatic phyllodes tumor and its implications was likewise done to complete this study.
Results: A total of 200 patients with phyllodes tumor surgically managed within the study period were reviewed and followed up. One hundred sixty one out of 200 (80.5%) patients were histologically classified as benign. Twelve patients out of 200 (6.0%) developed distant metastasis on follow up, 1 (0.62% of 161 benign phyllodes tumors) of whom had benign phyllodes tumor.
Conclusions: The authors show that distant metastasis from benign phyllodes tumor can occur here in the Philippines. Therefore, the subtype of phyllodes tumor alone, especially in benign lesions, does not absolutely predict biological behavior and risk of recurrence. A better understanding of the true nature of metastasis in these tumors is highly anticipated.

Key words: Breast surgery, Phyllodes, metastasis, benign

Phyllodes tumors (PTs) of the breast are an uncommon and heterogenous group of fibroepithelial neoplasms classified by the World Health Organization (WHO) into benign, borderline or malignant on the basis of histopathological features such as stromal cellularity, atypia and overgrowth and mitotic activity. Compared to Western countries where PTs represent 0.3 - 1% of primary breast tumors occurring mostly in middle-aged women (average 40-50 years old), PTs account for a higher proportion of primary breast tumors and may occur at a younger age (average 25-30 years old) in Asians.[1] Most PTs are benign (60-75%) and distant or hematogenous metastasis, albeit few, is seen almost exclusively in malignant PTs.[1] Prognosis in metastatic disease is poor as this condition remains incurable and generally unresponsive to chemotherapy. As there is a dearth of information and data on PTs in the Philippines yet these ultimately impact on the management and survival of Filipino patients, the authors reviewed their surgical cases of PTs, focusing in this report, for the first time in Philippine literature, on the real risk of distant metastasis from the more common benign variety of PTs, not only to raise awareness and disseminate recognition, but also to influence better surgical practice and inspire research on the treatment of this rare but universally fatal condition.

Methods

A chart and records review of all adult patients (> 18 years of age) managed surgically with a histopathologic diagnosis of PT at the University of the Philippines College of Medicine-Philippine General Hospital (UPCM-PGH) Medical Center Department of Surgery charity

services from January 1, 2005 to December 31, 2014 was done. Data from patients who on follow up were found subsequently to have distant metastasis were gathered and further reviewed. An extensive literature search on metastatic PTs and their implications was likewise done to complete this study. This study had been approved by the University of the Philippines Manila Research Ethics Board.

Results

A total of 200 patients with PTs and surgically managed by the Service within the study period were identified, followed-up, reviewed and analyzed. One hundred sixty one out of the 200 (80.5%) patients were histologically classified as benign. Twelve patients out of the 200 (6.0%) patients developed distant metastasis on follow up, 1 (0.62% of benign PTs) of whom had benign PT. This was in a 51 year old female from Manila who underwent mastectomy of a 15-centimeter non-ulcerating benign PT of the left breast of 10 months duration. A review of the histopathologic examination reveals adequate sampling of the mass as at least 15 random sections (pathologic standard for a 15-centimeter specimen) were taken with a final pathologic reading of benign or low grade phyllodes tumor, no unusual features such as dysplasia, in-situ or invasive carcinoma, and negative surgical margins and lymph nodes sampled. She developed radiologic evidence of distant metastases to the lungs 22 months after surgery with a concurrent local chest recurrence extending to the forearm and suspicious metastasis to the L2 vertebra on x-ray. Further work-up, evaluation and treatment were planned but patient was lost to follow-up.

Another case of benign PT in a 40-year old patient who underwent total mastectomy of a 10-centimeter right breast mass and developed an upper lip mass 20 months post-surgery was excluded as a distant recurrence from phyllodes tumor could not be confirmed. After a wide excision of the upper lip mass, pathology report revealed spindle cell neoplasm which could be considered as a metastasis since phyllodes tumors do have spindle cell components and although rare, there have been 2 cases reported from Mexico of malignant phyllodes tumor metastasizing to soft tissues of the oral cavity namely, the tongue and lower lip.[2] However, confirmation to this effect via further review and/or immuno-histochemistry could not be obtained.

Discussion

Metastatic disease from PTs, mostly from the malignant variety and often to the lungs, appearing as solid nodules or thin-walled cavities[3], has been reported to range from about 1.7 - 27.1% in a 2017 overview[4] to 13 - 40% of patients with a mean overall survival of 30 months in another 2017 review.[5] In a large series of 293 patients from the Memorial Sloan-Kettering Cancer Center in New York, USA, all 5 patients who developed distant metastasis in the bone, brain, epidural space, supraclavicular fossa, chest wall, vertebra and lung were from malignant PTs.[6]

Benign PTs, on the other hand, belying the term 'benign', have been reported to metastasize, even if rarely. In a Polish (Krakow, Poland) case series, first reported in 1996 involving 170 cases of PTs[7], later updated in 2016 with 295 cases[8], 3 out of 160 benign PTs (1.9%) were documented to develop metastasis. These were the same 3 cases of metastases from 2861 benign PTs (0.1%) identified in a 2013 review of literature by the European Institute on Oncology in Milan, Italy, of 5530 cases of PTs reported from 1951 until April 2012.[9] In another series of 101 patients from the MD Anderson Cancer Center in Houston, Tx, USA, 8 patients subsequently developed distant metastasis in the lung, brain and pelvis, 7 from malignant phyllodes and 1 from benign tumor.[10] One (1) case each of distant metastasis from benign PT was similarly reported by Mangi et al (1999)[11] out of 40 cases of PTs from the Massachusetts General Hospital in Boston, Ma, USA; by Asoglu, et al. (1999)[12] out of 50 cases from the Mayo Clinic in Rochester, Mn, USA; and by Abdalla, et al. (2006)[13] out of 79 cases from Cairo University in Cairo, Egypt. The average rate of metastasis from benign PTs is calculated to be 0.4% (the above 7 cases/1915 cases) from a 2017 literature review from Singapore.[4] Although most of the above reports on metastasis in benign PTs did not specify the particular site or organ involved of each

patient, sites mentioned include the lungs, bones, brain, and pelvis. By comparison, our study yielded an overall metastatic disease rate from PTs of 6.5% and a 1.24% rate from benign PTs. This documentation is evidence that this rare phenomenon can occur among Filipinos as well. Whether these cases in literature, including patient on this study, represent distant metastasis from a local recurrence and malignant transformation, or true metastasis from the initial benign PT, is difficult to ascertain, except when the metastasis is solitary or isolated to a particular distant site.

Although it is well known that the prognosis of metastatic disease from PTs and soft tissue sarcomas in general, to which treatment in systemic recurrence of PTs are patterned after[3], is dismal, efforts other than development of better chemotherapeutic drugs like doxorubicin and ifosfamide[8] are still rightfully undertaken. As unusual features like hyperplasia, metaplasia, dysplasia, in-situ or even frank invasive malignancy have been shown to occur in some benign PTs[14], clinico-pathologic factors other than histologic classification have been studied to better predict the likelihood of recurrence and metastasis and influence not only adjuvant treatment such as endocrine[15], radiation[16] and chemo-therapy[17] which have largely been with no proven role or controversial[3] especially in benign PTs, but also impact postoperative surveillance or follow-up strategy[18] and formation of consensus guidelines.[19] In a review from the City of Hope Comprehensive Cancer Center in Los Angeles, CA, USA of 478 patients with PTs, post-operative adjuvant radiation therapy was recommended for malignant PTs >2cm treated by lumpectomy alone and tumors >10 cm treated by mastectomy alone as local recurrence was shown to adversely impact survival rates.[20] Over time, radiation therapy utilization has been seen to increase significantly attributed to concern about more advanced disease.[21] Age, tumor border, size, necrosis, ulceration grade, nuclear pleomorphism, heterologous stromal elements and surgical margins as sole predictors of distant metastasis have all been explored with varying success partly due to infrequency of metastatic events. For benign PTs, a recent review from the UK[22] of 1702 patients, showed no difference in recurrence rates between a 1 and 10 mm surgical margin, similar to a smaller and earlier Danish study of 354 cases revealing no justification for wide excision margins in benign PTs.[23] The Singapore Nomogram for Outcome Prediction in breast phyllodes tumors developed in 2012[24] and based on 4 predictive factors namely, stromal atypia, mitoses, overgrowth and surgical margins (AMOS) is being further validated in larger cohorts.[25,26] Biomarkers such as high expressions of IMP3[27], CD105[28], CD10[29], Axl and SST6GalNAcII[30], Six1[31], EGFR, c-kit, Wnt5a, stromal p16, and pRb[9] have been associated with metastasis in PTs and show promise as predictors in the future. Genomic profiling[32] and its correlation to metastatic risk and chemotherapeutic benefit, as recognized in breast carcinomas but not yet well understood currently in PTs, is another potential area of research and development.

Conclusions

The subtype of PT alone, especially in benign PT, does not absolutely predict biological behavior and risk of recurrence. A better understanding and documentation therefore, of the true nature and mechanisms of metastasis in benign, and even malignant PTs, perhaps through biomarkers or molecular targets, is definitely awaited and warranted. Even as the outcome of treatment in metastatic PTs is suboptimal at the present time, the recognition of metastatic potential can influence proper oncologic management and even appropriate surgical approach and postoperative follow-up. Together with advances in the aspects of adjuvant therapy, conventional treatments such as chemotherapy and radiotherapy, and novel approaches like immuno- and targeted therapy, a specific approach to each particular variant of PT can then best be achieved.

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