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Cystosarcoma phyllodes with muscular and lymph node metastasis

Our experience and review of the literature

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Cystosarcoma phylloides with muscular and lymph node metastase. Our experience and review of the literature

BACKGROUND: *Phyllodes tumors are biphasic fibroepithelial neoplasms of the breast. While the surgical management of these relatively uncommon tumors has been addressed in the literature, few reports have commented on the surgical approach to tumors greater than ten centimeters in diameter – the giant phyllodes tumor.*

CASE REPORT: *We report a case of a 45-year-old woman who presented with a large lump in her right breast, involvement of multiple ipsilateral axillary lymph nodes and pectoralis major muscle. Clinical findings and cytologic examination (fine-needle aspiration) were suggestive of cystosarcoma phyllodes and we discuss the techniques utilized for pre-operative diagnosis, tumor removal, and breast reconstruction. A review of the literature on the surgical management of phyllodes tumors was performed.*

CONCLUSION: *Management of the phyllodes tumor presents the surgeon with unique challenges. The majority of these tumors can be managed by simple mastectomy. In our case clinical findings and cytologic examination (fine-needle aspiration) were suggestive of cystosarcoma phyllodes, for which the patient underwent a modified radical mastectomy. Post-operative radio therapy was given to the loco regional area.*

KEY WORDS: Immediate reconstruction, Phylloides tumors, Post-operative radio therapy, Radical surgery.

Background

Phyllodes tumor had been described as early as 1774, as a giant type of fibroadenoma.¹ It was described in 1838 by Muller who used the name Cystosarcoma Phyllodes to qualify the leaf like and fleshy gross appearance of this tumor. Since then this term was used. Though it is confusing, many other names were used such as pseudosarcomatous fibroadenoma, giant intracanalicular

fibroadenoma and Brodie's serocystic disease. In 1981, the world health organization (WHO) adopted the term phyllodes tumor because this term does not imply any biological behavior, and it has gained wide acceptance.² The majority of studies in the literature classify Phyllodes tumor into three subgroups as described by Rosen.³ They are benign, malignant low-grade, and malignant high-grade. The distinction between these subgroups is based on histological characteristic of the tumors and the predictive of probable clinical course.

Case history

A 45 year old female, mother of two, presented with a large, painful mass in her right breast. She had noticed a small mass 5 years prior, while breast feeding her youngest child, which she then correlated with trauma and ignored. For 5 years, the mass stayed the same size

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and was painless. Six months prior to admission, however, the mass started increasing in size and became painful. Clinical examination revealed a well-nourished woman whose right breast was replaced by a large, solid, irregular mass fixed to the chest wall. No ulceration, bleeding, or discharge was observed. The axillary lymph nodes were palpable. Results of a routine blood and urine analysis were normal, as were a chest x-ray film, a computed tomographic scan of the chest and abdomen, and a bone scan. Pre-operative CT scan revealed a 7.5 x 11 cm mass in the anterior portion of the breast, with no apparent mediastinal, lung or neck lymphadenopathy. Fine-needle aspiration cytology from the mass revealed features of cystosarcoma phyllodes. The patient was clinically diagnosed with a stage IIIB (T4a, N1, M0) breast tumor. Right modified radical mastectomy with dissection of level I and level II lymph nodes was performed. A left mastopexy was performed for purposes of symmetry. An elliptical incision encompassing the entire mass and the overlying skin was made. Collaterals in the skin supplied the tumor, and no deep invasion was identified. The superior and inferior skin flaps included skin that had been overlying the tumor. The tumor was excised along with the pectoralis muscle fascia. Axillary dissection was undertaken because of the presence of palpable level I and II nodes intra-operatively. A tissue expander was placed before final closure, as the patient desired reconstruction. The pathologic findings of this procedure were consistent with a cystosarcoma phyllodes tumor. The tumor measured 10.0 x 8.0 x 5.0 cm *ex vivo*. Microscopic sections showed large branching ducts surrounded by a uniform, loose stroma; areas of hyalinization and myxoid change were rare. The margin of resection was negative for the tumor with a tumor-free zone that ranged from over 0.5 to 1.0 cm. The Ki67 proliferation index of the tumor was 0.8 and 4 for the epithelial and stromal component, respectively. Significant cytologic atypia and mitotic activity was noted. Nineteen lymph nodes were obtained, all of which were site of metastatic diseases. The patient had an unremarkable post-operative course and was able to start tissue expansion 19 days after her surgery. She had exchange of her tissue expander for a permanent implant 6 months after her mastectomy. She had an uneventful recovery from these surgical procedures and is currently 6 years post-surgery without complication.

Discussion

Phyllodes tumors are fibroepithelial neoplasms with epithelial and cellular stromal components, the latter of which represents the neoplastic process³. The presence of an epithelial component differentiates the phyllodes tumor from other stromal sarcomas. They make up 0.3 to 0.5% of female breast tumors¹ and have an incidence of about 2.1 per million, the peak of which occurs

in women aged 45 to 49 years^{4,5}. The tumor is rarely found in adolescents and the elderly^{6,7}. Classically, patients present with a firm, mobile, well defined, round, macro lobulated, and painless mass. There are no pathognomonic mammographic or ultrasound features. Hence the phyllodes tumor can be extremely difficult to differentiate from a fibroadenoma, which is sometimes treated with a non-operative approach³. For this reason, early diagnosis of the phyllodes tumor is crucial so that the correct management of the tumor, which often does include surgery, can be pursued as early as possible. This may also prevent the growth of phyllodes tumors into giant ones. In a series of 106 patients by Chua et al., 71% of patients with a post-operative diagnosis of phyllodes tumor had a presumptive diagnosis of fibroadenoma at the time of surgery⁸. Another series showed a pre-operative diagnosis of phyllodes tumors in only 10 to 20% of patients¹.

A variety of techniques have been utilized to improve the pre-operative diagnosis of phyllodes tumors. Cole-Beuglet et al. performed a retrospective study on 8 cases of histologically proven phyllodes tumors that were evaluated by mammography and ultrasound. They determined that while certain ultrasound findings (low-level internal echoes, smooth walls, good through transmission, and smooth margined fluid-filled clefts in a predominantly solid mass) may suggest a phyllodes tumor, there is no consistent and reliable way to distinguish between phyllodes tumors and other benign appearing tumors on ultrasound or mammography⁹. In a recent review examining the use of ultrasound in the diagnosis of phyllodes tumors, Chao et al. identified three sonographic features that are characteristic of these tumors: well circumscribed, lobulated masses, heterogeneous internal echo patterns, and a lack of microcalcifications¹⁰. In addition, the authors shed light on the pre-operative distinction between fibroadenomas and phyllodes tumors. Patients with fibroadenomas are generally younger than the patients with phyllodes tumors; fibroadenomas have a larger ratio of length to antero-posterior diameter; and phyllodes tumors are generally larger than fibroadenomas¹⁰.

Another group investigated the possibility of establishing a pre-operative diagnosis of malignant or benign phyllodes tumor through the use of color Doppler ultrasound. They concluded that although several ultrasonographic features are characteristic of a malignant phyllodes tumor, a histologic specimen should be obtained for definitive diagnosis. The features that suggested a malignant behavior were "marked hypoechogenicity, posterior acoustic shadowing, and higher values of RI (resistance index), PI (pulsatility index), and Vmax (systolic peak flow velocity)"¹¹. Another potentially useful diagnostic modality is magnetic resonance imaging (MRI). One article discussed the use of MRI in characterizing benign phyllodes tumors. Findings consistent with a benign phyllodes tumor included a lobulated or polyg-

onal shape with smooth borders, cystic or septated features, and a gradual or rapid pattern of time-signal intensity curve¹². In a recent correspondence, Cheung et al. discussed the pathological features typical of phyllodes tumors and how they are manifested in MRI. The authors went so far as to suggest that the findings of "characteristic leafy internal morphology, best shown on subtraction MRI, which highlighted the enhancing cotyledonous solid portions within irregular blood-filled cystic spaces" are pathognomonic for a phyllodes tumor¹³.

Fine needle aspiration (FNA) has also been proposed as a method to improve pre-operative diagnosis; however, existing reports are not promising. Salvadori et al. found the FNA to be diagnostic in only 4 of 30 cases⁵. Other investigators have obtained similar results and have concluded that FNA is usually non-diagnostic¹⁴. The difficulty in diagnosing the phyllodes tumor by FNA is compounded by the fact that it shares many cytologic features with fibroadenoma^{15,16}. Core tissue biopsy is an attractive alternative to FNA, and several authors have suggested its use as a diagnostic procedure^{8,17}.

Interestingly, our patient had a core tissue biopsy only, which provided a preliminary diagnosis of phyllodes tumor. We believe that core tissue biopsy represents the preferred means of pre-operative diagnosis for giant breast tumors, and the histologic information gained from this procedure is important in guiding surgical treatment. Phyllodes tumors are divided into benign, borderline, and malignant histotypes based on the microscopic appearance of the stromal component. Approximately 15 to 30% of all phyllodes tumors are classified as malignant^{5,18-20}. Histologic appearance may not, however, correlate with clinical behavior^{17,18,20,21}, as both malignant and borderline tumors have been shown to be capable of metastasizing. Reinfuss *et al.*, using histotype criteria developed by Azzopardi and Salvadori et al.⁵, showed that the histotype of the tumor was an independent prognostic factor, with 5-year survivals of 95.7% for benign tumors, 73.7% for borderline tumors, and 66.1% for malignant tumors². A study by Chaney *et al.*, which combined the benign and borderline tumors into a single category, found 5-year survival rates of 91% for benign tumors and 82% for malignant tumors. Ten-year survival rates, however, dropped to 79% and 42%, respectively²⁰.

A recent review and clinical follow-up of 33 cases concluded that histopathological classification is the strongest prognostic factor for this disease²². Others have failed to duplicate the correlation between histotype and survival¹⁷. Metastasis is seen in 25 to 31% of malignant tumors^{1,20}, but only in 4% of all phyllodes tumors⁵. The most common sites for metastasis include the lungs, bone, liver, and distant lymph nodes. Skin involvement with tumor does not appear to be a predictor of metastasis²³.

While the use of chemotherapy and radiotherapy have shown promise in a few small trials, their role in the

treatment of metastatic phyllodes tumors remains unproven. Hormonal therapy has also been attempted, but with limited efficacy^{20,24-26}. Pathologic factors associated with poor prognosis include greater than 3 mitotic figures per high power field, infiltrating margins, severe atypia, stromal overgrowth, stromal component other than fibromyxoid, and tumor necrosis^{20,27-30}. Hawkins et al. reported a strong correlation between stromal overgrowth and metastasis, finding that 72% of tumors with stromal overgrowth will eventually develop a metastasis²⁷. Variables such as age, symptom duration, and tumor growth rate are not of prognostic value²⁷⁻³⁰. Phyllodes tumors do not typically metastasize via the lymphatics. About 20% of patients have palpable axillary lymph nodes on presentation, but only 5% of these show histologic evidence of metastasis upon pathologic examination. Of the phyllodes tumors with a malignant histotype, up to 15% will metastasize to the axilla³⁰. In a 1972 retrospective report, Kessinger et al. found that all metastatic lesions described in the literature contained only stromal elements. No malignant epithelial elements were observed. Since most sarcomas metastasize hematogenously, this finding may explain why axillary metastasis is so rare²⁴.

Palpable lymphadenopathy is typically attributed to the patient's immune response to tumor necrosis. The rare patient who does have lymph node metastases tends to have a poor prognosis [30]. Observing the rarity of lymph node involvement, most authors have concluded that removal of axillary lymph nodes is not warranted unless there are palpable nodes^{2,14,20,29,31,32}.

Data regarding sentinel lymph node biopsy in phyllodes tumors are lacking. In patient A, 3 lymph nodes were included as part of the mastectomy specimen. In patient B, palpable nodes were present, therefore axillary dissection was performed. However, neither patient showed evidence of tumor spread to the lymph nodes. Theoretically, the axillary nodal basin can be evaluated with sentinel lymph node biopsy and subsequent frozen section in patients that have clinically negative axillary nodes. However, patients with giant phyllodes may have clinically enlarged axillary lymph nodes that may be suspicious for metastatic disease. Sentinel lymph node biopsy may not be accurate in these patients and the surgeon may be forced to proceed with axillary lymph node dissection.

About 20% of phyllodes tumors would be considered giant, or greater than 10 cm in maximum diameter². As mentioned before, the importance of this cut-off value has been disputed. There is a continuing debate that exists over the prognostic significance of tumor size^{23,26,28,32}. Thus, appropriate cut off values for tumor size and associated prognosis have never been defined¹⁸. There is also disagreement as to whether malignant histology correlates with size. Some investigators show that malignant tumors tend to be larger than benign ones^{8,26}, while others have failed to duplicate this association^{2,20}.

Surgical management of the phyllodes tumor has also been a source of debate over the years. Some authors have argued for simple mastectomy for phyllodes tumors because of the risk of local recurrence after more conservative procedures^{23,24,30,31}. However, studies have shown no differences between breast conserving surgery versus mastectomy in terms of metastasis-free survival or overall survival, despite the higher incidence of local recurrence that comes with breast conserving surgery²⁸. Most experts currently advocate that surgeons obtain at least 1 cm margins on primary excision or re-excision of a tumor removed with close margins, as long as the tumor to breast size will permit^{1,2,5,8,14,17,20,30,33}. However, an excision with the required margins is often impossible in giant phyllodes tumors such as the cases reported here. Mastectomy should be reserved for larger tumors^{18,26} and should be considered in recurrent tumors, especially of the malignant histotype giant phyllodes tumors, particular emphasis should be placed upon complete removal of all visible tumor. Local recurrence in phyllodes tumors has been associated with inadequate local excision and various histological characteristics, including mitotic activity, tumor margin, and stromal cellular atypia³⁴. Because of the danger of recurrence that accompanies an incomplete resection or a resection characterized by close margins, the surgeon is often faced with the need for mastectomy for phyllodes tumors that are greater than 10 cm. Depending on the size of the breast and the location of the phyllodes tumor, mastectomy may also be required for tumors that are between 5 and 10 cm in diameter³⁵. It should be emphasized that by the time a phyllodes tumor becomes giant, there is no guarantee that the remaining breast tissue has not been infiltrated by tumor cells. Hence, the emphasis should be on complete extirpation of all visible tumor and breast tissue during mastectomy. If all breast tissue has been removed, and all tumor infiltrated soft tissues have been removed, then the tumor is unlikely to recur locally. In both of our cases, mastectomies were considered the appropriate surgical procedure because of the large size of the tumors when compared to the overall amount of breast tissue. This procedure provides the best opportunity for obtaining clear margins, thereby reducing the likelihood of tumor recurrence.

We found that normal skin overlying the tumor could be preserved with the expectation of close but negative margins. This approach permitted skin closure without the need for split thickness skin grafting and allowed placement of a tissue expander. The ability to preserve the overlying skin flaps is an important consideration in the surgical management of giant phyllodes tumor as it generally allows for a more satisfying cosmetic result.

Chest wall invasion appears to be an uncommon event with phyllodes tumors. Reinfuss et al. reported that 2.4% of phyllodes tumors in their series had clinically recorded infiltration into the pectoralis major muscle.² Moore and Kinne recommend extended excision of involved

pectoralis muscle, followed by reconstruction of the chest wall with Marlex mesh and methylmethacrylate³².

Some have recommended the consideration of post-operative radiation for cases of chest wall infiltration¹⁴. Although patient showed evidence of pectoralis major muscle invasion, the involvement was not extensive and was easily managed by excision of a portion of the muscle. No invasion of deeper structures was noted in the other case. Foreknowledge of the location of the tumor's blood supply can be vital information when removing large tumors. Little has been written on the subject with regard to giant phyllodes tumors or breast cancers in general. A case report by Jonsson and Libshitz documented the angiographic pattern of a 25 cm phyllodes tumor. The tumor was hypervascular with irregular and tortuous arteries. Blood supply to the tumor was via one large and several smaller perforating anterior branches of the internal mammary, lateral thoracic, acromio-thoracic arteries, and branches of the axillary artery³⁶.

We found that the giant tumors in the present report derived the majority of their blood supply from skin collaterals. Thus, the surgeon can expect the majority of blood loss during resection to come from the creation of the skin flaps. In this situation, the surgeon need not routinely obtain an angiogram.

In general, immediate breast reconstruction can be performed at the time of mastectomy for phyllodes tumors¹⁴. Mandel et al. reported a case in which subcutaneous mastectomy was performed for a large phyllodes tumor, followed by immediate implantation of a breast prosthesis. They cite minimal interference with the detection of recurrent lesions and the minimization of emotional distress as advantages to the procedure³⁷. Orenstein and Tsur described a similar case in an adolescent female in which a silicon implant was placed under the pectoralis major, where it would not impair the recognition of recurrent disease³⁸. Local recurrence rates for phyllodes tumors are 15 to 20% and are correlated with positive excision margins, rather than with tumor grade or size^{1,8,14,31}. Other studies have shown a higher risk of local recurrence in borderline and malignant tumors. In a series of 21 patients by Salvadori *et al.*, 51 patients were treated with breast conserving surgery (enucleations, wide excisions), and 14 of the tumors recurred locally. In contrast, the 20 patients treated with mastectomy (subcutaneous, modified radical, or radical) showed no evidence of local recurrence⁵. Importantly, there is no contraindication to immediate reconstruction after mastectomy in cases of giant phyllodes tumor, and this decision can be made solely based upon patient preference^{37,38}.

Conclusion

In summary, management of the giant phyllodes tumor presents the surgeon with unique challenges.

Diagnostically, we believe that core tissue biopsy repre-

sents an attractive means for pre-operative diagnosis and aids in the differentiation of phyllodes tumors from fibroadenomas. The majority of these tumors can be managed by simple mastectomy. Axillary lymph node metastasis is rare, and dissection should be limited to patients with pathologic evidence of tumor in the lymph nodes. There is no contraindication to immediate reconstruction after mastectomy.

Riassunto

I tumori filloidi sono neoplasie ad andamento bifasico, il loro trattamento è raramente descritto in letteratura per lesioni con diametro superiore ai 10 cm. Descriviamo il caso di una paziente quarantacinquenne con tumore Filloide della mammella destra, metastasi ai linfonodi ascellari omolaterali ed al M. Grande Pettorale. Riportiamo i dati clinico-strumentali ed il trattamento chirurgico demolitivo e ricostruttivo. Effettuiamo, inoltre, la revisione della letteratura circa la possibilità di effettuare, per determinati casi, chirurgia radicale seguita da radioterapia post operatoria.

“Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.”

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