Review Article

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Approaches to phyllodes tumour of the breast: a review article

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ABSTRACT

Phyllodes tumours are rare entities of fibroepithelial diseases. The exact pathogenesis and their relationship with fibroadenomas are oblivious. Women aged between 35 to 55 years are commonly affected, even younger in Asian population. Triple assessment should be applied as a guide to management in any breast pathology. Clinical appearances are typically diagnostic for phyllodes tumours. Even though sometimes inconclusive, mammography and ultrasonography are the main imaging modalities. Although the role of cytology is debatable, presence of both epithelial and stromal elements supports the diagnosis especially in malignant type. Core biopsy is rather favored in view of higher accuracy for the diagnosis. Accurate preoperative assessment and histologic diagnosis allow correct surgical intervention and subsequent avoidance of reoperation. Surgical management can be either wide excision with more than 1 cm margins or mastectomy without axillary surgery. Local recurrence has been associated with inadequate excision of the pseudopod. Adjuvant radiotherapy is recommended for positive surgical margin and for local control of borderline and malignant phyllodes tumors. The role of chemotherapy and endocrine therapy has not been fully studied.

Keywords: Cystosarcoma phyllodes, Fibroadenoma, Phyllodes tumours, Pseudopod, Triple assessment

INTRODUCTION

Phyllodes tumour is a rare entity in the annals of mammary pathology. They originate from the Greek word, "phyllon" meaning a leaf, which is histologically classical for phyllodes tumour. It is also known as a disease of Brodie. It accounts for 0.3-0.5% of any female breast tumours. It has a distinct biphasic characteristics of fibroepithelial diseases namely epithelial and stromal components. In a phyllodes tumour, there is evidence of stromal overgrowth rather than epithelial elements.

Presence of an epithelial component differentiates phyllodes tumor from other stromal sarcomas. Historically, phyllodes tumors were known as a giant type of fibroadenoma as early as 1774 and then followed by Chelius as a way to describe this tumour. ^{2,3} Back in 1838 Johannes Muller introduced the tumours as cystosarcoma phyllodes. ⁴ Despite of sarcoma-term from their name, they were believed to be benign initially. However, in 1931 Lee and Park reported the first case of metastatic phyllodes tumour. ⁵ World Health Organization started to use the term phyllodes tumour in 1981. ⁶ Rosen

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later sub-classified them histologically as benign, borderline, or malignant according to their distinct features.⁷

Phyllodes tumours are not uncommon for 35 to 55 year olds, however Asian populations tend to develop it at an earlier age of 25 to 30 years old. 8,9 There were incidences of phyllodes tumours younger than 25 years old, even as early as 10 years old. 10 A descriptive epidemiology study by Bernstein revealed the average annual incidence rate is 2.1 per 1 million women. 11 Latina whites have a higher risk of this cancer than other ethnicity. 11 Even majority are exclusively among female gender, there also have been reported cases of phyllodes tumours in men and few developed within gynaecomastia. 12,13 Based on a local study, Malay ethnicity accounts for the highest number of cases, which then followed by Chinese, India and others.¹⁴ Among them, 59.7% are benign, 22.1% are borderline dan 18.2% are malignant. 14 All phyllodes tumours encountered among the Malay patients were of the benign variety in comparison with the Chinese and Indians.9

PATHOGENESIS

At present, the exact pathogenesis of phyllodes tumours is obscure, whether they originate from existing fibroadenomas or arise de novo. Most fibroadenomas have polyclonal elements and are regarded as hyperplastic rather than neoplastic lesions. 15 Despite of having similar polyclonal element, a somatic mutation is postulated to develop resulting in a monoclonal proliferation with a propensity to progress to phyllodes tumour.15 It has also been postulated that stromal proliferation can occur as a result of growth factors induction in the breast epithelium. Increased endothelin-1 levels have been demonstrated within phyllodes tumours. 16,17 Trauma, lactation, pregnancy and increased estrogen activity occasionally have been implicated as factors stimulating tumor growth. Even, a genetic predilection namely Li-Fraumeni syndrome is the most commonly quoted genetic alterations in phyllodes tumours.9

CLINICAL FEATURES

Phyllodes tumours usually present with a painless breast lump, representing more than 70% of the cases. Usually it will be noticeable by the patient herself. Infrequently, mastalgia can also be part of the presentation. Up to 96% are unilateral with very few cases of bilaterality reported. They are more commonly found in upper outer quadrant, whereas huge lesions tend to involve more than one quadrant. The side of tumour (left versus right breast) is not significantly different between benign, borderline and malignant tumours. This is similar to the occurrence of infiltrative breast carcinoma. There were few cases of phyllodes tumour arising within the axilla and vulva. Upon presentation, the tumor size varied and ranged between 5 and 250 mm with a mean size of

83 mm. ⁸ Giant phyllodes tumour is considered if the size is more than 10 cm. The largest ever reported case of giant phyllodes tumour was 50 x 50 cm. ²²

Phyllodes tumours tend to rapidly grow. In some patients, a mass may have been overt for several years, which sudden increment of the size happened. In certain condition, neglect or refusal for primary surgery leads to a next visit with a worsening breast lesion.²² Hence it will complicate subsequent surgical undeniably intervention. There are distinct characteristics to suggest phyllodes tumour clinically. The mass will be bosselated with shiny thin skin and dilated surrounding superficial veins (Figure 1). Skin over the tumour might be ulcerated leading to secondary infection, bleeding or foul-smelling discharge. Nipple retraction or destruction is rare unless in fungating lesion. Gigantic mass tends to cause heaviness causing patient's immobility, thus exposing to risk of deep vein thrombosis. Quality of life might be impaired in massive phyllodes tumours as a result of immobility, need for frequent dressing and even cosmetic issues.



Figure 1: A picture of a bosselated breast with shiny skin and dilated veins. Presence of ulcerated fungating mass involving outer lobe of the breast with contact bleeding.

Palpable axillary lymphadenopathy can be identified in up to 10-15% of patients but less than 1% have nodes.22 pathologic positive Presence lymphadenopathy should raise a suspicion of concomitant invasive ductal carcinoma. Mostly, lymphadenopathy in phyllodes tumours occurs due to reactive hyperplasia from tumor necrosis or secondary to ulcerated lesions. Phyllodes tumours are spread hematogenously rather than using lymphatic route. Any metastatic features namely pleural effusion, hepatomegaly, or pathological fractures, malignant phyllodes tumours should be suspected as the top priority.

DIAGNOSIS

Anybody who presented with breast pathology should follow triple assessment as a guide to management. This is inclusive of phyllodes tumour. Other differential diagnoses that should be considered include benign conditions such as fibroadenoma, hamartoma, and lipoma or malignant lesions such as carcinoma, sarcoma, and metastatic tumour. Apart from history and clinical examination; imaging and core biopsy are confirmatory for the diagnosis. Imaging modalities which include ultrasound and mammography are the mainstay of radiological investigation. Phyllodes tumours appear as a well-defined oval, lobulated mass with rounded borders, mammographically are identical fibroadenoma.²³ In view of the compression to the surrounding breast stroma, a radiolucent "halo" may be seen.²³ Coarse calcification may be present but a typical popcorn calcification in fibroadenoma is not visualized in phyllodes tumours. On sonography, they often show smooth contours with low level homogenous internal echoes and absence of posterior shadowing.²³

Fine needle aspiration cytology (FNAC) is diagnostic for fibroadenoma. It is applied for a clinically apparent fibroadenoma. The pathognomonic features consisting of bare nucleus and bipolar cells (both epithelial and stromal elements) will be visualized. However, those features are conspicuous in phyllodes tumour as well making the diagnosis challenging. Both entities have an overlapping feature. It is often easier to separate benign from malignant phyllodes tumours rather than to differentiate benign phyllodes tumors from fibroadenomas. The presence of both epithelial and stromal elements are necessary to confirm the diagnosis. It is substantial in using core biopsy especially to differentiate between benign and borderline or malignant phyllodes tumours. Core biopsy represents the best modality for preoperative diagnosis with a sensitivity of 99%, negative predictive value and positive predictive value 93% and 83%, respectively.²⁴ Core biopsy using 14-gauge needle enables to provide an extra-architectural information provided by histology compared with cytology.²⁵ In the case of ulcerated lesion, wedge biopsy is needed instead.

On macroscopy, benign phyllodes tumours show a well-circumscribed lobulated and solid firm mass with a white tan whorling cut surface, similar to a fibroadenoma. Occasionally, larger tumours especially malignant type tend to develop a hemorrhagic and necrotic areas with curved protrusions into the parenchymal spaces. Microscopically, they are characterised by stromal overgrowth with intracanalicular growth pattern pushing the epithelium to the periphery forming a leaf-like contour (Figure 2). The stroma is cellular in comparison to fibroadenoma which is hypocellular. It can be uniform to pleomorphic with plump spindle-shaped cells, hence determines its poorer pathological behaviour. In fact, only the stromal cells potentiate to metastasise. Unlike phyllodes tumours, fibroadenomas have a true capsule.

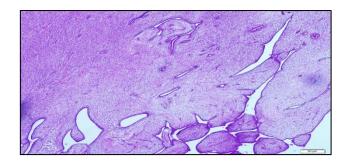


Figure 2: Phyllodes tumour showing a stromal overgrowth with intracanalicular growth pattern pushing the epithelium to the periphery forming a leaf-like contour.

According to Azzopardi and Salvadori, they had proposed a widely acceptable definitions for phyllodes tumour between benign, borderline and malignant type. 27,28 They have described on the tumour margins (pushing or infiltrative), stromal cellularity (low, moderate or high), mitotic rate (less than 5, between 5-9 or more than 10 per 10 high power field) and pleomorphism (mild, moderate or severe). World Health Organization added stromal atypia (mild, moderate or marked) and malignant heterologous elements in the criteria for diagnosis. While these features are observed in combination, they may not present concomitantly. Presence of a malignant heterologous elements will indicate the lesion as a malignant phyllodes tumours.

The role of immunohistochemistry in diagnosis of phyllodes tumours is still promising. Studies have shown that p53, Ki67, CD117, EGFR, p16 and VEGF are associated with histological grades.²⁹ The results indicate that the lowest expression is correlated with benign phyllodes tumours, meanwhile the highest is in malignant type. In fact, they may be valuable in differentiating fibroadenomas from phyllodes tumors and even to separate between grades of phyllodes tumours. Up to date, none has been proven to be clinically useful.²⁹

MANAGEMENT

Surgery is generally the mainstay of management in phyllodes tumours. Although the optimal choice of surgery is still debatable, most agree and opt for adequate surgical resection for better disease-free survival and subsequent improvement of overall survival. In borderline and malignant phyllodes tumours exceptionally, extensive preoperative assessment and staging are compelling. Hence, histological diagnosis via tissue biopsy is essential beforehand.

Surgical management can either be breast conserving surgery or mastectomy without axillary staging. In wide excision, the tumour should be resected with margin of more than 1 cm. Routine axillary dissection is not recommended as phyllodes tumours are spread hematogenously. Only less than 1% produce pathologic

nodes.²² Axillary dissection is only required upon histologically positive malignant cells. In benign phyllodes tumours, observation alone after surgery is considered safe. Study has advocated that local recurrence and 5 years survival rates are 4% and 96% respectively in benign phyllodes tumours.³⁰ The treatment of choice for borderline and malignant type is simple mastectomy traditionally. Malignant phyllodes tumors are more likely to recur after breast conserving surgery than benign types.³¹ In certain cases, immediate breast reconstruction especially rotational flap can be performed at the time of mastectomy for skin closure or cosmetic purposes.²² 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. Nevertheless, certain authors favor breast conserving surgery instead as local recurrences do not appear to cause systemic spread of the disease.32

The role of adjuvant breast radiotherapy is still unclear and widely under study. It is recommended for positive surgical margin postoperatively and for local control of borderline and malignant phyllodes tumors.³³ It is even suggested by National Comprehensive Cancer Network especially in malignant types.³⁴ Even the usage is controversial, the result is encouraging in patients with high risk features such as bulky tumors, hypercellular stroma, high nuclear pleomorphism, high mitotic rate, presence of necrosis, and increased vascularity within the tumor.³³ A study has concluded that the local recurrence with adjuvant radiotherapy was significantly lesser than patients treated with margin-negative resection alone.³⁵ Hence, by giving adjuvant radiotherapy in marginnegative resection can provide an effective way for local control of borderline and malignant phyllodes tumors.

The role of endocrine therapy, such as tamoxifen has not fully understood in phyllodes tumours. Oestrogen and progesterone receptor expression has been shown in 40% and almost 100%, respectively from the breast epithelium.36,37 Even, there has been a local study to address the co-expression of estrogen receptor beta and smooth muscle actin in phyllodes tumour. 14 Still, the use of endocrine therapy in either adjuvant or palliative setting has not been proven.³⁸ Stromal c-kit positivity and epithelial endothelin-1 negativity are more often associated with malignant phyllodes tumour. The overall positive rate of c-kit immunoreactivity was 13% in benign and 67% in malignant phyllodes tumour. 17 Endothelin-1 epithelial cytoplasmic staining was seen in 100% of benign and 17% of malignant phyllodes tumour.17

The role of chemotherapy remains uncertain but consideration can be given for their use in cases of malignant phyllodes tumours. Adjuvant chemotherapy using doxorubicin and ifosfamide 6 cycles with an interval of 28 days between each cycle has been practiced with promising result.³⁹ Even after chemotherapy, the

long-term survival is still associated with complete resection and histopathological type of tumor. This is practically beneficial for malignant phyllodes tumors. Local recurrence is regarded as a failure of primary surgical treatment. It has been associated with inadequate excision of the pseudopod. Local recurrence can be controlled by further wide excision (with 1 cm margins) or mastectomy. Lung is the most common distant metastatic area, followed by bone and abdominal viscera. They can develop without evidence of local recurrence. These often occur in the absence of lymph node metastases and histologically contain only the stromal element. ²³

CONCLUSION

Phyllodes tumors of the breast are rare neoplasms. Diagnosis is obtained by clinical appearance and core biopsy. The option of treatment depends on histological diagnosis either wide excision or mastectomy without axillary surgery. Radiotherapy and chemotherapy are reserved for selected cases with specific indications. Further studies need to be organized regarding role of adjuvant treatment especially in borderline and malignant phyllodes tumours.

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