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Phyllodes Tumor

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Introduction: Phyllodes tumor (PT) is a rare tumor of breast. It has many terminologies in the literature; the most recent and accepted one is PT by world health organization classification of breast tumors.

Objectives: The objective of this retrospective study is to reclassify all cases diagnosed as PT into benign and malignant PT (low grade and high grade), and to evaluate the clinical outcome of these cases.

Setting: King Abdul Aziz University hospital.

Methods: Eight cases were found over 18 years (1985 to March 2003). Histological slides and reports are examined and their clinical data and charts are reviewed. Six cases were malignant (2 low grades and 4 high grades) and two cases were benign. Follow-up periods varied between several weeks to seven years.

Conclusion: Although PT is a rare tumor of breast, however, it has to be differentiated from other benign lesions such as giant fibroadenoma. It also has to be classified properly to differentiate its benign type from the malignant counterpart that require long time follow-up.

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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.

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The objective of this retrospective study is to reclassify all cases diagnosed as PT into benign and malignant PT (low grade and high grade), and to evaluate the clinical outcome of these cases.

METHODS

In retrospect all cases diagnosed as Phyllodes tumor present in the archives of department of pathology at KAAUH from 1985 – March 2003 are examined and reclassified into benign, malignant, (low grade and high-grade). The gross description of the tumor is obtained from the patient pathology reports. The patient's files were reviewed to obtain clinical information and follow-up.

RESULT

We found 8 cases with 10 biopsies and lumpectomies. The age ranges from 29 to 54 years. All these cases presented with a palpable right or left breast mass of variable sizes range from 4 to10 cm diameter (Table 1). Case number 1 and 4 had two specimen needle biopsies and lumpectomy.

Table 1. **Phyllodes tumor patients cases**

Cases	Age	Procedure	Site	Natio-nality	Clinical Presentation	Macroscopic Appearance
1	44	Tru-cut biopsy Lumpectomy	Rt breast	Saudi	Breast mass, tender, mobile for 1 ½ month	5 cores
2	33	Excision	Rt breast	Ethiopian	Breast mass for 15 years. Mobile& firm.	Fibrofatty tissue with cystic lesion an contain soft irregular projections
3	41	Excision	Rt breast	Saudi	Breast lump. By self examination. Previous right medullary carcinoma 7 yrs back	Fibrofatty tissue
4		Tru-cut biopsy & excisional biopsy	Rt breast	NA	NA	Multiple
5	36	Lumpectomy	Rt breast	Philipino	Breast mass for 7 years suddenly increased in size. Mobile & firm.	Oval mass, well-circumscribed
6	27	Lumpectomy	Lt breast	Saudi	Left breast mass for 2 years. Painful for the last 4 months. History of trauma 2 years ago. Right breast lumpectomy 2 years ago	Oval firm encapsulated mass
7	42	Excision	Lt breast	NA	NA	3 fragments
8	33	Lumpectomy	Lt. brest	Malaysian	Left breast mass for 7 years. increased in size in last year. Retracted nipple, with yellow discharge on examination.	Whorly appearance of the nodule

DISCUSSION

Phyllodes tumor (PT) is uncommon neoplasm of breast, accounting for 0.3-0.9% of all breast tumors[4]. The malignant variant of phyllodes tumor is even lower. It is usually present as solitary unilateral tumor in one breast or rarely multifocal in or both breasts. The median age is 45 years, ranges from 10 to 86 and it is uncommon to occur in patients younger than 30 years of age. Isolated examples of PT have been described in men.

Phyllodes tumor is usually presented as a firm to hard, discrete, palpable mass, there is no clinical feature to distinguish benign or malignant phyllodes tumor from fibroadenoma[5]. A diagnosis of phyllodes tumor may be favored clinically if the tumor size measures more than 4 cm with history of rapid growth. However, giant fibroadenoma is always in the differential diagnosis. The average size is 4 to 5 cm ranging from 1 to 20 cm. Malignant tumor tends to be larger than benign variants. Large tumor may invade and ulcerate the skin or extend into the chest wall[6].

Breast mammography of PT appeared as rounded or lobulated, sharply defined, opaque mass in most cases; indistinct border were seen in minority of cases[7]. Ultrasound of PT reveal a well circumscribed not homogenous mass may be due to dilatation of ducts with cysts like formation and presence of epithelium-lined clefts[8]. Cystic components, evident by ultrasound slightly more frequently seen in malignant PT[9]. Classifications are uncommon and occur with equal frequency in benign and malignant PT. It is not possible to distinguish reliably between benign and malignant patients by mammography or ultrasound[7, 9].

Coexistance of PT with fibroadenoma histologically is seen in approximately 40% of cases[10]. It could be suspected clinically if the patient reports enlargement of a pre-existing tumor that was previously stable for years[11]. Cytogenetic Studies revealed no karyotypic changes in benign and malignant tumors[12]. The abnormalities are more complex in the malignant lesions. Biochemical analysis has detected progesterone receptor in the stromal of many patients, whereas only few of the tumors shows stromal expression of estrogen receptors[13]. PT appears grossly as well-circumscribed but not encapsulated. It may be a single mass, or multinodular. Tumors with microscopically invasive borders usually appear to be well-circumscribed grossly. The cross section of the tumor is composed of firm, bulging gray to tan tissue. Foci of degeneration, necrosis, and infarction may appear gelatinous or hemorrhagic. These alterations are more common in malignant patients but may occur in large benign lesions. Cysts that may contain necrotic debris are rarely present. An unusual variant of tumors has an exaggerated cystic component resulting in a gross appearance that is difficult to distinguish from cystic papilloma[14]. Microscopically the tumor arise form periductal rather than from intralobular stroma, and usually contain sparse lobular elements. It is characterized by its biphasic growth pattern in which stromal proliferative and hypercellularity around ducts result in projection of the ductal structure into the lumen forming leaf like structure. Most patients have a heterogeneous histological appearance.

In numerous cases, the intracanalicular patterns of clefts are obscured by hyperplasia of the ductal epithelium, or there may be conspicuous lobular component. Depending on cellularity, invasiveness of the tumor cytological atypia and mitotic count, phyllodes tumor is classified into benign, and malignant of low grade or high grade based on histology. Immunohistochemistry or molecular genetics has no role in diagnosis[3,8,15].

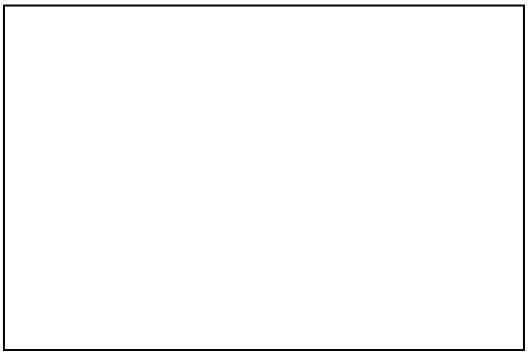

Figure 1. Stromal cellular overgrowth with leaf like projection into the ducts (Phyllodes pattern) 100 X.

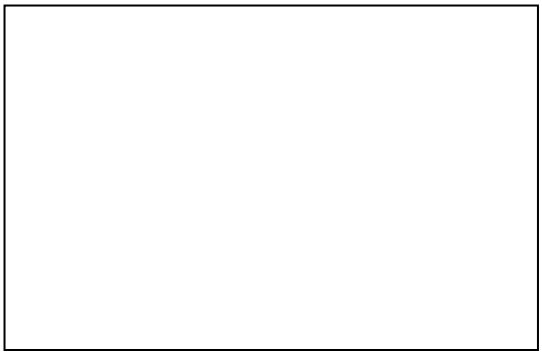

Figure 2. Heterogenous stromal expansion, predominantly around ducts (40 X magnification).

The most important differential diagnosis of benign PT is fibroadenoma. Several features must be taken into consideration in making this distinction. Patients are characterized in most cases by: younger age group in fibroadenoma cases, smaller size, mobile mass. Histologically, PT characterized by expansion and increased cellularity of the stromal compared with fibroadenoma. In some patients, stromal cellularity is more dense in the zone adjacent to epithelial components, the so called periductal stroma. Mitotic activity also may be accentuated in this distribution (periductal stroma) whereas mitoses are virtually absent from fibroadenomas as described by Rosen, although Page stated that mitosis is sometimes numerous in fibroadenoma but no abnormal forms[3,15]. However, a substantial group of patients exhibit little or no zonal stromal distribution. The presence of elongated epithelial-lined clefts is a feature associated with PT, occasionally these spaces are dilated and may be surrounded by cellular stroma (Fig 1). Epithelial clefts also can occur in fibroadenoma, especially in large or giant fibroadenoma, but the stroma in intracanalicular fibroadenomas tend to be hypocellular and uniform myxoid or fibrotic. Myxoid changes in the stroma of PT may be patchy and undergo degenerative changes, (Fig 2, 3) but in fibroadenoma it tends to be homogeneously distributed. Pseudoangiomatous stromal hyperplasia (PASH) occurs in patient with PT and in some instances it is a prominent feature of the lesion. Rarely multinucleated stromal giant cells are found in a patient with PASH, with bizarre forms, in typical benign stroma this criterion should not be interpreted as criterion of malignancy[3] (Fig 4). The stroma of PT is usually stain positive with antibodies for vimenting filaments and usually gives a negative stain with S 100 protein antibodies[17]. Estrogen receptors positivity is variable; however, progesterone receptors stain is more frequent[13]. Although no single criterion is used to differentiate benign and malignant Phyllodes; therefore, we applied multiple criteria for this differentiation. Excisional biopsy is required to determine the grade of the tumour based on stromal cellularity, mitotic activity, and microscopic character of tumor border (Fig5).

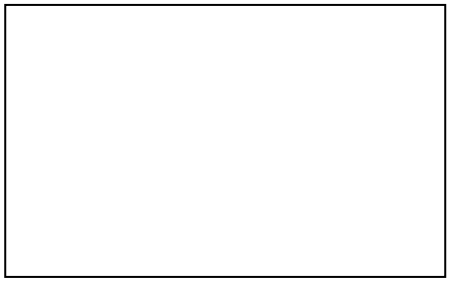

Figure 3. Epithelial hyperplasia of ducts epithelium with fibromyomatous stroma (250 X magnification).

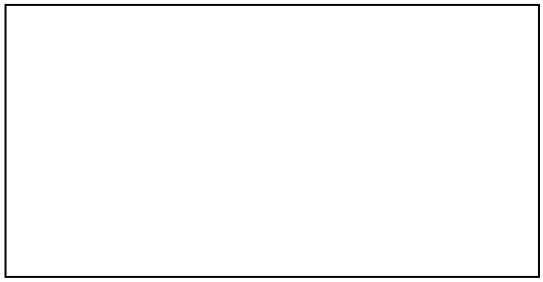

Figure 4. Metaplastic sarcomatous stroma.

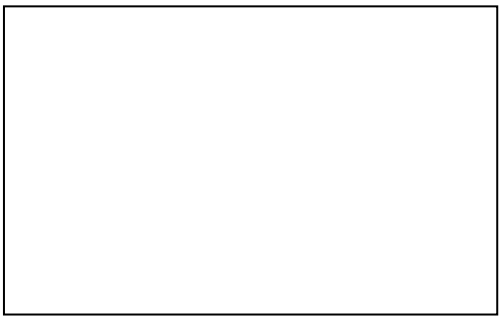

Figure 5. Microscopic invasive border of malignant phyllodes tumor (100 X magnification)

The sub-classification of tumours based on histology encompasses 3 groups of lesions; benign, Low-grade malignancy, and High-grade malignancy. Patient with benign phyllodes tumor usually curable by complete local excision with adequate margins of normal breast tissue, and it shows less risk of local recurrence, and no metastasis. The interval of recurrence tends to be longer, in addition whenever recurrence occur it always benign. The malignant phyllodes tumor have the capacity for local recurrence which is usually of high grade. It is also has the ability to metastasize either at presentation or later on in its course by hematogenous spread usually to the lungs[3].

Most reports in the literature emphasize on the clinico-pathological features of the tumor, and very few reports concentrate on management. Surgery is the treatment of choice. In the past radical surgery was the best choice, however nowadays more conservative surgery is recommended. The treatment of choice include, wide local excision or simple mastectomy without lymph node clearance, since axillary metastasis is extremely rare. The local recurrence of malignant phyllodes tumor, after limited local excision is 43%[18].

Radiotherapy can be used to decrease local failure rate after wide local excision, however it shows no significance effect on survival[19]. Various chemotherapy are used in phyllodes tumor with radiotherapy and shows no value in controlling the disease but it may improve survival[18,20]. Approximately 3-12% of the patient die from either extension into chest wall in local recurrence or from distance metastasis to lung or bones[20]. Negative surgical margin of excision is an important prognostic factor that control local recurrence[20]. Tumor size of 5 cm or more are more liable for local recurrence. Therefore, maintaining adequate margin for tumor larger than 5 cm will help in controlling local recurrence.

Table 2. **Microscopic**

Case No	STROMAL CELLULAR GROWTH	STROMAL EXPANSION	MITOTIC FIGURES	C. P.	CAPSULE & BORDER	METAPLASIA	GIANT CELLS	STRO
1	Moderate - marked	Uniform	4/10 HPF	Moderate	-Invasive borders	No	present	collage
2	Moderate Periductal	Heterogeneously distributed	2/10 HPF	Mild	-No invasive borders -No capsule	Appocrine metaplasia	No	Fibroco -nous myxo stron
3	Moderate around duct	Heterogeneous	2/10 HPF	Mild	-No capsule -No invasive borders	No	No	collage
4	Marked expansion cystic duct dilatation around ducts (periductal)	Heterogeneous	>7/10 HPF	Mild - moderate	Cannot be detected	angiomatous metaplasia focally	Present	Foca collage
5	Moderate – marked stromal prolifiration	Uniform expansion	>20/10 HPF	Marked	-No capsule - invasive borders	No	Prominent (sarcomatous)	collage
6	Marked	Uniform with focal sclerosis	>16/10 HPF	Mild	-No capsule -Invasion of borders	No	No	collage
7	Marked	Uniform	>10/10 HPF	Moderate	-No capsule - Invasive borders	Angiomatous metaplasia	No	Myxo degener focal
8	Moderate	Heterogeneous	3/10 HPF	Absent	-No capsule - Invasive borders	Appocrine metaplasia	No	Fibro stron

C.P. = Cytological Pleomorphism
E.P. = Epithelial Proliferation
NRD = No Recurrent Disease

If we compare our finding to the literature, although we had very small number of patient, yet we find that the most significant histological criteria to diagnose malignant phyllodes tumor is stromal invasion, and mitotic rate. Both low and high grade phyllodes tumor have microscopic invasive border, but the low grade have mitosis less than 5/10 high power field (HPF), while the high grade have more than 5 mitosis/10 HPF (Table 2). The size of the tumor has no significance on grading of phyllodes tumor.

CONCLUSION

Although PT is a rare tumor of breast, however, it has to be differentiated from other benign lesions such as giant fibroadenoma. It also has to be classified properly to differentiate its benign type from the malignant counterpart that require long time follow-up.

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