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Phyllodes Tumor: A Retrospective Analysis of 4 Years, At a Rural Based Tertiary Care Center

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Abstract

Aim: The present study demonstrates the recent experiences in histopathological diagnosis of phyllodes tumor of breast. *Material & Methods*: Histopathological slides and medical records of eleven cases of phyllodes tumor of breast diagnosed at the Department of Pathology, SRMS-IMS, Bareilly from January 2013 to December 2016 were reviewed. Cases were evaluated for degree of stromal cellularity and atypia, mitotic count, stromal overgrowth, and the nature of the tumour borders. *Results:* The median age at diagnosis was 45 years (range 30 years to 58 years). Mean tumor size was 10.2 cm (range 22cm to 6cm). Tumors predominated on the right side (54.5%). Wide tumorectomy was performed in seven patients and four patients underwent mastectomy. FNAC was performed in seven cases out of which 3 cases were diagnosed as phyllodes, 2 cases showed possibility of phyllodes and 2 cases were diagnosed as fibroadenomas. Histopathologically 10 cases were diagnosed as benign phyllodes and one case was diagnosed as borderline or low malignant potential. There were two cases of recurrent benign phyllodes tumor. *Conclusions*: The confrontation of our results to the data of the medical literature shows that histological confirmation is required for the diagnosis of phyllode tumors. The treatment of choice is surgery. The prognosis depends on the histological characteristics of these tumors.

Keywords: Phyllodes Tumor; Prognosis; Tumorectomy.

Introduction

Phyllodes tumors are rare but fascinating group of fibroepithelial neoplasms of the breast. They display a morphological resemblance spectrum ranging from, fibroadenomas at the benign end of the spectrum to pure stromal sarcomas at the malignant end of the spectrum. Phyllodes tumors are classified into three tier grading system i.e benign, borderline and malignant grade. The histological parameters used for this classification include: degree of stromal cellularity and atypia, mitotic count, stromal overgrowth, and the nature of the tumor borders. Accurate and reproducible categorization of these tumors is challenging as these histomorphological parameter have two to three tiers of stratification [1].

Phyllodes tumors are rare is males and children. Recurrence rates for benign, borderline and malignant phyllodes tumors are 10–17%, 14–25% and 23–30% respectively. Distant metastasis occurs in almost 22% of malignant phyllodes tumors [1]. A large series study of phyllodes tumours in Asian population showed recurrence rates of 10.9%, 14.4% and 29.6% for benign, borderline and malignant phyllodes tumors, respectively [2].

Accurate preoperative histopathological diagnosis of phyllodes tumors helps in correct surgical planning and tumor excision [3]. Benign phyllodes tumors are often indistinguishable from fibroadenomas and can be cured by local surgery. Importance of phyllodes tumors lies in the need to differentiate them from fibroadenomas. Surgery may involve either wide local excision or mastectomy, provided histologically clear specimen margins are ensured [4,5].

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Material & Methods

Histopathological slides and medical records of cases of phyllodes tumor of breast diagnosed at the Department of Pathology, SRMS-IMS, Bareilly from January 2013 to December 2016 were reviewed.

Inclusion Criteria

- Histpathological biopsy report of phyllodes tumor.
- Patient receiving treatment at SRMS-IMS.

Exclusion Criteria

- Patients with final fibroadenoma diagnosis.
- Phyllodes tumor that had associated in situ or infiltrating carcinoma

Institutional medical records were fetched for medical records of these patients. Data was gathered regarding the history, age, sex, size, clinical features, treatments undertaken, and recurrence data. Histopathological, cytological and mammography reports were also collected.

All the histopathology slides were re-examined in the Department of Pathology, of the institution and were classified as benign, borderline, or malignant, in compliance with the criteria proposed by Azzopardi and Salvadori and adopted by WHO [6]. Cases were evaluated for degree of stromal cellularity and atypia, mitotic count, stromal overgrowth, and the nature of the tumor borders.

Table 1: Three tiered grading system for phyllodes

	Benign	Borderline	Malignant
Stromal Cellularity	mild	moderate	marked
Stromal Atypia	MILD	moderate	marked
MITOSIS(/10hpf)	<5	5-9	>=10
Tumor Margins	Well Defined	Well Defined or focally invasive	invasive
Stromal Overgrowth	Absent	Absent or focal	Present

Details of various histological parameters used for grading of Phyllodes tumors [7]:

- Mitotic activity- Evaluated in more cellular areas and quantified per 10 HPF (X40)
- Stromal overgrowth- Stromal proliferation without accompanying epithelial elements in at least 1 low-power field (X4)
- Stromal cellularity - Evaluated in the most cellular areas.
  - Mild - Twice cellularity of normal perilobular stroma with evenly spaced nuclei without overlapping
  - Moderate - Intermediate in degree between mildly and markedly
  - Marked - Stromal cells in close contiguity with nuclei appearing to touch and overlapping
- Stromal atypia
  - Mild - Small, uniform nuclei, with absent or inconspicuous nucleoli
  - Moderate - Intermediate in degree between mildly and markedly
  - Marked - Marked variation in nuclear size and shape, irregular nuclear membrane, and prominent nucleoli
- Infiltrative tumor margin - Projections of tumor stroma into the peritumoral stroma or adipose tissue

Results

During the period of the study, at the SRMS-IMS a total of 11 patients with phyllodes tumor were diagnosed and analysed. During the period of study not a single case of malignant phyllodes tumor was diagnosed at our institution.

Table 2: General characteristics of Phyllodes tumors

Characteristic	Number of cases
Sample number	11
Mean age (yrs)	45
Laterality	
Right	6 (54.5%)
Left	5 (45.5%)
Surgical management	
Mastectomy	4 (36.4%)
Conservative surgery	7 (63.6%)
Mean size (cm)	10.2

The median age at diagnosis was 45 years (range 30 years to 58 years). Mean tumor size was 10.2 cm (range 6cm to 22cm). Tumors predominated on the right side (54.5%). Wide tumorectomy was performed in seven patients and four patients underwent mastectomy.

FNAC was performed in seven cases out of which 3 cases were diagnosed as phyllodes, 2 cases showed possibility of phyllodes and 2 cases were diagnosed as fibroadenomas.

Histopathologically 10 cases were diagnosed as benign phyllodes and one case was diagnosed as borderline or low malignant potential. There were two cases of recurrent benign phyllodes tumor.

Histopathological study of the benign Phyllodes tumors biopsy showed cellular atypia which was mild in most of cases along with mild stromal atypia, while one case presented with a scant cellularity. Stromal fragments were present at least one in every microscopic field. Semi-quantitative assessment revealed that the all cases (ten cases) are characterized by few if any mitoses, moderate to marked cellular overgrowth, and slight to moderate cellular pleomorphism.

Histopathological study of the single case of borderline phyllodes tumors showed an average of 5 to 6 mitoses per 10 high-power field, moderate stromal cellularity that is irregularly distributed in hypocellular areas. Stroma comprises of fibroblastic cells which at places are showing myxomatous changes. Stromal cells display mild to moderate degree of nuclear atypia.

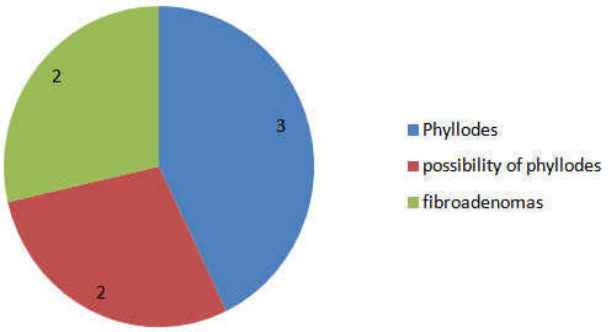

Fig. 1: Different cytological diagnosis before histopathological confirmation of phyllodes tumours

Discussion

The diagnosis of phyllodes tumor is made when an increased intracanalicular pattern is seen with leaf-like fronds protruding into cystically dilated spaces along with stromal hypercellularity. A benign phyllodes tumor when compared with fibroadenoma show slight increase in cellularity of stroma and have minimal nuclear atypia, pushing borders, and mitotic figures ≤4/10 High Power Fields (HPFs). Stromal overgrowth is absent. Whereas, a malignant phyllodes tumor shows markedly increased cellularity of stroma and atypia, has permeative margins, and has mitotic figures > 10/10 HPFs. Overgrowth of stroma is easily identified. Borderline phyllodes tumors have intermediate features between these two spectrums [6].

Stromal cellularity is assessed in most cellular areas. Mild hypercellularity is characterized by a slight increase in stromal cells when compared with normal perilobular stroma, with nuclei that are evenly spaced and not overlapping or touching. Marked cellularity shows merged areas of densely overlapping nuclei, while moderate cellularity has intermediate findings, with occassional overlapping stromal nuclei. When comparing atypia- Mild stromal atypia is characterized by nuclei with smooth nuclear contours and with little variation in nuclear size. Marked atypia is characterized by marked variation in nuclear size, irregular nuclear membranes with discernible nucleoli and coarse chromatin. Moderate atypia is characterized by some variation in nuclear size, with wrinkled nuclear membranes, to an extent lying between that in mild atypia and marked atypia [8].

In a study of 605 cases of phyllodes tumor to assimilate the important microscopic features which independently ascertain the clinical behaviour of phyllodes tumors, by Tan et.al. found that atypia, mitoses, overgrowth and surgical margins (AMOS criteria) were of great significance in predicting the clinical behaviour, with surgical margin being the most important feature. They developed a nomogram using a mathematical formula that could be used to calculate the risk of recurrence [2].

In a large Asian study of phyllodes tumors the recurrence rates were found to be 10.9%, 14.4% and 29.6% for benign, borderline and malignant phyllodes tumors, respectively [2]. In another study of 33 cases from Germany, the recurrence rates were found to be 8%, 20% and 50% for benign, borderline and malignant tumors, respectively [1]. The recurrence rates as per WHO literature are 10–17%, 14–25% and 23–30% for benign, borderline and malignant phyllodes tumors, respectively [1]. An interesting clinicopathological analysis conducted by Karim et al. suggested that recurrence rates were higher in Asian patients than those of non-Asian ethnicity [9]. In our study 2(18%) cases of recurrent benign phyllodes tumor were identified.

It is observed that grade progression can occur during local recurrence of phyllodes tumors. Various reasons explaining this have been proposed like, lack of proper representative sampling of the tumor, presence of stromal subclones and tumor heterogeneity [10], and stromal–epithelial interdependency loss [11].

In a phyllodes tumors study of 335 cases, it was found that metastases and death due to phyllodes tumors were consistently anteceded by a diagnosis of a primary malignant phyllodes tumor [12]. Prognosis in metastatic phyllodes tumors is very poor, with ensuing death [2,13]. Common sites of metastasis are lung and skeleton, but may involve any other organ. Histologically, the components of metastases include the malignant stromal elements with the absence of accompanying epithelium [12,14,15].

Many biological markers like MicroRNAs [16], Ki-67, CD10, CD34, p53, CD117 [17], Pax3 [18], actin, Vimentin [19], VEGF and β-catenin [20] have been studied in phyllodes tumors. Many have shown association with grade but none have been successful in defining clinical behaviour and grade in specific cases [21].

The recommended treatment of phyllodes tumor is surgical excision with wide tumor free margins of at least 1cm or larger [22]. However, in a recent study of 164 cases of phyllodes tumors it was found that a 1 cm negative margin thickness did not provide any significant advantage over a negative margin of thinner width [23]. Using radiotherapy, chemotherapy or both as adjuvant therapy for treatment of phyllodes tumors has not played a clear and definite role with lots of contradictory results in literature [24,25,26].

Conclusion

The comparison of our results to the data of the medical literature shows that histological confirmation is required for the diagnosis of phyllode tumors. The treatment of choice is surgery. The prognosis depends on the histological characteristics of these tumors. The diagnosis, classification, behaviour prediction and clinical management of phyllodes tumors are quiet challenging. The aim of grading of phyllodes tumors should be to distinguish accurately benign and malignant phyllodes tumors. The term benign fibroepithelial lesion/neoplasm should be used sparingly where a clear distinction between cellular fibroadenoma and benign phyllodes tumors is not possible.

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