

Phyllodes Tumour of Breast: Ki 67 Expression in Various Histological Subtypes

B.R. Vani^{1*}, Deepak Kumar B¹, Padma Priya K², Sandhyalakshmi B.N.¹ and Srinivasamurthy¹

¹Department of Pathology, ESIC Medical College and PGIMSR, Rajajinagar, Bangalore, India

²Department of Pathology, Sapthagiri Institute of Medical Sciences and Research Institute, Hesarghatta, Bangalore, India

Keywords: *Phylloides, Borderline Malignant, Ki 67, Breast*

ABSTRACT

Background: Phyllodes tumours [PT] are uncommon fibroepithelial tumours with marked stromal proliferation over epithelial component with majority being benign. Along with grade, additional study of proliferative markers such as p 53, Ki 67 are essential to identify those with potential for aggressive behaviour. In this background study was undertaken to assess the histopathological characters and correlate Ki 67 expression in different subtypes of PT.

Methods: A total of 21 cases were studied. Clinical details, gross features and primary histologic features were taken into consideration. Immunostaining for Ki 67 were performed. Ki 67 immunoeexpression was categorised as 0-10, 11-30, 31 and above depending on the percentage of positive tumor cells in each case. Ki 67 immunoeexpression was correlated with histologic grade and clinical features.

Result: 14 cases (66.7%) of Benign, 03 cases (14.3 %) of borderline, and 04 cases (19 %) cases of malignant phylloides tumor were seen. Average Ki 67 expression in BPT and BIPT was 4.5 % (range 1-8%) and 14 % (range 13-15 %) respectively. MPT exhibited Ki range of 41-80 % with average LI of 56 %. A significant association was seen between expression of Ki 67 in different grades of phyllodes tumour.

Conclusion: Inclusion of Ki 67 in routine histopathology reporting of phylloides is mandatory as Ki LI proves to be of paramount importance in sub categorisation of phylloides.

***Corresponding author:**

Dr B.R. Vani, 169/B, 4th Main, 3rd cross, J P Nagar, # rd phase, Bangalore-78, INDIA.

Phone: +91 9945511383

Email: vanibr@yahoo.in



Introduction

Phyllodes tumours [PT] are uncommon fibroepithelial tumours with marked stromal proliferation over epithelial component. Majority are benign and constitutes 0.3-1.5% of breast neoplasms. [1,2,3,4,5]. Common clinical presentation is of rapidly growing lump in the breast with median age of occurrence being 45 years and 10-20 years later than fibroadenoma. [2,6,7,8,9].

PT encompasses benign (BPT), borderline (BIPT) and malignant subtypes (MPT) with varied propensity for recurrence, over all incidence being 8-40%. [3,5]. Metastasis corresponds with grade of phylloides and is 4%, 22% in BIPT and MPT respectively. [8,9]. MPT has poor prognosis with 5 year survival rate of 66% [4].

Histological grade is based on semiquantitative assessment of degree of stromal cellularity, cellular pleomorphism, mitotic activity, and tumour margins. [8]. Additional study of proliferative markers such as p53, Ki67 are essential to identify those with potential for aggressive behaviour. [3]. Literature data shows tumour grade corresponds with p53, and Ki 67 expression. [10].

In this background study was undertaken to assess the histopathological characters and correlate Ki 67 expression in different subtypes of PT.

Materials and Methods

The study was undertaken in department of pathology, ESIC MC & PGIMS, RNR, Bangalore from January 2010-December 2013. Total number of PT cases were 21. Clinical details including age of patient, nature of surgery etc were collected from medical records. Gross features of the specimen and appearance at cut section were noted. During this period cases of PT if recurred were also studied. Primary histologic criteria defining PT considered is stromal overgrowth with absence of epithelial component in atleast one low power field. [1]. Further depending on histological features PT were graded as BPT, BIPT, MPT. [8].

PT with mitotic activity (MA) less than 5/ 10 high power field (hpf) and any one or more of the features as described for BPT were categorised as BPT. Tumours with MA more than 10 / 10 hpf and any one or more of the features describing those of MPT were categorised as MPT. Tumours with MA more than 5/10 hpf but less than 9/10 hpf and intermediate features describing those of BIPT were categorised as BIPT. [8]

Immunostaining for Ki 67 were performed. Positive and negative controls were run with each batch of IHC for Ki 67. The proportion of nuclear positivity defined by any detectable brown staining of the nucleus above the

background level were scored as positive and labelling index [LI] was determined by counting a minimum number of 1000 cells in the most active areas. Ki 67 immunexpression was categorised as 0-10, 11-30, 31 and above depending on the percentage of positive tumor cells in each case.

Data was analysed using descriptive statistics such as mean and standard deviation. Difference between 2 categories were evaluated by using chi square test of significance for independence. A p value less than 0.05 was considered to be significant.

Result

During the four year study period total phylloides case were 21. Age range was 24-64 years with mean age of 38.2 years. [Table 1]. Majority presented as solitary lump in breast (95.23%). One patient had synchronous fibroadenoma [FA] in left breast with PT affecting right breast. Lumpectomy was the nature of surgery in 85.7% cases. Modified radical mastectomy [MRM] was performed in three cases since FNA reported as malignancy.

Over all PT size ranged from 2 to 26 cms with mean of 9.7 cms. Average size in BPT is 6.9 cms (2- 14 cms range), BIPT 9.3 cms (7-14 cms range), MPT 19.7 cms (12-26 cms). [Table 2].

Histologically BPT were 14 cases (66.7%), BIPT 03 cases (14.3%), MPT 04 cases (19%). [Table 3]. All BPT exhibited histological features as defined by WHO. In BIPT uniform stromal cellularity was a feature noted in 2 cases. Third case with heterologous stromal expansion; though had well circumscribed margins, recurred and this recurred tumour had intermediate margins with areas of necrosis and other histological features defining BIPT. IHC for Ki 67 done on this recurred BIPT had same score as primary tumour.

All MPT exhibited the classical features defined by WHO with monomorphic or pleomorphic sarcomatous stroma. Axillary lymphnode dissection was accompanied with MRM performed in two cases and all the lymphnodes were free of tumour microscopically. IHC for vimentin was positive, while EMA, SMA, CK was negative.

Average Ki 67 expression in BPT, BIPT was 4.5% (range 1-8%) and 14% (range 13-15%) respectively. MPT exhibited Ki range of 41-80% with average LI of 56%. [Table 4] [Fig 1,2]

Upon statistical analysis, a significant association was seen between tumor size and various grades of phyllodes tumour. Expression of Ki 67 in different grades of phyllodes tumour was also statistically significant.

Table 1: Age distribution in different grades of phylloides tumor.

Age (yr)	Benign PT (N= 14)	Borderline PT (N=3)	Malignant PT (N=4)
< 30	04	00	00
31-40	09	01	01
41-50	01	01	01
51-60	00	01	01
>60	00	00	01

Table 2: Tumor size in different grades of phylloides tumor.

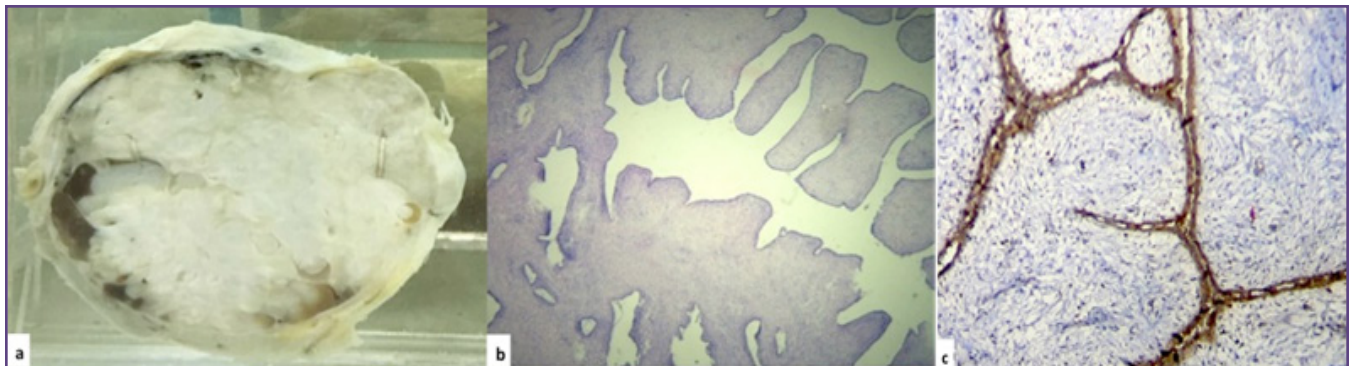
Tumor size	Benign PT (N= 14)	Borderline PT (N=3)	Malignant PT (N=4)	P value
< 10 cm	10	02	00	0.019
10-20cm	04	01	02	
>20cm	00	00	02	

Table 3: Histological features in different grades of phylloides tumor.

Histological features	Benign PT (N= 14)	Borderline PT (N=3)	Malignant PT (N=4)
Stromal cellularity	Low (14)	Moderate (3)	High (3)
Cellular pleomorphism	Mild (14)	Moderate (2)	Marked (3)
Mitotic index	<5/10 hpf (14)	5-9/10 hpf	>10/10hpf
Margins	Well circumscribed (14)	Well circumscribed (2) pushing (1)	Infiltrating (3)
Stromal proliferation	Uniform (14)	uniform	Irregular (3)

Table 4: Average[A_v] Ki 67 expression in different grades of phylloides tumor.

Ki 67 expression	Benign PT cases(A _v Ki in %)	Borderline PT cases(A _v Ki in %)	Malignant PT cases(A _v Ki in %)
< 10	14 (4.5)	--	--
11-30	--	3 (14)	--
>31	--	--	4 (56)

**Fig. 1: Benign Phyllodes tumor; (a) Gross ; (b) H&E - 4x; (c) Ki67 IHC 10x..**

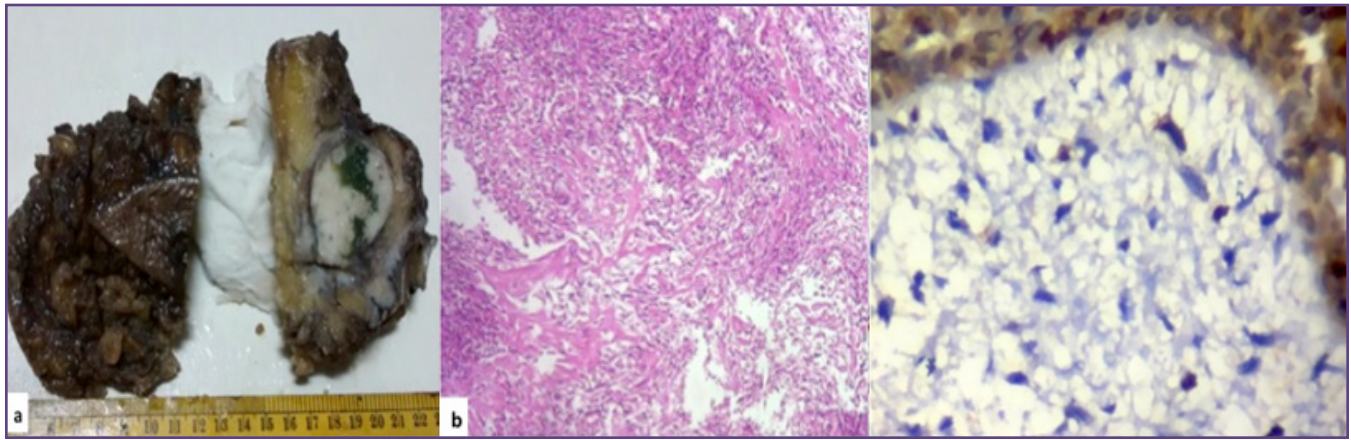


Fig. 2: Borderline Phyllodes tumor; (a) Gross ; (b) H&E - 4x; (c)IHC Ki 67 IHC 40x.

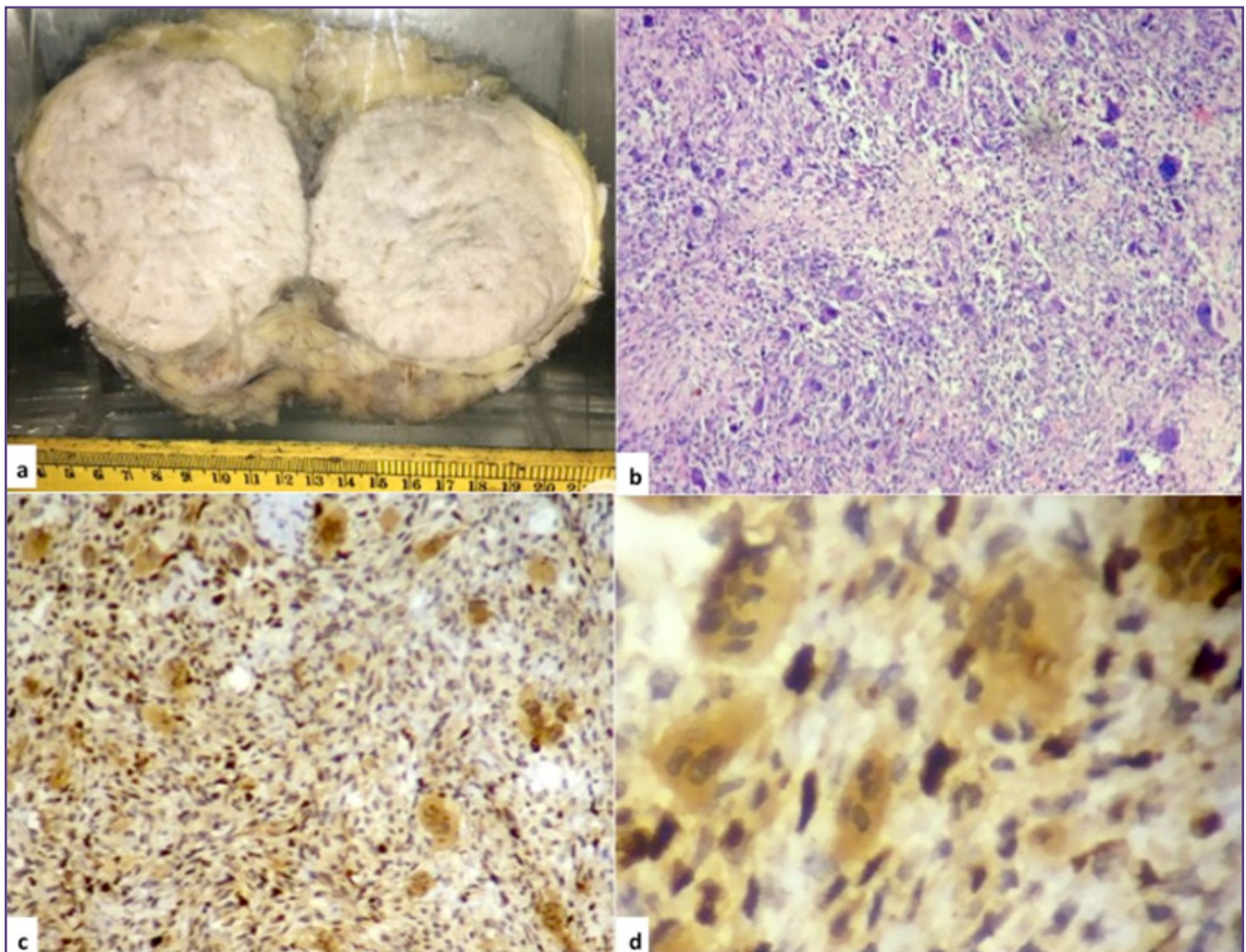


Fig. 3: Malignant Phyllodes tumor; (a) Gross ; (b) H&E - 10x; (c) Ki67 IHC 10x; (d) Ki 67 IHC 40x.

Discussion

Johannes Muller in 1838 coined the term cystosarcoma phylloides due to morphologic leafy bulbous protrusion of epithelium covering proliferating stroma and often extending into cystic space. [4,6,7,11] Majority were benign and not all cases exhibited cystic degeneration, hence WHO renamed the misleading nomenclature as phylloides tumour. [4,7,8,11,12]

PT constitutes 0.3 to 1 % of primary breast neoplasm and 2.5 % of fibroepithelial breast lesions. [4,6,12,13]. In our institution breast lesions during the study period constituted 6.7% of total histopathology specimens. Prevalence of PT was 2.3 % of breast lesions and is in concordance with literature available. [6,7].

Median age group of presentation is 40-50 years. [2,6]. Occurrence at younger age with average of 25- 30 years reported in Asians. [2,7]. In the present study maximum number of cases were seen in age group of 31-40 years (52.4 %) with median age of presentation of 38.2 yrs, which is in concordance to the data available in literature. [6,13].

Phylloides present as painless, palpable mass in upper outer quadrant frequently affecting right breast [6,13]; bilaterality reported in 3.4-3.8%. [6]. In our case series all were solitary, majority occurring in upper outer quadrant with 12 cases affecting right breast and 9 cases involving left breast. One patient presented with synchronous FA of opposite breast. Literature search revealed concomitant FA in 4.2 % to 1/3 rd of women with PT and in proportion of FA somatic mutation result in monoclonal stromal proliferation progressing to PT. [4,6]. In our patient probably an existing FA would have shown monoclonal proliferation and hence patient presented with PT. This underscores the fact that FA and PT represent two ends of a single spectrum with origin being intralobar stroma.

In present study tumour size varied from 2-26 cms, with average size of 9.7 cm and is in concordance with average size reported in literature. [6]. Mean tumour size of BPT, BIPT, MPT is 6.9 cm, 9.3 cm and 19.7 cm respectively. No single morphologic feature predicted clinical tumour behavior and histologic grade is independent of size, presentation, clinical behaviour. [4,6]. In our study increased size had increased grade and was statistically significant. Tumours were lobulated, fleshy, grey white to grey tan with cystic change in few. In malignant phylloides, patient presented with sudden growth and tumours were bulky varying in size from 12-26 cm. Areas of haemorrhage, necrosis, microcysts and infiltrating nodules were a feature in MPT. The skin over the tumour exhibited dilated veins; however no ulceration noted in our study. [5,12].

On cytology smears showed large and increased stromal fragments with plump spindle cells in the background, suggesting phylloides, however a differential of fibroadenoma was offered. Smears exhibiting marked nuclear pleomorphism, increased mitotic activity prompted malignancy of breast; epithelial or stromal.

Phylloides histology exhibited proliferating fibroblastic stroma lined by ductal epithelial cells projecting into cleft like spaces, appearing morphologically as leaf like pattern. In a typical benign phylloides, stroma was reminiscent of exaggerated intracanalicular pattern of fibroadenoma. Borderline tumours exhibited heterogeneity with hypercellular and hypocellular areas and mitotic count of < 10/10hpf. The sarcomatous stroma ranged from monomorphic to pleomorphic resembling fibrosarcoma, malignant fibrous histiocytoma or liposarcoma. [11]

According to various studies malignancy in PT range from 7 to 45 %. [4,6]. In our study MPT comprised 1.7 % of all type of primary malignant lesions of breast. Of all the PT; MPT accounted for 19.04 % and this in concordance with study by Eroglu E et al. [13]

A remarkable feature observed in 2 cases [50 %] of MPT was secondary changes comprising of osteoclastic giant cells and areas of necrosis. The stroma in these osteoclast rich lesion showed a high Ki 67 LI of 80 % and 56 %; the same has been notified as a case report. [15]

Metastasis is 25-50 % [6,7] and is via blood often to lungs, pleura, bone, CNS. [6,11] Axillary metastasis is uncommon, while axillary lymphadenitis seen in 10- 20% patients exhibits reactive histology as noted in 2 cases of MPT that we studied. [6,7,11,14].

Chan Y J et al stated that BPT with Ki expression more than 10 % needs to be treated and followed up to avoid recurrence and malignant transformation. [1]. In our study all BPT had Ki less than 8 % with average of 4.5 %. Gatalica et al reported mean Ki of 7.73 and 23.42 in BPT and MPT respectively. [16]. The more obvious increased Ki LI was seen as expected in malignant phylloides category and our study showed a high mean Ki 67 LI of 56 % as compared to Gatalica et al. We conclude that expression of Ki 67 correlated well with morphologic grade and was statistically significant similar to Chan Y J et al.

Conclusion

Inclusion of Ki 67 in routine histopathology reporting of phylloides is mandatory as Ki LI proves to be of paramount importance in sub categorisation of phylloides.

Acknowledgement

Nil

Funding

None

Competing Interests

None Declared

Reference

1. Chan YJ, Chen BF, Chang CL, Yang TL, Fan CC. Expression of p53 Protein and ki 67 Antigen in Phylloides Tumor of the Breast. *J Chin Med Assoc* 2004;67:3-8.
2. Khurshid A, Kayani N, Bhurgri Y. Phylloides Tumors in Adoloscet Girls and Young Women in Pakistan. *Asian Pacific J Cancer Prev*. 7:563-566.
3. Esposito NN, Mohan D, Bruhky A, Lin Y, Kapali M, Dablo DJ. Phyllodes Tumor. A Clinicopathologic and Immunohistochemical Study of 30 cases. *Arch Pathol Lab Med*. 2006;130:1516-21.
4. Parker SJ, Harries SA. Phyllodes Tumors. *Postgrad Med J* 2001;77:428-35.
5. Carter D, Schnitt SJ, Mills RR. The Breast. In: Carter D, Greenson JK, Reuter VE, Stoler MH, Mills SE, Sternberg's Diagnostic Surgical pathology. 5th ed. Philadelphia: Lippincott Williams and Wilkins;2010, The Breast;285-350.
6. Abdelkrim SB, Trabelsi A, Bouzrara M, Boudagga MZ, Memmi A, Bakir DA, Mokni M. Phyllodes tumors of the Breast: A review of 26 cases. *World Journal of Oncology* 2010,1(3):129-34.
7. Lester SC. The Breast. In: Kumar V, Abbas AK, Fausto N, Aster JC, editors. *Robbins and Cotran Pathologic Basis of Disease*. 8th ed. India: Elsevier India Pvt Ltd;2010.
8. Tavassoli FA, Devilee P, editors. *World Health Organization of Tumors. Pathology and Genetics of Tumors of the Breast and Female Genital Organs*. Lyon: IARC Press; 2003.
9. Rosen PP. *Rosen's Breast Pathology*. 3th ed. Philadelphia: Lippincott William and Wilkins; 2009.
10. Kuruk U, Bayol U, Pala EE, Cumureu S. Importance of P53, Ki-67 expression in the differential diagnosis of benign/malignant phyllodes tumors of the breast. *Indian J Pathol and Microbiol* 2013; 56(2): 129-34.
11. Rosai J. *Rosai and Ackerman's Surgical Pathology*. 10th ed. New Delhi: Reed Elsevier India Private Limited; 2011. Chapter 20, Breast;1659-1770.
12. Stamatakos M, Tsaknaki S, Kontzoglou K, Gogas J, Kostakis A, Safioleas. Phyllodes tumor of the breast: a rare neoplasm, though not that innocent. *Internal Seminars in Surgical Oncology*. 2009.
13. Eroglu E, Irkkan C, Bulak H, Kilicoglu B, Oral S. Phyllodes tumor of the breast: case series of 40 patients. *Gazi Medical journal* 2003;14:29-34.
14. Ahmed S, Rahman MA, Murshed KM, Shirin L. Phyllodes Tumor of Breast: BSMMU Experience. *J Bangladesh CollPhySurg* 2007;2570-72.
15. Vani BR, Kumar BD, Sandhyalakshmi B N, Geethamala K, Murthy V S, Radha M. Malignant phyllodes tumor with osteoclastic giant cells. *Saudi J Health Sci* 2014;3:124-6.
16. Gatalica Z, Finkelstein S, Lucio E, Tawfik O, Palazzo J, Hightower B et al. p 53 protein expression and gene mutation in phyllodestumour of the breast. *Pathol Res Pract* 2001;197:183-7.