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ORIGINAL ARTICLE

Phyllodes tumours of the breast: retrospective analysis of a University Hospital's experience

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Abstract

Taking cognizance of the purported variation of phyllodes tumours in Asians compared with Western populations, this study looked at phyllodes tumours of the breast diagnosed at the Department of Pathology, University of Malaya Medical Centre over an 8-year period with regards to patient profiles, tumour parameters, treatment offered and outcome. Sixty-four new cases of phyllodes tumour were diagnosed during the period, however only 30 (21 benign, 4 borderline and 5 malignant) finally qualified for entry into the study. These were followed-up for 4-102 months (average = 41.7 months). Thirteen cases (8 benign, 3 borderline, 2 malignant) were Chinese, 9 (all benign) Malay, 7 (4 benign, 1 borderline, 2 malignant) Indian and 1 (malignant) Indonesian. Prevalence of benign versus combined borderline and malignant phyllodes showed a marginally significant difference ($p=0.049$) between the Malays and Chinese. Patients' ages ranged from 21-70 years with a mean of 44.9 years with no significant difference in age between benign, borderline or malignant phyllodes tumours. Except for benign phyllodes tumours (mean size = 5.8 cm) being significantly smaller at presentation compared with borderline (mean size = 12.5 cm) and malignant (mean size = 15.8 cm) ($p<0.05$) tumours, history of previous pregnancy, breast feeding, hormonal contraception and tumour laterality did not differ between the three categories. Family history of breast cancer was noted in 2 cases of benign phyllodes. Local excision was performed in 17 benign, 2 borderline and 3 malignant tumours and mastectomy in 4 benign, 2 borderline and 2 malignant tumours. Surgical clearance was not properly recorded in 10 benign phyllodes tumours. Six benign and all 4 borderline and 5 malignant tumours had clearances of <10 mm. Two benign tumours recurred locally at 15 and 49 months after local excision, however information regarding surgical clearance was not available in both cases. One patient with a malignant tumour developed a radiologically-diagnosed lung nodule 26 months after mastectomy, was given a course of radiotherapy and remained well 8-months following identification of the lung nodule.

Keywords: phyllodes tumour, breast, Malaysian

INTRODUCTION

Phyllodes tumours are uncommon biphasic fibroepithelial tumours constituting 0.3 to 1.0% of all breast tumours in females.[1] Interestingly some authors have suggested peculiarities of the "Asian" variant including an earlier age of 25-30 years at presentation, in comparison with the usual 40-50 years of age generally reported for other populations.[2, 3] Although this tumour was described as early as 1774,[4] there are still areas of ambiguity regarding histological diagnostic criteria, prognostic factors and optimal treatment. Little research has been carried out in this area in the Malaysian context with its noteworthy mix of Malays constituting about 63%, Chinese 25% and Indians 7% of the total population.[5] Taking cognizance of the said differences amongst Asian cases, this study aimed to analyse histologically-confirmed cases of phyllodes tumours diagnosed at the Department of Pathology, University of Malaya Medical Centre over an 8-year period with regards to patients' profiles, tumour parameters, type of treatment offered and clinical outcome in an attempt to gain increased insight into this tumour in our local context.

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MATERIALS AND METHODS

All cases of breast phyllodes tumour, diagnosed for the first time at the Department of Pathology, University of Malaya Medical Centre in an 8-year period from 1st January 2004 till 31st December 2011 were retrieved from the Department of Pathology archives. The following information were obtained from either the histopathology request forms or the patients' medical records: patient's age, ethnicity, history of pregnancy, breast feeding, hormonal contraception (for a period of at least 12 months prior to diagnosis), family history of breast cancer (limited to first degree relatives viz parent, siblings or offspring), tumour laterality and tumour size. The type of surgery performed and follow-up details were also retrieved from the patients' medical records. For patients to qualify for entry into the study, they had to be followed for a minimum of 4 months following definitive surgical intervention at the University of Malaya Medical Centre except if the patient succumbed to the disease at an earlier date.

Following retrieval of the above data, all the histopathological slides of the cases which could be entered into the study were reviewed and classified according to the current World Health Organization (WHO) classification criteria into benign (Figure 1A), borderline (Figure 1B) and malignant (Figure 1C) categories.[6] The review also took into account any alteration in the classification from the original WHO classification system[7] which had been used earlier to classify the tumours. Surgical clearance was also assessed during the histological review. The surgical clearance was charted as the tumour being ≥10 mm or <10 mm from the nearest surgical resection margin based on the National Comprehensive Cancer Network's guidelines for breast cancers.[8] The histopathology slides were reviewed using an Olympus BX51 (Olympus, Japan) microscope. Statistical analysis was carried out using the Fisher exact test or Student's t-test with statistical significance set as $p < 0.05$.

RESULTS

In the 8-year period from 1st January 2004 till 31st December 2011, a total of 64 patients were histologically-diagnosed for the first time at the Department of Pathology, University of Malaya Medical Centre with phyllodes tumour. All the patients were females. Unfortunately, 33 cases had defaulted follow-up early and before 4 months following surgery and 1 case had concurrent infiltrating lobular carcinoma and could not be entered into the study. Finally 30 cases qualified for entry.

Of the 30 cases, 21 were categorised as benign, 4 borderline and 5 malignant according to the current WHO classification.[6] All the cases remained in the same categories as when classified under the earlier WHO classification system[7] and no case had to be re-categorised. Among the 30 cases, 13 patients were Chinese, 9 Malay, 7 Indian and 1 Indonesian. Amongst

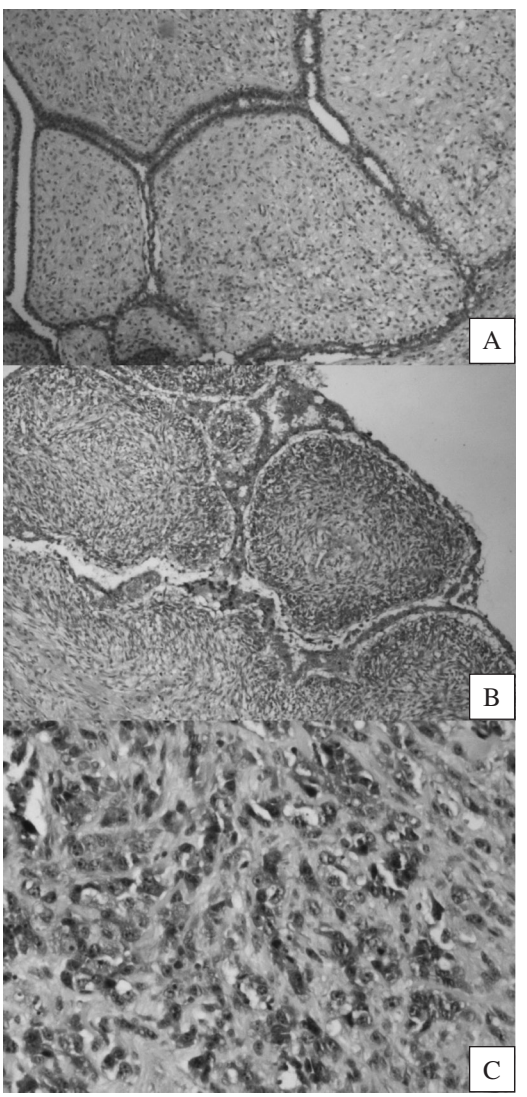

FIG 1: Phyllodes tumours with mildly (A) and moderately cellular (B) stroma compressing breast ducts in a characteristic intracanalicular pattern in a benign and borderline case respectively. (C) Malignant phyllodes tumour with cytological atypia, increased cellularity and stromal overgrowth. (Haematoxylin and Eosin stain x 100)

TABLE 1: Demographics of the benign, borderline and malignant phyllodes tumours (n=30)

		Benign n=21	Borderline n=4	Malignant n=5
Ethnicity				
	Chinese	8 (28.1%)	3 (75.0%)	2 (40.0%)
	Malay	9 (42.9%)	0 (0.0%)	0 (0.0%)
	Indian	4 (19.0%)	1 (25.0%)	2 (40.0%)
	Others	0 (0.0%)	0 (0.0%)	1 (20.0%)
Age (years)	Range	21-66	45-54	31-70
	Mean	43.4	49.8	47.2

the Chinese, 8 were benign, 3 borderline and 2 malignant while the Indians had 4 benign, 1 borderline and 2 malignant tumours. In contrast, all the phyllodes tumours in the Malays were benign. A marginal difference (p=0.049) was noted between the prevalence of benign versus combined borderline and malignant phyllodes tumours in the Malay and Chinese population but not amongst the Indians. The Indonesian patient had a malignant phyllodes tumour. The patients' ages ranged from 21-70 years with a mean of 44.9 years. Patients with benign tumours had an age range between 21-66 years (mean=43.4 years), borderline 45-54 years (mean=49.8 years) and malignant 31-70 years (mean=47.2 years) with no significant difference noted in the age of patients at presentation of benign, borderline or malignant phyllodes tumours. Table 1 illustrates the demographics of benign, borderline and malignant phyllodes tumours in this study.

The history of previous pregnancy, breast feeding, hormonal contraception, family history of breast cancer, tumour laterality and tumour size in benign, borderline and malignant phyllodes tumours are captured in Table 2. Pregnancy status, breast feeding, hormonal contraception, family history of breast cancer or location of tumour to the left or right breast were not significantly different between benign, borderline and malignant phyllodes tumour cases.

TABLE 2: History of previous pregnancy, breast feeding, hormonal contraception, family history of breast cancer, tumour laterality and tumour size of the benign, borderline and malignnat phyllodes tumours (n=30)

		Benign n=21	Borderline n=4	Malignant n=5
History of previous pregnancy	Yes	11 (52.4%)	2 (50.0%)	3 (60.0%)
	No	10 (47.6%)	2 (50.0%)	2 (40.0%)
History of breast feeding	Yes	8 (38.1%)	1 (25.0%)	2 (40.0%)
	No	13 (61.9%)	3 (75.0%)	3 (60.0%)
History of hormonal contraception	Yes	2 (9.5%)	1(25.0%)	1 (20.0%)
	No	19 (90.5%)	3 (75.0%)	4 (80.0%)
Family history of breast cancer	Yes	2 (9.5%)	0 (0.0%)	0 (0.0%)
	No	19 (90.5%)	4 (100.0%)	5 (100.0%)
Tumour laterality	Right	9 (42.9%)	2 (50.0%)	4 (80.0%)
	Left	12 (57.1%)	2 (50.0%)	1 (20.0%)
Tumour size (cm)	Range	1-16	4-29	4-30
	Mean	5.8	12.5	15.8

About equal number of patients were nulliparous, or had been previously pregnant in the benign, borderline and malignant categories. Thirty-eight percent of patients with benign, 25.0% with borderline and 40.0% with malignant phyllodes tumours had breast-fed previously while 9.5% of patients with benign, 25.0% with borderline and 20.0% with malignant phyllodes tumours gave a history of hormonal contraception. Two cases of benign phyllodes had a family history of breast cancer. Fifty-seven percent of the benign tumours were on the left and 80.0% malignant phyllodes were on the right while borderline tumours were distributed equally between the two sides. Malignant tumours averaged at 15.8 cm, borderline 12.5 cm and benign 5.8 cm in size at presentation, with malignant tumours and borderline tumours being significantly larger ($p<0.05$) at presentation compared with benign.

Table 3 shows the type of surgery, surgical clearance, local recurrence, metastases and period of follow-up for patients with the benign, borderline and malignant phyllodes tumours in this study. Local excision was carried out for 17 patients with benign, 2 borderline and 3 malignant phyllodes tumours. Simple mastectomy was carried out for one patient with benign and one patient with a malignant tumour while mastectomy with axillary clearance was performed in 3 of the benign cases, 2 borderline and 1 malignant phyllodes tumour. All lymph nodes were free of tumour involvement in cases where lymphadenectomy was carried out. Surgical clearance of ≥10 mm was documented in 5 benign phyllodes tumours while clearance of <10 mm was observed in 6 benign and all 4 borderline and 5 malignant phyllodes tumours. In 10 benign phyllodes tumour the surgical clearance could not be determined with certainty due to piecemeal removal of the tumour or unclear recording during the macroscopic examination and subsequent cut-up for histopathological examination. Local recurrence was noted in 2 benign cases 15 months and 49 months respectively following local excision. Both recurrences remained in the benign category. Information regarding surgical clearance was however not available in both these cases. A nodule in the lung, radiologically diagnosed as a metastasis, was detected in a case of malignant phyllodes tumour, 26 months after simple mastectomy. The patient underwent a course of radiotherapy and remained well during follow-up at our hospital. The patient was subsequently discharged and referred back to her home state hospital, 8 months after identification

TABLE 3: Type of surgery, surgical clearance, occurrence of local recurrence and metastases and the follow-up period of the benign, borderline and malignant phyllodes tumours (n=30)

		Benign n=21	Borderline n=4	Malignant n=5
Type of surgery	Local excision	17 (81.0%)	2 (50.0%)	3 (60.0%)
	Simple mastectomy	1 (4.8%)	0 (0.0%)	1 (20.0%)
	Mastectomy with axillary clearance	3 (14.3%)	2 (50.0%)	1 (20.0%)
Surgical clearance	≥10 mm	5 (23.8%)	0 (0.0%)	0 (0.0%)
	<10 mm	6 (28.6%)	4 (100.0%	5 ((100.0%)
	Not known	10 ((47.6%)	0 (0.0%)	0 (0.0%)
Locally recurrent	Yes	2	0	0
	No	19	4	5
Metastatic	Yes	0	0	2
	No	21	4	3
Period of follow-up (months)	Range	4-102	5-54	20-72
	Mean	44.2	26.5	43.6

of the lung nodule. For the cases in this study, the follow-up period ranged from 4-102 months with an average of 41.7 months. Among the benign tumours, the cases were followed up between 4-102 months (mean=44.2 months), borderline between 5-54 months (mean=26.5 months) and malignant 20-72 months (mean=43.6 months). No patient succumbed to the disease during the period of study.

DISCUSSION

Of the 30 cases of phyllodes tumours finally entered into the study, 21 (70.0%) were benign, 4 (13.3%) borderline and 5 (16.7%) malignant, the relative proportions of the 3 categories being similar to what is generally observed.[6] Interestingly, in our study all phyllodes tumours encountered among the Malay patients were of the benign variety in comparison with the Chinese and Indians in whom all 3 categories; benign, borderline and malignant varieties were encountered. This preponderance of the benign variant among the Malay cases in our study was significantly different from the pattern seen in the Chinese patients who had less benign lesions compared with combined borderline and malignant phyllodes tumours. Although the number of cases in this study is small and does not make it prudent for definite conclusions, various studies have indicated differences in phyllodes tumours associated with ethnicity[3,9] and this observation should be further verified in a larger study. The mean age at presentation of the cases was 44.9 years with no significant difference in mean age between the benign, borderline or malignant categories. It is notable that the age at presentation of phyllodes tumours in our patients appears more akin with that of "Western" populations than the younger age reported amongst Asian patients.[6]

Benign, borderline and malignant phyllodes tumours in this study did not demonstrate any association with pregnancy, breast feeding or hormonal contraception although loose associations with these factors have been alluded to before in some studies.[10-12] About 5-15% of breast cancers have a hereditary basis and the most commonly implicated are the Hereditary Breast and Ovarian Cancer (HBOC) syndrome involving mutations in the BRCA1 and BRCA2 genes and Li-Fraumeni syndrome resulting from germline mutation in TP53 with phyllodes tumours as one of the prominent tumours occurring in the latter.[13-15] Although Li-Fraumeni syndrome is most commonly quoted, other genetic alterations have also been implicated in phyllodes tumours.[16-18] The two cases of benign phyllodes tumour in this study with family history of breast cancer will require further in-depth investigation for clarification. As expected, the side of tumour location (left versus right breast) was not significantly different between benign, borderline and malignant tumours. As in other studies, malignant (mean size = 15.8 cm) and borderline (mean size = 12.5 cm) phyllodes tumours in this study also presented at a larger size compared with their benign counterparts with a mean size of 5.8 cm.[19, 20] Although this would usually reflect a more rapid growth rate of the more aggressive malignant and borderline tumours, it may also be worth considering if these larger more aggressive tumours transformed and progressed from smaller benign tumours.[21, 22]

In this study, the period of follow-up of the cases ranged from 4-102 months with a mean of 41.7 months. At this juncture, it is noteworthy to mention that of 64 new cases of phyllodes tumours diagnosed during the 8-year period of this study, 33 defaulted with follow-up less than 4-months following surgery. The reason for this is unclear but may be because the University of Malaya Medical Centre is a tertiary referral centre and patients who come from other parts of the country find it inconvenient to return for long-term assessment and follow-up. Surgery, which is generally advocated for phyllodes tumours, was the mainstay of management for the patients in this study. Although the optimal type of surgery is still debated, most agree that adequate surgical clearance is of more importance than the type of surgery in determining overall survival.[19, 23-26] It is unfortunate that information pertaining to surgical clearance was not available in the 2 benign cases which recurred after 15 months and 49 months respectively following local excision. The case of malignant phyllodes tumour who developed a radiologically-diagnosed lung metastasis had surgical clearance of <10 mm following simple mastectomy.

In conclusion, this study has provided a few valuable insights into phyllodes tumours in the Malaysian setting which may have clinical relevance, but which will require larger studies for proper confirmation. Firstly, the age at presentation does not seem to parallel the younger age reported amongst Asians. The Malays appear to be less prone to malignant phyllodes. Reproductive history does not seem to have a role in the development of malignancy, whereas

a genetic or hereditary basis is worthy of further investigation. Finally a large size at presentation should heighten suspicion of malignancy.

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