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RESEARCH COMMUNICATION

Phylloides Tumors in Adolescent Girls and Young Women in Pakistan

Amna Khurshid, Naila Kayani, Yasmin Bhurgri*

Abstract

The objective of this study was to determine the frequency of phylloides tumor (PT) in adolescent girls and young women (less than and equal to 25 years of age) and to define the clinico-pathological features of PT in this unusual clinical setting. This descriptive study was carried out at the Aga Khan University Hospital (AKUH) pathology department. All consecutive cases of PT diagnosed during the last sixteen years in the section of histopathology from 1st January 1990 to 31st June 2005 were included. Selection of cases was restricted to patients up to 25 years of age. A total of 42 cases of PT in up to 25 years of age were diagnosed. This comprised 11% of the total PT cases (total n=363). The number of benign (BPT), borderline (BLPT) and malignant (MPT) was identical i.e. 14 (33.3%) each. Clinically all cases presented with a solid, mobile, palpable mass. The mean age was 19.1 years (95% CI, 16.7-21.6), 21.9 years (95% CI, 20.7-21.9) and 19.7 years (95% CI, 17.2-22.3) in BPT, BLPT and MPT respectively. In majority of cases the surgical procedure performed was lumpectomy (50% of BPT, 78% of BLPT and 64% of MPT). High grade PT (BLPT and MPT) is an uncommon mammary tumor in adolescent girls and young women but seems to be occurring with increased frequency in the study population. This observation may indicate the biological behavior of PT in a high risk population, though chances of referral bias are also present. In view of the rarity of the disease, larger population studies are suggested to confirm our findings.

Key Words: Phylloides tumors - adolescent females - Pakistan

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Introduction

The phylloides tumor (PT) was first described by Mullaer in 1838 as a rare breast neoplasm of fibro-epithelial origin. Ever since then there has been a controversy regarding its nomenclature. It was previously called cytosarcoma phylloides but at present the WHO recommended term 'Phylloides Tumor' is largely used (WHO, 1981). These tumors are large, bulky, fast growing masses that originate from the intralobular stroma of the breast. PTs are histologically classified as benign (BPT), borderline (BLPT), or malignant (MPT) depending on cellular atypia, anaplasia, and degree of mitotic activity and infiltration. Overall, PTs account for less than 1% of all breast neoplasms (Tavassoli and Devilee, 2003) and are only very rarely seen in adolescent females. The average age of presentation is 40-50 years, around 15-20 years older than fibroadenomas (FAs) (Tavassoli and Devilee, 2003; Azzopardi, 1979; Chu et al., 1988). Malignant PTs develop on the average 2-5 years later than benign PTs. In Asians, however, PT occurs at a younger age, with an average of 25-30 years (Chua et al., 1988).

PTs are a group of biphasic tumors basically analogous to FAs, characterized by a double layered epithelial

component, arranged in clefts. The epithelial components are surrounded by an over-growing hypercellular mesenchymal component typically organized in leaf-like structures. The PT is usually benign but recurrences are not uncommon (Tavassoli and Devilee, 2003). Metastases are blood borne involving most frequently the lung and bones. Treatment protocols are dependent upon tumor categorization. This makes recognition of the entity important both for clinicians and patients. The biological behavior and prognosis of malignant PT is similar to sarcomas of the breast.

The presentation of PT is of a relatively large, movable, painless mass with a short history and rapid growth. The lesion lacks complete encapsulation and extends into surrounding tissue in multiple projections of different sizes. Thus assessment of the margins is important to predict the biological behavior of the lesion. Clinically PT is difficult to evaluate. On mammogram, PT appears well defined with a smooth and sometimes lobulated border. Fine needle aspiration (FNA) cytology is often diagnostic but may not include sufficient tissue for microscopic evaluation of these tumors; therefore, core biopsies are preferred. Complete evaluation of PT may require several diagnostic tools

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including gross examination, radiology and cytological or histological examination.

The objective of this study was to observe the frequency of PT in adolescent girls and young women (less than and equal to 25 years of age) and to define the clinico-pathological features of PT in this unusual clinical setting.

Materials and Methods

This descriptive study was carried out at the Aga Khan University Hospital (AKUH) pathology department. All consecutive cases of PT diagnosed during the last sixteen years in the section of histopathology from 1st January 1990 to 31st June 2005 were reviewed for the study. This included cases primarily diagnosed at AKUH pathology department and also second opinion slides of PT. Selection of cases was restricted to patients up to 25 years of age, though the frequency of all PT was also noted.

The incident cases of PT, ICD-O3 (WHO, 2000) categories M-9020 were categorized by the age of the patient and biological presentation of the tumor. All morphological and biological types were included, BPT, BLPT and MPT. Clinical and macroscopic information was taken from archived pathology reports. The reported data were rechecked. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, topography, morphology, grading and staging.

Originally all specimens had been fixed in 10% buffered formalin, grossed and representative sections taken according to established protocols. The sections had been routinely processed under standardized conditions for paraffin embedding. The sections had been cut and stained with hematoxylin and eosin (H&E) using a standard format incorporating all the relevant parameters.

The reviewed cases were initially evaluated on archived H&E stained sections and subsequently, where required immunohistochemical analysis was performed by employing envision technique. Immunohistochemical stains for desmin, smooth muscle actin, S-100 etc. were examined to further characterize the stromal elements. Only H&E slides were available for a few of the second opinion cases, thus limiting the use of immunochemistry in these cases.

The pathology department of AKU receives surgical specimens from AKUH, Karachi and through 84 AKU pathology laboratory collection points in Pakistan. It covers a large geographical area, with collection points located in all major cities like Karachi, Hyderabad, Multan, Lahore, Quetta, Peshawar, Islamabad, Rawalpindi, Larkana and also many rural locations.

The diagnosis of PT and its categorization into BPT, BLPT and MPT was based on established criteria recommend by WHO (WHO, 1981) to standardize with the classification in other parts of the world. The criteria used to classify histological types of PT included tumor margins (pushing to infiltrating), stromal cellularity (low, moderate, high) mitotic rate (per 10 HPF; <5, 5-9 and >10) and pleomorphism (mild, moderate and severe). Stromal

overgrowth was defined as stromal proliferation to the point where the epithelial elements are absent in at least 1 HPF (40X) (Mollitt DL et al, 1987). The data were analyzed using SPSS 13.0.

Quality control for diagnostic pathology is maintained through internal and external quality checks. External quality assurances for diagnostic pathology are maintained by the College of American Pathologists (CAP) surveys. Internal quality assurances are maintained by the use of histochemical stains, immunohistochemical techniques. Biological markers are used for malignancies, which necessitates cellular typing and sub typing. The departmental consensus committee confirms diagnosis.

Results

A total 42 cases of PT in up to 25 years of age were selected for the study. This comprised 11% of the total PT cases (total n=363). The number of BPT, BLPT and MPT was identical i.e. 14 (33%) each. Thirty three cases were primarily diagnosed at AKUH pathology department and 9 were second opinion slides of PT, originally diagnosed elsewhere.

Data for patient age and tumor size are given in Table 1. Clinically all cases presented with a single solid, mobile, palpable mass. In the majority of cases in all three categories of PT the surgical procedure was lumpectomy, which was performed in 50% of the cases of BPT, 79% of BLPT and 64% of MPT. Mastectomy was performed in 7% BLPT and 28% MPT, but in none of the cases of BPT. A clinical history of the surgical procedure performed was not available in 50% cases of BPT, 14% BLPT and 8% MPT. However the specimen received suggested lumpectomy as the surgical procedure performed. There was a marginal predisposition to develop PT in the right breast (BPT 70%; BLPT 66.7%; malignant 50.0%).

Microscopically tumor margins/borders were

Table 1. Phylloides Tumours in Karachi Comparative Studies

		Mean	Minimum	Maximum
Age	Benign	19.1 (95% CI, 16.7-21.6)	13	25
	Borderline	21.9 (95% CI, 20.7-21.9)	19	25
	Malignant	19.7 (95% CI, 17.2-22.3)	13	25
Size	Benign	6.5 (95% CI, 4.1-8.9)	1.5	14
	Borderline	8.9 (95% CI, 4.5-13.3)	2.0	19
	Malignant	11.0 (95% CI, 7.6-14.4)	5.0	19

Table 2. Comparison of Studies of Phylloides Tumours

Year	Authors	Total	Pathological Diagnosis (%)		
			BPT	BPLT	MPT
1983	Briggs et al	44	84.1	2.3	13.6
1987	Mollitt et al	5	80.0	-	20.0
1992	Vesely et al	4	100.0	-	-
1998	Prabha et al	45	75.6	17.8	6.6
2006	Current study	42	33.3	33.3	33.3

BPT, benign PT; BPLT, borderline PT; MPT, malignant PT

circumscribed in 46% of BPT cases. In BLPTs the borders were circumscribed (16%), pushing (18%), or infiltrating (6%). In the other 60% the border could not be assessed. For MPTs the border was infiltrating in 28% and unclear in the remainder. Among MPTs a single case each of chondroid differentiation, liposarcomatous change and osteosarcoma was seen.

The microscopic morphology of PT in adolescent and younger females was not distinguishable from PT that occurs in old age, in our study. Among various histological features stromal cellularity was mild in the majority of cases of BPT, moderate in BLPT and marked in MPT. The mean number of mitotic figures was 7/HPF (95% CI 3.0-11.8) minimum 4/HPF, maximum 17/HPF in BLPT and 13/HPF (95% CI 7.3-19) minimum 8/HPF, maximum 20/HPF in MPT. The mitotic activity was infrequent in BPT.

Discussion

The results of the current study indicate that there is an equal distribution of BPT, BLPT and MPT in the study population. As this is an uncommon breast tumor and very infrequent in the young age, no literature has yet been published for Karachi, and/or for Pakistan. There are very few international studies published on subject, thus restricting comparison (see Table 2).

In the series of cases up to 25 years of age published in 1998 by Prabha et al less stringent criteria were used to classify histological subtypes of PT. According to their criteria the mitotic rate for BPT, BLPT and MPT was 0-1, 2-5 and >5 per high power field (HPF), respectively, whereas we used the WHO classification which has a higher mitotic count for sub-categorization of PT i.e. <5, 5-9 and >10 per HPF for BPT, BLPT and MPT respectively. If we had used Prabha's criteria we would have had a much higher frequency of BLPTs and MPTs in our series. Thus we suggest that there is probably a more aggressive disease in our population.

The findings of Briggs et al (1983) also supported an excess of lesions with poorer prognosis in our population.

We also compared our data with a study in India (Inder et al, 2001) extending over a 20 year contemporary period, in a similar geographical area. Only 1 case of BPT was reported. Mollitt et al in 1987 reported a single case of MPT out of 5 PTs in their series of adolescent females, with a range of 13 to 18 years. The other 4 cases were BPTs. Vesely et al in 1992 presented 4 cases of PT all benign in their study of in-pubertal girls aged 11-15 years. Unfortunately, there have not been enough statistical numbers of studies or cases in studies to study this lesion more adequately. On the basis of the limited published data available for comparison, we suggest that we not only have a more aggressive disease, but also at a younger age. This is an important point to appreciate as WHO indicates that PT usually arises in the 4th or 5th decade and the MPT develops 4 to 5 years later than BPT.

We reached similar conclusions when our study was compared with other published studies. An article published

from Athens (Elshiekh et al, 2000) regarding breast tumors during adolescence showed that in a 22 years period there was only one case of PT. No explanation of the low frequency was given. The probable explanation that the upper limit of age in their study was 20 years, does not entirely explain the low frequency of BLPT and MPT. Histologically PT occurring in young women are indistinguishable from PT in older women (Prabha et al 1998).

FA is widely accepted as the most common neoplasm in adolescent girls (Prabha B et al 1998). Therefore FA comes in close differential diagnosis of BPT. It is difficult clinically to differentiate FA from BPT, except by histological confirmation. Though the size of the lesion is important for differentiation, it is not a very helpful parameter. The average size of juvenile fibroadenoma (JFA) in literature is 3.8 cm which is only slightly smaller than the mean size of BPT in our study i.e. 6.5 cms.

Tumor borders are important for the assessment of the malignant potential of PT. We could not assess the borders in some of the lumpectomy cases as in these cases we had received enucleated excision specimens and adjacent normal breast tissue was not available for. In cases where the margins could not be assessed the diagnosis was based on the other 3 recommended criteria.

A precise histopathological assessment of PT is essential, as the management depends on histopathology and the treatment of PT remains controversial. In the current study, lumpectomy was performed in all the cases of BPT, 78% of BLPT and 64% of MPT, this seems to be in line with advocated management. Most studies advocate that benign lesions can be managed with local excision (enucleation) using a cosmetic incision. Borderline or malignant cases should be treated with wide local excision (simple mastectomy) or re-excision to negative margins. Failure of complete excision results in local recurrence. Recurrence of PT is usually treated with further surgery. Since lymph node involvement is rare (10%) in MPT, axillary dissection may or may not be done. Axillary dissection is recommended only if nodes are palpable. When PT's metastasize, they usually do so through the blood vessels, with no lymph node involvement. Most common sites for metastatic growth are the lungs, bone, and abdominal viscera.

Benign tumors can be very aggressive in their growth and recurrence rates. Consequently, it has been suggested that all PT should be regarded as having a malignant potential. Life-time close follow-up is therefore mandatory. In our study we were unable to follow-up the patients, therefore are unable to determine the rate of recurrence, if any.

In conclusion, high grade PT (BLPT and MPT) is an uncommon mammary tumor in adolescent girls and young women but seems to be occurring with increased frequency in the study population. This observation may indicate the biological behavior of PT in a high risk population, though chances of referral bias are also present. In view of the rarity of the disease, larger population studies are suggested to confirm our findings.

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