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HISTOPATHOLOGICAL PATTERN OF RISK ASSOCIATED PROLIFERATIVE BREAST DISEASE AMONG WOMEN ATTENDING A REFERRAL CENTER IN KINGDOM OF SAUDI ARABIA

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ABSTRACT

***Background*:** Proliferative breast lesions (PBL) with or without atypia (PBLWA/PBLWOA) are a significant risk factors for breast Cancer.

***Aim*:** The aim of this study is to determine the histopathological pattern of risk associated PBLWA and PBLWOA among women attending King Abdulaziz University Hospital(KAUH).

***Settings and Design*:** This is study is conducted between Jan 2007 to Dec 2016 using breast specimens with histologically confirmed diagnosis of PBL

***Materials and Methods*:** Computerized data was filtered to identify target breast biopsies and specimens .Two pathologists separately reviewed the slides and reports of all patients with PBL to arrive at consensus. Updated diagnostic criteria were used for classification of PBL.

***Statistical Analysis*:** Data was analyzed using the program statistical package for social science version 15.0

***Results*:** The most common PBLWOA was multiple papillomas (MPLS 36 %) followed by usual ductal hyperplasia(UDH 31% . Both Atypical ductal hyperplasia and Atypical lobular hyperplasia were almost in equal frequency(50%).

Conclusion: MPLS was the most common PBLWOA followed by UDH with peak incidence between 40-49 years among women attending KAUH.

KEYWORDS : Proliferative, breast, atypia,sclerosis,hyperplasia

Introduction

The easy access and availability of radiological techniques such as mammography(MMG), ultrasound (US) and magnetic resonance imaging (MRI) of the breast along with the extensive use of percutaneous needle biopsies has made it possible to accomplish the diagnosis of proliferative breast lesions (PBL) without surgery in the majority of patients. The identification of proliferative lesions within the mammary terminal ducto-locular unit (TDLU) has outstanding prognostic and therapeutic implications as each of lesions is associated with a variable degree of risk of developing subsequent breast cancer (BC) combined with either an increased probability of finding cancer after surgery, a possible malignant transformation (to in situ or invasive cancer), or an increased probability of developing BC in the long term. Accordingly therapeutic implications may involve either surgical excision or abstention [1,2]. As such the management of these lesions is determined by the heightened risk of BC [3].

Proliferative breast lesions with or without atypia (PBLWA/PBLWOA) are a significant risk factors for BC, even when adjusted for the influence of demographic characteristics. The risks associated with different histological classifications of PBL have remained same across different races [1,2,4,5].

It is therefore essential for the practicing pathologist to recognize these lesions and render accurate and clinically relevant diagnoses. Better knowledge and understanding of such lesions would also enhance the ability of surgeons and oncologists to follow up such patients and prevent morbidity resulting from BC. Given the paucity of knowledge regarding the histopathological pattern of PBL among women in Kingdom of Saudi Arabia (KSA) we designed this study.

Aim

The aim of this study is to determine the histopathological pattern of risk associated proliferative breast lesions with and without atypia among women attending King Abdulaziz University Hospital between Jan 2007 to Dec 2016.

Materials and Methods

Study Setting and Design

This is a retrospective study conducted at King Abdulaziz University Hospital (KAUH), Jeddah, KSA between Jan 2007 to Dec 2016. Initially all surgical specimens for female breast were identified by performing a computerized search through the electronic archives of the Anatomic Pathology Department and were classified into benign and malignant diagnosis. From this all specimens with histologically confirmed diagnosis of PBL were identified to be studied further.

Materials and Methods

The database was filtered using appropriate Systematized Nomenclature of Human Medicine (SNOWMED) morphologic codes, to identify breast biopsies and cases were divided according to age groups. The specimens included those from both Saudi and Non Saudi patients. Two pathologists separately reviewed the slides and reports of all patients with PBL arrived at a consensus. One of the two pathologists is a breast pathologist. PBLs were classified into two diagnostic categories as : proliferative breast lesions without is a breast pathologist(PBLWOA), and proliferative breast lesions with atypia (PBLWA) based on Dupont and Page criteria with sub categorization from the most recent WHO classification of breast tumors [6,7]. Only independent pure forms of PBLWOA and PBLWA were included while those associated with preinvasive or invasive lesions were excluded. In instances when more than one PBL was observed in the same patient the most dominant pattern was scored in order to reflect the most reliable frequency of a particular lesion.

For the sake of common understanding the following diagnostic criteria were used to subcategorize PBL.

Usual Ductal Hyperplasia (UDH): Increased number of admixed epithelial, myoepithelial and metaplastic apocrine cells without architectural distortion or distension of duct was used to denote usual ductal hyperplasia. It was further sub classified into mild with epithelial proliferation three to four cell layer, moderate with epithelial proliferation more than four cell layers encompassing bridging of luminal space and florid with epithelial proliferation distending or obliterating the lumen. Variation in the appearances of epithelial cells and their nuclei was considered the most important distinguishing feature.

Solitary Papilloma(SP): Single intraductal, central papilloma characterized microscopically by formation of epithelial fronds that have both the luminal epithelial and the outer myoepithelial cell layers, supported by a fibrovascular stroma was considered as SP.

Multiple Papillomas(MPLS) : Papillomatosis or multiple papillomas were defined as a minimum of five clearly separate papillomas within a localized segment of breast tissue, usually in a peripheral or subareolar location.

Sclerosing adenosis (SA): Sclerosing Adenosis was considered as swirling lobulocentric,elongated and compressed glandular proliferation characterized by preferential preservation of myoepithelial cells and variable atrophy of epithelial cells, accompanied by lobular fibrosis and obliteration to cystic dilation of lumens. When presence of myoepithelial cells was doubtful on microscopic examination in hematoxylin and eiosin staining immunohistochemical marker such as p63 was used to highlight them.

Columnar Cell Change (CCC): CCC was used to denote thin, single or one to two cell deep epithelial layers composed of predominantly cuboidal to tall columnar cells distributed in a uniform patterm in variably and irregularly dilated glands. The nuclei of these cells were relatively large and oriented perpendicular to the underlying basement membrane and myoepithelial cells .The apical surfaces of the cells showed presence of cytoplasmic snouts.

Radial sclerosing lesions (RSLs) : Radial sclerosing lesions were considered as proliferative abnormalities with stellate configuration radiologically and histologically. Histologic structure characterized by a sclerotic center with a central core containing obliterated duct (s), elastin deposits, and mostly infiltrating tubules was considered as diagnostic criteria .

*Atypical Ductal Hyperplasia (ADH):*Small and focal ductal hyperplasias measuring less than 2mm in dimensions with characteristic partial structural or cytological features of DCIS (Ductal carcinoma in situ) intermingling with UDH were considered as atypical ductal hyperplasia.

Atypical Lobular Hyperplasia (ALH): This diagnosis was rendered using both quantitative and qualitative criteria. Quantitatively criteria included that less than 50- 75% of a lobule showing features of LCIS. Qualitatively, ALH was characterized by the presence, within one or more lobules or ductules, of abnormal cells similar to those found in LCIS accompanied by acinar expansion, but indistinct borders of individual acinar units or intralobular ductules.

Statistical Analysis

Data was analyzed using the program statistical package for social science version 15.0 (SPSS Inc., Chicago,IL, USA). Descriptive and frequency statistics were obtained for the variables studied. The procedures followed in the present study were in accordance with the ethical standards of the hospital ethical committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.The study was approved by the institutional "Ethics Committee on Human Experimentation and Research".

Results

A total of 1881 breast cases (1039 malignant, 769 benign and 74 atypical) were identified between Jan 2007 and Dec 2016.Among the benign category 416(22%) were classified as non proliferative while 353(19%) were classified as PBLWOA. PBLWA formed 74(4%). The most common PBLWOA was MPLS (N=127; 36 %) peak incidence 40-49 years, followed by UDH (N=109; 31%) peak incidence 40-49 years. The most common age group affected by PBLWOA in general was that of peri-menopausal and menopausal women *Table 1 A*. 303(86 %) of PBLWOA were unilateral lesions while 50(14%) were bilateral. Among the UDH 14 (13%) were classified as mild,65(60%) as moderate and 30(27 %)as florid. Both categories of PBLWA affected women in their fifth and sixth decade of life with equal frequency *Table1 B*. Except for a single case of CCC no other PBL were noted in less than 20 years of age group.A total of 199 (46%) patients among both PBLWOA and PBLWA together had more than one lesion. Different combinations were noted between the PBLWOA and PBLWA. The most frequent associations are presented in *Table 2*.Among the SP, 45 (78%) were present on core biopsies while their subsequent excision specimens demonstrated the association with other lesions. Crystalline intraluminal calcifications were seen among 19 (76 %) of CCC and 11 (30%) of SP and MPL taken together. Pure form of ADH was most common in the 6th decade 35% while ALH as most common in the 5th decade 35%.

Table 1 A) showing the age and form(pure v/s combined) distribution of PBLWOA among patients attending KAUH between Jan 2007 and Dec 2016

Age group	PBLWOA												
	MPLS N=137 (39%)		UDH N=109 (31 %)		SP N=58(16%)		SA N=30(8%)		CCC N=25(7%)		RSL N=4(1%)		TLIEAG
	P=82	C=55	P=71	C=38	P=29	C=29	P=10	C=20	P=7	C=18	P=2	C=2	
less than 20	0	0	0	0	0	0	0	0	0	1	0	0	1
20-29	2	3	8	2	3	1	2	2	2	2	0	0	27
30-39	22	15	14	8	3	7	3	7	1	6	1	1	88
40-49	25	12	28	18	10	14	4	6	3	6	1	0	127
50-59	20	5	18	7	11	3	1	4	1	3	0	1	74
60-69	10	12	2	1	1	4	0	0	0	0	0	0	30
More than 70	3	8	1	2	1	0	0	1	0	0	0	0	16

*PBLWOA: Proliferative breast lesions without atypia,UDH;Usual ductal hyperplasia, SP;Solitary papilloma, MPLS; Multiple papillomas, CCC; Columnar cell change, SA;Sclerosing adenosis, RSL; Radial sclerosing lesion, P:Pure form, C; Combined with others, TLIEAG: Total lesions in each age group

Table 1B) showing the age and form(pure v/s combined) distribution of PBLWA among patients attending KAUH between Jan 2007 and Dec 2016

Age group	PBLWA				
	ADH N=37 (50 %)		ALH N= 37 (50 %)		TLIEAG
	P=23	C=14	P=14	C=23	
20-29	0	2	1	0	3
30-39	7	3	1	6	17
40-49	6	3	6	7	22
50-59	8	5	4	3	20
60-69	2	0	1	5	8
More than 70	0	1	1	2	4

*ADH;Atypical ductal hyperplasia,ALH;Atypical lobular hyperplasia, P:Pure form ,C; Combined with others, TLIEAG:Total lesions in each age group

Table 2 showing the frequency of association of PBLWOA among patients attending KAUH between Jan 2007 and Dec 2016

PBL	CO EXISTING LESIONS
MPLS	38 UDH 16 FCC
UDH	38 MPLS
SP	9 SA 8 ADH 12 ALH
SA	9 SP 5 ADH 6 ALH
CCC	6 SA 5 ALH
RSL	1 ADH
ADH	8 SP 5 SA 1 RS
ALH	5 CCC 12 SP 6 SA

*PBL; Proliferative breast lesion,UDH;Usual ductal hyperplasia, SP;Solitary papilloma,MPLS;Multiple papillomas,CCC; Columnar cell change,SA;Sclerosing adenosis,RSL;Radial sclerosing lesion, ADH;Atypical ductal hyperplasia,ALH;Atypical lobular hyperplasia

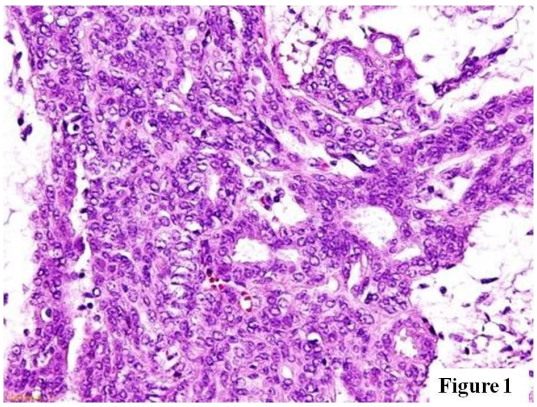

Figure 1: Usual ductal hyperplasia at 20x showing moderate mixed epithelial and myoepithelial cells proliferation encompassing bridging of luminal space

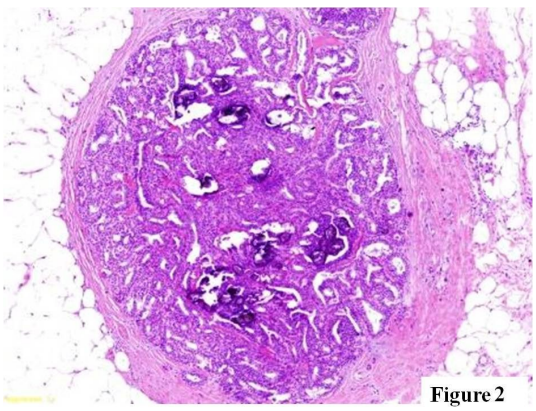

Figure 2: Solitary Papilloma at 20x showing formation of epithelial fronds that have both the luminal epithelial and outer myoepithelial cell layers, supported by a fibrovascular stroma .Note the presence of calcifications

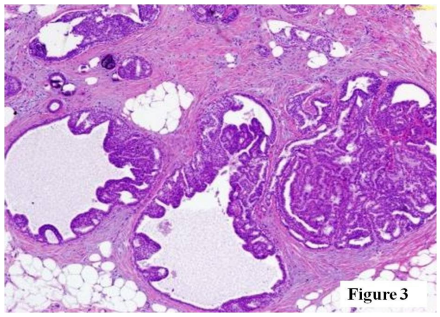

Figure 3: Multiple Papillomas at 20x showing five clearly separate papillomas within a localized segment of breast tissue composed of epithelial fronds that have both the luminal epithelial and outer myoepithelial cell layers, supported by a fibrovascular stroma

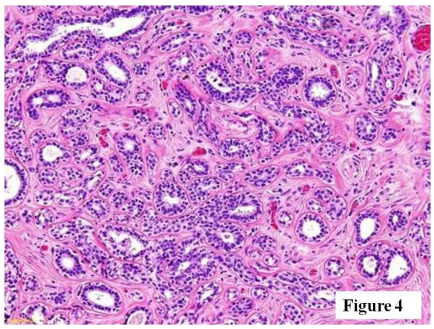

Figure 4 :Sclerosing adenosis at 20x showing elongated and compressed glandular proliferation with preserved myoepithelial cells and variable atrophy of epithelial cells.Note the presence of lobular fibrosis and obliteration to cystic dilation of lumens.

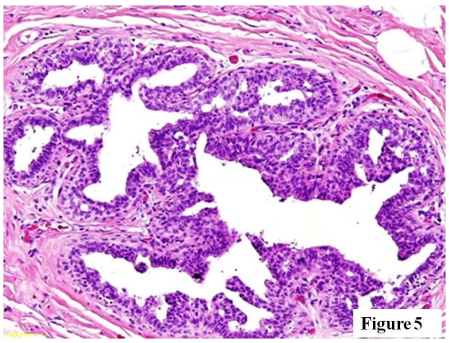

Figure 5:Columnar cell change at 20x showing two cell deep epithelial layers composed of uniformly distributed tall columnar cells predominantly with irregularly dilated glands.

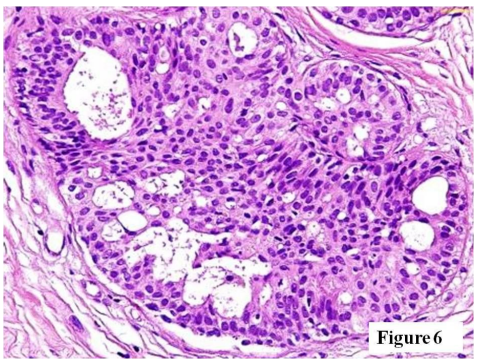

Figure 6: Atypical ductal hyperplasia at 20x showing small focal ductal hyperplasia with characteristic partial structural or cytological features of DCIS(red arrows) intermingling with UDH

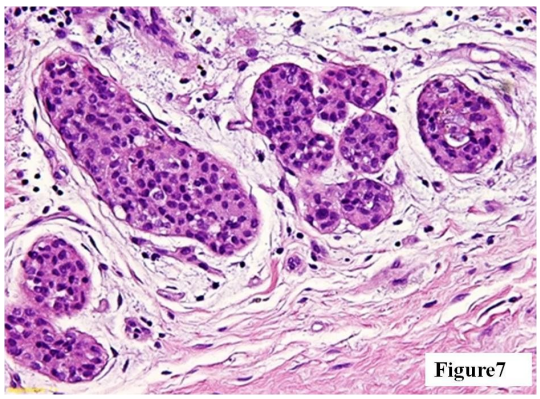

Figure 7: Atypical lobular hyperplasia at 20x showing the lobule partially occupied by abnormal cells accompanied by acinar expansion, but indistinct borders of individual acinar units

Discussion

There has been an increase in BC among Saudi women of different ages from 24.3% in 2005 to 27.4% in 2010[8,9].The most recent Saudi Cancer Registry report estimates the BC reports at 29.1% in 2013[10]. A recent study reported an incidence of 31.2 to 38.6% among women of age 45-59 and 30-44 years respectively [11]. Ibrahim et al. reported that the incidence of BC in KSA is expected to increase by about 350% by the year 2025 [12,13].In the light of these facts it becomes more important to further broaden our understanding of the risk factors that have been identified to contribute to the pattern of BC including PBL [7]. To the best of our knowledge so far, this is the first study reporting the histopathological pattern of PBL among women in KSA within the context of currently used international subcategorization and risk of BC [14] .PBL are very common among women of reproductive to middle age group [15] . A previous study from KAUH reported a frequency of 0.5 % for PBLWA and 9.3 % for PBLWOA (N=1504) with no other specifications [16].Comparatively this study reflects an increase in frequency of both PBLWA (4%) and PBLWOA(19%) , which can be partly explained by the easy access and availability of radiological techniques for diagnosis such as MMG,US and MRI along with the extensive use of percutaneous needle biopsies for the purpose of diagnosis and partly by the increasing awareness of BC and its risk factors in the region.

A large cohort study of benign breast disease demonstrated that women with atypical hyperplasia (AH) have a substantially increased risk of BC while those with PBLWOA have a modestly increased risk [5]. Another population based study showed a rate ratio of 4.56 for BC among women having PBLWA and a lower rate ratio of 3.58 among those with PBLWOA [17]. Castells X et al [17] found that although a family history of BC increased the risk of cancer in women with PBL it was not of any statistical significance. However other studies have reported statistically significant contribution of family history of BC in aggravating the risk further among women with PBL [2,18].

The type of PBL identified at biopsy is a major predictor of BC risk [19]. Large studies have proven beyond doubt that the magnitude of BC risk varies with the histological type of PBL [20-23]. In *Table 3* [5,7,18,20-30] we present the relative risk for BC among currently used sub-categories of PBL.In large cohort studies Collins et al [20] have re-demonstrated 4.5-fold increase in BC risk associated with a diagnosis of AH and a 1.6-fold increase with PBLWOA. Furthermore, when the risk is examined according to the type of atypia (ADH vs ALH), they reported that a greater elevation in risk is conferred by a diagnosis of ALH with OR(odds ratio), 6.6; 95% CI (confidence interval) 4.2-10 versus ADH with OR, 3.2; 95% CI, 2.1-4.7 .Similar findings were reported by, Zhou et al [18] in a meta-analysis evaluating BC risk among women with histologically confirmed benign breast disease.

Table 3.Relative risk of breast cancer among various categories of PBLWOA and PBLWA.

PBL	Relative risk of BC
Without atypia	
Intraductal proliferative lesions • Usual ductal hyperplasia (moderate/ florid) • Columnar cell lesion Intraductal papilloma • Large /solitary/central • Micropapillomas/multiple/peripheral	 1.5-2[7] 1.5[7] 2.04-2.1 [24] 3.01-3.54[24]
Sclerosing adenosis	1.91-3.3%[25]
Radial Scar	1.82[26,27]
With atypia	
Flat epithelial atypia	1.23-3.91[5,28,29]
Atypical hyperplasia • Ductal • Lobular	 2.1-4.7 [20-23,30] 4.2-10.3 [18,20-23,30]

* PBL; proliferative breast lesions, BC; breast cancer * Relative risk is the risk compared to women without any risk factors

They demonstrated an OR(odds ratio) of 5.14 for women with ALH (95% CI, 3.5-7.5) and an OR of 2.9 for women with ADH (95% CI, 2.2-4.0) [18]. Notably, this contrasts with data from the Mayo Benign Breast Disease Cohort, in which is no significant difference in BC risk was observed by the subtype of atypia ALH versus ADH [30]. A large multicenter cohort study by Kabat et al [5] and another cohort study by Hartmann et al [30] reported a stronger association of AH with BC among younger and premenopausal women compared to older and postmenopausal women. However the modifying effect of age or menopausal status on risk among women with PBLWOA remains less clear. Kabat et al [5] found no difference in risk among pre and post menopausal women with PBLWOA whereas Hartmann et al[30] reported a somewhat higher risk among women less than 45 years of age compared to women more than 55 years of age. In our study women having atypical lesions were post menopausal Table 1B.

We would like to make a special mention of the newly added category " flat epithelial atypia"(FEA). This proliferative columnar lesion with cytologic atypia now called "flat epithelial atypia" is described by multiple terms such as columnar alteration with prominent apical snouts and secretions and columnar cell lesion with atypia[28,31,32]. Several prior studies have evaluated the BC risk attributable to FEA with variable and inconclusive results and its relationship to AH and BC remains unclear. Another retrospective study by Martel et al [32] involving 1,751 core needle biopsies reported 63 FEA (3.6%) without associated BC or AH. Of note, in another retrospective study of 84 patients who had surgical biopsy with "pure" FEA (i.e. no AH or lobular neoplasia present), none developed subsequent invasive cancer after median follow up of 13.3 years [33]. Lack of evidence to support independent BC risk among women with "pure" FEA argues against it as a precursor of BC and thus, so far most of the previous studies are unable to answer the question of risk conclusively. This could probably explain why most of our regional pathologists are not currently using this diagnostic terminology.

SP may occur at any age from infancy to the ninth decade, but they are most frequent in the sixth and seventh decades of life. Women with MPLS tend to be younger than women with SP and most often present in their 40s and early 50s [34]. Contrary to the literature, in our study SP were most common in the fifth decade while the frequency of MPLS was noted across women in their 30s through their 60s. SP are considered markers of risk only when they are associated with atypia. Lewis et al [24] report that when atypia is associated this risk increases between 5.1 to 13.1 for SP. Therefore, if atypia is

encountered in a papilloma on an excisional biopsy, the surrounding breast tissue should be carefully examined [34]. MPLS are more likely to occur bilaterally and their probability of having an in situ or invasive carcinoma is higher than with the SP[34].

SA arises in TDLUs thus maintaining a lobulocentric pattern with closely proliferating epithelial cells nests which closely resemble that of insitu and invasive ductal BC making differentiation between the two difficult. SA is strongly associated with various PBL including UDH,SP and with calcification and apocrine changes [35]. The relative risk of BC might increase to 5.5, translating to a 1.2% risk per year of BC if atypia is associated with the SA [35].

The strength of this study was that histopatholological confirmation of all PBL ensured the quality of the histological classification among included cases using strict diagnostic criteria besides the consistent histopathologic review done by an expert breast pathologist. While this study is one of its kind among women in KSA, it has certain limitations. The fact that a good number of patients had more than one lesion could have led to imprecise quantitative estimates for some histological types of PBL causing some degree of detection bias. Small numbers of AH also restricted our ability to examine it in combination with other histological features. Lack of systemic follow-up limited the further study of appropriate BC risk assessment.

In conclusion MPLS (36 %) was the most common PBLWOA with peak incidence between 40-49 years, followed by UDH (31%) with peak incidence also between 40-49 years , among women attending KAUH. Both categories of PBLWA were noted with almost equal frequency (50%) with peak age between 50-59 years for ADH and 40-49 years for ALH. Larger prospective cohort studies need to be performed to follow up patients with PBLWOA and PBLWA in order to study the causal relationship of risk between PBL and BC risk.

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