

Histomorphological and immunohistochemical study of benign tumors and tumor like conditions of breast

¹Amrisha Jaiswal, Senior Resident, Department of Pathology, Dr. BC Roy Post Graduate Institute of Pediatric Sciences

²Nishi Tandon, Professor, Department of pathology, Era's Lucknow Medical College and Hospital

³Reeta Chaudhary, Junior Resident, Department of pathology, Era's Lucknow Medical College and Hospital

³Moniza Ilyas, Junior Resident, Department of pathology, Era's Lucknow Medical College and Hospital

²Nirupma Lal, Professor, Department of pathology, Era's Lucknow Medical College and Hospital

⁴Salim Tahir, Professor, Department of surgery, Era's Lucknow Medical College and Hospital

Corresponding Author: Nishi Tandon, Professor, Department of pathology, Era's Lucknow Medical College and Hospital, Lucknow, U.P.

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Abstract

Background and Objective: Breast cancer remains to be the most common malignant condition in the women yet majority of breast lesions are benign in nature. This study aimed to carry out a histopathological and immunohistochemical evaluation of benign breast disease including benign tumor and tumor like conditions, using S-100, and myoepithelial cytokeratin markers.

Materials and Methods: The present study was an Observational cross sectional study. Paraffin embedded specimen of breast tissue from the Lab of Department of Pathology, Era's Lucknow Medical College, Lucknow 4 ½ years (18 months prospective and 36 months

retrospective) starting from July 2013 to December 2017.

Results: Majority of cases were diagnosed as benign tumors (n=159; 75.4%) followed by inflammatory lesions (n=34; 16.1%) and benign breast disease (n=18; 8.5%) respectively. Among benign tumors, fibroadenoma (n=130; 81.8%) was the most common followed by phyllodes (n=11; 6.9%), gynecomastia (n=6; 3.8%), juvenile fibroadenoma (n=3; 1.9%), tubular adenoma, lactating adenoma, lipoma and nipple adenoma (n=2; 1.3% each). There was 1 (0.6%) case of duct papilloma too. Among 34 cases with inflammatory conditions, maximum (n=15; 44.1%) had chronic granulomatous mastitis followed by breast abscess (n=6; 17.6%), duct ectasia with adenosis, tubercular lesion and

acute on chronic inflammation (n=3; 8.8% each), fat necrosis (n=2; 5.9%) and pyogenic granuloma and eosinophilic granuloma (n=1; 2.9% each).

Conclusion: the present study revealed that hematoxylin and eosin (H&E) stain and histomorphological assessment is sufficient to rule out malignancy and determine the nature and type of benign breast conditions.

Keywords: Breast, Benign Breast Disease, Myoepithelial Cytokeratin, S100

Introduction

Although, breast cancer remains to be the most common malignant condition in the women yet majority of breast lesions are benign in nature. [1] The incidence of benign breast lesions begins to rise during the second decade of life and peaks in the fourth and fifth decades, as opposed to malignant diseases, for which the incidence continues to increase after menopause, although at a less rapid pace. [2] In different studies from India, the peak incidence of benign breast disease has been reported to take place between 21 and 40 years of age, [3,4] thus it mainly affects in the reproductive age group. The spectrum of benign breast conditions consists of fibroadenoma, phyllodes tumor, gynaecomastia, breast abscess, chronic mastitis, etc.. Evidence from clinical follow-up studies has indicated that there is a relationship between the presence of histologically proven benign breast disease and breast cancer risk and that the level of risk for development of breast carcinoma varies according to the histologic category of benign breast disease. [5] Hence, their early identification and management is quite essential. The majority of benign lesions are not associated with an increased risk for subsequent breast cancer, unnecessary surgical procedures should be avoided. It is important

for pathologists, radiologists, and oncologists to recognize benign lesions, both to distinguish them from in situ and invasive breast cancer and to assess a patient's risk of developing breast cancer, so that the most appropriate treatment modality for each case can be established. [6]

Triple assessment, which includes clinical examination, imaging and histopathological examination, is now considered the gold standard approach to the diagnosis of all breast lumps. [7] In the majority of cases, diagnoses of benign and malignant epithelial lesions of the breast are achievable using H & E microscopic sections alone. However, in some circumstances, such as in atypical and borderline breast lesions, as well as in core needle biopsy (CNB), this morphological distinction can be problematic. [8]

Although microscopic examination of the routine H&E-stained sections is the gold standard for the histopathological diagnosis of breast specimens, immunohistochemistry (IHC) remains an integral part of this process.[9]

Keeping in view the importance of immunohistochemical studies in differentiation, diagnosis and prognosis of benign breast disease the present study was planned out with an aim to carry out a histopathological and immunohistochemical study of benign breast disease including benign tumor and tumor like conditions, using S-100, and myoepithelial cytokeratin markers.

Materials & Methods

The present study was an Observational cross sectional study. The sample size was 328 were based on the on the study. [10] The study was done in the Department of Pathology, Era's Lucknow Medical College, Lucknow 4 ½ years (18 months prospective and 36 months

retrospective) starting from July 2013 to December 2017. All diagnosed cases of benign tumor and tumor like conditions including pre malignant conditions of breast were included in the study. All malignant tumors, inflammatory conditions, tumors associated with paraneoplastic syndromes and metastatic neoplasms and Immunocompromised patients were excluded from the study. Ethical clearance was taken from Institutional Ethical committee. (ELMC/R_cell/EC/2017/35).

All the specimens obtained were processed in the department. They were stained routinely with haematoxylin and eosin stain All the benign lesions were categorized into three categories as follows:

1. **Benign tumors:** These included fibroadenoma, phyllodes, gynecomastia, different types of adenomas, lipoma and papilloma.
2. **Inflammatory conditions:** These included cases of mastitis, abscesses, granuloma, chronic inflammation, necrosis and other like inflammatory conditions.
3. **Benign breast disease:** These included adenosis, hyperplasia, fibrocystic disease and other benign breast diseases.

The confirmation of diagnosis was done by two observers. In case of a disagreement regarding diagnosis between the two observers, or both the observers suspecting a malignant condition / coexisting malignant condition, immunohistochemistry was performed. Cytokeratin 5/6 and S100 [11] were performed on formalin fixed paraffin embedded tissue sections cut into approximately 4- μ m by streptavidin biotin method as per Protocol standardized in our laboratory.

For Cytokeratin 5/6 (LOT-AM1331112) and S100 (LOT-AM0580808) Mouse Monoclonal Antibody in PBS with carrier protein and preservative, Ready-to-use (Biogenex) and was used to detect Myoepithelium in

human breast tissue semi-quantitatively in high pH. This antibody labels and assesses cytokeratin and S100 in benign breast lesion.

For secondary antibody Dako REAL HRP RABBIT/MOUSE (ENV) was used.

Staining evaluation

STAINING INDEX (SI): It is calculated by *Intensity Proportion of immunopositive cells*; 0 No staining; 1+ Weak staining 1+ <10%; 2+ Moderate staining 2+ 10-50%; 3+ Strong staining 3+ >50% [11]

The data so obtained was fed into computer using MS-Excel software which was used for the purpose of statistical analysis.

Statistical analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean \pm SD. *Differences at P<0.05 will be considered significant*

Results

During the study period, a total of 328 breast tissue specimen were obtained at our Department, out of which 211 (64.3%) were taken as benign conditions. On yearwise assessment, maximum samples were obtained in the year 2016 (n=87/328; 26.5%) while minimum samples were obtained in the years 2014 and 2017 (n=55/328; 16.8% each). Maximum specimen of benign conditions were seen in the year 2016 (n=54/209; 25.8%) followed by year 2015 (n=53/209; 25.4%), year 2017 (n=37/209; 17.7%), year 2014 (n=35/209; 16.7%) and year 2013 (n=32/209; 15.3%) respectively. Proportionally, the detection rate for benign conditions was maximum in the year 2015 (73.6%) and minimum in the year 2013 (54.2%). On evaluating the data statistically, there was no significant difference in

detection rate of benign conditions in different years (p=0.234).

Distribution of cases according to age, gender and predominant clinical complaint at presentation was described (Table 1)

Table 1: Distribution of cases according to age, gender and predominant clinical complaint at presentation (n=211)

Sn.	Variable	No. of cases	Percentage
1.	Age (Years)		
	11-20 Years	72	34.1
	21-30 Years	76	36.0
	31-40 Years	40	19.0
	41-50 Years	18	8.5
	51-60 Years	5	2.4
	Mean Age ± SD (Range)	27.56±10.43 (11-60)	
2.	Gender		
	Female	205	97.2
	Male	6	2.8
3	Predominant clinical complaint		
	Lump	126	59.7
	Pain	52	24.6
	Tenderness	22	10.4
	Lump with heaviness	11	5.2

Right side was more commonly involved (n=106; 50.2%) as compared to left side (n=98; 46.4%). There were 7 (3.3%) cases with bilateral involvement. Majority of cases were diagnosed as benign tumors (n=159; 75.4%) followed by inflammatory lesions (n=34; 16.1%) and benign breast disease (n=18; 8.5%) respectively. Spectrum of cases according to diagnosis on H&E. (Table 2)

Table 2: Spectrum of cases according to diagnosis on H&E (n=211)

Sn.	Diagnosis	No. of cases	Percentage
1.	Benign tumors	159	75.4
	Fibroadenoma	130	81.8
	Phyllodes	11	6.9
	Gynecomastia	6	3.8
	Juvenile fibroadenoma	3	1.9
	Tubular adenoma	2	1.3
	Lactating adenoma	2	1.3
	Lipoma	2	1.3

	Nipple adenoma	2	1.3
	Duct papilloma	1	0.6
2.	Inflammatory lesions	34	16.1
	Chronic granulomatous mastitis	15	44.1
	Breast abscess	6	17.6
	Duct ectasia with adenosis	3	8.8
	Tubercular lesion	3	8.8
	Acute on chronic inflammation	3	8.8
	Fat necrosis	2	5.9
	Pyogenic granuloma	1	2.9
	Eosinophilic mastitis	1	2.9
3.	Benign breast disease	18	8.5
	Sclerosing adenosis	6	33.3
	Adenosis with hyperplasia	5	27.8
	Fibrocystic disease	5	27.8
	Atypical ductal hyperplasia	1	5.6
	Usual ductal hyperplasia	1	5.6

Mean age of patients with benign tumors was 25.91±9.82 years followed by those with inflammatory conditions (32.41±10.30 years) and benign breast disease (33.00±11.66 years). On evaluating the data statistically, mean age of patients with benign tumors was significantly lower as compared to that of patients with inflammatory and benign breast disease (p<0.001). For benign and inflammatory conditions majority of cases had involvement of right side whereas for cases clustered under benign breast disease majority had

involvement of left side. However, the association between side and type of benign breast condition was not significant statistically (p=0.663).

Most of the cases (n=197; 93.3%) could be diagnosed successfully using routine histopathology with the help of haematoxylin and eosin stain. There were 14 (6.63%) cases in which IHC was required to confirm the benign etiology. Assessment of suspicious cases under IHC evaluation with Staining Index (SI) (Table 3)

Table 3: Assessment of suspicious cases under IHC evaluation with Staining Index (SI)

S No.	Diagnosis	Total No. of cases (n=152)	No. of cases considered under IHC evaluation (%) (n=14)	CYTOKERATIN 5/6(SI) (n=14)	S 100(SI) (n=14)
1.	Sclerosing Adenosis	6	4(66.7)	All Cases SI= 9	3 Cases SI= 9 1 Case SI= 2
2.	Atypical ductal hyperplasia	1	1(100)	SI= 9	SI= 9
3.	Usual ductal hyperplasia	1	1(100)	SI= 9	SI= 6

4.	Juvenile fibroadenoma	3	1(33.3)	SI= 9	SI= 9
5.	Nipple adenoma	2	1(50)	SI= 9	SI= 6
6.	Duct ectasia with adenosis	3	1(33.3)	SI= 9	SI= 9
7.	Fibroadenoma	130	2(1.5)	Both Cases SI= 9	Case 1 SI= 6 Case 2 SI= 9
8.	Adenosis with epithelial hyperplasia	6	3(50)	All Cases SI= 9	All Cases SI= 9

The findings were in general suggestive of strong benign nature of the suspected lesions.

Discussion

During the blocked period (2013 to 2017), a total of 328 breast tissue specimen were obtained at Department of Pathology, Era’s Lucknow Medical College, Lucknow, out of which 211 (64.3%) were benign in nature, thus prevalence of benign tumors and tumor like conditions in our set-up was 64.3%. Similar to observations of present study, Albasri [12] in their study among western Saudi Arabian women reported the prevalence of benign breast conditions as 60%. Hiremath and Hegde [10] in their study reported prevalence of benign breast conditions to be 70.87%. On the other hand, Ahmed and Awal (2018) [13] in their study found benign conditions in 96.51% of women presenting to their clinic for evaluation of breast disease. In present study, annual incidence of benign tumor and tumor like conditions ranged from 54.2% (Year 2013) to 73.6% (Year 2015). However, there was no statistically significant difference in annual incidence of benign tumor and tumor like conditions during the blocked period. The findings in effect confirm that despite slight variation in annual prevalence, benign breast conditions comprised the major proportion of breast disorders thus reemphasizing the fact that benign conditions are more prevalent as compared to malignant conditions

In present study, age of patients ranged from 11 to 60 years. Majority of patients (70.1%) were ≤30 years of age. Only 5 (2.4%) patients were above 50 years of age. Mean age of women was 27.56 years. As compared to malignant diseases of breast which are reported to be more common in older and post-menopausal phase of women, benign conditions are more common in relatively younger age. Similar to observations of present study, Khanzada *et al.* [14] in their study also had majority of patients in ≤30 years age range (54.2%). Majority of patients in present study were female (n=205; 97.2%). Only 6 (2.8%) patients were males. Srivastava *et al.* [15] in their study had a high male representation (8.3%). Most of the other studies [13, 14, 16, 17] had only female patients in their study. In general, the studies show that male comprise a negligible proportion of total burden of benign diseases of breast as also observed in present study.

In present study, majority of cases presented with lump (n=126; 59.7%) followed by those presenting with pain (n=52; 24.6%), tenderness (n=22; 10.4%) and lump with heaviness (n=11; 5.2%) respectively. Similar to findings of present study, Saraswat and Vyas [18] also reported presence of a lump (58%), pain or discharge as the major presenting complaints of patients with benign breast

conditions. Hiremath and Hegde [10] also reported breast lump alone was the commonest symptom overall, seen in 329 patients (36.4%) followed by multiple symptoms seen in 254 patients (28.12%). In present study too, a number of patients presented with multiple conditions, however, only the chief presenting complaint was reported and coincided with the findings of previous studies too.

Right side was more commonly involved (n=106; 50.2%) as compared to left side (n=98; 46.4%). There were 7 (3.3%) cases with bilateral involvement. As far as side involved is concerned, though a higher predisposition of left as compared to right side has been reported for breast cancer [19], however, no such side-associated predisposition for benign conditions of breast has been reported. Incidentally, similar to present study, Albasri [12] too in their study found right side to be more commonly involved (49.2%) as compared to left side (45.3%) or bilateral involvement (7.5%) respectively. However, Srivastava *et al.* [15] found left side to be more commonly involved (46.67%) as compared to right side (35.83%) or bilateral involvement (17.5%) respectively.

In present study, majority of cases were diagnosed as benign tumors (n=159; 75.4%) followed by inflammatory lesions (n=34; 16.1%) and benign breast disease (n=18; 8.5%) respectively. Similar to our findings, Albasri who classified their cases into three – benign tumors, non-neoplastic conditions and inflammatory conditions also found dominance of benign tumors (52.9%) followed by non-neoplastic conditions (32.7%) and inflammatory conditions (13.9%) respectively. [12]

In present study, chronic granulomatous mastitis comprised the second most common condition

(n=15/211; 7.1%) followed by Phyllodes (n=11/211; 5.2%). They have been shown to comprise from 1.4% to 6.8% [12, 13, 20, 21] and from 1.6% to 5.4% [20, 15, 22] of benign conditions in different studies. Among different studies, the second and third positioned benign conditions have shown a considerable variability. Khanzada *et al* [14] in their study had fibrocystic disease (20.7%) and abscess (16.4%) as the next most common disease, however, in present study they comprised only 2.4% and 2.8% of study population. The present study did not find a significant association between between side involved and different benign tumor and tumor like conditions. No such association has either been reported in previous studies.

In present study, all the cases were histopathologically diagnosed cases of benign breast disease including both prospective as well as retrospective data. However, on review we found a total of 14 cases to have slight suspicion of malignant, for these cases IHC evaluation were done

Conclusion

The findings of present study thus showed that incidence of benign tumor and tumor like conditions among suspicious breast pathologies was quite prevalent in our setup. Among different benign conditions, fibroadenoma, inflammatory conditions and benign phyllodes were quite dominant. In general the benign conditions could be successfully confirmed using normal histomorphological assessment using haematoxylin and eosin stain only, however, certain conditions categorized under benign breast disease and other benign conditions required confirmation using IHC stains. However, none of the suspected cases turned out to be malignant on IHC, thus showing that H&E stain and histomorphological assessment is sufficient to rule out

malignancy and determine the nature and type of benign breast conditions

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