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Original Research Article

Histological variations in fibroadenoma of breast

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Abstract

Background: Fibroadenoma of the breast is a relatively frequently occurring tumor. Although often considered a benign tumour, several reports describe a higher risk of subsequent breast carcinoma in patients diagnosed with fibroadenoma. Increased risk depends on presence of complex changes within fibroadenoma, presence of hyperplasia and positive family history for breast cancer. But surprisingly not much literature is available on the variations within the fibroadenoma of the breast.
Aims and Objectives: Our main aim was to study the histological variations within the fibroadenoma of the breast. We also tried to identify those lesions with the possible risk of malignancy.
Materials and Methods: A total of 100 specimens of fibroadenoma of breast between May 2013 and April 2015 were studied at our institute. Slides were stained with Hematoxylin and Eosin (H & E) and were thoroughly reviewed. Slides were screened for proliferative epithelial changes, fibrocystic epithelial changes, stromal changes and various other changes such as foci of tubular adenoma and phyllodes tumour. Slides with invasive malignancies were excluded from the study.
Results: Mild hyperplasia was the commonest variation within the fibroadenoma. Complex hyperplasia was seen in older age groups.
Conclusion: Fibroadenoma is a common tumour of breast, more frequently occurring in 2nd and 3rd decade. Since malignant transformation is not seen or is extremely rare under 35yrs of age, only fibroadenomas in women above this age should be considered for excision biopsy.
Keywords: fibroadenoma, epithelial hyperplasia, intracanalicular, pericanalicular.

1. Introduction

Fibroadenoma of the breast is a relatively frequently occurring tumor. Women can present with fibroadenoma at any age, but the peak incidence is in the second and third decade. [1] Although often considered a benign tumor, several reports describe a higher risk of subsequent breast carcinoma in patients diagnosed with fibroadenoma.[2-4]

Fibroadenoma is a biphasic tumor, i.e. it is composed of an epithelial and a stromal component. The epithelial component of fibroadenoma can display similar aberrations as the epithelial component of the normal breast.

Dupont *et al* [5] assigned the term complex fibroadenoma to those fibroadenomas associated with sclerosing adenosis, epithelial calcifications, cyst formation and apocrine changes. Patients with such an association bear a higher risk of developing an invasive breast cancer.

Since there are clues that fibroadenoma indicates a higher risk of subsequent carcinoma and little is known about lesions occurring within and adjacent to fibroadenomas, the aim of this study was to make a thorough inventory of the histologic features of the epithelium and stroma within breast fibroadenomas in a large group of cases.

2. Material and Methods

All specimens of fibroadenoma of breast were subjected for histopathological examination in our institute. 100 consecutive specimens of clinically suspected and pathologically proven fibroadenoma of the breast in females were sectioned, processed and subjected for Haematoxylin and Eosin staining and included in

study. Slides were screened for proliferative epithelial changes (hyperplasia, carcinoma *in situ* [CIS], invasive carcinoma), fibrocystic epithelial changes (apocrine metaplasia, cysts, squamous metaplasia, sclerosing adenosis, microglandular adenosis, blunt duct adenosis, papilloma, lactational changes, calcifications), stromal changes (foci of pseudoangiomatous stromal hyperplasia, presence of smooth muscle, hyalinization, myxoid change), and various other changes such as foci of tubular adenoma and phyllodes tumor.

Informed consent of the patient for the present study was not required as it was a retrospective laboratory study.

3. Results and Analysis

3.1 Patients

A total of 100 specimens of fibroadenoma of breast processed between May 2013 and April 2015 in our department were studied.

The average age of the patients was 29.82yrs (range 18-52 years). About 80% were in 2nd and 3rd decade of their life which was extremely statistically significant (p= <0.0001).

Most of the patients (82%) presented with lump without pain in the breast. Few presented with lump with pain (18%).

Most of them were left sided (53) compared to right (47), but it was not statistically significant (p=0.5485).

The mean size of the fibroadenoma, expressed by the largest diameters varied between 1.0 and 8.0 centimeters, with a mean of 3.1 centimeters.

3.2 Histopathology

Slides were stained with hematoxylin and eosin (H&E) (on average 3) and were thoroughly reviewed. Fibroadenomas were classified as pericanalicular or intracanalicular when 90% of the tumor displayed that particular type of growth pattern. If neither type could be assigned to a tumor, it was diagnosed it as mixed histological type.

3.3 Changes within the fibroadenoma

The frequencies of histopathological changes found within the fibroadenomas are shown in Table No. 1. 46% of fibroadenomas were of the pericanalicular type, 37% were classified as intracanalicular and 17% were of the mixed histological type, but this difference was statistically insignificant.

In this series, hyperplasia was a common feature of fibroadenoma. Mild ductal hyperplasia was found in 26% of cases. Moderate ductal hyperplasia was seen in 2% and florid ductal hyperplasia in 1% of cases. Atypical ductal hyperplasia (ADH) was detected once, in same patient as florid ductal hyperplasia. All together, in 29% of fibroadenomas some form of hyperplasia was found. However, since in the otherwise normal breast an elevated risk for invasive carcinoma has been proven only for moderate, florid and atypical hyperplasia, we excluded mild ductal hyperplasia from further considerations.

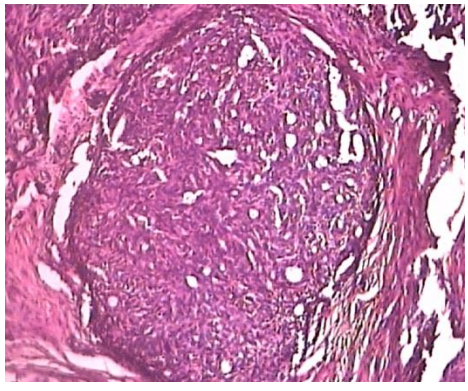

Figure 1: Florid ductal hyperplasia in Fibroadenoma

Within fibroadenomas, hyperplasia of higher grade than mild was found in 3% of fibroadenomas, and was present in older age groups (mean age 45.66 years), which is statistically very significant p <0.005(p=0.0013).

Lobular carcinoma *in situ* (LCIS) was not found in our series. However Ductal carcinoma *in situ* (DCIS) was seen in one (1%). Age of this patient was 50 years, which is significantly older than those without this lesion (p<0.0001).

The so-called complex features were frequently seen, apocrine metaplasia being most frequent (19.0%). Taken together, 29% of fibroadenomas in this series were complex. Seven (24.13%) of the complex fibroadenomas harbored more than one complex feature. None harbored more than two complex features. Complex fibroadenomas were seen more often at higher age (mean age 35.68 years), which is extremely statistically significant with a p value of <0.001(p =0.0009).

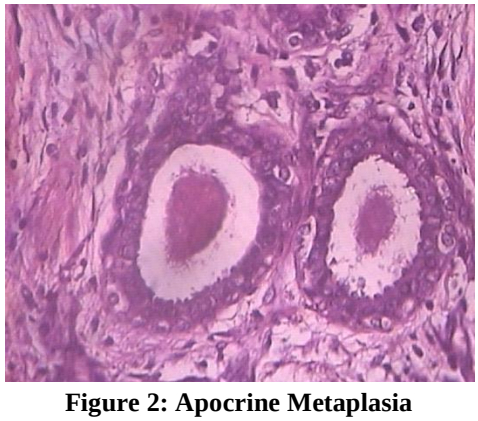

Figure 2: Apocrine Metaplasia

Stromal Hyalinization was seen in 18% of fibroadenomas. It was seen more often in older age groups (mean age 34.66 years), but was not statistically significant (p= 0.8058). Myxoid change in stroma was seen in 16% of fibroadenomas.

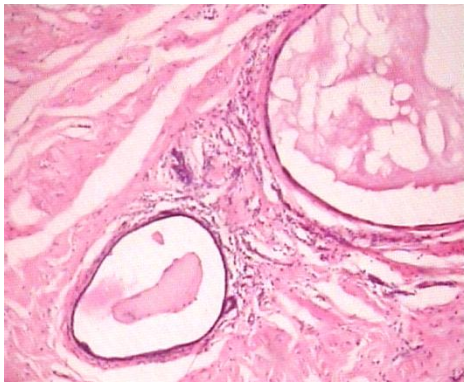

Figure 3: Cystic Change

In eight cases we observed foci of tubular adenoma. In one fibroadenomas we detected a part of the tumor which had to be classified as a focal phyllodes tumor, which was benign (Table 1).

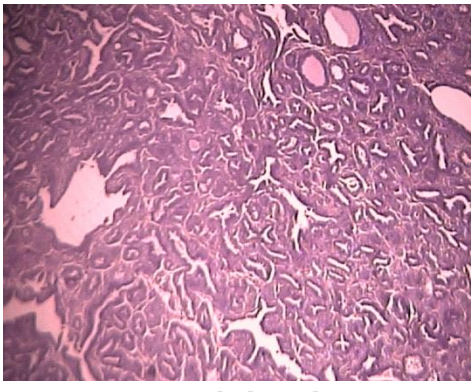

Figure 5: Tubular Adenoma

Table No.1: Frequency of histopathological changes within fibroadenoma

Lesion	No. of Cases
Proliferative Epithelial Changes	
Mild ductal Hyperplasia	26
Moderate ductal hyperplasia	2
Florid ductal hyperplasia	1
Atypical ductal hyperplasia	1
LCIS	0
DCIS	1
Fibrocystic epithelial changes	
Apocrine metaplasia	19
Cysts	14
Sclerosing Adenosis	3
Calcifications	0
Microglandular adenosis	5
Stromal Changes	
Myxoid Change	16
Hyalinization	18
Others	
Foci of tubular adenoma	8
Foci of phyllodes tumour	1

4. Discussion

This is the study reviewing in detail the histologic features of a large group of 100 fibroadenomas. Although fibroadenoma is associated with a higher risk for invasive breast cancer, few data on histological changes inside fibroadenomas were available in literature. We found that the fibroadenoma displays a large variety of histological changes, some of which are expected to be of importance.

On the whole, the fibroadenoma of the breast presenting in the 2nd and 3rd decade of life was 80%.

Fibroadenoma of the breast usually form during menarche (15-25yrs of age) [6], a time at which lobular structures are added to the ductal system of the breast. The mean age in our series was 29.82 yrs which was comparable with Carty N.J. *et al*. [7]

4.1 Histopathology

Fibroadenomas are considered to be an abnormality of normal development and involution. They are essentially an exhuberant overgrowth of elements thought to be derived from the terminal duct lobular unit, the epithelial component giving the impression of being compressed (‘intracanalicular’) or not (‘pericanalicular’) although the last distinction would appear to have no clinical relevance. [8]

Hyperplasia within fibroadenoma was frequently seen in this series, it was present in 29% of cases. It can be found at all ages. We cannot exclude the possibility of observer subjectivity, but we have been strict in using Page’s [9] criteria for hyperplasia and included an additional feature (dispersed myoepithelial cells) which, in our opinion, denies hyperplasia. Further, we excluded a hyperplasia like pattern which is caused by curling up of the epithelium of larger ducts when it is disrupted and detached. Dupont and Page [5] gave relative risks for hyperplasia in breast parenchyma ranging from 2 to 5. It is tempting to apply these relative risks to hyperplasia found within fibroadenomas, but nothing has been proven regarding this matter. However, if hyperplasia within fibroadenoma behaves in the same way as in the otherwise normal breast, it could make a contribution to the increased relative risk associated with fibroadenoma and may be a reason for excision. It is conceivable that part of the increased relative risk associated with complexity of the fibroadenoma, as described by Dupont *et al*[2], can be attributed to hyperplasia within the fibroadenoma since the presence of the former was correlated with presence of the latter in our study. Therefore, the meaning of hyperplasia within fibroadenomas in terms of progression risks remains to be determined. Dupont *et al* [2] found an incidence of 13.7%, which was associated with a relative risk of 3.9. Likewise, McDivitt *et al* [4] reported an odds ratio of 3.7.

Since most specimens did not meet the requirement of 0.5 cm² of surrounding tissue we couldn’t study the changes in surrounding tissue. In order to identify women with this risk factor, it would be preferable to include, if possible, a small rim of surrounding tissue when resecting a fibroadenoma.

A frequency of 1.0% for CIS within fibroadenoma was found. One case of DCIS was detected. However no case of LCIS was detected in our series. Few heterogeneous figures describing the occurrence of *in situ* and invasive carcinoma within fibroadenoma exist. Ozello and Gump[10] found an incidence of 0.3% for invasive and *in situ* carcinoma taken together and Deschenes *et al* [11] found one carcinoma *in situ* and one invasive carcinoma in 70 fibroadenomas (1.4% each). Further, Buzanowski *et al* [12] reported five cases of LCIS in 4000 fibroadenomas (0.1%). Our percentage seems similar, but this figure is nevertheless realistic (Table 2).

Table No.2: Histopathological variations in different series

	Present series	Kuijper *et al* [14]	Shabtai *et al* [20]
Mild ductal Hyperplasia	26%	11.6	
Moderate ductal hyperplasia	2%	26.8	
Florid ductal hyperplasia	1%	5.3	12.9%
Atypical ductal hyperplasia	1%	0.3	
LCIS	0%	0.8	0.6%
DCIS	1%	1.3	3.4%
Apocrine metaplasia	19%	28	16.3%
Cysts	14%	5.1	
Sclerosing Adenosis	3%	12.4	23%
Calcifications	0%	3.8	14.2%
Microglandular adenosis	5%	0.3	
Foci of tubular adenoma	8%	0.5	
Foci of phyllodes tumour	1%	0.8	

In our series, mean age of patients with CIS within fibroadenoma was relatively high (50 years), comparable to the study by Diaz *et al*. [13]

We could classify as many fibroadenomas as complex in comparison with Dupont *et al* [2], but less than Kuijper *et al* [14]. There is a tendency for complex fibroadenomas to occur at higher age.

Several authors have opted for conservative management of the fibroadenoma below a certain age. 25 years [15], 35 years [16] and 40 years [17] have been suggested as age thresholds. Another study demonstrated that a large proportion of fibroadenomas in women under 20 years of age will resolve. [18] In dealing with fibroadenoma, two problems need to be acknowledged. First, stroma and 'epithelium of the fibroadenoma itself can undergo malignant transformation. As underlined by this study, CIS arising within fibroadenoma is found mostly at older age. In our study the only patient with this lesion was 50 years of age. Therefore, removal of fibroadenomas in women over the age of 45 may tackle the problem of epithelial progression.

A criterion to distinguish between fibroadenoma and phyllodes tumor is rapid growth. Therefore, rapid growth in a tumor previously diagnosed as fibroadenoma should raise suspicion of stromal transformation (and possibly epithelial transformation). Malignancy arising within fibroadenoma should be treated as in the otherwise normal breast. Second, fibroadenoma is associated with a long-standing increased risk of invasive breast cancer. Depending on presence of hyperplasia in adjacent tissue, complexity of the fibroadenoma and a positive family history for breast cancer the RR may rise to 4, nearly twice the RR for women with a first degree relative with breast cancer. [19]

Since 45.0% of fibroadenomas harbor either complex features or hyperplasia in adjacent tissue, it would be ideal to remove all fibroadenomas in order to identify all women at increased risk for breast cancer. However, since fibroadenoma is a frequently occurring tumor often only seen on ultrasonography, this has major clinical implications. As long as it is unclear whether the indicated RR is high enough to have clinical consequences such as intensive follow-up or chemoprevention, there are no clear-cut arguments to advise removal of all fibroadenomas.

Of course, the diagnosis of fibroadenoma first needs to be established before a wait-and-see approach can be advised in individual cases. To this end, a triple diagnostic procedure including clinical investigation, mammography/ sonography and fine needle aspiration (FNA)/ needle core biopsy (NCB) can be useful [14]. The advantage of NCB over FNA may be that it more easily reveals complex changes and epithelial proliferations. Excision of fibroadenomas above the age of 35 years will remove all malignant lesions arising within fibroadenomas. Surveillance may be warranted for women with a known family history for breast cancer diagnosed with fibroadenoma with complex features or hyperplasia in adjacent tissue on NCB or excision. For this group, removal may not be necessary since the RR associated with such lesions appears to be bilateral and not specific to the site or the fibroadenoma.

5. Summary and Conclusion

Fibroadenoma is the most prevalent of the fibroepithelial tumours and is generally regarded as a benign tumour. It is common in 2nd and 3rd decade. Upper outer quadrant is the most commonly involved quadrant. Most of them present with lump in the breast. Left breast has got more incidence than the right.

Histologically, mild hyperplasia is the commonest variant within the fibroadenoma. Moderate and florid hyperplasia can also be present but in few of them and mostly in elderly age groups.

Large epidemiological studies relate the presence of fibroadenoma to an increased relative risk for invasive breast cancer. The mechanism for this association is unknown, but it seems to be related in part to microscopical features of the fibroadenoma.

Since malignant transformation of the epithelium of fibroadenomas is not seen or is extremely rare under 35 years of age, only fibroadenomas in women above this age should be excised.

References

[1] Foster ME, Garrahan N, Williams S. Fibroadenoma of the breast. *J R Coll Surg Edinb* 1988; 33:16-19.

[2] Dupont WD, Page DL, Parl FF, *et al*. Long-term risk of breast cancer in women with fibroadenoma. *N Engl J Med* 1994; 331:10-15.

[3] Carter CL, Corle DK, Micozzi MS, *et al*. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am J Epidemiol* 1988; 128:467-477.

[4] McDivitt RW, Stevens JA, Lee NC, *et al*. Histologic types of benign breast disease and the risk for breast cancer. *Cancer*. 1992; 69:1408-1414.

[5] Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med*. 1985; 312:146-151.

[6] Greenberg R, Skornick Y, Kaplan O. Management of Breast Fibroadenomas. *JGIM*. 1998; 13: 640-645.

[7] Carty NJ, Ravichandran D, Carter C, Royle GT, Rubin C, Taylor I. Management of Fibroadenoma of the breast. *Ann R Coll Surg Eng*. 1995; 77:127-130.

[8] Dent DM, Cant PJ. Fibroadenoma. *World J Surgery*. 1989; 13:706 – 710.

[9] Page DL, Anderson TJ, Rogers LW. Epithelial hyperplasia and carcinoma *in situ* (CIS). In: Page DL, Anderson TJ, eds. *Diagnostic Histopathology of the Breast.* Edinburgh, Scotland: Churchill Livingstone; 1987.p.120-92.

[10] Ozello L, Gump FE. The management of patients with carcinomas in fibroadenomatous tumors of the breast. *Surg Gynecol Obstet*. 1985; 160:99-104.

[11] Deschenes L, Jacob S, Fabia J, *et al*. Beware of breast fibroadenomas in middleaged women. *Can J Surg*. 1985; 28:372-374.

[12] Buzanowski-Konakry K, Harrison EG Jr, Payne WS. Lobular carcinoma arising in fibroadenoma of the breast. *Cancer*. 1975; 35:450-456.

[13] Diaz NM, Palmer JO, McDivitt RW. Carcinoma arising within fibroadenomas of the breast: a clinicopathologic study of 105 patients. *Am J Clin Pathol* 1991; 95:614-622.

[14] Kuijper A, Mommers EC, van der Wall E, van Diest PJ. Histopathology of fibroadenomas of the breast. *Am J Clin Pathol.*2001; 115: 736-742.

[15] Cant PJ, Madden MV, Close PM, *et al*. Case for conservative management of fibro-adenomas of the breast. *Br J Surg*. 1987; 74: 857-859.

[16] Wilkinson S, Anderson TJ, Rifkind E *et al*. Fibroadenoma of the breast: a follow up of conservative management. *Br J Surg*. 1989; 76: 390-391.

[17] Dixon JM, Dobie V, Lamd J, *et al*. Assessment of the acceptability of conservative management of fibroadenoma of the breast. *Br J Surg*. 1996; 83:264-265.

[18] Cant PJ, Madden MV, Coleman MG, *et al*. Non-operative management of breast masses diagnosed as fibroadenoma. *Br J Surg*. 1995; 82:792-794.

[19] Pharoah PDP, Day NE, Duffy S, *et al*. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer*. 1997; 71:800-809.

[20] Shabtai M, Malinger PS, Shabtai E, Rosin D, Kuriansky J, Megido MR. Fibroadenoma of the Breast: Analysis of Associated Pathological Entities – A Different Risk Marker in Different Age Groups for Concurrent Breast Cancer. *IMAJ* 2001; 3: 813-817.