PROSPECTIVE STUDY OF HISTOLOGICAL PROLIFERATIVE CHANGES IN ADJACENT AREAS OF BREAST CANCER

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ABSTRACT

BACKGROUND

Breast cancer remains a global health problem with an increasing incidence. Proliferative breast diseases are recognised as one of the risk factors in the development of carcinoma. This study was undertaken to know the frequency of proliferative lesions and other lesions in association with breast carcinomas in mastectomy specimens.

MATERIALS AND METHODS

100 cases of excised carcinoma breast sent to the Department of Pathology for a three-year period at tertiary care centre was thoroughly examined and changes adjacent to the tumour was recorded and tissue was subjected for histopathological examination and results tabulated.

RESULTS

Infiltrating duct cell carcinoma, Not Otherwise Specified (NOS) type was present in 89% of cases. Among the associated lesions, nonproliferative lesions constituted 16%, proliferative breast disease without atypia 29%, proliferative breast disease with atypia 10% and others 45%. Fibrocystic disease constituted 14% of cases, epithelial hyperplasia 15%, sclerosing adenosis 12% and atypical ductal hyperplasia in 10% of cases. Other types of associated lesions were duct carcinoma in situ in 4 cases.

CONCLUSION

Proliferative lesions adjacent to carcinoma breast were seen in 39% of cases. Fibrocystic disease, epithelial hyperplasia, sclerosing adenosis and atypical ductal hyperplasia being the commonest lesions adjacent to carcinoma breast in the present study.

KEYWORDS

Proliferative Lesions, Carcinoma Breast, Adjacent Tissue.

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BACKGROUND

Early detection of breast lesions continues to be an important goal in the management of breast cancer. Breast masses continue to be a source of dread for the patients and the treating surgeons with risk of cancer and the disfigurement it brings on surgery in spite of the cosmetic implants. Hormones play a major role in the development of breast cancer. Role of hormones involves their effects on breast cell proliferation and that this increased cell division is vital for the genesis of human cancer. During the adolescent and reproductive age, major hormonal changes result in the growth of the mammary tissue. This directly or indirectly influences the formation of the various breast lesions that commonly occurs that may or may not result later in a malignant change.

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AIM AND OBJECTIVES

Epithelial proliferative lesions extend from the common epithelial hyperplastic process, Ductal Hyperplasia of Usual Type (UDH) to high-grade Ductal Carcinoma in Situ (DCIS). Intermediary forms include intermediate and low-grade forms of DCIS and Atypical Ductal Hyperplasia (ADH). The lobular neoplastic epithelial proliferations, Atypical Lobular Hyperplasia (ALH) and Lobular Carcinoma in Situ (LCIS) form a similar parallel spectrum of risk lesions. Clinical followup studies have indicated that these intraductal proliferative lesions are associated with different levels of risk for subsequent development of invasive breast cancer that ranges from approximately 1.5 times that of the reference population for UDH, 4- to 5-fold (range, 2.4- to 13.0-fold) for ADH and 8-to 10-fold for DCIS. However, the overall biological significance of these lesions is unknown.[1,2,3,4] The role of the pathologist evaluating the specimens of breast mass is very vital and significant in not only differentiating between benign and malignant lesions,

but also to assess the potential risks associated with the various proliferating benign lesions giving an early warning for a follow up.

MATERIALS AND METHODS

100 cases of excised carcinoma breast sent to the Department of Pathology for a three-year period at tertiary care centre were included in the study. The specimens received were excision biopsies and mastectomy specimens. On grossing, the changes adjacent to the tumour were recorded and the tissue was subjected for histopathological examination. All the sections were stained routinely with Haematoxylin and Eosin and the results tabulated.

Inclusion and Exclusion Criteria

The total number of cases with carcinoma breast studied was 100 during this period. One case was of that of a male and the rest were from female. 59% of the cases were from the age group of 30-50 years. The youngest case recorded in the study was of 25 years and the oldest was that of a 72-year-old lady (Table 1A). Infiltrating duct cell carcinoma, NOS type was present in 89%; malignant phyllodes tumour was 4%, colloid carcinoma 2%, medullary carcinoma 2%, papillary carcinoma 1%, metaplastic carcinoma 1%, comedocarcinoma 1%, non-Hodgkin's lymphoma 1% and scirrhous carcinoma 1%. No cases of lobular carcinoma were recorded (Table 1B). Various changes were studied in the adjacent areas of cancer. They were broadly divided into 1) Non-proliferative breast disease, 2) Proliferative breast disease without atypia, 3) Proliferative breast disease with atypia and 4) other associated changes. Non-proliferative lesions constituted 16%, proliferative breast disease without atypia 29%, proliferative breast disease with atypia 10% and others 45% (Table 2).

RESULTS

Fibrocystic disease constituted 14% of cases, epithelial hyperplasia 15%, (Figure 1, 2, 3) sclerosing adenosis 12%, papillomatosis 2% and atypical ductal hyperplasia in 10% (Figure 5). Other types of associated lesions; DCIS was observed in 4 cases, fibroadenoma seen in 2 cases, intraductal papilloma was recorded in 1 case, papillomatosis 2, metaplasias were seen in 14 cases: squamous metaplasias in 2, 1 case showed chondroid metaplasia, 11 cases had apocrine change, (Figure 4). Calcifications were seen in 13 cases (Figure 5). Granulomatous reaction was seen in ten cases with one case with history of a previous lumpectomy. Duct ectasia seen in 1 case (Table 3).

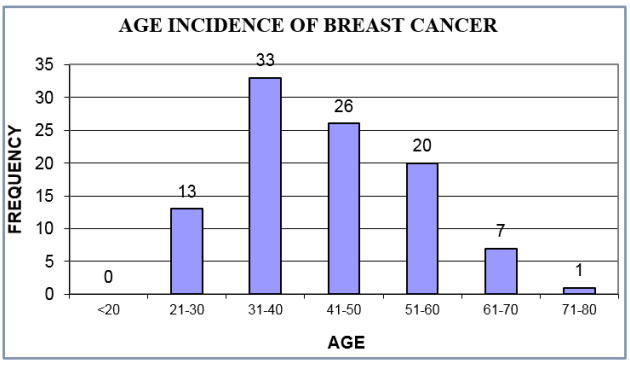

Table 1A

Malignant Tumours	Number of Cases	Percentage
Infiltrating duct cell carcinoma (NOS)	89	89
Medullary carcinoma	02	2
Colloid carcinoma	01	1
Comedocarcinoma	01	1
Papillary carcinoma	01	1
Metaplastic carcinoma	01	1
Malignant phyllodes tumour	04	4
Non-Hodgkin's lymphoma	01	1
Total	**100**	

Table 1B. Relative Frequency of Carcinoma Breast-100

Lesions	Number of Cases	Percentage
Nonproliferative lesions	16	16
Proliferative lesions without atypia	29	29
Proliferative lesions with atypia	10	10
Others	45	45
Total	**100**	**100**

Table 2. Associated Changes in Adjacent Tissue in Carcinoma Breast

Lesions	Number of Cases	Percentage
Nonproliferative lesions		
Fibrocystic disease	14	14
Adenosis	02	2
Proliferative lesions without atypia		
Epithelial hyperplasia	15	15
Sclerosing adenosis	12	12
Papillomatosis	02	2
Proliferative lesions with atypia		
Atypical ductal hyperplasia	10	10
Others		
DCIS	04	4
Fibroadenoma	02	2
Intraductal papilloma	01	1
Apocrine metaplasia	11	11
Squamous metaplasia	02	2
Chondroid metaplasia	01	1
Calcifications	13	13

Duct ectasia	01	1
Granulomatous reaction	10	10
Total	**100**	**100**

Table 3. Associated Changes in Adjacent Tissue in Carcinoma Breast

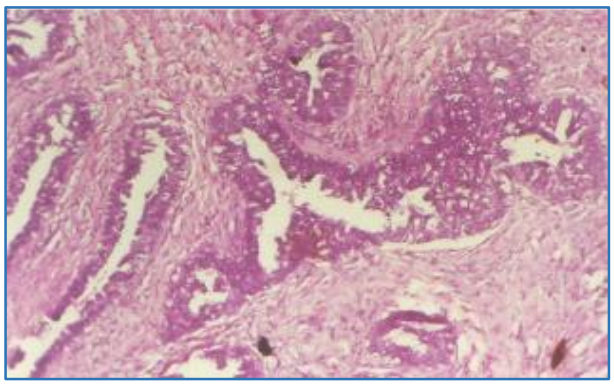

Figure 1. Microphotograph Showing Fibrocystic Disease with Moderate Epithelial Hyperplasia (H and E, 100X)

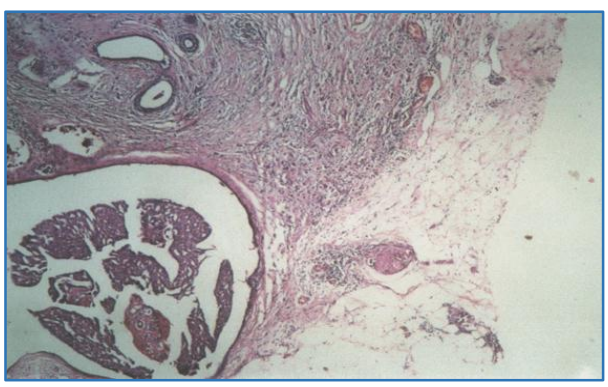

Figure 2: Microphotograph Showing Fibrocystic Disease with Florid Epithelial Hyperplasia (H and E, 100X)

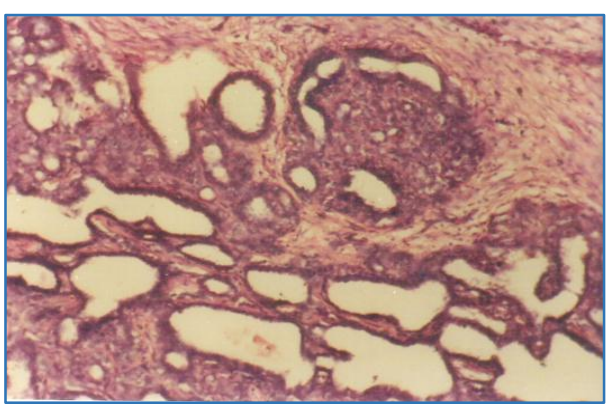

Figure 3. Microphotograph Showing Fibrocystic Disease with Atypical Ductal Hyperplasia (H and E, 100X)

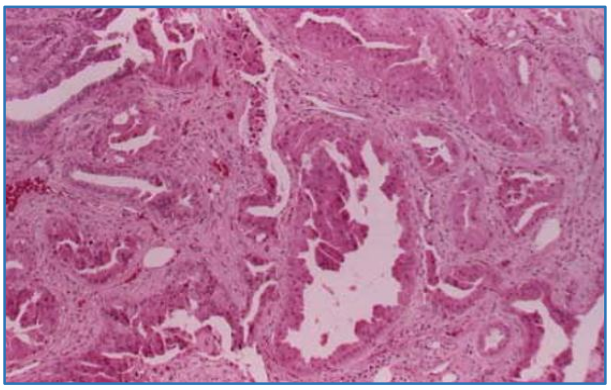

Figure 4. Microphotograph Showing Apocrine Metaplasia (H and E, 100X)

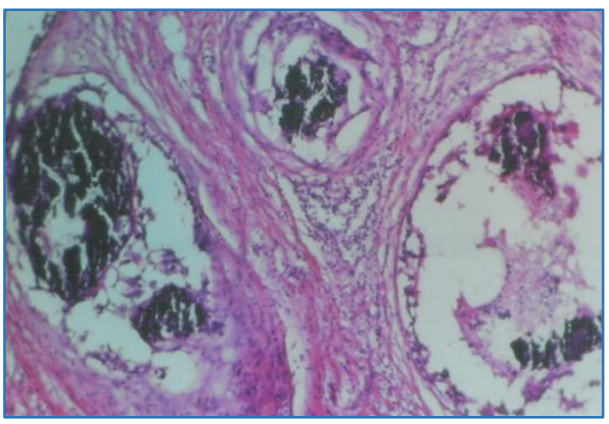

Figure 5. Microphotograph Showing Calcifications (H and E, 100X)

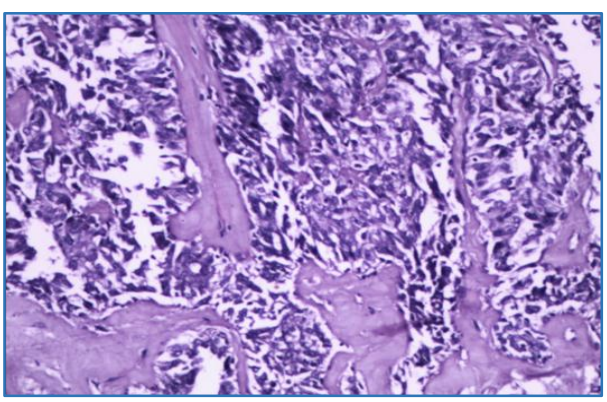

Figure 6. Microphotograph Showing Intraductal Papilloma (H and E, 100X)

DISCUSSION

Breast carcinoma is among the most common and lethal malignancies in women in western countries.[5] Because this malignancy is very common and difficult to treat, there is growing interest in studying early premalignant changes of invasive breast cancer to prevent and control this disease. The possibility of detecting precursor lesions of invasive neoplasms is of paramount importance from the diagnostic, prognostic and therapeutically points of view. An evidence favouring a direct relationship between benign and malignant breast lesions relied mainly on histological grounds where a coexistence and a continuum between these lesions are seen.[6,7]

It is still uncertain whether the pathogenesis of breast cancer can be assimilated to the multistep model of carcinogenesis according to which tumours develop and progress as a result of changes in oncogene and tumour suppressor gene loci. Women with proliferative breast lesions such as usual hyperplasia, atypical hyperplasia and in situ carcinoma have approximately 2-, 4- and 10-fold increased relative risks, respectively, of eventually developing invasive breast cancer.[8] Epithelial hyperplasia is characterised by increase in the number of cells in relation to basement membrane. It is classified as mild, moderate and florid hyperplasia. In mild epithelial cell proliferation, the epithelium is increased three to four layers. Moderate epithelial cell proliferation fills nearly 70% of the lumen and in florid - epithelial cell proliferation more than 70% of lumen shows clefts, papillomas, arches and bridges (Figure 2). Hyperplasia with atypical shows nuclear pleomorphic. Shashikala R et al[9] examined 100 cases of carcinoma with adjacent changes in the breast. The sections from the surrounding breast tissue showed proliferative lesions in 38 cases (38%) and nonproliferative lesions in 27 cases (27%). In the remaining 35 cases, there were no changes noted microscopically. Of these, 38 cases of proliferative lesions, 20 cases showed atypia and 18 cases did not show atypia. The 20 cases of proliferative lesions with atypia in the surrounding breast tissue had moderate epithelial hyperplasia in 9 cases and florid epithelial hyperplasia in 11 cases. Apocrine metaplasia, sclerosing adenosis and cystic change were noted in these cases along with epithelial hyperplasia (Figure 4). London SJ et al[10] observed nonproliferative lesions in 46 cases (38.0%), proliferative lesions without atypia in 48 cases (39.6%) and proliferative lesions with atypia in 27 cases (22.3%). Breast cancer risk was more strongly associated with atypical hyperplasia among premenopausal women than postmenopausal women. Hartmann LC et al[11] in their study identified that out of 9087 women 66.6% showed nonproliferative lesions, proliferative lesions without atypia in 29.6% and atypical hyperplasia in 3.6% of cases. In the present study, proliferative lesions without atypia were 29 (29%) and proliferative lesions with atypia were 10 (10%), 5 in association with fibrocystic change. Fibrocystic disease of breast is one of the commonest diseases affecting women in age group of 30-50 yrs. Traditionally, the disease has always been described as benign in nature with very low or almost no potential to develop into a malignant lesion. However, studies now reveal that not all cases of fibrocystic disease are absolutely benign, but a select few can progress to malignant transformation.[12] The disease has been reported to be present and undergo malignant change even in males.[13] Fibrocystic disease of breast can be divided into nonproliferative and proliferative patterns. Nonproliferative patterns are associated with cystic changes and fibrosis.[14] The lesions are characterised by increase in fibrous stroma associated with dilatation of ducts leading to cysts, which may either be single or multiple varying in size ranging from 1 cm to 5 cm. Multiplicity of cyst and recurrent disease, apocrine metaplasia, atypical ductal hyperplasia and sclerosing adenosis are important determinants for malignant transformation in a patient suffering from fibrocystic disease of breast.[15,16] In the present study, fibrocystic disease (Figure 1) constituted 14% of cases, 3 with focal atypical ductal hyperplasia (Figure 3). One of the case showed an intraductal papilloma adjacent to it (Figure 6). Sclerosing Adenosis (SA) is a common proliferative lesion of the breast, which as a single feature, conveys an approximate doubling of breast cancer risk. Its role in breast carcinogenesis remains undefined; its presence may aid in risk prediction for women after a breast biopsy. SA was present in 62.4% of biopsies with proliferative disease without atypia and 55.1% of biopsies with atypical hyperplasia. The presence of SA stratified risk in subsets of women defined by age, involution status and family history. However, SA does not further stratify risk in women diagnosed with other forms of proliferative breast disease either with or without atypia "which implies the relative cancer risk of 1.5 to 2.0 times.[17] In the present study, there are 12 cases of sclerosing adenosis associated with carcinoma with a peek incidence in the age group of 31-40 years.

R. Ali-Fehmi[18] in a study of 28 patients with breast lesions characterised by presence of Multiple Papilloma (MP) found Atypical Hyperplasia (AH) in 12 of 28 cases. Proliferating epithelium may project as multiple small papillary excrescences into ductal lumen classically describes as ductal papillomatosis. These changes can be malignant precursors. In few cases, the hyperplastic cells have features resembling carcinoma in situ. Such lesions can be described as atypical ductal hyperplasia. Both atypical ductal hyperplasia and lobular hyperplasia are associated with increased risk of invasive cancer. We observed papillomatosis in 2 cases and atypical ductal hyperplasia in 10 cases. Fibroadenomas associated with cysts, epitheliosis, sclerosing adenosis, papillary apocrine changes are described as "complex" fibroadenomas. These have a long-term risk for developing breast carcinoma. The relative risk increased to 3.1% among patients with complex fibroadenomas and remained elevated for decades after diagnosis. Patients with a family history of breast cancer in whom such fibroadenoma were diagnosed had a relative risk of 3.72 compared to general population. Patients with benign proliferative disease in the parenchyma adjacent to the fibroadenoma had a relative risk of 3.88.[19] In our study, 2 cases of fibroadenoma were recorded with one patient aged 40 years showing extensive florid epitheliosis was associated with invasive ductal carcinoma NOS type. The other case aged 46 years showing calcifications and was associated with cystosarcoma phyllodes in which the epithelial elements were benign, but the stromal tissue was malignant. DCIS has been linked to subsequent invasive carcinoma by various studies. In most women, CIS and subsequent invasive cancer showed the same morphological (i.e., ductal or lobular) features. The cumulative risk of breast cancer was 16%, 10 years after DCIS was diagnosed thus emphasising the importance of adequate surveillance of women with DCIS of the breast. DCIS is present in 80%

of invasive breast cancers with morphological similarities to invasive carcinoma.[20,21] In our study, there were only 4 cases of DCIS. This low incidence might be related to the fact that in our study 96% of the cases presented in late stages of cancer. Introduction of mammographic breast screening has increased many fold in incidence rates of Carcinoma in Situ (CIS) of the breast and as a proportion of new breast cancers following them.

CONCLUSION

Fibrocystic disease, epithelial hyperplasia, sclerosing adenosis and atypical ductal hyperplasia were the commonest lesions adjacent to carcinoma breast. Proliferative lesions in the breast are recognised as one of the risk factors in developing breast carcinoma.

In the present study, proliferative lesions without atypia was seen in 29% of cases and proliferative lesions with atypia in 10% of cases of carcinoma breast. All cases of proliferative lesions in the breast carry an increased risk especially when there is atypia. Women who have been diagnosed as having proliferative breast disease require careful follow-up with annual mammographic screening being mandatory for women with atypical hyperplasia.

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