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Original Article

Study of CK5/6 in Benign and Malignant Breast Lesions

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Abstract
Background: *The presence or absence of a myoepithelial cell layer around carcinoma cells is the basis for dividing tumors into in situ and invasive types. Cytokeratin (CK) is a family of intracytoplasmic intermediate filament proteins present in almost all epithelial cells, which can be used to identify these myoepithelial cells and thus differentiate benign from malignant lesions. Moreover, If CK positivity is seen in malignant lesion, it indicates a basal type of carcinoma and have bad prognosis.*
Aims: *The present study is designed to differentiate Benign Lesions and Malignant lesions and detect basal like carcinomas*
Material and Methods: *This is a Cross – Sectional, Laboratory based comparative type of observational study in which immunohistochemical staining for cytokeratin 5/6 was applied on paraffin embedded sections of 100 breast lesions using avidin biotin peroxidase technique. The distribution and intensity of staining was recorded and graded semi quantitatively.*
Results: *There were 50 cases of benign lesion, all of which were positive for CK5/6 except two cases of lactating adenoma. The malignant lesions comprised eleven cases of ductal carcinoma in situ (DCIS) and 39 cases of infiltrating carcinoma, not otherwise specified, IDC (NOS). None of the DCIS cases showed a positive immunoreaction but 19 cases of IDC were positive for CK5/6. The staining reaction in the malignant lesions was significantly less than that of benign lesions.*
Conclusion: *The majority of carcinoma arising in women with BRCA 1 mutation are 'basal like. 'Due to high proliferation and rapid growth, they carry an adverse prognosis. CK 5/6 can be used to identify these basal like subgroup and thus by screening there family members with BRCA1, prophylactic measures can be taken at an early stage..*
Keywords: *CK, DCIS, IDC.*

Introduction

Cytokeratin (CK) is a family of intra cytoplasmic intermediate filament proteins present in almost all epithelial cells. Expression of each CK molecule depends on cell type and differentiation status, thus CKs can be markers to identify

particular type of epithelial tumours.[1]The presence of the myoepithelial cell (MEC) in intimate relationship with the epithelial cells of the lesions is what differentiates in situ from invasive disease. The proliferated luminal cells in benign lesions show a large number of CK5/6 positive cells because of proliferation of both glandular and basal cells. Most malignancies are derived from differentiated glandular cells and do not reveal immunochemical staining with CK5/6.[2,3]

Material and Methods

This is a Cross – Sectional, Laboratory based comparative type of observational study in which immunohistochemical staining for cytokeratin 5/6 was applied on paraffin embedded sections of 100 breast lesions using avidin biotin peroxidase technique. The distribution and intensity of staining was recorded and graded semi quantitatively (Table1)

Results

The present study included 100 cases of Breast neoplasm out of which 50 were Benign and 50 were malignant.Maximum number of benign cases were of fibroadenoma (54%) (table 2). All the benign lesions were positive for CK5/6 with the staining index 6-9 except for two cases of lactating adenoma. (Table 2)

There were 38 cases of IDC, 11cases of DCIS and 1 case of medullary carcinoma. All the cases of DCIS were immune negative for CK5/6 staining.18 cases of IDC and one case of medullary carcinoma showed positivity for CK5/6 but had staining index less than benign lesions in most of the cases (Table 3). Maximum CK5/6 positive cases of infiltrating carcinoma had age below 50 yrs (89%), tumor size >2 cm (95%) and histological grade 2or3(85%). Morever majority of CK5/6 positive cases of IDC had nodal involvement, lymphovascular invasion and necrosis. 75 % of triple negative cases were CK5/6 positive & 63% cases of CK5/6 positive infiltrating carcinoma were triple negative.

Table1: CK5/6 Staining Index

Intensity	Proportion of immunopositive cells
0=No staining	
1+=Weak staining	1+=<10% cells
2+=Moderate staining	2+=10-50% cells
3+=Strong staining	3+=>50% cells

Table 2: CK5/6 positive cases in Benign Breast Disease

S.No.	Lesions	Total cases	Positive	Negative
1	Fibroadenoma	27	27 (100%)	0
2	Fibrocystic disease	11	11 (100%)	0
3	Duct Ectasia	3	03 (100%)	0
4	Lactating Adenoma	2	00 (0%)	2(100%)
5	Usual Ductal Hyperplasia	7	07 (100%)	0
Total		50	48	2

Table 3: CK5/6 positive cases in Malignant Breast Disease

S.No.	Lesions	Total number of cases	Positive CK5/6	Negative CK5/6
1	Ductal Ca In Situ	11	00 (0%)	11 (100%)
2	Infiltrating Ductal Carcinomas	38	18 (47.4%)	20 (62.6%)
3	Medullary Carcinoma	1	1 (100%)	00(0%)
Total		50(100%)	19 (38%)	31 (62%)

Table 4: Comparison ofCK5/6 positive cases in Benign Breast Disease

	Akhtar et al	Bhalla et al	Present study
Fibrocystic	6/6(100%)	12/12(100%)	12/12(100%)
Fibroadenoma	20/20(100%)	9/9(100%)	27/27 (100%)
Duct ectasia	8/8(100%)	1/1(100%)	3/3(100%)
Lactating adenoma	0/0	0/1 (0%)	0/2 (0%)
UDH	4/4(100%)	0/0 (0%)	6/6 (100%)
Total	38(100%)	21/23 (95.3%)	48/50 (96%)

Table 5: Comparison ofCK5/6 positive cases in Malignant Breast Disease

	Akhtar et al	Bhalla et al	Ding et al	Present Study
IDC	6/22	6/22	0/19	18/38
DCIS	0/18	0/3	0/19	0/11
Medullary carcinoma	0	0	-	1/1
Total	40	25	38	50

Table 6: Comparison of CK5/6 positivity in triple negative cases of breast carcinoma

	Akhtar et al	Pillai et al	Present Study
Triple Negative	6/6 (100%)	13/18 (72.2%)	11/17 (64.7%)

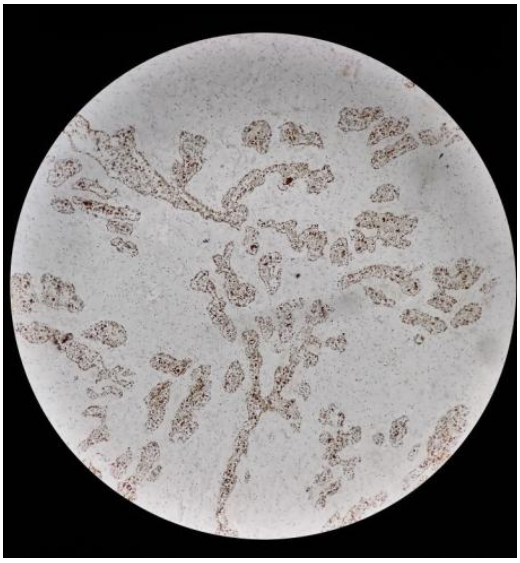

Figure 1: Immunohistochemical staining with CK5/6 in a case of fibbroadenoma

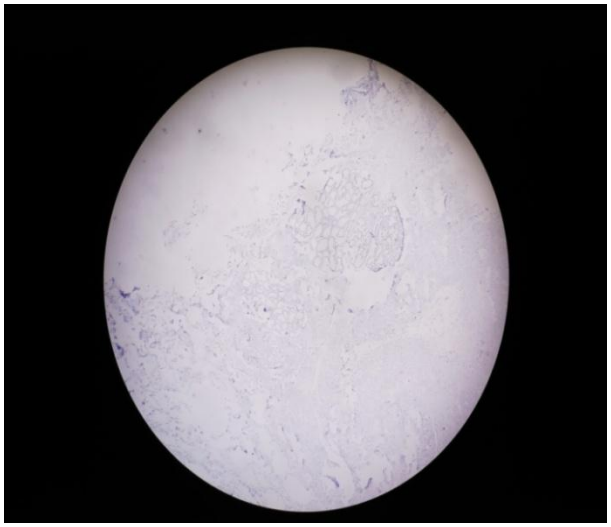

Figure 2: Immunohistochemical staining with CK5/6 in a case of Lactating adenoma

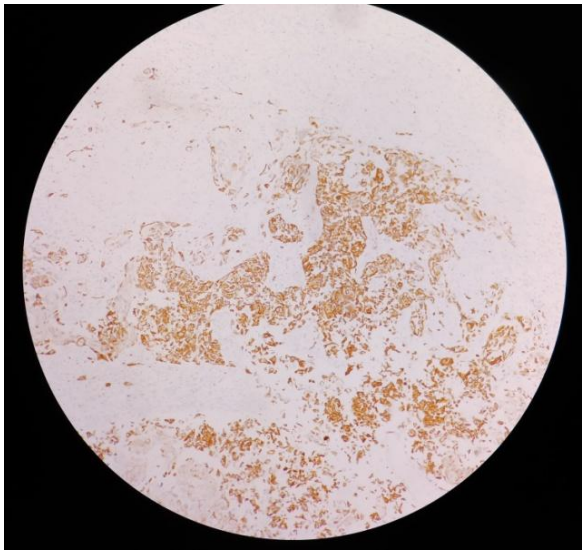

Figure 3: Immunohistochemical staining with CK5/6 in a case of IDC showing positive staining

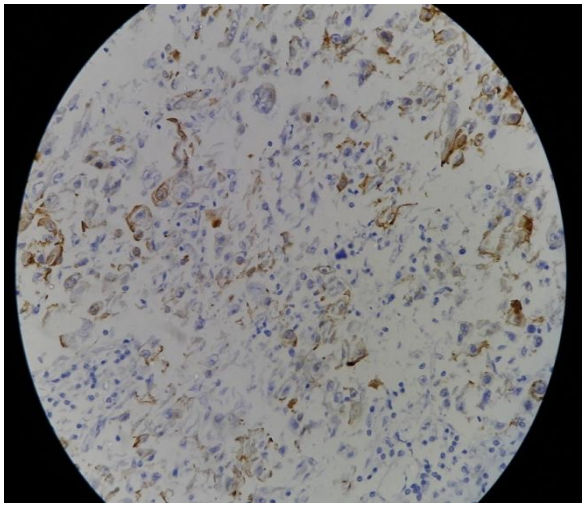

Figure 4: Immunohistochemical staining with CK5/6 in a case of Medullary carcinoma showing positive staining

Discussion

Amongst 50 benign cases, 48 cases were immunopositive for CK5/6. These findings are similar to the studies of Akhtar et al[4], Bhalla et al[5] and Bocker et al[6] (Table 4). Of the total 50 cases of malignant breast lesion in our study,19 cases showed CK5/6 positive immunoreactions. Akhtar, Bhalla, Bocker and Takie reported positive CK5/6 expression in 27%, 24%, 5% and 21.1% respectively in malignant lesions.[4,5,6,7] (Table5). CK5/6 antibody is applied to differentiate radial scar verses invasive cancer, intraductal papilloma versus papillary intraductal carcinoma and microglandular adenosis versus tubular carcinomas. In radial scar, the myoepithelial layer is retained around the glandular structures and therefore show positive staining with CK5/6. In foci of sclerosing adenosis the staining is heterogenous. In low grade invasive carcinoma, CK5/6 staining is negative [8].

Similar to our study, Rehim et al showed on inverse correlation of CK5/6 with patients age.[9] In Akhtar et al, Bhalla et al and Lakhani et al study, positive correlation of CK5/6 positive cases with histological grade, lymph node metastasis and necrosis was seen which was similar to our results.[4,5,10] In our study Out of 17 triple negative IDC cases 11 cases were positive for CK5/6.In Akhtar et al study, all the triple negative malignant cases showed positive immunoreactions for CK5/6.[4] Naim et al have reported strong CK5/6 positivity in triple negative breast carcinoma[11] Pillai et al reported that 13 out of 18 cases of TNBC expressed CK5/6 positivity[12] (Table 6).

Conclusion

The basal/ myoepithelial cells express CK5/6 and thus can be used to identify myoepithelial cells in various tissue sections.

Basal like subtype accounts for 15% to 20% of all breast cancers and confers a markedly poor prognosis. If IDC cases were positive for CK5/6 then they imply a basal like molecular phenotype. This subtype is highly associated with BRCA1 mutation. Thus patient with this subtype along with their first degree relative must be subjected for BRCA1 mutation testing.

Moreover identifying them is important as they are also unlikely to respond to anti estrogen chemohormonal therapy or trastuzumab

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