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Immunostaining Patterns of CD10 in Fibroadenomas and Phyllodes Tumours of Breast

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ABSTRACT

Background: Accurate differentiation between fibroadenomas and phyllodes tumours (PTs) is challenging due to overlapping morphological features. CD10, an immunohistochemistry (IHC) marker, has shown promise in distinguishing these breast lesions. This study aimed to evaluate CD10 expression patterns in fibroepithelial lesions (FELs) of the breast.

Methods: This cross-sectional study was conducted in the Histopathology Department, at Dow University of Health Sciences over 1 year (01st Jan 2023 to 15th Dec 2023). Through the purposive sampling technique, the female patients having FELs were diagnosed by Consultant Pathologists as fibroadenomas or PT and were included in the study by employing specific histological parameters on H & E slides. Immunohistochemistry with CD10 antibody was conducted on a total of 120 samples with an equal split of fibroadenomas, benign PT, borderline PT, and malignant PT (30 cases each), assessing stromal cell staining and categorizing expression as negative (<10% positivity), weak (10–30% positivity), or strong (>30% positivity). Data was statistically analyzed by using SPSS version 26 including reporting mean ± S.D for continuous data and utilizing the Chi-square test to assess associations, with significance set at $p<0.05$.

Results: Negative CD10 expression was observed in fibroadenomas and benign PT, while borderline and malignant PT exhibited weak and strong positive CD10 expression. The analysis revealed a highly significant association (p-value < 0.001) between CD10 expression levels and the various forms of breast lesions. This strong statistical correlation indicates that CD10 could be an important biomarker for assessing the nature of breast lesions. A low p-value reinforces the reliability of the findings, suggesting that the observed differences in CD10 expression are unlikely to be due to random chance.

Conclusion: The findings of the study suggest that CD10 expression could assist as a valuable marker for differentiating between FELs of the breast. Moreover, it may serve as an indicator of the aggressiveness and metastatic potential of PT.

Keywords: Fibroadenomas lesion, CD10, Immunohistochemistry, Breast lesions.

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INTRODUCTION

Fibroepithelial tumours are a diverse category of biphasic tumours that are distinguished by the growth of both epithelial and stromal components. Under this category of tumors, fibroadenomas and phyllodes tumours (PT) tend to be important entities, each with distinctive histopathological and clinical characteristics[1,2]. Fibroadenomas, which are frequently identified in younger women, are characterized by a well-defined ovoid mass with a grey-white to yellow color on macroscopic examination. Microscopically, they show expansion of the stromal component around epithelial structures, with two recognized patterns: pericanalicular and intracanalicular. In addition to the conventional type, there are variants such as myxoid fibroadenoma and cellular fibroadenoma. The presence of atypical epithelial hyperplasia or malignant changes within fibroadenomas is rare[3]. A recent study from Pakistan in 2020 highlighted this, revealing fibroadenomas to dominate, comprising over half of all cases and the majority of benign lesions[4]. Consistently, other research in the region echoed this trend, highlighting benign breast diseases as the predominant afflictions in breast pathology[5, 6].

PT is a rare type of primary breast tumour, accounting for 0.3% to 1% of cases. They typically occur in older individuals, distinguishing them from fibroadenomas. Macroscopic findings of PT typically include a well-defined, firm mass with a smooth surface. These tumours often exhibit a macro-lobulated appearance and are mobile within the breast tissue[7]. Microscopically, PT exhibits a diverse range of histological features, spanning from benign to malignant. Grading of these tumors involves the evaluation of parameters such as stromal cellularity, atypia, mitotic activity, and necrosis or malignant elements. Benign tumours manifest specific histological criteria, while malignant tumours display distinct features indicative of malignancy. PTs exhibit higher frequency, particularly among Asian women, occurring at a younger age compared to other populations[3]. A study in Pakistan revealed that benign PTs constituted approximately 2.24% of cases, with borderline PTs and malignant PTs representing 0.07% and 0.26%, respectively[6]. Recurrence rates vary across tumour grades, with malignant cases demonstrating a higher propensity for recurrence and the potential for distant metastasis. Local recurrences typically manifest within a two-year timeframe and can be either biphasic or monophasic, while distant metastases predominantly affect systemic organs[7].

Considering the importance of differences in their treatment and outcomes, it is imperative to accurately differentiate between fibroadenomas and PTs. Literature suggests that distinguishing between the two can be difficult, especially when dealing with limited biopsy samples. To help with this differentiation and to sub-classify PTs into prognostically relevant categories—benign, borderline, and malignant—several ancillary studies, including immunohistochemical (IHC) markers, have been investigated[3].

CD10, also known as common acute lymphoblastic leukemia antigen or CALLA, is a zinc-dependent metalloprotease typically expressed on the cell surface of epithelial cells in various tissues such as the prostate, stomach, liver, colon, and apocrine breast lesions, as well as in the endometrial stroma. Similar to many matrix metalloproteinases (MMPs), CD10 plays a role in degrading extracellular matrix components and regulating the biological activities of peptide substrates by modulating their local concentrations. Its overproduction in tumour stroma has been implicated in tumour development and progression by facilitating extracellular matrix degradation and promoting local invasion.[8] Recent studies, particularly those focused on the breast, have revealed its (CD10) existence in a variety of neoplasms as well as normal tissues[9,10,11,12]. Particularly, myoepithelial cells, in situ adenocarcinomas, and other cell types in the breast have been found to express CD10[13,14].CD10 has also been studied for its possible utility to differentiate between different grades of PTs[15]. Studies, particularly those focused on borderline and malignant PTs, have indicated a correlation between CD10 expression and PT grades[15,16,17]. The primary objective of this study was to investigate the expression of CD10 immunohisto-chemical staining in FELs of the breast (fibroadeno-mas and PTs), and the histopathological character-istics of FELs, particularly its association with tumour grade.

METHODS

This research was designed as a prospective, cross-sectional study, conducted in the Histopathology Department of Dow Diagnostic, Research and Reference Laboratory (DDRRL)at Dow University of Health Sciences (DUHS), Ojha Campus, Karachi, Pakistan over a period of 1 year (01st Jan 2023 to 15th Dec 2023). Eligible participants included those with specimens that displayed clinical suspicions of fibroepithelial lesions. Through the purposive sampling technique, breast tissue obtained from surgical excisions, which were documented and reported in DDRRL, and females of all age groups were considered eligible for participation. Conversely, participants were excluded from the study if they met any of the following criteria: a diagnosis of invasive carcinoma of the breast, specimens of pregnant women, incomplete patient particulars on requisition forms, or instances where patient consent was not obtained. Ethical approval of the research was obtained from the institutional board of review of the University. The total sample size of the study was 120 which was divided into 4 groups

(30 in each group), determined using the OpenEpi calculator (version 3.01), was based on achieving 80% statistical power at a confidence level of 95%. This calculation was influenced by findings from Puri et al.,[18] which observed a 50% positive expression of grade 1 CD10 in benign PT, contrasting with 0% positivity in malignant PT. Breast tissue specimens from female patients were obtained from the Histo-pathology Department of DDRRL/DUHS. These patients/ attendants were contacted for consent by a phone call given on their form. The purpose and objective of the research were explained and 3 days were given to them for decision making. The patients were contacted again via phone call after three days and written informed consent was taken from them. After the consent taking, these speci-mens were subjected to macroscopic examination following established International Grossing Proto-cols and subsequently processed for slide prepara-tion. FFPE blocks containing fibroepithelial tumors were prepared and stained with hematoxylin and eosin (H&E) dye. Subsequently, all the slides under-went a thorough review, and the histological diag-noses were confirmed as either fibroadenomas or PT by the Consultant Pathologists. In PT, the stromal component exhibited a cellular and expanded pattern reminiscent of leaves. To determine the degree of malignancy, PT is classified by the WHO into benign, borderline, and malignant categories based on various histopathologic parameters, including stromal cellularity and atypia, stromal overgrowth, mitotic count, and tumor border char-acteristics[19,20].Stromal overgrowth was designated as either present or absent, and the mitotic count was quantified as mitotic figures per 10 high-power fields. A diagnosis of benign PT was established when the tissue displayed low cellularity, lacked stromal overgrowth, exhibited mild pleomorphism, featured a rounded margin, and had a mitotic count of ≤2/10 high-power fields. Malignant PT was diagnosed when the mitotic count was ≥5/10 high-power fields, accompanied by stromal overgrowth and an infiltrative margin. PT of border-line malignancy was identified when the criteria for malignant PT were not entirely met[21]. For fibroade-nomas, confirmation of diagnosis was based on the presence of a biphasic pattern characterized by a bland epithelial component and a stromal compo-nent with low cellularity, minimal to absent stromal mitoses, and the absence of an extensive frond-like stromal growth pattern[22].

After diagnosing FELs, 120 slides were immunos-tained with CD10 antibody (Clone 56C6) and observed again under a light microscope. For the evaluation of CD10 expression, stromal cell staining was assessed, using cytoplasmic staining of the breast myoepithelium as an internal control (Fig 1). Staining intensity was graded as 0 (no staining), weak, moderate, or strong, corresponding to much weaker, slightly weaker, or similar intensity as the myoepithelium, respectively. Additionally, the percentage of stained cells was assessed as nega-tive, Grade-1 (<10% positive cells), Grade-2 (10-30% positive cells), and Grade-3 (>30% positive cells)[15, 18].

Figure 1: Internal Control Showing Cytoplasmic Staining of Breast Myoepithelium

IBM SPSS version 26 was used for the statistical analysis. Continuous data (age and size of lesion) were reported in mean ± S.D and the Chi-square test was employed to assess the association between two categorical variables (grades of PT and CD10 expression as negative, weak, and strong while the expression of CD10 was expressed in count as well in percentages). A p-value of <0.05 was considered as significant.

RESULTS

A total of 120 cases were included in the study. The distributions of diagnoses among the cases of the study were as follows: Fibroadenoma (30 cases, 25%), Benign PT (30 cases, 25%), Borderline PT (30 cases, 25%), and Malignant PT (30 cases, 25%). The participant's ages ranged from 20 years to 65 years, with a mean age of 39.12 years (S.D 10.8). Regarding the tumor size in cm, it ranged from 1.00 to 22.00, with a mean tumor size of 8.47cm (S.D 5.1).

The characteristics of the lesions are presented in Table 1. Fibroadenoma and benign PT often had circumscribed borders, while malignant PTs displayed permeative borders. The leaf-like architecture was common in benign and borderline PTs. Malignant PTs were characterized by severe nuclear atypia, stromal overgrowth, higher mitotic activity, and necrosis. Most tumours were completely excised, with single tumour focus being the most common.

Table 1: Characteristics of FELs of the Breast

Characteristics of Tumor		Diagnosis				Total
		Fibroadenoma N (%)	Benign PT N (%)	Borderline PT N (%)	Malignant PT N (%)	
Tumor borders	Circumscribed	30 (25%)	30 (25%)	27 (22.5%)	8 (6.6%)	95 (79.1%)
	Permeative	0 (0%)	0 (0%)	3 (2.5%)	22 (18.33%)	25 (20.8%)
Leaf-like architecture	Present	0 (0%)	30 (25%)	28 (23.3%)	18 (15%)	76 (63.3%)
	Absent	30 (25%)	0 (0%)	2 (1.6%)	12 (10%)	44 (36.6%)
Nuclear atypia	None	30 (25%)	1 (0.8%)	0 (0%)	0 (0%)	31 (25.8%)
	Mild	0 (0%)	17(14.1%)	30 (25%)	2 (1.6%)	49(40.8%)
	Moderate	0 (0%)	12 (10%)	0 (0%)	6 (5%)	18 (15%)
	Severe	0 (0%)	0 (0%)	0 (0%)	22 (18.33%)	22 (18.33%)
Stromal overgrowth	Present	0 (0%)	0 (0%)	19 (15.8%)	27 (22.5%)	46 (38.3%)
	Absent	30 (25%)	30 (25%)	11 (9.1%)	3 (2.5%)	74 (61.6%)
Stromal hypercellularity	None	30 (25%)	0 (0%)	0 (0%)	0 (0%)	30 (25%)
	Mild	0 (0%)	14 (11.6%)	28 (23.3%)	6 (5%)	48 (40%)
	Moderate	0 (0%)	16 (13.3%)	2 (1.6%)	14 (11.6%)	32 (26.6%)
	Severe	0 (0%)	0 (0%)	0 (0%)	10 (8.3%)	10 (8.3%)
Mitotic activity	0-4	30 (25%)	29 (24.1%)	17 (14.1%)	0 (0%)	76 (63.3%)
	5-10	0 (0%)	1(0.8%)	10 (8.3%)	22 (18.33%)	33 (27.5%)
	> 10	0 (0%)	0 (0%)	3 (2.5%)	8 (6.6%)	11 (9.1%)
Heterologous element	Present	0 (0%)	1 (0.8%)	0 (0%)	10 (8.3%)	11 (9.1%)
	Absent	30 (25%)	29 (24.1%)	30 (25%)	20 (16.6%)	109 (90.8%)
Necrosis	Present	0 (0%)	0 (0%)	0 (0%)	30 (25%)	30 (25%)
	Absent	30 (25%)	30 (25%)	30 (25%)	0 (0%)	90 (75%)
Surgical margins	Completely excised	7 (5.8%)	28(23.3%)	22(18.33%)	26(21.6%)	83(69.1%)

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Strong CD10 expression was absent in fibroadenoma and benign PT but present in 36.7% of borderline and 60% of malignant PTs. The association between CD10 expression and breast lesion types was highly significant (p < 0.001) Table 2.

Table 2: Expression of CD10 in FELs of the Breast

Type of Tumor	Negative	Weak positive	Strong positive	P-Value
Fibroadenoma	22 (73.4%)	8 (26.6%)	0 (0%)	<0.001
Benign PT	17 (56.6%)	13 (43.4%)	0 (0%)	
Borderline PT	4 (13.3%)	15 (50%)	11 (36.7%)	
Malignant PT	3 (10%)	9 (30%)	18 (60%)	

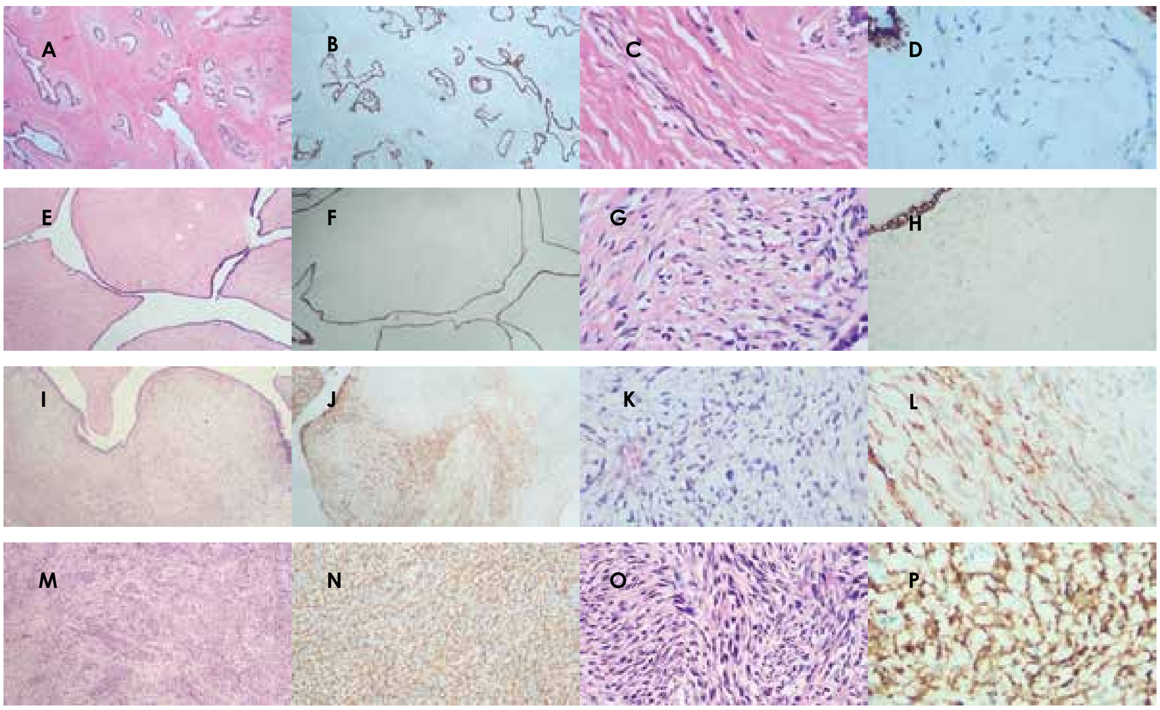

Figure 1: Photomicrograph of FEL of Breast

A-D: Photomicrograph of Fibroadenoma (A: H&E at 40x magnification showing proliferating ducts and stroma, B: Negative CD10 expression at 40x magnification with internal control of myoepithelium, C: H&E at 400x magnification, and D: Negative CD10 expression at 40x magnification)

E-H: Photomicrograph of Benign Phyllodes Tumor (E: H& E at 40x magnification, F: Negative CD10 expression at 40x magnification, G: H&E at 400x magnification, and H: Negative CD10 expression at 400x magnification)

I-L: Photomicrograph of Borderline Phyllodes Tumor (I: H&E at 40x magnification, J: Strong CD10 expression at 40x magnification, K: H&E at 400x magnification, and L: Strong CD10 expression at 400x magnification

M-P: Photomicrograph of Malignant Phyllodes Tumor (M: H&E at 40x magnification, N: Strong CD10 expression at 40x magnification, O: H&E at 400x magnification, P: Strong CD10 expression at 400x magnification

DISCUSSION

Fibroepithelial lesions (FELs) are a varied group of biphasic tumours that include both epithelial and stromal components. This research aimed to assess CD10 expression in breast FELs, particularly focusing on fibroadenomas and phyllodes tumours (PTs). Distinguishing between fibroadenomas and PTs is essential for guiding treatment decisions and predicting clinical outcomes as fibroadenomas can be simply observed if small or simply excised but phyllodes tumor requires wide local excision with clear margin and follow-up due to the risk of recurrence and metastasis. CD10 has attracted interest in breast cancer studies due to its potential role in tumour formation and progression. CD10 is implicated in modulating cellular functions and degrading the extracellular matrix, thereby influencing the dynamics of the tumour microenvironment[8]. This study aimed to find out the association between CD10 expression and the histopathological characteristics of the patients diagnosed with fibroadenomas and PTs.

The current study encompassed a diverse range of participants, with ages spanning from 20 to 65 years and a mean age of 39.12 years. These findings resonate with those of previous researchers, as evidenced by the broader age range reported in their studies. Conversely[18, 23, 24]. Other studies reported a narrower age range of 14 to 55 years[25, 26]. The range of tumour sizes observed in our study population varied from 1 to 22 cm, with a mean size of 8.47 cm and a standard deviation of 5.1. However, the mean tumour size reported by some researches , was 7.56 ± 4.24 cm, with sizes ranging from 2.5 to 18 cm and 2.5 cm to 15 cm with a mean of 3.75 cm respectively[18, 26]. This suggests a similar range of tumor sizes compared to our study, albeit with a slightly lower mean size. The variation in tumour size observed between studies may be attributed to several factors, including differences in patient demographics, sample selection criteria, and tumour measurement methods.

Histopathological analysis of the current study revealed similarities in various features between FA and PT, including tumour boundary, mitotic activity, stromal cellularity, stromal overgrowth, and no lesions as well as the overall structure of the PT. However, as the tumours progressed from benign to borderline and malignant PT, remarkable differences in these histopathological characteristics became evident, corresponding to the increasing grade of the tumour. While some previous studies, support these findings, indicating a clear distinction between different grades of PT, other research, such as the study did not find mitosis to be significantly correlated with tumour progression[27, 28, 29]. Despite observing a certain level of overlap in mitotic activity between FA and PT, the study did not establish a significant correlation between mitosis and tumour grade. This suggests that while some histopathological features may evolve with tumour progression, the significance of certain criteria, like mitotic activity, may vary and require further investigation.

The current findings revealed variation in CD10 expression across different types of FELs. In fibroadenomas and benign PTs, CD10 expression was predominantly negative, indicating a minimal presence of CD10 in the stromal component of these tumours. This aligns with findings of previous studies, that have suggested a lack of CD10 expression in benign breast lesions[25, 29]. While other studies, found a higher prevalence of positive CD10 expression in benign PT cases[18]. Additionally, their study reported positive CD10 expression in all malignant PT cases, indicating a consistent presence of CD10 in the stromal component of these tumours.

However, as tumours progressed from benign to malignant PTs, we observed an increase in CD10 expression. Malignant PTs exhibited a higher proportion of positively stained stromal cells compared to benign lesions. This finding is consistent with the previous studies, implicating CD10 overexpression in tumor stroma and its potential role in tumor progression by promoting extracellular matrix degradation and facilitating local invasion[15, 18]. However, a research found inconsistent findings for the pattern of CD10 expression[23]. They observed higher CD10 expression in both benign and malignant PT cases, contrasting with our findings and highlighting the variability in CD10 expression patterns observed across different studies.
In this study, we observed distinct staining patterns associated with different grades of PTs. Benign and borderline PTs showed weak CD10 staining, whereas malignant PTs exhibited strong staining. This suggests a potential association between CD10 expression intensity and tumour aggressiveness, implying that higher CD10 expression levels may indicate more advanced disease stages.

Comparisons with previous studies yielded both concordant and discordant findings regarding CD10 expression in FELs. While few studies reported similar trends of increased CD10 expression in malignant PTs, others observed contrasting results, or found no significant associations, Between CD10 expression and tumour grade[15, 18, 29, 26, 23, 25]. These discrepancies underscore the complexity of CD10's role in breast tumorigenesis and the need for further investigation into its molecular mechanisms and clinical implications.

The study has several limitations. It does not assess the association of CD10 expression with the long-term follow-up data/clinical outcomes such as recurrence or survival. Another is the small sample size, despite including 30 samples of each tumour type. Furthermore, the study does not cover the full spectrum of

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molecular and genetic factors that could impact FELs.

CONCLUSION

Our study concluded that CD10 differential expression can assist particularly in grading phyllode tumor next to the histopathological characteristics of FELs. By incorporating CD10 expression analysis alongside conventional histopathological methods, histopathologists have the potential to enhance diagnostic precision and improve patient outcomes in breast cancer management.

DECLARATIONS

Not applicable

CONFLICT OF INTEREST

None to declare

ETHICAL APPROVAL

Ethical approval was taken from the institutional review board (IRB) of DUHS (reference number:(Ref # IRB-2794/DUHS/Approval/2023/177).

FUNDING

Nil

PATIENT CONSENT

The patient/guardian was taken

AUTHORS CONTRIBUTION

FMA: Conceptualized the study, designed the research methodology, and played a major role in drafting and revising the manuscript.**SHS :**Conducted the literature review, assisted in data analysis, and contributed to the interpretation of results. **FD:** Partici-pated in data collection, andi mmunohistochemical staining, and contributed to manuscript writing. **LA** Assisted in data collection and analysis, as well as in the interpretation of histopathological findings. **UB** Provided critical revisions to the manuscript, ensured the accuracy of the scientific content, and supervised the overall project. **ST** Contributed to the statistical analysis, helped in preparing tables and figures, and was involved in manuscript editing.

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