

Original Research Article


Stromal expression of CD34 immunohistochemical antigen in proliferative lesions of breast

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Abstract

Introduction: CD34 Immunohistochemical antigen serves as a tool in differentiating between benign and malignant conditions. Hence, the study was conducted to determine the stromal expression of CD34 antigen by immunohistochemical method in proliferative lesions of the breast and to evaluate the loss of CD34 antigen expression in stromal cells is specific for malignant lesions.

Materials and methods: 108 cases of proliferative lesions of the breast were studied from January 2016 to December 2017 for some time of 2 years. Paraffin-embedded blocks were retrieved for all the cases and underwent routine processing followed by Hematoxylin and Eosin staining. 84 cases of the benign lesion, one case of the borderline lesion and 23 cases of the malignant lesion were studied for CD34 immunohistochemical staining, and semi-quantitative assessment was done.

Results: On Hematoxylin and Eosin staining, we have found benign lesions includes 63 cases of fibroadenoma, 7, 4, and 3 cases of the fibrocystic disease, fibro adenosis and fibroadenoma respectively with apocrine metaplasia. Malignant lesions include 22 cases of infiltrating ductal carcinoma, one case of infiltrating lobular carcinoma. One case of borderline phyllodes tumor was also included in this study. In normal breast tissue, stroma was positive for CD34 IHC stain. All the malignant cases are showing loss of CD34 staining. Only one case of borderline phyllodes tumor shows grade 2 staining with CD 34 Antigen.

Conclusion: We can concluded that the use of CD34 Immunohistochemical marker positivity as an adjuvant tool in differentiating between benign and malignant conditions where the morphology is equivocal.

Key words

Serum Magnesium, Mean Platelet Volume, Acute Myocardial Infarction, Renal Profile. CD34 Immunohistochemical antigen, Breast cancer, Tumors.

Introduction

Normal mammary stroma contains a large number of CD34 positive fibroblasts which can be detected at the 10th week of gestation and in developmental phase these can be found in the majority of stromal cells [1]. Normal breast shows CD34 positivity in both intralobular and interlobular stroma where the intralobular stromas has strong positivity, and interlobular stroma has weak positivity for CD34. CD34 positive stromal cells can also be present in endothelial cells of vessels. In many studies, the malignant transformation of the tumours shows a reduction of CD34 positive stromal fibroblasts [2, 3]. The importance of stromal interaction with the ductal system is important for normal breast development and tumorigenesis in malignancy [4-6].

During the tumorigenesis, mutation in the premalignant ductal epithelial cells activated the adjacent stroma, and the activated stromal fibroblast undergoes morphological and phenotypical alterations which include a loss of CD34 expression and acquire smooth muscle actin when it becomes myofibroblast-like cells which allow the malignant cells disseminate through the stroma because of the contractile property [7]. Expression of CD34 IHC staining in the blood vessel endothelial lining and normal breast stroma present in the proliferative lesion of the breast are taken as internal controls.

Materials and methods

108 cases of proliferative lesions of the breast were studied throughout 2 years (January 2016 to December 2017) which includes cases of lumpectomy, mastectomy, modified radical mastectomy and also small biopsies from the breast lesions. 84 cases of the benign lesion, one case of the borderline lesion and 23 cases of malignancy were studied for CD34

immunohistochemical staining and graded as 0, 1, 2, 3 as follows.

<5% of CD34 positivity was considered as grade 0,

5 to 25 % of CD34 positivity was considered as grade 1,

25 to 50 % of CD34 positivity was considered as grade 2,

>50% of CD34 positivity was considered as grade 3.

The following methods did a semi-quantitative assessment.

Grade 0 – Interpreted as complete loss of CD34

Grade 1 – Interpreted as reduced expression

Grade 2 and Grade 3 - Interpreted as a retained expression.

Results

Out of 83 cases of benign cases, 62 cases of fibroadenoma, 7 cases of fibrocystic disease, 4 cases of fibro adenosis, 2 cases of fibroadenoma with apocrine metaplasia, 2 cases of fibroadenoma with focal ductal hyperplasia, 2 cases of fibroadenoma with fibrocystic disease, and 2 cases of benign phyllodes tumour shows retained CD34 expression and graded as Grade 2 and Grade 3. One case of fibroadenoma and one case of fibroadenoma with apocrine metaplasia show reduced expression of CD34 antigen and graded as Grade 1. One case of complex fibroadenoma showed loss of CD 34 antigenic expression and graded as Grade 0. All the Malignant lesions include 22 cases of infiltrating ductal carcinoma and one case of infiltrating lobular carcinoma showed loss of CD34 staining and graded as Grade 0. We encounter one borderline lesion which shows retained expression of CD34 and graded as Grade 2 (Table – 1).

Discussion

Normal mammary stroma contains CD34 positive fibroblasts/fibrocytes. The CD34 positive fibroblasts distribution is like that of normal skin. This is due to the development of mammary glands from solid epithelial cords growing from the epidermal layer into the underlying mesenchyme. CD34 is a transmembrane glycoprotein that is involved in modulation of cell adhesion and signal transduction and is expressed in mesenchymal cells of the prostate, urinary bladder, fallopian

tube, thyroid, pancreas, colon, uterine cervix and testis [2, 3]. On endothelial cells, CD34 acts as a ligand for L-selectin. They constitute a population of stromal cells that are capable of synthesising connective tissue matrix. CD34 positive stromal fibroblasts are potent antigen presenting cells, and they play a major role in host response to tissue damage [1, 8]. Loss of CD34 expression is noted in malignant transformation of mesenchymal cells in the stroma.

Table – 1: Histopathological diagnosis.

Histopathological diagnosis and number of cases	Grading of CD34 stromal positivity			
	(< 5%) Grade 0	(5% to 25%) Grade 1	(25% to 50%) Grade 2	(>50%) Grade 3
Fibro adenoma (63)	0	01	05	57
Fibro adenoma with apocrine metaplasia (3)	0	01	01	01
Fibrocystic disease (7)	0	0	0	7
Fibro adenosis (4)	0	0	1	3
Fibro adenoma with focal ductal hyperplasia (2)	0	0	0	2
Fibro adenoma with fibrocystic disease (2)	0	0	0	2
Complex fibro adenoma (1)	1	0	0	0
Benign phyllodes (2)	0	0	2	0
Borderline phyllodes (1)	0	0	1	0
Invasive ductal carcinoma (22)	22	00	00	00
Invasive lobular carcinoma (1)	01	00	00	00
Total = 108	24	02	10	72

This study shows retained CD34 expression (grade 2 and 3) in the entire benign lesion of breast except for 3 cases which includes fibro adenoma, fibro adenoma with apocrine metaplasia and complex fibro adenoma. Reason for loss of expression in the above cases are poorly understood and needs further studies.

In the present study loss of CD34 expression is found in the malignant transformation of proliferating breast lesions. The change in the CD34 expression is localised as the stroma which surrounds the ductal system which has invasive carcinoma but the other areas which are not involved by invasive carcinoma retaining the expression of CD34 antigen in the corresponding stroma. This strongly implicates the epithelial and mesenchymal interaction in the control of

CD 34 expression. This raises the possibility of “loss of CD34 expression is related to malignant transformation”. The importance of loss of CD34 expression of stromal cells in reactive fibrosis may be due to the terminal differentiation.

This potential for the stromal response to the tumour is becoming a target for the treatment of breast malignancy. It is essential that the changes in fibroblast phenotype associated with malignancy are carefully dissected not only to validate their use as possible diagnostic markers but also to establish their potential as therapeutic targets. The functional relevance of stromal fibroblast CD34 expression and its loss is unclear although it may represent a change from a multipotent mesenchymal cell to committed cell type.

The data suggest that there is a strong correlation between the loss of CD34 expression in stroma and malignant transformation. Several mechanisms may explain the promotion of tumor invasion that induces the transformation of CD34 fibrocytes/fibroblasts into myofibroblasts. CD34 positive fibrocytes are potent antigen presenting cells capable of priming naive T cells so might be involved in specific immune surveillance [9, 10]. CD34 positive stromal cells are involved in remodelling of stromal tissue damage via TGT-beta, synthesis of collagen 1 and 2 and SMA and also in terms of migration factors within the injured tissue via CCR7, CXCR4, SLC and CXCL12. CD34 positive fibroblasts also play a role in angiogenesis. Loss of CD34 expression leads to loss of most essential functions includes immunity, cell adhesion, motility, stromal remodelling and angiogenesis inhibition which promote the invasion of tumor cells into the stroma and also helpful in metastasis [11].

In our study loss of CD34 expression is seen in all malignant cases which also support the above theory. Hence the use CD34 Immunohistochemical marker positivity as an adjuvant tool in differentiating between benign and malignant conditions where the morphology is equivocal.

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