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The Association between CD10 Expression and Histological Grade in Invasive Breast Carcinoma of No Special Type

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Abstract: ***Breast carcinoma is the commonest malignancy in women. Histological grade is one of independent prognostic factor of its. Breast carcinoma is an epithelial malignancy, however stromal plays an important role in breast carcinoma progression. Stromal marker is now emerging as a new marker in assessing the prognosis of breast carcinoma. Stromal CD10 expression associated with more aggressive tumor behavior. Some studies linking CD10 expression with histological grade still show conflicting result. The aim of this study was to prove the association between CD10 expression and histological grade in invasive breast carcinoma of no special type. This study was performed using a cross sectional observational analytical method. Immunohistochemical staining of CD10 was performed in 50 samples invasive breast carcinoma of no special type that met inclusion and exclusion criteria. The study results were analyzed with Chi-Square test with significancy level at p < 0.05. The highest number of cases were in the 40-50 years (44%) age group. There was an association between the CD10 expression and histological grade (p=0.001; p<0.05). Assessment of CD10 expression can be used as a marker of tumor aggression levels based on histological grade, so it could determine prognosis and for more effective therapies.***

Keywords: invasive breast carcinoma of no special type, histological grade, CD10 expression

1. Introduction

Breast carcinoma is still a major health problem faced by developing and developed countries. The incidence and death rates of breast carcinoma are still high due to its causes and carcinogenesis is not fully known. Invasive breast carcinoma of no special type is the most frequent histological type of breast carcinoma, accounting for approximately two-third of cases [1]. Its prognosis depends on biological factor and the extent of carcinoma [2]. One of the biological factor is histological grade and its remains an independent prognostic factor in invasive breast carcinoma [1].

Although breast carcinoma is an epithelial malignancy, stromal microenvironment plays an important role in carcinoma development. Stromal contributes in carcinoma progression that promote tumor cell growth, dedifferentiation, invasion, and ectopic survival of tumor cells [3], [4]. It gives the reason for the importance of stromal markers in assessing prognosis of invasive breast carcinoma.

One of the stromal marker is CD10, also known as neprilysin or common acute lymphoblastic leukemia/lymphoma antigen (CALLA). CD10 is a zinc dependent metalloproteinase which regulate many peptides by lowering their extracellular concentration so they can't binding to their receptor [5]. CD10 is not expressed in stromal cells of normal breast. However in invasive breast carcinoma, CD10 abnormally expressed in stromal around the invasive area [5], [6]. Several study reported that stromal CD10 expression associated with biological aggressiveness in invasive breast carcinoma.

The aim of this study was to prove the association between CD10 expression and histological grade in invasive breast carcinoma of no special type.

2. Material and Methods

2.1 Specimens

Slides and paraffin embedded tissue blocks from 50 patients invasive breast carcinoma of no special type were retrieved from the histopathology archives in Anatomic Pathology Laboratory of Sanglah Hospital, Bali in the period January 1st 2015- June 30th 2017.

2.2 Histopathologic evaluation

The slides from these cases were reviewed, and histopathologic diagnoses in the histopathologic reports were confirmed independently by two pathologists and one resident.

2.3 Histological grade evaluation

Invasive breast carcinoma of no special type is divided into histological grade 1, 2, and 3 according to Nottingham Combined Histologic Grade (Elston-Ellis Modification of Scarff-Bloom-Richardson Grading System) [1] . It is depends on:

A. Tumor tubule and gland formation:

>75% of tumor	score 1
10-75% of tumor	score 2
<10% of tumor	score 3

B. Nuclear pleomorphism

Small, regular uniform cells	score 1
Moderate increase in size and variability	score 2
Marked variation	score 3

C. Mitosis counts

Number of mitotic figures in most active area. This is performed by counting 10 high power field. This study used Olympus binocular microscope CX22 with field diameter 0.65.

<13	score 1
13-24	score 2
>25	score 3

2.4 Immunohistochemistry and interpretation

Tissue section at 3 µm thickness from each case were prepared for immunostaining. After incubated overnight, deparaffinization, and rehydration, tissue section were incubated with (3%) hydrogen peroxide. The slides were washed with PBS, placed in coplin jars containing citrate buffer, and then incubated with primary Mouse Monoclonal Antibody Against human CD10, Abcam diluted to 1:100. The colour was visualized by DAB as chromogen.

Immunohistochemistry results evaluated by a semiquantitative approach and interpreted independently by two pathologists and one resident. Pattern of staining for CD10 is cytoplasmic and or membranous positivity in stromal cells with desmoplastic picture throughout the invasive area. The staining has interpreted as negative (no staining), weak positive (either diffuse weak staining or strong focal staining in less than 30% of stromal cells), and strong positive (strong staining of 30% or more of the stromal cells) [7]. Both negative and weak positive expression were considered as negative. Only strong positive CD10 expression was considered as positive [8] [Figure 1].

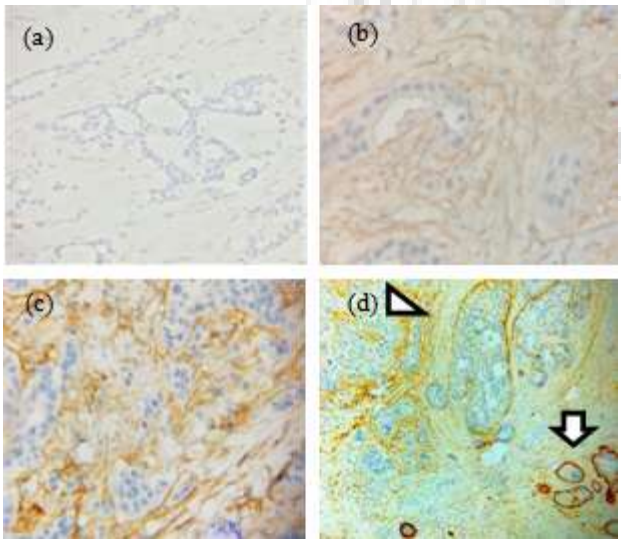

Figure 1: CD10 staining. (a) Negative (400x). (b) Weak positive (400x). (c) Strong positive (400x). (d) Variation of CD10 staining in one lesion, arrow in myoepithelial of non neoplastik gland and arrow head in stromal cells of invasive area (100x).

2.5 Statistical analysis

Descriptive statistics were calculated. Chi square test was used to assess the association between CD10 expression and histological grade. P value less than 0.05 was considered significant. All statistical analyses were performed using SPSS 20.0

3. Result

Sample distribution by age and histological grade of invasive breast carcinoma of no special type are shown in Table 1. In this study, total 50 cases of breast carcinoma were included. The ages ranged from 29 to 78 years. The mean age was 49,24±9,54 years. Majority of cases (22 cases, 44%) were within the age of 40-50 years.

Table 1: Sample distribution by age and histological grade

Age (years)	Invasive breast carcinoma of no special type			Total n (%)
	Histological grade 1 n	Histological grade 2 n	Histological grade 3 n	
<40	0	1	5	6 (12%)
40-50	6	4	12	22 (44%)
51-60	2	8	7	17 (34%)
61-70	2	2	0	4 (8%)
>70	0	0	1	1 (2%)

Table 2. shows CD10 expression in different histological grade of invasive breast carcinoma of no special type. Ten cases of histological grade 1, none of that is positive for CD10. Fifteen cases of histological grade 2 and among them 8 (32%) showed positive CD10 expression while 7(28%) showed negative CD10 expression. Twenty-five cases of histological grade 3 and among them 17 (68%) showed positive CD10 expression while 8(32%) showed negative CD10 expression. The association between CD10 expression and histological grade in this study is statistically significant, p=0,001 (p value is less than 0,05, Chi-square test)

Table 2: CD expression and histological grade

CD10 expression	Histological grade			Total	p
	1	2	3		
Positive	0 (0%)	8 (32%)	17 (68%)	25 (100%)	0,001
Negative	10 (40%)	7 (28%)	8 (32%)	25 (100%)	
Total	10 (20%)	15 (30%)	25 (50%)	50 (100%)	

4. Discussion

In present study, age of the sample ranged from 29 to 78 years with mean age being 49,24±9,54 years. Majority of the patients i.e 44% (n=22) belonged to the age group 40-50 years. Similar result were obtained from study of Hartaningsih & Sudarsa, Rahayu, and Simon [9]-[11].

In our study, 50% of cases (25 from total 50 cases) showed positivity for CD10 immunostaining in the stromal surrounding the invasive area. This is in concordance with the results of several recent studies, i.e 48.6% in study by Jana et al. [12], 49.5% by Vo et al. [13], and 53.4% by Sadaka et al [14]. Other studies showed higher percentages

of CD10 positivity including 80% in study by Nema et al. [15], 81,6% by Anuradha Devi et al. [16], and 64% by Balajji et al. [8]. The discrepancy in this result might due to different cutoff points in evaluate the positivity of CD10 between studies.

Positive CD10 expression in the studied cases of invasive breast carcinoma of no special type suggested that CD10 stromal expression implicated in breast carcinoma tumorigenesis. In breast carcinoma, C10 expression has contradictory findings. In early stage of tumorigenesis, its disappearance from myoepithelial leads progression of DCIS to invasive carcinoma. However in invasive breast carcinoma, upregulation of abnormal CD10 enzymatic activity leads to accumulation of cleaved peptides [6], [12].

In the present study, a statistically significant association was found between CD10 expression and histological grade (p=0,001) (CI 95% and p<0,05). This result in agreement with those reported by other recent study i.e p<0,001 by Sadaka et.al [14], p=0,04 by Balajji et.al [8], and p<0,0001 by Prabhakaran [17]. In contrast with these findings, p=0,5624 in study by Iwaya et.al [18], p=0,139 by Puri et. al [19], and p=0,151 by Vo et.al [13] reported that there was no statistically significant correlation between CD10 expression and tumor histological grade. Lack of standardized methodology for measuring stromal CD10 expression and the use of different cutoff points might explain these different findings. In our study, only strong positive expression in >30% tumor stromal around the invasive area is considered as positive.

Accumulation of cleaved peptides resulted by increased abnormal CD10 enzymatic activity in invasive breast carcinoma, could inhibit epithelial cell differentiation. In breast carcinoma condition, intracellular CD10 signaling could also modified. These signaling alterations could block PTEN function and activation of Akt pathway. All of it lead to apoptosis inhibition, tumor cell proliferation, and angiogenesis. So with a stronger CD10 expression, the histological grade of breast carcinoma becomes worse [6], [12].

In conclusion based on the results of this study, there was an association between the CD10 expression and histological grade in invasive breast carcinoma of no special type. CD10 expression can be used as a marker of tumor aggressiveness based on histological grade and associated with poorer patient prognosis.

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