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RESEARCH ARTICLE

The Validity Assessment of E-Cadherin Expression to Differentiate Ductal and Lobular Type Invasive Breast Carcinoma

I Gusti Ayu Sri Mahendra Dewi[1*], Ni Putu Ekawati[1]

Department of Pathology Anatomy, Faculty of Medicine Udayana University/ Sanglah General Hospital Denpasar-Bali.

***Corresponding Author: I Gusti Ayu Sri Mahendra Dewi**

Abstract

Introduction: Currently, breast cancer is one of the leading causes of cancer related death in women worldwide. The diagnosis of breast cancer still depends on biopsy to determine the histopathological subtype and the nature of the cancer. However, the subtypes alone could not differentiate between lobular and ductal carcinoma. Therefore, this study aimed to evaluate the validity of E-cadherin expression as biomarker to differentiate ductal and lobular invasive breast carcinomas. Methods: An analytic observational cross sectional study was conducted using 47 biopsy samples of ductal and lobular type invasive breast carcinoma examined at Anatomical Pathology Laboratory Faculty of Medicine, Udayana University/ RSUP Sanglah Denpasar in 2017. The samples were evaluated using H & E staining while E-cadherin expression was examined by using Immunohistochemistry technique (IHC). Pearson chi-square was performed to analyze the data with p-value less than 0.05 was considered significant or valid. Result: Descriptive statistics showed that the samples were homogeneous in term of age between ductal and lobular types (p=0.668). Breast cancer was found to be more prevalent on the left breast compared to the right one in both in ductal and lobular types. IHC staining showed that E-cadherin expression was significantly lower in lobular types (9.1% positive) compared to ductal (60.0% positivity) and, thus, can be used to differentiate them (p=0.000). Conclusion: E-cadherin expression was a valid biomarker to differentiate ductal and lobular type invasive breast carcinoma. More comprehensive study with larger number of samples is required to assess the generality of this finding

Keywords: *E-cadherin, Breast carcinoma, Ductal type, Lobular type.*

Introduction

Cancer is still poses as a health problem worldwide both in developed and developing countries including Indonesia. Breast cancer is the most common cancer in women and also the leading cause of death in women in developing countries. However, the patients tend to be diagnosed at advanced stages which limit the treatment option and also poses worse prognosis. According to WHO classification 2012, breast carcinoma classified into several subtypes [1].

The most common subtypes of invasive breast carcinoma are ductal and lobular type which differentiated through histologic examination [2]. Histopathological type determination is important because it has implications in the prognosis of the patient. However, determination of the type is sometimes difficult to do especially in indeterminate cases due to the overlapping of the histopathologic feature [3, 6]. Lobular type of invasive breast carcinoma has a different clinical behavior compared to ductal type [3, 7]. Histopathologically, lobular type is characterized by the presence of discohesive cells that distributed between the fibrous stroma which often have characteristics such as small to medium in size with mild to moderate atypia. These characteristics are sometimes difficult to identify by pathologists when screening the tissue samples.

The dis-cohesive growth pattern occurs due to the deregulations of intercellular adhesion, especially those mediated by E-cadherin. E-cadherin is calcium-dependent trans-membrane protein, which mediates intercellular adhesion and cell polarity. E-cadherin maintains cell viability and loss of cadherin adhesion often resulted in apoptosis

induction [7]. Most of the lobular type invasive carcinomas are indicated by loss of E-cadherin expression 3, 8]. In one study, it was found that E-cadherin was not expressed in 93.3% of lobular type cases compared with 15% in ductal type [2]. Other studies have shown that the negative expression of E-cadherin is a sensitive and specific biomarker for confirmatory diagnosis of lobular invasive carcinoma, [3, 4] whereas Singhai et al (2011) suggest that there was a correlation between E-cadherin expression and histologic types, but no correlation with other prognostic factors [3, 9]. However, there still no study that evaluate the validity of E-cadherin in diagnostic setting. Therefore, this study aims to prove the validity of differential expression of E-cadherin expression in ductal and lobular type invasive breast carcinoma.

Methods

Study Design and Specimen Collection

A cross-sectional analytic observational study was conducted in 2017 at Anatomical Pathology Department Faculty of Medicine Udayana University/ Sanglah General Hospital. The samples used in this study were biopsy or surgically removed breast cancer tissue from patients with invasive ductal and lobular breast carcinomas that matched the inclusion and exclusion criteria. Samples were collected on a consecutive basis until the required samples size was met.

Histopathological and Immunohistochemical of E-Cadherin Examination

The IHC staining was conducted in Pathological laboratory of Sanglah General Hospital/Udayana University. Initially, the specimens were processed and then stained with conventional Hematoxylin-Eosin and histopathologic examination was performed to determine the type of carcinoma. To determine the expression of E-cadherin, the paraffin-embedded tissues from biopsy or surgery of patients with ductal or lobular type invasive breast carcinoma, were examined immunohistochemically using The Cell Marque Rabbit Antibody E-cadherin (EP700Y) (Vantagebio).

Statistical Analysis

Initially, the descriptive characteristic of the subject was tabulated and normality testing was conducted by using Kolmogorov-Smirnov Test. Then, the Levene-T Test was performed to find homogeneity of the variance which then continued by chi-square to determine the significance of E-cadherin expression toward breast cancer type with p-value less than 0.05 was considered significant or valid.

Results

Sample distribution based on patient age, location, and E-cadherin expressions are summarized in Table 1, Table 2, and Table 3 respectively. The histopathology features of ductal and lobular type invasive breast carcinoma are showed in Figure 1 and the results of E-cadherin expression are showed in Figure 2.

Table 1: Baseline characteristics of study samples

Parameters	Breast Cancer Type		Total
	Ductal type n=25	Lobular type n=22	
Mean Age	50.1 ± 8.45	48.8 ± 12.20	49.5 ± 10.28
Age Range			
31-40	2 (8.0%)	8 (36.4%)	10 (21.3%)
41-50	10 (40.0%)	5 (22.7%)	15 (31.9%)
51-60	11 (44.0%)	6 (27.3%)	17 (36.2%)
61-70	2 (8.0%)	1 (4.5%)	3 (6.4%)
71-80	0 (0.0%)	2 (9.1%)	2 (4.2%)
Location			
Right breast	12 (48.0%)	9 (40.9%)	
Left breast	13 (52.0%)	13 (59.1%)	
E-Cadherin*			
Positive	15 (60.0%)	2 (9.1%)	
Negative	10 (40.0%)	20 (90.9%)	

*significant at p<0.05; Chi-square test

A total of 47 samples were included in this study. According to histopathological type, 25 samples were invasive carcinoma of no special type (ductal type) and 22 samples were invasive lobular carcinoma (lobular type). The Kolmogorov-Smirnov Test was performed to assess the distribution of age and it proved to be normally distributed (p= 0.200) and homogenous (Levene-T test) (p=0.057). The youngest patient of invasive breast carcinoma was 33 years old while and the oldest was 73 years old. Most patients with ductal type were aged between 51-60 year (44.0%) while younger age distribution was found in patients with lobular type (31-40 years/36.4%). Overall, the mean age of all samples was 49.5 ± 10.28 with 50.1 ± 8.45 for ductal type and 48.8 ± 12.20 in the lobular type group. As for the initial analysis, there was no significant difference in mean age between ductal and lobular types (p=0.668).

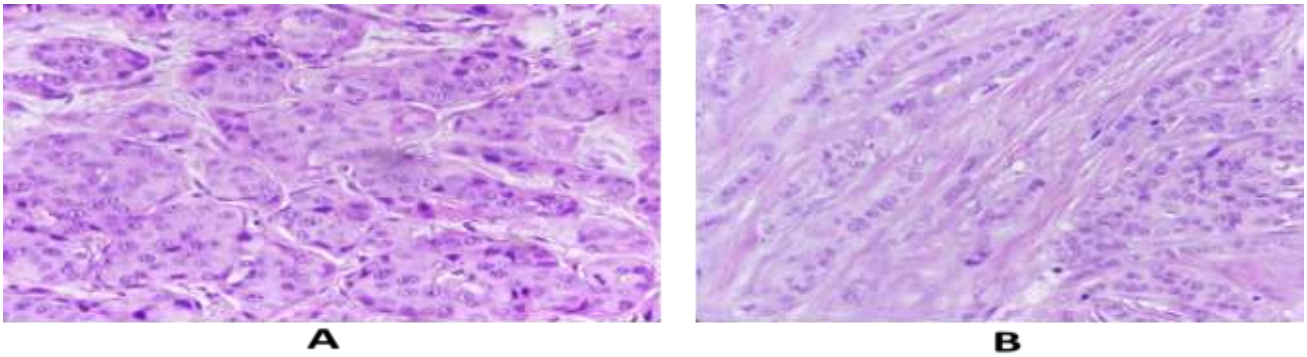

Figure 1: A. Ductal Type Invasive Breast Carcinoma (H&E, 400x); B. Lobular Type Invasive Breast Carcinoma (H&E, 400x)

Based on the location of the affected breast, the left breast was affected more often than the right one in both ductal and lobular types with frequency of 52.0% and 59.1% respectively. Regarding E-cadherin expression, positive result was found in 60% (15/25) of invasive ductal breast carcinoma while only 9.1% (2/22) samples in lobular type group were positive (Table 1; Figure 2). Analysis by Pearson chi-square test showed that the E-cadherin expression is significantly different between the two grous and thus can be considered as valid to differentiate ductal and lobular type invasive breast carcinoma (p=0.000).

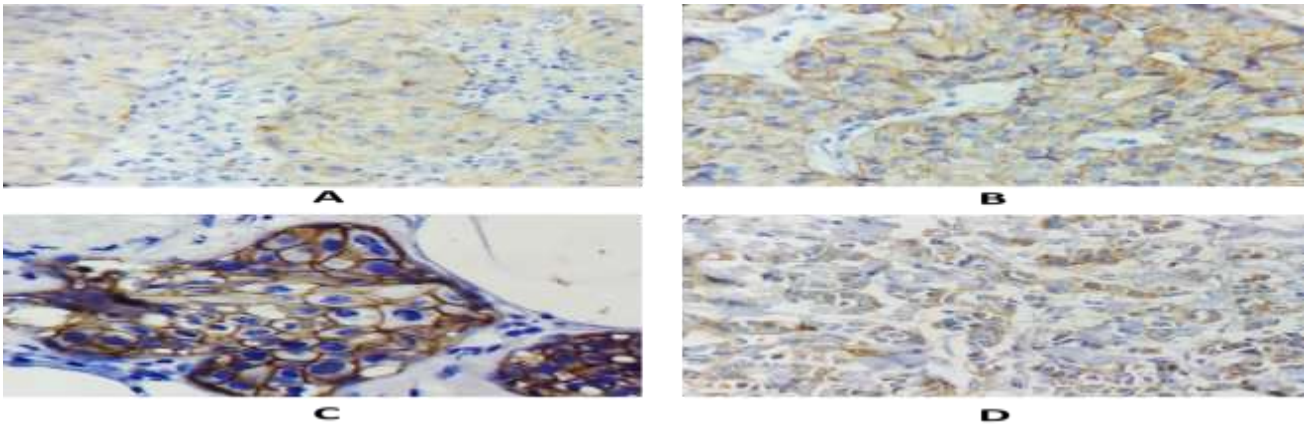

Figure 2: A. Ductal Type Invasive Breast Carcinoma, weak positive expression in >10% neoplastic cells (IHC E-Cadherin, 400x); B. Ductal Type Invasive Breast Carcinoma, moderate positive expression in >10% neoplastic cells (IHC E-Cadherin, 400x); C. Ductal Type Invasive Breast Carcinoma, strong positive expression in >10% neoplastic cells (IHC E-Cadherin, 400x); D. Lobular Type Invasive Breast Carcinoma, negative expression (IHC E-Cadherin, 400x)

Discussion

In this study, the term ductal type invasive carcinoma is carcinoma in accordance with the terminology of invasive ductal carcinoma, not otherwise specified (NOS) (2003) or identical to invasive carcinoma of no special type (NST) (2012). This groups consist of tumor without feature of specific differentiation that characterize other types of breast cancer [10].Ductal type invasive carcinoma is the most common type of breast

carcinoma and contributes to 55% of breast cancer while lobular type tends to be less frequent with prevalence about 10%. Both this types are distinguished by their histopathologic features [11, 12]. Lobular type invasive carcinoma has different characteristics compared to ductal type, such as onset at older age, larger tumor size, multifocal and higher multi-centric proportion.

It also behaves differently and has different prognosis which underlie the importance to differentiate both of them [7, 13].The incidence of breast cancer increases with age. During the premenopausal period the incidence rate increases at 8-9% per year and decreases after menopause at 2-3% per year [14]. In the past decade the incidence of breast cancer has doubled in countries that were previously classified as low risk, such as Japan, Singapore, and urban areas in China. This change corresponds to an increase in economic status and increased risk for breast cancer such as age at menarche, fertility and nutritional status [14]. Another study found that the average age of invasive carcinoma lobular type was 3 years older than the ductal type [12]. Most breast cancers are diagnosed in the left breast compared to the right [15, 17].

However, the underlying reason for this phenomenon is still unknown. A possible explanation is that the left breast tend to be slightly larger than the right, so more breast tissue is at risk of developing cancer.[15,18] Right breast is also tend to be more often used for breastfeeding which could confer some degree of protection against cancer development. Furthermore, women who are predominantly right handed will check left breast more often than the right one and, thus, increase the chance of finding a lump in it [15]. Study by Zeeneldin et al. (2013) found the ratio of laterality of left breast compared with right breast is 1.16. Breast cancer in the left breast is more commonly found at <46 years old and older age.

Ductal type carcinoma tends to be more common in the right breast, whereas the lobular type is more common in the left breast [16]. Consistent with those study, the left breast was found to be more often involved than the right in this study. Lobular type breast carcinoma is an important subtype in breast cancer, which has certain biological and clinical characteristics. This lobular type also has heterogeneous biological nature, so the identification of patients with a poor prognosis is important in order to be assigned to more individualized treatments [7]. However, proper biomarkers that able to differentiate both of these types are yet to be found. E-cadherin is largely expressed by normal epithelial cells.

Selective loss of E-cadherin expression often associated with cellular dedifferentiation and enhancement of invasive properties of cancer cells, thus, E-cadherin is classified as a classic tumor suppressor gene [3, 4]. Immunohistochemical evaluation of E-cadherin can be used to differentiate between well and poorly differentiated breast cancer. Thus, determination of E-cadherin expression could be a highly usefull tool in differentiating ductal and lobular type breast cancer, mainly because loss of E-cadherin expression is rare in non-lobular carcinoma [4]. In this study, positive E-cadherin staining was found in 60% (15/25) of patients with ductal type breast cancer whereas in the lobular type, 90.9% (20/22) of them were negative. This finding is consistent with several previous studies. Turashvili et al. (2007) found that the negative E-cadherin staining was found in 93.3% on the lobular type and only 15% on the ductal type [2].

Other study by Qureshi et al. (2006) found 99.5% positive E-cadherin expression in ductal type while 90% of the lobular type patients had negative staining [4]. In tubule-lobular variant of lobular type invasive carcinoma, E-cadherin expression was 15% [10]. Pai et al. (2013) suggested that E-cadherin expression can be used as a marker to differentiate ductal and lobular type invasive breast carcinoma. In all cases of ductal type, the E-cadherin were expressed in moderate to strong intensity while only 1 case was found with moderate intensity in the lobular type [8].

Kowalski et al. (2003) showed that in ductal type, as much as 55% (12/22) of subjects had normal E-cadherin expression, whereas in the metastatic area all cases showed positive E-cadherin expression. In the lobular type, only 12% were positive in the primary tumor while all metastatic regions showed negative staining. This study proves the relationship between decreased or unexpressed E-cadherin metastasis in patients with breast

carcinoma [19, 20]. In contrast, strong E-cadherin expression has strong correlation with the absence of lymph node metastasis [9].

Other studies also had shown a positive correlation between the prevalence of E-cadherin expression with lobular type invasive breast carcinoma, but it was not correlated with other prognostic variables such as tumor size, tumor grade, ER, PR, and HER-2 expression [3,4,9,19]. Loss of E-cadherin expression also often found in advanced cancer, thus, loss of E-cadherin expression also can be used as a marker of tumor aggressiveness [9].Negative expression of E-cadherin is a sensitive and specific biomarker to confirm the diagnosis of lobular type invasive breast carcinoma, with the specifity of 97.7%, negative predictive value of 96.8%, sensitivity 88.1%, and positive predictive value of 91.2% [3, 4].

Also, the mean overall survival and disease-free survival in patients without E-cadherin expression was shorter than patients with E-cadherin expression [19]. Therefore, E-cadherin is a prospective molecular biomarker that could help pathologists confirming the diagnosis of breast cancer and determining patients with grave prognosis for more comprehensive treatments.

Conclusion

E-cadherin is differentially expressed in ductal and lobular type breast cancer and can validly differentiate both types of breast cancer. However, a larger prospective study is needed to confirm this finding and to rationalize it clinical use.

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Ethic Approval

This study was approved by Ethical Commission of Faculty of Medicine Udayana University with approval letter number 2032/UN.14.2?KEP/2017

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