CHARACTERISTICS AND EXPRESSION OF IMMUNOHISTOCHEMISTRY MUCIN 1 (MUC1) OF INVASIVE BREAST CARCINOMA AT THE H. ADAM MALIK CENTRAL GENERAL HOSPITAL MEDAN

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ABSTRACT

Background: MUC1 has become a topic of concern in cancer treatment because of its upregulation which might influence the invasion, proliferation, and survival of tumor cells by reducing cell adhesion and extracellular cell-matrix adhesion. Besides, stray overexpression from MUC1 is associated with angiogenesis and chemoresistance in cancer. Thus MUC1 has a role in tumorigenesis, progressive and metastasis, this can function as an underlying prognostic factor. An accurate biomarker for early diagnosis and a more accurate prognosis can improve the efficiency of current treatment in breast cancer and is a molecular marker for target therapy.

Objective: Assessing the characteristics and immunohistochemical expression of MUC1 of invasive breast carcinoma.

Materials and Methods: A descriptive study with a cross-sectional approach, using tissue paraffin blocks from 42 patients with invasive breast carcinoma and given a MUC1 immunohistochemistry appearance, then a broad percentage of MUC1 expression was assessed.

Results: MUC1 immunohistochemistry expression in invasive breast carcinoma was mostly positive (76.2%). Based on the involvement of MUC1 immunohistochemistry expression based on the presence or absence of distant invasive breast carcinoma found in M1 the highest shows positive MUC1 expression (100%). Immunohistochemistry expression of MUC1 based on histopathological grading was obtained at the highest grade 3 showing positive MUC1 expression (93.8%).

Conclusion: The presence of distant metastases tends to show high positive MUC1 expression and there is also a tendency that if a histopathological grading is high then it will show that MUC1 expression is also highly expressed

Keywords: invasive breast carcinoma, MUC1 immunohistochemistry expression, metastasis.

Introduction

Breast cancer is a malignancy that is formed from breast epithelial cells that grow and proliferate uncontrollably. Breast cancer is the most common type of cancer in women (154 countries worldwide) and the most common cause of cancer death in women (103 countries worldwide). There are more than 2 million women diagnosed with breast cancer in 2018, and more than half a million women die from this disease. According to data from Global Burden Cancer (GLOBOCAN) in 2018 that breast cancer ranks second most frequently in the world, which found 2,088,849 cases (11.6%) with a mortality rate of 626,279 cases, in Asia showing that breast cancer occupies the second most common cancer with 911,014 new cases (22.3%) and the fifth cause of death with 310,577 cases (6.05%), whereas in Indonesia alone breast cancer was the first cancer with 58,256 new cases (19.18%) and also the main cause of death in women with an estimated 22,692 cases (12.75%). The World Cancer Organization and the World Health Organization estimate an increase in the incidence of cancer in the world around 300 percent by 2030, and the majority occur in developing countries including Indonesia.[1-7]

In the 2013 Basic Health Research Data, the Health Research and Development Agency of the Ministry of Health of the Republic of Indonesia shows that breast cancer is cancer with the highest prevalence in Indonesia, amounting to 0.5 ‰. Yogyakarta Province ranks first at 2.4 ‰, while in North Sumatra Province at 0.4 ‰. According to research conducted by Lingga in 2016 found that as many as 447 breast cancer patients were treated at Medan Haji Hospital in 2014-2015. While research conducted at H. Adam Malik Central General Hospital on breast cancer was reported as many as 222 cases in 2009 by Banurekhaa, as many as 312 cases in 2010 by Taha, and as many as 167 cases in 2016 by Fandini. The incidence of breast cancer increases with age, where breast cancer rarely occurs under the age of 25 years, but its incidence increases rapidly after age 30 and is highest in the perimenopouse age group.[7-13] Breast cancer is a heterogeneous disease of various entities with different morphological appearance and nature. In recent years, it has been proven that diversity is due to genetic changes.[14]

Mucin 1 (MUC1) is a transmembrane glycoprotein and has been investigated as a tumor-associated antigen like a cell membrane glycoprotein, MUC1 is usually expressed at low levels on the apical surface of epithelial cells, including in the pancreas, breast, lung and digestive tract. Excessive expression of MUC1 in breast cancer is a result of some genetic changes and dysregulation of transcription. The MUC1 gene is located on chromosome 1q21, a place that is often changed in breast cancer cells.[15-19]

Changes in mucin expression or changes in glycosylation accompany cancer development and affect cell growth, differentiation, transformation, adhesion, invasion, and immune surveillance. MUC1 is detected on the apical surface of most normal glandular epithelial tissue. In contrast, MUC1 shows diverse localization in malignant tissue, including expression in the cytoplasm and on the membrane.[20]

In a study conducted by Patel et al., found 58% of cases were positively expressed with MUC1. The Do et al. study reported 93.6% positive MUC1, and Else et al. 72.5%.[21-23] Besides, MUC1 has become a topic of concern in cancer treatment because of its upregulation which might influence invasion, proliferation, and survival of tumor cells by reducing cell adhesion and matrix cell-extracellular adhesion. MUC1 has also been shown to be associated with epidermal growth factor receptors (EGFRs), β-catenin and nuclear factor (NF) -κB signaling in regulation of progressive and cancerous invasion. Besides, stray overexpression from MUC1 is associated with angiogenesis and chemoresistance in cancer. Thus MUC1 has a role in tumorigenesis, progressive and metastasis, this can function as an underlying prognostic factor.[15-17]

Material and Methods

We examined 42 samples from cases of invasive breast carcinoma at H. Adam Malik General Hospital in 2018 who were diagnosed histopathologically with hematoxylin-eosin (HE) staining. This study was a descriptive cross-sectional study in which each sample in this study was observed once and only at one time aimed at assessing the characteristics and expression of immunohistochemistry of MUC1 in invasive breast carcinoma in H. Adam Malik General Hospital. Immunohistochemistry expression of MUC1 was assessed based on characteristics including age, tumor size, lymph node involvement (LN), presence or absence of distant metastases, clinical-stage, histopathological type, and histopathological grading. This study also assessed the pattern of immunoreactivity of MUC1 immunohistochemistry expression in invasive breast carcinoma.

The sample used is a sample that meets the inclusion and exclusion criteria, ie the inclusion criteria are all slides and paraffin blocks originating from postoperative breast tissue which are diagnosed as an invasive breast histopathology in an adequate and representative histopathology after staining with hematoxylin-eosin (HE) in H. Adam Malik Central General Hospital Medan in 2018 and has medical record data that includes clinical data, namely age, tumor size, LN involvement, presence or absence of distant metastases and clinical stage. As for the exclusion criteria, the slides and paraffin blocks derived from breast tissue biopsy were diagnosed as histopathologically invasive breast carcinoma and the slides and paraffin blocks could not be re-evaluated or re-cut for examination with MUC1 immunohistochemistry.

The evaluation of MUC1 immunohistochemistry expression in invasive breast carcinoma in this study was considered negative if not expressed or ≤ 10% expressed and positive if expressed > 10% divided into 3 groups, namely 11-49% (low expression), 50-74% (50-74% (intermediate expression) and ≥ 75% (high expression).[24] Immunoreactivity patterns of MUC1 immunohistochemistry expression were assessed based on five patterns, namely the entire membrane, apical, focal cytoplasmic, diffuse cytoplasmic, and 'inside-out'.[25] This research was approved by the Health Research Ethics Committee of the Faculty of Medicine Universitas Sumatera Utara Medan, No: 703/TGL/KEPK FK USU-RSUP HAM/2019.

Results

In this study, 200 cases of invasive breast carcinoma patients were obtained in 2018 at H. Adam Malik General Hospital Medan. Of all cases, researchers took a minimum sample of 42 cases diagnosed histopathologically by conforming to the inclusion and exclusion criteria. The following are the results of the research obtained.

The sample in this study, based on clinical data from the medical records, showed an average age of 50.45 years with the youngest age being 23 years and the oldest age being 70 years. Based on the age of invasive breast carcinoma patients, the highest age group was found in the age group of 50-59 years with 15 cases (35.7%), followed by the age group of 40-49 years with 14 cases (33.3%), the age group > 59 years as many as 7 cases (16.7%), the age group of 30-39 years were 5 cases (11.9%) and the least were found in the age group of 20-29 years as many as 1 case (2.4%). Based on tumor size, the highest tumor size was T4 in 21 cases (50%), followed by T3 in 13 cases (31%), T2 in 4 cases (9.5%) and T1 in 4 cases (9.5%). The highest number of LN involvement was N0 with 28 cases (66.6%), followed by N1 with 13 cases (31%), and N2 with 1 case (2.4%).

Based on the presence or absence of distant metastases, the highest number was M0 in 35 cases (83.3%), followed by M1 in 7 cases (16.7%). The most common clinical stage was stage III with 21 cases (50%), followed by stage II with 10 cases (23.8%), stage IV with 7 cases (16.7%) and the least was stage I with 4 cases (9.5%) (Table 1).

Microscopic examination of preparations with HE staining showed the most common type of histopathological type was invasive carcinoma no special type, as many as 30 cases (71.4%), whereas 12 other cases encountered histopathological type of breast type special carcinoma which consisted of 6 cases (14.3%)

invasive lobular carcinoma, 3 cases (7.1%) mucinous carcinoma, 1 case (2.4%) carcinoma with medullary features, 1 case (2.4%) carcinoma with apocrine differentiation and 1 case (2.4 %) carcinoma with signet-ring cell differentiation (Table 1). Based on histopathological grading, it was found that the most frequently found was grade 2 and grade 3, each of which were 16 cases (38.1%), followed by grade 1 as many as 10 cases (23.8%) (Table 1).

Table 1 Frequency Distribution of Characteristics of Invasive Breast Carcinoma

Characteristics (n=42)	Total (n)	Persentage (%)
Age (years), mean ± SD	50,45 ±9,83	
20 – 29	1	2.4
30 – 39	5	11.9
40 – 49	14	33.3
50 – 59	15	35.7
>59	7	16.7
Tumor Size		
T1	4	9.5
T2	4	9.5
T3	13	31
T4	21	50
Lymph Node (LN)		
N0	28	66.6
N1	13	31
N2	1	2.4
Distant Metastasis		
M0	35	83.3
M1	7	16.7
Stage		
I	4	9.5
II	10	23.8
III	21	50
IV	7	16.7
Histopathological Type		
Invasive carcinoma of no special type	30	71.4
Invasive lobular carcinoma	6	14.3
Mucinous carcinoma	3	7.1
Carcinoma with medullary features	1	2.4
Carcinoma with apocrine differentiation	1	2.4
Carcinoma with signet ring cell differentiation	1	2.4
Histopathological Grading		
Grade 1	10	23.8
Grade 2	16	38.1
Grade 3	16	38.1

The distribution of MUC1 immunohistochemical expression in patients with invasive breast carcinoma in this study, obtained more positive MUC1 expression in 32 cases (76.2%) compared to the negative 10 cases (23.8%). MUC1 expression in the positive invasive breast carcinoma group, there were 14 cases (33.3%) with high expression, followed by low expression 13 cases (31%), and intermediate expression 5 cases (11.9%) (Table 2).

Table 2 Frequency Distribution of MUC1 Immunohistochemistry Expression of Invasive Breast Carcinoma

MUC1 expression	Total (n)	Persentage (%)
Positive		
Low expression	13	31.0
Intermediate expression	5	11.9
High expression	14	33.3
Negative	10	23.8
Total	42	100

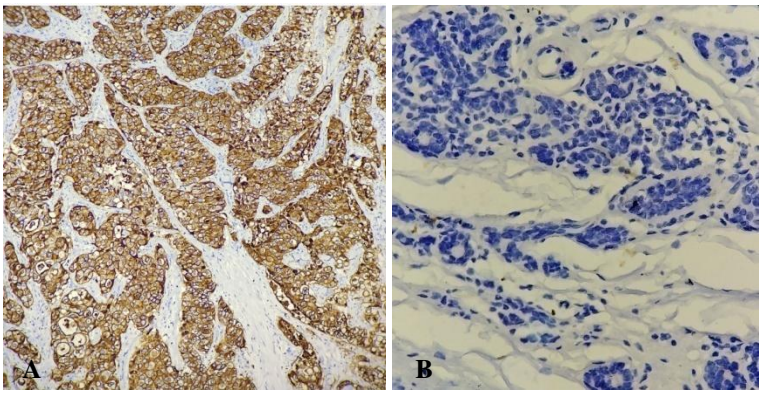

Figure 1. MUC1 immunohistochemistry expression. **A**. Positive MUC1 expression. **B**. Negative MUC1 expression (x100 Magnitude).

Distribution of MUC1 immunohistochemistry expression based on age of patients with invasive breast carcinoma for the age group of 20-29 years was obtained from 1 case found showing positive MUC1 expression (100%). The 30-39 years age group obtained from 5 cases showed positive MUC1 expression was 3 cases (60%) and negative expression was 2 cases (40%). The age group of 40-49 years was obtained from 14 cases showing positive MUC1 expression was 11 cases (78.6%) and negative expression 3 cases (21.4%). The age group of 50-59 years was obtained from 15 cases showing positive MUC1 expression was 12 cases (80%) and negative expression was 3 cases (20%), and in the > 59 years group it was found out of 7 cases showing positive MUC1 expression was 5 cases (71 , 4%) and negative expression in 2 cases (28.6%) (Table 3).

Based on tumor size in invasive breast carcinoma, results in T2 showed positive MUC1 expression of all (100%) of the 4 cases encountered. For T4 obtained from 21 cases showing positive MUC1 expression were 17 cases (81%) and negative expression 4 cases (19%). In T1 obtained from 4 cases showing positive MUC1 expression were 3 cases (75%)% and negative expression in 1 case (25%)%, whereas T3 obtained in 13 cases showing positive MUC1 expression were 8 cases (61.5%) and expression negative 5 cases (38.5%) (Table 3).

Based on the involvement of LN in invasive breast carcinoma, the results showed that N2 showed positive MUC1 expression (100%) of 1 case found. For N0, it was obtained from 28 cases showing positive MUC1 expression was 22 cases (78.6%) and negative expression 6 cases (21.4%). Whereas the N1 obtained from 13 cases showed positive MUC1 expression was 9 cases (69.2%) and negative expression 4 cases (30.8%). (Table 3).

Based on the presence or absence of distant metastases, the results showed that M1 showed a positive MUC1 expression of all (100%) of the 7 cases encountered. Whereas in M0, 35 cases showed positive MUC1 expression in 25 cases (71.4%) and negative cases in 10 cases (28.6%) (Table 3).

Based on clinical stage it was found that at stage IV all MUC1 expressions were positive (100%) of the 7 cases encountered. In stage II, 10 cases showed positive expression of MUC1, 8 cases (80%) and negative cases 2 cases (20%). For stage I obtained from 4 cases showing a positive MUC1 expression was 3 cases (75%) and negative expression 1 case (25%). Whereas in stage III, it was found out of 21 cases showing positive MUC1 expression, 14 cases (66.7%) and negative expression 7 cases (33.3%) (Table 3).

Based on the histopathological type of invasive breast carcinoma in this study it was found that mucinous carcinoma, carcinoma with medullary features, carcinoma with apocrine differentiation, all showed positive MUC1 expression (100%), each of which was obtained from 1 case found. In invasive carcinoma of no special type obtained from 30 cases found showing positive MUC1 expression was 24 cases (80%) and negative expression 6 cases (20%). Invasive lobular carcinoma obtained from 6 cases showed positive expression of MUC1 in 3 cases (50%) and negative expression in 3 cases (50%). Whereas carcinoma with signet-ring cell differentiation showed negative MUC1 expression (100%) from 1 case found (Table 3).

Based on histopathological grading, it was found that in grade 3 out of 16 cases obtained showed more positive MUC1 expression, namely, 15 cases (93.8%) while negative expression was found in 1 case (6.2%). In grade 2 out of 16 cases found showing positive MUC1 expression was found in 12 cases (75%) and negative expression in 4 cases (25%). Whereas grade 1 out of 10 cases obtained showed positive MUC1 expression found in 5 cases (50%) and negative expressions in 5 cases (50%) (Table 3).

Table 3 Frequency Distribution of MUC1 Immunohistochemical Expression Based of Characteristics of Invasive Breast Carcinoma Patient

Characteristics (n=42)	MUC1 immunohistochemistry expression				Total
	Positive (n=32)		Negative (n=10)		
	n	%	n	%	n
Age (years)					
20-29	1	100	0	0	1
30-39	3	60	2	40	5
40-49	11	78.6	3	21.4	14
50-59	12	80	3	20	15
>59	5	71.4	2	28.6	7
Tumor Size					
T1	3	75	1	25	4
T2	4	100	0	0	4
T3	8	61.5	5	38.5	13
T4	17	81	4	19	21
Lymph Node (LN)					
N0	22	78.6	6	21.4	28
N1	9	69.2	4	30.8	13
N2	1	100	0	0	1
Distant Metastasis					
M0	25	71.4	10	28.6	35
M1	7	100	0	0	7
Stage					
I	3	75	1	25	4
II	8	80	2	20	10
III	14	66.7	7	33.3	21
IV	7	100	0	0	7
Histophatology Type					
IC NST	24	80	6	20	30
ILC	3	50	3	50	6
Mucinous carcinoma	3	100	0	0	3
Carcinoma with medullary features	1	100	0	0	1
Carcinoma with apocrine differentiation	1	100	0	0	1
Carcinoma with signet ring cell differentiation	0	0	1	100	1
Histophatology Grading					
Grade 1	5	50	5	50	10
Grade 2	12	75	4	25	16
Grade 3	15	93.8	1	6.2	16

Distribution of immunoreactivity patterns of MUC1 expression in invasive breast carcinoma found that the majority of immunoreactivity patterns were diffuse cytoplasmic, found in 11 cases (26.2%), followed by apicals for 9 cases (21.4%), all membranes by 8 cases (19 %), focal cytoplasmic in 8 cases (19%), and the least encountered was 'inside-out' in 1 case (2.4%). This immunoreactivity pattern of MUC1 expression was not found or negative in 5 cases (11.9%) (Table 4).

Table 4 Frequency Distribution of Immunoreactivity Patterns of MUC1 Immunohistochemistry Expression of Invasive Breast Carcinoma

Immunoreactivity Patterns MUC1 Expression	Total (n)	Persentage (%)
Entire membrane	8	19
Apical	9	21,4
Focal cytoplasmic	8	19
Diffuse cytoplasmic	11	26,2
'Inside-out'	1	2,4
Negative	5	11,9
Total	42	100

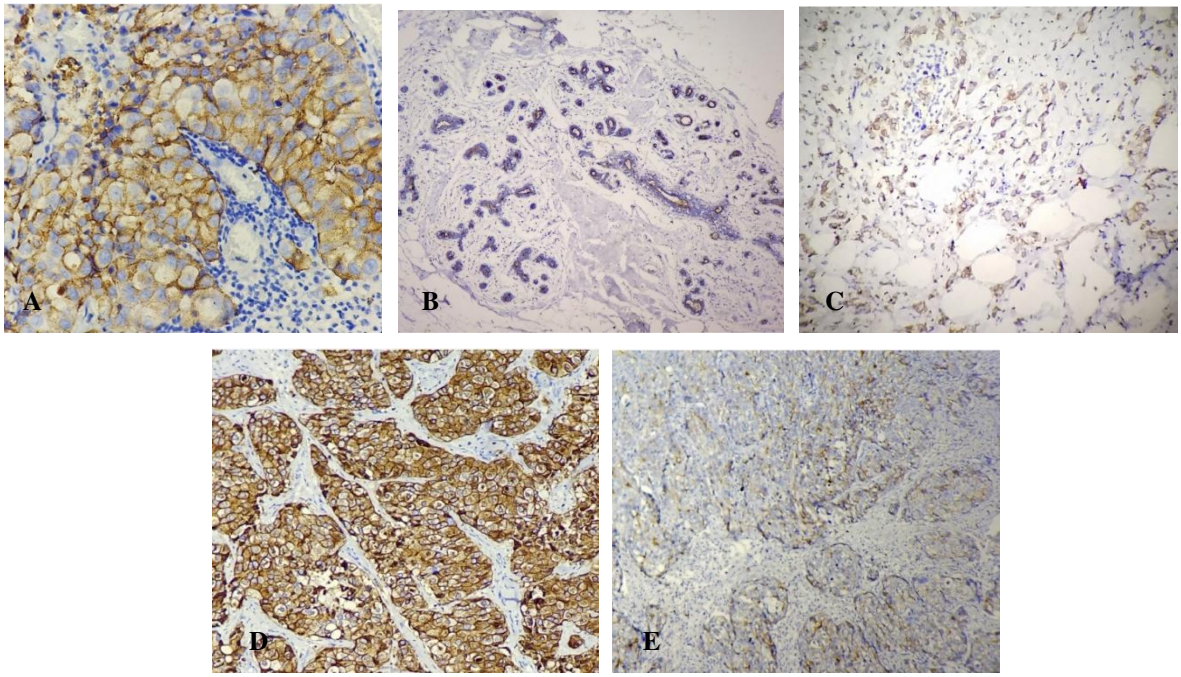

Figure 2. Immunoreactivity patterns of MUC1 expression. **A**. Entire membrane. **B**. Apical. **C**. Focal cytoplasmic. **D**. Diffuse cytoplasmic. **E**. 'Inside-out' (x100 magnitude).

Discussion

Research results from 42 cases of invasive breast carcinoma for the age group were found to be more common in the 50-59 years age group ie, 15 cases and were found at least in the age group 20-29 years ie, 1 case. The average age of 50.45 years, with the youngest age is 23 years and the oldest age is 70 years. This is slightly different in the research conducted by Fandini at H. Adam Malik General Hospital Medan, where the most common age group was 40-49 years with 63 cases from 167 cases overall, while for the 50-59 years age group there were 50 cases but the least age group was found to show the same results, namely the age group of 20-29 years as many as 3 cases.[12] According to the research conducted by Lingga in Medan Haji General Hospital, it was found that the most age group was the age group ≥ 40 years as many as 71 cases out of 96 overall cases,[9] and research conducted by Baldus et al. found the average age was 61.8 years.[26] From the results of this study showed that breast carcinoma incidence is more common in women aged > 50 years. The biggest risk for developing breast cancer is prolonged exposure to estrogen, which makes female sex and old age a significant risk factor. Risk is largely based on age, and is often estimated based on decades. After menopause, and especially after the age of 65, the risk increases several fold. For example, for ages 30-39, the risk is 0.43%, for ages 40-49, the risk is 1.44%, for ages 50-59, the risk is 2.63%, and for ages 60-69, the risk is 3.65%.[27]

In this study also found cases of invasive breast carcinoma at a younger age, namely the age group 20-29 years found 1 case, and 5 cases in the 30-39 years age group. Breast cancer in young women is uncommon, affecting only 4-6% of women under the age of 40 years,[28] and has risk factors, namely familial breast cancer syndromes and genetic testing for mutations of BRCA1 or BRCA2 and, more rarely, mutations TP53. In a population-based case control study, it was found that a woman with breast cancer under the age of 35 had a detected BRCA1 or BRCA2 mutation of 9.4%.[29] Usually, breast cancer in young women is more aggressive, a prognosis that is more less favorable, and worse survival rate compared to older patient.[28]

Based on tumor size, in this study it was found that the most frequently encountered was T4 in 21 cases. This is not in line with research conducted by Patel et al. which obtained the most tumor size was T2 in 28 cases out of 50 overall cases.[21] and the study of Peters et al. obtained the highest tumor size as well as T2 in 12 cases out of 24 overall cases.[30] The study conducted by Garbar et al. found that the highest tumor size was T1 in 33 cases out of 55 cases overall,[31] and the study conducted by van der Veght et al. obtained the highest tumor size in T1 and T2 respectively 109 cases out of 243 cases overall.[25] The differences that occur can be said due to differences in the location of research conducted in this regard relating to socio-economic, education, environment and people's lifestyles. Indonesian people's awareness in examining their health, especially breast health, is still very low, in addition to the low economy and health insurance system that has not protected it thoroughly so that it is difficult to do breast screening such as mammography examinations, this is different that occurs outside Indonesia, so that sufferers are more quickly detected early, therefore there are many tumors that are still relatively small.

The involvement of lymph nodes (LN) in this study which was more common was N0 or LN involvement was absent, as many as 28 cases. This is in line with research conducted by Patel et al. which was found to be more N0 as many as 17 cases out of 50 overall cases[21] and according to the study of Peters et al. also found similar things that N0 was more frequently found, 13 cases out of 24 cases overall.[30] Based on the presence or absence of distant metastases found in this study the most were M0 or no distant metastases were found ie 35 cases, whereas for M1 or the presence of distant metastases in 7 cases. This is in line with research conducted by Tang et al. which is found to be slightly more found M0 than M1 which is as many as 64 cases (51.2%) of 125 overall cases.[32] See the results of this study and other studies that found more for which there are no metastases, either regional metastases (LN) or distant metastases. This can be caused by the fact that breast cancer can develop if genetic information from cells carries a mutation and this change occurs depending on many factors that influence each other, such as age, height and weight, the immune system and hormones.[33] These cancer cells requires a metastatic cascade of steps to get out of the primary place to spread to various organs, and to reach these stages cancer cells must face many natural barrier layers.[34]

The clinical stage of this study found more in stage III as many as 21 cases, while stage IV as many as 7 cases. This is in line with research conducted by Lingga et al. in Haji General Hospital Medan, it was found that more stages were stage III with 58 cases, while stage IV had 7 cases out of 96 overall cases,[9] but differed from the results of research from Patel et al. which gets the most staging is stage II as many as 25 cases out of 50 overall cases.[21] The results of this study indicate that many patients are diagnosed with advanced stages (stage III and stage IV). The existence of this difference is due to the unequal location of the study, socio-economic, completeness of supporting facilities and infrastructure, as well as the awareness of the patient himself to conduct an early examination of the breast.

The most common histopathological type found in this study was invasive carcinoma of no special type in 30 cases. Research conducted by Patel et al. obtained the same results that the most common histopathological type was invasive carcinoma of no special type as many as 46 cases out of 50 overall cases,[21] and research from Garbar et al. also found the most was invasive carcinoma. of no special types as many as 55 cases out of 71 overall.[31] This is consistent with the literature which states that invasive carcinoma of no special type is the largest group of invasive breast carcinomas, which occurs in about 40-75% of all invasive breast carcinomas.[35]

Histopathological grading in this study was found in grade 2 and grade 3 in 16 cases respectively. This is in line with the research of Patel et al. which obtained the most results in grade 2 with 23 cases, while grade 3 was found in 19 cases out of 50 overall cases,[21] and research from Garbar et al. also getting the most grade is grade 2 as many as 23 cases and grade 3 as many as 22 cases out of 55 cases overall.[31] More high grade was found in this study so we can measure the picture of a tumor that has a the potential to metastasize or cause death due to high grade is characterized by a poor prognosis.[36]

The results of 42 cases of invasive breast carcinoma with MUC1 expression found that the majority of cases showed positive expression in 32 cases (76.2%) compared with negative expression in 10 cases (23.8%). This result is no different from the study conducted by Wu et al. which showed more positive expressions, 16 cases (76.2%) out of 21 cases overall,[24] studies of Do et al. 206 cases (93.6) %) out of 220 cases overall.[22] and Patel et al. 29 cases (58%) out of 50 overall cases.[21] In this study, of the three groups of MUC1 expressions that were positively expressed, tended to be more frequent in the high expression group of 14 cases (33.3%). This is in line with research by Rakha et al. which divides MUC1 expression into 3 groups, namely negative, low expression and high expression, and the result is that high expresion is more often found (42%), [37] and according to research by Wang et al. which divides MUC1 expression into 2 groups namely low expression and high expression, it was found that the high expression group was also found as many as 109 cases (83.21%) of 131 cases overall.[38] However, in other studies conducted by Wu et al. showed different results, namely positive MUC1 expression was slightly more common in the 11-49% group (low expression), ie as many as 6 cases (29%) out of 21 overall cases.[24] The presence of positive expressions was more common than the negative expressions according to the researchers due to the occurrence of abberant glycosylation is more often found in the samples of this study, while the presence of negative expressions due to not the occurrence of abberant glycosylation so that it is not expressed.

MUC1 immunohistochemical expression based on age of patients with invasive breast carcinoma found that in the age group 20-29 years showed 100% positive expression of MUC1. Whereas for other age groups the expression of positive MUC1 was also found more than the negative MUC1 expression. The results were not different from the study of Wang et al. who examined the relationship between the MUC1 staining pattern (CD227) with the clinicopathological parameters by dividing the age group into 2 groups, namely the age group < 49 years and the age group ≥ 49, with the results in the age group < 49 years showed the expression of MUC1 positive was more common, namely 98 cases (54.1%) of 181 cases overall. In the study of Wang et al. the research results were obtained which showed no significant relationship between MUC1 expression with age.[38]

Immunohistochemistry expression of MUC1 based on tumor size showed T2 with more positive MUC1 expression (100%) than 4 cases and T3 showed more negative expression (38.5%) than 13 cases. This is in line with research from Patel et al. which was found in T2 positive MUC1 expression (30%) of 50 overall cases.[21] From the results of this study it can be seen that there is no apparent tendency to occur, where if the tumor size is large then the MUC1 expression is positive also high. According to research conducted by Patel et al. it was found that there was no significant relationship between tumor size and MUC1 expression.[21]

MUC1 expression based on LN involvement showed that in N2 there was 100% positive MUC1 expression, whereas negative MUC1 expression was more in N1 (30.8%). This result is different from the study conducted by Do et al. which found that N0 was more likely to be found with positive MUC1 expression (92.7%) out of 82 cases.[22] Research from Patel et al. found that N1 was more likely to have positive MUC1 expression (24%) of 50 overall cases.[21] From the results of this study it was found that the presence of LN (N2) showed a tendency for high positive MUC1 expression. This is confirmed by research conducted by Wang et al. finding that there is a significant relationship between LN involvement and the expression of MUC1.[38]

MUC1 expression based on the presence or absence of distant metastases found that M1 showed positive MUC1 expression of all (100%) of the 7 cases obtained. Whereas in M0 out of 35 cases obtained, it showed that not all of them were positively expressed (71.4%), but there were also those who were negatively expressed (28.6%). Researchers see a tendency that in cases with distant metastases will be positively higher expression. No studies that have described the expression of MUC1 and distant metastases have been found in the literature. MUC1 is greatly increased during clinical development from normal tissue to metastasis.[39]

Based on clinical stage, it was found that more positive MUC1 expression was stage IV (100%) of the 7 cases obtained. For stage I and II from this study, it was found that MUC1 expression was more positive than stage III. This is not in line with the study of Patel et al. which gets more positive expression is stage II (30%) of 50 overall cases.[21] The results of this study do not show a tendency that if the higher the stage of the patient the higher the positive MUC1 expression will be, although in stage IV all positive expressions were obtained. According to research conducted by Patel et al. it was found that there was no significant relationship between staging and MUC1expression.[21]

Immunohistochemistry expression of MUC1 based on histopathological type found that from the histopathological type of mucinous carcinoma, carcinoma with medullary features, and carcinoma with apocrine differentiation, all three showed more positive MUC1 expression (100%). Whereas carcinoma with signet-ring cell differentiation showed more negative MUC1 expression (100%). For the most common invasive carcinoma of no type found in this study, it showed more positive expression of MUC1 (80%) while the rest found negative MUC1 expression (20%). The presence of negative MUC1 expression in several types of histopathology according to researchers due to the influence of the presence or absence of abberant glycosylation, which can affect the expression of MUC1. According to the results of research from Lau et al. it was found that invasive carcinoma of no special type, invasive lobular carcinoma, and mucinous carcinoma were each positively expressed MUC1 100%.[40] The results of this study indicate that there is a tendency for mucinous carcinoma to show MUC1 expression which is positive, because mucinous carcinoma also contains extracellular mucin components. Whereas the carcinoma with signet ring cell differentiation showed negative MUC1 expression because it contained many intracellular components of mucin.

MUC1 expression based on histopathological grading showed that in grade 3 there were more positive expressions (93.8%) while negative expressions were less (6.2%) of the 16 cases obtained. For grade 2 there were fewer positive expressions (75%) but more negative expressions (25%) from 16 cases were obtained compared to grade 3. While in grade 1 out of 10 cases there were fewer positive expressions (50%) but more negative expressions were found (50%) compared to grade 2 and grade 3. The results of this study showed a tendency that the higher the histopathological grading, the higher the positive expression of MUC1, and vice versa. This is different from the study conducted by Patel et al. which showed that positive MUC1 expression was more common in grade 2 (28%) of 50 overall cases.[21]

This study also examined the pattern of immunoreactivity of MUC1 expression, with the most common pattern was diffuse cytoplasmic in 11 cases. This is not much different from the results of research from van der Vegt et al. found that the most frequent pattern was cytoplasmic diffuse in 173 cases out of 237 cases overall.[25] Research from Do et al. also found that the most pattern was cytoplasmic in 137 cases of 220 cases overall,[22] and in line with research conducted by Garbar et al. and Wang et al. obtained the most patterns were cytoplasmic each 66 cases from 71 cases overall and 101 cases out of 131 cases overall.[31;38] For apical patterns from the results of this study found 9 cases while the pattern 'inside out' obtained 1 case. The results of the study from van der Vegt et al. found 64 cases of apical patterns and 23 cases of inside out obtained 23 cases from 237 cases overall.[25] While the results of Wang et al. showed no apical patterns from 131 overall cases.[38] Patterns based on the location of MUC1 expression i.e apical membrane expression and 'inside-out' expression, both are associated with less aggressive biological profiles.[25] Apical expression is associated with good functional differentiation and prognosis whereas cytoplasmic and / or membrane are associated with poor survival compared to apical expressions.[37]

Conclusion

The MUC1 immunohistochemistry expression showed that the highest positive expression was 76.2%, with the highest expression group being the most positive. The presence of distant metastases tends to show high positive MUC1 expression and there is also a tendency that if a histopathological grading is high then it will show that MUC1 expression is also highly expressed. Immunoreactivity pattern of MUC1 immunohistochemistry expression in invasive breast carcinoma showed the most diffuse cytoplasmic pattern associated with poor survival compared to apical expressions.

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