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STUDY OF ASSOCIATION BETWEEN EXPRESSION OF MUC 1 AND CLINICOPATHOLOGICAL PARAMETERS OF BREAST CARCINOMA

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ABSTRACT

Background: Breast carcinoma is a heterogeneous malignancy requiring reliable prognostic biomarkers. MUC1, a transmembrane glycoprotein, is frequently overexpressed and aberrantly localized in breast cancer, contributing to tumor progression and metastasis. Its association with clinicopathological parameters and therapeutic potential makes MUC1 a promising prognostic marker and target for personalized treatment. The aim and objective is to study the expression of MUC1 in different molecular subtypes of breast carcinoma and evaluate its association with molecular classification based on immunohistochemical markers.

Materials and Methods: This hospital-based observational study was conducted in the Department of Pathology, Guntur Medical College, from October 2020 to June 2022. A total of 72 breast carcinoma cases were analysed. Histopathological evaluation, grading, and staging were performed using standard WHO, Nottingham, and AJCC criteria. Immunohistochemistry for ER, PR, HER2/neu, Ki-67, and MUC1 was carried out in 40 cases. Associations between MUC1 expression and clinicopathological parameters were analysed using the Chi-square test.

Results: A total of 72 breast carcinoma cases were analysed, of which 40 underwent immunohistochemical evaluation. Most patients were above 45 years of age (82%), with a mean age of 55.3 years. Invasive Breast Carcinoma of No Special Type was the predominant histological subtype (93.1%). Grade II tumours (56%) and Stage II disease (64%) were most common. Hormonal receptor positivity was observed in 42.5% of cases, while triple-negative breast carcinoma constituted 37.5%. MUC1 expression showed significant association with age, tumour stage, histological subtype, and HER2-enriched molecular subtype, but not with tumour grade, lymph node status, or hormonal receptor status.

Conclusion: The study showed that breast carcinoma predominantly affected women above 45 years and was mainly of the IBC-NST subtype. Hormone receptor-negative and triple-negative tumours were common and associated with adverse prognostic factors. MUC1 expression correlated with tumour stage, histological subtype, and HER2-enriched cancers, indicating potential prognostic significance.

Keywords: Breast Carcinoma, Immunohistochemistry, Clinicopathological Parameters, Breast Cancer Biomarkers.

INTRODUCTION

Breast carcinoma is the most frequently diagnosed cancer among women worldwide and remains one of the leading causes of cancer-related mortality. Despite considerable advances in early detection, diagnosis, and treatment, breast cancer continues to pose a major public health challenge due to its heterogeneous nature and variable clinical outcomes. Traditional prognostic factors such as tumor size, histological grade, lymph node status, clinical stage,

and hormone receptor expression are commonly used for patient management. However, these factors alone may not accurately predict disease progression and survival in all patients. Therefore, there is a growing interest in identifying molecular biomarkers that can improve prognostic assessment and facilitate personalized treatment strategies.[1,2] Mucins are a family of high-molecular-weight glycoproteins expressed on the surface of epithelial cells, where they play an important role in protecting and lubricating epithelial tissues. Among the different mucins, Mucin 1 (MUC1) has attracted significant attention because of its involvement in the development and progression of several epithelial malignancies, including breast carcinoma. MUC1 is a transmembrane glycoprotein encoded by the MUC1 gene located on chromosome 1q21. Under normal physiological conditions, MUC1 is expressed on the apical surface of glandular epithelial cells and contributes to maintaining epithelial integrity and protecting tissues from environmental injury.[1-8] During malignant transformation, MUC1 undergoes several structural and functional alterations. Breast carcinoma cells commonly exhibit overexpression of MUC1, loss of normal apical localization, abnormal glycosylation, and redistribution of the protein over the entire cell surface. These changes expose novel antigenic sites and contribute to tumor progression. Aberrant MUC1 expression has been associated with increased cellular proliferation, reduced apoptosis, enhanced invasion, metastatic spread, and immune evasion. Consequently, MUC1 is considered an important molecule involved in breast cancer pathogenesis.[1,2,8] The biological significance of MUC1 extends beyond its role as a structural membrane protein. The cytoplasmic domain of MUC1 interacts with several intracellular signaling molecules and pathways involved in cell growth and survival. Studies have demonstrated that MUC1 can regulate signaling pathways associated with tumor progression, including those involving β-catenin and growth factor receptors. These interactions promote epithelial-mesenchymal transition, facilitate tumor invasion, and increase metastatic potential. Furthermore, MUC1 has been implicated in resistance to apoptosis and therapeutic interventions, highlighting its role in promoting aggressive tumor behavior.[2,8] A large proportion of breast carcinomas demonstrate increased MUC1 expression when compared with normal breast tissue. Immunohistochemical studies have shown that normal breast epithelium exhibits a polarized apical staining pattern, whereas malignant cells display diffuse membranous and cytoplasmic staining. This altered pattern of expression has been linked to tumor aggressiveness and adverse clinical outcomes. As a result, MUC1 has emerged as a potential biomarker for evaluating the biological behavior and prognosis of breast cancer.[3,4] Several studies have investigated the association between MUC1 expression and clinicopathological characteristics of breast carcinoma. Increased MUC1 expression has been reported in association with higher tumor grade, lymph node metastasis, advanced disease stage, and poorer survival outcomes. McGuckin and colleagues demonstrated that elevated MUC1 expression was significantly associated with lymph node involvement and reduced survival, suggesting its role in tumor dissemination and progression.[3] Additionally, abnormal localization patterns of MUC1 have been shown to correlate with unfavorable pathological features and worse clinical outcomes.[4]

The relationship between MUC1 expression and hormone receptor status has also been explored extensively. Evidence suggests that MUC1 expression is frequently observed in estrogen receptor-positive breast cancers, indicating possible hormonal regulation of the protein. Hormonal influences on MUC1 synthesis and expression have been demonstrated in both laboratory and clinical studies.[5] Furthermore, lower MUC1 expression has been reported in triple-negative breast cancers, which are generally associated with aggressive clinical behavior and poorer prognosis.[6] These findings indicate that MUC1 may have an important role in defining the molecular characteristics of breast carcinoma.In addition to its prognostic value, MUC1 has emerged as a promising therapeutic target. Tumor-associated MUC1 exhibits abnormal glycosylation patterns that create unique antigenic epitopes, making it distinguishable from MUC1 expressed in normal tissues. This property has led to the development of MUC1-directed therapeutic strategies, including cancer vaccines, monoclonal antibodies, antibody-drug conjugates, and cellular immunotherapies. Recent advances in precision oncology have further strengthened interest in MUC1 as a target for individualized cancer treatment.[8,10] Although numerous studies have evaluated the significance of MUC1 in breast carcinoma, conflicting findings regarding its prognostic value still exist. Differences in patient populations, immunohistochemical techniques, scoring methods, and molecular subtypes may contribute to these variations. Therefore, further studies are needed to clarify the relationship between MUC1 expression and established clinicopathological parameters. The present study is undertaken to evaluate the expression of MUC1 in breast carcinoma and to determine its association with various clinicopathological parameters. Understanding these associations may provide valuable insights into tumor behavior and help establish the role of MUC1 as a prognostic biomarker and potential therapeutic target in breast cancer.[1-10]

Aim and objectives: To study the expression of MUC1 in different molecular subtypes of breast carcinoma and evaluate its association with molecular classification based on immunohistochemical markers.

MATERIALS AND METHODS

The present study was a hospital-based observational study conducted in the Department of Pathology, Guntur Medical College, Guntur, Andhra Pradesh. The study was carried out over a period of twenty-one months, from October 2020 to June 2022. During this period, all eligible cases of breast carcinoma that satisfied the inclusion criteria were enrolled in the study. A total of 72 cases were included for analysis. The study comprised mastectomy and lumpectomy specimens that were histopathologically diagnosed as carcinoma breast. Cases diagnosed on tru-cut biopsy alone were excluded from the study. Other exclusion criteria included benign breast tumours, inflammatory and infective lesions of the breast, recurrent carcinoma breast cases, and patients who had received any form of treatment before surgical intervention. Prior approval was obtained from the Institutional Ethics Committee before initiation of the study. Patient confidentiality and ethical standards were maintained throughout the research period. Relevant clinical information such as age, presenting symptoms, tumour characteristics, and other pertinent findings were collected from medical records and documented in a structured case proforma. Gross examination of the surgical specimens was performed according to standard guidelines recommended for oncological pathology specimens. Important gross findings, including tumour size, site, appearance, status of surgical margins, nipple-areola complex involvement, and lymph node status, were carefully recorded. All tissue specimens were fixed in 10% neutral buffered formalin and subjected to routine histopathological processing. Formalin-fixed paraffin-embedded tissue blocks were prepared following standard laboratory procedures. Sections of appropriate thickness were cut from the paraffin blocks and stained with Haematoxylin and Eosin (H&E). The stained sections were examined under light microscopy for detailed histomorphological evaluation. The histological classification of breast carcinomas was performed according to the World Health Organization (WHO) Classification of Breast Tumours, 2019. Tumour grading was carried out using the Nottingham Histological Grading System, also known as the Elston–Ellis modification of the Scarff–Bloom–Richardson grading system. The grading was based on assessment of tubule formation, nuclear pleomorphism, and mitotic count. Pathological staging was assigned according to the American Joint Committee on Cancer (AJCC) TNM staging system, 8th edition. Histopathological reporting was done following the recommendations of the College of American Pathologists (CAP) protocol. For immunohistochemical evaluation, representative tumour areas were selected from H&E-stained sections. Fresh sections were obtained from the corresponding paraffin blocks and subjected to immunohistochemical staining using standard protocols. The markers studied included Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor-2 (HER2/neu), Ki-67, and MUC1. ER and PR expressions were assessed using the Allred scoring system. HER2/neu status was interpreted according to established reporting guidelines. The Ki-67 proliferation index was recorded as the percentage of positively stained tumour cell nuclei. MUC1 expression was evaluated based on the extent and intensity of staining in tumour cells. Based on the immunohistochemical findings, cases were categorised into molecular subtypes such as Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Carcinoma. The expression of MUC1 was analysed in relation to various clinicopathological parameters including age, tumour size, histological grade, pathological stage, lymph node involvement, and molecular subtype. The collected data were entered into Microsoft Excel and analysed using SPSS software version 16.0. Descriptive statistics were used to summarise the study findings. Associations between MUC1 expression and clinicopathological variables were evaluated using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 72 cases of breast carcinoma were analysed in the present study. Immunohistochemical evaluation for ER, PR, HER2/neu, Ki-67, and MUC1 expression was performed in 40 cases. The mean age of the patients was 55.3 years, with the majority (82%, n=59) being above 45 years of age. Most patients were multiparous, with 72% (n=52) having more than two children, while 17% (n=12) were nulliparous. A positive family history of breast carcinoma was noted in 19% (n=14) of cases. Tumour size ranged widely, with the majority of tumours (69%, n=50) measuring between 2 and 5 cm. Tumours larger than 5 cm constituted 21% (n=15) of cases, whereas only 10% (n=7) measured less than 2 cm. Lymph node metastasis was observed in 57% (n=41) of cases. Histological grading using the Nottingham–Bloom–Richardson system showed that Grade II tumours were most common (56%, n=40), followed by Grade III (33%, n=24) and Grade I (11%, n=8). According to AJCC staging, Stage II disease was predominant, accounting for 64% (n=46) of cases, followed by Stage IIIA (16%, n=12), Stage I (11%, n=8), and Stage IIIB (9%, n=6). Overall, most patients presented with intermediate-grade, Stage II breast carcinoma [Table 1]. Histopathological examination revealed that Invasive Breast Carcinoma of No Special Type (IBC-NST) was the predominant histological subtype, accounting for 93.1% (n=67) of the total cases. This was followed by Mucinous carcinoma, which constituted 2.8% (n=2) of cases. Solid papillary carcinoma with invasion and Invasive lobular carcinoma were comparatively uncommon, with each subtype representing 1.4% (n=1) of cases.

The findings indicate a clear predominance of IBC-NST among breast carcinoma cases in the present study, while special histological variants were encountered only occasionally [Table 2]. Immunohistochemistry for ER, PR, HER2/neu, and Ki-67 was performed in 40 breast carcinoma cases. ER positivity was observed in 42.5% (n=17) of cases, while 57.5% (n=23) were ER negative. PR expression was seen in 37.5% (n=15) of cases and absent in 62.5% (n=25). HER2/neu overexpression was identified in 37.5% (n=15) of cases. Concordant positivity for both ER and PR was noted in 37.5% (n=15) of cases, whereas 57.5% (n=23) were negative for both receptors. Overall, hormonal receptor positivity was observed in 42.5% (n=17) of cases [Table 3]. Analysis of clinicopathological parameters showed that hormone receptor (HR)-negative tumours were significantly associated with age above 45 years (p=0.0067), tumour size (p=0.012), higher tumour grade (p=0.021), and lymph node metastasis (p=0.043). Triple-negative breast carcinoma was more frequently observed in older patients, tumours measuring 2–5 cm, higher-grade lesions, and cases with lymph node metastasis; however, these associations were not statistically significant. Invasive Breast Carcinoma of No Special Type (IBC-NST) was the predominant histological subtype, with the majority of HR-negative and triple-negative tumours belonging to this category [Table 4]. MUC 1 IHC (100X) was presented in [Figure 1].

Table 1: Clinicopathological parameters of breast carcinoma (n=72)

Parameter		No. of cases	Percentage
Age group	≤45 years	13	18%
	>45 years	59	82%
Parity	Nulliparous	12	17%
	≤2 children	8	11%
	>2children	52	72%
Family history	Present	14	19%
	Absent	58	81%
Tumor size	< 2cm	7	10%
	2 to 5cm	50	69%
	>5cm	15	21%
Lymph node involvement	Present	41	57%
	Absent	31	43%
NBR grade of the tumor	1	8	11%
	2	40	56%
	3	24	33%
AJCC staging	Stage I	8	11%
	Stage II	46	64%
	Stage III a	12	16%
	Stage III b	6	9%

Table 2: Proportion of various Histological types (n =72)

Histological tumor type	No. of cases	Percentage
Invasive breast carcinoma of no special type	66	92.1%
IBC – NST with medullary features	1	1.3%
Mucinous carcinoma	2	2.7%
Invasive lobular carcinoma	1	1.3%
Solid papillary carcinoma with invasion	1	1.3%
Metaplastic carcinoma	1	1.3%
Total	72	

Table 3: Proportion of ER, PR, Her 2 neu, Ki 67 receptors in breast carcinoma cases (n=40) and concordance

Hormone receptor	Status	No. of cases (n)	%
Estrogen receptor	+	17	42.5
	-	23	57.5
Progesterone receptor	+	15	37.5
	-	25	62.5
Her 2 neu	+	15	37.5%
	-	25	62.5%
Ki 67 index	Low	27	67.5%
	High	13	32.5%
Concordant and discordant			
Concordant	ER +, PR +	15	37.5%
	ER -, PR -	23	57.5%
Discordant	ER +, PR -	2	5%
	ER -, PR +	--	--
Hormonal receptor-positive tumors	ER +, PR +	17	42.5%
Hormonal receptor-negative tumors	ER -, PR -	23	57.5%

Table 4: Association of clinicopathological parameters with MUC 1 median score (n=40)

Clinicopathological parameter			The median score of MUC 1		
		N	High [>150], n (%)	Low [<150], n(%)	P value
Age	≤45 years	6	3(7.5)	3(7.5)	0.027
	>45 years	34	19(47.5)	15(37.5)	
Tumor size	<2cm	6	4(10)	2(5)	0.248
	2 to 5cm	27	11(27.5)	16(40)	
	>5cm	7	7(17.5)	0	
Lymph node involvement	Present	20	11(27.5)	9(22.5)	1
	Absent	20	11(27.5)	9(22.5)	
NBR grade of the tumor	1	6	5(12.5)	1(2.5)	0.20
	2	19	9(22.5)	10(25)	
	3	15	8(20)	7(17.5)	
AJCC staging	Early	33	16(40)	17(42.5)	0.033
	Late	7	6(15)	1(2.5)	
Histological type	Invasive breast carcinoma of no special type	37	19(47.5)	18(45)	0.0006
	Mucinous carcinoma	1	1(2.5)	--	
	Invasive lobular carcinoma	1	1(2.5)	--	
	Solid papillary carcinoma with invasion	1	1(2.5)	--	

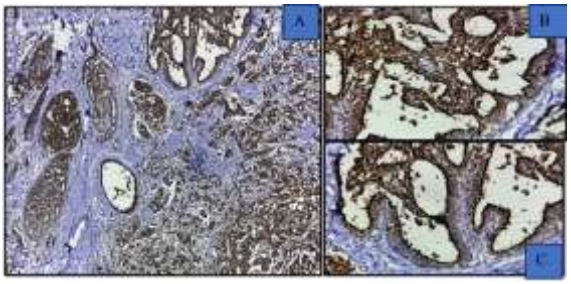

Figure 1: MUC 1 IHC (100X)
A) MUC 1 IHC (100X)
B) MUC 1 IHC showing membranous & cytoplasmic expression(400X)
C) MUC 1 IHC with Luminal & cytoplasmic expression(400X)

DISCUSSION

Breast carcinoma is a heterogeneous malignancy with diverse clinicopathological and molecular characteristics that influence prognosis and therapeutic response. The present study evaluated the clinicopathological profile, molecular subtypes, and MUC1 expression in breast carcinoma and correlated these findings with established prognostic parameters. The majority of patients in the present study were above 45 years of age, with a mean age of 55.3 years. Similar observations have been reported by earlier studies, who documented a higher incidence of breast carcinoma among middle-aged and older women in the Indian population.[11-13] A positive family history was observed in a small proportion of cases and was associated with earlier disease onset, which is in agreement with previous studies.[14-16] Most tumours measured between 2 and 5 cm at diagnosis. Comparable findings have been reported by earlier studies.[14-17] The relatively larger tumour size at presentation compared to Western populations may be attributed to delayed diagnosis, limited awareness, and inadequate screening programmes. Lymph node metastasis was identified in more than half of the cases, reflecting a considerable burden of locally advanced disease, similar to observations made by earlier studies.[18,19] Histological grading revealed a predominance of Nottingham Grade II tumours, followed by Grade III lesions. Similar findings have been documented by earlier studies.[20] Stage II disease constituted the majority of cases, which is in concordance with the observations of Mohapatra et al. and other Indian studies.[21] These findings indicate that most patients present after local tumour progression but before the development of extensive advanced disease.Invasive Breast Carcinoma of No Special Type (IBC-NST) was the predominant histological subtype in the present study. Similar results have been reported by Sharma et al., Gogia et al., and Pandit et al., confirming that IBC-NST remains the most common histological variant of breast carcinoma.[22-25] Immunohistochemical evaluation demonstrated hormonal receptor positivity in 42.5% of cases, while 57.5% were negative for both ER and PR receptors. Comparable findings have been reported by Kiranjot Kaur et al. Triple-negative breast carcinoma (TNBC) was the most common molecular subtype, accounting for 37.5% of cases. Similar frequencies have been documented by earlier studies.[20-22] The high prevalence of TNBC among Indian women is clinically significant because this subtype is associated with aggressive biological behaviour and limited therapeutic options. Hormone receptor-negative tumours showed significant associations with older age, larger tumour size, higher histological grade, and lymph node metastasis. Triple-negative tumours were also more commonly associated with larger tumour size and higher tumour grade, supporting their aggressive nature. The principal objective of the present study was to evaluate MUC1 expression in breast carcinoma. High MUC1 expression demonstrated significant associations with age above 45 years, tumour stage, and histological subtype. However, no significant association was observed with tumour size, tumour grade, lymph node status, ER, PR, HER2/neu

expression, or Ki-67 index. Similar findings have been reported by earlier studies.[13] Conversely, it was demonstrated a positive association between MUC1 expression and hormone receptor positivity.[14] A significant association was observed between MUC1 expression and the HER2-enriched molecular subtype. This observation supports previous evidence suggesting an interaction between MUC1 and HER2 signalling pathways and highlights the potential role of MUC1 as a therapeutic target in selected breast carcinoma patients.[9] Overall, the present study suggests that MUC1 may serve as a useful biomarker in breast carcinoma and could have prognostic and therapeutic relevance. Further studies involving larger sample sizes and long-term follow-up are required to establish its precise clinical utility.

CONCLUSION

The present study demonstrated that breast carcinoma predominantly affected women above 45 years of age and was most commonly diagnosed as Invasive Breast Carcinoma of No Special Type. Hormone receptor-negative and triple-negative breast carcinomas constituted a significant proportion of cases and were associated with adverse clinicopathological features such as larger tumour size, higher histological grade, and lymph node metastasis. MUC1 expression showed significant association with age, tumour stage, histological subtype, and HER2-enriched molecular subtype. However, no significant correlation was observed with tumour grade, lymph node status, hormonal receptor status, or Ki-67 index. These findings suggest that MUC1 may serve as a useful prognostic biomarker and a potential therapeutic target in breast carcinoma.

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