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Potential of Serum IL-6 as a Predictor of Tumor Histological Manifestations in Premenopausal Breast Cancer with Metabolic Syndrome

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ABSTRACT

Backgrounds: All of the elements of the metabolic syndrome (MS) can affect the development of breast cancer (BC) and its manifestations through different mechanisms. This study aims to evaluate the manifestation of pathomorphological features of cancer in BC women with MS and evaluate the relationship between serum level of IL-6 and hystological characteristics of tumor in BC.

Methods: The present cross-sectional study included 55 patients with a diagnosis of premenopausal BC in the Department of Breast Cancer, Republican Cancer Center of Uzbekistan, from October 2022 to November 2023. We determined the effect of MS on clinicopathological features of breast cancer. The serum level of IL-6 was determined using IFA.

Results: Overall, 31 patients (56.36%) suffered from MS, and 24 (43.63%) did not. The results of our study suggest that MS may affect the histological manifestations of BC in premenopausal women. Serum IL-6 levels in premenopausal BC women with MS are positively correlated with classic clinicopathological parameters indicative of cancer-aggressive phenotype.

Conclusion: There is a significant correlation between the presence of MS and premenopausal BC. Serum levels of IL-6 can be an independent indicator in evaluating clinical and pathomorphological features of the disease in women with MS.

INTRODUCTION

BC is a disease characterezid by the uncontrolled proliferation of cells within breast tissue, encompassing lobules and duct.[1] The incidence of the disease is increasing, which is found in every eighth woman.[2] Classic risk factors for breast cancer involve processes that contribute to hormonal imbalances, such as early menarche, late menopause, number of births and abortions, duration of breastfeeding, and obesity. In addition, some comorbid conditions increase the risk of disease incidence and impact treatment processes and the overall survival of patients. MS represents processes that cause metabolic, hormonal, and clinical changes in the body, affecting BC risk, pathophysiology, and development.[2] MS is a combination of pathological disorders in the body, such as abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDLP-C in serum, which increase the risk of developing BC by 17%, triple disease recurrence, and double mortality.[3]

Over the past decade, researchers have focused on the relationship between MS criteria and cancer. In

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particular, some experimental studies have shown that BC cells consume cholesterol for promotion and proliferation processes.[4] It is hypothesized that hyperinsulinemia and insulin resistance may increase the risk of BC because insulin increases proliferation processes in breast cells and inhibits sex hormone-binding globulin, which leads to an increase in the level of active estrogen. Hyperglycemia, hyperinsulinemia, increased inflammation, and dyslipidemia commonly accompany obesity and diabetes. These metabolic changes are considered factors that increase the risk of cancer and death.[5,6] For example, hyperglycemia may supply cancer cells with additional glucose, facilitating proliferation. Hyperglycemia can lead to an increase in residual products of glycolysis and reactive oxygen species, which can cause DNA damage.[7,8] Hypertension is also an essential criterion for MS, and some scientists argue that it plays a role in the development of cancer. According to the conclusion of a cohort study conducted by Largent *et al.*,[8] taking antihypertension drugs for five years or longer increases the risk of developing invasive BC. In particular, the ER-positive type of cancer is more common in hypertensive patients during the premenopausal period.

In 20% of patients, chronic inflammation or infection leads to cancer. If there is no chronic inflammation at the onset of the development of cancer, later infiltrative processes appear in the patient's body.[9] Moreover, a high concentration of interleukins is observed in the tumor microenvironment. Due to chronic inflammation, normal cells do not respond to apoptosis. A high level of IL-6 promotes the proliferation of cancer stem cells.[9] IL-6 not only causes cancer-related inflammation, but also participates in the repair of damaged DNA fragments, antioxidant defense systems, proliferation, invasion, metastasis, and angiogenesis processes.[10]

Autocrine and paracrine IL-6 signaling pathways control cancer cell proliferation, stimulate cancer stem cells (CSCs), and participate in metastasis. There is a high level of IL-6 in cancer-associated fibroblasts (CAF) in human breast cancer tissue, and this complex process of carcinogenesis - angiogenesis of tumor cells stimulates proliferation and invasion. IL-6 is also involved in the emergence of an aggressive tumor phenotype. The IL-6-JAK1-STAT3 signaling pathway ensures the transformation of non-cancerous stem cells into cancer stem cells.[11] Due to the expression of IL-6 and its receptor, the cells do not respond to apoptosis. The expression of IL-6 has also been detected in the metastatic area in patients resistant to chemotherapy.[12,13]

IL-6 is essential in maintaining the balance of CSC (senescent cells) and non-cancerous stem cells, normal and tumor cells in the tumor microenvironment.[14] In recent studies, it has been found that a high IL-6 increase in the Her2/neu positive subtype of CSC in the late stages is related to these old (senescent) cells. The relationship between apoptotic cells and inflammation leads to chronic inflammation that affects tumor progression. It should be noted that the observed reduction in disease recurrence and mortality, when patients continue to receive anti-inflammatory drugs after removal of the primary tumor, also supports the relationship between chronic inflammation and tumor progression.[15]

Our research aims to evaluate the impact of MS criteria on the pathomorphological-clinical characteristics of BC and to evaluate the relationship between serum levels of IL-6 and cancer characteristics in premenopausal BC patients.

METHODS

Patient selection

For this cross-sectional study, we selected participants through the non-random sampling method. The study sample (n=55) was recruited from patients who referred to the Republican Oncology Center from October 2022 to November 2023. The stage of the disease (I-III), the absence of surgery, and the number of chemotherapy courses (no more than 1-2 courses) were taken into account to avoid errors in evaluating the results. Inclusion criteria were early and locally advanced BC, and being in the premenopausal status. Exclusion criterion was having metastatic BC. Patient consent was obtained verbally. The study was conducted based on the approval of the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan (report No. 4/6-1876).

Anthropometric measurement

Body mass index (BMI) was calculated using the formula (BMI= weight(kg)/height(m2)) in patients by measuring their height and weight.

Laboratory examination

In order to evaluate the criteria for MS in the study, patients' fasting blood was collected from the wrist vein on fasting. Centrifugation separated the blood into serum, and lipid and glucose profiles were evaluated. A diagnostic kit (Spinreact, Spain) was used for total cholesterol, HDL-C, LDL-C, and TG. Glucose content was determined using a glucose liquidator (Human, Germany). Also, serum levels of IL-6 ELISA (Elabscience, USA) and insulin (OOO XEMA, Russia) were studied using the IFA method. Atherogenic index, HOMO/IR, and

triglyceride/glucose index were calculated using relevant formula.

Pathomorphological report analysis

The pathomorphological and immunohisto - chemical characteristics of the tumor were studied. The tumor's localization, size, degree of differentiation, lymph nodes status, ER, PR, Her2/neu receptors status, and the level of epithelial proliferative activity of the tumor cell (Ki-67%) were evaluated. The immunohistochemical study was done by freezing the biopsied material in paraffin, making a block, and using monoclonal antibodies of "Dako" company. After IHC, tissue sections are made using an indirect immunoperoxidase-anti peroxidase reaction. Diaminobenzidine was used as a chromogen, and Mayer's hemotoxylin was used for control staining.

Definition of metabolic syndrome

Several researchers have given different explanations for MS. We used the WHO definition of MS[16]: BMI ≥30 kg/m2, serum TG >1.7 mmol/l, HDL-ch <1 mmol/l, and blood pressure ≥140/90 mmHg or/and antihypertensive medication, urinari albumin excterion rate ≥20 µg/min or albumin/creatinin ratio ≥3.4 mg/mmol. We calculated the atherogenic index and HOMO/IR to measure insulin resistance. According to WHO's criteria, if insulin resistance (type 2 diabetes, imparied fasting glucosae, impaired glucosae tolerance) and two of the above criteria were positive, we considered patients as having MS.

A slight finding here is the absence of urinary albumin excretion. However, it did not affect assessing the presence of MS in these patients.

Statistical analysis

Statistical analyses were performed using the program "Origin Pro" (2021) and online program "DataTab". All indicators' average value and standard deviation (mean ± SD) were analyzed. We used the Chi-square test to evaluate categorical variables. We used the independent sample t-test to determine the difference between the groups. We did a univariable and multivariable analysis by the binary logistic regression method with IL-6 as the dependent variable and tumor histological characteristics as the independent variable. A P-value of less than 0.05 and a significance level of 95% were considered significant.

RESULTS

Patient characteristics

In our study, we checked 55 BC patients overall. They were divided into two groups according to MS measurements, 31(56.36%) of the patients with MS, and 24 (43.63%) without MS. The results of assessing MS criteria and other indicators of the patients are given in Table 1.

All patients were married, had a sex life, gave birth to children, breastfed them, and had no unhealthy behavior (drug addiction, smoking, drinking alcohol). Rejecting the main risk factors of BC helped us to assess the effect of MS factors correctly. The age means were 40.1±5.46 and 38.61±4.71 years in the group with MS and the one without MS, respectively (P=0.001). *Analysis of the effect of metabolic*

syndrome on the tumor histological phenotype

Anatomo-histological features of the tumor were analyzed in both groups of the patients. The results of the comparisons of these characteristics of BC in patients with and without MS are presented in Table 2.

Table 1. Results of assessing metabolic criteria in the patients

Characteristics	With MS and BC n=31	Without MS and BC n=24	P-value*
BMI(kg/m^2)	33.7±2.8	26.6±1.3	0.001
Systolic blood pressure(mm.Hg)	121.9±2.02	119±1.83	0.22
Diastolic blood pressure (mm. Hg)	82.2±1.56	80.7±2.48	0.54
Serum Total cholesterol (mmol/l)	5.9±0.44	5.16±0.55	0.052
Serum HDL-ch(mmol/l)	1.3±0.04	1.39±0.02	0.031
Serum TG (mmol/l)	1.59±0.12	2.1±0.21	0.046
Serum LDL-C(mmol/l)	4.7±0.26	3.85±0.26	0.001
Serum VLDL-C (mmol/l)	0.9±0.13	0.7±0.05	0.78
Atherogen index	3.4±0.37	2.7±0.43	0.001
Serum glucosae(mmol/l)	5.9±0.42	4.97±0.56	0.42
Serum insulin (mlU/l)	29.2±4.51	21.6±3.35	0.02
Serum IL-6(pg/ml)	38.4±4.81	26.6±3.13	0.01
HOMO/IR	7.05±1.88	3.66±0.57	0.05

BC- breast cancer, MS – metabolic syndrome *P-value was <0.05 considered statistically significant.

Table 2. Comparison of anatomopathological and IHC characterictics in breast cancer patients with MS and without MS

Characteristics		With MS n=31 n(%)	Without MS n=24 n(%)	P-value	Chi^2
Tumor location	Right breast	16(51.61)	13(54.16)	0.721	0.13
	Left breast	15(48.38)	11(45.83)		
Tumor size	≤2 cm	3(9.67)	6(25.0)	0.028	7.15
	2-5 cm	17(54.81)	16(66.7)		
	> 5 cm	11(35.48)	2(8.33)		
Histology	Ductal invasive	24(77.41)	24(100.0)	0.051	5.97
	Ductal infiltrative	3(9.67)	0(0.0)		
	Rare type	4(12.9)	0(0.0)		
Histological grade	G1	5(16.12)	4(16.7)	0.98	0.04
	G2	20(64.51)	16(66.7)		
	G3	6(19.35)	4(16.7)		
Lymph nodes	Positive	25(80.64)	20(83.3)	0.854	0.03
	Negative	6(19.35)	4(16.7)		
ER receptor	Positive	17(54.81)	16(66.7)	0.325	0.97
	Negative	11(35.48)	8(33.3)		
PR receptor	Positive	14(45.16)	18(75.0)	0.096	2.76
	Negative	14(45.16)	6(25.0)		
Her2/neu	Positive	9(29.03)	15(62.5)	0.031	4.76
	Negative	17(54.81)	9(37.5)		
Ki-67	30%>	8(25.81)	10(41.7)	0.173	1.86
	30%<	23(74.19)	14(58.3)		

BC- breast cancer, MS – metabolic syndrome, ER- estrogen receptor, PR- progesterone receptor, Her2/neu- human epidermal growth factor receptor, Ki-67 – cell proliferative activity

Based on the results presented in Table 2, we analyzed the effect of MS on the tumor histological phenotype. In the MS group, the large tumor size was 11 (35.48%), ductal infiltrative tumor was observed in 3 patients (9.67%), rare tumor histological types in 4 cases (12.9%), negative Her2/neu receptors in 17 patients (54.81%), and Ki -67 protein over 30% was shown in 23 (74.19)% of this group. These four indicators – large tumor size, infiltrative and rare histological types, negative Her2/neu receptor, and Ki-67 <30% in metabolically healthy BC patients were 2 (8.33%), 0 (0%), 9 (37.5%) and 14 (58.3%), respectively. These differences in the groups, the rapid progress of the disease (high proliferative activity, large tumor size), lack of sensitivity to target drugs (Her2/neu receptor negative), the presence of aggressive and severe histological types (infiltrative forms and rare histological types) were observed in patients with MS more than in those without MS.

Evaluation of quantitative changes in serum IL-6 about tumor histological characteristics

According to the results of the study, IL-6 serum concentration is about 1.5 times higher in women with MS compared to metabolically healthy women (P=0.001)(Table 1). A weak positive correlation exists between BMI and IL-6 serum level (pg/ml) (r=0.58, p-0.12, r=0.05, P=0.84 in the two study groups, respectively). Since the histological heterogenity was observed in BC patients with MS, we compared the concentration of the serum IL-6 in the histological groups. The average level of IL-6 in BC (mean) is 37.6±1.6 pg/ml; in other rare histological types, it is 42.5±3.3 pg/ml, and in tumor-infiltrative cancer type, it is -56.5±14.8 pg/ml (P=0.051). The results of the analysis of molecular subtypes is shown in Figure 1.

Table 3 shows the quantitative changes in IL-6 serum concentration relative to other tumor characteristics.

According to Table 3, there are statistically significant differences in IL-6 levels between patients with and without MS for tumors ≤2 cm and 2-5 cm (P= 0.016 and P= 0.032, respectively). Statistically significant differences in IL-6 levels are observed for both positive and negative lymph node status in both groups (P= 0.027 and P= 0.001, respectively). No significant differences in IL-6 levels are observed across different histological grades (G1, G2, G3) and ER/PR-positive or ER/PR-negative patients with and without MS. Overall, significant differences in IL-6 levels are observed mainly in tumor size and lymph node status between patients with and without MS.

In order to evaluate the changes of IL-6 depending on tumor characteristics, logistic regression analysis was performed. We used the unvariable and multivariable logistic regression method and estimated the Odds ratio (Tables 4 and 5).

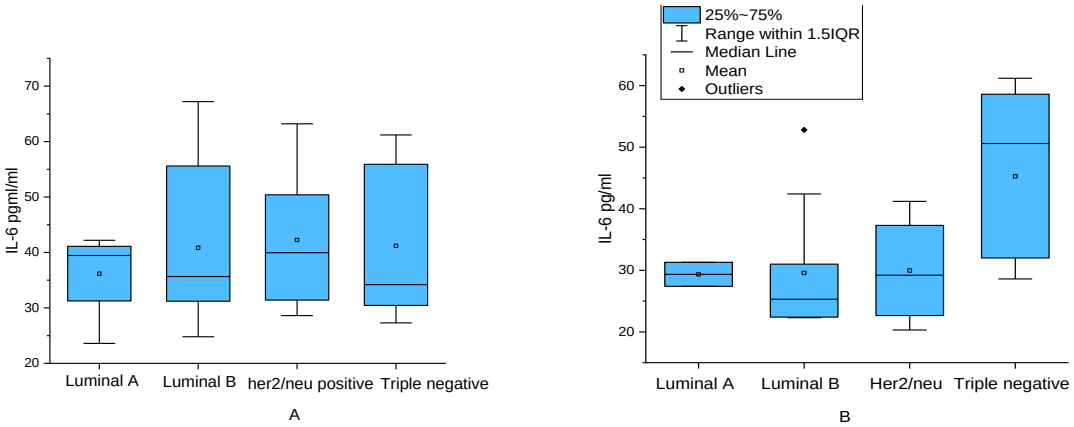

Figure 1. Comparative picture of IL-6 (pg/ml) by molecular subgroups in study groups (A- group with MS and B- without MS, respectively: Luminal A 36.17±8.49 vs 29.35±2.75 (P= 0.001); Luminal B 40.84±14.35 vs 29.55±9.65 (P= 0.001); Her2/neu 42.25±12.87 vs 29.97±9.23 (P=0.001), Triple negative 41.2±14.03 vs 45.25±13.76 (P= 0.05).

Table 3. Changes in IL-6 concentration associated with tumor characteristics

Characteristics		With MS n=31 n(IL-6, Mean±SD)	Withot MS n=24 n(IL-6, Mean±SD)	P-value
Tumor size	≤2 cm	3(29.8)*	6(25.3±3.2)	0.016
	2-5 cm	17(35.6±5.9)	16(28.8±6.3)	0.032
	>5 cm	11(60.1±5.2)	2(31.5)*	0.841
Histological grade	G1	5(37.7)*	4(25.5)*	0.232
	G2	20(38.9±6.1)	16(29.4±4.7)	0.659
	G3	6(26.5±4.1)	4(29.7)*	0.531
Lymph nodes	Positive	25(42.2±5.3)	20(29.6±7.3)	0.027
	Negative	6(28.9±3.4)	4(26.8±6.4)*	0.001
ER receptor	Positive	17(34.0±4.5)	16(29.4±5.4)	0.258
	Negative	11(41.3±5.3)	8(28.2±6.1)	0.052
PR receptor	Positive	14(34.4±6.2)	8(26.5±3.7)	0.102
	Negative	14(34.9±4.6)	6(24.9±5.4)	0.087

*only the average value (mean) was reported when the number of cases (n) was less than 6.

Table 4. Unvariable analyze of serum IL-6 according to tumor characteristics.

Tumor characteristics		With MS OR (CI 95%)	Without MS OR (Cl 95%)
Tumor size	2>cm	1 (0.91-1.03)	1 (0.7-1.03)
	2≤cm	1.03 (0.97-1.09)	1.18 (0.97-1.44)
		P=0.026	P=0.21
Lymph node status (mts)	Yes	1.22 (1-1.48)	1.05 (0.9-1.23)
	No	1 (0.68-1.)	1 (0.87-1.11)
		P=0.003	P=0.473
Ki-67(%)	30%≥	1 (0.9-1.02)	1 (0.87-1.06)
	30%<	1.9(0.98-1.11)	1.04(0.94-1.15)
		P=0.129	P=0.426

MS- metabolic syndrome, OR – Odds ratio, Cl-confidence interval.

For patients with MS, there is a statistically significant difference in tumor size (P= 0.026), indicating that tumor size distribution is affected by the presence of MS (2>cm and 2≤cm size of tumor OR – 0.97, Cl 95% -0.91-1.03, OR – 1.03 Cl 95% 0.97-1.09, respectively). The OR indicates that patients with MS are more likely to have positive lymph node status, suggesting that the presence of MS affects lymph node involvement (P= 0.003). The results for Ki-67 indicate that Ki-67 is not strongly associated with MS status.The observed P-values indicate that tumor size and lymph node status are significantly different in patients with MS, while Ki-67 levels are not significantly different in either group.

Table 5. Multivariable analysis of serum IL-6 according to tumor characteristics.

Tumor characteristics		P	With MS OR(95%CI)
Tumor size	2≤cm	0.261	0.32 (0.04 – 2.34)
	2>cm		1 (0.43-23.03)
Lymph node	Yes	0.997	2.15 (0.23 – 15.6)
	No		1 (0.05 – 1.32)
Ki-67	30%<	0.546	1.87 (0.25 – 14.2)
	30%≥		1 (0.07-4.07)

MS- metabolic syndrome, OR – Odds ratio, Cl-confidence interval.

According to the multivariable regression analysis (Table 5), the odds of having a tumor size ≤2 cm / >2 cm in patients with MS are not statistically significant

(P=0.261). The odds of having lymph node positivity/negativity and Ki-67<30% / ≥30% are not statistically significant in the two groups (P=0.997; P=0.546, respectively).

DISCUSSION

The results of our study suggest that MS may affect the histological manifestations of BC in premenopausal women. We observed that some aggressive phenotypes of the tumor were manifested in BC patients with MS. Three or more MS criteria predict a higher percentage of rare BC histological forms and infiltrative cancer types. Also, the negativity of Her2/neu receptors is more common in this category. A Ki-67 protein above 30% indicates an active proliferative process in more tumor cells in MS patients. Tumor size is more significant in patients with MS than those without MS. No significant difference was found between the two groups in terms of lymph node damage, differentiation level, and ER and PR receptors. These results suggest that MS affects the manifestation of aggressive characteristics of BC.

In the second part of our study, we evaluated the relationship between serum levels of IL-6 and tumor histological characteristics BC in patients with MS. Our results revealed a correlation between serum levels of Il-6 and tumor size, lymph node damage, and tumor cell proliferative activity in patients with MS. We obtained statistically significant results regarding the relationship between IL-6 and lymph node status in BC patients with MS. According to the regression analysis, the confidence intervals for the odds ratios were wide, indicating a high degree of uncertainty in the estimates, which might be due to the small sample size or high variability within the data.

However, this study has some limitations, such as the non-random selection of the patients. Many studies have found that there is no relationship between serum levels of IL-6 and BC[17] and that systemic IL6 levels may be an indicator of BC risk in healthy women. Long-term use of anti-inflammatory drugs reduce the risk of BC in older adults.[18,19] This means that inflammatory mediators, including cytokines, can promote cancer. Two prospective studies in older populations have not found any association between IL6 and BC risk, but these studies were limited by low predictive power.[18,20]

Tripsianis and his team concluded that IL-6 can be an independent predictor for BC.[22] Accordingly, a high concentration of IL-6 in the blood plasma predicts the spread of the process to the lymph nodes and short survival. When comparing the amount of IL-6 in the blood plasma of healthy patients and patients with BC, it was found that it was ten times higher, which may be due to the clinical stage of the disease, its spread to the lymph nodes, disease recurrence, and metastasis.[23] Elevated levels of IL-6 in locally advanced breast cancer are a poor prognostic marker for overall and disease-free survival.[24,25]

Dysregulation of the IL-6 signaling pathway is also essential in cancer initiation, promotion, progression, metastasis, and invasion. It is also an essential factor that determines the viability of tumor cells, protects cells from cytotoxic drugs and stress, forms their resistance, and increases their viability.[26,27]

CONCLUSION

Our study reported a significant correlation between MS and histological characteristics of BC. Serum IL-6 levels in premenopausal women with MS are positively correlated with classic clinicopathological parameters that indicate an aggressive cancer phenotype. Considering this, IL-6 can be used as an independent biomarker to assess the aggressiveness of the disease. In BC patients with MS, IL-6 can be used to evaluate the lymph node status. The results of our study are important for research investigating the clinical significance of IL-6 in the evaluation of metastatic BC.

ETHICAL CONSIDERATIONS

The study was approved by the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan (report No. 4/6-1876).

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CONFLICT OF INTEREST

The authors declare no confilict of interest for this article.

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