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HISTOLOGICAL PRESENTATION OF BREAST CANCER AND ITS ASSOCIATION WITH METABOLIC SYNDROME

Matluba A. Mirzaeva[1], Bakhtiyor U. Iriskulov[2], Lola T. Alimhodjaeva[3]

1 PhD student, Department of Normal and Pathological Physiology, Tashkent Medical Academy, Tashkent, Uzbekistan

2 Professor, DSc, Department of Normal and Pathological Physiology, Tashkent Medical Academy, Tashkent, Uzbekistan

3 DSc, MD, Department of Breast Cancer, Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan

ABSTRACT

Backgrounds. Metabolic syndrome(MS) is associated with an increased risk of cardiovascular disease, type II diabetes, and recurrence of disease in breast cancer(BC) patients. In this cross-sectional study, we analyzed the histological demonstration of MS-associated BC. **Methods and materials.** We interviewed 74 women with diagnosed breast cancer at the Republican Cancer Center in Uzbekistan. All MS criteria were evaluated in every patient, and the histological performance of the tumors was based on pathomorphological analysis. **Results.** 41 of 74 patients have three or more MS elements. In these groups, diversified histological types of tumors occur. Tumor size is the most significant, and proliferative activity of tumor cells is higher than in the group without MS. Triple negative molecular subtypes occur more in women who have MS. We didn't find significant differences in other histological criteria between the two groups. **Conclusion.** MS can affect some histological demonstrations of BC, such as tumor size, tumor histological types and subtypes, and cancer cell proliferation activity.

Key words: breast cancer, metabolic syndrome, lipid profile, insulin resistance, body mass index.

INTRODUCTION

The relationship between metabolic syndrome (MS) and breast cancer (BC) is important in terms of influencing morbidity and mortality. Metabolic syndrome is a complex of metabolic, hormonal, and clinical changes, with its pathogenesis linked to immune-inflammatory processes. Metabolic syndrome is characterized by abdominal obesity, hypertension, hyperglycemia, decreased serum high-density

lipoprotein (HDL-C) levels, and increased serum triglycerides (TG).[4] The presence of at least three of these five components, according to the NCEP and ATP III criteria, indicates the presence of MS.[5]

While individual components of MS may not directly correlate with the development of BC, their combination can increase the risk of the disease. For instance, MS can activate various molecular pathways through changes seen in endocrine, metabolic, and immune cells, which in turn can influence the development of BC.[1,6]

These pathways can promote breast cell proliferation and inhibit apoptosis through effects, such as increasing estrogen levels, endogenous insulin levels, reducing adiponectin, and increasing cytokine levels like TNF-alpha and IL-6.[7] MS is a crucial risk factor for cardiovascular disease and diabetes, and it may also be important in the development of BC. There are many studies on the relationship between MS and BC in postmenopausal women. [10, 11] But area of premenopausal BC researchs results are controvercially issue. Therefore, in this study, we analyzed the relationship between the MS and histological manifestations of premenopausal BC.

Aim: to study the influence of MS on the histological presentation of BC.

Material and methods. *Patient selection*. For the study, 74 BC patients were collected in the Department of Breast Cancer of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology. Patients were collected based on some criteries. Inclusion criteries were early and locally advanced stage BC, premenopausal status, having sex, giving birth, and breastfeeding. Exclusion criteries were metastatic breast cancer, postmenopausal status, and women who have not given birth and are not breastfeeding.

Methods. In order to evaluate the criteria of MS in the study participants' fasting blood was collected from the wrist vein. Centrifugation separated 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). Arterial blood pressure was measured. Body mass index (BMI) was calculated based on patients' weights and heights. In addition, we calculated the atherogenic index(AI) and HOMO/IR to measure insulin resistance. The pathomorphological and immunohistochemical characteristics of the tumor were studied from case-history. The tumor's localization, size, degree of differentiation, damaged lymph nodes, status of ER, PR, HER2/neu receptors, and level of epithelial proliferative activity of the tumor cell (Ki-67%) were evaluated.

Statistical analysis. Statistical analyses were performed using the program "Origin Pro" (2021). All indicators' average value and standard deviation (mean ± standard deviation) were analyzed. A p-value of less than 0.05 and a significance level of 95% were considered reliable.

Result. *Patients characteristics.* All of the patients were divided into two groups according to manifestation metabolic syndrome. The first group consists of 41 patients who have 3≤ MS positive elements. The second group includes 33 patients who have less than three MS elements. The median age of patients was 40,1±5,46 and 38,61±4,71, respectively, in the first and second groups. Other characteristics of patients are given in Table 1.

Table 1.

Character of patients

Criteria	with MetS	without MetS
Age	40,1±5,46	38,61±4,71
BMI(kg/m^2)	33,7±2,8	26,6±1,3
Systolic blood pressure(mm.Hg)	121,9±2,02	119±1,83
Diastolic blood pressure (mm. Hg)	82,2±1,56	80,7±2,48
Serum Total cholesterol (mmol/l)	5,9±0,44	5,16±0,55
Serum HDL-ch(mmol/l)	1,3±0,04	1,39±0,02
Serum TG (mmol/l)	1,59±0,12	2,1±0,21
Serum LDL-C(mmol/l)	4,7±0,26	3,85±0,26
Serum VLDL-C (mmol/l)	0,9±0,13	0,7±0,05
Atherogen index	3,4±0,37	2,7±0,43
Serum glucosae(mmol/l)	5,9±0,42	4,97±0,56
Serum insulin (mlU/l)	29,2±4,51	21,6±3,35
Serum IL-6(pg/ml)	38,4±4,81	26,6±3,13
HOMO/IR	7,05±1,88	3,66±0.57

**p-value was <0,05 considered statistically significant.*

In the second group of patients, invasive carcinomas were found in 32(78.0%) cases, infiltrative carcinomas in 4(9.75%) cases, and less common histological types (medullary, tubular, cribriform, mucinous, and adenocarcinoma) in 5(12.19%) cases(Figure 1). According to the G grade (tumor differentiation grade), G1-7(17.07%) cases were observed, G2 -19(46.3%) cases, and G3-4 (9.75%) cases. In the first group, all (100%) cases were invasive carcinomas. Based on the tumor differentiation grade, G1-10 (30.3%) cases were observed, G2-15 (45.5%) cases, and G3-2(6.06%) cases.

According to the results of the immunohistochemical examination, in the main group, luminal A was found in 4(9.76%) patients, luminal B in 16(39.0%) patients, Her/2 positive in 10 (24.4%) patients, and triple-negative in 9(21.9%) patients. In the first group, luminal A was found in 4(12.2%) patients, luminal B in 12(36.6%) patients, Her/2 positive in 5 (15.2%) patients, and triple-negative in 5(15.2%) patients (Figure 2).

We observed that some aggressive phenotypes of the tumor manifested in MS-associated BC. In particular, the large tumor size is 35% (tumor size > 5 cm are not present in metabolically healthy patients), infiltrative or rare aggressive tumor histological types are 22.5%, negative Her2/neu receptors -55%, Ki -67 protein over 30% is shown in 74% of this group. These four indicators - tumor size, infiltrative or rare histological types, negative HER2/neu receptor, Ki-67 <30% in metabolic healthy BC patients are 0%, 0%, 37.5%, and 58.3%, respectively(Table 2).

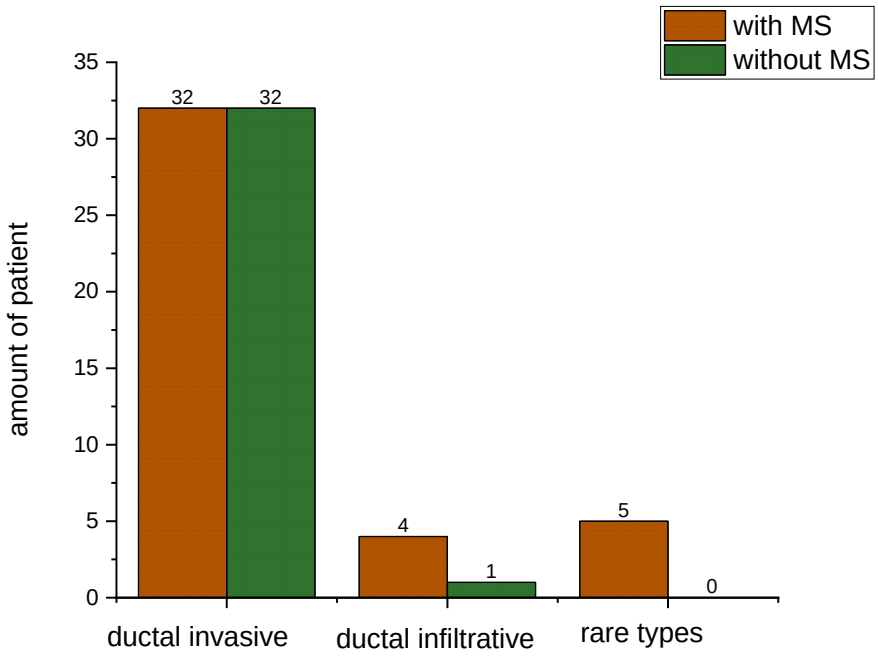

Figure 1. Differences of histological types of tumors between groups

Table 2.

Histological manifestation of tumor		with MetS (n-41) n(%)	without MetS (n-33) n(%)
Tumor location	Right breast	19(46,3)	15(45,5)
	Left breast	20(48,8)	16(48,5)
	Both	2(4,88)	2(6,06)
Tumor size	≤2sm	3(7,32)	6(18,2)
	2-5 sm	22(53,7)	21(63,6)
	> 5sm	16(39,0)	7(21,2)
Histologycal type	Ductal invasive	32(78,04)	33(97,0)
	Ductal infiltrative	4(9,76)	1(3,0)
	Rare histological type	5(12,2)	0(0,0)
Histological grade*	G1	7(17,1)	10(30,3)
	G2	19(46,3)	15(45,5)
	G3	4(9,7)	2(6,1)
Lymph nodes	Positive	35(85,3)	28(83,3)
	Negative	6(14,6)	5(16,7)
ER reseptor *	Positive	21(51,2)	21(84,8)
	Negative	10(24,4)	11(33,3)
PR receptor *	Positive	22(53,7)	18(54,5)
	Negative	8(19,5)	20(60,6)
HER2/neu*	Positive	14(34,1)	17(51,5)
	Negative	21(51,2)	14(42,4)
Ki-67*	30%≤	29(76,3)	17(65,4)
	30%>	9(23,7)	9(34,6)

* if this criterion was not determined in patients, it was not given in the table.

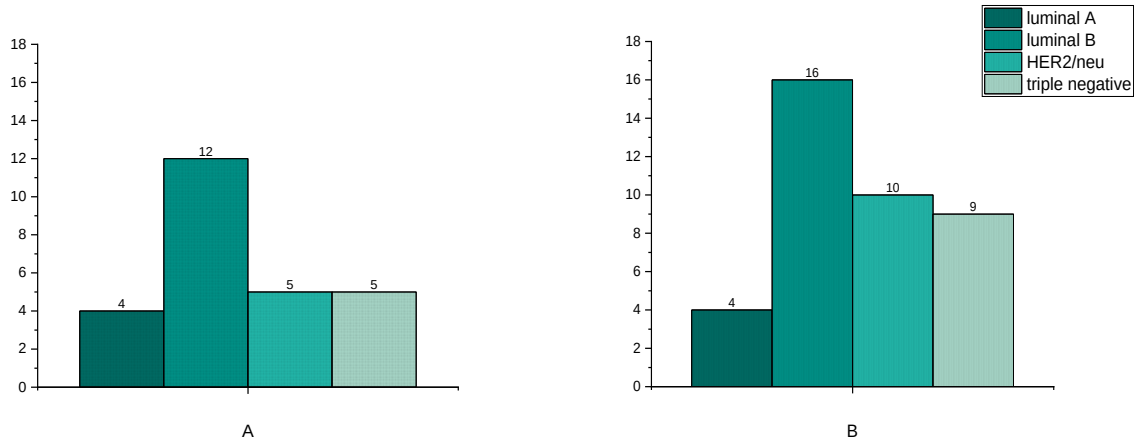

Figure 2. Occurrence molecular subtypes in groups: A-without MS, B-with MS.

Discussion. Relationships between MS and BC have been established in several research studies. MS and its components have indeed been linked to an increased risk of BC. Several studies have shown that factors such as obesity, insulin resistance, elevated levels of certain blood lipids (e.g., triglycerides), and hypertension, which are characteristic components of MS, can contribute to the development and progression of breast cancer. These factors can influence hormone levels, promote inflammation, and affect cellular processes related to cancer growth and spread. Understanding these associations is crucial for developing strategies for prevention and management in individuals with MS.[8] Opportunistic screening for breast cancer should indeed be considered for women with MS especially considering the increased risk associated with MS components like obesity, insulin resistance, and hormonal changes.[3, 9] The presence of 1 or 2 components of MS among patients without a full diagnosis of MS has been associated with worse survival outcomes in some studies. This suggests that even partial manifestations of Mets could still confer increased risk, potentially due to the individual components' effects on health and disease progression. Understanding these associations can be valuable for risk assessment and developing targeted interventions to improve outcomes in at-risk patient populations. [2]

Our study findings indicate that MS might influence some histological presentations of BC in premenopausal women. Patients with three or more MS criteria have a higher percentage of aggressive rare BC histological forms and infiltrative cancer types. Furthermore, this subgroup of women observes a higher frequency of Her2/neu receptor negativity. Ki-67 protein level exceeding 30% suggests an active proliferative process involving more tumor cells among women with MS. Tumor size appears to carry more larger in women with MS compared to

the group without MS. However, no significant differences were noted between the two groups concerning lymph node status, differentiation level, and estrogen receptor (ER) and progesterone receptor (PR) status.

Conclusion. Our study demonstrated that MS is highly related to aggressive phenotype - tumor size, proliferative activation of tumor cells, and receptor status of premenopausal breast cancer. In premenopausal women with ≥3 components of MS, routine BC screening could help to detect the early stage of BC.

REFERENCES

1. A.-S. Furberg, M. B. Veierшd, T. Wilsgaard, L. Berstein, and I.Thune, "Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk," Journal of the National CancerInstitute, vol. 96, no. 15, pp. 1152–1160, 2004.

2. Buono, G., Crispo, A., Giuliano, M. et al. Metabolic syndrome and early stage breast cancer outcome: results from a prospective observational study. Breast Cancer Res Treat 182, 401–409 (2020). https://doi.org/10.1007/s10549-020-05701-7

3. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, Sami N, Lee K, Buchanan TA, Spicer DV, Tripathy D, Bernstein L, Mortimer JE. Effects of Aerobic and Resistance Exercise on Metabolic Syndrome, Sarcopenic Obesity, and Circulating Biomarkers in Overweight or Obese Survivors of Breast Cancer: A Randomized Controlled Trial. J Clin Oncol. 2018 Mar 20;36(9):875-883. doi: 10.1200/JCO.2017.75.7526.

4. Danesh H, Anbiaei R, Ziamajidi N, Farhadian M, Barartabar Z, Abbasalipourkabir R. Association between Metabolic Syndrome Risk Factors and Immunohistochemical Profile in Women with Breast Cancer. Iran J Med Sci. 2023 Sep;48(5):456-464. doi: 10.30476/IJMS.2022.95039.2673. PMID: 37786471; PMCID: PMC10541543.

5. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care. 2012 Nov;35(11):2402-11. Doi: 10.2337/dc12-0336. PMID: 23093685; PMCID: PMC3476894.

6. L. A. Healy, A. M. Ryan, P. Carroll, et al., "Metabolic syndrome, central obesity, and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer," Clinical Oncology, vol. 22, no. 4, pp. 281–288, 2010.

7. LM Lashinger, EL Rossi, and SD Hursting. Obesity and Resistance to Cancer Chemotherapy: Interacting Roles of Inflammation and Metabolic

Dysregulation Clinical Pharmacology & Therapeutics | VOLUME 96 NUMBER 4 | October 2014

8. Mohammed, A.M., Hamed, H.B., Noaman, M.K. et al. Metabolic syndrome and breast cancer risk. J Egypt Natl Canc Inst 35, 42 (2023). https://doi.org/10.1186/s43046-023-00203-1

9. Negi, Preety; Kingsley, Pamela A.; Jacob, Jubbin Jagan1; Sachdeva, Jaineet; Jomi, Chinnu. Metabolic Syndrome and Breast Cancer: Is There a Cause-and-Effect Relationship? Journal of Radiation and Cancer Research 14(3):p 144-149, Jul–Sep 2023. | DOI: 10.4103/jrcr.jrcr_43_22.

10. Zhao P, Xia N, Zhang H, Deng T. The Metabolic Syndrome Is a Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis. Obes Facts. 2020;13(4):384-396. doi: 10.1159/000507554. Epub 2020 Jul 22. PMID: 32698183; PMCID: PMC7590763.

11. Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A, Negri E, La Vecchia C. Metabolic syndrome and the risk of breast cancer in postmenopausal women. Ann Oncol. 2011 Dec;22(12):2687-2692. doi: 10.1093/annonc/mdr025. Epub 2011 Mar 17. PMID: 21415236.