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Inflammatory Markers in Patients with Breast Cancer at the National Oncology Center, Aden, Yemen, 2023

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Abstract

Introduction: Chronic inflammation can predispose to different forms of cancer. It was found to play a role in the development and progression of breast cancer. This study was conducted to evaluate some inflammatory markers at diagnosis of patients with breast cancer compared to those under chemotherapy.

Methods: This is a cross-sectional study, enrolled 150 female patients with breast cancer at the National Oncology Center, Aden, from August 1st, 2022 to August 1st, 2023. Sixty patients were newly diagnosed breast cancer cases (group I) and 90 patients were under chemotherapy (group II). Demographic, clinical and histologic data were collected, and patients were tested for the following inflammatory markers; white blood cells count (WBC), platelets count, erythrocytes sedimentation rate (ESR), serum ferritin, lactate dehydrogenase (LDH), beta -2- macroglobulin (β2-M), C-reactive protein (CRP), cancer antigen 15-3 (CA 15-3), and carcinoemberyonic antigen (CEA).

Results: The mean age of patients was 48.8 ± 11.2 years, and mean body mass index (BMI) of 25.2 ± 4.8 Kg/m^2. Most of them were ever married (88.0%), postmenopausal (62.7%), parous (79.3%), with family history of breast cancer (50.0%). Histologically, higher percentages of them had invasive ductal carcinoma (85.3%), late stages breast cancer (63.3%), positive estrogen and progesterone receptors (67.3% and 60.0%, respectively), positive human epidermal growth factor receptor-2 detected in (35.3%) and lymphovascular invasion in (29.3%). All the studied inflammatory markers showed significantly lower mean or median values in group II when compared to group I, with higher significance level for total WBC count, ESR, and β_2M.

Conclusion: Different simple inflammatory markers can be used in assessment of newly diagnosed breast cancer patients and in follow-up of chemotherapy response.

Keywords: Breast Cancer, Inflammatory, Markers, Chemotherapy, Response.

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العلامات الالتهابية لدى مرضى سرطان الثدي في المركز الوطني للأورام بعدن

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ملخص الدراسة

المقدمة: من الممكن أن تؤدي الالتهابات المزمنة إلى الإصابة بأنواع مختلفة من السرطان، حيث أنها تلعب دورًا في حدوث وتطور سرطان الثدي. تم إجراء هذه الدراسة لتقييم بعض علامات الالتهاب عند تشخيص مرضى سرطان الثدي مقارنة بمن يخضعون للعلاج الكيميائي.

المنهجية: أجريت هذه الدراسة المقطعية، وشملت 150 مريضة مصابة بسرطان الثدي في المركز الوطني للأورام بعدن، للفترة من 1أغسطس2022 إلى 1أغسطس 2023م. ستون مريضة تم تشخيصهن بسرطان الثدي حديثًا (المجموعة الأولى) و90 مريضة تحت العلاج الكيميائي (المجموعة الثانية). تم جمع البيانات الديموغرافية والسريرية والنسيجية للمرضى، وتم سحب التحاليل للعلامات التالية: عدد كريات الدم البيضاء، عدد الصفائح الدموية، معدل ترسيب كريات الدم الحمراء، الفيريتين، خميرة اللاكتات ثنائية الهيدروجين، بيتا -2- مايكروجلوبولين، بروتين سي التفاعلي، مستضد السرطان 15-3، ومستضد السرطان الجنيني.

النتائج: كان جميع المرضى من الإناث بمتوسط عمر 11.2 ± 48.8 سنة ومتوسط مؤشر كتلة الجسم 4.8 ± 25.2 كجم/م^2. وكان معظمهن متزوجات (88.0٪)، بعد انقطاع الطمث (62.7٪)، ولودات (79.3٪)، ولديهن تاريخ عائلي للإصابة بسرطان الثدي (50.0٪). من الناحية النسيجية، كانت النسب الأعلى منهن مصابات بسرطان القناة الغازية (85.3٪)، سرطان الثدي في مراحله المتأخرة (63.3٪)، إيجابية لمستقبلات هرمون الاستروجين والبروجسترون (67.3٪ و60.0٪ على التوالي)، وإيجابية لمستقبلات عامل نمو البشرة البشري الثاني في (35.3٪)، وغزو الأوعية اللمفاوية في (29.3٪). كانت قيم المتوسطات أو القيم الوسطى لجميع علامات الالتهاب الخاضعة للدراسة أقل بشكل ذو دلالة أحصائية هامة في المجموعة الثانية مقارنة بالمجموعة الأولى، مع مستوى أعلى من الأهمية لعدد كريات الدم البيضاء ومعدل ترسيب كريات الدم الحمراء وبيتا - 2- مايكروجلوبولين.

الخلاصة: خلصت هذه الدراسة إلى أنه من الممكن استخدام علامات الالتهابات المتعددة والبسيطة في تقييم مرضى سرطان الثدي الذين تم تشخيصهم حديثًا ومتابعة استجابتهم للعلاج الكيميائي.

كلمات مفتاحية: سرطان الثدي، الالتهابات، العلامات، العلاج الكيميائي، الاستجابة.

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Introduction

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast. Human breast cancer is originally a colonial disease. A single transformed cell is the product of a series of somatic (acquired) or germ-line mutations and is eventually able to express full alignment and potential [1,2].

According to estimates by the International Agency for Research on Cancer, female breast cancer is the leading cause of cancer incidents worldwide in 2020 with nearly 2.3 million incident cases representing 11.7% of all cancer cases and 1 in 4 cancer cases in women. It was the fifth leading cause of cancer mortality worldwide with around 685,000 deaths in 2020 [3].

Recently, attention has been paid to the renaissance of the inflammation - cancer connection, and according to epidemiological studies, chronic inflammation can predispose to different forms of cancer [4]. Observational studies have increasingly explored the link between inflammation and incident breast cancer through the use of systemic inflammatory markers [5,6]. Most of these studies utilized the acute-phase reactant excessively produced by the liver during inflammation, as C-reactive protein (CRP) [7], and ferritin [8], other markers as white blood cells count (WBC), platelets count (Plt) [9], serum lactate dehydrogenase (LDH) enzyme,[10] beta -2- macroglobulin (β2-M) [11], erythrocytes sedimentation rate (ESR)[12].

Other serum biomarkers such as carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) are useful in metastatic disease surveillance, but not for the diagnosis of localized breast cancer [7].

In Aden, there is no previous study conducted to investigate these biomarkers in patients with breast cancer. This gave us the justification to conduct this study with the aim of determining these biomarkers in newly diagnosed breast cancer compared to those under chemotherapy at the National Oncology Center (NOC), in Aden. Thus, the purpose of this study is to evaluate some inflammatory markers at diagnosis of patients with breast cancer compared to those under chemotherapy.

Methods

Study design and setting

This study is a cross-sectional study conducted at the National Oncology Center in Aden.

Study population

All patients with a histological diagnosis of breast cancer at the National Oncology Center in Aden, from August 1st, 2022 to August 1st, 2023, were included in the study. This encompassed both newly diagnosed patients who had not yet started chemotherapy and those already undergoing chemotherapy, regardless of the cycle or treatment protocol.

Sampling

A non-probability convenience sampling method was used to include all breast cancer cases diagnosed in the study period. All participants were female patients, divided into two

groups. Group I consisted of 60 newly diagnosed patients during the study period who underwent surgery and were evaluated before the initiation of chemotherapy. Group II included 90 patients already undergoing chemotherapy

Data collection

Data were collected from 150 patients with breast cancer who were interviewed and enrolled in the study. All included patients were subjected to face-to-face interview between the researcher and the newly diagnosed and managed cases of breast cancer under study.

A structured questionnaire, was employed to obtain data about sociodemographic, and medical conditions and a blood sample (7mL) was taken from each participant with minimal stasis from the antecubital vein using a dry, sterile disposable syringe and needle. Two ml of blood was dispensed into a tube containing the anticoagulant ethylene diamine tetra acetic acid (EDTA) to test complete blood cells count (CBC), and 1.6ml was added to the black lidded sedimentation tubes that contained 3.8% sodium citrate for ESR. Three milliliters of blood were collected in a dry, clean, plain test tube with gentle handling to avoid hemolysis. The tube was kept in a slanting position until clot formation, then centrifuged at 3000 rpm for 5 minutes at 25°C. The separated serum was transferred into properly labeled Eppendorf tubes. From each Eppendorf, approximately 1000 µL of serum was used for the measurement of serum ferritin, CEA, and CA 15-3; another 1000 µL was used for LDH and C-reactive protein; and 100 µL was used for β2-microglobulin analysis.

Statistical analysis

Data collected were analyzed by the SPSS program version 24. Qualitative data were presented as frequency and percentages. Quantitative data were first tested for normality distribution by the Kolmogorov-Smirnov test, which revealed parametric distribution for all data except (CRP, CA 15-3, and CEA). Parametric data were presented as mean with standard deviation (SD) and tested by parametric test (Paired t-test). Non-parametric data were presented as median with range, and tested by non-parametric test (Mann Whitney U-test). All tests were applied at the 95% confidence limits and a level of significance ($\alpha = 0.05$) with p-values of ≤ 0.05 were considered statistically significant.

Ethical considerations

This study was approved by the committee of Research Ethics Committee of the Faculty of Medicine and Health Sciences, University of Aden. A permission request letter for data and sample collection was taken from all the patient's breast cancer administrations. After giving, full details of the objectives, benefits, and risks of the study voluntary verbal consent was required from all the patients under study. On the other hand, their refusal was respected. Personal information was saved and not published.

Results

Of the 150 participants, 60 patients (40.0%) were newly diagnosed, had undergone surgery, and were assessed prior to the initiation of chemotherapy, while 90 patients (60.0%) were receiving chemotherapy.

The mean age of the patients was 48.8± 11.2 years, with a mean BMI of 25.2± 4.8 kg/m². The majority (88.0%) were ever married. Postmenopausal women constituted a higher proportion than premenopausal women (62.7% vs. 37.3%, respectively). As shown in Table 1, most patients (79.3%) were parous, and half (50.0%) reported a family history of breast cancer.

Table 1: Baseline Characteristics of the Studied Patients (n = 150)

Item	№.	%
Mean age ± SD (Min.-Max.) years	48.8 ± 11.2 (22 – 88)	
Mean BMI ± SD (Min.-Max.) Kg/m^2	25.2 ± 4.8 (15.6 – 37.7)	
Marital status		
Unmarried	18	12.0
Ever married	132	88.0
Menopausal status		
Premenopausal	56	37.3
Postmenopausal	94	62.7
Parity		
Parous women	119	79.3
Non Parous women	31	20.7
Family history of breast cancer	75	50.0

SD: standard deviation. BMI: body mass index.

Regarding the clinical staging of breast cancer, Table 2 shows that only 36.7% of the cases were diagnosed at early stages—14.0% in stage I and 22.7% in stage II—while the highest percentage (63.3%) were in advanced stages, with 35.3% in stage III and 28.0% in stage IV. Histologically, the predominant type was invasive ductal carcinoma, accounting for 85.3% of cases, while 14.7% were invasive lobular carcinoma. Lymphovascular invasion was present in 29.3%, estrogen receptor (ER) positivity in 67.3%, progesterone receptor (PR) positivity in 60.0%, and HER2 positivity in 35.3%. [Table 2].

Table 2: Characteristics of Breast Cancer in the Studied Patients (n = 150)

Item	№.	%
Clinical staging		
I	21	14.0
II	34	22.7
III	53	35.3
IV	42	28.0
Histologic type		
Invasive ductal carcinoma	128	85.3
Invasive lobular carcinoma	22	14.7
Lympho-vascular invasion		
Positive	44	29.3
Negative	106	70.7

Estrogen receptor		
Positive	101	67.3
Negative	49	32.7
Progesterone receptor		
Positive	90	60.0
Negative	60	40.0
Human epidermal growth factor receptor two (Her2)		
Positive	53	35.3
Negative	97	64.7

All the studied inflammatory markers showed significantly lower mean or median values in group II when compared to group I, with higher significance level for total WBC count, ESR, and β_2M [Table 3].

Table 3: The Mean/ Median Values of Inflammatory and Tumor Markers in the Studied Groups

Item	Group I (n = 60)	Group II (n = 90)	*p*
	Mean ± SD (Min.-Max.)	**Mean ± SD (Min.-Max.)**	
WBCs (x10^9/L)	7.8 ± 3.4 (3.5 – 19.5)	6.0 ± 2.9 (2.2 – 17.2)	0.001*
Platelets (x10^9/L)	322.7 ± 114.6 (151 – 787)	269.6 ± 94.9 (94 – 592)	0.002*
ESR (mm/hr)	45.4 ± 29.7 (15 – 150)	31.1 ± 15.8 (10 – 91)	0.001*
Ferritin (ng/mL)	227.2 ± 188 (24 – 1117)	152.6 ± 119 (26.6 – 700)	0.003*
LDH (U/L)	274.6 ± 105 (110 – 520)	231.6 ± 71 (115 – 422)	0.003*
β_2M (mg/L)	3.8 ± 0.95 (2.5 – 5.9)	3.3 ± 0.82 (2.0 – 5.6)	0.001*
	Median (Min.-Max.)	**Median (Min.-Max.)**	
CRP (mg/L)[#]	10.0 (0.4 – 80)	6.0 (0.14 – 44)	0.008*
CA 15-3 (µ/ml)[#]	24.1 (3.0 – 567)	17.2 (5.3 – 160)	0.029*
CEA (ng/ml)[#]	3.0 (0.3 – 81.0)	2.1 (0.4 – 13.6)	0.030*

*p-value ≤ 0.05 is statistically significant.
[#] Values expressed as median and tested by the Mann-Whitney-U test for non-parametric data.
Hb: hemoglobin concentration. WBCs: White blood cells count.
ESR: Erythrocytes Sedimentation Rate. LDH: Lactate dehydrogenase.
CRP: C- reactive protein. β_2M: beta 2-microglobulin.
CA 15-3: cancer antigen 15-3 CEA: Carcinoembryonic antigen

Discussion

Inflammation is a term describing a sequence of reactions of the immune system in response to often, but not always, harmful stimuli such as infections, injuries, physical and chemical phenomena, auto-immune or hypersensitivity reactions [13]. In cancer, inflammation may have beneficial effects, acting as a link between the innate and adaptive immune systems and potentially enhancing the antitumor immune response [14]. However, it can also have several negative consequences for functional, behavioral, and clinical outcomes, as it has been associated with skin alterations, pain, fatigue, cognitive problems, and overall symptom burden in cancer patients [15].

Studies in breast cancer utilized variable inflammatory markers, as the first line of defense circulating cytokines as interferons (IF) and interleukins (IL) [16.17], and the second line defense, the acute phase proteins as CRP, and ferritin [7,8]. Other studies utilized other markers that were noticed to be changed with inflammation, as WBC, platelets count, LDH, β2-M, and ESR [9-12]. In the current study, breast cancer patients were investigated with the available inflammatory markers, including the acute phase proteins and other markers that changed during inflammation, in addition to the tumor related antigens; CA15-3 and CEA.

This study found that at diagnosis of patients with breast cancer, no patient found with stage 0, all of them from stage I to IV. It was found that all the studied markers were elevated at diagnosis, which might be attributed to the fact that these markers are related to the tumor burden.

This elevation at diagnosis reflects the effect of the tumor on these markers, or that these elevated markers started earlier and were associated with increased risk of breast cancer [18]. However, the study of Zhao *et al*. [19], found that after the development of cancer, malignant cells and cells found in their microenvironment evoke inflammatory responses via many pathways.

Similar finding to the current study were reported by Petekkaya *et al*. [20], who observed evaluation of serum inflammatory markers in newly diagnosed patients with breast cancer as high serum CRP, ESR, ferritin, LDH, and β2-M, with higher percentage of patients with high CA15-3 and CEA. Consistent findings were also reported by Muhesin and Hadi [21], who observed an elevated serum ferritin, with higher percentage of elevated CA15-3 and CEA. As well, Ali *et al*., discovered an increase in platelets and white blood cell count in patients with newly diagnosed breast cancer [22].

Conventional cancer treatments as chemotherapy were developed based on their ability to destroy malignant cells. Based on this fact this will lead to decreased production of some inflammatory markers [7]. In the current study, among patients who were already started chemotherapy, significantly lower values were observed.

The currently studied patients showed higher significance of decreased marker level for WBCs, ESR, and β2M. The study of Abulkassim *et al*. [23], depicted that chemotherapy leads to a decrease in leukocyte and platelets count in breast cancer patients. Therefore, these changes in these parameters must be taken into account when treating these patients.

For the ESR, the study of Alshamly and Bshaena [24], observed that ESR is significantly raised in breast cancer patients, which is attributed to the elevation of the acute phase reactant as fibrinogen and globulins. The significant decrease in ESR after chemotherapy may be utilized as a marker for monitoring response to therapy. As the Guidelines for the Management of Metastatic Bone Disease in Breast Cancer, blood markers (CA15-3, CEA and ESR) measurement are also recommended as a valuable tool in monitoring therapy [25].

Beta-2-microglobulin has been demonstrated as a growth factor and signaling molecule in breast cancer [26]. The study of Jongvilaikasem *et al.* [27], showed decreased level of β2M after treatment of breast cancer, which is similar to the current study finding. This study showed that a combination of different markers is better than any single marker in evaluation of newly diagnosed patients with breast cancer and in monitoring therapy response.

Conclusion

The different simple inflammatory markers can be used in assessment of newly diagnosed breast cancer patients and in follow-up of chemotherapy response. It is recommended to use these simple, cheap, easy and always available tests in evaluation and monitoring patients with breast cancer and to conduct similar studies for other types of cancers.

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