RESEARCH ARTICLE

Editorial Process: Submission:11/21/2022 Acceptance:05/16/2023

Comparison of Interleukin-33 Serum Levels in Patients with Breast Cancer and Idiopathic Granulomatous Mastitis

Marzieh Haghbin[1], Abdolreza Sotoodeh Jahromi[1], Reza Ranjbaran[2], Mojdeh Abbasi[3], Akbar Hashemi Tayer[1]*

Abstract

Background: Breast cancer (BC) is the main cause of cancer death in women. Idiopathic granulomatous mastitis (IGM), a rare chronic disease that clinically mimics breast carcinoma, and is associated with high mortality and morbidity, but an immediate and accurate diagnosis can substantially decrease these rates. Expressed by numerous human tissues, interleukin-33 (IL-33) has an inductive role in the network of pro-inflammatory cytokines. The aim of this study was to investigate the serum levels of IL-33 in BC and IGM patients in comparison with healthy women. **Materials and Methods:** This descriptive-analytical study was carried out on 28 patients with BC and 25 patients with IGM as the patient groups and 25 healthy volunteers with normal screening reports as the control group. Histopathological pattern of BC and IGM were confirmed by specialized pathologists. The serum concentration of IL-33 was measured using enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. **Results:** The mean age of the patients with BC and IGM and the control group was 49.1, 37.1, and 36.8 years, respectively. There was no significant difference in IL-33 expression among the participants with regard to age, marital status, body mass index (BMI), and menopausal status. IL-33 assay indicated a significant difference between the BC (P=0.011) and IGM (P=0.031) groups compared to the controls, although no substantial differences were observed between the IGM and BC groups. **Conclusion:** IL-33 can be considered a significant factor distinguishing IGM and BC patients from controls, although it cannot be applied to diagnose and differentiate BC from IGM patients.

Keywords: Breast Cancer- idiopathic Granulomatous Mastitis- Interleukin-33

Asian Pac J Cancer Prev, **24 (5)**, 1629-1634

Introduction

Breast cancer (BC) is one of the most common cancers diagnosed in females that is considered a major public health concern (Chen et al., 2020; Haghbin et al., 2021). Although men are also at risk of this cancer, the prevalence of developing or dying from breast cancer in men is approximately 1:1,000 compared to 1:8 for women (Giordano, 2018). Due to the increasing incidence and mortality rate of BC, early diagnosis and suitable treatment are vital, as they can lead to a significant reduction in the rates of death in the long term (Lin Teoh and Das, 2017; Wang, 2017). Studies have shown that chronic inflammation predisposes to the development of various forms of cancer, including BC (Mantovani et al., 2007; Bhatelia et al., 2014). IL-33 therefore plays an important role in tumour progression.

IL-33 is a member of the IL-1 family of cytokines that is actively released as an alarmin after cell damage (Liew et al., 2016; Shen et al., 2018). IL-1 gene family induces a complex network of pro-inflammatory cytokines, and by expressing integrins on endothelial cells and leukocytes, this family regulates and initiates pro-inflammatory responses (Shen et al., 2018). While IL-33 is released by numerous human tissues, it is mainly expressed in endothelial and epithelial cells that are exposed to the outside environment (Kurowska-Stolarska et al., 2011). The specific cell membrane receptor for IL-33 is ST2, also known as IL-1 receptor-like 1, which, upon binding, can activate NF-kB and MAP kinase and eventually result in biologic effects for this factor (Ali et al., 2011; Pisani et al., 2021). IL-33 stimulates innate lymphoid cells (ILC2s), T helper 1 (TH1) cells, regulatory T (Treg) cells, natural killer (NK) cells, and CD8+ T cells, and this pleiotropic nature is reflected in the role of IL-33 in tissue, infection, central nervous system disease, metabolic hemostasis, inflammation, and cancer (Liew et al., 2016). The signalling pathway of IL-33/ST2 can induce cell-dependent inflammatory responses, such as cancer (Larsen et al., 2018). Some studies have shown

*[1]Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran. [2]Diagnostic Laboratory Sciences and Technology Research Center, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. [3]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden. *For Correspondence: hashemiakbar@yahoo.com*

that IL-33 expression is correlated with the progression of BC and these patients have higher serum levels of IL-33 compared to normal individuals (Yang et al., 2015; Larsen et al., 2018).

Moreover, there is a hypothesis that IL-33 has a pro-tumorigenic function in cancer cell lines and causes increased invasion and migration (Pisani et al., 2021). On the contrary, some studies have pointed out the anti-tumor properties of this factor, which result in tumor growth inhibition. Qin et al. reported that IL-33 significantly repressed cancer growth and prolonged the survival of cancer-bearing mice by increasing IFN-γ production in tumors (Qin et al., 2016). The expression of IL-33 also reportedly inhibits tumor progression and results in tumor eradication through the CD8+ T cells (Gao et al., 2015). It is proposed that IL-33 might exert anti-cancer activities and suppress tumor growth under specific circumstances.

Moreover, as a rare, chronic, inflammatory and benign breast disease, idiopathic granulomatous mastitis (IGM) mostly affects women of reproductive age with a recent history of pregnancy and breastfeeding (Patel et al., 2010; Martinez-Ramos et al., 2019; Cakir et al., 2022). IGM mimics breast carcinoma clinically and radiologically (Bani-Hani et al., 2004). The main challenge in the diagnosis of IGM is distinguishing it from malignancy (Evans et al., 2021). Yigitbasi et al., (2017) showed that IL-33 and IL-33-ST2 receptor have high sensitivity and specificity to differentiate IGM from BC. Also, Halim et al., (2018) revealed that compared to BC patients, individuals with IGM have higher levels of IL-33.

IGM and BC patients are similar in their first presentation and also their radiological features (Wolfrum et al., 2018; Zangouri et al., 2022). The misdiagnosis of these diseases will have adverse life impacts for patients, including very costly treatments, poor quality of life, inappropriate medicine use, metastasis in BC patients misdiagnosed with IGM, and even death due to the increasing rate of BC mortality. Based on a study by Azamjah et al., findings from a 25-year-long study revealed a critical increase in the BC mortality rate. These researchers also illustrated that an accurate diagnosis made in a timely manner can be crucial for BC patients (Azamjah et al., 2019).

Hence, in this study, we evaluated the IL-33 serum level in BC patients compared to patients with IGM and its possible potential as a discriminative marker.

Materials and Methods

Patient characteristics

In this descriptive-analytical study, 78 women who were referred to Khatam al-Anbia clinic at Paymaneh Hospital of Jahrom University of Medical Sciences participated in three groups, as follows: Patients with histologically-confirmed BC (n=28), patients with IGM (n=25) and healthy volunteers (n=25).

Patients with BC and IGM were histopathologically confirmed by a specialized pathologist. The healthy participants with a normal screening report and no underlying diseases were selected as the control group. Demographic data including age, marital status, body mass index (BMI), and menopausal status were collected by a specific checklist. The participants in the healthy control group were selected such that they had no statistically significant differences with the participants in the BC and IGM groups in terms of demographic information. The participants with an active infection or underlying diseases and those with a history of smoking or drug abuse were excluded from the study.

Written informed consent was obtained from the candidates prior to participation in this study. The research project was approved by the ethics committee of Jahrom University of Medical Sciences (IR.JUMS.REC.1398.003) and performed in accordance with the Declaration of Helsinki.

Sample collection and preparation

Blood samples of patients and healthy volunteers were drawn from the antecubital vein through a 21-gauge needle (BD Vacutainer needles). Blood samples were collected in anticoagulant-free tubes. Serum samples for IL-33 analyses were separated immediately by centrifugation of the clotted samples for 10 minutes at 1,200×g and were stored at -20°C until the analysis.

Measurement of serum IL-33 level

The IL-33 level was measured using a commercially-available ELISA kit (Human IL-33 ELISA kit, Shanghai Crystal Day Biotech Co., China, Cat. No. E0044Hu) and was compared to the standard graph that had been validated for measuring IL-33 according to the kit manufacturer's instructions.

Statistical analysis

All the statistical analyses were performed in SPSS software version 21 (IBM, USA). The normal distribution of the data was determined using the Kolmogorov-Smirnov test. The descriptive data were presented as mean ± standard deviation, and the analytical data were compared using the one-way analysis of variance (ANCOVA) and Duncan's test. P-values ≤0.05 were considered statistically significant.

Results

In this study, the mean age of the participants with BC and IGM was 49.1±10.5 and 37.1±10.2 years, respectively. Most participants were married, had a history of underlying diseases and a history of BC in their family. The statistical analysis showed that the BC, IGM and control groups were similar in terms of marital status (p=0.25), smoking (p=0.11), BC history (p=0.054) and history of underlying diseases (p=0.81). Meanwhile, there was a significant difference in terms of age and menopausal status between the three groups (p=0.001) (Table 1).

The mean concentration of IL-33 in the BC, IGM, and control groups was 581.0±312.5, 486.6±307.8, and 301.2±67.4 pg/mL, respectively. The ELISA analysis showed no significant difference in serum levels of IL-33 with regard to age (p=0.279), marital status (p=0.622), BMI (p=0.402), and menopausal status (p=0.999) in the patients with BC. Similarly, no substantial difference was

Table 1. Description of Demographic Variables in BC, IGM, and Control Groups

		Patients, n (%)		Control, n (%)	p-value
		BC	IGM		
Age	<30	0 (0.0)	8 (32.0)	7 (28.0)	0.001
	31-40	5 (17.9)	8 (32.0)	8(32.0)	
	41-50	8 (28.6)	8 (32.0)	8 (32.0)	
	>50	15 (53.6)	1 (4.0)	2 (8.0)	
BMI	Normal	8 (28.6)	4 (16.0)	8 (32.0)	0.31
	Overweight	14 (50.0)	16 (64.0)	13 (52.0)	
	Obese	6 (21.4)	5 (20.0)	4 (16.0)	
Marital status	Single	3 (10.7)	0 (0.0)	3 (12.0)	0.25
	Married	25 (89.3)	25 (100)	22 (88.0)	
Smoking	Yes	4 (14.3)	0 (0.0)	1 (4.0)	0.11
	No	24 (85.7)	25 (100)	24 (96.0)	
Menopause	Yes	12 (42.90	1 (4.0)	2 (8.0)	0.001
	No	16 (57.1)	24 (96.0)	23 (92.0)	
BC history	Yes	6 (21.4)	2 (8.0)	0 (0.0)	0.054
	No	22 (78.6)	23 (92.0)	25 (100)	
Underlying disease*	Yes	6 (21.4)	4 (16.0)	4 (16.0)	0.81
	No	22 (78.6)	21 (84.0)	21 (84.0)	

*Cardiovascular diseases, Renal disease, Diabetes, Liver disease, Lung disease, Hypertension

observed between the patients with IGM and the healthy subjects in terms of IL-33 serum levels and the other discussed factors (Table 2).

According to the ANCOVA, after modifying the effect of age and menopausal status, a significant difference was observed in terms of IL-33 levels among the BC, IGM, and control groups (Figure 1). The results of the LSD analysis showed a significant difference between the BC and control groups (p=0.011) and between the IGM and control groups (p=0.031) in terms of IL-33 expression. In addition, IL-33 was higher in the BC and IGM groups than the control group. Nonetheless, there was no significant difference in IL-33 levels between the BC and IGM groups (p=0.43) (Table 3).

Discussion

Although there are advances in the use of herbal medicine in cancer treatment (Shakeri et al., 2020; Jahromi et al., 2021; Muhammad et al., 2022), pharmaceutical treatments and their side effects are still a major challenge in cancer therapy (Khamisipour et al., 2016; Kokhaei et al., 2016). The use of immunological biomarkers can therefore be useful in the differential diagnosis or targeted treatment of different types of cancer (Berraondo et al., 2019).

In this study, serum levels of IL-33 were evaluated in patients with BC and IGM, and the final results showcased a significant difference between the BC and control group.

Table 2. IL-33 Levels in the Groups of BC Patients, IGM, and Control Group based on Age, Marital Status, BMI, and Menopause Status

		Patients, (mean±sd)		Control, (mean±sd)	p-value
		BC	IGM		
Age	<30	0	360.3 ± 54.8	316.8 ± 62.6	BC= 0.27
	31-40	464.2 ± 45.2	719.6 ± 464.2	293.2 ± 51.6	IGM=0.07
	41-50	560.2 ± 115.9	401.8 ± 116.2	309.8 ± 89.6	Control=0.73
	>50	631.0 ± 416.2	311.0 ± 0.0	268.3 ± 57.5	
BMI	Normal	486.2 ± 56.2	694.2 ± 671.3	320.5 ± 70.8	BC= 0.40
	Overweight	678.2 ±421.4	431.8 ± 139.7	282.6 ± 55.6	IGM=0.93
	Obese	480.3 ± 89.6	496.0 ± 319.4	292.6 ± 95.8	Control=0.56
Marital status	Single	511.6 ± 32.5	441.1 ± 180.2	354.5 ± 65.7	BC= 0.62
	Married	589.3 ± 330.3	486.6 ± 307.8	295.2 ± 66.8	IGM=0.41 Control=0.62
Menopause	Yes	597.7 ± 365.2	311.0 ± 0.0	280.5 ± 75.6	BC= 0.99
	No	568.4 ± 278.5	312.2 ± 493.9	303.5 ± 68.5	IGM=0.24 Control=0.75

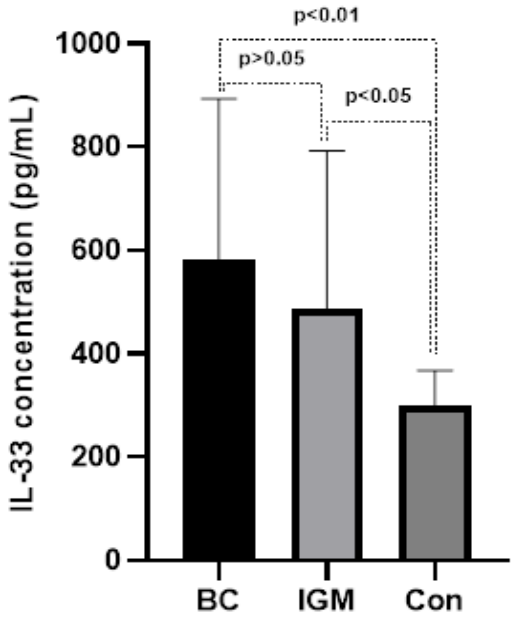

Figure 1. Comparison of IL-33 in Three Groups of Participants. There was a significant difference between IL-33 level in BC (p< 0.01; by ANCOVA), and IGM (p< 0.05; by ANCOVA) patients compared to control. Results are mean ±SD.

Also, the results showed the same difference between the IGM and control groups, although the level of IL-33 did not differ significantly between the IGM and BC groups, which demonstrates the doubtful use of IL-33 as a distinguishing factor between these diseases, which have similar presentations.

IGM is correctly known as a rare and benign breast disease that usually affects fertile women with a history of breastfeeding. Although IGM is rare, since its diagnosis is based on the disease presentations and given its great similarity to BC, distinguishing between IGM and BC is difficult, even based on radiological patterns (Halim et al., 2018). In addition, with the advances in science in recent years, increases in IL-33 levels have been more notably detected in patients with IGM and BC (Yang et al., 2015; Hu et al., 2017; Yigitbasi et al., 2017). The role played by IL-33, which has been unclear until the recent years, focuses on the IL-33/ST2 axis (Milovanovic et al., 2012; De la Fuente et al., 2015).

Abundant evidence suggests that cytokines are involved in carcinogenic pathways (Haghshenas et al., 2022). As a member of the IL-1 family, IL-33 has receptors with three different isoforms, including ST2L, sST2, and ST2V (Milovanovic et al., 2012). ST2L, a membrane-anchored receptor, is responsible for IL-33 signaling. In contrast, sST2 acts as a decoy receptor with a decreasing effect on IL-33 signaling, and ST2V acts similar to sST2 but lacks a third extracellular immunoglobulin domain (Li et al., 2000; De la Fuente et al., 2015).

Our study showed that the serum levels of IL-33 were significantly higher in patients with BC and IGM compared to healthy controls. In addition, there were no significant differences in any of the studied groups in terms of age, marital and menopausal status and BMI with regard to serum levels of IL-33. In accordance with the present study, Yang et al., (2015) also conducted a study to evaluate the relationship between sST2 and IL-33 in breast cancer patients. They apparently found a higher level of IL-33 and sST2 in BC patients compared to the control group. Also, due to the higher level of vascular endothelial growth factor (VEGF) among BC patients, which has a major impact on angiogenesis, these researchers suggested that IL-33 and sST2 are also linked to angiogenesis and have a pivotal role in the development and metastasis of BC (Yang et al., 2015). Another study by Lu et al., (2014) showed a poor prognosis of BC among patients with higher levels of sST2, IL-33, and VEGF. These results are consistent with the outcomes among BC patients in our study. Besides, there is a lack of evidence on the differential diagnosis of IGM and BC, and due to the malignant features of BC, reaching an exact diagnosis is crucial. The accuracy of IL-33 in the differential diagnosis of BC and IGM was also examined by Yigitbas et al., (2017), and in contrast to the current study, they found a significant difference in the levels of IL-33 between primary BC and IGM. Their results showed that IL-33 is significantly higher in IGM patients compared to BC patients. Also, the study indicated a specificity of 96% and sensitivity of 93.75% for IL-33 accuracy, and the researchers finally suggested that IL-33 can be considered a useful inflammatory biomarker for differential diagnosis between IGM and BC (Yigitbasi et al., 2017).

Table 3. Comparisons of IL-33 Level in the Studied Groups with the Adjustment of Age and Menopausal Status

Groups		p-value	95% CI
	IGM	0.427	(-0.171, 0.400)
BC	Control	0.011	(0.111, 0.816)
	BC	0.427	(-0.400, 0.171)
IGM	Control	0.031	(0.032, 0.666)

The present finding is in line with the results of Cohen's research, who reported that IL-33 decreases CD8 T cell activity (Cohen et al., 2015), and this mechanism could also potentially explain the increase in serum levels of IL-33 in the patients compared to the healthy individuals.

Finally, given the different outcomes observed in our study and the increased incidence of BC, further studies with larger population sizes are required before we can accept IL-33 as a reliable discriminative and prognostic factor for IGM and BC patients.

Our study also had some limitations; first, we included only patients without acute infection and did not perform a full examination for obscure symptoms, which should be covered in future research. Second, the patients' drug history was not evaluated. Last, the duration of IGM or BC diagnosis was not taken into consideration in our study.

In conclusion, Based on the present study, there was no significant difference in serum levels of IL-33 in BC patients compared to IGM patients. Therefore, IL-33 assay cannot be used to diagnose and differentiate BC patients

from IGM. The higher IL-33 level in IGM and BC patients compared to the control group suggests Th2 response dominance in the patient group, which may contribute to tumor development and/or IGM. In addition, there was no significant difference between the three study groups in terms of age, marital and menopausal status and BMI with regard to the level of IL-33. It may therefore be wise to perform more detailed investigations for evaluating this important marker to help differentiate the two diseases from each other.

Author Contribution Statement

Akbar Hashemi Tayer participated in the design of the study, carried out the experiments, analyzed and interpreted the results, and drafted the manuscript; Reza Ranjbaran, and Mojdeh Abbasi revised the manuscript critically and contributed to the writing of the manuscript; Marzieh Haghbin was responsible for getting informed consent and the recruitment of the volunteers; Abdolreza Sotoodeh Jahromi conducted the experiments. All of the authors approved the final version of this paper for publication.

Acknowledgements

This study has been supported by Jahrom University of Medical Sciences. We would particularly like to thank all the volunteers who participated in this study.

Statement of Funding

The study was funded by Jahrom University of Medical Sciences.

Statement of Ethics

The study complied with the guidelines for human studies. The study was approved by the ethics committee of Jahrom University of Medical Sciences (IR.JUMS.REC.1398.003). Written informed consent was obtained from the patients and the healthy volunteers prior to participation in this study.

Availability of Data

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None of the authors have any conflicts of interest to declare.

References

Ali S, Mohs A, Thomas M, et al (2011). The dual function cytokine IL-33 interacts with the transcription factor NF-κB to dampen NF-κB–stimulated gene transcription. *J Immun*, **187**, 1609-16.

Azamjah N, Soltan-Zadeh Y, Zayeri F (2019). Global Trend of Breast Cancer Mortality Rate: A 25-Year Study. *Asian Pac J Cancer Prev*, **20**, 2015-20.

Bani-Hani KE, Yaghan RJ, Matalka, II, et al (2004). Idiopathic granulomatous mastitis: time to avoid unnecessary mastectomies. *Breast J*, **10**, 318-22.

Berraondo P, Sanmamed MF, Ochoa MC, et al (2019). Cytokines in clinical cancer immunotherapy. *Br J Cancer*, **120**, 6-15.

Bhatelia K, Singh K, Singh R (2014). TLRs: linking inflammation and breast cancer. *Cell Signal*, **26**, 2350-57.

Cakir C, Nayci A, Ferlengez E, et al (2022). Cytokines the Etiology of Idiopathic Granulomatous Mastitis. *J Coll Physicians Surg Pak*, **32**.

Chen Z, Xu L, Shi W, et al (2020). Trends of female and male breast cancer incidence at the global, regional, and national levels, 1990-2017. *Breast Cancer Res Treat*, **180**, 481-90.

Cohen ES, Scott IC, Majithiya JB, et al (2015). Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation. *Nat Commun*, **6**, 1-10.

De la Fuente M, MacDonald TT, Hermoso MA (2015). The IL-33/ST2 axis: role in health and disease. C*ytokine Growth Factor Rev*, **26**, 615-23.

Evans J, Sisk L, Chi K, et al (2021). Concurrent granulomatous mastitis and invasive ductal cancer in contralateral breasts—a case report and review. *J Surg Case Rep*, **2021**, rjab519.

Gao X, Wang X, Yang Q, et al (2015). Tumoral expression of IL-33 inhibits tumor growth and modifies the tumor microenvironment through CD8+ T and NK cells. *J Immunol*, **194**, 438-45.

Giordano SH (2018). Breast cancer in men. *N Engl J Med*, **378**, 2311-20.

Haghbin M, Hashemi Tayer A, Kamravan M, et al (2021). Platelet-Derived Procoagulant Microparticles as Blood-based Biomarker of Breast Cancer. *Asian Pac J Cancer Prev*, **22**, 1573-9.

Haghshenas MR, Saffarian A, Khademolhosseini A, et al (2022). Simultaneous Increase in Serum Levels of IL-37 and IL-18 Binding Protein In Low-Grade and High-Grade Brain Tumors. *Asian Pac J Cancer Prev*, **23**, 2851-6.

Halim NA, Uthman I, Rammal R, et al (2018). Idiopathic Granulomatous Mastitis Presenting as a Breast Pseudotumor: Case Reports with Review of the Literature. *Case Rep Rheumatol*, **2018**, 4264012.

Hu H, Sun J, Wang C, et al (2017). IL-33 facilitates endocrine resistance of breast cancer by inducing cancer stem cell properties. *Biochem Biophys Res Commun*, **485**, 643-50.

Jahromi AS, Kargar M, Kafilzadeh F, et al (2021). Crocin promotes apoptosis in human EBV-transformed B-lymphocyte via intrinsic pathway. *Mediterr J Hematol Infect Dis*, **13**.

Khamisipour G, Jadidi-Niaragh F, Jahromi AS, et al (2016). Mechanisms of tumor cell resistance to the current targeted-therapy agents. *Tumor Biol*, **37**, 10021-39.

Kokhaei P, Jadidi-Niaragh F, Sotoodeh Jahromi A, et al (2016). Ibrutinib-A double-edge sword in cancer and autoimmune disorders. *J Drug Target*, **24**, 373-85.

Kurowska-Stolarska M, Hueber A, Stolarski B, et al (2011). Interleukin-33: a novel mediator with a role in distinct disease pathologies. *J Intern Med*, **269**, 29-35.

Larsen KM, Minaya MK, Vaish V, et al (2018). The Role of IL-33/ST2 Pathway in Tumorigenesis. *Int J Mol Sci*, **19**.

Li H, Tago K, Io K, et al (2000). The cloning and nucleotide sequence of human ST2L cDNA. *Genomics*, **67**, 284-90.

Liew FY, Girard J-P, Turnquist HR (2016). Interleukin-33 in health and disease. *Nat Rev Immunol*, **16**, 676-89.

Lin Teoh S, Das S (2017). The role of MicroRNAs in diagnosis, prognosis, metastasis and resistant cases in breast cancer. *Curr Pharm Des*, **23**, 1845-59.

Lu Dp, Zhou Xy, Yao Lt, et al (2014). Serum soluble ST2 is associated with ER-positive breast cancer. *BMC Cancer*, **14**, 1-8.

Mantovani A, Marchesi F, Porta C, et al (2007). Inflammation

and cancer: breast cancer as a prototype. *Breast J*, **16**, 27-33.
Martinez-Ramos D, Simon-Monterde L, Suelves-Piqueres C, et al (2019). Idiopathic granulomatous mastitis: A systematic review of 3060 patients. *Breast J*, **25**, 1245-50.
Milovanovic M, Volarevic V, Radosavljevic G, et al (2012). IL-33/ST2 axis in inflammation and immunopathology. *Immunol Res*, **52**, 89-99.
Muhammad N, Usmani D, Tarique M, et al (2022). The role of natural products and their multitargeted approach to treat solid cancer. *Cells*, **11**, 2209.
Patel RA, Strickland P, Sankara IR, et al (2010). Idiopathic granulomatous mastitis: case reports and review of literature. *J Gen Intern Med*, **25**, 270-3.
Pisani LF, Tontini GE, Gentile C, et al (2021). Proinflammatory Interleukin-33 Induces Dichotomic Effects on Cell Proliferation in Normal Gastric Epithelium and Gastric Cancer. *Int J Mol Sci*, **22**, 5792.
Qin L, Dominguez D, Chen S, et al (2016). Exogenous IL-33 overcomes T cell tolerance in murine acute myeloid leukemia. *Oncotarget*, **7**, 61069-80.
Shakeri M, Tayer AH, Shakeri H, et al (2020). Toxicity of saffron extracts on cancer and normal cells: A review article. *Asian Pac J Cancer Prev*, **21**, 1867.
Shen J-X, Liu J, Zhang G-J (2018). Interleukin-33 in malignancies: friends or foes? Front immunol, 9, 3051.
Wang L (2017). Early diagnosis of breast cancer. *Sensors*, **17**, 1572.
Wolfrum A, Kümmel S, Theuerkauf I, et al (2018). Granulomatous mastitis: a therapeutic and diagnostic challenge. *Breast Care*, **13**, 413-8.
Yang ZP, Ling DY, Xie YH, et al (2015). The Association of Serum IL-33 and sST2 with Breast Cancer. *Dis Markers*, **2015**, 516895.
Yigitbasi MR, Guntas G, Atak T, et al (2017). The Role of Interleukin-33 as an Inflammatory Marker in Differential Diagnosis of Idiopathic Granulomatous Mastitis and Breast Cancer. J *Invest Surg*, **30**, 272-6.
Zangouri V, Niazkar HR, Nasrollahi H, et al (2022). Benign or premalignant? Idiopathic granulomatous mastitis later diagnosed as ductal carcinoma breast cancer: Case report and review of literature. *Clin Case Rep*, **10**, e6323.