Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 11172 - 11181
Received 05 March 2021; Accepted 01 April 2021.

Association of IL-17 and IFN-g in Patients of Breast CancerInfected and non-Infected with Toxoplasmosis

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Abstract

Background: Breast cancer is the most frequent malignant disease and the leading cause of death from cancer among women worldwide, both economically developed and developing countries.*T.gondii* is the more common protozoan parasites that cause opportunistic infections in individuals of immunocompromising.

Aims of the Study: Association the cytokines IL-17 and IFN-g in breast cancer patients Infected and non-Infected with toxoplasmosis andtoxoplasmosis only group.

Materialsand Methods: The case control study was conducted on 240 (60) patients with CA. Breast infected toxoplasmosis group, 60 patients with CA. Breast non-infected toxoplasmosis group, 60 patients infected toxoplasmosis without cancer group and 60 healthy controls group) . Both groups patients with CA. Breast were referred to Middle Euphrates cancer center in Najaf and private the clinics for Physicians Oncology , patients infected toxoplasmosis without cancer group were referred to Hospitals in Najaf during the period November2019 to October 2020. Measurement of IgG *Toxoplasma* and cytokines (IL-17 and IFN-g) by using Enzyme Linked Immunosorbant Assay.

Results: The showed a levels of IgG *Toxoplasma*(144 ± 83.4 IU/ml), IL-17 (154.1 ± 55.9 ng/L) and IFN-g(46.6 ± 17.5 ng/ml) in patients of breast cancer infected toxoplasmosis higher than in other studying groups.

Conclusions:A significant elevation levelsIL-17 and IFN-g in breast cancer groups and toxoplasmosis only group in comparison with control and higher a significant elevation levels of IgG, IL-17 and IFN-g in breast cancer infected toxoplasmosis in comparison with breast cancer non-infected toxoplasmosis.

Keywords :IL-17, IFN-g,IgG, Breast cancer, ELISA.

Introduction

Breast cancer is the most frequent malignant disease and the leading cause of death from cancer among women worldwide, both economically developed and developing countries[(1)]. Breast cancer is the most prevalent form of cancer in women worldwide, accounting for 25 percent of all cancer cases [(2)]. In 2018, it resulted in two million new cases and 627,000 deaths[(3)]. It is more prevalent in developed countries[(2)]and more than 100 times higher in the women than in the men[(4)].In uncontrolled breast cell proliferation, breast cancer occurs in the form of a tumour. Malignant breast cancer is

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 11172 - 11181
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an irreversible process without treatment. The patient may die early stages on if the malignant tumour is not removed[5].

Toxoplasmosis is a disease caused by the parasite *Toxoplasma gondii*. Toxoplasmosis infections in adults usually have on noticeable symptoms. People may experience a few weeks or months of mild flu-like symptoms, such as muscle aches and tender lymph nodes, occasionally[6].Parasite infections are more frequent in people with cancer patients due to immunocompromised, which is why people with cancer are more likely to develop antibodies to this kind of protozoan[7]. *T*oxoplasma *gondii*can manipulate the gene expression by miRNAs in host cell and can thus cause cancer onset[8]. Furthermore, toxoplasmosis can result from anti-cancer treatments for people with leukemia, lymphoma, breast tumors, ovarian tumors, lung tumors and malignant tumours[7].

IL-17 shows a pro-inflammation effect on adiversity of the cell types which induces prostaglandns, nitrogen oxides, cytokines and chemokine's. IL‑17 is cytokines have a protumour effect on tumour cells or on a collateral basis by affecting the anti-tumour response of the patient and by causing changes in the microenvironment that aggravate disease's invasive and the metastatic profile[9]. In 2013, reported a correlation between high IL-17 levels in breast cancer[9]. High expression levels of IL-17producing mammalian tumour cells correlate with a weak prognostic factor for stage, overall, and sickness-free survival[10].

Interferons are a protein family that plays a role in preventing viral replication, inhibiting cell growth, and modulating cell differentiation[11]. IFN-g activates a variety of anti-parasite pathways in cell body, one of them is an increase in the production of nitric oxide in infected the cell [12]. Besides its function in the immune cells, IFN-g inhibits the growth of a number of non-hematopoietic forms of cells, including many types of tumour. It was actually used as an antitumor agent [13,14].The IFN-g has shown in different studies the ability to inhibit the growth of many tumour cell lines includingcells of breast cancer [15]. IFN-g exposure has the ability to stimulate cancer growth. Furthermore, new research shows that IFN-g induces tumour metastasis as well [16].

Materialsand Methods

The case-control study was conducted on 240 (60) patients with CA. Breast infected toxoplasmosis group, 60 patients with CA. Breast non-infected toxoplasmosis group, 60 patients infected toxoplasmosis without cancer group and 60 healthy controls group) and their age between (31-70 years old). Both groups of patients with from breast cancer were referred to Middle Euphrates cancer center in Najaf and private oncological

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clinics, patients infected toxoplasmosis without cancer group were referred to the Hospitals in Najaf between November2019 toOctober 2020.

Preparation of samples and ELISA detection ofIgGToxoplasma and cytokines

Five ml of blood samples were obtained using disposable syringes from each woman's redial vein.The tubing was then centrifuged for 10 minutes in 3000 rounds (rpm) to collect the serum. For future immunological study, all sera were stored at -20ºC. Anti*Toxoplasma* IgG and cytokines(Interleukin-17 and IFN-g) measurement by using Enzyme Linked Immunosorbant Assay (ELISA)

Statistical Analysis

This study was a type of case-control study. The statistical significance was done by using SPSS (statistical package for social sciences)version 17 computer software for the analysis purpose of the data. The ANOVA test was used to determine the statistical significance of the difference in mean between more than two groups. P-value of less than 0.05 level was considered statistically significant[(17)].

Results

Mensuration Mean of anti- *Toxoplasma* IgG titer

The present results revealed high percentages of positivity for anti-*Toxoplasma* IgG in patients with breast cancer infected Toxoplasmosis with titer mean(144 ± 83.4 IU/ml) and Toxoplasmosis only group who is seropositive to anti-*Toxoplasma*IgG with titer mean(122.6 ± 55.5 IU/ml) compared with healthy control with a statistically significant differences (P<0.01).

Furthermore,results of the study revealed percentages of seropositivity for IgG *Toxoplasma* titerin patients of CA. Breast infected Toxoplasmosis compared with Toxoplasmosis only group with a statistically significant differences (P<0.05) as shown in Figure (1).

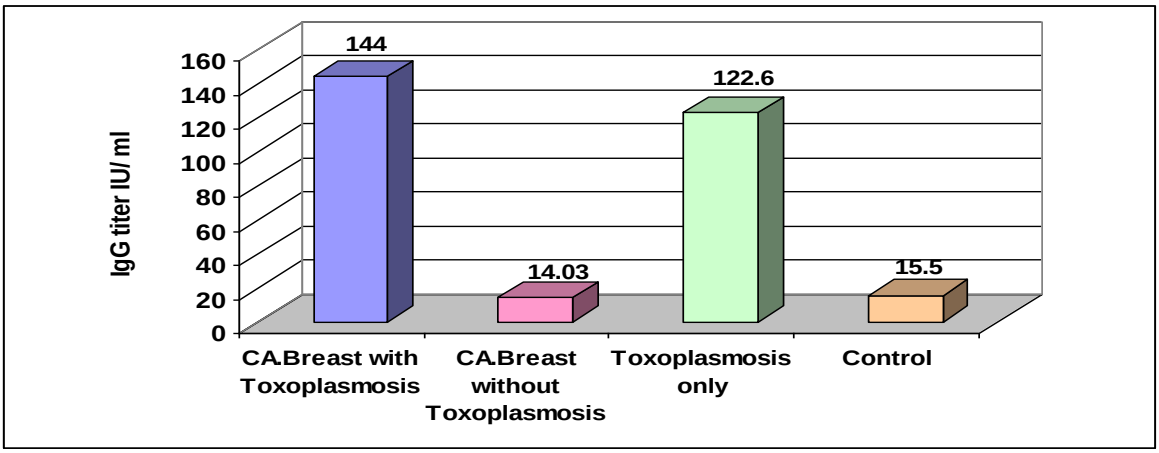

Figure (1): Comparison the mean levels of IgG titer according to between groups

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Mensuration Mean of IL-17

Figure (2) showed high significant differences (P<0.01) in mean of IL-17 in CA. Breast patients infected with toxoplasmosis was (154.1 ± 55.9 ng/L) when compared with mean of IL-17 in other groups (CA. Breast patients without toxoplasmosis (95.4 ± 26.6 ng/L), the patients infected toxoplasmosis only(130 ± 48.9 ng/L) and healthy control group (50.2 ± 17.7 ng/L)). The showed significant differences (P<0.01) in mean of IL-17 in CA. Breast patients without toxoplasmosis when compared with healthy control and showed significant differences (P<0.01) in mean of IL-17 in patients infected toxoplasmosis only was (130 ± 48.9 ng/L) compared with mean of healthy control (50.2 ± 17.7 ng/L).

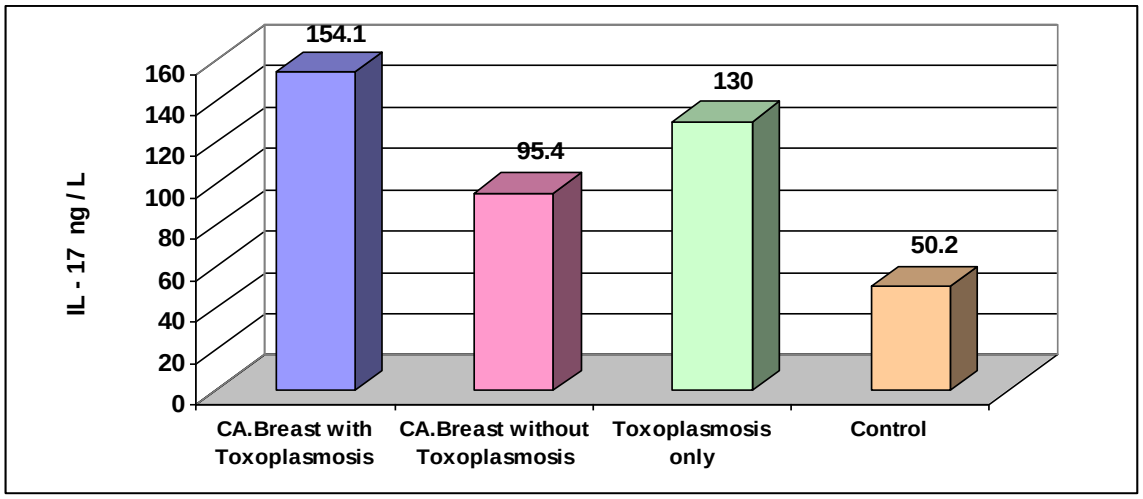

Figure (2): Comparison the mean levels of IL-17according to between groups

Mensuration Mean of IFN-g

Figure (3) showed significant differences (P<0.01) in mean of IFN-g in CA. Breast patients infected with toxoplasmosis was (46.6 ± 17.5 ng/ml) compared with mean of CA. Breast patients without toxoplasmosis(23.2 ± 11.7 ng/ml) and mean of healthy control (20.6 ± 12.8 ng/ml). The showed significant differences (P<0.01) in mean of IFN-g in patients infected toxoplasmosis only was (41.5 ± 20.2 ng/ml) compared with mean of healthy control (20.6 ± 12.8 ng/ml) and showed no significant differences in mean of IFN-g in CA. Breast patients without toxoplasmosis (23.2 ± 11.7 ng/ml) with healthy control (20.6 ± 12.8 ng/ml).

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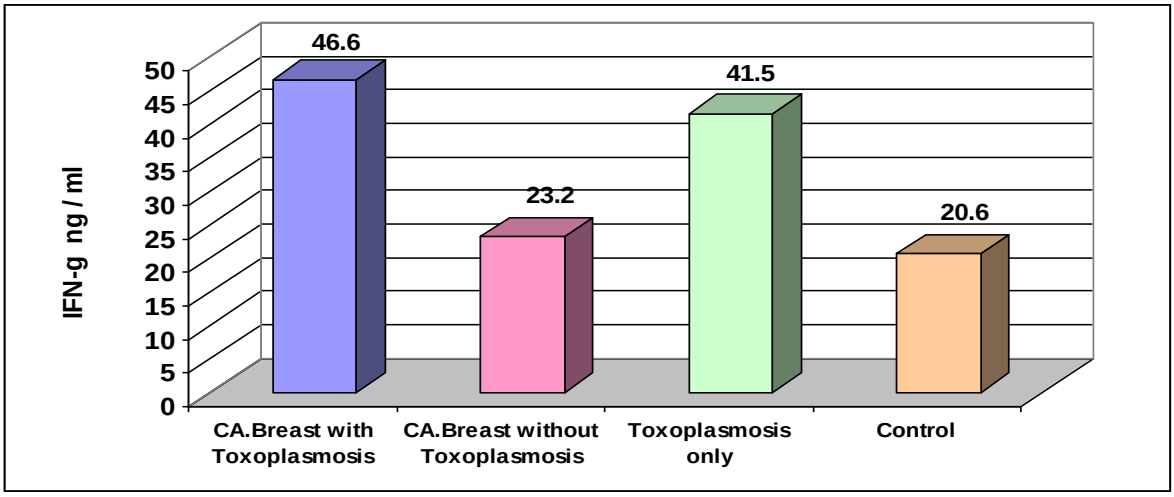

Figure (3): Comparison the mean levels of IFN - g according to between groups

Discussion

Breast cancer is the most common form of cancer in women worldwide. Despite the fact that this malignant has a good prognosis, that was the major cause of death associated with cancer [(18)]. In Iraq, a study found that women had a 33.81 percent share of breast cancer. Compared to other Arab countries in Kuwait, Jordan and Bahrain, the proportion of breast cancer has been lower. Through contrast, the average was higher in other Arab countries such as Saudi Arabia, Oman, the United Arab Emirates, and Qatar, as well as in neighbouring countries Iran and Turkey [(19,20)].

Toxoplasmosis is a complex infection that is considered a seriour disease in immunocompromised patients, where the reactivation of a latent infection can result in death.The prevalence and concentration of IgG antibodies can influence the occurrence of reactivated toxoplasmosis[(21)]. The results of present study showed that the higher percentages of positivity for anti-*T. gondii* IgG titer was (144 ± 83.4 IU/ml) in CA. Breast patients compared with Toxoplasmosis only group was (122.6 ± 55.3 IU/ml). This result agrees with a previous study in Iraq found that the higher titer of positivity for anti-*Toxoplasma* IgG was among patients with CA. Breast (220.718 ± 19.33 IU/ml) compared with the controls (140.575 ± 12.65 IU/ml) [(22)], and other study showed that higher titer of positivity for *Toxoplasma* IgG was between patients with breast cancer (266.36 ± 18.52 IU/ml)compared with the controls infected toxoplasmosis (127.58 ± 11.49 IU/ml) [(23)]. Other studies showed that the overall IgG antibody levels in patients with *Toxoplasma gondii*, cancer group, and a control group were (87.32 ± 35.6 IU/ml, 105.80 ±.96.11IU/ml, 63.26 ±14.20IU/ml, respectively)[(24)]. These results, regardless of the type of cancer, are consistent with other studies that have shown that the

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seroprevalence rate of toxoplasmosis in cancer patients is higher than in healthy individuals[18,25,26].

Despite IL-17 is well-known role in enhancing the inflammatory responses, reports on cytokine's role and involvement in cancer cell growth and development are inconsistent [27]. IL-17 is apart from tumor-promoting properties, IL-17 has also been shown to have antitumor properties.[27]The release of IL17 via Th17-polarized cells was more effective than by Th1 cells in the elimination of established tumors[28]. This study showed significant differences level of IL-17 between breast cancer groups and control group. The results agreed with study in Shiraz, Iran and study inTunisia,who found the highest mean level of IL-17 in breast cancer when compared with control groups[29,30]. Other study, reported that IL-17 expression in breast cancer tissue is mostly confined to macrophages and this finding was interpreted by authors as evidence of the potential macrophage role of IL-17 in promoting tumour progression and invasion [31]. Another study, the reported that IL-17 could promote tumour cell growth, an effect mediated by the IL-17-induced IL-6 release by signal transducer activation and the transcription 3 factor activator (STAT 3) in both tumour and nonmalignant stromal cell[32]. In addition, that showed significant increases in IL-17 and IL-6 mRNA tumour expression that promoted tumour development [33]. In the present study, the results showed that there was an increase in concentration of IL-17 in both breast cancer patient's infected toxoplasmosis group, breast cancer patient's non-infected toxoplasmosis group and toxoplasmosis only group . The results of study agreed with study in Diyala-Iraq, who found increase in concentration of IL-17 in both cancer patient's seropositivity and healthy seropositivity[34].The results of the study in the high mean of IL-17 in toxoplasmosis group agreed with study in Sudan findings, which found a higher significant rise in the mean serum IL-17level in toxoplasmosis patients (203.15pg/ml) as compared to control group(54.8 pg/ml)[35].Numerous regulatory immune functions have been reported for the IL-17 cytokine family, probably due to the induction of several immune signallingmolecules[36.37]. The most well-known function of IL-17 is that it plays a role in inducing and mediating proinflammatory responses[38].

In several studies, IFN-g can prevent the growth of many lines of tumour cell, including breast cancer cells [15,39]. Since signal transduction through the IFN-g receptor is required for this effect, tumour proliferation was the highest in animal cells with a lower number of functional receptor[40], the IFN-g has an antitumor effect in breast cancer cell lines by upregulating the expression of p21 and inducing arrest of cell cycle [41,42], have reported that while IFN-g promotes angiostasis, IFN-g-mediated

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signallingoften separates perivascular cells from blood vessels, accelerating tumour metastasis [(16)]. This study showed no significant differences level of IFN-g between breast cancer non-infected Toxoplasma and healthy control group, while patients of breast cancer infected Toxoplasmosis had higher mean of IFN-g than breast cancer non-infected *Toxoplasma* (P<0.01).The results agreed with study inEgypt, who found that the median of IFN-g level was comparable between cancer and control groups, but that Toxoplasma seropositive individuals had a higher mean level of IFN-g than seronegative individuals[(43)]. This study showed significant differences(P<0.01) in mean level of IFN-g between females infected *Toxoplasma* only group in comparedwith control group, these similar research estimating the serum IFN-g level in this patients category, this finding corroborated a study by AL-Sherees, which discovered a significant increase (P= 0.01) in IFN- levels in toxoplasmosis patients compared to control groups[(44)].This data are currently being used to improve the immune system's function in tumour cell eradication and subsequent tumour cell repertoire immunoediting[(45)]. Researchers are currently investigating the older notion that different bacterial, viral, parasitic, yeast, and biological agents could be used as cancer therapeutics.*Toxoplasmgondii*infection, a protozoan parasitic infection, has been shown to increase resistance to certain forms of tumours[(46)].

Conclusions:A significant elevation levelsIL-17 and IFN-g in breast cancer women groups and toxoplasmosis only group in comparison with control group and higher a significant elevation levels of IgG, IL-17 and IFN-g in breast cancer infected toxoplasmosis in comparison with breast cancer non-infected toxoplasmosis group. That demonstrates the importance of these cytokines in promoting or suppressing immunity toward breast cancer and resistance to *Toxoplasma* infection.

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