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The Association of *Toxoplasma gondii* Infection in Breast and Colorectal Cancer Patients

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Abstract: *Toxoplasma gondii* is an obligatory intracellular protozoan parasite which is a major opportunistic pathogen in patients who are immunocompromised that having cancer disease. Little is known about the epidemiology of *T. gondii* infection in patients who are immunocompromised. This study investigate the possible association of *T. gondii* infection with cancer disease via determining the seropositivity rate of anti *T. gondii* antibodies (IgG and IgM) in Iraqi patients infected with breast and colorectal cancer and investigate the level of IL-6 in the studying groups. Overall 223 women serum samples that included 112 healthy controls samples and 111 samples with breast cancer (CA. Breast) and colorectal cancer (CA. CRC) enrolled in this study. The participants were tested for *T. gondii* immunoglobulins (IgG and IgM) antibodies and (IL-6) levels. The results showed that 86 (77.46%) cancer sample out of 111 samples and 23 (20.54%) out of 112 control samples were positive to anti *T. gondii* IgG. The seropositive rate of anti *T. gondii* IgG in CA. Breast and CA. CRC patients (77.50%, 77.42%) respectively compared with control group (20.54%). The present results revealed that the higher percentages for anti-*T. gondii* IgG and IL-6 titer was among patients with CA. Breast and CA. CRC whose are seropositive to anti *T. gondii* IgG. In regard to the tumor size, higher mean levels of IgG and IL-6 was shown in the tumor size (> 5 cm). Concerning to the tumor stages, the highest mean titer of IgG and IL-6 in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG was in stage (IIIC). According to the grade status, the highest mean titer of IgG Abs and IL-6 was in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG was in grade (G3). The increased levels of anti-*T. gondii* IgG and IL-6 was significantly higher in CA. Breast and CA. CRC patients that infected with *T. gondii* compare with healthy control. Thus, anti-*T. gondii* IgG test and circulating levels of inflammatory cytokines has to be taken into consideration as markers for staging of the cancers.

Keywords: *Toxoplasma gondii*, IL6 Levels, Breast, Colorectal Cancer

1. Introduction

Toxoplasma gondii is an obligate apicomplexan intracellular protozoan parasite and considered the most common global parasite [1]. *T. gondii* infection in immune-competent individuals is rarely symptomatic, but toxoplasmosis occurred in fetus and immunocompromised hosts may result in a severe disease or even lethal damage [2]. Cell-mediated immunity plays a major role against *T. gondii*. It is accompanied by the transformation of the parasite into tissue cysts resulting in chronic infection [3]. This invasion process involved two special organelles, rhoptries and micronemes, each organelle secreting proteins during the invasion process [4]. *T. gondii* resides within a vacuole after rapid cellular invasion, derived from the host cell's plasma membrane. *T. gondii* multiply asexually and cause cellular distraction, leading to cell death [5]. *T. gondii* triggers an innate immune response characterized by a rapid recruitment of neutrophils to the site of infection, followed by a strong Th1 protective response associated with the production of proinflammatory cytokines such as Interleukin-6 (IL-6) in murine toxoplasmosis, a gradual increase in serum IL-6 is correlated with clinical signs [6, 7]. Inflammatory response is the major pathology in the infected hosts. Around three weeks post infection, resistance of individual develops and tissue cysts may form in numerous organs, primarily in brain and muscles. These quiescent cysts permit the parasite

to evade the adaptive host immune. When the tissue cysts rupture, the released quiescent cysts (bradyzoites) are killed by the host immune system. If immune system becomes compromised, such as due to chemotherapy in cancer or AIDS, these bradyzoites develop into tachyzoites, causing active toxoplasmosis [8].

Cancer disease affecting both developing and developed countries [9], about 14.1 million new cancer cases and 6.2 million deaths occurred in 2012 worldwide. In Eastern Mediterranean regions, they observed noticeable increase in the prevalence rate of illness, higher frequencies of younger ages and advanced stages. Colorectal cancer represents a significant cause of morbidity and mortality worldwide [10]. Some medical cases patient require immunosuppressive drug: as in some types of cancer and organ transplantation, during combination with toxoplasmosis infection often lead to severe morbidity and mortality [11]. Patients with immunosuppressive therapy have deficient in cellular immunity, and this makes them more susceptible to the infection [12].

Cytokines are soluble mediators secreted by the cells without any specificity for antigens and which exert their biological action at very low concentrations. IL-6 is an inflammatory cytokine and it is secreted from the activated monocyte, macrophage, or tumor cell [10]. Cytokines are secreted by the breast tumors of which IL-6 is one of them [13]. One important cytokine in colon cancer is IL-6 with its pleiotropic properties. Serum levels of IL-6 are increased in colon cancer patients and correlate with prognosis. Circulating IL-6 might be a prognostic indicator in colorectal cancer [10]. Cytokines production leads to over secretion of superoxide (free radicals) and hydrogen peroxide H_2O_2 that helps mechanical O_2-independent killing of *T. gondii* [14]. Resistance to early *T. gondii* infection is a faint balance between the production of proinflammatory cytokines, which control parasite growth, and regulatory cytokines, which limit host pathology [15]. The molecular pathogenesis of cancer is still poorly understood [10]. The parasitic infection with *T. gondii* considers the most frequent protozoan causing opportunistic infections in immunocompromised individuals. However, little is known about the epidemiology of *T. gondii* infection in patients who are immunocompromised that having immunosuppressive therapy [16].

2. Material and Methods

2.1. Blood Collection

Overall 223 women serum samples included 112 healthy controls samples and 111 samples with CA. Breast and CA. CRC enrolled in this study. They were attended to Oncology Teaching Hospital in the Medical city hospital in Baghdad province from October, 2016 to February, 2017. Blood samples of 5ml were taken from redial vein of each woman by using disposable syringes. The blood was placed in sterilized (Gel Clot activator vacuum tubes) and left for 30 minutes at room temperature for clotting. Then, the samples were centrifuged at 3000 round per minute (rpm) for 10 minutes for serum aspiration and dispensed into 3 eppendroff- tubes by using micropipette and stored at -20°C for future immunological analysis. ELISA kits (Acon *Toxoplasma* IgG ELISA (I231-1091), IgM ELISA (I231-1101), and the cusabio human interleukin 6 kits (CBS-E04638h) kits was used in this study.

2.2. Data Analysis

The Statistical Analysis System- SAS (2012) program was used to study the effect of difference factors in study parameters. Chi-square test was used for significant compare between percentage and least significant difference –LSD test was used for significant compare between means in this study.

3. Results

3.1. Serological Examination of IgG-Abs to T. Gondii in Patients with CA. Breast, CA. CRC and the Control Group

The serological examination for anti- *T. gondii* IgG of patients with CA. Breast and CA. CRC and the control group was (77.46% and 20.54%) respectively. There were no positivity rates of anti-*T. gondii* IgM among the cancer patients and control group. The seropositive rates of anti- *T. gondii* IgG were (77.50%, 77.42% and 20.54%) in CA. Breast, CA. CRC and control group respectively.

Table 1. *Serological examination of anti- T. gondii IgG-Abs to in patients with CA. Breast, CA. CRC and the control group.*

Antibody	Healthy control N = 112		Breast cancer patients N = 80		Colorectal cancer patients N = 31		Chi-square
	No	%	No	%	No	%	
IgG (+)	23	20.54	62	77.50	24	77.42	12.67 **
IgG (-)	89	79.46	18	22.50	7	22.58	12.52 **
IgM (+)	0	0.00	0	0.00	0	0.00	0.0000 NS
IgM (-)	112	100	80	100	31	100	0.0000 NS

** (P<0.01), NS: Non-significant.

3.2. Compare IgG and IL-6 Levels Between Control Group and Patients with CA. Breast and CA. CRC

The present results revealed that the higher titer of positivity for anti-*T. gondii* IgG was among patients with CA. Breast and CA. CRC (220.718 ± 19.33 IU/ml, 225.401 ± 22.07 IU/ml) respectively compared with the controls (140.575 ± 12.65 IU/ml) with a statistically significant

differences (P < 0.01). Also the present results revealed that the higher titer of IL-6 was among patients with CA. Breast, CA. CRC whose are seropositive to anti *T. gondii* IgG were (7.659 ± 0.38 pg/ml, 21.216 ± 1.18 pg/ml) respectively compared with mean value in control groups (5.752 ± 0.33 pg/ml) with a statistically significant differences (P < 0.01).

Table 2. *Compare IgG and IL-6 levels among control group and patients with CA. Breast and CA. CRC.*

Studying groups	IgG (IU/ml)		P-value
	Toxo (-)	Toxo (+)	
Healthy control	2.452 ± 0.08	140.575 ± 12.65	0.0001 **
CA. Breast	3.402 ± 0.17	220.718 ± 19.33	0.0001 **
CA. CRC	6.664 ± 0.47	225.401 ± 22.07	0.0001 **
P-value	0.044 *	0.0053 **	---
	IL-6 (pg/ml)		
Healthy control	4.726 ± 0.37	5.752 ± 0.33	0.076 NS
CA. Breast	7.508 ± 0.42	7.659 ± 0.38	0.866 NS
CA. CRC	18.245 ± 1.06	21.216 ± 1.18	0.061 NS
P-value	0.0001 **	0.0001 **	---

* (P<0.05), ** (P<0.01), NS: Non-significant.

3.3. The Serological Examination of Anti- T. gondii IgG Antibodies and Clinicopathological Factors in Patients with CA. Breast and CA. CRC

In regard to the tumor size, higher mean levels of IgG was shown in tumor size (> 5 cm), the mean titer of IgG in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG was (186.525 ± 18.61 IU/ml, 246.921 ± 22.03 IU/ml) respectively, while in patients whose are seronegative to anti-*T. gondii* IgG, the titer was (1.327 ± 0.012 IU/ml, 5.302 ± 0.43 IU/ml) respectively (P < 0.01). Concerning the tumor stages, the highest mean titer of IgG Abs in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG was in stage (IIIC) (287.288 ± 23.75 IU/ml, 131.454 ± 11.57 IU/ml) respectively while in patients whose are seronegative to anti-*T. gondii* IgG was (1.668 ± 0.04 IU/ml, 1.668 ± 0.05 IU/ml) respectively (P< 0.05). According to the grade status, the highest mean titer of IgG Abs in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG were shown in grade (G3) (51.06 ± 2.71 IU/ml, 378.61 ± 21.83 IU/ml) respectively, compared with patients whose are seronegative to anti-*T. gondii* IgG was (4.279 ± 0.52 IU/ml, 7.914 ± 0.35 IU/ml) respectively (P< 0.01).

Table 3. *The serological examination of anti- T. gondii IgG antibodies and clinicopathological factors in patients with CA. Breast and CA. CRC.*

Clinicopathological factor	IgG (IU/ml)				P-Value
	CA. Breast		CA.CRC		
	Toxo (-)	Toxo (+)	Toxo (-)	Toxo (+)	
Cancer size					
<5	1.196 ± 0.005	168.49 ± 16.54	4.620 ± 0.51	173.665 ± 16.29	0.0001 **
>5	1.327 ± 0.012	186.525 ± 18.61	5.302 ± 0.43	246.921 ± 22.03	0.0001 **
P-Value	0.0735 NS	0.139 NS	0.061 NS	0.0251 *	---
Cancer stage					
IIIA	0.864 ± 0.02	192.564 ± 15.32	0.33 ± 0.02	95.524 ± 6.42	0.0001 **
IIIB	0.873 ± 0.02	197.377 ± 16.07	0.697 ± 0.02	115.973 ± 7.93	0.0001 **
IIIC	1.668 ± 0.04	287.288 ± 23.75	1.668 ± 0.05	131.454 ± 11.57	0.0001 **
P-Value	0.0375 *	0.0218 *	0.0255 *	0.0382 *	---
Cancer grade					
(G1) Well differentiated	0.964 ± 0.06	21.54 ± 1.16	1.411 ± 0.04	150.32 ± 8.92	0.0001 **
(G2) Moderately differentiated	3.598 ± 0.46	41.90 ± 2.54	4.961 ± 0.27	307.91 ± 24.94	0.0001 **
(G3) Poorly differentiated	4.279 ± 0.52	51.06 ± 2.71	7.914 ± 0.35	378.61 ± 21.83	0.0001 **
P-Value	0.0001 **	0.0001 **	0.0001 **	0.0001 **	---

* (P<0.05), ** (P<0.01).

3.4. The Serological Examination of IL-6 and Clinicopathological Factors in Patients with CA. Breast and CA. CRC

In regard to the tumor size, higher mean levels of IL-6 was shown in the tumor size (> 5 cm), the mean titer of IL-6 in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG was (7.299 ± 0.65 pg/ml, 12.097 ± 0.86 pg/ml) respectively, while in patients whose are seronegative to anti-*T. gondii* IgG was (6.76 ± 0.37 pg/ml, 4.561 ± 0.39 pg/ml) respectively (P< 0.01). Concerning to the tumor stages, the highest mean titer of IL-6 in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG was in stage (IIIC) IL-6 was (10.387 ± 0.78 pg/ml, 24.109 ± 1.40 pg/ml) respectively while in patients whose are seronegative to anti-*T. gondii* IgG was (6.805 ± 0.44 pg/ml, 7.308 ± 0.33 pg/ml) respectively (P< 0.01). According to the grade status, the highest mean titer of IL-6 in patients with CA. Breast and CA.CRC whose are seropositive to anti-*T. gondii* IgG were shown in grade

(G3) was (7.158 ± 0.48 pg/ml, 19.848 ± 1.06 pg/ml) respectively, compared with patients whose are seronegative to anti-*T. gondii* IgG which was IL-6 was (2.740 ± 0.03 pg/ml, 9.745 ± 0.61 pg/ml) respectively (P< 0.01).

Table 4. *The serological examination of IL-6 and clinicopathological factors in patients with CA. Breast and CA. CRC.*

Clinicopathological factor	IL-6 (pg/ml)				P-Value
	CA. Breast		CA.CRC		
	Toxo(-)	Toxo (+)	Toxo(-)	Toxo (+)	
Cancer size					
<5	4.14 ± 0.25	5.971 ± 0.41	4.578 ± 0.24	7.162 ± 0.51	0.0291 *
>5	6.76 ± 0.37	7.299 ± 0.65	4.561 ± 0.39	12.097 ± 0.86	0.00744 **
P-value	0.0485 *	0.064 NS	0.892 NS	0.0079 **	---
Cancer stage					
IIIA	5.146 ± 0.31	7.756 ± 0.36	3.63 ± 0.09	5.824 ± 0.24	0.0264 *
IIIB	5.887 ± 0.36	8.131 ± 0.62	3.537 ± 0.12	6.231 ± 0.30	0.0031 **
IIIC	6.805 ± 0.44	10.387 ± 0.78	7.308 ± 0.33	24.109 ± 1.40	0.0001 **
P-value	0.074 NS	0.0352 *	0.0103 **	0.0001 **	---
Cancer grade					
(G1) Well differentiated	1.021 ± 0.03	5.424 ± 0.11	1.352 ± 0.04	8.145 ± 0.54	0.0001 **
(G2) Moderately differentiated	2.247 ± 0.07	6.981 ± 0.32	3.852 ± 0.08	16.432 ± 0.94	0.0001 **
(G3) Poorly differentiated	2.740 ± 0.03	7.158 ± 0.48	9.745 ± 0.61	19.848 ± 1.06	0.0001 **
P-value	0.0461 *	0.0474 *	0.0001 **	0.0001 **	---

* (P<0.05), ** (P<0.01).

4. Discussion

The susceptibility to the infection with toxoplasmosis in immunocompromised could be due to many reasons such as the geographical variation, customs, habits, difference in genetic susceptibility and the acquisition method of *Toxoplasma* infection [17, 18]. Persistent infections may promote cancer because long-term host defensive responses induce inflammation, which increases mutation rates [19]. IgG antibodies indicate chronic infection and an increased titer of IgG antibodies might show reactivation [20]. These chronic infections probably persist throughout the life and may remain undiagnosed until or unless it is reactivated as a result of severe immune suppression [21]. In this study, raised serum IL-6 was present in CA. Breast and CRC patients in compare with healthy control. *T. gondii* patients had a higher level of IL-6 as compared to healthy subjects, which seems to confirm the presence of an inflammatory state. Recent years focused on the identification of cytokines as prognostic factors. Both the innate and acquired immune system are believed to play crucial roles in the anti-tumor response, and the interaction between host immune system and tumor cells has been the subject of intense research over the past decades [22, 23]. According to these results, this study revealed that mean titer of anti-*Toxoplasma* IgG was increased exponentially with tumor size, and the heights mean titer was shown in CA. CRC. It has been long established that the pathologic variables of tumor size is significant prognostic indicator in breast carcinoma [24-27]. In addition, intracellular pathogens may disrupt cell barriers to cancer, allowing oncogenic mutations to accumulate through time [28]. An association between serum IL-6 and size of tumor in patients with cancer has been reported [10, 29]. With increasing tumor size, the higher frequency of positivity of IL-6 was noted. Clinicopathological significance of IL-6 in breast cancer was significantly associated with the tumor sized ≥ 5 cm [30-32].

Patients with high IL-6 were more often found to have advanced disease [29]. The staging of CA. CRC relies on histopathologic criteria of tumor invasion (T), spread to local lymph nodes (N), and tumor metastases to distant organs (M) in the TNM classification system, and tumor cell differentiation [33]. In patients with cancer, immune function is impaired and this is the main reason for the increase of *Toxoplasma* antibodies and duration of chemotherapy [34]. This study showed that the IL-6 levels are correlated with the increasing tumor stages and these finding agree with other studies [30]. IL-6 is a pleiotropic cytokine that plays a significant role in the growth and differentiation of cells [35]. People with immunocompromised systems, especially those with higher chronic infection risk due to cellular immune deficiency, as well as patients with cancer are more susceptible to be infected with *T. gondii* [36]. IL-6 contributes to the proliferation of CA. CRC cells and other cancers, especially at the advanced stage of development [37]. Human tumor cell lines have been reported to produce IL-6 [29]. Patients with high IL-6 were more often found to have advanced disease [29].

The levels of IL-6 associate with TNM staging of the disease of breast cancer. As IL-6 has a direct correlation with the stage of the disease it may indirectly correlate with the prognosis of the patient [13]. IL-6 activity on cancer cells and their environment might actually shift from growth inhibition and differentiation to proliferation and antiapoptosis [38-40]. This could explain the prognosis associated with the presence of tumor IL-6 in early-stage breast cancer and the poor survival associated with high serum IL-6 levels in this series of metastatic breast cancer patients [41]. The stage III breast cancer patients also had advanced histological grade (II or III) of tumors [42]. Serum IL-6 in cancer stages III–IV subgroups was significantly higher than in cancer stages 0–II sub-groups. Accordingly, these variables might be clinically relevant

biomarkers in patients with CA. CRC [43]. According to different stages of CA. CRC, there is a significant association between increasing levels of IL-6 and staging of the tumor [44]. IL-6 can accelerate tumor progression towards malignancy [37]; [45]. As the stage of the disease increased, serum IL-6 level increased proportionately [13]. These diseases have an association with defects in cell-mediated immunity, which is described as T cell exhaustion phenomenon, when strengthened by the use of immune depressive therapies, inclines towards the development of toxoplasmosis, which makes the host unable to control intracellular pathogen infections or tumors [46-48]. Increased levels of immunoglobulins (Ig) in neoplastic microenvironments also result in accumulation of immune complexes (ICs) that engender tumor-promoting inflammatory responses [49, 50]. Ig-IC formation is a significant feature of cancer development: high circulating levels of ICs are associated with increased tumor and poor prognosis in patients with breast, head and neck malignancies [51, 52]. This finding concluded that expression of this cytokine was associated with histological tumor grade in breast cancer and colorectal cancer. IL-6 level is low in normal human mucosa and rises only moderately during progression from adenomatous to low grade (G1 and G2) cancer lesions. High levels of IL-6 were observed in rather undifferentiated lesions (G3–G4). IL-6 is required for protective immunity against *T. gondii* infection [53] and it is contributes in the progress of specific cellular and humeral immune responses, including cell differentiation, immunoglobulin secretion and T cell activation. Thus, IL-6 level might potentially be a clinically relevant biomarker of tumor growth [54]. Breast tumor cells not only produce more IL-6 than normal breast epithelial cells, but also the response on the tumor cells to this interleukin is greater [55]. IL-6 was increased during chronic infection with *T. gondii* parasites [56]. Serum IL-6 concentration in patients is associated with the progression, histological grade [44] as well as tumor size [57].

5. Conclusion

Taking together, these results demonstrate that the increased incidental rate of toxoplasmosis may consider as an indication to the high risk of cancer due to the fact that the latent *Toxoplasma* infection may be trigger long term chemotherapy leading to the compromised immunity of the patients. Moreover, the increased levels of anti- *T. gondii* IgG and IL-6 was significantly higher in CA. Breast and CA. CRC patients that infected with *T. gondii* in compare with healthy control. Thus, anti- *T. gondii* IgG test and circulating levels of inflammatory cytokines has to be taken into consideration as markers for staging of the cancers.

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