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ORIGINAL ARTICLE

Toxoplasma gondii in cancer patients receiving chemotherapy: seroprevalence and interferon gamma level

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Abstract *Toxoplasma gondii* is an opportunistic parasite causing life-threatening diseases in immune-compromised patients. The purpose of the study is to determine the seroprevalence of *Toxoplasma gondii* in chemotherapy receiving cancer patients in relation to different types of malignancies, and to estimate the level of interferon gamma in *Toxoplasma* seropositive and seronegative cancer patients and healthy controls. Anti-*Toxoplasma* IgG and IgM antibodies, and interferon gamma were analyzed in 120 cancer patients receiving chemotherapy (60 having hematological malignancies and 60 with solid organ tumors) and 60 healthy controls using ELISA method. *Toxoplasma* (IgG and IgM) were determined in (66.7% and 9.2%) of the cancer group compared to (33.3% and 6.7%) of the control group with statistical significance only in IgG seropositivity ($p < 0.001$, OR = 4). Patients with hematological malignancies had higher IgG seropositivity than solid organ tumors (40% vs 26.7%). The difference between the groups was statistically significant ($p = 0.002$, OR = 3.5). Median level of interferon gamma was in the same range between cancer patients and control group. However, it was highly elevated in *Toxoplasma* seropositive (76 pg/ml) than seronegative (44.5 pg/ml) cases with statistical significance ($p < 0.001$). *T. gondii* infection remains a major threat to cancer patients and still needs proper screening, diagnosis and treatment.

Keywords *Toxoplasma gondii* · Seroprevalence · Cancer patients · Interferon gamma

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Introduction

Toxoplasma gondii (*T. gondii*) is an intracellular protozoan parasite, which has the ability to invade and replicate in various host organs. This apicomplexan coccidian parasite is frequently encountered in diverse ranges of living hosts. The global prevalence of *T. gondii* infection was estimated to be 30% with variations mainly depending on climatic conditions, dietary habits, and socioeconomic standards (Pappas et al. 2009; El Deeb et al. 2012).

Toxoplasma infections are transmitted mainly through ingestion of undercooked meat containing tissue cysts, or food contaminated with oocysts in cats' feces. Congenital transmission, blood transfusion, and tissue transplantation are other possible routes for spread of the infection (Polat et al. 2012).

In immunocompetent individuals, *Toxoplasma* infection often passes unnoticed leaving the person immune against reinfection. Conversely, it causes fulminant life threatening disseminated disease in the immunosuppressed individuals including cancer patients (Wang et al. 2017; Alim et al. 2018).

Toxoplasma gondii infection stimulates strong protective T helper1 (Th1) response resulting in production of interferon gamma (IFN-γ), tumor necrotizing factor alpha

(TNF-α), and interleukin 12 (IL-12) from T-lymphocytes. This stimulated cell mediated immunity protects the host from the tachyzoite multiplication and prevents the occurrence of the pathology (Filisetti and Candolfi 2004). Humoral immune response has also a role in preventing reinfection with the parasite (Evering and Weiss 2006; Phuangphet 2008).

IFN-γ is important in activating the human macrophages and has antimicrobial activity (Denkers and Gazzinelli 1998). Also, it directly controls the parasite growth (Halonen 2004). Neutrophils are also essential in the early course of toxoplasmosis and play an important role in the protection from the rapidly replicating tachyzoites (Bliss et al. 2001).

Cancer, the principal cause of death both in developing and developed countries, occurs when the immune system can't destroy or eliminate the abnormally dividing cells and fails to contain the tumor (Mellman et al. 2011; Fox et al. 2017).

The relationship between toxoplasmosis and cancers remains dual. Most cancer patients are in a state of impaired cellular and humoral immune systems either from the primary disease, or from chemotherapy and/or radiotherapy administration. Chemotherapeutic drugs work by killing both fast growing cancer cells, and healthy white blood cells causing neutropenia. So, patients receiving chemotherapy are more susceptible to *Toxoplasma* infections. Many studies have reported that the rate of reactivation of a latent *T. gondii* infection was higher in different types of cancers particularly those of the eye, brain, blood and breast (Maciel et al. 2000; Khurana et al. 2005; Kojima et al. 2010; Kalantari et al. 2017).

On the other side, *T. gondii* was also implicated as possible oncogenic pathogen with suggested role in induction and progression of malignant diseases. This was explained by many theories such as preventing apoptosis, enhancing the motility of dendritic cells and macrophages (Carmen and Sinai 2007; Baumgartner 2011), or accumulating oncogenic mutations due to disruption of the traditional cell barriers (Ewald 2009).

Cancer immunotherapy is primarily based on rescuing the normal ability of the immune system to eradicate cancer. Interestingly, *T. gondii* protein extracts were reported to elicit partial antitumor effects. Safe non-replicating *T. gondii* vaccine was found to effectively stimulate potent immunity against existing cancer, hence increasing survival, and preventing its recurrence (Mellman et al. 2011; Fox et al. 2013, 2017).

The primary purpose of the present study is to investigate the seroprevalence of toxoplasmosis in cancer patients receiving chemotherapy attending Beni-Suef University Hospital, Egypt and its relation to different types of malignancies. Also, it aims to estimate the level of serum IFN-γ in *Toxoplasma* seropositive and seronegative cancer patients and healthy controls.

Materials and methods

Population study and blood sampling

A case–control study was performed from February to November 2017 on a total of 180 individuals aged between 18 and 77 years. The study population included 120 cancer patients receiving chemotherapy referred to Oncology Department of Beni-Suef University Hospital and 60 immunocompetent healthy individuals as controls. Cancer patients were classified into 2 groups; the first group included patients having solid organ tumors (no. = 60), while the second group was patients with hematological malignancies (no. = 60). The patients and the control subjects were interviewed using questionnaire containing all sociodemographic data. In addition, the history and stage of cancer, radiological imaging, and treatment regimen were all recorded to the cancer patients. Approximately, 3 ml blood samples were collected from each patient. Sera were separated in 1.5 ml labeled Eppendorf tube, and stored in a deep freezer at − 20 °C until used (Hassanain et al. 2018).

Determination of anti-*Toxoplasma* antibodies and interferon gamma level

Toxoplasma antibodies (IgG and IgM) were serologically screened in all participants' sera using the commercial Pre Check ELISA kits (Pre Check Bio, Inc., USA) according to the manufacturer's manual. The optical density (O.D) was read at 450 nm with a microplate reader, and cut-off value was calculated as 2.1 × mean negative control O.D.

Quantitative measurement of IFN-γ in serum of studied population was done using Human Interferon γ Elisa kit (My Bio Source Inc., San Diego, USA) following manufacturer instructions. O.D was determined at 450 nm, the standard curve was constructed and concentration of samples corresponding to the mean absorbance from the standard curve was calculated.

Ethical approval

The study was approved by the Research Ethical Committee of the Beni-Suef University, Faculty of Medicine, Egypt (No. FWA 00015574) and written consent was obtained from all the participants after explaining the purpose of the study.

Statistical analysis

All data were tabulated and entered into SPSS Version 23 (IBM, Somers, NY, USA) program for statistical analysis. Categorical data were presented as numbers and percentages. Mean with standard deviation were calculated for continuous numerical variables. Chi-square (χ^2) and Odds Ratio (OR) were used to compare any two qualitative variables. p value equal to or < 0.05 was considered of significant value. Univariate logistic regression was used to detect the relation between *Toxoplasma* seropositivity and different risk factors. Independent samples T test (Mann–Whitney U test) was used to differentiate between significant means.

Results

The present study was conducted on a total of 180 individuals with mean age of 49 ± 14.9 years. The age of the cancer patients ranged between 20 and 77 years (mean; 54 ± 13 years) which is comparable to the age range, 18–68 years of healthy individuals (mean; 40.5 ± 14 years). Females were 55% of the studied cases (59.2% in cancer cases, 46.7% in controls), while males represented 45% (40.8% in cancer cases, 53.3% in controls).

Cancer group included 60 cases of solid organ tumors distributed in descending manner as follows: 17 breast cancers, 13 gynecological malignancies, 11 colon cancers, 6 lung cancers, 5 bladder cancers, 4 soft tissue sarcomas, 2 stomach cancers, 1 brain cancer, 1 bone cancer. While, hematological malignancies (60 cases) included: 39 Hodgkin's/non-Hodgkin's lymphomas, 15 chronic lymphocytic/myelocytic leukemias and 6 multiple myelomas.

Toxoplasma IgG antibodies were detected in 100 (55.5%) out of the total 180 screened cases represented as follows; 80/120 (66.7%) of cancer patients compared to 20/60 (33.3%) of the healthy controls and the difference was found to be highly significant. Presence of cancer increases the level of *Toxoplasma* IgG 4 times more than the healthy group ($p \leq 0.001$, OR = 4, 95% CI = 2.073–7.719). Concerning *Toxoplasma* IgM, the total positive cases were detected in 15 (8.3%) cases; higher in cancer patients than control group, 9.2% versus 6.7% respectively. Although, the difference between both groups was found to be insignificant, cancer still increase risk of *Toxoplasma* IgM 1.4 than healthy controls (OR = 1.4, 95% CI = 0.430–4.639) (Table 1).

Patients having hematological malignancies had higher IgG seropositivity than solid organ tumors (40% and 26.7% respectively) with statistical significance ($p = 0.002$, OR = 3.5). Although the same pattern was also shown regarding *Toxoplasma* IgM; 5.8% versus 3.3% in hematological malignancies and solid organ tumors, respectively; it was of non-significant value (Table 2).

Distribution of total seropositive *Toxoplasma* cases in different kinds of tumors was demonstrated in (Table 3) where lymphomas and multiple myelomas among all hematological malignancies had the highest percentages of *Toxoplasma* IgG antibodies representing 84.6%, and 83.3% respectively. Concerning solid organ tumors, all cases of bone and stomach cancers were *Toxoplasma* IgG positive (100%). Highest IgM seropositivity was detected both in lymphomas and gynecological malignancies in approximate proportion; 15.1% and 15.4% respectively. However, in both cases p value was non-significant.

The overall seroprevalence of *Toxoplasma* antibodies (IgM and/or IgG) were 104 cases; 83 cancer cases (69.2%) and 21 (35%) controls with high significance ($p < 0.001$). *Toxoplasma* seropositive percentages were higher in females (59.6%) than males (40.4%), in old-aged individuals (55.8%) than other two age groups and in urban areas (57.6%) than rural areas (42.3%). However, all these differences were of non-significant values (Table 4).

IFN-γ was quantitatively estimated to all participants and the readings ranged between 29.3 and 153.1 pg/ml with mean of 67.4 ± 30.3 pg/ml, and normal range was estimated from 39 to 50 pg/ml. Increased level of IFN-γ was reported in 63 cases (44 in cancer patients and 19 in control). The median level of INF-γ was in the same range between cancer and control groups. However, *Toxoplasma* seropositive cases had higher median of IFN-γ compared to the seronegative group with statistical p value (Table 5).

Discussion

Intact immune system has a critical role in combating any parasitic infection (Sanad et al. 2014). In many instances, immunocompromised individuals including cancer patients may catch opportunistic infections such as toxoplasmosis (Mohammadi Manesh et al. 2014).

In the present study, both anti-*Toxoplasma* IgG and IgM antibodies were higher in cancer patients (66.7% and 9.2%) than healthy controls (33.3% and 6.7%) respectively, showing a significant difference for IgG only. This is typically may be due to weakened host immunity in cancer patients which may allow the reactivation of past chronic *Toxoplasma* infection or increasing the possible risk of acquiring new infection.

Many similar studies in accordance with our results were conducted worldwide. Anti *T. gondii* IgG was reported in 63% and 60% in Turkish cancer patients receiving chemotherapy versus 19.4% and 27% in healthy individuals (Yazar et al. 2004; Alim et al. 2018). In Nepal,

Table 1 Association of anti-*Toxoplasma* antibodies (IgG and IgM) in cancer and healthy control groups

Anti-*Toxoplasma* antibodies			Total (no. = 180)	Cancer group (no. = 120)	Control group (no. = 60)	*p* value	OR*
IgG	Positive	No. (%)	100 (55.6%)	80 (66.7%)	20 (33.3%)	< 0.001*	4
	Negative	No. (%)	80 (44.4%)	40 (33.3%)	40 (66.7%)		
IgM	Positive	No. (%)	15 (8.3%)	11 (9.2%)	4 (6.7%)	0.567	1.4
	Negative	No. (%)	165 (91.7%)	109 (90.8%)	56 (93.3%)		

*Significant *p* value, *OR* odds ratio

Table 2 Relation of anti-*Toxoplasma* antibodies (IgG and IgM) to cancer type

Anti-*Toxoplasma* antibodies			Cancer type (no. = 120)		*p* value	OR*	95% CI
			Hematological malignancies	Solid organ tumors			
IgG	Positive	No. (%)	48 (40%)	32 (26.7%)	0.002*	3.5	1.556–7.874
	Negative	No. (%)	12 (10%)	28 (23.3%)			
IgM	Positive	No. (%)	7 (5.8%)	4 (3.3%)	0.343	1.8	0.512–6.681
	Negative	No. (%)	53 (44.1%)	56 (46.7%)			

*Significant *p* value, *OR* odds ratio

Table 3 Distribution of seropositive *Toxoplasma* IgG and IgM in different classifications of hematological malignancies and solid organ tumors

Classification of Tumor		Total no.	IgG		IgM	
			No. (%)	*p* value	No. (%)	*p* value
Hematological malignancies	Lymphomas	39	33 (84.6)	0.357	4 (15.1)	0.298
	Chronic Leukemias	15	10 (66.7)		3 (13.3)	
	Multiple myelomas	6	5 (83.3)		0	
Solid organ tumors	Breast	17	8 (47.1)	0.680	2 (11.8)	0.657
	Gynecological	13	7 (53.8)		2 (15.4)	
	Colon	11	6 (54.5)		0	
	Lung	6	3 (50)		0	
	Bladder	5	3 (60)		0	
	Soft tissue sarcomas	4	2 (50)		0	
	Stomach	2	2 (100)		0	
	Bone	1	1(100)		0	
	Brain	1	0		0	

IgG seroprevalence was 68.7% among patients having ocular malignancies (Rai et al. 2003). Also, in Korea, cancer patients group had the highest titers of *Toxoplasma* IgG antibodies (Shin et al. 2009).

Lower seroprevalence rates were recorded in different studies conducted on cancer patients; 20%, 19%, 20.6%, 26% (Huang et al. 2000; Wang et al. 2000; Jiang et al. 2015; Wang et al. 2017 respectively). These obvious variations may be attributed to different social and cultural habits, distinct environmental and geographical factors, and different practices in livestock farming.

In Egypt, scarce studies were conducted on the prevalence of *T. gondii* infection in cancer patients. Previously, Khalil et al. (1991) reported the prevalence of 36% *T. gondii* IgG antibodies while, El Shazly et al. (1996) reported 92% IgG and 24% IgM seropositivity in cancer patients after chemotherapy. In recent studies, Mostafa et al. (2018) and Abdel Malek et al. (2018) had detected

Table 4 Association between the overall *Toxoplasma* seropositivity and different variables by univariate analysis

Variable		Group		Total (no. = 104)	*p* value	OR
		Seropositive Cases (no. = 83)	Seropositive Control (no. = 21)			
Gender	Male (81)	32 (38.5%)	10 (47.6%)	42 (40.4%)	0.128	1.599
	Female (99)	51 (61.4%)	11 (52.3%)	62 (59.6%)	Reference	
Age Group	18–30 (37)	8 (9.6%)	11 (52.3%)	19 (18.2%)	0.196	0.595
	31–50 (50)	21(25.3%)	6 (28.5%)	27 (26%)	0.287	1.466
	> 51(93)	54 (65.1%)	4 (19%)	58 (55.8%)	Reference	
Residence	Urban (102)	44 (53%)	16 (76.2%)	60 (57.6%)	0.707	0.889
	Rural (78)	39 (46.9%)	5 (23.8%)	44 (42.4%)	Reference	

*Significant *p* value, *OR* odds ratio

Table 5 Levels of IFN-γ (pg/ml) according to the group and seropositivity

IFN-γ (pg/ml)		Median	*p* value
Group	Cancer patients	60.9	0.338
	Healthy controls	52.65	
Toxoplasma seropositivity	Seropositive	76	< 0.001*
	Seronegative	44.5	

Data were non-parametric and presented by median and Mann–Whitney test to calculate significance between groups

*Significant *p* value, *OR* odds ratio

anti *T. gondii* IgG antibodies in 55.8%, and 20%, and IgM in 3.8%, and 4% cancer patients, respectively.

Our results revealed that patients with hematological malignancies had higher IgG seropositivity than solid organ tumors (40% and 26.7% respectively) with significant statistical value ($p = 0.002$). This is in compliance with Young and McGwire (2005) but contrary to Abdel Malek et al. (2018) who revealed that patients with solid organ tumors (24%) had the higher prevalence of toxoplasmosis than patients having hematological malignancies (12%). However, they reported that the difference was of non-significant value.

Nevertheless, our results can be clarified by two explanations. The first is that most of hematological malignancies patients have impaired cellular immunity. They are considered as intermediate and high risk neutropenic patients by definition. Secondly, corticosteroids are one of the cornerstones in most chemotherapy regimens given to patients having hematological malignancies.

In this study, all cases of bone and stomach cancers were IgG positive (100%) and this is relatively in accordance with Mostafa et al. (2018) who found the highest positivity of IgG was in breast cancer and bone carcinoma (80%). However, our results may be insufficient due to low number of cases of stomach and bone tumors in the study. Variations in seroprevalence of anti-*Toxoplasma* IgG and IgM antibodies in solid organ tumors may be owed to the type of selected immune-suppressed patients, virulence of different *T. gondii* strains and patients' genetic susceptibility.

In the preceding literature, the overall prevalence of toxoplasmosis was higher in females (59.6%) than males (40.4%) with non-significant statistics. This finding partially agrees with Mostafa et al. (2018) who recorded 90.9% and 30% anti-*Toxoplasma* IgG antibodies in females and males, respectively, and may throw light on congenital toxoplasmosis as an important public health problem. This result may be attributed to more susceptibility of females to indoor activities dealing with raw or undercooked meat, raw unwashed fruits or vegetables and/or farming and their greater proximity to cats as well as other animals during daily cleaning activities.

On the other hand, Wang et al. (2015) and Abdel Malek et al. (2018) revealed the higher prevalence of toxoplasmosis in males (8.96%, 18%) than females (7.45%, 16%) respectively, with no significant differences. Meanwhile other studies reported higher rate of toxoplasmosis in males than in females with statistically significant values (Shimelis et al. 2009; Jones et al. 2014).

This study detected higher seropositive cases in higher old age group (55.8%) compared to other two groups. Taking into consideration that more than 50% of participants were from this age group, this finding is in agreement with other studies (Jumaian 2005; El-Geddawi et al. 2016). This is may be due to the fact that impairment of the immune system and exposure to infection become greater with age. In contrast, Abd El Wahab et al. (2018) had revealed higher toxoplasmosis seropositivity in a younger age group (18–24 years).

Toxoplasma seropositive cases were detected in 57.6% of individuals living in urban areas while 42.4% in those living in rural areas, and also this result was of non-significant value. This is in accordance with Walle et al. (2013) and Abdel Malek et al. (2018) who clarified this finding by consuming undercooked meat, environmental variation, and keeping cats indoors.

This study showed the same median level of IFN-γ between cancer and control groups while *Toxoplasma* seropositive persons had higher median of IFN-γ than seronegative ones. In spite of scarcity of similar studies estimating IFN-γ serum level in this category of patients, this result partially agrees with Abdul-Lateef et al. (2012) who found increased IFN-γ level in asymptomatic toxoplasmosis in comparison to healthy control. This finding confirmed that toxoplasmosis induces a highly strong type-1 cytokine response including IFN-γ especially during acute initial infection due to early stimulation of T cell and natural killer cell (Denkers and Gazzinelli 1998; Abou-Bacar et al. 2004).

Immunity to toxoplasmosis is a widely T-cell mediated immunity. Establishment of a symbiosis between *T. gondii* and its host may rely on the role of several inflammatory cytokines such as IFN-γ, TNF-α and IL12 (Shen et al. 2001). This immune response leads to conversion of the parasite to bradyzoites, and limits the parasite tissue extension (Filisetti and Candolfi 2004; Abdul-Lateef et al. 2012). However, *T. gondii* infection has an absolute need to IFN-γ during the acute stage of the disease for controlling tachyzoite replication, and during the chronic infection to maintain the latency and prevent infection reactivation (Suzuki et al. 2012).

Although, overproduction of IFN-γ is associated with highly virulent *T. gondii* infection (Gavrilescu and Denkers 2001), the evidence that IFN-γ can limit neoplastic growth in both chemically induced and transplantable tumors had been reported as well (Kaplan et al. 1998; Shankaran et al. 2001; Street et al. 2002). These data were currently used to enhance the role of immune system in tumor cells eradication, and subsequent immunoediting in tumor cell repertoires (Dunn et al. 2002).

Currently, the ancient idea that different bacterial, viral, parasitic, yeast, and biological agents may be used as cancer therapeutics has attracted the researchers' interest. Hibbs et al. (1971) had proved that *T. gondii* as a protozoan parasitic infection can enhance resistance against certain types of tumors.

Interestingly, *Toxoplasma* infection had elicited a significant antitumor response against development of B16F10 melanoma, aggressive ovarian cancer, and pancreatic cancer in mice. Treatment with non-replicating *Toxoplasma* uracil auxotrophs (NRTUAs) rapidly increases Th1 cytokines, IFN-γ and IL12 production. On the other hand, depletion of these cytokines can abolish this antitumor response (Hunter et al. 2001; Baird et al. 2013; Sanders et al. 2015; Fox et al. 2016).

Conclusion

Toxoplasmosis represents a major cause of morbidity in cancer patients undergoing chemotherapy regimens with predominance in hematological malignancies, and therefore, those patients still need proper screening, diagnosis and treatment. *T. gondii* infection increases the level of interferon gamma than normal individuals. Further studies concerning prevalence of toxoplasmosis in other categories of malignancies and radiotherapy receiving cancer patients are highly recommended.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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