Int.J.Curr.Microbiol.App.Sci (2019) *8*(5): 80-90

International Journal of Current Microbiology and Applied Sciences
***ISSN: 2319-7706* Volume 8 Number 05 (2019)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2019.805.011

Toxoplasma gondii Infection Delays the Onset and Decreases the Severity of Rheumatoid Arthritis in a Programmed Death-1 Mediated Mechanism

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Keywords

Rheumatoid arthritis, Toxoplasmosis, Programmed death-1, Immunomodulation

Article Info

Accepted:
04 April 2019
Available Online:
10 May 2019

A B S T R A C T

Rheumatoid arthritis (RA) is a common autoimmune disorder that affects around 1% of the world's population. The associating morbidity extends out of the joints to involve many vital organs in addition to increased mortality rates. Environmental infections are one of the accused elements to be a risk factor for RA. The relationship between RA and toxoplasmosis was a point of controversy where most of the human studies reported either absent or positive correlation. They usually linked toxoplasmosis to suppressed immunity by the drugs used for RA treatment which enhances activation of latent infections. The current work studied the actual effect of toxoplasmosis on RA by excluding the immune-suppressive action of drugs. The studied population was all newly diagnosed cases who did not start RA treatment. We also studied the effect of programmed death-1, PD-1 (which is overexpressed in chronic toxoplasmosis) on RA severity. We recorded a higher age of onset and decreased severity markers of RA in toxoplasmosis positive patients. The higher lymphocytic PD-1 expression that associated toxoplasmosis was negatively correlated to RA severity. We concluded that toxoplasmosis delayed onset of RA and decreased its severity. These effects can be related to the toxoplasmosis associated increase in lymphocytic PD-1 expression.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that results in progressive articular destruction and many comorbidities in vascular, metabolic, bone and psychological domains (McInnes and Schett, 2017). It affects 0.3-1% of the population allover the world. 0.8 % of all disability-adjusted life years lost in Europe is caused by RA. According to the World Health Organization (WHO), 50% of RA patients can't continue their work within 10 years of disease onset. In addition to depression which is a common sequel of the associating pain, disability, and increased health care

expenditures. The associating increased mortality rate is usually related to cardiovascular problems that complicates RA (Englbrecht *et al.,* 2013; Gulácsi *et al.,* 2015; Taylor *et al.,* 2016; Deb *et al.,* 2018).

Genetic architecture of RA patients revealed that most of the 100 loci responsible for disease susceptibility or progression implicate immune effector or regulatory gene products (McInnes and Schett, 2017). That's why blocking the proinflammatory or enhancing the immune-regulatory mediators are the main targets for drug research to overcome the unresponsiveness of some patients to the traditional disease-modifying agents. One of the important molecules that suppress the immune response and is usually deficient, mutated or malfunctioning in RA patients is programmed death-1 (PD-1). This molecule is expressed on a wide variety of immune cells. Once activated, it inhibits both T cell and B cell activation cascade. It was also proved to directly affect RA severity. Moreover, RA susceptibility is affected by PD-1 polymorphisms (Prokunina *et al.,* 2004; Raptopoulou *et al.,* 2010; Liu *et al.,* 2014; Sandigursky *et al.,* 2017). These findings highlight the potential importance of devising future therapies that can modulate lymphocyte activation through targeting of the PD-1/programmed death ligands (PD-Ls) pathways. This immune-modulating element, PD-1 is also expressed on lymphocytes in chronic infections and is responsible for reactivation of latent infections of the protozoan parasite, *T. gondii* (Bhadra *et al.,* 2011, 2012; Moretto *et al.,* 2017; Xiao *et al.,* 2018).

T. gondii is an obligatory intracellular parasite that can infect any vertebrate animal and remains in his tissues for-life. Its infections usually pass unnoticed in immunocompetent hosts and can be reactivated if host immunity is suppressed (Halonen and Weiss, 2013). The relationship between RA and toxoplasmosis is a point of controversy (Hosseininejad *et al.,* 2018). Some experimental studies reported a negative correlation (Washino *et al.,* 2012) while many human studies reported the reverse where *T. gondii* immunoglobulins (Ig) were detected in sera of RA patients more than healthy controls. These studies usually explained this link by the fact that patients who develop autoimmune diseases have disturbed immune responses that facilitate reactivation of latent infections. Others regarded it to the usage of immune-suppressive drugs that renders the patients more susceptible to opportunistic infections. Other studies supported both points of view and suggested a reciprocal relationship theory (Listing *et al.,* 2013; El-Henawy *et al.,* 2017; Tian *et al.,* 2017). The sharing point among these studies is that all of them were held on patients who are already on treatment that may be the cause of *T. gondii* infection or at least reactivation of latent infections. Previously we reported on the PD-1-mediated protective effect of *T. gondii* antigens against experimental autoimmune encephalomyelitis – the animal model of multiple sclerosis – (Sharaf EL-Deen *et al.,* 2018). In the present study, we investigated its role in RA. Unlike the previous similar studies, our studied population was recently diagnosed RA patients who didn't start RA therapy nor received any immune-suppressive drugs that may increase the risk of *T. gondii* infection. The present work also studied the possible influence of *T. gondii*-induced PD-1 on the severity of RA.

Materials and Methods

Ethical considerations

This study was approved by the Research Ethics Committee of Faculty of Medicine, Menoufia University, Egypt. The aim of the study was explained to all participants and

informed consents were obtained from all of them.

Subjects and study design

This study was a case-control study. It was performed on 100 RA patients attending the outpatient clinic of Physical Medicine, Rheumatology and Rehabilitation Department at Menoufia University Hospitals, Menoufia, Egypt. Duration of the study extended from January 2017 to Mars 2019. All patients underwent full history taking, clinical examination and they were classified according to the classification criteria of the American College of Rheumatology/ European League against Rheumatism (Aletaha *et al.*, 2010). Inclusion criteria were, recently diagnosed RA patients and didn't start treatment. Exclusion criteria were other types of arthritis, encountering immune-suppressive diseases or receiving any immune-suppressive drugs. A control group of 50 healthy non-rheumatoid individuals [negative rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACCPA)] and with matched age and sex was included.

Patients were divided into two groups. GI: non-rheumatoid healthy controls (HC). GII: RA patients. Each group was further subdivided into two subgroups, GIa: RA and *T. gondii* negative (HC/T^{--}). GIb: RA negative and *T. gondii* positive (HC/T^{+}). GIIa: RA positive and *T. gondii* negative (RA/T^{--}). GIIb: RA and *T. gondii* positive (RA/T^{+}).

Diagnosis of RA and assessment of degree disease of severity

Peripheral blood samples were collected from patients and controls. Laboratory tests included erythrocyte sedimentation rate (ESR) by Westergren method (Gilmour and Sykes, 1951), C-reactive protein (CRP), RF using nephelometric technology on MISPA-i2 analyzer (Agappe Diagnostics Ltd., Kerala, India); and ACAPA using electrochemiluminescence on Cobas e411 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany). Steps of tests were performed according to manufacturers' protocols.

Disease activity score 28, DAS28 index was calculated after the examination of 28 swollen and tender joints involving hands, arms and knees and linking results of their examination in a mathematical formula with results of ESR and CRP. The DAS28 ranges from 1 to 9 where a low score (< 3.2) indicates a low disease activity, a moderate score (3.2–5.1) indicates moderate disease activity and a high score (> 5.1) indicates high disease activity (Anderson *et al.*, 2011).

Assessment of *T. gondii* positivity

Serum samples of all participants were analyzed for anti- *T. gondii* IgG antibodies using commercial enzyme immunoassay, Human Anti-*T. gondii* IgG kit (ab108776, Abcam, USA) in accordance with manufacturer's recommendations. Positive samples were analyzed for anti- *T. gondii* IgM antibodies using Human Anti-*T. gondii* IgM Kit (ab108778, Abcam, USA) to exclude acute infection. Anti- *T. gondii* IgG and IgM antibody levels were expressed as U/ml.

Assessment of PD-1 expression on $CD4^{+}$ lymphocytes by flow cytometry

25 µl of EDTA-anti-coagulated blood was mixed thoroughly with 2 µl of the following mouse anti-human monoclonal antibodies, CD279 (PD-1) phycoerythrin, PE (**lot** 5181224067, MiltenyiBiotec, USA) and CD4 fluorescein isothiocyanate, FITC (BD 7156809, Biosciences, USA). Blood samples were incubated for 20 min. at room

temperature in the dark. Red blood cells were lysed by adding 1 ml of lysing solution for 5 min. Then, samples were washed twice using phosphate buffered saline (PBS) and finally, the cells were suspended in 200 µl of PBS for flow cytometric analysis.

$PD\text{-}1^{+}CD4^{+}$cell percentage was determined by analysis on FACS Calibur (Becton Dickinson Immunocytometry Systems, San Jose, CA, USA), gating was done on lymphocytes using side versus forward scatter and at least 10,000 events were acquired.

Statistical analysis

SPSS was used for data analysis (SPSS Inc. Released in 2015. IBM SPSS statistics for windows, version 23.0, Armonk, NY: IBM Corp). The Normality of the data was tested by Kolomogrov and Shapero tests. Chi-square test ($\chi 2$) was used to study the association between qualitative variables and whenever any of the expected cells were less than five, Fischer's Exact test was used. Data of the quantitative type were expressed in Mean and Standard Deviation. Mann Whitney's test was used for comparison of quantitative variables between two groups. Spearman correlation was used to express the correlation between different variables. Kruskal Wallis test was used for comparison of quantitative variables between more than two groups of not normal distributed data with Tamhane's test as a post hoc test. The level of significance of the present data was 95%, so, p-value >0.05 was considered as non-statistically significant difference, while p-value < 0.05 was considered as statistically significant difference.

Results and Discussion

Prevalence of toxoplasmosis is not different between RA patients and HC

Insignificant difference was detected between both groups regarding positivity for toxoplasmosis [Figure 1a]. Opposing results were obtained by Shapira *et al.,* (2012); El-Sayed *et al.,* (2016); El-Henawy *et al.,* (2017); and Tian *et al.,* (2017) who recorded higher prevalence of toxoplasmosis among RA patients compared non-RA individuals. Unlike our work, their studies were held at least 6 months after onset of treatment which by itself is a risk factor for encountering infections due to the associating immune-suppression (Young and McGwire, 2005; Lassoued *et al.,* 2007; El-Sayed *et al.,* 2015). Actually, they assessed the effect of RA on *T. gondii* not the reverse. Some of these authors related the higher incidence of RA in *T. gondii* positive patients to the geographical distribution of patients who share genetic susceptibility to autoimmune diseases and lifestyles that facilitates infection (Shapira *et al.,* 2012; Tian *et al.,* 2017).

Despite the absence of the significant difference between HC and RA groups regarding *T. gondii* IgG positivity, mean IgG titer was significantly higher in RA than the HC group with negative IgM in both groups [Figure 1b]. This finding may reflect reactivation of latent infection. Activation of infection is a common sequela of RA due to the associating premature aging of the immune system with increased apoptosis and/or malfunction of innate and adaptive immune cells. Moreover, the immune-suppressing drugs enhance this reactivation in a dose-dependent manner (listing *et al.,* 2013). Similarly, El-Sayed *et al.,* (2016) and El-Henawy *et al.,* (2017) reported a statistically significant higher anti-*T. gondii* antibody titers in RA patients than control non-RA individuals.

RA/T^{+} patients have delayed disease onset

A statistically significant difference was detected between the mean ages of both RA subgroups where RA/T^{+} patients had a higher mean age of onset than RA/T^{-}ones [Figure

1c]. This can be related to the statistically significant increase of the immune-suppressing molecule PD-1 that occurred in RA/T^+ patients and correlated negatively with the age of RA onset.

Similarly, Washino *et al.,* (2012) recorded a delay in the onset of spontaneous arthritis (an animal model of RA) in *T. gondii* infected IL-1Ra-deficient mice than non-infected ones. They related this delay to the immune-downregulation that associated *T. gondii* infection at both cellular and transcriptional levels. Also, the human study held by Fischer *et al.,* (2013) reported that RA appeared at an older age in chronic toxoplasmosis patients.

Delayed onset of RA manifestations is supported by findings of our previous work on the experimental model of the autoimmune disease, multiple sclerosis. Immunization of mice with soluble antigens of *T. gondii* tachyzoites was associated with a PD-1-dependent suppression of the proinflammatory cytokines, IL-17, and INF-ɣ with a subsequent delay in the appearance of the clinical manifestations of the disease (Sharaf El-Deen *et al.*, 2018).

RA/T^+ patients have decreased disease activity scores and severity markers

All laboratory investigations for disease severity – and subsequently prognosis – (i.e. RF, ACAPA, ESR, and CRP) and DAS28 scores were lower in RA/T^+ patients than RA/T^- ones. Differences were statistically significant in comparison of all assessed parameters.

This can be related to the statistically significant increase of the immune-suppressive PD-1 expression on $CD4^+$ lymphocytes which correlated negatively with all assessed parameters of severity [Figures 1d-1h]. Similarly, Washino *et al.,* (2012) postulated an immune modulating action of *T. gondii* which could decrease disease severity in RA-animal model through suppression of the proinflammatory cells, Th17.

The contradicting results of El-Sayed *et al.,* (2016) and El-Henawy *et al.,* (2017) who reported a positive correlation between latent toxoplasmosis and severity of RA manifestations can be explained by the higher degree of immune dysregulation - that appeared clinically as higher activity scores even with the use of drugs-. The higher the RA severity, the more the risk of acquiring *T. gondii* infection or at least activation of latent infections (Doran *et al.,* 2002).

RA/T^+ patients have a higher lymphocytic expression of PD-1

Because RA is more T helper cell-controlled, we focused on PD-1 expression on $CD4^+$ lymphocytes. We found that percentage of $CD4^+$ lymphocytes that expressed PD-1 was statistically higher in RA/T^+ patients than RA/T^- ones. Moreover, this percent correlated negatively with all scores of disease severity [Figure 2]. These findings are supported by Ceeraz *et al.,* (2013) and Li *et al.,* (2014). They reported decreased PD-1 expression on both $CD4^+$ and $CD8^+$ lymphocytes of RA patients. They correlated degree of disease severity scores to the degree of reduction of lymphocytic PD-1 expression because PD-1 and its ligands are responsible for downregulation of the effector lymphocytes - with subsequent immune suppression - through induction of lymphocytic apoptosis.

Greisen *et al.,* (2017) reported similar results. They even reported a failure of upregulation of the miRNAs of synovial fluid mononuclear cells, PD-1 upon stimulation.

Fig.1 Comparison between the studied groups regarding **a.** Prevalence of toxoplasmosis in HC and RA patients; **b.** Serum levels of *T. gondii* IgG in HC and RA patients; **c.** Mean age of disease onset in RA/T^{-} and RA/T^{+} patients; **d.** ESR of RA/T^{-} and RA/T^{+} patients; **e.** CRP of RA/T^{-} and RA/T^{+} patients; **f.** ACAPA of RA/T^{-} and RA/T^{+} patients; **g.** RF of RA/T^{-} and RA/T^{+} patients; **h.** DAS28 of RA/T^{-} and RA/T^{+} patients

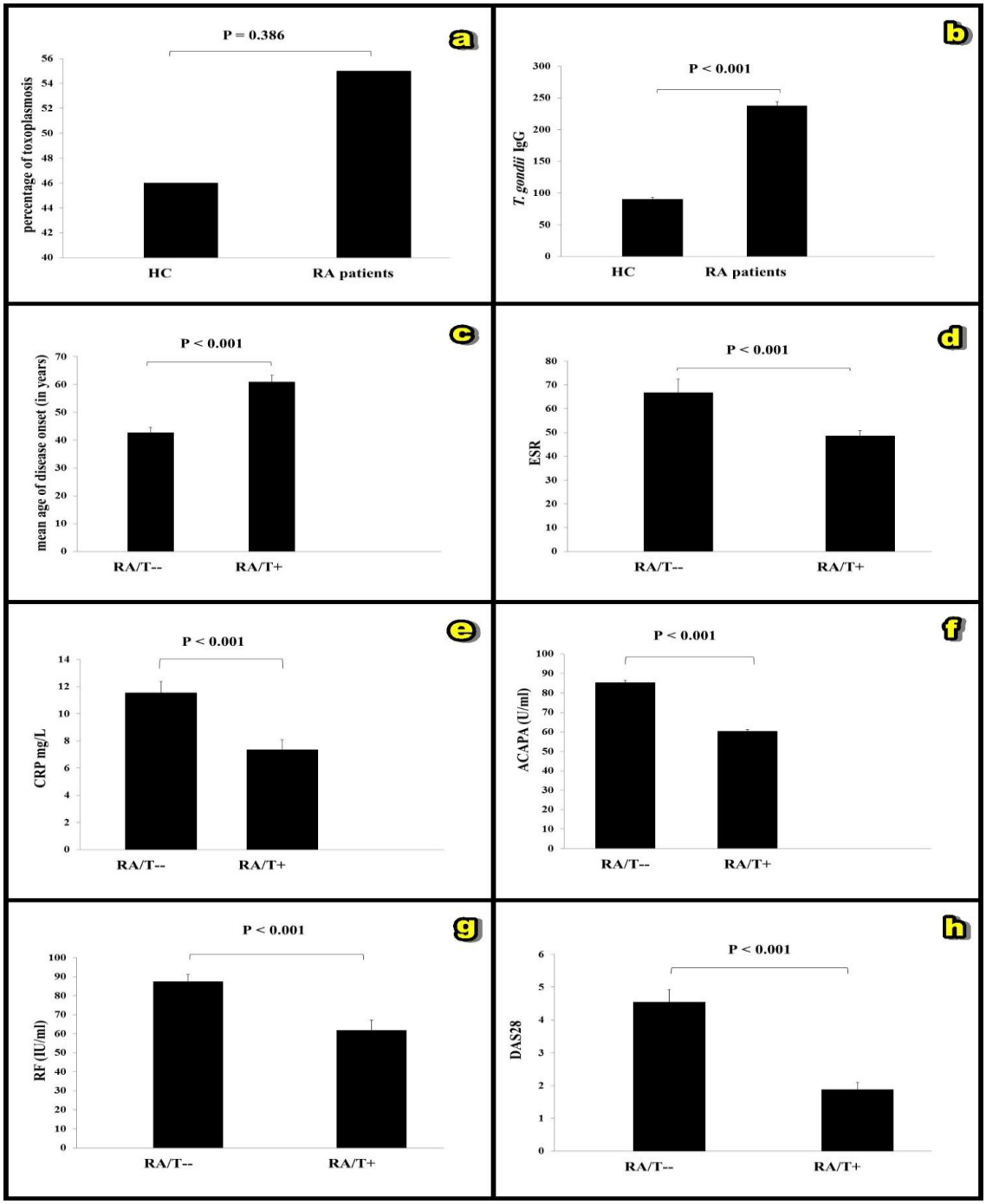
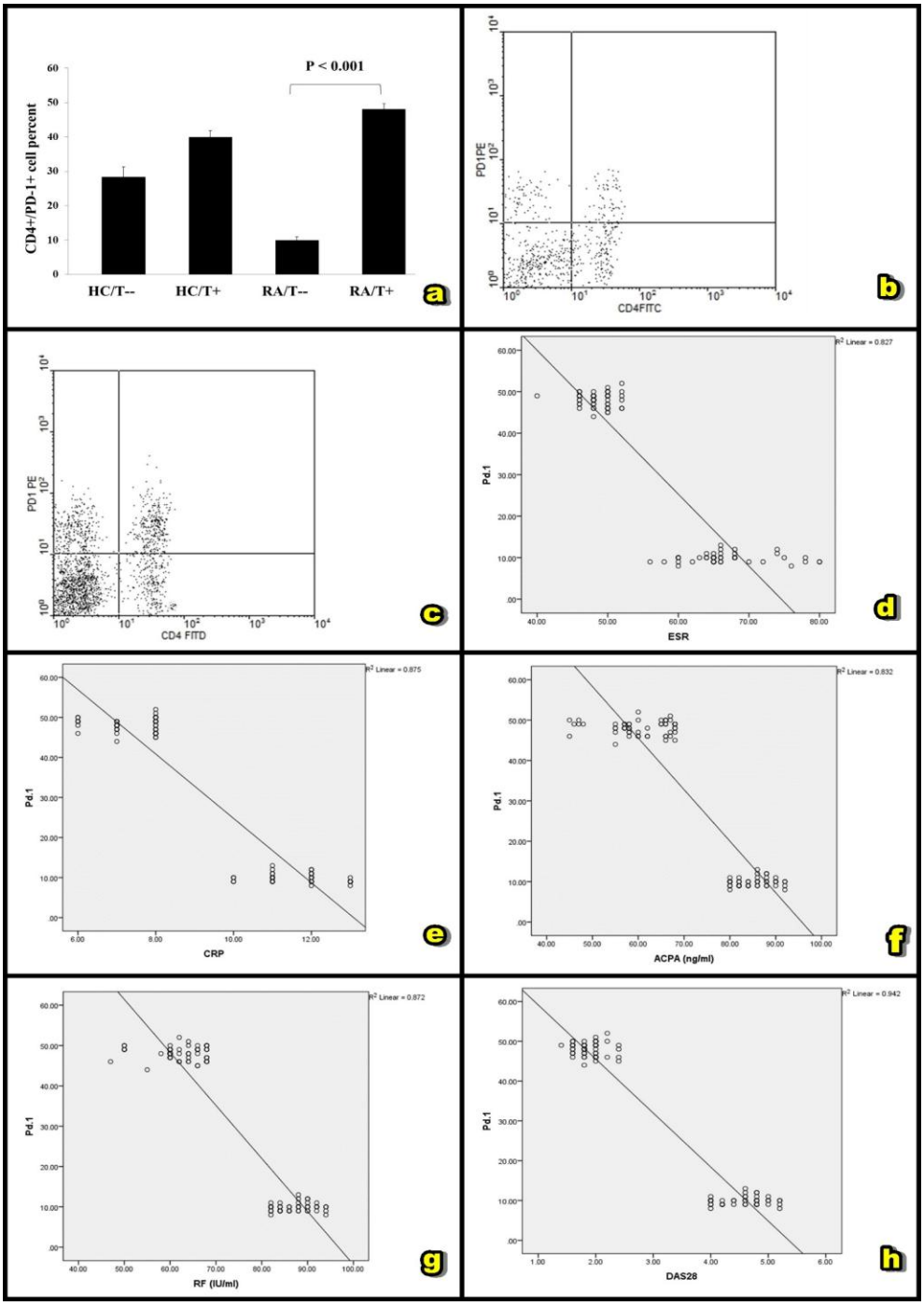


Fig.2 a. Comparison of $CD4^+$ lymphocytic PD-1 expression among the studied groups.
b. Flowcytometric data of $CD4^+$ lymphocytes' PD-1 expression in RA/T^- patients.
c. Flowcytometric data of $CD4^+$ lymphocytes' PD-1 expression in RA/T^+ patients.
d. Correlation between $CD4^+$ lymphocytes' PD-1 expression and ESR.
e. Correlation between $CD4^+$ lymphocytes' PD-1 expression and CRP level.
f. Correlation between $CD4^+$ lymphocytes' PD-1 expression and ACAPA level.
g. Correlation between $CD4^+$ lymphocytes' PD-1 expression and RF level.
h. Correlation between $CD4^+$ lymphocytes' PD-1 expression and DAS28 score.



Influence of *T. gondii* on PD-1 expression on both $CD4^+$ and $CD8^+$ lymphocytes was recorded in many previous studies. Bhadra *et al.,* (2011 and 2012) and Moretto *et al.,* (2017) reported an increased lymphocytic expression of PD-1 in chronic toxoplasmosis due to lymphocytic exhaustion and this PD-1 increase was responsible for reactivation of latent infections. Xiao *et al.,* (2018) also documented the important role of PD-1 in toxoplasmosis reactivation. Its blockade was found to preserve potent immune response that could reduce brain cysts of *T. gondii*. Hwang *et al.,* (2018) reported that increased expression of inhibitory molecules starts once infection turns into the chronic stage and gradually increases. The significant variation in PD-1 expression of lymphocytes of RA/T^- and RA/T^+ patients can explain the delayed onset of RA manifestations. Results of Belkhir *et al.,* (2017) supports ours. They recorded RA incidence in 60% of patients who received anti-PD1 antibodies as a part of cancer immunotherapy. Manifestations appeared in patients who were totally negative for RA. The relation between decreased severity markers and increased PD-1 in RA/T^+ patients is supported by findings of Menzies *et al.,* (2017) who reported flaring of RA and other autoimmune diseases in patients who received anti-PD-1 immunotherapy and had a previous autoimmune disease.

In conclusion, *T. gondii* infection enhanced the $CD4^+$ lymphocytic expression of the immune-suppressive molecule, PD-1. It caused the delayed onset of RA and decreased its severity markers. So, better disease prognosis is expected in presence of *T. gondii* infection.

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How to cite this article:

Sharaf El-Deen, S.A., R.M. Brakat, R.M. El-Kholy, D.S. Saif, Soliman, S.A. 2019. *Toxoplasma gondii* Infection Delays the Onset and Decreases the Severity of Rheumatoid Arthritis in a Programmed Death-1 Mediated Mechanism. *Int.J.Curr.Microbiol.App.Sci.* 8(05): 80-90.
doi: https://doi.org/10.20546/ijcmas.2019.805.011