

TOXOPLASMA GONDII INFECTION IN PATIENTS WITH MALIGNANT AND BENIGN BONE TUMOURS

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Abstract. *Toxoplasma gondii* (*T. gondii*) is an intracellular parasite that infects humans, and seroprevalence of its infection varies from about 10 to 80 percent in different countries with a higher prevalence in warmer and humid regions. In this study, the rate of acute and chronic toxoplasmosis in patients with benign or malignant bone tumours was investigated. Fifty-three patients who suffered from various bone tumours, as well as sixty-five healthy controls with an unknown serological profile for anti-*Toxoplasma* antibodies, were enrolled in this cross-sectional study. Anti-*Toxoplasma* antibodies were detected in serum samples using enzyme-linked immunosorbent assay (ELISA) and blood samples of them were used for real-time PCR. Thirty-two (60.32%) and twenty-one (39.63%) of patients had malignant tumours and benign tumours, respectively. The results showed a higher and significant seropositivity rate of IgM antibodies in primary bone tumour patients compared to the control group and *Toxoplasma* DNA became positive in 18.86% of patients with primary bone tumours and 6.15% of controls. Surprisingly, the high presence of parasite DNA was detected in patients with malignant tumours. The seroprevalence of *T. gondii* IgM antibodies and DNA positivity among the cancer patients were significantly higher than healthy individuals. Also, chronic toxoplasmosis (it was shown with IgG positive) appears to be more common in people with benign cancers than malignancies. The study showed a relatively high seroprevalence of anti-*T. gondii* antibodies in patients with primary bone cancer. However, the considerable rate of positive blood samples for the presence of parasite's DNA should not be ignored. A key to the effective management of diseases in immunosuppressed individuals is prompt and accurate diagnosis of toxoplasmosis. Moreover, it seems that PCR tests may be more reliable than serological methods and it could be considered as a precise method for diagnosis of acute toxoplasmosis.

Key words: primary bone tumour, malignant tumour, benign tumour, toxoplasmosis, *Toxoplasma gondii*, real-time PCR.

ИНФЕКЦИЯ, ВЫЗВАННАЯ TOXOPLASMA GONDII, У БОЛЬНЫХ ЗЛОКАЧЕСТВЕННЫМИ И ДОБРОКАЧЕСТВЕННЫМИ ОПУХОЛЯМИ КОСТИ

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Резюме. *Toxoplasma gondii* (*T. gondii*) — это внутриклеточный паразит, патогенный для человека. Распространенность соответствующей инфекции колеблется от 10 до 80% и наиболее высока она в странах с теплым и влажным климатом. В настоящем исследовании изучалась частота острого и хронического токсоплазмоза у паци-

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ентов с доброкачественными или злокачественными опухолями костей. В данном поперечном исследовании приняли участие 53 пациента, страдающих различными новообразованиями костей, а также 65 здоровых людей с неизвестным серологическим профилем антител против токсоплазмы, составивших контрольную группу. Антитела против токсоплазмы были обнаружены в образцах сыворотки с помощью твердофазного иммуноферментного анализа (ELISA), а образцы крови были использованы для ПЦР в реальном времени. 32 (60,32%) и 21 (39,63%) пациент имели злокачественные и доброкачественные опухоли соответственно. Более высокий и значимый уровень IgM-антител отмечен у пациентов с первичной опухолью кости в сравнении с группой контроля, а ДНК *Toxoplasma* была обнаружена у 18,86% пациентов с первичными опухолями костей и у 6,15% пациентов из контрольной группы. Неожиданным оказалось высокое содержание ДНК паразита у пациентов со злокачественными опухолями. Распространенность антител IgM к *T. gondii* и обнаружение ее ДНК среди онкологических больных были значительно выше, чем у здоровых людей. Кроме того, хронический токсоплазмоз (диагностированный по положительному результату теста на IgG), по-видимому, чаще встречается у людей с доброкачественными формами рака, чем со злокачественными новообразованиями. Исследование показало относительно высокую распространенность анти-*T. gondii* у пациентов с первичным раком кости. Однако нельзя не учитывать значительный процент положительных образцов крови на наличие ДНК паразита. Ключом к эффективному лечению заболеваний у людей с ослабленным иммунитетом является своевременная и точная диагностика токсоплазмоза. Более того, по-видимому, тесты ПЦР могут быть более надежными, чем серологические методы, и их можно рассматривать как точный метод диагностики острого токсоплазмоза.

Ключевые слова: первичная опухоль кости, злокачественная опухоль, доброкачественная опухоль, токсоплазмоз, *Toxoplasma gondii*, ПЦР в реальном времени.

Introduction

Toxoplasma gondii (*T. gondii*) is an obligatory intracellular parasite that infects humans and many animal species and approximately one-third of the world's population is at risk of infection with this protozoan [11, 25]. Seroprevalence of *T. gondii* infection varies from about 10 to 80 per cent in different countries with a higher prevalence in warmer and humid regions [8, 9, 26]. Host immune system plays the most important role in pathological symptoms of toxoplasmosis, for example, immunocompetent individuals rarely show considerable signs, however, this infection in immunocompromised persons may lead to severe diseases such as encephalitis, pneumonia, retinochoroiditis and even death [1, 31].

B lymphocytes produce various classes of antibodies in response to *T. gondii* infection which could be applied for serodiagnosis, like specific IgM which can be detected within 7–15 days in acute infection, however, class switching to IgG antibodies and production of a higher titer and avidity of this class of antibody is observed in chronic toxoplasmosis [12, 28]. Therefore, one of the easiest diagnostic tests for the routine detection of toxoplasmosis is a screening of specific IgG and IgM antibodies in serum, however; the application of molecular techniques may be more sensitive and appropriate methods for diagnosis of acute toxoplasmosis in high-risk patients especially in cancerous people with low traceable antibodies in consequence of radio or chemotherapy [2, 22, 25].

Cancer is one of the major causes of mortality worldwide and is the second leading one in developing countries [18]. Primary bone tumours impose a burden of mortality and morbidity with a wide range of clinical manifestations including pain, peripheral

inflammation and bone fractures on the patients, worldwide. Various histological types of primary bone tumours include benign (osteochondroma, giant cell tumour, exostosis) and malignant (osteosarcoma, Ewing's sarcoma, chondrosarcoma) tumours with nonspecific symptoms which make it difficult to be managed by clinicians [10, 30].

Toxoplasmosis can cause opportunistic life-threatening infection in cancer patients [4]. On the other hand, several studies hypothesized that *T. gondii* infection is responsible for the progression of malignant diseases due to inhibition of apoptosis and motility of macrophages [6]. Therefore, epidemiological studies are required to estimate the rate of infection in high-risk individuals, especially in immunocompromised patients with malignancies undergoing chemotherapy [1, 27]. A case-control study of 900 different cancer patients and 900 controls was conducted in China for evaluating the epidemiology of *T. gondii* infection and the results showed a high significant prevalence of anti *T. gondii* IgG in cancer patients but because of rare incidence of different bone tumours, this type of tumour hadn't been mentioned [7], so in this study, we aimed to evaluate the serum levels of IgG and IgM using enzyme-linked immunosorbent assay (ELISA) and determine parasite-specific DNA by quantitative real-time polymerase chain reaction (qPCR) in aforementioned patients.

Materials and methods

Fifty-three patients who suffered from various bone tumours, as well as sixty-five healthy controls with an unknown serological profile for anti-*Toxoplasma* antibodies, were enrolled in this cross-sectional study.

tional study with local ethical approval and informed consent, from March to August 2019. The blood samples were collected from patients who were diagnosed for primary bone cancer and subjected to surgery at the Shafa Orthopedic Hospital. The patient group was divided into patients with benign tumour subgroups including osteochondroma, giant cell tumour (GGT), exostosis, and other types and patients with malignant tumour subgroups including osteosarcoma, Ewing's sarcoma, chondrosarcoma, and other sarcomas. Approximately five ml of blood was obtained from each participant and divided into two tubes. The tube with no anticoagulant was used for serum isolation to be applied in serological tests and the second tube containing EDTA was used for isolation of buffy coat leukocytes and subsequently DNA purification. All samples were stored at -20°C until use. The serum titre of anti-*T. gondii* antibodies (IgG and IgM) were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's setting (Pishtazteb, Iran) and the absorbance was read by ELISA reader (Biohit, BP800, Finland) at 450 nm versus 630 nm. All experiments were performed in duplicate and equivocal results were repeated [2, 29].

Genomic DNA was extracted from the isolated buffy coat samples using DNA extraction mini kit (YTA Co., Iran) according to the manufacturer's instruction. Specific primers for repeated element (RE) gene of *T. gondii* (F 5'-AGG GAC AGA AGT CGA AGG GG-3' and R 5'-GCA GCC AAG CCG GAA ACA TC-3') was designed using NCBI blast software [3]. The DNA samples were tested for the presence of the 164-bp fragment of RE gene of *T. gondii* by real-time PCR machine (Rotor-Gene Q, Qiagen, USA), in 20 μl volumes, as previously described [3]. Briefly, 1 μg of DNA template was added to SYBR Green PCR Master Mix (YTA Co., Iran). Afterwards, 0.8 μl of each forward and reverse primers with a concentration of 1 pmol/ μl was added and distilled water was used for volume adjustment. Quantitative PCR (qPCR) was performed at 95°C for 10 min, followed by 40 cycles at 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s. The PCR experiments were repeated three times.

Statistics. Data were recorded and analysed with the SPSS v.18 software (SPSS Inc., Chicago, ILL, USA) using Mann-Whitney and Chi-square tests. The p-value < 0.05 was considered as significant.

Table 1. Demographics data of bone cancer patients and healthy individuals

Characteristics		Number of patients (n = 53)	Number of healthy individuals (n = 65)
Gender	Female	24 (45.28%)	51 (78/46%)
	Male	29 (54.71%)	14 (21/53%)
Age	< 20 years old	14 (26.14%)	4 (6/15%)
	20–40 years old	26 (49%)	43 (66.15%)
	40–60 years old	7 (13.2%)	14 (21.53%)
	> 60 years old	6 (11.3%)	4 (6/15%)

Results

The demographic data of the participants are presented in Table 1. Thirty-two (60.32%) and twenty-one (39.63%) of patients had malignant tumours and benign tumours, respectively. The results showed a higher and significant seropositivity rate of IgM antibodies in primary bone tumour patients compared to the control group (Table 2). All samples were tested by real-time PCR for *Toxoplasma* DNA which became positive in 18.86% of patients with primary bone tumours and 6.15% of controls. Surprisingly, the high presence of parasite DNA was detected in patients with malignant tumours (Table 2). We founded a higher IgG and IgM titer against *T. gondii* in patients with benign versus malignant bone tumours but PCR results in malignant patients had a higher percentage than benign patients and control group.

A p-value less than 0.05 was considered significant statistically and the seroprevalence of *T. gondii* IgM antibody and DNA positivity among the cancer patients were significantly higher than healthy individuals ($p = < 0.001$ and $p = 0.005$ respectively). Also, chronic toxoplasmosis (it was shown with IgG positive) appears to be more common in people with benign cancers than malignancies.

Discussion

One of the accepted hypothesis is a higher incidence of opportunistic infections such as toxoplasmosis in cancer patients as a group of immunocompromised individuals [20], for example, the seroprevalence rate of *T. gondii* infection in Iran

Table 2. Seropositivity rates for anti-*T. gondii* antibodies and parasite DNA positivity in primary malignant, benign bone tumour patients and control group

Group	Subgroups	Number of samples	IgG positive			IgM positive			PCR positive		
			No.	%	p-value	No.	%	p-value	No.	%	p-value
Cancer patients	Malignant bone tumours	32	14	43.75	0.44	4	12.50	< 0.001	7	21.87	0.001
	Benign bone tumours	21	11	52.38	0.06	4	19.04	< 0.001	3	14.28	0.06
	Total patients	53	25	47.16	0.23	8	15.09	< 0.001	10	18.86	0.005
Controls	Controls	65	25	38.46		0	0		4	6.15	

was 45–51% in cancer patients but 39% in healthy individuals [1, 8]. However, the geographical factors, eating habits and livestock farming practices can be effective in the prevalence of this infection. Khabaz et al. showed that anti-*T. gondii* IgG was detected in 63.6% of patients with neoplasia and 58% of healthy controls, although, all of the participants (case and control groups) were negative for anti-*T. gondii* IgM antibodies [19]. *T. gondii* seroprevalence was 60.3% in immunocompromised patients and 33.3% in healthy individuals in other provinces during 2014–2015 [17]. Otherwise, the higher rate of *T. gondii* infection in immunocompromised individuals, such as cancer patients could be due to many reasons such as a difference in genetic susceptibility and the source of *Toxoplasma* infection [1, 32]. So, it might be concluded that a high incidence of acute toxoplasmosis in bone cancer patients could be due to impaired genetic system or decreased immunity to encounter this protozoan. The high rate of PCR results obtained for *T. gondii* DNA in cancer patients (18.86% against 6.15% in a healthy individual) could be a witness of this hypothesis and the lower immunity in malignant patients may be explained with more incidence of this infection in patients with malignant tumours versus benign types (21.87% and 14.28%, respectively). On the other hand, this parasite could remain silent in tissue cysts that are commonly formed in different organs such as the central nervous system and the situations such as the immune suppression in cancer patients or the therapeutic process can cause reactivation of parasite and latent toxoplasmosis [24]. So, this can account as another reason for a high percentage of positive PCR and IgM results in cancer.

In the current study, the findings emphasize raising the possible role of cancer on *T. gondii* infection susceptibility, because the seroprevalence of anti-*Toxoplasma* antibodies in patients was higher (47.16% versus 38.46%). The other hypothesis is the effect of persistent infection on the promotion of cancer due to rising mutation rates as a result of long-term host defence responses in inflammation situations [15]. Also, intercellular pathogens like *T. gondii* may disrupt cell barriers against oncogenic agents and might cause mutations after accumulating over time [14].

Interestingly, we observed that two PCR positive patients in the malignant group were negative for anti-

Toxoplasma IgM and IgG antibodies in ELISA which might be due to the recent infection or impaired immune response following immunosuppressive therapy. It was mentioned that serological tests could be sometimes inadequate for detecting active infection in immunosuppressed individuals, because the antibody titre may not rise enough to be detected [13, 23]. Overall, these patients are incapable of developing high titres of antibodies against *T. gondii*. Moreover, anti-neoplastic drug therapy could impair specific anti-*Toxoplasma* antibody production [16, 21].

Hence, serological methods alone have low reliability in both patients and healthy; it was strongly recommended that serologic tests should be combined with other diagnostic methods like gene amplification for accurate clinical diagnosis of active toxoplasmosis. Molecular methods are efficient techniques that allow specific amplification of DNA. The real-time qPCR could be successfully used to *T. gondii* diagnosis and is capable to detect low concentrations of target DNA [3, 22, 32]. Besides, to increase the specificity and sensitivity of immunological assays in immunocompromised patients, new antigenic targets should be designed the parasite to have a potential immunogenic antigen in immunodiagnostic tools of toxoplasmosis in patients with cancer [5].

Conclusion

The study showed a relatively high seroprevalence of anti-*T. gondii* antibodies in patients with primary bone cancer. However, the considerable rate of positive blood samples for the presence of parasite's DNA should not be ignored. A key to the effective management of diseases in immunosuppressed individuals is prompt and accurate diagnosis of toxoplasmosis. Moreover, it seems that PCR tests may be more reliable than serological methods and it could be considered as a precise method for diagnosis of acute toxoplasmosis.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article. The sponsor or funding organization had no role in the design or conduct of this research.

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