Investigation of anti-Toxoplasma gondii antibodies in patients with neoplasia

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This study aimed to determine the prevalence of anti-Toxoplasma gondii antibodies in patients with neoplasia. One hundred and eight patients with neoplasia and 108 healthy controls were studied for the presence of anti-T. gondii antibodies using a micro ELISA and peroxidase-labelled anti-human IgG (rabbit) and IgM (goat). Anti-T. gondii IgG antibodies were detected in 68 (63.0 %) patients and in 21 (19.4 %) of the controls, which was a statistically significant difference. In addition, anti-T. gondii IgM antibodies were detected in seven (6.5 %) patients and in one (0.9 %) control. A high percentage of positivity for Toxoplasma antibodies in patients with neoplasia was detected. Therefore, parasitological surveys of this patient group should be periodically performed.

INTRODUCTION

Toxoplasmosis represents an important public health problem, considering that 0.25–5 cases of congenital infection occur per 1000 live births; that approximately 10 to 20 % of uveitis cases are caused by this parasite; and that the prevalence of Toxoplasma gondii-induced encephalitis can reach up to 40 % in patients with AIDS (Krück & Remington, 1978; Frenkel, 1973; Luft & Remington, 1988). Therefore, toxoplasmosis is of great clinical importance in man in two major situations: as a cause of congenital infection, with 5–24 % of children becoming ill and dying during the neonatal period, in addition to the high rate of children with severe physical, neurological and visual sequelae who require special education and costly care (Frenkel, 1973; Remington & Desmonts, 1990), and as an opportunistic infection with high mortality in immunosuppressed individuals (Carey et al., 1973; Ambroise-Thomas & Pelloux, 1993).

Toxoplasmosis can vary from an asymptomatic, self-limiting infection to a fatal disease, as seen in patients with congenital infections or in debilitated patients in whom underlying conditions may influence the final outcome of the infection (Ambroise-Thomas & Pelloux, 1993).

In individuals with normal immunity and acute acquired Toxoplasma, infection is usually self-limiting and rarely requires specific treatment (Israelski & Remington, 1993). In immunocompetent hosts, the infection is frequently benign, with parasitaemia being self-limiting, resulting in an asymptomatic clinical form of the disease in most cases. However, in about 20 % of Toxoplasma cases, acute infection is accompanied by febrile lymphadenopathy, asthenia and lymphomonocytosis, with the course of infection being self-limited (Feldman, 1968; Darcy & Santoro, 1994). After this period, T. gondii remains viable in the form of tissue cysts, which reproduce slowly throughout the life of the host, thus characterizing the chronic phase of infection. During this phase, the tissue cysts are controlled by the humoral and cellular immune system, involving T-lymphocytes and macrophages, which are continuously stimulated by parasite antigens. As a result, parasite multiplication is more active and persists for longer periods of time in less immunologically active tissues such as the central nervous system (Darcy & Santoro, 1994; Sims et al., 1989).

Immunocompromised hosts, especially those with deficient cellular immunity, are at risk of recrudescence of chronic infection and dissemination, with the occurrence of fulminating disease. Patients with neoplasia, collagen tissue disease, transplant recipients under immunosuppressive therapy or haemodialysis patients with chronic renal failure have deficient cellular immunity, and this makes them susceptible to the infection (Yazar et al., 2003). In immunocompromised patients, the infection most often involves the nervous system, with diffuse encephalitis, meningoen cephalitis or cerebral mass lesions (Garcia & Bruckner, 1997).

The most frequent protozoan causing opportunistic infections in immunocompromised individuals is T. gondii. Its association with severe manifestations of immunosuppression has been known for several decades, and the occurrence of encephalitis and disseminated disease has since been observed in different clinical conditions such as lymphoreticular neoplasias, solid organ transplants, and at present, mainly in patients with AIDS (Ferreira & Borges, 2002).

Toxoplasmosis in patients who are immunocompromised by virtue of underlying neoplastic disease has received relatively little attention. In this study, the seropositivity rate of anti-
T. gondii antibodies in patients with neoplasia was evaluated. This patient group was immunocompromised because of the underlying disease and/or immunosuppressive therapy so they were at risk from opportunistic infection. The aim of this study was to assess the risk of severe toxoplasmosis in patients with neoplasia by monitoring IgG and IgM antibodies to T. gondii.

**METHODS**

**Subjects.** One hundred and eight (51 men, 57 women) patients with neoplastic disorders who presented to Erciyes University Medical Faculty Oncology and Haematology Department in 2000–2002 and 108 healthy volunteers (52 men, 56 women) were included in the study. The age of the patient group was 18 to 82 with the mean age of 50.9 ± 13.9 and 27 to 64 with the mean age of 51.9 ± 12.2 in the control group. Blood was taken from all patients under sterile conditions and was centrifuged at 1000 r.p.m. and the sera separated. The sera were stored at −20°C until tested.

**Serological technique.** ELISA was used for determination of anti-T. gondii IgG and IgM antibodies. The ELISA kit was provided by a commercial manufacturer (EUROIMMUN). This procedure was performed according to the manufacturer’s instructions. Peroxidase-labelled anti-human IgG (rabbit) was used and the cut-off value recommended by the manufacturer of 10 IU ml⁻¹ for the detection of IgG was used. Peroxidase-labelled anti-human IgM (goat) was used for the detection of IgM antibody. The cut-off of the IgM ELISA kit was used. The absorbance of serum samples was divided into the absorbance of the calibrator, if the ratio was ≥1 the sample was considered as positive for IgM antibody.

**Statistics.** SPSS version 9.0 for Windows pocket program was used. Chi-squared test and Kolmogorov–Smirnov one sample test were used. \( P < 0.05 \) was accepted as statistically significant.

**RESULTS AND DISCUSSION**

IgG antibodies to T. gondii were found by ELISA in 68 (63.0%) patients with neoplasia and in 21 (19.4%) healthy volunteers. IgM antibodies were found by ELISA in seven patients (6.5%) with neoplasia and in one healthy volunteer (0.9%) in the control group. The sero-prevalence distributions of the two groups are shown in Table 1. The difference in the IgG seropositivity rate between the patient and the control group is statistically significant \( (P < 0.05) \). The seropositivity rate of anti-T. gondii IgM was higher in the patient group but statistically significant \( (P < 0.05) \) (Table 1).

The distribution of the neoplasia amongst the patient group and the seropositivity rates of anti-T. gondii IgG and IgM are shown in Table 2. We found the seropositivity rates of anti-T. gondii IgG in Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, leukaemia, multiple myeloma, lung carcinoma, larynx carcinoma, hepatocellular carcinoma, breast cancer, ovarian cancer and their ratios were as follows: 68.0, 60.0, 66.7, 73.3, 38.5, 50.0, 80.0, 60.0, 80.0 and 63.0 %, respectively. We performed statistical analysis to determine the positivity rates of anti-T. gondii IgG antibodies in each neoplasia patient group. The results were not statistically significant \( (Z = 1.024, P > 0.05) \).

Serological results are normally used to diagnose toxoplasmosis. All other procedures’ results must be interpreted in light of the serological findings. The Sabin–Feldman dye test, one of the first methods used to diagnose toxoplasmosis, is based on the fact that T. gondii, in the presence of immune serum, loses its affinity for methylene blue stain. Because this test uses live Toxoplasma trophozoites, however, most

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**Table 1.** The results of serological examination for antibodies to T. gondii of patients with neoplastic disorders and the control group

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Patients with neoplasia (( n = 107 ))</th>
<th>Healthy controls (( n = 107 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Anti-T. gondii IgG</td>
<td>68</td>
<td>63.0</td>
</tr>
<tr>
<td>Anti-T. gondii IgM</td>
<td>7</td>
<td>6.5</td>
</tr>
</tbody>
</table>

**Table 2.** The seropositivity rates of anti-T. gondii IgG and IgM in the neoplasia patient group

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>No. patients</th>
<th>IgG-positive</th>
<th>IgM-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>25</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>10</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>15</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>15</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>13</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Larynx carcinoma</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>10</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>108</td>
<td>68</td>
<td>7</td>
</tr>
</tbody>
</table>
laboratories do not provide it routinely. The serologic
diagnosis of toxoplasmosis is very complex and has been
discussed extensively in the literature; a number of additional
procedures, some of which are automated, have been de
doped and reported in the last few years. These methods
include enzyme immunoassays, some of which are auto-
mated, ELISAs, direct agglutination, an immunofluores-
cence assay (IFA), immunocapture and immunoblot. The
ELISA is the method used most routinely because of its
efficacy, ease of use, and its low cost and availabilty (Garcia &
Bruckner, 1997).

The diagnosis of acute toxoplasmosis is mainly based on a
combination of clinical and laboratory data. In clinical
practice, serological tests are routinely employed to detect
IgM- and IgG-specific antibodies, including indirect imm-
unofluorescence and immunoenzymatic tests. The use of more
sensitive and specific methods, such as PCR, has been shown
to be effective (Ferreira & Borges, 2002).

It is known that T. gondii infection produces IgM, IgA, IgE
and IgG antibodies, with the first three being detected early
during the course of infection. IgM antibodies indicate acute
infection, are the first to occur and can be detected 7–15 days
after infection, with maximal concentrations being observed
during the second month, followed by a progressive decline
and disappearance of these antibodies within a few months.
However, low antibody titres may persist for a prolonged
period of time (months or years). IgG antibodies indicate
chronic infection and an increased titre of IgG antibodies
might show reactivation (Ferreira & Borges, 2002).

We evaluated the seropositivity rate of toxoplasmosis in
patients with neoplasia, using ELISA to determine levels of
anti-T. gondii IgG and IgM antibodies. The present results
revealed higher percentages of positivity for T. gondii IgG and
IgM antibodies in patients with neoplasia (52.9%) compared
with the controls (20%) with a statistically significant
difference (Table 1). These findings may be due to the fact
that patients with neoplasia are immunocompromised,
which increases their susceptibility to this infection.

It has recently been shown that the seropositivity rate of
patients with neoplasia (65.5%) was statistically higher than
the control group (Hökelek et al., 2001). In addition, studies
indicated that the seropositivity for IgG of patients with
Hodgkin’s and non-Hodgkin’s disease was 42.8% (Altıntas,
1983) and in acute leukaemia patients was 63.3% (Güngör
et al., 1993). Our results also agreed with these studies.

The immune system functions are disturbed in patients with
neoplasias. This is the main reason for the high seropositivity
results. Toxoplasmosis has been most often described in
association with some specific malignancies such as Hodg-
kin’s disease, lymphoma, acute and chronic leukaemias or
multiple myeloma. Moreover, patients being treated with
anti-neoplastic agents for solid tumours including those of
the breast, ovary and lung have been associated with
toxoplasmosis. The mechanisms by which these diseases
predispose to development of toxoplasmosis have not been
well characterized. Whether it is the disease itself or the
immunosuppressive therapy used for its treatment that it is
of greater importance in suppressing immunity against
Toxoplasma is unclear. However, these diseases are associated
with defects in cell-mediated immunity, and it is clear that
T-cell dysfunction, when augmented by the use of immuno-
suppressive therapies, predisposes to the development of
toxoplasmosis (Israelski & Remington, 1993).

Individuals under immunosuppressive therapy such as pa-
tients with neoplasia, who had been previously infected with
T. gondii, might show an altered serological profile for this
protozoan compatible with reactivation, such as increased
IgG antibody titres or, less frequently, increased titres of
acute-phase antibodies thus, the patients with neoplasia may
undergo acute reactivation. In the routine serological survey
of cancer patients, results compatible with reactivation or
acute infection could influence the treatment protocol.
Severe toxoplasmosis can be prevented by therapy and, if
necessary, a change in the chemotherapy protocol. The
results of our study clearly support this interpretation.

In conclusion, patients with neoplasias should be screened
for Toxoplasma routinely. Clinicians should be more careful
with this patient group and parasitological surveys of pa-
tients with neoplasia should be periodically performed to
prevent the possibility of severe toxoplasmosis.

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akut lösemili hastalarda Toxoplasma IgM, IgG ve Sabin Feldman

Kemoterapi uygulanan kanser hastalarında Toxoplasma antikorların


