Risk Factors, Clinical Features, and Outcomes of Toxoplasmosis in Solid-Organ Transplant Recipients: A Matched Case-Control Study

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Background. Solid-organ transplant (SOT) recipients are considered to be at increased risk for toxoplasmosis. However, risk factors for this infection have not been assessed. The aim of this study was to determine the risk factors, clinical features, and outcomes of toxoplasmosis in SOT recipients.

Methods. A multicenter, matched case-control study (1:2 ratio) was conducted between 2000 and 2009. Control subjects were matched for center, transplant type, and timing. Cases were identified from the hospitals’ microbiology and transplantation program databases. Logistic regression was performed to identify independent risk factors.

Results. Twenty-two cases (0.14%) of toxoplasmosis were identified among 15 800 SOTs performed in 11 Spanish hospitals, including 12 heart, 6 kidney, and 4 liver recipients. Diagnosis was made by seroconversion (n = 17), histopathologic examination (n = 5), polymerase chain reaction (n = 2), and autopsy (n = 2). In a comparison of case patients with 44 matched control subjects, a negative serostatus prior to transplantation was the only independent risk factor for toxoplasmosis (odds ratio, 15.12 [95% confidence interval, 2.37–96.31]; P = .004). The median time to diagnosis following transplantation was 92 days. Primary infection occurred in 18 (81.8%) cases. Manifestations included pneumonitis (n = 7), myocarditis (n = 5), brain abscesses (n = 5), chorioretinitis (n = 3), lymph node enlargement (n = 2), hepatosplenomegaly (n = 2), and meningitis (n = 1). Five patients (22.7%) had disseminated disease. Crude mortality rate was 13.6% (3 of 22 patients).

Conclusions. Although uncommon, toxoplasmosis in SOT patients causes substantial morbidity and mortality. Seronegative recipients are at high risk for developing toxoplasmosis and should be given prophylaxis and receive careful follow-up.

Despite new immunosuppressive regimens, opportunistic infections still constitute a major drawback to patients undergoing solid organ transplantation (SOT) [1]. Toxoplasmosis is a worldwide parasitic zoonosis transmitted to humans by ingestion of raw or undercooked meat containing Toxoplasma gondii cysts or by ingestion of oocysts from fecally contaminated foods. Seroprevalence of Toxoplasma varies geographically, with lower rates in the United States (3%–35%) and higher rates reported in Western Europe, Africa, and South and Central America. In Spain, Toxoplasma seroprevalence has been assessed in women of childbearing age, where it ranged from 18% to 34% [2]; in a group of human
immunodeficiency virus (HIV)–infected patients and drug
addicts, seroprevalence ranged from 27% to 37% [3]. In
immunocompetent individuals, acute infection is asymptomatic
in >80% of cases. The acute infection is followed by a latent
chronic phase with persistence of the cyst in tissues, especially
in the muscles, brain, eye, and, more rarely, other organs [4].

SOT recipients are considered to be at increased risk for
toxoplasmosis. They are susceptible to toxoplasmosis by con-
sumption of contaminated food, reactivation of latent disease
through immune suppression, or transmission from the organ
donor [5, 6], especially in the case of heart recipients [7–10].
Although sporadic cases of toxoplasmosis in SOT recipients
have been reported [11–14], comprehensive information on
Toxoplasma infection in this population is scarce. Significantly,
risk factors for toxoplasmosis in SOT recipients have not been
formally assessed. The present multicenter study, with a 1:2
matched case-control study design, was conducted in order to
identify the risk factors for toxoplasmosis in SOT recipients and
to analyze the clinical features and outcomes of toxoplasmosis
for all case patients.

MATERIALS AND METHODS

Setting and Study Population

The study was conducted in 11 Spanish tertiary care hospitals
with active organ transplantation programs, including liver,
kidney, heart, lung, pancreas, intestinal, and multivisceral
transplantation. All patients with toxoplasmosis diagnosed
from January 2000 through December 2009 were included in
the study. Patients were identified from the hospital micro-
biology and transplantation program databases; initial identi-
fication was followed by a detailed review of patient medical
records. The study was approved by the institutional review
board of the coordinating center, Institut d’Investigació
Biomèdica de Bellvitge (IDIBELL)—Hospital Universitari de
Bellvitge (reference: PR248/10).

For the purposes of risk factor analysis, a matched case-
control study (1:2 ratio) was performed. Two control subjects
were included for each case patient with toxoplasmosis. The
control subjects were matched for 3 characteristics: (1) institu-
tion, (2) type of transplantation, and (3) time of transplantation.
The recipients who underwent transplants immediately before
and after the index case patient and who survived at least as long
as the time to diagnosis of toxoplasmosis were categorized as
control subjects.

Clinical Data and Definitions

Toxoplasmosis diagnosis was established in the presence of
compatible clinical manifestations plus at least 1 of the following:
(1) posttransplantation seroconversion in pretransplantation
seronegative recipients for T. gondii; (2) a positive polymerase
chain reaction (PCR) result in peripheral blood, bronchoalveolar
lavage, or cerebrospinal fluid samples; or (3) the demonstration
of parasites by direct histopathologic examination from tissue
biopsy specimens. For case patients, the time of event was de-
defined as the time of toxoplasmosis diagnosis; for control sub-
jects, the time of toxoplasmosis infection in the corresponding
case patient was used. Variables analyzed for both case patients
and control subjects included donor and recipient Toxoplasma
pretransplantation serostatus, patient demographic data, trans-
plant type, prior transplantation, presence of diabetes mellitus,
immunosuppressive drugs at the time of the event, an elevated
mean calcineurin inhibitor level within the preceding 30 days
(>$15 \mu g/mL for tacrolimus and >300 ng/mL for cyclosporin),
history of high-dose prednisone therapy within the preceding
6 months ($20 mg of prednisone for >1 month or >2 pulses
of 1 gram of intravenous methylprednisolone), receipt of
a lymphocyte-depleting antibody within the preceding 12 months,
trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis or
pyrimethamine prophylaxis at any time since transplantation
for at least 1 month, allograft rejection within the preceding
6 months, history of cytomegalovirus (CMV) infection or dis-
ease within the preceding 6 months, and mean lymphocyte and
neutrophil counts within 30 days of the event.

In the participating centers, use of TMP-SMZ (a single
double-strength tablet given 3 times per week) for 3 to 6 months
as prophylaxis against Pneumocystis jiroveci was recommended.

For all case patients, clinical characteristics and laboratory
data at the time of toxoplasmosis infection, treatment, and
outcomes were exhaustively evaluated. CMV infection and
disease were defined as described elsewhere [15].

Microbiological Studies

Toxoplasma serology was performed using chemiluminescent
microparticle immunoassay as a screening test (ARCHITECT,
Abbott). In the event of a positive screening result, enzyme-
linked fluorescent assay was used for immunoglobulin M
detection (MiniVidas, BioMerieux). All serological tests were
carried out according to the manufacturers’ instructions.
PCR for the detection of T. gondii was performed as described
elsewhere [16].

Statistical Analysis

To detect statistically significant differences between speci-
fied groups, we used the \( \chi^2 \) test with continuity correction
for categorical variables and the Student \( t \) test for continuous
variables. Univariate odds ratios (ORs) were calculated for
the potential risk factors for toxoplasmosis. Multivariate
logistic regression analysis of factors potentially associated
with toxoplasmosis included all statistically significant vari-
bles in univariate analysis and all clinically relevant vari-
ables, whether statistically significant or not [17]. The analysis
was performed with the stepwise logistic regression model of the SPSS software package (SPSS, an IBM Company). In all analyses, P values < .05 were considered to be statistically significant. All reported P values are 2-tailed.

RESULTS

Epidemiology
Twenty-two cases of toxoplasmosis were identified among 15 800 transplant recipients in 11 hospitals with active organ transplantation programs. This figure represented 0.14% of all transplant recipients and included 12 of 1979 (0.61%) heart recipients, 6 of 7709 (0.08%) kidney recipients, and 4 of 4872 (0.08%) liver recipients. There were no cases of toxoplasmosis among pancreas, lung, or small bowel recipients. The frequency of toxoplasmosis was significantly higher in heart recipients compared to the kidney and liver recipients (12 of 1979 [0.61%] vs 10 of 12 581 [0.08%]; P < .001). The median time to diagnosis of toxoplasmosis after transplantation was 92 days (range, 24–7111 days). Ten of the 22 (45%) case

### Table 1. Univariate Analysis of Risk Factors for Toxoplasmosis in Solid-Organ Transplant Recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Patients (n = 22)</th>
<th>Control Subjects (n = 44)</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Male sex</td>
<td>16 (72.7)</td>
<td>35 (79.5)</td>
<td>1.45</td>
<td>(.44–4.79)</td>
<td>.547</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>50.5 (20–68)</td>
<td>53.9 (18–67)</td>
<td>0.98</td>
<td>(.94–1.03)</td>
<td>.476</td>
</tr>
<tr>
<td>D/R Toxoplasma serostatus*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+/R–</td>
<td>9 (40.9)</td>
<td>2 (4.5)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>D unknown/R–</td>
<td>8 (36.4)</td>
<td>3 (6.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D–/R–</td>
<td>1 (4.5)</td>
<td>6 (13.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+/R+</td>
<td>…</td>
<td>1 (2.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/unknown/R+</td>
<td>1 (4.5)</td>
<td>9 (20.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+/R unknown</td>
<td>1 (4.5)</td>
<td>2 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/unknown/R unknown</td>
<td>1 (4.5)</td>
<td>12 (27.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative serostatus before transplantationb</td>
<td>18 (90.0)</td>
<td>11 (36.7)</td>
<td>15.54</td>
<td>(3.02–80.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (13.6)</td>
<td>7 (15.9)</td>
<td>0.83</td>
<td>(.19–3.59)</td>
<td>1.000</td>
</tr>
<tr>
<td>Previous blood transfusions</td>
<td>3 (13.6)</td>
<td>4 (9.1)</td>
<td>1.58</td>
<td>(.32–7.77)</td>
<td>.429</td>
</tr>
<tr>
<td>Prophylaxis with TMP-SMZ at any time since transplantation</td>
<td>8 (36.4)</td>
<td>20 (45.5)</td>
<td>0.69</td>
<td>(.24–1.96)</td>
<td>.481</td>
</tr>
<tr>
<td>Prophylaxis with pyrimethamine at any time since transplantation</td>
<td>2 (9.1)</td>
<td>…</td>
<td>0.31</td>
<td>(.217–.45)</td>
<td>.108</td>
</tr>
<tr>
<td>Receipt of antifungal prophylaxis at the time of the eventb</td>
<td>2 (9.1)</td>
<td>5 (11.4)</td>
<td>0.78</td>
<td>(.14–4.38)</td>
<td>1.000</td>
</tr>
<tr>
<td>Receipt of CMV prophylaxis at the time of the eventb</td>
<td>4 (18.2)</td>
<td>6 (13.6)</td>
<td>1.41</td>
<td>(.35–5.62)</td>
<td>.720</td>
</tr>
<tr>
<td>CMV disease within preceding 6 monthsc</td>
<td>8 (36.4)</td>
<td>3 (6.8)</td>
<td>7.81</td>
<td>(1.81–33.59)</td>
<td>.004</td>
</tr>
<tr>
<td>Allograft rejection within preceding 6 months</td>
<td>8 (36.4)</td>
<td>9 (20.5)</td>
<td>2.22</td>
<td>(.71–6.93)</td>
<td>.164</td>
</tr>
<tr>
<td>Lymphocyte count within preceding 30 days, median cells/mm³ (range)</td>
<td>1195 (252–3500)</td>
<td>1750 (520–6700)</td>
<td>0.99</td>
<td>(.99–1.00)</td>
<td>.070</td>
</tr>
<tr>
<td>Neutrophil count within preceding 30 days, median cells/mm³ (range)</td>
<td>2789 (220–34 440)</td>
<td>3500 (1650–18 600)</td>
<td>0.586</td>
<td>(1.00–1.00)</td>
<td>.524</td>
</tr>
<tr>
<td>Receipt of high-dose prednisone within preceding 6 monthsc</td>
<td>11 (50.0)</td>
<td>9 (20.5)</td>
<td>3.89</td>
<td>(1.20–11.82)</td>
<td>.014</td>
</tr>
<tr>
<td>Elevated median calcineurin inhibitor level within preceding 30 daysd</td>
<td>…</td>
<td>2 (16.7)</td>
<td>0.56</td>
<td>(.37–.84)</td>
<td>.495</td>
</tr>
<tr>
<td>Receipt of lymphocyte-depleting antibody within preceding 12 months</td>
<td>7 (31.8)</td>
<td>12 (27.3)</td>
<td>1.24</td>
<td>(.41–3.79)</td>
<td>.701</td>
</tr>
</tbody>
</table>

Data are No. (%) of patients, unless otherwise indicated.
Abbreviations: CI, confidence interval; CMV, cytomegalovirus; D, donor; OR, odds ratio; R, recipient; TMP-SMZ, trimethoprim-sulfamethoxazole.

a Toxoplasma serostatus was available in 32 of 66 (48.4%) of the donors and in 50 of 66 (75.7%) of the recipients.
b Time of event was defined as the time of toxoplasmosis for the case patients and as the equivalent time since transplantation for the matched control subjects.
c Site of CMV disease. Control patients: viral syndrome (n = 2), digestive disease (n = 1); case patients: viral syndrome (n = 3), digestive disease (n = 3), pneumonitis (n = 2).
d High-dose prednisone was defined as ≥20 mg of prednisone for ≥1 month or ≥2 pulses of 1 gram of intravenous methylprednisolone.
e Elevated median calcineurin inhibitor level was defined as >15 µg/mL for tacrolimus and >300 ng/mL for cyclosporine.
patients received a diagnosis of toxoplasmosis within the first 3 months after transplantation and 4 were diagnosed between 3 and 6 months after transplantation. Overall, 14 of the 22 (64%) case patients received a diagnosis of toxoplasmosis within the first 6 months after transplantation.

### Risk Factors for Toxoplasmosis

The risk factors analyzed for the 22 case patients and 44 matched control subjects are shown in Table 1. In univariate analysis, a negative *Toxoplasma* serostatus prior transplantation, diagnosis of CMV disease within the preceding 6 months, and receipt of high-dose prednisone prior to transplantation were significantly associated with toxoplasmosis.

After application of a logistic regression model (Table 2), a negative *Toxoplasma* serostatus prior transplantation was found to be the only independent risk factor for toxoplasmosis in SOT recipients (OR, 15.12 [95% confidence interval {CI}, 2.37–96.31]; *P* = .004).

### Clinical Characteristics of Toxoplasmosis in SOT Recipients

The clinical characteristics of the 22 SOT recipients with toxoplasmosis are shown in Table 3. Sixteen patients (72.7%) were men, with a median age of 50 years. Diagnosis was made a mean of 12 days after clinical manifestations appeared. Eighteen SOT recipients with toxoplasmosis (81.8%) developed primary infections.

Seronegative SOT recipients who had received TMP-SMZ prophylaxis or pyrimethamine prophylaxis (7 of 18 case patients) developed toxoplasmosis later after transplantation (476.28 ± 415.70 days vs 48.81 ± 28.93 days; *P* = .035). Toxoplasmosis did not occur in any patient while receiving TMP-SMZ prophylaxis or pyrimethamine prophylaxis.

More than half the patients had fever at diagnosis. Other clinical manifestations are detailed in Table 3, with respiratory and neurologic symptoms being the most frequent. Pulmonary involvement was common (31.8%) as was disseminated disease, which was present in 5 patients. Other manifestations included myocarditis, brain abscesses, chorioretinitis, hepatosplenomegaly, lymph node enlargement, and meningitis. Two patients had septic shock at presentation. Five SOT recipients with toxoplasmosis (22.7%) had a coexisting CMV infection.

### Diagnosis

The diagnosis of toxoplasmosis was established by ≥1 of the following methods: seroconversion in 17 cases, histopathologic examination in 5 cases (percutaneous myocardial biopsy in 4 cases, brain biopsy in 1 case), and a positive PCR result in 2 cases (a positive blood sample in 1 case and a positive bronchoalveolar lavage fluid in 1 case). PCR testing was performed in samples of 5 patients: peripheral blood in 3 cases, cerebrospinal fluid in 2 cases, and bronchoalveolar lavage in 2 cases.

### Treatment and Outcomes

As shown in Table 3, 20 patients were treated with sulfadiazine plus pyrimethamine. In the 2 SOT recipients diagnosed by necropsy, no specific antibiotic treatment had been initiated. Because sulfadiazine has associated side effects, treatment had to be switched in 1 case to clindamycin and in another case to atovaquone. The median duration of antimicrobial administration was 42 days.

Four patients (18.2%) required admission to the intensive care unit; 3 underwent mechanical ventilation. Crude mortality rate was 13.6% (3 of 22 patients). Two patients who were diagnosed at necropsy had disseminated disease and died of multiorgan failure. The remaining patient died 36 days after toxoplasmosis diagnosis due to respiratory failure and concomitant CMV lung infection.

### DISCUSSION

Information regarding the frequency of toxoplasmosis in a broad range of organ transplant types is scarce. In the present multicenter study, the frequency of toxoplasmosis in SOT recipients was 0.14%. The frequency was highest in heart recipients (0.6%). This latter figure concurs with that found in another Spanish study reporting 2 cases of toxoplasmosis among 315 heart recipients (0.6%) at a single institution [18]. By contrast, no episode of toxoplasmosis was observed in a cohort of 1006 SOT recipients in Canada, where the seroprevalence was low [19].

In the present matched case-control study, the only independent risk factor for toxoplasmosis in SOT recipients was a negative *Toxoplasma* serostatus prior to transplantation. This finding correlates with previous observational
studies, mainly involving cardiac recipients. The incidence of toxoplasmosis in seronegative heart recipients receiving an organ from a seropositive donor has been reported to be as high as 50%–75% [7, 8]. Indeed, in 1 report, toxoplasmosis occurred in 3 of the 4 seronegative patients who received cardiac allografts from seropositive donors but in none of the 10 seropositive patients [10]. Previous reports of toxoplasmosis involving nonheart SOT recipients also suggested that seronegative patients are at high risk for developing this infectious complication [11, 12].

TMP-SMZ is usually indicated as prophylaxis for *P. jiroveci* pneumonia in SOT recipients [20]. Moreover, it has recently been found to be a protective factor against listeriosis [21]. Results from observational studies, including a large number of transplant patients, suggest that TMP-SMZ may also be effective in preventing toxoplasmosis, even in cardiac recipients [18, 19, 22–24]. Importantly, none of the patients in the present study developed toxoplasmosis while receiving TMP-SMZ prophylaxis.

Most of our cases of toxoplasmosis (81.8%) were primary infections and occurred within the first 6 months after transplantation. Fever, pneumonitis, myocarditis, and brain abscesses were the most common manifestations. It should be noted that pulmonary involvement and disseminated disease were particularly frequent. Other investigators have previously documented similar clinical manifestations in transplant recipients [25–31].

Table 3. Clinical Characteristics, Treatment, and Outcomes of 22 Solid-Organ Transplant Recipients With Toxoplasmosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>50.02 (20–68)</td>
</tr>
<tr>
<td>Transplant</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>12 (54.5)</td>
</tr>
<tr>
<td>Kidney</td>
<td>6 (27.2)</td>
</tr>
<tr>
<td>Liver</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Primary toxoplasmosis*</td>
<td>18 (81.8)</td>
</tr>
<tr>
<td>Days to symptom onset after transplantation, median (range)</td>
<td>86.5 (12–7097)</td>
</tr>
<tr>
<td>Days of symptoms until diagnosis, median (range)</td>
<td>12 (0–53)</td>
</tr>
</tbody>
</table>

Clinical manifestations

| Temperature >38°C                       | 14 (63.6)         |
| Dyspnea                                 | 7 (31.8)          |
| Cough                                   | 6 (27.3)          |
| Headache                                | 6 (27.3)          |
| Confusion                               | 6 (27.3)          |
| Focal neurologic signs                  | 5 (22.7)          |
| Visual abnormalities                    | 3 (13.6)          |
| Hepatosplenomegaly                      | 2 (9.1)           |
| Lymph node enlargement                  | 2 (9.1)           |
| Shock at presentation                   | 2 (9.1)           |

Site of *Toxoplasma* infection

| Pneumonitis                             | 7 (31.8)         |
| Myocarditis                             | 5 (22.7)         |
| Brain abscesses                         | 5 (22.7)         |
| Chorioretinitis                         | 3 (13.6)         |
| Meningitis                              | 1 (4.5)          |
| Disseminated disease                    | 5 (22.7)         |
| Serum creatinine >1.5 mg/dL at presentation | 6 (30.0)      |
| Leukocyte count >10 000 cells/mm³ at presentation | 4 (18.2)       |

Diagnostic method

| Seroconversion                          | 17 (77.3)        |
| Histopathologic examination             | 5 (22.7)         |
| Positive PCR sample                     | 2 (9.1)          |
| Autopsy                                 | 2 (9.1)          |
| Coexisting infection                    | 6 (27.3)         |
| Bacterial infection                     | 2                |
| CMV infection                           | 5                |
| Fungal infection                        | 1                |
| ICU admission                           | 4 (18.2)         |
| Mechanical ventilation                  | 3 (13.6)         |
| Antimicrobial treatment                 |                   |
| Sulfadiazine plus pyrimethamine         | 20 (90.9)        |
| Days of antimicrobial treatment, median (range)b | 42 (14–180) |

Data are no. (% of patients, unless otherwise indicated. Abbreviations: CMV, cytomegalovirus; ICU, intensive care unit; PCR, polymerase chain reaction; TMP-SMZ, trimethoprim-sulfamethoxazole.

* Eighteen patients were seronegative before transplantation and were considered primary infections.

* Patients who died were excluded from the analysis.

Crude mortality rate in our SOT recipients with toxoplasmosis was 13.6%. In previous reports, mortality was found to be higher, especially among untreated patients [11, 12]. Death in most reported cases of toxoplasmosis has been related to a delay in diagnosis and targeted treatment...
and receive careful follow-up. However, it may be necessary to give a further prophylactic course when rejection episodes necessitate increased immunosuppressive treatment.

In conclusion, toxoplasmosis in SOT recipients is uncommon but causes substantial morbidity and mortality, especially when it is not recognized early and properly treated. Based on our findings, recipients who are seronegative prior to transplantation have the highest risk for developing this opportunistic infection and should be given TMP-SMZ prophylaxis for 6 months and receive careful follow-up. However, it may be necessary to give a further prophylactic course when rejection episodes necessitate increased immunosuppressive treatment.

**Notes**

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**


