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 consumption 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 microbiology and transplantation program databases; initial identification 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) institution, (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 defined as the time of toxoplasmosis diagnosis; for control subjects, 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, transplant 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 μg/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 disease 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, enzymelinked 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 specified groups, we used the χ² 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 variables in univariate analysis and all clinically relevant variables, 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>
</thead>
<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(^a)</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>&lt;.001</td>
<td></td>
<td></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+/R+</td>
<td>1 (4.5)</td>
<td>9 (20.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D unknown/R+</td>
<td>1 (4.5)</td>
<td>2 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D−/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 transplantation(^b)</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 event(^d)</td>
<td>2 (9.1)</td>
<td>5 (11.4)</td>
<td>0.78</td>
<td>(.14–.438)</td>
<td>1.000</td>
</tr>
<tr>
<td>Receipt of CMV prophylaxis at the time of the event(^d)</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 months(^c)</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/mm(^3) (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/mm(^3) (range)</td>
<td>2789 (220–34440)</td>
<td>3500 (1650–18600)</td>
<td>0.586</td>
<td>(1.00–1.00)</td>
<td>.524</td>
</tr>
<tr>
<td>Receipt of high-dose prednisone within 6 months(^d)</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 days(^e)</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; T/M-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 \( \geq 20 \) mg of prednisone for \( \geq 1 \) month or \( \geq 2 \) pulses of 1 gram of intravenous methylprednisolone.

\(^e\) Elevated median calcineurin inhibitor level was defined as \( > 15 \mu \text{g/mL} \) for tacrolimus and \( > 300 \text{ng/mL} \) 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].

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Seroconversion was the most frequent method used to establish the diagnosis of toxoplasmosis in the present study. It is therefore clinically important to determine Toxoplasma serostatus prior to transplantation. However, it should be noted that some severely immunosuppressed patients with toxoplasmosis may not develop a measurable serological response [32]. In this regard, PCR testing has been reported to be a useful tool for diagnosing toxoplasmosis in AIDS patients, bone marrow transplant patients, and SOT recipients [16, 33, 34]. The specificity of PCR techniques has been estimated to be 100%, with sensitivity ranging from 16% to 100% depending on the assay and sample used [34, 35].

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.
Therefore, physicians should consider toxoplasmosis in the differential diagnosis of seronegative SOT recipients with fever, pulmonary infiltrates, neurological symptoms, or multiorgan failure during the early posttransplantation period. The present multicenter and retrospective study has some limitations that should be acknowledged. First, the number of case patients was relatively small. Second, as occurs in retrospective analysis, the data collection is dependent upon the accuracy of clinical data that was recorded at the time of the clinical event. Third, the practices may have varied across participating centers in Spain and among various types of transplants.

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