Toxoplasmosis in Kidney Transplant Recipients: Report of Six Cases and Review

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Six patients with toxoplasmosis complicating renal transplantation are described, and 25 other reported cases are reviewed. The mean age of the 31 patients was 35.16 years. Most of the recipients (25 of 29) showed signs of toxoplasmosis within 3 months post-transplantation, with fever, neurological disturbances, and pneumonia as the main clinical features. Diagnosis was established at autopsy in 15 cases, by serology in 13 cases, and by direct examination, culture, or polymerase chain reaction of biological samples in 5 cases. Seventeen patients also had concomitant infections. The donor was the likely source of transmission to 10 recipients; reactivation was suspected in two cases. The source of transmission could not be determined for the remaining 19 patients. The mortality rate was 64.5%. Ten of the 11 patients given specific treatment survived, indicating that early diagnosis and therapy are essential.

Toxoplasmosis is an infectious disease caused by *Toxoplasma gondii*. It can be life-threatening in immunocompromised subjects, including persons infected with HIV [1] and organ transplant recipients. Infection has been reported to be a particular complication of cardiac transplantation [2]. It is somewhat surprising that there have been few reports of toxoplasmosis in kidney transplant recipients, despite the degree of immunosuppression associated with this condition. This report summarizes our experience with six cases of toxoplasmosis in kidney transplant recipients and reviews the existing English- and French-language literature on this subject.

Case Reports

Toxoplasmosis occurred in six of 373 consecutive kidney transplant recipients treated in our unit from July 1989 to June 1995. The first and second cases have been reported previously [3] and will be summarized here. Patients 1 and 2 and patients 3 and 4 received kidneys from the same donors.

The titers of antibody to *T. gondii* in transplant recipients was measured by an immunofluorescence assay for IgG (BioMérieux, Lyon, France), an ELISA for IgM (Toxo-M EIA, Abbott Laboratories, North Chicago, IL), an immunosorbent agglutination assay (ISAGA) for IgM (BioMérieux), and an ELISA for IgA (Toxo IgA, SFRI, St. Jean d’Illac, France).

Case 1

A 30-year-old woman who had undergone dialysis because of IgA nephropathy underwent a second transplantation in July 1989. She received methylprednisolone and antithymocyte globulin for the first 4 weeks. Cyclosporine was added to the regimen during the third week. She developed a fever with leukopenia and thrombocytopenia and hepatic cytolysis on day 27 post-transplantation. The patient’s temperature had decreased by day 39, but she was still suffering from a cough, dyspnea with hypoxemia, and pulmonary infiltrates. The patient died soon after.

Postmortem examination revealed disseminated toxoplasmosis. Light microscopy showed multiple toxoplasmic cysts in the lungs, liver, myocardium, brain, and pancreas (figure 1). The results of serological tests for *Toxoplasma* species, determined retrospectively, were negative for samples obtained 7, 21, and 35 days after transplantation.

Case 2

A 58-year-old man with end-stage renal failure due to extracapillary glomerulonephritis received the left kidney from the donor in case 1. Initial immunosuppression consisted of administration of antilymphocyte serum with methylprednisolone for 26 days. Treatment with azathioprine was begun on day 8 and that with cyclosporine on day 23. He became febrile (temperature, 40°C) 40°C on day 41 and had isolated tremors of the hands. Twelve hours later, he developed diarrhea, hyperventilated, and became confused.

Laboratory tests showed arterial hypoxemia, thrombocytopenia, and elevated levels of transaminases. Chest radiographs revealed bilateral lung infiltrates. The CSF and findings from cerebral tomodensitometry were normal. He suffered cardiac arrest soon after bronchoalveolar lavage (BAL) and died on day 43.

Cultures of blood, urine, and BAL and CSF specimens were all negative for bacterial pathogens. Postmortem examination revealed edematous lungs. Light microscopy showed multiple toxoplasmic cysts in the lungs, myocardium, brain, and liver.
Figure 1. In the postmortem examination in case 1, histologic sections of the lungs (A) and liver (B) were found to contain intracellular aggregates (arrows) of T. gondii organisms (stain, hematoxylin-eosin; original magnification, ×1,000).

Cell inclusions of cytomegalovirus (CMV) were detected in esophageal sections.

The patient was seropositive (IgG, 500 IU/mL; no IgM antibodies), as determined by testing of the antemortem serum sample, the only sample available for testing. The titers of IgG antibodies against herpes simplex virus had increased significantly, and CMV early antigen was detected in his blood the day before his death. Analysis of the BAL specimen enabled direct visualization of Toxoplasma tachyzoites, and inoculation of this fluid into a mouse yielded evidence of toxoplasmosis after 2 weeks.

The donor of the kidneys in cases 1 and 2 was a 32-year-old man with no history of recent clinical disease. He was declared to be brain-dead immediately after sustaining head trauma. His serum was not stored, and there was no serological evidence of T. gondii. The recipient of the heart harvested from this donor was treated with pyrimethamine and sulfonamide when an asymptomatic but significant rise in titers of antibodies to T. gondii was noted on days 19–25 after transplantation. His clinical course was uneventful. The recipient of the liver from the same donor experienced hepatitis due to CMV 1 month after transplantation. There was no change in the titers of antibodies to T. gondii.

Case 3

A 40-year-old man underwent a cadaveric renal transplantation in October 1994 because of chronic renal failure due to reflux nephropathy. Induction immunosuppressive treatment
consisted of administration of thymoglobulin for the first 10 days. Treatment with cyclosporine was started on day 2. A herpes-zoster rash appeared on the skin over the right T-5 area on day 21. The patient was given acyclovir for 10 days.

Fever developed and continued despite regression of the rash. Thrombocytopenia (107,000/mm³) appeared on day 23, and leukopenia (2,760/mm³) on day 29. Chest radiographs were normal. No organisms were recovered from his urine or from repeated blood cultures. The thorax and abdomen CT scan showed no abnormalities.

Ganciclovir therapy was started to thwart any CMV disease. Fever persisted without any site of infection. Antibiotics (cefotaxime, ofloxacin) were administered without success. On day 32 it was decided to initiate empirical treatment with pyrimethamine, sulfadiazine, and folic acid. Cyclosporine was withdrawn and the prednisone dosage was tapered to 10 mg/d.

Toxoplasma serology performed before transplantation showed an absence of immunity to T. gondii in the recipient. PCR of the blood for T. gondii was performed before treatment started on day 31 and was positive; serological values included a low titer of IgG, considered to be transmitted by thymoglobulins or by CMV-specific immunoglobulins. IgM antibodies to T. gondii were detected 4 days later and IgA antibodies 8 days later.

A bone marrow aspirate (BMA) studied on day 37 was positive by PCR. Direct visualization of this sample for T. gondii, with use of May-Grünwald-Giemsa (MGG) staining and direct immunofluorescence, was negative. One month after mouse inoculation, Toxoplasma species organisms were isolated from the first blood sample (day 31) and from the BMA.

His general condition improved. Inflammation decreased in 7 days after the treatment with pyrimethamine/sulfadiazine was started, and the fever disappeared in 6 days. Cyclosporine therapy was started again on day 49. The anti-Toxoplasma treatment was stopped after 2 months because of anemia and thrombocytopenia. The titers of IgG and IgA antibodies to Toxoplasma increased (to 2,000 IU/mL and 2.51, respectively) after the specific antimicrobial therapy was stopped. The patient was doing well 2 months after the end of the treatment, and his serum creatinine level was 123 μmol/L.

Case 4

A 29-year-old man with end-stage renal disease due to IgA nephropathy had been undergoing dialysis for 2 years. He was given a cadaveric renal transplant from the same donor as in case 3. Antithymocyte globulin was given prophylactically for the first 12 days. Cyclosporine therapy was begun on day 2. The posttransplantation period was complicated by ureteral necrosis, which was treated by ureteropyelostomy (day 10), and by pneumonia due to Legionella pneumophila serogroup 1 (day 17).

The patient’s fever abated after 3 days of ofloxacin therapy, but his body temperature increased to 38.3°C 10 days later, without any other abnormality. Chest radiographs were normal. Transmission of toxoplasmosis via the organ was considered because of a slight increase in titer of specific IgG (60 IU/mL from transplantation until day 19, increasing to 250 IU/mL on day 26) and because of the toxoplasmosis noted in the recipient of the other kidney from the same donor.

Serum IgA antibodies to Toxoplasma species were then detected. PCR showed no Toxoplasma DNA in the blood. The treatment was completed with pyrimethamine, sulfadiazine, and leucovorin. Immunosuppressive treatment (with cyclosporine and prednisone) was not changed. The fever disappeared in 24 hours. The patient was then treated with ofloxacin for 6 weeks and with pyrimethamine and sulfadiazine for 2 months. His titer of IgG antibody to T. gondii peaked at 1,000 IU/mL on day 53 and then decreased. The IgM antibody titer remained negative.

The kidneys used in cases 3 and 4 were harvested from the same donor, a 20-year-old man who had suffered severe cranial trauma. The serology of the donor, which had initially been reported as seropositive for IgG to T. gondii, was rechecked and found to be IgA positive as well, suggesting a recent infection. Although the titer of IgM to T. gondii was negative by ELISA, it was positive by ISAGA.

Case 5

A 50-year-old man received a kidney transplant in July 1993. He had been undergoing regular hemodialysis for 5 months because of end-stage renal disease due to IgA nephropathy. Induction immunosuppressive therapy consisted of administration of thymoglobulin and methylprednisolone (40 mg/d). Cyclosporine therapy was started 7 days post-transplantation. His postoperative course was unremarkable until day 15, when he developed a fever (38.5°C) and thrombocytopenia (118,000/mm³). These signs were associated with leukopenia (2,500/mm³, with 83.5% neutrophils) and hepatic cytolysis from day 23.

The cause of fever remained unexplained despite multiple cultures for bacteria, viruses, and fungi, as well as numerous serological studies for CMV, T. gondii (IgG level, 250 IU/mL), and Epstein-Barr virus. Ganciclovir therapy was started for presumptive CMV infection. The symptoms did not abate. His left eye was red, but this was not associated with any pain or loss of vision. Repeated funduscopic examinations revealed no abnormalities.

His leukopenia and thrombocytopenia worsened (420/mm³ and 27,000/mm³, respectively), and hypoxemic pneumonia developed 3 days later. The chest radiograph showed diffuse bilateral pulmonary infiltrates. The BAL specimen contained 410 cells (10% neutrophils). The Candida albicans found on
direct examination and culture was considered to be secondary to oral candidosis.

Because of the severity of the clinical condition and the leukopenia, empirical therapy with imipenem, vancomycin, ciprofloxacin, itraconazole, pyrimethamine, clindamycin, and folinic acid was started on day 26. The occurrence of pulmonary toxoplasmosis in this immunocompromised patient with pulmonary infiltrates was considered. Cyclosporine was withdrawn for 10 days and the prednisone dosage was tapered to 10 mg/day.

The patient's condition improved clinically with treatment, and his temperature became normal in 11 days. Serological tests showed a rise in level of T. gondii–specific IgG between day 31 (500 IU/mL) and day 38 (2,000 IU/mL) and the appearance of specific IgA but no specific IgM antibodies. Very rare trophozoites of T. gondii were retrospectively seen on MGG-stained smears of BAL fluid. The parasite was demonstrated in 10 days by inoculation of mice with BAL fluid. Reactivation of CMV was found.

After 6 days leukopenia disappeared, and imipenem, vancomycin, and ciprofloxacin were withdrawn. Anti-CMV therapy (with ganciclovir and then foscavir) was maintained for 1 month, as well as that with itraconazole. Cyclosporine treatment was started again. Administration of antitoxoplastic agents was continued for 2 months. The patient developed toxoplasmic retinochoroiditis 10 months later, which responded rapidly to use of pyrimethamine and sulfadiazine. Antiparasite therapy was discontinued after 12 weeks.

The level of IgG to Toxoplasma species remained stable (2,000 IU/mL). The specific IgA antibodies found on day 31, which persisted to day 87, were detected again from day 165, 1 month before the retinopathy. IgM antibody to Toxoplasma species (revealed by ISAGA) was found only during IgA reactivation. At the time of this report (1 year after the end of antibiotherapy), the patient was without clinical manifestations of infection. His serum creatinine level was 170 μmol/L.

The donor was a 29-year-old man who died of a head injury. His Toxoplasma serology (by dye test and IgM ELISA) was negative. The recipient of the other kidney and that of the liver never developed any clinical or serological toxoplasmosis.

Case 6

A 42-year-old woman, who had been undergoing peritoneal dialysis since March 1992 because of renal dysplasia, was given a cadaveric donor renal transplant in June 1995. One month after the beginning of dialysis, the patient showed signs of hemiplegia and had epileptic seizures, suggesting an air embolism, from which she had neurological sequelae (left hemiplegia and clonic manifestations). Immunosuppressive therapy consisted of administration of antithymocyte globulins for the first 18 days post-transplantation. Cyclosporine therapy was initiated on day 11.

She developed a fever 1 month after transplantation. Multiple blood cultures and viral screens (i.e., for herpes simplex virus, CMV, and Epstein-Barr virus) were all negative. Klebsiella species organisms were found in the urine, and she was treated with clavulanate/amoxicillin. Her condition worsened despite urine sterilization. No abnormalities were detected by auscultation or chest radiography, but measurements of arterial blood gas yielded a pH of 7.45, a PacO₂ of 29.2 mm Hg, and a PacO₂ of 69.2 mm Hg.

Bronchoscopy with BAL demonstrated scant secretion, and stains were negative for acid-fast bacilli, Pneumocystis carinii, and T. gondii. The BAL fluid culture was positive for Staphylococcus aureus, and the patient was given vancomycin. The patient became confused and had seizures. A cranial CT scan showed cerebral atrophy, right ventricular dilatation, and leukoencephalopathy. Analysis of the CSF showed 2 WBCs/mm³, a glucose level of 55 mg/dL, and a protein level of 42 mg/dL.

Bacterial and viral cultures of the spinal fluid were sterile. The results of the CT scan led to diagnosis of sequelae of the air embolism, and seizures were considered to have been brought on by low serum concentrations of antiepileptic drugs. A presumptive diagnosis of toxoplasmosis was made. Pyrimethamine and sulfadiazine were administered on day 44, but because of severe leukopenia they were replaced by pyrimethamine and clindamycin. The patient's fever subsided within 72 hours, and her condition gradually improved. Therapy was discontinued after 3 months.

The donor's Toxoplasma pretransplantation serology was completely negative. Before transplantation, the recipient had IgG antibodies to T. gondii. An IgM ELISA and IgA ELISA were negative. The level of specific IgG antibodies increased between day 37 (60 IU/mL) and day 44 (500 IU/mL). Specific IgA antibodies appeared later (day 58). The patient remained IgM negative.

PCR studies showed T. gondii DNA in the blood (from day 44 to day 59), in the BMA (day 43), in the CSF (day 43), and in the BAL fluid (day 44). A few intracellular and extracellular tachyzoites of T. gondii were seen on stained smears of BMA on careful examination (figure 2). T. gondii was isolated from the peritoneal exudate of mice inoculated with blood, BAL, and CSF samples from the patient. Results of parasite detection in CSF were considered with caution, as the fluid was initially slightly bloody because of a “traumatic tap.”

Review and Discussion

Although T. gondii is known to be a pathogen of persons with impaired cell-mediated immunity, it remains an unusual pathogen in renal transplant recipients. In addition to the six cases described in this report, we found reports of only 25 other cases of visceral toxoplasmosis complicating renal transplantation. One patient [4] was exposed to additional risk factors: kidney transplantation and Hodgkin's disease. All the
were found in four patients [8, 9, 11, 25]. Intestinal bleeding before or after the onset of pneumonia was noted in two cases [8, 14], and a rash occurred in one case [13].

Routine laboratory studies showed no consistent abnormalities. However, leukopenia and/or thrombocytopenia were noted in 54% of the reported kidney transplant recipients, including patients 1, 2, 3, 5, and 6.

Concomitant infection with another pathogen may add to diagnostic confusion. Of the 31 cases, 17 (54.8%) involved coinfections. Viruses were the most frequent coexisting infectious agents, including CMV (3 patients), herpes simplex virus (3 patients), and varicella-zoster virus (2 patients). Bacteria (usual infectious bacteria, Mycobacteria species, and opportunist bacteria species such as L. pneumophila in case 4) and fungi (Candida species and Aspergillus species), were also noted.

The frequent concomitant isolation of Toxoplasma species and other pathogens was noted in other immunocompromised patients, such as bone marrow transplant recipients [28] and patients with cancer [29]. This finding may be related to the severity of immunosuppression or to the fact that the copathogen may modify the T-cell immune response and increase susceptibility to T. gondii. For example, CMV [30] is known to modify T lymphocyte subsets, natural killer cells, and cytokines, which play an important role in the pathogenesis of toxoplasmosis [26].

Toxoplasmosis was diagnosed at autopsy in 48% of the reported cases. Seroconversion was noted before death in two patients, and diagnosis was confirmed at autopsy [15, 16]. The organs most frequently affected at autopsy were the brain (93% of the 16 cases in which this organ was examined), the heart (70%), and the lungs (52%). No T. gondii tachyzoites or cysts were found in the transplanted kidneys.

The other 14 cases were diagnosed by serology (11) and/or direct examination of a BMA smear (2) and/or blood culture (1) and/or PCR of the blood (2), BMA (2), and BAL fluid (1). Tests for specific IgG and IgM antibodies are the most widely used means of diagnosing toxoplasmosis. Serological examination is reliable in kidney transplant recipients, but seroconversion may take up to 6 weeks after the onset of infection. Detection of IgA antibody may be helpful in identifying recent primary infections or reactivations (as shown in case 5). Specific IgM may persist for a year or more after infection, whereas specific IgA disappears between 6 and 10 months [31, 32].

The varying clinical presentation makes specific diagnostic studies for toxoplasmosis necessary. There is no single serological test that is accurate enough to be recommended for diagnostic use. Diagnosis is more reliable when several tests are performed as a panel. Animal inoculation or cell culture methods are sensitive but time-consuming; T. gondii may be isolated within a few days to a few weeks after inoculation [33]. BAL fluid may be used to identify the organism in patients with pulmonary symptoms, by means of MGG, immunoperoxidase, or eosin–methylene blue staining or immunofluorescence with...
### Table 1. Characteristics of 31 kidney transplant recipients with toxoplasmosis.

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Age (y)</th>
<th>Sex</th>
<th>R/D serology</th>
<th>Signs (day of occurrence)</th>
<th>Source of diagnosis</th>
<th>Treatment*</th>
<th>Coinfection</th>
<th>Drugs used for initial immunosuppressive treatment*</th>
<th>Rejection</th>
<th>Outcome</th>
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<td>[6] 1966</td>
<td>20/M</td>
<td></td>
<td>-/Na³</td>
<td>Fever (d 0), leukopenia,</td>
<td>Autopsy</td>
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<td>None</td>
<td>Aza + Prd</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>thrombocytopenia (d 3),</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>headaches, dizziness (d 15), abnormal movements (d 15), pneumonia (d 20), seizures (d 25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[7] 1967</td>
<td>25/M</td>
<td></td>
<td>NA/NA¹</td>
<td>Fever (d 68), abnormal movements (d 68), pneumonia (d 94)</td>
<td>Autopsy</td>
<td>None</td>
<td>None</td>
<td>Aza + Prd</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>[8] 1970</td>
<td>44/F</td>
<td></td>
<td>-/Na¹</td>
<td>Tachycardia (d 31), bloody stools (d 36), coma and seizures (d 39)</td>
<td>Autopsy</td>
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<td>None</td>
<td>VZV, E. coli (trachea) Aza + Prd (Dact and irrad, d 8)</td>
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<td>[9] 1970</td>
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<td>Fever (d 30), lethargy, pericarditis, heart failure, jaundice</td>
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<td>Lethargy, pneumonia</td>
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<td>None</td>
<td>S. aureus (abdominal wall abscess) Aza, Prd, irrad</td>
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<td>NA NA</td>
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<td>Aza + Prd, MP</td>
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<td>Sfso</td>
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<td>Died</td>
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<td>OKT3, MP + Aza</td>
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Table 1. (Continued)

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<th>Signs (day of occurrence)</th>
<th>Source of diagnosis</th>
<th>Treatment*</th>
<th>Coinfection</th>
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<th>Rejection</th>
<th>Outcome</th>
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<td>HSV</td>
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<td>Survived</td>
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<td>Serology</td>
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<td>No</td>
<td>Survived</td>
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<td>[23] 1993 37/M</td>
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<td>Autopsy, serology†</td>
<td>None</td>
<td>S. epidermidis</td>
<td>Aza + Prd + Cyp</td>
<td>Yes</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>[24] 1995 37/F</td>
<td>-/IgG+, IgM+</td>
<td>Fever (d 16), acute renal failure (d 16), hemolytic anemia (d 16), thrombocytopenia (d 16), leuokpenia (d 16), hepatic cytolysis (d 28), hypoxemia</td>
<td>BMA, serology†</td>
<td>None</td>
<td>S. epidermidis (blood)</td>
<td>ALT, Aza + Cysp + Prd</td>
<td>Yes</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>[25] 1995 74/F</td>
<td>IgG+/NA+</td>
<td>Renal failure (y 6), heart failure, seizures</td>
<td>Autopsy</td>
<td>None</td>
<td>CMV</td>
<td>NA</td>
<td>Yes</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>[PR] 1 30/F</td>
<td>-/NA</td>
<td>Fever (d 27), leuokpenia (d 27), thrombocytopenia (d 27), hepatic cytolysis (d 27), pneumonia (d 39)</td>
<td>Autopsy</td>
<td>None</td>
<td>E. coli</td>
<td>ALT, Cyp + Prd</td>
<td>No</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>[PR] 2 58/M</td>
<td>NA/NA+</td>
<td>Fever (d 41), diarrhea (d 42), abnormal movements (d 41), confusion (d 42), pneumonia (d 42), leuokpenia (d 42), thrombocytopenia (d 42), hepatic cytolysis (d 42)</td>
<td>Autopsy, BAL†</td>
<td>None</td>
<td>HSV, E. coli (urine), CMV (esophagus)</td>
<td>ALT, Aza + Cysp + Prd</td>
<td>No</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>[PR] 3 40/M</td>
<td>-/IgG+, IgA+, IgM+</td>
<td>Fever (d 24), thrombocytopenia (d 23), leuokpenia (d 29)</td>
<td>Blood PCR, serology, PCR of BMA</td>
<td>Pyr + Sdz</td>
<td>VZV</td>
<td>ALT, Cyp + Prd</td>
<td>No</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>[PR] 4 28/M</td>
<td>IgG+/IgA+, IgM+</td>
<td>Fever (d 23)</td>
<td>Serology</td>
<td>Pyr + Sdz</td>
<td>Legionella pneumophila</td>
<td>ALT, Cyp + Prd</td>
<td>No</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>[PR] 5 50/M</td>
<td>IgG+/IgA+, IgM+</td>
<td>Fever (d 16), thrombocytopenia (d 15), leuokpenia (d 23), hepatic cytolysis (d 23), pneumonia (d 26)</td>
<td>Serology, BAL†</td>
<td>Pyr + Cn</td>
<td>Candida (tongue), CMV</td>
<td>ALT, Cyp + Prd</td>
<td>No</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>[PR] 6 42/F</td>
<td>IgG+/Ig-</td>
<td>Fever (d 30), pneumonia (d 43), leuokpenia (d 44), seizures (d 44)</td>
<td>Serology, blood PCR, BMA PCR, BAL PCR, BMA</td>
<td>Pyr + Sdz, then Pyr + Cn</td>
<td>Klebsiella (urine), S. aureus (BAL)</td>
<td>ALT, Cyp + Prd</td>
<td>No</td>
<td>Survived</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. BAL = bronchoalveolar lavage; BMA = bone marrow aspirate; D = donor; HSV = herpes-simplex virus; NA = not available; PR = present report; R = recipient; VZV = varicella-zoster virus; + = positive; − = negative.

* ALT = antilymphocyte therapy; Aza = azathioprine; Cn = Clindamycin; CP = cyclophosphamide; Cysp = cyclosporin A; Dact = dactinomycin; 5-FU = 5-fluorouracil; irrad = irradiation; MP = methylprednisolone; Prd = prednisone; Pyr = pyrimethamine; Sfdo = sulfadoxine; Sfso = sulfisoxalone; Smz = sulfamethoxazole; Sp = spiramycin; T = trimethoprim-sulfamethoxazole.

† Indeterminate source of infection.

‡ Reactivated infection.

Donor transmission.

II Retrospective determination.

Chemotherapy for Hodgkin's disease was administered.
monoclonal antibodies. Direct examination for parasites with these techniques can be performed on any tissue or biological fluid, but their degree of sensitivity is low [21, 34].

Gene amplification for toxoplasmal DNA by PCR proved to be quite useful for two of our patients (cases 3 and 6). The method is a sensitive and specific tool for the rapid, early detection of *T. gondii* in sputum, tissues, and fluids, provided it is performed in a well-qualified laboratory [35, 36]. Since the clinical manifestations are not specific, many cases of toxoplasmosis in kidney transplant recipients are probably missed. Toxoplasmosis might have gone undiagnosed in some patients who died but who were not autopsied. These cases could be easily diagnosed if tests for parasitemia with PCR were more widely available. Our findings suggest that kidney transplant recipients with unexplained fever should be tested for parasitemia.

Of the 19 recipients for whom results of serology were available, 14 (73%) were seronegative before transplantation. The serological status of the organ donor was known in nine (64%) of these cases. In all cases but one, the donor had antibodies to *T. gondii* and was the likely source of transmission. Reactivation of latent *T. gondii* probably occurred in cases 5 and 6 because of the negative serology of the donors. In contrast, patient 4, who was also seropositive before transplantation, was probably reinfected by a recently infected donor.

Acute toxoplasmosis in two recipients of renal allografts from the same donor was reported five times ([16, 19, 21] and twice at our center). The serologies of two of these donors ([19] and cases 3 and 4) suggested a recent acute infection. In the case reported by Guérin et al. [17], it was unclear how the patient was exposed to the organism since the donor and recipient were both seronegative before transplantation. It may have been due to ingestion of oocysts or to tissue cysts. The importance of this mechanism in the transmission of toxoplasmosis in kidney transplant recipients is unknown.

In our unit, recipients are given general recommendations about the prevention of animal-associated infections (avoid direct contact with pet feces; wash hands after handling pet). We do not advise the patients to change their eating habits or to eat only well-cooked meat, especially as *T. gondii* infections often occur during the early posttransplantation period (mostly in the hospital).

Our data show that a patient (particularly a seronegative one) receiving a kidney from a seropositive donor has the greatest risk of developing clinically significant toxoplasmosis, especially if the donor had just become infected or, worse yet, was parasitic. This last point may account for the absence of donor-acquired *T. gondii* infection in 20 antibody-negative recipients who were given a kidney from an antibody-positive donor, as in the serological survey of Speirs et al. [37].

Accordingly, the systematic serological screening of transplant donors and recipients is essential. In France, where the seroprevalence of toxoplasmosis is high, compulsory serological studies of a potential donor include tests for antibody to *T. gondii*. In countries with different regulations and a lower seroprevalence, banking donors' serum for later study (and particularly *Toxoplasma* serology) could be wise in case of unexpected infections.

The presence of IgM specific antibody in the donor is not necessarily a reason to reject the kidneys, but it must lead to a close clinical and laboratory monitoring of the recipients to ensure the earliest start of specific treatment if toxoplasmosis is suspected. As shown in cases 3 and 4, donor serology must be performed in detail to detect asymptomatic recent infection; specific IgA antibody detection may help [32].

Of the patients reviewed, 20 (64%) died of toxoplasmosis. One recipient [16] died for another reason: she refused dialysis. Toxoplasmosis was lethal in all but one of the untreated recipients, who developed infection 13 months after transplantation [13]. Ten of the 11 patients who were given treatment survived the disease. Thus, early diagnosis and treatment of the disease is important for a favorable outcome. Presumptive or proven diagnosis of toxoplasmosis must lead to prompt, acute therapy.

Our recipients appeared to respond well to pyrimethamine/sulfadiazine or pyrimethamine/clindamycin. The two cases described by Jacobs et al. [21] show that trimethoprim-sulfamethoxazole is also active against *T. gondii* [38]. However, antibiotic combinations, including cotrimoxazole, may not be the best for treating toxoplasmosis. At present, the combination of oral pyrimethamine with a dihydrofolate reductase inhibitor and sulfadiazine (4–6 g/d), a competitive inhibitor of dihydrofolate synthetase, in association with oral folinic acid (10–20 mg/d) is the treatment of choice.

The exact dosing schedule for pyrimethamine in treatment of kidney transplant recipients has not been defined. High dosages are recommended (a 200-mg loading dose followed by 50–75 mg/d) to treat toxoplasmosis in patients with AIDS [1] or cancer [29]. Toxicity commonly complicates the treatment of toxoplasmosis. Dose-related cytopenia, fever, and rash are the main side effects of pyrimethamine, whereas adverse responses to sulfadiazine include rash, nausea, cytopenia, and nephrotoxicity [39], including crystalluria, hematuria, radiolucent stones, interstitial nephritis, and renal failure.

Oral pyrimethamine plus oral or parenteral clindamycin is a reasonable alternative for intolerant or refractory patients. Again, the incidence of toxic effects is high (nausea, vomiting, diarrhea, rash, neutropenia, myopathy, and pseudomembranous colitis). A dose of 600 mg orally or intravenously every 6 hours is recommended. Higher doses (1,200 mg every 6 hours) also have been used successfully. Sulfadiazine dosages must be adjusted to the degree of renal failure [40]. Pyrimethamine, sulfadiazine, and clindamycin did not interact with cyclosporine in our patients.

The new macrolide antibiotics (azithromycin, roxithromycin, and clarithromycin) may be promising when used in combination with pyrimethamine or sulfadiazine, but controlled, pro-
spective studies are necessary to assess their role in treating toxoplasmosis [41–43]. The optimal duration of acute treatment remains undetermined. Because of the risk of relapse, as case 5 illustrates, the question is whether maintenance therapy is necessary. There are no standard recommendations for maintenance therapy. At this time, further studies are needed.

The efficacy of the antitoxoplasmonic agents may also be improved by reducing the doses of the immunosuppressive treatments, as was done in 10 cases. Immunosuppression may allow invasion and multiplication of the proliferative stage of the organism released from tissue cysts within adjacent cells.

In summary, T. gondii, while still relatively uncommon, may cause significant infection in renal transplant recipients. The disease may result from reactivation of latent infection or, more frequently, from transmission to the host from a recently infected donor. This emphasizes the importance of screening for toxoplasmosis in donors and in recipients.

In addition, disseminated toxoplasmosis in kidney transplant recipients must be considered in the differential diagnosis of an unexplained infection occurring within the first 3 months following transplantation. Early diagnosis and therapy can lead to a successful outcome. PCR assays of body fluids or tissue, tissue culture isolation, mouse inoculation, and serological tests should be performed if there is any serious doubt about the diagnosis.

Acknowledgments

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References


