NDT Plus (2008) 6: 429–432
doi: 10.1093/ndtplus/sfn159
Advance Access publication 18 October 2008

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

Unusual presentation of primary toxoplasmosis infection in a kidney-transplant patient complicated by an acute left-ventricular failure

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Abstract

Although primary toxoplasmosis is a rare event following kidney transplantation, it can be life threatening. This report describes this complication. The patient presented with high-grade fever, haemolytic anaemia and haemophagocytic-syndrome-related pancytopaenia. *Toxoplasma gondii* diagnosis was ascertained by blood and bone-marrow PCR assays. After 6 weeks with Clindamycin plus pyrimethamine therapies and despite negativation of *T. gondii* blood PCR assay, the patient developed left-ventricular failure. After adding sulfamethoxazole/trimethoprim, ramipril, digoxine, bisoprolol and spironolactone, he progressively recovered. Anti-*T. gondii* therapy was continued for 6 months. Four years later he received a third kidney allograft: at that time anti-*T. gondii* antibodies had become negative. The outcome was uneventful despite immunosuppression but with inclusion of sulfamethoxazole/trimethoprim prophylaxis. More than 3 years after the third kidney transplantation the patient has had no toxoplasmosis reactivation. This case report highlights that *T. gondii* can be the cause of myocarditis in a renal transplant recipient.

Keywords: chronic kidney disease; haemophagocytic syndrome; heart failure; toxoplasmosis; myocarditis

Toxoplasmosis is a worldwide infectious disease caused by the protozoan *Toxoplasma gondii*. The disease has a favourable outcome in almost all immunocompetent individuals, whereas it can be life threatening in those who are immunocompromised, such as organ-transplant patients [1]. In the latter setting, the disease can result from *T. gondii* transmission either within the allograft from a seropositive donor into a seronegative recipient [2–4] or via blood [5] from immunocompetent donors. In organ-transplant recipients, the most usual mechanism is the reactivation of latent infection in the recipient [1]. In immunocompromised patients, toxoplasmosis can present as central nervous system (CNS)-related symptoms, chorioretinitis, pneumonitis or multiorgan involvement, presenting with acute respiratory failure or haemodynamic abnormalities similar to septic shock [1]. *T. gondii*-related haemophagocytic syndrome has also been reported [6,7] as well as *T. gondii*-related haemolytic anaemia [8–11]. In heart-transplant recipients who are *T. gondii* seronegative and who receive a *T. gondii* seropositive allograft, primary toxoplasmosis can present as myocarditis or cardiomyopathy [12]. A case of an unusual presentation of primary toxoplasmosis complicated by a probable toxoplasmosis-induced acute left-ventricular heart failure in a patient with failed renal allograft is reported.

Case report

A male patient, born in 1982, had bilateral congenital kidney hypoplasia and underwent a first kidney transplant, from a living donor, in 1984, and did not experience acute rejection. Immunosuppression consisted of cyclosporine, steroids, plus azathioprine (AZA) until 1989. At this point he lost his allograft due to chronic rejection. A second kidney transplantation, from a deceased donor, was performed in 1990. At that time his toxoplasmosis serology was negative. Immunosuppression included induction therapy with antithymocyte globulins, AZA, steroids and cyclosporine, without methylprednisolone pulses. He progressively developed chronic allograft nephropathy in 2000 and cyclosporine was replaced by tacrolimus, and AZA by mycophenolate mofetil (MMF). In the spring of 2001, his serum creatinine was 522 μmol/L, i.e. calculated creatinine clearance (Cockcroft–Gault formula) was 16 mL/min. The immunosuppression was based on tacrolimus

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(4 mg/day, i.e. trough levels of 5 ng/mL), MMF (1 g/day) and prednisolone (0.19 mg/kg/day). In June 2001, daily hyperthermia (above 39°C), maculo-papular skin eruptions, diarrhoea, vomiting and weight loss (−10% within 2 weeks) developed and he was admitted in our unit. The body temperature was 39°C, blood pressure was 150/85 mmHg, with regular pulse at 100/bpm and no oedema was noted. A biological work-up revealed a serum creatinine of 1077 μmol/L and BUN of 43 mmol/L. He had haemolytic anaemia: haemoglobin was 7.8 g/dL, the reticulocyte count was 85 000/mm^3, and a low haptoglobin level (<0.06 g/L) and high lactate dehydrogenase (4500 IU/L; $N < 500$) were found. Schistocytes, antinuclear autoantibodies and a Coomb's test were all negative. Platelet count was 105 000/mm^3 and leucopaenia was 900/mm^3, of which 315 were polymorphonuclear cells. A bone-marrow aspiration disclosed increased cellular density, associated with features of haemophagocytic syndrome. Blood was assessed for viraemias by PCR. Cytomegalovirus (CMV), Epstein–Barr virus, herpes simplex type 6 virus and parvovirus B19 were negative while CMV and hepatitis serology were also negative. He did have protective antibodies against hepatitis B virus (anti-HBs). Blood, urine, stool and bone-marrow cultures were negative for bacteria and fungi. Conversely, blood and bone-marrow samples, assessed by PCR, were positive for *T. gondii.* Serology testing with an immuno-enzymatic method (AXSYM, Abbott Laboratories, UK) found specific *T. gondii* IgM (index 0.94; $N < 0.6$) without specific IgG, whereas 1 month earlier *T. gondii* serology had been negative. A central nervous system (CNS) computed tomography was normal, and the CNS fluid examination was negative for bacteria, viruses, fungi and parasites, including *T. gondii* (as assessed by PCR). At that time, no transthoracic echocardiogram was performed. Because of the allograft failure, the patient was placed on daily haemodialysis for three consecutive days, and then scheduled for sessions lasting 4 h, three times a week. Tacrolimus and MMF therapy were stopped, whereas prednisolone was continued. Because primary toxoplasmosis diagnosis had been confirmed, therapy with clindamycin (2 g/day) and pyrimethamine (50 mg/day) plus folinic acid was initiated. He was discharged 21 days after initial admission with a temperature of 38°C, blood pressure of 145/85 mmHg and a regular heart rate at 110/bpm. White blood cell and platelet counts were normal, whereas he still had haemolytic anaemia (Hb 9.7 g/dL, reticulocytes of 229 000/mm^3 and haptoglobin of 0.06 g/L). The C-reactive protein was 9.7 mg/L. The toxoplasmosis blood PCR test had become negative, whereas toxoplasmosis serology still demonstrated both specific IgM and IgG. Six weeks after anti-toxoplasmosis treatment had been initiated the patient complained of severe dyspnoea [grade III (NYHA classification)], which was not improved by the dialysis sessions. His blood pressure was low at 100/70 mmHg. An electrocardiogram showed sinusal tachycardia at 140 bpm. A chest radiograph showed the heart area to be enlarged and a transthoracic echocardiogram showed a hypokinetic left ventricle with an ejection fraction of 10%; the right ventricle was not dilated. There was no evidence of pulmonary hypertension. These findings were confirmed by two different operators. Isotopic left ventriculography estimated the left ventricular ejection fraction to be 20%. The 24-h cardiac rhythm data displayed no abnormalities. The VO_2-max was measured to be 12 mL/kg/min. A percutaneous angiocoronarography was normal. The patient declined an endomyocardic biopsy. Selenium as well as vitamin B1 plasma levels were within the normal ranges. The work-up for infections (bacterial, viral, fungal, parasitical) was negative, apart from an increase in the anti-*T. gondii* IgM and IgG titres. A repeated blood PCR test for toxoplasmosis remained negative. In addition to Clindamycin and pyrimethamine, sulfamethoxazole/trimethoprim at a dose of 800/120 mg given after each dialysis sessions, ramipril 2.5 mg/day, digoxine three tablets per week, bisoprolol 1.25 mg/day and spironolactone 25 mg/day were added. Finally, the patient was placed on a heart-transplant waiting list. Cardiac function remained poor within the following month but had improved by 2 months later (by November 2001), with a left ventricular ejection fraction of 47% (at which point he was removed from the heart-transplant waiting list). The ejection fraction further increased to 60% by October 2002. Anti-toxoplasmosis therapy was given for a total of 6 months. In March 2005, the patient underwent a successful third kidney transplantation: at this point the toxoplasmosis serology had became negative. He received a T-cell depleting therapy, i.e. antithymocyte globulins, tacrolimus, MMF and steroids. In addition, he also received toxoplasmosis prophylaxis with sulfamethoxazole/trimethoprim (400/80 mg every other day) for 1 year. More than 3 years after his third kidney transplantation no toxoplasmosis reactivation occurred and the serum creatinine was 130 μmol/L.

Discussion

Toxoplasmosis infection is considered to be rare after kidney transplantation. A retrospective survey of 657 consecutive kidney-transplant patients, from 2001 to 2005, revealed only one single case of clinical toxoplasmosis, occurring in an otherwise immunized patient [13]. Iqbal *et al*. [14] found that only 33.1% of patients had antibodies against *T. gondii* before transplantation. Within the first year posttransplantation, however, 19 seronegative patients out of 111 seroconverted for *T. gondii*. Of these, none developed clinical toxoplasmosis. In the seropositive patients, 34 out of 49 patients had an increase in *T. gondii* antibodies, although none developed toxoplasmosis [14]. In a review article, Renoult *et al*. reported on 29 kidney transplant patients with posttransplant toxoplasmosis: this originated from the donor in 10 cases; the mortality rate was as high as 64.5% [15].

In kidney-transplant patients toxoplasmosis can be associated in rare cases with haemophagocytic-related pancytopaenia [6,7]. This situation can be life threatening; the diagnosis is based on a bone-marrow aspiration, which can sometimes find tachyzoites that are pathognomonic for toxoplasmosis. Blood and bone-marrow PCR tests are also of value in rapidly detecting *T. gondii* infections in these circumstances [16], and is now the most sensitive method. Toxoplasmosis has also been associated with haemolytic

anaemia [8–11], though its mechanisms are still poorly understood. Our patient had previously received high amounts of immunosuppressive therapy and two kidney transplants, thus totalling 16 years of immunosuppressive therapy plus an induction therapy with antithymocyte globulins. He presented with both haemophagocytic and haemolytic syndromes and 6 weeks after the start of clindamycin and pyrimethamine he presented with myocarditis. Myocarditis can be suspected from symptoms of fever, sudden onset of global heart failure and biventricular hypokinesia. He fulfilled these three criteria, except that ventricular hypokinesia was located only in the left chamber. No other cause for myocarditis was found. Although we could not directly demonstrate that the myocarditis was related to primary toxoplasmosis infection, we strongly suspected a toxoplasmosis-induced myocarditis based on the recent medical history of the patient, the increase in the anti-*T. gondii* IgM and IgG titres and the improvement after sulfamethoxazole/trimethoprim therapy had been added to previous therapies. A confirmation by endomyocardial biopsy [17] was not possible. At that time, his blood PCR test for toxoplasmosis was negative, which is not surprising because the parasite, i.e. tachyzoites, can only be detected during the transient parasitaemic phase. After the phase, the parasite forms cysts within the tissues that can only be detected by a biopsy. Tachyzoites are disseminated via the bloodstream and infect many tissues, including the CNS, eye and skeletal and heart muscles. We can speculate that *T. gondii* may persist in the myocardium even though it is not detected in the blood. Our case report highlights how a patient with a failed allograft can present with the same infectious complication as a transplant patient receiving a high immunosuppressive regimen. Mariani *et al*. [18] reported a complete atrioventricular block associated with toxoplasmosis myocarditis, but in this case, toxoplasmosis-induced myocarditis diagnosis was based only on positive anti-*T. gondii* IgM and IgG, and neither the blood PCR test nor the endomyocardial biopsy was performed.

Cases of *T. gondii*-related clinical myocarditis are very rare but fulminant disseminated toxoplasmosis has been observed after heart transplantation [19]. Moreover, it has been shown among heart-transplant recipients that pre-transplant *T. gondii* seropositivity is associated with an increased risk of all-cause and cardiac mortality, with an increase in the development of advanced cardiac allograft vasculopathy [20]. The risk of toxoplasmosis in heart-transplant recipients can be decreased by prophylaxis [21–23]. In human immunodeficiency virus (HIV)-positive patients before the era of antiretroviral therapy, a series of necropsies in 182 HIV patients found cardiac toxoplasmosis in 12% (n = 21), of whom one out of seven cases were not associated with CNS involvement. However, in these 21 patients, cardiac toxoplasmosis was suspected in only three [24]. After kidney transplantation, so far, only one case of *T. gondii*-related myocarditis has been reported in a patient who had *T. gondii*-related encephalitis; however, this diagnosis was established on postmortem analysis [25].

In immunocompromised patients, the most frequently used successful regimen for toxoplasmosis is a combination of pyrimethamine/sulfadiazine and folinic acid for 4–6 weeks; in HIV patients sulfamethoxazole/trimethoprim appears to be equivalent to the latter regimen [1]. In our patient, we initially replaced sulfadiazine with clindamycin because he presented with end-stage kidney disease because of his failing renal allograft. After 1 month of this therapy he developed cardiac failure, which demonstrates that our therapeutic choice was probably insufficient, but the addition of sulfamethoxazole/trimethoprim therapy rapidly improved the patient's clinical situation.

Regarding *T. gondii* prophylaxis, kidney-transplant patients usually receive sulfamethoxazole/trimethoprim as prophylaxis for *Pneumocystis jiroveci* within the first 6 months posttransplantation and this prophylaxis also prevents toxoplasmosis. After that period, only those who have low TCD4 lymphocyte counts and are at risk for *T. gondii*, i.e. donor (+)/recipient (−), should be considered for subsequent *T. gondii* screening and possible long-term prophylaxis.

We conclude that primary toxoplasmosis in kidney-transplant patients can be life-threatening, particularly when complicated by haemophagocytic syndrome and acute left-ventricular heart failure.

Conflict of interest statement. None declared.

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Received for publication: 17.4.08
Accepted in revised form: 18.9.08