Nephroquiz for the Beginner
(Section Editor: M. G. Zeier)

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A patient with neurological deficits and seizures after renal transplantation

Case

A 56-year-old man with end-stage renal disease due to autosomal dominant polycystic kidney disease had continuous ambulatory peritoneal dialysis for 2 years and intermittent haemodialysis for an additional 5 years. In March 1998 his 49-year-old wife donated a kidney to him for renal transplantation.

Immunosuppressive treatment consisted of prednisone, antithymocyte globulin, cyclosporin, and mycophenolate mofetil. There was delayed recovery of transplant function because of cyclosporin toxicity 1 month after transplantation. Cyclosporin dosage was reduced and mycophenolate dosage was tapered to 2 g/day for 1 month. Four months after transplantation cyclosporin was replaced by tacrolimus because of gingival hyperplasia and a raised serum creatinine. The blood levels of cyclosporin and tacrolimus were within therapeutic ranges.

The patient’s course was unremarkable until 6 months post-transplantation, when his condition deteriorated progressively, and was complicated by drowsiness, headache, impaired co-ordination and speech impediment.

Axial T2 and post-contrast T1 MRI scans (Figure 1) showed multiple ‘target’-appearing ring enhancing masses in the right basal ganglia with slightly perifocal vasogenic oedema, and left frontal subcortical with central hypodensity consistent with necrosis.

Question

What is your diagnosis?

Fig. 1. Axial T2 and post-contrast T1 MR scans on admission show multiple ‘target’-appearing ring enhancing masses in right basal ganglia with perifocal vasogenic oedema, and left frontal subcortical with central hypodensity consistent with necrosis.

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Answer to the quiz on the preceding page

The MRI scans of our patient were suggestive of toxoplasmosis. Histopathological examination of an immediately performed stereotaxic brain biopsy revealed acute encephalitis. The diagnosis was confirmed by serological tests. Retrospectively, serological tests showed IgG antibodies to *T. gondii* before transplantation (titre 1:96), whereas IgM was negative. Six-month post-transplantation IgG titre was 1:256. IgM antibodies to *T. gondii* were now positive (titre 1:96), consistent with reactivation of toxoplasmosis. The titre of IgG antibody to *T. gondii* increased dramatically and peaked at 1:16 000, whereas the IgM titre rose to 1:768 during the next 2 months and then decreased. Eight months after transplantation serological tests showed a low titre of IgG antibodies but IgM antibodies were absent. The serology of the donor was found to be IgG positive (titre 1:64).

The treatment of this patient was extremely difficult. The physicians’ aim was to stop immunosuppressive therapy and to remove the transplant. Although repeatedly discussed, the patient and his wife refused this course, since he valued her donated kidney. Therefore, initially immunosuppressive therapy (mycophenolate) was only reduced and dexamethasone was added because of cerebral oedema. Toxoplasmosis-specific treatment was started, including pyrimethamine (75 mg/day), sulphadiazine (3 g/day), clindamycin (900 mg/day), and folic acid (10 mg/day). The patient’s condition worsened. He developed epileptic seizures with left hemiplegia. Figure 2 shows axial T2 and post-contrast T1 MR scans 2 months after making the diagnosis. Despite the above therapy, the masses increased, with strong rim enhancement patterns and wide perifocal oedema. Fever developed and the chest radiograph showed pulmonary infiltrates. Therefore immunosuppressive therapy except for dexamethasone was discontinued. Three months after beginning specific antiparasite therapy, the patient’s general condition improved and he was transferred to a rehabilitation centre. At that time, he was without clinical manifestations of infection. Subsequently immunosuppressive therapy was restarted. Two weeks later the patient became confused and again had seizures. He died 3 days later. There was only consent to autopsy of the brain. Macroscopy showed subdural haematoma, oedematization and herniation. Microscopy revealed multiple disseminated lesions characterized by a central zone of necrosis, surrounded by microglial cells and macrophages consistent with a status after treated toxoplasmosis.

Immunosuppressed individuals are susceptible to infectious diseases. *Toxoplasma gondii* is a protozoan of worldwide distribution. Serological surveys show increasing infection rate with age, ranging from 10 to 67% among those over 50 years. In immunocompetent people, postnatal toxoplasmosis is usually asymptomatic. Fatal infections may develop in patients with AIDS [1] or in immunosuppressed individuals, resulting in encephalitis, pneumonia, or other conditions. Brain involvement (encephalitis) occurs in more
than half of the cases. In organ transplant recipients, the disease may result from a newly acquired infection, or reactivation of a previous infection. However, most disease processes result from transmission to the transplant recipient from a recently infected donor [2]. Toxoplasmosis is well known after allogeneic bone marrow transplantation [3] or cardiac transplantation [4]. After renal transplantation, however, cerebral toxoplasmosis is a rare event. Literature survey revealed 31 case reports of visceral toxoplasmosis complicating renal transplantation [2]. There is a maximum of disease incidence 3 months post-transplantation. Because of the great variability of signs and symptoms, the diagnosis of toxoplasmosis remains difficult and in most cases was not considered during life. Therefore, among renal transplant patients toxoplasmosis may be underdiagnosed. The main clinical features are neurological signs. Extraneurological toxoplasmosis-associated features may be pneumonia, cardiac abnormality [5], and intestinal bleeding. The transplanted kidney is generally unaffected. Therefore a renal transplant patient with unexplained fever and neurological symptoms should be considered to have toxoplasmosis.

The diagnosis of toxoplasmosis rests on changing titres of specific IgG, IgM, and IgA anti-toxoplasma antibodies or on isolation of the parasite from infected tissue (e.g. cerebral or lymph nodes biopsies). In our case the diagnosis was established by serology and typical MRI lesions. These are in good agreement with necrotizing encephalitis [6]. Western-blot analysis of blood or bone marrow aspirate (BMA) and PCR of blood, BMA smear or bronchial lavage fluid [7] may confirm the diagnosis [8,9].

Sixty-four per cent of the reported cases died of T. gondii infection [2]. If untreated, toxoplasmosis was lethal in all but one case. In contrast, 10 of 11 renal allograft recipients who were treated either with pyrimethamine and sulfadiazine or with pyrimethamine and clindamycin, in association with oral folinic acid, survived if immunosuppression was stopped or at least reduced. Sulfadiazine dosage must be adjusted to the degree of renal failure. However, the optimal duration of treatment and its dosage regimen have not yet been determined. Treatment is complicated by enzyme induction, thrombocytopenia, and leukopenia. In such cases clindamycin has been recommended instead of sulfadiazine [10].

The efficacy of antitoxoplasma therapy may be enhanced by reducing or stopping immunosuppressive agents.

References


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