TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Progressive multifocal leuko-encephalopathy after ABO-incompatible kidney transplantation

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Dear Sirs,

With the increased burden of immunosuppression in ABO-incompatible renal transplantation worries exist regarding infectious risks [1]. JC-virus (JCV), a polyomavirus, is the cause of progressive multi-focal leukoencephalopathy (PML), a rapidly progressing demyelinating disease of the central nervous system that results in the death of the patient usually within 3–6 months after diagnosis. A total of 69 PML cases post-transplantation, of whom 44 in solid organ, have been described and were recently reviewed [2]. Here we describe the first case of JCV-induced PML after ABO-incompatible renal transplantation.

At presentation in 2002, a 48-year-old white Caucasian male with IgA nephropathy was treated with a 6-month course of cyclofosfamide and prednisolone. This treatment resulted in stabilization of renal function, but later on renal function deteriorated progressively. In May 2009, at the age of 55, he underwent a pre-emptive living-unrelated ABO-incompatible renal transplantation. The living donor was his wife; she had blood group B, the recipient's blood group was A. Pre-transplant anti-B titers were 1:32. According to the protocol, 30 days before transplantation he was given Rituximab 375 mg/m^2; subsequently, 14 days before transplantation, immunosuppressive drugs were started including mycophenolate mofetil 2 dd 1000 mg, tacrolimus 2 dd 7 mg, and prednisolone 1 dd 30 mg [3]. One day before transplantation he received intravenous immunoglobulins 0.5 g/kg. After three immuno-adsorptions his anti-B titer was 1:1. The kidney transplantation was uncomplicated and primary renal function was excellent; at discharge, serum creatinine was 123 μmol/l, his tacrolimus level was 13.8 μg/l and his anti-B titer 1:1.

Two and a half months after transplantation the patient reported mild left-sided anesthetic feeling, particularly in his hand. He experienced difficulties playing the piano. Subsequently, there was a rapid deterioration with decreased left-sided sensitivity, proprioception, and also motoric abnormalities. He was referred to a neurologist and on a CAT scan white lesion abnormalities were detected.

The patient was admitted, viral and serological tests were done and tacrolimus was stopped. A lumbal punction was performed. In the liquor glucose was 4.0 mmol/l (normal 2.2–4.4 mmol/l) and protein 0.4 g/l (normal range 0.290–0.670 g/l). In the liquor, JCV was detected by real-time polymerase chain reaction (RT-PCR). RT-PCR of liquor for CMV, EBV, HSV type 1, HSV type 2, VZV and HHV 6 were all negative. JCV was not detected in urine or plasma of the patient, neither was any other of the aforementioned viruses. An MRI scan was performed which showed right frontoparietal peri-Rolandic subcortical confluating white matter lesions continuing parietal until the ventricle. No cerebral masses and no contrast enhancement were detected. We diagnosed the patient with PML caused by JCV. Subsequently, all immunosuppression was stopped, except prednisolone 20 mg, and the patient was started on leflunomide 20 mg. After cessation of the immunosuppressive treatment neurological symptoms progressed for a few days but then rapidly came to a standstill.

Ultimately, he developed a complete left-sided hemiparesis of his arm, leg, and face. He did not have problems regarding diuresis and stool. He was discharged to a revalidation clinic and started an intensive revalidation program for 4 months as an inpatient. At discharge, he was able to walk with a stick; unfortunately, he could not use his left arm. During the follow-up, prednisolone was gradually reduced to 10 mg, leflunomide was continued once daily 20 mg. No other viral infections have occurred. One year later his neurological situation is stable and his renal function remains excellent with last serum creatinine 102 μmol/l, low anti-B antibodies 1:1 and no detectable CD19-positive B cells.

Here we describe the first patient after an ABO-incompatible renal transplantation following this protocol using antigen-specific immunoadsorption and Rituximab who developed PML due to JCV infection. Fortunately, after drastic reduction of immunosuppression and initiation of

leflunomide, the neurological symptoms stabilized and subsequently improved. Meanwhile his renal transplant function remained remarkably excellent.

The gold standard of diagnosing PML requires identification of the characteristic pathological changes on brain biopsy. JCV DNA is normally found in brain biopsies and cerebrospinal fluid (CSF) of PML patients [4]. However, JCV can be detected in the CSF of some patients with no clinical evidence of PML, and can therefore not be used to diagnose PML in the absence of compatible clinical and radiological findings. In our patient, PML was diagnosed by the presence of neurological symptoms, the detection of the JC virus in the liquor by RT-PCR and matching MRI images with the characteristics of PML. Brain biopsy was not performed.

Both current peri-operative and long-term immunosuppression in patients after an ABO-incompatible renal transplantation are intensive. In particular, Rituximab has been associated with the occurrence of PML [5]. However, although rare, also in patients undergoing an ABO-compatible renal transplantation cases of PML have been reported previously with an incidence of 14.4 cases/100 000 person years [6].

Currently, no effective antiviral therapy exists for polyomavirus infections. In solid organ transplant recipients diagnosed with PML it is recommended to stop or reduce the immunosuppression. In a recent large case series, including a literature review, a total of 69 patients with post-transplantation PML were identified and multiple treatments were reported, often with poor outcome [2]. The patient presented in this case report was treated with leflunomide and prednisolone after stopping all other immunosuppressive drugs. This therapeutic option was based on a review of PML that showed a change in the natural course of PML in one patient after the experimental start of leflunomide [7]. In accordance with these results our patient stabilized after reduction of immunosuppression and start of leflunomide; no adverse effects were seen and even renal function remained excellent. Further research is needed to investigate the role of leflunomide in anti-PML therapy.

In conclusion, ABO-incompatible kidney transplantation could be associated with increased risk of viral infections. The outcome of ABO-incompatible renal transplantation should be carefully monitored and whenever deemed possible protocols should be adapted to reduce the total immunosuppressive burden.

J.S.F. Sanders,[1] A. Riezebos-Brilman[2] and J.J. Homan van der Heide[3]
1 Division of Nephrology, Department of Internal Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
2 Division of Clinical Virology, Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
3 Department of Nephrology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
e-mail: j.sanders@umcg.nl

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