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LETTER TO THE EDITOR

Remission of multiple sclerosis in a patient with insulin dependent diabetes mellitus following combined kidney–pancreas transplantation

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We would like to add a case report to the literature in response to the letter by Behrbohm *et al.* [1], who described a transplanted liver recipient with co-morbidity of multiple sclerosis (MS). We report for the first time on a patient with disseminated encephalitis and diabetic nephropathy who successfully underwent combined renal/pancreas transplantation. Combined renal/pancreas transplantation has evolved as an excellent treatment option for patients with diabetic nephropathy. According to recent developments, this was achieved by several improvements in surgical techniques, immunosuppression, and patient care [2–4]. Of note, co-occurrence of insulin-dependent diabetes mellitus (IDDM) and MS has been recently reviewed [5]. Diabetes mellitus causes severe neurological complications including peripheral neuropathy or autonomic failure. For patients with other neurological disorders this can add up to severe debilitation and immobilization with significant diminution in quality of life. In these patients combined renal/pancreas transplantation might be associated with an increased risk for surgical and infectious complications, however, if transplantation is successful, they would significantly benefit from this therapy [6]. Only few patients with MS thus far have undergone solid-organ transplantation [1,7,8]. Arguments against transplanting these patients include possible requirement for interferon therapy and the subsequent risk of triggering organ rejection. Additionally, the unpredictable course of MS and limited life expectancy raise debate over the potential waste of an organ of which another individual could have benefited more effectively. Finally, if the initial transplantation were successful, there may be an impaired ability to cope with secondary surgical or medical complications in the setting of neurological impairment. Conversely, it has been hypothesized that the required immunosuppression following solid-organ transplantation might have a beneficial effect on the course of MS [9–11]. Significant clinical improvement or even complete remission of MS following liver transplantation has been reported [1,7].

Our patient was a 40-year-old male who was listed for combined renal/pancreas transplantation for diabetic nephropathy in July 2002. He had been diagnosed with IDDM in 1969 at the age of 7 years and end-stage renal failure in 2002. His co-morbidities included diffuse coronary artery disease (CAD) and hypertension. In 1993, the patient presented with optic neuritis, and the diagnosis of MS was obtained by magnetic resonance imaging (MRI) and cerebrospinal fluid examination. Treatment with Glatiramer (Copaxone ®; Teva Pharmaceutical Industries Ltd, Utrecht, the Netherlands) at a dose of 20 mg/day was initiated. In 1996, the patient experienced paresthesias in the right hand. MRI studies demonstrated progression of demyelinated intracerebral lesions. Further neurological and electrophysiological examination revealed profound neuropathy. Interferon was not given since the patient was awaiting organ transplantation. The patient was felt to be physically and mentally fit enough to undergo combined renal/pancreas transplantation, which took place without complication in January 2004. The cold ischemia for the renal graft and the pancreas were 11.7 and 13.6 h respectively. Immunosuppression consisted of anti-thymocyte globulin (ATG) induction (4 days ATG Fresenius at a dosage of 4 mg/kg BW), tacrolimus (trough levels of 8–12 ng/ml), sirolimus (trough levels of 6–10 ng/ml) and rapidly tapered steroids; Glatiramer was withdrawn. Somatostatin was given at a dosage of 6 mg/24 h. Perioperative antimicrobial prophylaxis consisted of clindamycin (600 mg q 8 h for 3 days), levafloxacin (400 mg q 12 h for 5 days) and fluconazole (400 mg daily). Initial functioning of the renal graft was poor on account of acute tubular necrosis, however, within 3 weeks the renal graft recovered and diuresis increased to 2000 ml/day and serum creatinine declined to 2 mg/dl. Also the pancreas graft was functioning well and the patient required only minimal exogenous insulin during the immediate postoperative phase. Perioperative complications included a thrombosis of the arteriovenous fistula, which was treated by thrombectomy and a dislocation of the ureteral splint. During the second post-transplant week, the patient developed graft pancreatitis with significant fluid collection, which was drained percutaneously. Specimens grew *Candida krusei*, which

was treated with voriconazole (200 mg q 12 h, i.v. for 1 week followed by oral maintenance therapy) in combination with caspofungin (initial dose 70 mg followed by 50 mg/day for a total of 2 weeks). He complained of general weakness during the entire hospital stay; however no symptoms specific for MS were noted. The abdominal drain was removed but CT-scan revealed again a large peripancreatic fluid collection, which was again treated with pigtail drainage. Once the fistula output had decreased and no pathogens were cultured, the drain was removed. Voriconazole maintenance therapy was given for a total of 8 weeks. Two years post-transplant, the patient underwent coronary arterial stenting for CAD. After a 4-year follow-up, the patient is doing well and both grafts are functioning normally (C-Peptide 3.5 μg/l, HbA1c 5.6%, serum creatinine 1.2 mg/dl). Neurological follow-up examination showed no signs and symptoms typical for both disseminated encephalitis and diabetic polyneuropathy. No spinal tapping was performed. A repeat MRI showed complete remission of the previously diagnosed MS pathology.

This case demonstrates that similar to other types of solid-organ transplantation for various end-stage organ failures, combined kidney/pancreas transplantation is the best treatment option for patients with diabetic nephropathy and concurrent MS [1,7,8]. This therapy can provide superior survival when compared to any other treatment and a significant improvement in the quality of life of these patients. Although our patient observation time is still short, there was no observed deterioration in the course of disseminated encephalitis. In fact, the patient subjectively reported an improvement in his overall health, diabetic as well as neurological. Independence from dialysis and insulin injections may have the greatest impact on this improvement. Additionally, diabetic neuropathy has also improved over time. Little is known how DM and dialysis influence the course of MS, as both are associated with neurological symptoms and a negative impact is likely [12]. Given the now well-known link between DM and MS [5,13–15], it is surprising that thus far there have been no reports of MS patients undergoing pancreas transplantation. Although there has been vivid discussion concerning this issue, an increased risk for the development of MS in patients suffering from DM type I at least for some subpopulations now seems to be a plausible hypothesis. Certainly underreporting should be suspected, however, it is possible that patients with MS thus far have been excluded from pancreas transplantation for the above-mentioned reasons. When looking at the perioperative course in our patient, no major neurological problems were observed. In general we attempted to avoid any unnecessary drugs, which might cause neurological side effects. Immunosuppression consisted of ATG induction, tacrolimus, sirolimus and a rapid steroid taper. We aimed at keeping trough levels of tacrolimus below 10 ng/ml, which has been shown to be the most effective immunosuppressive drug in pancreas transplantation. Immunosuppressive agents remain therapeutic options in the treatment of MS. In a recent study, disease-modifying treatments for MS, including therapy with human antibody and oral immunosuppressive agents were investigated [16]. Also other treatment options have been suggested [17–23]. After control of the severe intra-abdominal infection, no other complications were observed and the patient is doing exceptionally well and reports a significant improvement in his well being. This case report suggests that patients with MS should not be excluded from pancreas transplantation. With the use of immunosuppressive agents, rejection is prevented and MS is treated. The mammalian target of rapamycin inhibitors may have a particularly positive effect on MS as recently suggested. On the other hand transplant outcome may be inferior with usage of sirolimus/TAC when compared with that of mycophenolate-mofetil/TAC [23,24]. Further case reports are required to confirm our observation and a longer follow-up is required to determine final outcome in our patient because a remitting or relapsing MS cannot be excluded after 4 years. On account of the co-occurrence of MS and IDDM, repeat cases of such patients should be expected in the future [5,15].

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