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Human islet retransplantation in a patient with type I diabetes

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Sir: Islet transplantation in type I diabetic patients with end-stage kidney failure has had some important but still unreliable success [1, 3, 4, 6]. Recently, the Edmonton group reported on a series of successful islet allografts in non-uremic type I diabetic patients using a steroid-free immunosuppressive regimen and repeated islet injections until achieving insulin-independence [5]. This remarkable breakthrough in the field of islet transplantation raises several questions on the reasons for the previous frequent graft failures. It will be of importance to elucidate whether the high islet mass or the steroid-free medication was the key point for success in the Edmonton protocol. We present the case of islet retransplantation in a type I diabetic patient having completely lost the function of a first islet graft. This case illustrates the difficulty in overcoming the diabetogenicity of a cyclosporine- and steroid-based immunosuppression and the inability to prevent islet graft loss.

The 66-year-old man with a 32-year history of type I insulin-dependent diabetes (negative C-peptide) suffered from diabetic complications including end-stage renal disease, for which a cadaveric kidney transplantation had been performed when the patient was 56 years old. The patient had brittle diabetes with frequent hypoglycemic events. At age 61, the patient was accepted for islet transplantation. The first islet graft failed after 3 months and, due to recurrent hypoglycemic episodes, the patient asked for islet retransplantation. At age 62, 20 months after the first islet graft, the patient received another islet graft. Both transplantations were performed by transcutaneous transhepatic access of the portal vein with monitoring of the portal pressure. The data of the two transplantations are summarized in Table 1.

For both transplantations, crossmatches were negative and there was no HLA repeat of the islet grafts on the grafted kidney (Table 2).

Following the first intrahepatic islet allotransplantation, the patient had increased serum C-peptide levels (Fig. 1a), a decreased number of hypoglycemic episodes and reduced HbA1c levels, indicating that the grafted islets were functional. Insulin requirements sharply increased, and basal C-peptide levels were non-physiologically high (Fig. 1a), suggesting a marked insulin resistance. After steroid dose reduction, insulin requirements did not decrease significantly below the pretransplant requirements indicating a too low functional islets mass. Three months later, C-peptide was undetectable and the patient again had recurrent hypoglycemic events. The islet graft function was completely lost, the cause remaining unknown.

Following the second islet graft, the patient again had a sharp in-

Table 1. Features of the first and of the second islet transplantation

	First islet transplantation	Second islet transplantation
TOT	400,000 (including 113,000 cryo)	615,000
EIN	330,000 (including 65,000 cryo)	505,000
EIN/kg	4,700	7,200
Purity	80%	60%
Immunosuppression	Cyclosporine, corticosteroids, mycophenolate, ATGAM for 10 days	Cyclosporine, corticosteroids, mycophenolate, basiliximab on days 1 and 4

Table 2. HLA typing of the patient and of donors (kidney and islets)

Patient	A 2, 24(9)	B 8, 27	DR 2, 3
Kidney graft	A 28, 30 (19)	B 17, X	DR 3, 7
First islets			
Fresh	A 2, 3	B 15(5), 7	DR 2, 8
Cryo 1	A 3, 23(9)	B 14, 49(21)	DR 1, 4
Cryo 2	A 2, 32(19)	B 7, 34	DR 15, 11
Second islets	A 3, 11	B 55(22), 65(14)	DR 13(6), 14(6)

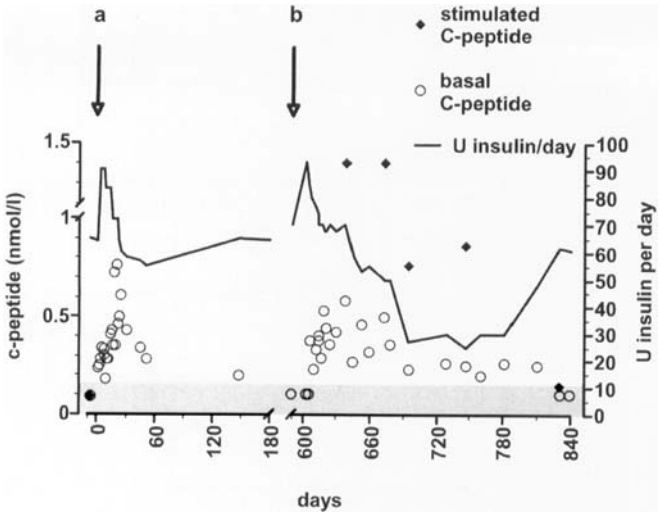

Fig. 1. C-peptide levels and daily insulin requirements after first (*a*) and second (*b*) islet allotransplantation in a type I diabetic patient with a functional kidney graft. Basal C-peptide levels below 0.16 nmol/l (=0.5 ng/ml) were considered as negative (*dashed area*). Stimulated C-peptide levels were measured 6 min after an intravenous bolus of 1 mg glucagon

crease in both insulin requirements and basal C-peptide levels (Fig. 1b). However, the second graft had an excellent basal and stimulated C-peptide release, allowing a dramatic reduction of the daily insulin doses, while the percentage of glycosylated hemoglobin normalized (5.6% 3 months after the procedure as compared to between 8.5 and 10% before the islet transplantation). Most importantly for the patient, disabling hypoglycemic episodes disappeared. However, in spite of an excellent endocrine function of the graft for 6 months, complete insulin withdrawal was not possible. Moreover, we were not able to avoid a slow decrease in islet function, as demonstrated by the decrease of basal and stimulated C-peptide and the increase of daily insulin requirements and of HbA1c. At 10 months after retransplantation, the graft function was again lost. Kidney function remained stable (creatinine clearance of 50 ml/min) and there were no signs of kidney rejection on a routine biopsy performed during follow-up.

This case illustrates with two consecutive grafts that a high islet mass is required to overcome a steroid- and cyclosporine-induced insulin resistance [2]. Moreover, the patient twice presented with late graft loss using steroid-, cyclosporine- and mycophenolate-based immunosuppression together with an anti-T-cell induction therapy. However, the absence of an accelerated rejection and the excellent metabolic control after the second islet graft are reasons for optimism that the new Edmonton protocol may also be applied successfully with lower islet masses, but concomitantly preventing steroid-induced insulin resistance and late graft failure.

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