EVIDENCE OF RECURRENT TYPE I DIABETES FOLLOWING HLA-MISMATCHED PANCREAS TRANSPLANTATION


SUMMARY - Type 1 diabetes mellitus is considered as an autoimmune disease against beta cells. Diabetes recurrence after pancreas transplantation is well known in HLA-identical twins while it is rarely reported in recipients of cadaveric pancreatic grafts. In the present case report, diabetes recurrence occurred in a recipient who underwent cadaveric combined pancreas kidney transplantation. Seven years after transplantation the patient exhibited progressive hyperglycemia needing insulin therapy while the renal graft was well functioning. The diagnosis of recurrent disease was obtained on the histological features such as selective loss of beta cells without clear signs of insulitis and on the presence of markers (GAD 65 and IA-2) for humoral autoimmunity. It is intriguing that, at the time of recurrence of type 1 diabetes, the patient had stopped steroids and azathioprine, while only cyclosporine was maintained as immunosuppressive treatment. Our case report underlines the relevance of studying the humoral autoimmune response directed to islet autoantigens in cadaveric pancreas allograft recipients. Furthermore, it suggests that an efficient immunosuppressive treatment after transplantation may be able to reduce the autoimmune response against the pancreatic allograft.

Key-words: diabetes recurrence, autoimmunity, HLA-mismatched pancreas transplantation.

RÉSUMÉ - Récidive d’un diabète de type 1 après transplantation pancréatique HLA incompatibles.
Le diabète de type 1 est une maladie auto immune dirigée contre les cellules β. La récidive du diabète de type 1 après transplantation pancréatique a déjà été rapportée chez des jumeaux homozygotes HLA identiques et rarement dans le cas de greffon provenant de donneur cadavérique. Nous rapportons la récidive du diabète de type 1 chez un receveur qui a bénéficié d’une double greffe rein pancréas HLA incompatible. Sept ans après la transplantation, l’insulinothérapie a du être reprise alors que le greffon rénal restait fonctionnel. Le diagnostic de récidive du diabète de type 1 a été affirmé sur la perte sélective des cellules β du greffon (en l’absence de signes d’insulite) associée à la positivité des anticorps anti-GAD 65 et anti-I2. Il était intéressant de noter qu’au moment de la récidive du diabète la patiente avait arrêté d’elle-même la corticothérapie et l’azathioprine et que la ciclosporine était le seul immunosuppresseur poursuivi. Notre observation souligne l’utilité de l’étude des marqueurs d’auto immunité chez les receveurs de greffon pancréatique. De plus, notre observation suggère qu’une immunomodulation efficace pourrait réduire la survenue d’une réaction auto immune dirigée contre le greffon pancréatique.

Mots-clés : récidive de diabète, transplantation pancréatique, incompatibilité HLA, auto immunité.

Type 1 diabetes mellitus is considered as a chronic destructive organ-specific autoimmune disorder in which the occurrence of islet cell autoantibodies (ICAs) and glutamic acid decarboxylase (GAD 65) antibodies is concomitant or preceding the clinical onset of the disease as well as the presence of mononuclear cell infiltrates in the islets [1-3]. Type 1 diabetes develops in the setting of genetic susceptibility and the resulting selective beta-cell destruction is associated with specific HLA-DR antigens [4].

Although pancreas transplantation, usually in combination with kidney transplantation, is at the present time the most effective treatment for type 1 diabetic patients with end-stage renal failure, recurrence of diabetes can be the cause of graft failure [5, 6]. The present case supports the possibility that diabetes recurrence may adversely affect pancreatic graft function in type 1 diabetic patients who received HLA-mismatched pancreas transplants from cadaveric donors as previously described by Tyden in 1996 [7].

CASE REPORT

A 32-year-old blood type 0 + woman with type 1 diabetes for 16 years and an end-stage renal disease underwent combined cadaveric renal and pancreatic transplantation.

The recipient’s HLA haplotype were A1 B44 B63 DR3 DR4 DR52 DR 53 DQ2 DQ8.

The multiorgan cadaveric donor was a 16-year-old blood 0 + woman with brain death secondary to a vehicle accident. The donor’s HLA haplotype were A3-28 B 7-35 DR 10-11.

Graft of the whole pancreas was performed with systemic and enteric exocrine drainage.

Maintenance immunosuppressive therapy consisted of cyclosporine (6 mg/Kg/day depending on renal function and cyclosporin serum levels), azathioprine (25 mg/kg/day) and prednisolone (5 mg/day).

An acute rejection episode that was successfully treated with antihuman thymocyte globulin and high dose steroids was evidenced on day 10; then, both grafts functioned well for seven years. At day 30 post-transplantation, the fasting C-peptide was 7.8 µg/L while the patient had no detectable C-peptide before transplantation; Hb A1c, 24-h profiles of glucose, insulin and C-peptide concentrations were performed every year.

Five years after transplantation, steroids and azathioprine were stopped by the patient herself and cyclosporine was the unique immunosuppressive treatment. At this time point, the patient was insulin independent, Hb A1c was 5.4% and the oral glucose tolerance test was normal (glycemia was 7.3 mmol/l, insulin 51 µU/l and C peptide 8.3 µg/l at 120 minutes during the oral glucose tolerance test). At seven years post-transplantation, she exhibited progressive hyperglycemia and insulin therapy was resumed while the renal graft was well functioning.

Three years later, the pancreatic graft was replaced. The excised graft looked normal without evidence of thrombosis and inflammation. Histologic examination revealed a normal lobular architecture with no endovasculitis (Fig. 1). Although light mononuclear-cell infiltration was evidenced in a few islets, the immunohistochemical studies, using polyclonal antibodies, showed glucagon secreting cells but no insulin secreting cells (Fig. 2 and Fig. 3).

Serum from the patient was screened before grafting and at the time of graft failure for the presence of specific antibodies against cytoplasmic islet cells (ICA), glutamic acid decarboxylase (GAD 65) and tyrosine phosphatase (IA-2) using ICA assay, a combi-GAD and IA-2 test as well as individual GAD and IA-2 assays [8, 9]. Antibodies levels were expressed...
as index values according to a positive standard serum. At time of graft failure a significant increase in serum antibody levels was evidenced (0.13 to 0.73 units for anti-GAD 65 antibodies and 29 to 112 units for IA-2 antibodies).

A second pancreatic graft was performed but had to be removed after 5 months because of rejection. Microscopical evaluation of the second graft revealed clear signs of rejection such as loss of the lobular architecture, mono-nuclear cell infiltration, endovascularitis, necrosis of the exocrine and endocrine tissue.

**DISCUSSION**

Recurrence of type 1 diabetes in pancreas transplants was defined by Sutherland as “hyperglycemia associated with selective loss of beta-cells, with or without accompanying isletitis. Vasculitis and, in some cases, isletitis with non selective destruction of all endocrine cell types were features of rejection” [6].

The incidence of selective beta-cell destruction after pancreatic transplantation is unknown. An association between the reappearance of islet-cell antibodies and the failure of a cadaveric pancreatic graft has been suggested from several authors [5, 10, 11] as well as the recurrence of type 1 diabetes has been identified in recipients of an HLA-identical sibling or twin donor graft [6]. Although diabetes recurrence is usually not observed in a cadaveric allograft recipient probably because immunosuppression efficiently blocks the autoimmune mechanism, Tyden et al. [7] described two cases of IDDM recurrence that occurred in recipients who received cadaveric pancreatic grafts.

The diagnosis of recurrent disease in our case was obtained on the histological features — selective loss of beta-cells — and on the presence of markers for humoral autoimmunity. It was impossible to evidence clear signs of insulitis, but several years had elapsed between the deterioration of the graft function and the removal of the pancreas.

It is intriguing that after a good long-term function of the pancreatic graft with steroids, azathioprine and cyclosporin as immunosuppression, graft failure occurred when cyclosporin was solely maintained as immunosuppressive treatment. Consequently, in the present case it is difficult to affirm as Tyden et al. that immunosuppressive therapy does not prevent autoimmune destruction of the graft. Conversely, it seems to suggest the important role of the immunosuppressive therapy used after transplantation in preventing the recurrence of the disease. Moreover, in order to preserve beta-cell function in individuals at risk for development of type 1 diabetes, several trials used non-specific immunosuppressive therapies and included prednisone, anti-thymocyte globulin, prednisone plus azathioprine and cyclosporine A. These studies demonstrated that insulin dependency could be delayed with generalized immunosuppression, but metabolic remission of diabetes was lost with the withdrawal of therapy [12, 13].

In our case GAD65 and IA-2 Ab presence clearly indicates the humoral immune response against beta-cell constituents, suggesting the importance of monitoring pancreas transplants from cadaveric donors. Several authors suggested the possible association between the persistence of high levels of GAD65 and IA-2 Abs and the failure of a cadaveric pancreatic graft [5, 10] as well as pancreatic islet allograft [14]. Presence of autoimmune markers in a HLA mismatched patient was also surprising. Two studies in BB rats [15, 16] hosting islet allografts demonstrated islet specific destruction despite MHC incompatibility. It cannot be excluded that donor beta cell antigens have been presented by self MHC on recipient antigen presenting cells through an indirect pathway. A second hypothesis is that the process of beta cell loss is not directly mediated by T cells. It is possible that multiple mechanisms may be involved in beta cell damage including apoptosis or toxicity of the immunosuppressive drugs leading to the release of beta cell antigens.

Although the incidence of diabetes recurrence in patients with whole pancreas allotransplantation seems to be lower than in pancreatic islet recipients during the first year of transplantation, specific beta cell destruction may increase during the follow-up particularly in previously immunized hosts.

In conclusion, our case report underlines the possibility of recurrence of type 1 diabetes in cadaveric pancreas allograft recipients as well as of modifying this risk with a potent immunosuppressive regimen. In addition the screening of autoantibodies against beta-cell constituents may be an useful tool to predict the risk of type 1 diabetes recurrence in pancreatic transplants.
REFERENCES