

Brief Report

RECURRENCE OF AUTOIMMUNE DIABETES MELLITUS IN RECIPIENTS OF CADAVERIC PANCREATIC GRAFTS

GUNNAR TYDÉN, M.D., FINN P. REINHOLT, M.D.,
GÖRAN SUNDKVIST, M.D., AND JAN BOLINDER, M.D.

INSULIN-DEPENDENT diabetes mellitus is an autoimmune disease in which the beta cells of the islets of Langerhans are selectively destroyed.¹ In a patient with this disease, a transplanted pancreas should be as susceptible to the autoimmune process as the native pancreas. Indeed, insulin-dependent diabetes mellitus can recur in an immunocompetent or minimally immunosuppressed recipient of a pancreatic transplant from an identical twin or HLA-identical sibling.² Usually, however, the degree of immunosuppression required to prevent rejection is sufficient to prevent autoimmune damage to the pancreatic graft.³ We report on two patients who underwent pancreatic transplantation with poor HLA matching and in whom the beta cells in the transplants were subsequently destroyed despite standard immunosuppressive therapy.

CASE REPORTS

Patient 1

A 34-year-old man with insulin-dependent diabetes mellitus underwent combined renal and pancreatic transplantation with cadaveric grafts because of end-stage diabetic nephropathy. The donor's HLA haplotypes were HLA-A2,3; B12,15; and DR4,7; those of the recipient were HLA-A2; B5,27; and DR1,4. The pancreatic graft was anastomosed to the common iliac artery and the vena cava.⁴ The postoperative course was uneventful, and both grafts functioned well. Maintenance immunosuppressive therapy consisted of cyclosporine, azathioprine, and prednisolone. The patient had no detectable C peptide in serum before transplantation but had high serum C-peptide concentrations both while fasting and postprandially afterward, indicating the systemic delivery of insulin.⁵

Twenty-nine months later, insulin therapy was resumed because of hyperglycemia, and although serum C peptide was still detectable in the fasting state, there was no increase in the concentration two hours after a standard meal (Fig. 1). The renal graft was functioning well.

From the Divisions of Transplantation Surgery (G.T.), Pathology (F.P.R.), and Medicine (J.B.), Karolinska Institute, Huddinge Hospital, Huddinge, and the Department of Endocrinology, Malmö University Hospital, Malmö (G.S.) — both in Sweden. Address reprint requests to Dr. Tydén at the Division of Transplantation Surgery, Karolinska Institute, Huddinge Hospital, 141 86 Huddinge, Sweden.

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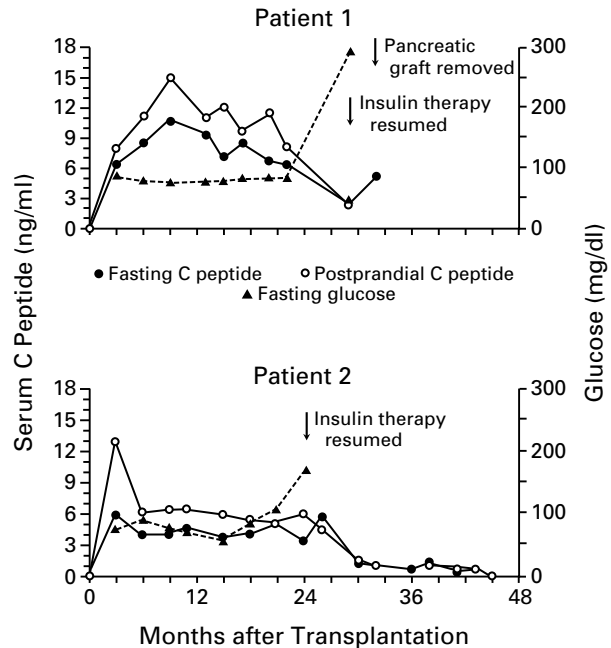


Figure 1. Fasting and Postprandial Serum C-Peptide Concentrations and Fasting Serum Glucose Concentrations in Two Recipients of Pancreatic and Kidney Transplants Who Had Recurrent Diabetes.

In Patient 1, serum C peptide was still detectable after the pancreatic transplant had been removed. However, the postprandial response (two hours after a standard meal) was abolished. In Patient 2, the pancreas was removed six years after the loss of beta-cell function. To convert the values for C peptide to nanomoles per liter, multiply by 0.331. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

Three months later, the pancreatic graft was replaced. The excised graft looked normal, and histologic examination revealed almost normal exocrine pancreatic tissue (Fig. 2A). There was no evidence of rejection, such as mononuclear-cell infiltration or endovasculitis.³ The islets, however, were infiltrated with mononuclear cells (i.e., insulinitis was present). Immunohistochemical studies showed many cells with strong staining for glucagon and chromogranin A, but a smaller number of cells stained for insulin, and the staining was weaker (Fig. 2B, 2C, and 2D). Some cells that stained for common leukocyte antigen were seen in islets with weak staining for insulin. Tests for antibodies against islet cells⁶ and glutamic acid decarboxylase⁷ were negative in serum obtained five months after the first transplantation (no earlier samples were available) but were positive in serum obtained two months before retransplantation and at the time of retransplantation. The second pancreatic transplant had to be removed after six weeks because of a serious infection. Microscopical evaluation of that graft did not reveal any signs of beta-cell destruction.

Patient 2

A 34-year-old woman with insulin-dependent diabetes mellitus underwent combined transplantation with cadaveric renal and pancreatic grafts because of end-stage diabetic nephropathy. The donor's HLA haplotypes were HLA-A2,11; B12,40; and DR5,6; those of the recipient were HLA-A1,9; B8,16; and DR1,3. Maintenance immunosuppressive therapy consisted of cyclosporine, azathioprine, and prednisolone. The patient had no detectable C peptide in serum before transplantation. Afterward, the serum

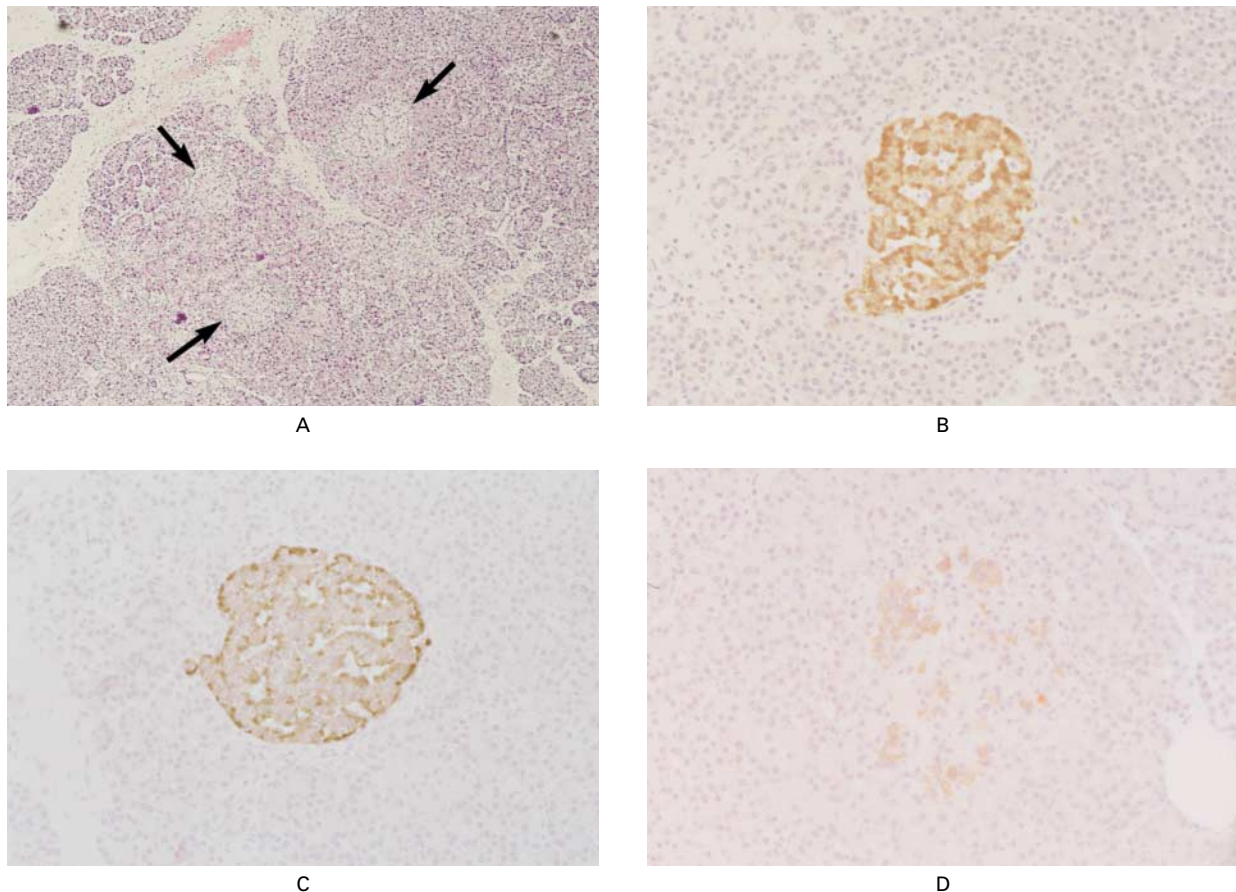


Figure 2. Photomicrographs of Sections of the Pancreatic Graft Removed from Patient 1.

Panel A shows a slight lymphocytic inflammation in and adjacent to islets (arrows) — that is, insulinitis — but only a minimal increase in interstitial fibrous tissue and no signs of rejection, such as diffuse parenchymal mononuclear-cell infiltration or endovasculitis (hematoxylin and eosin, $\times 31$). Panels B, C, and D show the results of immunoperoxidase staining of an islet with polyclonal antibodies against human glucagon, chromogranin A, and insulin, respectively (Dakopatts, Copenhagen, Denmark) ($\times 125$). In Panel B, many cells are stained with antibodies against glucagon. In Panel C, about the same number of cells are stained with antibodies against chromogranin A. In Panel D, a moderate number of cells are stained with antibodies against insulin, but the intensity of the staining is lower than in normal islets.

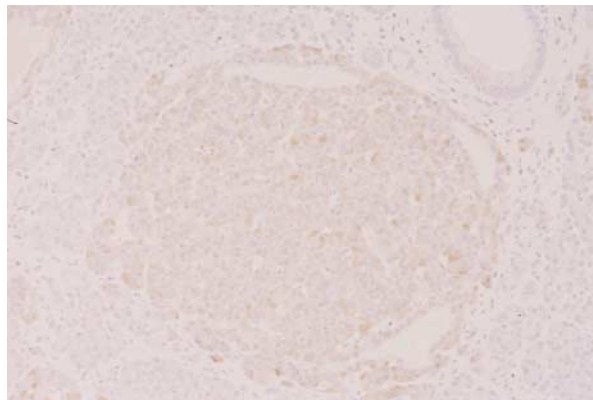
C-peptide concentration ranged between 3 and 6 ng per milliliter (1 and 2 nmol per liter) (normal range, 0.9 to 5.1 ng per milliliter [0.3 to 1.7 nmol per liter]) in the fasting state and increased after a standard meal (Fig. 1).

Two years later, the patient's beta-cell function began to deteriorate, and exogenous insulin therapy was resumed. The serum creatinine concentration ranged from 1.7 to 2.8 mg per deciliter (150 to 250 μmol per liter). Six years later, the pancreatic graft was removed because of recurrent acute episodes of abdominal pain with tenderness over the graft and high serum amylase concentrations. The pancreatic graft appeared normal on gross examination. Histologic examination revealed essentially normal exocrine pancreatic tissue, with no signs of rejection. The islets showed no signs of insulinitis. Immunohistochemical studies showed staining for glucagon and chromogranin A but no staining for insulin (Fig. 3A, 3B, and 3C). Cells stained for common leukocyte antigen were seen in the exocrine pancreatic tissue and in a few of the islets. Tests for antibodies against islet cells and glutamic acid decarboxylase in serum samples obtained at the time of transplantation, immediately afterward, six months after the loss of endocrine function, and at the time of transplant removal were all negative. A second transplantation was not performed.

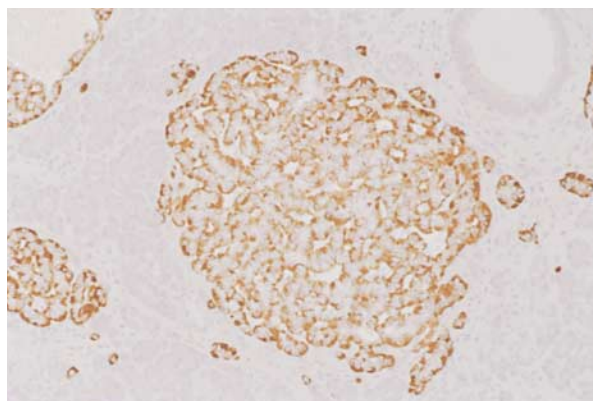
DISCUSSION

Many diseases treated by organ transplantation are believed to have an autoimmune origin, and theoretically, any transplanted organ is as susceptible to the autoimmune process as the organ being replaced. Indeed, in the early era of transplantation, it was feared that all transplanted organs would be affected by the original disease. This has not proved to be the case, probably because the immunosuppressive therapy required to prevent rejection is sufficient to prevent autoimmune damage to the graft. If the donor is an identical twin and immunosuppressive therapy is not needed to prevent rejection, however, the autoimmune disease may rapidly recur.² Thus, in patients with autoimmune disease, the advantage of transplanting tissue from an identical twin is lost.

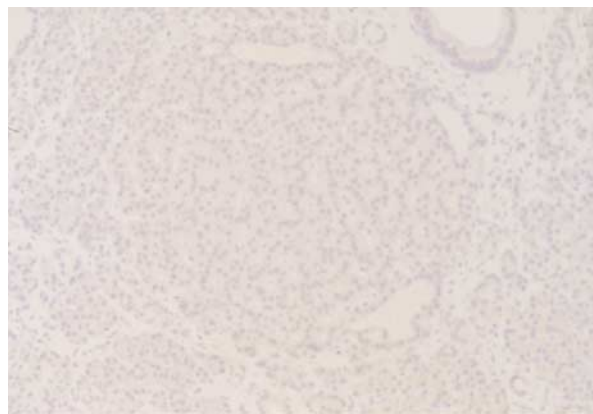
To our knowledge, there have been no reports of



A



B



C

Figure 3. Photomicrographs of Sections of the Pancreatic Graft Removed from Patient 2.

Panels A, B, and C show the results of immunoperoxidase staining of an islet with polyclonal antibodies against human glucagon, chromogranin A, and insulin, respectively (Dakopatts) ($\times 125$). In Panel A, many cells are stained (although somewhat weakly) with antibodies against glucagon. In Panel B, many cells are stained with antibodies against chromogranin A. In Panel C, none of the cells are stained with antibodies against insulin.

recurrent diabetes in patients with insulin-dependent diabetes mellitus who received cadaveric pancreatic grafts. The pattern of selective destruction of beta cells in our two patients, with the preservation of alpha and delta cells, resembles that in pancreatic islets from patients with long-standing insulin-dependent diabetes mellitus⁸ and suggests that the autoimmune disease had recurred. Furthermore, there were no signs of acute rejection (diffuse parenchymal mononuclear-cell infiltration, endovasculitis, or both) or chronic vascular rejection (fibrous intimal proliferation in the arteries).³

The physiologic data support the same conclusion. In both patients, after long-term functioning of the pancreatic grafts, beta-cell function gradually decreased over a period of 6 to 12 months. The first sign of deterioration was a decline in the rise in the serum C-peptide concentration after a meal, followed by a decrease in the serum C-peptide concentration in the fasting state. This gradual decline in beta-cell secretory capacity is similar to that which occurs in adults with insulin-dependent diabetes mellitus.⁹

Lastly, in Patient 1, serum tests for antibodies against islet cells and glutamic acid decarboxylase were initially negative, but both types of antibodies were detected at high titers at the time of overt beta-cell dysfunction. Moreover, there was histologic evidence of insulinitis in association with the recurrence of markers for humoral autoimmunity. Hence, this patient had the characteristic features of insulin-dependent diabetes mellitus of recent onset.⁸ In Patient 2, neither of these antibodies was detected, but several years had elapsed between the time when serum C peptide was last detected and the removal of the pancreas (when samples were obtained for the antibody tests). By the time the graft was removed, the islets were devoid of beta cells, and there were no signs of insulinitis.

The incidence of selective beta-cell destruction after pancreatic transplantation is unknown. However, a possible association between the reappearance of islet-cell antibodies and the failure of a cadaveric pancreatic graft has been suggested.¹⁰ In our series of 155 patients who received cadaveric pancreatic transplants, 20 patients with recurrent diabetes under similar circumstances (a slow decline in insulin secretion after a prolonged period of stable function) have undergone pancreatic biopsies or removal of the transplants. Of these 20 patients, only the 2 described here had a selective loss of beta cells. Eleven other patients had pancreatic grafts that gradually failed after functioning for several years, but since these patients did not undergo biopsy or graft removal, histologic studies were not performed. Some of these patients may have had recurrent autoimmune disease.

Our findings clearly suggest that selective destruction of beta cells may occur despite sustained immunosuppressive therapy with cyclosporine, azathioprine,

and prednisolone. Similarly, immunosuppressive therapy does not prevent progressive beta-cell dysfunction in patients with insulin-dependent diabetes mellitus of recent onset.¹¹ Finally, it has been suggested that a poor HLA match between donor and recipient may reduce the risk of recurrent autoimmune diabetes after pancreatic transplantation.² Our findings clearly demonstrate that the donor and recipient of a pancreatic graft do not have to share HLA alleles for autoimmune destruction of the graft to occur.

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CORRECTION

Recurrence of Autoimmune Diabetes Mellitus in Recipients of Cadaveric Pancreatic Grafts

Recurrence of Autoimmune Diabetes Mellitus in Recipients of Cadaveric Pancreatic Grafts . On page 860, in the legend to Figure 1, the sentence that begins on line 5 should have read, "In Patient 1, serum C peptide was still detectable *just before the pancreatic transplant was removed*," not "was still detectable *after the pancreatic transplant had been removed*," as printed. We regret the error.