

1761

Insulin Independence for 58 Months Following Pancreatic Islet Cell Transplantation in a Patient Undergoing Upper Abdominal Exenteration

H.L.R. Rilo, P.B. Carroll, A. Tzakis, R. Jaffe, C. Ricordi, T.E. Starzl and A.S. Rao

THE most successful outcome of pancreatic islet allotransplantation has been in patients with upper abdominal malignancies who have undergone cluster resection followed by liver replacement.^{1,2} Between January 1990 and June 1992, 11 patients underwent this procedure; six (55%) of whom were insulin-independent until demise, due to recurrence of the primary disease. We report herein, a 58-month postoperative metabolic course of the longest survivor of islet allotransplantation, who underwent upper abdominal exenteration for hepatocellular carcinoma necessitating combined liver and islet transplantation.

MATERIAL AND METHODS

Patient

At the time of surgery (1/90), the patient was 15 years of age and had previously been diagnosed as having fibrolamellar hepatocellular carcinoma that did not respond to repeated transcatheter hepatic intra-arterial administration of chemotherapeutic agents (Adriamycin and cis-platinum). She had no metastatic lesions and underwent upper abdominal exenteration that included total pancreatectomy followed by orthotopic liver allotransplantation. At the culmination of this procedure, 4.7×10^5 islets (5.1×10^5 IEq), isolated from the pancreas of the cadaveric liver donor were infused into the portal vein. For postoperative immunosuppression, only tacrolimus (FK506, Fujisawa Pharmaceutical Co., Deerfield, IL) was used.

Isolation of Pancreatic Islets

Islets were isolated by a modification of the automated method,³ and further purified by velocity sedimentation on a discontinuous Euro-Collins-ficoll density gradient using a cell separator (COBE 2991™, COBE Laboratories Inc., Lakewood, CO). Islet number, purity and viability were determined by dithizone staining.

Postoperative Assessment of Islet Cell Function

For precise evaluation of transplanted islets cell function, serial determination of levels of plasma glucose, C-peptide and glycosylated hemoglobin (HbA_{1c}) were performed. Additionally, at regular intervals posttransplantation, attempts were also made to assess islets cell responses to stress by oral glucose tolerance test (OGTT), Sustacal challenge test and by IV glucose tolerance test (IVGTT).

From the Pittsburgh Transplantation Institute and the Departments of Surgery (H.L.R.R., T.E.S., A.S.R.) and Pathology (A.S.R.) and the University of Miami, School of Medicine, Miami Florida (P.B.C.A.T., C.R.) and Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania (R.J.).

This work supported by Project Grant No DK 29961 from the National Institute of Health, Bethesda, Maryland.

Address Reprint Requests to: Abdul S. Rao, Pittsburgh Transplantation Institute, E1545 Biomedical Science Tower, 200 Lothrop Street, Pittsburgh, PA 15213.

© 1995 by Appleton & Lange
0041-1345/95/\$3.00/+0

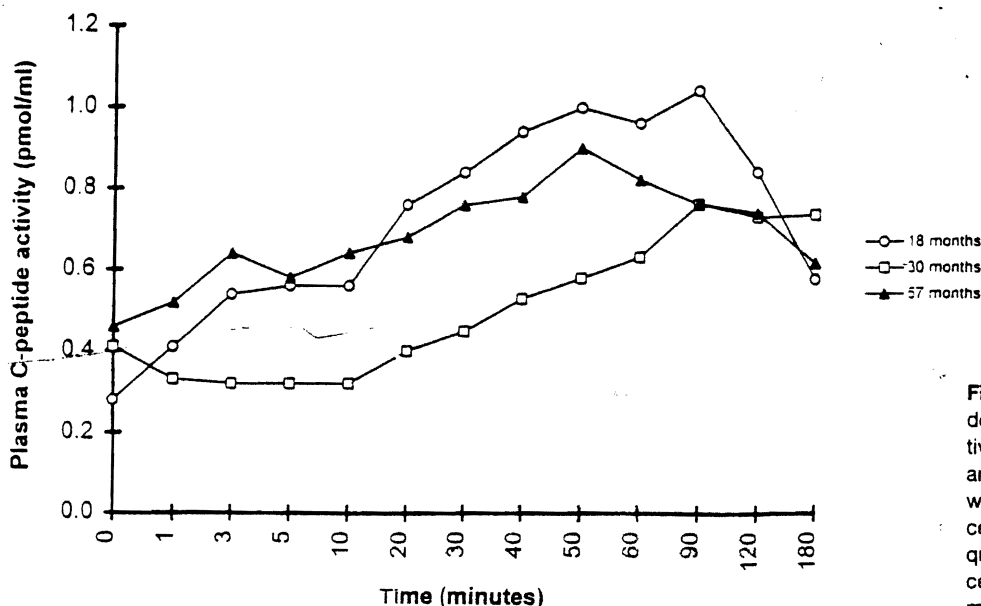


Fig 1. Serial posttransplant determinations of C-peptide activity following IV glucose tolerance test (IVGTT), in a patient who underwent liver and islets cell allotransplantation subsequent to cluster resection necessitated by upper abdominal malignancy.

RESULTS AND DISCUSSION

The clinical and metabolic course during the first 36 months following islets cell and liver transplantation have been detailed elsewhere.² The patient achieved complete independence from exogenous insulin at approximately 16 weeks posttransplantation, and continued to maintain this status for up to 58 months, at which time she died due to multiple system organ failure precipitated by widespread metastases. It must be noted, that at 18 months posttransplantation, the first recurrence of the malignancy was observed which manifested itself as a solitary tumor, limited to the jaw, necessitating surgical resection followed by a course of chemotherapy and local radiation. At that time, involvement of the regional lymph nodes was confirmed, however, there was no evidence of distant metastases.² Similar to our earlier observations,² IVGTT test performed at 57 months posttransplantation revealed a normal C-peptide response (Fig 1), confirming the preservation of transplanted islets cell function. Immunohistochemical analysis of liver sections obtained at autopsy revealed the presence of transplanted islets, which in addition to exhibiting normal morphology, stained positively for insulin, glucagon, somatostatin, and pancreatic polypeptides. Additionally, the presence of S100⁺ and UVEC⁺ cells suggested innervation and organization of vasculature respectively, within the islet cell mass.

In conclusion, islets obtained from a single donor, when infused into a recipient undergoing a "cluster" procedure, reversed diabetes and rendered the patient insulin-free for up to 58 months posttransplantation. Similar success has also been achieved in 5 of 10 additional cluster recipients who died insulin-free at various times posttransplantation.² On the contrary, long-term insulin-independence has not been accomplished in transplant recipients of islets and other whole organ allografts.⁴ Our ongoing clinical trials of delayed islets cell infusion, which in the rodent model has yielded indefinite graft survival,⁵ may however ameliorate this discouraging initial outcome witnessed in type I diabetics.

REFERENCES

1. Tzakis AG, Ricordi C, Alejandro R, et al: *Lancet* 336:402, 1990
2. Carroll PB, Rilo HLR, Alejandro R, et al: *Transplantation* 59:875, 1995
3. Ricordi C, Lacy PE, Finke EH, et al: *Diabetes* 37:413, 1988
4. Ricordi C, Tzakis A, Carroll PE, et al: *Transplantation* 53:407, 1992
5. Ricordi C, Murase N, Rastellini C, et al: *Transplant Proc* 26:3358, 1994