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Case Report

Detection of Intrahepatic Human Islets Following Combined Liver-Islet Allotransplantation

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Summary: This article describes the localization of intact insulin-containing intrahepatic islets after combined liver-islet allotransplantation. The patient was a 36-year-old woman who underwent upper abdominal exenteration for neuroendocrine carcinoma: 289,000 islets were transplanted via portal vein infusion immediately after complete revascularization of the liver. Immunosuppression was with low-dose FK-506. OKT3 and steroids were used to treat one rejection episode 2 weeks after transplantation, but the patient subsequently developed multiple infections and died 109 days after transplantation. At autopsy, the transplanted liver did not show any sign of rejection and well-preserved islets were present in portal triads sampled from the anterior inferior edge of the right lobe. Immunohistochemical labeling confirmed the presence of insulin-containing cells. This finding indicated that human islets can survive after intrahepatic allotransplantation, despite positive cross-match with no HLA antigen match, suggesting that upper abdominal exenteration and liver transplantation may constitute a protective factor for the survival of allogeneic human islets. Key Words: Human—Islet—Transplantation.

Recent improvements in islet separation and purification procedures (1–6) have resulted in prolonged insulin independence after human islet allotransplantation (7–10), demonstrating that it is possible to reverse diabetes with islets obtained from one (7) or multiple (8,9) pancreas donors. The major obstacle to wider clinical application of islet transplantation is the vulnerability of the human islets to immune rejection.

It has been shown in both animals and humans that liver allografts can induce a state of donor-specific unresponsiveness to vascularized organ al-

lografts such as the heart or kidney (10). Similar results can be achieved with infusion of allogeneic intrahepatic islets when islets are infused 24 h after a liver transplant (10).

This article describes localization of insulin-containing intrahepatic islets at autopsy in a 36-year-old woman who underwent upper abdominal exenteration and combined liver-islet allotransplantation (7).

CASE REPORT

The patient was a 36-year-old woman with a history of neurofibromatosis since childhood. In 1986, she developed biliary obstruction and secondary biliary cirrhosis with portal hypertension and esophageal varices (treated with endoscopic sclero-

therapy). In 1989, she was found to have a periampullary pancreatic mass diagnosed by biopsy to be a neuroendocrine carcinoma. After exploratory laparotomy, a portal angiogram was done, demonstrating splenic vein invasion by the tumor, which excluded a splenorenal shunt as a therapeutic option. A decision was made to perform a liver transplant and not to decompress the portal system with an alternative procedure, to avoid subsequent hepatic encephalopathy.

On February 10, 1990, the patient underwent combined liver and islet allotransplantation following resection of a cluster of abdominal organs including the liver, stomach, duodenum, proximal jejunum, transverse colon, spleen, and the entire pancreas. The patient was not diabetic before surgery and thus had not been on insulin. There was no C-peptide response to glucagon in the interval between native organ removal and islet infusion, indicating that all native insulin-producing cells were removed.

Pancreas and liver were obtained from a multiorgan, 19-year-old, female, cytomegalovirus (CMV)-seropositive donor. The recipient was CMV-seronegative. The islets were separated by a modification (2) of the automated method for human islet isolation (1). Purification of the endocrine component was by Eurocollins-Ficoll discontinuous gradients (11), using a cell separator (3,4) (COBE 2991, Lakewood, CO, U.S.A.). Immediately following complete liver allograft revascularization (7), 289,000 islets, average diameter of 150 μ
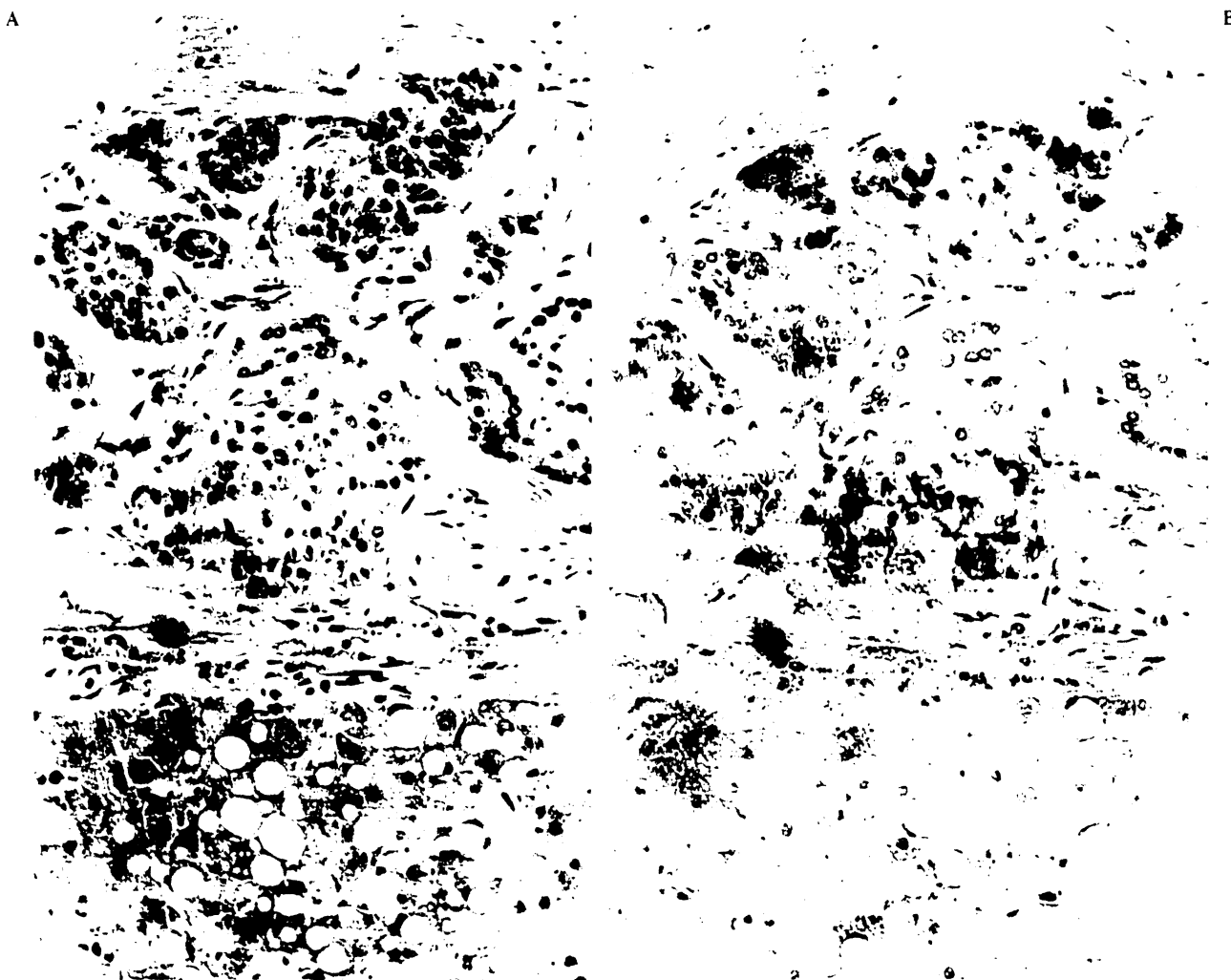

FIG. 1.   A: Photomicrograph of human islets (top) in a portal triad 109 days following human islet allotransplantation. The islets were contained within small venules in the interstitium of the portal tract. The liver showed steatosis and cholestasis but no inflammatory cell infiltrate. The parenchymal changes were attributed to the sepsis and total parenteral nutrition (hematoxylin-eosin, ×85). B: Immunohistochemical stain (immunoperoxidase) for insulin revealed beta cells (darkly staining cells, ×85).

(12,13), were transplanted via portal vein infusion. The cytotoxic cross-match was strongly positive (100%), and there was a complete six-antigen HLA mismatch. Immunosuppression was with FK-506 (4 mg twice a day, i.v.). Two weeks after transplantation, a liver biopsy was performed because of hepatic dysfunction: the biopsy demonstrated acute cellular rejection. The patient was treated with 7 days of OKT3 and steroids, but she subsequently developed CMV hepatitis, which was treated with ganciclovir (DHPG). Her clinical status deteriorated because of multiple respiratory complications, renal infections (*Klebsiella, Aeromonas*), and the CMV hepatitis.

On May 16, 1990, the patient developed gramnegative sepsis (*Aeromonas hydrophilia*), and all immunosuppressive therapy was discontinued on May 19. Despite aggressive antibiotic and supportive medical therapy, the patient became progressively obtunded and died 109 days after transplantation. Postmortem examination revealed enteritis and bronchopneumonia, with subsequent sepsis as the cause of death. The liver allograft showed steatosis and cholestasis, but no inflammatory cell infiltrate or CMV inclusions. The parenchymal changes noted above were attributed to the sepsis and total parenteral nutrition. Pancreatic islets were detected in several portal triads in tissue sections from the anterior inferior edge of the right lobe of the liver. The islets were contained within small venules in the interstitium of the portal tracts (Fig. 1A). An immunohistochemical stain for insulin confirmed the presence of insulin-containing cells (Fig. 1B).

It is of note that the patient never became insulin independent after islet allotransplantation. We attributed the exogenous insulin requirement to the complicated postoperative course (sepsis) and the need for continuous total parenteral nutrition. Nevertheless, significant plasma C-peptide levels (14) were observed during the postoperative course: 2.15 ± 1.27 pM, n = 30, versus C-peptide plasma levels in normal controls of 2.19 ± 1.22 pM, n = 10.

DISCUSSION

The findings in this patient indicated that human islets can survive in the liver of transplanted patients, despite positive cross-match, no HLA antigen match, and immunosuppressive monotherapy with low-dose FK-506, which was discontinued 12 days before the patient died. Also, the findings sug-

gest that upper abdominal exenteration and liver transplantation may constitute a favorable environment for allogeneic human islets, providing additional evidence in support of previous experimental results on combined liver-islet transplantation (10). Since this patient, we have been able to document the presence of insulin-containing cells in both wedge and needle liver biopsies in patients who received either liver-islet or kidney-islet allografts (15).

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