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Vanishing Pancreatic Grafts

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Comparison of pancreaticoduodenal transplants (PDT) and duct-ligated pancreas transplant (DLPT) were performed using syngeneic and allogeneic studies in rats. Both DLPT and PDT allogeneic grafts showed mild rejection. DLPT groups showed disorganized pathology and acini replaced by fat. Eventually, massive fibrosis was seen in the Islets of Langerhans, as well as rejection cellular infiltrates. In both PDT groups, normal histology was observed in the same period. Thus the effect of duct occlusion is highly detrimental for the grafts.

Key Words: Pancreaticoduodenal transplants, duct-ligated pancreas transplants

INTRODUCTION

Since we reported our technique for rat pancreaticoduodenal transplantation (PDT) in 1972, we have extensively studied the immunopathological and pathophysiological[1-5] aspects of this model. Associated with these studies of acute and chronic PDT in allogeneic models, either internal or external blockage of the pancreatic duct system occurred with subsequent complicating pancreatic cyst and abscess formation of the pancreatic parenchyma, with the replacement of pancreatic acini and consequent displacement of pancreatic islets of Langerhans by fat, leading to the vanishing of these grafts. A recent report by Humar et al.[6] prompted us to reexamine our animal model to clarify the nature of the vanishing grafts.

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MATERIALS AND METHODS

Lewis (LW) and Sprague Dawley (SD) rats, weighing 250g to 300g of mixed sex were employed for syngeneic and allogeneic studies, respectively. Though SD strains of rats were inbred at the San Diego Microsurgical Institute for over 15 generations, transplantation of solid organs (heart or pancreas) between SD strains still shows mild to moderate rejection phenomena. Grafts between in-bred LW strains showed no signs of rejection. SD strain was used to study allogeneic grafts, and in-bred LW strain was used for syngeneic grafts. In SD and LW rats, both pancreaticoduodenal transplants (PDT) and pancreatic duct-ligated transplants (DLPT) were performed. In order to compare these groups, transplants were performed according to the initial protocol of our technique utilizing venous drainage[1] into the inferior vena cava (IVC). The pancreatic duct-ligated model eliminated the duodenal segment by serial ligation of minute pancreatic duct branches and blood vessels originating from the pancreas. The transplants were harvested periodically up to 6 months, placed in 10% formalin, and stained with H&E.

RESULTS

In syngeneic studies, Low and high magnification microphotographs (Fig. 1A, B) of PDT grafts show normal pancreatic acini and islets of Langerhans in transplants at one month post-transplant, whereas Fig. 1C and 1D show DLPT grafts with acini replaced by fat and islets of Langerhans

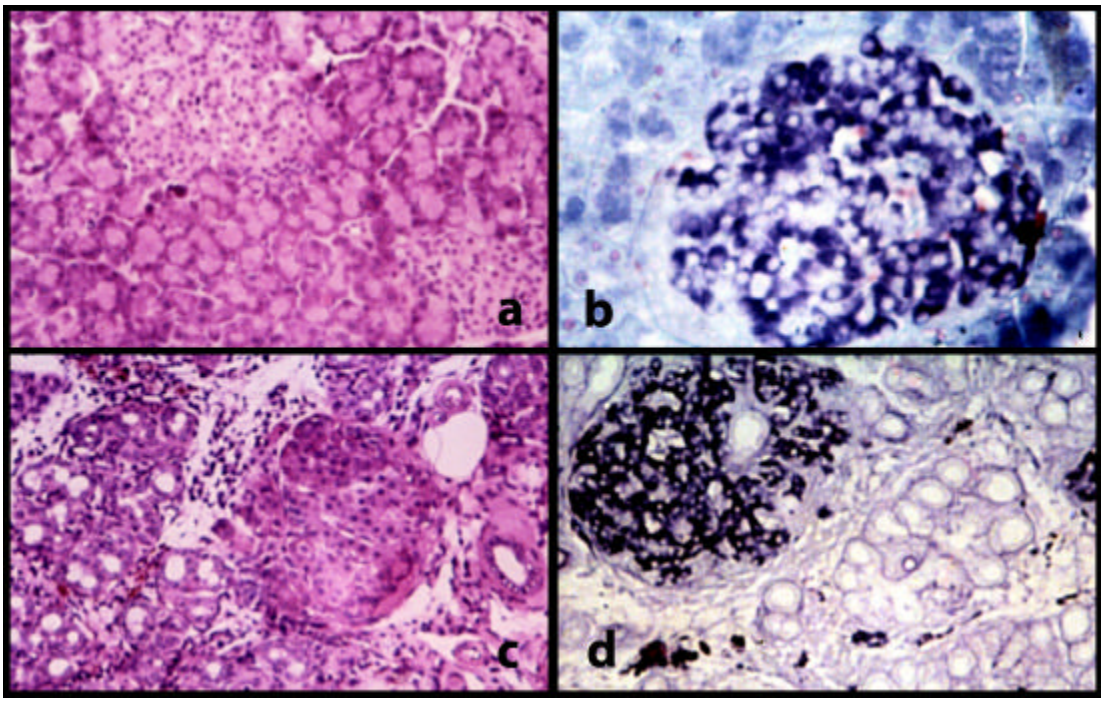

Fig. 1. Syngeneic grafts at one month post-transplant (a) Pancreaticoduodenal transplant (PDT) at low magnification; (b) PDT at high magnification, showing intact islets of langerhans and acini; (c) Duct-ligated pancreas transplant (DLPT) at low magnification; (d) DLPT at high magnification, showing fat replacement of acini and disturbance of islets of Langerhans.

Table 1. Pathological Changes in Duct-Ligated Allo-Pancreatic Grafts in Rats*

POD†	Incidence of lymphocytic infiltration / total No	Incidence of necrosis and abcesses / total No	Incidence of Fibrosis / - total No
4 - 7	4 / 4	4 / 4	4 / 4
10 - 14	4 / 4	4 / 4	4 / 4
21 - 35	6 / 6	6 / 6	6 / 6
60 - 90	5 / 5	2 / 5	5 / 5

*Sprague Dawley Rats.
†Postoperative days.

remaining intact at the same period of one post-transplant month. At six months post-transplant, PDT (Fig. 2A, B) grafts show normal islets of Langerhans and normal acini; pancreatic ducts in these transplants are neither dilated nor constricted. In contrast, DLPT 6-month old grafts show massive fat replacement of acini (Fig. 2C, D) and diffuse fibrosis including islets of Langerhans, with fewer cells remaining in the islets of Langerhans.

In the allogeneic transplant cohort, the DLPT grafts showed multiple cysts, abscesses and necrosis within and surrounding the grafts (Table 1). In addition to the rejection lymphocyte cell infiltration, there was development of acute pancreatitis with massive early fibrosis and fat replacement of the acini. At 5 post-transplant weeks, (Fig. 3A, B) the pancreas tissue showed disorganized acini with the majority of acini replaced by fat and moderate fibrosis. On the other hand, during the same period, the chronically rejected PDT grafts (Fig. 3C) showed normal islets of Langerhans and acini with the exception of a few rejection lymphocyte cells at 10 post-transplant weeks (Fig. 3D).

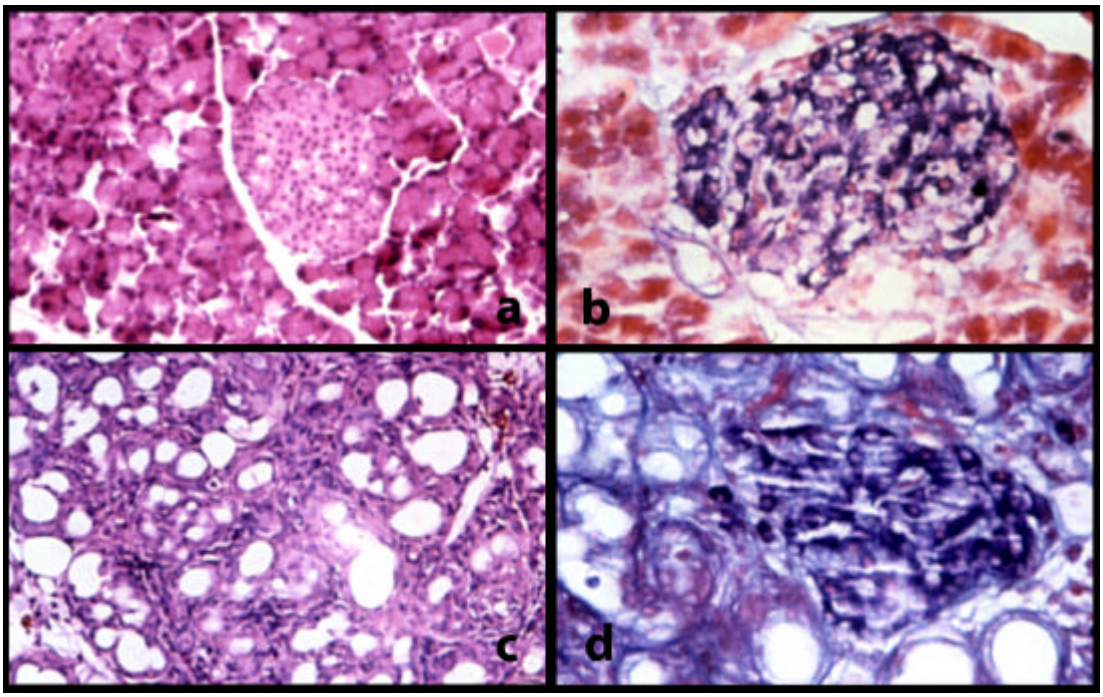

Fig. 2. Syngeneic Grafts at six months post-transplant (a) Normal pancreas tissue from a PDT graft at low magnification (b) and high magnification; (c) DLPT graft at low magnification and (d) high magnification indicate fat replacement of acini as well as islets of Langerhans showing early fibrosis, with a loss of a few islet cells.

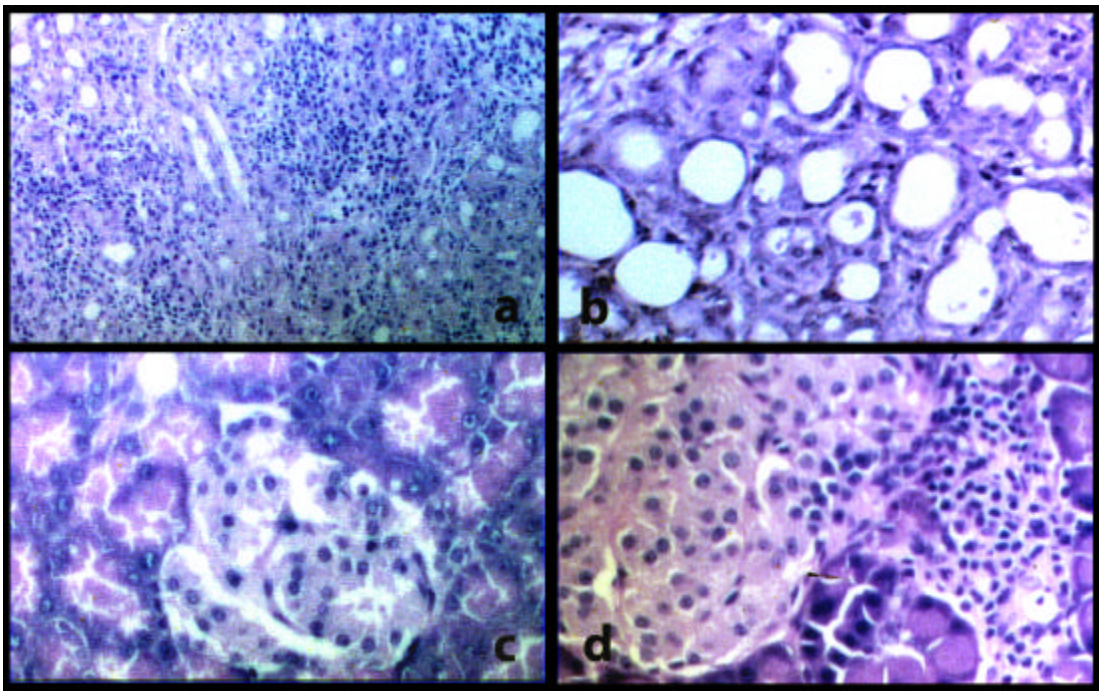

Fig. 3. Allogeneic Pancreatic Grafts (a) Five weeks post-transplant DLPT grafts at low and (b) high magnification show fat replacement throughout a majority of the acini. (c) PDT at five weeks and (d) ten weeks post-transplant show normal islets of Langerhans and acini that has not been replaced by fat, despite rejection with inflammatory lymphocyte cell infiltration.

DISCUSSION

In order to alleviate Diabetes Mellitus, various pancreatic transplant techniques are available. Kelley, Lillehei[7,8] and their associates utilized pancreaticoduodenal transplants combined with other organ transplants, including simultaneous kidney transplants. Starzl's group[9] adopted and refined such procedures in clinical pancreaticoenteric whole organ transplantation with or without kidney transplants. On the other hand, others[10,11] adopted the technique of inserting the pancreatic duct into the urinary system to monitor the rejection process of the pancreas graft. These two transplant techniques are well-accepted procedures in clinical practice, though in either procedure, pancreatic duct occlusion may occur and the grafts undergo fat replacement and the islets of Langerhans finally vanish. The solution for preventing the vanishing islets requires further scientific investigation.

CONCLUSION

Both pancreaticoduodenal and pancreatic duct-ligated transplants in syngeneic (Lewis rats) and allogeneic (Sprague Dawley rats) studies have been performed to observe any pathological changes in the period of six post-transplant months. Both syngeneic and allogeneic PDT groups preserved normal morphology of the islets of Langerhans and acini, while approximately 70% of DLPT syngeneic grafts exhibited acini replaced by fat, and fibrosis. DLPT allografts at 5 weeks typically showed widespread disorganization due to fat replacement of islets of Langerhans cells, rejection with lymphocyte inflammatory cell infiltration, and progressively worsening fibrosis. At 6 months, syngeneic DLPT grafts showed fibrosis with loss of islets of Langerhans cells, thus the fates of cells in the islets of Langerhans has not been determined; we are now investigating which specific cells are being lost.

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