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Three Cases of Pancreas Allograft Dysfunction

We present clincopathologic features of three cases of biopsy-proven pancreas allograft dysfunction in Korea. All patients had advanced insulin-dependent diabetes mellitus (IDDM). Case 1 was a 30-year-old woman who underwent a simultaneous pancreas-kidney transplantation. Urinary infection developed 6 days after the operation, which remitted and reappeared, when urine amylase level was normal. Since the 55th day after the operation, intermittent hematuria has persisted. Cytomegalovirus inclusions were detected on the urinary bladder and grafted duodenal mucosa. The graft was removed due to perforation of the grafted duodenum and panperitonitis. Case 2 was a 27-year-old man undergoing pancreas transplantation alone (PTA). Ten days after the transplatation, the level of 24 urine amylase decreased and the graft was not delineated by ^{99m}Tc DTPA scintigraphy. Allograft needle biopsy revealed multiple acinar cell necrosis and mild lymphocytic infiltration which were compatible with mild acute rejection. Case 3 was a 25-year-old man undergoing cadevaric PTA. Three months after the transplantation, graft was removed due to gastric perforation associated with cytomegalovirus and angiodestructive fungal infection. Various causes of pancreas allograft dysfunction can be diagnosed by needle biopsy, thus appropriate biopsy specimen should be taken using improved biopsy technique.

Key Words: *Pancreas Transplanation; Biopsy, Needle; Transplantation, Homologous; Graft Rejection; Fungi; Cytomegalovirus Infections*

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INTRODUCTION

Pancreas and pancreas-kidney transplantation are considered an acceptable alternative for the treatment of type I diabetic patients particularly if there is already significant diabetic nephropathy (1-3). The first pancreas transplantation was performed in 1966, and at the end of 1996, more than 8,800 pancreas transplants have been reported to the International Pancreas Transplantation Registry (4). A total of 22 cases of pancreas transplantation have been performed in Asan Medical Center from 1990 until the end of 1998 (5).

The major cause of pancreas allograft loss is irreversible rejection. This is particularly true in pancreas after kidney transplantation (PAK) and pancreas transplantation alone (PTA) cases since the clinical diagnosis of rejection remains relatively non-specific. Pathologic examination of pancreas allograft biopsy has been used as one of parameters for the diagnosis of pancreas rejection (6). Although biopsy materials have been obtained through cystoscopy-guided transduodenal pancreatic biopsy or percutaneous pancreatic biopsy, the experience with needle biopsies of pancreas allograft is small compared with other solid organs such as kidney, liver and heart (7-9). The number of pancreas transplantation is few and no biopsy-proven case of pancreas allograft dysfunction has been reported yet in Korea.

We report three cases of pancreas allograft dysfunction, one of which was diagnosed by needle biopsy and the others were finally evaluated with the removed graft.

CASE REPORT

Case 1

Clinical findings

A 30-year-old female underwent a simultaneous pancreas-kidney transplantation (SPK) due to a 9-year history of insulin dependent diabetic mellitus (IDDM) with retinopathy and nephropathy. After the transplantation, immunosuppression was done using FK506 and the levels of 24-hr urine amylase and serum creatinine were used to monitor allograft rejection. Six days after the operation, urine color change was detected. Thus urine culture was performed and urinary tract infection by *Serratia* was

confirmed. She received antibiotic therapy for 10 days. Fifteen days after the operation, the serum creatinine level increased, indicating acute rejection of the kidney, while urine amylase was maintained at a constant level (93,424 U/24h). The renal biopsy, however, showed only FK506-associated changes without evidences of acute rejection. Thus, insulin administration was stopped by 27 day post-transplantation. Another urinary tract infection by *Enterobacter cloacae* was confirmed on 34 day post-transplantation, which was improved by antibiotic treatment for 5 days. She was discharged on 39 day post-transplantation, when urine amylase level was 120,000 U/24h. About 15 days after discharge, she complained of hematuria, but no active bleeding lesion was found by cystoscopy. Intermittent hematuria recurred 27 days after discharge. Cystoscopic biopsy specimen revealed cytomegalovirus (CMV) infection in the grafted duodenum and urinary bladder wall. Despite treatment of ganciclovir, panperitonitis developed due to perforation of grafted duodenum. Primary closure of the perforated site was done, but hematuria and dysfunction of grafted pancreas continued. Therefore, the allograft pancreas was removed on 135 day post-transplantation. Blood glucose level has been controlled by insulin injection.

Pathologic findings

Cystoscopic allograft biopsy specimen consisted of the duodenal tissue and urinary bladder. Surface epithelium was eroded or ulcerated with moderate chronic inflammation. In contrast, glandular cells of duodenal mucosa were enlarged with characteristic intranuclear viral inclusions of cytomegalovirus (Fig. 1). The bladder mucosa was edematous and was infiltrated by lymphocytes. Capillaries and veins were dilated and were filled with fibrin thrombi. Some endothelial cells or perivenular stromal cells were markedly enlarged with amphophilic intranuclear and cytoplasmic inclusions which were immunostained for CMV antigen. A few endothelial cells were detached into the venous channel. Characteristic owl's eye nuclei with perinuclear halo were rarely present.

The removed pancreas allograft was grossly normal without necrosis or fibrosis. Attached duodenal mucosa was slightly eroded, and serosa was irregularly thickened. Microscopically, the duodenal mucosa was atrophic and eroded with mild chronic inflammation. In the pancreas, septal inflammation was focal and mild, and ductal epithelium was intact. The acinus was multifocally infiltrated only by lymphocytes, where isolated acinar cells revealed cytopathic changes and viral inclusions (Fig. 2). Although arteritis was frequently noted, parenchymal necrosis was not identified. Arterial occlusion with foam cells was rarely identified. A few glandular cells contained amphophilic viral inclusions. Subserosal lymph nodes were multifocally infarcted and adjacent large arteries revealed endothelialitis and necrotizing arteritis with organized thrombi.

Case 2

Clinical findings

A 27-year-old man underwent PTA due to 9-year-

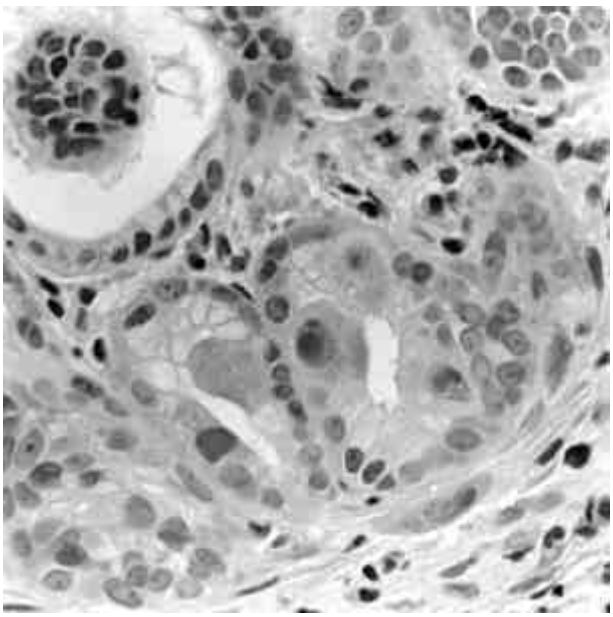

Fig. 1. Cystoscopic biopsy of pancreas allograft with duodenum: A few duodenal mucosal epithelial cells are enlarged and reveal intranuclear and/or cytoplasmic cytomegalovirus inclusions (H&E, ×200).

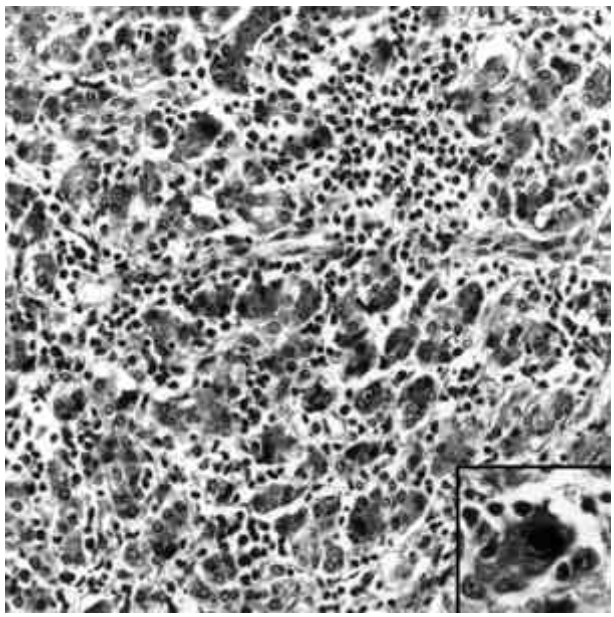

Fig. 2. Removed allograft pancreas: Infiltration of lymphocytes are mild and acinar cells reveal cytomegalic changes with typical intranuclear cytomegalovirus inclusions (inset) (H&E, ×100).

history of IDDM and retinopathy. After the transplantation, FK506 was administered continuously and OKT3 transiently for 8 days. Ten days after the operation, the level of 24 hr urine amylase decreased and the grafted pancreas was not delineated on ^{99m}Tc DTPA scintigraph. Cystoscopic needle biopsy of the pancreas allograft was performed at that time and a diagnosis of mild acute rejection was made. The level of FK506 increased and OKT3 was readministered for 14 days. The level of 24 hr urine amylase began to increase from 13 day post-transplantation and was recovered to that before the episode of rejection on 23 day post-transplantation. The grafted pancreas was recognized by the ^{99m}Tc DTPA scintigraphy on 29 day post-transplantation. He has been well without evidences of rejection for 7 months.

Pathologic findings

The pancreas allograft biopsy specimen consisted of 3-4 lobules with intervening septa. A few foci of acinar cell necrosis were associated with mild infiltration of lymphocytes, neutrophils and rare plasma cells (Fig. 3). No eosinophils were identified. Single acinar cell degeneration was noted multifocally, showing pyknotic nuclei and eosinophilic cytoplasm. Mitotic figures were rarely noted. Islets of Langerhans were intact. The inflammation was accentuated around a small venule, leading to focal venular endothelialitis (Fig. 4). However, no arteritis was confirmed due to sampling limitation. These features were consistent with mild acute rejection (acute rejection grade III).

Case 3

Clinical findings

The 25-year-old male patient had had IDDM for 6 years and controlled his blood sugar level by insulin medication. He underwent cadeveric PTA. Three weeks after the transplantation, hemoptysis developed and reactivation of old tuberculosis was suspected in left lung radiologically. The left lung lesion progressed and superimposed aspergillosis was suspected clinically. Three months after the transplantation, abdominal distension due to fluid collection developed and has persisted in spite of drainage by pigtail catheter. Thus, a leakage at the graft anastomosis site was suspected. On exploratory laparatomy, gastric perforation and necrosis of the adjacent omental tissue were identified, but the grafted pancreas itself appeared unremarkable grossly. Debndement of the gastric perforation site and graft removal were done. On 98 day post-transplantation, heart failure with valve insufficiency due to association with fungal endocarditis occurred and died of systemic fungal infection on 126 day post-transplantation.

Pathologic findings

The transplanted pancreas and a part of the duodenum were removed in addition to the perforated portion of the stomach and omentum. The pancreas was slightly edematous. Neither hemorrhage nor necrosis was noted. Attached duodenal mucosa showed no abnormal findings grossly. Fragments of peritoneal and gastric tissues were necrotic. Microscopically, the pancreas tissue revealed

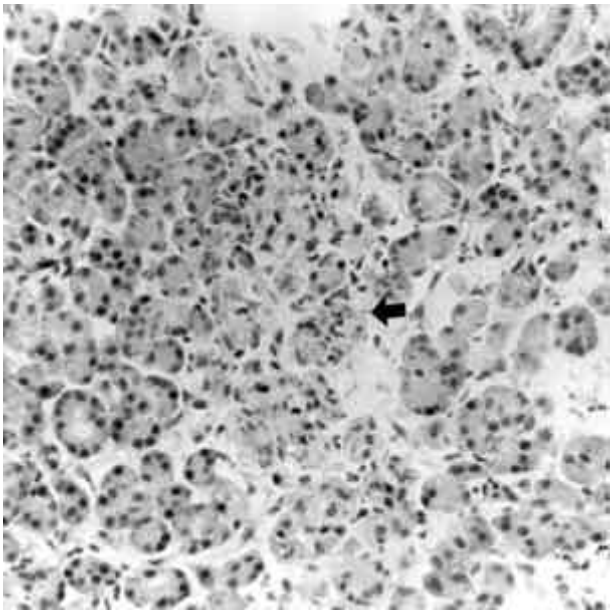

Fig. 3. Needle biopsy of allograft pancreas: Acinar cells are necrotic and are associated with mild mononuclear cell infiltration (arrow) (H&E, ×100).

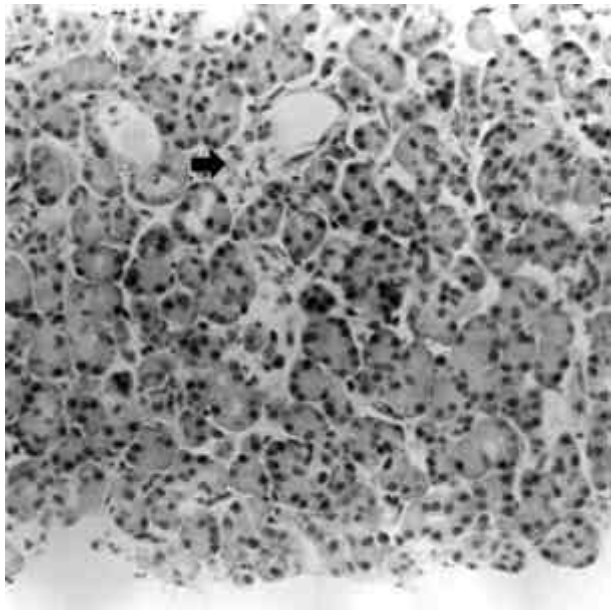

Fig. 4. Needle biopsy of allograft pancreas shows focal venular endothelialitis (arrow) (H&E, ×100).

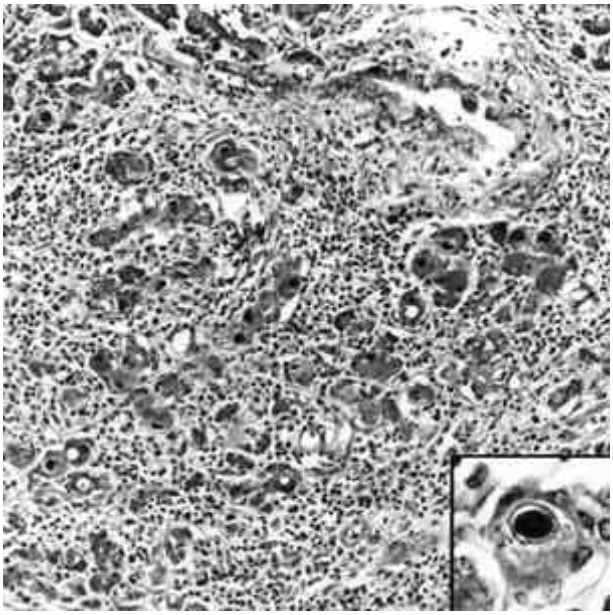

Fig. 5. Removed allograft pancreas: Interstitial and septal infiltration of mononuclear cells is moderate and multiple cytomegalovirus inclusions are frequently noted in acinar and ductal cells (H&E, ×100). Note typical owl's eye appearance of intranuclear cytomegalovirus inclusion in addition to cytoplasmic viral inclustion (inset) (H&E, ×100).

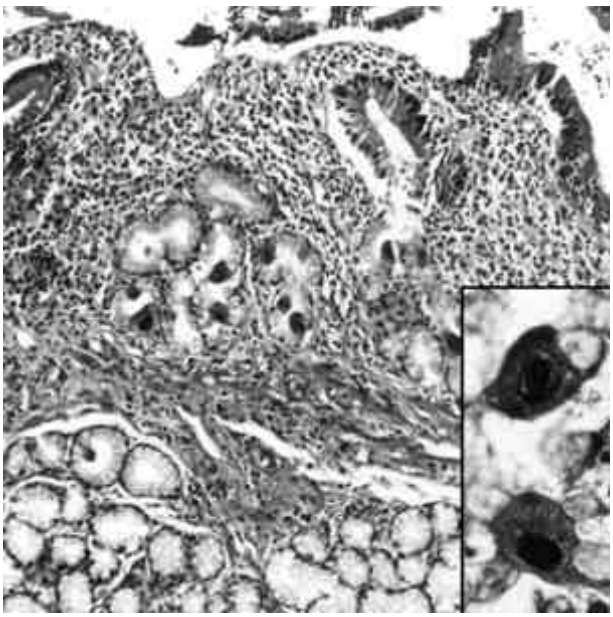

Fig. 6. Duodenum of the removed allograft pancreas: Mucosal glandular epithelial cells have many cytomegalovirus inclusions (inset) (H&E, ×100).

moderate chronic inflammatory cell infiltration where many acinar cells were markedly enlarged with intranuclear and cytoplasmic CMV inclusion. The inclusions were mostly noted in acinar or ductal cells, while they were rarely detectable in islet cells or stromal cells (Fig. 5). No endothelialitis was noted. Although the duodenal mucosa was grossly unremarkable, viral inclusions were easily detected in glandular epithelium (Fig. 6). The perforated gastric mucosa was necrotic where characteristic CMV inclusion containing cells and fungal hyphae were admixed. The fungi were variable in diameter, but revealed right-angle branching without septation, which suggested mucormysosis (Fig. 7). Angioinvasion and angiodestruction by the fungi were noted.

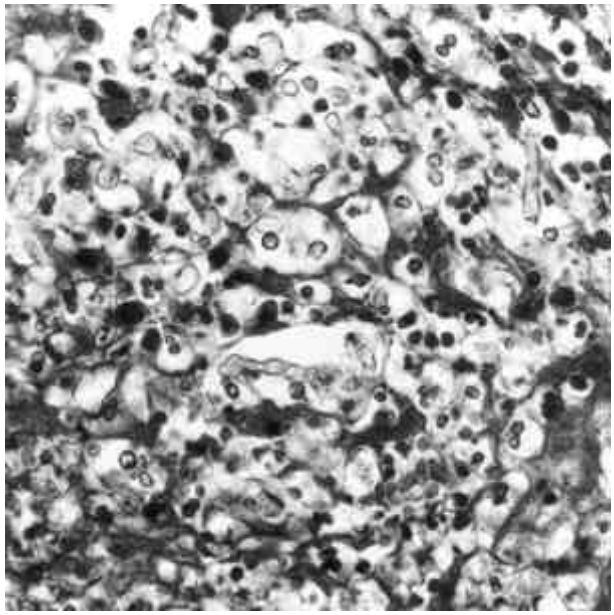

Fig. 7. Perforated stomach wall: Note septated fungal hyphae and enlarged degenerated cells which are consistent with aspergillosis (H&E, ×100).

DISCUSSION

We presented clinicopathologic findings of three patients with different causes of pancreas allograft dysfunction. They underwent two different types of pancreas transplantation, SPK or PTA. Pancreas transplantation can be done simultaneously with kidney transplantation (SPK), after kidney transplantation (PAK) or pancreas alone (PTA). SPK is the most common type of pancreas transplantation and the treatment of choice in uremic type I diabetics (3). The overall one year graft survival for SPK (79%) is reported to be higher than that of PAK (60%) and PTA (57%) (4).

Case 1 was one from SPK, in which kidney biopsy was performed first for the diagnosis of acute rejection due to increased serum creatinine level without evidences of pancreatic dysfunction. In cases of SPK or PAK, the co-transplanted kidney is thought to provide a reliable indicator for rejection through serial determinations of the recipient's serum creatinine. In case 1, there was no evi-

dence of rejection in renal allograft biopsy and the normal level of urine amylase and persistent hematuria suggested a possibility of complications by infection rather than acute rejection. Thus, duodenal and bladder biopsies were done later, which confirmed CMV infection demonstrating viral inclusions in venous endothelium, stromal cells and glandular epithelium. CMV pancreatitis was prevented using antiviral agents such as gancyclovir (11, 12), but occasional patients presented with abnormal pancreatic function secondary to graft involvement by CMV infection, and severe cases may present intractable hemorrhage and duodenal-cuff perforation (13, 14). Since acute allograft rejection and mild CMV pancreatitis with scanty cytopathic changes can show overlapping morphological features, CMV graft pancreatitis should always be ruled out with a thorough examination of the tissue available. In addition, special stains and/or molecular approach should be applied, if necessary, before a diagnosis of rejection is rendered. Although prominent arteritis and luminal narrowing with foam cell collection could be suggestive of acute rejection in case 1, inflammation was mild and localized only in areas showing CMV inclusions. These findings may suggest that arteritis can be prominent in CMV pancreatitis.

Multiple infection is a serious complication in organ transplantation. In case 3, the patient had tuberculosis, aspergillosis and CMV infection. Gastric perforation, the direct cause of graft failure was also due to CMV-associated gastric ulcer and angiodestructive fungal infection.

The incidence of acute rejection is reported to be higher in pancreas allograft than that of the other solid organ, ranging 70-80% (1, 15, 16). In addition, irreversible rejection, a major cause of graft loss is particularly important for pancreas after PAK and PTA, since the clinical diagnosis of rejection remains relatively nonspecific. In case 2, urine amylase level has been serially checked for the diagnosis of acute rejection, which decreased markedly at 10 days post-transplantation. In addition to urine amylase, ^{99m}Tc DTPA scintigraphy was used for the diagnosis of pancreas rejection, which showed no uptake in pancreas. ^{99m}Tc DTPA scintigraphy is one of the parameters used for the diagnosis of pancreas rejection including decrease in urinary insulin and C peptide, increase in serum amylase, lipase, anodal trypsinogen and pancreas specific protein, cytologic evaluation of pancreatic juice and urine, urinary amylase and allograft biopsy.

The adequacy of biopsy material in allograft pathology is very important and two or three segments of parenchymal lobules with corresponding fibrous septa are known to be suitable for the evaluation of the pancreas allograft biopsy. The cystoscopy-guided transduodenal pancreatic biopsy specimen in case 2 was small, but was adequate since the biopsy contains more than three segments of parenchymal lobules and fibrous septa.

The experience with needle biopsies of transplanted pancreas is small compared with other solid organ transplants. With the development of percutaneous biopsy technique, pathology of pancreas transplant needle biopsy has been systematically evaluated (17-22). Drachenberg et al. (1996) proposed five-grading schema for acute rejection in pancreas (20). Multifocal involvement of mild parenchymal inflammation and associated acinar cell necrosis in case 2 were characteristics of mild acute rejection, although vasculitis was suspicious and septal inflammation was not identified due to the limitation of sampling. Needle biopsy of pancreas allograft for the differential diagnosis of pancreas dysfunction is a gold standard, and thus appropriate biopsy specimen should be taken using improved biopsy technique for the definite diagnosis of acute rejection and other causes of graft dysfunction.

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