Transpl Int (1997) 10: 451–456

ORIGINAL ARTICLE

Interstitial and vascular pancreas rejection in relation to graft survival

Joke G. Boonstra
Johan W. van der Pijl
Yves F. C. Smets
Herman H. P. J. Lemkes
Jan Ringers
Leendert A. van Es
Fokko J. van der Woude
Jan A. Bruijn

Received: 6 March 1997
Received after revision: 5 June 1997
Accepted: 30 June 1997

J.G. Boonstra (✉) · J.W. van der Pijl
L.A. van Es · F.J. van der Woude[1]
Department of Nephrology, Building 1, C3-P,
University Hospital Leiden,
P.O. Box 9600
NL-2300 RC Leiden, The Netherlands
Fax: + 31 71 524 8118
e-mail: Boonstra@rullf2.leidenuniv.nl

Y.F.C. Smets · H.H.P.J. Lemkes
Department of Endocrinology,
University Hospital Leiden,
P.O. Box 9600
NL-2300 RC Leiden, The Netherlands

J. Ringers
Department of Surgery,
University Hospital Leiden,
P.O. Box 9600
NL-2300 RC Leiden, The Netherlands

J.A. Bruijn
Department of Pathology,
University Hospital Leiden,
P.O. Box 9600
NL-2300 RC Leiden, The Netherlands

[1] *Present adress*: V. Medizinische Klinik, Klinikum Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer, D-68135 Mannheim, Germany

Abstract To examine the incidence of interstitial and vascular rejection in pancreas allografts and its impact on graft survival, we studied 36 percutaneous pancreas biopsies and 10 pancreas transplantectomy specimens from 32 patients who had undergone simultaneous pancreas-kidney transplantation. Interstitial rejection (IR) was predominantly found in the biopsies, while vascular rejection (VR) was most prominent in the transplantectomies. Pancreas graft survival was significantly decreased for pancreas grafts that had suffered from vascular rejection when compared to those with only interstitial rejection. Potential rejection markers, i.e., serum amylase, glucose, creatinine, and urinary amylase, did not correlate with histological signs of rejection, although increased levels of serum amylase were, in all but one case, associated with rejection. We conclude that a percutaneous pancreas biopsy remains the most reliable method to determine pancreas rejection, and that by distinguishing between IR and VR, a pancreas biopsy may provide important diagnostic as well as prognostic information.

Key words Pancreas transplantation, biopsy, rejection · Biopsy, pancreas transplantation, rejection · Vascular rejection, biopsy, pancreas · Interstitial rejection, biopsy, pancreas

Introduction

Simultaneous pancreas-kidney transplantation (SPK) is performed in patients with diabetes mellitus type I and end-stage renal failure. Rejection is a major complication after SPK, as with other types of transplantation. It may occur isolated in the pancreas or kidney, or concurrently in both grafts [8, 10, 11, 25, 28]. We previously reported that SPK recipients suffered from more interstitial rejection (IR) episodes of the kidney than did re-

cipients of a kidney transplant alone, while the incidence of vascular rejection (VR) episodes was comparable between the groups [3]. Clearly, much less is known about pancreas rejection than about kidney rejection, as experience with the former is more limited.

While laparotomy used to be necessary to perform pancreas biopsies [27], several transplant centers have, in the past few years, started using the percutaneous biopsy technique for the pancreas allograft [1, 19]. This enables an accurate diagnosis of rejection. There is, however, no generally accepted classification for pancreas rejection, such as the Banff classification for kidney rejection, although suggestions have been put forward by Nakhleh and Sutherland, and Drachenberg et al. [6, 15]. Carpenter's group [4] reported that histological changes in duodenal biopsies from pancreaticoduodenal grafts parallel the findings in the pancreas biopsy and that both accurately reflect the state of the graft. A more recent report [17] however, shows that pancreas and duodenum can suffer independently from a rejection episode. Since isolated pancreas rejection episodes are also reported [10], monitoring pancreas rejection by performing only a kidney or duodenum biopsy will not always give accurate information.

The decision to perform a pancreas biopsy is often based on changes in the values of blood glucose, urinary amylase, and serum amylase, but also on serum creatinine as a marker for simultaneous kidney rejection. Since the pancreas and kidney can reject independently after SPK, serum creatinine will not always be a good marker for pancreas rejection. Serum amylase and pancreas-specific protein have been shown to be sensitive, but not specific, markers for rejection [5, 13, 29]. Hypoamylasuria may be used as a marker in bladder-drained transplants as it correlates with histologically defined pancreas rejection; however, major differences in specificity have been reported [2, 12, 14, 18]. Serum anodal trypsinogen has been reported to be a reliable, graft-specific rejection marker [5, 12, 20]. However, no pancreas core biopsies were performed in these studies to confirm rejection. Another method for the early detection of pancreas rejection may be the use of protocol biopsies. However, Stratta et al. could not demonstrate a difference in 1-year actuarial graft survival for patients with or without protocol cytoscopic transduodenal pancreas biopsies [26].

We have previously shown that in both SPK and kidney transplantation alone, vascular kidney rejection is associated with significantly decreased renal graft survival [3, 22]. In pancreas rejection, however, no studies have been performed in which IR and VR were analyzed separately and related to graft survival.

In this study, we analyzed 36 pancreas biopsies and 10 transplantectomies from 32 patients who had undergone a bladder-drained pancreas-kidney transplantation for the presence of IR and VR, and we studied the impact of these types of rejection on pancreas graft survival. Tissue sections were also stained for the presence of insulin- and glucagon-producing cells. The type and severity of rejection were compared between pancreas sections and kidney material simultaneously obtained in 23 instances. Furthermore, we studied the relationship between histological parameters and several routinely used laboratory parameters that might be indicative of pancreas rejection.

Materials and methods

Patients

We studied 32 patients who had undergone an SPK at our institution as well as one or more percutaneous pancreas biopsies and/or a pancreas transplantectomy. Pancreaticoduodenocystostomy was performed in all patients to ensure exocrine drainage. Patients were followed for at least half a year or until end of follow-up. The mean age of the patients at the time of transplantation was 37.6 years (SD ± 8.3 years) and the mean duration of diabetes was 23.7 years (SD ± 6.7 years). The mean warm and cold ischemia times of the pancreas were 23.0 (± 4.6) min and 11.8 (± 3.7) h, respectively.

The immunosuppressive regimen consisted of cyclosporin A, prednisone, and azathioprine. Cyclosporin A was used at a starting dose of 3 mg/kg per day i.v. and was changed to 8 mg/kg per day p.o. according to whole blood trough levels as determined by radioimmunoassay (Cyclotrac-SP; Incstar, Stillwater, Minn., USA): 250–500 ng/ml during the first 3 months and 50–150 ng/ml thereafter. Prednisone was used at a starting dose of 25 mg/day and was tapered to 20 mg/day after 1 month and again after 3 months to 15 mg/day. Azathioprine was used at a constant dosage of 1.5 mg/kg per day. OKT3 (Orthoclone Muromonab CD3, Janssen-Cilag, The Netherlands) induction therapy (5 mg/day for 10 days) was given to 13 patients. Rejection episodes were treated with methylprednisolone (1 g i.v. for 3 days), rabbit antithymocyte globulin (RIVM, Bilthoven, The Netherlands) for 10 days (5 mg/kg per day on the 1st day, with subsequent doses given when the absolute number of lymphocytes was more than 300/mm^3 [9]), or OKT3 (5 mg/day i.v. for 10 days) according to a fixed schedule. The type of rejection, i.e., interstitial or vascular, was not taken into consideration.

Biopsies

A total of 36 percutaneous biopsies and 10 transplantectomies were performed in the 32 patients studied. Biopsies of the pancreas were taken with ultrasound guidance using an 18-gauge Biopty needle (Biopty, Lund, Sweden). Indications for biopsy were: (1) hypoamylasuria (25% decrease in 24-h urinary amylase when compared to two prior samples), (2) an edematous pancreas on CT scan, (3) an elevated serum amylase (> 600 U/l), and (4) hyperglycemia (fasting and postprandial). One biopsy was performed because of severe hematuria. When clinical and laboratory indications for pancreas rejection were present but a pancreas biopsy could not be performed to confirm rejection (due to exudative lesions or overlying intestinal loops), these episodes were not considered in the present study.

The mean time from transplantation to biopsy was 60 days. Indications for transplantectomy were: graft failure ($n = 6$), surgical site infections and the need to stop immunosuppression ($n = 2$),

thrombosis ($n = 1$), or a combination of pain, fever, and a rise in serum creatinine ($n = 1$). Sections from paraffin-embedded tissues were stained with hematoxylin-eosin, silver methenamine, and periodic acid-Schiff (HE staining). Furthermore, sections were stained with mouse anti-human leukocyte common antigen (DAKO, Glostrup, Denmark) and with rabbit anti-human insulin and glucagon, using an indirect three-step immunoperoxidase method with diaminobenzidine.

Sections were evaluated for the presence of mild, moderate, or severe IR and VR. For IR, we used the grading system presented by Benedetti et al. [2], based on the mononuclear infiltrate and involvement of morphological changes in the acinar area. For the definition of mild, moderate, and severe VR, we used the grading system used before for the definition of VR in the kidney [3]; this was somewhat more detailed than the gradation proposed by Benedetti et al. Leukocyte common antigen staining was used in additional to HE staining to evaluate the amount of infiltration. Insulin- and glucagon-stained sections were evaluated for the presence or absence of positive cells. Simultaneously taken kidney biopsies and transplantectomies were evaluated for the presence of IR and VR, using a modification of the Banff classification, as described before [3].

Retrospectively, all 36 pancreas transplant biopsies were evaluated with regard to complications due to the procedure. Hemoglobin counts until 1 week after biopsy, clinical records, and ultrasound investigations of the pancreas (performed on indication) were used as indicators for possible complications.

Laboratory parameters

Urinary (24-h collection) and serum amylase, glucose, and creatinine levels were determined at the diagnostic laboratory of our hospital. Amylase was determined using an enzymatic colorimetric test, and glucose using a UV test (all from Boehringer Mannheim, Mannheim, Germany).

Statistical analysis

Estimated graft survival rates were calculated from transplantation until graft loss or end of follow-up using the Kaplan-Meier method and were compared with the log-rank test. Pancreas graft loss was defined as a return to insulin dependency, and death with a functioning graft was considered as censoring. The Cox proportional hazards analysis was used to determine the relative risk of pancreas graft loss for patients who had suffered from VR (and IR) during follow-up, compared to those with only IR. Spearman's correlation coefficients were calculated for the relationship between histological and laboratory parameters at the time of biopsy and for the relationship between the severity of IR (expressed as 0, 1, 2, or 3 for no rejection, mild, moderate, and severe rejection, respectively) in simultaneously taken pancreas and kidney biopsies. Differences in glucose, creatinine, and serum and urinary amylase on the day of biopsy between the groups with and without rejection were compared using the Mann-Whitney test. Changes in laboratory parameters were compared 7 days before biopsy and on the day of biopsy using the Wilcoxon test. Statistical analyses were performed with the SPSS program (SPSS, Chicago, Ill., USA).

Table 1 The incidence of interstitial and vascular rejection in pancreas biopsies and transplantectomies

Type of rejection		Biopsies $n = 36$	Transplantectomies $n = 10$
No rejection		10 (31 %)	2 (20 %)
Interstitial rejection	Mild	17 (47 %)	1 (10 %)
	Moderate	8 (22 %)	6 (60 %)
	Severe	1 (3 %)	1 (10 %)
Vascular rejection	Mild	2 (6 %)	3 (30 %)
	Moderate	0	3 (30 %)
	Severe	1 (3 %)	1 (10 %)

Results

Histology

Table 1 shows the incidence of mild, moderate, and severe IR and VR in the pancreas biopsies and transplantectomies. IR was seen in 26 of 36 (72 %) biopsies and was mild in most cases. VR was seen in 3 biopsies, in addition to an interstitial infiltrate. Vascular changes were more prominent in the transplantectomies (70 %), while IR was seen in 80 % of the transplantectomies, although it was predominantly moderate. Interstitial infiltration was mainly found in the acinar tissue and consisted predominantly of mononuclear cells, although one biopsy also contained granulocytes. The latter findings might have been associated with a simultaneous *E. coli* pyelonephritis that occurred in this patient.

In some cases, very few mononuclear cells were also found in the islets of Langerhans. Immuno-peroxidase staining showed the presence of insulin-producing cells in all samples except one biopsy and two transplantectomies, and glucagon-producing cells in all but two biopsies and two transplantectomies. Ten biopsies and two transplantectomies were without signs of rejection. In one of these transplantectomies, severe thrombosis was found.

In the case of 20 pancreas biopsies and 3 transplantectomies, the kidney graft was biopsied or removed at the same time. Vascular rejection was seen in two cases of a simultaneous transplantectomy and was present in the pancreas and in the kidney. In six cases (30 %) of a simultaneous biopsy, one of the organs did not suffer from rejection, while mild or moderate IR was found in the other graft. Overall, the severity of IR in the pancreas correlated significantly with the severity of IR in the kidney ($r = 0.60$, $P = 0.003$).

Major complications were not observed in relation to the percutaneous pancreas biopsies. No infectious sequelae occurred, and only minor changes in hemoglobin concentration were found (a maximum decrease of 10 %). In three cases, a slight lesion, a suspected hematoma, was found at ultrasound investigation 1 day after biopsy. These lesions resolved without additional therapy.

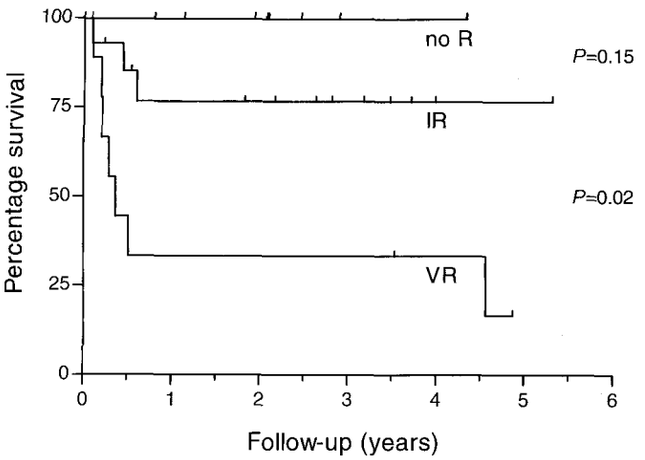

Fig. 1 Kaplan-Meier graft survival curves for grafts that never suffered from rejection (*R*, $n = 8$), grafts with only interstitial rejection (IR) during follow-up ($n = 15$), and grafts with one or more vascular rejection (VR) episodes ($n = 9$). Survival curves for IR and VR were significantly different (log-rank, $P = 0.02$). No difference was found between survival curves for IR and no rejection (log-rank, $P = 0.15$)

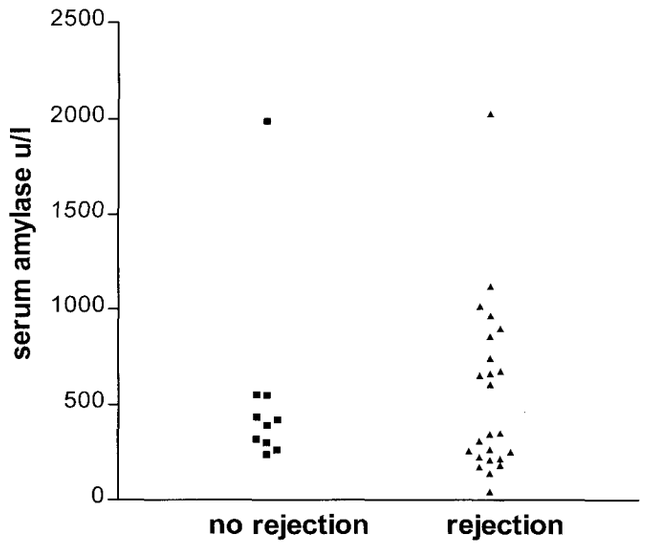

Fig. 2 Serum amylase (U/l) on the day of biopsy for biopsies without rejection ($n = 10$) and biopsies with rejection ($n = 24$)

Graft survival

To study the impact of IR and VR in the pancreas on survival of the graft, Kaplan-Meier graft survival curves were calculated for grafts without rejection, grafts with only IR during follow-up, and grafts that had suffered from one or more VR episodes (with or without IR; Fig. 1). Grafts were lost due to rejection or, in two cases, due to thrombosis. Graft survival differed significantly between the group with IR only and the group with VR (log-rank, $P = 0.02$). One-year survival for grafts with IR was 77 % and for grafts with VR 33 %. The relative risk of graft loss for VR over IR was 4.2 (95 % CI 1.3–18.6). There was no significant difference between the survival curves for grafts without rejection and those with IR. Variations in graft survival were not caused by differences in the number of HLA-A, B, or DR mismatches between the groups.

Correlation of histological rejection with laboratory parameters

To find out whether standard laboratory parameters could be predictive for histological rejection, we studied the concentrations of serum amylase, glucose, creatinine, and urinary amylase from 7 days before until the day of biopsy. Transplantectomies were not considered because 90 % of these suffered from thrombosis, which might influence the levels of potential rejection markers. Biopsies were divided into two groups: those without rejection and those with mild, moderate, or severe IR, with or without VR. No significant difference was observed between the two groups regarding concentrations of serum amylase, glucose, creatinine, or percentage decrease in urinary amylase on the day of biopsy. However, for all but one biopsy, an increased serum amylase (> 600 U/l) was associated with rejection (Fig. 2), indicating that serum amylase is still a useful marker.

To study whether the increase in serum amylase, glucose, and creatinine prior to the day of biopsy might be more informative than concentrations on the day of biopsy, we compared the concentrations of these parameters from 7 days before biopsy with those from the day of biopsy using a Wilcoxon test for paired observations. No significant difference was observed between these time points for either the group without rejection or the group with histologically proven rejection, indicating that there was no significant increase in serum amylase, glucose, or creatinine prior to the taking of biopsies with or without rejection.

Discussion

In this study we showed that leukocytes infiltrating the pancreas during rejection are predominantly localized in the exocrine part, i.e., acinar tissue, while in some biopsies and transplantectomies an infiltrate was also seen in the islets of Langerhans. Nakhleh et al. [16] have shown that an infiltrate in the islets of Langerhans is associated with recurrent diabetes, but if normal percentages of insulin- and glucagon-positive cells are present, this can also indicate rejection. Recently, two cases were reported of SPK recipients with recurrent diabetes

in their pancreas grafts showing infiltration in the islets but not in the exocrine tissue and a decrease or absence of insulin-positive cells [30]. In our tissue samples with isletitis, there was always normal insulin and glucagon staining and an exocrine infiltration that was, in several cases, moderate to severe. We, therefore do, not consider the presence of isletitis in our series as recurrence of diabetic disease in these grafts but rather as an expression of more severe IR. This is in agreement with the findings from a recent study by Drachenberg et al. [7], who were also unable to demonstrate the recurrence of diabetes in their series.

In 9 % of the biopsies and 70 % of the transplantectomies studied, we found signs of endovasculitis associated with intimal or medial thickening, indicating that the rejection process also involved the vessels of the graft. However, we cannot exclude the possibility that VR might have been missed in some biopsies due to a sampling error.

In a large study on open duct, enteric-drained, and silastic and prolamine duct-injected grafts, the Minnesota group showed that endovasculitis is a useful feature to distinguish acute rejection from pancreatitis [23]. In their study on cystoscopic biopsies in bladder-drained grafts, however, interstitial and vascular pancreas rejection could occur independently [2]. In our study, we also often found acute interstitial rejection in percutaneously taken biopsies without the presence of VR. A polymorphonuclear infiltrate was found in one biopsy that could be explained by a concurrent *E. coli* pyelonephritis in this patient.

The presence of one or more VR episodes during follow-up resulted in significantly decreased graft survival when compared to grafts that had only suffered from IR. We previously found that renal graft survival in SPK recipients was also significantly decreased when VR episodes occurred during follow-up [3]. A study on rejection after kidney transplantation alone in our hospital also showed decreased graft survival for patients with VR and an adjusted relative risk of graft loss of 4.92 (95 % CI 3.25–7.43) [22]. Thus, VR is an important factor in determining the prognosis of both kidney and pancreas allografts. This supports the use of a histological classification system that distinguishes between IR and VR. Until now, no distinction has been made between the presence of IR and/or VR in antirejection treatment. However, future pancreas rejection episodes that also involve the vessels of the graft may be treated more stringently than episodes with only IR.

For 23 of the 46 pancreas biopsies and transplantectomies, concurrent kidney tissue was obtained. A positive correlation was found between the severity of IR in the kidney and in the pancreas. A study by Allen et al. [1] showed comparable findings in kidney and pancreas in 69 % of the cases and no isolated pancreas rejection, while others have reported the latter [10]. In our group, we found isolated pancreas rejection in 4 out of 20 simultaneously taken pancreas and kidney biopsies. This is, however, probably an underestimation of its occurrence since, for 16 of the 36 pancreas biopsies studied, no concurrent kidney biopsy was taken. In light of this and the fact that isolated kidney rejection is also a common phenomenon after pancreas-kidney transplantation, a biopsy of one of the grafts cannot predict the status of the other. However, our data show that when both grafts suffer from rejection, the type (IR or VR) and severity of IR can, in theory, be determined by performing only one biopsy.

In 31 % of the biopsies, we found aberrant laboratory parameters but no histological signs of rejection. This group could theoretically include clinical situations such as CMV infection or pancreatitis. However, these biopsies were completely normal, and CMV could be excluded both clinically and with the pp56 immunofluorescence test [24].

Monitoring pancreas graft rejection should ideally be performed with the help of a reliable serum or urinary marker, facilitating an early and less invasive diagnosis. Klassen et al. [10] showed, in a recent study, that at the time of suspected pancreas rejection, changes are seen in commonly used laboratory markers, but they concluded that these are only 80 % specific for acute rejection. Here, we have studied the levels of serum amylase, glucose, and creatinine, and the percentage decrease in urinary amylase for biopsies with and without histologically proven rejection, but we found no significant difference between the groups. High serum amylase levels (> 600 U/l), however, were nearly always associated with an interstitial infiltrate and might, therefore, still be clinically useful. Some promising results have been found in studies regarding the use of serum anodal trypsinogen as a putative marker for pancreas rejection [5, 12, 20]. Further studies, correlating serum anodal trypsinogen with pancreas core biopsy-proven rejection, are needed to determine whether it may be a useful rejection marker. Our group has recently shown that pancreatitis-associated protein (PAP) may be a new and useful serum marker for pancreas rejection and that it is also detectable in situ by immunohistochemical staining of pancreas biopsies with rejection [21].

We conclude that vascular pancreas rejection is an important factor in determining the prognosis of the graft. Laboratory rejection markers did not correlate significantly with histologically defined rejection, suggesting that a percutaneous pancreas biopsy, which is a safe procedure, remains the most reliable method for determining the type and severity of pancreas rejection.

Acknowledgements This study was supported by a grant from the Dutch Diabetes Foundation, grant number 92–125.

References

1. Allen RDM, Wilson TG, Grierson JM, Greenberg ML, Earl MJ, Nankivell BJ, Pearl TA, Chapman JR (1991) Percutaneous biopsy of bladder-drained pancreas transplants. Transplantation 51: 1213–1216
2. Benedetti E, Najarian JS, Gruessner AC, Nakhleh RE, Troppmann C, Hakim NS, Pirenne J, Sutherland DER, Gruessner RWG (1995) Correlation between cytoscopic biopsy results and hypoamylasuria in bladder-drained pancreas transplants. Surgery 118: 864–872
3. Boonstra JG, Bruijn JA, Hermans J, Lemkes HHPJ, Ringers J, Pijl H van der, Woude FJ van der (1995) The incidence of interstitial and vascular kidney rejection after pancreas-kidney transplantation. J Am Soc Nephrol 5: 1918–1925
4. Carpenter HA, Engen DE, Munn SR, Barr D, Marsh CL, Ludwig J, Perkins JD (1990) Histologic diagnosis of rejection by using cytoscopically directed needle biopsy specimens from dysfunctional pancreatoduodenal allografts with exocrine drainage into the bladder. Am J Surg Pathol 14: 837–846
5. Douzdjian V, Cooper JL, Abecassis MM, Corry RJ (1994) Markers for pancreatic allograft rejection: comparison of serum anodal trypsinogen, serum amylase, serum creatinine and urinary amylase. Clin Transplant 8: 79–82
6. Drachenberg C, Klassen D, Bartlett S, Hoehn-Saric E, Schweitzer E, Johnson L, Weir M, Papadimitriou J (1996) Histologic grading of pancreas acute allograft rejection in percutaneous needle biopsies. Transplant Proc 28: 512–513
7. Drachenberg CB, Papadimitriou JC, Weir MR, Klassen DK, Hoehn-Saric E, Bartlett ST (1996) Histologic findings in islets of whole pancreas allografts. Transplantation 62: 1770–1773
8. Frisk B, Hedman L, Andersson C, Nyberg G, von Schenck H, Brynger H (1989) Discrepancy between renal and pancreatic rejection in combined transplantation. Transplant Proc 21: 2835–2836
9. Hoitsma AJ, Lier HJJ van, Reekers P, Koene RAP (1985) Improved patient and graft survival after treatment of acute rejections of cadaveric renal allografts with rabbit antithymocyte globulin. Transplantation 39: 274–279
10. Klassen DK, Hoehn-Saric EW, Weir MR, Papadimitriou JC, Drachenberg CB, Johnson L, Schweitzer EJ, Bartlett ST (1996) Isolated pancreas rejection in combined kidney pancreas transplantation. Transplantation 61: 974–977
11. Margreiter R, Klima G, Bosmuller C, Konigsrainer A, Schmid T, Steiner E (1989) Rejection of kidney and pancreas after pancreas-kidney transplantation. Diabetes 38: 79–81
12. Marks WH, Borgstrom A, Sollinger H, Marks C (1990) Serum immunoreactive anodal trypsinogen and urinary amylase as biochemical markers for rejection of clinical whole-organ pancreas allografts having exocrine drainage into the the urinary bladder. Transplantation 49: 112–115
13. Minakawa R, Brattstrom C, Tyden G, Tibell A, Pousette A, Bergstrom K (1995) Serum levels of pancreatic amylase and pancreas-specific protein as markers of pancreatic graft rejection episodes. Transplant Proc 27: 1329–1330
14. Munn SR, Engen DE, Barr D, Carpenter HA, Perkins JD (1990) Differential diagnosis of hypoamylasuria in pancreas allograft recipients with urinary drainage. Transplantation 49: 359–362
15. Nakhleh RE, Sutherland DER (1992) Pancreas rejection. Significance of histopathologic findings with implications for classification of rejection. Am J Surg Pathol 16: 1098–1107
16. Nakhleh RE, Gruessner RWG, Tzardis PJ, Brayman K, Dunn DL, Sutherland DER (1991) Pancreas transplant pathology: an immunohistochemical comparison of allografts with rejection, syngenic grafts, and chronic pancreatitis. Transplant Proc 23: 1598–1599
17. Nakhleh RE, Benedetti E, Gruessner A, Troppmann C, Goswitz JJ, Sutherland DER, Gruessner RWG (1995) Cytoscopic biopsies in pancreaticoduodenal transplantation. Transplantation 60: 541–546
18. Nankivell BJ, Allen RDM, Bell B, Taylor N, Wilson T, Grierson JM, Greenberg M, Chapman JR (1991) Factors affecting measurement of urinary amylase after bladder-drained pancreas transplantation. Clin Transplant 5: 392–397
19. Osama-Gaber A, Gaber LW, Shokouh-Amiri MH, Hathaway D (1992) Percutaneous biopsy of pancreas transplants. Transplantation 54: 548–550
20. Perkal M, Marks C, Lorber MI, Marks WH (1992) A three-year experience with serum anodal trypsinogen as a biochemical marker for rejection in pancreatic allografts. Transplantation 53: 415–419
21. Pijl JW van der, Boonstra JG, Barthellemy S, Smets YFC, Hermans J, Bruijn JA, Fijter JW de, Daha MR, Dagorn J (1997) Pancreatitis-associated protein: a putative marker for pancreas graft rejection. Transplantation 63: 995–1003
22. Saase JLCM van, Woude FJ van der, Thorogood J, Hollander AAMJ, Es LA van, Weening JJ, Bockel JH van, Bruijn JA (1995) The relation between acute vascular and interstitial renal allograft rejection and subsequent chronic rejection. Transplantation 59: 1280–1285
23. Sibley RK, Sutherland DER (1987) Pancreas transplantation. An immunohistologic and histopathologic examination of 100 grafts. Am J Pathol 128: 151–170
24. Smets YFC, Pijl JW van der, Dissel JT van, Ringers J, Fijter JW de, Lemkes HHPJ (1997) Infectious disease complications of simultaneous pancreas kidney transplantation. Nephrol Dial Transplant 12: 764–771
25. Stratta RJ, Sollinger HW, Perlman SB, D'Alessandro AM, Groshek M, Kalayoglu M, Pirsch JD, Belzer FO (1988) Early diagnosis and treatment of pancreas allograft rejection. Transpl Int 1: 6–12
26. Stratta RJ, Taylor RJ, Grune MT, Sindhi R, Sudan D, Castaldo P, Cushing CA, Radio SJ, Wisecarver JL, Matamoros A, Nelson NL, Hapke MR, Pillen TJ, Markin RS (1995) Experience with protocol biopsies after solitary pancreas transplantation. Transplantation 60: 1431–1437
27. Sutherland DER (1987) Role of pancreas graft biopsy in the diagnosis and treatment of rejection after pancreas transplantation. Transplant Proc 19: 2323–2331
28. Tesi RJ, Henry ML, Elkhammas EA, Davies EA, Ferguson RM (1994) The frequency of rejection episodes after combined kidney-pancreas transplant – the impact on graft survival. Transplantation 58: 424–430
29. Tyden G, Lundgren G, Gunnarsson R, Ostman J, Groth CG (1984) Laboratory findings during rejection of segmental pancreatic allografts. Transplant Proc 16: 715–717
30. Tyden G, Reinholt FP, Sundkvist G, Bolinder J (1996) Recurrence of autoimmune diabetes mellitus in recipients of cadaveric pancreatic grafts. N Engl J Med 335: 860–863