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Banff Schema for Grading Pancreas Allograft Rejection: Working Proposal by a Multi-Disciplinary International Consensus Panel

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Accurate diagnosis and grading of rejection and other pathological processes are of paramount importance to guide therapeutic interventions in patients with pancreas allograft dysfunction. A multi-disciplinary panel of pathologists, surgeons and nephrologists was convened for the purpose of developing a consensus document delineating the histopathological features for diagnosis and grading of rejection in pancreas transplant biopsies. Based on the available published data and the collective experience, criteria for the diagnosis of acute cell-mediated allograft rejection (ACMR) were established. Three severity grades (I/mild, II/moderate and III/severe) were defined based on lesions known to be more or less responsive to treatment and associated with better- or worse-graft outcomes, respectively. The features of chronic rejection/graft sclerosis were reassessed, and three histological stages were established. Tentative criteria for the diagnosis of antibody-mediated rejection were also characterized, in anticipation of future studies that ought to provide more information on this process. Criteria for needle core biopsy adequacy and guidelines for pathology reporting were also defined.

The availability of a simple, reproducible, clinically relevant and internationally accepted schema for grading rejection should improve the level of diagnostic accuracy and facilitate communication between all parties involved in the care of pancreas transplant recipients.

Key words: Acute allograft rejection, acute cellular rejection, allograft arteriopathy, allograft function, allograft loss, allograft monitoring, anti-HLA antibodies, antibody-mediated rejection, Banff schema, biopsy specimen, pancreas, pancreas allograft, pancreas and kidney, pancreatic islets, pathology

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Introduction

Pancreas transplantation is an effective treatment option for patients with either brittle or complicated diabetes mellitus (DM). A successful pancreas transplant results in disappearance of the acute complications of DM (i.e. hypoglycemia, severe hyperglycemia, and ketoacidosis), and may stabilize or even reverse some of the long-term complications of the disease (1–3).

The first pancreas transplant was performed in 1966, but routine application of this procedure did not occur until the 1980s. The slower progress for pancreas transplantation in comparison to other organ transplants was related both to technical and immunological challenges inherent to the graft itself (4). Maintenance of parenchymal architecture and preservation of endocrine function in whole pancreas transplantation requires concurrent surgical management of exocrine secretions. This is most commonly accomplished by pancreatico-duodenal transplantation with anastomosis of a portion of the donor duodenum either to the recipient small intestine or urinary bladder. Venous drainage of the pancreas (and consequent insulin delivery) can be performed either into the systemic (iliac vein or vena cava in cases of bladder or enteric exocrine drainage) or portal system (mesenteric vein in cases of enteric exocrine drainage) (5). Pancreas transplantation is performed in three different situations, depending on the patient's native kidney function: simultaneous pancreas-kidney (SPK) is used in diabetic patients with uremia/end-stage renal disease. This is the most common type of pancreas transplant performed, and currently accounts for 60–65% of new cases. Alternatively, the pancreas can be transplanted after a successful (previous) kidney transplant (sequential pancreas after kidney, (PAK)). Pancreas transplantation alone (PTA) is used to treat nonuremic diabetic patients (6).

Results of pancreas transplantation have continued to improve, with current 1-year graft survival (complete insulin independence) rates of 85% for SPK, 78% for PAK and 77% for PTA. One-year patient survival rates are excellent in all three categories, ranging from 95% to 97% (7). As of 2007, more than 20 000 pancreas transplants have been performed in the United States (8).

The mechanisms of acute rejection in the pancreas allograft are not different from those in other solid transplants, although distinctive rejection patterns are seen for the exocrine and endocrine components that likely reflect variations in major histocompatibility complex (MHC) expression, type and quality of the micro-vasculature, and sensitivity to ischemia (9–13). Experimental, as well as clinical, studies have shown that vessels, ducts and acini are the preferential targets of cell-mediated rejection, in contrast to the islets of Langerhans that are neither directly nor immediately affected (14–25) (Figures 1–4). On the other hand, the few documented cases of antibody-mediated rejection of the pancreas have presented with hyperglycemia, suggesting that the islets may be susceptible to micro-vascular injury associated with antibody deposition (26–28). MHC disparities in general, and specifically class II alloantibodies, have been associated with an increased risk of pancreas allograft loss (28). Antibody-mediated rejection has become increasingly recognized in pancreas transplantation (29) (Figure 5).

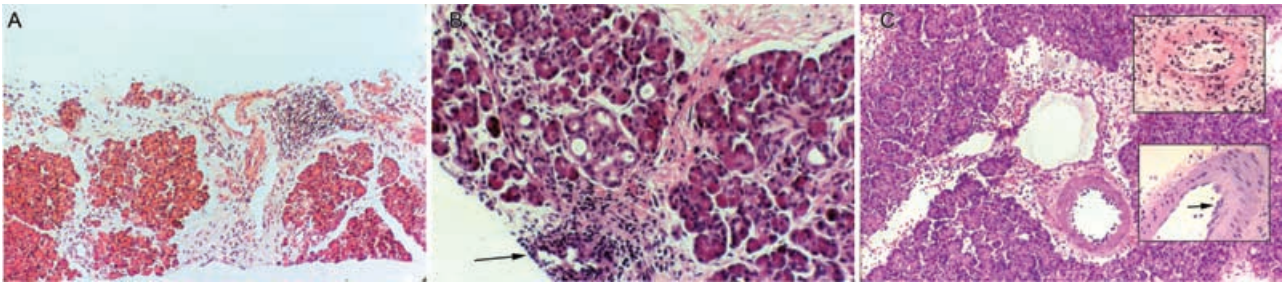

Figure 1: Inflammation in septa and septal structures. (A) Inactive appearing, mononuclear septal infiltrates that are not involving septal structures or acini. In the absence of more specific findings this case would be classified as 'indeterminate' for rejection. (B) Venulitis (arrow) representing mild/grade I ACMR in a biopsy done 5 days posttransplantation. There is minimal acinar inflammation (toward the left). The acini show patchy luminal dilatations (rounded empty spaces) consistent with ischemic injury. (C) Moderate/grade II ACMR defined by active septal inflammation in association with venulitis in two cross-sections of veins and intimal arteritis in the artery below. Top insert: from a different biopsy, necrotizing arteritis (the wall is replaced by amorphous eosinophilic material). There is also transmural inflammation and moderate-severe intimal arteritis. Note endothelial cell injury (swelling, sloughing). Bottom insert: minimal intimal arteritis consisting of a few of lymphocytes beneath the endothelium (arrow). There is no clear evidence of endothelial injury.

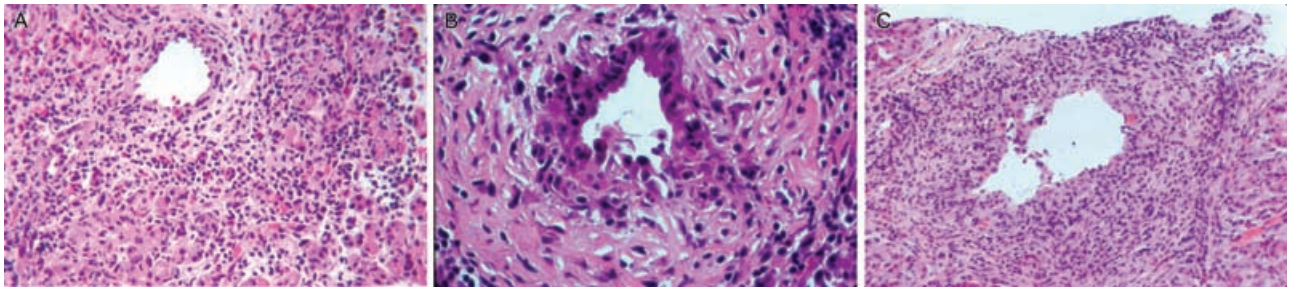

Figure 2: Venous and ductal inflammation in ACMR. (A) Active septal inflammation with numerous eosinophils and venulitis (upper middle field). (B) Ductal inflammation and associated reactive/regenerative epithelial changes. (C) Severe ductal inflammation. Dense infiltrates around a duct with extensive denudation of its epithelial lining. Few epithelial clusters on the left upper contour were positive for cytokeratin stain (not shown).

Significant and/or persistent acinar damage and chronic vascular injury (transplant arteriopathy) trigger a progressive fibrogenic reaction, which eventually impairs endocrine function (Figure 6). As with all other allografts, repeated episodes of acute rejection, and particularly late acute rejection, significantly increase the risk for graft loss due to chronic rejection (19,30–34).

Clinical diagnosis of acute rejection

Pancreas allograft rejection is usually asymptomatic so the clinical diagnosis relies heavily on laboratory markers of acinar cell injury (i.e. increase in serum amylase and lipase levels) or abnormalities in the exocrine or endocrine functions (decrease in urine amylase in bladder-drained grafts or hyperglycemia, respectively).

Increase in serum amylase and/or lipase is seen in a majority of rejection episodes, correlating with biopsy-proven rejection in approximately 80% of cases (35,37,38). Additionally, in patients with bladder exocrine drainage, decrease in amylasuria from baseline has been reported to correlate with histologically proven acute rejection in 53% of cases (35,36,39).

Hyperglycemia occurs only in the more severe, often irreversible, forms of acute rejection (16,17). The differential diagnosis in patients with hyperglycemia also includes early or late large vessel thrombosis, recurrence of autoimmune disease, islet cell drug toxicity and advanced stages of chronic rejection/graft sclerosis (30,31,40–42). Serial serum creatinine levels, with confirmation by renal allograft biopsy, are used as surrogate markers for pancreatic acute rejection in patients with simultaneous pancreas kidney transplants. Despite the general acceptance of this practice, the occurrence of asynchronous rejection has been well documented with isolated rejection of either the pancreas or the kidney allograft occurring in up to 30% of cases (43–45).

Rejection occurs earlier and is more common in PTA (9,46), which also has a higher rate of graft loss from irreversible rejection in comparison to SPK (9% and 30% in PTA vs. 2% and 7% in SPK transplants at 1 and 5 years, respectively) (8). Routine performance of percutaneous pancreas allograft biopsies has significantly improved outcomes in PTA because as mentioned above, timely diagnosis and treatment of acute rejection are essential to prevent irreversible graft sclerosis (6,43,46,47).

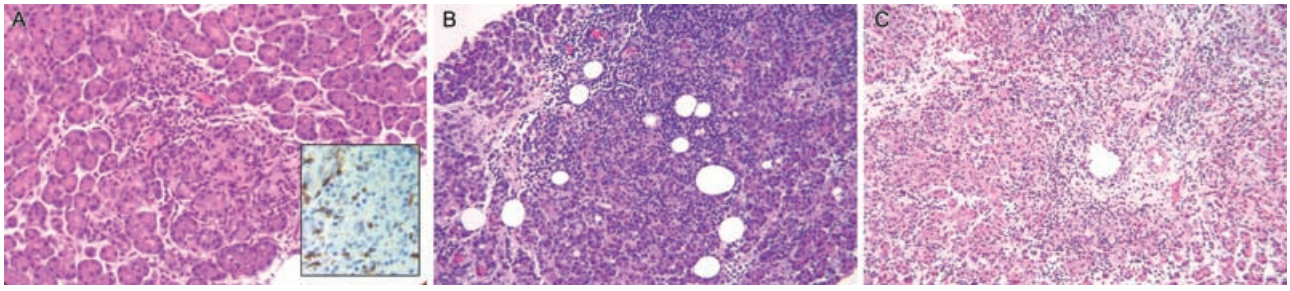

Figure 3: Acinar inflammation in ACMR. (A) Acinar inflammatory focus (center field), that is in continuity with a small inflamed septal area above. Insert: CD3 stain highlights T lymphocytes and their tight relationship to the acinar cells as is typically observed in ACMR. Also see Figure 6A. (B) Dense septal inflammation (upper left) that spills extensively in the neighboring acinar areas. There is also mild fatty infiltration. (C) Example of grade II/moderate acute cell-mediated rejection defined by the presence of multi-focal acinar inflammatory infiltrates in addition to the septal inflammation. All acinar areas are affected, but high magnification (not depicted) showed that acinar cell injury/necrosis was only seen in isolated cells (i.e. multi-cellular or confluent acinar cell injury/necrosis was not present).

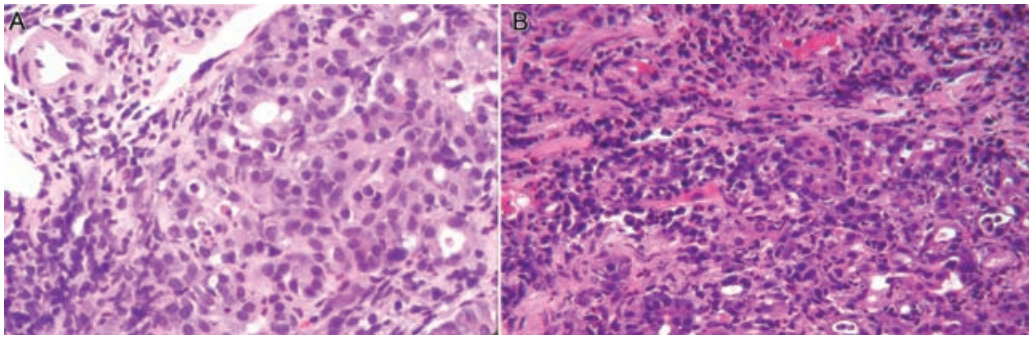

Figure 4: Focal versus multi-cellular/confluent acinar cell injury/necrosis. (A) Acinar cell injury/necrosis in occasional acinar cells. Note an apoptotic cell distinguished from the adjacent cells by a clear halo and few apoptotic bodies (lower left of apoptotic cell). Most acinar areas in this biopsy were free of inflammation. (B) Extensive septal and acinar inflammation with multi-cellular acinar cell injury/necrosis. The acinar architecture is distorted, there are empty spaces indicating acinar cell drop-out and patchy amorphous eosinophilic foci representing necrosis (top right and lower right). The depicted findings were seen throughout the acinar areas indicating severe/grade III ACMR.

Needle core biopsies

In contrast to kidney and liver transplantation, procurement of tissue samples from pancreas allografts was uncommon until the early 1990s when Allen et al. introduced a safe and reproducible technique of percutaneous needle biopsy (15). Due to the lack of specificity of serum and urine markers, needle core biopsies have become the standard for the diagnosis of acute pancreas allograft rejection (47–53).

Core biopsies are usually performed with 18 or 20 gauge needles, under ultrasound or computer tomographic guidance (53,54). Adequate tissue can be obtained in 88% to 90% of cases and complications are rare (2–3%, i.e. bleeding, mild pancreatitis) (38,46,52–55). Laparoscopic or open biopsies may be required if bowel loops are interposed between the abdominal wall and the graft (56). Cystoscopic transduodenal biopsies are now performed rarely in patients with bladder drainage, with adequate samples of pancreatic tissue obtained in 57–80% (57,58).

Biopsy adequacy

The adequacy of any particular biopsy sample is ultimately determined by the examining pathologist, but based on the current understanding of pancreas allograft rejection, it is recommended that at least three lobular areas and their associated inter-lobular septa are evaluated. Arterial branches follow a less-predictable course and are sampled with more difficulty. Due to the diagnostic importance ascribed to the arterial lesions, the absence of arterial branches in the biopsy core should be noted in the pathology report (17,59,60).

The presence of islets in pancreatic core biopsies is similarly unpredictable and is not necessary in the determination of allograft rejection (or biopsy adequacy) because

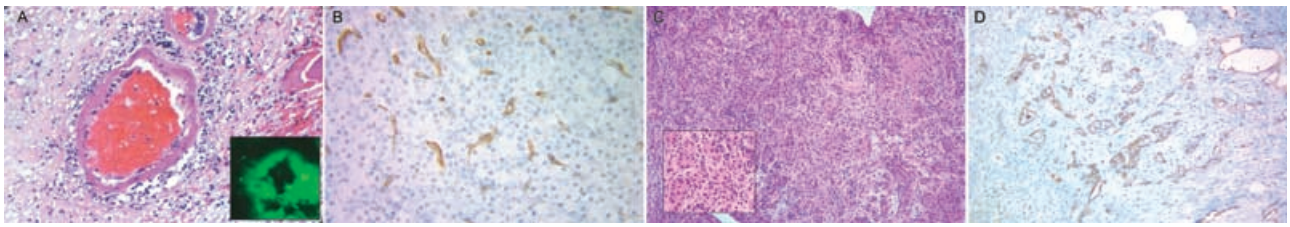

Figure 5: Antibody-mediated rejection (AMR). (A) Arterial fibrinoid necrosis due to accelerated AMR in a graft pancreatectomy performed 30 h posttransplantation. Insert: immuno-fluorescence stain is strongly positive for IgG. C4d stain (not represented) was also positive in all size vessels. (B) C4d stain in pancreatic capillaries in patient with acute AMR biopsied 10 days posttransplantation. (C) Same patient as part B, biopsied 18 days posttransplant, continues to have strong positivity for C4d (not represented) and extensive inter-acinar neutrophilic inflammation. Note foci of necrosis (upper right). (D) Same patient as parts B and C: strong C4d staining in pancreas lost due to persistent AMR, 3 months posttransplantation. Note extensive fibrosis with associated obliteration of the endocrine and exocrine components (chronic active AMR).

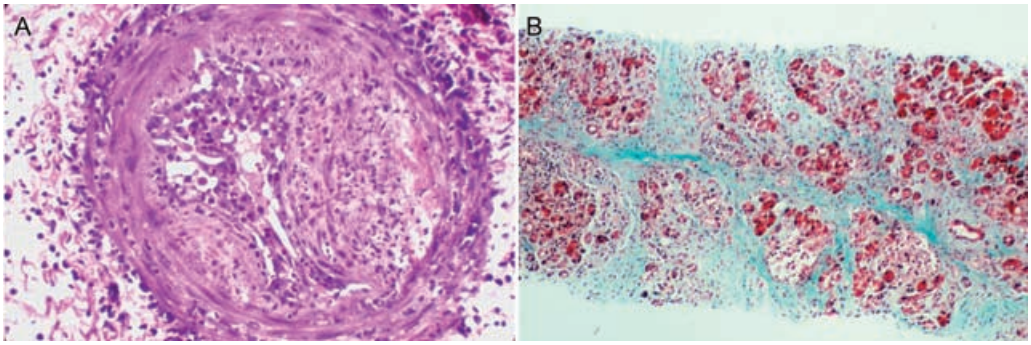

Figure 6: Chronic rejection/graft sclerosis. (A) Artery with severe luminal narrowing due to a combination of acute (intimal arteritis) and active chronic cell-mediated allograft rejection. The latter appears as two 'cushion-like' areas of intimal fibrosis with mononuclear inflammation. (B) Stage II of chronic rejection/graft sclerosis characterized by septal and acinar fibrosis that extends to the center of the acinar lobules.

inflammation affects the exocrine before the endocrine elements of the pancreas in most cases.

Guidelines for processing pancreas allograft biopsies

A methodical and rational approach to the utilization of needle core biopsies can maximize diagnostic yield. A description of routine and ancillary studies recommended is presented in Table 1. In biopsies used to assess hyperglycemia, insulin and glucagon immunostains should be performed to identify selective loss of beta cells (40,61). Masson's trichrome stain is particularly useful to demonstrate inter-acinar fibrosis in the earlier stages of graft sclerosis and to assist in the identification of specific structures or pathological changes (i.e. denuded ducts, fibrinoid necrosis in arterial walls, etc.).

Similar to the kidney, antibody-mediated rejection may be unrecognizable in the absence of C4d staining. There is no general agreement with respect to the best technique for C4d staining. Although the immuno-fluorescence technique is more sensitive, C4d staining of formalin-fixed paraffin-embedded sections is widely used with clinically acceptable results (59). It is currently recommended that the extent of C4d staining (i.e. % of positive inter-acinar capillaries) be reported (Table 2). In cases of C4d positivity, the need for correlation with serological studies (donor-specific antibodies -DSA) should be also stated in the pathology report (59).

Table 1: Recommended guidelines for processing pancreas allograft biopsies. Greater than or equal to 10 slides containing sequential sections are used as follows:

- Three for hematoxylin and eosin staining
- One for trichrome (collagen) staining
- One for C4d immuno-histochemistry
- Five or more intervening unstained sections for additional stains as needed (i.e. insulin and glucagon immuno-histochemistry if the biopsy is done for hyperglycemia; CMV, EBV, etc.).

Histological diagnosis and grading of acute pancreas rejection

The pioneering studies of Nakhleh and Sutherland, in which they compared tissue from failed and functioning allografts, identified intimal and transmural arteritis as features of the more severe forms of acute rejection. This observation led to the first proposal for a rejection grading schema (60). In subsequent years, routine availability of needle core biopsies allowed for the recognition of a broader spectrum of pathological changes in biopsies from functioning as well as rejecting or failing allografts (47–52). Based on a comparison of surveillance versus clinically indicated biopsies, a schema for grading acute rejection with six grades (0 to V) was developed at the University of Maryland (17). The latter schema emphasized progressive changes ranging from lack of inflammation (grade 0), to isolated involvement of fibrous septa (grade I) and septal structures (grade II), to acinar (grade III) and arterial involvement (grade IV). Parenchymal necrosis characterized the most severe form of rejection (grade V). Overall, the Maryland grading schema was shown to have good correlation with ultimate graft outcomes, clinical laboratory parameters and response to treatment (17). However, long-term outcomes and response to antirejection treatment between grades II and III were similar, both likely reflecting grafts with milder forms of acute rejection in contrast to the higher grades (IV and V) (16,17).

In 2005, a multi-disciplinary group of physicians with particular expertise and interest in the field of pancreas transplantation initiated consensus discussions at the 8th Banff Conference on Allograft Pathology (Edmonton, Alberta, Canada), following the successful model used for the development of the Banff schemas for grading rejection in kidney and liver transplantation (59,62). The working proposal presented here was generated after extensive, ongoing, consensus discussions that culminated at the 9th Banff conference on Allograft Pathology in 2007 (La Coruña, Spain).

Table 2: Histological definitions used for the diagnosis of rejection

Septal inflammatory infiltrates: predominantly mononuclear, including 'blastic' (activated) lymphocytes and variable numbers of eosinophils. Eosinophils may be the predominant cell type.
Venulitis: circumferential cuffing of septal veins with sub-endothelial accumulation of inflammatory cells and endothelial damage/lifting.
Ductitis: infiltration of ductal epithelium by mononuclear and/or eosinophillic inflammatory infiltrates and ductal epithelial cell damage. May lead to epithelial denudation.
Neural and peri-neural inflammation: septal inflammatory infiltrates in and around nerve branches (rare finding in needle biopsies).
Acinar inflammation: inflammatory infiltrates with similar characteristics as the septal infiltrates amidst the exocrine acini.
Acinar inflammatory lesion/focus: collection of $\geq$10 lymphocytes/eosinophils within an acinar area.
Focal acinar inflammation: $\leq$2 inflammatory foci per lobule with no evidence of acinar cell injury.
Multi-focal acinar inflammation: $\geq$3 foci of inflammation per lobule with single/isolated acinar cell injury/necrosis. Intervening uninflamed acinar areas.
Severe/extensive acinar inflammation: confluent, diffuse (widespread) acinar inflammation with focal or diffuse multi-cellular/confluent acinar cell injury-necrosis. No or very rare uninflamed acinar areas.
Acinar cell injury/necrosis: cytoplasmic swelling and vacuolization and/or nuclear pyknosis, apoptotic bodies, lytic necrosis leaving empty spaces equaling the size of individual cells (cell drop-out).
Single cell/spotty acinar cell injury/necrosis: only isolated cells are affected, with a vast majority of cells appearing preserved.
Multi-cellular/confluent acinar cell injury-necrosis: acinar cell damage /apoptosis involving multiple acinar cells (clusters).
Minimal intimal arteritis: rare, occasional, clearly defined sub-endothelial (intimal) inflammatory infiltration composed of mononuclear cells but with no evidence of activation or damage of the endothelial lining/intima (see below).
Moderate-severe intimal arteritis: easily identifiable mononuclear cells within the intima of an involved muscular artery and evidence of intimal injury, including any of the following: endothelial cell hypertrophy, activation or sloughing, fibrin leakage, neutrophil margination, macrophage activation, activation/proliferation of intimal myofibroblasts.
Necrotizing arteritis: focal or circumferential fibrinoid necrosis of the arterial wall with or without transmural inflammation.
Transplant arteriopathy: fibrointimal arterial thickening with narrowing of the lumen. Grading is done in the most affected artery as mild, up to 25% of luminal area; >25% but $\leq$50% of luminal area and severe, >50% of luminal area.
'Active' transplant arteriopathy: narrowing of the arterial lumen by a sub-endothelial proliferation of fibroblasts, myofibroblasts and smooth muscle cells with infiltration of the sub-intimal fibrous proliferation by mononuclear cells (T cells and macrophages).
Capillaritis: neutrophil and mononuclear cell margination in dilated inter-acinar and islet capillaries.
C4d semiquantitative grading: diffuse positive, $\geq$50% of inter-acinar capillaries; focal positive, 5–50% of inter-acinar capillaries; minimal positive/negative, <5 % of inter-acinar capillaries. Staining of larger vessels including arterioles is considered nonspecific.

Histological features of rejection and diagnostic categories: specific considerations

The specific histological features utilized in the 2007 Banff working schema are presented in Table 2. The schema consists of six main diagnostic categories, some of which may occur concurrently (Table 3). The severity of the pathological process is graded based on the global assessment of the biopsy. In addition, the extent of fibrosis and parenchymal atrophy are also assessed to determine the 'stage' of graft sclerosis. Reproducibility of the proposed working grading schema has not been yet tested and future studies are warranted to demonstrate its practical usefulness.

Normal: Inflammatory infiltrates are either absent, or very sparse with no features of activation (i.e. small lymphocytes, rare plasma cells). If any inflammation is present, it is focal, mononuclear and confined to the septa with lack of involvement of any of the septal structures such as vessels, ducts or nerves. Acinar inflammation and acinar cell damage are absent.

Normal-appearing biopsies are more often encountered in protocol biopsies of well-functioning grafts (17,49,51,63). An adequate biopsy (see above) with these histological characteristics essentially rules out a diagnosis of acute cell-mediated allograft rejection (ACMR). Thus, even in patients biopsied for graft dysfunction, empirical antirejection treatment has not been shown to be of clear benefit in the presence of a normal biopsy (16,17,63).

'Normal' or near-normal pancreas allograft biopsies may be also encountered under other clinical circumstances (see Table 4). Specifically, in patients biopsied for hyperglycemia, the differential diagnosis of a normal biopsy includes: (i) late phase of recurrent autoimmune disease (DM), that is, after resolution of isletitis and disappearance of beta cells (40,61); (ii) drug toxicity (41), and (iii) acute antibody-mediated rejection, as described in the case reported by Melcher et al. (26).

Indeterminate for Rejection

This category is defined by the presence of focal septal inflammation that displays features of activation (i.e. blastic' lymphocytes, variable numbers of eosinophils), but the overall features do not fulfill the criteria for mild rejection (i.e. partial cuffing of a septal vein or duct but lacking any evidence of endothelial or epithelial involvement, etc.) (Figure 1A). The clear identification of venulitis, and/or ductal inflammation and damage, even if only focal, places the biopsy in the category of grade I/Mild ACMR (see below).

Table 3: Diagnostic categories Banff working grading schema*,[a]

1. Normal. Absent inflammation **or** inactive septal, mononuclear inflammation not involving ducts, veins, arteries or acini. There is no graft sclerosis. The fibrous component is limited to normal septa and its amount is proportional to the size of the enclosed structures (ducts and vessels). The acinar parenchyma shows no signs of atrophy or injury.

2. Indeterminate. Septal inflammation that appears active but the overall features do not fulfill the criteria for mild cell-mediated acute rejection.

3. Cell-mediated rejection

Acute cell-mediated rejection

- Grade I/Mild acute cell-mediated rejection

Active septal inflammation (activated, blastic lymphocytes, ± eosinophils) involving septal structures: venulitis (sub-endothelial accumulation of inflammatory cells and endothelial damage in septal veins, ductitis (epithelial inflammation and damage of ducts). Neural/peri-neural inflammation.

and/or

Focal acinar inflammation. No more than two inflammatory foci^per lobule with absent or minimal acinar cell injury.

- Grade II/Moderate acute cell-mediated rejection

Multi-focal (but not confluent or diffuse) acinar inflammation (≥3 foci^per lobule) with spotty (individual) acinar cell injury and drop-out.

and/or

Minimal intimal arteritis

- Grade III/Severe acute cell-mediated rejection

Diffuse, (widespread, extensive) acinar inflammation with focal or diffuse multi-cellular /confluent acinar cell necrosis.

and/or

Moderate- or severe-intimal arteritis

and/or

Transmural inflammation-Necrotizing arteritis

Chronic active cell-mediated rejection. Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

4. Antibody-mediated rejection = C4d positivity** + confirmed donor specific antibodies + graft dysfunction

Hyperacute rejection. Immediate graft necrosis (≤1 h) due to preformed antibodies in recipient's blood

Accelerated antibody-mediated rejection. Severe, fulminant form of antibody-mediated rejection with morphological similarities to hyperacute rejection but occurring later (within hours or days of transplantation).

Acute antibody-mediated rejection. Specify percentage of biopsy surface (focal or diffuse). Associated histological findings: ranging from none to neutrophilic or mononuclear cell margination (capillaritis), thrombosis, vasculitis, parenchymal necrosis.

Chronic active antibody-mediated rejection. Features of categories 4 and 5.

5. Chronic allograft rejection/graft sclerosis

- Stage I (mild graft sclerosis)

Expansion of fibrous septa; the fibrosis occupies less than 30% of the core surface but the acinar lobules have eroded, irregular contours. The central lobular areas are normal.

- Stage II (moderate graft sclerosis)

The fibrosis occupies 30–60% of the core surface. The exocrine atrophy affects the majority of the lobules in their periphery (irregular contours) and in their central areas (thin fibrous strands criss-cross between individual acin).

- Stage III (severe graft sclerosis**)**

The fibrotic areas predominate and occupy more than 60% of the core surface with only isolated areas of residual acinar tissue and/or islets present.

6. Other histological diagnosis. Pathological changes not considered to be due acute and/or chronic rejection. e.g. CMV pancreatitis, PTLD, etc. (Table 4)

[a] Categories from 2 to 6 may be diagnosed concurrently and should be listed in the diagnosis in the order of their clinico-pathological significance.

*See Table 2 for morphological definition of lesions.

**If there are no donor-specific antibodies or these data are unknown, identification of histological features of antibody-mediated rejection may be diagnosed as '*suspicious for acute antibody- mediated rejection*', particularly if there is graft dysfunction.

Similarly, sparse- and inactive-appearing inflammation involving acini but not fulfilling the criteria for focal acinar inflammation described in ACMR would also fall into this category (see Tables 2 and 3).

'Indeterminate' histological features can be seen in protocol biopsies of well-functioning grafts as well as in patients biopsied for graft dysfunction. Similar to the 'borderline' category in kidney allografts, these changes might represent early as well as treated acute rejection, or alternatively might be entirely nonspecific (16,49). The treatment of patients with biopsies showing 'indeterminate' features will vary depending on the indication for biopsy, and ultimately depends on clinical judgment. In accordance with the heterogeneous nature of the 'indeterminate' histological changes, clinical response to treatment varies significantly in comparison to biopsies with definite mild ACMR that are usually responsive to treatment (9,16,17).

Table 4: Pathological changes 'other' than rejection in pancreas needle biopsies

Diagnosis	Main histological findings	Clinical presentation
Posttransplant ischemic pancreatitis	Inflammation: neutrophils, foamy macrophages. Location: septal if mild or diffuse if severe Other features: fat necrosis, edema and interstitial hemorrhage. Patchy coagulation necrosis of clusters of acinar cells may be present. No fibrosis, the septa may be expanded due to edema/fat necrosis.	Increase in amylase and lipase in serum. Decrease in urinary amylase.* Hyperglycemia if there is extensive necrosis.
Peripancreatitis/peri-pancreatic fluid collection	Inflammation: mixed (lymphocytes, plasma cells, eosinophils, neutrophils). Location: septa and periphery of lobules Other features: dissecting bundles of active fibroblastic proliferation with obliteration of septal structures, relative preservation of the center of lobules ('cirrhotic appearance')	Local or systemic infectious symptoms, abdominal pain, peri-tonitis. Peripancreatic fluid accumulation.Increase in amylase and lipase in serum.
Cytomegalovirus pancreatitis	Inflammation: mostly mononuclear. Location: septal and acinar, patchy. Other features: cytomegalovirus cytopathic changes in acinar, endothelial or stromal cells.	Increase in serum amylase and lipase. Decrease in urinary amylase.* Systemic symptoms if generalized disease. Other: Duodenal cuff perforation.
Posttransplant lymphoproliferative disorder	Inflammation: ranging from polymorphic with lymphoblasts, plasma cells, eosinophils in low-grade disease, to monomorphic, predominantly lymphoid in high-grade disease (lymphoma). Other features: lymphoid proliferation is nodular, expansive. Necrosis may be present.	Asymptomatic, or increase in serum amylase and lipase. Lymphadenopathy. Tumor mass. May coexist with acute rejection.
Bacterial or fungal infection	Inflammation: variable; acute, chronic, purulent, necrotizing (abscess), granulomatous. Location: random. Other features: same as bacterial and fungal infections in other organs.	Systemic and/or localized infectious symptoms. Peritonitis, duodenal cuff perforation. Increase in serum amylase and lipase.
Recurrent autoimmune disease/diabetes mellitus	Inflammation: islet-centered lymphocytic inflammation (isletitis). No inflammation in late stages after disappearance of beta cells. Other features: immuno-histochemical stains for insulin and glucagon demonstrate absence of insulin producing beta cells in some or all islets depending if early or late disease.	Acute or chronic deterioration in glucose metabolism with increasing need for insulin. Although not pathognomonic, islet cell auto-antibodies typically present (i.e. GAD 65, IA-2, etc.).
Acute calcineurin inhibitor toxicity	Absence of inflammation. Variable degrees of islet cell injury (cytoplasmic swelling, vacuolization, islet cell drop-out. formation of empty spaces (lacunae), apoptotic fragments). Immuno-peroxidase stains: markedly diminished staining for insulin in comparison to controls and to glucagon stain. Electron microscopy: loss of insulin dense core granules with preservation of glucagon dense core granules.	Acute hyperglycemia. High levels of cyclosporine or tacrolimus with return to normoglycemia with adjustment of drug dose or discontinuation.

*In bladder-drained grafts.

Cell-Mediated Rejection

Three grades of acute cell-mediated rejection (ACMR), grade I or mild, grade II or moderate, and grade III or severe, are defined based on the identification of specific lesions that predict progressively worse outcomes (9,15–17,60).

Intimal arteritis and necrotizing arteritis define the more severe forms of ACMR. These are less likely to respond to antirejection treatment and are known to carry an increased risk for immediate and subsequent graft thrombosis/loss and transplant arteriopathy (30). Because affected arteries are not always sampled, the presence and the extent of acinar inflammation (focal vs. multi-focal-diffuse) and the presence of acinar cell injury are also used to define the severity of ACMR because if left untreated or under-treated these findings correlate with development of fibrosis and accelerated graft loss (18).

Inflammation confined to the septa and septal structures (veins, ducts) is typically responsive to antirejection treatment and is therefore less likely to result in irreversible sequelae (9,16,60).

Mild ACMR (grade I)

This grade is defined by predominantly mononuclear septal inflammation that shows features of activation ('blastic' lymphocytes, variable numbers of eosinophils). The inflammation often extends into the sub-endothelial space of veins and inside the basement membrane of pancreatic ducts (Figure 1B and Figure 2). The inflammation can vary from septal area to area, but the presence of venulitis (see Table 2) or any degree of lymphocytic ductitis is sufficient for the diagnosis of grade I/mild ACMR. Inflammation of peripheral nerve branches coursing through the parenchyma is also a feature of rejection, although nerves are rarely sampled in needle biopsies.

Focal acinar inflammation is usually present at the interface between the septal connective tissue and the acinar lobules (e.g. periphery of the exocrine areas). Due to sampling variations, foci of acinar inflammation might be discontinuous from the septal inflammation (i.e. within 'deeper' areas of the lobules) or associated with inconspicuous septal inflammation. In such cases the diagnosis of grade I/mild ACMR depends on mild (focal) acinar cell inflammation and injury, as defined in Table 2. The acinar inflammatory foci are easily identified at low (100 ×) or medium (200 ×) magnification and the composition of the infiltrates is similar to that seen in the septa.

Biopsies with features of grade I/mild ACMR are occasionally found in patients with well-functioning grafts (63) but are significantly more common in patients with graft dysfunction (i.e. increase in serum amylase or lipase levels, or decrease in urinary amylase levels in bladder-drained grafts) (16,49–53). Response to treatment approaches 90% (16). The main histological differential diagnosis is CMV pancreatitis (64).

Moderate ACMR (grade II)

This grade can be defined by two histological features that may be identified either in isolation or concurrently.

The most common presentation consists of multiple foci (≥3 foci per lobule) of acinar inflammation with associated single-cell (individual) acinar cell injury and drop-out (Figures 3 and 4). The inflammatory foci are easily identified at low magnification, although examination at higher magnification is usually needed to exclude confluent acinar cell injury, which increases the grading to 'severe'. In other words, completely un-inflamed acinar/exocrine areas should be easily identified between the inflamed foci. Significant acinar inflammation is always associated with evidence of acinar cell injury (65), but in this grade the latter is spotty (i.e. affects only isolated acinar cells, Table 2).

Alternatively, moderate ACMR is defined by the presence of *minimal intimal arteritis*, recognized by the presence of occasional, clearly identified lymphocytes underneath the arterial endothelium (i.e. within the intima of a muscular artery) but lacking clear evidence of endothelial activation or injury (Figure 1C lower insert, and Table 2).

Biopsies with features of moderate ACMR are typically obtained from patients with graft dysfunction and response to antirejection treatment ranges from 71% to 85% (16).

Severe ACMR (grade III)

This grade is defined by three histological lesions that may be identified either in isolation or concurrently.

Severe acinar inflammation and damage are defined by confluent/diffuse (widespread, extensive) acinar inflammation with associated focal or diffuse multi-cellular/confluent acinar cell injury/necrosis (see Table 2) and (Figure 4B). The inflammation may be predominantly lymphoid or contain abundant eosinophils or variable numbers of neutrophils. Interstitial edema and/or hemorrhage signal severe tissue damage. By definition, there should be no or only rare, focal areas of completely uninflamed acinar/exocrine parenchyma (see Moderate ACMR).

Moderate-severe intimal arteritis: Alternatively, severe ACMR can be defined by easily identifiable intimal arteritis, characterized by mononuclear cells within the intima of an involved muscular artery with additional evidence of intimal injury or response to injury, such as endothelial cell hypertrophy, fibrin leakage, coating neutrophils and/or macrophages, and activation of intimal myofibroblasts, etc. (see Table 2).

Arteritis (vasculitis): Complete or partial circumferential necrosis often secondary to transmural arterial inflammatory infiltrates is also diagnostic of grade III/severe ACMR. On the other hand, arterial fibrinoid necrosis is also associated with antibody-mediated rejection (20,59). Therefore, the identification of this lesion should always trigger staining for C4d and a search for donor-specific antibodies in serum (Figure 1C, upper insert).

Each of the three lesions capable of defining grade III/severe ACMR portends a poor outcome. The short- and long-term impact to the organ will depend on the extent of acinar damage and the size and number of arteries affected by intimal arteritis or necrosis.

Confluent acinar inflammation and necrosis is invariably followed by atrophy or eventual disappearance of the exocrine component in the affected area. Changes of this nature markedly alter the micro-vascular environment of the graft on which the islets depend to maintain adequate function (13,29).

Similar to other solid organ transplants, intimal arteritis is associated with an increased risk of immediate or delayed thrombosis. This lesion is also a precursor of transplant arteriopathy (29). Transmural arteritis/vasculitis is associated with an immediate likelihood of thrombosis and secondary parenchymal infarction.

Biopsies with histological findings corresponding to this category are characteristically associated with graft dysfunction/failure, often including hyperglycemia (16,29,42). Response to antirejection treatment is poor (16,17,60).

Chronic active cell-mediated rejection

This category is defined by the presence of 'active' transplant arteriopathy (Table 2). Although rarely seen in needle biopsies due to sampling issues, this lesion is consistently present in pancreatectomies from failed grafts due to chronic cell-mediated rejection (29).

The entity of active transplant arteriopathy is included in the grading schema because according to clinical and experimental studies, this lesion appears to represent an intermediate stage between intimal arteritis and chronic transplant arteriopathy (Figure 6A). The extent of the histological changes and the amount of inflammatory infiltrates have been shown to correlate with sub-optimal immunosuppression. The identification of this lesion has potential clinical impact, as the process of ongoing cell-mediated vascular injury leading to further arterial narrowing may be halted with optimization of the immuno-suppressive regimen (66).

Antibody-Mediated Rejection (AMR)

This category is poorly characterized in pancreas transplantation. The proposed diagnostic criteria are based on inferences from the few well-documented cases reported in the literature and theoretical analogy to other organs (20,26,27,60). A broad spectrum of clinico-pathological manifestations of AMR are also recognized in the pancreas allograft ranging from fulminant graft failure in the setting of hyperacute rejection to its incidental identification in grafts with stable function.

AMR is characterized by a constellation of histological, clinical and serological features consisting of: (i) complement deposition in vessels (i.e. capillary C4d deposition) that can be accompanied by monocyte/macrophage and neutrophil margination within interstitial capillaries; (ii) graft dysfunction; and (iii) donor-specific antibodies (DSA) in serum.

AMR has been associated with hyperglycemia, suggesting that compromise of the islet micro-vasculature may play a pathogenic role different from cell-mediated injury in which the islets remain largely spared of direct immune damage (20,26,27).

Hyperacute rejection

Routine pretransplant cross-matching to rule out preformed DSA and ABO matching has virtually eliminated this catastrophic form of antibody-mediated rejection. Hyperacute rejection is characterized by extensive, vascular deposition of immune reactants (typically containing IgG), leading to intimal arteritis, arterial necrosis and thrombosis of veins, which in turn, cause widespread hemorrhagic necrosis. Allograft failure occurs immediately (typically $<$60 min) after the vascular anastomoses are completed.

Accelerated antibody-mediated rejection

So-called 'accelerated rejection' or 'delayed hyperacute rejection' is a severe form of AMR that presents clinically as an attenuated form of hyperacute rejection (Figure 5A). The histological findings are, therefore, similar (generalized immuno-globulin and complement vascular deposition, thrombosis and necrosis), but the event occurs within hours or days (rather than minutes) after revascularization of the allograft. The extent of parenchymal involvement is less diffuse in comparison to hyperacute rejection but the prognosis is equally poor. In well-documented cases of accelerated AMR, there has been retrospective documentation of existing DSA despite a negative pretransplant cross-match (29). Accelerated AMR clinically resembles graft thrombosis attributed to 'technical failure' from which it needs to be differentiated by careful histological and immuno-histochemical evaluation (C4d, immunoglobulin staining). Whereas hyperacute rejection is exceedingly rare ($<$0.01% of pancreas transplants), accelerated rejection was found in 2.5% of pancreatectomies in a clinico-pathological study (29).

Acute AMR

Acute AMR manifests typically in the first weeks posttransplantation with the development of allograft dysfunction and the appearance of DSA in the serum (26). On histological evaluation, there is generalized C4d staining of capillaries with no evidence of an underlying chronic injury (i.e. fibrosis). The reported spectrum of associated histological changes varies, from none (normal hematoxylin and eosin [H & E] histology) (26), to widespread thrombosis and parenchymal necrosis (20). Neutrophil and mononuclear cell margination (similar to capillaritis in the kidney) can be seen in association with C4d positivity in inter-acinar capillaries (20) (Figure 5B and C).

In the absence of graft dysfunction or if DSA are not found, a diagnosis of 'suspicious for acute antibody-mediated rejection' may be considered when there is extensive C4d positivity. The immediate- or long-term significance of this finding is currently unknown.

Chronic active antibody-mediated rejection

Humoral mechanisms have been clearly implicated in the development of chronic rejection (28). A diagnosis of

chronic active AMR is applied to biopsies showing features of chronic rejection/graft sclerosis, together with C4d positive staining in parenchymal capillaries. This scenario has been well described in the report of Carbajal et al. (27) (Figure 5D).

Vascular fibrinoid necrosis, with recent or organized thrombosis is supportive of ongoing antibody-mediated rejection. As in all situations in which antibody-mediated rejection is suspected, correlation with the presence of DSA is required for diagnosis (59).

Staging of Graft Sclerosis

The extent of fibrosis on pancreatic needle biopsies correlates with graft survival. The progression of graft sclerosis over time is well documented, particularly in patients with repeated rejection episodes (67). The progressive nature of pancreatic fibrogenesis lends itself to the application of a histological staging schema. Three stages are defined based on the identification of <30%, 30–60% and >60% of fibrosis in the biopsy core (stages I-III, respectively) with corresponding atrophy of the lobular parenchyma directly correlating with the extent of septal fibrosis. In stage I, most of the acinar lobules are preserved and only show focal erosion and irregularities of their contours. With progression of the fibrosis, as is seen in stage II, exocrine atrophy affects the majority of the lobules both in the peripheral (irregular contours) and central areas (Figure 6B). The latter change is best appreciated in collagen stains that show thin fibrous strands crisscrossing between individual acini. Stage III is characterized by diffuse fibrosis with near total or complete absence of functional parenchyma. The proposed staging schema has been shown to be reproducible in needle core biopsies and has significant prognostic value (67).

Transplant arteriopathy (arterial fibrointimal thickening with luminal narrowing) closely parallels the degree of fibrosis. When transplant arteriopathy is identified, this should be graded as mild, moderate or severe using the same morphological criteria applied to kidney biopsies (i.e. Banff cv1–3, Table 2) (68). Despite their major physio-pathological importance, the vascular lesions are not used for staging, because vascular disease is under-represented in needle biopsies (18,29). Similarly, evaluation of endocrine islets is not used for grading because their disappearance does not follow a predictable course in relationship to the overall degree of graft fibrosis (25,67).

Inflammatory infiltrates associated with ongoing acinar cell injury, venulitis and/or intimal arteritis and ductal inflammation indicate active ACMR that should be graded independently based on the key histological features specified above.

Other Histological Diagnosis

Given that acute rejection episodes have become less common under current immuno-suppressive protocols, a variety of other pathological processes are often encountered in pancreas biopsies from patients with graft dysfunction. These include infections, recurrence of autoimmune disease, or graft sclerosis/chronic rejection that may be identified in isolation or concurrently with other diagnostic categories in the schema (Figure 7; Table 4).

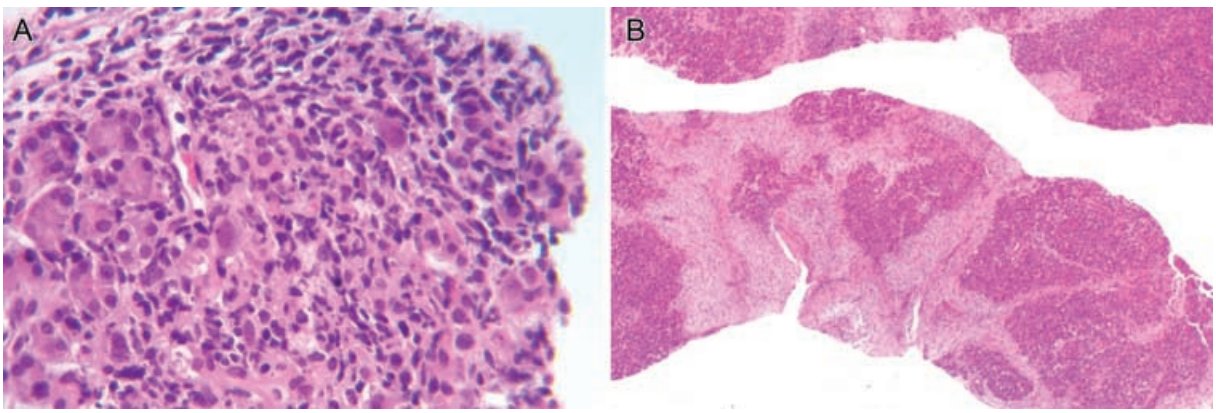

Figure 7: Other pathological processes. (A) Focus of CMV pancreatitis, with acinar inflammatory infiltrates resembling acute cell-mediated allograft rejection. Two cells with viral cytopathic changes (left of center and right above center) have large ground glass nuclei and abundant cytoplasm. (B) Peri-pancreatitis/peri-pancreatic fluid collection occurring in the early posttransplantation period is in the histological differential diagnosis of acute rejection. The pancreatic septa are expanded by an active fibroblastic proliferation that contains mixed inflammation. The septal inflammation and fibrosis push the acinar lobules apart and erodes their periphery, but their central areas are typically not affected (see also Figure 6B).

Concluding remarks

This work summarizes the current knowledge on pancreas allograft pathology and represents the clinical and histopathological cumulative experience of a large number of pancreas transplant centers. Purely morphological classifications of rejection such as this one, are limited by our insufficient understanding of the mechanisms and pathways of allograft injury (69). On the other hand, the availability of generally accepted morphological definitions is an absolutely necessary condition for any further investigational or clinical progress in pancreas transplantation.

The current 'working grading schema' provides specific diagnostic guidelines that should allow for a more accurate diagnosis of rejection, encourage the use of pancreas graft biopsies and should result in improved pancreas transplantation outcomes.

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