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Meeting report

Banff 2022 pancreas transplantation multidisciplinary report: Refinement of guidelines for T cell–mediated rejection, antibody-mediated rejection and islet pathology. Assessment of duodenal cuff biopsies and noninvasive diagnostic methods

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Abbreviations: AI, artificial intelligence; AMR, antibody-mediated rejection; AR, acute rejection; C4d, complement component 4d; CD3, cluster of differentiation 3; CD68, cluster of differentiation 68; CIN, calcineurin inhibitor; CMV, cytomegalovirus; dd cf DNA, donor-derived cell-free DNA; DGF, delayed graft function; DM, diabetes mellitus; dnDSA, de novo donor-specific antibody; DSA, donor-specific antibody; GEP, gene expression profiles; HbA1c, hemoglobin A1c; IAC, interacinar capillaries; Igls criteria, combination of elements used to define outcomes of β-cell replacement therapy; PAK, pancreas after kidney transplant; PNF, primary graft nonfunction; PTA, pancreas transplant alone; PTLD, posttransplant lymphoproliferative disorder; PTxBx, pancreas transplant biopsy; SPK, simultaneous pancreas and kidney transplant; T1DR, type 1 diabetes mellitus recurrence; TCMR, T cell–mediated rejection; TF, technical failures.

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ABSTRACT

The Banff pancreas working schema for diagnosis and grading of rejection is widely used for treatment guidance and risk stratification in centers that perform pancreas allograft biopsies. Since the last update, various studies have provided additional insight regarding the application of the schema and enhanced our understanding of additional clinicopathologic entities. This update aims to clarify terminology and lesion description for T cell–mediated and antibody-mediated allograft rejections, in both active and chronic forms. In addition, morphologic and immunohistochemical tools are described to help distinguish rejection from nonrejection pathologies. For the first time, a clinicopathologic approach to islet pathology in the early and late posttransplant periods is discussed. This update also includes a discussion and recommendations on the utilization of endoscopic duodenal donor cuff biopsies as surrogates for pancreas biopsies in various clinical settings. Finally, an analysis and recommendations on the use of donor-derived cell-free DNA for monitoring pancreas graft recipients are provided. This multidisciplinary effort assesses the current role of pancreas allograft biopsies and offers practical guidelines that can be helpful to pancreas transplant practitioners as well as experienced pathologists and pathologists in training.

1. Introduction

Currently, pancreas transplantation is the only available treatment leading to durable euglycemia in selected patients with insulin-dependent diabetes mellitus. Following transplantation, patients may demonstrate stabilization/reversal of diabetic complications, improved quality of life, and survival.[1-5]

The pancreas Banff schema provides guidelines for the diagnosis and treatment of T cell–mediated rejection (TCMR) and antibody-mediated rejection (AMR) and facilitates graft

loss risk stratification.[6-11] Nevertheless, pancreas transplant biopsies (PTxBx) remain underutilized due to misperceptions regarding a high risk of complications and difficulty in safely obtaining adequate tissue.[12] The small number of PTxBx has fostered the view that interpretation is difficult and clinical correlations uncertain.

The success of pancreas transplantation demands a team approach with collaboration between the medical-surgical team that will decide treatment interventions and the pathologists that interpret PTxBx.[4,13-23]

This report presents progress in areas related to pancreas graft histopathology as discussed at the Banff session on September 21, 2022, reflects extensive discussions by the pathology working group, and incorporates input sought from the wider pancreas transplant community.

1.1. Indications for PTxBx

Careful donor and recipient selection, potent immunosuppression, and systematic posttransplant monitoring have helped improve outcomes. Nevertheless, the incidence of allograft rejection remains significant, according to reports from the International Pancreas Transplant Registry and the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients .[24,25] Immunologic loss is higher following solitary pancreas transplantation, including the pancreas transplant alone (PTA) and sequential pancreas after kidney (PAK) categories. However, even in simultaneous kidney-pancreas transplants (SPK) after the first year, acute and/or chronic rejection are the major causes of death-censored graft loss (15% and 28%, respectively).[24,25] PTxBx remains the gold standard to confirm active rejection, as neither serologic blood tests nor radiological imaging are diagnostic.

International guidance for metabolic and immunologic monitoring, including indications for PTxBx, has recently been published.[12,19]

Performance of a PTxBx is strongly recommended when there is exocrine graft dysfunction or clinical suspicion of rejection to establish a diagnosis and tailor treatment.[6,12,19,23,26,27] In SPK transplantation, kidney biopsies play an important role, but PTxBx are indicated when there is pancreas dysfunction and particularly when the kidney biopsy is negative.[28] Discordant rejection in SPK transplantation occurs in 26% to 37% of cases.[15,18,29,30] PTxBx are also indicated in patients with recurrent hyperglycemia and/or increasing hemoglobin A1c (HbA1c) levels to identify islet pathology, particularly when the graft is not small (fibrotic/atrophic) on imaging.[11,31]

1.2. Surveillance or protocol biopsies

Surveillance PTxBx are used to monitor PTA and PAK transplants in $<$ 30% of centers[12,32-36] and may be useful for patients with donor-specific antibodies (DSA).[37] Outcomes with PTxBx performed at 4 months and 1 year highlighted the impact of subclinical and acute rejection (AR) on graft failure.[9]

1.3. Clinical correlations

For all PTxBx, it is important to emphasize the importance of clinicopathological correlations. Consideration of the clinical presentation can improve pathologic diagnostic accuracy and result in feedback that is more meaningful to the clinical care team (Table 1).

2. 2022 update to the Banff diagnostic categories

The reevaluation of the diagnosis and grading schemas had the main purpose of making them more comprehensive and easier to apply in the diagnostic setting. Table 2 presents the current updated working schema. For the most recent updates, visit https://banfffoundation.org/central-repository-for-banff-2019-resources-3/

2.1. Category 3–TCMR

- A subsection on chronic active TCMR was added to recognize the continuum between ongoing TCMR and evolving graft fibrosis (Fig. 1). This subsection also provides the basis for a more accurate diagnosis of chronic rejection vs graft fibrosis of a different or unknown etiology.

2.2. Category 4 –AMR

- The diagnosis of AMR was initially based on limited experience and using features of AMR in the kidney.[22] Subsequently, several groups have confirmed their usefulness for PTxBx.[6,8,15-18,37-40] In the current update, the diagnosis of AMR remains founded on the presence of microvascular inflammation/injury , documented DSA, and complement component 4d (C4d) positivity. However, it is recognized that biopsies with only 2 features of AMR are not uncommon, typically prompting therapeutic interventions.[8,37,38,41] Although C4d positivity is associated with inferior graft outcomes, C4d staining appears to be less reliable than the identification of microvascular inflammation/injury together with documented DSA.[8,38,41] Based on current clinical practices and reflecting the consensus discussions for the 2022 kidney update, the category "suspicious" is replaced by "probable" active AMR, for cases with incomplete AMR features (2 out of 3). The relative importance of each of the 3 components has not been determined for the pancreas; however, the presence of microvascular inflammation objectively reflects a morphologic abnormality that requires further investigation and follow-up.

- The presence of DSA (particularly class II), is associated with an increased incidence of rejection of all types (TCMR, AMR, and mixed), also conferring a greater risk of graft failure.[41] A footnote that applies to all rejection categories is added, to emphasize the importance of recognizing mixed rejection (TCMR + AMR),[39,40-42] and also listing the main features of each rejection type.[43]

- Chronic active AMR is also added to category 4, with the specific features listed in Table 2 and Figure 2.

Table 1
Clinical information potentially useful for the pathologic evaluation[a].

Information	Rationale
Time post transplant	Septal chronic inflammation is more common in long-term transplants. Ischemic injury/peripancreatic reaction is more common in the first few weeks posttransplant.
Reason for biopsy	Surveillance vs increased enzymes (acute, persistent, fluctuating), hyperglycemia, and so on will prompt consideration of other differential diagnoses and/or special studies.
Presence of DSA and history of DSA	Search for subtle features of antibody-mediated rejection and the possible use of ancillary stains.
Immunosuppression: Optimal vs suboptimal	In addition to rejection, lower immunosuppression can lead to subtle or unusual patterns of inflammation.
Previous rejection/previous treatment	Residual inflammation may persist weeks or months after rejection treatment; accurate information may help categorize active vs residual inflammation.
Peripancreatic infection/fluid collection	Acute and chronic phases can lead to inflammation and fibrosis in the more superficial parenchyma and require differentiation from T cell–mediated rejection (TCMR) and chronic rejection.
Cytomegalovirus (CMV) viremia	May prompt the use of deeper sections or CMV stains for differentiation from TCMR.
SPK: kidney rejection, BK nephropathy	Information regarding the pair organ can help interpret pancreatic pathology.
Imaging studies: Small vs normal-size graft	A biopsy showing a fibrotic graft from a graft of normal size may suggest a sampling error. Pancreas enlargement/mass may represent an infiltrative process (eg, PTLD, tumor, or cyst).

DSA, donor-specific antibody; SPK, simultaneous pancreas and kidney transplant; PTLD, posttransplant lymphoproliferative disorder.
[a] This is not meant to be a complete list of clinical scenarios, but it exemplifies the type of information that, when available and shared with the pathology team, can facilitate the pathology evaluation.

2.3. Previous category 5

- Chronic allograft arteriopathy, defined as "arterial intimal fibrosis with mononuclear cell infiltration in fibrosis,"[44] is now incorporated into the chronic active TCMR and AMR descriptions. Chronic allograft arteriopathy is more common in pancreatectomies from failed grafts with chronic or ongoing rejection (TCMR or AMR).[44-46] Active and chronic arterial changes may be caused by both TCMR and AMR.[47-52]

3. Rationale for the evaluation of cluster of differentiation 3 (CD3) and cluster of differentiation 68 (CD68) stains to determine the extent and pattern of inflammation

From a practical point of view, inflammation in the pancreatic septal connective tissue and septal structures (veins, ducts, and arteries) and in atrophic exocrine lobules is easily identified on routine hematoxylin and eosin staining. In contrast, assessment of mononuclear inflammatory infiltrates in well-preserved, tightly packed acinar glandular tissue may be difficult. Accurate and timely identification of acinar inflammation is essential to preventing the development of lobular fibrosis. Accordingly, the extent and severity of lobular inflammation/acinar cell damage are essential for grading TCMR in the Banff schema.[21,22] The CD3 and CD68 immunostains can help estimate the density and distribution of T cells and monocytes/macrophages against the background staining.[53]

In preliminary studies, the extent of CD3 staining in acini correlated linearly with the presence and severity of TCMR, whereas the absence of TCMR had no or minimal CD3 staining. Furthermore, the cumulative load of acinar T cells and macrophages correlates with an incremental risk of graft failure.[53] The contribution of CD68 staining to the diagnosis of early or mildly active AMR was discussed previously.[22]

Currently, 50% of the pathologists in the pancreas working group use CD3 (pan-T cell) and CD68 (monocyte/macrophage) immunostains routinely or for difficult cases to more accurately assess the amount and distribution of the inflammatory infiltrates.

The pathology working group recommends that the diagnosis and grading of rejection remain based on the evaluation of routine stains and the application of the Banff working schema. Careful evaluation of the acinar parenchyma with an assessment of the extent of inflammation and associated acinar cell injury is essential for the grading of TCMR and the recognition of early AMR. CD3 and CD68 stains can be helpful in ambiguous cases, particularly with inconspicuous lobular mononuclear infiltrates, and for discrimination from nonrejection related processes (Figs. 1 and 3).

Systematic analysis of CD3 and/or CD68 scoring in PTxBx to determine whether these are clinically useful is a main area of future research (Table 3).

3.1. Category 5—graft sclerosis

This category provides guidelines for assessing the degree of fibrosis (stage), as this carries important prognostic impli-

Table 2
Banff pancreas allograft rejection grading schema—2022 update diagnostic categories[a,b].

1. **Normal**

- Absent inflammation or inactive focal, septal, or mononuclear inflammation (small lymphocytes only), not involving ducts, veins, or arteries.
- There is no graft fibrosis. 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 inflammation, acinar cell injury, or atrophy.

2. **Indeterminate**[c]

- Septal inflammation that appears mostly inactive but is multifocal or has isolated features of activity (eg, focal activated lymphocytes and focal eosinophils). There is no venulitis or ductitis.[d]

3. **T cell–mediated rejection**[c]

Mild active T cell–mediated rejection/grade I

- Active septal inflammation (activated, blastic lymphocytes, ± eosinophils) involving septal structures as indicated by venulitis (perivenular inflammation/cuffing and venous endothelitis in septal veins, subendothelial accumulation of inflammatory cells and endothelial injury, activation, swelling, and/or lifting) and/or ductitis (epithelial inflammation and ductal epithelial injury, reactive features, disarray, sloughing).

and/or

- Focal acinar inflammation. No more than 2 inflammatory foci per lobule with absent or minimal acinar cell injury.

Moderate active T cell–mediated rejection/grade II [b]

- Multifocal (but not confluent or diffuse) acinar inflammation (≥ 3 foci per lobule) with spotty (individual) acinar cell injury and drop-out, focal encroachment by lymphocytes, replacement of acinar cells by inflammation, and/or incipient fibrosis. Active septal inflammation, as in grade I, is often present.

and/or

- Mild intimal arteritis/arterial endothelitis (with minimal, < 25% luminal compromise) with any degree of septal and/or lobular inflammation.

Severe active T cell–mediated rejection/grade III [b]

- Diffuse, widespread, and extensive acinar inflammation with focal or diffuse multicellular/confluent acinar cell necrosis. Active septal inflammation, as described for grade I, is often present.

and/or

Moderate or severe intimal arteritis/arterial endothelitis (> 25% luminal compromise) with or without transmural inflammation/necrosis with any degree of septal and/or lobular inflammation

Chronic active T cell–mediated rejection

Defined as ongoing inflammation in acini and/or ducts and/or arteries with features of chronic injury, fibrosis, or remodeling.

- Predominantly mononuclear inflammation in fragmented acini with increased interacinar fibrosis. Overall, ≥ stage 1 graft fibrosis is required.
- Ductal inflammation in ducts with periductal fibrosis and/or degenerative atrophic or metaplastic epithelial changes.
- Chronic transplant arteriopathy: arterial intimal fibrosis with mononuclear cell infiltration in fibrosis (typically T cells ± macrophages).

Concurrent active T cell–mediated rejection should be separately diagnosed and graded as per guidelines, and listed as the primary diagnosis because it may be amenable to treatment.[b]

4. Antibody-mediated rejection (AMR, see diagnostic components below*)

Active antibody-mediated rejection

*Confirmed circulating donor-specific antibody

*Morphologic evidence of active tissue injury (interacinar inflammation/capillaritis, acinar cell damage, swelling/necrosis/apoptosis/drop-out, vasculitis, thrombosis)

*C4d positivity in interacinar capillaries (IAC, ≥1% of acinar lobular surface) [e]

(*continued on next page*)

Table 2 (*continued*)

- **Active AMR** 3 of 3 diagnostic components.*
- **Probable active AMR** 2 of 3 diagnostic components.*
- Heightened clinical vigilance and exclusion of AMR are recommended when only 1 diagnostic component* is present.

Guidelines for histologic grading of active AMR

Grade I/mild: Well-preserved architecture, mild monocytic/macrophagic, and/or neutrophilic infiltrates with rare acinar cell damage.

Grade II/moderate: Overall preserved architecture with obvious monocytic/macrophagic, and/or neutrophilic infiltrates with multicellular acinar cell damage. Capillary dilatation, capillaritis, congestion, and extravasation of red blood cells.

Grade III/severe: Architectural disarray, scattered inflammatory infiltrates in a background of interstitial hemorrhage, multifocal parenchymal necrosis, arterial and venous necrosis, and thrombosis.

Chronic active antibody-mediated rejection

*Morphologic evidence of active (as above) and chronic tissue injury with evolving parenchymal fibrosis (≥ stage I graft fibrosis) and/or vascular changes indicating thrombosis, recanalization, vascular remodeling, and/or chronic transplant arteriopathy.

*Confirmed circulating DSA.

*C4d positivity in interacinar capillaries (≥ 1% of acinar lobular surface).

- **Chronic active AMR:** 3 of 3 diagnostic components*
- Probable chronic active AMR: 2 of 3 diagnostic components*

5. **Graft fibrosis**[f]

- **Mild graft fibrosis/stage**

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

- **Moderate graft fibrosis/stage II**

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 crisscross between individual acini).

- **Severe graft fibrosis/stage III**

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

6. **Islet pathology**[g]

- **Islet injury due to parenchymal ischemia.**
- **β cell injury due to calcineurin inhibitors toxicity.**
- **Recurrence of autoimmune DM**
  - Insulitis
  - Selective β cell loss
- **Features of type 2 DM**
  - Islet amyloid deposition
- **Nonspecific reactive/regenerative changes**
  - Nesidioblastosis
  - Islet hyperplasia

7. **Other histologic diagnosis.** Pathologic changes are not considered to be due to active and/or chronic rejection. eg, peripancreatic reaction, ductal issues, cytomegalovirus pancreatitis, posttransplant lymphoproliferative disorder, and others.

For most updated version, see Banff website: https://banfffoundation.org/central-repository-for-banff-2019-resources-3/.
DM, diabetes mellitus.

[a] Sample adequacy: 3 lobular areas and associated septal connective tissue. The report should state the number of lobular areas and mention whether arteries are present or absent. Recommended stains are hematoxylin and eosin (H&E), trichrome, and C4d. Section thickness: 4 μm.

[b] The diagnostic categories can be used concurrently as applicable and should be listed in the pathology report according to their clinico-pathologic significance/severity. When mixed active TCMR and AMR are identified, it is necessary to estimate the degree of activity (mild, moderate, or severe) for each process and also

indicate the extent of overall fibrosis (stage). histologic features favoring active TCMR are septal infiltrates, eosinophils, venulitis, ductitis, and mononuclear acinitis. Histologic features favoring active AMR are Neutrophilic acinar or septal infiltrates, capillaritis, necrotizing vasculitis, interstitial hemorrhage, and hemorrhagic necrosis.

[c] CD3 and CD68 immunostains can highlight differences in the composition and distribution of T cells and monocytes/macrophages. This may be helpful for the diagnosis and grading of rejection and to distinguish other pathologic processes, particularly when the routine light microscopy findings are ambiguous.

[d] Patchy perivenular mononuclear inflammation with no endothelial involvement and/or rare intraepithelial lymphocytes in an otherwise unremarkable duct are not sufficient to diagnose rejection.

[e] Findings in all published studies are based on C4d immunohistochemical staining. C4d immunofluorescence staining could be more sensitive based on studies in other organs, but systematic studies in pancreas transplant biopsies are not available.

[f] This category provides guidelines for the assessment of fibrosis independently of the etiology of scarring; however, rejection is the most common case of graft fibrosis (chronic rejection). When features of TCMR or AMR are identified, the diagnosis is to be made according to specified guidelines. In the absence of specific features, a descriptive diagnosis can be used.

[g] Evaluation of insulin and glucagon immunostains is required in most instances for the evaluation of islet pathology. The vast majority of adequate percutaneous biopsies contain islets. Insulin/glucagon stain may highlight islets that are not recognized on H&E stain. Normal insulin and glucagon staining are common in some forms of graft dysfunction (eg, insulin resistance, progressive graft fibrosis, and others).

cations.[54] Morphologic criteria for semiquantitative evaluation of graft scarring are based on the identification of progressive fibrosis with replacement of the normal parenchyma.[21,24,54-56]

Histologic examination of failed grafts is only performed when a graft pancreatectomy is deemed clinically necessary.[38,45,57-60] In the absence of pathologic evaluation, a presumed diagnosis of chronic rejection is often made based on clinical findings, particularly when the graft appears small/sclerotic on imaging studies.[11,31,61] Although rejection is by far the most common cause of graft atrophy, in rare cases, the fibrosis can be attributed to other causes, including thromboembolic or ischemic complications, as well as other processes such as previous infections.[45,62]

Chronic rejection is histologically defined as progressive fibrosis/scarring resulting from persistent, repeated, or untreated allograft rejection.[54] At the time of histologic evaluation, chronic rejection can be inactive; previous history of rejection episodes or suboptimal immunosuppression supports a diagnosis of chronic rejection. In the absence of specific diagnostic features or a lack of clinical history consistent with chronic rejection, the noncommittal term graft sclerosis should be used.

Even in grafts that have clinically lost endocrine function, irregularly shaped islets with both insulin and glucagon-producing cells often remain within the fibrous tissue. In some patients, graft function may persist for some time despite significant parenchymal fibrosis.[63]

3.2. Category 6—islet pathology

The development of diagnostic criteria for this category has progressed slowly due to the limited number of PTxBx done solely for hyperglycemia. Timely diagnosis of the cause of islet insufficiency may allow for the development of interventions to prevent or delay failure.

After successful pancreas transplantation, insulin therapy is discontinued and glucose metabolism is normalized.[64-67] On the other hand, organs with partial function may still provide clinical benefits. The Igls criteria propose 4 levels of graft function status: optimal, good, marginal, and failure, by evaluating HbA1c and C-peptide levels, severe hypoglycemia events/year, and total daily insulin requirements.[68,69]

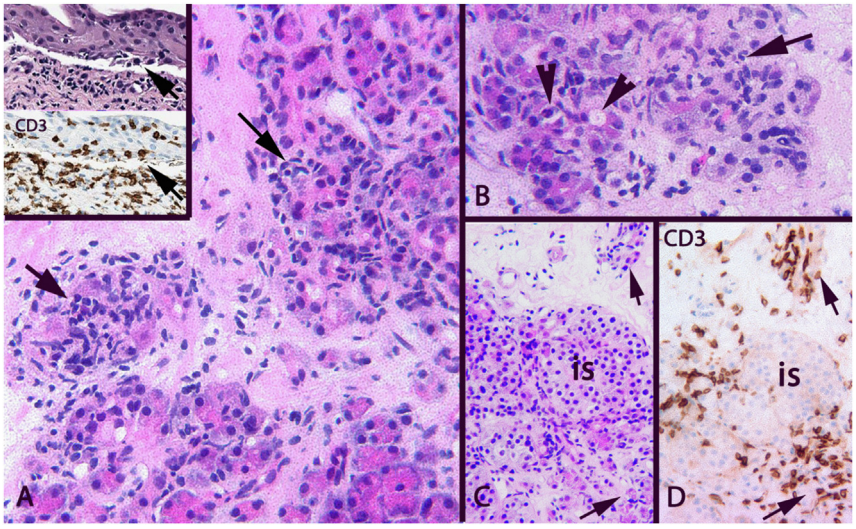

Figure 1. Chronic active T cell–mediated rejection (TCMR). (A and B) Septal and interacinar fibrosis with mononuclear inflammation predominantly around the acini (arrows). Arrowheads mark acinar cell injury/loss. Top inset: Chronically injured pancreatic duct with detachment from the subepithelial area (arrows). Both the epithelium and the underlying connective tissue show prominent T cell infiltrates (CD3 stain). (C and D) Inflamed, atrophying acini with interacinar fibrosis. The CD3 stain highlights the T cell infiltrates. Note that the islet (is) has proportionally minimal inflammation; islets are not primarily targeted by active TCMR.

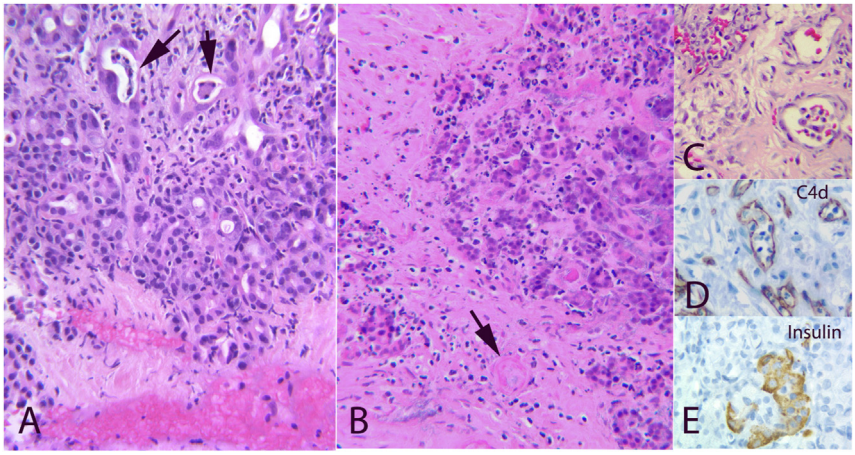

Figure 2. Chronic active antibody-mediated allograft rejection. (A) Evolving fibrosis surrounding partially atrophic acini with mixed infiltrates, including neutrophils in the interstitium, and focal congestion/hemorrhage (lower area). Degenerated acini with desquamated cells can be present and should be differentiated from capillaritis (arrows). (B) Atrophic acini in areas of evolving fibrosis. The arrow marks a small vessel with organized thrombosis. (C and D) Distended capillaries with clusters of luminal inflammatory cells (capillaritis) marked with the C4d stain. (E) Insulin stain highlights β cells in residual distorted islets.

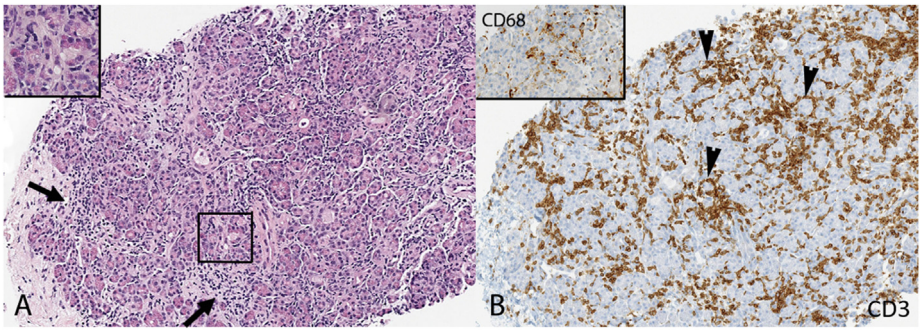

Figure 3. Immunohistochemical findings in T cell–mediated rejection (TCMR) assessment of the extent and density of inflammatory infiltrates. (A) Hematoxylin and eosin stain of a pancreas needle biopsy with mononuclear inflammation in the septal (arrows) and acini. The inset shows distortion of the acinar organization and spotty cell loss. (B) The CD3 stain highlights the T cell infiltrates. Prominent acinar inflammation and associated acinar cell damage are consistent with moderately active TCMR (Banff II). Multifocal encroachment of acinar cells by T cells (arrowheads). Inset: The CD68 stain demonstrates clusters of monocytes/macrophages that are less pronounced in the same sample.

For practical purposes, most patients with islet dysfunction after transplantation fall into one of the following 4 categories:

1. Early posttransplant dysfunction/failure: Delayed graft function (DGF) and primary nonfunction (PNF)

Graft dysfunction after a technically successful, well-vascularized transplant may resolve after a period of time (DGF) or may persist permanently (PNF). Criteria defining DGF and PNF have been proposed.[25,64,66,67]

PNF occurs in 0.5% to 4% of all pancreas transplants,[58,70] and, together with technical failure, is the main cause of graft loss in the first 3 months posttransplant.[24] Regarding DGF, the reported incidence varies significantly.[64,67]

In the absence of rejection, DGF and PNF in the pancreas are often related to ischemic injury-triggering changes akin to those seen in DGF and PNF in the kidney.[71]

Histologic studies of pancreas graft PNF are limited because, unless active rejection is suspected, these organs are not usually biopsied.

A few reported cases of PNF[72] and DGF[73] showed ischemic/degenerative changes that involved all pancreatic compartments, including acinar cells, ductal epithelium, and islet cells (see below for ischemic features). Both insulin- and glucagon-producing cells are present in these cases, albeit showing features of cellular injury (Fig. 4).

2. Islet dysfunction/failure accompanying active rejection

Hyperglycemia may be present in patients with active rejection.[73,74] Islets are not specifically targeted by the alloimmune process,[75-82] but islet inflammation, islet cell damage, and occasional islet necrosis may occur in TCMR and AMR to a degree proportional to the severity of AR. In mild (Banff I) TCMR with predominant septal infiltrates, the islets are not affected. When there is islet inflammation in moderate and severe TCMR (Banff II and III), typically characterized by prominent acinar inflammation, the islet infiltrates have the same composition as the surrounding acinar infiltrates.[81,83] Similarly, in AMR, microvascular inflammation, capillaritis, and hemorrhagic necrosis (in severe cases) may involve all tissue components, including the islets.[22] Both insulin- and glucagon-producing cells are found in islets from cases affected by TCMR and AMR, although heterogeneous abnormalities can be observed correlating with the overall degree of tissue injury.

3. Islet dysfunction/failure due to progressive graft fibrosis/chronic rejection

Severe or persistent TCMR leads to graft fibrosis.[30,84-86] Progressive scarring leads to irreversible distortion and obliteration of the vascular milieu that supports endocrine function, resulting in graft failure.[7,45,54,55,85,86-90] Less commonly, evolving AMR also results in progressive graft fibrosis following damage and eventual destruction of the microvasculature.[22,91]

4. Islet dysfunction/failure in the absence of allograft rejection or fibrosis

A proportion of patients return to a state of diabetes requiring insulin or antidiabetic agents months or years after pancreas transplantation. Several donor and recipient risk factors have been identified, but the etiology appears to be heterogeneous.[92-95] Hyperglycemia in these patients is secondary either

Table 3
Future research directions.

Topic	Issues to address	Required evidence	Research plan
Surveillance biopsy	Incidence of subclinical rejection	Ideal timing toward the performance of surveillance biopsies	Standardization of protocol biopsies between centers could provide further evidence of the ideal timing to perform these biopsies
	Impact on graft outcomes	Impact on long-term graft survival	
Histologic classification	AMR C4d is negative.	Impact of C4d negative AMR on graft outcomes (with and without DSAs)	Retrospective cohort analysis (single or multicenter)
	CD3 and CD68 immunohistochemistry	Histologic scoring of CD3 and/or CD68 positive immunohistochemistry staining	Retrospective cohort analysis (single or multicenter)
Blood-based molecular biomarkers (dd-cfDNA/ GEP)	Utility for longitudinal pancreas graft monitoring	Superiority to the current standard of care (amylase/lipase/glucose)	Multicenter prospective randomized clinical trial
	Between organ discrimination (in PAK)	Ability to discriminate between pancreas and kidney graft rejection in PAK	Large prospective clinical trial
Graft transcriptomics	Active rejection gene signatures	Identification of active rejection gene signatures with impact on graft outcome (response to treatment/survival)	Retrospective cohort analysis
Digital pathology/ artificial intelligence (AI)	Standardization of graft classification	Ability of AI for automated histologic classification	Multicenter centralized scanned biopsy slides

AMR, antibody-mediated rejection; dd-cfDNA, donor-derived cell-free DNA; DSA, donor-specific antibodies; GEP, gene expression profiles; PAK, pancreas after kidney.

to inadequate production of insulin by the transplant (ie, β cell injury or loss) or to excessive insulin requirements leading to β cell dysfunction (ie, insulin resistance or weight gain).[96,97]

Calcineurin inhibitor (CNI) islet toxicity is associated with β cell injury, most commonly occurring in the first year posttransplant, in patients with high levels of either cyclosporine or tacrolimus.[98] The islet cell abnormalities are limited to the β cell population and show cytoplasmic clearing and vacuolization on light microscopy, weak insulin staining, and paucity of secretory granules; cytoplasmic swelling is observed on electron microscopy.[98] The glucagon stain marks well-preserved α cells.

The histologic and clinical abnormalities in CIN toxicity may be reversible with a reduction or discontinuation of the drug. Selective β cell injury in CNI toxicity contrasts with the ischemic changes that affect all cell types and can spontaneously resolve over time (Fig. 4).

Type 1 diabetes mellitus recurrence (T1DR)

The first cases of T1DR were recognized by Sibley et al[99] and Sutherland et al[100] but a more complete understanding of this entity comes from seminal studies at the University of Miami.[101-103] In one study, T1DR was identified in 2.5% of SPK transplant recipients.[104]

PTxBx in T1DR generally exhibits insulitis (inflammatory damage of the islets), the typical lesion of type 1 diabetes. The active destructive phase, consisting of insulitis with progressive and selective loss of β cells, is transient and may be patchy. Paradoxical areas of prominent insulin staining can result from attempts at β cell regeneration.[105] Due to the lack of findings of rejection or fibrosis, the pancreas and islets in the inactive phase (after disappearance of β cells and associated insulitis) may look superficially normal on routine stains.[106] The diagnosis requires immunohistochemical demonstration of lack of insulin-producing cells in the islets.[100,102,106,107] After a prolonged period of time, the islets as a whole can disappear.[87,99] Most but not all patients experience seroconversion for multiple islet antigen-specific autoantibodies and islet autoantigen-specific memory T cells that have been identified in the peripheral blood, pancreas allograft, and peripancreatic lymph nodes.[103,107-110] Diagnosis of insulitis can be facilitated by CD3 immunostaining showing inflammation circumscribed to the islets (mononuclear cuffing and intraislet infiltrates), whereas the exocrine tissue overall has insignificant inflammation (Fig. 5).

Development of type 2 diabetes

A more common but multifactorial presentation resembles type 2 diabetes with insulin resistance and associated β cell failure.[111] This process is often associated with amyloid deposition and degenerative changes in islets.[112] The specific phenotype is difficult to characterize morphologically as the changes are progressive, amyloid can be present before islet dysfunction is clinically manifested, and the β cell changes are poorly defined.[111,113,114] Amyloid is best demonstrated with the Congo red stain or using electron microscopy (Fig. 5).

Table 4 lists the main clinicopathological features of islet dysfunction after pancreas transplantation.

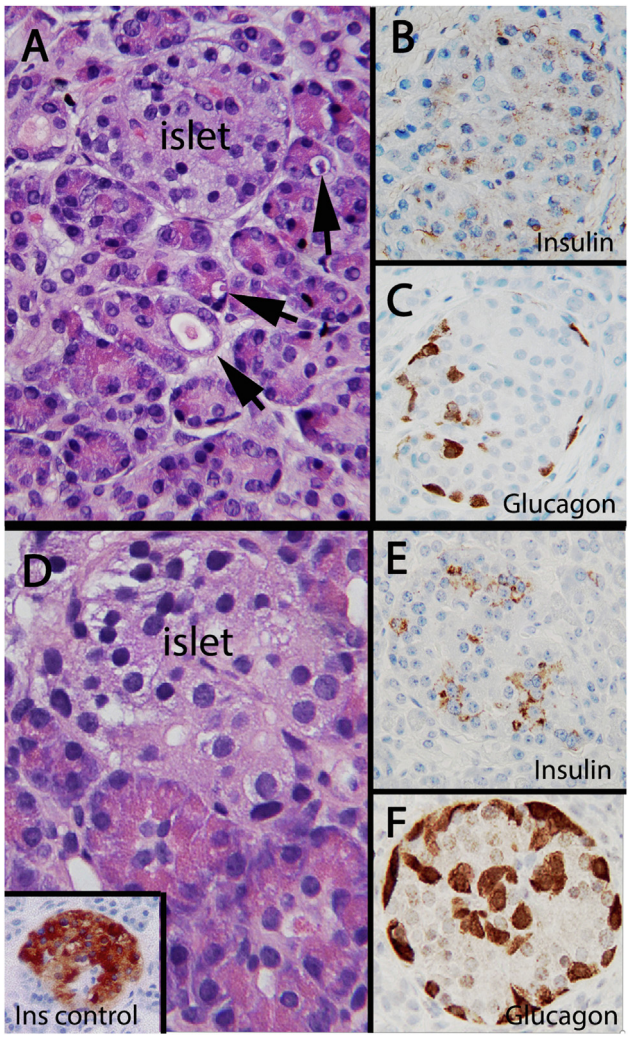

Figure 4. Ischemic graft injury (A, B, and C) and CIN islet toxicity (D, E, and F). (A) Generalized graft injury involves islets and exocrine tissue in patients with ischemic graft dysfunction. Exocrine ischemia appears most commonly with microcystic degeneration in the acini (lower arrow) as well as more subtle cell loss/apoptosis in individual acinar cells (middle and upper arrows). The islets show various degrees of islet cell vacuolization, often staining paler than normal. (B and C): Ischemic injury affects the totality of the islet cells. (B) Insulin and (C) glucagon stains demonstrate diminished insulin and glucagon secretion in both β and α cells (compare with D inset and F showing normal staining for insulin and glucagon, respectively). (D) Islet cell vacuolization and clearing, but without significant changes in the acini, characterize β cell injury in calcineurin inhibitor toxicity. Inset: Insulin staining in a control sample for comparison. (E) insulin shows very weak, spotty staining. (F) Glucagon stain marks α cells with expected strength and distribution.

Other nonspecific reactive reparative islet changes

In grafts that have lost function secondary to chronic rejection, normal or fragmented islets, as well as clusters of enlarged islets (hyperplasia), may be present. Although both insulin- and glucagon-producing cells are found in the residual islets, the atrophic/fibrotic parenchyma lacks the supportive microvasculature necessary for effective endocrine function.

Insulin- or glucagon-producing cells located within the ductal epithelium (nesidioblastosis) are found in approximately 4% of biopsy samples. These changes have no clear clinical correlation and likely represent a reactive/regenerative change after graft injury.[81,82]

Small pale acinar nodules, also representing a reactive/regenerative change in exocrine lobules, can resemble islets architecturally, but careful evaluation reveals their acinar cell composition.[115]

Specific recommendation for islet evaluation: In patients with recurrent hyperglycemia and/or increasing HbA1c levels, particularly when there is no evidence of evolving allograft rejection, the performance of insulin and glucagon staining is necessary to accurately determine the etiology of islet dysfunction.

In islets with the expected population of alpha cells (normal glucagon staining), the absence of β cells (negative insulin staining) is diagnostic of T1DR; in the same context, weak or sparse insulin staining likely represents selective β cell injury. In contrast, normal insulin and glucagon staining, highlighting the expected population of α and β cells, is common in other forms of islet dysfunction (eg, insulin resistance, progressive graft fibrosis, and others).

4. Category 7 other histologic diagnosis

4.1. Early graft thrombosis due to surgical complications vs active rejection

Technical failures (TF) account for 5.5% to 6.4% of graft losses in the first 3 months posttransplant. The most common cause of TF is graft thrombosis. Pathology analysis is important because thrombosis due to TF can be misdiagnosed as rejection, and vice versa.[24,38,45,59]

In the study of Wallace et al[59], 9 of 23 allograft pancreatectomy specimens diagnosed as TF on clinical grounds had histologic features of rejection (39%). All 9 cases had features of active TCMR, with 4 of them also showing evidence for AMR.

Proposed diagnostic terminology for the pathologic evaluation of pancreatectomy specimens performed in the first 90 days posttransplant:

- Thrombosis—with no underlying vascular or parenchymal pathology
- Thrombosis—with the following pathologic findings: (List all findings, eg, active rejection, arterial dissection, abscess formation, C4d positivity, and others).

Specify in the description of thrombosis:

- Recent, organized, or mixed
- Type of vessel: arterial and/or venous
- Size of involved vessels—large extrapancreatic vessels and/or intraparenchymal vessels
- Extent of thrombosis—focal/multifocal/diffuse

Specific recommendations for gross and histology evaluations:

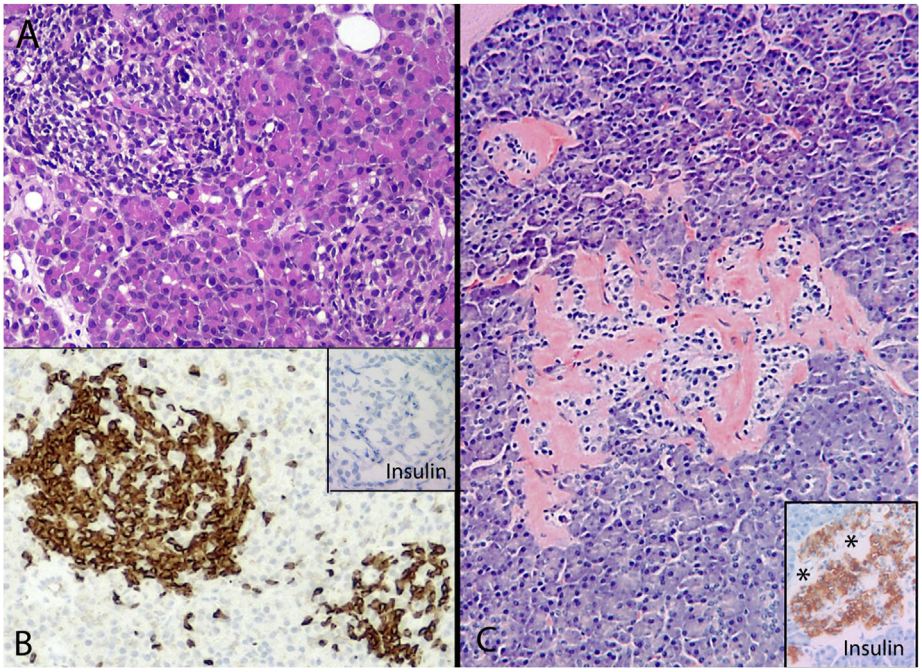

Figure 5. Recurrence of type 1 diabetes mellitus (DM) (A and B) and type 2 DM after pancreas transplantation (C). (A) Insulitis in recurrent autoimmune diabetes is characterized by dense lymphocytic infiltration in and around 2 islets. (B) CD3 stain indicates a predominance of T cells involving the islets, with sparse inflammation in the surrounding acinar tissue. Inset: Insulin stain is negative in the islet and confirms complete loss of insulin-producing β cells. (C) Type 2 DM after pancreas transplantation often presents with islet amyloid deposition. These amorphous, acellular deposits are highlighted using the Congo red stain. Bulky amyloid deposits lead to the depletion of normal islet vascularization and the eventual disappearance of the islet cells. Inset: Insulin stain highlights distortion of persisting functional β cells in an islet with amyloid deposits (asterisks).

- Evaluate large vessels, random sections from the lobular parenchyma, and C4d stain.
- Assess the duodenal cuff anastomosis to identify dehiscence (leak) and serositis.
- Perform histologic sections of any discrete lesions (abscesses, tumors, lymph nodes, and others).

4.2. Peripancreatic inflammation and ischemic pancreatitis

Inflammation of the peripancreatic connective tissues in the early posttransplant period, with and without infection or fluid collection, may lead to histologic features in the pancreas parenchyma that need to be differentiated from active rejection. On H&E stain, there is irregular septal expansion due to a fibroblastic reaction with mononuclear or mixed septal inflammation and overall preservation of the exocrine/acinar lobules. Lymphocytic lobular inflammation should be absent or only minimal in the periphery of the lobules.

Ischemic pancreatitis is characterized by septal and connective tissue edema with variable macrophage and neutrophilic infiltrates, as well as enzymatic fat necrosis. The lobules show spotty acinar cell drop-out and microcystic degeneration.

4.3. Ductal issues

Ductal reactive changes (likely representing some impairment of exocrine secretion drainage) affect interlobular or small acinar ducts. The changes are heterogeneous, including periductal fibrosis (trichrome stain), ductal dilatation, squamous metaplasia, the accumulation of secretions, and/or ductal proliferation. Lymphocytic infiltrates are not significant. Additional studies are necessary to better understand the nature and significance of this process.

5. Additional topics

Duodenal donor cuff biopsies as surrogates for pancreatic biopsies

In pancreas transplants with gastric or duodenal drainage, the duodenal cuff may be accessible endoscopically, and mucosal biopsy samples can be obtained to monitor the status of the graft.[16,115–117]

Severe or advanced rejection usually involves both the duodenal cuff and the pancreatic parenchyma,[118-120] but cystoscopically obtained duodenal cuff biopsies in patients with bladder drainage have shown isolated rejection of one or the other component.[121]

Brockman et al,[122] performed prospective duodenal cuff biopsies and identified AR in 30% of SPK and 82% of PAK recipients, with subsequent histologic improvement after treatment and good clinical outcomes. Nordheim et al,[123] performed 113 prospective biopsies of both the duodenal cuff and the pancreas (97 for surveillance and 16 for graft dysfunction) and found that the duodenum was an inadequate surrogate for pancreas rejection, with a sensitivity of only 9%; rejection was identified in 27% of PTxBx. Perosa et al,[16] used duodenal cuff biopsies for prospective graft surveillance but also obtained concurrent PTxBx in patients with graft dysfunction. In the latter group, there was 70% concordance of rejection in duodenal and pancreatic samples, but the grade of rejection was only in agreement in the more severe cases. Both Perosa et al[16], and Nordheim et al[123], identified cases of isolated pancreas or duodenal rejection. Duodenal biopsies have also been used to identify patients with cytomegalovirus infection (unpublished data presented at the 2022 Banff meeting).

In summary, the most accurate diagnosis of rejection grade and type (TCMR vs AMR) is achieved with PTxBx, but a surrogate

Table 4
Main diagnostic criteria for the evaluation of islet dysfunction in pancreatic allograft biopsies.

Clinical setting	Main hematoxylin and eosin histologic findings	Insulin stain	Glucagon stain	Possible outcomes
DGF due to ischemic injury	Islet morphology: Global islet injury with architectural disarray, islet cell vacuolization, and islet cell drop-out. No significant inflammation. Exocrine morphology: Acinar cell injury, vacuolization and drop-out, pseudocystic acinar changes, ductal cell injury (swelling, loss of polarity). No significant inflammation. Ischemic injury with pancreatitis: Same as above, with variable septal edema, septal and acinar infiltration by macrophages and neutrophils, fat enzymatic necrosis, and rarely small thrombi.	Islets with variable staining of β cells ranging from strong to weak depending on the degree of ischemic cell injury	Islets with variable staining of α cells ranging from strong to weak depending on the degree of ischemic cell injury	-Resolution leading to normal function within days or weeks - Partial resolution (good or marginal function)[a] -No resolution Primary nonfunction, graft thrombosis
Dysfunction 1st year posttransplant due to selective β cell injury CNI toxicity, or other cause	Islet morphology: Islet cell vacuolization with clear, swollen cytoplasm. Spotty cell drop-out. In more severe cases, loss of islet cell polarity is associated with islet disorganization. Exocrine morphology: Normal. There is no significant acinar cell damage, no inflammation, and no significant fibrosis.	Islets with weak or variable staining of β cells Granular staining alternating with washed-out staining	Islets with strong, normal staining in a normal population of α cells	-Resolution of dysfunction with adjustment or change in maintenance regimen - Partial resolution (good or marginal function)[a] - Progression to graft failure
Unexpected dysfunction due to DM autoimmune recurrence (T1DR)	Islet morphology: Active phase has insulitis (dense lymphocytic infiltrates in and around islets). Injury and reactive changes in islet cells. Late phase: Disappearance of β cells and clearing of inflammation. Islet hyalinization. Exocrine morphology: Normal. There is no significant acinar cell damage, no inflammation, and no significant fibrosis.	Islets in the early phase show a decrease or rarely patchy strong staining in β cells Complete loss of β cells in the late phase	Islets with persistence of α cells despite variable to complete loss of β cells	Progression to graft failure. Currently, no treatment is available
Persistent or progressive	Islet morphology: Ranging from normal to enlarged with irregular	Islets with overall normal staining of β cells but	Islets with overall normal staining of α cells but	Variable clinical course, persistence of good or

(*continued on next page*)

Table 4 (*continued*)

Clinical setting	Main hematoxylin and eosin histologic findings	Insulin stain	Glucagon stain	Possible outcomes
dysfunction due to type 2 DM	shapes. Variable islet cell vacuolization. Irregular amyloid deposition (amorphous pink material subtle of diffuse). Exocrine morphology: Normal or nonspecific changes. There are no features of rejection. There is no significant fibrosis.	distorted islet architecture when there is amyloid deposition	distorted islet architecture when there is amyloid deposition	marginal graft function[a], or progression to graft failure

CNI, calcineurin inhibitors; DGF, delayed graft function; DM, diabetes mellitus; T1DR, type 1 diabetes mellitus recurrence.

[a] Based on outcomes of β cell replacement as presented in reference[68].

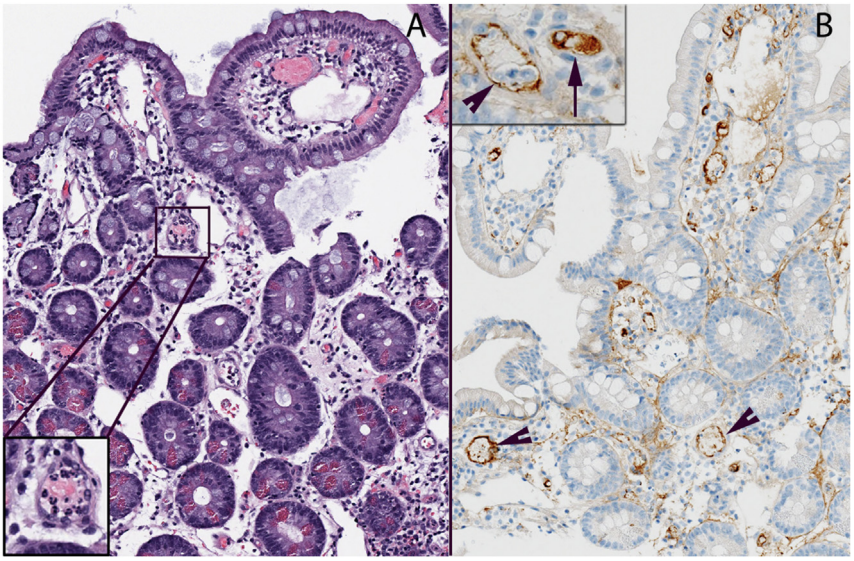

Figure 6. Active antibody-mediated allograft rejection in a duodenal cuff biopsy. The pancreas was not accessible for percutaneous biopsy in this patient with graft dysfunction and high-level class II donor-specific antibodies. (A) Duodenal mucosa with edema of the lamina propria, dilatation of capillaries, and capillaritis (inset). (B) C4d stain marks the outline of most capillaries in the lamina propria. Inset contrasts linear/granular capillary wall staining (arrow heads) with nonspecific reactivity in plasma (inset, arrow).

duodenal cuff biopsy may be helpful when the pancreatic parenchyma is inaccessible (Fig. 6). Duodenal cuff biopsies in patients with enteric—duodenal or gastric drainage can be used for graft surveillance, with the recognition that discrepant findings between the duodenum and the pancreas may occur in up to one-third of cases.[16]

Specific recommendations:

- The diagnosis of rejection is based on guidelines used for small intestinal transplantation.[124-126]
- Obtain 3 to 5 biopsy fragments to avoid sampling issues.[126]
- Rule out a cytomegalovirus infection.[16,117]

6. Noninvasive biomarkers in pancreas transplantation

Noninvasive monitoring of pancreas graft rejection relies traditionally on serum amylase and lipase measurements, that are known to have poor specificity.[10]

There is a benefit of monitoring for antihuman leukocyte antigens DSA in pancreas transplantation[127] because up to 39% of patients develop de novo DSA (dnDSA)[128,129] and dnDSA is associated with an inferior pancreas graft survival rate.[39,129,130] Protocol biopsies in SPK recipients with dnDSA revealed subclinical rejection in up to 47% of cases, of which only 57% were AMR.[42] Therefore, the presence of dnDSA is a risk factor for AMR, as well as rejection in general, and can be considered an indication to perform a PTxBx.

More recently, blood-based molecular biomarkers, such as donor-derived cell-free DNA (dd-cfDNA) and gene expression profiles (GEP), have emerged as sensitive monitoring tools in other abdominal solid organ transplants.[131-136] Dd-cfDNA is particularly useful for the diagnosis of AMR,[132] whereas the GEP has demonstrated a good ability to predict TCMR.[134] Major advantages of these biomarkers include their relative independence from functional markers (ie, serum lipase), the fact that they are donor- or graft-specific, and the fact that their increase in

the presence of graft injury typically occurs prior to changes in standard clinical markers.[137] In an analysis including pancreas biopsy-matched samples, dd-cfDNA was significantly increased in patients with biopsy-proven AR diagnosed beyond day 45 posttransplant.[138] Dd-cfDNA outperformed serum lipase in the diagnosis of pancreas AR, with an area under the curve of 0.84 compared with 0.74 for lipase. Of relevance, this performance was achieved with a cut-off value of dd-cfDNA of 0.7% instead of the 1% previously described for kidney transplantation.[132] Dd-cfDNA elevation was shown to precede the clinical rejection episodes.[139] A recent multicenter study confirmed that the mean dd-cfDNA level for all pancreas transplant recipients is $< 1.0\%$; subsequent increases in dd-cfDNA levels were correlated with rejection and infection.[140]

Dd-cfDNA increased significantly in the immediate post-transplant period, likely due to the ischemia-reperfusion injury, but normalized within 45 to 80 days.[138-140]

Dd-cfDNA is potentially useful for the longitudinal monitoring of pancreas transplantation and can be considered a useful biomarker for monitoring graft dysfunction after the early post-transplant phase.

Additional studies should focus on the integration of these blood-based molecular diagnostic tools with graft transcriptomics,[141] peripheral blood immune cell phenotyping,[142,143] functional studies.[21] This integration may provide further insights into the pathophysiology of pancreas graft rejection, the correlation between blood-based biomarkers and graft outcomes (ie, response to treatment), and identifying organ specific molecular biomarkers/signatures (ie, cfDNA-INS)[144] or islet specific exosomes.[145] See Table 3 for areas for future research.

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Declaration of competing interests

The authors of this manuscript have no conflicts of interest to disclose, as described by the American Journal of Transplantation.

Data availability statement

Details on the process used for developing these guidelines can be obtained from the Banff 2022 video recordings. Records of written pancreas Banff group discussions are availabe and can be made availalbe upon request.

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