Pathology of Pancreas Transplantation

22

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22.1 Introduction

Diabetes mellitus (either overt or undiagnosed) is the principal indication for pancreas transplantation. In the USA in 2015, an estimated 30.3 million people, equivalent to 9.4% of the population, had diabetes mellitus (DM) with 5–10% having type 1 diabetes mellitus (T1DM) [1]. Diabetes is also the most common cause of end-stage renal failure, blindness, and a major contributing factor for peripheral vascular and coronary artery disease [2, 3]. Administration of exogenous insulin is an effective treatment for T1DM and selected patients with type 2 diabetes, and tight control of blood glucose levels reduces or slows down complications [4]. However, large fluctuations in levels of glucose (including hypoglycemia) remain serious concerns particularly in T1DM, and annual mortality rates of up to 3–6% have been attributed to insulin-related hypoglycemic crises [5].

Pancreatic transplantation improves quality of life and is potentially curative for patients who are insulin-dependent, because of type 1 or type 2 DM, or following total pancreatectomy. In the long term, it prevents, arrests, or reverses the onset or progression of DM complications and restores hypoglycemic counter-regulation [6]. At the molecular level, circulating microRNAs associated with diabetic nephropathy and systemic microvascular damage are normalized after simultaneous pancreas-kidney transplantation [7].

22.1.1 History and Outcomes of Pancreas Transplantation

The history of pancreas transplantation, reviewed elsewhere in detail [8, 9], is inextricably intertwined with the history of DM. The first human pancreas transplant (combined with a renal transplant) was performed in 1966 by Kelly and colleagues [10]. Between the first pancreas transplant in 1966 and the end of 2011, the International Pancreatic Transplant Registry (IPTR) recorded over 27,000 pancreas transplants in the USA, and more than 15,000 elsewhere in the world [5, 11]. The annual number of transplants in the USA peaked between 2002 and 2005 at over 1400, and then decreased by 20% between 2005 and 2014. In 2017, adult transplant recipients numbered 971, including

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retransplants, of which over 80% were simultaneous pancreas-kidney (SPK) transplants, 8% pancreas after kidney (PAK), and 10% pancreas transplants alone (PTA) [3, 12].

In the USA at present, five-year patient survival rates are 93% for SPK, 91% for PAK, and 78% for PTA recipients, respectively, whereas five-year graft survival rates are 73% for SPK, 65% for PAK, and 53% for PTA [3].

22.1.2 Indications for Pancreas Transplantation

According to the OPTN/SRTR 2017 Annual Data Report, approximately 80% of transplants are performed for T1DM, 14% for T2DM, and 6% for "other" indications (e.g., chronic pancreatitis, benign neoplasms) [12, 13]. The type of pancreas transplant procedure depends on several clinical factors [3, 5]. Patients with dialysis-dependent advanced renal disease and insulin dependence undergo SPK, freeing them from both dialysis and insulin therapies. However, if the patient receives a kidney from a living donor, this may be followed by a PTA. Patients who have previously undergone renal transplantation and have brittle DM and secondary complications, including in the renal allograft, are candidates for PAK. Pancreatic transplant alone (PTA) is reserved for patients suffering from brittle DM with preserved renal function.

22.1.3 Alternatives to Whole Pancreas Transplantation

The principal alternatives to whole pancreas transplantation are islet cell transplantation and living donor pancreas transplants, omitting the more exotic xenotransplants and bionic pancreata [14].

22.1.3.1 Islet Cell Transplantation

A total of 1086 allogeneic islet cell transplants were performed between 2002 and 2015 [15]. Islet cell transplantation in patients with TIDM has been successful recently in achieving insulin independence in over 50% of well-selected patients at 5 years and can be considered in patients at high cardiovascular risk, those reluctant to undergo abdominal surgery, or in selected non-uremic patients with a low body mass and low insulin requirements [16]. Drawbacks include a reduced chance of achieving insulin independence (50% vs. 70% in SPK at 5 years), a continued need for immunosuppression (albeit at reduced dosages), and the need for 2–4 donors per transplant [14]. **Autologous islet cell transplants**, extracted predominantly from pancreata of patients with chronic pancreatitis, cumulatively numbered 819 between 1999 and 2015 [17]. Insulin independence rates following autologous islet cell transplantation show considerable variability, related to age and other factors [17].

22.1.3.2 Living Donor Transplantation

Since 1979, the year of the first living donor segmental pancreas transplant, over 160 have been performed globally [18]. Advantages include shorter waiting times and improved outcomes, particularly if the recipient is highly sensitized. Furthermore, it provides an opportunity for a simultaneous pancreas-kidney transplant from the same donor. Drawbacks include hyperglycemia (or overt diabetes) in the donor (mandating careful selection) and surgical complications in both donor and recipient [18–20].

22.2 Role of the Pathologist in Pancreas Transplantation

Pancreas transplants are broadly separated into whole/segmental organ transplant and islet transplant. Pathologists are principally involved in the assessment of the former. That said, pancreas allografts in the setting of simultaneous pancreas-kidney (SPK) transplant are infrequently biopsied in most centers. The pathologist has several important responsibilities in the management of **whole pancreas transplantation**. These include the interpretation of **post-transplant core biopsies**, obtained by CT or ultrasound. The primary indications for biopsy are concerns over rejection, heralded by an elevated serum amylase and/or lipase, or falling urinary amylase in bladder-drained allografts. However, as in liver and kidney transplantation, the biochemical alterations are

relatively non-specific, and biopsy is very useful to distinguish acute rejection from other processes. Another critical role of the pathologist is **assessment of the failed allograft** at the time of re-transplantation or post mortem examination. In most centers, biopsies are not obtained to evaluate the donor organ at the time of transplantation (although this may be performed for the kidney in SPK procedures). Another important responsibility of the pathologist is the detailed examination of the **native pancreas explant**, which can follow available protocols [21–23] (see also Chaps. 2 and 3).

The role of pathologists in **islet cell transplantation** is limited. There may be occasions to examine the allograft such as post mortem or to assess the liver or other organs for concomitant abnormalities [24, 25].

22.3 Pathologic Alterations Related to Operative Complications, and Examination and Findings in Failed Allografts

22.3.1 Surgical Procedure of Pancreas Transplantation

A brief review of the surgical procedure of whole organ pancreatic transplantation is relevant to understanding the complications, and for optimal handling and examination of the failed allograft. The entire graft consists of the pancreas per se, the attached segment of donor duodenum, the venous and arterial anastomoses, and a route for drainage of exocrine secretions [20, 26].

The venous anastomosis is established with the recipient's systemic or portal venous system. At present, 80–90% of transplants are performed with the **systemic venous drainage** from the pancreatic portal vein connected to the right common or external iliac vein or the inferior vena cava. The advantage of this approach is its relative simplicity. The principal disadvantage is peripheral hyperinsulinemia that may promote insulin resistance and increased atherosclerosis.

The arterial anastomosis is more complex and involves the preparation of a Y-graft from the donor common, external, and internal iliac arteries, followed by anastomosis of its two peripheral branches to the donor superior mesenteric and splenic arteries. The final step is the surgical connection of the main segment of the Y-graft to the recipient common iliac artery or aorta.

Drainage of the exocrine secretions occurs via the urinary bladder or small bowel. Although the former was previously preferred, at present over 80–90% of pancreatic transplants utilize enteric drainage. The donor "C" loop of duodenum attached to the pancreas is anastomosed to the recipient small bowel, most often without a Roux-en-Y. This shift in drainage to the enteric route was driven by the side effects of urinary bladder drainage, which include reflux pancreatitis, metabolic acidosis, dehydration, and hematuria. These disadvantages outweigh the potential benefit of monitoring for allograft rejection by reductions of urinary amylase in pancreas transplant alone (PTA) and pancreas after kidney (PAK) transplant recipients.

22.3.2 Surgical Complications of Pancreas Transplantation

The principal surgical complications are vascular thrombosis of the graft, bleeding, anastomotic leaks, fluid collections in the abdomen, and infections, including pancreatitis. These remain significant issues compared to transplantation of other solid organs. In the 1980s, graft failure rates caused by technical issues hovered around 25%, but currently are below 10% [27, 28].

22.3.3 Vascular Thrombosis

Large venous or arterial thrombosis remains the chief cause of non-immunological allograft loss, with enteric-drained pancreas after kidney (PAK) and pancreas transplant alone (PTA) patients at greatest risk [29]. Pathogenetic factors include an intrinsically lower blood flow compared with other solid organs (e.g., liver, heart, and kidney), operative trauma, donor pancreas-related preservation injury, and a hypercoagulable state [20, 27, 30, 31]. Vascular thrombosis usually occurs early, within the first 2 weeks post-transplant.

Late onset thrombosis should prompt investigation for other etiologies such as rejection or atherosclerotic vascular disease.

Thrombosis may cause stenosis or complete obstruction of the affected vessel. Occlusion of the splenic or superior mesenteric artery may produce partial infarction of the allograft, the extent of injury depending on collateral circulation. The corresponding clinical picture ranges from minimal effect to complete loss of the graft. Elevation of blood glucose levels should raise clinical suspicion, and Doppler ultrasound can assess flow in the arterial Y-graft, venous outflow, and flow to the pancreatic parenchyma [29, 32]. Without early diagnosis and intervention (anticoagulants, thrombectomy), arterial or venous thrombosis results in irreversible infarction necessitating removal of the entire transplanted pancreas and duodenal cuff [33].

22.3.4 Examination of the Failed Allograft

Examination of the failed allograft by the pathologist requires knowledge of (1) the precise surgical procedure utilized, (2) the interval from transplant, (3) clinical findings, laboratory data, and imaging studies focused on peri- and post-operative events, and (4) any prior episodes of acute cellular rejection (ACR) or antibody-mediated rejection (AMR).

22.3.4.1 Macroscopic Examination

Macroscopic examination of the failed allograft entails weighing, measuring, and describing the specimen including (1) the segments of recipient small bowel (generally jejunum) and donor duodenum, (2) the pancreas, and (3) the arterial and venous segments, carefully sectioning the latter to look for thrombosis or other causes of obstruction (e.g., atherosclerosis, stenosis). The pancreas is serially sectioned, and generous sampling is taken from multiple sites for microscopic examination.

22.3.4.2 Macroscopic Pathologic Findings in Vascular Thrombosis

The macroscopic pathologic findings in vascular thrombosis (Fig. 22.1) include the presence of (1) an intact segment of recipient small bowel since its vascularization is independent of the donor, (2) thrombus within the lumen of a vessel, (3) pancreas and donor duodenal segment displaying hemorrhagic necrosis (depending on whether the thrombosis is arterial or venous in origin) with dark red parenchyma and duodenal mucosa, and possibly pancreatitis (see Sect. 22.3.5).

22.3.4.3 Histopathologic Findings in Vascular Thrombosis

The histopathologic findings in vascular thrombosis include classic ischemic and/or hemorrhagic necrosis of the duodenal segment and pancreatic parenchyma and vessels, with variable acute inflammation. Secondary abscess formation and opportunistic infections, including fungal (particularly candidiasis), can develop [34]. Histopathologic examination may elucidate the underlying etiology. "Idiopathic" causes may be related to surgical or technical complications and reveal organizing thrombotic occlusion of large arteries and/or veins and ischemic necrosis. Antibody-mediated rejection (AMR) including "hyperacute rejection", is characterized by fibrinoid necrosis or necrotizing vasculitis in arteries and/or veins of any size [30]. In some cases, primary vascular injury can be difficult to distinguish from necrotic vessels embedded within infarcted pancreatic parenchyma. To circumvent this problem, the pathologist should search for evidence of vasculitis in the least necrotic or damaged areas or ideally in viable areas. In addition, immunohistochemistry for C4d and correlation with donor-specific antibodies (DSA) may be of value. A comment should be included in the pathology consultation report that in view of the extensive infarction, the possibility of AMR cannot be entirely excluded. Graft vascular thrombosis related to acute cellular rejection (ACR) is discussed below (see Sect. 22.5.2).

22.3.5 Post-Transplant Ischemic and Infectious Pancreatitis

Graft pancreatitis is often caused by several interacting factors including ischemia/reperfusion injury and technical/surgical complications. It may lead to anastomotic leaks, intra-abdominal

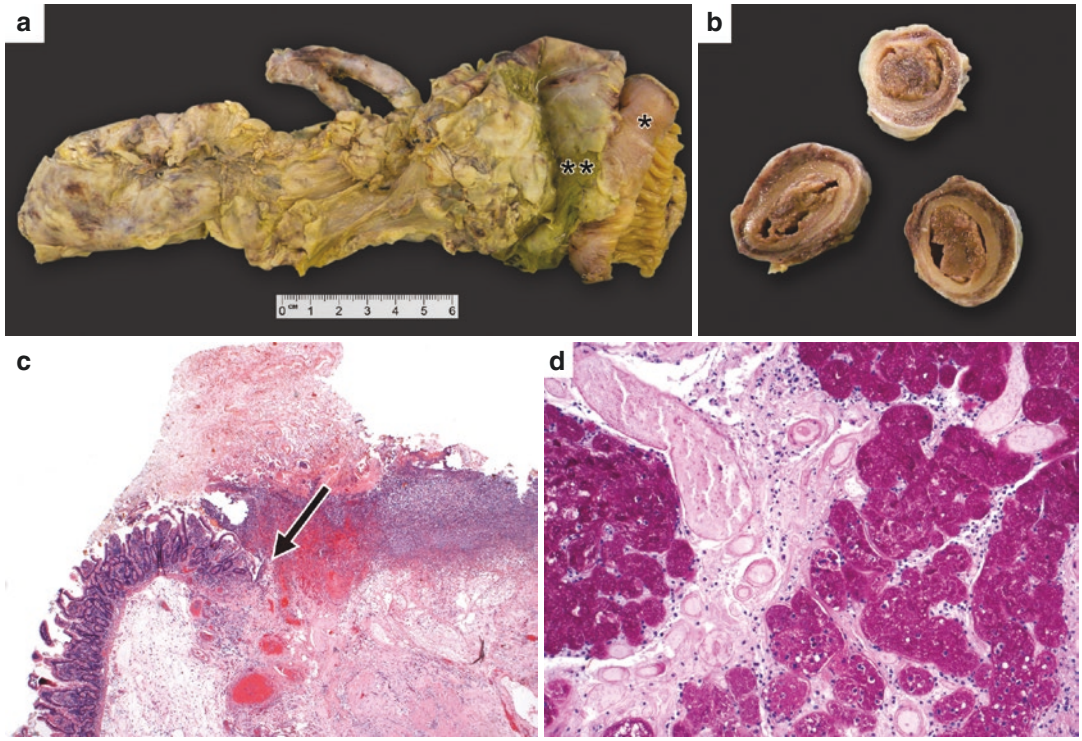

Fig. 22.1 Pancreas allograft removed following arterial thrombosis: the viable recipient small bowel (*) is anastomosed to the necrotic donor duodenum (**) and necrotic pancreatic allograft (**a**). The arterial segment enters the pancreas at the top. The sectioned arterial segment shows total thrombotic occlusion (**b**). Low power shows the junction (*arrow*, **c**) between the intact recipient small bowel and the necrotic, inflamed donor duodenum. PAS stain shows the necrotic pancreatic tissue (**d**)

fluid accumulations and superimposed infections. If extensive, this complication frequently requires removal of the graft. The pathologic features of graft pancreatitis mimic those of necrotizing pancreatitis in the non-transplant setting with macroscopic fat necrosis, parenchymal necrosis, and/or hemorrhage (Fig. 22.2) (see also Chap. 7). Microscopic examination reveals acinar (and variable islet cell) necrosis, infiltration of neutrophils and macrophages, edema, and hemorrhage. Secondary infectious pancreatitis can be caused by a variety of microbial agents, notably bacterial and fungal [30, 35].

22.3.6 Post-Transplant Ischemia/Reperfusion Injury

Ischemic/reperfusion injury resembles that in other transplants. Its pathogenesis centers on microvascular injury due to donor- and recipient-related factors. Microscopic alterations (generally in core biopsies) (Fig. 22.3) include interstitial and intracellular edema, focal acinar cell or adipocyte necrosis, and a variable neutrophilic infiltrate [35, 36]. Both ischemic/reperfusion injury and post-transplant pancreatitis are in the differential diagnosis of acute rejection in core biopsies, and indeed may co-exist with rejection.

22.4 Core Biopsy Specimens in Pancreas Transplantation: Procedures and Technical Aspects

The role of the pathologist in pancreatic transplantation is more restricted than in most other solid organ transplants, and largely limited to the assessment of core biopsies. These are generally

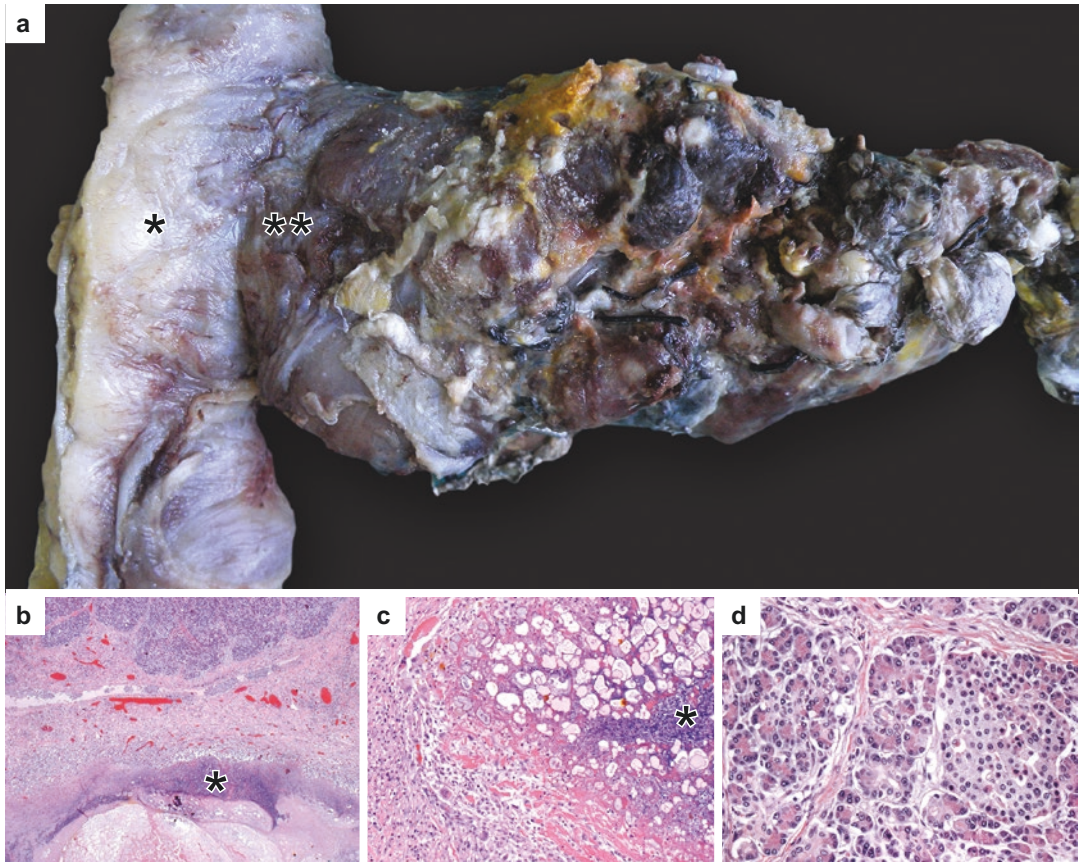

Fig. 22.2 Peripancreatitis and pancreatitis secondary to partial vascular thrombosis in a resected transplant: the pancreas (*right*) with recipient small bowel (*) and donor duodenum (**) shows prominent surface fibrinous exudate (**a**). Low power shows fat necrosis (*bottom*), adjacent abscess (*), a layer of active chronic inflammation and early granulation tissue and intact parenchyma (*top*) without overt necrosis (**b**). Medium power shows fat necrosis (*right*) admixed with acute inflammation (*), and a layer (*left*) of active chronic inflammation (**c**). The adjacent parenchyma is intact (**d**)

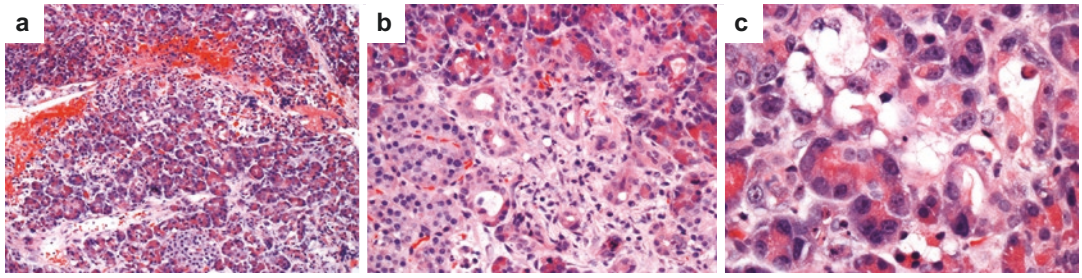

Fig. 22.3 Mild ischemia-reperfusion injury in a core biopsy 9 days post-transplant: there is septal hemorrhage, damage to acini at the periphery of the lobule, and mild acute inflammation (**a**). Note the small area with damage and dropout of acini, and mild neutrophilic infiltrate (**b**). High power shows swelling, hypereosinophilia, and dropout of acinar cells (**c**)

performed for elevated serum amylase, lipase, and/or glucose, or to assess reduced urinary amylase in patients with bladder drainage of pancreatic exocrine secretions. The principal goal is to identify acute cellular rejection (ACR), chronic rejection (CR), and less commonly antibody-mediated rejection (AMR), and their morphologic mimics. Ultrasound- or CT-guided percutaneous core needle biopsies, with an 18 g or 20 g needle, are currently the gold standard to evaluate pancreas allografts, yielding adequate tissue in 88% to 96% of cases with minimal complications [37–39].

22.4.1 Surrogate Biopsy Options to Assess Rejection in the Pancreas Allograft

The first option is the **kidney** in the setting of simultaneous pancreas-kidney (SPK) or pancreas after kidney (PAK) transplants. Although experimental animal models previously suggested that both kidney and pancreas are rejected simultaneously, this has not been borne out in human transplant recipients. Indeed, the conclusion to draw from several studies is that between a quarter and a third of rejection episodes in SPK and PAK transplant biopsies can be discordant, the pancreas being more sensitive to rejection than the kidney [35, 40–43]. Furthermore, even in the cases concordant for rejection, over one third can have different types of rejection (i.e., acute cellular vs. antibody-mediated vs. mixed) [43]. Therefore, until proven otherwise, it is recommended to biopsy both organs at the same time, or at least, if the kidney allograft biopsy shows no rejection, to then biopsy the pancreas allograft [42].

The second surrogate biopsy site potentially applicable to all three types of pancreas transplants is the **donor duodenal cuff** that forms part of the allograft, sampled either endoscopically near the enteric anastomosis or cystoscopically for bladder-drained pancreata. A few studies using this method have shown that a diagnosis of rejection is possible, albeit with significant disagreements with concurrent pancreas allograft biopsies [44, 45]. However, the discrepancies, including potentially missing cases of vascular or chronic rejection, and the lack of criteria to precisely grade ACR or interpret C4d staining, have impeded this approach [44–47].

In summary, at present, neither renal nor duodenal cuff biopsy sampling, at least alone, is clearly recommended to accurately assess rejection in the pancreas allograft.

22.4.2 Protocol or Surveillance, and Post-Therapy Core Biopsies

Protocol or surveillance biopsies are not widely accepted in pancreas transplantation. Nevertheless, a few studies have recommended surveillance biopsies, particularly when initiated early after transplant and in pancreas transplant alone (PTA) or PAK recipients, as they can detect clinically significant rejection in about 20–50% of patients before demonstrable clinical or biochemical alterations. However, surveillance biopsies showing minimal or mild rejection rarely progress, and indeed, rejection may persist in a significant number of patients with biopsy-proven rejection after therapy. Therefore, although early detection of rejection may improve survival of the allograft, additional longitudinal studies are needed [41, 46, 48, 49].

22.4.3 Pancreas Allograft Core Biopsy: Handling and Processing

The pancreas allograft core biopsy obtained under CT or ultrasound guidance using 18 or 20 g needles should be fixed immediately in 10% neutral buffered formalin or a comparable fixative. Depending on clinical circumstances, it can be processed for emergent same day interpretation or overnight for the next day. The Banff

multidisciplinary international consensus panel [39] recommends that at least 10 sequential slides be cut and prepared as follows: 3 H&E-stained slides (e.g., cuts 1, 5, 9), 1 slide for C4d immunohistochemistry (e.g., cut 4), and 1 slide for Masson trichrome or other collagen stain to assess fibrosis or to highlight fibrinoid necrosis in arteritis associated with high-grade rejection. Immunohistochemistry for CMV and in situ hybridization for EBV are optional. If the indication for the biopsy is hyperglycemia and/or a strong clinical suspicion for recurrent type 1 diabetic autoimmune isletitis (or insulitis), immunohistochemistry for insulin and glucagon can be performed (discussed in Sect. 22.7).

22.4.3.1 Adequacy of the Pancreas Allograft Core Biopsy

For adequacy of the pancreas allograft core biopsy, the 2008 Banff panel's guidelines [39] propose the presence of **at least three lobular areas** and their associated inter-lobular septa. Although arteries are desirable in the biopsy, their presence is variable. In view of the diagnostic importance of arterial lesions (particularly for the higher grades of ACR), their presence or absence should be mentioned in the pathology report. Islets of Langerhans may or may not be seen but are not strictly necessary to assess adequacy or rejection, because the inflammation affects predominantly the exocrine component. Of note, the Banff panel emphasizes that the final determination of biopsy adequacy rests with the individual pathologist. Certainly, even in the face of a suboptimal biopsy, any diagnostic findings should be clearly indicated, thereby averting the need for re-biopsy.

22.5 Pancreas Allograft Rejection

Rejection represents the recipient's immune response to antigens in a non-syngeneic graft. Its pathogenesis implicates the innate and adaptive immune systems, the latter mediated by combinations of antibodies and mononuclear and polymorphonuclear cells (lymphocytes, monocytes, plasma cells, eosinophils) [50, 51]. Allograft rejection of the pancreas is classified into antibody-mediated (AMR), acute cellular rejection (ACR), and chronic rejection (CR). The loss of pancreas allografts from chronic allograft rejection at 2 years post-transplant is 1.5% for simultaneous pancreas-kidney (SPK), 5.7% for pancreas after kidney (PAK), and 10.3% for pancreas transplant alone (PTA) transplants [52].

22.5.1 Antibody-Mediated Rejection (AMR)

The spectrum of the clinicopathological manifestations of AMR is broad, ranging from fulminant graft failure ("hyperacute rejection") to its incidental identification in otherwise stable grafts. **The clinicopathological findings and criteria for AMR** are as follows [53]:

- Circulating donor-specific antibodies (DSA)
- Morphologically discernible tissue injury
  - Capillaritis
  - Interacinar inflammation
  - Acinar cell damage (swelling, necrosis, or apoptosis)
  - Vasculitis or thrombosis
- Immunopositivity for C4d of interacinar capillaries in ≥5% of the acinar lobular surface area

Of note, the requirement of "graft dysfunction" (a component of the 2008 Banff Schema) is no longer a requirement for AMR [39].

22.5.1.1 Hyperacute Rejection

Now very rare, hyperacute rejection (HAR) typically occurs in the setting of circulating preformed anti-donor antibodies [27, 53]. The pathologic findings in hyperacute rejection in its earliest stages are rarely encountered in patients, but have been described in experimental animals. They include margination of neutrophils in capillaries and venules, congestion, interstitial edema, and focal acinar cellular damage (vacuolization, degranulation, and necrosis) [54]. Later alterations observed in biopsy specimens or explanted failed allografts comprise extensive

vascular deposition of immune complexes and complement (typically IgG and C4d), resulting in endotheliitis or intimitis, arterial and venous fibrinoid necrosis and thrombosis, a prominent neutrophilic infiltrate, culminating in widespread hemorrhagic necrosis of the parenchyma. The differential diagnosis of hyperacute rejection includes other causes of vascular thrombosis [53]. As previously indicated, distinguishing AMR from other causes includes the presence of the aforementioned alterations in viable tissue sections (particularly bona fide vasculitis), positive donor-specific antibodies (DSA) and C4d deposition in the vasculature [39].

Of note, the term "accelerated AMR" or "delayed hyperacute rejection" is not included in the latest Banff schema for AMR, but is defined as delayed onset (hours to days) of hyperacute AMR, with similar histopathologic and serologic findings [27].

22.5.1.2 Acute Antibody-Mediated Rejection AMR

About 75% of patients who develop acute AMR present in the first 6 months, although a minority present much later [53]. **Clinically**, most patients with acute AMR exhibit graft dysfunction with one or more of the following: elevation of serum amylase and/or lipase, reduction in urinary amylase, and less commonly, hyperglycemia. There is an overlap of clinical findings in AMR and ACR so that a biopsy is required to establish the diagnosis.

Pathologic Features of Acute AMR

The pathologic features of acute AMR include some or all the following (Fig. 22.4) [53]:

- **Acinar and interacinar inflammation** with infiltration of neutrophils, monocytes, and macrophages. In those instances where the neutrophils are inconspicuous, the monocytes can be highlighted by immunohistochemistry for CD68.
- **An interacinar capillaritis** with variably prominent and distributed intraluminal neutrophils and monocytes. Microvascular damage can result in prominent interstitial edema and hemorrhage in the severe forms.

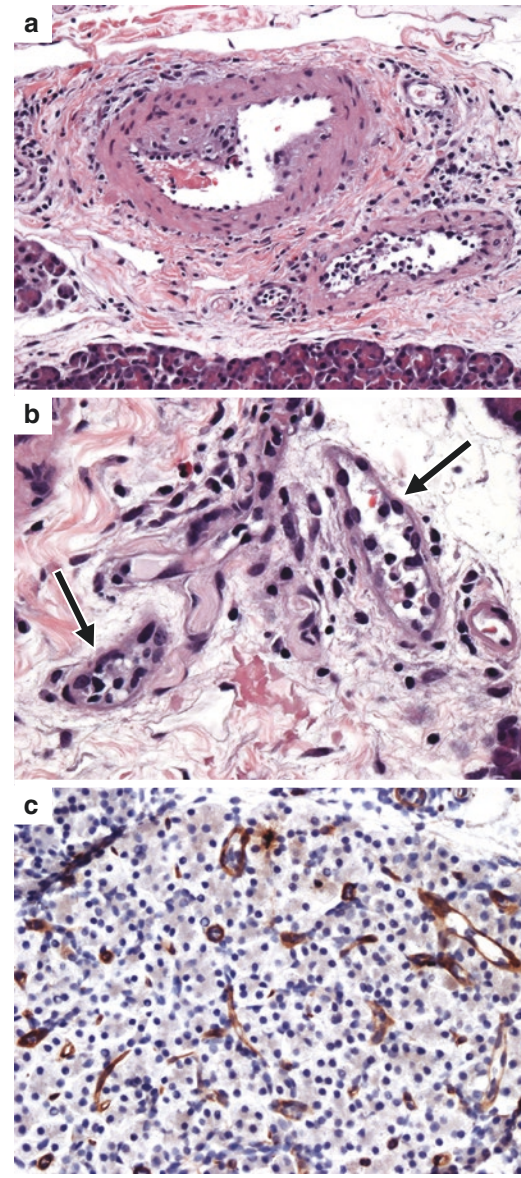

Fig. 22.4 Antibody-mediated rejection in a pancreas core biopsy from a patient post kidney-pancreas transplant: there is focal arteritis and intravascular inflammatory cells in a small artery, as well as capillaritis (**a**). Arteritis may be a sign of both acute cellular and antibody-mediated rejection. Capillaries with increased intraluminal inflammatory cells are indicative of capillaritis (*arrows*, **b**). There is positive staining of interacinar capillaries for C4d (**c**)

- **Damage to acinar cells** and pancreatic parenchyma, with variable cellular swelling, vacuolization, apoptosis, and necrosis. In severe

AMR, these findings can overlap with those encountered in hyperacute rejection [30, 53].

Histopathologic Grading of Acute AMR

The histopathologic grading of acute AMR according to the 2011 Banff schema is:

- **Grade I or mild acute AMR:** preserved architecture with mild monocytic or mixed monocytic and neutrophilic inflammatory infiltrates and sparse acinar cellular damage.
- **Grade II or moderate acute AMR:** largely preserved architecture with interacinar monocytic or mixed monocytic and neutrophilic infiltrates, dilated capillaries with capillaritis, congestion and extravasation of erythrocytes, and multifocal acinar cellular dropout or necrosis.
- **Grade III or severe acute AMR:** variably disordered architecture, preponderance of interstitial hemorrhage, multifocal or confluent parenchymal necrosis, thrombosis and necrosis of arteries and veins, and sparse monocytic and/or neutrophilic inflammatory infiltrates.

Immunohistochemistry for C4d in Pancreas Allografts

Immunohistochemistry for C4d in pancreas allografts is key for the diagnosis of AMR and should be performed in all cases of suspected AMR [53, 55–57]. In the **assessment of staining for C4d**, only linear or granular staining pattern of interacinar capillaries in exocrine lobular parenchyma is considered positive, as it correlates with serum donor-specific antibodies (DSA) and with clinical outcomes. The presence of C4d staining of arteries or veins, of the interstitial connective tissue, or extra pancreatic tissues is nonspecific, although helpful as an internal quality control for the staining technique. The threshold for positive staining remains at ≥ 5% as established by the 2008 Banff grading schema [39, 58, 59].

The recommended grading scheme for C4d staining is [53]:

- **Negative**: absence or <5% interacinar capillary staining in exocrine lobules
- **Focal positive**: 5–50% staining of capillaries
- **Diffuse positive**: >50% of capillaries staining

Reporting Nomenclature for AMR

The final clinical diagnosis of acute AMR requires the combination of (1) histopathologic features, (2) positive immunohistochemistry for C4d, and (3) serological evidence of DSA. The recommended reporting nomenclature is the following [53]:

- **Acute AMR** (i.e., definite) when all 3 above diagnostic criteria are present.
- **"Consistent with acute AMR"** when 2 of 3 criteria are present.
- **"Requires exclusion of AMR"** when only 1 of 3 criteria is present.

Of note, the concept of AMR in the absence of immunopositivity for C4d, i.e., "C4d-negative AMR", mirrors that observed in heart and kidney allografts [55–57].

22.5.1.3 Chronic Active Antibody-Mediated Rejection

"Humoral" mechanisms in general, and particularly circulating DSA, have been implicated in the pathogenesis of the graft fibrosis and failure characteristic of chronic rejection. Thus, the diagnosis of chronic active AMR is established in allograft biopsies exhibiting the following [53]:

- Histopathologic and immunopathologic features of acute AMR (including C4d positivity)
- Features of chronic rejection/graft sclerosis in absence of other etiologies of fibrosis (see below)
- Absence of acute cellular rejection (ACR)

Other findings supporting a component of AMR include vascular mural fibrinoid necrosis and the presence of organizing luminal thrombi. To make a definitive diagnosis of chronic active AMR, all three components of AMR are required as detailed above, in addition to the sclerotic changes of CR. If only 2 of the 3 are present, then the term "suspicious for chronic active AMR" should be reported.

22.5.1.4 Mixed AMR and ACR

Perhaps unsurprising in view of the nature of immune mechanisms in transplantation, both AMR and ACR can be observed in the same biopsy. Histopathologic features include the interstitial mononuclear infiltrate of ACR (detailed in the next section) along with the classic triad of findings in AMR [53]. Each component should be evaluated, graded, and reported separately using the Banff schema.

22.5.2 Acute Cellular Rejection (ACR)

22.5.2.1 Clinical and Laboratory Features of ACR

Cellular rejection rarely produces overt clinical symptoms or signs, so suspicion is driven by altered biochemical parameters. In about 80% of cases of ACR, exocrine dysfunction is characterized by a rise in serum amylase and/or lipase, reflecting acinar cell injury. In patients with bladder-drained grafts a fall in urinary amylase is seen in over 50% of cases of ACR. In contrast, endocrine dysfunction i.e., hyperglycemia (or a reduction in urinary insulin or peptide C) is usually indicative of severe ACR or another severe insult to the allograft, such as a surgical complication (e.g., vascular thrombosis), chronic rejection, or recurrent autoimmune isletitis [27, 39].

22.5.2.2 Histopathologic Findings of ACR in the Pancreas Allograft

The 2008 Banff schema provides clear definitions and descriptions of the histopathologic findings in ACR (as well as in AMR) [39]. The histopathologic features are summarized below (Figs. 22.5, 22.6, 22.7, 22.8, 22.9, 22.10, 22.11):

- **Septal inflammatory infiltrates** composed of activated lymphocytes and monocytes with a variable number of eosinophils (Fig. 22.5).
- **Acinar inflammatory infiltrates** composed of mononuclear cells permeating the acini (Fig. 22.8a). These may take the form of (1) an acinar inflammatory focus with ≥10 inflammatory cells, (2) "focal acinar inflammation" with 2 or more inflammatory foci per acinar lobule, but without acinar cell injury, (3) "multifocal acinar inflammation" with 3 or more foci of inflammation per acinar lobule and with single or focal isolated acinar cell damage or necrosis in the midst of uninvolved acini, or (4) "severe or extensive acinar inflammation" with marked diffuse acinar inflammation with extensive acinar cell damage or necrosis and few, if any, spared acinar areas. These inflammatory infiltrates damage the exocrine acini.
- **Inflammation of veins and venules (venulitis)** characterized by perivascular and mural

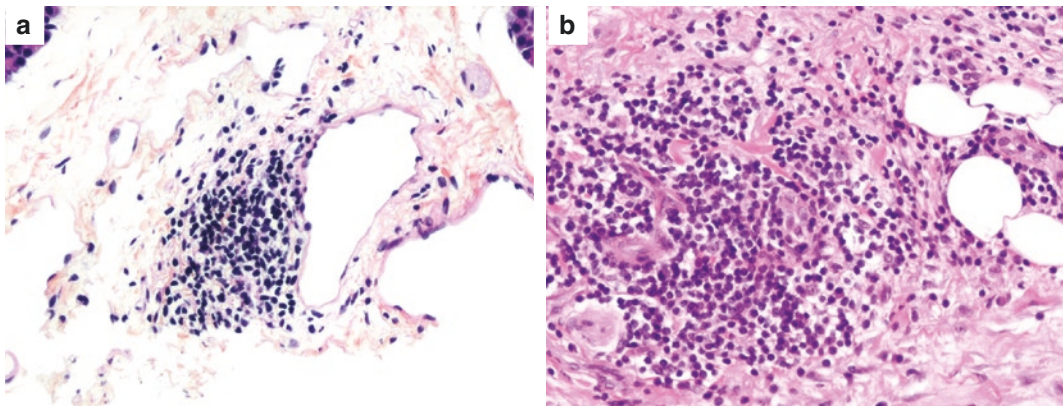

Fig. 22.5 "Indeterminate" grade of acute cellular rejection: septal lymphocytic infiltrates can be either focal (**a**) or more extensive (**b**). Findings of grade I or higher were absent. Note the absence of venulitis in (**a**)

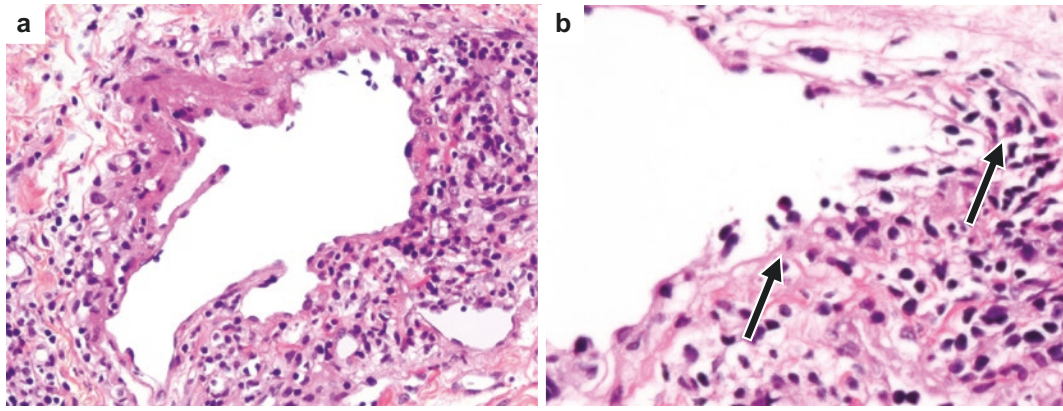

Fig. 22.6 Acute cellular rejection grade I: venulitis is characterized by activated lymphocytes cuffing and infiltrating the venular subendothelial space (**a**), lifting and damaging the endothelium (*arrows*), and spilling into the lumen (**b**)

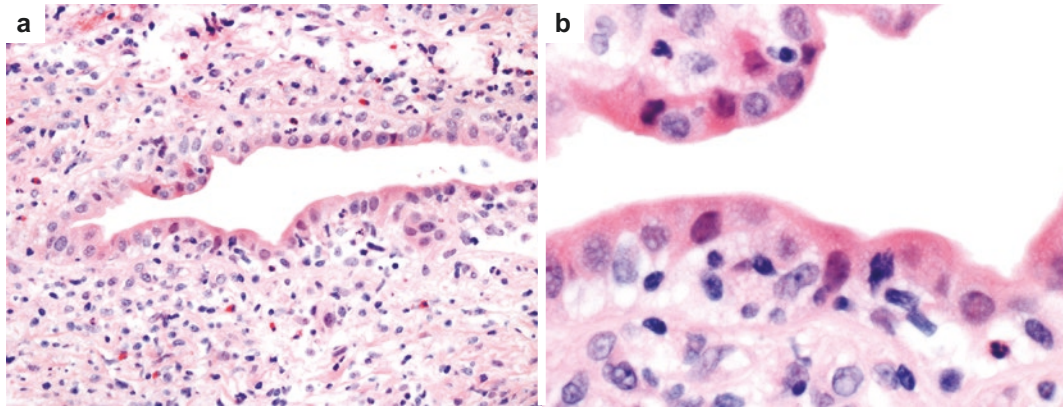

Fig. 22.7 Acute cellular rejection at least grade I: in ductitis, the duct is surrounded (**a**) and infiltrated by lymphocytes admixed with a few eosinophils (**b**)

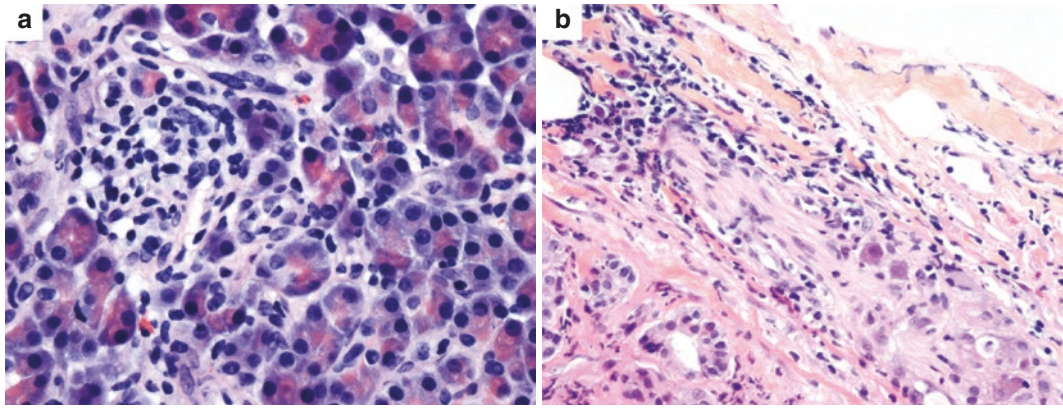

Fig. 22.8 Acute cellular rejection (ACR) at least grade I: there is a focus of acinar inflammation with ≥10 inflammatory cells and no definite acinar cell damage (**a**). With ≥ 2 of these foci per acinar lobule, the descriptor is "focal acinar inflammation". This core biopsy shows a nerve surrounded and infiltrated by lymphocytes, a feature also found in higher grades of ACR (**b**)

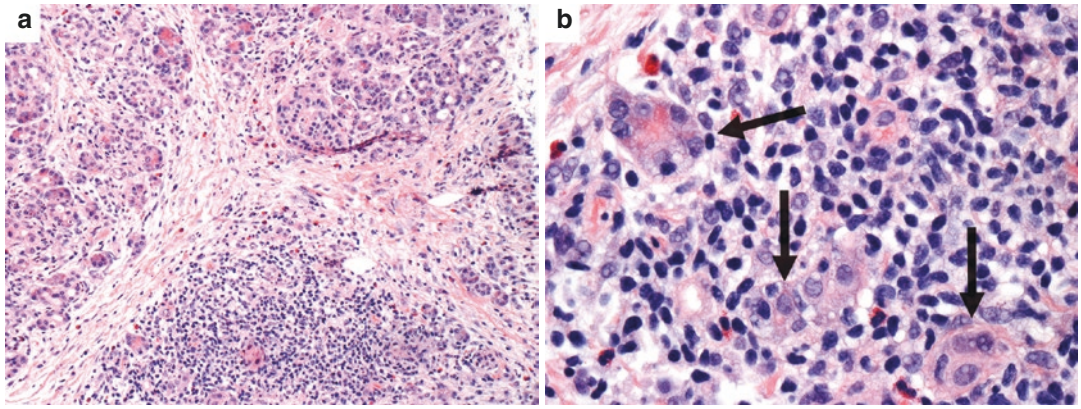

Fig. 22.9 Acute cellular rejection grade III: low power shows lobules of acini with variable inflammation separated by mildly to moderately thickened fibrous septa (**a**). The lobule at the top is least affected, the one on the left shows "multifocal acinar inflammation" with focal acinar cell damage or necrosis, and the one at the bottom shows extensive activated lymphocytic and eosinophilic infiltrate and loss of many acini. High power shows extensive lymphocytic infiltrate with eosinophils, together with degranulating and damaged acini (*arrows*, **b**)

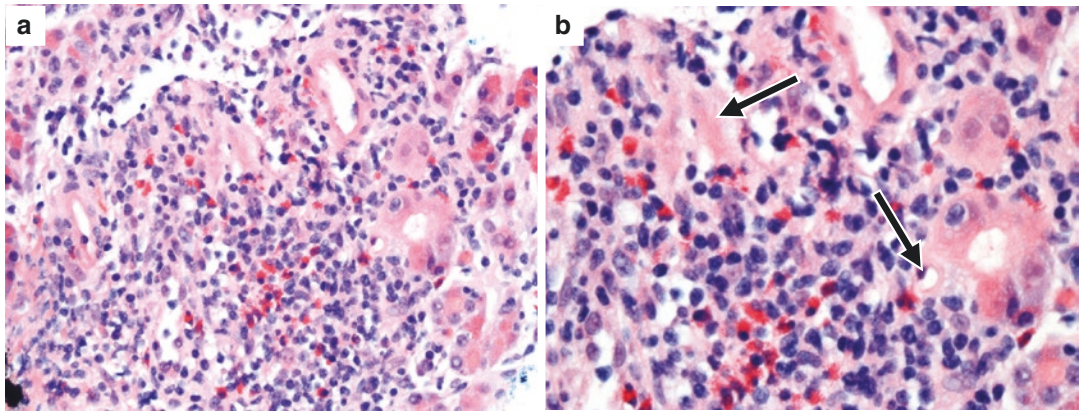

Fig. 22.10 Acute cellular rejection grade III with severe or extensive acinar inflammation: there is a prominent activated lymphocytic and eosinophilic infiltrate with loss of many acini (**a**). There is acinar epithelial cell damage with hypereosinophilia (*arrows*, **b**)

infiltrates of mononuclear inflammatory cells and/or eosinophils with lifting of the endothelium (Fig. 22.6).

- **Inflammation of interlobular ducts (ductitis)** with infiltration of ductal epithelium (i.e., localized to the mucosal epithelium inside the basement membrane) by mononuclear cells and/or eosinophils, plus ductal epithelial damage and/or denudation (Fig. 22.7).
- **Inflammation in and around the nerves** in interlobular septa (Fig. 22.8b).
- **Acinar cell injury or necrosis**, characterized by swelling or vacuolization of the cytoplasm, nuclear pyknosis, as well as apoptosis or necrosis leaving an empty space, i.e., dropout (Figs. 22.9 and 22.10). This may take the form of (1) "single cell/spotty acinar cell injury/necrosis" with preservation of the majority of acinar cells, or (2) "multicellular/confluent acinar cell injury/necrosis" with involvement of groupings of acinar cells of variable size.
- **Inflammation of arteries (arteritis)** that can take the form of (1) a "minimal intimal arteritis" with occasional very focal intimal inflammatory infiltrates of mononuclear cells without activation or damage of the endothe-

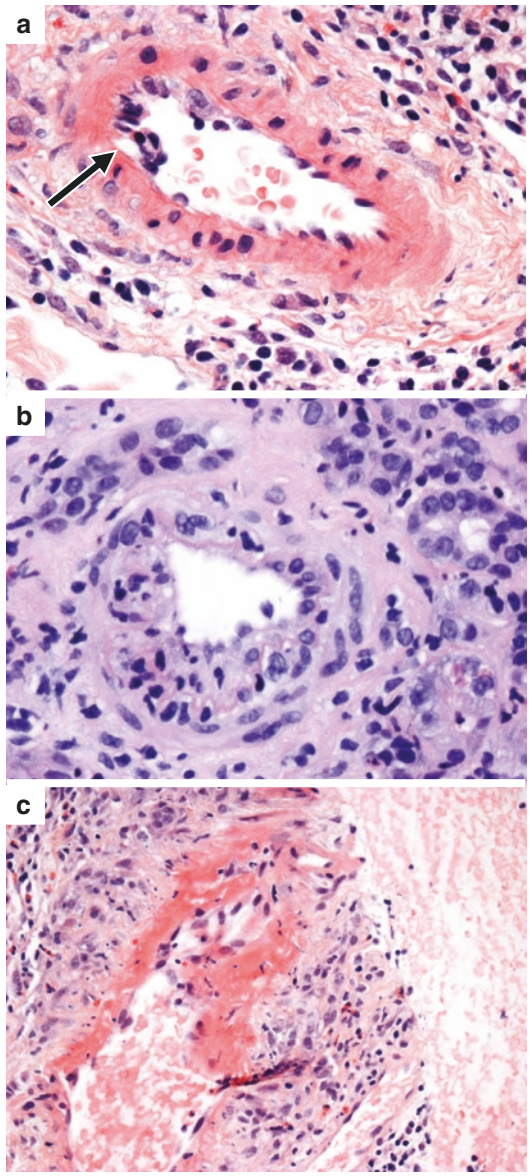

Fig. 22.11 Arteritis in acute cellular rejection (ACR): minimal intimal arteritis with focal infiltration of intima by inflammatory cells (*arrow*) is indicative of moderate ACR (**a**). Note also the lymphocytes and eosinophils around the artery. Moderate arteritis with infiltration of the intima and media by lymphocytes, and with endothelial damage, is a criterion of severe ACR (**b**). This medium-sized artery shows severe transmural arteritis with fibrinoid necrosis and endothelial damage (**c**). Note that vasculitis is also a feature of antibody-mediated rejection and an indication for C4d immunohistochemistry

lial cellular layer (Fig. 22.11a), (2) "moderate to severe intimal arteritis" with a clearly evident intimal mononuclear inflammatory infiltrate, plus damage to the intima, i.e., endothelial hypertrophy or sloughing, presence of fibrin, margination of neutrophils, or activation or proliferation of myofibroblasts (Fig. 22.11b), and (3) a "necrotizing arteritis" i.e., the presence of localized or circumferential mural fibrinoid necrosis and/or a transmural inflammatory infiltrate (Fig. 22.11c).

Note that these features do not include a description of inflammation or damage to the islets of Langerhans. Indeed, the prime target of the cell-mediated immune reaction is the acinar compartment. As in chronic pancreatitis, the islets are spared significant damage unless the process is severe or longstanding, or if the microvasculature supplying the islets is compromised.

22.5.2.3 Grading of ACR in the Pancreas Allograft

The diagnostic features and criteria are incorporated into the rejection **categories of the 2008 and 2011 Banff schemes for grading ACR** [39, 53]. They reflect the components that should be included in the pathology consultation report.

- **Normal:** characterized by absence of, or very minimal, inflammation composed of only small lymphocytes and/or rare plasma cells in septa only. Nerves, acini, ducts, and vessels are normal.
- **Indeterminate for rejection:** shows only focal septal or rarely acinar infiltrates of activated lymphocytes and/or eosinophils but without any of the definite criteria of ACR (Fig. 22.5). This category may be seen in protocol biopsies or with graft dysfunction and is either of unclear significance or may represent early or treated ACR. Management of these patients varies depending on clinical findings.

- **Mild or grade I ACR:** defined as septal inflammatory infiltrates (activated lymphocytes ± eosinophils) with either (1) venulitis and/or (2) ductitis, and/or less commonly (3) inflammation of nerves. Instead of the septal inflammatory component, there may be occasional focal acinar inflammation or spotty acinar cell injury or necrosis (Figs. 22.6, 22.7, 22.8). Grade I ACR usually manifests with graft dysfunction but is reversible with immunosuppressive therapy in about 90% of patients.
- **Moderate or grade II ACR:** defined as one or both of the following histopathologic features: (1) three or more foci of inflammation per acinar lobule, i.e., multifocal, with isolated or spotty acinar cell damage and dropout, and/or (2) a "minimal intimal arteritis", defined as very focal intimal inflammatory infiltrates of mononuclear cells and without endothelial activation or damage. Patients with grade II ACR usually have graft dysfunction and respond to immunosuppressive medications in 70–85% of cases [39].
- **Severe or grade III ACR:** defined as one or more of the following 3 histopathologic features: (1) **severe acinar inflammation and damage** plus focal or "multicellular/confluent acinar cell injury/necrosis" (Fig. 22.9, 22.10). Biopsies may show (a) polymorphous infiltrates of neutrophils, mononuclear cells and eosinophils, and (b) interstitial edema and hemorrhage. There should be minimal, if any, spared exocrine parenchyma; (2) **moderate to severe intimal arteritis** (Fig. 22.11b), and/or (3) a necrotizing arteritis (Fig. 22.11c). The prognosis of Grade III ACR is poor on account of inflammatory injury progressing to exocrine parenchymal loss, compromise of the microvasculature, and consequent loss of islets. The advanced vascular lesions increase the risk of thrombosis or may initiate or promote transplant arteriopathy. These biopsies are encountered in patients with prominent graft dysfunction including hyperglycemia. Response to augmented immunosuppression is generally poor [39].

22.5.2.4 Chronic Active Cell-Mediated Rejection

This subtype of ACR was included in the 2008 Banff schema and refers to the presence of an "active transplant arteriopathy" within the spectrum of chronic ACR. It is indicative of a pattern intermediate between the intimal arteritis of moderate or severe ACR and established "chronic transplant arteriopathy" [39]. These lesions, readily found in excised failed pancreatic allografts, are seldom encountered in core biopsies because they are generally not sampled. They arise in the setting of suboptimal immunosuppression, and if detected and promptly treated, potential arrest or partial reversal of the rejection may be achieved [30, 39].

22.5.3 Chronic Rejection or graft sclerosis in the pancreas allograft

Chronic rejection (CR) is the principal cause of late pancreas allograft loss. Indeed, whereas allograft loss due to acute rejection peaks between 3 and 12 months post-transplant, loss from chronic rejection continually rises after transplant and is one of the principal causes of long-term allograft loss after one year, the other being death from other causes [5].

Unlike acute cellular rejection that is "graded", chronic rejection is "staged", and the stage of CR is a good predictor of remaining graft function [60]. Moreover, the good correlations between ACR and CR, and between AMR and CR highlight the shared pathogenetic mechanisms [53].

22.5.3.1 Clinical and Laboratory Features of Cellular Rejection (CR)

The clinical and laboratory features of CR are nonspecific, and the diagnosis rests principally on manifestations related to loss of β-cell mass and function, i.e., blood glucose levels and/or measurements of C-peptide. Other causes of islet cell injury include calcineurin inhibitor toxicity or recurrence of autoimmune isletitis. It is noteworthy that the pancreas requires a substantial portion of islet cell mass loss before glucose or C-peptide abnormalities appear and therefore, by the time hyperglycemia occurs, the changes are largely irreversible. Furthermore, measurements of lipase and amylase, which herald ACR, lack sensitivity and specificity in the context of CR, due to the destruction of acini [60]. Therefore, the diagnosis of CR rests with the pathologist, and percutaneous core biopsies remain the gold standard.

22.5.3.2 Histopathologic Features of CR

The morphologic hallmark of CR in core biopsies is **graft sclerosis or fibrosis**, with concomitant atrophy and loss of acinar lobules (Figs. 22.12, 22.13) [39, 53]. Chronic vascular lesions may be present, but are rarely encountered in core biopsies and thus are not criteria in the staging scheme. The fibrosis, with admixed mononuclear infiltrates, starts in the interstitial perivascular areas of septa and gradually encroaches upon and obliterates the acinar lobules. The process culminates in subtotal replacement of the pancreas by dense collagenous tissue interspersed with residual atrophic acini, rare ducts, and a few islets. In addition, there is periductal fibrosis, and the ductal epithelial changes may show dysmorphic alterations (Fig. 22.14). The islets disappear relatively late in this fibrosing process and loss of α- and β-cells can be assessed with immunohistochemistry (Fig. 22.15). Masson's trichrome stain can be very useful in delineating the extent of fibrosis in CR.

22.5.3.3 Staging of CR in the Pancreas Allograft

The 4-point scheme for CR (stages 0-III) is primarily based on the percent surface area of the biopsy occupied by fibrous tissue [39, 53, 60]. The extent of acinar atrophy accompanying the fibrosis is not directly taken into account. The scheme is elucidated below and illustrated in Figs. 22.12 and 22.13.

- **Stage 0, normal pancreas:** the fibrous septa are of normal width and do not extend beyond the confines of the adjacent ducts and vessels; the acinar parenchyma is normal.

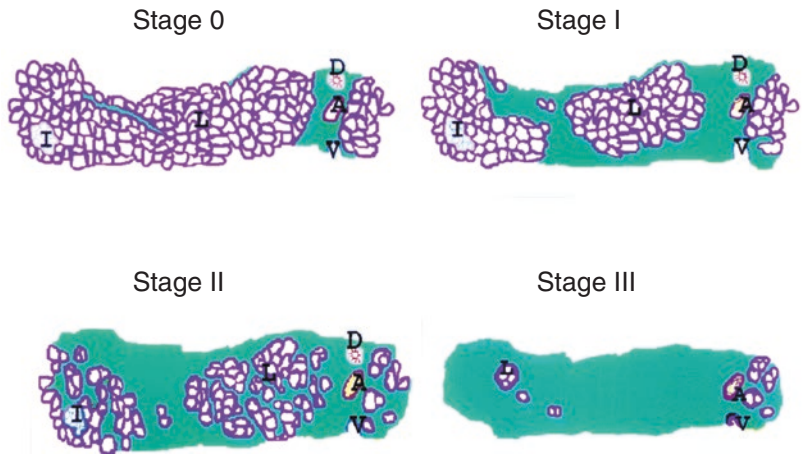

Fig. 22.12 Diagrammatic representation of the stages of chronic rejection according to the Banff scheme. Stage 0 is normal, with normal narrow interlobular septa; stage I has <30% of the biopsy area replaced by fibrous tissue, stage II, 30–60%, and stage III, >60% occupied by fibrous tissue. A, artery, D; duct, I, islet; L; lobule; V, vein (Reproduced with permission from Papadimitriou et al. [60], John Wiley and Sons)

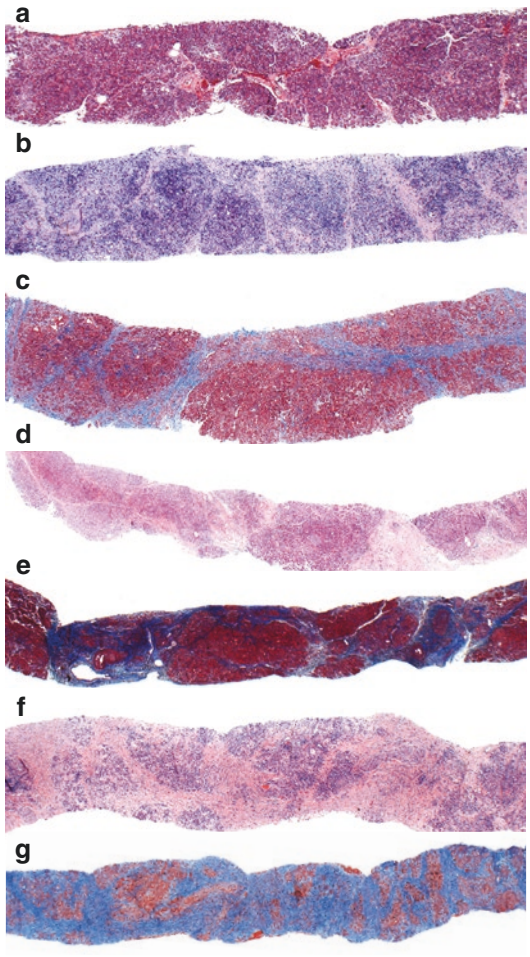

Fig. 22.13 Chronic rejection: normal parenchyma with thin interlobular septa corresponds to "stage 0" in the chronic rejection scheme (**a**). Stage I, mild chronic rejection shows large areas of preserved lobular tissue, and fibrous septa occupying <30% of the area of the biopsy (**b**, **c**). In chronic rejection stage II (**d**, **e**), and stage III (**f**, **g**), there is gradual atrophy of lobules and an increase in the proportion of septa giving the appearance of "cirrhosis". Masson trichrome (**c**, **e**, **g**)

- **Stage I, mild CR:** the fibrous septa are expanded, but the fibrosis comprises under 30% of the surface area of the biopsy. The centers of most acinar lobules are preserved, but the periphery can be irregular and focally eroded.
- **Stage II, moderate CR:** the fibrosis occupies 30 to 60% of the area of the biopsy and all lobules show some fragmentation and atrophy with focal drop-out of acini; the peripheral contours of most lobules are irregular with some atrophy in central areas. New fibrous septa traverse the lobules between acini.
- **Stage III, severe CR:** the fibrosis occupies over 60% of the surface area of the biopsy, with few remaining acini and islets.

22.5.3.4 Chronic Allograft Arteriopathy in the Pancreas Allograft

Chronic allograft arteriopathy is a distinctive intimal fibroproliferative and inevitable obliterative vascular lesion associated with chronic rejection that is similar in all solid organ transplants. Its **histopathologic features** include proliferation of intimal myofibroblasts, fibroblasts, and smooth muscle cells to form a concentrically thickened intimal layer, often accompanied by a variable mononuclear inflammatory cell infiltrate including foamy histiocytes (i.e., an endarteritis) (Fig. 22.16). These lesions produce ischemic damage to the graft and may predispose to thrombotic events.

The 2008 Banff schema distinguishes between **"transplant arteriopathy"** and **"active transplant arteriopathy"**. The former is characterized by predominantly fibrous thickening of the arterial intima, leading to narrowing of the lumen. It is graded based on the most advanced lesions into mild (< 25% of luminal area), moderate (25–50% of luminal area), or severe (>50% of luminal area). **Active transplant arteriopathy**, in addition to the above findings, also shows infiltration by mononuclear inflammatory cells (Fig. 22.16). This must be distinguished from the classic intimal arteritis found in severe ACR (Fig. 22.11) and in the vasculitis of AMR, in which necrosis and inflammation (acute and chronic) occur without substantial intimal myofibroblastic or smooth muscle proliferation.

In summary, paraphrasing the 2011 Banff conceptual approach to chronic allograft arteriopathy (or vasculopathy) [53], it is a relatively nonspecific entity that combines cellular and antibody-mediated immune mechanisms, and

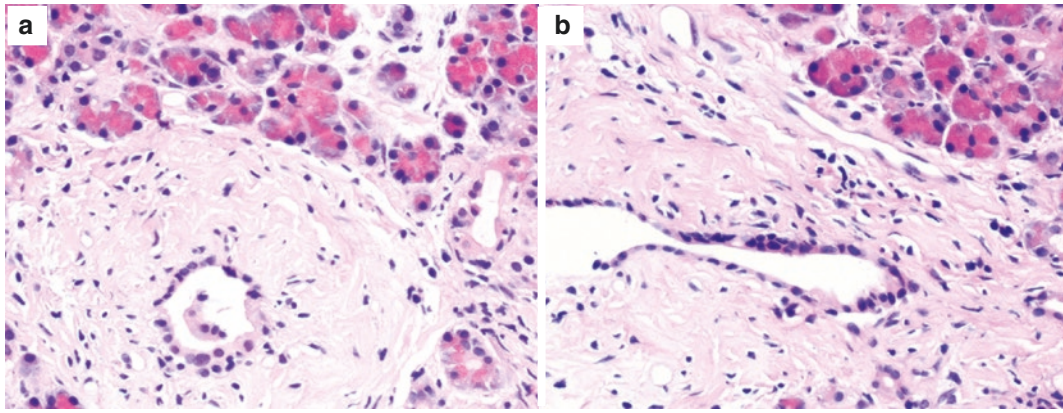

Fig. 22.14 Chronic rejection: the interlobular ducts in chronic rejection are surrounded by dense fibrosis and show irregularities and pleomorphism of the ductal cells (**a**, **b**)

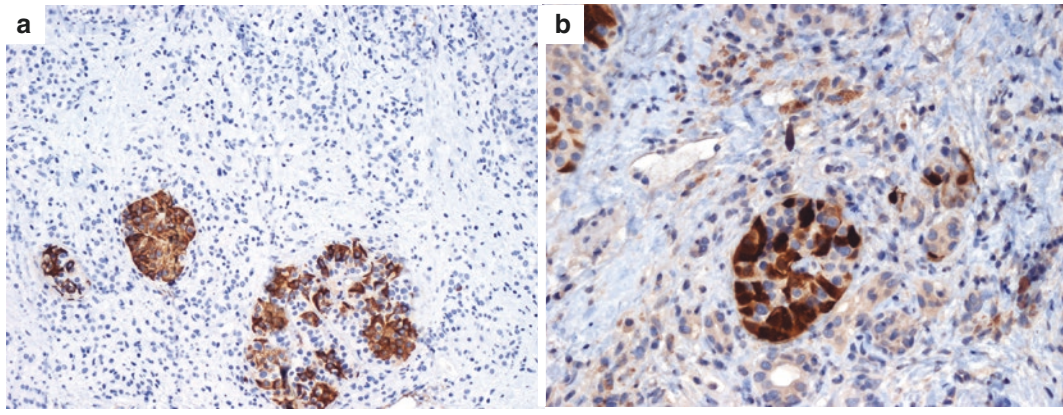

Fig. 22.15 Chronic rejection: there is variable atrophy and loss of cells in the islets, although this is much less marked than the loss of acinar parenchyma. Immunohistochemistry for insulin (**a**) and for glucagon (**b**)

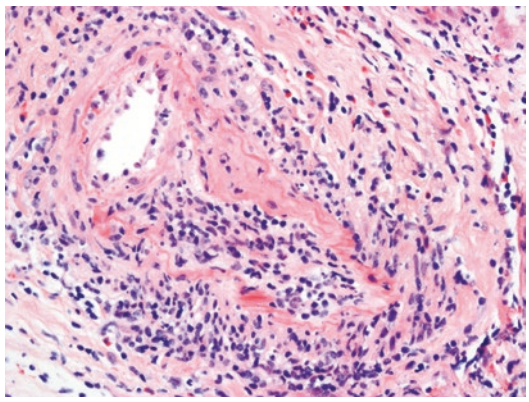

Fig. 22.16 Active transplant arteriopathy: there is a combination of mononuclear cells in the intima and media, and some fibrous thickening with luminal stenosis

is seen at the more severe end of the spectrum of ACR and AMR, as well as in CR. In other words, it fits into a continuum that starts with moderate or severe ACR and AMR, traverses through chronic active cell-mediated rejection and chronic active antibody-mediated rejection, and with time or perhaps if suboptimally treated, terminates in chronic rejection. In practice, it is recommended that finding either intimal arteritis or chronic allograft arteriopathy should prompt the search for other pathological features of both ACR and AMR, including immunopositivity for C4d, as well as an assessment of the fibrosis to accurately stage the CR.

22.5.4 Differential Diagnosis of Forms of Rejection, and Distinction from Other Entities Encountered in Core Biopsies

Acute cellular rejection (ACR) must be differentiated from antibody-mediated rejection (AMR) because the clinical management differs. That said, both ACR and AMR can co-exist. Helpful morphologic clues that aid in their distinction include the following [53]:

- **Features predominating in AMR** are (1) an inflammatory infiltrate composed of neutrophils and monocytes/macrophages; (2) acinar cell injury; (3) interacinar capillaritis; (4) necrotizing arteritis ± thrombosis; (5) hemorrhagic necrosis if severe; and importantly (6) focal or diffuse immunopositivity for C4d in interacinar capillaries.
- **Features predominating in ACR** are (1) septal infiltrates composed predominantly of mononuclear cells, i.e., T-cells ± eosinophils (neutrophils can be found in severe ACR); (2) acinitis with infiltration of mononuclear cells inside the acinar basement membrane; (3) venulitis and/or ductitis and/or peripheral nerve inflammation.
- **Features shared by AMR and ACR** are (1) to some extent acinar cellular injury and (2) active transplant arteriopathy in severe or advanced lesions.

The other differential diagnostic considerations of acute allograft rejection, and to a lesser extent chronic rejection (CR), are summarized in Table 22.1. Parenthetically, these other disorders are now infrequently observed in core biopsies [44].

Table 22.1 Pathologic alterations in the differential diagnosis of rejection

Diagnostic entity	Histopathologic and related features	Type of rejection with key differentiating features
Ischemia-reperfusion injury and ischemic pancreatitis	Ischemic damage or necrosis of acini (vacuolization, apoptosis, necrosis, drop-out). Principally interlobular septal acute inflammation with neutrophils, foamy macrophages, fat necrosis, interstitial edema ± hemorrhage. Fibrosis typically absent.	Principally AMR: necrotizing vasculitis ± fibrinoid necrosis; positive staining for C4d.
Infectious pancreatitis, peripancreatitis and peripancreatic fluid collection	Mixed septal and peripheral lobular acute and chronic inflammation with neutrophils, some lymphocytes, plasma cells, and eosinophils. May be granulomas, abscesses, and bacterial or fungal organisms (special stains useful). May be bundles of active fibroblastic proliferation in interlobular septa at periphery of acinar lobules.	AMR: vasculitis, interacinar capillaritis; positive staining for C4d. ACR: predominantly septal and acinar activated lymphocytes ± eosinophils, venulitis, ductitis. When severe, neutrophils and arteritis. CR: occurs later, dense septal fibrosis, acinar ± islet atrophy, vasculopathy.
Pancreatitis due to CMV	Predominantly mononuclear inflammation, focal in septa and acini, with viral cytopathic changes in endothelium, acinar or stromal cells. Positive immunohistochemistry for CMV. Correlate with serum PCR studies.	Mostly mild ACR: venulitis, ductitis. Absent viral cytopathic changes, negative immunohistochemistry and PCR for CMV.

(continued)

Table 22.1 (continued)

Diagnostic entity	Histopathologic and related features	Type of rejection with key differentiating features
Recurrent autoimmune isletitis, diabetes mellitus	Lymphocytic infiltration of specifically islets (isletitis). Absence of inflammation in late stages after disappearance of β-cells. Immunohistochemical stains for insulin and glucagon show preferential loss of β-cells. Correlate with autoantibodies to islet cells, insulin, GAD.	ACR: lymphocytic infiltration predominantly in acini, not in islets. CR: fibrosis, acinar atrophy; loss of both insulin- and glucagon-producing cells.
Acute islet cell toxicity from calcineurin inhibitors (cyclosporine, tacrolimus)	**Islet cell damage**: vacuolization or swelling of cytoplasm, loss of islet cells replaced by lacunae, focal necrosis or apoptosis. Absence of isletitis. **Immunohistochemistry**: markedly decreased staining for insulin compared with glucagon. **Electron microscopy**: vacuolization of β-cells with specific loss of insulin dense core granules. Observed more with tacrolimus (dose-dependent and reversible).	Recurrent autoimmune diabetes: associated with isletitis, autoantibodies.
Post-transplant lymphoproliferative disorder (PTLD)	Polymorphic type: infiltrate of variably atypical lymphocytes, polyclonal or monoclonal plasma cells, few eosinophils. Monomorphic type: infiltrate of large atypical B-cells (diffuse large B-cell lymphoma or other). Frequent positivity for EBV (in situ hybridization for EBER). May form a mass (correlate with clinical findings and imaging studies).	ACR: infiltrating lymphocytes small or activated, not frankly atypical; venulitis, ductitis; no mass; EBV absent.

Abbreviatons: *ACR* acute cellular rejection, *AMR* antibody-mediated rejection, *CR* chronic rejection, *EBV* Epstein-Barr virus, *EBER* EBV-encoded small RNA, *GAD* glutamic acid decarboxylase, *PCR* polymerase chain reaction
See also references [27, 35, 39]

22.6 Infections in Pancreas Allografts

Bacterial and fungal infections may occur because of surgical complications, and the findings resemble those of acute pancreatitis in the non-transplant setting (Figs. 22.17 and 22.18). Of the fungal infections, *Candida* species are the most common [34, 61].

Infections due to cytomegalovirus (CMV) remain a lingering concern despite prophylaxis. Up to 44% of CMV-negative recipients of a pancreas from a CMV-positive donor developed CMV infection/disease, despite CMV prophylaxis. **Pathologic findings** are detailed in Table 22.1. Immunohistochemistry and PCR studies of the blood are helpful if histopathologic findings are equivocal.

Other viral infections can occur in pancreatic transplant recipients, particularly those in the *Herpes* family. Two studies report the incidence of Herpes simplex infection of about 10% and Varicella zoster virus around 11%, primarily involving the gastrointestinal tract and skin, but not the allograft [62, 63].

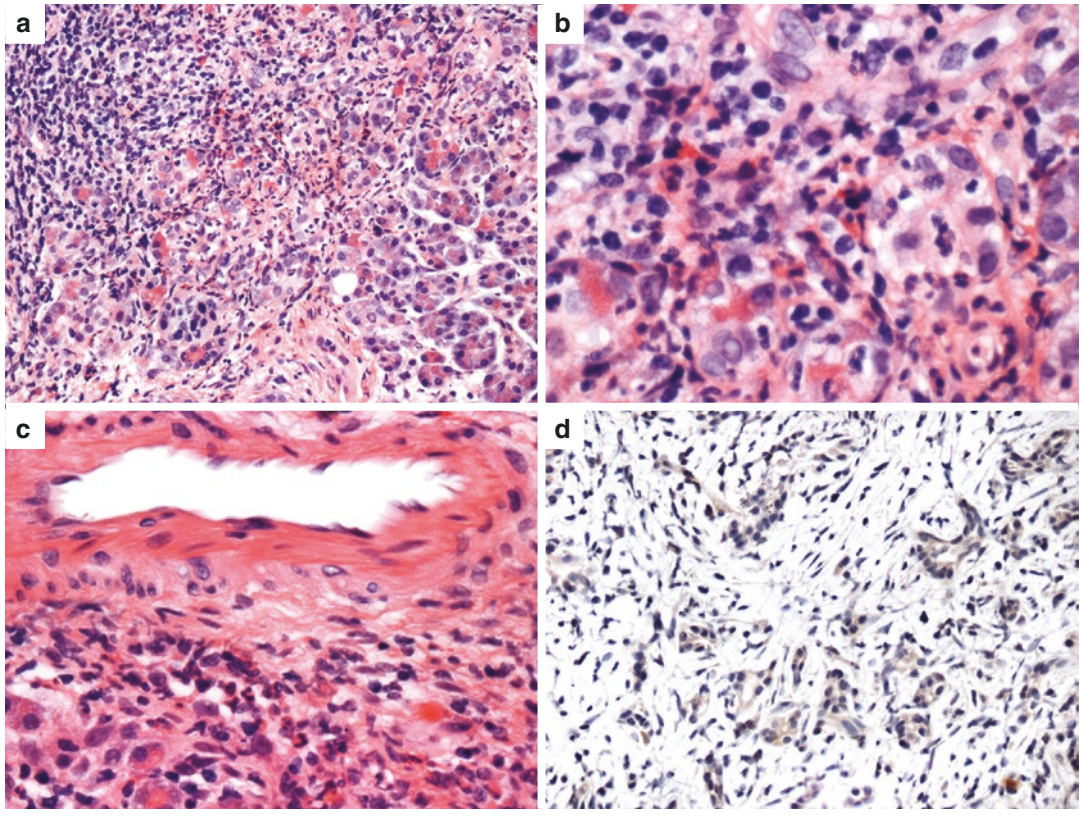

Fig. 22.17 Post-transplant patient with acute pancreatitis: the core biopsy shows a predominantly neutrophilic infiltrate in the septum and amongst acini (**a**, **b**). The differential diagnoses include acute cellular rejection (ACR) and particularly antibody-mediated rejection (AMR). However, note the absence of arteritis (**c**), and the negative C4d immunohistochemistry (**d**)

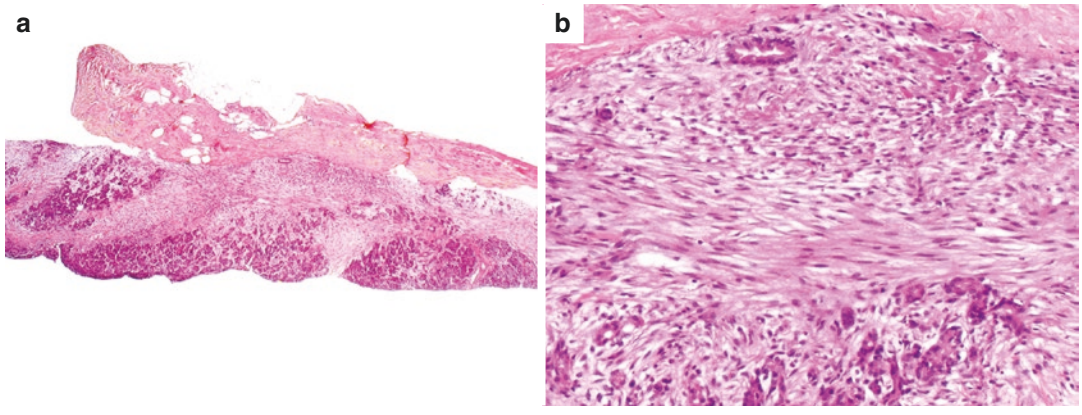

Fig. 22.18 Post-transplant patient with peripancreatitis: there is active granulation tissue at the surface (**a**) and dissecting between lobules (**b**)

22.7 Recurrent Autoimmune Isletitis (Insulitis) and Diabetes Mellitus

The incidence of recurrent TIDM, initially reported in sets of identical twins, approaches 17% for T1DM after a median follow-up of 39 months [27, 64–68]. However, recurrent autoimmune DM is not the only cause of hyperglycemia. In one long-term study, 15% of recipients presented with significant hyperglycemia associated with different etiologies, including chronic rejection (5–6%), post-transplant DM with insulin resistance secondary to weight gain and/or medications (6–7%), recurrent T1DM in 5–6%, and rarely, vascular thrombosis [65].

The pathogenesis of recurrent autoimmune isletitis recapitulates that of the original disease. The β-cells are targeted specifically by immune mechanisms involving B- and T-cells, and antibodies, leaving α- and δ-cells unharmed [64, 65, 69].

Clinically, there is gradual or rapid loss of glycemic control and the variable appearance of serum autoantibodies. Although these autoantibodies are good predictors of autoimmune DM, biopsy is frequently required to confirm the diagnosis [27, 69].

22.7.1 Pathologic Findings in Recurrent Autoimmune Isletitis

Pathologic findings in recurrent autoimmune isletitis include early infiltration of the islets (not acini as in rejection) by predominantly T-cells, followed by gradual disappearance of β-cells, and of the lymphocytes [66, 67]. Immunohistochemistry using antibodies against insulin and glucagon is useful to demonstrate the selective loss of β-cells (Fig. 22.19).

22.8 Acute Islet Cell Toxicity from Calcineurin Inhibitors

Another cause of post-transplant hyperglycemia is targeted damage to β-cells by calcineurin inhibitors, particularly tacrolimus, a dose-related, reversible effect [27, 39]. Light microscopy shows cytoplasmic swelling and vacuolization of β-cells, with apoptosis. Immunohistochemistry shows decreased staining for insulin compared with glucagon. The inflammation seen in recurrent autoimmune isletitis is lacking in calcineurin inhibitor toxicity. The findings can be correlated with the serum tacrolimus and/or with serum autoantibodies.

22.9 Reporting Checklists

A list of macroscopic and microscopic features to consider when reporting failed allografts is shown in Table 22.2. A list of microscopic features to consider when reporting an allograft core biopsy for the principal forms of rejection and other findings is shown in Table 22.3. These checklists are meant only as guidelines and should be adapted to local reporting practices.

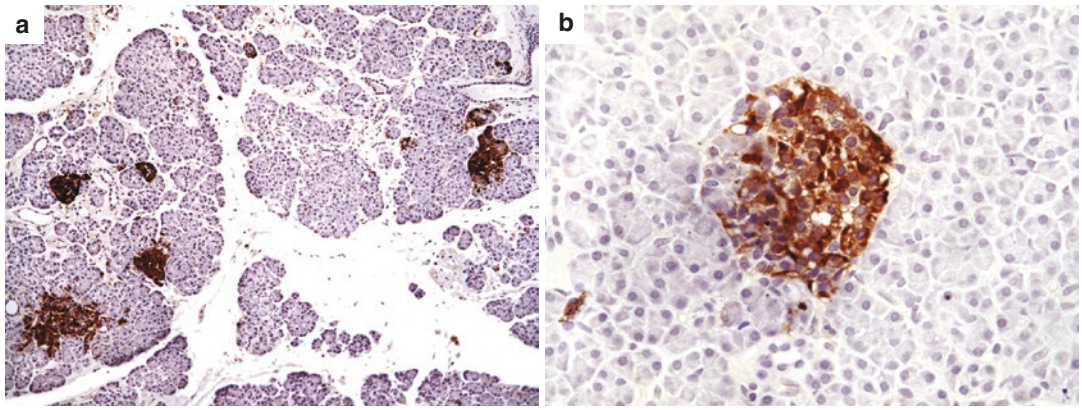

Fig. 22.19 Recurrent isletitis of type I diabetes: immunohistochemistry for glucagon (**a**, **b**) and for insulin (**c**, **d**) shows the selective loss of insulin-producing β-cells

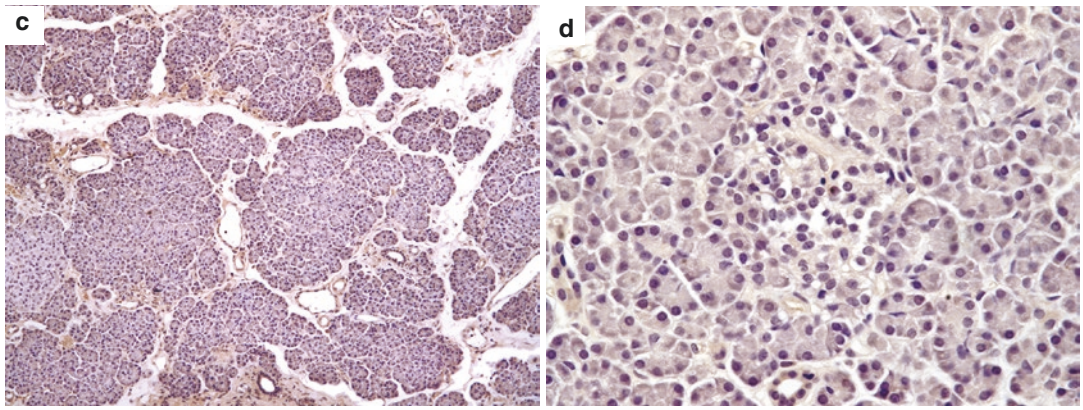

Fig. 22.19 (continued)

Table 22.2 Reporting of failed pancreas allograft

Macroscopic assessment
Specimen type (e.g., pancreas allograft, with or without donor duodenum, recipient small bowel)
Pancreas, donor duodenum, recipient small bowel, artery, vein
Weight of specimen
Dimensions of each part
Other features
Appearance of
Pancreas (necrotic, viable, hemorrhagic, inflamed, other)
Donor and recipient small bowel (necrotic, viable, hemorrhagic, inflamed, other)
Arteries, veins (patent, thrombosed, other)
Microscopic assessment
Pancreatic parenchyma
Total, subtotal, partial necrosis with edema, hemorrhage, abscess formation, organisms, other
Donor duodenum
Total, subtotal, partial necrosis, ulceration, edema, hemorrhage
Recipient small bowel
No necrosis, focal, partial necrosis, inflammation, other
Artery
Patent, partial or complete thrombosis
Vein
Patent, partial or complete thrombosis
Other findings

Table 22.3 Reporting of pancreas allograft core biopsies (template) [53]

Antibody-mediated rejection
Adequate biopsy showing capillaritis, interacinar inflammation, acinar cell damage, vasculitis or thrombosis, most consistent with antibody-mediated rejection, grade I (mild), grade II (moderate), grade III (severe)
C4d stain negative/faintly/moderately/strongly positive in about % of interstitial capillaries
Conclusion (with or without presence of DSA): definite acute antibody-mediated rejection (AMR) / consistent with acute AMR/requires exclusion of AMR.
Acute cellular rejection, grade I out of III
Adequate biopsy showing active septal inflammation, and venulitis with lymphocytes, and few eosinophils most consistent with acute cell-mediated rejection, mild, grade I out of III
Two to three small arteries and few arterioles present on biopsy with no diagnostic abnormality.
Masson trichrome stains shows minimal if any septal and acinar fibrosis.
C4d stain negative/faintly/moderately/strongly positive in about % of interstitial capillaries
Acute cellular rejection, grade II or III out of III
Adequate biopsy showing inflammation with mostly lymphocytes and few eosinophils, multifocal acinar inflammation, with acinar cell injury, ductitis, venulitis and minimal arterial arteritis /necrotizing arteritis, consistent with acute cell-mediated rejection, moderate, grade II or III out of III

(continued)

Table 22.3 (continued)

Masson trichrome stains shows minimal if any septal and acinar fibrosis.
C4d stain negative/faintly/moderately/strongly positive in about % of interstitial capillaries
Chronic rejection, grade I, II, or III out of III
Adequate biopsy showing mild/moderate/severe septal fibrosis and acinar atrophy, with or without arterial changes/foam cell arteriopathy, consistent with chronic allograft rejection/graft sclerosis, mild/moderate/severe, grade I or II or III out of III
Masson trichrome stains shows mild/moderate/severe septal fibrosis.
C4d stain negative/faintly/moderately/strongly positive in about % of interstitial capillaries
Other findings
Infections (CMV, other…)
Inflammation, pancreatitis
Ischemia/reperfusion injury
Changes of calcineurin inhibitor toxicity
Recurrent isletitis

Abbreviations: *CMV* Cytomegalovirus, *DSA* Donor-specific antibodies

References

1. National Diabetes Statistics Report, 2017. Estimates of diabetes and its burden in the United States Atlanta, Georgia: Center for Disease Control and Prevention; 2017 [updated 06/2019; cited 2019 December 11, 2019]. https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf.
2. American Diabetes Association. Statistics about diabetes data from the national diabetes statistics report, 2015 2015 [cited 2019 December 11]. https://www.diabetes.org/resources/statistics/statistics-about-diabetes.
3. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. BMJ. 2017;357:j1321.
4. Nathan DM. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2014;37(1):9–16.
5. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nat Rev Endocrinol. 2013;9(9):555–62.
6. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. Lancet. 2009;373(9677):1808–17.
7. Bijkerk R, Duijs JM, Khairoun M, Ter Horst CJ, van der Pol P, Mallat MJ, et al. Circulating microRNAs associate with diabetic nephropathy and systemic microvascular damage and normalize after simultaneous pancreas-kidney transplantation. Am J Transplant. 2015;15(4):1081–90.
8. Sutherland DER, Gruessner RWG. History of pancreas transplantation. In: Gruessner RWG, Sutherland DER, editors. Transplantation of the pancreas. New York, NY: Springer-Verlag; 2004. p. 39–68.
9. Squifflet JP, Gruessner RW, Sutherland DE. The history of pancreas transplantation: past, present and future. Acta Chir Belg. 2008;108(3):367–78.
10. Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery. 1967;61(6):827–37.
11. Gruessner AC, Gruessner RW. Pancreas transplant outcomes for United States and non United States cases as reported to the United Network for Organ Sharing and the International Pancreas Transplant Registry as of December 2011. Clin Transpl. 2012:23–40.
12. Kandaswamy R, Stock PG, Gustafson SK, Skeans MA, Urban R, Fox A, et al. OPTN/SRTR 2017 annual data report: pancreas. Am J Transplant. 2019;19(Suppl 2):124–83.
13. Mehrabi A, Golriz M, Adili-Aghdam F, Hafezi M, Ashrafi M, Morath C, et al. Expanding the indications of pancreas transplantation alone. Pancreas. 2014;43(8):1190–3.
14. Bux Rodeman K, Hatipoglu B. Beta-cell therapies for type 1 diabetes: Transplants and bionics. Cleve Clin J Med. 2018;85(12):931–7.
15. CITR Tenth Annual Report (2016) Rockville, MD: Collaborative Islet Transplant Registry; 2017. https://citregistry.org/system/files/10th_AR.pdf. Accessed 14 Dec 2019.
16. Wisel SA, Braun HJ, Stock PG. Current outcomes in islet versus solid organ pancreas transplant for beta-cell replacement in type 1 diabetes. Curr Opin Organ Transplant. 2016;21(4):399–404.
17. Inaugural Report on Autologous Islet Transplantation Rockville, MD: CITR Coordinating Center; 2017. https://citregistry.org/system/files/10th_AR.pd. Accessed 14 Dec 2019.
18. Han DJ, Sutherland DER. Living donor pancreas transplantation. In: Oniscu GC, Forsythe JLR, Pomfret EA, editors. Transplantation surgery. Springer surgery atlas series, vol. 1. Berlin, Germany: Springer-Verlag; 2019. p. 485–500.
19. Choi JY, Jung JH, Kwon H, Shin S, Kim YH, Han DJ. Pancreas transplantation from living donors: a single center experience of 20 cases. Am J Transplant. 2016;16(8):2413–20.
20. Samoylova ML, Borle D, Ravindra KV. Pancreas transplantation: indications, techniques, and outcomes. Surg Clin North Am. 2019;99(1):87–101.
21. Kakar S, Shi C, Adsay NV, Fitzgibbons P, Frankel WL, Klimstra DS, et al. Protocol for the examination of specimens from patients with carcinoma of the exocrine pancreas. College of American Pathologists (CAP), 2017. www.cap.org. Accessed 8 Jan 2020.
22. Campbell F, Cairns A, Duthie F, Feakins R. Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. London: The Royal College of Pathologists; 2017.

23. The Royal College of Pathologists of Australasia. Cancer of the exocrine pancreas, ampulla of Vader and distal common bile duct. Structured reporting protocol, 2014. www.rcpa.edu.au/Library/Practising-Pathology/Structured-Pathology-Reporting-of-Cancer/Cancer-Protocols. Accessed 8 Jan 2020.
24. Westermark GT, Davalli AM, Secchi A, Folli F, Kin T, Toso C, et al. Further evidence for amyloid deposition in clinical pancreatic islet grafts. Transplantation. 2012;93(2):219–23.
25. Desai CS, Khan KM, Megawa FB, Rilo H, Jie T, Gruessner A, et al. Influence of liver histopathology on transaminitis following total pancreatectomy and autologous islet transplantation. Dig Dis Sci. 2013;58(5):1349–54.
26. Laftavi MR, Gruessner A, Gruessner R. Surgery of pancreas transplantation. Curr Opin Organ Transplant. 2017;22(4):389–97.
27. Patil DT, Yerian LM. Pancreas transplant: recent advances and spectrum of features in pancreas allograft pathology. Adv Anat Pathol. 2010;17(3):202–8.
28. Troppmann C. Complications after pancreas transplantation. Curr Opin Organ Transplant. 2010;15(1):112–8.
29. Farney AC, Rogers J, Stratta RJ. Pancreas graft thrombosis: causes, prevention, diagnosis, and intervention. Curr Opin Organ Transplant. 2012;17(1):87–92.
30. Drachenberg CB, Papadimitriou JC, Farney A, Wiland A, Blahut S, Fink JC, et al. Pancreas transplantation: the histologic morphology of graft loss and clinical correlations. Transplantation. 2001;71(12):1784–91.
31. Drachenberg CB, Papadimitriou JC. The inflamed pancreas transplant: histological differential diagnosis. Semin Diagn Pathol. 2004;21(4):255–9.
32. Khaja MS, Matsumoto AH, Saad WE. Vascular complications of transplantation: part 2: pancreatic transplants. Cardiovasc Intervent Radiol. 2014;37(6):1415–9.
33. Delis S, Dervenis C, Bramis J, Burke GW, Miller J, Ciancio G. Vascular complications of pancreas transplantation. Pancreas. 2004;28(4):413–20.
34. Bono B. Managment of infections in pancreatic transplant recipients. In: Kumar D, Humar A, editors. AST handbook of transplant infections, vol. 2. Hoboken, NJ, USA: Wiley-Blackwell; 2011. p. 22.
35. Drachenberg CB, Papadimitriou JC. Pancreas transplantation pathology. In: Ruiz P, editor. Transplantation pathology. Cambridge: Cambridge University Press; 2009. p. 249–89.
36. Maglione M, Ploeg RJ, Friend PJ. Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation. Curr Opin Organ Transplant. 2013;18(1):83–8.
37. Klassen DK, Weir MR, Cangro CB, Bartlett ST, Papadimitriou JC, Drachenberg CB. Pancreas allograft biopsy: safety of percutaneous biopsy-results of a large experience. Transplantation. 2002;73(4):553–5.
38. Atwell TD, Gorman B, Larson TS, Charboneau JW, Ingalls Hanson BM, Stegall MD. Pancreas transplants: experience with 232 percutaneous US-guided biopsy procedures in 88 patients. Radiology. 2004;231(3):845–9.
39. Drachenberg CB, Odorico J, Demetris AJ, Arend L, Bajema IM, Bruijn JA, et al. Banff schema for grading pancreas allograft rejection: working proposal by a multi-disciplinary international consensus panel. Am J Transplant. 2008;8(6):1237–49.
40. Gruessner RW, Nakhleh R, Tzardis P, Schechner R, Platt JL, Gruessner A, et al. Differences in rejection grading after simultaneous pancreas and kidney transplantation in pigs. Transplantation. 1994;57(7):1021–8.
41. Troxell ML, Koslin DB, Norman D, Rayhill S, Mittalhenkle A. Pancreas allograft rejection: analysis of concurrent renal allograft biopsies and posttherapy follow-up biopsies. Transplantation. 2010;90(1):75–84.
42. Assalino M, Hadaya K, Andres A, Berney T. Discordant rejection in simultaneous pancreas and kidney transplantation: true discordance or analysis artefact? Transpl Int. 2018;31(1):17–9.
43. Parajuli S, Arpali E, Astor BC, Djamali A, Aziz F, Redfield RR, et al. Concurrent biopsies of both grafts in recipients of simultaneous pancreas and kidney demonstrate high rates of discordance for rejection as well as discordance in type of rejection – a retrospective study. Transpl Int. 2018;31(1):32–7.
44. Redfield RR, Kaufman DB, Odorico JS. Diagnosis and treatment of pancreas rejection. Curr Transplant Rep. 2015;2(2):169–75.
45. Gunther Brockmann J, Butt A, AlHussaini HF, AlMana H, AlSaad K, Al-Awwami M, et al. Protocol duodenal graft biopsies aid pancreas graft surveillance. Transplantation. 2019;103(3):622–9.
46. de Kort H, Roufosse C, Bajema IM, Drachenberg CB. Pancreas transplantation, antibodies and rejection: where do we stand? Curr Opin Organ Transplant. 2013;18(3):337–44.
47. Drachenberg CB. Is the duodenum trustworthy? Transplantation. 2019;103(3):463–4.
48. Casey ET, Smyrk TC, Burgart LJ, Stegall MD, Larson TS. Outcome of untreated grade II rejection on solitary pancreas allograft biopsy specimens. Transplantation. 2005;79(12):1717–22.
49. Drachenberg CB, Papadimitriou JC, Schweitzer E, Philosophe B, Foster C, Bartlett ST. Histological findings in "incidental" intraoperative pancreas allograft biopsies. Transplant Proc. 2004;36(3):780–1.
50. Chinen J, Buckley RH. Transplantation immunology: solid organ and bone marrow. J Allergy Clin Immunol. 2010;125(2). Suppl 2:S324–35.
51. Farrar CA, Kupiec-Weglinski JW, Sacks SH. The innate immune system and transplantation. Cold Spring Harb Perspect Med. 2013;3(10)
52. Singh R, Sutherland DER, Kandaswamy R. Pancreas transplantation. In: Mamode N, Kandaswamy R, editors. Abdominal organ transplantation. Oxford, UK: John Wiley & Sons, Ltd; 2013. p. 80–106.
53. Drachenberg CB, Torrealba JR, Nankivell BJ, Rangel EB, Bajema IM, Kim DU, et al. Guidelines for the

diagnosis of antibody-mediated rejection in pancreas allografts-updated Banff grading schema. Am J Transplant. 2011;11(9):1792–802.
54. Hawthorne WJ, Griffin AD, Lau H, Hibbins M, Grierson JM, Ekberg H, et al. Experimental hyperacute rejection in pancreas allotransplants. Transplantation. 1996;62(3):324–9.
55. Haas M. An updated Banff schema for diagnosis of antibody-mediated rejection in renal allografts. Curr Opin Organ Transplant. 2014;19(3):315–22.
56. Haas M, Sis B, Racusen LC, Solez K, Glotz D, Colvin RB, et al. Banff 2013 meeting report: inclusion of C4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant. 2014;14(2):272–83.
57. Berry GJ, Burke MM, Andersen C, Bruneval P, Fedrigo M, Fishbein MC, et al. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2013;32(12):1147–62.
58. Torrealba JR, Samaniego M, Pascual J, Becker Y, Pirsch J, Sollinger H, et al. C4d-positive interacinar capillaries correlates with donor-specific antibody-mediated rejection in pancreas allografts. Transplantation. 2008;86(12):1849–56.
59. De Kort H, Munivenkatappa RB, Berger SP, Eikmans M, Van Der Wal A, De Koning EJ, et al. Pancreas allograft biopsies with positive C4d staining and anti-donor antibodies related to worse outcome for patients. Am J Transplant. 2010;10(7):1660–7.
60. Papadimitriou JC, Drachenberg CB, Klassen DK, Gaber L, Racusen LC, Voska L, et al. Histological grading of chronic pancreas allograft rejection/graft sclerosis. Am J Transplant. 2003;3(5):599–605.
61. Fallatah SM, Marquez MA, Bazerbachi F, Schiff JR, Cattral MS, McGilvray ID, et al. Cytomegalovirus infection post-pancreas-kidney transplantation – results of antiviral prophylaxis in high-risk patients. Clin Transplant. 2013;27(4):503–9.
62. Netchiporouk E, Tchervenkov J, Paraskevas S, Sasseville D, Billick R. Evaluation of herpes simplex virus infection morbidity and mortality in pancreas and kidney-pancreas transplant recipients. Transplant Proc. 2013;45(9):3343–7.
63. Netchiporouk E, Tchervenkov J, Paraskevas S, Sasseville D, Billick R. Evaluation of varicella zoster virus infection morbidity and mortality in pancreas and kidney-pancreas transplant recipients. Transplant Proc. 2013;45(2):701–4.
64. Tyden G, Reinholt FP, Sundkvist G, Bolinder J. Recurrence of autoimmune diabetes mellitus in recipients of cadaveric pancreatic grafts. N Engl J Med. 1996;335(12):860–3.
65. Burke GW 3rd, Vendrame F, Pileggi A, Ciancio G, Reijonen H, Pugliese A. Recurrence of autoimmunity following pancreas transplantation. Curr Diab Rep. 2011;11(5):413–9.
66. Sibley RK, Sutherland DE. Pancreas transplantation. An immunohistologic and histopathologic examination of 100 grafts. Am J Pathol. 1987;128(1):151–70.
67. Sibley RK, Sutherland DE, Goetz F, Michael AF. Recurrent diabetes mellitus in the pancreas iso- and allograft. A light and electron microscopic and immunohistochemical analysis of four cases. Lab Invest. 1985;53(2):132–44.
68. Dean PG, Kudva YC, Larson TS, Kremers WK, Stegall MD. Posttransplant diabetes mellitus after pancreas transplantation. Am J Transplant. 2008;8(1):175–82.
69. Martins LS, Henriques AC, Fonseca IM, Rodrigues AS, Oliverira JC, Dores JM, et al. Pancreatic autoantibodies after pancreas-kidney transplantation – do they matter? Clin Transplant. 2014;28(4):462–9.