Pancreas Transplant Pathology

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Pancreas and simultaneous pancreas-kidney transplantation (SPK) are indicated for the treatment of type 1 diabetic patients, in particular, patients with diabetic nephropathy. Pancreas transplant alone may be indicated for type 1 diabetic patients with unstable "brittle diabetes" but no significant renal disease [1]. Pancreas transplantation is also infrequently performed to treat patients with type 2 diabetes. Diabetes mellitus and the sequelae of hyperglycemia is a major cause of end-stage renal disease, vascular disease, diabetic gastroparesis, neuropathy, and retinopathy. With a functional pancreatic graft, there is a stabilization of glucose levels and a decrease in the long-term consequences of hyperglycemia [2].

Pancreatic transplant was first performed in 1966 for endocrine dysfunction. Although at first graft survival was poor, over time, outcomes have progressively improved [3]. Initial surgical procedures involved whole graft transplant with polymer duct obliteration. Complications included vascular thrombosis, pancreatitis, and fistula formation. Bladder-drained grafts achieved an improved outcome, with the exocrine secretions drained into the bladder and insulin released to the venous system through the iliac veins. An advantage to this technique was the ability to monitor for rejection by quantification of exocrine enzymes such as amylase and lipase in the urine. Complications of this technique included hematuria, urine leak, urinary tract infection, and reflux pancreatitis. Another complication of this technique was hyperinsulinemia, because insulin was directly released into the systemic circulation [4].

Most pancreatic transplants are now performed via pancreatic-duodenal transplantation [5]. The donor duodenum is anastomosed to the recipient small bowel or bladder. Venous drainage can be made to the portal system in these enteric-drained grafts, which is similar to the drainage of the native pancreas. There have been reports of lower complications with enteric-drained grafts, as well as fewer and less severe episodes of rejection [6].

Owing to the variation in major histocompatibility complex (MHC) expression in the various cellular components of the pancreas, acute cellular rejection (ACR) has been associated with damage to the exocrine function of the pancreas [7]. ACR preferentially affects the ducts, vessels, and acini. In contrast, antibody-mediated rejection (AMR) has been associated with hyperglycemia and islet injury, suggesting a vulnerability to microvascular injury and ischemia [8, 9].

Pancreatic allograft rejection is clinically asymptomatic, and detection relies on serum measurement of increased acinar enzymatic products such as amylase and lipase. Endocrine abnormalities in the form of hyperglycemia may also be noted in cases of severe rejection as well as in large vessel thrombosis and chronic rejection. Serum creatinine may also be used as a surrogate marker for pancreatic rejection in patients with SPK, although rejection is not always congruent between the two organs [10].

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8.1 Acute Cell-Mediated Rejection

The following are adapted from the Banff Schema for Grading Pancreas Allograft Rejection [11, 12] (Table 8.1).

8.1.1 Normal Pancreas

The normal pancreas shows absent to sparse inflammatory infiltrates, confined to the fibrous septa without involvement of septal structures. The fibrous septa are proportional to the size of the associated duct and vessels.

8.1.2 Indeterminate for Rejection

Focal active septal inflammation is present; however, the overall features do not fulfill the criteria for mild ACR

Table 8.1 Histological grading of ACR in pancreas transplant biopsies [11]

Category	Histology	Comments
Normal	Absent or inactive septal inflammation	Active inflammation includes blastic lymphocytes and/or eosinophils
Indeterminate for ACR	Active septal inflammation without additional findings	No ductitis or venulitis
Grade I/mild ACR	Active septal inflammation with ductitis or venulitis And/or 1–2 foci per lobule of acinar inflammation	Absent/minimal acinar injury
Grade II/moderate ACR	Minimal intimal arteritis (<25 % luminal compromise) And/or multiple foci (≥3 foci/lobule) of acinar inflammation with individual cell injury	No confluent or diffuse inflammation Requires differentiation from AMR
Grade III/severe ACR	Diffuse acinar inflammation with focal or diffuse confluent acinar cell necrosis And/or moderate to severe intimal arteritis And/or necrotizing arteritis	Requires differentiation from AMR

8.1.3 Grade I (Mild)

Active inflammation, including activated blastic lymphocytes and/or eosinophils, involving septal structures is present. This inflammatory infiltrate may be variable. Foci of venulitis are seen, which is characterized by circumferential lymphocytic/inflammatory accumulation in the subendothelium with associated endothelial injury (Figs. 8.1 and 8.2). Ductal injury (ductitis) should also be present and will show lymphocytic or eosinophilic inflammation within the ductal epithelium. As a result of the inflammatory infiltrate, the ductal epithelial cells often show irregular spacing of the nuclei, anisonucleosis, and reactive changes (Fig. 8.3). Denudation of the epithelial cells may also be seen. The presence of venulitis or ductitis is sufficient for the diagnosis of mild ACR. In the absence of venulitis and ductitis, mild ACR may be diagnosed by the presence of focal acinar inflammation, limited to no more than two inflammatory foci per lobule with absent to minimal acinar cellular injury or dropout (Fig. 8.4).

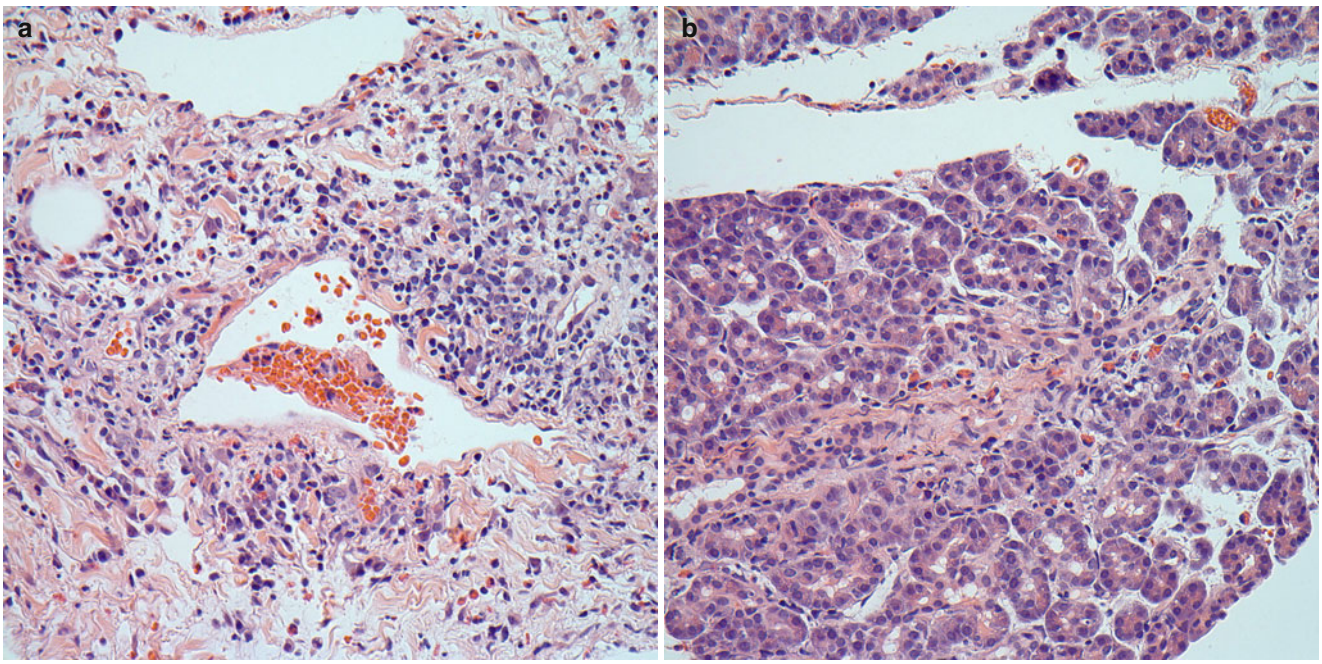

Fig. 8.1 (**a**, **b**) Mild ACR. (**a**) Interlobular septa show inflammation including activated blastic lymphocytes, plasma cells, eosinophils, and rare neutrophils. (**b**) The inflammatory infiltrate may be rich in eosinophils

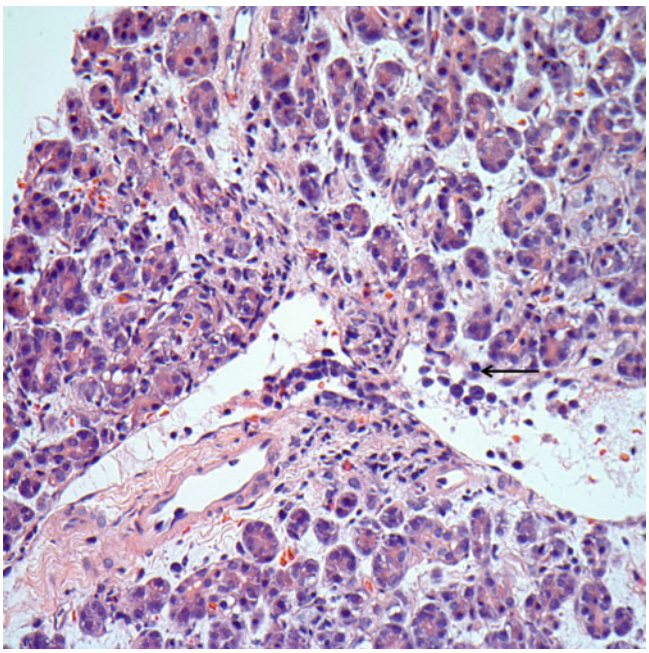

Fig. 8.2 Mild ACR. Septal vein shows venulitis with subendothelial accumulation of lymphocytes, activated blastic lymphocytes, and endothelial cell lifting and damage (*arrow*)

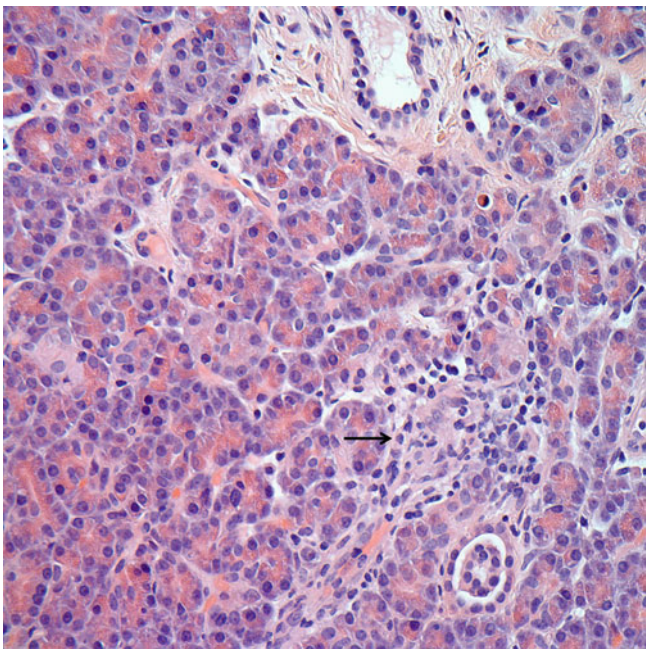

Fig. 8.4 Mild ACR. Spotty acinar inflammation and injury with minimal (*arrow*) to absent acinar dropout. These findings in isolation may also be diagnostic of mild ACR

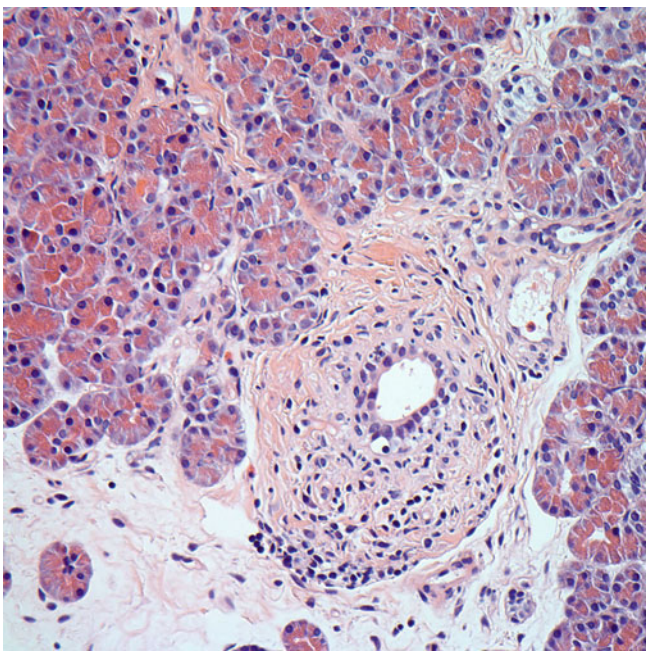

Fig. 8.3 Mild ACR. Interacinar duct with infiltration by lymphocytes and epithelial injury. The ductal epithelium shows cytoplasmic vacuolization, irregular nuclear spacing, and scattered apoptotic nuclei

8.1.4 Grade II (Moderate)

In addition to the histological findings of mild rejection, moderate ACR includes the finding of multifocal acinar inflammation (three or more foci per lobule) with individual acinar cell injury/dropout (Fig. 8.5). Alternatively, the diagnosis of moderate ACR may be defined by the presence of mild intimal arteritis, which is characterized by rare or occasional subendothelial inflammation by mononuclear cells without activation of or damage to the overlying arterial endothelium. The extent of the arteritis should compromise less than 25 % of the vessel lumen (Fig. 8.6).

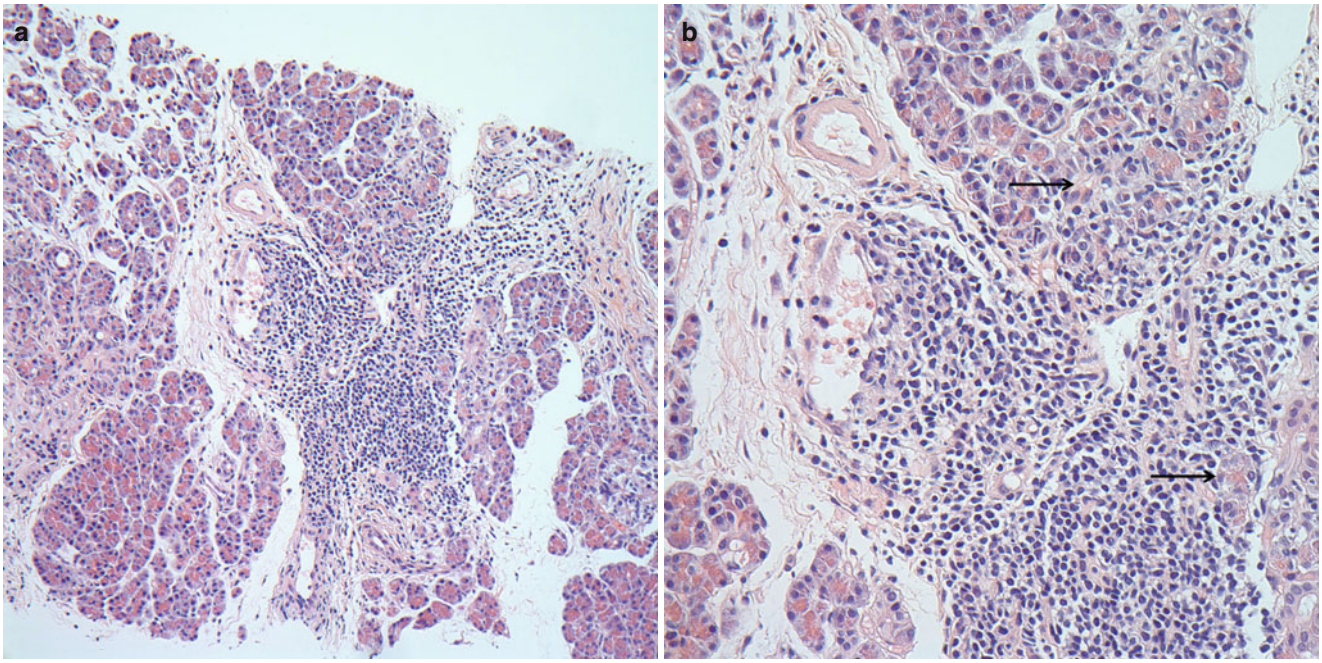

Fig. 8.5 (**a**, **b**) Moderate ACR. (**a**) Septal inflammation with lymphocytes, plasma cells, and rare eosinophils. (**b**) Focal acinar inflammation with spotty multifocal acinar injury/dropout (*arrows*). Septal venulitis is also identified

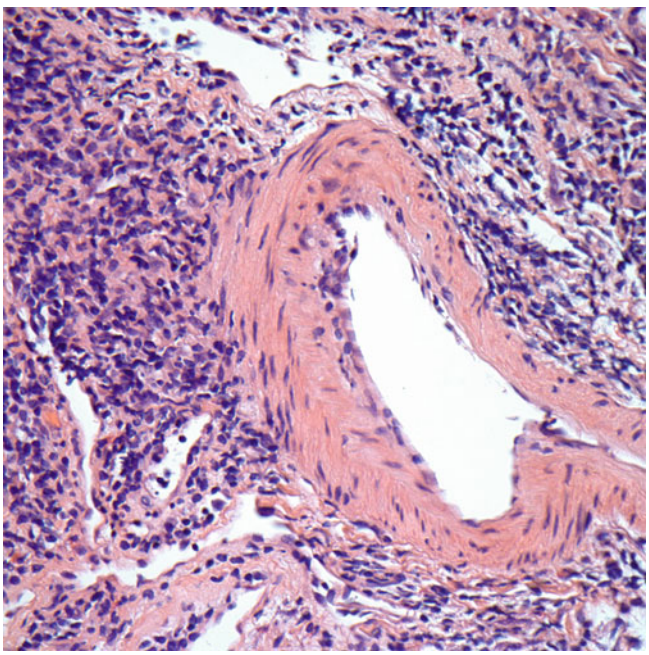

Fig. 8.6 Moderate ACR. Intimal arteritis with mononuclear cells in the subendothelium of this muscular artery. There is focal endothelial swelling and lifting/damage. The damage seen occupies less than 25 % of the arterial lumen

8.1.5 Grade III (Severe)

Severe ACR is characterized by diffuse acinar inflammation (confluent) with associated focal or diffuse confluent acinar cell necrosis. Interstitial edema and hemorrhage are characteristic of severe tissue damage. There should be no significant acinar tissue present without inflammatory infiltrate. Severe ACR may also be diagnosed by moderate to severe intimal arteritis, in which mononuclear cells are seen within the intima of a muscular artery with evidence of injury. This injury can manifest as endothelial cell activation or sloughing, margination of neutrophils, macrophage activation, proliferation of myofibroblasts within the intima, and fibrin leakage. Greater than 25 % of the vessel lumen should be compromised by the injury. Necrotizing arteritis, with focal or circumferential fibrinoid necrosis, may be seen with or without transmural inflammation. This finding can also be seen in AMR and should raise this possibility.

8.2 Antibody-Mediated Rejection

8.2.1 Hyperacute Rejection

This type of rejection is immediate graft rejection (within 1 h) due to preformed antibodies in the recipient serum. The histological findings include edema, acinar cell injury with vacuolization, degranulation, and spotty necrosis. Neutrophilic margination in capillaries and veins may be seen. In later stages, hemorrhagic necrosis is seen throughout the graft. Widespread fibrinoid vascular necrosis and thrombosis are present. C4d staining is seen throughout graft vasculature.

8.2.2 Accelerated AMR

Accelerated AMR is similar to hyperacute rejection, but occurs hours to days after transplantation.

8.2.3 Acute AMR

The diagnosis of acute AMR involves the combination of three criteria. These criteria include laboratory-confirmed circulating donor-specific antibodies (DSA), morphological evidence of tissue injury (see grading criteria later), and C4d positivity in interacinar capillaries (>5 % of acinar lobular surface) by immunostaining. When three of three criteria are met, the findings are diagnostic of AMR. If two of three criteria are met, the findings are consistent with AMR. If only one of three criteria is met, the finding requires exclusion of AMR. The grading of AMR is based on the histological features seen in the biopsy material (Table 8.2).

Table 8.2 Histological grading of AMR in pancreas transplant biopsies [12]

Category	Histology
Grade I/mild acute AMR	Well-preserved architecture
	Mild macrophage or mixed macrophage/neutrophilic infiltrates
	Rare acinar cell damage
Grade II/moderate acute AMR	Overall preserved architecture
	Interacinar macrophage or mixed macrophage/neutrophilic infiltrates
	Capillary dilation, capillaritis
	Congestion
	Multicellular acinar dropout
	Extravasated red blood cells
Grade III/severe acute AMR	Architectural disarray
	Scattered inflammatory infiltrates with interstitial hemorrhage
	Multifocal parenchymal necrosis
	Arterial and venous wall necrosis and thrombosis

8.2.4 Grade I/Mild Acute AMR

The pancreatic tissue shows well-preserved architecture. There are mild mononuclear and/or neutrophilic infiltrates with only rare acinar cell dropout/apoptosis (Fig. 8.7).

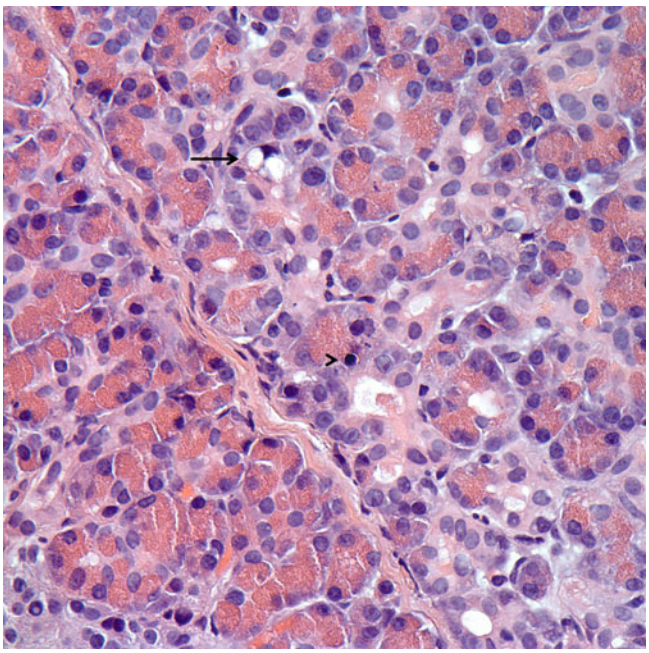

Fig. 8.7 Mild AMR. Subtle acinar cell injury with cytoplasmic swelling and vacuolization (*arrow*) and nuclear pyknosis/apoptosis (*arrowhead*)

8.2.5 Grade II/Moderate Acute AMR

There is overall preservation of pancreatic tissue architecture. Interacinar mononuclear, macrophage, and/or neutrophilic infiltrates are present. An immunostain for CD68 can highlight mononuclear infiltrate in cases without prominent neutrophils. See Table 8.2 for other histological features that may also be seen.

8.2.6 Grade III/Severe Acute AMR

The pancreatic tissue will show architectural disarray, with scattered inflammatory infiltrates in a background of interstitial hemorrhage.

8.2.7 C4d Staining Interpretation

C4d staining should be interpreted in interacinar capillaries. Immunohistochemical staining may be performed; however, immunofluorescence staining may be more sensitive. The staining pattern must be linear or granular. If the extent of lobular surface area is less than 5 %, the result is deemed negative. If there is staining of 5–50 % of the lobular surface area, the result is deemed focally positive (Fig. 8.8). If greater than 50 %, the result is deemed diffusely positive. Staining of the endothelium of larger arteries and veins, as well as septal and peripancreatic connective tissues is considered nonspecific staining.

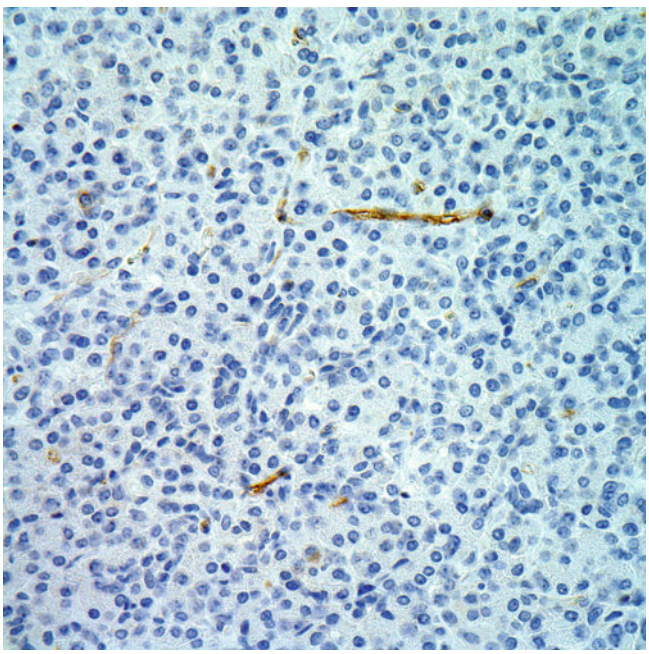

Fig. 8.8 AMR. Immunohistochemical staining for C4d shows focal positivity defined as between 5 and 50 % of the interacinar capillaries. In combination with the DSA studies as well as histological features, this may be supportive of AMR

8.3 Chronic Active AMR

Chronic active AMR is defined as the combination of features of AMR and chronic allograft rejection in the absence of acute T-cell–mediated rejection. Histological findings include arterial intimal fibrosis and infiltration of mononuclear cells with formation of a neointima.

8.4 Chronic Allograft Arteriopathy

Chronic allograft arteriopathy is characterized by arterial intimal fibrosis with mononuclear cell infiltration. Foam cell arteritis may also be seen (Figs. 8.9 and 8.10).

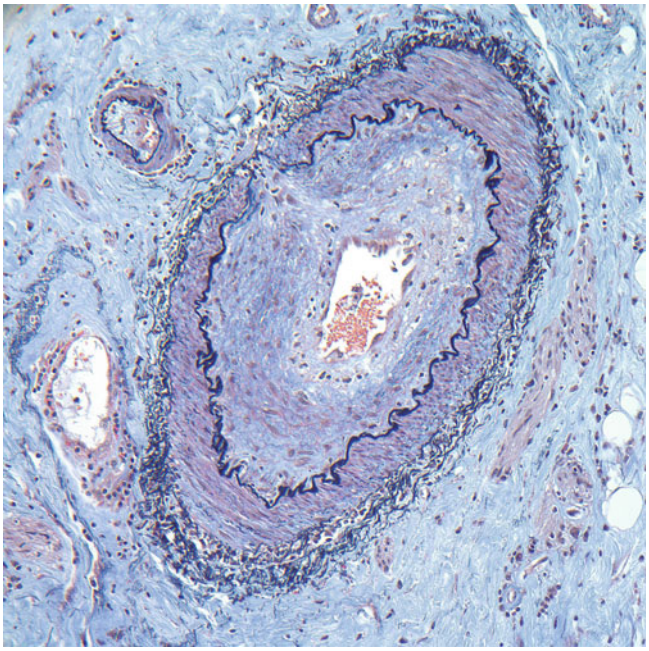

Fig. 8.9 Chronic allograft arteriopathy. Trichrome-elastin stain highlights arterial intimal fibrosis and neointima formation, with narrowing of the vessel lumen

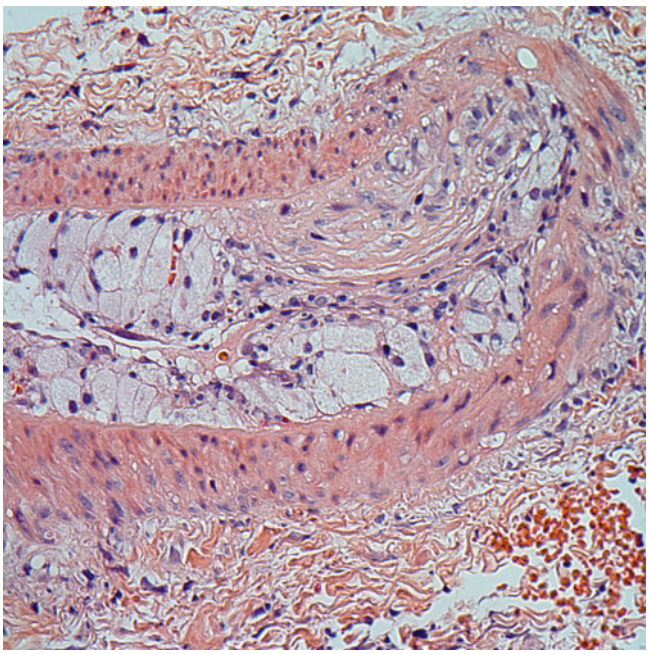

Fig. 8.10 Foam cell arteritis. Muscular artery with an intimal proliferation of fibroblasts and foamy macrophages. These findings may be seen in chronic allograft arteriopathy

8.5 Chronic Allograft Rejection/Graft Sclerosis

Staging of chronic rejection in pancreas transplant biopsies is based on the Banff Schema (Table 8.3) [11, 12].

Table 8.3 Histological staging of chronic rejection in pancreas transplant biopsies [11]

Category	Histology
Stage I (mild graft fibrosis)	Expansion of fibrous septa
	Acinar lobules show eroded, irregular contour
	Central lobules are normal
	Fibrosis <30 % of core surface
Stage II (moderate graft fibrosis)	Exocrine atrophy in the majority of lobules
	Acinar lobules show eroded, irregular contours
	Thin fibrous strands transverse individual acini
	Fibrosis occupies 30–60 % of core surface
Stage III (severe graft fibrosis)	Isolated residual acinar or islets present
	Fibrotic areas occupy >60 % of the core surface

8.5.1 Stage I (Mild Graft Fibrosis)

The pancreatic tissue shows mild expansion of fibrous septa. On biopsy, fibrosis occupies less than 30 % of the core surface. The acinar lobules show eroded and irregular contours; however, the central lobules are normal (Fig. 8.11).

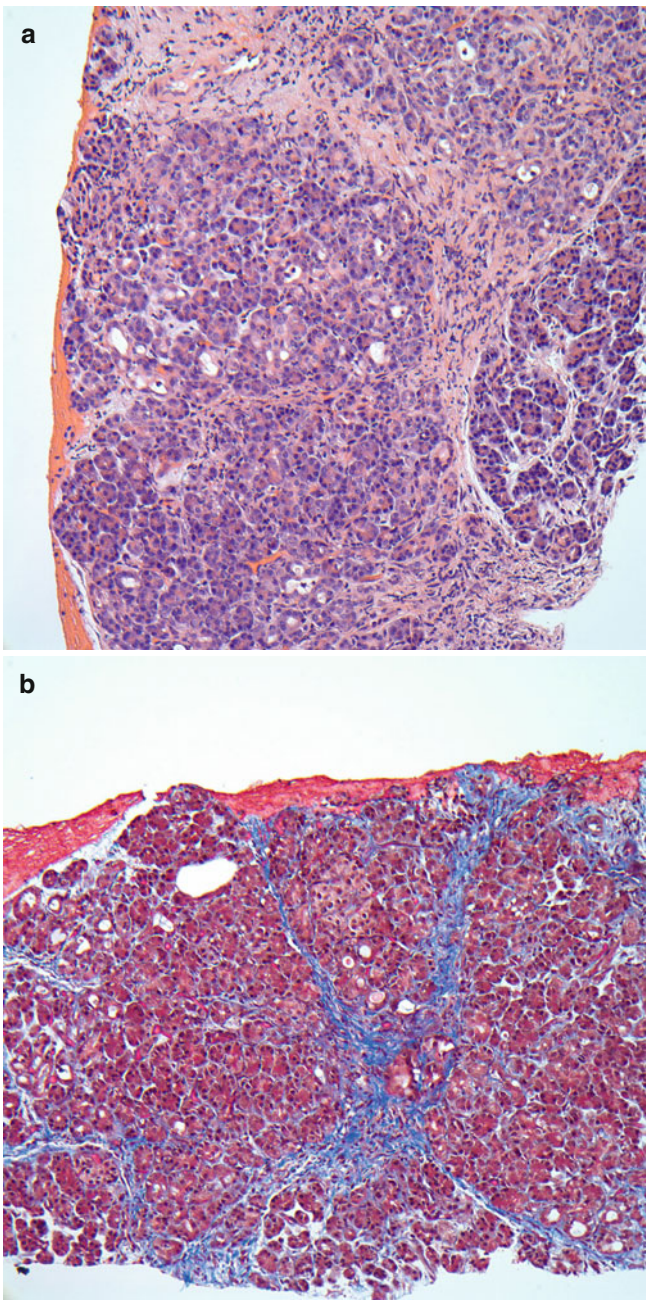

Fig. 8.11 (**a**, **b**) Stage 1 (mild) graft fibrosis. Subtle fibrous expansion of the septa and eroded, irregular contours of the acinar lobules. The central lobules remain without fibrosis. (H 200×) (**b**) Trichome stain highlights a mild increase in septal fibrosis as well as subtle fibrosis at the edge of the lobules, with sparing of the central lobules

8.5.2 Stage II (Moderate Graft Fibrosis)

There is moderate expansion of fibrous septa. On biopsy, fibrosis occupies 30–60 % of the core surface. Acinar lobules show exocrine atrophy with irregular contours involving most lobules. Central lobules show thin fibrous strands traversing individual acini (Fig. 8.12).

8.5.3 Stage III (Severe Graft Fibrosis)

Fibrosis is the predominant histological finding with involvement of greater than 60 % of the core surface. Only isolated residual acini or islets are present (Fig. 8.13).

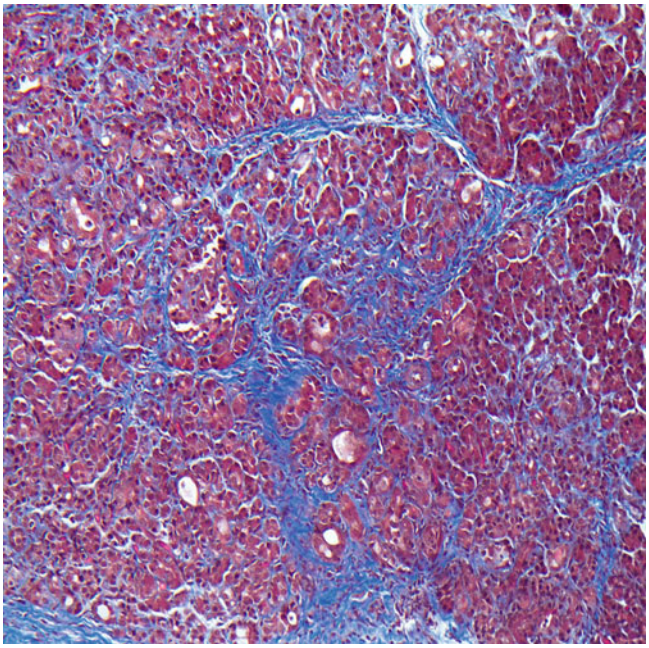

Fig. 8.12 Stage 2 (moderate) graft fibrosis. Trichrome-stained section shows moderate expansion of the fibrous septa with erosion of the contours of the lobules. Thin bands of fibrosis traverse the individual acini in both peripheral and central lobules. The patient was 10 years post pancreatic transplant

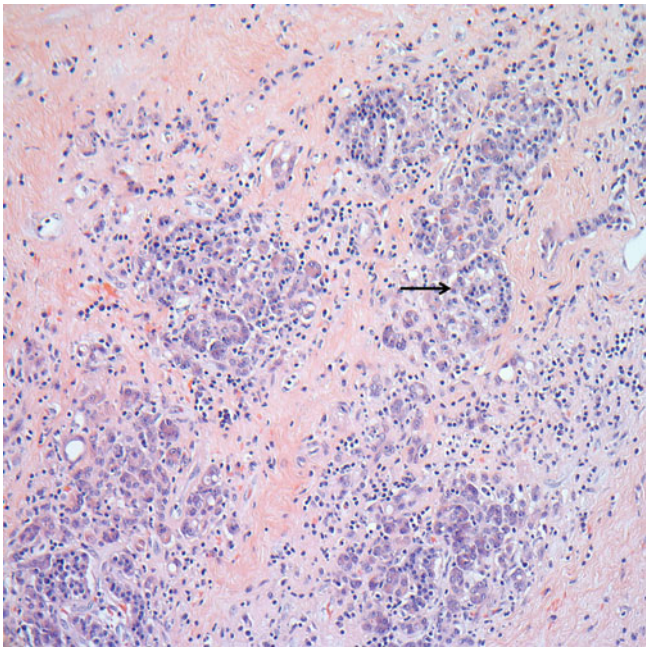

Fig. 8.13 Stage 3 (severe) graft fibrosis. There is severe graft fibrosis with atrophic acini and rare residual islets (*arrow*). The patient was 6 years post pancreatic transplant

8.6 Other Causes of Allograft Dysfunction

8.6.1 Ischemic Pancreatitis

Patients present with increased serum amylase and lipase or decreased urine amylase. Inflammation including foamy macrophages and neutrophils is seen within the pancreatic parenchyma. In mild disease, these findings are confined to the septa, but they may become diffuse in severe disease. Fat necrosis, edema, and coagulative necrosis can be seen.

8.6.2 Peripancreatitis

Patients present with systemic infectious symptoms and abdominal pain. Signs of peritonitis are seen. There may be peripancreatic fluid collections. Histologically, there is inflammation consisting of lymphocytes, plasma cells, eosinophils, and neutrophils present in the septa and at the periphery of lobules. The peripancreatic connective tissue may demonstrate necrosis and predominantly neutrophilic inflammation. Activated fibroblasts are seen with obliteration of septal structures and preservation of the center of the lobules (Fig. 8.14).

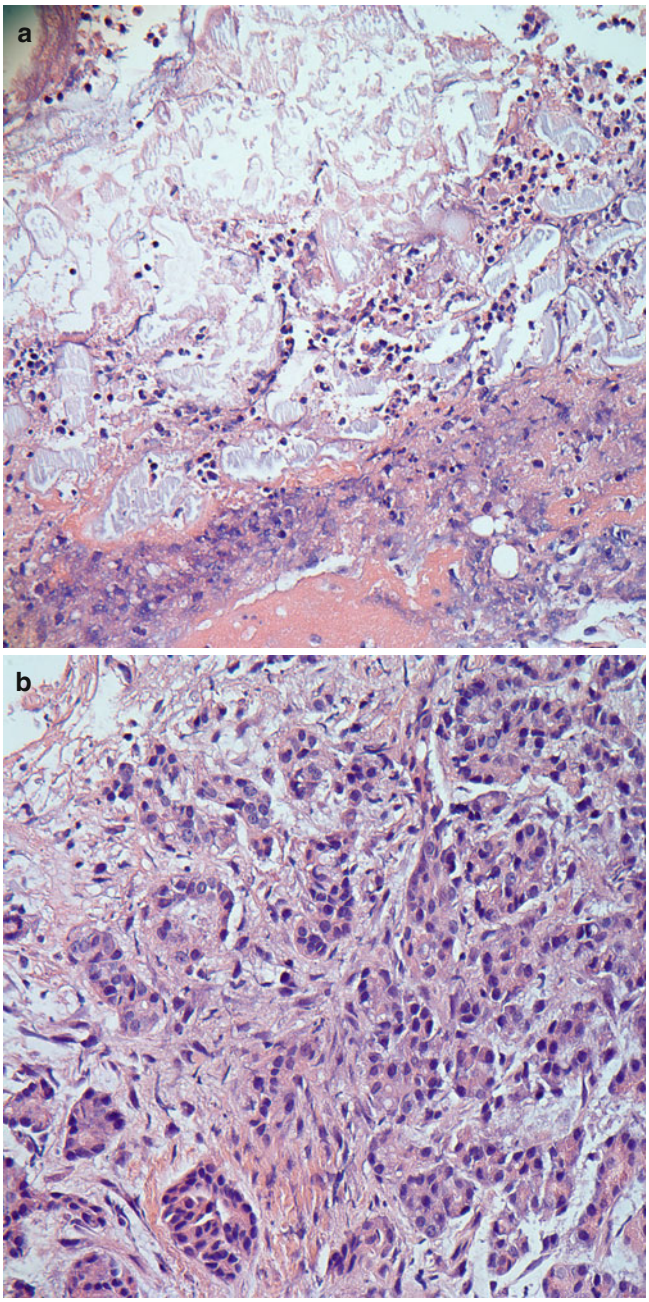

Fig. 8.14 (**a**, **b**) Peripancreatitis. (**a**) Acute inflammation and fat necrosis are seen in this graft biopsy. (**b**) The adjacent pancreatic tissue shows activation of fibroblasts and extension into the pancreatic parenchyma. This fibroblast proliferation should not be interpreted as chronic rejection

8.6.3 Infections

8.6.3.1 Cytomegalovirus Pancreatitis

Patients with cytomegalovirus (CMV) pancreatitis present with increased serum amylase and lipase. The tissue shows patchy mononuclear inflammation in septa and acini. The characteristic nuclear and cytoplasmic inclusions and cytomegaly are seen within infected acinar, endothelial, ductal, or stromal cells [13].

8.6.3.2 Bacterial or Fungal Infection

A variable inflammatory infiltrate composed of neutrophils, mononuclear cells, or granulomatous inflammation is seen. The inflammation is often necrotizing. Special stains may be performed to visualize the infectious organisms.

8.6.4 Recurrent Disease

8.6.4.1 Recurrent Autoimmune Disease (Diabetes Mellitus)

Recurrent autoimmune disease presents with hyperglycemia and/or islet cell autoantibodies (GAD-65, IA,2). There is islet-centered lymphocytic inflammation (isletitis) seen on biopsy tissue. In late stages, little to no inflammation is seen after beta cells have been destroyed [14].

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