Pancreas

21

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21.1 Introduction

The IgG4-related lesion in the pancreas, now termed type 1 autoimmune pancreatitis (AIP), was first reported in 1991 under the descriptive moniker of lymphoplasmacytic sclerosing pancreatitis (LPSP) [1]. Kawaguchi and colleagues focused upon only two cases in their report but in doing so accounted for nearly all of the pathological characteristics of type 1 AIP recognized today. The authors demonstrated remarkable foresight in observing that the disease delineated by their cases must have a systemic distribution (see Chap. 2).

A similar report published by a European group in 1997 proposed the concept of nonalcoholic duct destructive chronic pancreatitis (NDCP) [2]. In retrospect, some of the cases seem to fall into the category of type 1 AIP/LPSP with an association of "Sjögren's syndrome" or "primary sclerosing cholangitis" or histological identification of numerous obliterated veins (this was detected only in one of twelve cases). However, cases with the pancreatic duct epithelium infiltrated by neutrophils and destroyed—a process highly reminiscent of type 2 AIP—are also included. The authors concluded that all of these histological features are a process of continual change, and neutrophilic inflammation seen in the duct causes the extensive fibrosis.

Other trends in the AIP literature confirmed the existence of a subset of patients with discordant features such as neutrophil infiltration into the pancreatic duct epithelium, similar (or identical) to that observed in NDCP. This entity, known for several years as idiopathic duct-centric chronic pancreatitis (IDCP) [3], or AIP with granulocytic epithelial lesion (GEL) [4], is now considered to be an entity distinct from LPSP.

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The confusing tale describing nomenclature changes within the two entities now considered to comprise AIP stems from the fact that the literature surrounding these entities was conceived, developed, and debated without the benefit of the immunostaining of tissues for IgG4. Subsequent to much of the discussion about LPSP, NDCP, and IDCP, Hamano et al. demonstrated that serum IgG4 values are elevated in AIP patients [5] and that tissue lesions are infiltrated by numerous IgG4-positive plasma cells [6]. The number of IgG4-positive plasma cells was then noted to be significantly higher in LPSP than in IDCP [7], leading to the realization that LPSP and IDCP are in fact different diseases and that LPSP is the IgG4-related condition.

The existence of various clinical differences between the two also became apparent [8]. At present, LPSP and IDCP are called type 1 and type 2 AIP, respectively [9], and in the International Consensus Diagnostic Criteria for AIP, separate diagnosis criteria for the two types have been proposed [10].

LPSP and IDCP are now recognized as related conditions that demonstrate the pathological features of type 1 and type 2 AIP, respectively. Yoshida et al. announced the concept of AIP in 1995 [11] and in that single case reported a clinical picture now regarded as classic for type 1 AIP.

Few inflammatory diseases of the pancreas other than AIP show major lymphoplasmacytic infiltration. For this reason, the attention of pathologists became focused upon this glaring anomaly within the spectrum of pancreatic disease. Indeed, the author considers it inevitable that the first IgG4-related lesion to be identified was that of the pancreas as opposed to any other organ. The highly specific nature of type 1 (IgG4-related) AIP, formerly known as LPSP, can be appreciated by reading the original report of Kawaguchi et al [1]. In describing the history of AIP, the importance of those initial observations pertaining to the histological features of this condition must be emphasized.

H. Umehara et al. (eds.), *IgG4-Related Disease*, DOI 10.1007/978-4-431-54228-5_21,

21.2 Pathological Characteristics of Type 1 AIP

21.2.1 Fibrotic Lesions

The basic pathological findings of type 1 (IgG4-related) AIP are marked lymphoplasmacytic infiltration and fibrosis that involve the exocrine tissues, including pancreatic ducts and lobules, peripancreatic adipose tissue, and blood vessels, resulting in the formation of characteristic lesions. Lymphoid follicle formation is also often present. Within these lesions eosinophilic infiltration is occasionally seen, while copious eosinophilic infiltrates are observed only rarely and neutrophil infiltrates almost never.

The storiform type of fibrosis seen in type 1 AIP is characterized by bands of fibrosis that radiate in various directions from the center, sometimes forming a characteristic swirling pattern. Despite its fibrotic nature, it is typically accompanied by a copious inflammatory cell infiltrate. These findings are fundamentally different from those of the forms of fibrosis seen in other types of chronic inflammation. Storiform fibrosis shows a range of changes varying from lesions with a cell-rich component to others that consist mainly of collagen. Within a single case, a mixture of lesions may be found. Lesions with a cell-rich component are comprised of small spindle cells, lymphocytes, and plasma cells, with little collagen content (cell-rich type; Fig. 21.1a). Over time, collagen formation progresses, with a gradual reduction in the cellular component of the inflammation (transitional type; Fig. 21.1b). The final stage of this process is the fibrotic stage, at which time fibrotic foci develop that consist mostly of collagen with a scanty cellular component (fibrotic type; Fig. 21.1c). Cell-rich and transitional types of storiform fibrosis are of the greatest diagnostic significance, because the diagnosis of type 1 AIP and IgG4-RD is difficult to render with conviction at the fibrotic stage.

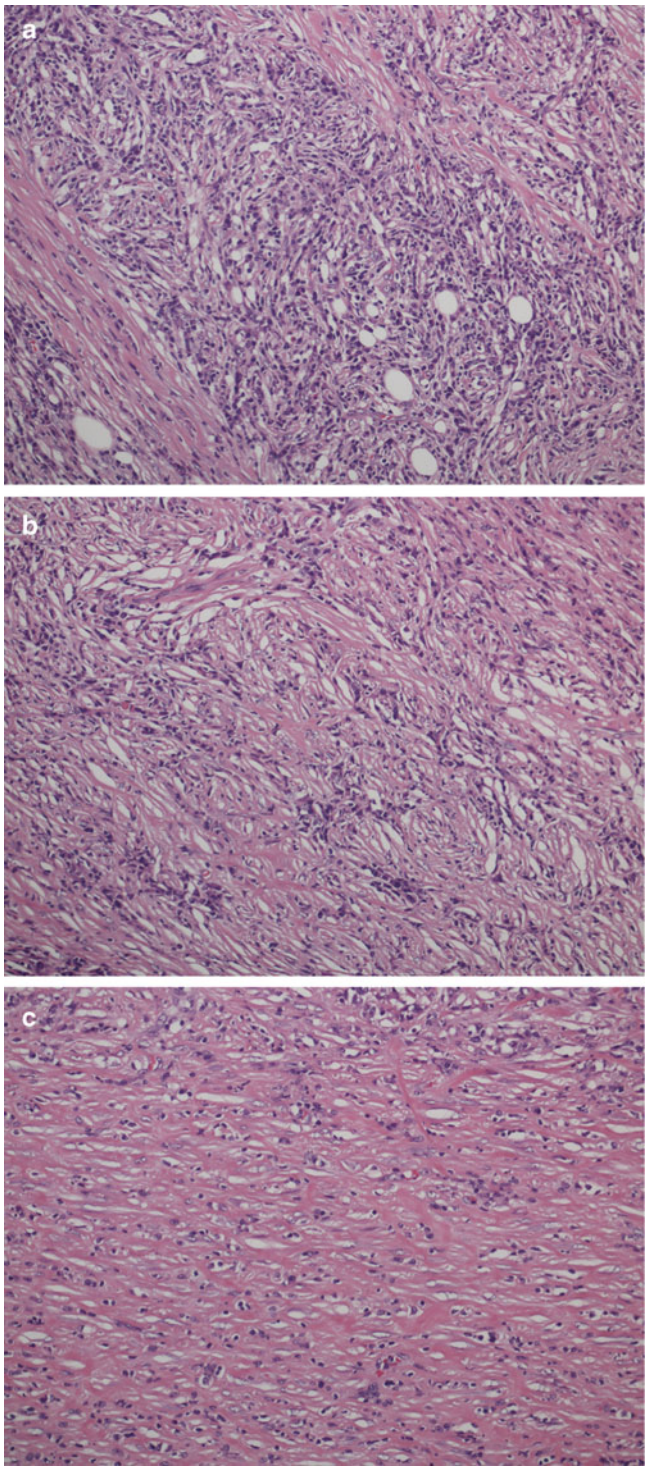

Fig. 21.1 Storiform fibrosis seen in type 1 AIP. (**a**) Cell-rich type; (**b**) transitional type; (**c**) fibrotic type

21.2.2 Pancreatic Duct Lesions

Lesions composed of lymphoplasmacytic infiltration and fibrosis form and surround the ductal epithelium of the pancreas. Inflammatory cell infiltration of the pancreatic duct epithelium, regressive epithelial changes, and regenerative findings are typically not seen in type 1 (IgG4-related) AIP, but rather are characteristic of type 2 AIP. Typical pancreatic duct lesions are easy to identify in the interlobular pancreatic ducts, and lesions are also often observed in the intralobular pancreatic ducts. Occasionally, a thin layer with a simple infiltration of lymphocytes and plasma cells just beneath the epithelium is surrounded by fibrosis. In others, a thick inflammatory band with storiform fibrosis surrounds the epithelium, creating the impression of a thickened pancreatic duct wall (Fig. 21.2) [12].

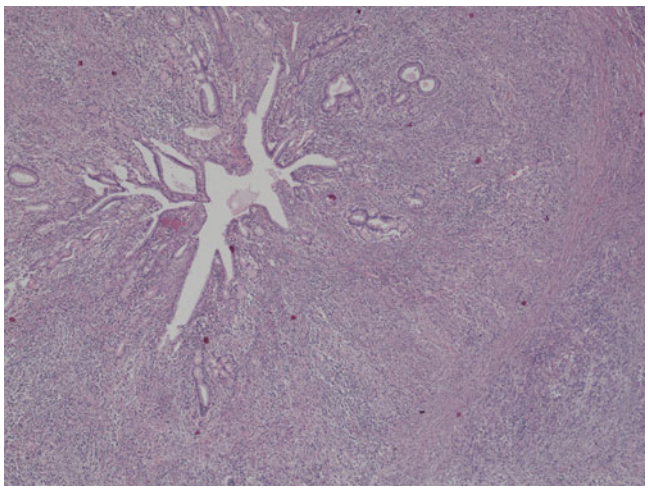

Fig. 21.2 Pancreatic duct lesions of type 1 AIP. Around the epithelium a thick inflammatory lesion associated with storiform fibrosis has formed, giving the appearance of a thickened pancreatic duct wall

21.2.3 Lobular Lesions

Lymphoplasmacytic infiltration of the lobules is frequently seen, with the development of interlobular fibrosis. Lymphoplasmacytic infiltration may be also present in interlobular fibrotic foci. Lobular atrophy generally ensues with pancreatitis of other causes, but in type 1 AIP, the inflamed lobules usually do not become atrophic and their borders remain well preserved (Fig. 21.3a) [12, 13]. On the other hand, acinar cell loss does occur (Fig. 21.3b). This is thought to reflect injury to the pancreatic parenchyma. The lobules also occasionally become edematous. When the lobular structure has been largely destroyed, the lobule and surrounding fibrosis merge, sometimes showing storiform fibrosis. This phenomenon is particularly common at the border between the pancreas and surrounding adipose tissue. In the absence of such findings, obvious storiform fibrosis is difficult to detect in the lobules.

21.2.4 Peripancreatic Adipose Tissue Lesions

Peripancreatic adipose tissue inflammation, virtually a sine qua non for the diagnosis of type 1 AIP, is the site where storiform fibrosis and obliterative phlebitis are most commonly observed. Inflammation involves the fat lobules and spreads by enclosing individual adipocytes, until they are gradually replaced by inflammatory foci (Fig. 21.4). At the pancreatic border, parenchymal injury is often severe, and the border between the pancreatic parenchyma and adipose tissue becomes indistinct.

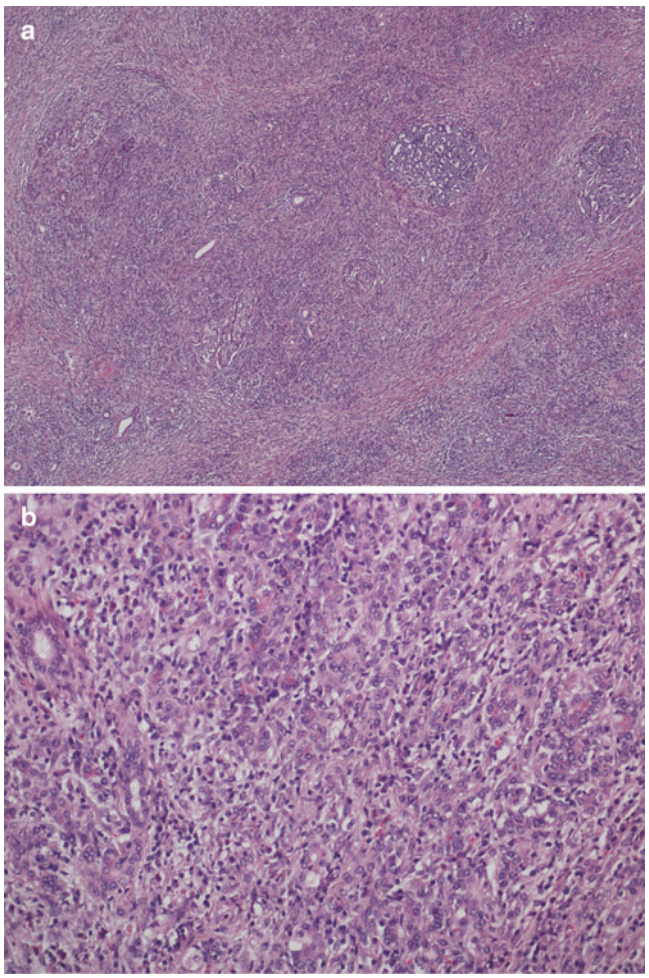

Fig. 21.3 Lobular lesions of type 1 AIP. (**a**) Lobular atrophy is absent, and the borders are preserved. (**b**) In the lobules there is loss of acinar cells, and lymphoplasmacytic infiltration is seen

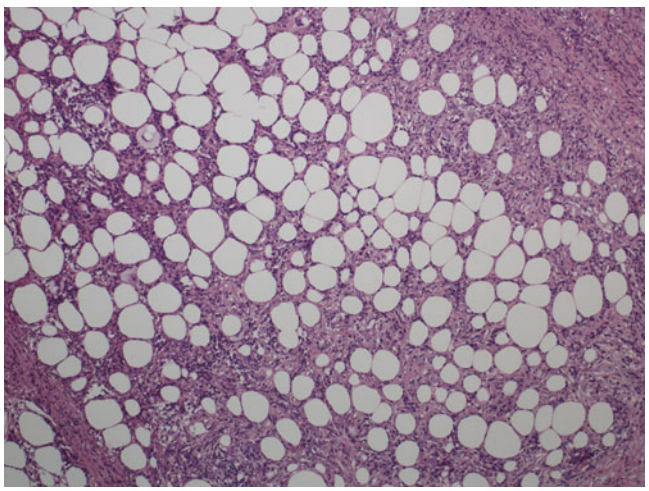

Fig. 21.4 Peripancreatic adipose tissue lesions of type 1 AIP. Inflammatory cell infiltrates spread between adipocytes, and in areas in which inflammation has advanced, adipocytes have become unclear

21.2.5 Vascular Lesions

Phlebitis is an essentially universal finding in type 1 AIP. Inflammation of the venules is the major finding, with lymphocytes and plasma cells infiltrating from the venous wall into the lumen, culminating in venous obliteration. For this reason, this condition is called "obliterative phlebitis." Phlebitis may also be found in large veins such as the splenic and portal veins, but in these instances the inflammation is limited to only a portion of the wall and rarely results in obliteration.

Obliterative phlebitis is usually easy to recognize on sections stained by hematoxylin and eosin and should be suspected when no vein is evident adjacent to an artery, because under normal circumstances in the pancreas, arteries and veins run in parallel (Fig. 21.5a). Staining of elastic fibers using a stain like elastica van Gieson also facilitates the identification of obliterated veins (Fig. 21.5b), but venous occlusion such as may be caused by an organizing thrombus in the setting of either chronic pancreatitis or pancreatic cancer must be differentiated carefully. The histological picture of obliterative phlebitis is identical to that of the surrounding inflammatory changes. Thus, obliterative phlebitis may blend into the inflammatory background of the surrounding tissue. Storiform fibrosis may also be found in involved veins.

Small arteries are also occasionally inflamed (arteriolitis) with type 1 AIP [3]. Arterial lesions frequently form by extension from the adventitia to the outer layer of the media (Fig. 21.5c). These arterial lesions are similar in morphology to those of the IgG4-related periarteritis detected in the aorta and its larger branches, with lumen occlusion observed rarely. Marked inflammation is present in the surrounding tissue in early lesions, making it difficult to judge whether the inflammation in the portion of the vessel corresponding to the arteriolar adventitia represents a true arteritis or not. For this reason, only few reports are yet available on the characteristics and frequency of such arterial lesions.

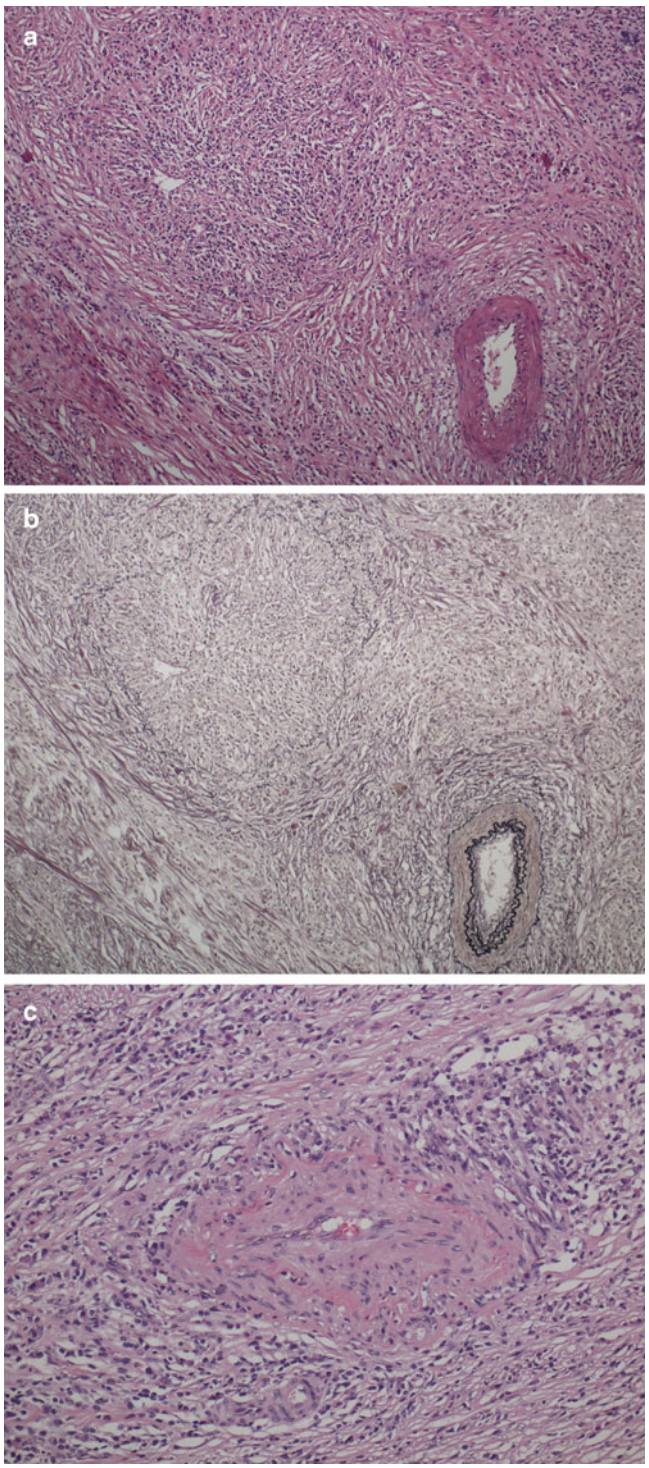

Fig. 21.5 Vascular lesions of type 1 AIP. (**a**) Obliterative phlebitis. A vein running in parallel with the artery cannot be identified, and at the site where the vein would be expected to be present, a nodule-like inflammatory focus has formed. (**b**) Obliterative phlebitis (elastica van Gieson stain). At the same site as (**a**) elastic fibers are stained, an obliterated vein is clearly observed. (**c**) Arteriolitis. Inflammation extends from the adventitia to media, and the medial smooth muscle layer has become obscured

21.2.6 IgG4-Positive Plasma Cells

Abundant IgG4-positive plasmacytic infiltration is present in type 1 AIP (Fig. 21.6). In resected materials, usually >50 positive cells per high-power field (HPF) are noted [14]. However, because this criterion is only rarely satisfied in biopsy materials, the number of IgG4-positive plasma cells has been set at >10/HPF in some proposed diagnostic criteria [10]. Setting the cutoff point at only 10 IgG4-positive plasma cells per HPF in the pancreas lowers the diagnostic specificity

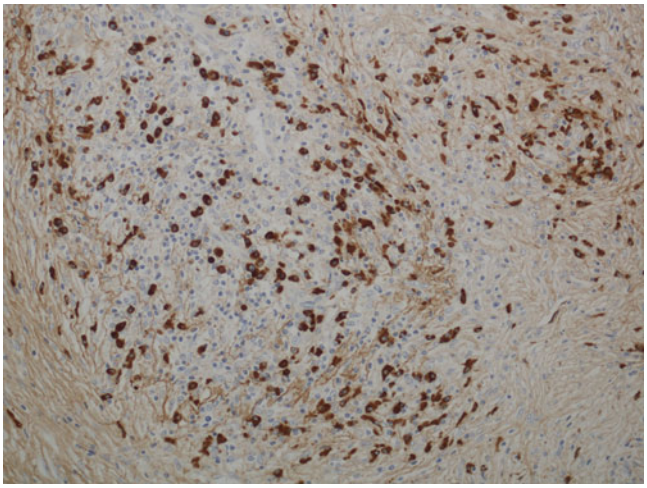

Fig. 21.6 Abundant IgG4-positive plasmacytic infiltration seen in type 1 AIP

of this finding, because such tissue concentrations of IgG4-positive cells are also observed occasionally in conditions other than type 1 AIP (e.g., in the inflammation associated with pancreatic cancer [7]). Thus, this tissue finding alone is not diagnostic of type 1 AIP.

In the pancreas as well as other organs, determination of the IgG4/IgG ratio within tissue is a useful diagnostic indicator, sometimes more useful than the simple count of IgG4-positive plasma cells per HPF. The IgG4/total IgG ratio may be conceptualized to be more useful than the count of IgG4-positive plasma cells as the degree of fibrosis within a tissue waxes and the cellular inflammatory component wanes. In type 1 AIP, the IgG4/total IgG ratio is usually >0.40, though exceptions to this guideline certainly exist.

In the International Consensus Diagnostic Criteria for AIP, a diagnosis of type 1 autoimmune (IgG4-related) pancreatitis can be established when ≥3 of the following histological items are satisfied: (1) periductal lymphoplasmacytic infiltration without granulocytes; (2) storiform fibrosis; (3) obliterative phlebitis; and (4) numerous (>10/HPF) infiltrating IgG4-positive cells [10]. These criteria emphasize the importance of the histological picture in the diagnosis of type 1 AIP. For example, even if the number of infiltrating IgG4-positive plasma cells exceeds 10/HPF, the diagnosis of type 1 AIP cannot be rendered if neither storiform fibrosis nor obliterative phlebitis is present. The strict requirement for the characteristic histopathological findings of storiform fibrosis and obliterative phlebitis compensates to some degree for the relatively low diagnostic hurdle of only >10 IgG4-positive plasma cells per HPF.

21.3 Pathological Characteristics of Type 2 AIP

The lesions of type 2 AIP extend from the pancreatic ducts to within the lobules, involving mainly the exocrine tissue. It is clearly an epithelium-centric inflammation, with the lumen and/or epithelium of the pancreatic ducts infiltrated by neutrophils—the so-called GEL—resulting in epithelial degeneration and loss and the finding of regenerative changes (Fig. 21.7a, b). Lymphoplasmacytic infiltration surrounds the epithelium but there is not a predominance of IgG4 staining among the plasma cells present. Pathological evaluation is essential to making the diagnosis of type 2 AIP, and the presence of GEL in the interlobular pancreatic duct establishes this diagnosis. This epithelium-centric inflammation further extends from the peripheral intralobular pancreatic duct to the acinar cells (Fig. 21.7c, d), and lymphoplasmacytic infiltration is seen within the intralobular stroma. Fibrosis is seen in the interlobular regions, but this differs from the interlobular inflammation seen in type 1 AIP because the inflammatory cell infiltration in this area is sparse by comparison to type 2 AIP. Storiform fibrosis and obliterative phlebitis, so characteristic in type 1 AIP, are absent in the type 2 subset. Finally, the degree of peripancreatic adipose tissue inflammation is substantially less in type 2 AIP than in type 1 AIP.

In the diagnosis of type 2 AIP, GEL is emphasized as a specific finding. In the opinion of this author, this emphasis is misguided. Although the finding of GEL is useful in differentiating type 2 AIP from type 1, the epithelium-centric inflammation observed in type 2 AIP is not specific for this disease and cannot be differentiated from similar or identical lesions detected in *Helicobacter pylori* gastritis and ulcerative colitis. (In ulcerative colitis, the finding that corresponds to GEL is called "crypt abscess.") In contrast, the histological picture of type 1 AIP is unique, with similar features found in no other diseases.

21.4 Similarity to Other IgG4-Related Lesions

Compared with the pathological features of IgG4-related lesions in other organs, the marked inflammation that occurs in both the exocrine pancreas and the adjacent adipose tissue marks a relatively distinct phenomenon within IgG4-RD. In contrast, for example, salivary gland lesions in IgG4-RD (IgG4-related sialadenitis involving the submandibular glands, parotid glands, or both) show inflammation that primarily affects the lobules, with inflammation of adipose

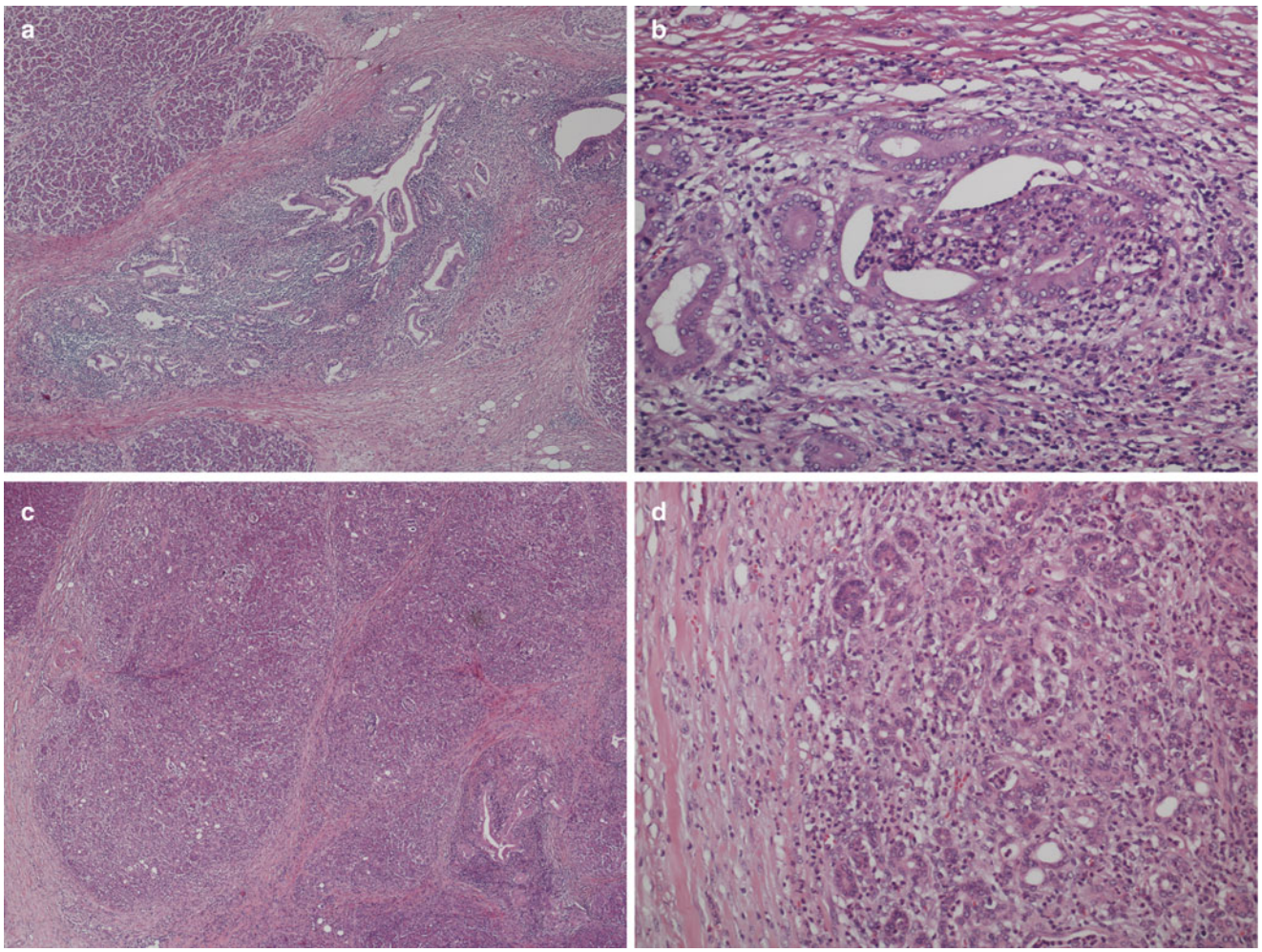

Fig. 21.7 Type 2 AIP. (**a**, **b**) Interlobular pancreatic duct lesions. Marked lymphoplasmacytic infiltration is seen surrounding the epithelium (**a**), and in the lumen, neutrophil infiltration (GEL) is found (**b**). Nuclear swelling in the pancreatic duct epithelium is seen and is interpreted as a regenerative change. (**c**, **d**) Lobular lesions. In the lobule, infiltrates consisting of neutrophils, lymphocytes, and plasma cells are seen, and neutrophils also infiltrate the lumen of the intralobular pancreatic ducts. In the fibrotic foci seen in the interlobular space (**d**: *left-hand side*) there is only scanty inflammatory cell infiltration

tissue rare. In bile duct lesions, adipose tissue inflammation is mild in the absence of pseudotumor formation. The lesion of the peripancreatic adipose tissue resembles that of retroperitoneal fibrosis, and it is appealing to believe that the marked inflammation of adipose tissue associated with type 1 AIP relates in some fashion to the location of the pancreas in the retroperitoneum.

21.5 Concluding Remarks

I reviewed type 1 AIP focusing on its pathological characteristics. The histological picture of type 1 AIP is unique, and its histological findings are essential to the pathological diagnosis.

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