Tumor-like Lesions of the Pancreas

17

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17.1 Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a "one of a kind" inflammatory disease of the pancreas since it differs clinically, pathologically, and instrumentally from all other types of pancreatitis. Many papers have been published since the introduction of the term "autoimmune pancreatitis" by Yoshida et al. in 1995 [1], focusing mainly on the dramatic and quick response to steroid therapy.

AIP has been recently classified as *type 1* (also called lymphoplasmacytic sclerosing pancreatitis, LPSP) and *type 2* (idiopathic duct centric pancreatitis, *IDCP*) [2]. Type 1 AIP is characterized by the presence of storiform fibrosis, with obstructive phlebitis (Fig. 17.1); high levels of serum IgG4; and IgG4+ plasma cells in the involved pancreatic tissue. Other pathologic findings may be observed in this form of AIP, but they are not specific and are shared with type 2 AIP (Fig. 17.2). Type 2 AIP is characterized mainly by the presence of *granulocytic epithelial lesions* (GEL), which are the expression of an aggressive cellular attack against the pancreatic epithelial ductal cells, with rupture and destruction of ductal structures [3].

The clinical profiles of patients suffering from AIP seems to differ in the two forms of the disease [4]. Patients with type 1 AIP are older, with a higher prevalence of males and a more frequent involvement of other organs, both of the gastrointestinal tract and extra-gastrointestinal. The main clinical implication of this classification seems to be that type 1 AIP is a systemic relapsing IgG4-associated disease, whereas type 2 AIP is a serum IgG4-negative disease that does not relapse. However, the frequency of relapse(s) seems to

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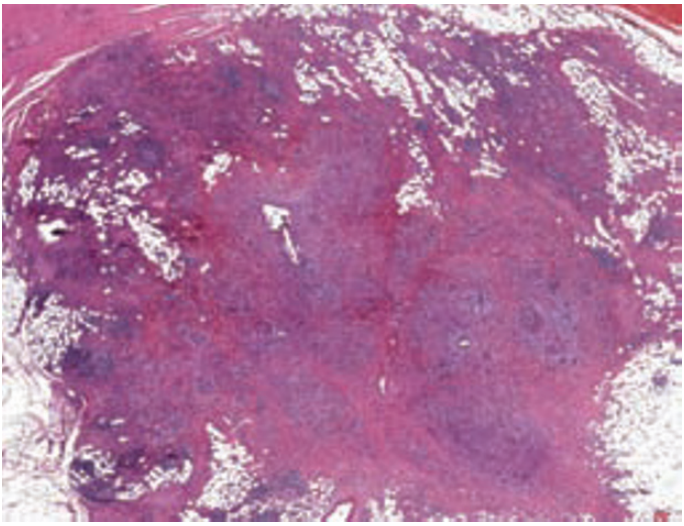

Fig. 17.1 Autoimmune pancreatitis Whole-mount section of the head of the pancreas: ill-defined, firm mass extending into the peri-pancreatic tissues and narrowing the secondary ducts

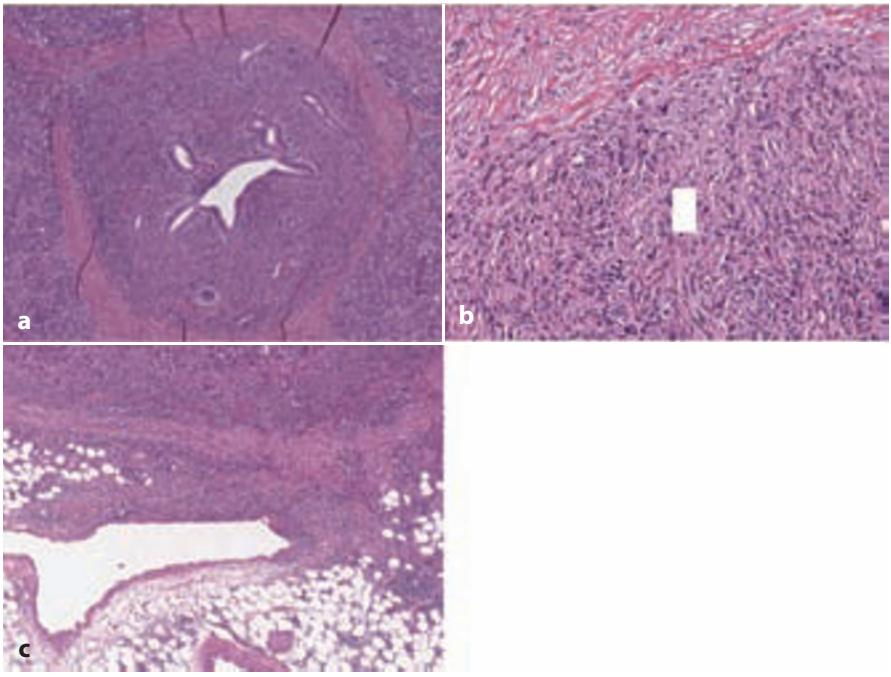

Fig. 17.2 Distinctive microscopic findings of autoimmune pancreatitis. **a** A dense inflammatory infiltrate is centered on medium-sized to large pancreatic duct. **b** Storiform pattern of fibrosis. **c** Obliterative venulitis: the inflammatory cells infiltrate a venous wall

be similar in the two forms of AIP, according to a recent paper from a French series [5].

AIP is a disease that quickly and fully responds to steroids [6-9]. The initial dosage of prednisolone ranges from 0.5 to 1 mg/kg/day, tapering to 2.5–5 mg every week.

The concept of the disease has changed over the time. Initially, AIP was considered to involve the entire pancreas, based on the Japanese experience. Later, the possibility of a segmental inflammatory involvement of the pancreas was proposed. Therefore, a clinically based classification of *focal* vs. *diffuse* AIP is now generally accepted [7, 10]. Focal AIP is defined as a segmental involvement of the pancreatic parenchyma with or without the presence of a low-density mass, as determined at imaging. In an Italian series, focal AIP was more frequent than diffuse AIP (63% vs. 37%) [7]. Compared to diffuse AIP, patients with focal AIP are older, more frequently males, and the main clinical presentation is jaundice. Since these findings are shared with pancreatic cancer, many patients with AIP undergo resective surgery (pancreaticoduodenectomy).

Indeed, this morphologically based classification has important clinical implications since in the presence of a focal disease, particularly if a low-density mass is detected at imaging, pancreatic cancer must be carefully and confidently excluded before steroid therapy is introduced [11]. The risk is, on the one hand, to operate on a patient with AIP that fully responds to steroids and, on the other, to treat a resectable cancer with steroids, delaying surgery and exposing the patient to the possibility of metastases or local invasion, both of which may preclude surgery. The diagnostic algorithm is therefore different in focal and diffuse forms of AIP.

In diffuse forms, a cholangiocarcinoma may be suspected in the presence of a single stenosis of the common bile duct. However, the probability of this being a malignancy (cholangiocarcinoma, peri-ampullar neoplasia) is very low and the differential diagnosis should mainly include acute pancreatitis (Figs. 17.3, 17.4).

By contrast, in the focal forms the likelihood of a cancer is very high. A recent review of the studies investigating the frequency of benign disease in patients who underwent pancreatic surgery for a resectable mass in the head of the pancreas found that 10% of these patients had an inflammatory pancreatic disease [11]. A recent study reported that half of these patients had a final diagnosis of LPSP. Therefore, in the presence of a pancreatic mass, only one patient in ten can be expected to have an inflammatory disease, while the large majority have a malignancy. The implication for clinical practice is that in the presence of a pancreatic mass pancreatic cancer needs to be excluded before patients are treated with steroids. Despite radiological, serological, and clinical findings highly suggestive of AIP, we strongly recommend that a biopsy of the pancreas be performed in such cases. For this purpose, fine-needle aspiration (FNA) biopsy is more accurate than core biopsy in the exclusion of cancer. Figure 17.5 shows the algorithm we propose in focal AIP with or without

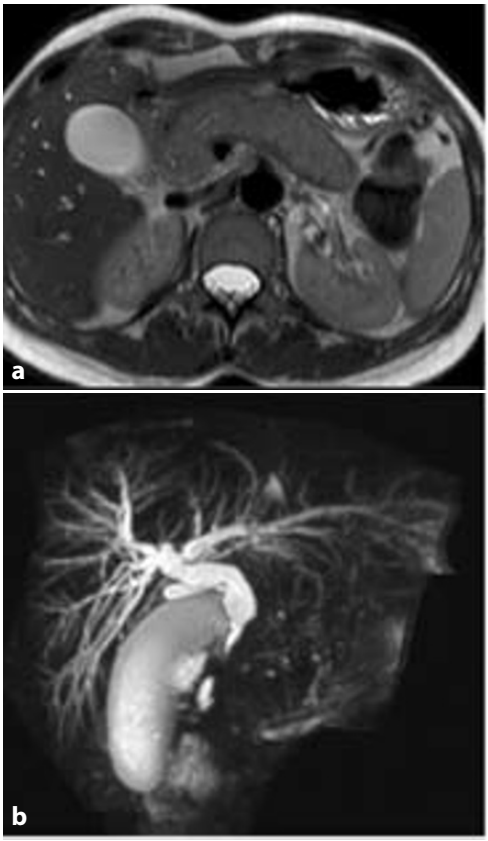

Fig. 17.3 MRI findings of a patient suffering from the diffuse form of autoimmune pancreatitis. **a** The axial sequence shows a diffuse enlargement of the pancreas, with a peripheral rim. **b** MRCP shows a stenosis of the intrapancreatic segment of the common bile duct with upstream dilation of the extra- and intrahepatic trees, without dilation of the main pancreatic duct

a hypodense mass at imaging. A trial with high-dose steroid therapy (1 mg/kg/day) may lead to a definitive diagnosis of AIP and should be made only if cytology is negative and the results of imaging, i.e., CT (Fig. 17.6), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), or contrast-enhanced EUS, are suggestive of AIP. At an international meeting held in Fukuoka, Japan, international consensus diagnostic criteria (ICDC) were recently proposed and can be used in this setting [12] (Figs. 17.5, 17.7). A second look after 3 weeks with the same imaging technique used at the basal examination is required. Normalization or significant improvement of the pancreatic morphology (disappearance of the hypodense mass, normalization of the pancreatic ductal system) is an important diagnostic finding. However, the decision to use steroids is difficult and should be made in an experienced tertiary center, after discussions among clinicians, radiologists, and surgeons.

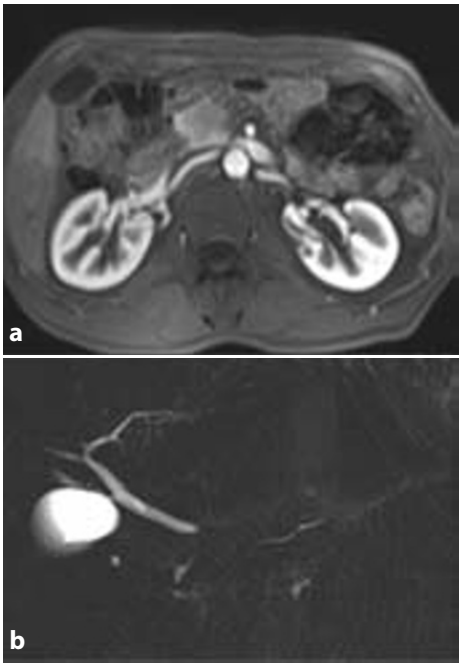

Fig. 17.4 MRI findings of a patient suffering from the focal form of autoimmune pancreatitis. **a** The axial sequence shows focal involvement in the head of the pancreas, with a hypodense mass mimicking a pancreatic adenocarcinoma. **b** MRCP demonstrates a stenosis of the intrapancreatic segment of the common bile duct, with upstream mild dilation of the extra- and intrahepatic trees, and a long stenosis of the main pancreatic duct in the head of the pancreas

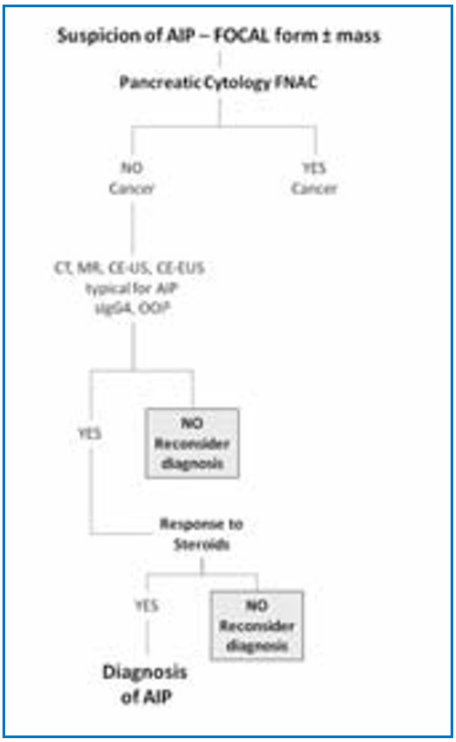

Fig. 17.5 Diagnostic algorithm for patients with the focal form of autoimmune pancreatitis according to the ICDC for AIP [12]

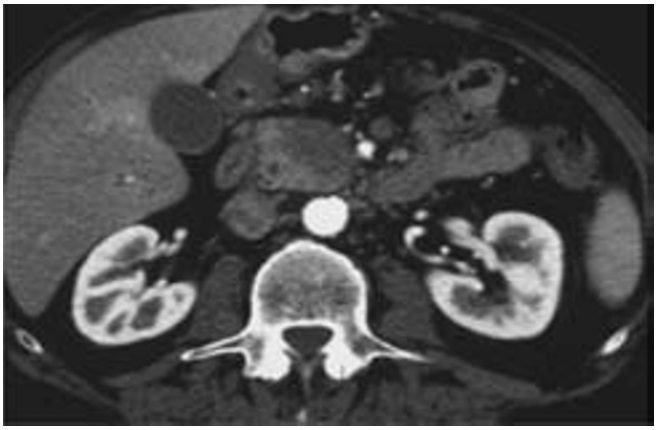

Fig. 17.6 CT findings of a patient suffering from the focal form of autoimmune pancreatitis

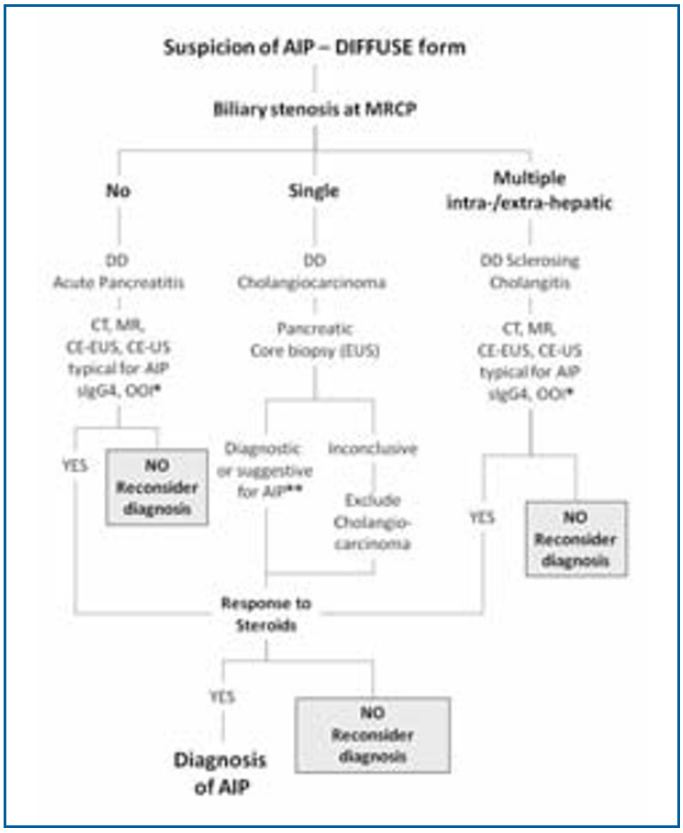

Fig. 17.7 Diagnostic algorithm for patients with the diffuse form of autoimmune pancreatitis, using the international consensus diagnostic criteria (ICDC) for AIP [12] (*) or the criteria of Zamboni et al. [3] (**)

17.2 Paraduodenal Pancreatitis

17.2.1 Epidemiology, Etiology and Pathogenesis

Chronic pancreatitis (CP) reflects a chronic inflammatory process involving the pancreas, with a final result of endocrine and exocrine pancreatic insufficiency. Reports of the prevalence of CP vary enormously, from 20 to 200 cases per 100,000 people described in the general population, with the increase due to the rising consumption of alcohol [13]. CP has a very long course and the involvement of the duodenal wall is typical; stenosis occurs in 19.6–31% of all cases of CP [14, 15]. The duodenal wall can be affected by other rare conditions, such as enterogenous duplication and retention cysts of the Brunner glands, or as a result of pancreatitis in duodenal heterotopic pancreas. The latter has been described under different names (para-ampullary duodenal wall cyst, cystic dystrophy of the duodenal wall, groove pancreatitis), but considering the clinical presentation along with the radiological and pathological features, we prefer the name paraduodenal pancreatitis (PP) [16]. Typically, PP is seen in male patients in their 40s who have a history of alcohol abuse; the disease involves principally the duodenal wall, near the minor papilla. The pathogenesis of PP has been related to functional and anatomical obstruction of the minor papilla.

Specifically, the minor papilla comprises a ductal system often surrounded by a sphincter-like structure and consistently associated with intraduodenal pancreatic tissue anatomically connected to the dorsocranial pancreas. Therefore, cysts can be considered as dilated ducts associated with intraduodenal pancreas. Of note, intraduodenal pancreatic tissue should be regarded as a bud of the dorsal pancreas entrapped within the duodenal wall during organogenesis, rather than ectopic pancreas. The presence of abundant pancreatic tissue associated with the minor papilla may reflect incomplete migration of the dorsal pancreatic bud and thereby explain the relatively high percentage (67%) of imperforated minor papilla occurring in the normal pancreas. In the presence of a closed minor papilla, countercurrent flow from the duct of Santorini through the duct of Wirsung is generated. It may be impaired by a particularly acute angle of the "Wirsungian knee" [16]. In this scenario, external factors, such as alcohol and smoking, can play a central role, rendering the pancreatic juice more viscous and inducing intrapancreatic calcification. Obstruction of the normal flow of pancreatic juice leads to a chronic inflammatory process and ultimately a paraduodenal mass mimicking a solid-cystic periampullary tumor.

17.2.2 Clinical Presentation and Pathological Features

The clinical presentation of PP reflects the particular location of the pathological process, i.e., the duodenal wall. The most frequent symptom is due to

stenosis of the second duodenal portion, causing pain that is typically ameliorated with vomiting. In a minority of patients with PP, the inflammatory process can involve the "groove" area, compressing the main biliary tract and thus resulting in jaundice.

Macroscopically, two types of PP may be distinguished. In the ''cystic'' type, multiple cysts ranging in diameter from 1 to 10 cm and protruding into the mucosa of the supra-ampullary duodenum are seen (Fig. 17.8). If the cysts are particularly large, they may be confused with an intestinal duplication. The second, ''solid'' type is characterized by a remarkable thickening of the duodenal wall, which contains cysts less than 1 cm in diameter (Fig. 17.9). Both types share variable degrees of thickening of the duodenal wall, which is more evident at the pancreatic side of the second portion of the duodenum, above the ampulla and connected to the minor papilla. The groove region is usually enlarged, either due to fibrotic tissue or to the presence of cysts within the duodenal wall. As a result of the former, narrowing of the common bile duct may occur, as well as duodenal stenosis secondary to the cysts.

The presence of numerous enlarged peri-pancreatic lymph nodes is also a typical characteristic of PP.

Histologically, the cysts are found in the submucosal and muscular layers of the duodenal wall and can often extend to the groove region. Observation of the cut surface shows that the internal layer of the cysts is mainly lined by columnar pancreatic ductal cells, which may be lost and replaced by inflammatory granulation tissue. Smooth-muscle hyperplasia and fibrosis, causing Brunner gland hyperplasia and variable thickening and disarray of the muscular layer in the duodenum, are additional features. The cysts are associated with heterotopic pancreatic tissue within the muscular or submucosal layer. More frequently the groove area is characterized by marked fibrosis and chronic inflammation. Ductal ectasia with stones, fibrosis, and an inflammatory reaction that includes myofibroblastic proliferation are also commonly observed in the pancreatic parenchyma [17, 18].

17.2.3 Diagnosis and Treatment

In most cases, the clinical and radiological presentations of PP are very similar to those of pancreatic and peri-ampullary tumors, making the differential diagnosis particularly difficult. The patient's medical history, his or her abuse of alcohol, weight loss, and the presence of steatorrhea can aid in ruling out the presence of malignancy. In case of a cystic mass in the groove area, the differential diagnosis is easier, whereas the presence of a solid mass poses a challenge. Imaging can demonstrate the non-specific features that PP shares with other tumors. Magnetic resonance cholangiopancreatography (MRCP) may reveal only abnormalities in the biliary and pancreatic ducts. US and contrast-enhanced CT may show a hypovascularized mass associated with ductal dilatation and calcification. The identification of small cystic formations in the

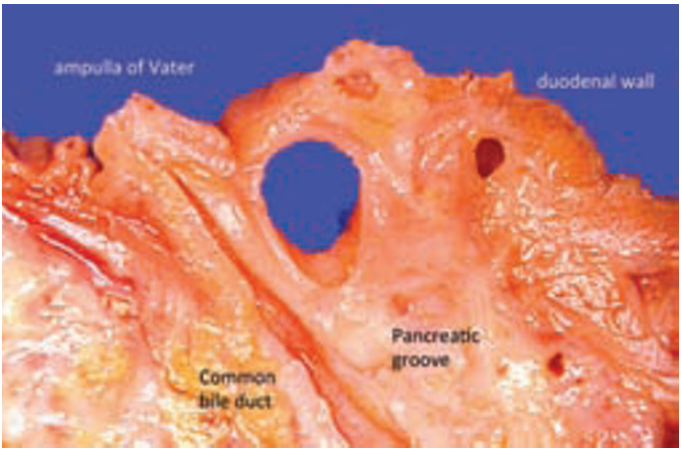

Fig. 17.8 Paraduodenal pancreatitis, cystic variant

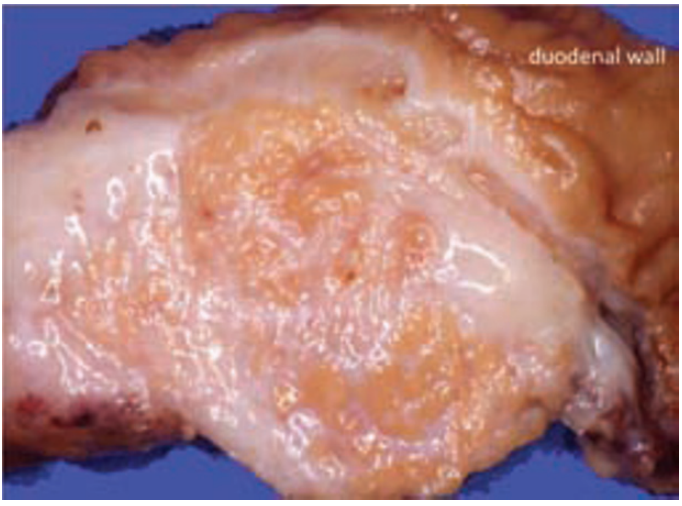

Fig. 17.9 Paraduodenal pancreatitis, solid variant

thickened duodenal wall on the pancreatic side is a specific finding for PP (Fig. 17.10). Procacci et al. [19] described the appearance of the thickened duodenal wall as a solid layer between the duodenal lumen and the pancreas, hypoechoic at US, isoattenuating at unenhanced CT, and hypoattenuating in the early phase and isoattenuating in the late phase on contrast-enhanced CT. The gastroduodenal artery is often dislocated to the left due to the growing mass.

However, the final diagnosis at CT can sometimes be difficult. Consequently, the role of EUS is central in the assessment of solid paraduodenal pancreatic masses. This imaging method is further improved with the use of the newest generation of intravenous contrast agents, but also allows EUS-

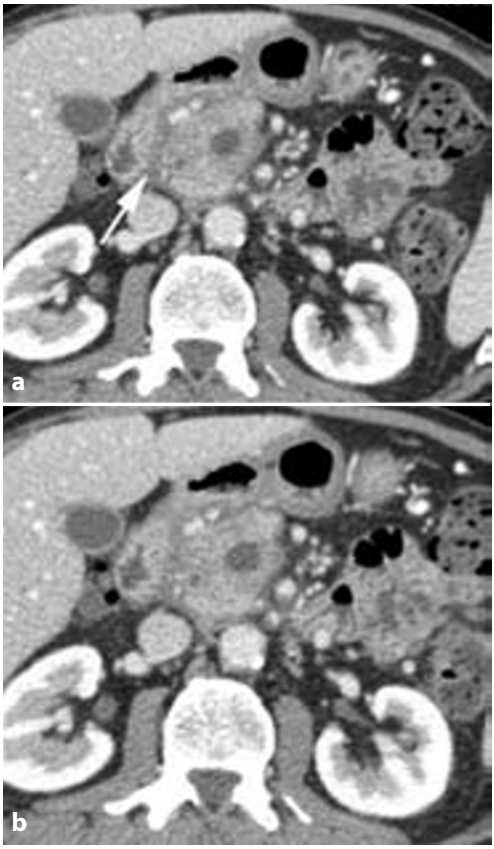

Fig. 17.10 Thickening of the duodenal wall in the groove region, with a hypovascularized appearance (*arrow*) at CT (**a**, **b**). In the pancreatic head, a small pseudocystic lesion is also visible

FNA [20]. The specificity and sensitivity of the latter are between 75–100% and 78–95%, respectively, with a complication rate of 0–2% [21]. EUS-FNA is cost-effective and in our experience is the second most preferred diagnostic method after percutaneous US-guided FNA biopsy.

Surgery represents the best treatment for uncertain pancreatic masses when doubts remain even after EUS-FNA [22]. In this case, surgeons should perform a pancreatoduodenectomy, while the Longmire-Traverso (PD-LT) is the procedure mostly performed for combined obstruction of the duct of Wirsung, main biliary duct, and duodenum [23]. A biliary and duodenal by-pass is indicated in case of duodenal stenosis and jaundice, when endoscopic treatment has failed. In patients with a definitive diagnosis of PP, the immediate elimination of all risks factors (alcohol, smoking) and enzyme replacement are mandatory.

17.3 Pancreatic Hamartoma

Histologically, pancreatic hamartoma is characterized by a focal overgrowth of mature tissue composed of normal cells with a disorderly arrangement [24, 25].

Although these tumors are very rare, their exact prevalence is difficult to determine as some of them are likely to be asymptomatic and remain undetected. In our hospital, a high-volume center for pancreatic pathology, only two cases of pancreatic hamartoma have been collected to date. In both of these, the tumors presented as a solid, well-circumscribed, whitish-gray mass, with a homogeneous appearance on the cut surface and a maximum diameter of 1.5 cm (Fig. 17.11).

Microscopically, pancreatic hamartomas are composed of well-differentiated acinar and ductal cells, without atypia, disposed in a radial trabecular arrangement. A wide sclerotic paucicellular area is usually present in the center of the lesions. Acini and small intralobular and interlobular ducts show atrophic aspects without any evidence of dysplasia. Discrete islets of Langerhans are usually lacking [25] (Fig. 17.12). At preoperative work-up, these lesions are usually misdiagnosed as pancreatic adenocarcinoma; therefore, careful pathological examination is of paramount importance. Of note, repetitive FNA shows normal acinar cells. If intraoperative histological and immunohistochemical findings suggest a diagnosis of pancreatic hamartoma, a minimal pancreatic resection can be performed, sparing the patient the unnecessary risk of postoperative complications associated with major resections [26].

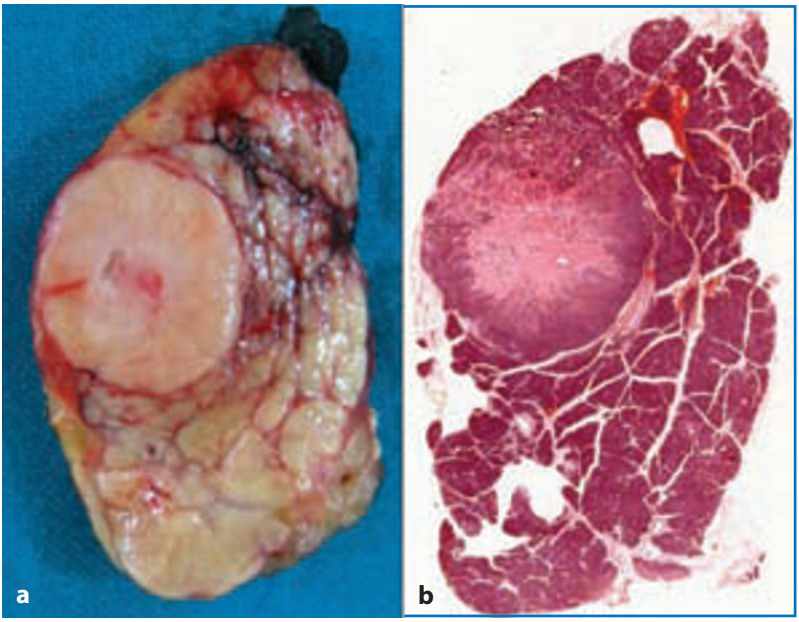

Fig. 17.11 Pancreatic hamartoma. **a** Gross appearance. **b** Whole-mount section

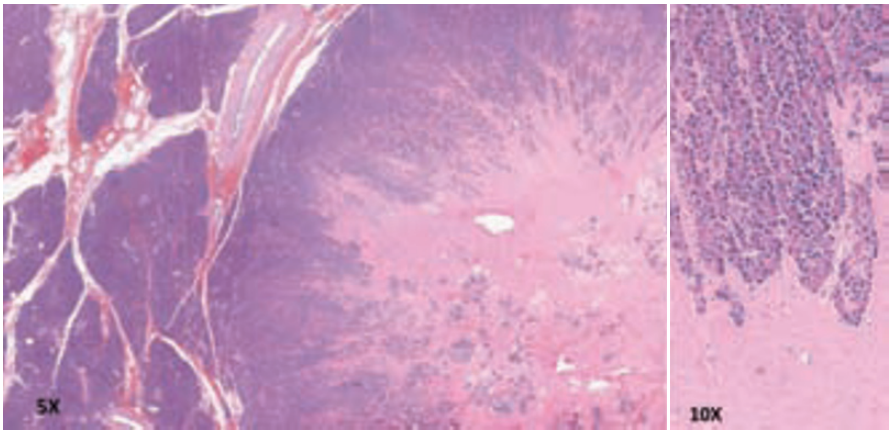

Fig. 17.12 Pancreatic hamartoma at histologic examination as seen at different magnifications: well-circumscribed lesion composed of disorganized acini with central fibroblastic, heavily collagenized stroma

17.4 Intrapancreatic Accessory Spleen

Intrapancreatic accessory spleen (IPAS) is a congenital anomaly that is due to the fusion failure of splenic primordial mesenchymal tissues, mimicking, in some case, a pancreatic neoplasm. A large study of approximately 3000 autopsies concluded that 10–12% of the populations examined had an accessory spleen. Most (80%) are situated in the adipose tissue at the splenic hilum, followed by the pancreatic tail (17%). Other, uncommon sites are the wall of the jejunum, mesentery, and pelvis [27].

Usually, IAPS are resected because they are misdiagnosed by imaging as pancreatic neoplasms. At ultrasonography, they appear as well-defined, usually well vascularized lesions [28]. On contrast-enhanced CT or MRI, the contrast enhancement of IAPSs at the arterial and portal phases is more intense than that of normal pancreatic parenchyma, simulating a pancreatic neuroendocrine neoplasm (PanNEN) [29-31]. The usefulness of octreotide scintigraphy is very limited for the differential diagnosis of IPAS and PanNEN, because splenic tissue, and in particular the white pulp, typically also expresses somatostatin receptors [32].

Three cases of resected IPAS have been seen at our institution. Interestingly, two of the three patients had undergone splenectomy for abdominal trauma some years before the finding of the IPAS, suggesting that a compensatory hyperplasia of the accessory splenic tissue may result in these tumor-like lesions. Therefore, in the case of a hypervascularized well-circumscribed nodule within the pancreatic tail (Fig. 17.13) in a patient who has previously undergone splenectomy, it is very important to distinguish IPAS from PanNENs, to avoid unnecessary surgery.

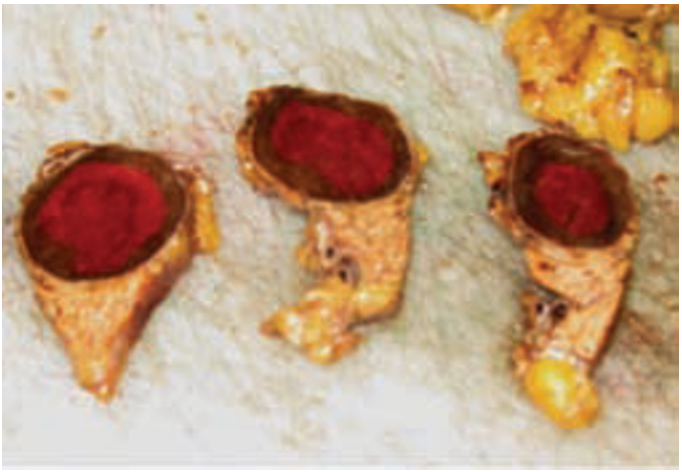

Fig- 17.13 Heterotopic spleen: gross appearance of a well-circumscribed nodule of red splenic tissue surrounded by normal pancreas

Accordingly, in our opinion IPAS should be suspected in the presence of hypervascular lesions located in the tail of the pancreas, in patients who have previously undergone splenectomy.

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