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Review

Inflammatory and tumor-like lesions of the pancreas

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Summary

Inflammatory/tumor-like lesions of the pancreas represent a heterogeneous group of diseases that can variably involve the pancreatic gland determining different signs and symptoms. In the category of inflammatory/tumor-like lesions of the pancreas, the most important entities are represented by chronic pancreatitis, which includes alcoholic, obstructive and hereditary pancreatitis, paraduodenal (groove) pancreatitis, autoimmune pancreatitis, lymphoepithelial cyst, pancreatic hamartoma and intrapancreatic accessory spleen. An in-depth knowledge of such diseases is essential, since they can cause severe morbidity and may represent a potential life-threatening risk for patients. Furthermore, in some cases the differential diagnosis with malignant tumors may be challenging. Herein we provide a general overview of all these categories, with the specific aim of highlighting their most important clinic-pathological hallmarks to be used in routine diagnostic activities and clinical practice.

Key words: chronic pancreatitis, paraduodenal pancreatitis, groove, autoimmune pancreatitis, pancreatic pathology

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Introduction

Inflammatory /tumor-like lesions of the pancreas represent a heterogeneous group of diseases that can variably involve the pancreatic gland causing a composite spectrum of different signs and symptoms. An in-depth knowledge of such diseases is very important, since they can cause severe morbidity and may represent a potential life-threatening risk for patients. For surgical pathologists, recognizing their histological features and morphological hallmarks is fundamental, since all these disorders can potentially mimic pancreatic ductal adenocarcinoma or other malignant neoplasms.

In the group of inflammatory/tumor-like lesions of the pancreas, the most important categories are: chronic pancreatitis (CP), paraduodenal (groove) pancreatitis (PGP), autoimmune pancreatitis (AP), lymphoepithelial cyst, pancreatic hamartoma and intrapancreatic accessory spleen. The key features of each category are summarized in Table I. Figure 1 shows some typical macroscopic aspects.

Table I. Main features of inflammatory and tumor-like lesions of the pancreas.

Pathological conditions	Etiology	Clinical issues	Macroscopic features	Microscopic features
Chronic pancreatitis	Alcoholic pancreatitis.	Clinical symptoms are very similar for the three subtypes, including severe abdominal pain and dysfunction of both exocrine and endocrine parenchyma	Irregular fibrosis (irregular whitish area). Intraductal calculi of calcium carbonate and pseudocysts.	Fibrosis and pseudocysts.
	Obstructive pancreatitis.		Clear localization of fibrosis (demarcated whitish area); multiple retention cysts. Pseudocysts very rare.	Fibrosis and retention cysts.
	Hereditary pancreatitis.		If *PRSS1* and *CFTR*-related: progressive lipomatous atrophy (yellowish areas); if *SPINK1*-associated: progressive fibrosis (withish areas).	Lipomatous atrophy *vs* progressive fibrosis.
Paraduodenal (groove) pancreatitis	Chronic obstruction of the minor papilla.	Severe waxing and waning upper abdominal pain, postprandial vomiting and weight loss due to duodenal stenosis.	Duodenal wall with trabeculated appearance and cystic change, especially in the proximity of the minor ampulla, which can be absent or largely obstructed by calcified, proteinaceous material. Epicenter in the groove area.	Dense fibrosis of the duodenal wall around the minor papilla, with variably extension to the groove area and the pancreatic parenchyma. Cysts are lined by ductal epithelium.
Autoimmune pancreatitis	Type 1: part of the systemic autoimmune immunoglobulin (Ig) G4+ related disease.	Men > 60 years, IgG4+; obstructive jaundice, vague abdominal pain. Involvement of different organs (systemic disease). Important response to corticosteroid-based therapy.	Grossly, type 1 and type 2 are undistinguishable. Most common appearance: pseudo-tumor aspect, whitish-yellowish area.	Compact inflammatory infiltrate of T cell-lymphocytes and plasma cells (IgG4+), fibrosis specifically localized in the periductal area, and a marked venulitis. The inflammation is centered around and within medium-to-large interlobular ducts.
	Type 2: autoimmune disorder, more pancreas-specific.	Male = female, younger patients (4^{th}-5^{th} decade). Limited to pancreas (15% of patients may have concurrent inflammatory bowel disease). Important response to corticosteroid-based therapy.		Lymphoplasmacytic inflammation located in the periductal regions of pancreatic parenchyma, presence of granulocytic epithelial lesions.
Lymphoepithelial Cyst	Unknown.	Usually, this is an asymptomatic lesion, discovered incidentally by imaging analysis due to unrelated reasons.	Unilocular or multilocular cyst, can be located or entirely within the pancreatic gland or in the periphery with exophytic growth. It can reach a large size (>5 cm), and shows a irregular capsule.	The cystic epithelium is multi-layered-squamous, and is surrounded by a dense layer of lymphoid tissue with prominent germinal centers. The adjacent pancreatic parenchyma is usually unremarkable.

▶

Table I. continues

Pathological conditions	Etiology	Clinical issues	Macroscopic features	Microscopic features
Pancreatic hamartoma	Malformation, disembryogenetic disorder.	Variable and dependent by size and location	Head of the pancreas, intrapancreatic mass.	Small ductal structures lined by columnar epithelial cells without atypia, surrounded by fibrous stroma and an unorganized acinar parenchyma. The presence of each component can vary, determining different morphological aspects, with ductal, stromal or acinar prominence.
Intrapancreatic accessory spleen	Unknown.	Variable and dependent by size and location; differential diagnosis with neuroendocrine tumors.	Brownish nodule (spleen appearance) surrounded by normal pancreas.	Mature splenic tissue, with a normal distribution of white and red pulp.

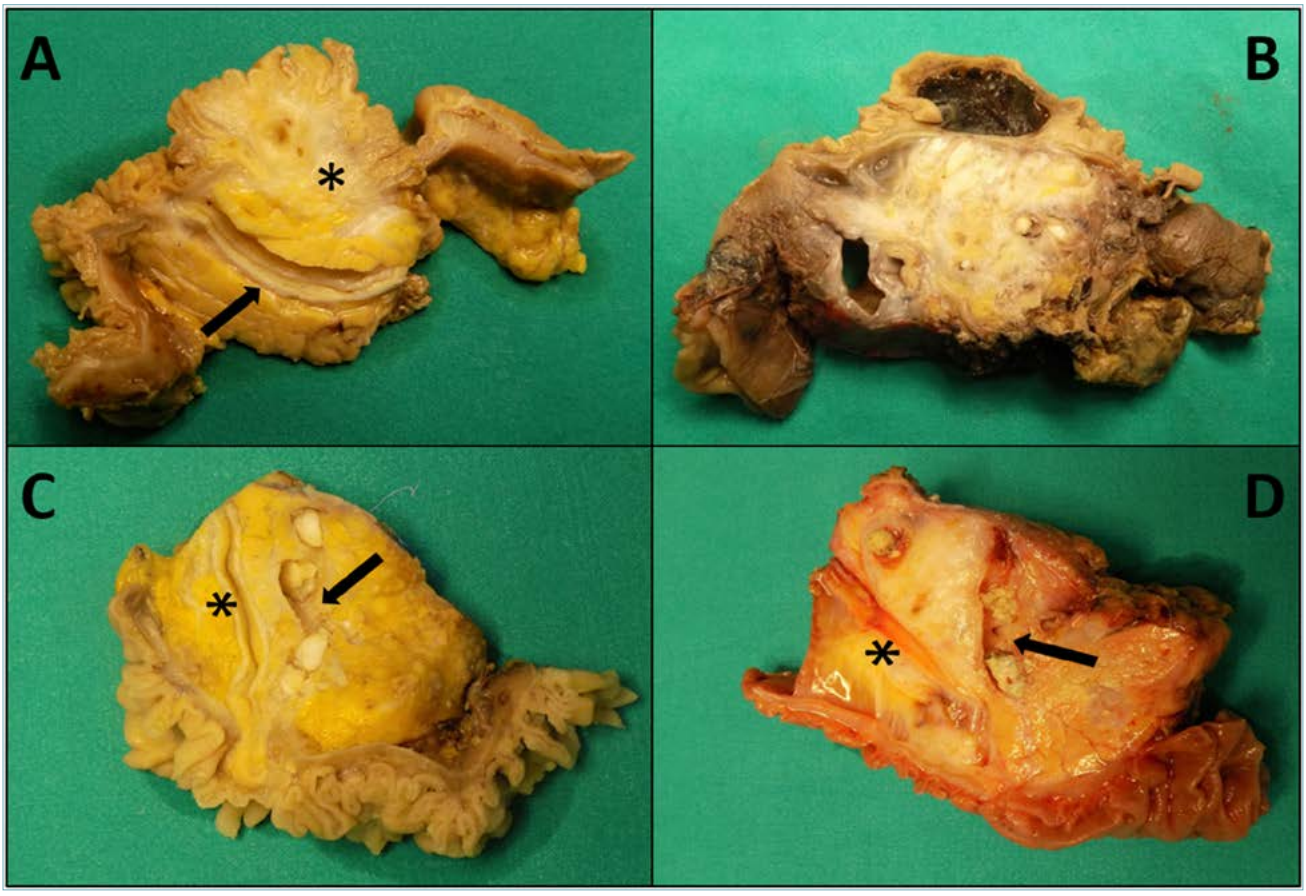

Figure 1. Paradigmatic images of PGP and CP. PGP, solid variant: marked expansion of the groove area (asterisk) and marginal involvement of the pancreatic parenchyma and of choledocus (black arrow) (A); PGP, cystic variant: diffuse presence of cysts and extensive pancreatitis of the pancreatic parenchyma (B); CP with intraductal calculi (asterisk: coledochus, black arrow: Wirsung's duct) (C); Macroscopic translucent/pearly appearance of CP can be better appreciated on fresh tissues (asterisk: coledochus, black arrow: Wirsung's duct) (D).

Chronic Pancreatitis (CP)

Definition and terminology

CP was first described in the scientific literature by Sir Thomas Cawley in 1788 [1]. He reported the history of a young man who died of diabetes, whose autopsy revealed a pancreas filled with calculi. Starting from this landmark publication, many studies aimed at clarifying the pathogenesis and pathophysiology of CP. This condition is now considered as a progressive, fibro-inflammatory disease characterized by irreversible damage to the pancreas [2]. Based on its diverse etiologies, CP is now grouped into three different categories: i) alcoholic pancreatitis, ii) obstructive pancreatitis, and iii) hereditary pancreatitis.

Clinical Issues and different etiologies

In Western Countries, the incidence of CP is around 10 cases per 100,000, with a prevalence up to 40 cases per 100,000 subjects [2-4]. Although the symptomatic spectrum may be underhand and unspecific, patients often present with severe abdominal pain and with dysfunction of both exocrine and endocrine parenchyma[3]. The abdominal pain usually have a classical back irradiation to the intra-scapular area. Therapeutic strategies for chronic pancreatitis are mostly supportive, without resolving the disease and its symptoms definitively. As a consequence and despite its low prevalence, CP represents a non-negligible cause for both hospital admissions and overall costs for the public health system[2]. Notably, patients with CP have also an increased risk for developing pancreatic ductal adenocarcinoma.

The underlying cause of chronic pancreatitis is multifactorial and involves a complex interaction of environmental, genetic, and/or other risk factors [5-10]. Alcoholic-CP is caused by a heavy and prolonged alcohol abuse, and usually affect the pancreas of young-to-middle aged male patients. Notably, fewer than 5% of alcoholic individuals develop chronic pancreatitis [2]. This observation indicates that the involvement of other additional insults or cofactors are needed for leading a subject to CP [7,9]. Indeed smoking, obesity, genetic background and infectious diseases have been suggested as important cofactors of alcohol in this condition [7-11]. Obstructive CP originates by an obstruction of the Wirsung's duct or of secondary ducts, which can be caused by different entities, such as tumors, of which benign (less commonly) or malignant (more commonly), ductal stones, scars, paraduodenal wall cysts, stenosis of the papillary region and congenital anomalies [10,11]. Differently from alcoholic-CP, obstructive CP affects the gland distal to the site of obstruction, being thus confined to a clearly delimited area in location. Based on the etiology of the obstruction, obstructive chronic pancreatitis affect equally male and female, and can occur over a extensive age distribution. Therapeutic approaches for obstructive chronic pancreatitis aim at removing the underlying cause, whenever possible (e.g.: interventional endoscopy, surgical resection) [2]. Hereditary CP describes an entity resulting from the presence of genetic factors playing a critical role in both the susceptibility and predisposition for CP developing. The 3 most common germline alterations associated with chronic pancreatitis involve the genes Serine Protease-1 *(PRSS1)*, Cystic Fibrosis Transmembrane-conductance Regulator (*CFTR*) and Serine Peptidase Inhibitor Kazal type 1 (*SPINK1*) [12-16]. Germline mutations resulting in *PRSS1* gain of function are responsible for a type of hereditary CP that mostly involves very young patients (< 20 years old) [12]. On the other hand, autosomal recessive alterations in *CFTR* gene represent the most common etiology of hereditary CP in children, within the cystic fibrosis syndrome spectrum [15]. Moreover, mutations of *SPINK1* gene are considered to be CP genetic moderators, which either lower the threshold of originating pancreatitis or worsen its severity because of other risk factors [2,16].

The common CP course, independent from these different etiologies, in the initial stages of the disease is clinically articulated in recurrent episodes of abdominal pain [5-10]. Over time, the pain attacks decrease in incidence and severity, but in parallel there is a progressive destruction of the glandular parenchyma, leading to irreversible endocrine and exocrine failure.

Macroscopic features

The macroscopic features of alcoholic CP differ based on the different stages of the disease. Indeed, in early stages there is a patchy distribution of parenchymal fibrosis, in both perilobular and and interlobular location [10,11,17]. Grossly, this feature usually results in an accentuation of individual pancreatic lobules, with dilation of distortion of the portion of the pancreatic ductal tree embedded in this fibrosis. In later stages, the pancreatic parenchyma is extensively atrophic, with consequent reduction of the size of the entire gland [17]. A diffuse loss of the normal pancreatic lobular architecture with replacement by diffuse fibrosis is associated with prominent changes of pancreatic ducts, including marked dilation and distortion. Intraductal calculi of calcium carbonate are frequently present, and pseudocysts are encountered in up to a half of alcoholic-CP, representing a macroscopic hallmark of alcoholic-CP [18].

The macroscopic features of obstructive-CP can differ based on the underlying etiology. However, the most

important points regard the clear localization of the disease, involving the pancreatic distal to the obstruction, and the distal ductal dilation and distortion[2]. The normal pancreatic architecture is lost and replaced by a whitish fibrosis and by the presence of multiple retention cysts, above all in longstanding cases. Pseudocysts are very rare in obstructive-CP.

In hereditary CP, *PRSS1* and *CFTR*-related CP show a progressive lipomatous atrophy; conversely, *SPINK1*-associated hereditary CP usually exhibits a pattern of progressive fibrosis [2,19].

Microscopic description with diagnostic criteria

Paradigmatic microscopic images of CP are presented in Figure 2.

Although, as described below, there are different histological features that are more often seen in the different types of CP, it is of importance acknowledging that the most common and cardinal features for CP histologic diagnosis are represented by the triad of fibrosis, loss of acinar tissue and duct changes. The presence of all the components of this triad represents the most important diagnostic criteria for CP [20].

Given that, from a microscopic point of view, the histological features mirror the gross alterations of each CP subtype. In early stage alcoholic CP, indeed, there is a perilobular and interlobular fibrosis, composed of spindled fibroblasts, which are dispersed in a thin wavy collagen [10,17,21]. Atrophic changes regard in this stage exocrine/acinar parenchyma. In this case, the remaining Langerhans islets can be visible in small aggregates, representing a differential diagnosis with neuroendocrine microadenoma /neuroendocrine tumors. In such cases. an immunohistochemical analysis for normal pancreatic hormones (including at least insulin and glucagon) will demonstrate the usual hormones' distribution, thus confirming the normal nature of the process. Usually there is also associated a patchy distribution of lymphocytes (above all T-cells), plasma cells and histiocytes [21]. In advanced stages, the dilated pancreatic ducts may show a prominent squamous metaplasia. There is an extensive loss of exocrine and also endocrine parenchyma, with replacement by not only perilobular and interlobular fibrosis, but also intralobular fibrosis [10,21]. Pseudocysts are composed of thick, fibrous walls that lack by definition an epithelial cell lining, and are filled with necrotic debris, fibrin, blood, and macrophages [17,21]. Foci of fat

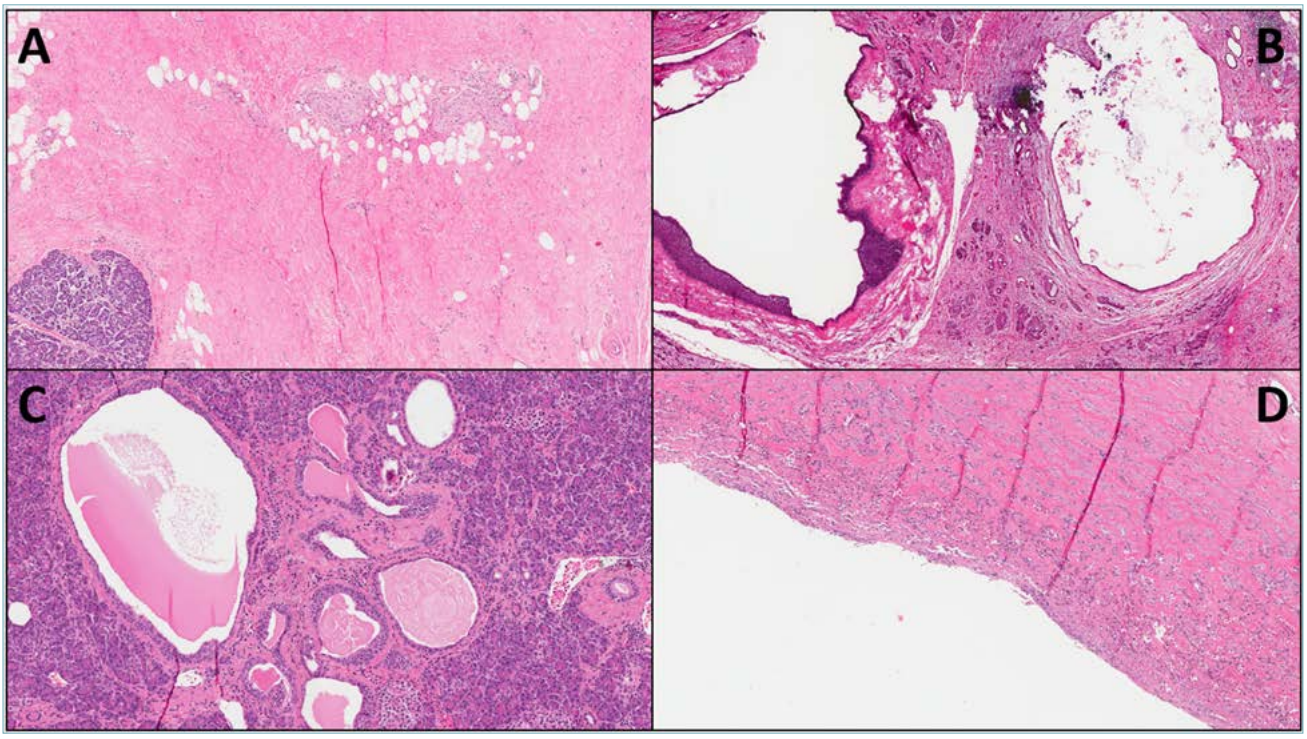

Figure 2. Important histological patterns of chronic pancreatitis. (A) Marked fibrosis with loss of normal pancreatic parenchyma (original magnification 4X); (B) calcification in pancreatic duct with focal squamous metaplasia of a duct (original magnification 10X); (C) calcific plugs in pancreatic duct with ductal changes (original magnification 10X); (D) pancreatic pseudocyst: the lack of epithelial lining is evident (original magnification 4X).

necrosis characterized by partially necrotic adipose tissue with foamy macrophages, multinucleated giant cells, and chronic inflammation may be also present [2]. Similarly to the macroscopic description, the morphology of obstructive CP is characterized by narrowed changes involving the pancreatic parenchyma distal to the obstruction. The normal pancreatic parenchyma is replaced by a variable amount of perilobular and interlobular fibrosis. The epithelium of the ductal tree may undergo hyperplasia and/or squamous metaplasia. In advanced stages, a diffuse loss of pancreatic parenchyma and a prominent fibrosis are typical. Another important aspect is represented by the presence of retention cysts, which represent dilated ducts lined by reactive cuboidal-to-columnar epithelium with intraluminal proteinaceous plugs and serous fluid [2,10].

The microscopic features of hereditary CP are heterogeneous, based on the stage of the disease but also on different etiologies. The morphology of PRSS1-related hereditary CP, for example, are dependent on patient age. In advanced age, pancreas of patients with *PRSS1* alterations show a diffuse parenchymal atrophy, with extensive replacement by mature adipose tissue [22]. Scattered endocrine islets and rare residual acinar cells, if present, are usually localized near Wirsung's duct. The ductal epithelium may undergo dysplastic changes consistent with low-grade pancreatic intraepithelial neoplasia (PanIN) [23]. On the other hand, in pediatric cases there is usually a central parenchymal loss with mild chronic inflammation and perilobular and/or interlobular fibrosis [2,24]. Noticeably, the periphery of the gland usually shows a patchy parenchymal replacement with mature adipose tissue. The fatty replacement of the pancreatic parenchyma is not randomly located; indeed, it extends from the periphery to the central areas of the pancreas [22]. Fibrosis may be present, but it is usually focal or mild. Hereditary CP associated with *CFTR* mutations are usually associated with ductal dilation, intraductal mucinous plugs and periductal fibrosis. Conversely, hereditary-CP associated with *SPINK1* mutations are characterized by loss of pancreatic parenchyma with concomitant perilobular and interlobular fibrosis. The ductal epithelium can be atrophic, with intraluminal proteinaceous plugs and calculi [2].

Paraduodenal (Groove) Pancreatits (PGP)

Definition and terminology

PGP (also reported as groove pancreatitis or cystic dystrophy of heterotopic pancreas) is a distinctive form of chronic pancreatitis occurring predominantly in and around the duodenal wall (near the minor papilla), with frequent involvement of anatomic region between the superior limit of the pancreatic head, duodenum, and common bile duct, which is the so-called "groove area" [24-28]. PGP can presents either as a pure lesion, as a result of pancreatitis of the intraduodenal pancreatic parenchyma associated with the minor papilla, or associated with chronic pancreatitis of the proper pancreas. PGP as a pure lesion is rare compared with PGP associated with CP.

Clinical issues

The vast majority of patients with PGP are middle-aged men (5th decade) with a history of alcohol abuse and smoking [26]. The clinical syndrome includes an important symptomatology with severe waxing and waning upper abdominal pain, disordered gastric emptying, postprandial vomiting and weight loss due to duodenal stenosis [2,26,27]. Although its pathogenesis remains not completely understood, the main hypothesis attributes the onset of this disease to a chronic obstruction of the minor papilla [24].

Imaging reveals thickening of the duodenal wall with associated cyst formation within the duodenum or the groove area, with a consequent radiographic appearance of a pseudocyst or of a cystic pancreatic neoplasm[2]. More rarely, cases with minor cystic changes or solid lesions, often related to the sclerotic changes in the periampullary region, may mimic a pancreatic or a periampullary malignancy [27-30]. The therapeutic strategies for PGP may be supportive/conservative but, in case of a severe and longstanding symptomatology, and/or also in case of a difficult differential diagnosis with cancer, the first choice is represented by pancreaticoduodenectomy [26-30].

Macroscopic features

The macroscopical examination of a surgically resected specimen of the pancreatic head region with a PGP shows a duodenal wall with a trabeculated appearance, often accompanied by cystic change, especially in the proximity of the minor papilla, which can be absent or largely obstructed by calcified, proteinaceous material [24-30]. On cut sections, the epicenter of PGP can be identified around the minor papilla, with variable involvement of the groove area, which can be relatively gelatinous to solid, or contain cysts. In some cases, cyst formation may be prominent, measuring up to several centimeters in size, mimicking intestinal duplication [27]. The cysts are filled with proteinaceous debris, usually have a smooth, opaque wall and may contain small calculi [2]. Typically, the duodenal wall and underlying pancreatic parenchyma are thickened and fibrotic between Vater's ampullary region and the minor papilla; the duodenal mucosa often acquires a

nodular or cobblestone appearance [2,31]. Although fibrosis is typically narrowed to the groove area, it may spill into the adjacent pancreatic tissue, leading to stenosis of the Wirsung's duct and of the common bile duct [2]. The fibrosis has a typical translucent-pearly appearance. It is also of interest to note that PGP is usually associated with the presence of enlarged "reactive" lymph nodes/lymphadenopathy, macroscopically evident, which are seen more rarely in the case of pancreatic cancer.

Microscopic description with diagnostic criteria

The typical histological appearance of PGP is shown in Figure 3.

From the histologic point of view, an important feature is the presence of a dense fibrosis of the duodenal wall around the minor papilla, with variable extension to the adjacent structures including the soft tissue of the groove area and the pancreatic parenchyma [24,26,31]. Disperse in this fibrotic background, there are fibroblasts, myofibroblasts and smooth muscle cells. In the duodenal wall, a marked, bulging Brunner gland hyperplasia is often present, contributing to the thickening of the intestinal wall [2,24,27,31]. The cysts can be either restricted to the submucosal and muscular layers of the duodenal wall, or extended to the groove region. The internal surface is mainly lined by columnar pancreatic duct-like epithelium, which may be lost and replaced by inflammatory granulation tissue. The cysts contain small calculi that may extravasate causing a foreign body giant cells reaction [2], which may call for a differential diagnosis with undifferentiated carcinoma of the pancreas with osteoclast-like giant cells [30]. In late stage of disease, the proper pancreas usually shows atrophy, fat necrosis, chronic inflammation and thick fibrosis [2,27]. Prominence of nerve bundles resembling traumatic neuroma is also a common finding in such area [27].

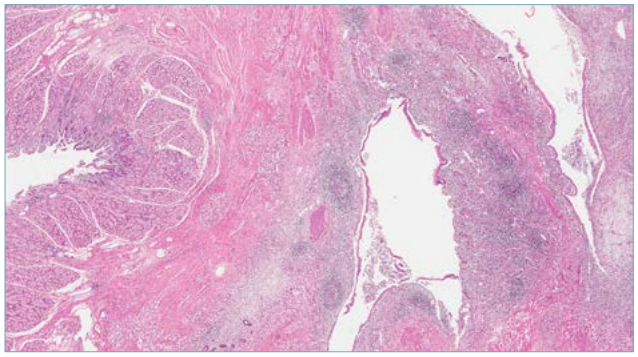

Figure 3. The histological appearance of paraduodenal groove pancreatitis is here shown. The cystic region usually includes multiple cysts lined by ductal epithelium (original magnification 2X).

Autoimmune Pancreatits (AIP)

Definition and terminology

AIP represents a heterogeneous disease process and is composed of 2 subtypes (type 1 and type 2). AIP is classified as type 1, which is often regarded as part of the systemic IgG4-related disease (IgG4-RD) that may involve other organs, or as type 2, which is more pancreas-specific [32-36].

Clinical issues

AP is a unique form of chronic pancreatitis. From a clinical point of view, the symptoms associated to this disease are heterogeneous; the most frequent is represented by obstructive jaundice, followed by vague abdominal pain. Both type 1 and type 2 AIP patients demonstrate significant response to corticosteroid-based therapy.

At clinical presentation, patients with AIP-type 1 are generally men, older than 60 years, and seropositive for IgG4 [33-37]. It is within the spectrum of IgG4-RD that often affects multiple organs and shares similar clinical, serologic and pathologic features [2,33-37]. Together with the pancreas, the other organs that are more frequently involved are liver, breast, lacrimal and salivary glands (Küttner tumor), but may other districts may be affected, as for example nasopharynx, bone marrow, extra-ocular muscles and retrobulbar space, kidneys, lungs, lymph nodes, meninges, arteries, skin, prostate, thyroid gland and even pericardium [34]. Despite a remarkable response to corticosteroid-based therapeutic strategies, patients are prone to frequent relapses [38].

Conversely, AIP-type 2 affects more often younger subjects (< 4-5th decade) and is equally distributed between male and females [37,38]. Clinical manifestations are limited to the pancreatic region, but a variable percentage (up to 15%) of patients have inflammatory bowel disease [38]. AIP-type 2 patients demonstrate a good response to corticosteroid-based therapy, with very low relapse rate [38].

A subset of patients of both types AIP may have also high blood levels of the antigen CA 19-9 (up to > 12,000 U/ml) [39]. This condition further complicates the clinical differential diagnosis with pancreatic cancer, which represents the most important differential diagnosis of both AI subtypes [39].

Macroscopic features

Macroscopically, the two different subtypes of AIP are indistinguishable [37]. Indeed, in both subtypes, the pan-

creatic resection specimen may present a narrowed, discrete area, with a "pseudo-tumor" appearance, or may show a more diffuse parenchymal enlargement, with a decrease of the physiological lobular structure, a white to yellow discoloration and a greater tissue hardness [2,37]. The pancreatic ductal tree and the common bile duct may be involved by these modifications, with a potential consequent obstruction. Lastly, there is no presence of calculi in AP.

Microscopic description with diagnostic criteria

Paradigmatic images of AI are shown in Figure 4.
Microscopically, type 1 and type 2 AIP present with two different and specific histologic framework, but there are some common aspects as well.
Type 1 AIP usually shows a compact inflammatory infiltrate, composed of T cell-lymphocytes and plasma cells, a fibrosis specifically localized in the periductal area, and a marked venulitis [37,40,41]. The inflammation as a typical localization within the pancreatic parenchyma: indeed, it is centered around and within medium-to-large interlobular ducts [2,37,40,41]. This specific phenomenon results in the infolding of the ductal epithelium with the consequent shrinkage of the ductal lumen. Regarding venulitis, the inflammatory infiltrate involves the venule and venous wall; in late-stage disease, such aspects may evolve in an obliterative phlebitis, with fibrosis of the lumen. Another common aspect is also represented by perineural inflammation. The inflammation, above all in late-stage diseases, may extend widely to the surrounding parenchyma, evocating fibrosis with secondary atrophy. In this stage, the fibrotic changes become more diffuse, assuming a whorled or storiform pattern [2,37]. Lymphoid aggregates can be identified in most cases in intrapancreatic and peripancreatic tissue [42]. Regarding IgG4 immunohistochemical research, this may represent a useful tool for supporting the diagnosis, and should highlight a high number of IgG4-positive plasma cells, above all in early stages. A significant count is considered as the presence of at least 10 IgG4-positive plasma cells per high-power field; verifying that the proportion of IgG4/IgG is assessed at least at 40-45% may be of help in some cases [42,43]. It should be highlighted that

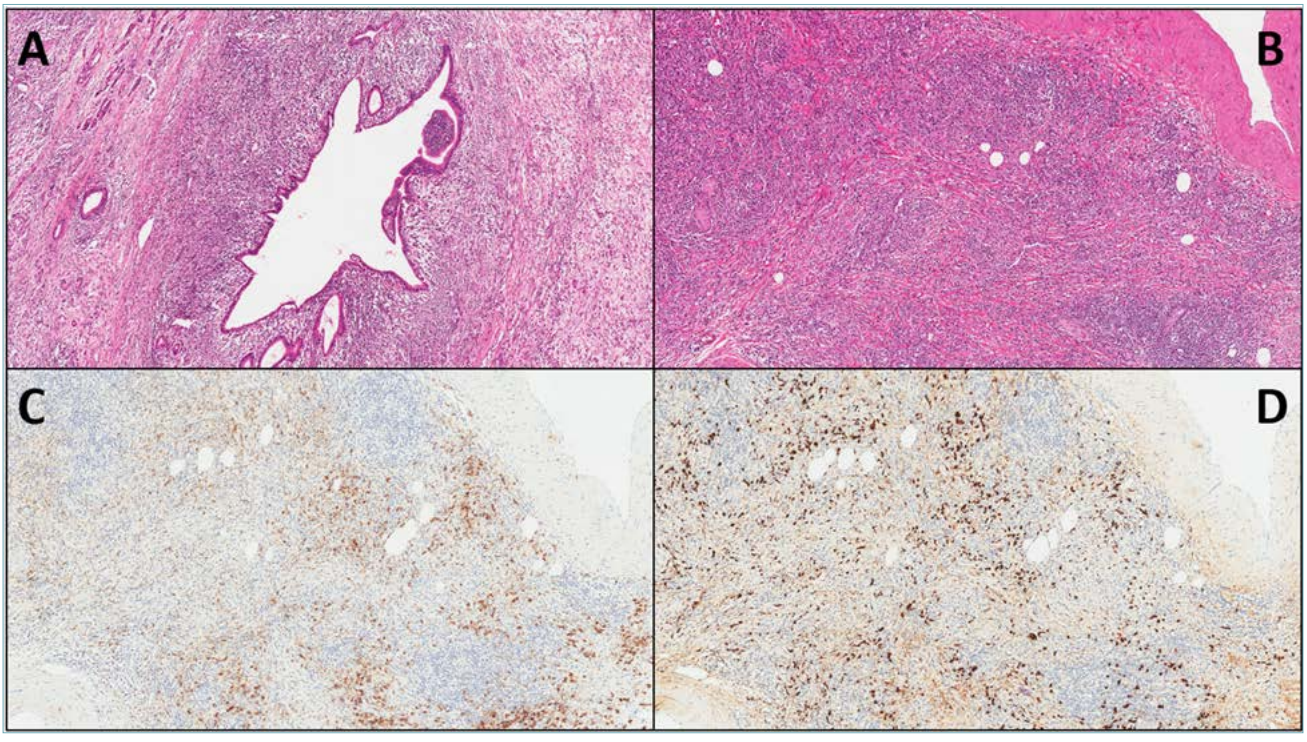

Figure 4. Key histological and immunohistochemical patterns of autoimmune pancreatitis. (A) Marked inflammatory infiltrate is typically centered around pancreatic ducts (original magnification 10X); (B) dense inflammatory infiltrate with secondary pancreatic parenchyma is encountered in late-stage autoimmune pancraetitis (original magnification 4X); (C) immunohistochemical analysis for CD138 highlights a diffuse infiltration by plasma cells (original magnification 4X); (D) immunohistochemical analysis for IgG4 indicates that a high number of plasma cells are also positive for IgG4 (original magnification 4X).

a "positive" count of IgG4 plasma cells may be possible also in up to 10% of pancreatic ductal adenocarcinoma and alcoholic chronic pancreatitis [42]. Thus, this finding should be interpreted with caution and correctly inserted in the pertinent clinical, radiological, laboratory and histological framework to support the diagnosis of AI.

Type 2 AIP, similar to type 1 AIP, usually shows a lymphoplasmacytic inflammation that is electively located in the periductal regions of pancreatic parenchyma; at the same time, acinar atrophy and periductal fibrosis may be also present, but such findings are less pronounced in type 2 AI [35-37]. Notably, the peculiar and diagnostic hallmark of type 2 AI is represented by the presence of granulocytic epithelial lesions [35-37]. They are characterized by periductal acute inflammation consisting of aggregates of neutrophils beneath the ductal epithelial cells and within the lumen; such acute inflammation brings to marked modifications of the ductal epithelium, including cell damage, detachment and obliteration [2,35-37]. Regarding IgG4 immunostaining, very few positive plasma cells might be present, or less commonly they could be totally absent [40-43].

It is also of importance to report that, in some cases of AIP, a marked inflammatory infiltrate may be seen between pancreatic parenchyma and peri-pancreatic adipose tissue. Notably, this feature may also be recognized by imaging, with typical radiological pancreatic aspects (e.g.: mass forming lesions, "sausage-shaped" appearance). Lastly, the evaluation of resection margins is a very important step during surgical resections for AIP. Indeed, pancreatic neck margin and biliary resection margin may be involved by the inflammatory process, and this aspect should be clearly stated in the pathology report, also for therapeutic purposes.

Other rare inflammatory/tumor-like lesions of the pancreas

Lymphoepithelial cyst

The finding of a lymphoepithelial cyst in the pancreas is a rare event. Usually, this is an asymptomatic lesion, discovered incidentally by imaging analysis due to unrelated reasons [44]. There are no associations with autoimmune or syndromic diseases, as described for the counterpart affecting salivary glands[27]. From the macroscopic point of view, lymphoepithelial cyst may be unilocular or multilocular, can be located or entirely within the pancreatic gland or in the periphery with exophytic growth [44,45]. Such cysts can reach a large size (> 5 cm), and show an irregular capsule. The fluid content can show variable presentations: indeed, it may be limpid/serous but also milky-necrotic, depending on the degree of keratin formation [45,46]. The pre-operative diagnosis is challenging, since neither imaging nor fine-needle aspiration can established a reliable diagnosis; the most important differential diagnosis that usually remains still open is represented by a pancreatic cystic neoplasm [46,47]. From the microscopic point of view (representative images are shown in Fig. 5), there is a multi-layered squamous epithelium, that can contain keratinaceous debris, surrounded by a dense layer of lymphoid tissue with prominent germinal centers [44,45]. The adjacent pancreatic parenchyma is usually unremarkable, but it can occasionally show granulomas or foci of steatonecrosis. There are no risk of malignant transformation but, due to the difficulties of pre-surgical diagnosis, patients are usually treated with curative surgical resection.

Pancreatic hamartoma

Hamartoma is defined as a focal overgrowth of cells and/or tissues that are inborn in the organ in which they are grown. Thus, its definition is closer to the concept of malformation rather than of a "true" neoplasm [48]. Pancreatic hamartoma is a rare condition, of which pathologists should be aware since it can mimic a malignant tumor, sometimes with a challenging diagnosis. Usually, it is located in the head of the pancreas and appears as a unique intrapancreatic mass [49], although rare cases with multiple and separated nodules have been described [50]. From a microscopic point of view, pancreatic hamartoma is composed of small ductal structures lined by columnar epithelial cells without atypia, surrounded by fibrous stroma and an unorganized acinar parenchyma, with at least partial loss of lobular architecture [51]. The presence of each component can vary, determining different morphological aspects, with ductal, stromal or acinar prominence. The presence of neuroendocrine islets is typically uncommon. In the case of complete/exclusive acinar component, acinar cell carcinoma can be ruled out thanks to some typical features of pancreatic-acinar hamartomas, including small dimensions and the absence of cell atypia. Notably, a previous consensus-paper has tried to provide reliable criteria for assessing the diagnosis of pancreatic hamartoma, as follows: i) presence of a well-defined mass; ii) composed of mature ductal structure and acini with distorted architecture; iii) absence of discrete islets of Langerhans [51] (Fig. 5). Typically, adjacent pancreatic parenchyma is conserved. From an immunohistochemical point of view, hamartomatous cells express all ordinary markers of the normal counterpart. Although morphology alone is the main diag-

nostic criterion, in some case of ductal predominance the use of P53 and DPC4 staining may be of help in ruling out a diagnosis of pancreatic ductal adenocarcinoma. The biological behavior of pancreatic hamartoma is benign, but, due to the difficulties in pre-operative differential diagnosis, it typically requires surgical resection [27].

Intrapancreatic accessory spleen

Intrapancreatic accessory spleen is a rare finding, which occur typically in the pancreatic tail [52-55]. It refers to the presence of an accessory spleen growing into the pancreatic parenchyma. From a macroscopic point of view, there is a brownish nodule surrounded by normal pancreas. This nodule has the gross features of the normal spleen. In case of large size, the center of the accessory spleen may remain reddish also after fixation, due to the large amount of blood. From the microscopic point of view (representative images are shown in Fig. 5), intrapancreatic accessory spleen is usually composed of mature splenic tissue, showing a normal distribution of white and red pulp [52]; CD8 is a very useful marker for the red pulp (vessels). A very rare condition that may occur in case of intrapancreatic accessory spleen is given by the internal growth of an epidermoid cyst [53]. This typically affects young adults and show a multilayered squamous epithelium surrounded by splenic tissue [53]. The impor-

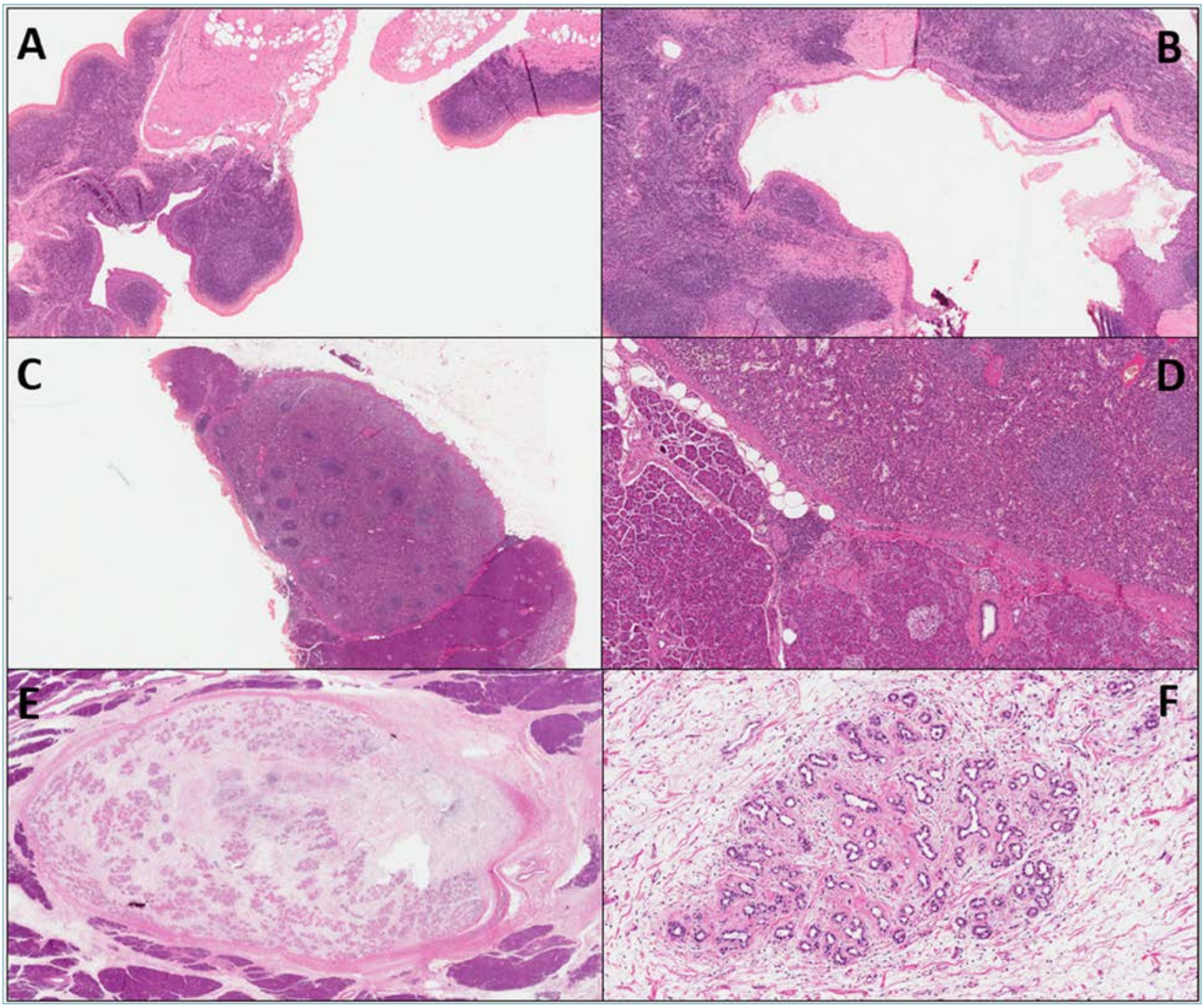

Figure 5. Typical microscopic appearance of lymphoepithelial cysts (A, B; original magnification A: 2X, B: 10X), of intrapancreatic accessory spleen (C, D; original magnification C:2X, D: 10X), and of pancreatic hamartomas (E, F; original magnification E:1X, F: 20X). Notably, the pancreatic hamartoma shows a ductal predominance (E, F).

tance of intrapancreatic accessory spleen is given by its typical differential diagnosis, which is represented by pancreatic neuroendocrine tumors. In some cases, fine-needle cytology with imaging can resolve this diagnostic challenge, but still most cases undergo surgical resection and the diagnosis is established on surgical specimens [54-55].

Differential diagnosis

The most important differential diagnosis of inflammatory and tumor-like lesions of the pancreas is represented by pancreatic ductal adenocarcinoma (PDAC). Unfortunately, in a significant proportion of cases it may be very difficult to differentiate inflammatory and tumor-like lesions of the pancreas from PDAC based on imaging, clinical presentation and laboratory markers. Pathologists that are called to provide this distinction on cytology and/or fine-needle biopsy should be aware that some features may be present in both inflammatory and neoplastic conditions.

Histologically, the most helpful aspects in distinguishing PDAC from reactive glands are represented by the location and structure of the glands, in addition to cytological features. Reactive glands/ducts are usually complete and well-demarcated, differently from neoplastic glands that are more often ruptured or incomplete. The presence of "naked" glands in peri-pancreatic adipose tissue is very suggestive for PDAC, but attention must be paid to the fact that the observed fat tissue might represent the final step of an involution process involving acinar parenchyma (this feature is clearly distinguishable for the presence of remnant of pancreatic islets) [56]. Mitotic figures, necrotic luminal debris, stromal desmoplasia and aberrant DPC4 and/or P53 expression may be also of help for a definitive PDAC diagnosis [56,57]. Perineural or vascular invasions are both highly diagnostic of an infiltrating tumor. Another significant microscopic feature that can support the diagnosis of PDAC is the finding of neoplastic glands in abnormal locations, such as immediately adjacent to muscular blood vessels. This criterion is very useful in the differential diagnosis with inflammatory conditions, also in the case of cytostatic evaluations.

Notably, it is of importance to report that ultrasound-guided fine needle biopsy is becoming a gold-standard in the pre-operative patients' evaluation for pancreatic masses. Thanks to the possibility of examining a relatively significant portion of tissue, this methodology can permit to avoid un-necessary surgery. This kind of biopsy, furthermore, can permit in depth evaluation also with immunohistochemistry, staining for example for IgG-IgG4 (AIP) or for P63 (squamous content of lympho-epithelial cysts).

Lastly, some cytological aspects should be mentioned in the differential diagnosis of inflammatory and tumor-like lesions of the pancreas with PDAC. Enlarged and hyperchromatic nuclei and irregular nuclear membranes support a diagnosis of PDAC. Notably, the undifferentiated PDAC variant with osteoclast-like giant cells could be misdiagnosed as PGP by cytology, due to the abundance of giant cells and necrotic-hemorrhagic changes [30,58-60]. This confirms the need of strong and reliable evidence in the difficult process of differential diagnosis.

Different from the other inflammatory/tumor-like lesions of the pancreas, the most important differential diagnosis for intrapancreatic accessory spleen is not represented by PDAC, but by neuroendocrine tumors. In some cases, fine-needle cytology with imaging can resolve this diagnostic challenge. In case of persisting doubts, a strict surveillance protocol can be observed. However, many cases still undergo surgical resection, and the diagnosis is established on surgical specimens with histological diagnosis.

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