Chapter 13
Pancreas

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Anatomy and Histology of the Pancreas

The pancreas is a hammer-shaped organ located deeply in the retroperitoneum. It is divided into four grossly indistinct regions: the head, neck, body, and tail. The pancreatic head, including a blunt extension portion known as the uncinate process, is adjacent to the proximal duodenum. The neck is a short, constricted area anterior to the mesenteric vessels. The body is the midportion of the pancreas resting on the aorta. The tail flattens out as it approaches the spleen. The anterior surface of pancreas is covered by peritoneum, especially at the body and tail regions.

The pancreas has exocrine and endocrine components. The exocrine pancreas is composed of lobules made up of numerous acini, separated by the fibrous septa (Fig. 13.1). Digestive enzymes secreted from the acini drain into the duodenum by the delicate ductal system, which is lined by flattened ductal epithelium. The endocrine component accounts for a very minor portion of pancreatic tissue and consists mostly of Islets of Langerhans cells. The islet cells are small polyhedral cells with amphophilic cytoplasm. Depending on the hormones produced, the islet cells may be classified as insulin-producing β cells, glucagon-producing α cells, somatostatin-producing δ cells, and pancreatic polypeptide-producing (PP) cells, which can be identified by immunohistochemistry or electron microscopy [1, 2].

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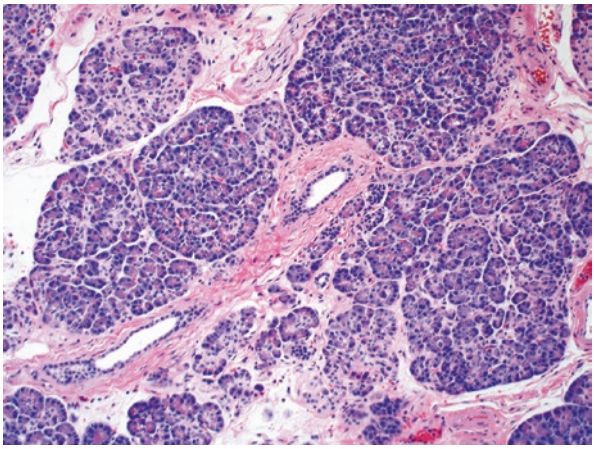

Fig. 13.1 Histopathology of the pancreas (hematoxylin-eosin stain)

Sampling Methods

Cytological assessment is an important modality in the diagnosis of the pancreatic lesion given its complex anatomy. Traditionally, various methods are available to collect cytologic samples from the pancreas, including duodenal lavage, endoscopic cytologic sampling via the common bile duct, using ultrasound or retrograde pancreatography or pancreatic juice collection [3]. With the advent of endoscopic ultrasound-guided find needle aspiration (EUS-FNA), diagnostic FNA has become the procedure of choice for establishing the diagnosis of pancreatic lesions. EUS-FNA provides real-time visualization of the needle tip, better visualization of small lesions than CT, and can identify local invasion or metastases, thus allowing simultaneous diagnosis and staging [4]. It is well known with excellent specificity (around 100% in nearly all studies), variable sensitivity (60–96%), and rare complications (<0.5%) [5, 6]. Whenever possible, rapid on-site evaluation (ROSE) should be performed to reduce the chance of adequate sampling, especially during the evaluation for solid mass [3].

Normal Pancreas Cytology

Adequacy: The entire slide should be quickly scanned at low magnification to assess preservation and cellularity. The sample adequacy depends on the nature of the sampled lesion [7]. There is no requirement for a specific number of cells to be evaluated. The cells of pancreatic origin include acinar cells, ductal cells, and islet cells (Table 13.1).

Acinar cells: Acinar cells are the predominant cell type found in FNA from normal pancreatic tissue. They are usually arranged in small cohesive clusters or acini,

Table 13.1 Cytomorphologic features of pancreatic cells

	Acinar cells	Ductal epithelial cells	Islet cells
Arrangement	Clusters or acini, grape-like, few stripped nuclei and isolated cells	Flat cohesive, monolayer sheet, honeycomb	Large or small aggregates, in ribbons or as single cells
Cytoplasm	Abundant granular, may have fine red granules, small vacuoles	Relatively abundant, may contain vacuoles	Scant granular
Nuclei	Round	Round to slightly oval	Round to oval
Nuclear contour	Smooth	Smooth	Smooth
Chromatin	Fine granular	Fine granular	Speckled, salt and pepper
Nucleoli	Distinct	Inconspicuous	Inconspicuous

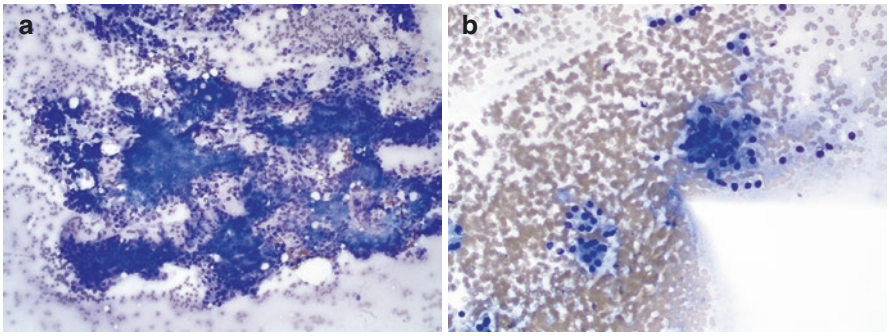

Fig. 13.2 Cytomorphology of pancreatic acinar cells. (**a)** Acinar cells in sheets and clusters; (**b)** acinar cells with acinar pattern (Diff-Quik stain)

lobulated groups, or less frequently as single cells (Fig. 13.2). The nuclei are round, relatively uniform, and often eccentrically located, with smooth nuclear contours and small but distinct nucleoli. Strapped naked nuclei are frequently seen. The chromatin is finely granular and evenly distributed. The cytoplasm is relatively abundant, which may contain small vacuoles and appear fine granular.

Ductal epithelial cells: The ductal cells are often seen as monolayered sheets of uniform cuboidal cells with centrally placed small round nuclei. The cell borders are often well defined, and the cytoplasm is transparent, giving the appearance of "honeycomb" pattern (Fig. 13.3). The nuclei have smooth contours, evenly distributed fine chromatin, and inconspicuous nucleoli. Occasionally, large areas of the ductal epithelium form thick, multilayered sheets with overlapping nuclei, raising a concern for malignancy. Close examination of the edges will reveal the above-mentioned normal cytologic features.

Islet cells: Islet cells less likely to be seen in the cytological samples of the pancreas. In the case of sclerosing cholangitis and atrophic pancreas, loose, spherical, or oval aggregates of islet cells may be present. Like other endocrine cells, islet cells have round to oval nuclei, granular "salt and pepper" like chromatin, small nucleoli, and ill-defined cell borders.

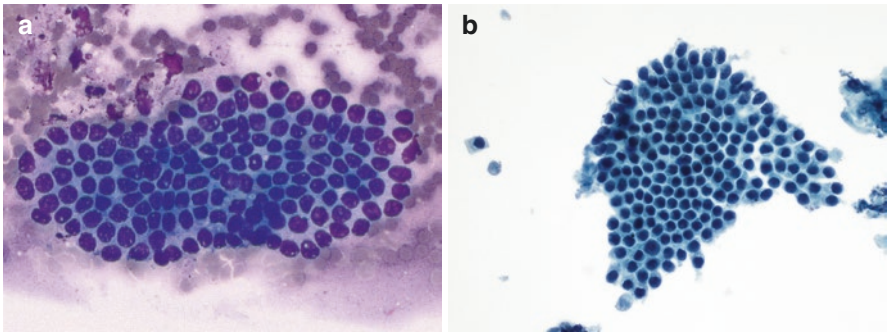

Fig. 13.3 Cytomorphology of pancreatic ductal cells. Uniform epithelial cells arranged in flat sheet. (**a**) Diff-Quik stain; (**b**) papanicolaou stain

Table 13.2 Common contaminants and their mimics

Cell type	Approach	Cytomorphology	Mimics
Gastric epithelial cells	Endoscopic transgastric (lesions in the body and tail)	Sheets of bland appearing cells with mucinous cytoplasm (foveolar cells)	Low-grade mucinous neoplasm
Gastric parietal cells and chief cells	Endoscopic transgastric (lesions in the body and tail)	In small clusters, or singly with granular cytoplasm (parietal cells)	Neuroendocrine cells
Intestinal epithelial cells	Endoscopic transduodenal (lesions in the head and uncinate)	Nonmucinous epithelium in large sheets, admixed with goblet cells, "starry sky" appearance. Intraepithelial lymphocytes are sprinkled among enterocytes "sesame seeds"	Epithelial neoplasm
Hepatocytes	Percutaneous	Polygonal cells with granular cytoplasm, prominent nucleoli, intranuclear inclusions, lipofuscin granules, and bile pigment	Oncocytic neoplasm
Mesothelial cells	Percutaneous	Flat sheets with intercellular windows	–
Splenic tissue	Percutaneous (lesions in the tail)	Predominantly lymphocytes in a vascular background	Neuroendocrine tumors; intraparenchymal lymph node

Possible cells from other organs/contaminants: Other cells may be aspirated as the needle passes through adjacent organs. Examples include gastric and intestinal epithelial cells, hepatocytes, and mesothelial cells [8] (Table 13.2). Both duodenal and gastric epithelial cells are ever-present contaminants in the EUS-FNA specimens. Like pancreatic ductal cells, they also appear as flat,

monolayer sheets with honeycomb pattern. The sheet of duodenal cells is intermixed with occasional goblet cells, given a "starry sky" appearance (Fig. 13.4). Intraepithelial lymphocytes are also seen sprinkled among the enterocytes. Surface gastric foveolar cells have mucinous cytoplasm (Fig. 13.5). Other cells of gastric epithelium including chief cells and parietal cells may also be present. Hepatocytes have modest amount of granular cytoplasm and round nuclei with prominent nucleoli and occasional intranuclear inclusions. Cytoplasmic lipofuscin granules and bile pigments are frequently seen. The mesothelial cells have round to oval nuclei containing finely granular chromatin. Intercellular spaces or "windows" are characteristic features. Reactive mesothelial cells contain large distinct nucleoli, which must be distinguished from malignancy. Benign splenic tissue may be also seen on the smear for pancreatic tail lesion [9].

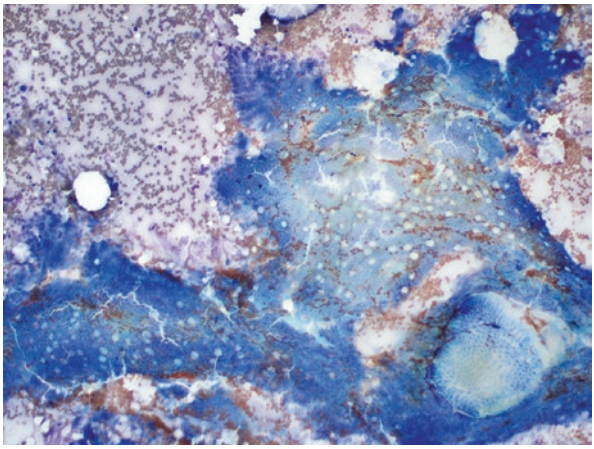

Fig. 13.4 Cytomorphology of duodenal epithelial contaminant (Diff-Quik stain)

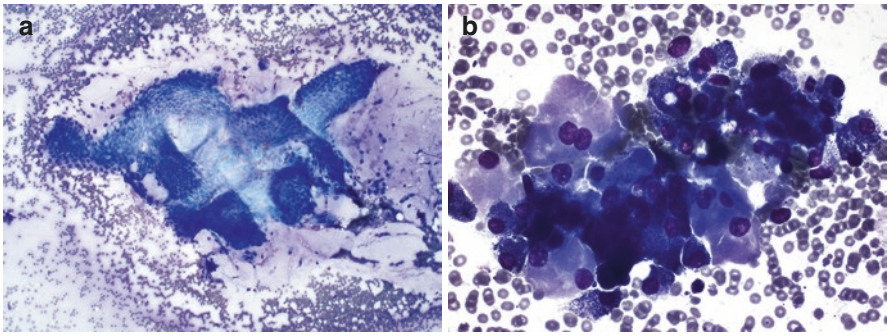

Fig. 13.5 Cytomorphology of gastric epithelial contaminant. (**a**) Foveolar epithelial cells; (**b**) mixed parietal cells and chief cells (Diff-Quik stain)

Reactive Changes

Acute Pancreatitis

The injury to the pancreatic parenchyma will result in the destruction by the digestive enzymes, leading to autodigestion of the pancreas and surrounding tissues. In the United States, acute pancreatitis is most often caused by alcohol use, followed by biliary stones, trauma, and medications and genetic factors. Classic clinical presentations, combined with lab findings including elevated white blood cell count, high amylase and lipase levels, often render the clinical diagnosis of acute pancreatitis. Radiologically, it seldom appears as a mass lesion. Thus, acute pancreatitis is rarely encountered in FNA specimens. When present, benign ducts and acinar cells admixed with fat necrosis and inflammation components are expected.

Chronic Pancreatitis

Chronic pancreatitis is a common but yet challenging diagnosis by cytology. Patients often have recurrent abdominal pain, with or without elevated serum amylase and lipase. There may be bile duct obstruction and jaundice, mimicking the presentation of pancreatic carcinoma. Chronic pancreatitis usually forms fibrosis, which appears as a mass like lesion on imaging. Therefore, FNA is a commonly used diagnostic method to rule out malignancy in such scenarios.

Histologically, chronic pancreatitis is characterized by fibrosis, atrophy and dropout of acini, and variable dilation of pancreatic ducts. Islets of Langerhans are embedded in the sclerotic tissue, which may be readily visible and appear enlarged than normal. The dilated ductal epithelium may show hyperplasia with reactive atypia, and even squamous metaplasia. Inflammatory cells such as lymphocytes and plasma cells infiltrate into the stroma. Ductal dilation and intraluminal protein plugs and calcifications are often seen in alcoholic chronic pancreatitis. In the end stage of the disease, the ducts may be distorted by diffuse fibrosis, with or without mucinous metaplasia.

Reactive atypia associated with chronic pancreatitis should be distinguished from well-differentiated ductal adenocarcinoma (Tables 13.3 and 13.4). Overall, there is low cellularity in pancreatitis comparing with ductal adenocarcinoma. At low power view, the cytological specimens of chronic pancreatitis show clusters of ducal cells, acinar cells, and mixed inflammation (Fig. 13.6). The inflammatory cells include neutrophils (early stage), histiocytes, lymphocytes, and plasma cells. Relatively clean background may be seen in the late stage of chronic pancreatitis.

Characteristic features for ductal adenocarcinoma include an uneven distribution of ductal cell clusters (drunken honeycomb) (Fig. 13.7). Isolated single abnormal cells are also seen. The cytological atypia include irregular nuclear contours and

Table 13.3 Cytomorphologic features of chronic pancreatitis and well-differentiated adenocarcinoma

	Chronic pancreatitis	Well-differentiated adenocarcinoma
Cellularity	Low to modest	Modest to high
Cell type	Mixed ductal and acinar cells	Predominantly ductal cells
Configuration of ductal cell clusters	Honeycomb	Drunk honeycomb
Single ductal cells	Minimal	Present
Nuclear size	Enlarged	Enlarged
Anisonucleosis	Absent	Present
Nuclear crowding and overlapping	Absent	Present
Nuclear contour	Smooth	Irregular
Nucleoli	Present	Present
Background	Mixed inflammation	Clear or scattered inflammation

Table 13.4 Cytomorphologic features of common reactive conditions

Conditions	Cytomorphologic features
Acute pancreatitis	• Rarely seen in FNA samples • Benign ducts and acinar cells, fat necrosis, and inflammatory cells
Chronic pancreatitis	• Background inflammation, fat necrosis, calcific debris • Pancreatic elements with mild atypia: – Monolayered sheets with few/rare isolated single cells – Smooth nuclear membranes – Low N/C ratio – Mild anisonucleosis – Occasional mitoses
Autoimmune pancreatitis	• Cellularly stromal fragments • Inflammatory cells including plasma cells admixed with reactive epithelial cells
Groove pancreatitis	• Spindled stromal cells, sometimes with atypia, foamy cells, and granular debris • Brunner glands can be seen
Ectopic splenic tissue	• Small lymphocytes in clusters admixed with other hematopoietic cells in a background of traversing vessels • CD8 highlighted endothelial cells of splenic sinus
Nesidioblastosis	• Neuroendocrine cells with positive insulin immunostaining

anisonucleosis. Prominent nucleoli and nuclear enlargement are common in both benign reactive and malignant conditions. Ductal carcinoma and chronic pancreatitis may co-exist, adding an additional layer of difficulty for diagnosis. A high threshold for malignancy is needed for diagnosis of malignancy in the presence of significant inflammation.

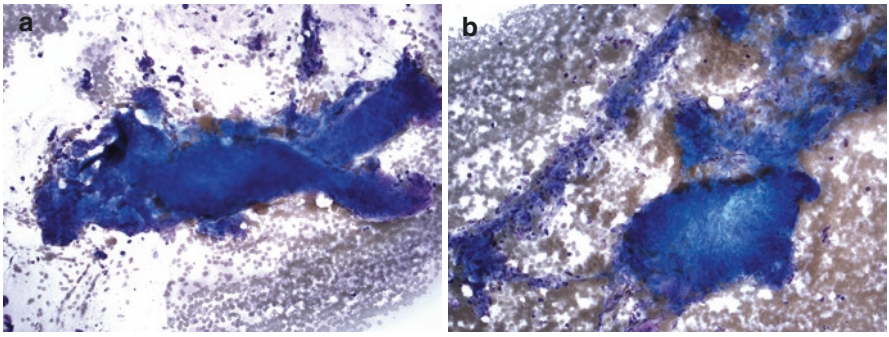

Fig. 13.6 Cytomorphology of chronic pancreatitis. (**a)** Mixed epithelial cells and stromal fragments; (**b)** stromal fragments with crushed lymphocytes (Diff-Quik stain)

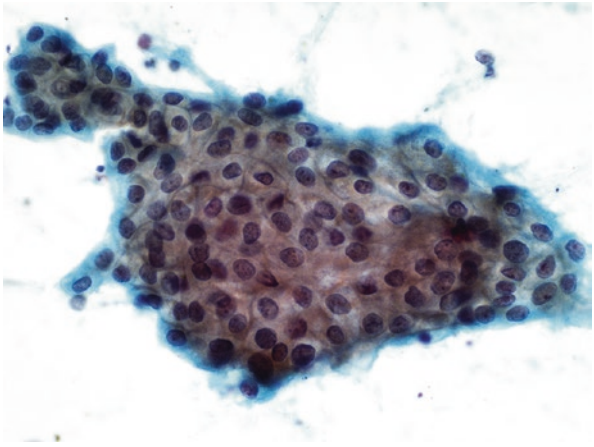

Fig. 13.7 Cytomorphology of well-differentiated ductal adenocarcinoma (Papanicolaou stain)

Autoimmune Pancreatitis (AIP)

AIP is a chronic inflammatory syndrome defined by clinical laboratory and pathologic criteria. Type 1 AIP is a systemic disease characterized by storiform-type fibrosis, obliterative phlebitis, and increased IgG4-positive plasma cells. Type 2 API is a pancreas-specific disorder with characteristic granulocytic epithelial lesions and occasional IgG-4 positive plasma cells [10]. It is well known that cytologic diagnosis is quite challenging given its overlapping clinical and imaging features with nonspecific chronic pancreatitis and ductal adenocarcinoma.

One of the diagnostic challenges is the cytologic atypia seen in autoimmune pancreatitis. At least 50% of cases showed varying degree of atypia, including severe atypia, as reported in the literature [10–12]. The presence of cellular stromal fragments and inflammatory cells admixed with epithelial cells may suggest the

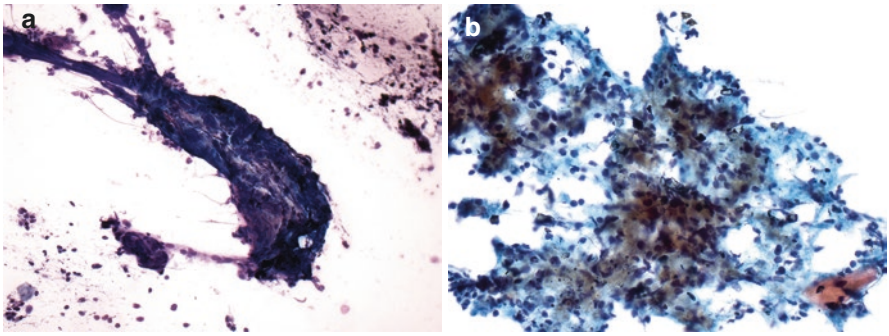

Fig. 13.8 Cytomorphology of autoimmune pancreatitis. (**a**) Stromal fragment with crushed lymphocytes, Diff-Quik stain; (**b**) loosely cohesive clusters of epithelial cells with crushed lymphocytes, Papanicolaou stain

diagnosis (Fig. 13.8). In addition, plasma cells can be rare and difficult to find in cytology samples although critical in the histological diagnosis. *KRAS* mutation may help with the differential diagnosis as it is more commonly associated with malignancy [11] although further studies are needed. Nevertheless, since the clinical management of AIP and adenocarcinoma differs significantly, it is important to keep AIP in the differential diagnosis, especially in cases with absence of classic malignant cytomorphology.

Groove Pancreatitis/Paraduodenal Pancreatitis

Groove pancreatitis, or paraduodenal pancreatitis, is an uncommon form of recurrent pancreatitis involving the "groove" region—the area between duodenum, the head of pancreas, and the common bile duct. This is an underrecognized entity often occurs in middle-aged men with alcohol use history [13]. Groove pancreatitis can cause duodenal wall fibrosis, inflammatory stroma, and duodenal wall/grove cysts mimicking mucinous cysts or pseudocysts [5]. There is limited knowledge regarding the cytopathologic features of groove pancreatitis, which are highly variable. The most common reported findings include spindled stromal cells, sometimes with atypia suggesting a spindle cell neoplasm, foamy cells, and granular debris [14]. When there forms paraduodenal wall cyst, it contains cystic contents such as debris and amorphous proteinaceous material. Bland epithelial cells with abundant foamy cytoplasm consistent with Brunner glands can also be seen [15]. Occasional mitotic figures with background necrotic debris are appreciated, leading to the suspicion for a neoplasm [13]. Florid spindle cell proliferation may also mimic gastrointestinal stromal tumor or a vascular neoplasm. Combination of clinical history, imaging studies, serology and cytologic features help leading to the suspicion for groove pancreatitis.

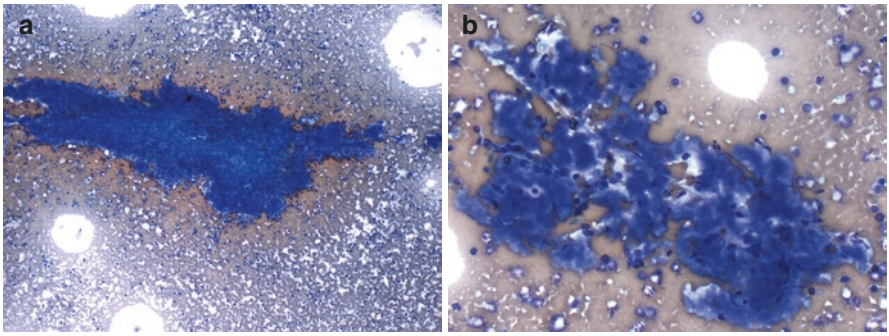

Fig. 13.9 Cytomorphology of accessary spleen. (**a)** Large lymphoid aggregate with dispersed lymphocytes; (**b)** large platelet aggregates (Diff- Quik stain)

Ectopic Splenic Tissue

Ectopic splenic tissue includes accessory spleen, a congenital anomaly, and splenosis, an acquired deposition of splenic tissue by autoimplantation after abdominal surgery or trauma. Both are not rare occurrences in the pancreas, easily mimicking a pancreatic neoplasm especially neuroendocrine tumor. The diagnosis should be considered when there are clusters of predominantly small lymphocytes admixed with other hematopoietic cells in a background of traversing small vessels [16]. Large platelet aggregates are frequently present (Fig. 13.9). The most helpful feature in the diagnosis of ectopic splenic tissue is the use of CD8 immunohistochemical staining in the cell block, which highlights the endothelial cells of the splenic sinus [17].

Nesidioblastosis

Nesidioblastosis is a heterogenous disease presented as persistent hyperinsulinemic hypoglycemia of infancy and rarely in adults. It is characterized by islet cell proliferation, thus mimicking pancreatic neuroendocrine tumor [18, 19]. Rare reports on cytologic features of nesidioblastosis showed neuroendocrine cells with positive immunostaining for insulin [20].

Cystic Lesions

The cystic lesions of the pancreas represent a broad-spectrum of entities including neoplastic and nonneoplastic. They are quite common but diagnostically challenging due to the sparse cellularity. Neoplastic cysts include mucinous (intraductal papillary mucinous neoplasms, IPMN and mucinous cystic neoplasms, MCN) and

Table 13.5 Characteristics of nonneoplastic cystic lesions in the pancreas

Entities	Cytomorphologic features	Cyst fluid analysis
Pseudocyst	• Degenerative debris, abundant inflammatory cells, histiocytes, sometimes yellow pigment and crystals • No epithelial components	High amylase (>250 U/L), often in thousands; low CEA
Retention cyst	• Nonciliated simple cuboidal or columnar epithelium which may contain mucin	
Squamoid cyst	• Squamous epithelium with eosinophilic cytoplasm may contain mucin	High CEA and amylase [24]
Lymphoepithelial cyst	• Squamous cells, squamous and amorphous debris, lymphocytes, macrophages, and cholesterol crystals	May have high CEA and amylase
Cystic lymphangioma	• Nonspecific findings including scattered lymphocytes and histocytes in the background of proteinaceous material • If applicable, CD31 and D2-40 highlight endothelial cells	High triglycerides Chylous appearance [25]
Dermoid cyst	• Benign mature squamous cells, inflammation, and keratin debris • Adnexal tissue in the cystic wall	
Epidermoid cyst of the accessory spleen	• Benign mature squamous cells, inflammation, keratin debris • Accessory splenic components	High CEA and CA19-9 reported [29, 31]
Duplication cyst/ ciliated foregut cyst	• Ciliated epithelial cells, mucinous material, histiocytes and amorphous proteinaceous debris • Duplication cyst has muscle layers	
ADPKD-associated cyst	• Simple epithelial cyst: small flat bland epithelial cells in a honey-comb pattern	
VHL-associated cyst	• Serous lining cyst, similar to serous cystadenoma	*VHL* gene mutation detected

nonmunicous cysts (serous cystadenomas, SCA, solid pseudopapillary tumors, cystic pancreatic neuroendocrine tumors, and other rare cystic malignancy). Nonneoplastic cysts include pseudocysts, lymphoepithelial cysts, retention cysts, cystic lymphangioma, and other congenital cysts. Here we will be focusing on the cytologic features and differential diagnosis for nonneoplastic cysts (Table 13.5).

Pseudocyst

As the most common nonneoplastic cystic lesion, pancreatic pseudocysts usually occur after acute or chronic pancreatitis. The diagnosis is often based on the patient's clinical history and imaging findings. Cytologically, it composed of degenerative debris, abundant inflammatory cells, histiocytes, and sometimes yellow pigment

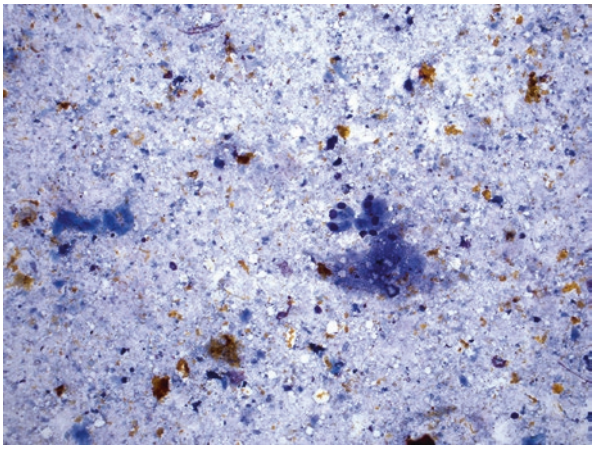

Fig. 13.10 Cytomorphology of pancreatic pseudocyst (Diff-Quik stain)

and crystals (Fig. 13.10) [21]. Pseudocysts have no epithelial lining by definition; thus, the presence of epithelial cells should raise a concern for a cystic neoplasm rather than pseudocysts. Pseudocysts should have high level of amylase (often in thousands) while low concentration of CEA, which is helpful for differentiation from IPMN and MCN [22].

Retention Cyst/Squamoid Cyst

Retention cysts are small (0.5–1.0 cm) cysts commonly associated with pancreatic duct obstruction or narrowing with upstream pancreatic duct dilation [21]. They are lined by nonciliated simple cuboidal or columnar epithelium which may contain mucin. A mucin-containing retention cyst should be differentiated from other neoplastic mucinous cysts, which often have intramural nodules or a solid component. Squamoid cyst is a distinct type of retention cyst lined by squamous epithelium, resulting from unilocular cystic dilatation of pancreatic ducts due to obstruction [23, 24].

Lymphoepithelial Cyst (LEC)

Pancreatic LECs are uncommon cysts that are similar to branchial cleft cysts in the neck, occurring predominantly in middle-aged men. Histologically, they are characterized by stratified squamous epithelium surrounded by dense lymphoid tissue with lymphoid follicles. On FNA aspirate, they typically contain squamous cells,

squamous and amorphous debris, lymphocytes, macrophages, and cholesterol crystals. LECs may contain elevated CEA and amylase, leading to potential confusion with mucinous neoplasms. Occasionally, mucus cells and the sebaceous differentiation are present, which should be differentiated from dermoid cysts.

Cystic Lymphangioma

Cystic lymphangiomas are congenital malformations of the lymphatic system resulted from the blockage of lymphatic flow leading to the development of lymphangiectasias. Pancreatic cystic lymphangiomas are rare indolent findings, tending to occur more commonly in women. The aspirate cyst fluid is usually chylous, serous, or serosanguineous [25]. High triglyceride contents, if present, can help confirm the diagnosis. FNA usually shows nonspecific findings such as scattered lymphocytes and histocytes in the background of proteinaceous material. Immunostains of endothelial markers CD31 and D2-40, if performed on the cell block, could highlight the cystic lining [21].

Dermoid Cyst

Dermoid cyst, also called cystic teratoma, is a rare benign lesion in the pancreas [26]. Cytomorphologic features include benign mature squamous cells, inflammation, and abundant keratin debris. Adnexal tissues are present within the cystic wall, which distinguishes dermoid cyst from epidermoid cyst. Mucicarmine stains may be helpful to rule out mucinous lesions.

Epidermoid Cyst of Accessory Spleen

An epidermoid cyst arising within an intrapancreatic accessory spleen is an extremely rare entity, the majority of which were reported from Asia [27–29]. The histogenesis is thought to be mesothelial cells from the spleen parenchyma form an inclusion cyst with subsequent squamous metaplasia [30]. While the detection of solid components associated with an accessory spleen might be the diagnostic clue, only a few cases were diagnosed preoperatively. In addition, cases with abnormally high CA19-9 and CEA have been reported [29, 31], making it difficult to distinguish from malignant tumors. Nevertheless, it is helpful to keep this entity in mind when a cystic lesion encountered especially in the pancreatic tail.

Duplication Cyst/Ciliated Foregut Cyst

Enteric duplication cysts are very rare congenital malformations of the foregut that can be found in the head of pancreas. The cytomorphologic features include a mix of epithelial cells, mucinous material, histiocytes, and amorphous proteinaceous debris. The epithelial lining can be squamous, columnar, gastric, or normal intestinal and is often ciliated [21]. On histological examination, duplication cysts contain layers of smooth muscle cells, recapitulating those of normal gut. Those without muscle cells should be designated as ciliated foregut cyst (CFC) [32]. The differential diagnosis includes bronchogenic cysts which contain cartilage and respiratory glands [33].

Others

Solitary cysts occur in patients with autosomal dominant polycystic kidney disease (ADPKD). Although the lesions are not often biopsied, FNA can help rule out other cystic lesions or malignancy in those patients. FNA aspirate has a simple epithelial cyst appearance, consisting of small flat group of uniform epithelial cells in a honeycomb pattern [34]. The pancreatic cysts seen in the patients with von Hippel-Lindau disease are similar to findings of serous cystadenomas, with serous lining cells with distinct cytoplasmic borders. Instead of forming a distinct lesion, VHL-associated cysts are often distributed irregularly. *VHL* gene mutations are detected in those lesions [35].

Ancillary Testing

As mentioned above, a number of ancillary tests have been utilized to help with the diagnosis of pancreatic cystic neoplasms. The cystic fluid biochemical analysis, including CEA and amylase levels, is one of the most important ones to help differentiate between mucinous and nonmucinous cysts [36, 37]. Of note, the cutoff value may differ among institutions and vary for different assays, which should be validated.

CEA: So far, the most accurate tumor markers for mucinous cysts remains CEA [38, 39]. It has been well known that high level of CEA is typically associated with cystic carcinomas and mucinous cysts [39]. While the generally accepted cutoff value is >192 ng/mL (accuracy of 79%), studies have shown the level >800 ng/mL are highly predicative for mucinous neoplasms (specificity of 98%). In contrast, a very low CEA level <5 ng/mL strongly suggests a serous cystadenoma or a pseudocyst (specificity of 95%) [38].

Amylase: This pancreatic enzyme levels are often used to distinguish between pseudocysts and neoplastic cyst [40]. Pseudocysts consistently contain elevated levels of amylase, typically in thousand units per liter.

Background Features

Necrotic background is one of the most common background features for pancreatic malignancy [41]; thus, nonneoplastic debris should be differentiated from tumor necrosis. Tumor necrosis associated with pancreatic ductal adenocarcinoma can be either diffuse or focal, associated with slightly atypical or evidently malignant cells [42]. As necrosis can be also seen in nonneoplastic conditions such as pancreatitis or cystic degeneration [43], investigating the presence and frequency of atypical and malignant cells is critical.

Mucinous background is one of the diagnostic findings for mucinous neoplasms such as IPMNs, MCNs, and colloid carcinomas. Therefore, it is important to avoid misinterpretation for mucinous background in the presence of gastric contamination. Gastroduodenal mucin seems to be watery or colloid-like, while neoplastic mucins are thicker [44]. In addition, conventional smear is superior than liquid-based cytology for the evaluation of mucinous background. Nevertheless, it is challenging to distinguish different types of mucins, the cytologic features should be interpretate in combination of the clinical context and imaging findings. For example, in the right clinical setting, abundant thick mucin alone may suggest the diagnosis of mucinous neoplasm [21]. On the other hand, scant thin mucin seen with low-grade mucinous epithelium is indistinguishable from that of normal gastric epithelium.

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Conflict of Interest None.

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