# Pancreas

# 11

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Cytologic study of pancreatic lesions has well-known utility. The differential diagnosis of mass lesions of the pancreas, the typical indication for pancreatic cytology studies, is extensive and encompasses benign and malignant entities. Fine needle aspiration (FNA) of pancreatic lesions has emerged as preferable to biopsy with large-core needles and frozen sections for diagnosing pancreatic carcinoma due to excellent diagnostic accuracy and relatively low morbidity associated with FNA [1, 2]. Results of FNAs or brushing of pancreatic lesions dictate subsequent treatment. Studies positive for malignancy are treated definitively with major surgery or chemotherapy depending on circumstances, usually without confirmation of the positive cytology with a small biopsy.

It is important for the cytopathologist to have knowledge of the radiographic findings of the lesion being sampled and the impression of the radiologist. Knowing whether the lesion is cystic or solid is important and can focus the differential diagnosis. Additional useful information includes size, location, association with the main duct (particularly for cystic lesions), and degree of demarcation. Associated pancreatic duct dilatation, an ominous finding in solid mass lesions, or lack thereof is also an important radiographic information [3]. In the experience of these authors, the on-site evaluation for adequacy of the FNA is also an ideal time to discuss the clinical and radiographic findings to obtain information that may not be gleaned in clinical and radiographic records.

## 11.1 Sampling Technique and Diagnostic Accuracy of FNA

Pancreatic FNA is always performed with either ultrasound (US) or computed tomography (CT) guidance. CT guidance provides better resolution than US; however, US offers the advantage of real-time visualization of the needle tip [4]. The approach of the pancreatic lesion can be either percutaneous or endoscopic. Endoscopic US (EUS) has emerged as the primary method of guidance for pancreatic FNA. Advantages include better visualization of small lesions, better visualization and control of the sampling needle, and assessment of regional lymph nodes and invasion of local structures. Thus, EUS-FNA often allows simultaneous diagnosis and staging of pancreatic tumors.

Recent studies report good sensitivity of FNA for pancreatic malignancy, ranging from 75 to 98 % [2, 5–8]. Prior studies reported lower sensitivities; it is thought that better sampling technique and improved recognition of subtle features of adenocarcinoma have enhanced the sensitivity of pancreatic FNA [9]. False-positive diagnoses are rare and positive predictive values approach 100 %. Thus, overdiagnosing malignancy is probably less of a problem than underdiagnosing, despite studies that have shown that FNA harboring "suspicious" cells is usually found to be malignant on repeat tissue studies [8]. Reasons for false negatives include paucity of tumor cells and failure to recognize tumor cells with subtle malignant features.

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## 11.2 Normal Elements

Acinar-type cells predominate in FNAs of normal pancreatic tissue. Architecturally, they show small, rounded clusters around a central lumen (*see* Figs. 11.1 and 11.2). The cells have a triangular shape, eccentric nuclei, and abundant granular cytoplasm. The presence of acinar cells in a pancreatic FNA is used by some as an indicator of adequacy. Ductal cells—the other predominate cell type in the pancreas—appear as flat sheets with a "honeycomb" architecture or "picket-fence" arrangements when seen on edge (*see* Fig. 11.3a, b). Contaminating gastrointestinal glandular mucosa can look similar to pancreatic ductal cells (*see* Fig. 11.3c), which is why acinar cells are considered a better indicator of pancreatic sampling. Endocrine or islet cells are only rarely seen in FNAs of the normal pancreas.

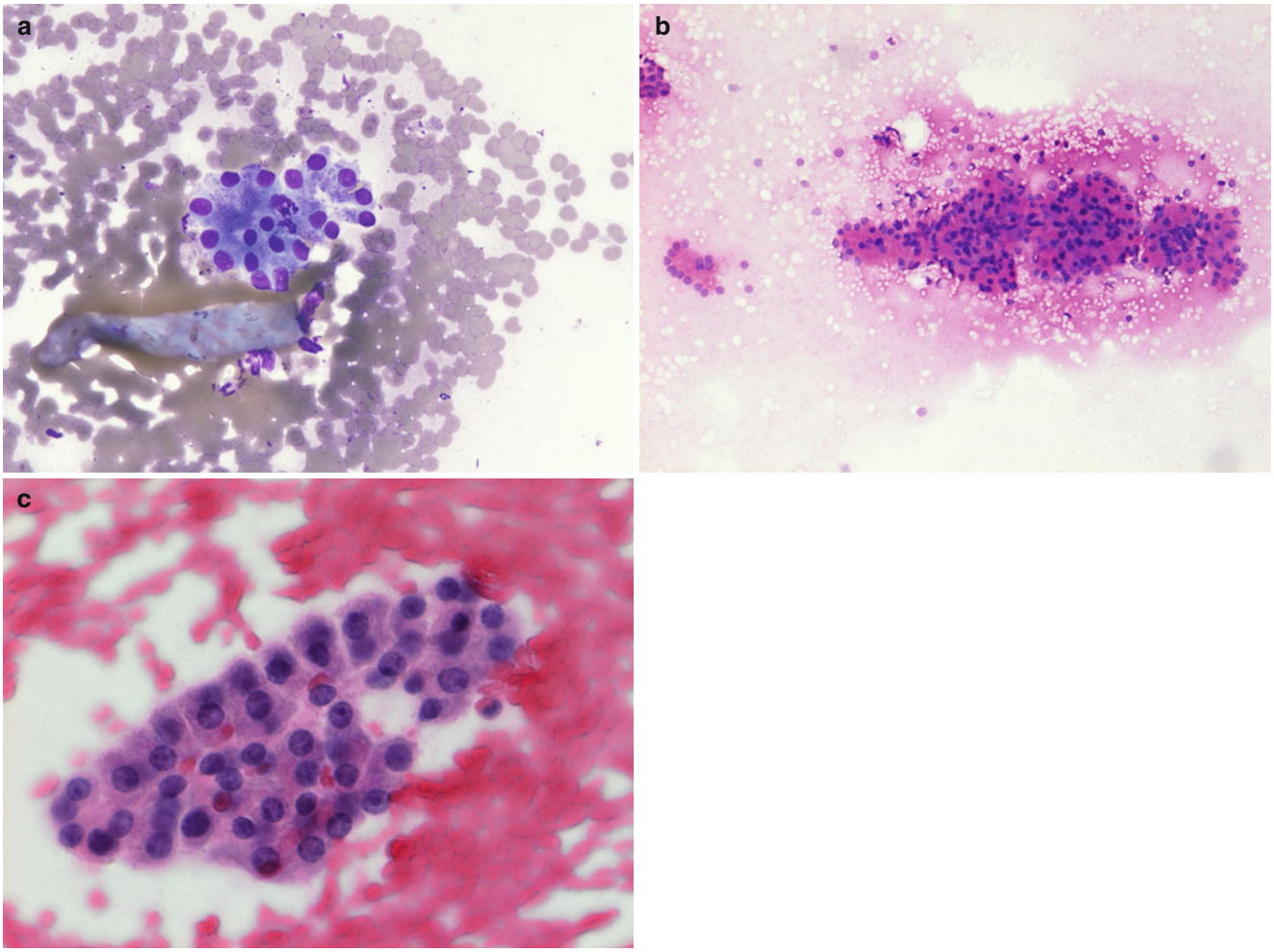


**Fig. 11.1** Normal pancreas. (**a** and **b**) Normal acinar cells characterized by eccentrically situated, abluminal, round, regular nuclei (Diff-Quik [DQ; Baxter Diagnostics; McGaw Park, IL, USA] and hematoxylin [HTX]). (**c**) In alcohol-fixed smears, the abundant granular cytoplasm is apparent (HTX)

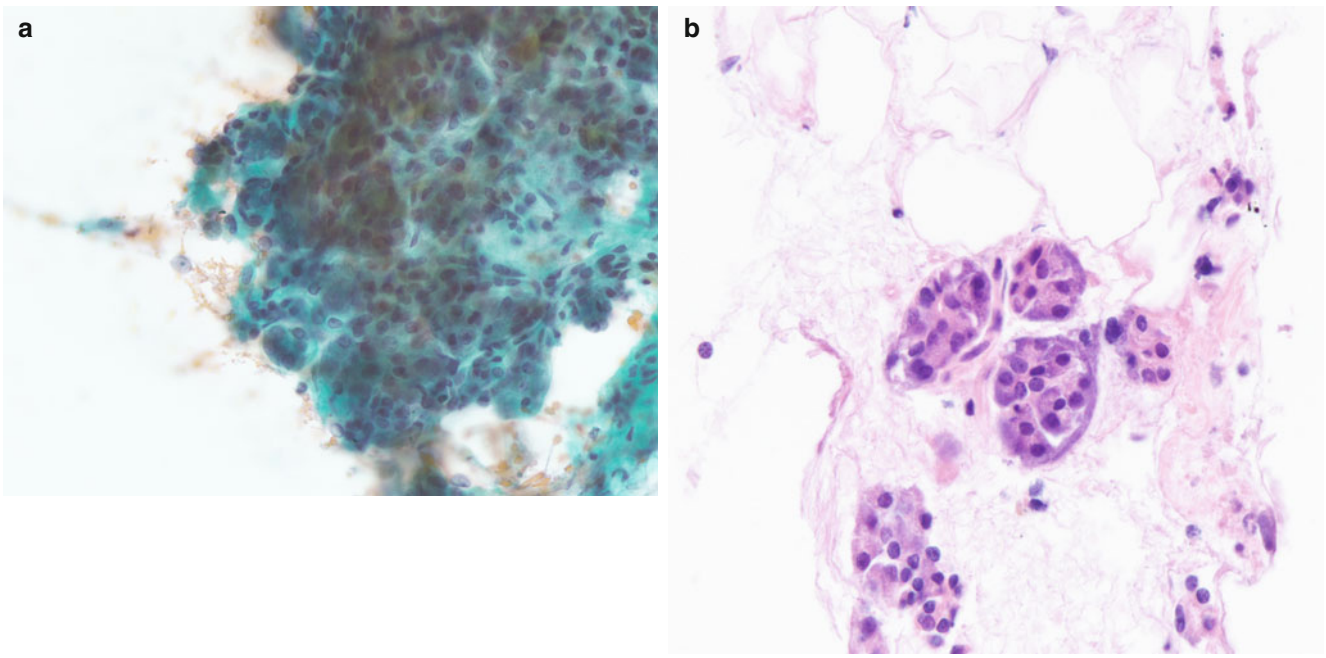


**Fig. 11.2** Normal pancreas. (**a**) Large intact tissue fragment with benign cells and recognizable acinar architecture toward the edge of the fragment (Papanicolaou [Pap] stain). (**b**) Normal pancreatic acini in cell block material (HTX)

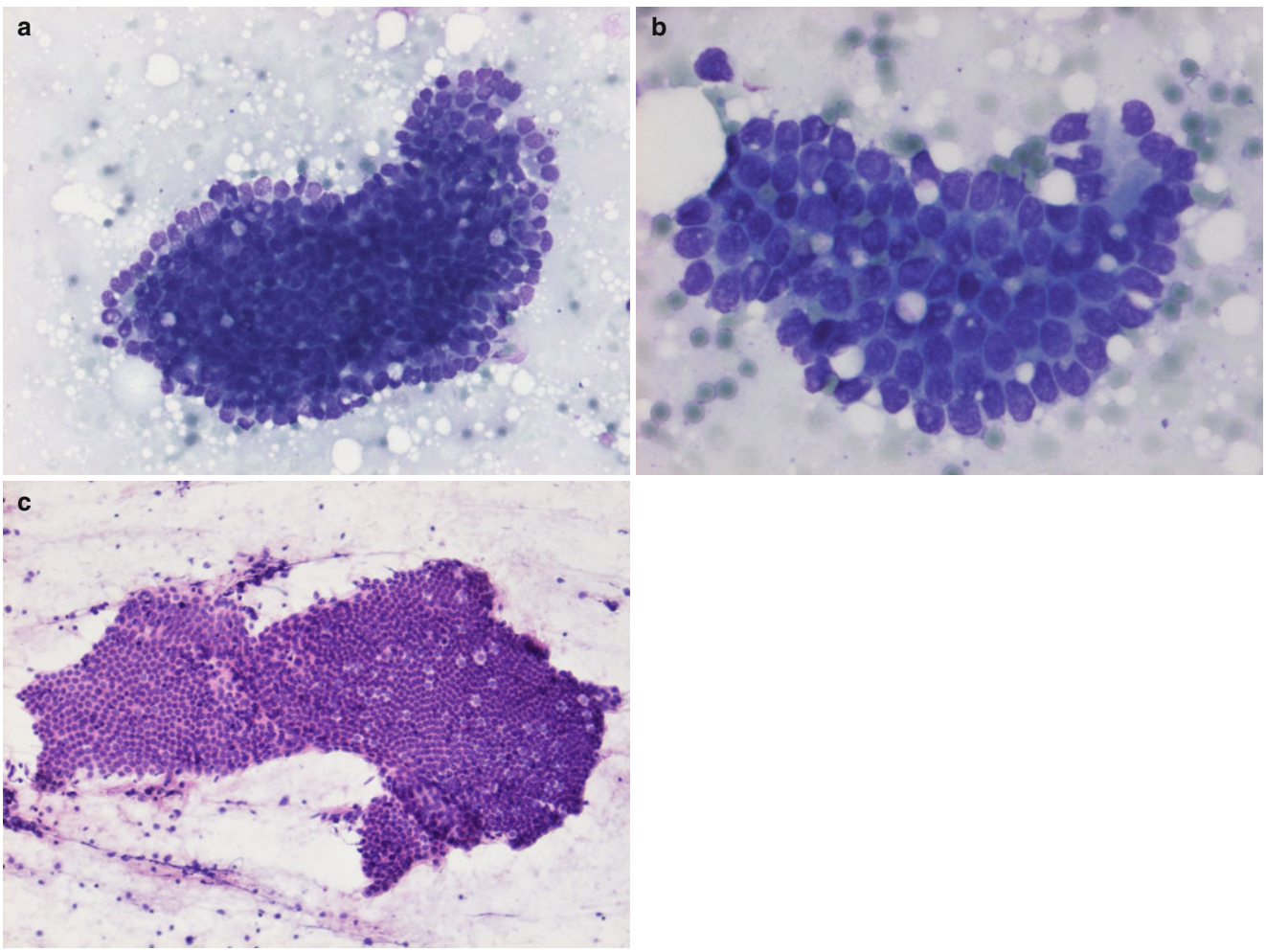


**Fig. 11.3** Normal pancreas. (**a** and **b**) Ductal cells in the pancreatic FNA appear as flat sheets with a "honeycomb" architecture (May-Grünwald-Giemsa [MGG]). (**c**) Contaminating gastrointestinal glandular mucosa can look similar to pancreatic ductal cells but interspersed goblet cells help to distinguish them from sheets of pancreatic ductal cells (HTX)

## 11.3 Pancreatitis and Nonneoplastic Entities

### 11.3.1 Acute Pancreatitis

Acute pancreatitis is the result of autodestruction of pancreatic parenchyma with inappropriately activated pancreatic enzymes. Although FNA biopsy would not normally be performed on a person suspected to have acute pancreatitis, occasionally patients with acute pancreatitis may present with a mass lesion and be referred for FNA. Acute pancreatitis typically yields cellular specimens, consisting of intact and degenerated neutrophils and histiocytes in a background of necrotic debris. Ductal epithelial cells in acute pancreatitis may show marked reactive-type changes and atypia that may be confused with ductal adenocarcinoma. Cytomorphologic features favoring reactive over ductal adenocarcinoma include uniform spacing of nuclei within epithelial sheets, round nuclear contours, lower cellularity, and an inflammatory background. In cases of acute pancreatitis, making the diagnosis is less important than overcalling the FNA as atypical or positive. It is also important to remember that malignant tumors can cause acute pancreatitis, so acute pancreatitis and pancreatic malignancy should not be considered mutually exclusive.

### 11.3.2 Chronic Pancreatitis

Chronic pancreatitis is defined as an ongoing inflammation of the pancreas with destruction of exocrine parenchyma and fibrosis. Chronic pancreatitis can lead to radiographic abnormalities that may be difficult to differentiate from a neoplastic process. Pseudocyst formation is also common in the setting of chronic pancreatitis, which could also lead to referral for FNA. In contrast to acute pancreatitis, FNAs of chronic pancreatitis are usually sparsely cellular due to tissue scarring and fibrosis. Ductal cells often with reactive changes can be seen in this setting (*see* Fig. 11.4). Mixed, mild inflammation, debris, and macrophages may also be seen. Again, establishing the diagnosis of pancreatitis is not the expectation of the FNA, but rather to declare it free or positive for malignancy. Because virtually all cases of pancreatic ductal adenocarcinoma coexist with chronic pancreatitis, they are not exclusive of each other.

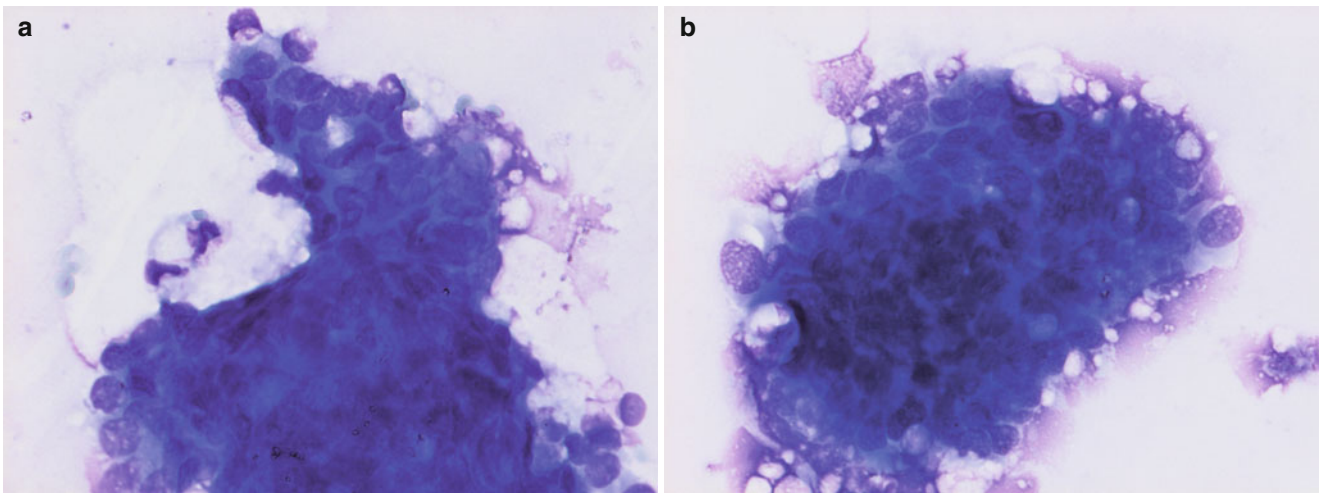


**Fig. 11.4** Chronic pancreatitis. (**a** and **b**) Clusters of glandular epithelium showing nuclear enlargement and crowding/overlapping of ductal cells consistent with reactive atypia (MGG)

## 11.4 Intrapancreatic Accessory Spleen

Accessory spleens are common, and when they occur in the pancreas, they can simulate a solid pancreatic neoplasm. The lesions are hypervascular and thus usually classified as a primary neuroendocrine tumor on radiographic studies if they are not recognized as an intrapancreatic accessory spleen (IPAS). Because IPASs are benign and do not need to be excised, recognizing the correct classification is important on FNA studies targeting IPASs.

Cytologic findings of IPAS have been described in the literature [10]. Most cases are reports of lesions that were ultimately excised, which is an unfortunate way to arrive at the diagnosis [11]. Cytologic findings included a mixed lymphoid population predominantly consisting of small mature lymphocytes with lesser numbers of plasma cells and eosinophils (*see* Fig. 11.5a). Prominent transgressing vessels are also typical. Direct smears are often more cohesive than are typical for a lymphoid population due to the sinus architecture of splenic tissue (*see* Fig. 11.5a). This false sense of cohesion can prompt one to consider a neuroendocrine tumor. Cell block material can confirm the diagnosis by proving that the lymphoid population is mixed and by decorating the splenic sinus endothelial cells with CD8, a pattern that is specific for splenic tissue (*see* Fig. 11.5c).

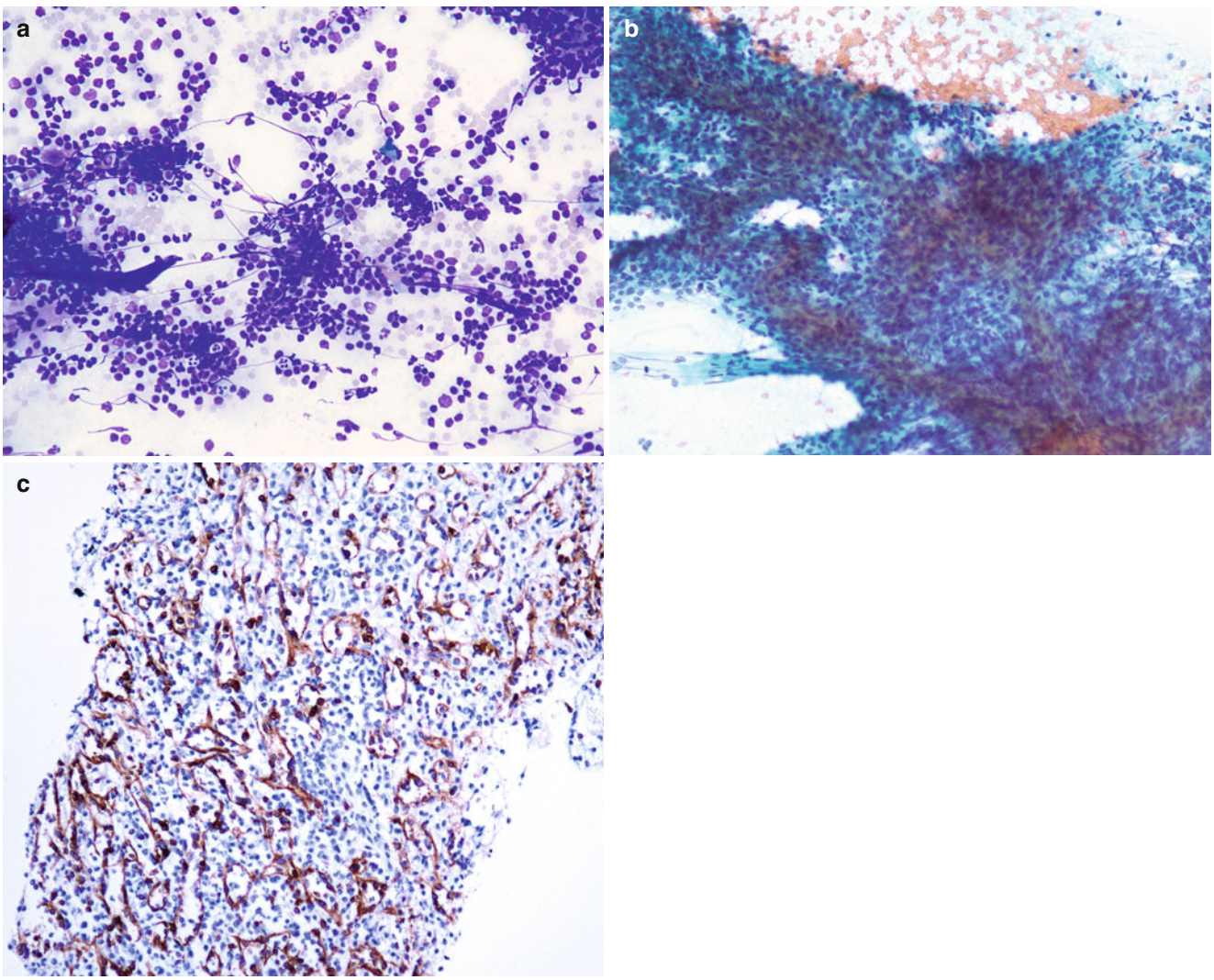


**Fig. 11.5** Intrapancreatic accessory spleen. (**a**) Cellular aspirate with loosely cohesive and dissociated lymphoid cells. The smearing process has disrupted some of the cells, producing nuclear streaks and lymphoid tangles (DQ). (**b**) Prominent transgressing vessels are also apparent (Pap stain). (**c**) CD8 immunostain demonstrating a sinusoidal pattern diagnostic of IPAS

## 11.5 Neoplasms

### 11.5.1 Pancreatic Ductal Adenocarcinoma

Infiltrating adenocarcinoma of the pancreas is a relatively common malignancy of middle-aged and older patients. Ductal adenocarcinoma is the most common variant and typically arises in the head of the pancreas and involves the distal common bile duct; thus, obstructive jaundice is a common presentation. The prognosis for infiltrating ductal adenocarcinoma is poor, with nearly every affected patient dying of the disease.

The diagnosis of pancreatic adenocarcinoma is usually established with pancreatic FNA. In most cases, the cytologic findings are not difficult and permit a definitive diagnosis. Well-differentiated adenocarcinomas, which are the exception, can be problematic and difficult to separate from benign aspirates. Similarly, a mucinous adenocarcinoma may be difficult to distinguish from nonmalignant mucinous neoplasms.

Well-differentiated ductal adenocarcinomas tend to maintain a flat honeycomb arrangement in aspirates that is very much akin to benign glandular elements. Cytologic clues to the malignant nature of the cells at scanning power include variation in nuclear size, nuclear crowding, and irregular spacing of the nuclei (*see* Fig. 11.6). The descriptor "drunken honeycomb" has been used to describe these subtle changes in well-differentiated tumors. Scrutiny of the nuclear membranes is critical to establishing a malignant diagnosis. Even well- and moderately differentiated tumors tend to have irregular nuclear contours with notches, convolutions, and nuclear grooves (*see* Fig. 11.7a, b). Chromatin is often irregular with hyperchromasia and areas of clearing. Prominent nucleoli are also a common finding (*see* Fig. 11.7c, d).

With increasing grade of tumor, loss of polarity and disorganization within cell groups increases (*see* Fig. 11.8a, b). Greater dyscohesion is typical of poorly differentiated tumors. The cytologic correlate is increased individual malignant cells (*see*

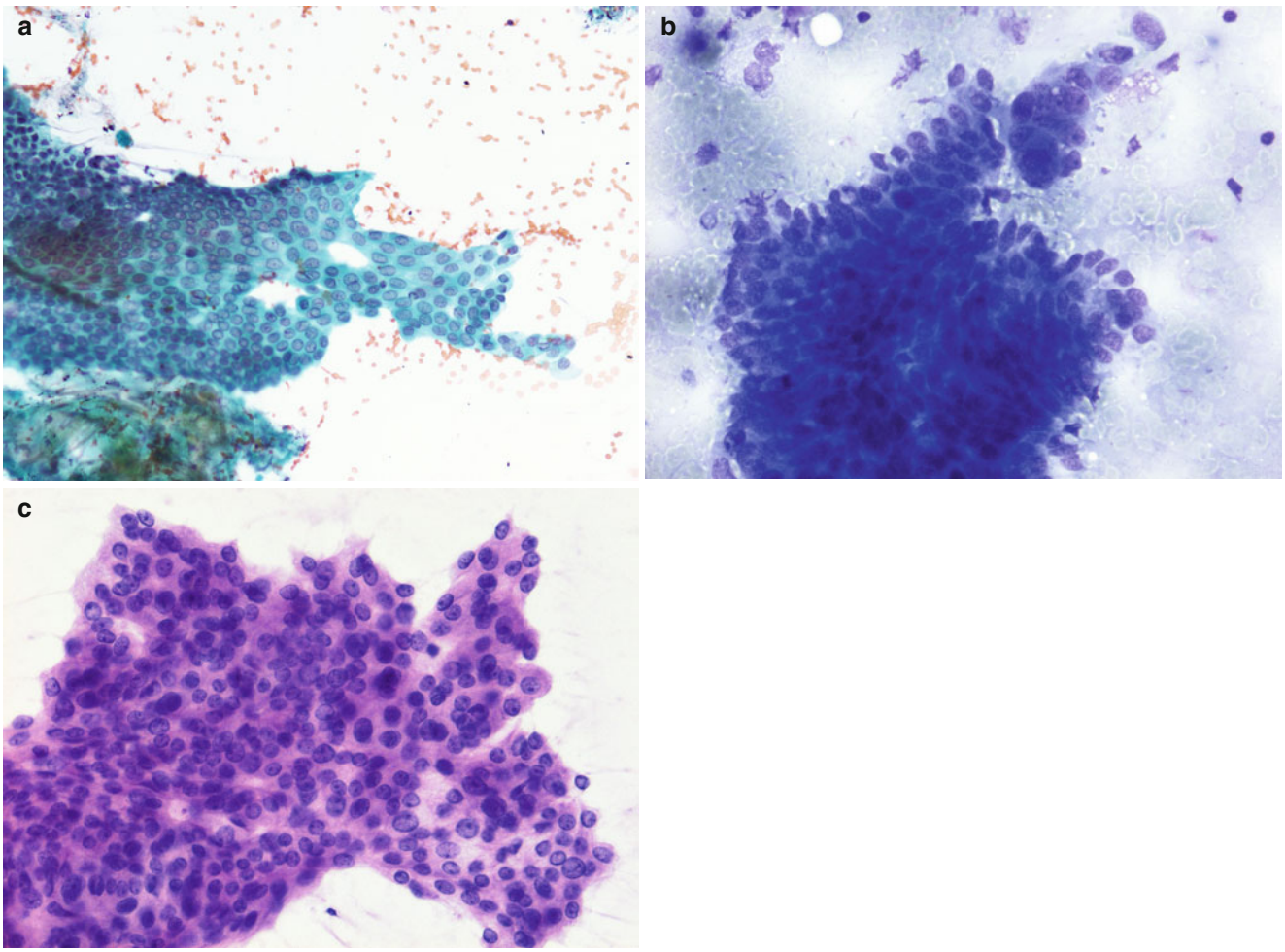


**Fig. 11.6** Well-differentiated adenocarcinoma of the pancreas. (**a**–**c**) Tumor cells arranged in a flat sheet and morphologically similar to benign ductal cells. However, scattered cells within these fragments show nucleomegaly, and, architecturally, the spacing is irregular. The nuclear contours of many tumor cells are smooth, whereas a few tumor cells have nuclear indentations (Pap stain, MGG, and HTX)

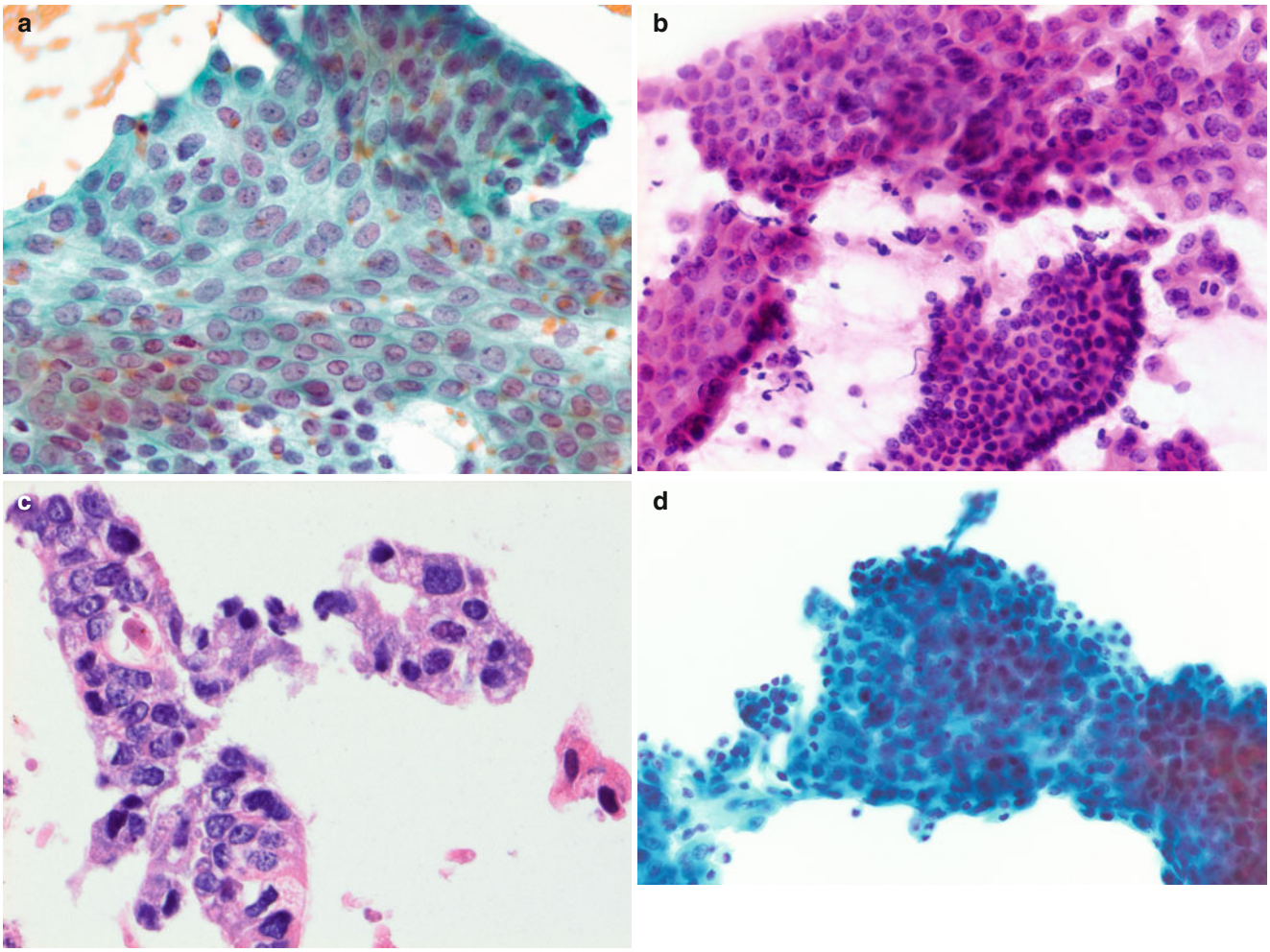


**Fig. 11.7** Moderately differentiated adenocarcinoma of the pancreas. (**a** and **b**) Sheet of glandular cells with up to fourfold nuclear size variation, irregular spacing, and irregular nuclear contours, which are features diagnostic of pancreatic adenocarcinoma (Pap stain, HTX). (**c**) Cell block section well demonstrates the architecture of the tumor and morphological details of tumor cells (HTX). (**d**) Liquid-based preparation of pancreatic FNA. Although nuclei are smaller due to shrinking artifact, diagnostic features are retained. Prominent nucleoli, crowding, and irregular nuclear contours are apparent in this field (ThinPrep)

Fig. 11.8c, d). Cell borders may become indistinct, imparting a syncytial appearance to the lesional cells. Squamous features are common in higher-grade tumors (*see* Fig. 11.9).

*Cytologic features:*

- Usually cellular smears.
- Flat honeycomb-arranged sheets of cells.
- Some dispersed cells.
- Moderate amounts of cytoplasm and occasional mucin vacuoles.
- Loss of polarity and disorganization within cell groups increases in higher grade.
- Irregular nuclear membrane with notches, convolutions, and nuclear grooves (more prominent changes in moderately and poorly differentiated carcinoma).
- Variation in nuclear size, nuclear crowding, and enlargement.
- Larger nucleoli than in benign ductal cells.
- Irregular chromatin and often hyperchromasia and areas of clearing.
- Squamous features are common in higher-grade tumors.

*Differential diagnosis and problems in diagnosis:*

- Pancreatitis
- Postirradiation atypia
- Distinguishing pancreatic adenocarcinoma from primary distal choledochus carcinoma (in tumors of the head of the pancreas)
- Metastases to the pancreas

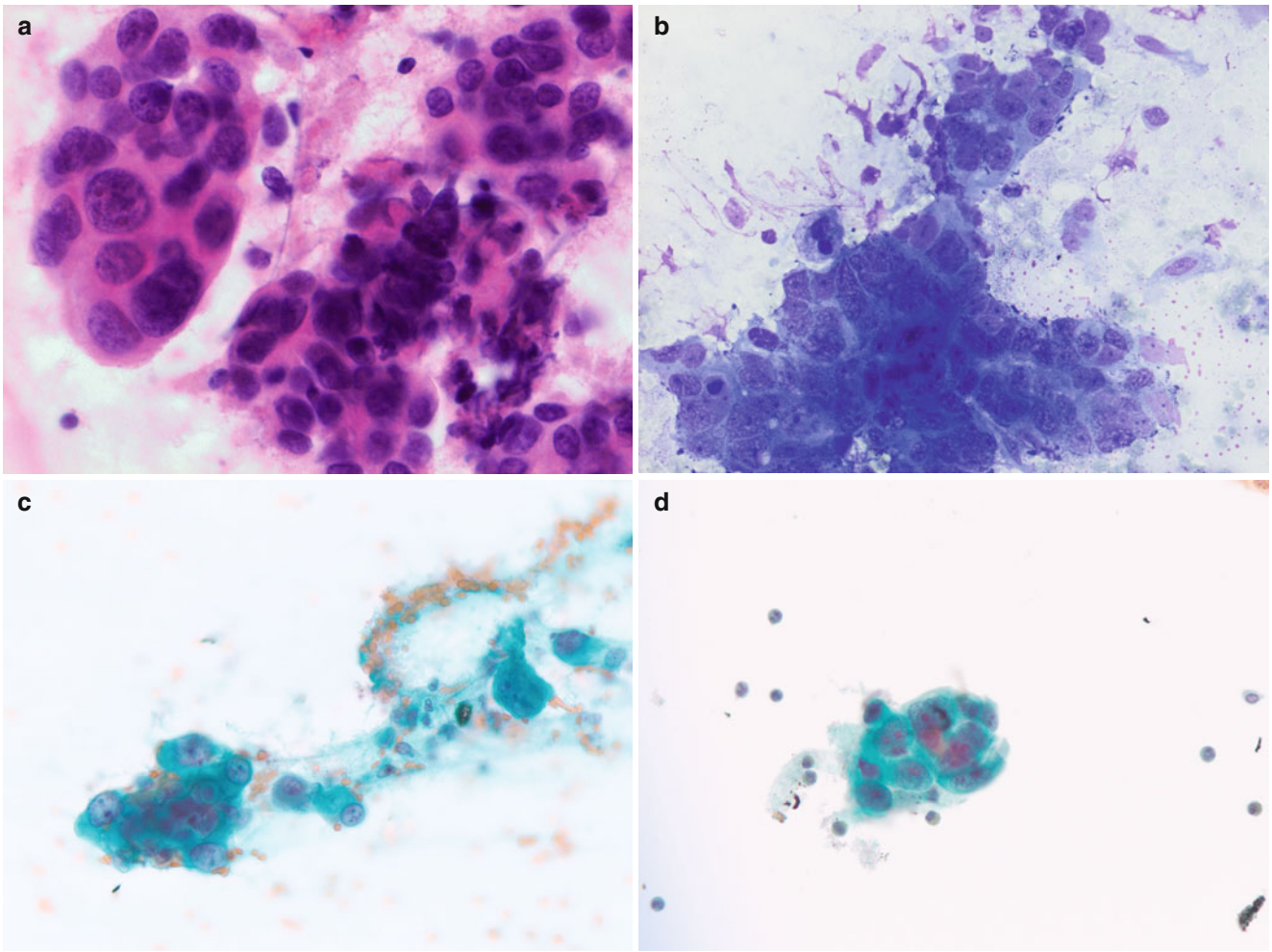


**Fig. 11.8** Poorly differentiated adenocarcinoma of the pancreas. (**a**) Variation in the nuclear size and shape, irregular nuclear contours, and chromatin distribution are obvious in smears (HTX). (**b**) Even in air-dried smears, macronucleoli are clearly visible in the tumor cells (MGG). (**c**) On the right, overtly malignant glandular cells are present. A loss of cell polarity and individual malignant cells are present on the left, features typical of poorly differentiated adenocarcinoma (Pap stain). (**d**) Glandular cluster with macronucleoli, anisokaryosis, and adjacent necrotic debris (ThinPrep)

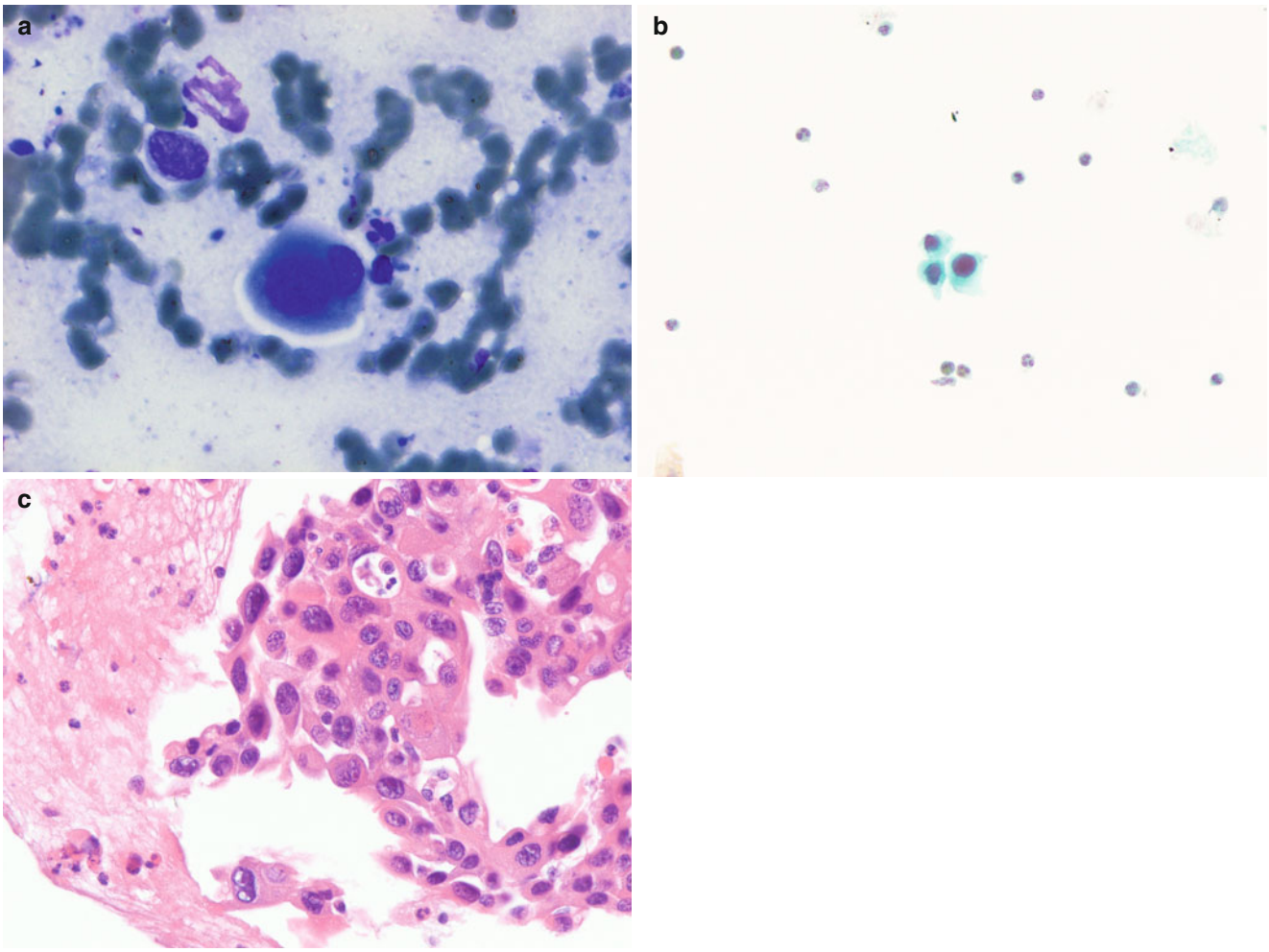


**Fig. 11.9** Poorly differentiated adenocarcinoma of the pancreas. (**a** and **b**) Squamous differentiation is commonly seen in poorly differentiated ductal adenocarcinoma (MGG, ThinPrep) and cell block material (**c**; HTX)

## 11.6 Variants of Ductal Adenocarcinoma

### 11.6.1 Adenosquamous Carcinoma

Adenosquamous carcinomas (ASC) of the pancreas are tumors showing dual differentiation containing both glandular and squamous elements. Focal squamous differentiation is very common in ductal adenocarcinoma and criteria for classification, as ASC require that 30 % of the tumors show squamous features. Cytologic features of squamous differentiation are the same as in other sites and include tumor cells with distinct cytoplasmic membranes, intracellular bridging, hard eosinophilic cytoplasm, and keratinization. Occasionally primary pancreatic carcinomas show such extensive squamous differentiation to raise consideration of metastatic disease to the pancreas. In such cases, identifying even focal glandular areas warrants a diagnosis of ASC. Pure squamous cell carcinoma of the pancreas is exceptional.

### 11.6.2 Undifferentiated (Anaplastic) Carcinomas

Undifferentiated (anaplastic) carcinomas of the pancreas show no obvious differentiation and include multiple recognized variants.

### 11.6.3 Pleomorphic Giant Cell Carcinoma

Pleomorphic giant cell carcinoma is a highly aggressive pancreatic tumor accounting for approximately 2 % of pancreatic malignancies and with similar patient demographics to conventional ductal adenocarcinoma. Aspirates are typically highly cellular, predominantly with individually placed tumor cells (*see* Fig. 11.10). The cells are highly pleomorphic with mononuclear, multinuclear, and bizarre tumor giant cells (*see* Fig. 11.11a, b). Cell shape is also variable with round, oval, and spindled tumor cells (*see* Fig. 11.11c). The nuclei have overtly malignant features. One distinctive feature of pleomorphic giant cell carcinoma is autophagocytosis of inflammatory cells by tumor giant cells (*see* Fig. 11.11d).

*Cytologic features:*

- Usually hypercellular smears
- Predominantly individual, isolated tumor cells
- Few cell clusters and poorly cohesive tumor cells within clusters

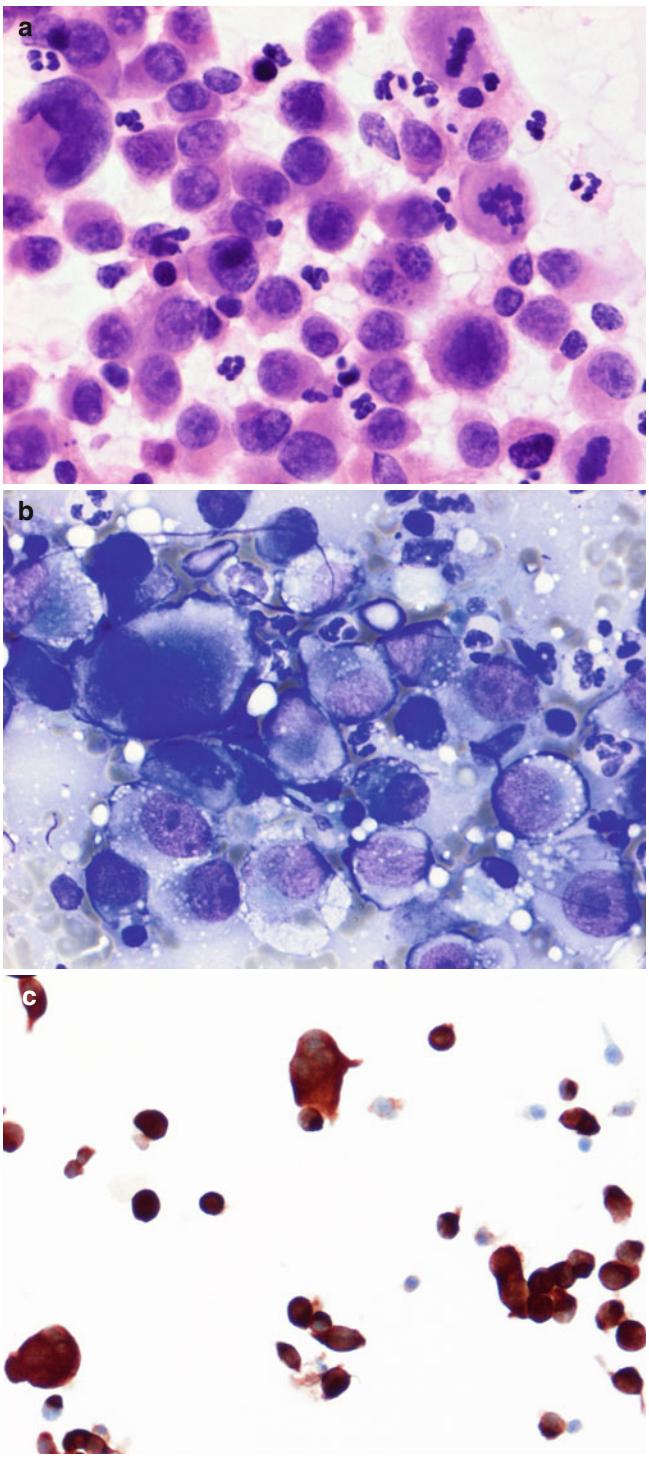


**Fig. 11.10** Undifferentiated (anaplastic) carcinoma of the pancreas (pleomorphic giant cell carcinoma of the pancreas). (**a** and **b**) Highly cellular smears with predominant, dissociated, pleomorphic tumor cells (HTX, MGG). (**c**) Positive keratin staining confirms a diagnosis of carcinoma (ThinPrep; Hologic; Bedford, MA, USA)

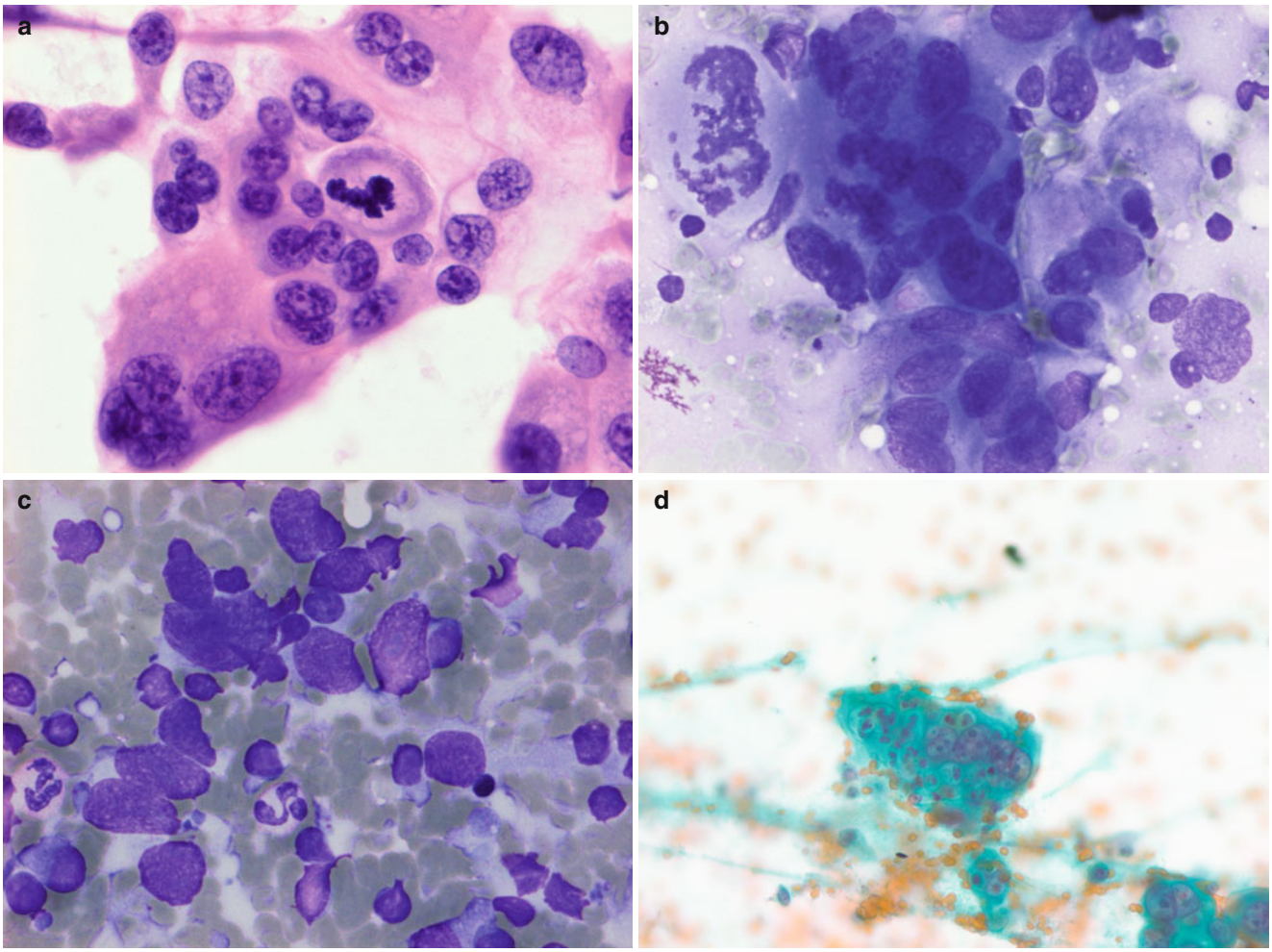


**Fig. 11.11** Undifferentiated (anaplastic) carcinoma of the pancreas (pleomorphic giant cell carcinoma of the pancreas). (**a** and **b**) In addition to marked anisonucleosis, hyperchromasia and obvious mitotic figures are present (HTX and MGG). (**c**) Sarcomatoid areas in the undifferentiated carcinoma may be occasionally sampled by FNA (MGG). (**d**) A bizarre multinucleated tumor giant cell is present and shows phagocytosis of numerous neutrophils (Pap stain)

- Markedly pleomorphic tumor cells and bizarre mononucleated and multinucleated giant cells
- Bizarre mitotic figures
- Occasionally spindled/sarcomatoid tumor cells
- Usually necrotic/inflammatory background
- Autophagocytosis of neutrophils

*Differential diagnosis and problems in diagnosis:*

- Metastatic malignant melanoma
- Metastatic germ cell tumors
- Pleomorphic sarcomas

### 11.6.4 Undifferentiated Carcinoma with Osteoclast-Like Giant Cells

Undifferentiated carcinoma with osteoclast-like giant cells is an extremely rare variant, with tumor cells resembling those of giant cell tumor of bone. Only a few descriptions of the cytologic findings of such tumors have been published. Highly cellular aspirates with mononucleated tumor cells admixed with diagnostic multinucleated (up to 20 nuclei per cell) histiocytic giant cells are characteristic (*see* Figs. 11.12 and 11.13). Undifferentiated carcinomas have an extremely poor prognosis compared to conventional ductal adenocarcinoma with an average survival of just 5 months [12].

*Cytologic features:*

- Usually hypercellular smears.
- Mononucleated tumor cells admixed with multinucleated osteoclast-like giant cells.
- Nuclei of mononuclear tumor cells resemble nuclei of giant cells but often with more obvious pleomorphism.
- Scattered mitotic figures.

*Differential diagnosis and problems in diagnosis:*

- Metastatic germ cell tumors
- Giant cell anaplastic carcinoma

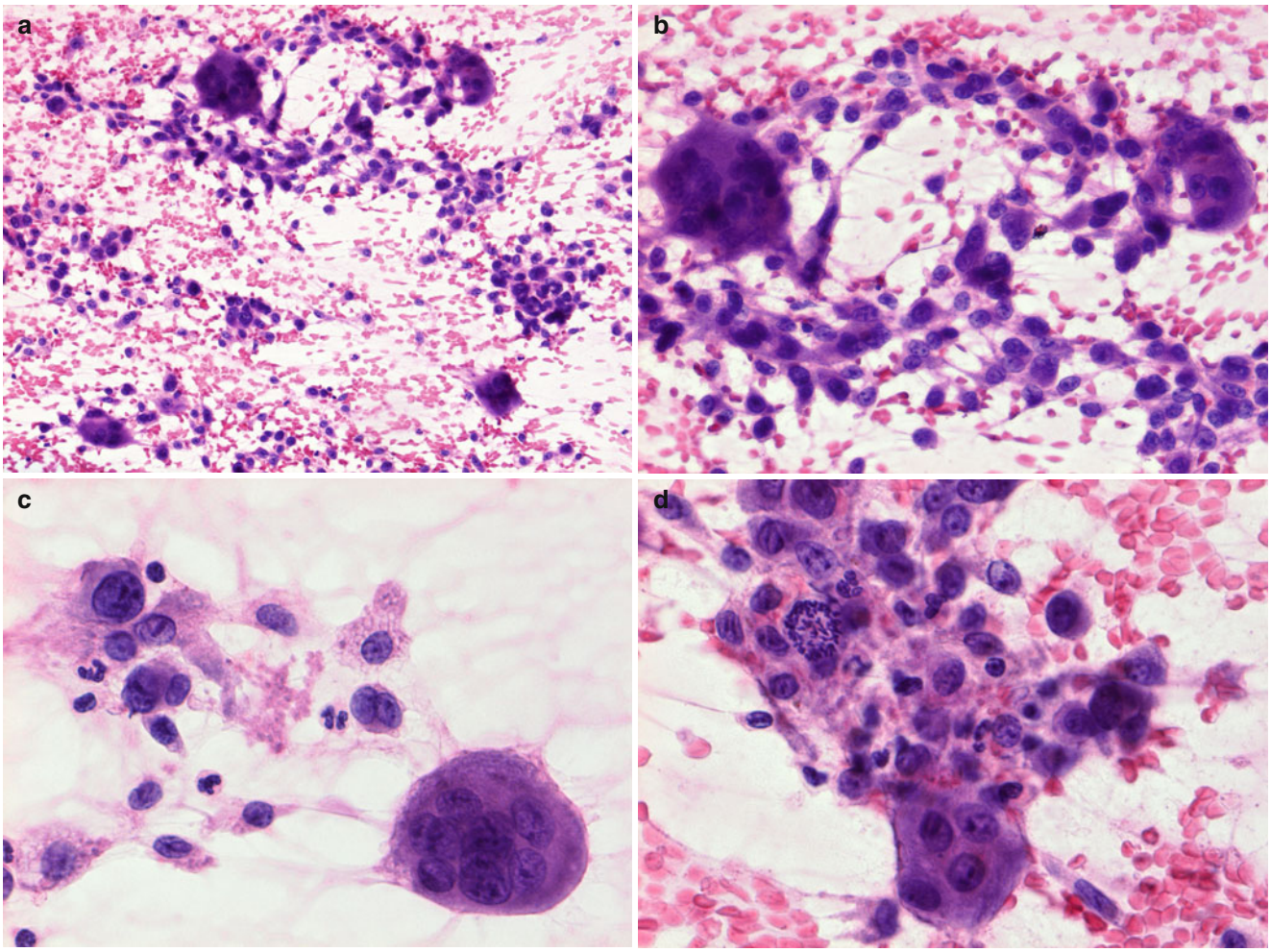


**Fig. 11.12** Undifferentiated (anaplastic) carcinoma of the pancreas with osteoclast-like giant cells. (**a** and **b**) Highly cellular aspirates with mononuclear tumor cells admixed with multinucleated histiocytic osteoclast-like giant cells are characteristic. (**c** and **d**) Poorly cohesive mononuclear cells show spindled and epithelioid morphology with nuclei resembling those of giant cells but often with obvious pleomorphism and scattered mitotic figures (HTX)

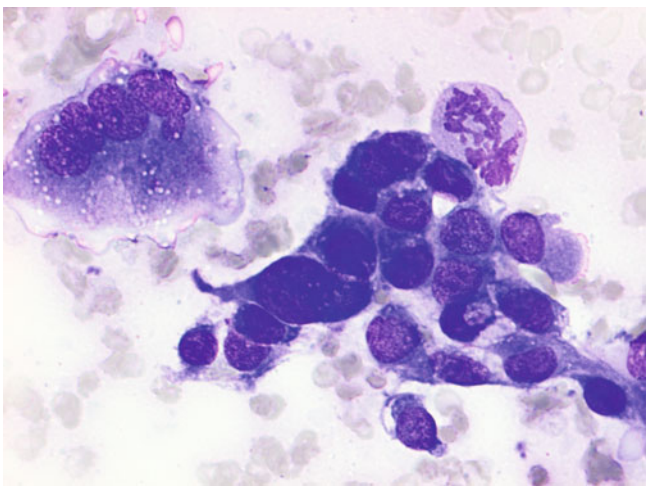

**Fig. 11.13** Undifferentiated (anaplastic) carcinoma of the pancreas with osteoclast-like giant cells. In air-dried smears, the fine cytoplasm granulation of the giant cells is visible. This appearance is similar to that of multinucleated osteoclasts present in smears from bone tumors (MGG)

### 11.6.5 Undifferentiated Carcinoma of the Small Cell Type

Undifferentiated carcinoma of the small cell type is another extremely rare variant of primary pancreatic tumor [13], morphologically indistinguishable from small cell carcinoma of the lung (*see* Fig. 11.14). Proper clinical information is crucial because tumor cells reminiscent of small cell carcinomas primary in the pancreas may be easily confused with metastatic small cell carcinoma.

*Cytologic features:*

- Usually hypercellular smears
- Mononucleated small tumor cells resembling small cell carcinoma primary in other organs

*Differential diagnosis and problems in diagnosis:*

- Metastatic small cell carcinoma

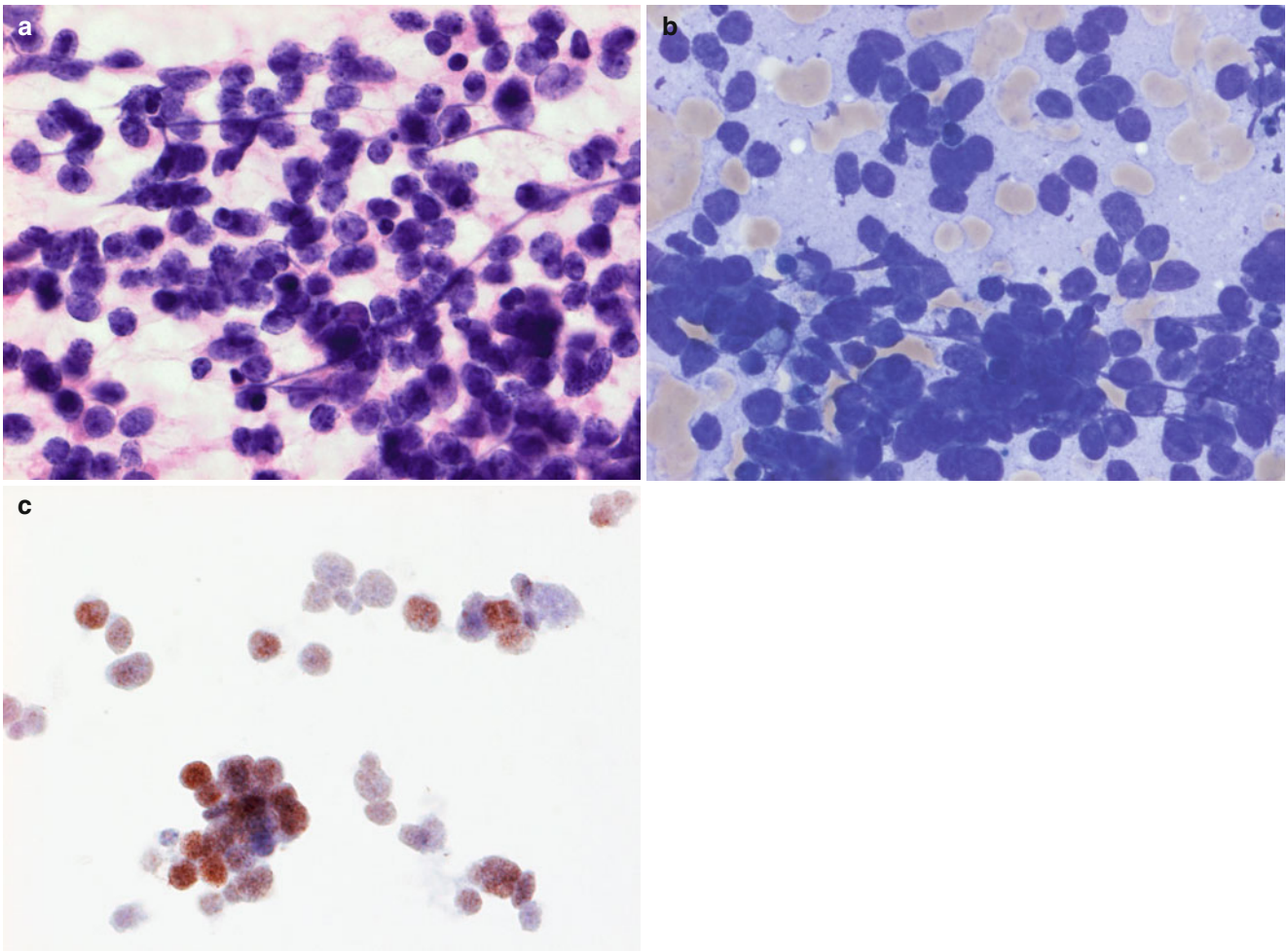


**Fig. 11.14** Undifferentiated (anaplastic) carcinoma of the pancreas, small cell variant. (**a** and **b**) FNA smears from extremely rare primary small cell undifferentiated carcinoma of the pancreas may be easily confused with metastatic small cell carcinoma of the lung (HTX, ThinPrep). (**c**) Similar to small cell carcinoma of the lung, tumor cells may express reactivity against thyroid transcription factor (TTF)-1 antibodies (ThinPrep)

## 11.7 Acinar Cell Carcinoma

Acinar cell carcinoma (ACC) is a malignant neoplasm composed of cells morphologically resembling normal pancreatic acinar cells and showing evidence of production of exocrine enzymes. Clinical and radiographic features of ACC are distinct as compared to ductal adenocarcinoma. ACCs are more circumscribed and tend to push rather than infiltrate adjacent structures. Obstructive jaundice is much less frequent with ACC. The outcomes of ACCs are better than for stage-matched ductal adenocarcinomas, with 5-year survival ranging from 25 to 50 % depending on the stage at diagnosis [14].

FNA of ACC is hypercellular and at scanning power shows small cohesive nests of tumor cells (*see* Fig. 11.15a). Typical architecture of an acinar unit of ACC is a central lumen surrounded by tumor cells with cytoplasm oriented toward the lumen and peripheral placement of the nuclei (*see* Figs. 11.15b and 11.16). The cytoplasm of ACC is usually eosinophilic and granular. On cytologic grounds, the cells of ACC may be quite bland but as compared to normal acinar cells have more prominent nuclei, nucleomegaly, altered polarity, and altered nuclear contours (*see* Fig. 11.17a, b). The overwhelming cellularity typical of ACC is inconsistent with benign acinar cells. Demonstrating pancreatic exocrine enzymes (trypsin, chymotrypsin, lipase, and amylase) with immunohistochemical stains (*see* Fig. 11.17c, d) is useful in differentiating ACC from pancreatic neuroendocrine tumors.

*Cytologic features:*

- Usually hypercellular smears.
- Small cohesive nests of tumor cells.
- Many dispersed cells but occasionally large clusters of tumor cells with preserved acinar architecture.
- Tumor cells resemble normal acinar cells showing moderate to abundant eosinophilic and granular cytoplasm.
- Round to oval nucleus with more prominent nucleoli; nucleomegaly and altered nuclear contours differ from normal acinar cells.
- Altered polarity and disorganization within cell groups.

*Differential diagnosis and problems in diagnosis:*

- Clusters of normal acinar cells
- Pancreatic endocrine neoplasm

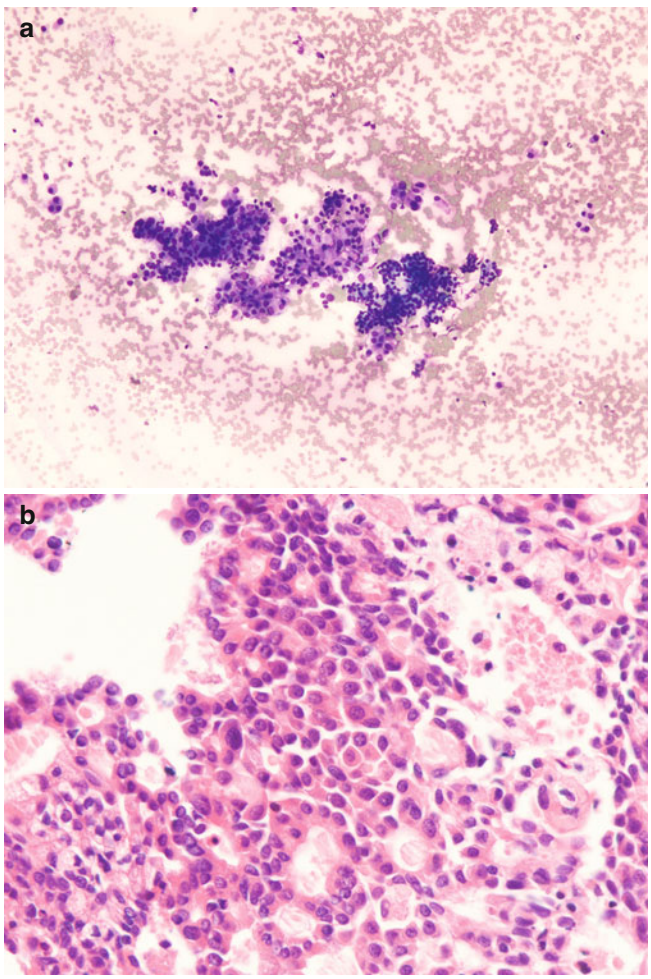


**Fig. 11.15** Acinar cell carcinoma of the pancreas. (**a**) Cellular specimen containing tumor cells that have an acinar architecture (DQ). (**b**) Cell block material containing low-grade tumor cells with abundant pink cytoplasm and acinar structures (HTX)

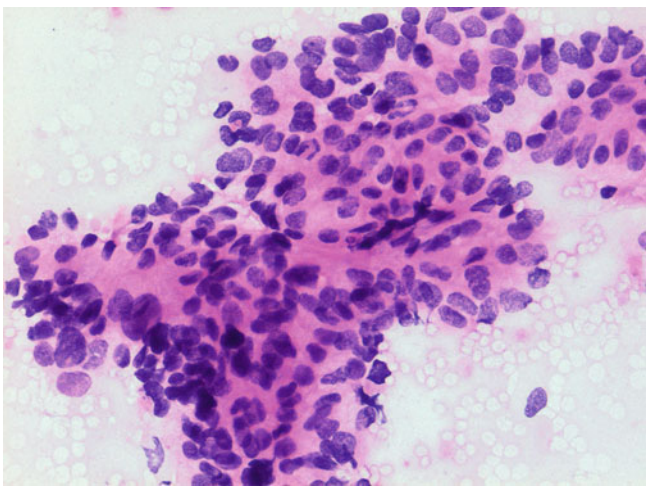

**Fig. 11.16** Acinar cell carcinoma of the pancreas. Another cytologic feature of acinar cell carcinoma. FNA showing a cohesive cluster of tumor cells. Obvious acinus-like structures are visible in the smears (HTX)

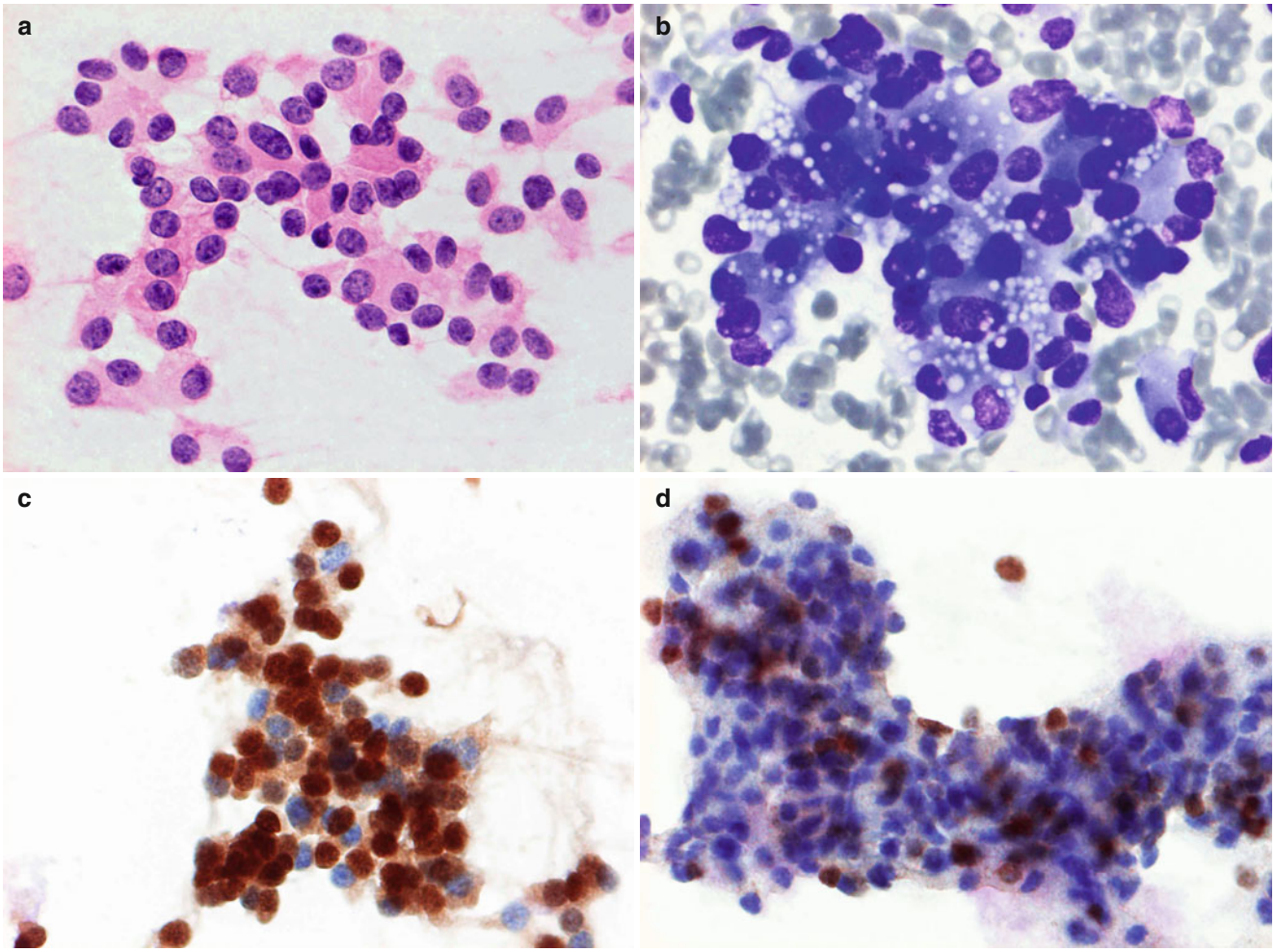


**Fig. 11.17** Acinar cell carcinoma of the pancreas. (**a** and **b**) Acinus-like structures of tumor cells with abundant cytoplasm reminiscent of normal pancreatic acini (HTX and MGG). (**c**) The cells are immunoreactive for **α**1-antitrypsin and chymotrypsin (**d**; ThinPrep)

## 11.8 Pancreatoblastoma

Pancreatoblastoma (PB) is a rare epithelial neoplasm and a common pancreatic tumor of childhood. The median age is 4 years and the tumor only rarely occurs in adult age groups. PB show acinar differentiation and distinctive squamoid nests a feature central to the diagnosis. Prognosis depends upon the respectability of the lesion at the time of discovery, and overall survival is approximately 50 % [15].

There are only a few reports of the cytologic findings in PB published in the peer-reviewed literature [16–19]. FNAs of PB are usually hypercellular with ovoid to cuboidal tumor cells that have a moderate amount of granular cytoplasm (*see* Fig. 11.18). Acinar and ductal arrangement of the tumor cells has been reported as well as blastemic elements. Notably squamoid features may not be readily identified in cytologic preparations and may be better appreciated in cell block material. The clinical and morphologic overlap with ACC and PB may make this distinction difficult in cytologic preparations, particularly if squamoid nests are not identified.

*Cytologic features:*

- Usually hypercellular smears
- Ovoid to cuboidal tumor cells that have a moderate amount of granular cytoplasm
- Acinar and ductal arrangement of the tumor cells
- Blastemic elements
- Squamoid corpuscles

*Differential diagnosis and problems in diagnosis:*

- ACC
- Solid pseudopapillary neoplasm of the pancreas (SPNP)
- Pancreatic endocrine neoplasms (PENs)

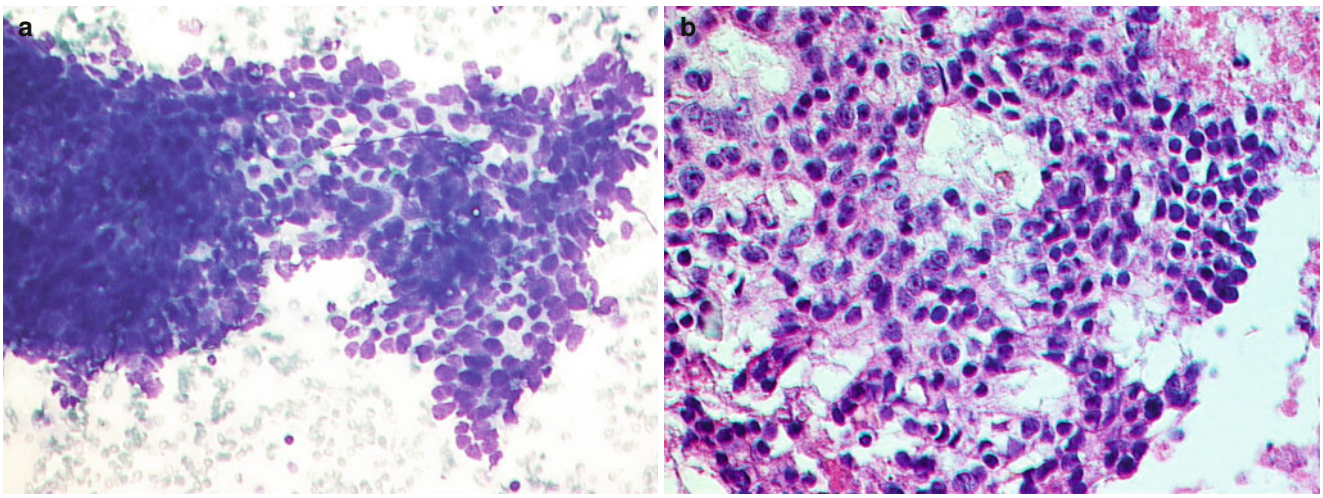


**Fig. 11.18** Pancreatoblastoma. (**a**) Direct smear of a pancreatic FNA in a pediatric patient with a nest of neoplastic epithelial cells without obvious differentiation (DQ). (**b**) Acinar differentiation is more apparent in the cellblock material. Helpful squamoid nests may not be identified and when present are usually found in the cell block material (HTX). Follow-up in this case confirmed pancreatoblastoma (*Images courtesy of* Jerzy Klijanienko, MD, Institut Curie, Paris, France)

## 11.9 Pancreatic Endocrine Neoplasms (Neuroendocrine Islet Cell Tumors)

PENs are pancreatic tumors with neuroendocrine differentiation and, by definition, are low grade. PENs usually occur in adult patients and represent about 1–2 % of pancreatic neoplasms. Radiographically, PENs are usually solid, well-demarcated lesions that may be seated anywhere in the pancreas. Functional PEN often presents with clinical syndromes related to hypersecretion of hormones.

FNAs of PEN are usually hypercellular, containing a monotonous population of tumor cells. The scanning power pattern of loosely cohesive tumor groups with interspersed single tumor cells is a good indicator of neuroendocrine differentiation, as is a rosette-like pattern in the FNA smears (*see* Figs. 11.19 and 11.20a, b). Round to oval, regular nuclei with finely stippled, evenly distributed "salt and pepper" chromatin are typical for low-grade PEN [20]. Nuclear eccentricity reminiscent of a plasma cell is also commonly seen. Decorating the tumor cells with neuroendocrine markers (chromogranin, synaptophysin, and CD56) can be used to confirm the diagnosis (*see* Fig. 11.20c, d). Overreliance on the immunoprofile for diagnostic purposes is discouraged, as other tumor may show spurious reactivity.

*Cytologic features:*

- Usually hypercellular smears
- Isolated cells and dyscohesive, loose cell clusters with occasional rosette-like structures
- Small- to medium-sized, monomorphic, or slightly pleomorphic tumor cells

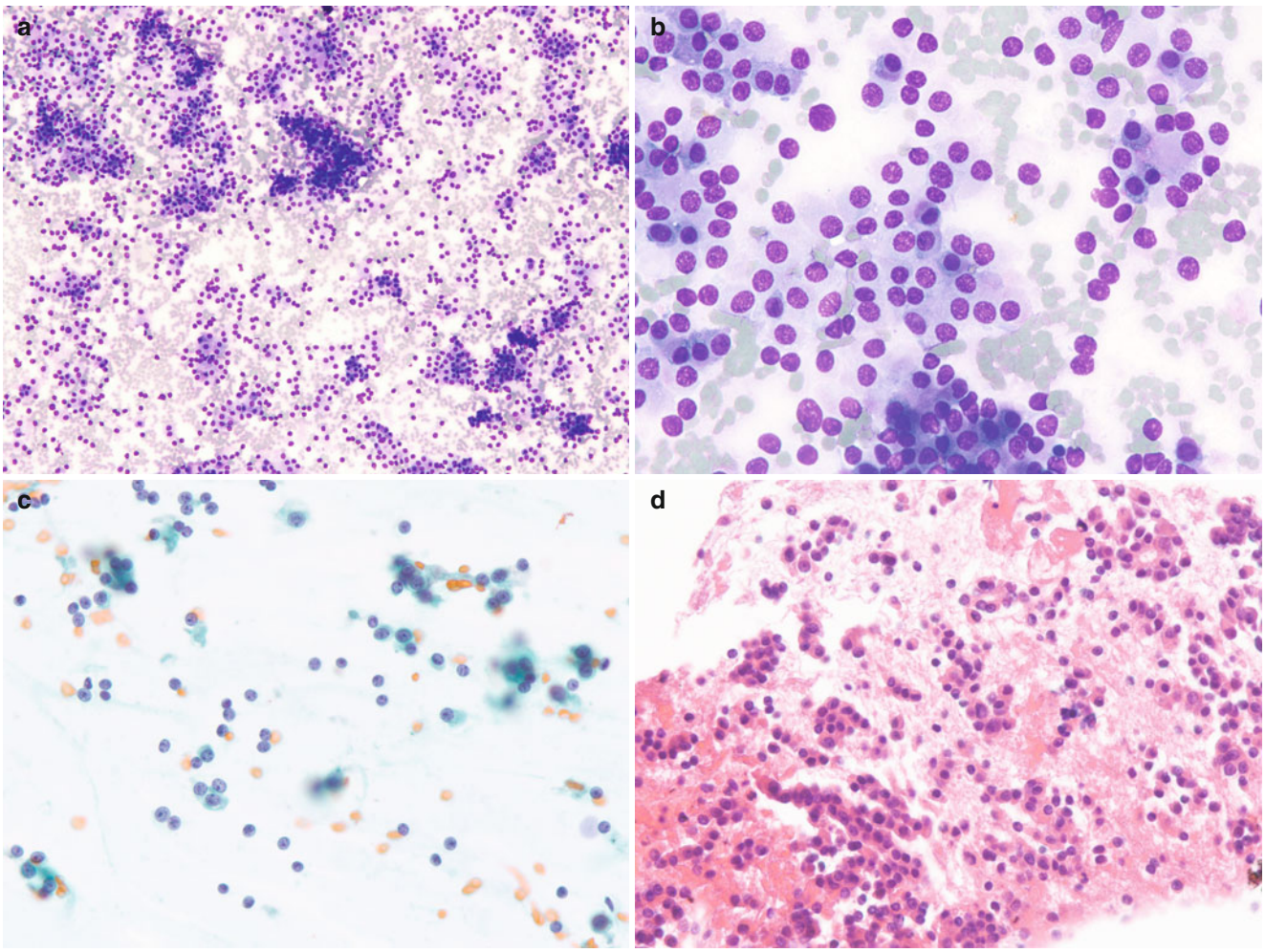


**Fig. 11.19** Pancreatic endocrine neoplasms (neuroendocrine islet cell tumor of the pancreas). (**a**) Scanning power shows a cellular aspirate with loosely cohesive groups of tumor cells and individual tumor cells. (**b**) The nuclei at higher power are round and regular with nuclear eccentricity imparting a plasmacytoid appearance to some of the cells (DQ). (**c**) Characteristic "salt and pepper" type of chromatin is readily apparent in this smear (Pap stain). (**d**) Cell block material is useful for confirming neuroendocrine differentiation and measuring proliferation index with immunohistochemical stains (HTX)

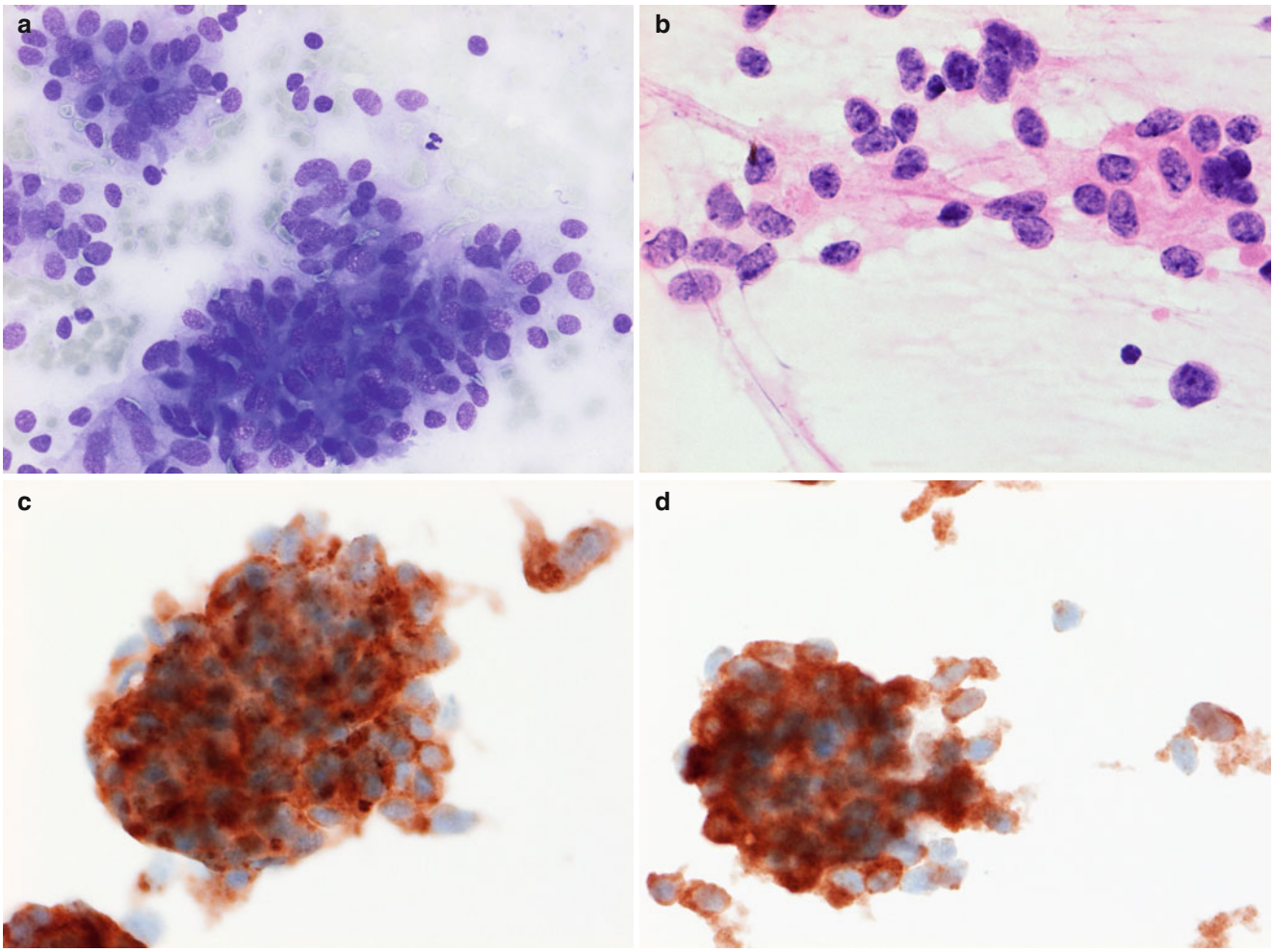


**Fig. 11.20** Pancreatic endocrine neoplasms (neuroendocrine islet cell tumor of the pancreas). (**a**) Different morphology in air-dried smears with a cellular aspirate of somewhat cohesive sheets of tumor cells showing oval to spindly nuclei and subtle pseudorosette formation (MGG). (**b**) Characteristic "salt and pepper" chromatin pattern in alcohol-fixed smears (HTX). (**c**) Immunostaining with tumor cells that expressed chromogranin A and synaptophysin (**d**) confirms diagnosis (ThinPrep)

- Occasionally cells with plasmacytoid morphology due to eccentrically placed nuclei
- Nuclei mostly uniform and round to oval with "salt and pepper" chromatin
- Scant to moderate cytoplasm

*Differential diagnosis and problems in diagnosis:*

- ACC
- SPNP
- Metastatic neuroendocrine carcinoma

### 11.9.1 Solid Pseudopapillary Neoplasm of the Pancreas

Solid pseudopapillary neoplasm of the pancreas (SPNP) is a low-grade epithelial neoplasm of uncertain histogenesis that occurs almost exclusively in young female patients. The prognosis is good, and most patients are cured with complete surgical resection. Local recurrence and metastatic spread occur in a minority of cases, but even in these cases, long-term survival has been documented [21].

The cytologic findings in FNAs of SPNP recapitulate the diagnostic features seen in histologic sections. Aspiration smears are frequently hypercellular showing pseudopapillary and papillary formation with fibrovascular or hyaline/myxoid cores and covered by one to several layers of cells (*see* Fig. 11.21). Tumor cells also may be arranged in scattered tight clusters, pseudorosettes, and as dispersed cells (*see* Fig. 11.22). Delicate vascular structures are seen lined by multiple layers of loosely cohesive tumor cells. When the structures are seen longitudinally in FNA preparations, they bear resemblance to a test-tube brush (*see* Fig. 11.23a). The tumor cells are low grade with round to oval uniform nuclei, bland nuclear chromatin, and scant cytoplasm. Nuclear grooves and inclusions are occasionally seen (*see* Fig. 11.23b). Intracytoplasmic or extracellular hyaline globules can also be seen (*see* Fig. 11.24). The primary differential is islet cell neoplasm. Pseudopapillary structures, nuclear grooving, and hyaline globules would not be expected in islet cell neoplasms. Radiographic evidence of cystic change in the tumor would also be in favor of SPNP (though cystic islet cell tumors do exist). SPNP are immunoreactive for CD10, vimentin, and B-catenin and nonreactive for cytokeratins and neuroendocrine markers.

*Cytologic features:*

- Usually hypercellular smears
- Pseudopapillary and papillary formation with fibrovascular or hyaline/myxoid cores covered by one to several layers of cells
- Tumor cells arranged in scattered tight clusters, pseudorosettes, and dispersed cells

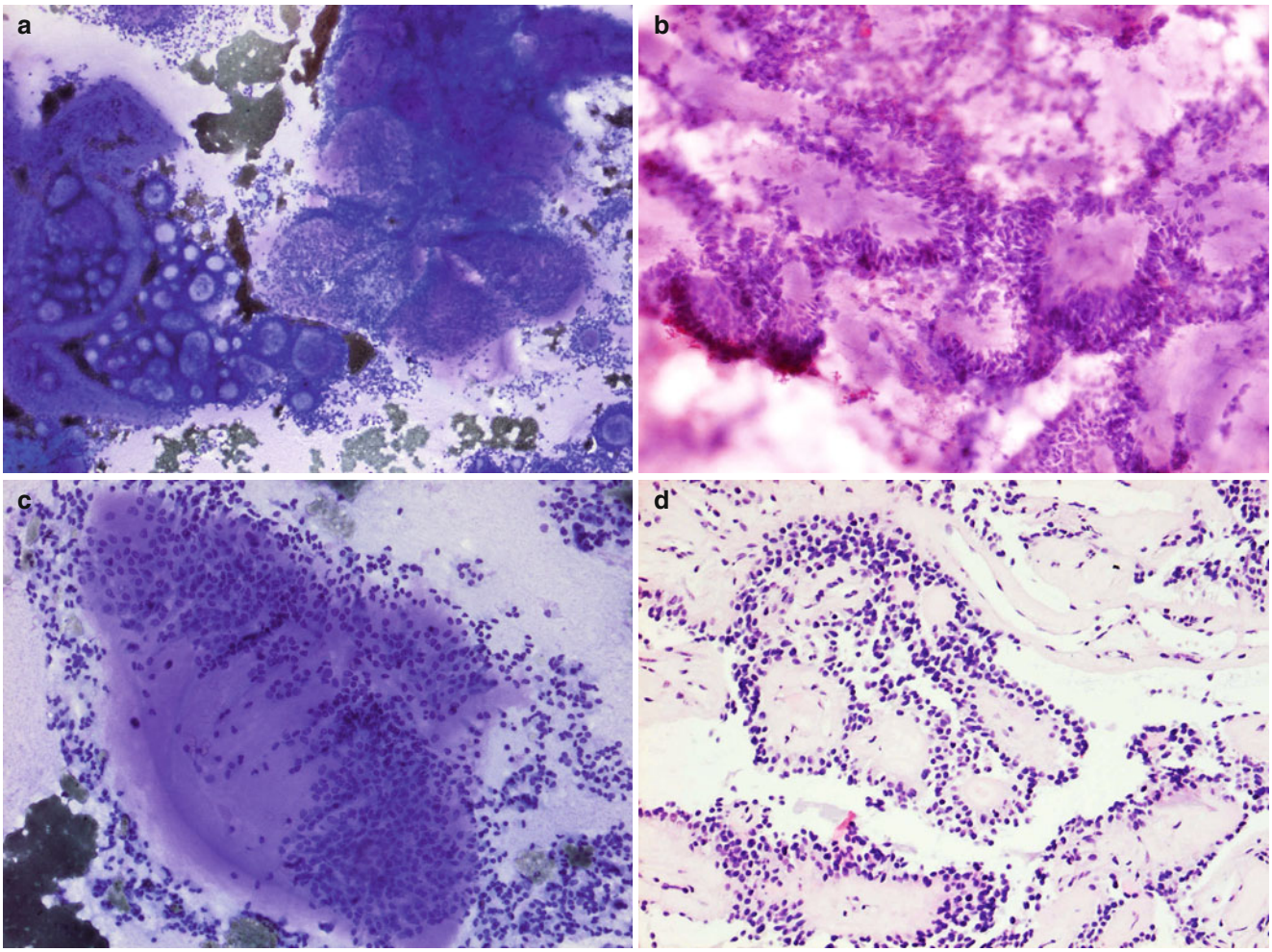


**Fig. 11.21** Solid pseudopapillary neoplasm of the pancreas. (**a**–**c**) Aspiration smears are frequently hypercellular showing pseudopapillary and papillary formation with fibrovascular or hyaline/myxoid cores and covered by one to several layers of cells (MGG and HTX). (**d**) Cell block prepared from aspirate showing similar microarchitecture (HTX)

- Delicate vascular structures lined by multiple layers of loosely cohesive tumor cells
- Monomorphic tumor cells with round to oval uniform nuclei, bland nuclear chromatin, and scant cytoplasm
- Intracytoplasmic or extracellular hyaline globules
- Occasional nuclear grooves and inclusions
- Foam cells and, occasionally, debris

*Differential diagnosis and problems in diagnosis:*

- ACC
- PEN

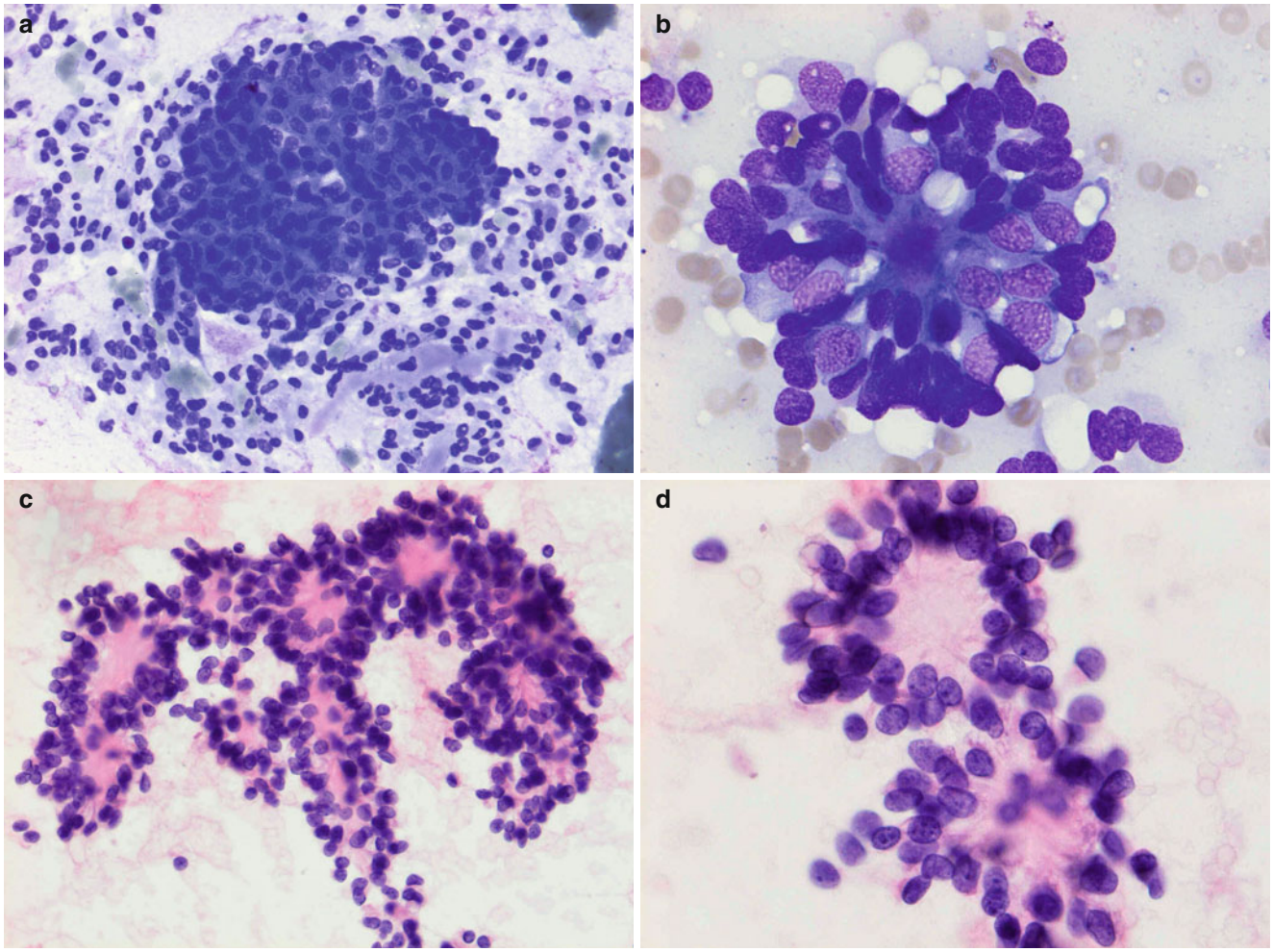


**Fig. 11.22** Solid pseudopapillary neoplasm of the pancreas. (**a**) Sheets of neoplastic cells show little pleomorphism with round to oval nuclei, finely textured chromatin and poorly preserved cytoplasm (MGG). (**b**–**d**) Rosette-like formations are occasionally visible in smears (MGG and HTX)

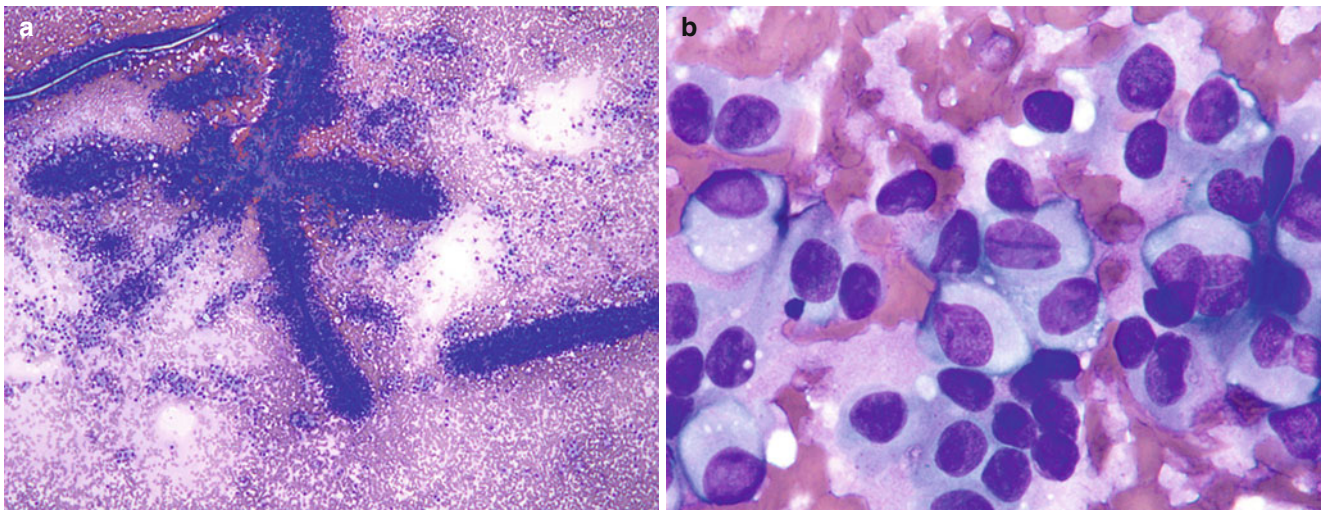


**Fig. 11.23** Solid pseudopapillary neoplasm of the pancreas. (**a**) Scanning power with vascular structures surrounded by multiple layers of tumor cells, reminiscent of a test-tube brush. (**b**) At higher magnification, low-grade tumor nuclei with nuclear grooves (DQ)

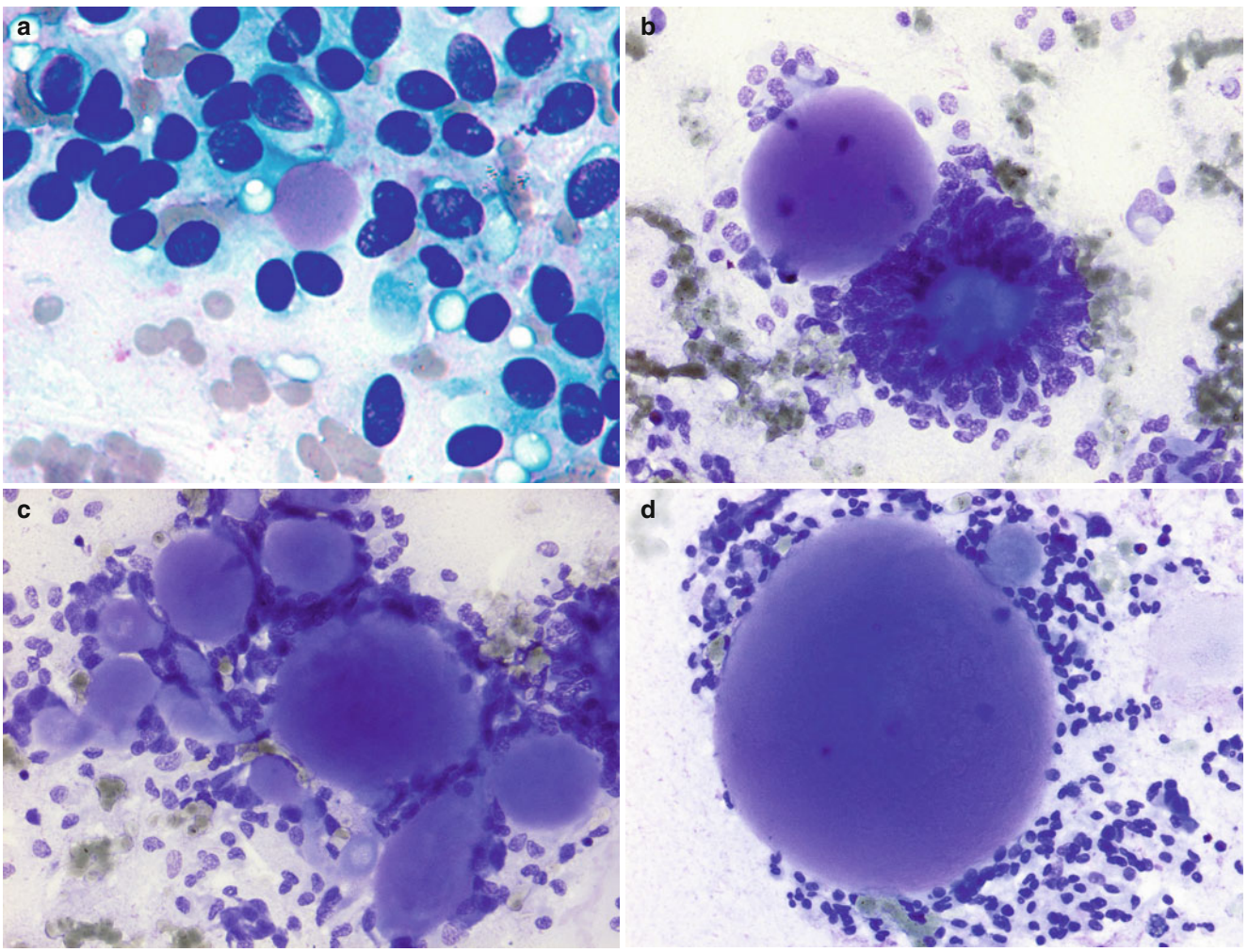


**Fig. 11.24** Solid pseudopapillary neoplasm of the pancreas. (**a**–**d**) Cellular smears with hyaline/myxoid stalks and globules lined or surrounded by neoplastic cells with round to oval nuclei are frequent findings in smears (DQ and MGG)

## 11.10 Mucin-Producing Cystic Neoplasia

Mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) are tumors that are distinct clinically and histologically but are considered together due to similar findings in cytology studies. Both tumors are thought to be uncommon, but increased usage of more sensitive cross-sectional imaging techniques has brought more cystic pancreatic lesions, and thus mucinous pancreatic neoplasia, to clinical attention in recent years. Both of these tumors are associated with invasive adenocarcinoma in a subset of cases.

The presence of thick, viscous, mucinous material is the first and often the only clue to the diagnosis of a cystic mucinous pancreatic tumor. Further classification of these entities is sometimes not possible, and a descriptive diagnostic line is often appropriate. Cytopathologists should not feel overly pressured to make specific diagnoses as the management is based upon several features including clinical findings, radiographic findings, chemical/molecular analyses of cyst fluid, and FNA findings. In FNA with findings consistent with a mucinous neoplasm, it is important to note whether or not cells with high-grade dysplasia are present.

*Cytologic features:*

- Usually hypocellular smears.
- Thick, viscous mucinous material.
- Neoplastic glandular cells often with cytoplasmic mucin.
- Morphology of the cells ranges from bland glandular cells to cytologically malignant, depending upon the degree of dysplasia.
- Finding papillary architecture would favor the diagnosis of IPMN over MCN.

*Differential diagnosis and problems in diagnosis:*

- Gastrointestinal contamination
- Pancreatic pseudocysts
- Parapancreatic cysts

## 11.11 Intraductal Papillary Mucinous Neoplasm

IPMN is a male-predominant tumor that usually occurs in the head of the pancreas and by definition involves the main pancreatic duct or a branch of the main duct (so-called side branch IPMN). The tumors produce mucin and usually grow within the duct in a papillary pattern. Mucin extrusion through the ampulla of Vater is an endoscopic finding virtually diagnostic of IPMN. Noninvasive IPMN is subtyped based upon the differentiation of the neoplastic glandular cell (gastric, intestinal, pancreatobiliary, or oncocytic) and classified according to the highest degree of dysplasia (low grade, intermediate grade, high grade) in well-sampled resected tumors. IPMNs associated with invasive adenocarcinoma are usually associated with high-grade dysplasia and tend to have a better prognosis than adenocarcinomas not associated with IPMNs (*see* Fig. 11.25). The histologic type of invasive adenocarcinoma may be colloid type or conventional.

Cytologic features of IPMN are abundant thick mucin with neoplastic glandular cells with cytoplasmic mucin. The tumor cells can be quite variable in appearance ranging from cytologically bland (*see* Figs. 11.26 and 11.27) where the primary differential would be gastrointestinal contamination to malignant if associated high-grade dysplasia or invasive adenocarcinoma is present. The cellularity of IPMN can also range from paucicellular (*see* Fig. 11.28) to overwhelming cellularity. Subtle cytologic features that have been reported to be helpful in predicting the histologic grade of cases of IPMN that lack obvious malignant cells include tight epithelial clusters with nuclear hyperchromasia and increased N/C ratios (indicative of at least moderate dysplasia). Admixed necrotic or inflammatory debris was a feature associated with high-grade dysplasia and invasive adenocarcinoma (*see* Fig. 11.29) [22].

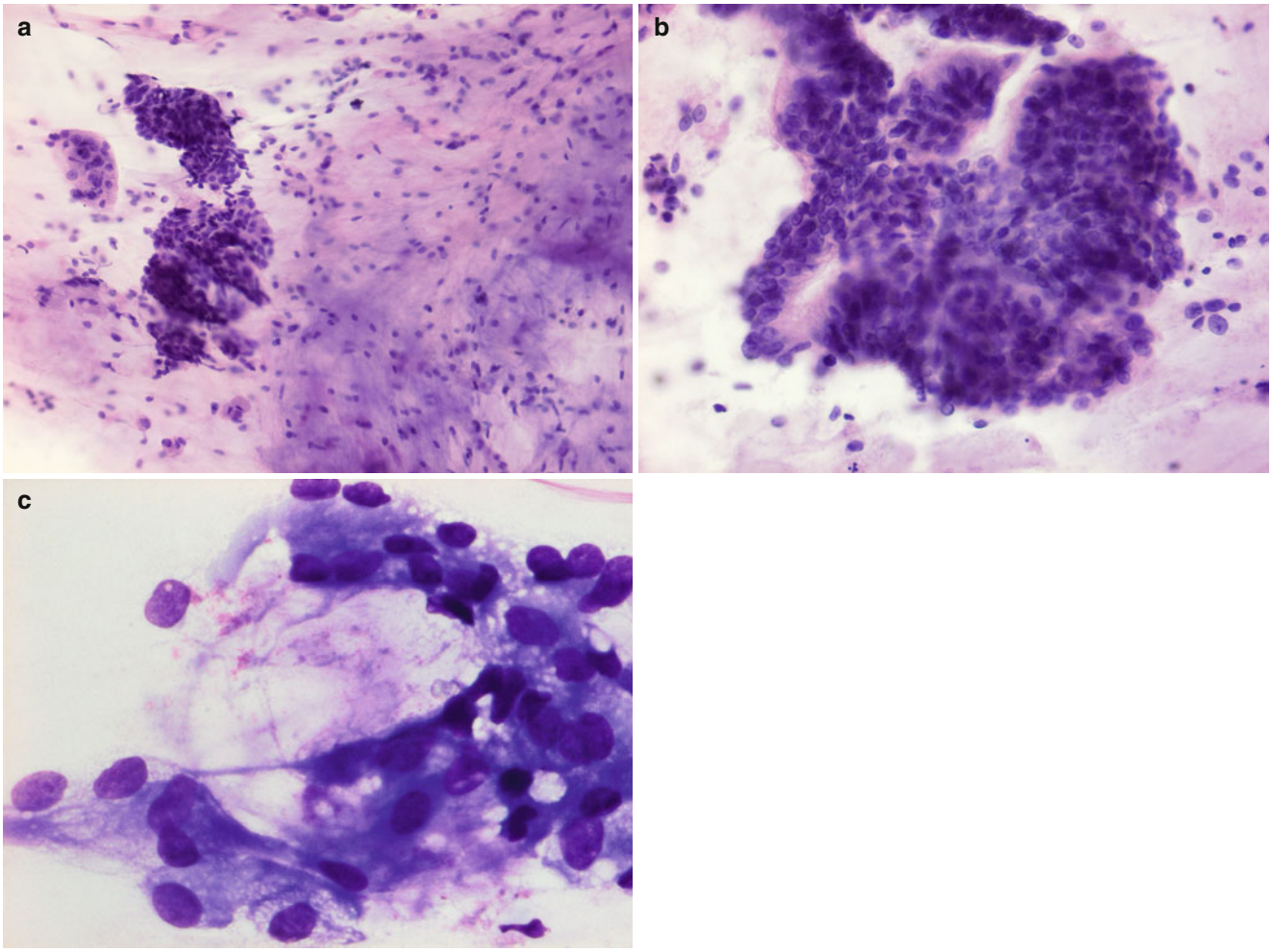


**Fig. 11.25** Mucinous neoplasm of the pancreas. (**a**–**c**) The neoplastic mucinous cells may be present in large numbers and show variable degrees of dysplasia. In these smears, high-grade dysplasia was indicative of invasive adenocarcinoma (HTX and MGG)

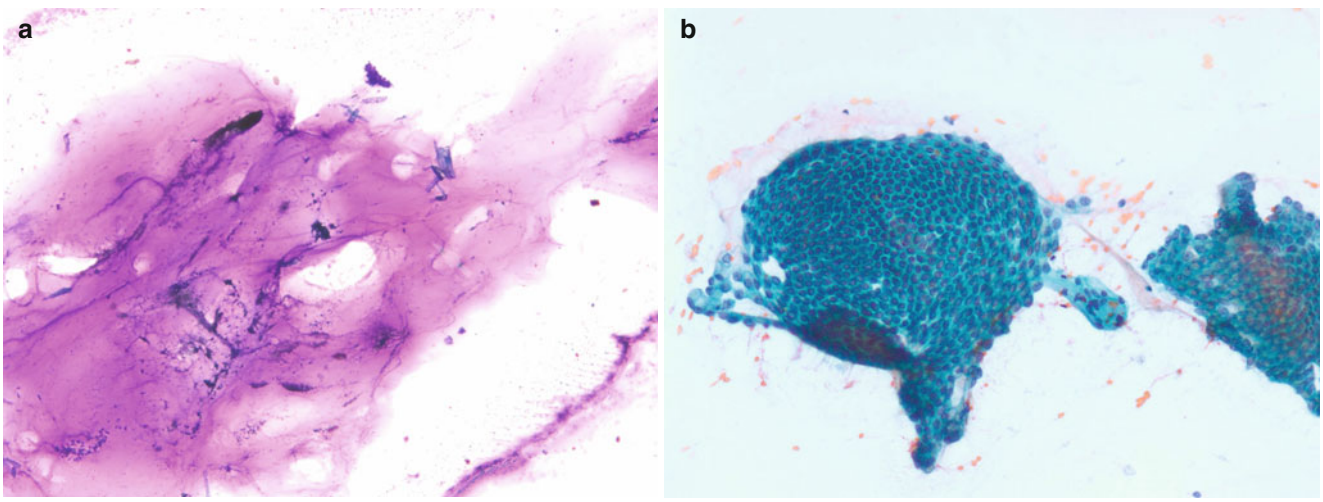


**Fig. 11.26** Mucinous neoplasm of the pancreas. (**a**) Thick mucin was grossly apparent to the aspirator and to the on-site cytopathologist and is readily seen in this direct smear (DQ). (**b**) Bland mucinous epithelium lacking high-grade dysplasia was also present (Pap stain). Surgical follow-up was IPMN with low-grade dysplasia

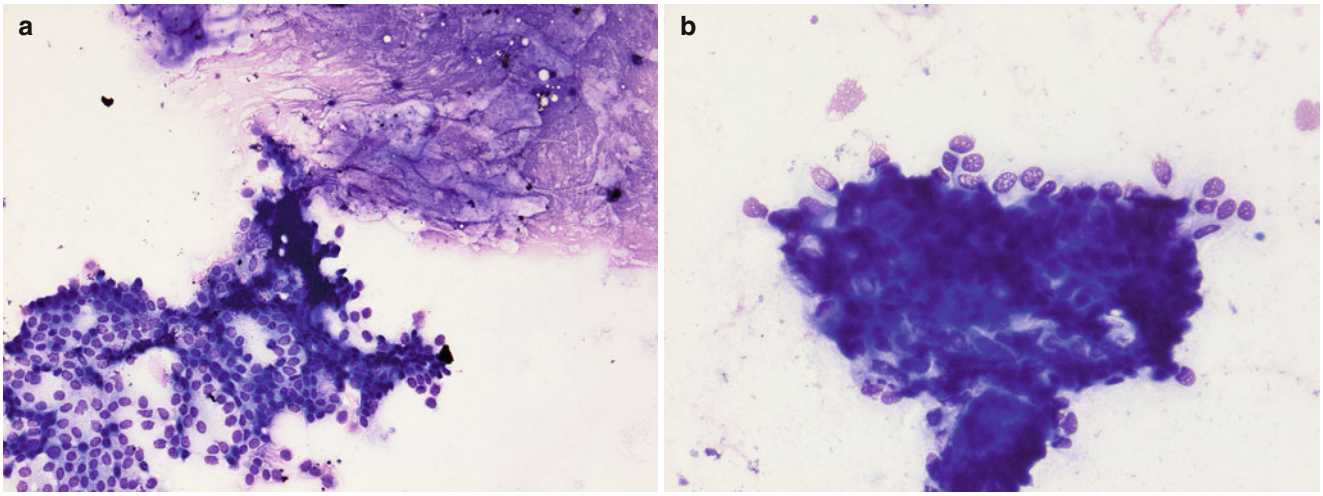


**Fig. 11.27** Mucinous neoplasm of the pancreas (IPMN with low-grade dysplasia). (**a**) Scanning power with smears containing sheets of epithelium with admixture extracellular mucin. (**b**) At moderate power, sheets of bland-looking epithelial cells with a few slightly atypical cells indicative of low-grade dysplasia (MGG)

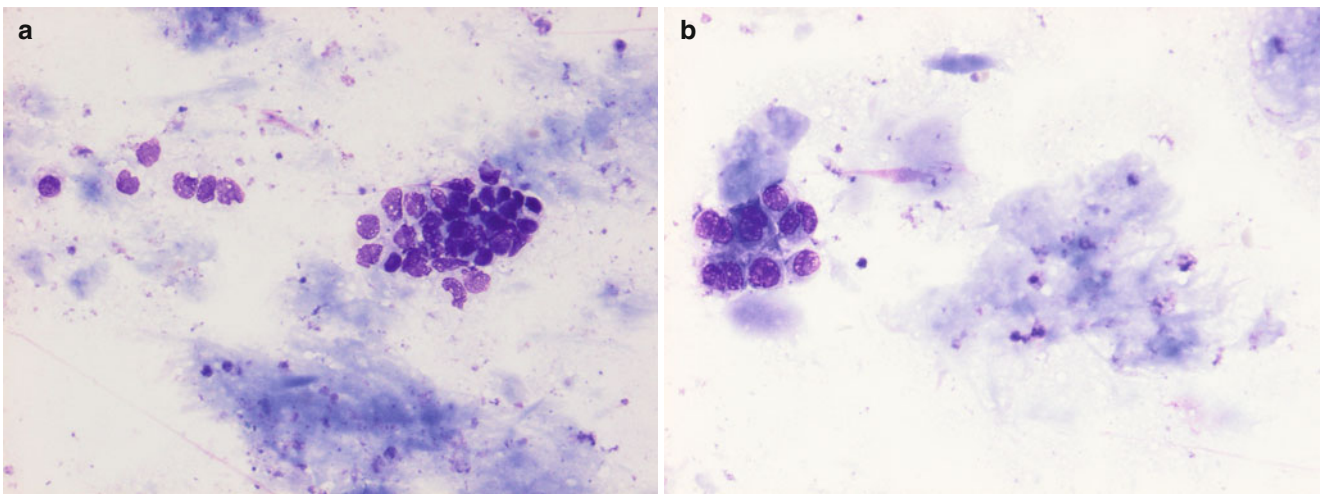


**Fig. 11.28** Mucinous neoplasm of the pancreas. (**a** and **b**) Paucicellular smears of IPMN: small epithelial sheets of poorly preserved cells with nuclear hyperchromasia and increased N/C ratios, indicative of at least moderate dysplasia (MGG). Surgical follow-up was IPMN of borderline malignancy grade

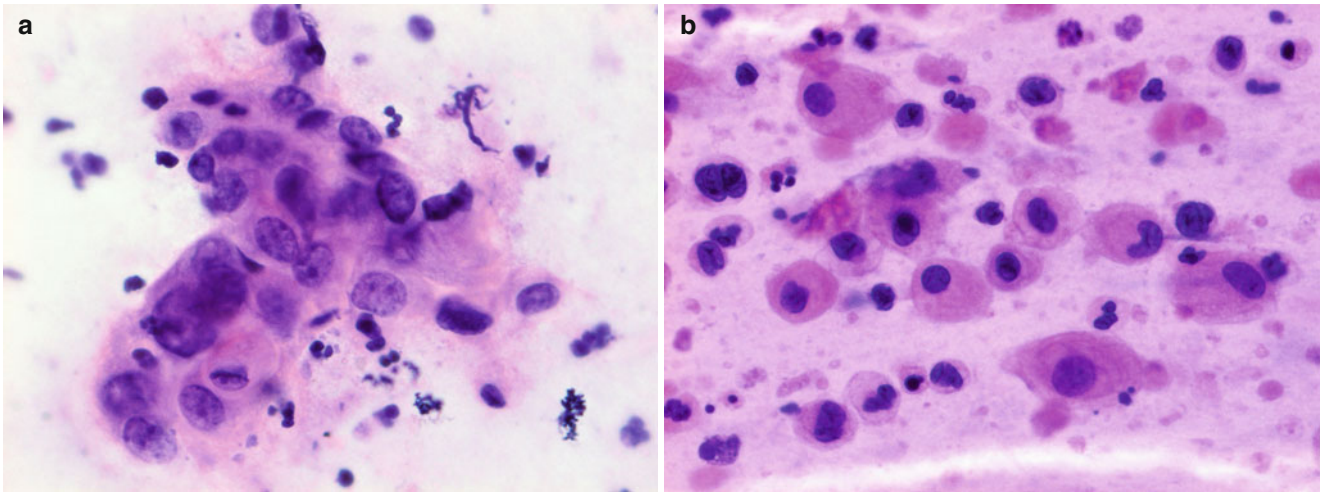


**Fig. 11.29** Mucinous neoplasm of the pancreas. Epithelial clusters with high-grade dysplasia (**a**) and admixed necrotic or inflammatory debris (**b**) are cytologic features associated with an invasive adenocarcinoma (HTX)

Differentiating IPMN from MCN may not be possible on FNA and usually would not be imperative for the cytopathologist to make this distinction. Finding papillary architecture would favor the diagnosis of IPMN over MCN. The much more important distinction is overcalling contaminating gastrointestinal mucin and glandular cells as IPMN or MCN. Duodenal mucosa can be recognized by the presence of Brunner's glands and gastric mucosa by tubular-shaped gastric pits. In cases with abundant contaminating gastrointestinal mucosa, mucin should be interpreted carefully as it is much more likely to be a contaminant rather than part of the targeted pancreatic lesion.

## 11.12 Mucinous Cystic Neoplasms

MCN is a cystic pancreatic neoplasm that does not communicate with the main pancreatic duct and occurs almost exclusively in women. MCNs are usually located in the body or tail of the pancreas and only rarely involve the head of the pancreas. Thus, the clinical and radiographic features are distinct from IPMN. Histologically, unilocular or multilocular cysts lined by mucinous columnar epithelium are characteristic. Associated ovarian-like stroma is another defining characteristic. Similar to IPMN, noninvasive MCN is histologically categorized into those with low-grade dysplasia (*see* Fig. 11.30), intermediate-grade dysplasia, and high-grade dysplasia depending upon the architectural and cytologic atypia present. Approximately one third of MCNs have an associated invasive adenocarcinoma (*see* Fig. 11.31).

As with IPMN, the most consistent finding is abnormally thick mucinous material. The neoplastic mucinous cells may be present in large quantities, and the morphology of the cells ranges from bland sheets of mucinous glandular cells to cytologically malignant depending upon the degree of dysplasia. Ovarian-type stroma is not seen in cytologic studies.

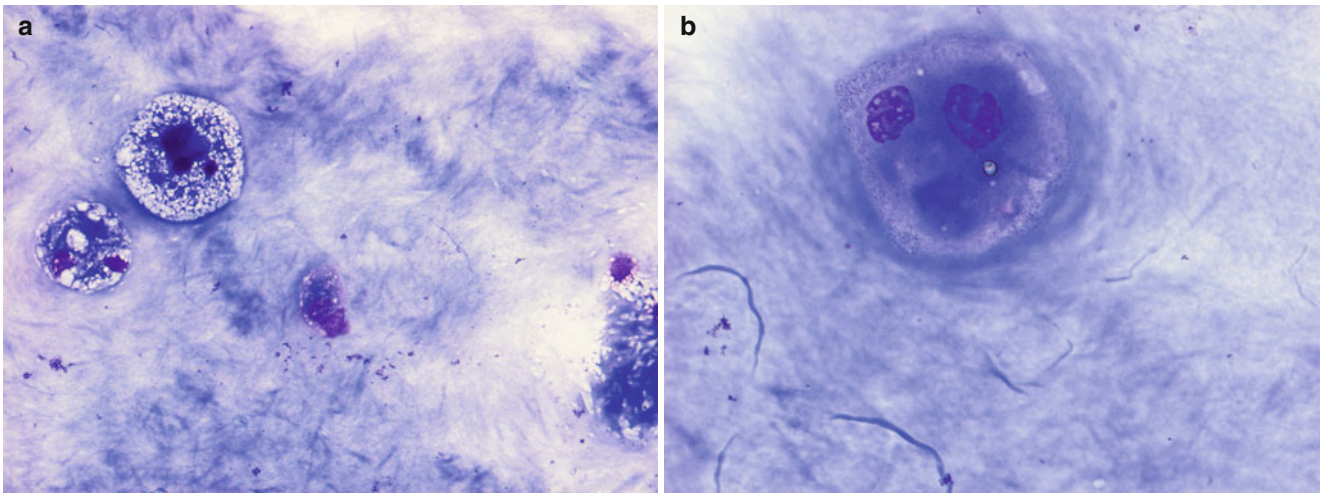


**Fig. 11.30** Mucinous neoplasm of the pancreas. (**a** and **b**) Paucicellular smears of MCN in the pancreatic tail with abundant extracellular and intracytoplasmic mucin and slight dysplasia (MGG). Surgical follow-up was MCN with low-grade dysplasia

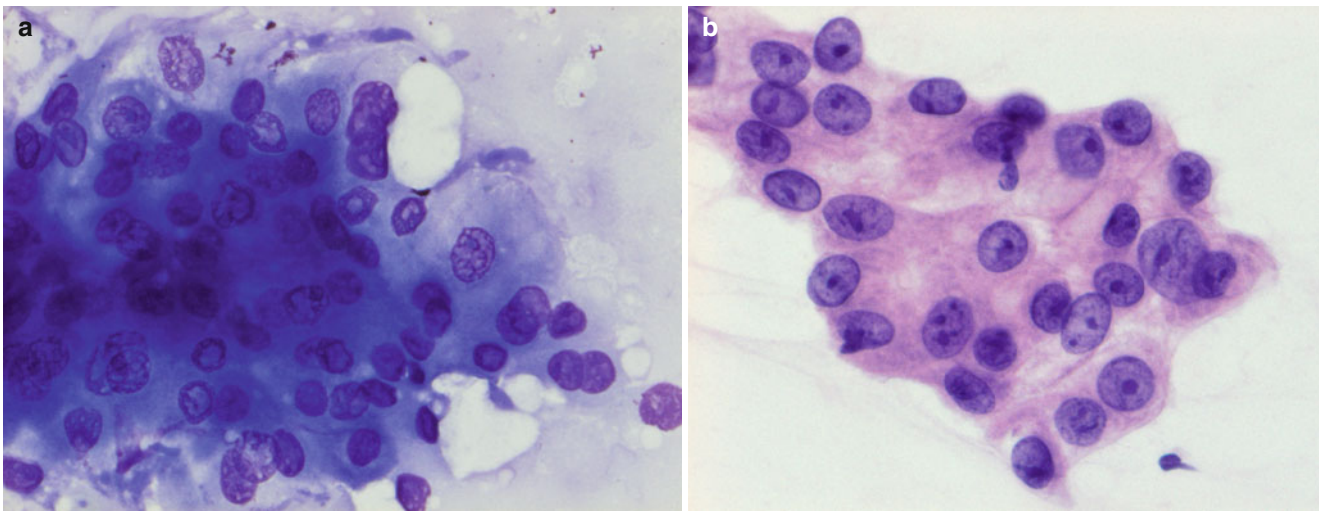


**Fig. 11.31** Mucinous neoplasm of the pancreas. Smears from MCN showing intermediate-grade (**a**) and high-grade dysplasia (**b**; MGG and HTX). Although FNA smears were reported as being MCN of borderline malignancy grade, surgical follow-up was MCN associated with invasive adenocarcinoma

## 11.13 Serous Cystadenoma

Serous cystadenoma of the pancreas (SCP) is a benign neoplasm composed of low-grade cuboidal epithelial cells that usually form microcysts containing serous fluid. If recognized on imaging studies as SCP, patients may be safely triaged for conservative management. In cases with macrocystic architecture, mucinous tumor would enter into the radiographic differential, and solid variants would raise the question of other solid pancreatic tumors. Nontypical radiographic appearance would likely trigger cytologic study for characterization; thus, serous cystadenomas that are referred for FNA represent a selected subset of cases.

Cytologic studies are typically paucicellular and lack thick mucinous material (*see* Fig. 11.32). The tumor cells are bland with centrally placed nuclei and are usually arranged in flat sheets, reminiscent of benign mesothelial cells. Occasionally, papillary arrangements are seen, and this can lead to diagnostic confusion with IPMN, particularly if the radiographic differential includes mucinous neoplasms. Similarly, contaminating gastrointestinal mucin can lead to an overdiagnosis of a mucinous neoplasm. Cytologic studies devoted to SCP are infrequent, but one retrospective study reported that only 25 % of cases were diagnosed as consistent with SCN [23]. The same series reported that 21 % of cases were misclassified as consistent with a mucinous neoplasm and 11 % were reported as suspicious for malignancy, reflecting the difficulty of establishing a definitive diagnosis in cytologic material.

*Cytologic features:*

- Usually sparse cellularity, often acellular
- Clean or bloody background
- Ovoid to cuboidal, bland tumor cells
- Uniform round to oval nuclei with fine chromatin
- Clear or somewhat granular, often finely vacuolated cytoplasm
- Extracellular or intracytoplasmic mucin absent

*Differential diagnosis and problems in diagnosis:*

- MCN
- Pancreatic pseudocysts
- Normal benign pancreatic ductal and acinar cells

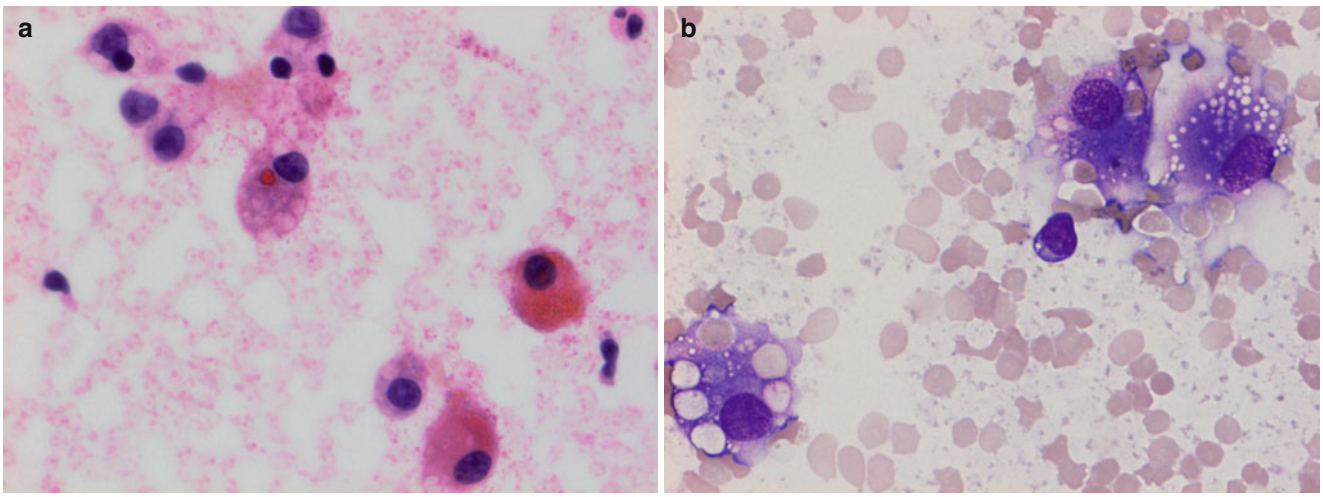


**Fig. 11.32** Serous cystadenoma. (**a** and **b**) Paucicellular smears containing bland tumor cells reminiscent of benign mesothelial cells. There is no thick mucinous material (HTX and MGG)

## 11.14 Secondary Tumors of the Pancreas

Metastatic tumors or systemic tumors involving the pancreas can mimic a primary neoplastic process, and such cases may be referred for FNA biopsy. Proper characterization is important to avoid an unnecessary surgical procedure. Pancreatic FNA containing tumor cells with features unusual for a primary pancreatic tumor, especially with features of the tumors mentioned above, should prompt consideration of secondary disease. In two cytologic series that reported nonhematopoietic metastatic disease to the pancreas, renal cell carcinoma was the most common tumor type diagnosed [24, 25]. Clear cell carcinomas of the kidney frequently show characteristic microscopic features, which are distinguishable from primary pancreatic neoplasms (*see* Fig. 11.33). Small cell carcinoma and melanoma have also been frequently reported in studies on metastatic disease of the pancreas [24–26]. As previously mentioned in this chapter, metastatic small cell carcinoma in the pancreas is morphologically indistinguishable from very rare cases of small cell carcinoma primary in the pancreas (*see* Fig. 11.34); even other neoplasms metastasizing to the pancreas may be morphologically and immunohistochemically indistinguishable from pancreas primaries (*see* Fig. 11.35). In such cases, clinical information regarding primary location outside of the pancreas is crucial in rendering a correct diagnosis. In many cases reported in the literature, the radiographic impression was that of primary pancreatic neoplasia. Cell block preparation, immunohistochemical work-up (*see* Fig. 11.36), and communication with treating clinicians (who may suddenly recall the remote skin excision when the question of melanoma is raised) (*see* Fig. 11.37) are critical for accurate diagnosis.

Lymphoma can also involve the pancreas (*see* Fig. 11.38). Most commonly, the tumors are high-grade B-cell lymphomas (*see* Fig. 11.39). The cytology of pancreatic lymphoma can be confused with acinar and neuroendocrine tumors,

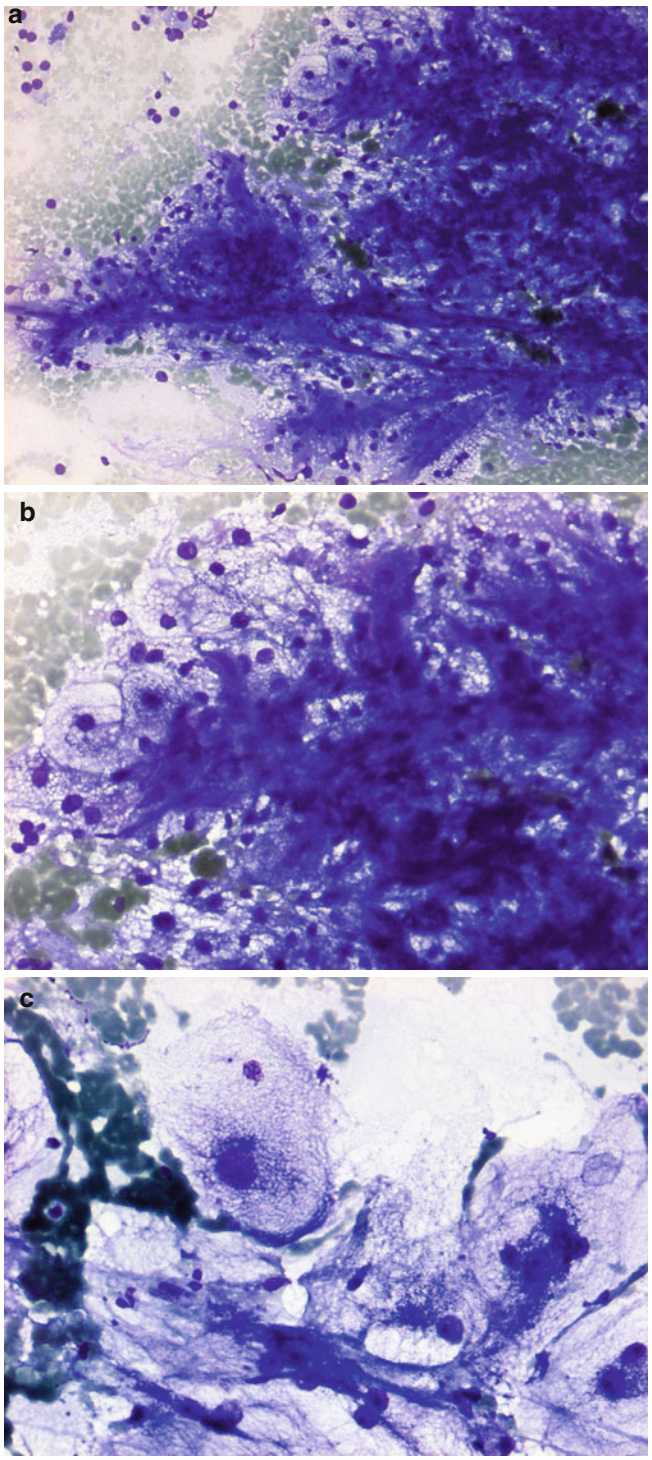


**Fig. 11.33** Secondary tumors of the pancreas. (**a**–**c**) Clear cell carcinomas of the kidney metastasizing to the pancreas frequently show the characteristic microscopic features, which distinguish it from primary pancreatic neoplasm (MGG)

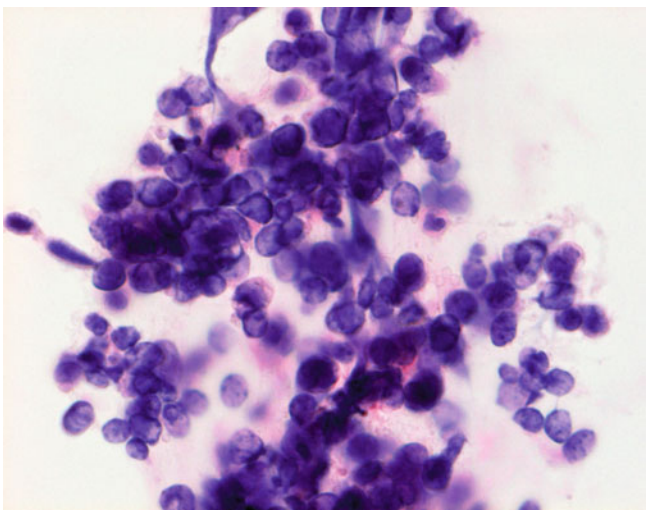

**Fig. 11.34** Secondary tumors of the pancreas. Metastatic small cell carcinoma of the lung is morphologically indistinguishable from the very rare cases of small cell carcinoma primary in the pancreas (HTX)

both of which can have a predominant population of dyscohesive cells [27]. Careful scrutiny of the neoplastic population should permit classification as a lymphoid neoplasm. Triage of material for flow cytometric analysis, as well as liquid-based and cell block preparation, should facilitate accurate diagnosis with cytologic material (*see* Fig. 11.40).

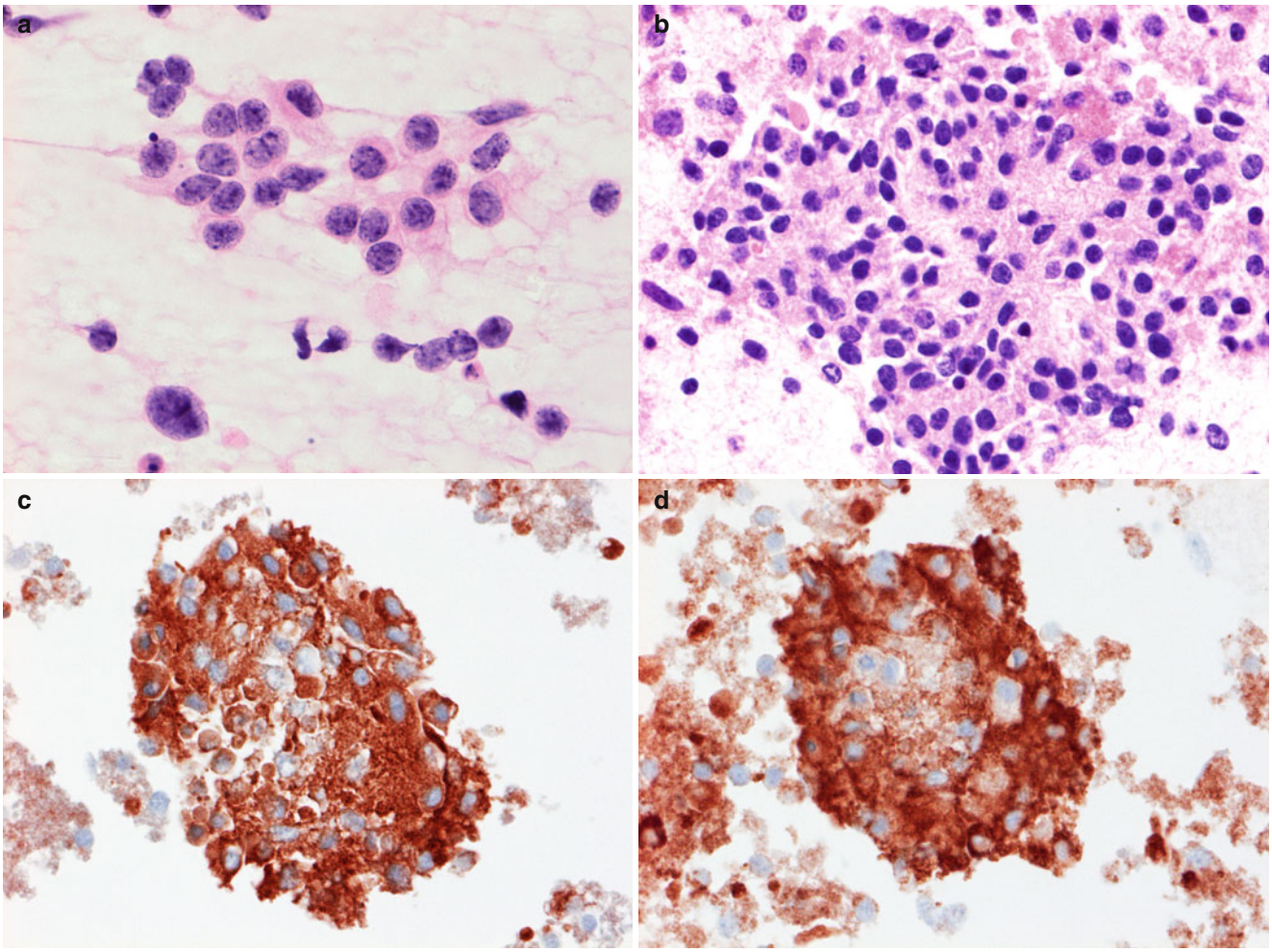


**Fig. 11.35** Secondary tumors of the pancreas. (**a**) FNA smears from lung carcinoid metastasizing to the pancreas (HTX). Smears complemented by a cell block preparation (**b**; HTX) and immunostains with synaptophysin (**c**) and chromogranin A (**d**) are indistinguishable from PEN primary in the pancreas. Without proper clinical information, correct diagnosis is not possible

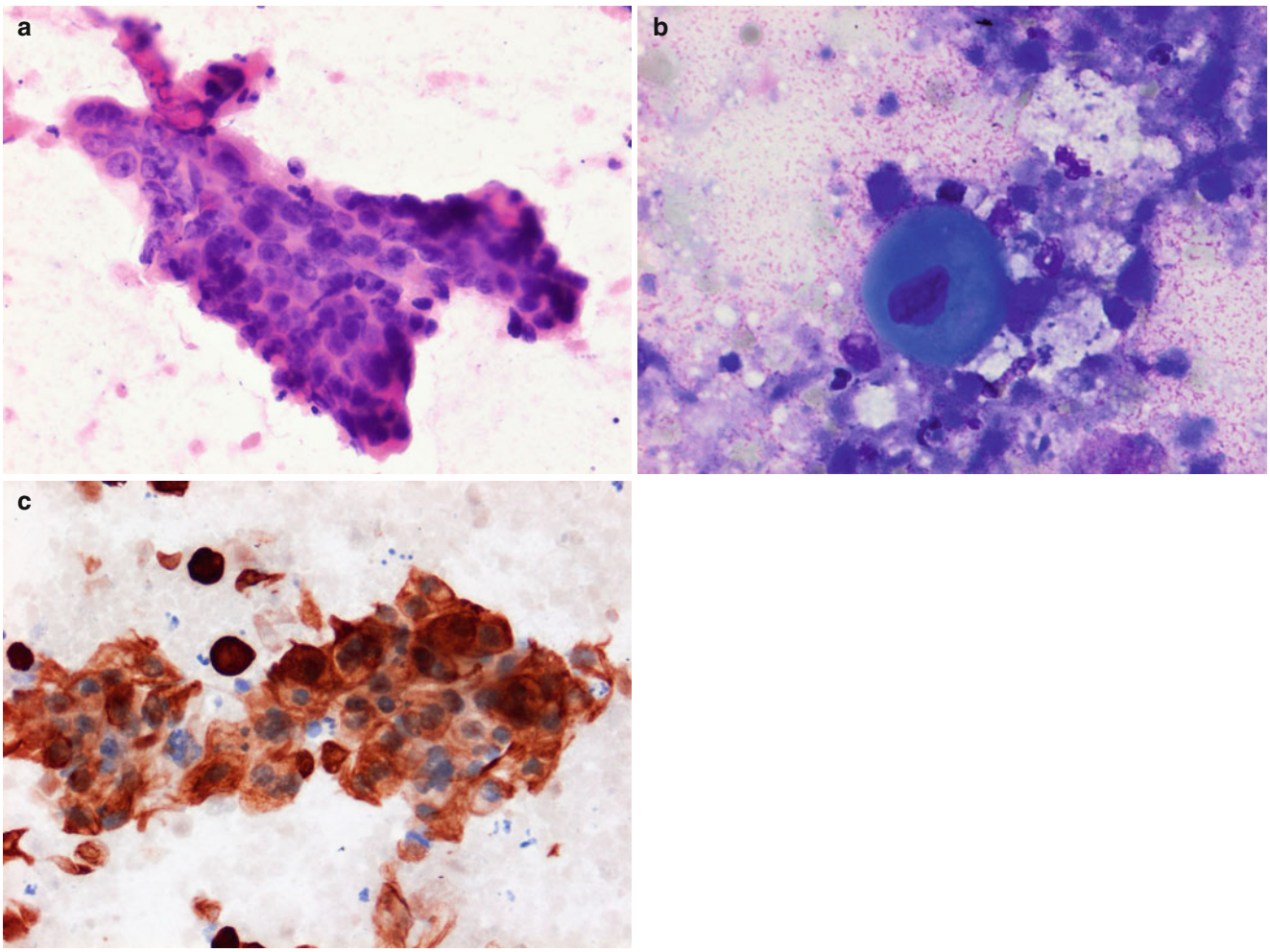


**Fig. 11.36** Secondary tumors of the pancreas. (**a**), FNA smears from metastatic squamous carcinoma of the esophagus show clusters of tumor cells with squamous differentiation (HTX) and obvious keratinization (**b**; MGG). (**c**) Note immunoreactivity with keratin CK5, indicative of squamous epithelium (direct smears)

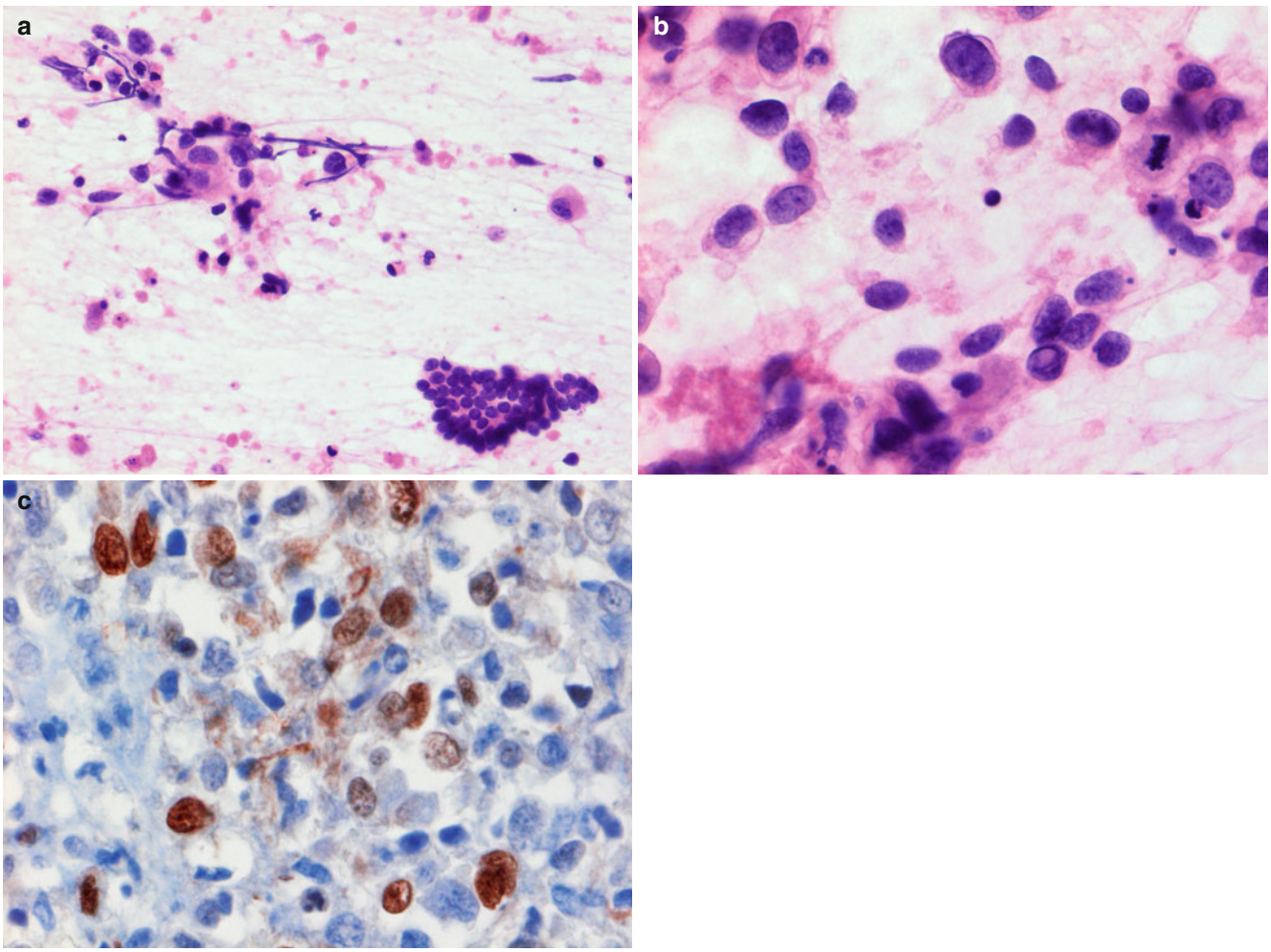


**Fig. 11.37** Secondary tumors of the pancreas. (**a** and **b**), FNA smears of malignant melanoma metastasizing to the pancreas (HTX). Without knowledge of clinical history and ancillary immunostains (**c**) with melanoma markers (cell block, S-100), correct diagnosis may be difficult to render from routinely stained smears

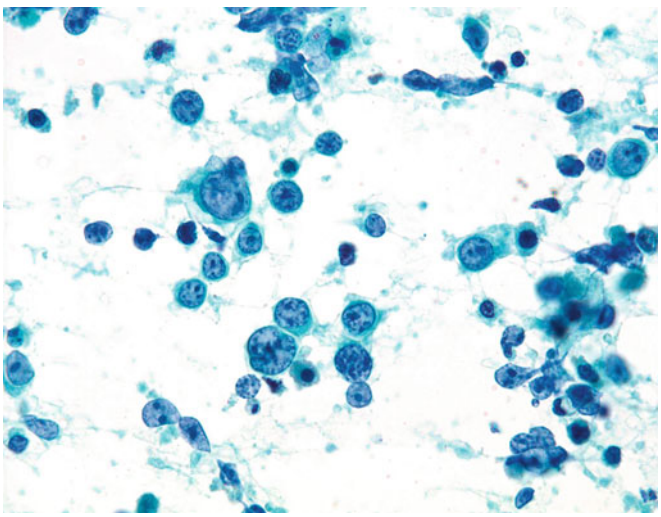

**Fig. 11.38** Lymphoma involving the pancreas. Sheets of dissociated large tumor cells with scant cytoplasm resembling immunoblasts are present. The cytomorphology is consistent with a high-grade lymphoma, and ancillary studies confirmed the diagnosis of diffuse large B-cell lymphoma (Pap stain) (*Image courtesy of* Dr. Syed Ali, Johns Hopkins Hospital, Baltimore, MD, USA)

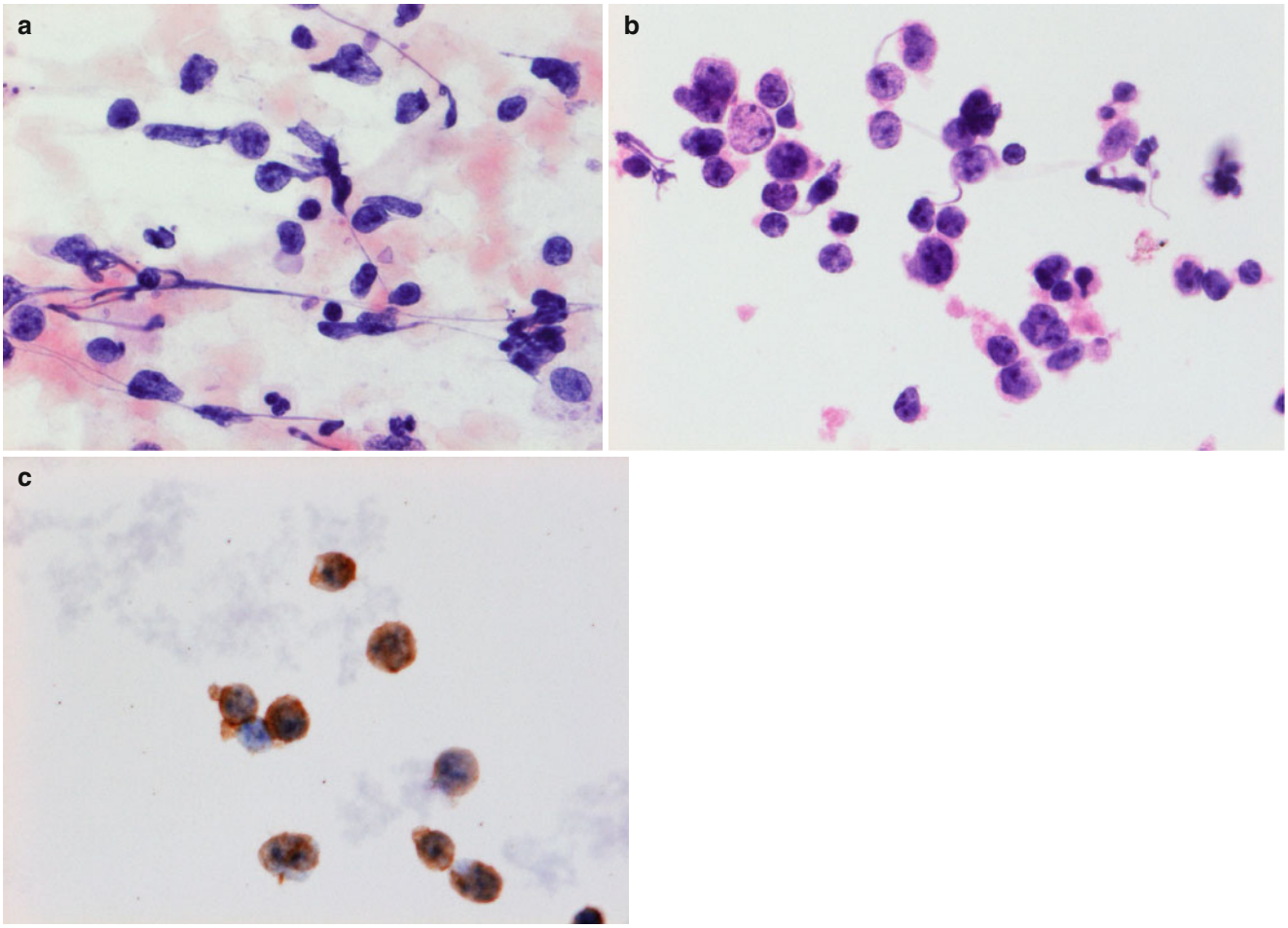


**Fig. 11.39** Lymphoma involving the pancreas. (**a** and **b**) Large-cell diffuse B-cell lymphoma: scattered large lymphoid cells (HTX and ThinPrep). (**c**) Lymphoid cells stain positive with CD20 (ThinPrep)

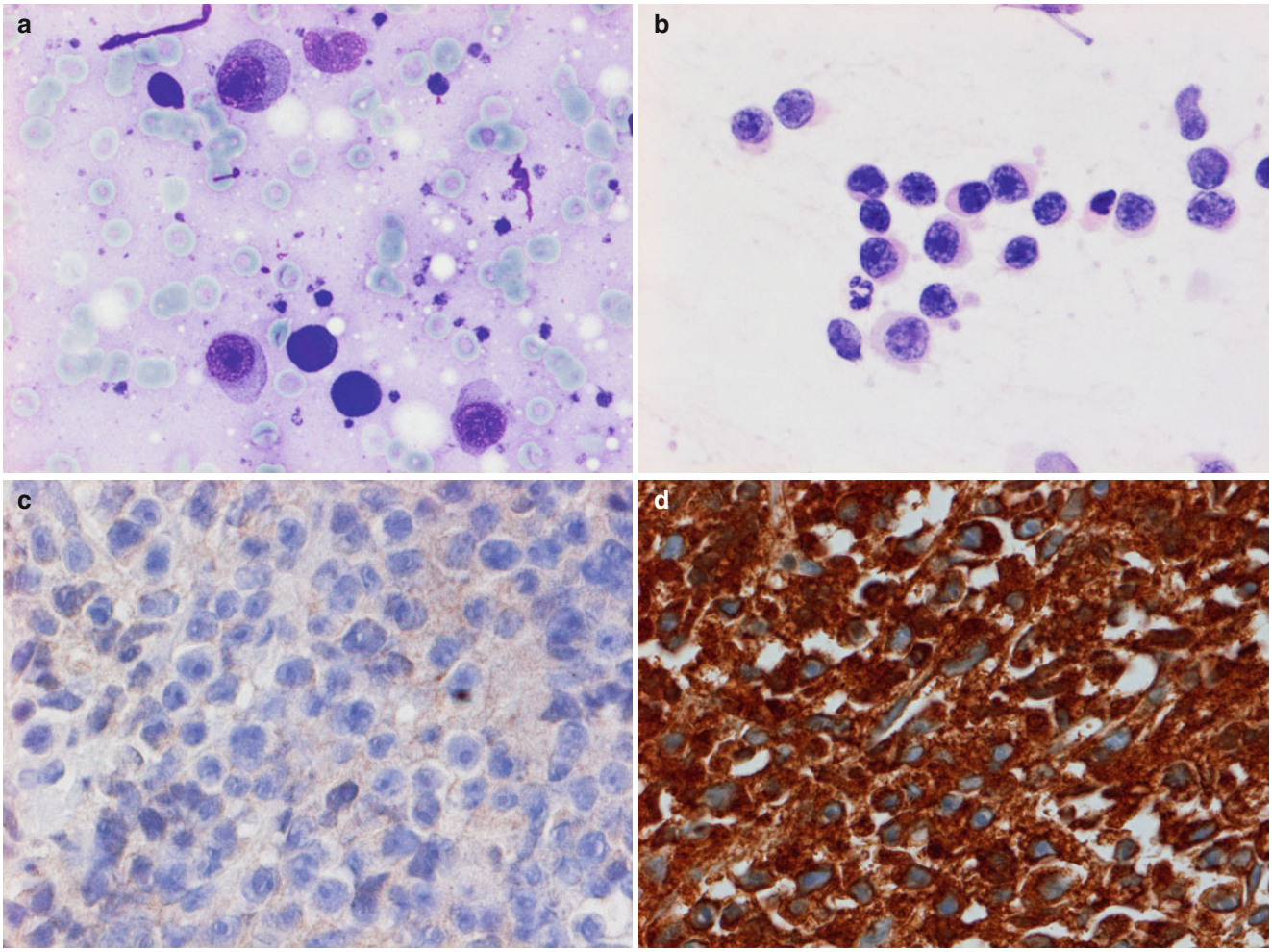


**Fig. 11.40** Lymphoma involving the pancreas. (**a** and **b**) FNA smears from plasmablastic NHL involving the pancreas, typical lymphoplasmacytoid morphology of lymphoid cells (MGG and HTX). (**c** and **d**) Light-chain lambda negativity and kappa positivity indicative of monoclonality (cell block)

## References


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