Mucinous Cystic Neoplasia

16

Mucinous cystic neoplasm is a cystic, epithelial, mucin-producing neoplasm with associated ovarian-type stroma. In contrast to intraductal papillary neoplasms (see Chap. 17), mucinous cystic neoplasms do not communicate with the pancreatic ductal system. Mucinous cystic neoplasms (MCNs) are solitary and may be unilocular or multilocular. The epithelial lining is composed of tall, columnar, mucin-producing epithelium, which may be flat or papillary depending on the degree of dysplasia. MCNs are generally considered to progress from low-grade dysplasia through high-grade dysplasia to invasive carcinoma and are one of the three main precursors of pancreatic invasive carcinoma, the other two being PanIN (see Chap. 8) and intraductal papillary neoplasm (see Chap. 17).

16.1 WHO Classification

Mucinous cystic neoplasms are included in 'benign epithelial tumors and precursors' in the 2019 WHO classification of tumors of the pancreas, [1] and are classified into the following three categories:

1. Mucinous cystic neoplasm with low-grade dysplasia.
2. Mucinous cystic neoplasm with high-grade dysplasia.
3. Mucinous cystic neoplasm with associated invasive carcinoma.

16.2 Terminology

Mucinous cystic neoplasm is the currently recognized terminology for this tumor, which has been referred to previously as mucinous cystadenoma and mucinous cystadenocarcinoma (non-invasive or invasive).

16.3 Epidemiology

MCN is relatively uncommon and accounts for approximately 10% of resected pancreatic cystic lesions. They occur almost exclusively in women (female to male ratio of 20:1) with a mean age of diagnosis at 45–50 years (range 16–95 years). Patients with associated invasive carcinoma tend to be 5–10 years older than those with non-invasive MCNs. Men appear to have a higher rate of high-grade MCN and MCN with associated invasive adenocarcinoma [2].

16.4 Clinical Features

Small MCNs are usually asymptomatic and found incidentally on imaging during clinical evaluation for other conditions. Larger MCNs may

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produce symptoms including abdominal pain, nausea and vomiting, anorexia, and weight loss. Patients may present with a palpable abdominal mass. In contrast to intraductal papillary neoplasms (see Chap. 17), there is no related history of pancreatitis. There are case reports describing rapid growth of MCNs during pregnancy, which may be related to the hormone sensitivity of the MCN ovarian-type stroma.

16.4.1 Associations

There are no well-established environmental etiological factors, and no associations with any genetic syndromes.

16.4.2 Imaging

Computed tomography (CT), magnetic resonance imaging (MRI), or endoscopic ultrasound (EUS) will reveal a solitary, sharply demarcated, thick-walled cyst that may be unilocular or multilocular. Often there is one large cyst, within which thin-walled, daughter cysts can be seen. Calcification may be present in the wall as a rim of peripheral 'eggshell' calcification in 20% of cases. There is no communication with the duct system. Features suggestive of malignancy include large size, irregular thickening of the cyst wall, mural nodules, and/or papillary excrescences projecting into the cyst lumen.

16.5 Macroscopy

The vast majority of MCNs (>98%) occur in the body or tail of the pancreas. They form a solitary large cystic mass, mean size 6–10 cm (range 2–35 cm), with smooth outer surface (Fig. 16.1) and thick fibrous capsule (Fig. 16.2), which may be calcified (Fig. 16.3). Opening may reveal a single cyst cavity, a multilocular cyst (with cysts ranging from a few millimeters to several centimeters in diameter), or one large cyst cavity with smaller thin-walled daughter cysts arising from the inner wall (Fig. 16.4). The cysts contain thick

Fig. 16.1 Mucinous cystic neoplasm: this large tumor in the tail of the pancreas has a smooth outer surface and abuts the spleen

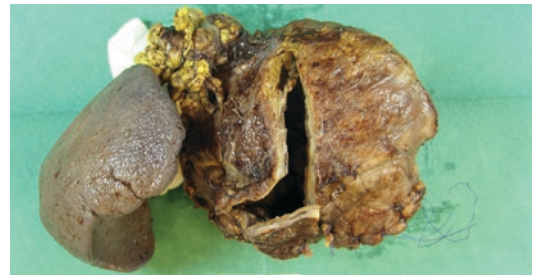

Fig. 16.2 Mucinous cystic neoplasm: the incised wall is thick and fibrotic

Fig. 16.3 Mucinous cystic neoplasm: this neoplasm has eggshell calcification throughout the wall

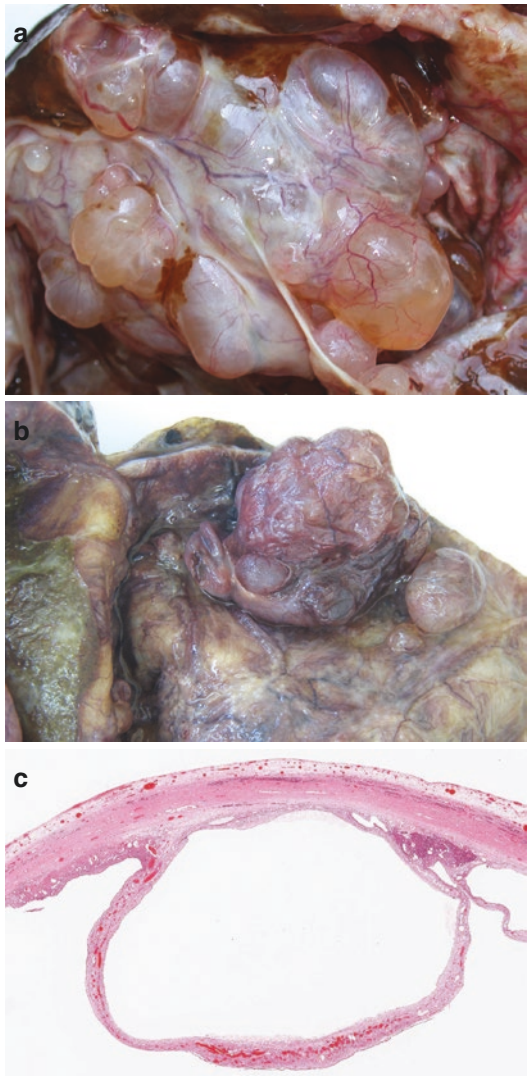

Fig. 16.4 Daughter cysts: there are smaller daughter cysts within this mucinous cystic neoplasm (**a**), which can be seen protruding from the smooth inner lining of the main cyst wall (**b**). These daughter cysts can be multilocular or unilocular (**c**)

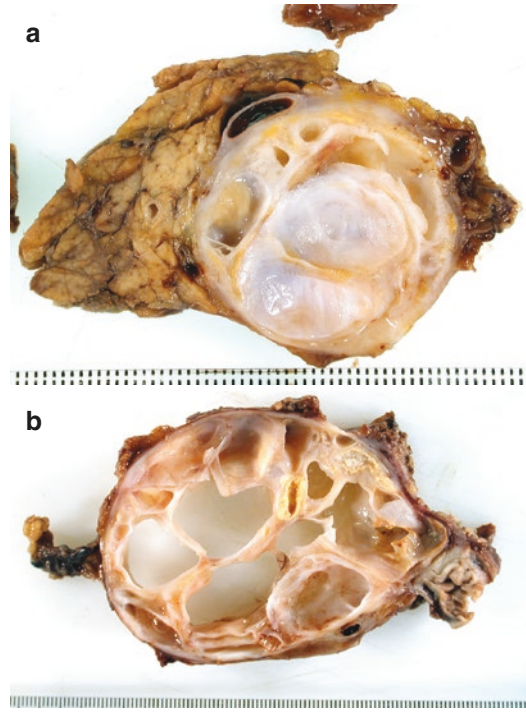

Fig. 16.5 Mucinous cystic neoplasm: cross-sections of these two tumors (**a**, **b**) show multilocular cysts with a glistening inner lining

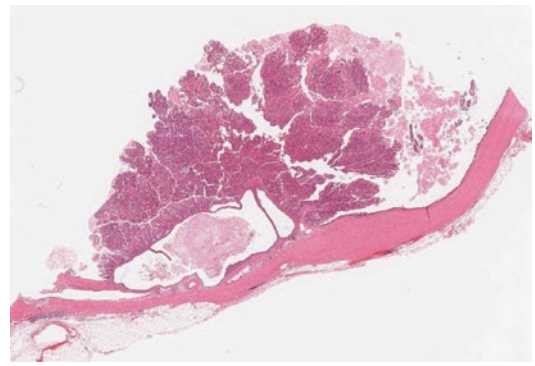

Fig. 16.6 Papillary projection: this single papillary projection, in an otherwise smooth-lined mucinous cystic neoplasm, showed low-grade and high-grade dysplasia

viscous mucin but may also contain hemorrhagic, watery fluid and necrotic debris. The inner surface of the cyst(s) is usually smooth and glistening (Fig. 16.5). When papillary projections are present, they should always be sampled because they usually represent high-grade foci (Fig. 16.6). MCNs do not communicate with the duct system, but, rarely, there may be erosion and fistula formation with the pancreatic ductal system.

MCNs with associated invasive carcinoma are usually large, multilocular cystic lesions with papillary projections, mural nodules (Fig. 16.7), or grossly visible invasion of the pancreas and adjacent structures. However, the invasive carcinoma may be very small and only detected microscopically. Lymph node metastases are rare.

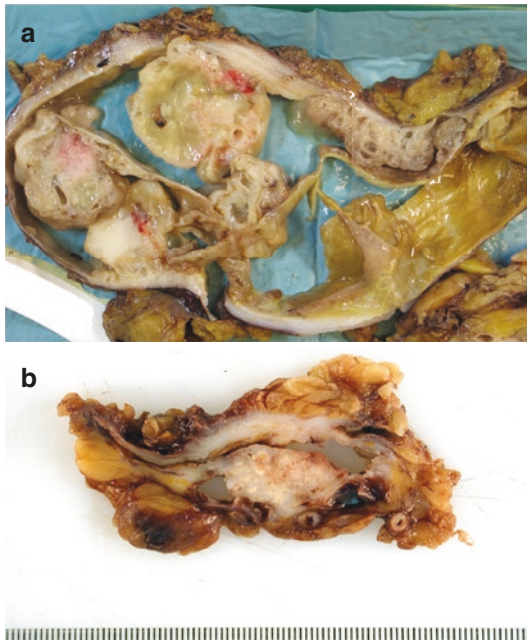

Fig. 16.7 Mural nodules: mural nodules in a mucinous cystic neoplasm should always be sampled. In both of these examples, a discrete focus of invasive carcinoma can be seen macroscopically, *lower left* (**a**) and *bottom center* (**b**)

16.5.1 Sampling

MCNs should always be sampled thoroughly to establish the diagnosis and the grade of dysplasia and to exclude invasive carcinoma. In larger lesions, much of the epithelium may be denuded (see Chap. 14, Sect. 14.2) and the capsule may be so sclerotic (Fig. 16.8) that it may be difficult to find the ovarian-type stroma to confirm the diagnosis. Papillary areas and solid areas (Figs. 16.6 and 16.7) must always be sampled because these are most likely to show high-grade dysplasia or invasive carcinoma. However, high-grade dysplasia and invasive carcinoma may be focal and not apparent macroscopically. In the absence of macroscopic invasive carcinoma, embedding the entire lesion may be considered, particularly if initial microscopic examination reveals high-grade dysplasia but no invasion.

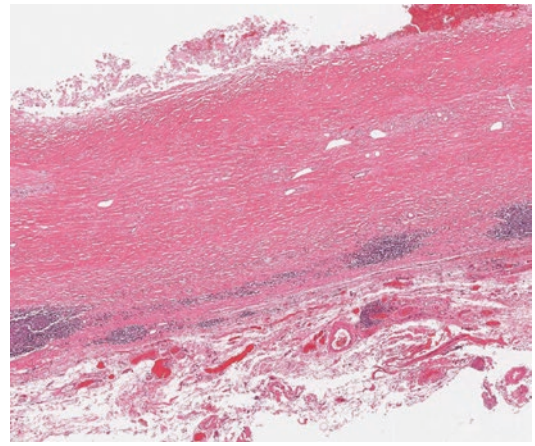

Fig. 16.8 Mucinous cystic neoplasm: the wall of this tumor is sclerotic with no evidence of epithelial lining (*uppermost*) or ovarian-type stroma

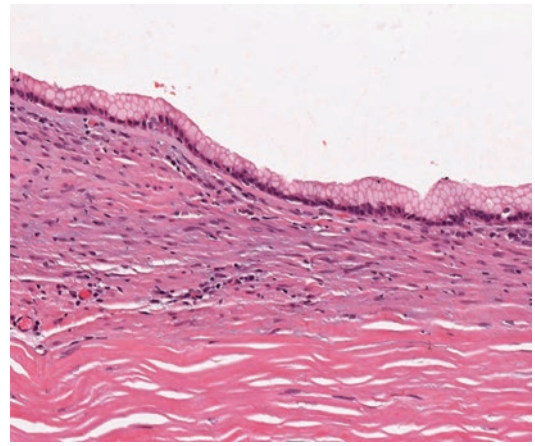

Fig. 16.9 Mucinous cystic neoplasm: this low-grade tumor is lined by tall, columnar, mucin-producing epithelial cells which resemble gastric-type epithelium

16.6 Microscopy

The cysts of MCN are lined by tall, columnar, mucin-producing epithelial cells (Fig. 16.9), which usually resemble gastric-type epithelium, but there may be intestinal differentiation with goblet cells and occasional paneth cells (Fig. 16.10). Nonmucinous, flat or cuboidal epithelium may also be present, as a minor or

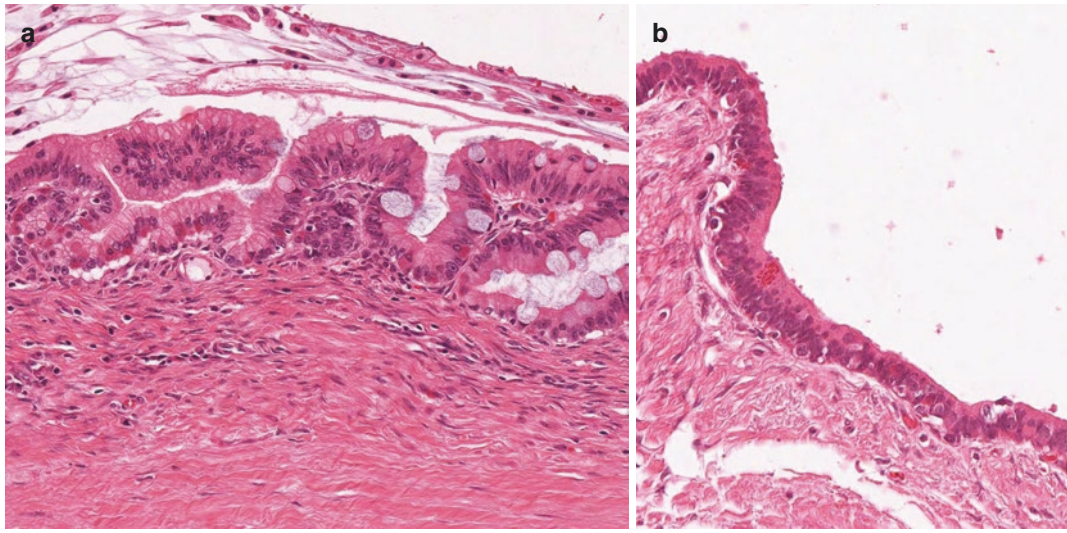

Fig. 16.10 Mucinous cystic neoplasm: there are goblet cells and prominent endocrine cells in this low-grade tumor (**a**). In another example of a low-grade tumor (**b**), there is a single paneth cell (*above center*) as well as endocrine cells

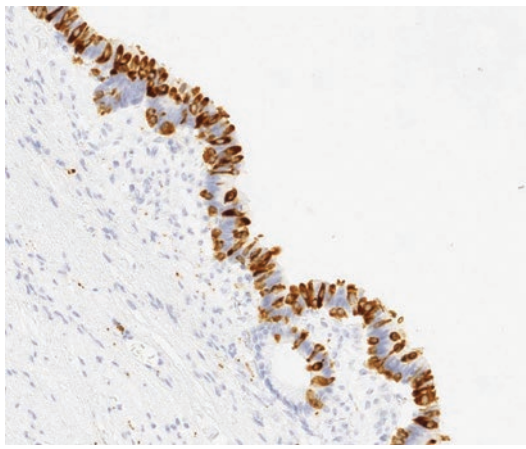

Fig. 16.11 Mucinous cystic neoplasm: synaptophysin immunohistochemistry shows abundant endocrine cells in the same tumor as shown in Fig. 16.10b

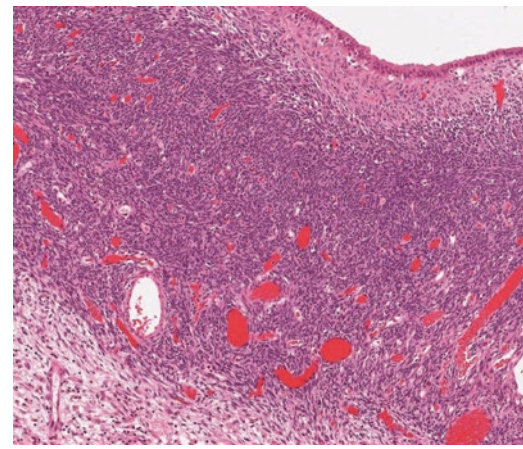

Fig. 16.12 Mucinous cystic neoplasm: typical ovarian-type stroma present as a thick subepithelial band in this tumor

major component [3], and particularly when there is marked hemorrhage and fibrosis. Very rarely, there may be squamous metaplasia [4]. Endocrine cells may be present within the epithelium and are reported to be more numerous in high-grade neoplasms (Figs. 16.10 and 16.11). In larger neoplasms, much of the lining epithelium may be denuded (Fig. 16.8) and thorough sampling is required to find it.

The ovarian-type stroma (Fig. 16.12) beneath the epithelium consists of closely packed spindle cells with round or elongated nuclei and sparse cytoplasm. There may be stromal luteinization (with epithelioid cells showing abundant clear or eosinophilic cytoplasm), but this is usually only seen in low-grade lesions. Mitotic figures are not present. There may be entrapped normal acini, islets, and ducts within the ovarian-type stroma.

The neoplastic epithelium may also invaginate into this ovarian-type stroma. In larger neoplasms, much of the stroma can become degenerate or sclerotic (Fig. 16.8) with only small foci of residual ovarian-type stroma (Fig. 16.13) or foci with the appearance of corpora albicantia.

There is usually a thick band of collagen, which may show focal calcification, between the cyst and the adjacent pancreas. The adjacent pancreas is usually fibrotic and atrophic.

The epithelium of MCNs can show different degrees of dysplasia within the same neoplasm, and there can be abrupt transition between low-grade and high-grade dysplasia. The grade of dysplasia is determined by the degree of architectural and cytological atypia, and until recently was classified as low grade, intermediate grade or high grade. Following a consensus meeting in Baltimore, it was recommended that this three-tiered grading system should be replaced by a two-tiered system [5], with the categories of low-grade dysplasia and intermediate-grade dysplasia being combined into low-grade MCN, and high-grade dysplasia remaining as high-grade MCN. This two-tiered system has been adopted into the 2019 WHO classification of tumors of the pancreas [1].

16.6.1 MCN with Low-Grade Dysplasia

MCN with low-grade dysplasia is characterized by tall columnar epithelium with small basally located nuclei (Fig. 16.14) or pseudostratified nuclei. The epithelium may be flat or have papillary projections and crypt-like invaginations (Fig. 16.15). There may be occasional mitotic figures.

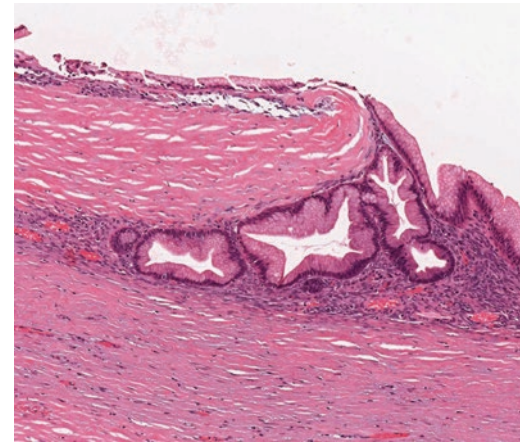

Fig. 16.14 Low-grade dysplasia: the epithelium is tall, columnar, and mucinous with basal nuclei and no atypia. Note the underlying ovarian-type stroma (*right*) and the sclerotic wall (*left*) where the epithelium is beginning to detach

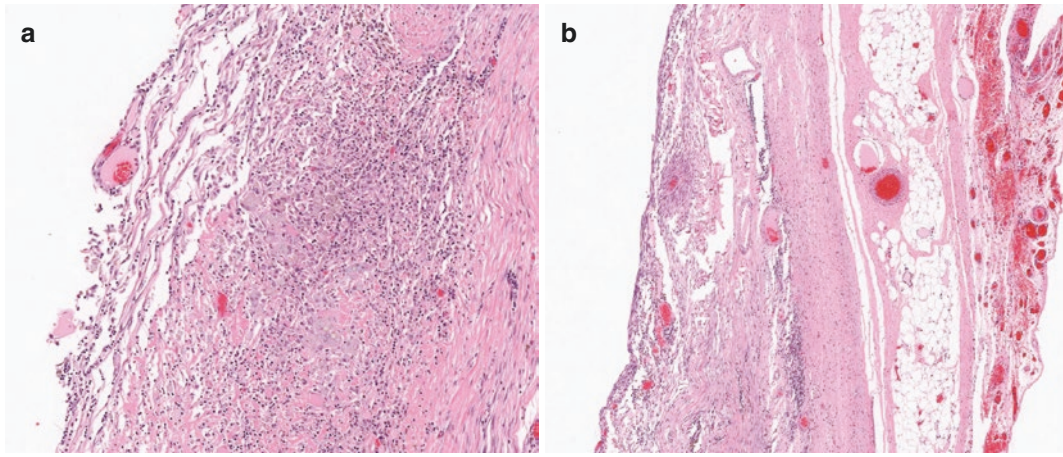

Fig. 16.13 Mucinous cystic neoplasm: there is loss of surface epithelium and a large focus of macrophages within the wall of this large degenerate tumor (**a**). There was only a single focus of residual ovarian-type stroma left in the wall (**b**), which is particularly cellular around the vessel (*center, left*)

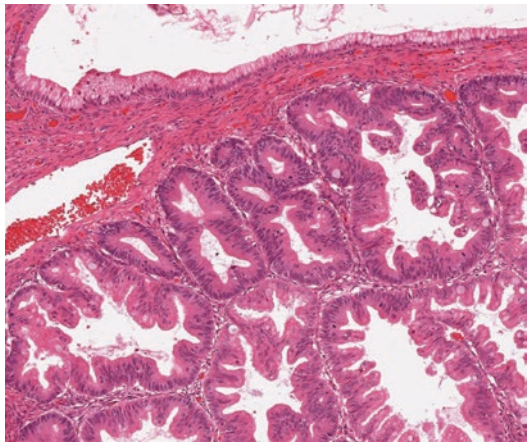

Fig. 16.15 Low-grade dysplasia: the low-grade epithelium in this case shows papillary architecture, pseudostratified elongated nuclei, and scattered mitotic figures, as well as flat columnar epithelium

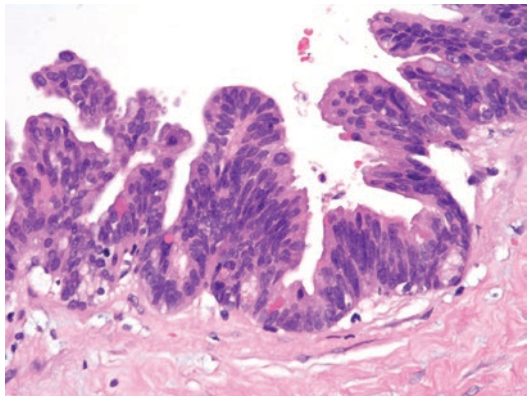

Fig. 16.16 High-grade dysplasia: there is micropapillary architecture with significant cytological atypia. There is nuclear stratification and pleomorphism, together with prominent nucleoli

16.6.2 MCN with High-Grade Dysplasia

MCN with high-grade dysplasia is characterized by significant architectural and cytological atypia with the formation of papillae with irregular branching and budding, nuclear stratification and pleomorphism, prominent nucleoli, and frequent mitotic figures, including atypical forms (Fig. 16.16).

16.6.3 MCN with Associated Invasive Carcinoma

Approximately 10–20% of MCNs have associated invasive carcinoma [6]. The carcinoma may be focal and small with limited invasion, or it may be more extensive and deeply invasive. The presence of desmoplastic stroma will distinguish invasive carcinoma from entrapped non neoplastic glands in the cyst wall. The invasive carcinoma may occur within intratumoral septa or intracystic nodules, as well as in the outermost wall of the MCN.

The invasive component usually resembles conventional pancreatic ductal adenocarcinoma (see Chap. 9, Sect. 9.6) but rare subtypes of pancreatic ductal adenocarcinoma have been described, including undifferentiated carcinoma (Fig. 16.17), undifferentiated carcinoma with

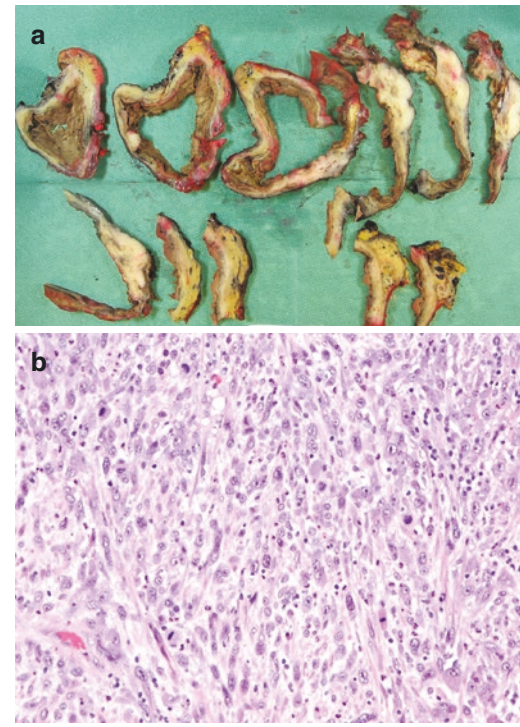

Fig. 16.17 Undifferentiated carcinoma arising in a mucinous cystic neoplasm: the solid white mural nodules in this tumor (**a**) are foci of undifferentiated carcinoma (**b**)

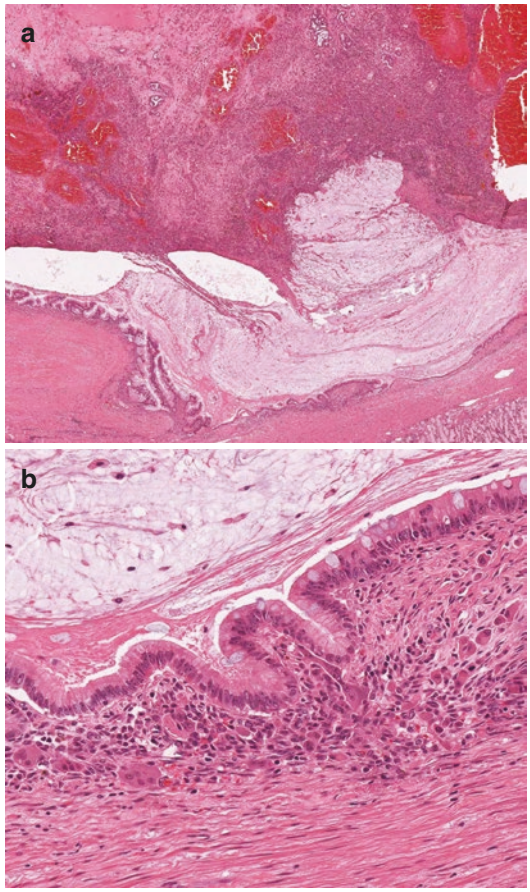

Fig. 16.18 Undifferentiated carcinoma with osteoclast-like giant cells arising in a mucinous cystic neoplasm: the low-power view shows typical mucinous cystic neoplasm *lowermost* with hemorrhagic carcinoma *uppermost* (**a**). At higher power, undifferentiated carcinoma and abundant osteoclast-like giant cells are present beneath mucinous epithelium, which contains scattered goblet cells (**b**)

osteoclast-like giant cells (Fig. 16.18), and adenosquamous carcinoma (see Chap. 9, Sect. 9.14). Invasive carcinomas arising in an MCN should be reported in the same way as a non-MCN-related invasive carcinoma (see Chap. 9, Sect. 9.11).

16.7 Immunohistochemistry

The epithelial cells express CK7, CK8, CK18, CK19, EMA, CEA, MUC5AC, and CA19-9. Scattered goblet cells express MUC2 and CDX2, while the intraepithelial endocrine cells express chromogranin A and synaptophysin (Fig. 16.11).

Ovarian-type stroma expresses vimentin, smooth muscle actin, progesterone receptor (60–90% cases) and, less frequently, ER (30%) (Fig. 16.19). It can also show immunopositivity for CD10, which is not expressed in normal ovarian stroma. Luteinized cells express alpha-inhibin and calretinin.

Immunohistochemistry is not usually needed to make the diagnosis of MCN, but progesterone receptor (PGR) may, on occasion, be helpful for confirming the presence of scanty ovarian-type stroma.

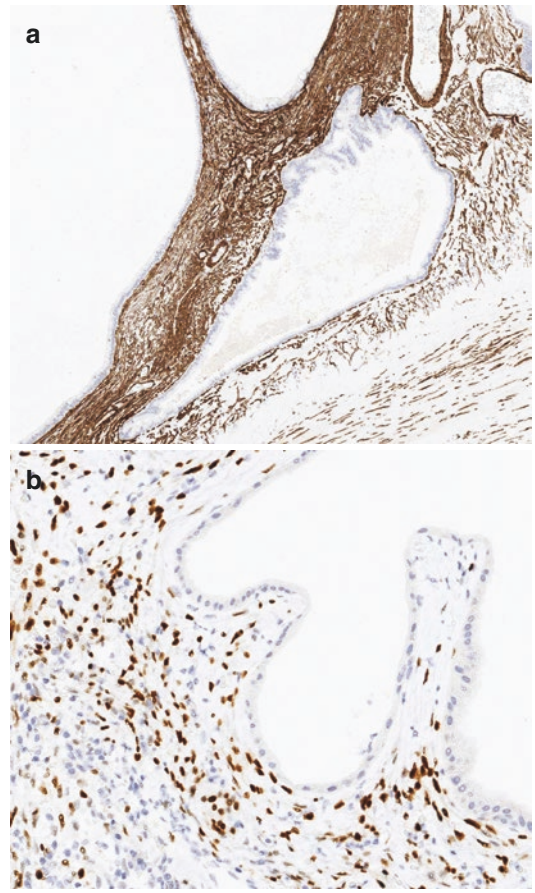

Fig. 16.19 Mucinous cystic neoplasm: the ovarian-type stroma is diffusely immunopositive with smooth muscle actin (**a**) and shows nuclear immunopositivity with progesterone receptor (**b**)

16.8 Molecular Pathology

Mutations in the *KRAS* gene can be detected in MCNs, in both the mucinous epithelium and the nonmucinous epithelium [7], and occur more frequently in high-grade tumors [8]. Mutations in the *PIK3CA* oncogene and the tumor suppressor genes *TP53*, *SMAD4*, *RNF43,* and *P16INK4A* appear to be associated with tumor progression.

16.9 Variants

16.9.1 MCN Involving the Main Pancreatic Duct

There is a single case report of MCN involving the entire main pancreatic duct [9]. This mucin-producing papillary neoplasm of the main pancreatic duct had clinical, radiological, and pathological features overlapping intraductal papillary mucinous neoplasm (see Chap. 17) and MCN. However, there was extensive ovarian-type stroma accompanying the neoplasm and, therefore, it was classed as an MCN of the main pancreatic duct.

16.9.2 MCN with Mesenchymal Overgrowth

In this rare benign tumor, the ovarian-type stroma predominates over the epithelial component, resulting in a solid tumor. There is abundant ovarian-type stroma, entrapped within which are small cysts lined by mucinous epithelium [10].

16.9.3 MCN with Sarcomatous Differentiation of the Stroma

There are case reports of sarcomatous differentiation of the stroma in MCNs characterized by hypercellular spindle cell sarcoma with numerous mitoses, including atypical forms, nuclear atypia, vascular invasion, and sarcomatous metastases [4, 11]. The accompanying epithelial component can be benign or malignant.

16.10 Differential Diagnosis

16.10.1 Intraductal Papillary Mucinous Neoplasm (IPMN) (see Chap. 17)

MCN may be confused with a branch-duct-type IPMN, but occurs almost exclusively in women, does not communicate with the duct system, is solitary, thick walled and, by definition, has ovarian-type stroma.

16.10.2 Simple Mucinous Cyst (Mucinous Nonneoplastic Cyst) (see Chap. 19, Sect. 19.2.1)

Simple mucinous cysts are benign, typically solitary, unilocular or multilocular cysts, lined by a single layer of bland, cuboidal to columnar mucinous epithelium. Beneath the epithelium, there is a thin band of paucicellular hyalinized stroma. They do not have nuclear atypia, papillae, or ovarian-type stroma.

16.10.3 Retention Cyst (see Chap. 19, Sect. 19.3.1)

Obstruction and fibrosis of a pancreatic duct may lead to cystic dilatation of the upstream ducts giving rise to so-called retention cysts. Retention cysts may be single or multiple, but are typically less than 1–2 cm in size, and are lined by pancreatobiliary-type epithelium. Occasionally, there may be low-grade PanIN within a retention cyst, with tall columnar mucinous epithelium. However, there is often a mixture of normal pancreatobiliary-type epithelium and PanIN within the same retention cyst, and ovarian-type stroma is lacking.

16.10.4 Retroperitoneal Mucinous Cystic Tumor

Primary retroperitoneal mucinous tumors are uncommon cystic neoplasms that occur almost exclusively in women, particularly those of reproductive age. They may be unilocular or multilocular, and the cysts are lined by mucin-producing epithelium and ovarian-type stroma similar to that seen in pancreatic MCNs. However, they do not involve the pancreas, which allows their distinction from pancreatic MCNs.

16.10.5 Pseudocyst or Macrocystic Serous Cystadenoma

Large MCNs may lose much of the epithelial lining and have abundant sclerotic stroma with only scanty foci of residual ovarian-type stroma. They may then be confused with a pseudocyst (see Chap. 7, Sect. 7.2.5), which lacks an epithelial lining, or a macrocystic serous cystadenoma (see Chap. 15, Sect. 15.6.2), which may also lose much of the epithelial lining.

Pseudocysts are associated with a history of pancreatitis. Macrocystic serous cystadenoma is usually a thin-walled cyst, and is lined by glycogen-rich, clear cuboidal cells. Thorough sampling of the cystic lesion may be needed to identify the defining ovarian-type stroma or the mucinous epithelium of MCN, neither of which are present in a pseudocyst or a macrocystic serous cystadenoma.

16.11 Staging

Invasive carcinoma arising with an MCN should be staged in the same way as conventional pancreatic ductal adenocarcinoma (see Chap. 9, Sect. 9.11).

16.12 Prognosis and Management

Given the risk of progression to invasive carcinoma, surgical resection is currently recommended for all surgically fit patients with an MCN [12, 13]. Surveillance, however, may be considered if the MCN is less than 4 cm in size and there are no risk factors such as a suspicious mural nodule or symptoms [13]. Complete resection of non-invasive MCNs is curative with a 5-year survival rate of 100%. Incomplete resection may lead to development of invasive carcinoma. The 5-year survival rate for resected MCN with associated invasive carcinoma is up to 60%, which is much better than for conventional, non-MCN-related pancreatic ductal adenocarcinoma. This probably reflects the earlier stage at diagnosis. Recently it has been suggested that T1a and T1b carcinomas may have a similar prognosis to non-invasive MCN [14].

Table 16.1 Reporting checklist for mucinous cystic neoplasm

Macroscopic assessment
• Specimen type
• Additional resected structures, e.g., spleen
• Tumor location
• Tumor size (3-dimensions)
• Involvement of adjacent organs
• Unilocular or multilocular tumor
• Invasive carcinoma identified or not
• Distance from resection margin(s)
Microscopic assessment
• Degree of dysplasia
• Invasive carcinoma present or not
• For invasive carcinoma:
Differentiation
Extent of invasion
Lymphatic, vascular or perineural invasion
Metastases
UICC TNM staging
• Completeness of excision/resection margin status
• Background changes

16.13 Reporting Checklist

A list of macroscopic and microscopic features to consider when reporting a mucinous cystic neoplasm is shown in Table 16.1.

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Further Reading

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