Mucinous Neoplasms of the Ovary

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Philip P.C. Ip and Annie N.Y. Cheung

Abstract

Primary mucinous tumors represent 15 % of all ovarian tumors and are classified as either benign, borderline, or malignant. More than 80 % of mucinous tumors are benign, while only 2–7 % are malignant. An overwhelming majority of tumors show gastrointestinal differentiation. Those of Müllerian differentiation are more commonly borderline tumors and rarely benign or malignant. Distinction between intestinal- and Müllerian-type carcinomas may not always be easy, owing to tumor heterogeneity and the fact that some tumors are mixed, such that components of benign, borderline, and carcinoma often coexist within an individual lesion. The diagnostic difficulty is further compounded by the fact that some tumors do not fit agreeably into the three biologic subcategories. Benign tumors containing <10 % of borderline features have been designated cystadenomas with focal atypia or focal proliferation. They are biologically benign. Borderline tumors have mild-to-moderate cytologic atypia, and almost all are followed by an uneventful outcome. In those with severe atypia and a complex architecture but without stromal invasion, the term mucinous borderline tumor with intraepithelial carcinoma is used. These latter tumors have a very low risk of recurrence. Microinvasion refers to borderline tumors, whether with or without intraepithelial carcinoma, that have ≥1 foci of tumor cells infiltrating the stroma but with each focus <10 mm^2. Provided the tumor has been adequately sampled to exclude occult foci of frank carcinoma, microinvasion does not seem to be an adverse prognostic factor. For mucinous carcinomas, the pattern of invasion is prognostically more relevant than grading, especially for stage I. Expansile-type stromal invasion refers to florid epithelial proliferation without intervening stroma. In infiltrative-type stromal invasion, there is irregular infiltration of the stroma by cells associated with stromal desmoplasia. The latter pattern is significantly associated with an adverse outcome.

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Molecular Pathology

The most common molecular change in mucinous tumors of the ovary is KRAS mutation at codon 12/13, involving >75 % of mucinous carcinomas and, to a lesser degree, their adjacent borderline and benign tumors. The latter supports the fact that there is a continuum of tumor progression from benign, borderline, to malignant and that KRAS mutation appears to be an early event in carcinogenesis [1–7]. Other early molecular events of crucial importance include p16 loss and RAS/RAF pathway alterations [8]. HER2 overexpression has been found in about 18 % of mucinous carcinomas and in 18 % of borderline tumors and is a potential target for therapy [9]. Tumors that showed both HER2 amplification and KRAS mutation have been shown to be prognostically favorable [9, 10].

Benign Mucinous Tumors

Synonyms

Mucinous cystadenoma

Clinical Features

Mucinous cystadenomas represent approximately 80 % of all ovarian mucinous tumors (Table 10.1). Some containing merely gastrointestinal epithelium may be of germ cell origin (monodermal teratoma). A minority may originate from Brenner tumors. The mean age of patients is 50 years and they usually present with a mass.

Gross Features

Mucinous cystadenomas are often unilateral and large, measuring 15–30 cm (mean, 10 cm) and weighing up to 4 kg [11]. They have a thick capsule and are either unilocular or multilocular (Fig. 10.1). The cyst wall may be either thin or thick and fibrous (adenofibromatous). Mucinous cystadenomas of Müllerian (endocervical-like) type are very rare. They are often uniloculated or have a few locules and do not have any grossly visible polypoid excrescences of a borderline tumor (see section "Endocervical-like mucinous borderline tumor"). They often contain altered blood or watery mucinous fluid. Some coexist with endometriosis.

Microscopic Features

The glands and cysts are usually separated by varying amounts of fibrous stroma, often with periglandular hypercellularity. Back-to-back

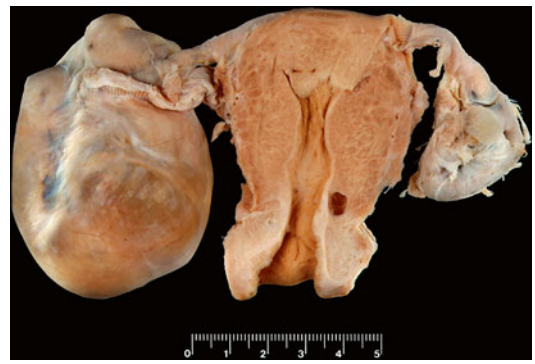

Fig. 10.1 Mucinous cystadenoma. The capsule is fibrous and thick

Table 10.1 Classification of ovarian mucinous tumors

Benign	Cystadenoma	
	Adenofibroma and cystadenofibroma	
Borderline	Intestinal type	*With microinvasion and/or intraepithelial carcinoma*
	Endocervical-like type (seromucinous)	
Malignant	Adenocarcinoma and cystadenocarcinoma	*With expansile invasion or with infiltrative invasion*
	Adenocarcinofibroma (malignant adenofibroma)	
	Mucinous tumor with mural nodules	
	Mucinous tumor with pseudomyxoma peritonei	

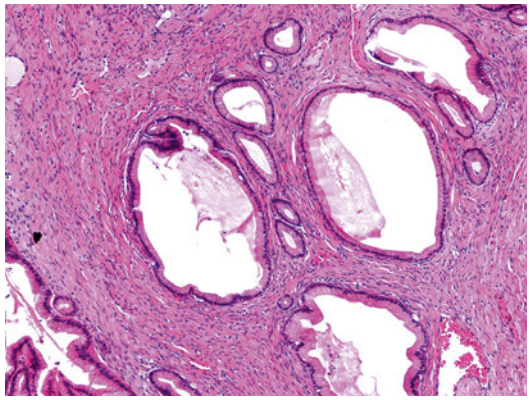

Fig. 10.2 Mucinous cystadenoma. The glands are surrounded by variable amount of fibrous stroma

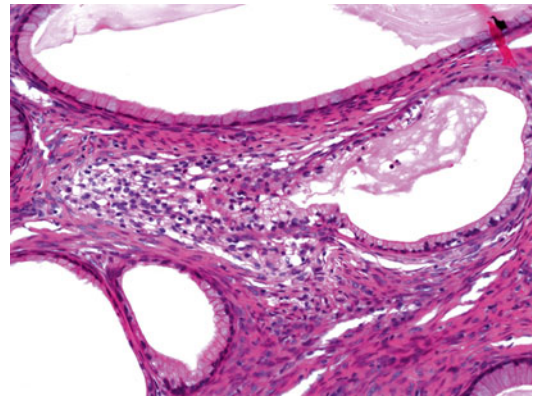

Fig. 10.4 Mucinous cystadenoma. Gland rupture with mucin granuloma

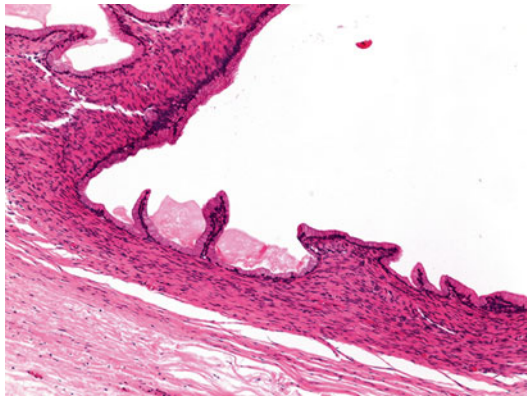

Fig. 10.3 Mucinous cystadenoma. Filiform papillae projecting into cystic space

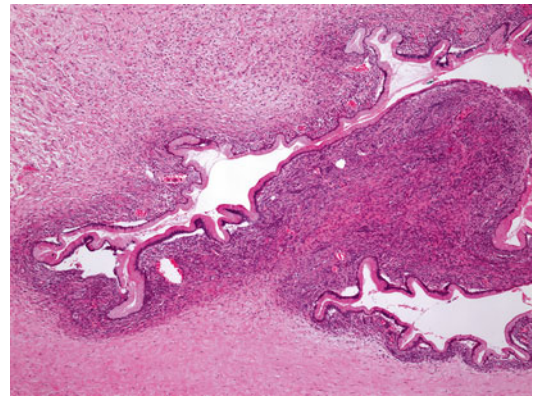

Fig. 10.5 Mucinous cystadenoma. The glands or cysts may be surrounded by a rim of condensed ovarian stroma

crowded glands may be seen, but there is almost always a thin rim of intervening stroma. The lining cells comprise a uniform layer of nonstratified columnar epithelium, with basally located nuclei and apical cytoplasmic mucin vacuoles. Almost all mucinous cystadenomas are of intestinal type. Although the "picket-fence" arrangement of the epithelium resembles that of endocervical mucosa, it has been noted that these epithelia more often show gastric pyloric differentiation (Figs. 10.2, 10.3, 10.4, 10.5, and 10.6) [11]. There should be no cytologic atypia. When there is mild-to-moderate atypia and nuclear stratification and tufting are present in mucinous borderline tumor, the designation of mucinous cystadenoma with focal atypia or focal proliferation may be used, provided the atypical component is <10 % of the entire tumor (Figs. 10.22, 10.23, 10.24).

The epithelium in mucinous cystadenomas of Müllerian (endocervical-like) type comprises single layer of cytologically bland mucous and eosinophilic cells. The latter may form epithelial tufts but true papillae with fibrovascular cores are not found. There is almost always striking inflammatory cell infiltration comprising neutrophils (Figs. 10.7 and 10.8).

Clinical Outcome and Prognosis

Mucinous cystadenomas are benign, even when there is focal atypia or focal proliferation (as defined above).

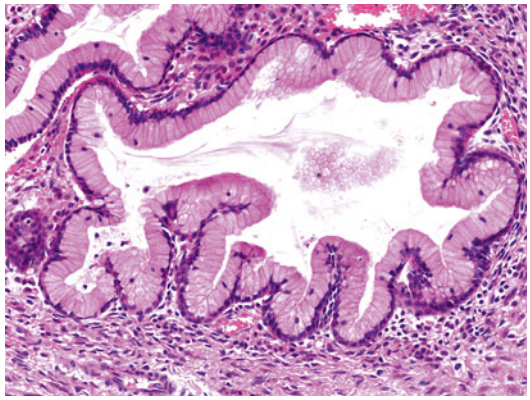

Fig. 10.6 Mucinous cystadenoma. The epithelial cells have basally located nuclei and apical mucin vacuoles

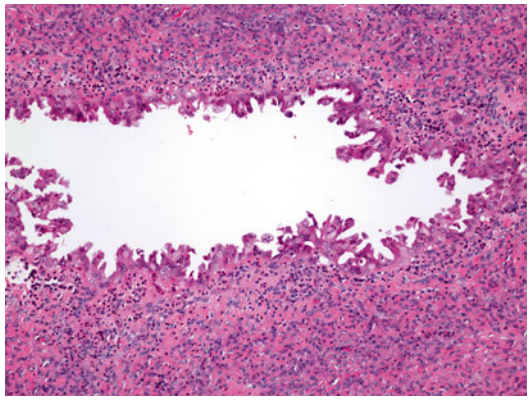

Fig. 10.7 Mucinous cystadenoma, endocervical-like. The epithelium may form tufts, but there is no intracystic papillary proliferation, in contrast to Fig. 10.25

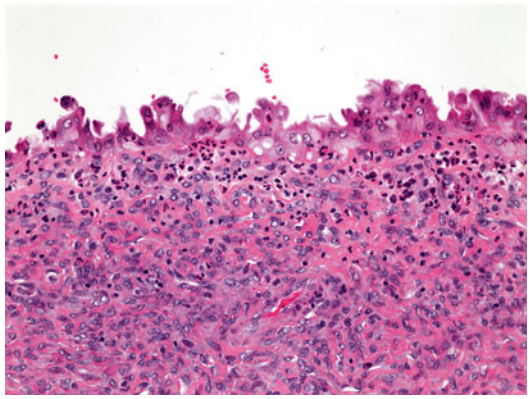

Fig. 10.8 Mucinous cystadenoma, endocervical-like. The lining epithelial cells comprise mucous cells and eosinophilic cells. Note prominent presence of inflammatory cells

Mucinous Borderline Tumors

Intestinal-Type Mucinous Borderline Tumors

Synonyms

(Intestinal-type) mucinous borderline tumor; Atypical proliferative mucinous tumor; Mucinous tumor of low malignant potential; Mucinous tumor of borderline malignancy

Clinical Features

Intestinal-type mucinous borderline tumors (IMBTs) usually affect women with a mean age of 51 years [11]. In the mucinous borderline tumor category, IMBT is the more common subtype and accounts for 85–90 % of cases. In >90 %, they are stage I, and 5–10 % are bilateral [12, 13]. When bilateral, a metastatic adenocarcinoma should always be excluded [14].

Gross Features

IMBTs are usually multiloculated and large, ranging from 18 to 22 cm and usually have a smooth and fibrous capsule (Figs. 10.9 and 10.10) [11].

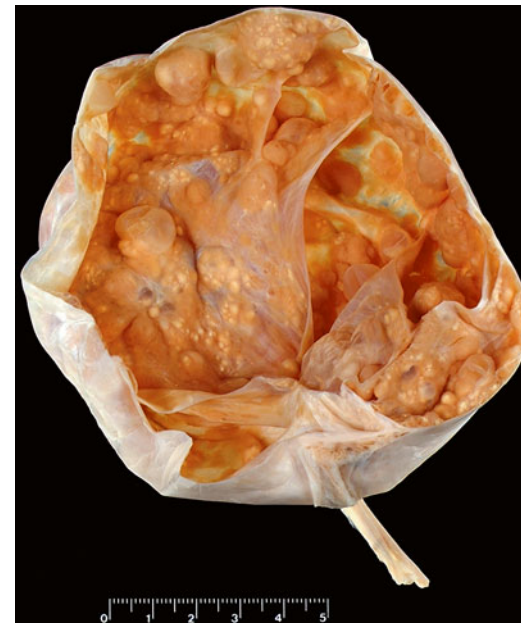

Fig. 10.9 Mucinous borderline tumor, intestinal type. Multiple internal locules of various sizes

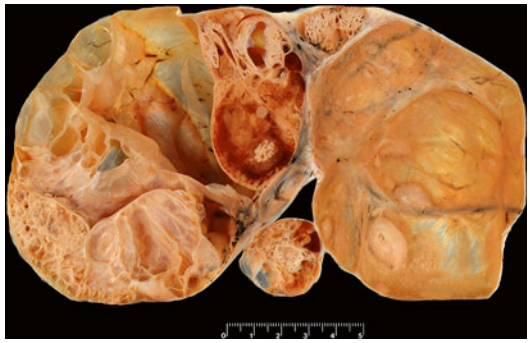

Fig. 10.10 Mucinous borderline tumor, intestinal type. Cross section of the small locules reveals even more internal loculations or septated cysts

The wall of the locules may be thin and translucent or may be thick and fibrous, rarely with polypoid excrescences. The locules usually contain clear and watery mucin but may be thick and viscous [1, 6, 15–18]. Hemorrhage and necrosis may be present and should not be interpreted as signs of malignancy. IMBTs are sometimes grossly indistinguishable from some benign cystadenomas or even carcinomas; generous sampling for microscopic examination is recommended. Although the general rule is to take 1 block for each centimeter of the tumor, it is equally important to note that this should be carried and focused on the solid areas, not just the thinner cyst lining.

Microscopic Features

The glands and cysts may be closely packed or widely separated by stroma. The glands may be fused, but true cribriform glands, i.e., those without any discernible stroma between individual glandular spaces, are infrequent. There are usually epithelial tufts or filiform papillae projecting into glandular spaces, but papillae with fibrovascular stromal cores, in particular those with hierarchical branching as encountered in serous borderline tumors, are not usually found. The cells lining the glands and cysts and those covering the filiform papillae are similar to those seen in a benign tumor but show mild-to-moderate pleomorphism (Figs. 10.11, 10.12, 10.13, 10.14, and 10.15). Goblet cells and, occasionally, Paneth cells and neuroendocrine cells are

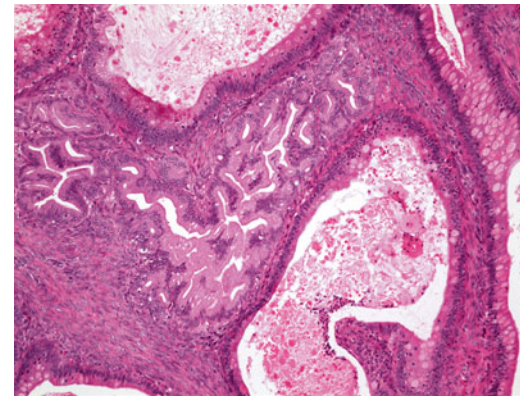

Fig. 10.11 Mucinous borderline tumor, intestinal type. Either the glands or cysts are lined by a single layer of epithelium, or there may be internal epithelial cross-bridges

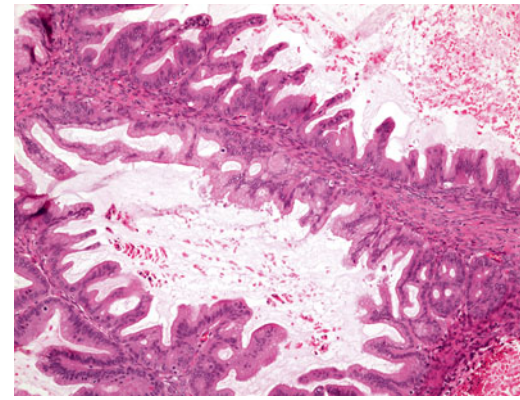

Fig. 10.12 Mucinous borderline tumor, intestinal type. Filiform papillae projecting into cystic spaces

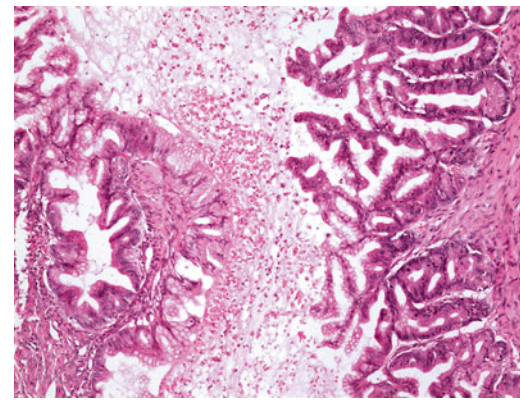

Fig. 10.13 Mucinous borderline tumor, intestinal type. Lining epithelium ranges from those resembling benign mucinous cystadenoma (*left*) to those that are architecturally complex and cytologically abnormal (*right*)

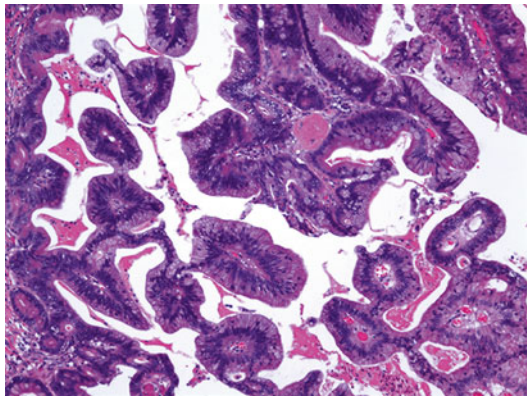

Fig. 10.14 Mucinous borderline tumor, intestinal type. Papillary pattern

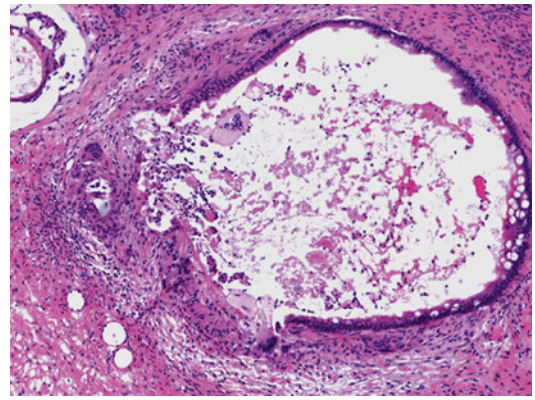

Fig. 10.16 Mucinous borderline tumor, intestinal type. A ruptured gland with mucin granuloma. This is sharply demarcated from the surrounding stroma

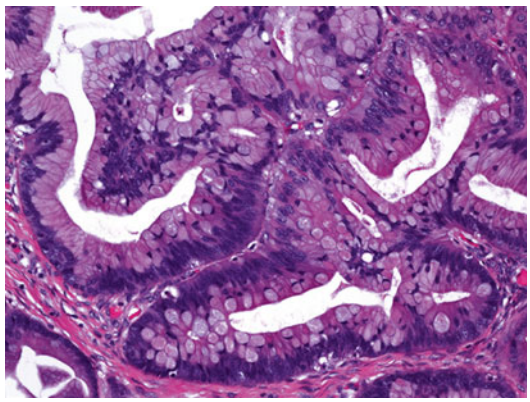

Fig. 10.15 Mucinous borderline tumor, intestinal type. The epithelium is enteric type, with prominence of goblet cells

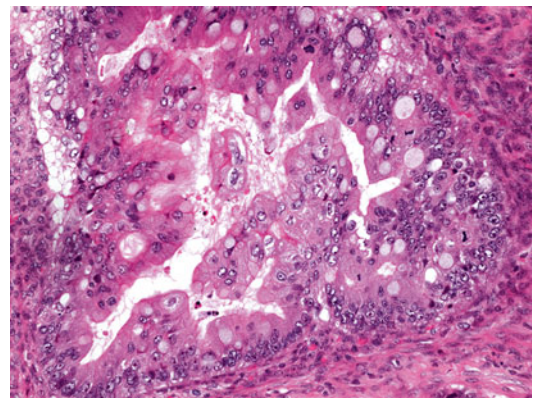

Fig. 10.17 Mucinous borderline tumor, intestinal type, with intraepithelial carcinoma. The epithelium is cytologically malignant

present. The nuclear features vary considerably within the same tumor, ranging from a single layer to stratified nuclei <4 cells in height with loss of the apical mucin vacuole. The range of atypical nuclear features is analogous to those of colorectal adenomatous polyps [6, 18–22]. Mucin granulomas are a result of rupturing of the glands or cysts and should not be misinterpreted as stromal invasion. These granulomas are often localized and do not show the widespread mucin dissection of stroma as in pseudomyxoma ovarii or pseudomyxoma peritonei. The isolated epithelial cells in mucin granulomas are almost always confined to the boundary of the latter (Fig. 10.16) [23].

Intraepithelial Carcinoma (Noninvasive Carcinoma). MBTs with intraepithelial carcinoma refer to tumors without unequivocal stromal invasion but show nuclear stratification of ≥4 cells in height, coarse chromatin, macronucleoli, and a high mitotic rate (Figs. 10.17, 10.18 and 10.19). The cytologic features, rather than the architecture, are more important in determining whether a component of the tumor is intraepithelial carcinoma or not [1, 6, 11, 24, 25]. When these foci are extensive, meticulous sampling for microscopy is necessary to exclude frank stromal invasion.

Microinvasion. IMBTs, particularly in those with intraepithelial carcinoma, may show foci of stromal microinvasion [18, 26]. The definition

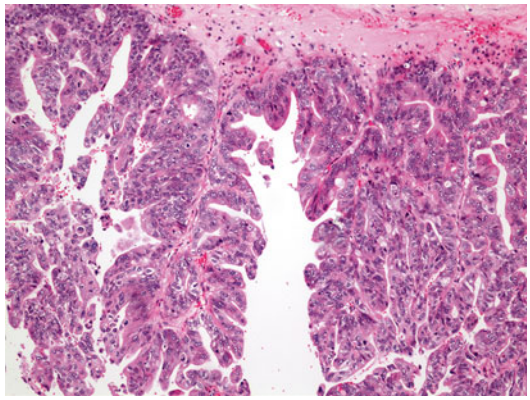

Fig. 10.18 Mucinous borderline tumor, intestinal type, with intraepithelial carcinoma. The malignant glands show back-to-back crowding, but the size of this area is less than that for diagnosing mucinous carcinoma with expansile invasion (see section "Intestinal-type mucinous carcinoma")

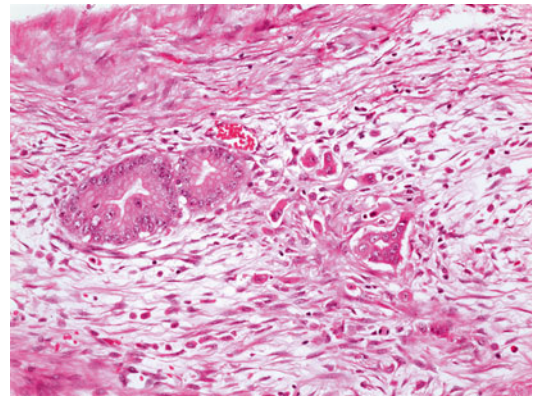

Fig. 10.20 Mucinous borderline tumor, intestinal type, with microinvasion. Invasive tumor cells with eosinophilic cytoplasm and surrounded by a clear space

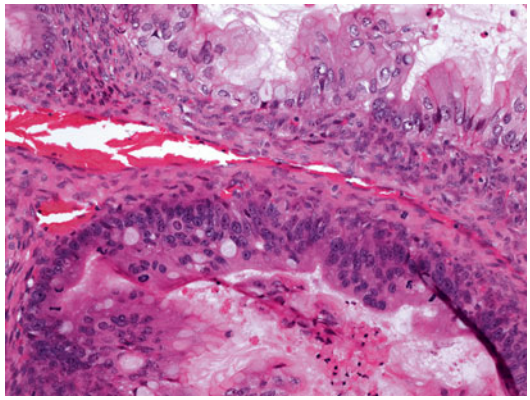

Fig. 10.19 Mucinous borderline tumor, intestinal type, with intraepithelial carcinoma. The intraepithelial carcinoma is usually localized. Note adjacent gland with lesser degree of cytologic atypia

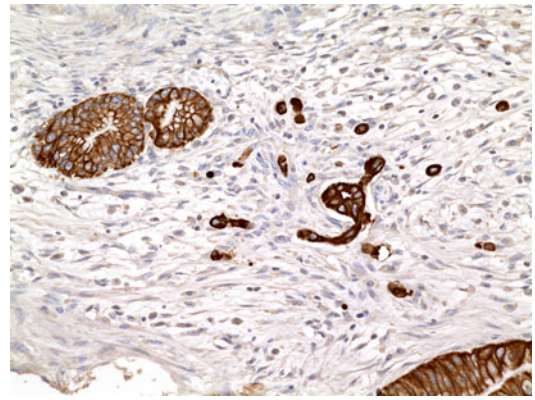

Fig. 10.21 Mucinous borderline tumor, intestinal type, with microinvasion (CK7). Invasive tumor cells may be readily identified using cytokeratin immunostains

of microinvasion varies, but most regard this to be either <5 mm in the greatest dimension or, more specifically, <10 mm^2 (or $\leq 3 \times 3$ mm in two linear dimensions) [24, 25]. Multifocal microinvasion may sometimes be found, but the significance is unknown. The focus usually consists of single cells, solid aggregates, and irregular isolated or confluent glands distributed haphazardly within a reactive fibrous stroma. Cytoplasmic eosinophilia is often seen. The cells are often surrounded by a clear space, which either contains mucin or is due to tissue retraction artifact (Fig. 10.20). The nuclear features in microinvasion are usually mild to moderate but may occasionally be severe. The latter are referred to as "microinvasive carcinoma." Foci of microinvasion may be difficult to appreciate and may go undetected, but a cytokeratin stain may help (Fig. 10.21) [23].

Differential Diagnosis

Mucinous Cystadenoma Versus IMBT: The presence of cribriform glands in cystadenomas, if unaccompanied by cytologic atypia, should not

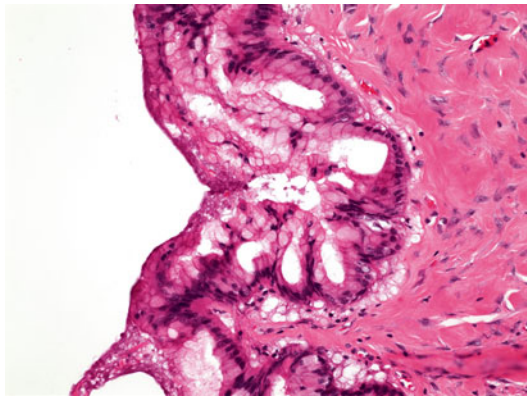

Fig. 10.22 Mucinous cystadenoma. Cribriform glands without cytologic atypia should not be classified as a borderline tumor

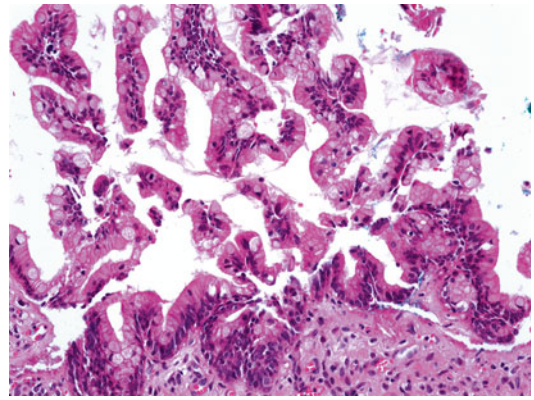

Fig. 10.24 Mucinous cystadenoma with focal atypia. Complex filiform papillae covered by cells with mild-to-moderate atypia

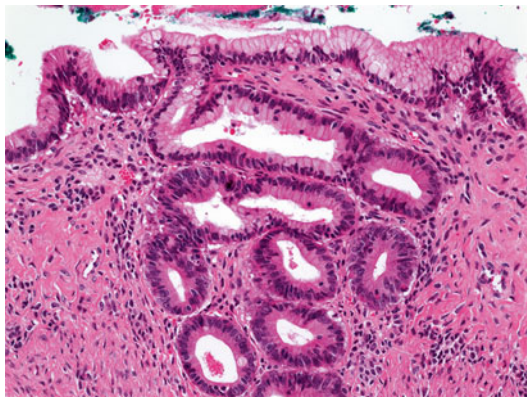

Fig. 10.23 Mucinous cystadenoma with focal atypia. Focal clusters of glands lined by cells with mild-to-moderate atypia. Note benign epithelium over the surface of the cyst lining (*top*)

be classified as borderline tumor (Fig. 10.22). The cribriform arrangement is usually related to tangential sectioning. When there is a minor focus (<10 %) of borderline tumor (i.e., tumor cells with cytologic atypia) in an otherwise benign tumor, the term mucinous cystadenoma with focal atypia (or focal borderline tumor) should be made (Figs. 10.23 and 10.24). The quantity of the borderline tumor (in percentage) should also be stated in the report.

IMBT Versus Mucinous Carcinomas: In mucinous carcinoma, any focus of stromal invasion must exceed that of microinvasion, as defined earlier.

Clinical Outcome and Prognosis

Most stage I IMBTs are benign. In about 6 % of either stage I or stage II/III IMBTs with intraepithelial carcinomas, there is a recurrence [1, 6, 18–22, 26–31]. This is most likely related to under-sampling of a borderline tumor containing occult foci of frankly invasive carcinomas [32]. Stage II/III IMBTs are usually associated with pseudomyxoma peritonei and are in fact almost always secondary tumors to the ovaries, commonly from the gastrointestinal tract (see section "Mucinous tumors associated with pseudomyxoma peritonei") [14, 33]. With rare exceptions, stage I, adequately sampled IMBTs with microinvasion reported had all been clinically benign [1, 6, 18, 21, 26, 31, 34, 35]. However, when the microinvasive tumor cells have high-grade malignant nuclear features, i.e., microinvasive carcinoma, an aggressive clinical behavior may be seen [32]. Treatment by cystectomy alone, as opposed to salpingo-oophorectomy, has been shown to be a significant factor in tumor recurrence [36, 37].

Endocervical-Like Mucinous Borderline Tumor

Synonyms

(Endocervical-like, Müllerian, or seromucinous-type) mucinous borderline tumor; Atypical

Table 10.2 Summary of ovarian mucinous borderline tumors

	Intestinal type	Endocervical-like
Proportion of borderline tumors	85 %	15 % (seromucinous)
Mean age (years)	51	34
Bilaterality	6 %	40 %
Mean size (cm)	19	8
Multilocularity	72 %	20 %
Goblet cells	100 %	0 %
Argyrophil cells	91 %	3 %
Acute inflammation	22 % (focal)	100 % (diffuse)
Endometriosis	6 %	50 %
Pseudomyxoma peritonei	17 %	0 %
Implants or lymph node metastasis	0 %	20 %

Modified and updated from Rutgers and Scully [12]

proliferative mucinous tumor; Mucinous tumor (cystadenoma) of low malignant potential; Mucinous tumor (cystadenoma) of borderline malignancy

Clinical Features

Endocervical-like mucinous borderline tumors (EMBTs) represent 10–15 % of mucinous borderline tumors. In >50 % there is preexisting endometriosis [6, 12, 38, 39]. The age of patients is younger than that for IMBTs, ranging from 19 to 59 years (mean, 34). One-fifth of cases are associated with extraovarian disease at the time of diagnosis. EMBTs have no association with pseudomyxoma peritonei.

Gross Features

EMBTs differ from their intestinal counterpart in several aspects (Table 10.2). They are usually smaller (mean diameter 8 cm), have fewer locules (≤3), are more often bilateral (40 %), have a stronger association with endometriosis (30–50 %), and almost always have an associated inflammatory reaction [12]. Polypoid excrescences, similar to those observed in serous borderline tumors, are usually found (Fig. 10.25) [12].

Microscopic Features

Club-shaped papillae with hierarchical branching, architecturally similar to those seen in serous borderline tumors, characterize EMBTs (Figs. 10.26, 10.27, 10.28, 10.29, 10.30, and 10.31). There is almost always some extracellular mucin, commonly infiltrated by neutrophils. The papillae have edematous fibrovascular cores and are covered by three cell types: mucinous cells, eosinophilic cells, and neutrophils. The mucinous cells are tall columnar and resemble those of the endocervix, while the polygonal eosinophilic cells are similar to those of serous borderline tumors and may show tufting and marked cellular stratification, sometimes to ≥20 cells in height.

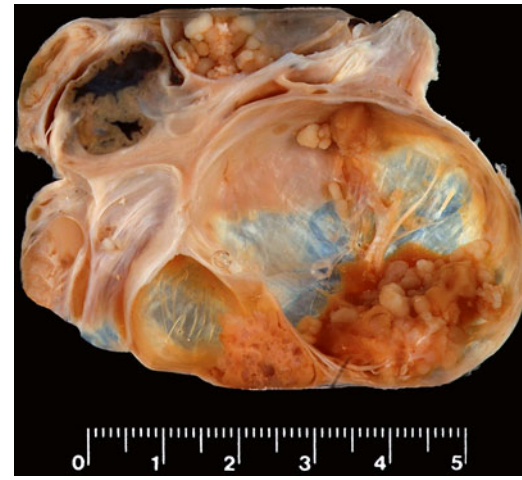

Fig. 10.25 Mucinous borderline tumor, endocervical-like. In contrast to borderline mucinous tumor of intestinal type, this is smaller, has fewer locules, and shows polypoid excrescences over the internal cyst lining

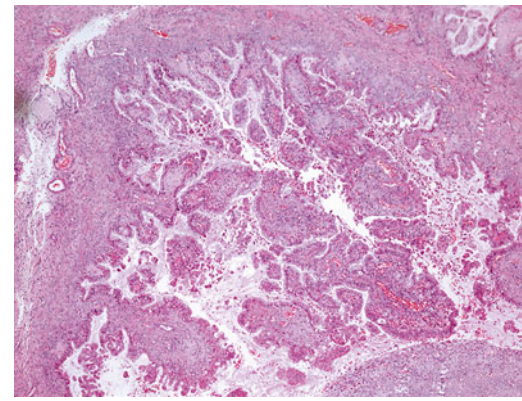

Fig. 10.26 Mucinous borderline tumor, endocervical-like. Club-shaped papillae project into cystic space

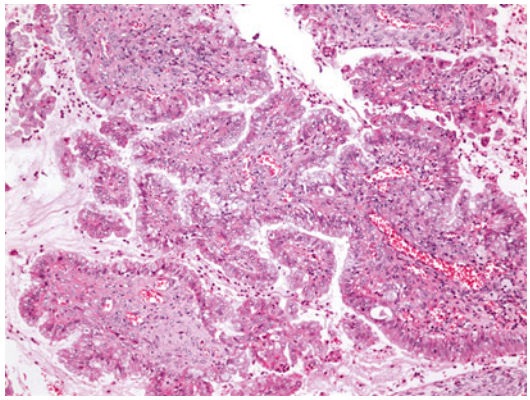

Fig. 10.27 Mucinous borderline tumor, endocervical-like. The papillae show hierarchical branching

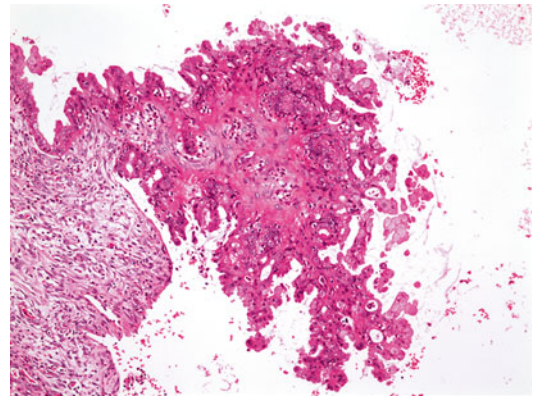

Fig. 10.30 Mucinous borderline tumor, endocervical-like. The cores of papillae are typically infiltrated by numerous neutrophils

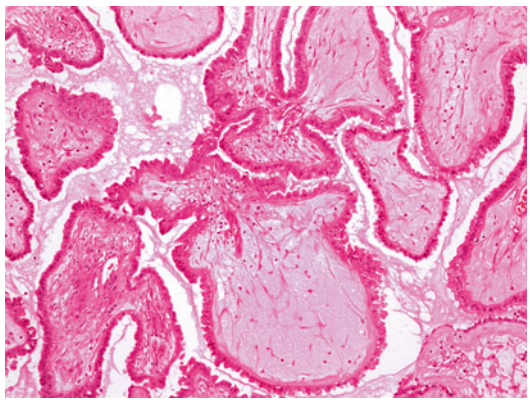

Fig. 10.28 Ovarian serous borderline tumor. The architecture is identical to mucinous borderline tumor, endocervical-like. The epithelial cells are predominantly eosinophilic but occasionally may have mucous cells

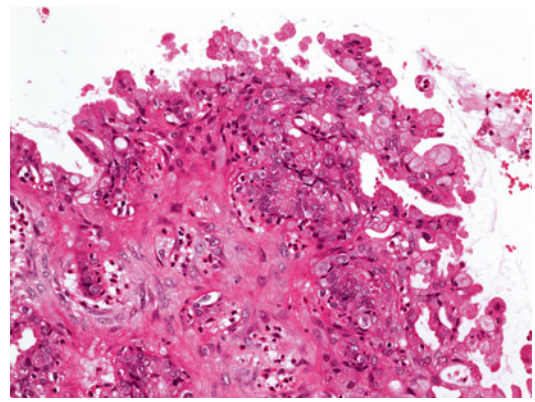

Fig. 10.31 Mucinous borderline tumor, endocervical-like. The epithelial cells may be highly stratified, but they show only mild-to-moderate cytologic atypia

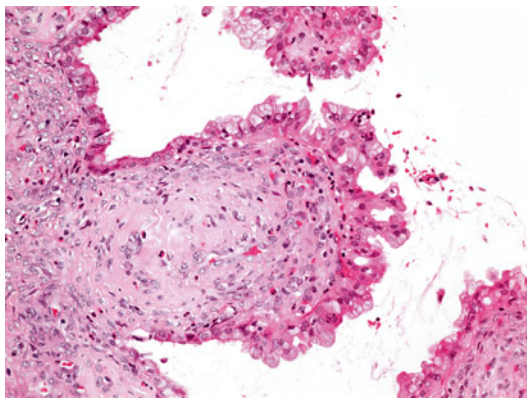

Fig. 10.29 Mucinous borderline tumor, endocervical-like. The papillae are covered by mucous cells and eosinophilic cells

Occasionally, ciliated cells are found. Cytologic atypia is usually mild to moderate although it may be focally severe. Like IMBTs, the combination of cellular stratification and severe atypia in EMBTs may be designated intraepithelial carcinoma (Figs. 10.32 and 10.33). In many cases, endometriosis, including atypical endometriosis, is found in the background cyst lining and may show transition to the EMBT. Microinvasion has been reported in 10–20 % of cases, and the definition is same as for IMBTs (see section "Intestinal-type mucinous borderline tumors"). When the microinvasive tumor cells exhibit only mild-to-moderate atypia, they are regarded as EMBTs with microinvasion; if they are severely atypical, the tumor should be diagnosed as EMBT

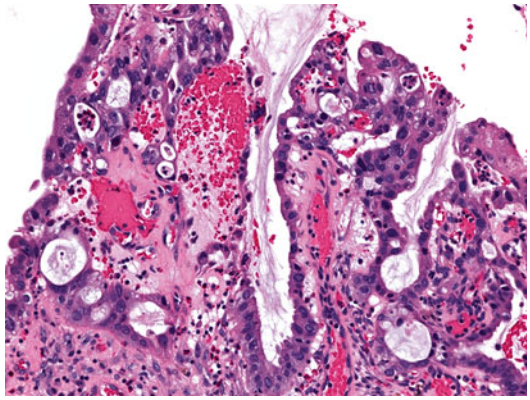

Fig. 10.32 Mucinous borderline tumor, endocervical-like, with intraepithelial carcinoma. There is glandular fusion and early cribriforming

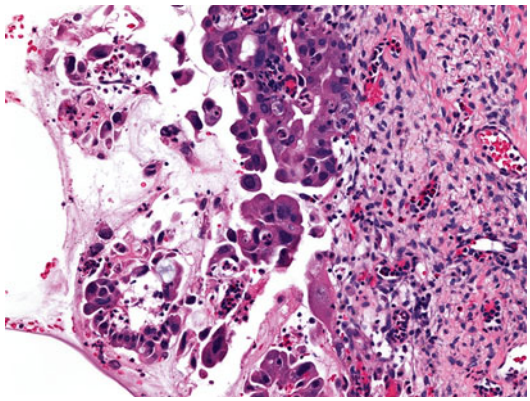

Fig. 10.33 Mucinous borderline tumor, endocervical-like, with intraepithelial carcinoma. The epithelial cells are cytologically malignant. In contrast to Fig. 10.31

with microinvasive carcinoma [34, 35, 40, 41]. The finding of microinvasion or microinvasive carcinoma should prompt additional sampling to exclude frank carcinoma.

Differential Diagnoses

Serous Borderline Tumor Versus EMBT: Serous borderline tumors, which share similar architecture with EMBTs, are distinguished from the latter by the absence of mucinous lining epithelial cells. Neutrophils and extracellular mucin are usually absent or less conspicuous than in EMBTs.

In addition to the mucinous and eosinophilic cells in EMBTs, the presence of serous, endometrioid, or squamous cell types has been reported in these tumors. Even though they were designated as EMBTs of mixed cell types in the older literature [38], they were noted to have the same clinical and pathologic features as EMBTs without these additional cell types, and placing these tumors with mixed cell types into the usual EMBT category is appropriate [41].

Clinical Outcome and Prognosis

The majority of EMBTs are stage I and are almost always followed by a benign clinical course [1, 12, 20, 21, 41, 42]. EMBTs with intraepithelial carcinoma or stromal microinvasion are not associated with a poorer prognosis. Patients with stage II or III disease have peritoneal implants or lymph node metastases, but these were not found to be of any prognostic significance. Fatal cases are exceptional and were described in cases with microinvasive carcinoma or intraepithelial carcinoma, which were most likely due to undetected foci of frankly invasive carcinoma in under-sampled tumors [41, 43].

Mucinous Carcinoma

Intestinal-Type Mucinous Carcinoma

Synonyms

(Intestinal-type) mucinous adenocarcinoma; Cystadenocarcinoma

Clinical Features

Mucinous carcinomas are uncommon and represent 2–7 % of all ovarian carcinomas [44–46]. The higher frequency in earlier studies is most likely related to the inclusion of some metastatic carcinomas that are morphologically indistinguishable from primary ovarian mucinous carcinomas. Patients with primary tumors usually present with an abdominal mass, and the serum levels of CA-125, CEA, and CA19.9 are frequently elevated [47]. The mean age is 45 years. About 75–80 % of cases are stage I. In >95 %, they are unilateral and usually >10 cm (mean, 18–22 cm). When bilateral and each <10 cm, metastases should always be excluded.

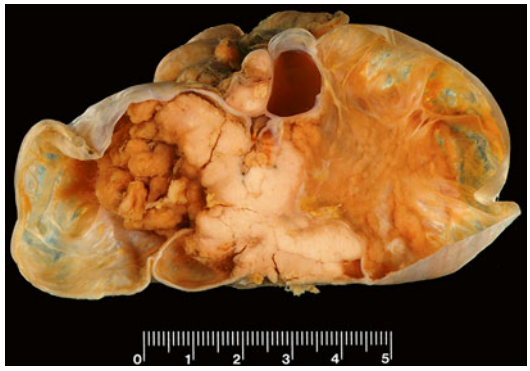

Fig. 10.34 Mucinous carcinoma. The carcinoma may be localized to the solid areas in a seemingly cystic tumor

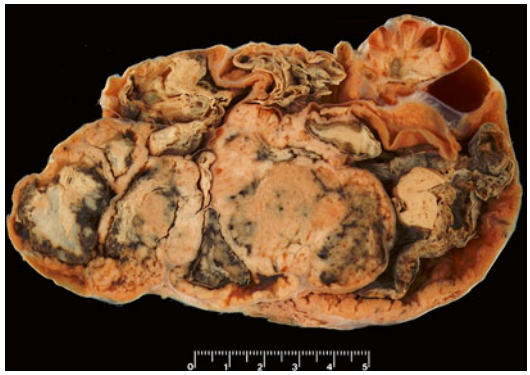

Fig. 10.35 Mucinous carcinoma. A predominantly solid tumor

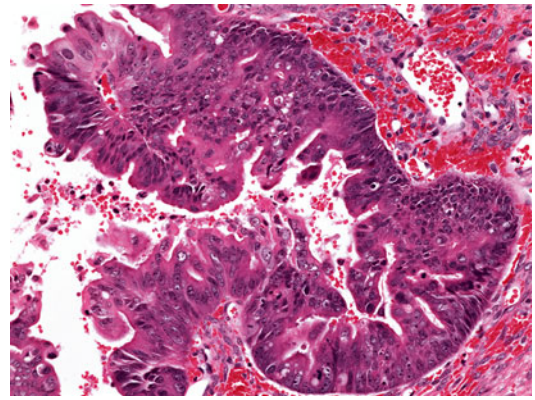

Fig. 10.36 Mucinous carcinoma. The glands are lined by malignant epithelial cells and almost complete loss of cytoplasmic mucin

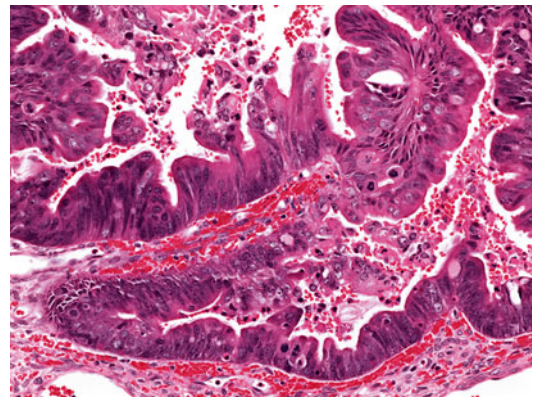

Fig. 10.37 Mucinous carcinoma. The tumor cells show variation in the degree of differentiation. Focally, goblet cells are still discernible

Gross Features

Tumors are usually large, solid, and cystic. Polypoid excrescences may be seen lining the cysts; soft or firm mucoid nodules may be found within the septa of the locules, often accompanied by necrosis and hemorrhage (Figs. 10.34 and 10.35). When sampling for histologic examination, it is crucial to take generous blocks from the solid areas, even though they may only represent a small portion in a large and seemingly cystic tumor.

Microscopic Features

Most cells show intestinal differentiation with prominent goblet cells, but some may represent endocervical-type cells [11]. The epithelium may form complex, crowded, fused, and cribriform glands, complex papillae, or solid nests. The cells usually are stratified to >4 cells in height, with loss of cytoplasmic mucin. The nuclei are severely pleomorphic (Figs. 10.36 and 10.37). In >80 % of carcinomas, there is often a coexisting benign and/or borderline tumor component. Presence of signet ring cells is exceptional, and a metastatic adenocarcinoma, particularly from the stomach, should always be excluded [48].

Mucinous Carcinoma with Expansile Invasion. About 50 % of mucinous carcinomas show expansile-type stromal invasion ("noninvasive," "intraglandular," or "confluent glandular" pattern) [6, 18, 31]. There is florid glandular proliferation without stromal support. The back-to-back

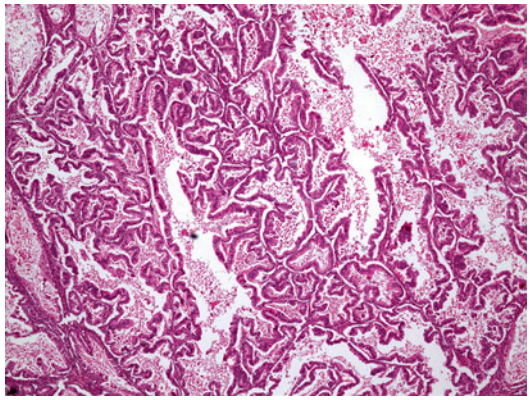

Fig. 10.38 Mucinous carcinoma, expansile invasion. Closely packed glands without intervening stroma

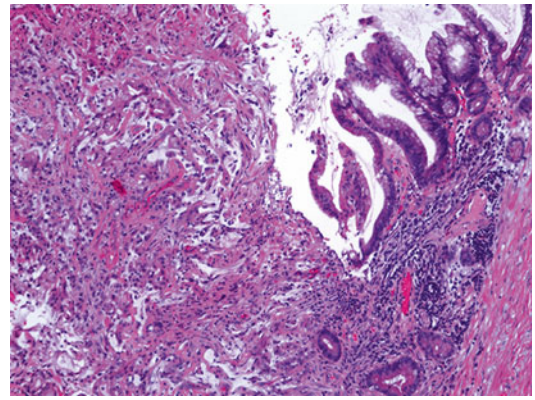

Fig. 10.40 Mucinous carcinoma, infiltrative invasion. Tumor glands irregularly infiltrate into the stroma

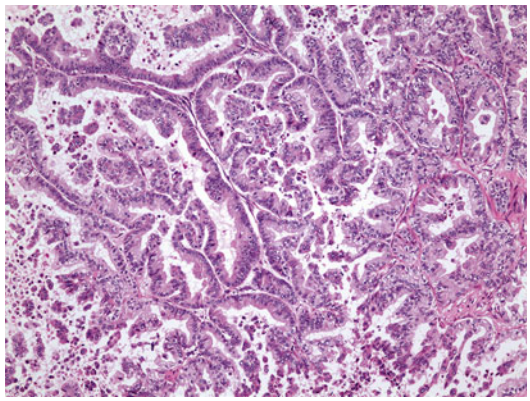

Fig. 10.39 Mucinous carcinoma, expansile invasion

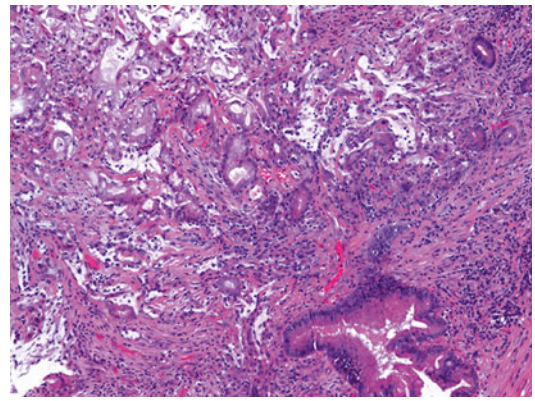

Fig. 10.41 Mucinous carcinoma, infiltrative invasion

cramped glands or cysts have almost no intervening stroma, creating a labyrinth or large cribriform gland patterns (Fig. 10.38 and 10.39).

Mucinous Carcinoma with Infiltrative Invasion. The invasion of interglandular space by irregular glands, cell clusters, or single cells results in destruction of the stroma and/or a desmoplastic reaction (Figs. 10.40, 10.41 and 10.42).

Differential Diagnosis

Mucinous Carcinoma with Expansile Invasion Versus IMBT with Intraepithelial Carcinoma: Distinguishing expansile invasion from IMBTs with intraepithelial carcinoma may be difficult and subjective. To qualify as frank mucinous

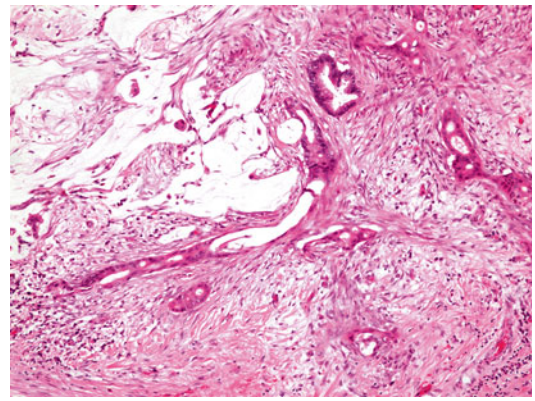

Fig. 10.42 Mucinous carcinoma, infiltrative invasion. Desmoplastic stromal reaction and mucin dissection of stroma

carcinoma, the focus of confluent glands in question should exceed the dimension for microinvasion (see section "Intestinal-type mucinous borderline tumors").

Mucinous Carcinoma Versus IMBT with Microinvasion: The invasive focus should exceed the dimension for microinvasion (see section "Intestinal-type mucinous borderline tumors").

Primary Versus Metastatic Mucinous Carcinoma: Metastatic mucinous carcinomas are more often bilateral, with a mean diameter of <10 cm, and commonly multinodular and show surface deposits. Histologically, a metastasis may show variation in the degree of cytologic atypia, ranging from areas resembling benign or borderline mucinous tumors to those with frankly malignant features. This has been described as the so-called maturation phenomenon and can potentially mimic a primary tumor [49]. The tumor glands are often arranged in nodules with variation in growth pattern between them, with infiltration of normal ovarian follicles or corpus albicans. Vascular invasion is usually prominent [50]. Immunohistochemistry is usually useful (see section "Immunohistochemistry of mucinous tumors").

Endometrioid Carcinoma Versus Mucinous Carcinoma: Endometrioid carcinomas may show abundant luminal mucin or mucin confined to the glycocalyx of the luminal aspect of the tumor cells. These should not be misinterpreted as mucinous carcinomas. Genuine mucinous differentiation should consist of cells with cytoplasmic mucin vacuoles stainable by mucicarmine in >50 % of cells.

Sertoli-Leydig Cell Tumor with Heterologous Elements Versus Ovarian Mucinous Tumor: Rarely, mucinous differentiation in a Sertoli-Leydig cell tumor may be overwhelming, and the gross appearance is that of a mucinous tumor. Histologically, however, typical sex cord tumor components are usually evident (Fig. 10.43) [51].

Prognostic Factors

FIGO stage is most important (Table 10.3). Approximately half of mucinous carcinomas are stage I, and the 5-year survival is 83 %. Those of stages II, III, and IV are 55, 21, and

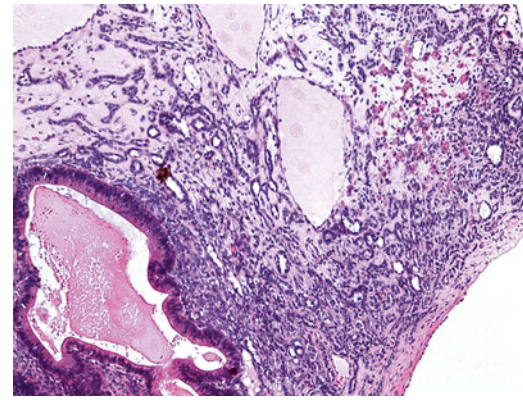

Fig. 10.43 Sertoli-Leydig cell tumor with heterologous mucinous epithelium

Table 10.3 International Federation of Gynecology and Obstetrics Staging System for Ovarian Cancer

I	Tumor limited to ovaries	
	Ia	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface, no malignant cells in ascites or peritoneal washings
	Ib	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface, no malignant cells in ascites or peritoneal washings
	Ic	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
II	Tumor involves one or both ovaries with pelvic extension	
	IIa	Extension and/or implants on uterus and/or tube(s); no malignant cells in ascites or peritoneal washings
	IIb	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings
	IIc	IIa or IIb with malignant cells in ascites or peritoneal washings
III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis	
	IIIa	Microscopic peritoneal metastasis beyond the pelvis
	IIIb	Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension
	IIIc	Peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis
	IV	Distant metastasis (excludes peritoneal metastasis)

Note: Liver capsule metastasis is stage III; liver parenchymal metastasis is stage IV. Pleural effusion must have positive cytology for stage IV

9 %, respectively [52]. The pattern of invasion appears to be more important than histologic grading. Mucinous carcinomas with expansile invasion are almost always stage I and are followed by an uneventful clinical course [1, 6]. Only two reported cases were associated with aggressive behavior [32]. The majority of stage II–IV mucinous carcinomas and stage I tumors that recurred were those with infiltrative invasion. Most of the latter were stage Ic. In excess of 90 % of patients, with high-stage carcinoma showing infiltrative invasion, died of their disease [6, 21, 22, 26–29]. An architectural grading using the same criteria as the FIGO grading for endometrial adenocarcinoma has not been shown to be useful in predicting outcome in stage I carcinomas [18, 21, 31]. However, higher architectural grade tumors were more likely to present at a higher stage [6]. In our experience, the majority of mucinous carcinomas are architecturally grade 2. In another study, nuclear grade 3 has been shown to be prognostically significant independent of stage [1].

Endocervical-Like Mucinous Carcinoma

Synonyms

(Endocervical-like, Müllerian, or seromucinous-type) mucinous carcinoma

Clinical Features

These are rare compared to those of intestinal type [39, 41]. The mean age of patients is 45 years, and the presentation is similar to those with mucinous carcinoma of intestinal type. There is also a strong association with endometriosis or endosalpingiosis [41]. Bilaterality is found in over 50 % of cases.

Gross Features

The tumors are usually cystic with either one or more locules. Their mean diameter is 12 cm. Polypoid excrescences may be found in the cyst lining, the ovarian surface, or both. The cyst content includes viscous brown to yellow mucin (Fig. 10.44).

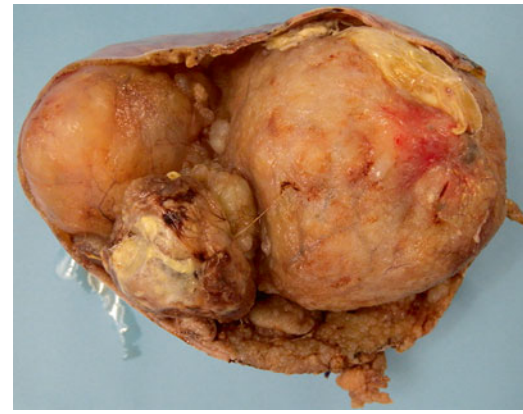

Fig. 10.44 Mucinous carcinoma, endocervical-like. There are often fewer locules compared with intestinal-type carcinomas. Note presence of smaller, polypoid excrescences (lower)

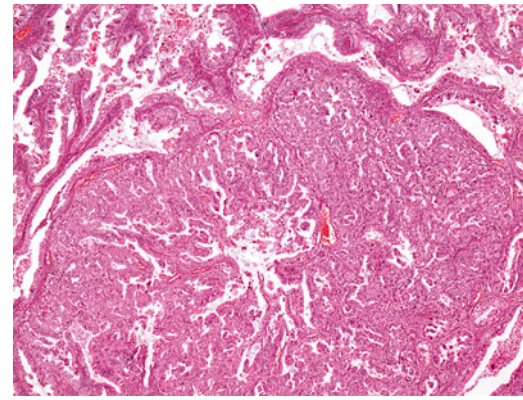

Fig. 10.45 Mucinous carcinoma, endocervical-like, with expansile invasion

Microscopic Features

Almost all endocervical-like mucinous carcinomas are found in association with EMBT. Patients who died of carcinomas of this subtype had tumors that showed, in addition to microscopic features of EMBTs, either frank stromal invasion or only a micropapillary architecture. All of these foci were >5 mm (Figs. 10.45 and 10.46) [41]. In addition to the usual cells types as found in EMBTs, some of these carcinomas also showed varying degrees of serous or endometrioid differentiation.

Prognostic Factors

Prognostic information on endocervical-like mucinous carcinoma is limited. Patients with

stage I tumors were followed by an uneventful outcome. At least half of those with stage II/III disease also had peritoneal invasive implants, two of which had a fatal outcome [39, 41, 53].

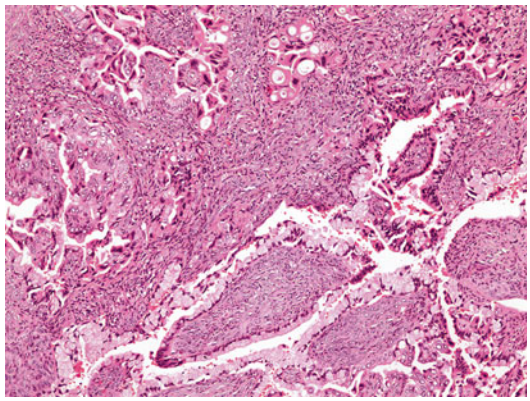

Fig. 10.46 Mucinous carcinoma, endocervical-like, with infiltrative invasion

Immunohistochemistry of Mucinous Tumors

Intestinal-type ovarian mucinous tumors express CK7 (diffusely), CK20, and CDX2 (patchily) (Fig. 10.47) [54–59]. Patchy staining with p16 may be observed and may be useful in distinguishing from metastatic endocervical carcinoma (diffusely positive) [60, 61]. DPC4 is usually expressed in primary mucinous tumors and may be useful for distinguishing from metastatic pancreatic and biliary tract carcinomas (negative in 50 %) [57, 62–64]. Intestinal-type ovarian mucinous tumors are generally nonimmunoreactive for estrogen and progesterone receptors, WT1, and CA-125 [54, 55, 65]. Tumors of teratomatous origin may exhibit typical colorectal carcinoma immunophenotype (CK20+, CDX2+, CEA+, and CK7−), and their use for distinguishing between the two may be impossible [65]. Endocervical-like mucinous

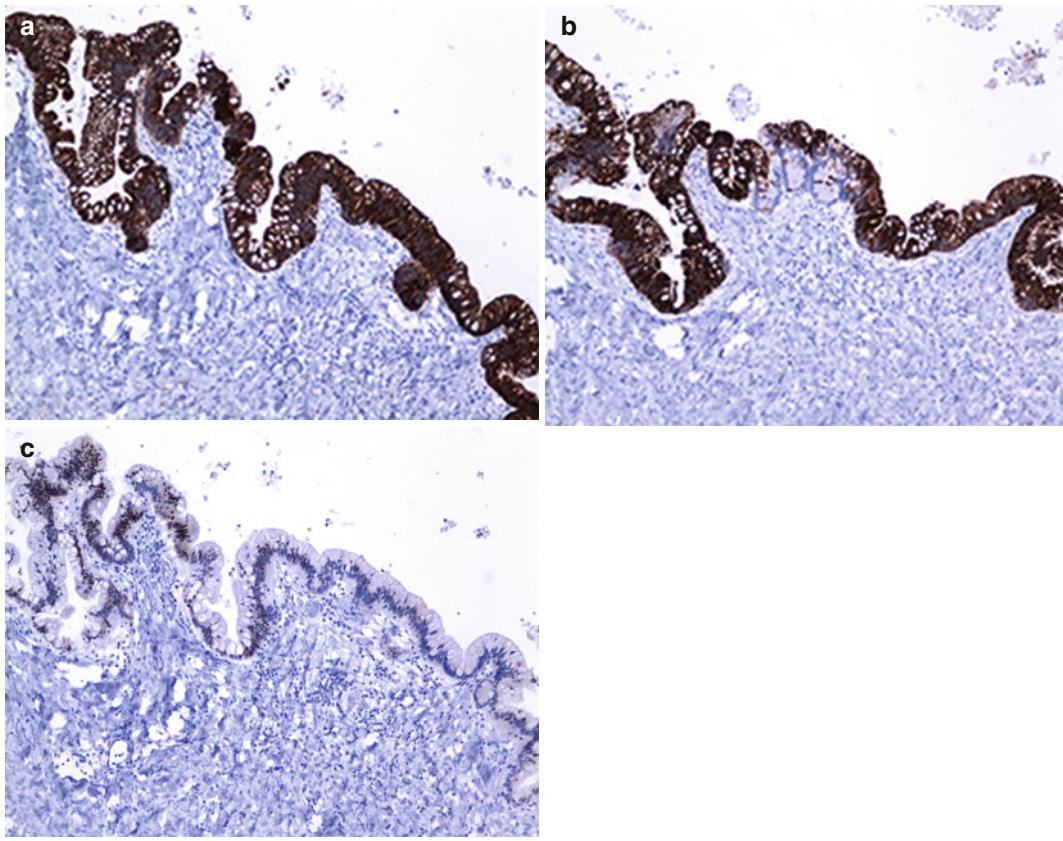

Fig. 10.47 Immunohistochemistry for a typical ovarian mucinous tumor with intestinal differentiation. (**a**) CK7, intense staining in all cells. (**b**) CK20, intense staining in most cells. (**c**) CDX2, moderate staining in a minority of cells

tumors are commonly positive for estrogen and progesterone receptors, CK7, and CA-125, but not for CK20, CDX2, or WT1 [56, 58, 59]. PAX8, a transcription factor for the paired box gene family, has been shown to be expressed in a variety of tumors of Müllerian and mesonephric origin and, in particular, is negative in gastrointestinal tumors and is therefore helpful in the differential diagnosis from metastatic adenocarcinoma. Probably because a large number of mucinous tumors show gastrointestinal differentiation, the expression of PAX8 is usually negative in those cases. In several studies, only 10–40 % of ovarian mucinous carcinomas and 19–23 % of mucinous cystadenomas/borderline tumors were positive for this marker [66–68]. PAX2, a transcription factor related to PAX8, is significantly less specific for use in female genital tract tumors than PAX8. In one study, none of the mucinous carcinomas were positive, and only 19 % of cystadenomas/borderline tumors were positive [66].

Mucinous Tumors Associated with Pseudomyxoma Peritonei

Pseudomyxoma peritonei (PP), or mucinous carcinoma peritonei [69], is a clinical syndrome referring to presence of abundant gelatinous, mucoid material adherent to peritoneal surfaces in the abdomen or pelvis (Fig. 10.48) [70]. Tumor cells are found within the mucin but the cellularity may be very low. The majority of PPs are a result of an appendiceal mucinous neoplasm with ovarian secondaries [14, 71–75]. Rarely, PP may be secondary to an intestinal tumor arising from an ovarian teratoma, commonly in a form of an IMBT [76, 77]. PP can also arise from mucinous carcinomas of other gastrointestinal sites, the breast and even lung, but these are exceptional [69].

In PP, the ovarian tumors are usually bilateral, but may be a unilateral right-sided tumor, often with surface involvement. The histologic appearance resembles ovarian IMBT (Figs. 10.49, 10.50, 10.51, and 10.52). In cases of appendiceal primaries, even though the appendix may be grossly normal, surgical resection with processing in its entirety for histologic examination is necessary.

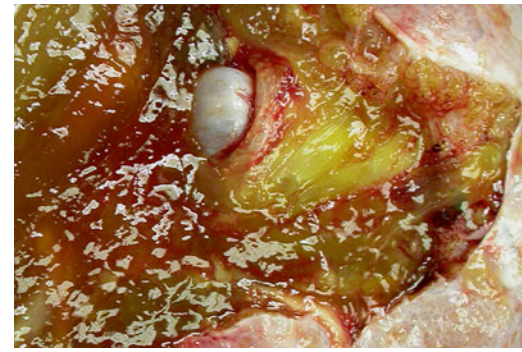

Fig. 10.48 Pseudomyxoma peritonei. Mucoid material occupies the peritoneum

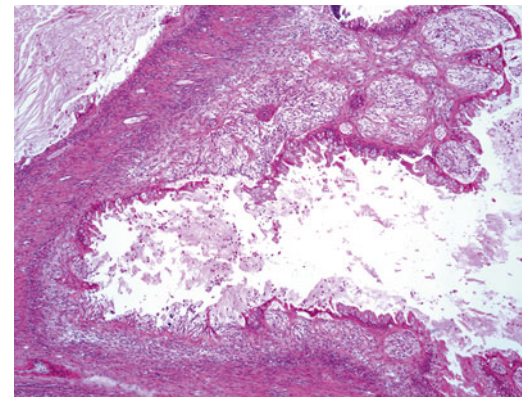

Fig. 10.49 Pseudomyxoma peritonei. Florid mucin granuloma formation in ovaries

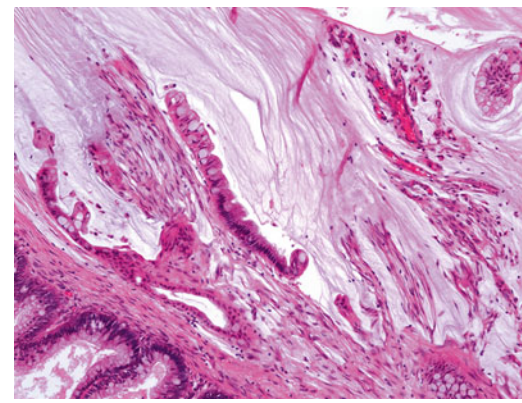

Fig. 10.50 Pseudomyxoma peritonei. Deceptively bland epithelial cells line the glands in the ovaries

This is because the lesion may be small and focal and may or may not show transmural invasion (Figs. 10.53, 10.54, and 10.55). The latter may

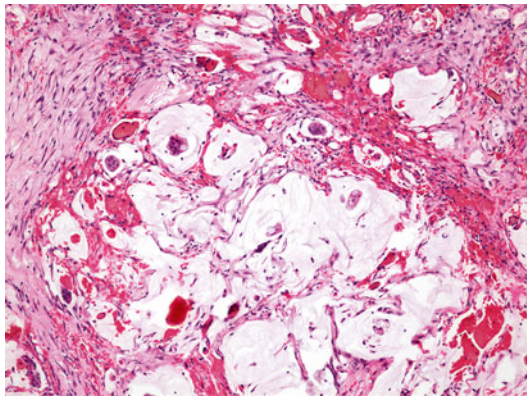

Fig. 10.51 Pseudomyxoma peritonei. Pseudomyxoma ovarii is present

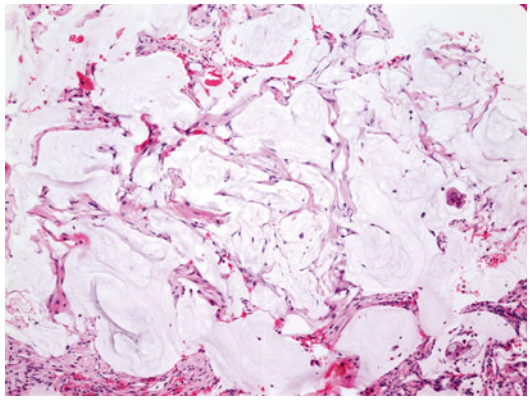

Fig. 10.52 Pseudomyxoma peritonei. Peritoneal mucin may be very low in cellularity

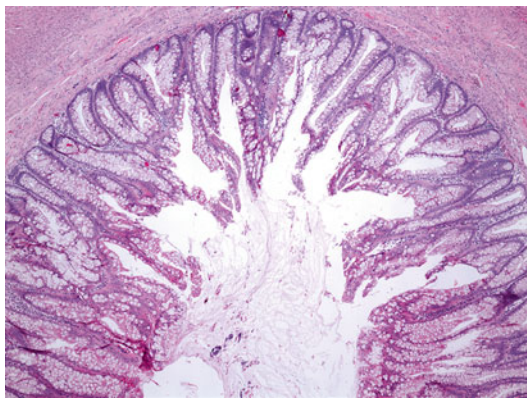

Fig. 10.53 Low-grade appendiceal mucinous neoplasm associated with pseudomyxoma peritonei. Mucosal proliferation without any invasion into the underlying muscularis propria

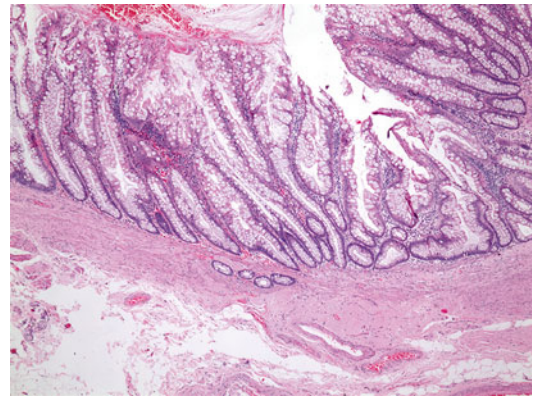

Fig. 10.54 Low-grade appendiceal mucinous neoplasm associated with pseudomyxoma peritonei. The mucosa shows villiform proliferation and covered by deceptively bland epithelium. Note localized thinning of the muscularis propria

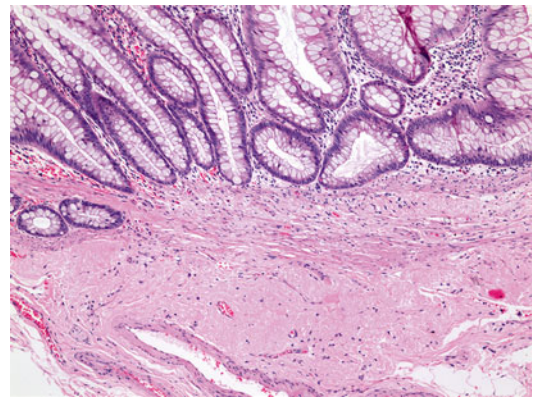

Fig. 10.55 Low-grade appendiceal mucinous neoplasm associated with pseudomyxoma peritonei. Thinning and interruption of the muscularis propria by fibrosis may be the only clue to a previously ruptured site

be due to the fact that the previously ruptured site has been sealed by fibrosis. The tumor may be a low-grade appendiceal mucinous neoplasm or a frank mucinous adenocarcinoma [69]. The incidence of detecting appendiceal mucinous neoplasms in cases of PP with ovarian mucinous tumors is, however, apparently less common in the Asian population [78].

Although immunohistochemistry is helpful in establishing the primary site in most cases, the intestinal-type immunoprofile of the appendix is identical to a minority of IMBTs arising from an

ovarian teratoma. In these cases, thorough histologic examination of the appendix is crucial. Currently, PP should be classified as high or low grade based on the architectural and cytologic features of the tumor cells inside the peritoneal mucin [69].

Mucinous Tumors with Mural Nodules

Benign, borderline, or malignant ovarian mucinous tumors may contain one or more mural nodules which are morphologically different from the preexisting mucinous epithelium. They have been classified into sarcoma-like mural nodules (SLMN), nodules of anaplastic carcinomas (NAC), and true sarcomas. Mixed forms also occur and sometimes it may be difficult to distinguish one from another [79–83]. Despite the favorable prognosis reported in SLMNs and NACs, it should be noted that the prognosis of such lesions would also be dependent on whether or not the preexisting mucinous tumor is a carcinoma and, if so, whether it shows expansile or infiltrative invasion.

SLMNs usually occur in young women (mean, 39 years). Grossly, they represent ≥1 discrete red-brown nodule usually 0.6–6 cm in size and sharply demarcated from the adjacent mucinous tumor. Histologically, the nodule shows a circumscribed proliferation of highly atypical cells comprising multinucleated epulis-like giant cells and malignant-looking spindle cells in a background of inflammatory cells (Figs. 10.56, 10.57, 10.58, and 10.59). The giant cells are usually immunoreactive for histiocytic markers, while the spindle cells are usually negative for cytokeratins [84]. In 50 %, the preexisting mucinous tumor is a carcinoma. Similar cases have been reported in extraovarian sites and rarely have heterologous elements such as osteoid [85]. Of the reported cases of SLMNs, the clinical courses have been benign [82].

NACs may be subclassified according to cell types. These include rhabdoid, sarcomatoid, or pleomorphic. Rhabdoid cells are large and have abundant eosinophilic cytoplasm, eccentric nuclei

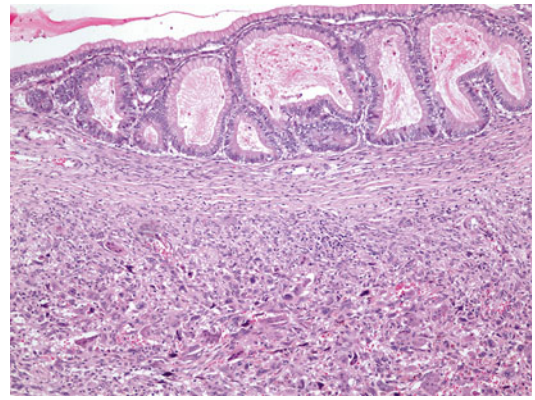

Fig. 10.56 Sarcoma-like mural nodule in mucinous neoplasm. The two components are sharply demarcated from one another

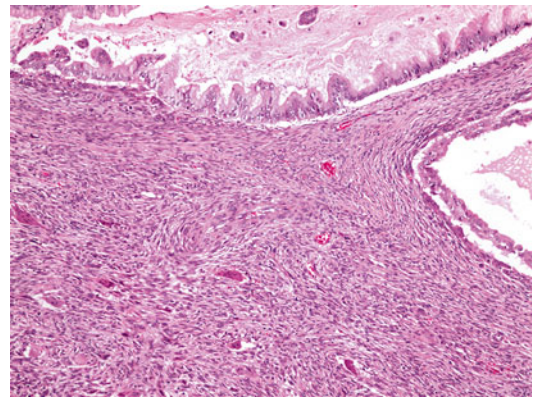

Fig. 10.57 Sarcoma-like mural nodule in mucinous neoplasm. The sarcomatous component contains spindle cells

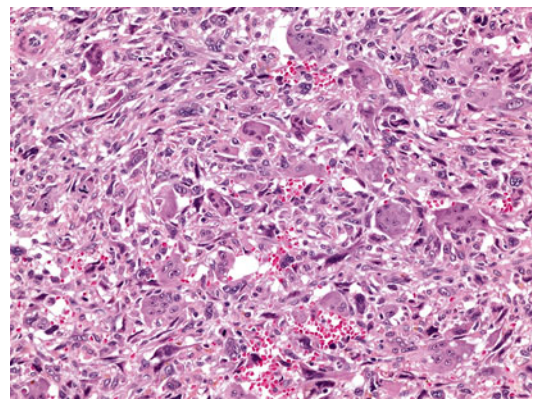

Fig. 10.58 Sarcoma-like mural nodule in mucinous neoplasm. The sarcomatous component is cytologically malignant

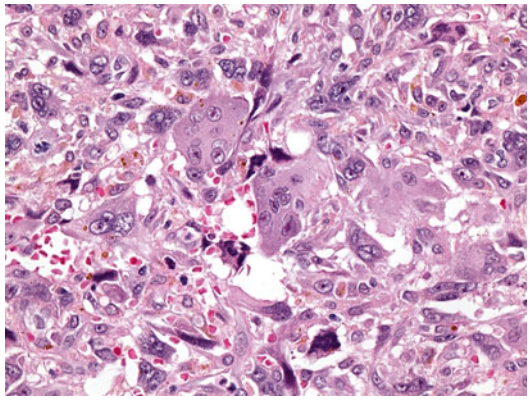

Fig. 10.59 Sarcoma-like mural nodule in mucinous neoplasm. Osteoclast-like giant cells

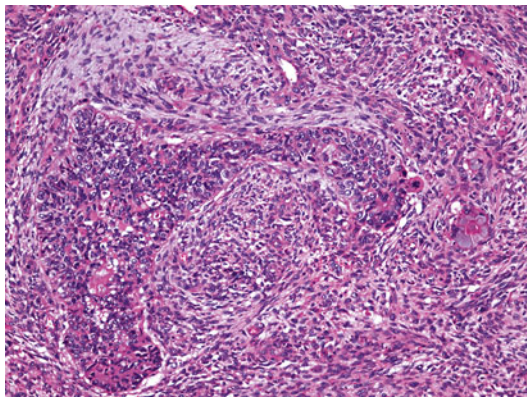

Fig. 10.60 Malignant Müllerian mixed tumor. The carcinomatous and sarcomatous components are well merged together, in contrast to sarcoma-like mural nodules in Fig. 10.56

with prominent nucleoli. The sarcomatoid cells are spindle cells arranged in a herringbone pattern and are immunoreactive for cytokeratin, in contrast to the spindle cells in SLMNs, as noted above. The pleomorphic subtype contains an admixture of rhabdoid and sarcomatoid spindle cells [83]. These nodules may measure up to 10 cm in size and can be multiple. In contrast to SLMNs, NACs have infiltrative borders and show invasion of the surrounding stroma, often with vascular invasion and coagulative tumor necrosis. Although the presence of NAC has not been shown to be an adverse prognostic factor for stage I mucinous tumors, experience with these cases is still limited and distinction from true sarcoma may be difficult in some cases.

True sarcomatous nodules such as fibrosarcoma and rhabdomyosarcoma are aggressive tumors [86, 87].

Mural nodules must be distinguished from carcinosarcoma (malignant mesodermal mixed tumors). In contrast to mural nodules, carcinosarcomas are biphasic and the carcinoma component is intimately mixed or merged with the malignant spindle cells (Fig. 10.60).

References

1. Rodriguez IM, Prat J. Mucinous tumors of the ovary: a clinicopathologic analysis of 75 borderline tumors (of intestinal type) and carcinomas. Am J Surg Pathol. 2002;26(2):139–52.
2. Cuatrecasas M, Villanueva A, Matias-Guiu X, Prat J. K-ras mutations in mucinous ovarian tumors: a clinicopathologic and molecular study of 95 cases. Cancer. 1997;79(8):1581–6.
3. Gemignani ML, Schlaerth AC, Bogomolniy F, Barakat RR, Lin O, Soslow R, et al. Role of KRAS and BRAF gene mutations in mucinous ovarian carcinoma. Gynecol Oncol. 2003;90(2):378–81.
4. Mayr D, Hirschmann A, Lohrs U, Diebold J. KRAS and BRAF mutations in ovarian tumors: a comprehensive study of invasive carcinomas, borderline tumors and extraovarian implants. Gynecol Oncol. 2006;103(3):883–7.
5. Kurman RJ, Shih IM. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. Int J Gynecol Pathol. 2008;27(2):151–60.
6. Lee KR, Scully RE. Mucinous tumors of the ovary: a clinicopathologic study of 196 borderline tumors (of intestinal type) and carcinomas, including an evaluation of 11 cases with "pseudomyxoma peritonei". Am J Surg Pathol. 2000;24(11):1447–64.
7. Mok SC, Bell DA, Knapp RC, Fishbaugh PM, Welch WR, Muto MG, et al. Mutation of K-ras protooncogene in human ovarian epithelial tumors of borderline malignancy. Cancer Res. 1993;53(7):1489–92.
8. Hunter SM, Gorringe KL, Christie M, Rowley SM, Bowtell DD, Campbell IG. Pre-invasive ovarian mucinous tumors are characterized by CDKN2A and RAS pathway aberrations. Clin Cancer Res. 2012; 18(19):5267–77.
9. McAlpine JN, Wiegand KC, Vang R, Ronnett BM, Adamiak A, Kobel M, et al. HER2 overexpression and amplification is present in a subset of ovarian mucinous carcinomas and can be targeted with trastuzumab therapy. BMC Cancer. 2009;9:433.

10. Anglesio M, Kommoss S, Tolcher M. Molecular characterization of mucinous ovarian tumors supports a stratified treatment approach with HER2 targeting in 19 % of carcinomas. J Pathol. 2013;229(1):111–20.
11. Scully RE, Young RH, Clement PB. Mucinous tumors and pseudomyxoma peritonei. In: Rosai JS, Sobin LH, editors. Atlas of tumor pathology tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Washington DC: Armed Forces Institute of Pathology; 1998. p. 81–105.
12. Rutgers JL, Scully RE. Ovarian mullerian mucinous papillary cystadenomas of borderline malignancy. A clinicopathologic analysis. Cancer. 1988;61(2):340–8.
13. Hart WR. Ovarian epithelial tumors of borderline malignancy (carcinomas of low malignant potential). Hum Pathol. 1977;8(5):541–9.
14. Young RH, Gilks CB, Scully RE. Mucinous tumors of the appendix associated with mucinous tumors of the ovary and pseudomyxoma peritonei. A clinicopathological analysis of 22 cases supporting an origin in the appendix. Am J Surg Pathol. 1991;15(5):415–29.
15. Hart WR. Borderline epithelial tumors of the ovary. Mod Pathol. 2005;18 Suppl 2:S33–50.
16. Hart WR. Mucinous tumors of the ovary: a review. Int J Gynecol Pathol. 2005;24(1):4–25.
17. Nomura K, Aizawa S, Hano H. Ovarian mucinous borderline tumors of intestinal type without intraepithelial carcinoma: are they still tumors of low malignant potential? Pathol Int. 2004;54(6):420–4.
18. Riopel MA, Ronnett BM, Kurman RJ. Evaluation of diagnostic criteria and behavior of ovarian intestinal-type mucinous tumors: atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive, and metastatic carcinomas. Am J Surg Pathol. 1999;23(6):617–35.
19. de Nictolis M, Montironi R, Tommasoni S, Valli M, Pisani E, Fabris G, et al. Benign, borderline, and well-differentiated malignant intestinal mucinous tumors of the ovary: a clinicopathologic, histochemical, immunohistochemical, and nuclear quantitative study of 57 cases. Int J Gynecol Pathol. 1994;13(1):10–21.
20. Siriaunkgul S, Robbins KM, McGowan L, Silverberg SG. Ovarian mucinous tumors of low malignant potential: a clinicopathologic study of 54 tumors of intestinal and mullerian type. Int J Gynecol Pathol. 1995;14(3):198–208.
21. Guerrieri C, Hogberg T, Wingren S, Fristedt S, Simonsen E, Boeryd B. Mucinous borderline and malignant tumors of the ovary. A clinicopathologic and DNA ploidy study of 92 cases. Cancer. 1994; 74(8):2329–40.
22. Hart WR, Norris HJ. Borderline and malignant mucinous tumors of the ovary. Histologic criteria and clinical behavior. Cancer. 1973;31(5):1031–45.
23. Kim KR, Lee HI, Lee SK, Ro JY, Robboy SJ. Is stromal microinvasion in primary mucinous ovarian tumors with "mucin granuloma" true invasion? Am J Surg Pathol. 2007;31(4):546–54.
24. Ronnett BM, Kajdacsy-Balla A, Gilks CB, Merino MJ, Silva E, Werness BA, et al. Mucinous borderline ovarian tumors: points of general agreement and persistent controversies regarding nomenclature, diagnostic criteria, and behavior. Hum Pathol. 2004; 35(8):949–60.
25. Seidman JD, Soslow RA, Vang R, Berman JJ, Stoler MH, Sherman ME, et al. Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. Hum Pathol. 2004;35(8):918–33.
26. Nomura K, Aizawa S. Noninvasive, microinvasive, and invasive mucinous carcinomas of the ovary: a clinicopathologic analysis of 40 cases. Cancer. 2000; 89(7):1541–6.
27. Chaitin BA, Gershenson DM, Evans HL. Mucinous tumors of the ovary. A clinicopathologic study of 70 cases. Cancer. 1985;55(9):1958–62.
28. Sumithran E, Susil BJ, Looi LM. The prognostic significance of grading in borderline mucinous tumors of the ovary. Hum Pathol. 1988;19(1):15–8.
29. Watkin W, Silva EG, Gershenson DM. Mucinous carcinoma of the ovary. Pathologic prognostic factors. Cancer. 1992;69(1):208–12.
30. Kikkawa F, Kawai M, Tamakoshi K, Suganuma N, Nakashima N, Furuhashi Y, et al. Mucinous carcinoma of the ovary. Clinicopathologic analysis. Oncology. 1996;53(4):303–7.
31. Hoerl HD, Hart WR. Primary ovarian mucinous cystadenocarcinomas: a clinicopathologic study of 49 cases with long-term follow-up. Am J Surg Pathol. 1998;22(12):1449–62.
32. Ludwick C, Gilks CB, Miller D, Yaziji H, Clement PB. Aggressive behavior of stage I ovarian mucinous tumors lacking extensive infiltrative invasion: a report of four cases and review of the literature. Int J Gynecol Pathol. 2005;24(3):205–17.
33. Young RH, Hart WR. Metastases from carcinomas of the pancreas simulating primary mucinous tumors of the ovary. A report of seven cases. Am J Surg Pathol. 1989;13(9):748–56.
34. Nayar R, Siriaunkgul S, Robbins KM, McGowan L, Ginzan S, Silverberg SG. Microinvasion in low malignant potential tumors of the ovary. Hum Pathol. 1996;27(6):521–7.
35. Khunamornpong S, Russell P, Dalrymple JC. Proliferating (LMP) mucinous tumors of the ovaries with microinvasion: morphologic assessment of 13 cases. Int J Gynecol Pathol. 1999;18(3):238–46.
36. Salomon LJ, Lhomme C, Pautier P, Duvillard P, Morice P. Safety of simple cystectomy in patients with unilateral mucinous borderline tumors. Fertil Steril. 2006;85(5):1510.e1–4.
37. Koskas M, Uzan C, Gouy S, Pautier P, Lhomme C, Haie-Meder C, et al. Prognostic factors of a large retrospective series of mucinous borderline tumors of the ovary (excluding peritoneal pseudomyxoma). Ann Surg Oncol. 2011;18(1):40–8.
38. Rutgers JL, Scully RE. Ovarian mixed-epithelial papillary cystadenomas of borderline malignancy of mullerian type. A clinicopathologic analysis. Cancer. 1988;61(3):546–54.

39. Dube V, Roy M, Plante M, Renaud MC, Tetu B. Mucinous ovarian tumors of Mullerian-type: an analysis of 17 cases including borderline tumors and intraepithelial, microinvasive, and invasive carcinomas. Int J Gynecol Pathol. 2005;24(2):138–46.
40. Rodriguez IM, Irving JA, Prat J. Endocervical-like mucinous borderline tumors of the ovary: a clinicopathologic analysis of 31 cases. Am J Surg Pathol. 2004;28(10):1311–8.
41. Shappell HW, Riopel MA, Smith Sehdev AE, Ronnett BM, Kurman RJ. Diagnostic criteria and behavior of ovarian seromucinous (endocervical-type mucinous and mixed cell-type) tumors: atypical proliferative (borderline) tumors, intraepithelial, microinvasive, and invasive carcinomas. Am J Surg Pathol. 2002; 26(12):1529–41.
42. Nomura K, Aizawa S. Clinicopathologic and mucin histochemical analyses of 90 cases of ovarian mucinous borderline tumors of intestinal and mullerian types. Pathol Int. 1996;46(8):575–80.
43. Korourian S, McKenney J, de Las Casas LE. Endocervical-like mucinous borderline tumors. Am J Surg Pathol. 2005;29(3):424; author reply.
44. Seidman JD, Horkayne-Szakaly I, Haiba M, Boice CR, Kurman RJ, Ronnett BM. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. Int J Gynecol Pathol. 2004;23(1):41–4.
45. Gilks CB. Subclassification of ovarian surface epithelial tumors based on correlation of histologic and molecular pathologic data. Int J Gynecol Pathol. 2004;23(3):200–5.
46. Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95 Suppl 1:S161–92.
47. Kelly PJ, Archbold P, Price JH, Cardwell C, McCluggage WG. Serum CA19.9 levels are commonly elevated in primary ovarian mucinous tumours but cannot be used to predict the histological subtype. J Clin Pathol. 2010;63(2):169–73.
48. McCluggage WG, Young RH. Primary ovarian mucinous tumors with signet ring cells: report of 3 cases with discussion of so-called primary Krukenberg tumor. Am J Surg Pathol. 2008;32(9):1373–9.
49. Young RH, Scully RE. Metastatic tumors in the ovary: a problem-oriented approach and review of the recent literature. Semin Diagn Pathol. 1991;8(4):250–76.
50. Lee KR, Young RH. The distinction between primary and metastatic mucinous carcinomas of the ovary: gross and histologic findings in 50 cases. Am J Surg Pathol. 2003;27(3):281–92.
51. Young RH. Sertoli-Leydig cell tumors of the ovary: review with emphasis on historical aspects and unusual variants. Int J Gynecol Pathol. 1993;12(2):141–7.
52. Pettersson F. Annual report of the results of treatment in gynecological cancer. Stockholm: International Federation of Gynecology and Obstetrics; 1991.
53. Lee KR, Nucci MR. Ovarian mucinous and mixed epithelial carcinomas of mullerian (endocervical-like) type: a clinicopathologic analysis of four cases of an uncommon variant associated with endometriosis. Int J Gynecol Pathol. 2003;22(1):42–51.
54. McCluggage WG. Immunohistochemical and functional biomarkers of value in female genital tract lesions. Int J Gynecol Pathol. 2006;25(2):101–20.
55. Baker PM, Oliva E. Immunohistochemistry as a tool in the differential diagnosis of ovarian tumors: an update. Int J Gynecol Pathol. 2005;24(1):39–55.
56. Vang R, Gown AM, Barry TS, Wheeler DT, Yemelyanova A, Seidman JD, et al. Cytokeratins 7 and 20 in primary and secondary mucinous tumors of the ovary: analysis of coordinate immunohistochemical expression profiles and staining distribution in 179 cases. Am J Surg Pathol. 2006;30(9):1130–9.
57. Ji H, Isacson C, Seidman JD, Kurman RJ, Ronnett BM. Cytokeratins 7 and 20, Dpc4, and MUC5AC in the distinction of metastatic mucinous carcinomas in the ovary from primary ovarian mucinous tumors: Dpc4 assists in identifying metastatic pancreatic carcinomas. Int J Gynecol Pathol. 2002;21(4):391–400.
58. Vang R, Gown AM, Barry TS, Wheeler DT, Ronnett BM. Ovarian atypical proliferative (borderline) mucinous tumors: gastrointestinal and seromucinous (endocervical-like) types are immunophenotypically distinctive. Int J Gynecol Pathol. 2006;25(1):83–9.
59. Vang R, Gown AM, Wu LS, Barry TS, Wheeler DT, Yemelyanova A, et al. Immunohistochemical expression of CDX2 in primary ovarian mucinous tumors and metastatic mucinous carcinomas involving the ovary: comparison with CK20 and correlation with coordinate expression of CK7. Mod Pathol. 2006; 19(11):1421–8.
60. Vang R, Gown AM, Farinola M, Barry TS, Wheeler DT, Yemelyanova A, et al. p16 expression in primary ovarian mucinous and endometrioid tumors and metastatic adenocarcinomas in the ovary: utility for identification of metastatic HPV-related endocervical adenocarcinomas. Am J Surg Pathol. 2007;31(5): 653–63.
61. Ronnett BM, Yemelyanova AV, Vang R, Gilks CB, Miller D, Gravitt PE, et al. Endocervical adenocarcinomas with ovarian metastases: analysis of 29 cases with emphasis on minimally invasive cervical tumors and the ability of the metastases to simulate primary ovarian neoplasms. Am J Surg Pathol. 2008;32(12): 1835–53.
62. Argani P, Shaukat A, Kaushal M, Wilentz RE, Su GH, Sohn TA, et al. Differing rates of loss of DPC4 expression and of p53 overexpression among carcinomas of the proximal and distal bile ducts. Cancer. 2001; 91(7):1332–41.
63. Tascilar M, Offerhaus GJ, Altink R, Argani P, Sohn TA, Yeo CJ, et al. Immunohistochemical labeling for the Dpc4 gene product is a specific marker for adenocarcinoma in biopsy specimens of the pancreas and bile duct. Am J Clin Pathol. 2001;116(6):831–7.
64. Schutte M, Hruban RH, Hedrick L, Cho KR, Nadasdy GM, Weinstein CL, et al. DPC4 gene in various tumor types. Cancer Res. 1996;56(11):2527–30.

65. McCluggage WG. Immunohistochemistry in the distinction between primary and metastatic ovarian mucinous neoplasms. J Clin Pathol. 2012;65(7):596–600.
66. Ozcan A, Liles N, Coffey D, Shen SS, Truong LD. PAX2 and PAX8 expression in primary and metastatic mullerian epithelial tumors: a comprehensive comparison. Am J Surg Pathol. 2011;35(12):1837–47.
67. Ozcan A, Shen SS, Hamilton C, Anjana K, Coffey D, Krishnan B, et al. PAX 8 expression in non-neoplastic tissues, primary tumors, and metastatic tumors: a comprehensive immunohistochemical study. Mod Pathol. 2011;24(6):751–64.
68. Nonaka D, Chiriboga L, Soslow RA. Expression of pax8 as a useful marker in distinguishing ovarian carcinomas from mammary carcinomas. Am J Surg Pathol. 2008;32(10):1566–71.
69. Carr NJ, Sobin LH. Adenocarcinoma of the appendix. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2010. p. 122–5.
70. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol. 1995;19(12):1390–408.
71. Chuaqui RF, Zhuang Z, Emmert-Buck MR, Bryant BR, Nogales F, Tavassoli FA, et al. Genetic analysis of synchronous mucinous tumors of the ovary and appendix. Hum Pathol. 1996;27(2):165–71.
72. Ronnett BM, Shmookler BM, Diener-West M, Sugarbaker PH, Kurman RJ. Immunohistochemical evidence supporting the appendiceal origin of pseudomyxoma peritonei in women. Int J Gynecol Pathol. 1997;16(1):1–9.
73. Ronnett BM, Shmookler BM, Sugarbaker PH, Kurman RJ. Pseudomyxoma peritonei: new concepts in diagnosis, origin, nomenclature, and relationship to mucinous borderline (low malignant potential) tumors of the ovary. Anat Pathol. 1997;2:197–226.
74. Cuatrecasas M, Matias-Guiu X, Prat J. Synchronous mucinous tumors of the appendix and the ovary associated with pseudomyxoma peritonei. A clinicopathologic study of six cases with comparative analysis of c-Ki-ras mutations. Am J Surg Pathol. 1996;20(6):739–46.
75. Szych C, Staebler A, Connolly DC, Wu R, Cho KR, Ronnett BM. Molecular genetic evidence supporting the clonality and appendiceal origin of Pseudomyxoma peritonei in women. Am J Pathol. 1999;154(6):1849–55.
76. McKenney JK, Soslow RA, Longacre TA. Ovarian mature teratomas with mucinous epithelial neoplasms: morphologic heterogeneity and association with pseudomyxoma peritonei. Am J Surg Pathol. 2008;32(5):645–55.
77. Vang R, Gown AM, Zhao C, Barry TS, Isacson C, Richardson MS, et al. Ovarian mucinous tumors associated with mature cystic teratomas: morphologic and immunohistochemical analysis identifies a subset of potential teratomatous origin that shares features of lower gastrointestinal tract mucinous tumors more commonly encountered as secondary tumors in the ovary. Am J Surg Pathol. 2007;31(6):854–69.
78. Shen DH, Ng TY, Khoo US, Xue WC, Cheung AN. Pseudomyxoma peritonei – a heterogenous disease. Int J Gynaecol Obstet. 1998;62(2):173–82.
79. Prat J, Scully RE. Ovarian mucinous tumors with sarcoma-like mural nodules: a report of seven cases. Cancer. 1979;44(4):1332–44.
80. Prat J, Scully RE. Sarcomas in ovarian mucinous tumors: a report of two cases. Cancer. 1979;44(4):1327–31.
81. Prat J, Young RH, Scully RE. Ovarian mucinous tumors with foci of anaplastic carcinoma. Cancer. 1982;50(2):300–4.
82. Bague S, Rodriguez IM, Prat J. Sarcoma-like mural nodules in mucinous cystic tumors of the ovary revisited: a clinicopathologic analysis of 10 additional cases. Am J Surg Pathol. 2002;26(11):1467–76.
83. Provenza C, Young RH, Prat J. Anaplastic carcinoma in mucinous ovarian tumors: a clinicopathologic study of 34 cases emphasizing the crucial impact of stage on prognosis, their histologic spectrum, and overlap with sarcomalike mural nodules. Am J Surg Pathol. 2008;32(3):383–9.
84. Matias-Guiu X, Aranda I, Prat J. Immunohistochemical study of sarcoma-like mural nodules in a mucinous cystadenocarcinoma of the ovary. Virchows Arch A Pathol Anat Histopathol. 1991;419(2):89–92.
85. Fan YS, Thomas TM, Ip PP, Cheung AN. Osteoid-forming sarcoma-like mural nodule in a retroperitoneal mucinous cystadenocarcinoma. Histopathology. 2006;49(2):201–4.
86. Scully RE, Young RH, Clement PB. Stroma tumors. In: Rosai JS, Sobin LH, editors. Atlas of tumor pathology tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Washington DC: Armed Forces Institute of Pathology; 1998. p. 189–202.
87. Scully RE, Young RH, Clement PB. Miscellaneous primary tumors. In: Rosai JS, Sobin LH, editors. Atlas of tumor pathology tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Washington DC: Armed Forces Institute of Pathology; 1988. p. 315–6.