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Borderline and Malignant Surface Epithelial – Stromal Tumors of the Ovary

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1. Introduction

Epithelial ovarian carcinoma (EOC) is the fourth leading cause of cancer mortality among women in western countries. The incidence of newly diagnosed EOC in the US is estimated to be 22,430 cases per year with 15,280 deaths (**Jamel A et al., 2006**). Surface epithelial-stromal tumors are the most common neoplasms of the ovary. Their origin is likely the epithelium lining the ovarian surface and/or invaginations of this lining into the superficial cortex of the ovary. They occur in women of reproductive age and older. They are usually subclassified as benign, borderline and malignant. Due to the numerous histologic types of ovarian neoplasms, we will limit our discussion to the most common epithelial stromal tumors. We will be discussing the gross appearances, microscopic patterns and differential diagnosis.

Based on the 2002 World Health Organization (WHO) classification of ovarian tumors (**Tavassoli FA and Devilee P, 2003**), Borderline and Malignant Surface-epithelial stromal tumors are classified as:

1.1 WHO classification

Serous tumors

Malignant

- Adenocarcinoma
- Surface papillary adenocarcinoma
- Adenocarcinofibroma

Borderline tumor

- Papillary cystic tumor
- Adenofibroma and cystadenofibroma

Mucinous tumors

Malignant

- Adenocarcinoma

- Adenocarcinofibroma
- Borderline tumor
 - Intestinal type
 - Endocervical type
- Mucinous cystic tumor with mural nodules
- Mucinous cystic tumor with pseudomyxoma peritonei

Endometrioid tumors including variants with squamous differentiation

- Malignant
 - Adenocarcinoma, NOS
 - Adenocarcinofibroma
 - Malignant mullerian mixed tumor (carcinosarcoma)
 - Adenosarcoma
 - Endometrial stromal sarcoma, low grade
 - Undifferentiated sarcoma
- Borderline tumor
 - Cystic tumor
 - Adenofibroma and cystadenofibroma

Clear cell tumors

- Malignant
 - Adenocarcinoma
 - Adenocarcinofibroma
- Borderline tumor
 - Cystic tumor
 - Adenofibroma and cystadenofibroma

Transitional cell tumors

- Malignant
 - Transitional cell carcinoma (non-Brenner type)
 - Malignant Brenner tumor
- Borderline
 - Borderline Brenner tumor

Squamous cell tumors

- Squamous cell carcinoma

Mixed epithelial tumors

Undifferentiated and unclassified tumors.

2. Serous tumors

2.1 Borderline tumors

Serous borderline tumors (SBT) represent 25% to 30% of non benign serous tumors and occur in women 30-50 years of age. In the majority of cases they are unilateral and usually present at an early stage (stage I) (Prat J and de Nictolis M., 2002). The WHO defines SBT as an “ovarian tumor of low malignant potential exhibiting an atypical epithelial proliferation of serous type cells greater than that seen in its benign counterpart but without destructive stromal invasion”.

Grossly, the mass is usually partially cystic and partially solid. Polypoid excrescences are present on the outer surface of the ovary or within the cyst lumen **Fig.2.1.a,b**.

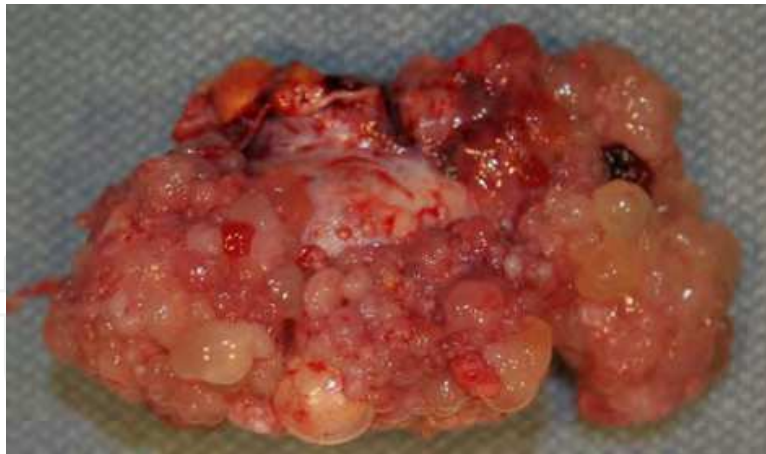


Fig. 2.1.a. Borderline serous tumor (BST). The ovary shows polypoid excrescences on its outer surface.

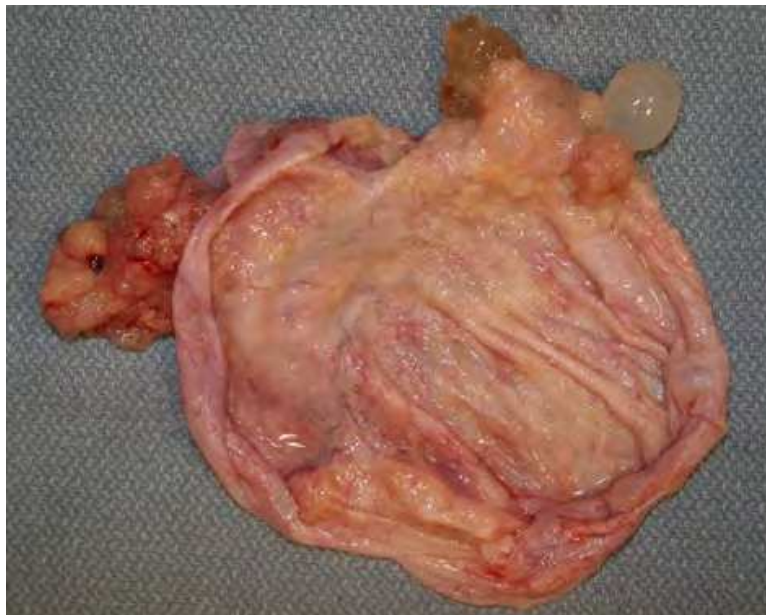


Fig. 2.1.b. BST. In another case, instead of polypoid excrescences on the outer surface of the ovary, papillary projections are seen within the cyst lumen of the ovary.

The papillary structures are yellowish, soft and friable. Grossly, SBT should be differentiated from the hard, stocky, white excrescences that are usually a characteristic of serous cystadenofibroma.

SBTs are divided into typical and micropapillary patterns.

2.1.1 Typical SBT

Typical SBT makes up the majority of SBT (90%). Microscopically, the papillae are lined by stratified cuboidal to columnar epithelial cells. These papillae show branching and complex structure. The epithelial cells have high nuclear cytoplasmic ratio (N/C), and the nuclei are hyperchromatic with prominent nucleoli. Mitotic figures are frequently present **Fig 2.1.1 a,b.**

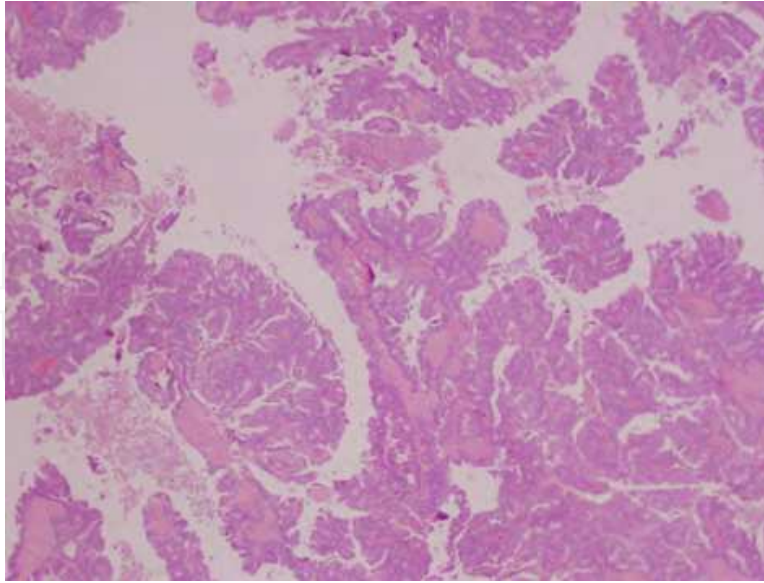


Fig. 2.1.1.a. BST: At the low magnification, the tumor is composed of papillary projections.

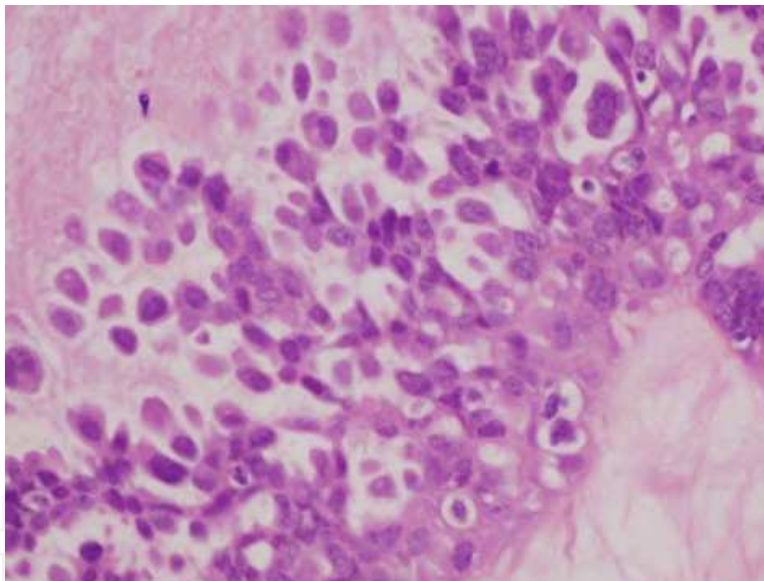


Fig. 2.1.1.b. BST: At higher magnification, the papillae are lined by epithelial cells exhibiting severe pleomorphism with moderate to severe atypia and with high nuclear/cytoplasmic ratio. They have big round nuclei and prominent nucleoli.

Caution should be practiced when one sees what appears to be epithelial proliferation without cytologic atypia, because tangential sectioning of the lining of a benign serous cystadenoma can give the impression of proliferation of the epithelial lining.

By definition, SBT lack stromal invasion. This is a major criterion to differentiate SBT from serous adenocarcinoma. Careful gross examination, as well several sections (1 section/1 cm of the tumor diameter) is needed. Finally, invasion of the stalk of the papillae should not be considered as ovarian stromal invasion.

2.1.2 SBT with micropapillary pattern or micropapillary SBT (MSBT)

SBT with micropapillary pattern or micropapillary SBT (MSBT) accounts 5-10% of all SBTs. The significance of this subtype has generated a lot of debate in pathology. Some authors have found a close association between MSBT and invasive implants and urged to call this entity as “micropapillary serous carcinoma”. Yet others prefer the terminology of MSBT, avoiding the use of the term of “carcinoma”, to minimize the possibility of over treating patients (Chang SJ et al., 2008; Sehdev S et al., 2003). The general agreement on the significance of micropapillary architecture in SBTs is that there is a significant increase in incidence of invasive peritoneal implants (Burks R et al., 1996). Molecular studies show that MSBT has a similar gene expression profile as low-grade serous carcinoma (LG-serous carcinoma) and distinct from typical SBT [May T et al., 2010]. The underlying genes involved in the pathogenesis of LG-serous carcinoma, and in MBST include mutations in a number of different genes including *KRAS* and *BRAF*. Actually, MSBT is the only surface-epithelial stromal tumor with a well defined adenoma-carcinoma sequence, where LG serous is thought to arise in a stepwise fashion from a benign cystadenoma through BST to an invasive LG-serous carcinoma (Kurman RJ et al., 2008). Microscopically, MSBTs shows highly complex micropapillary growth in a filigree pattern, growing in a nonhierarchical fashion from stalk. It has been described as “Medusa head” like appearance. Micropapillae are at least five times as long as they are wide. Fig 2.1.2 a,b.

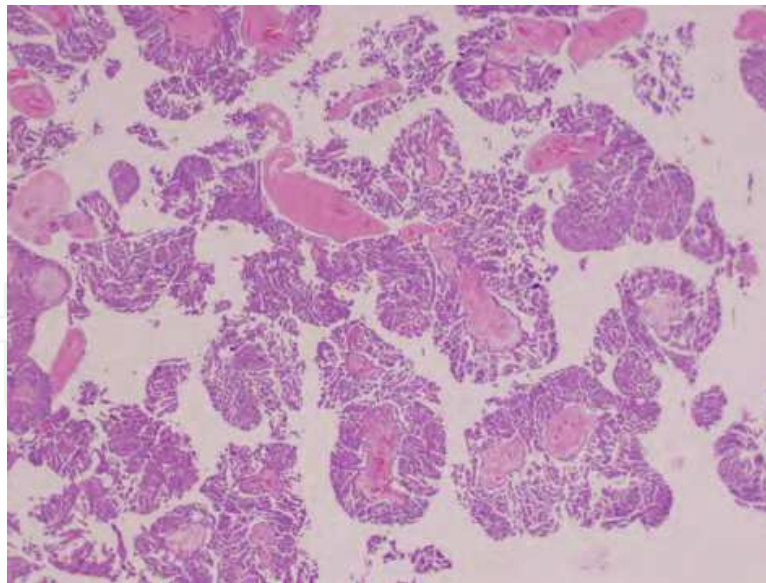


Fig. 2.1.2.a. Micropapillary SBT: Microscopic examination shows highly complex micropapillary growth in a filigree pattern, which is defined by a growth in a nonhierarchical fashion from fibrous stalk forming what we say “Medusa head’ like appearance.

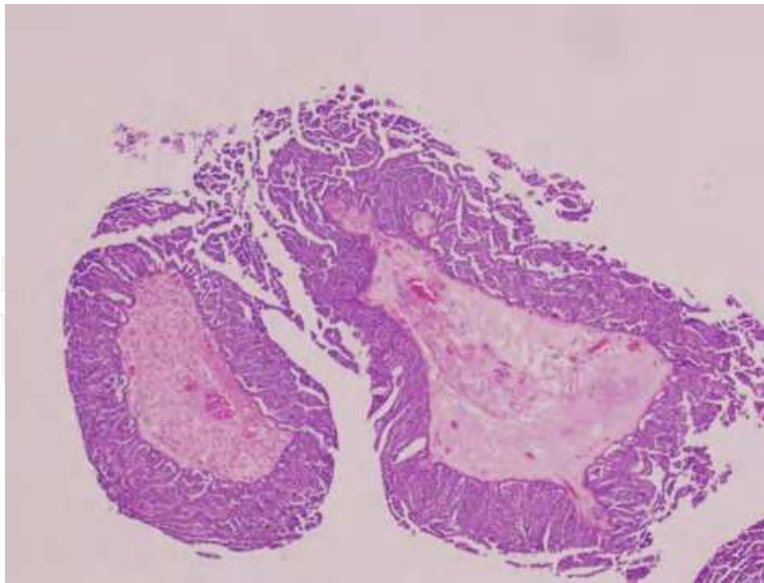


Fig. 2.1.2.b. Micropapillary SBT: The micropapillae are at least five times as long as they are wide.

Micropapillary foci should occupy an area of at least 5 mm, since micropapillary foci of less than 5 mm have no bearing on clinical outcome (Slomovitz MB et al., 2002).

2.1.3 Peritoneal implants

Peritoneal implants are classified into epithelial invasive and non-invasive implants, and desmoplastic invasive and non-invasive implants. Implants are a heterogeneous group and various types may coexist, therefore, multiple biopsies of numerous foci of suspicious lesions at the time of surgery and extensive tumor sampling by the pathologist, is the main key to exclude an invasive implant.

Epithelial non-invasive implants are characterized by the presence of branching, complex papillae within cystic spaces with no stromal reaction or destruction Fig 2.1.3.a.

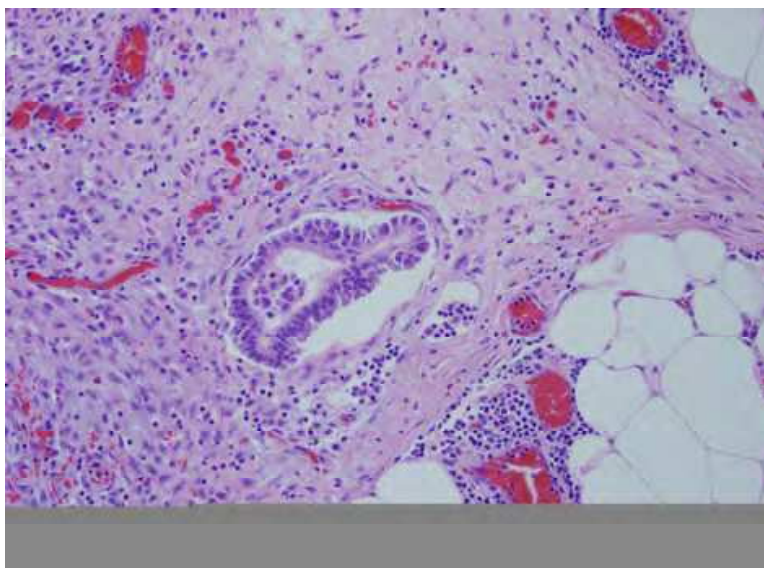


Fig. 2.1.3.a. Non-invasive peritoneal implant: The implant is defined by papillary structure in a space like structure with no evidence of invasion or destruction of the ovarian stroma.

SBT with non-invasive implants have been considered indolent, with 5-year survival rate of 95% and recurrence rate ranging from 8% to 32% (Silva EG et al., 2006).

Epithelial invasive implants are characterized by haphazardly distributed glands and clusters of branching papillae infiltrating the adipose tissue and stroma. The epithelial cells should have marked cytologic atypia. The associated stroma is composed of dense fibrous tissue Fig 2.1.3.b. Patients with SBT with invasive implants may develop low grade carcinomas many years after initial diagnosis. (McCluggage WG, 2010)

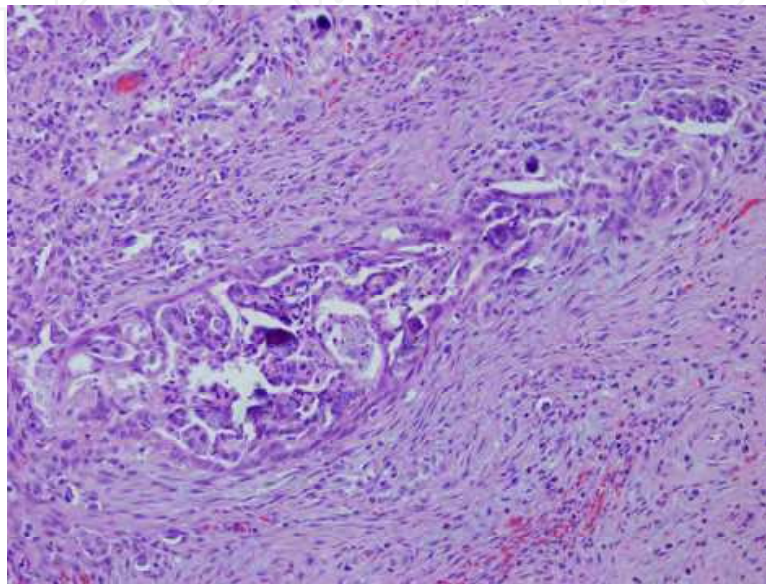


Fig. 2.1.3.b. Invasive implant: it is defined by complex structure of papillae where the neoplastic cells exhibit severe cytologic atypia and they seem to infiltrate a very dense stroma.

Desmoplastic non invasive implants are defined by clusters of tumor cells that are present in a loose fibrous stroma. The stroma may have granulation tissue like features with neutrophilic infiltrates and hemorrhage.

Differential diagnosis: Implants should be distinguished from benign epithelial inclusions or endosalpingiosis. Inclusions are defined by small glands lined by a single cell layer without atypia. Endosalpingiosis is characterized by a lining typical for tubal epithelium such as ciliated and intercalated cells.

2.1.4 SBT with microinvasion

Microinvasion is defined as single cells or few clusters of cells similar to those seen in the overlying SBT that infiltrate the stroma. One or more foci may be present but none should exceed 10 mm². SBT with microinvasion appears to have no significance on disease outcome, with 10 year survival rate is of 86% (Slomovitz BM et al, 2002).

2.1.5 Implants in a lymph node

Approximately 27% of surgically staged patients with SBT present with lymph node involvement by tumor. The most common lymph nodes involved are the pelvic and paraaortic groups. Recent molecular and morphologic data suggest that although most nodal implants are indeed metastatic from a concurrent ovarian neoplasms, small subsets arises de novo from nodal endosalpingiosis. It has also been suggested that the route of spread from an ovarian

SBT to lymph nodes might be via a peritoneal route and not lymphatic. The morphology of the implant is similar to that occurring in the ovary. Lymph node involvement does not adversely impact the overall survival of patients with SBT of the ovary [Fadare O, 2009]. The major differential diagnosis is endosalpingiosis and the criteria are cited previously in the text.

2.2 Serous carcinoma

Serous adenocarcinoma occurs in women a bit older than women with SBT, with an average age of 56 years. Patients with serous adenocarcinoma often present with advanced stage disease (stage III and IV) at first presentation.

Grossly, the tumor varies considerably in size from a few cm to 30 cm. The cut surface may be partially cystic and partially solid or it may be solid with areas of necrosis and hemorrhage Fig 2.2.a. When infiltrating the omental adipose tissue, the tumor creates what is called “omental caking” Fig 2.2.b.

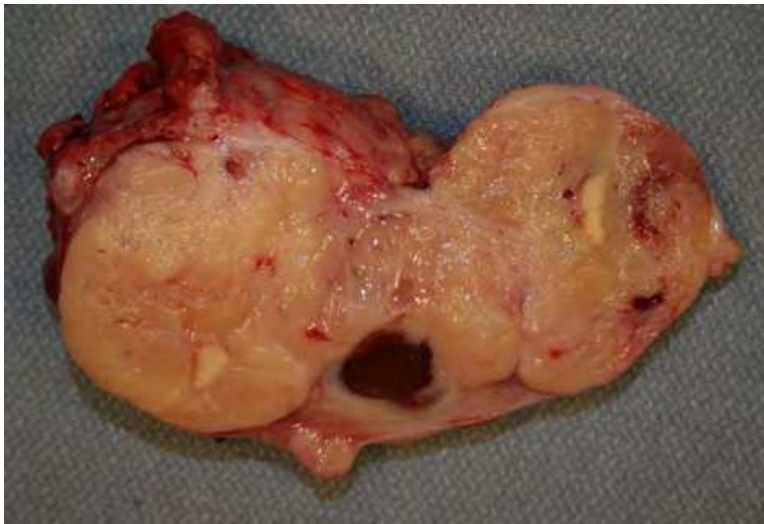


Fig. 2.2.a. Serous adenocarcinoma: the ovarian mass is solid with few cystic areas. The cut surface is firm, white with areas of necrosis and hemorrhage.

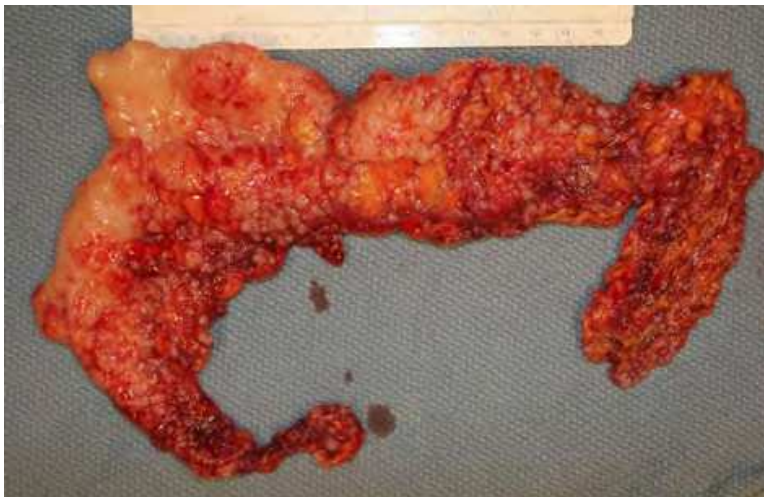


Fig. 2.2.b. Omentum: The tumor involves the omentum and create “omental cake” which is characterized by tumoral seeding of the adipose tissue. The cut surface is white, firm and homogenous.

2.2.1 Grading

Grading of surface epithelial stromal tumors is still performed haphazardly with several systems and non-systems used in different institutes and in different research studies. The lack of uniformity in grading has resulted in little consensus as to whether ovarian tumor grade has any significance in predicting disease outcome. The grading systems used most commonly worldwide are the International Federation of Gynecology and Obstetrics (FIGO) system, and the World Health Organization (WHO) system. The FIGO grading system for the ovary is similar to the grading system used in the uterus. It is based on architectural features. The grade depends on the ratio of glandular or papillary structures versus solid tumor growth. Grade 1 is equivalent to <5% solid growth, grade 2 to 5-50% solid growth and grade 3 to $\geq 50\%$ solid growth (**International federation of Gynecology & Obstetrics, 1971**). In the WHO system, the grade is assessed by both the architectural and cytologic features, without any quantitative values (**Tavassoli FA and Devilee P., 2003**). The Gynecologic Oncology (GOG) system is the most commonly used system in the United States (**Benda JA et al., 1994**). It employs a method based on the histologic type. For example, ovarian carcinoma of endometrioid type is graded similarly to the endometrial adenocarcinoma of endometrioid type. Ovarian carcinoma of transitional type is graded similar to transitional cell carcinoma (TCC) of the bladder. Clear cell carcinomas are not graded at all. Silverberg's et al proposed a new grading system similar to that used in breast carcinoma and it depends on architectural features (glandular 1, papillary 2 and solid 3), cytologic atypia (mild 1, moderate 2, severe 3), and mitotic rate (1 0-9 mitosis/10HPF, 2 10-24, 3 >25). A score is given by adding the parameters, a score of 3-5, is grade 1, a score of 6-7 is grade 2, and a score of 8 -9 is grade 3 (**Silverberg S, 200**). **Fig 2.2.1a and Fig 2.2.1.b** are examples of grade 1 and grade 3 serous carcinomas.

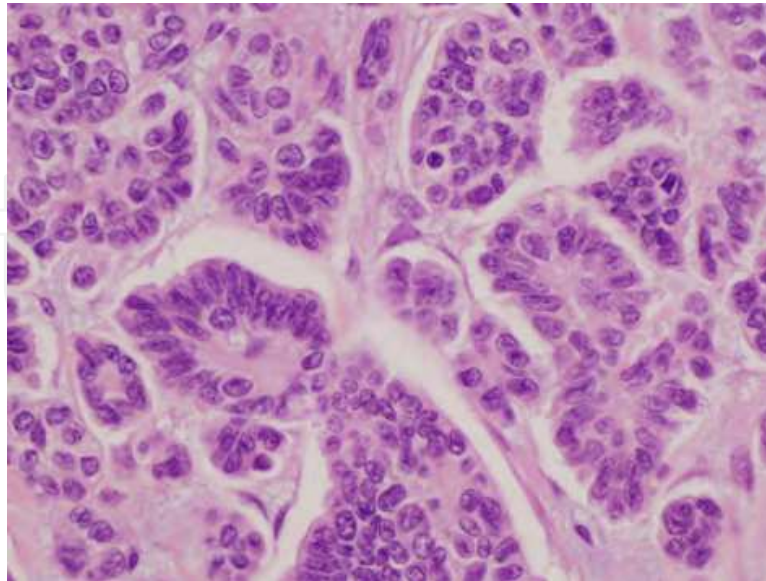


Fig. 2.2.1.a. Low grade serous carcinoma: The tumor has papillary features. The neoplastic cells have mild to moderate atypia and rare mitotic figures.

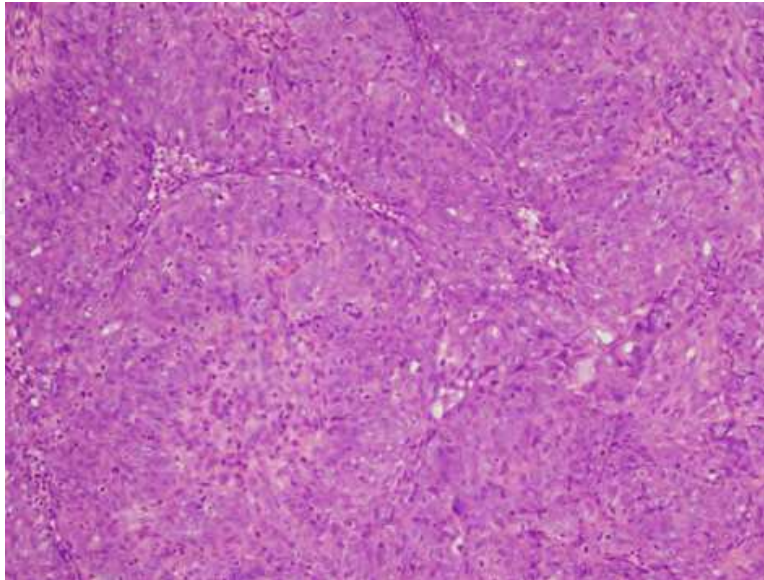


Fig. 2.2.1.b. High grade serous carcinoma: The tumor cells are arranged in solid sheets with very rare foci of papillary architecture. The cells exhibit severe atypia and frequent mitotic figures.

This grading system was confirmed to be reproducible in subsequent studies (Ishioaka SI et al., 2002). Another study from MD Anderson cancer center group suggested adopting a two-tier system that is based primarily on the assessment of nuclear atypia (uniformity vs. pleomorphism) in the worst area of the tumor (Malpica A et al., 2004). The tumor is graded into low grade and high grade. A few years after its introduction, the authors confirmed its reproducibility and urged its use to facilitate the clinical trials and protocols (Malpica A et al., 2007).

3. Mucinous tumors

3.1 Mucinous borderline tumors

Mucinous borderline tumors (MBT) (mucinous tumors of low malignant potential) as defined by the WHO, are tumors exhibiting an epithelial proliferation of mucinous type cells greater than that seen in their benign counterparts but without evidence of stromal invasion. MBT can be of intestinal type or endocervical-like type.

3.1.1 Mucinous borderline tumors of intestinal type

The intestinal type tumors are the most common type of MBTs, accounting for 85-90% of cases. They are not associated with peritoneal implants or lymph node involvement. Similar to low-grade serous tumors, intestinal type MBTs are thought to arise from a cystadenoma and to progress to carcinoma, following the adenoma-carcinoma sequence model. Grossly, they are usually a very large unicystic or multicystic mass filled with mucoid-gelatinous material **Fig 3.1.1a**.

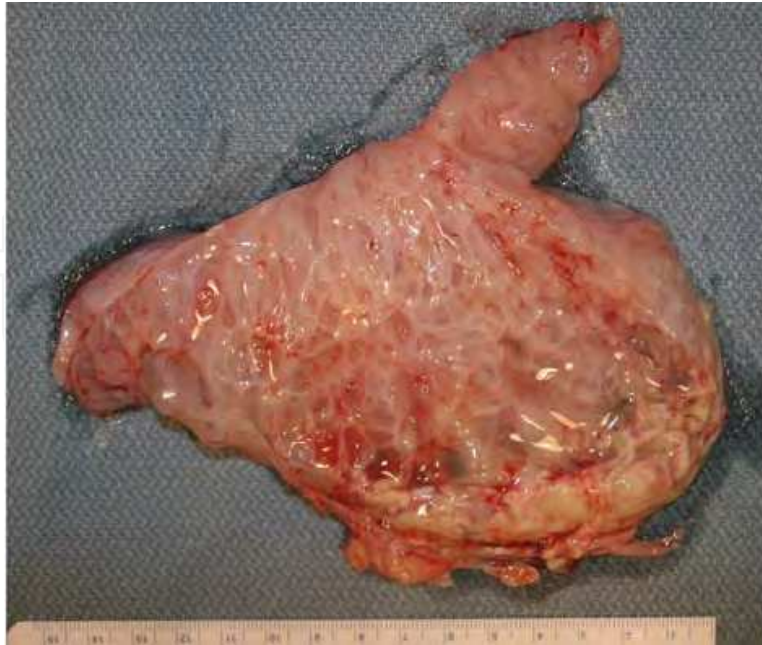


Fig. 3.1.1.a. Mucinous borderline tumor (MBT): The cut surface of the ovarian mass shows multiple cysts filled with gelatinous material. However in some areas the wall of the cyst seemed to be thickened.

Histologically, the lining of the cyst is composed of stratified lining of epithelial cells having high N/C ratio and prominent nucleoli **Fig 3.1.1.b,c**. Goblet cells and Paneth cells are present. No stromal invasion is seen.

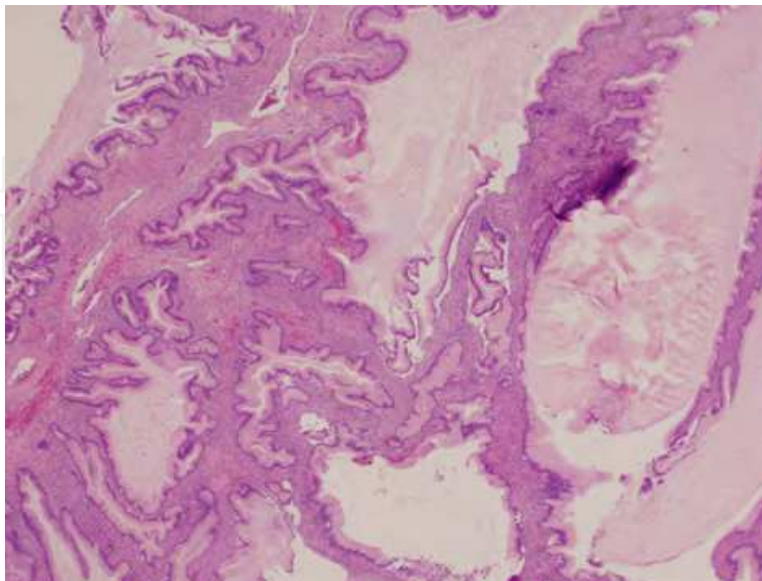


Fig. 3.1.1.b. MBT: At low magnification, the tumor is composed of proliferation of glands which some are cystically dilated separated by abundant intervening stroma.

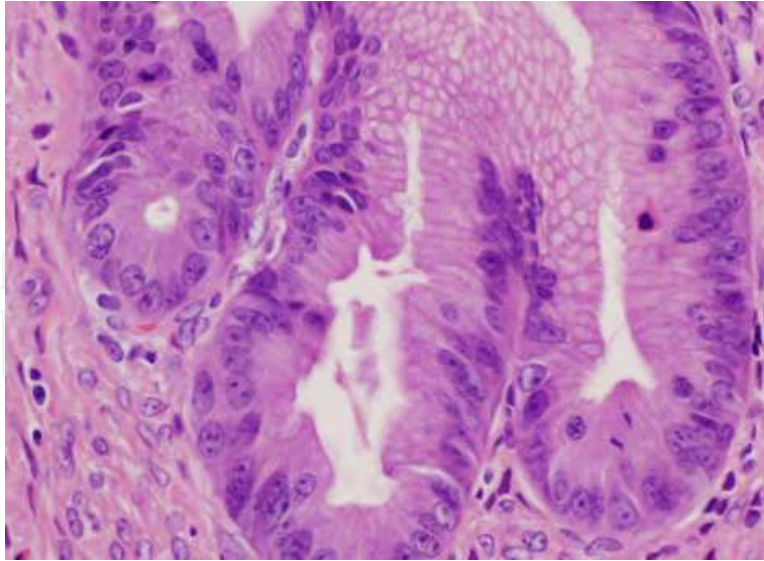


Fig. 3.1.1.c. Higher magnification showed that the glands are lined by mucin secreting cells exhibiting moderate to severe atypia, big nuclei and prominent nucleoli. In some areas, the cytoplasm shows mucin depletion. Mitotic figures are frequently present.

3.1.2 Mucinous borderline tumors of endocervical type

The endocervical type tumors are a less common and make up 10-15% of MBTs. They are usually smaller in size than their intestinal type counterparts and they are commonly bilateral (40%). They are thought to arise from endometriosis. Microscopically, the epithelial cells lining the cyst wall contain intracytoplasmic mucin, resembling endocervical cells.

3.1.3 Mucinous tumors with mural nodules

Mucinous tumors of the ovary, whether benign, borderline or malignant, may contain one or more nodules. These nodules are morphologically different than the overlying mucinous neoplasm. Grossly, nodules are yellow, pink with areas of hemorrhage and necrosis **Fig 3.1.3.a.**

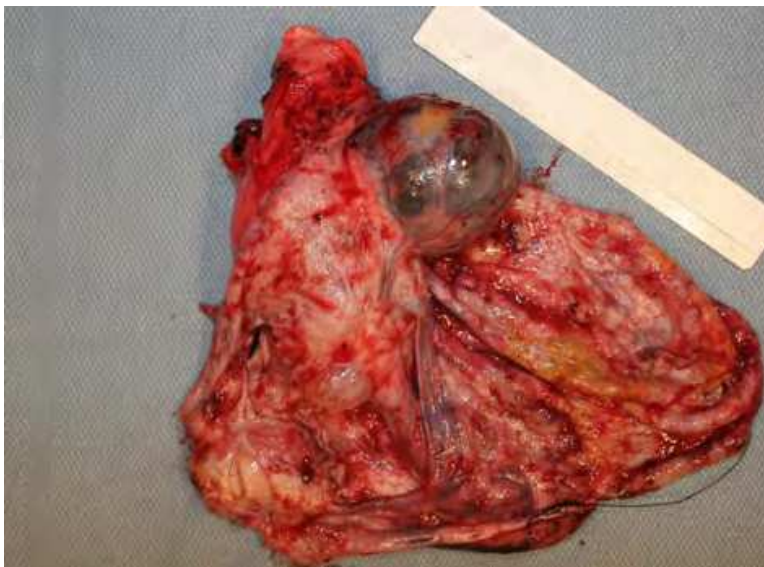


Fig. 3.1.3.a. Mural nodules: Mural nodules are grossly characterized by a well defined mass within the wall of the cyst. The cut surface is often hemorrhagic.

Microscopically, the mural nodules may be malignant (anaplastic, sarcoma or carcinosarcoma) or benign (sarcoma-like). It is important to distinguish between benign and malignant mural nodules, because benign mural nodules are of no prognostic significance. Immunohistochemistry is a very helpful tool for this purpose. Sarcoma-like nodules are composed of a heterogenous cell population of cells including spindle cells, giant cells, mononuclear cells and inflammatory cells. The cells of the sarcoma-like nodules are negative or very weakly positive for cytokeratin **Fig3.1.3.b**.

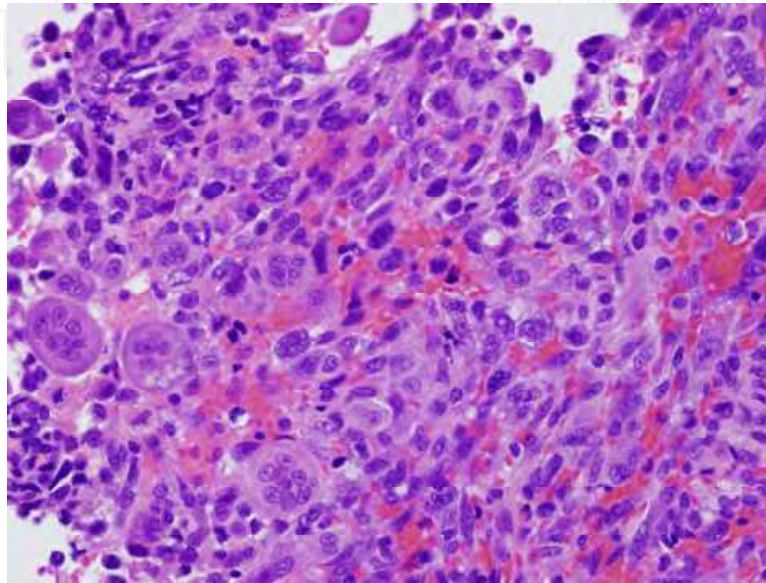


Fig. 3.1.3.b. Sarcoma-like nodules: They are composed of heterogenous cell population including spindle cells, giant cells, mononuclear cells and inflammatory cells.

Anaplastic sarcoma mural nodules are composed of diffuse sheets of spindled or large rhabdoid-looking cells with abundant eosinophilic cytoplasm and prominent nucleoli **fig 3.1.3.c,d**. These cells are usually strongly positive for cytokeratin **fig 3.1.3.e**.

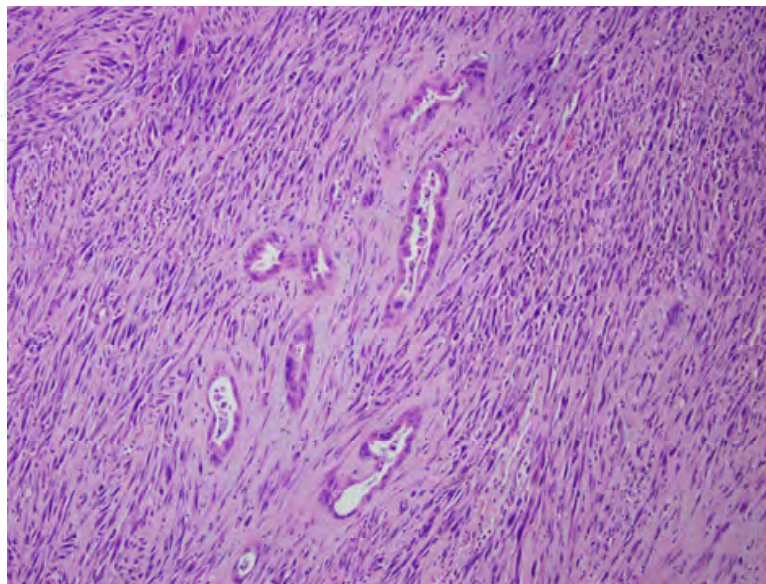


Fig. 3.1.3.c. Anaplastic nodules: They are characterized by proliferation of spindle cells.

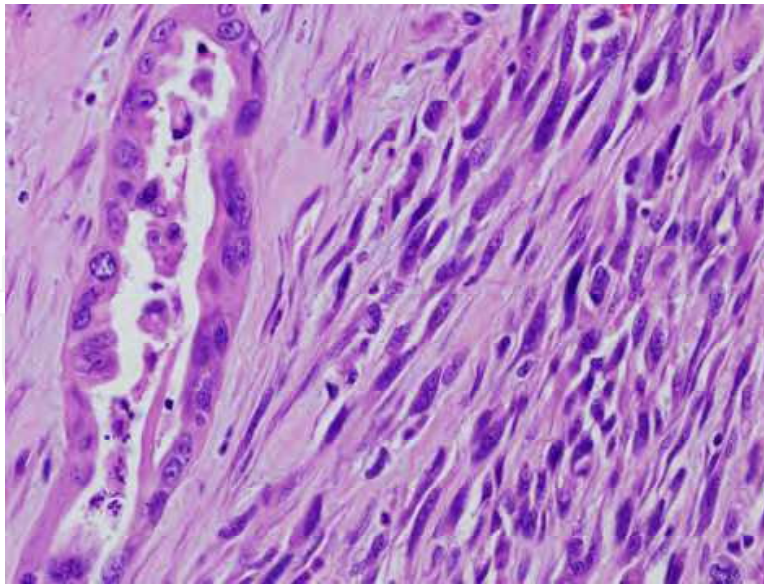


Fig. 3.1.3.d Anaplastic nodules: At higher magnification, the spindle cells exhibit severe atypia, hyperchromasia and numerous mitoses.

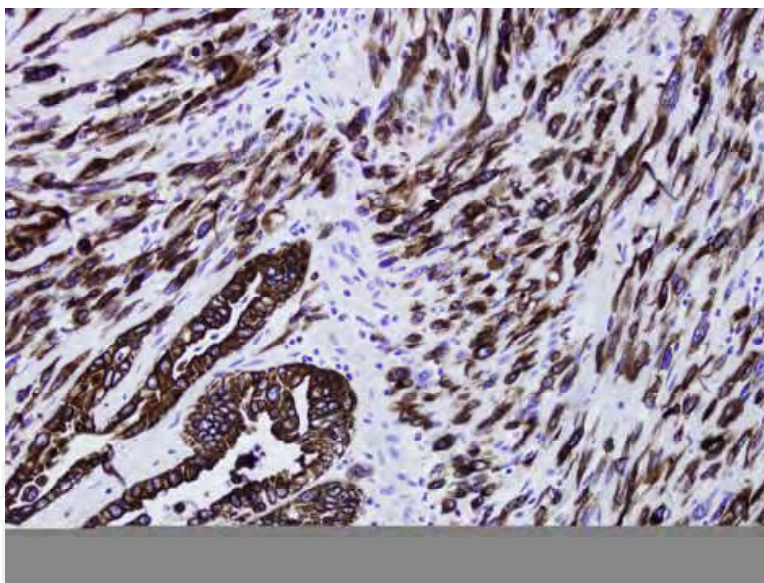


Fig. 3.1.3.e. Anaplastic nodules: The spindle cells in are strongly positive for total cytokeratin immunostain.

Lastly Sarcoma nodules exhibit a variety of patterns such as fibrosarcoma, rhabdomyosarcoma and undifferentiated sarcoma.

3.2 Mucinous adenocarcinoma

Mucinous adenocarcinomas (MAC) are very large tumors; many are 15 to 30 cm in diameter and weigh as much as 4 kgs. The cut surface can be cystic or solid and the content is composed of gelatinous, mucoid material **Fig 3.2a**.



Fig. 3.2.a. Mucinous cystadenocarcinomas: Grossly, they are characterized by partially cystic and partially solid mass. The cysts content is composed of gelatinous material.

These tumors are defined by invasion and adequate sampling is a key factor to document invasion process. Numerous sections (2 to 3 sections /1cm of tumor diameter) are required. Invasion can be defined as infiltration of ovarian stroma by neoplastic cells arranged in nests or as single cells with a stromal desmoplastic reaction **Fig 3.2.b,c**.

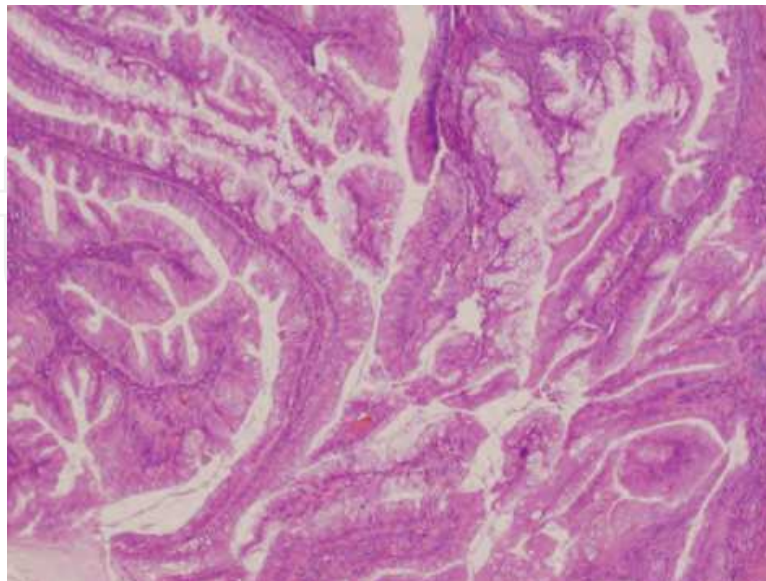


Fig. 3.2.b. Mucinous adenocarcinoma: It is also defined by proliferation of back to back glands with no or little interfering stroma.

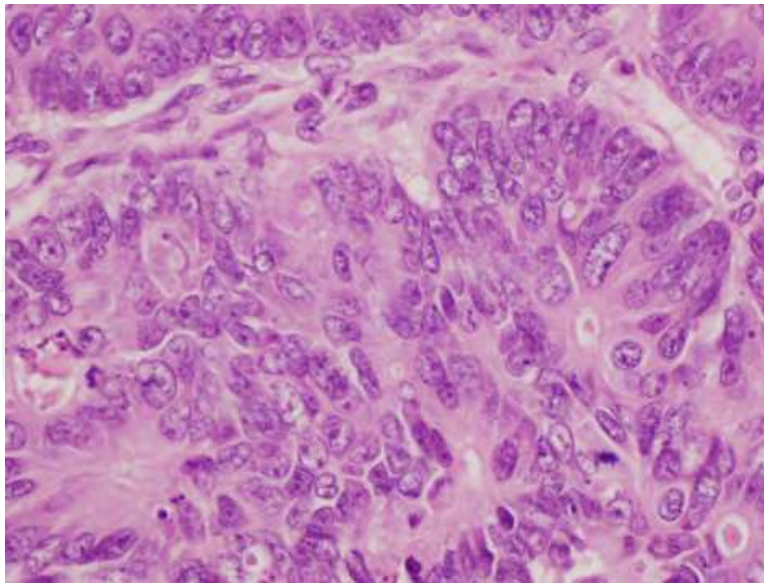


Fig. 3.2.c. Mucinous adenocarcinoma: These glands are cytologically malignant with severe atypia, large nucleoli, loss of cytoplasmic mucin and numerous mitosis.

However, one needs not to see typical stromal invasion with desmoplastic reaction to diagnose MAC, because invasion can also be defined as neoplastic glands which are back to back with no intervening stroma **Fig 3.2d**. Similar to MBTs, the epithelial lining in MAC can be of intestinal or endocervical type. MAC should be distinguished from metastatic adenocarcinoma from colonic origin. Metastatic colonic carcinomas are usually bilateral. Morphologically, they are characterized by glandular proliferation with abundant dirty necrosis and nuclear debris within amorphous necrotic tissue. The glands are lined by stratified cells with prominent atypia and mitosis **Fig 3.2.e**

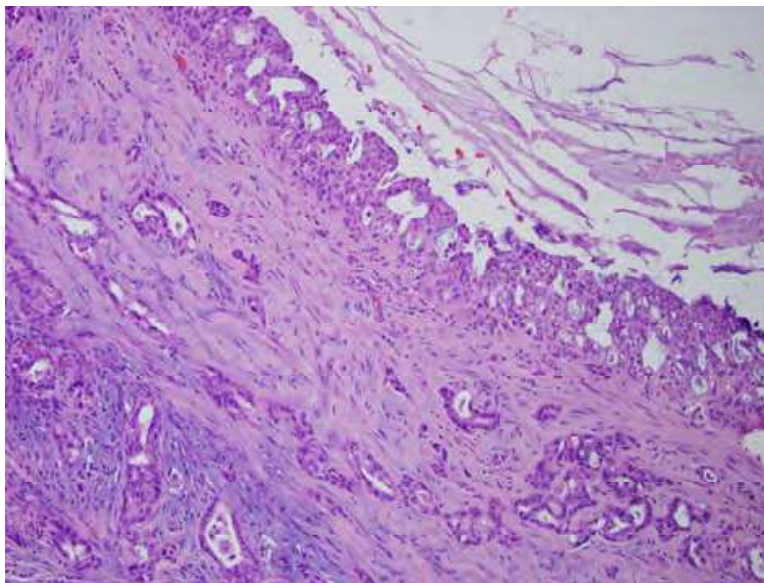


Fig. 3.2.d. Mucinous cystadenocarcinoma: It is defined by invasion of the ovarian stroma by small glands and nests of tumor cells . These glands are cytologically malignant and infiltrate the stroma in disorderly fashion.

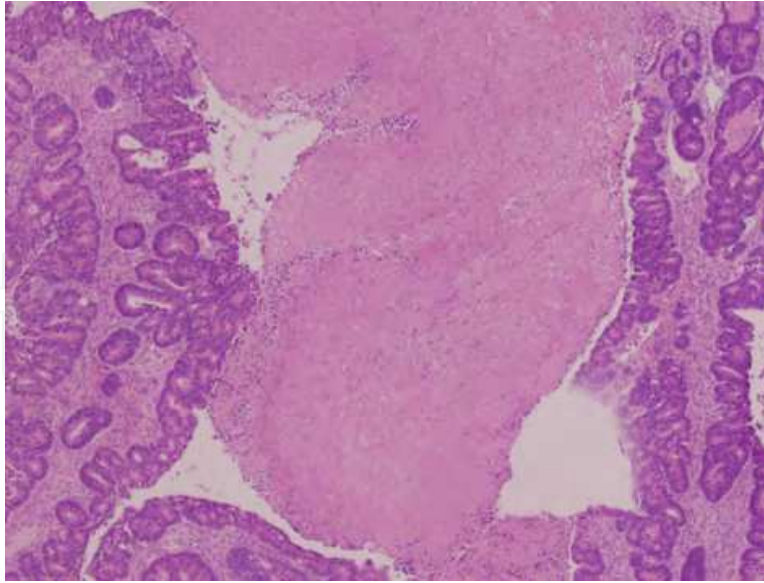


Fig. 3.2.e. Metastatic colon carcinoma: It is characterized by large glands with center “dirty” necrosis and nuclear debris within amorphous necrotic tissue.

3.3 Pseudomyxoma peritonei

Pseudomyxoma peritonei (PP) is a clinical term used to describe the finding of mucoid, gelatinous material in the abdominal cavity, often accompanied by an ovarian or gastrointestinal tumor. In 1995, Ronnett et al classified PP into low-grade variety “diffuse peritoneal adenomucinosis” (DPAM) and to high-grade variety “peritoneal mucinous carcinomatosis” (PMCA) (Ronnett BM et al, 1995). DPAM is defined as pools of mucin with few strips of mucinous epithelium exhibiting minimal cytologic atypia and rare mitotic figures Fig3.3.a. On the other hand, PMCA is characterized by abundant mucinous epithelium, glands or signet ring cells, showing severe atypia which are clearly malignant Fig3.3.b.

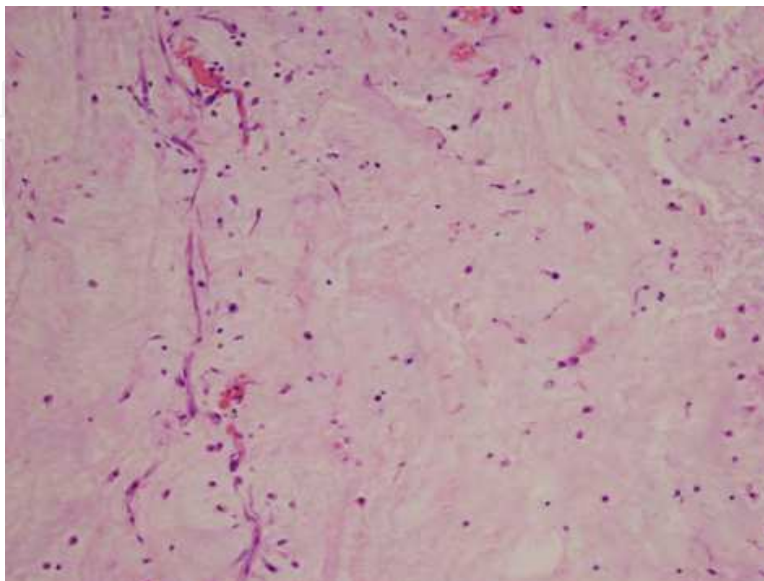


Fig. 3.3.a. Peritoneal mucinosis; It is characterized by pool of acellular mucin.

This classification is prognostically significant with 5-year survival rates of 84% for DPAM and 6.7% for PMCA (Ronnett BM et al, 2001). PP may originate from an ovarian primary or from an appendiceal primary. An appendectomy is necessary in those circumstances. Grossly, the appendix shows a dilated lumen filled with mucinous material. Histologically, depending upon the cytologic atypia, the appendiceal tumor may be a mucinous adenocarcinoma or a mucinous tumor of low malignant potential Fig3.3.c,d. (Misdraji J, 2009).

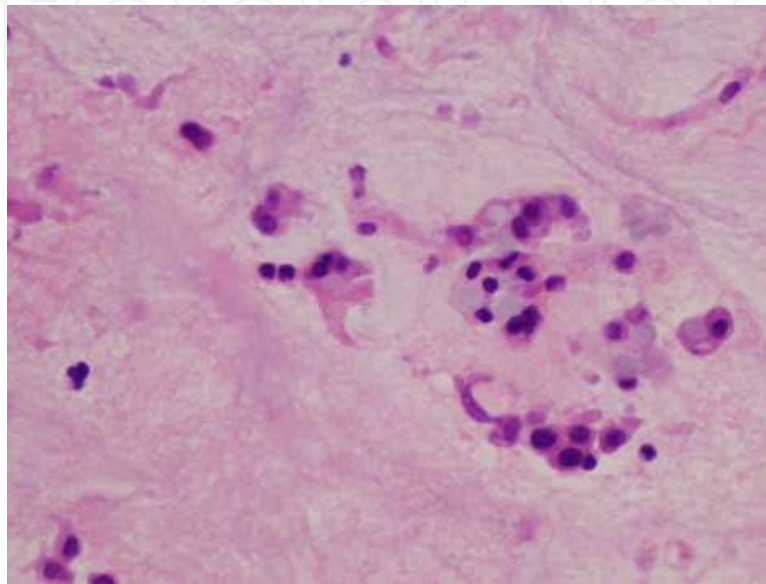


Fig. 3.3.b. Peritoneal adenocarcinomatosis: It is characterized by pool of mucin and clusters of malignant cells with signet-ring features.

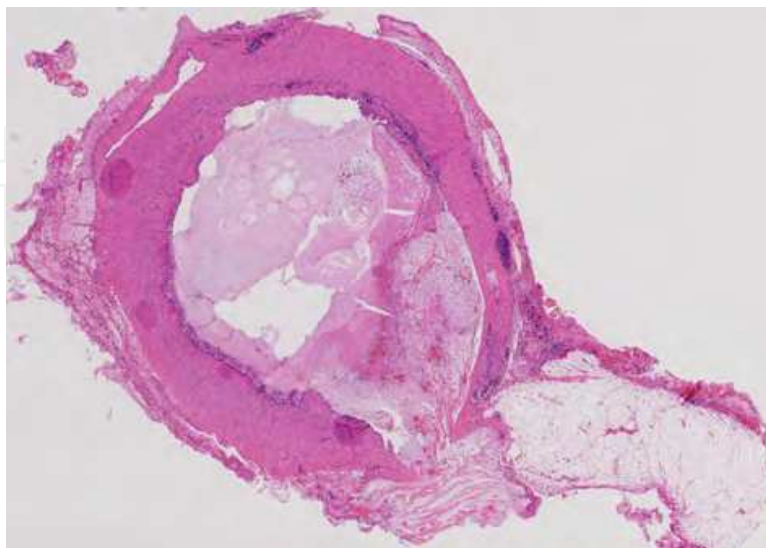


Fig. 3.3.c. Appendiceal mucinous tumor: The appendiceal lumen is dilated and filled with mucin which is dissecting the entire thickness of the wall.

In many cases, the appendix is encased by a very large mucinous mass, and histologically, the appendix is replaced by tumor, rendering the diagnosis of appendiceal primary very difficult.

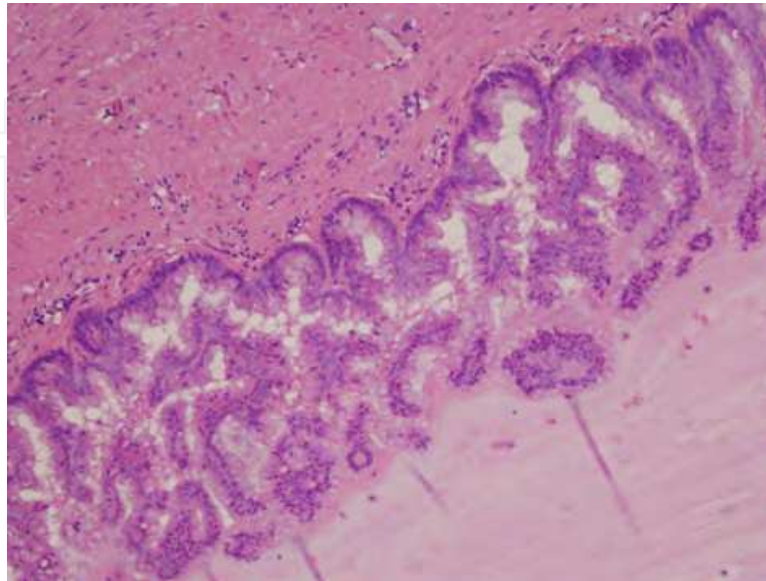


Fig. 3.3.d. Appendiceal mucinous tumor: The appendiceal mucosa shows proliferation of mucin-secreting cells that they are not frankly malignant. Due to the absence of glandular cribriform and submucosal invasion, this lesion is classified as mucinous tumor of low malignant potential.

Not so long ago, there was a considerable controversy about the origin of mucin in PP, in women with concomitant mucinous tumors of the appendix and the ovaries. Recent immunohistochemical, molecular, and genetic evidence supports the appendix as the primary tumor and secondary involvement of the ovary (**Ronnet BM et al, 2004**) In difficult cases, immunohistochemistry study including cytokeratin 7 (CK7), cytokeratin 20 (CK20) and CDX2 are useful to discriminate between primary appendix from primary ovarian mucinous tumors. At first CDX2 seemed to be a promising marker and its positivity was found to be very specific for lower gastrointestinal carcinomas but as more studies have been published, more cases of ovarian mucinous tumors have been found to be positive for CDX2 rendering its use of little value. On the other hand CK7/CK20 is more useful, as ovarian mucinous tumor are CK7+/CK20+ and appendiceal/ colon tumors are CK7-/CK20+. Thus, CK7/CK20 is the most useful and reliable combination in distinguishing appendiceal versus ovarian primary (**Chu P et al., 2000; Kaimaktchiev et al., 2004**).

4. Endometrioid tumors

4.1 Endometrioid adenocarcinoma

Endometrioid adenocarcinoma (EAC) account for 10-20% of ovarian carcinomas. They occur in postmenopausal women, with average age of 56 years. The frequent association with endometriosis and endometrioid adenocarcinoma of the endometrium suggested that some EAC of the ovary might have the same risk factors as those occurring in the endometrium. In contrary to serous carcinomas, about half of EAC cases present as early

stage disease (stage I and II). They are bilateral in 20% of cases. Microscopically, these tumors are usually well differentiated tumors (grade I). The tumor is microscopically very similar to those occurring in the endometrium, where back to back glands with no intervening stroma and squamous differentiation in the form of squamous morules and keratin pearls are present. **Fig 4.1a., b**

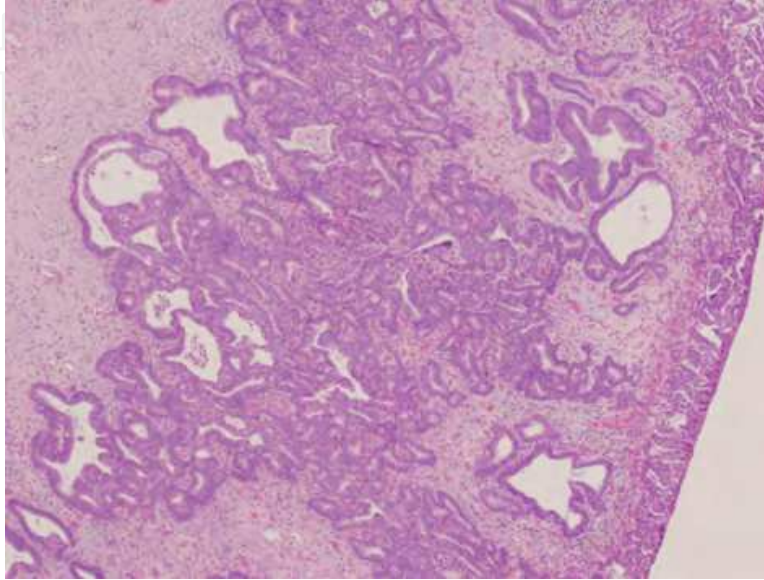


Fig. 4.1.a. Endometrioid adenocarcinoma (EAC): The morphologic features of this tumor are very similar to those occurring in the endometrium where back to back glands with no intervening stroma.

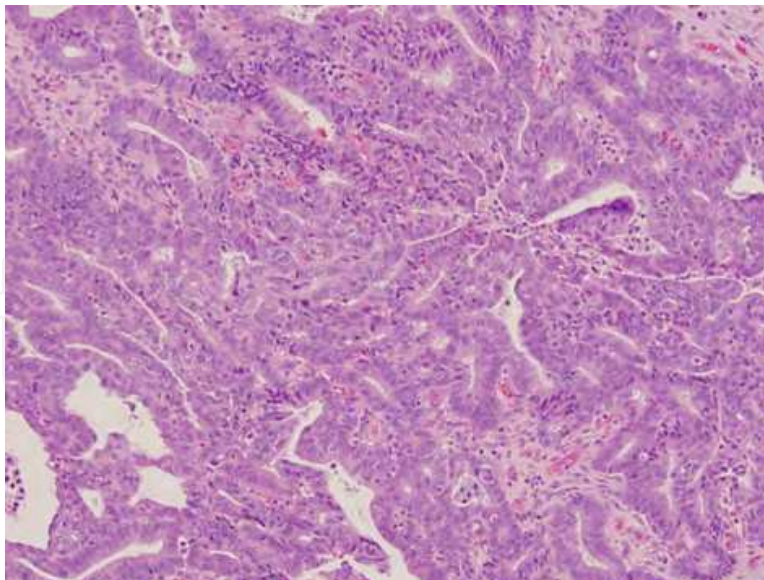


Fig. 4.1.b. EAC: The glands are cribriform and they are cytologically malignant.

Rare examples of mucin-rich, secretory, ciliated, and oxyphilic types have been described. Occasionally the tumor may resemble granulosa cell tumor, with the cells arranged in ribbons, and small glands, creating the illusion of Call-Exner bodies. Also, rare cases exhibit tubular glands resembling a Sertoli-Leydig cell tumor. In both cases alpha-inhibin is

excellent marker to differentiate between EAC and sex-cord tumors, where it is negative in EAC of the ovary and it is positive in sex-cord stromal tumors such as Sertoli-Leydig tumors and granulosa cell tumors **Fig 4.1.c.d** (Zhao C et al., 2007; Pelkey TJ et al., 1998).

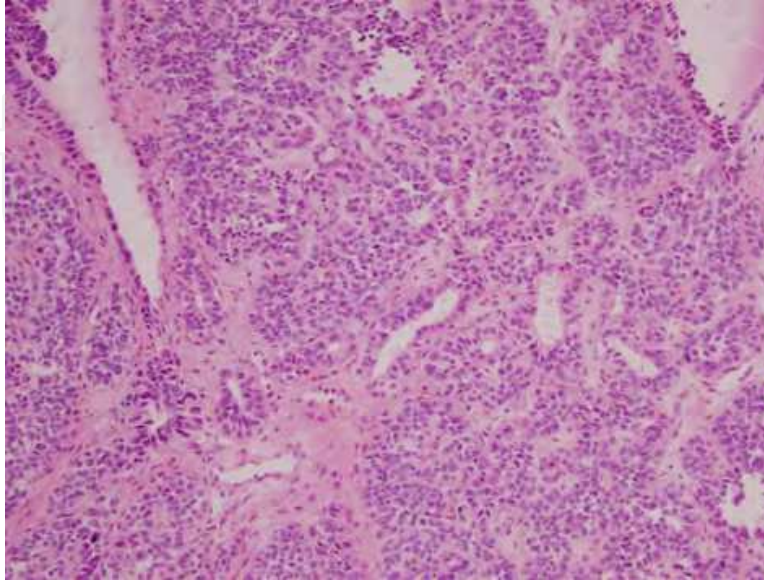


Fig. 4.1.c. Sertoli-Leydig cell tumor: They may be arranged in irregular tubules lined by stratified epithelium resembling endometrial adenocarcinoma.

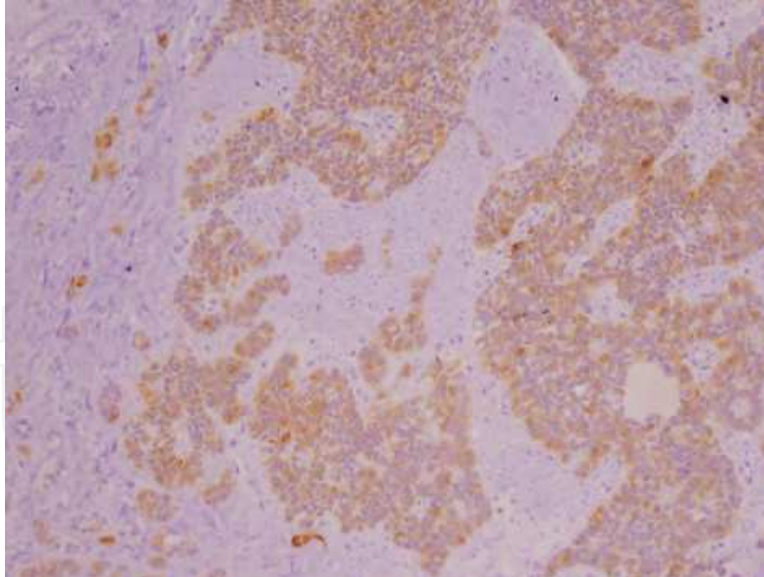


Fig. 4.1.d. Sertoli-Leydig cell tumor: Tumor cells are positive for inhibin immunostain.

4.2 Carcinosarcoma (mixed malignant mullerian tumor/MMMT)

Carcinosarcomas account for <1% of all ovarian cancers and occur in the sixth to eight decades. They are composed of two components; a malignant epithelial component and sarcomatous elements. The sarcomatous component may be homologous (tissue native to

the ovary) or heterologous elements (skeletal muscle, cartilage and bone). Molecular studies support a clonal origin of both components, leading some to propose designating carcinosarcoma as a “metaplastic carcinoma” (Thompson L et al, 1996; Mayall F et al, 1994). The epithelial component is usually of endometrioid type adenocarcinoma but other types like serous or mucinous may be found **Fig 4.2.a**. The sarcomatous component may be a homologous type such as fibrosarcoma, high-grade endometrial stromal sarcoma, or a heterologous type including chondrosarcoma or rhabdomyosarcoma **Fig 4.2.b**.

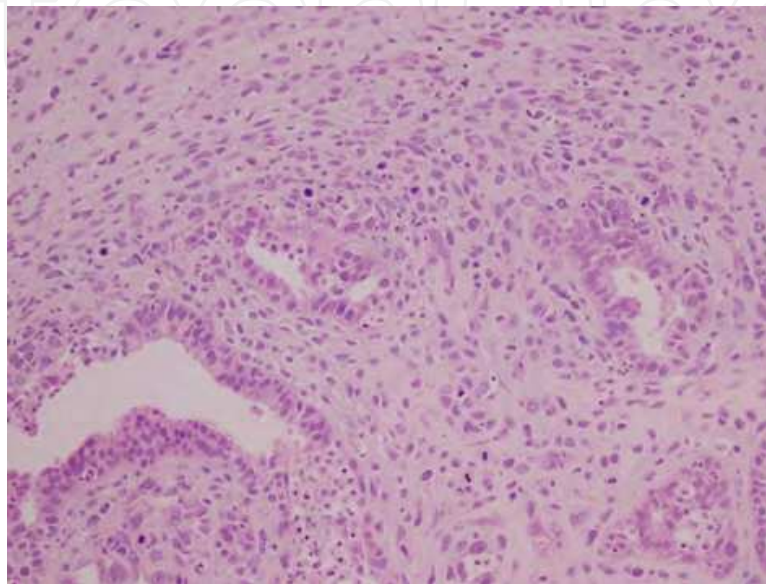


Fig. 4.2.a. MMTT: the tumor is composed of two components which are malignant, the epithelial component (adenocarcinoma) and the mesenchymal component (sarcoma).

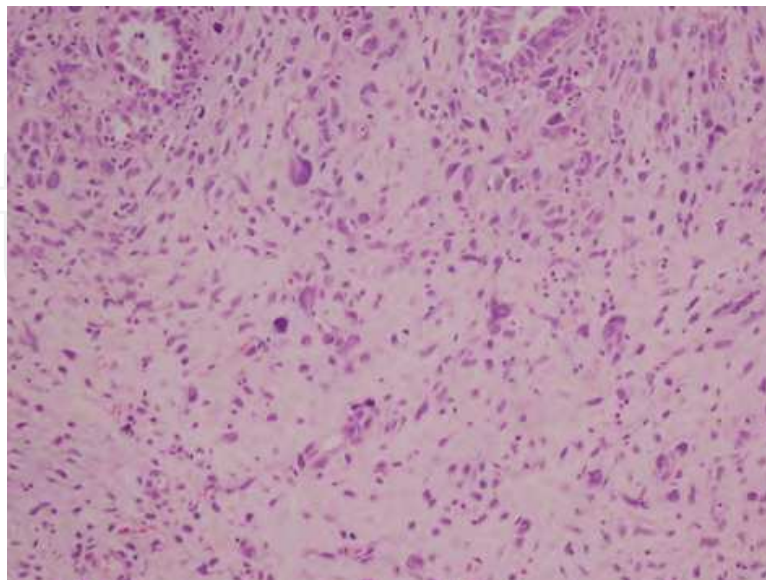


Fig. 4.2.b. MMTT: the mesenchymal component (sarcoma) is composed of very atypical, hyperchromatic cells. These cells have a high mitotic rate.

5. Clear cell tumors

Clear cell carcinoma

Clear cell carcinomas (CCC) represent 6% of surface-epithelial tumors. They occur in postmenopausal women, with a mean age of 57 years. CCC of the ovary has a few notable characteristics 1- they are almost always unilateral, 2- they are admixed with endometrioid type adenocarcinoma in 20-25% of cases, 3- they are often accompanied by endometriosis of the same ovary, 4- they may be associated with paraneoplastic hypercalcemia and 5- they have frequent mutations of ARID1A and PIK3CA genes (Anglesio MS et al., 2011). Histologically, CCC may exhibit various patterns of growth, including tubulo-cystic, papillary and solid patterns Fig 5.a. The papillae of CCC are unique in that they are composed of an extensive hyaline core which is different from the small, fibrovascular core papillae as seen in serous adenocarcinoma. In addition, CCC can display numerous cell types such as clear, hobnail, cuboidal, flat, oxyphilic and signet-cell types. The most common type, clear cell type, is defined by round to polygonal cells with a clear cytoplasm, eccentric nuclei and prominent nucleoli Fig5.b, c. The cytoplasm contains abundant glycogen which is Periodic acid-Schiff (PAS) positive, diastase digestion resistant. Numerous intracytoplasmic hyaline globules may be seen. Mucin can be found in the lumens of tubules and cysts and it is very abundant in the cytoplasm of the signet ring cell types.

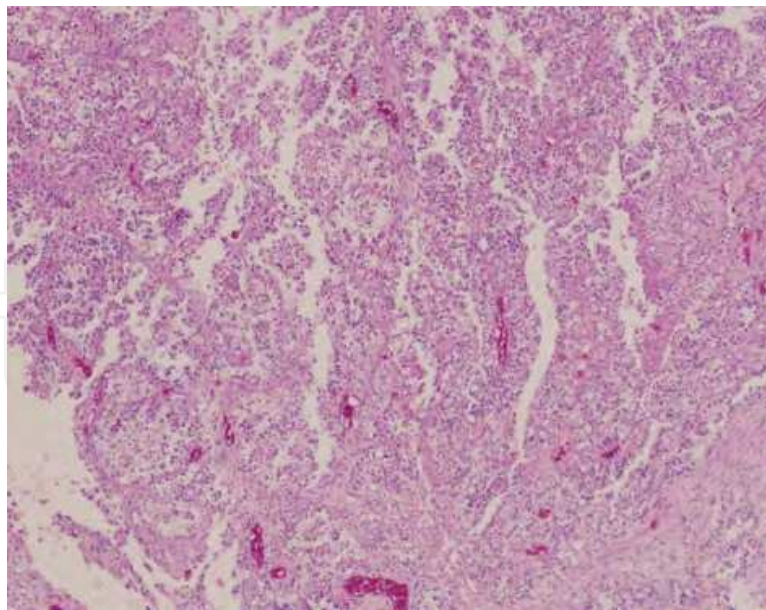


Fig. 5.a. Clear cell carcinoma (CCC): low magnification shows proliferation of neoplastic cells in form of solid sheets and papillary patterns.

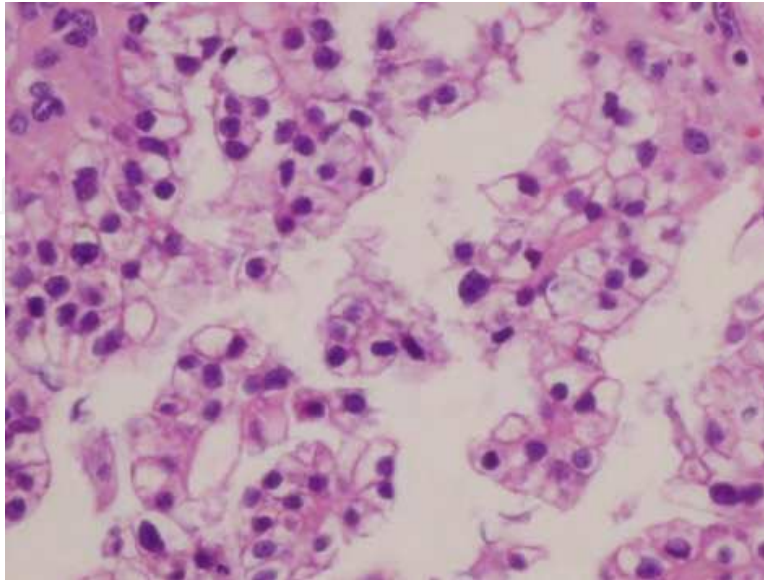


Fig. 5.b. CCC: The cells have a clear cytoplasm, and eccentrically located round nuclei.

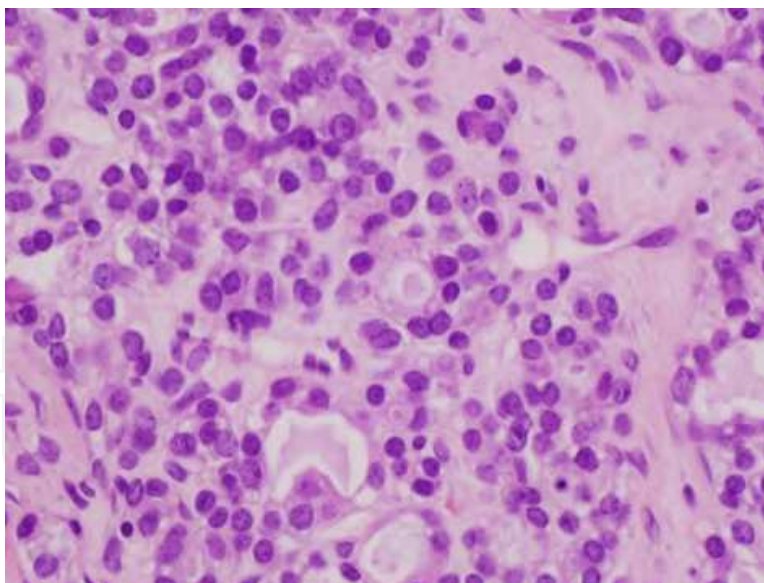


Fig. 5.c. CCC: some cells contain inspissated secretion that is mucicarmine positive creating a targetoid appearance.

Due to these various patterns, CCC can be mistaken for germ cell tumors including dysgerminoma, yolk sac tumors, endometrioid adenocarcinoma with secretory changes, and with metastatic renal cell carcinoma (RCC) **Fig 5.d,e**.

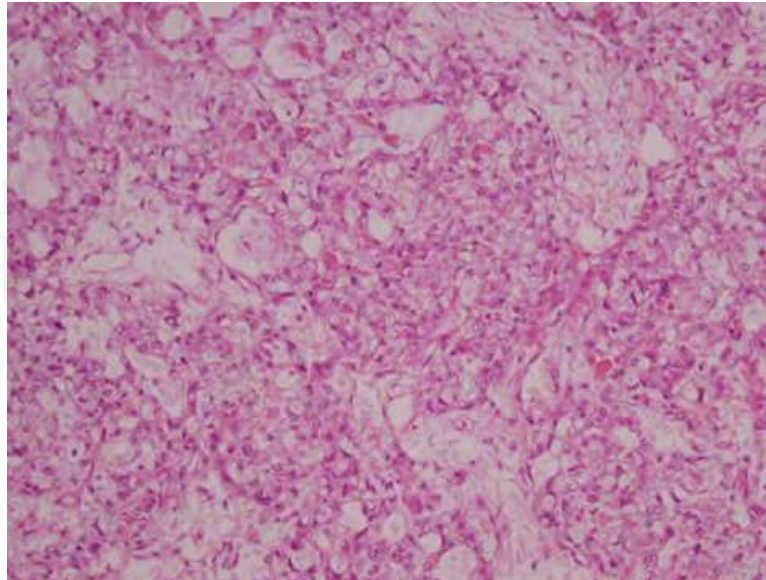


Fig. 5.d. Yolk sac tumor: The tumor is arranged in a loose stroma with small cystic structures.

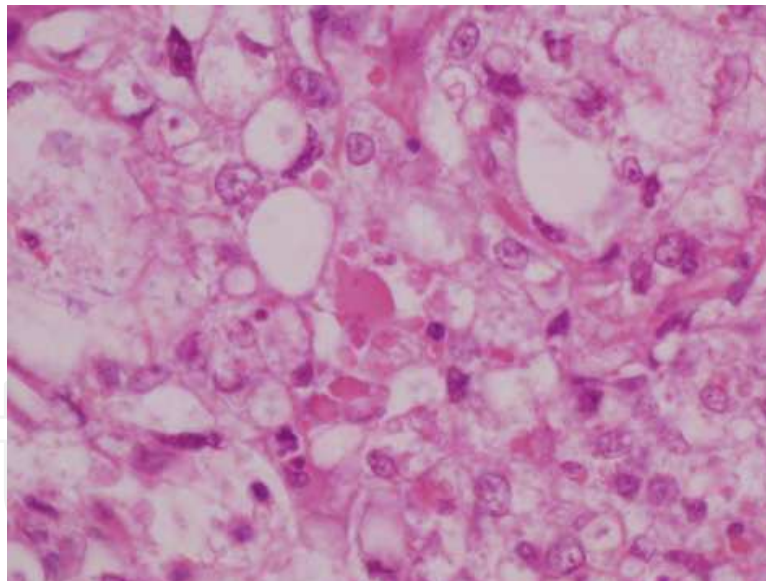


Fig. 5.e. Yolk sac tumor: The tumor cells have abundant eosinophilic cytoplasm and contain hyaline bodies.

Alpha-fetoprotein (AFP), placenta alkaline phosphatase (PLAP), cytokeratins and epithelial membrane antigen (EMA) are helpful immunohistochemistry stains to distinguish CCC from germ cell tumors. In germ cell tumors, AFP and PLAP are positive and cytokeratin and EMA are negative, while CCC cells are negative for AFP and PLAP and positive for cytokeratin and EMA (Mittal k et al 2008).

Metastatic RCC to the ovary, though rare, creates a major diagnostic challenge, when CCC of the ovary is of clear cell type. It is almost impossible to differentiate the two based solely on morphology. Therefore, IHC is helpful as RCC is usually negative for CK7 and positive for CD10 and CCC of the ovary is typically positive for CK7 and negative for CD10. In addition, correlation with radiologic findings is necessary to rule out metastatic RCC (Mittal K et al, 2008).

6. Transitional cell tumors

Transitional cell carcinoma and malignant Brenner tumors

The group of transitional cell tumors includes benign Brenner tumors, borderline and malignant Brenner tumors, and transitional cell carcinoma. By definition, transitional cell carcinoma of the ovary (TCC-O) and malignant Brenner tumors are composed of epithelial cells morphologically resembling urothelium. TCC-O is the least common surface epithelial tumor of the ovary, accounting 1-2% of all ovarian tumors. It may sometimes be associated with germ cell tumors. They are bilateral in 15% of the cases. Grossly they are cystic with intracystic papillary projections Fig 6.a.



Fig. 6.a. Transitional cell carcinoma of the ovary (TCC-O): The mass is mostly composed of one large cystic where a large vegetating tumoral mass protrudes in the lumen.

TCC-O can be already widespread disease at the time of diagnosis, however, malignant Brenner tumors are usually stage I disease at first presentation. Histologically, TCC-O and malignant Brenner tumors resemble TCC occurring in the urinary tract. They are composed of papillary projections protruding into a cystic lumen, lined by multilayered malignant transitional epithelium Fig 6.b.c.

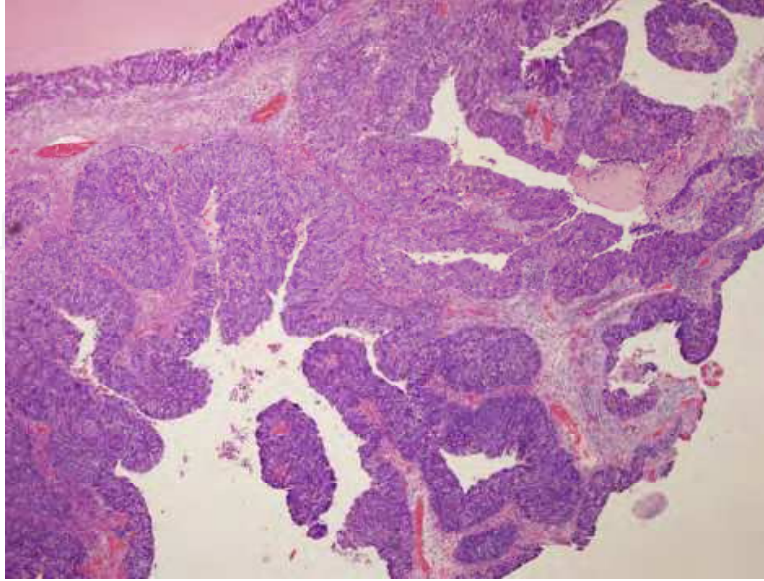


Fig. 6.b. TCC-O: The tumor is composed of broad undulating macropapillae with smooth borders.

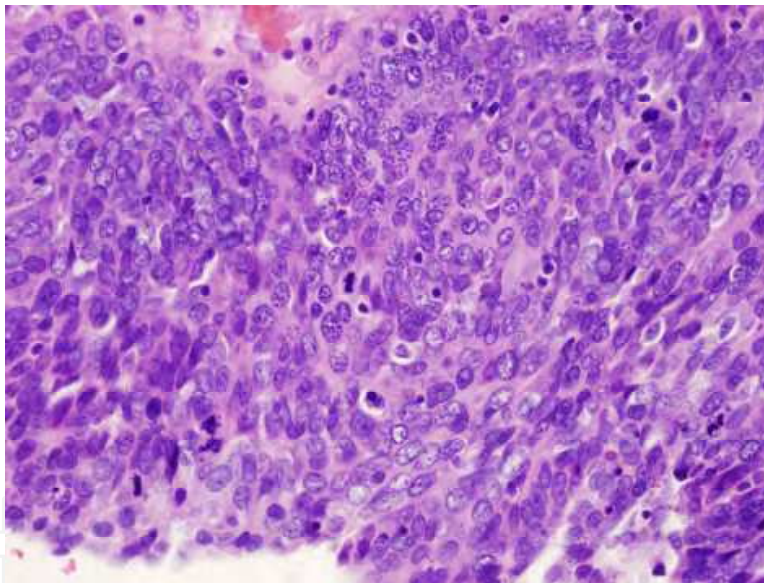


Fig. 6.c. TCC-O: At higher magnification, the macropapillae are composed of multilayered transitional cells resembling that of papillary transitional cell carcinoma of the bladder. These cells have high grade nuclei and numerous mitotic figures.

Foci of glandular differentiation and squamous metaplasia may also be seen. Very often, TCC can be mixed with serous adenocarcinoma. At matched stage, TCC-O has a worse prognosis compared to malignant Brenner tumors. Therefore, TCC-O should be differentiated from malignant Brenner tumors. Morphologically, TCC-O lack an associated benign or borderline Brenner tumor, whereas, malignant Brenner tumors are always accompanied by benign or borderline Brenner tumors (**Eichhorn JH et al., & Young RH, 2004**). Thus, extensive tumor sampling is needed to make an accurate diagnosis. The major differential diagnosis is metastatic TCC from the urinary tract and immunohistochemistry

can be very helpful. Numerous studies have dealt with this issue and concluded that the best IHC panel is CK20, uroplakin, and Wilm's tumor (WT). TCC-O are CK20-, uroplakin- and WT1+, whereas, metastatic TCC from the bladder are CK20+, Uroplakin + and WT1- (Logani S et al., 2003; Delair D et al., 2011 ; Ordonez NG, 2000).

7. Squamous cell carcinoma

Squamous cell carcinomas (SCCs) of the ovary are very rare. They arise most commonly from the lining of a dermoid cyst, endometriosis or a Brenner tumor (Acien P et al, 2010; Ba1 A et al, 2007). They have similar morphology to squamous cell carcinoma occurring in the cervix or vagina. Fig 7.a

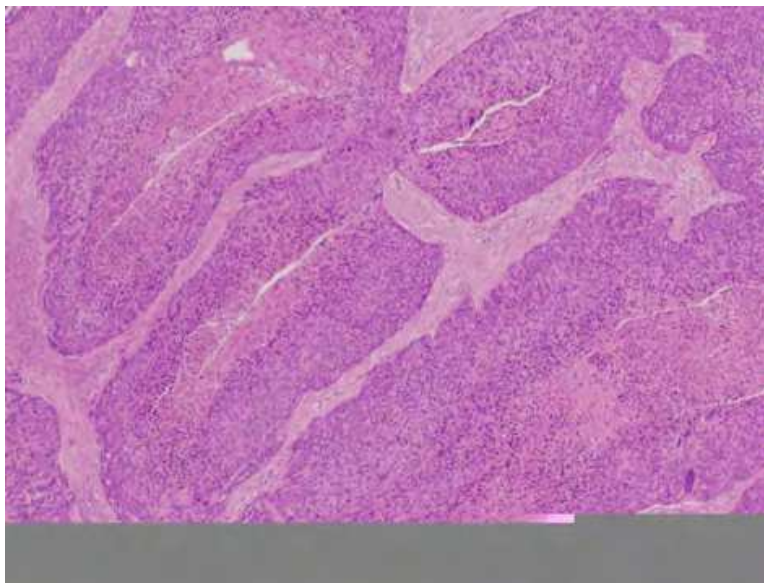


Fig. 7.a. Squamous cell carcinoma. Tumor cells are arranged in large nests. Keratin pearls and necrotic debris is also present. The tumor cells resembling squamous cell carcinoma of the cervix or squamous cell carcinoma of any origin.

Before the diagnosis of primary squamous cell carcinoma of the ovary is made, metastatic SCC from the cervix should be excluded. In addition, primary SCCs of the ovary should be distinguished from endometrioid adenocarcinoma with extensive squamous differentiation. Thus, extensive sampling is recommended. Cases of primary SCCs of the ovary frequently have spread beyond ovary at the time of presentation, leading to poor prognosis.

8. Ovarian carcinoma after neoadjuvant therapy

Traditionally, advanced stage ovarian carcinoma is treated by debulking surgery followed by chemotherapy. In some circumstances, neoadjuvant chemotherapy followed by debulking surgery may be done. Neoadjuvant chemotherapy is increasingly being used in the management of patients with advanced ovarian cancer and pathologists should be aware of the morphologic changes in ovarian cancer after neoadjuvant chemotherapy. For the inexperienced or those with no knowledge of the patients' history, treated tumors may be mistaken for metastatic carcinoma from breast primary or other sites. The morphologic

changes seen in response to neoadjuvant chemotherapy include small groups or single tumor cells in a densely fibrotic stroma **Fig 8.a**. The tumor cells are characterized by nuclear and cytoplasmic alteration making the grading and sometimes the tumor typing impossible and inaccurate. Nuclear changes include nuclear enlargement, hyperchromasia, irregular nuclear outlines and chromatin smudging. Cytoplasmic alterations include eosinophilic cytoplasm, vacuolation and foamy cell changes **Fig 8.b**. The stroma may have pronounced fibrosis, inflammation, foamy histiocytic infiltrates, hemosiderin deposits, necrosis, calcification and numerous free psammoma bodies (McCluggage WG et al., 2002; Chew I et al., 2009).

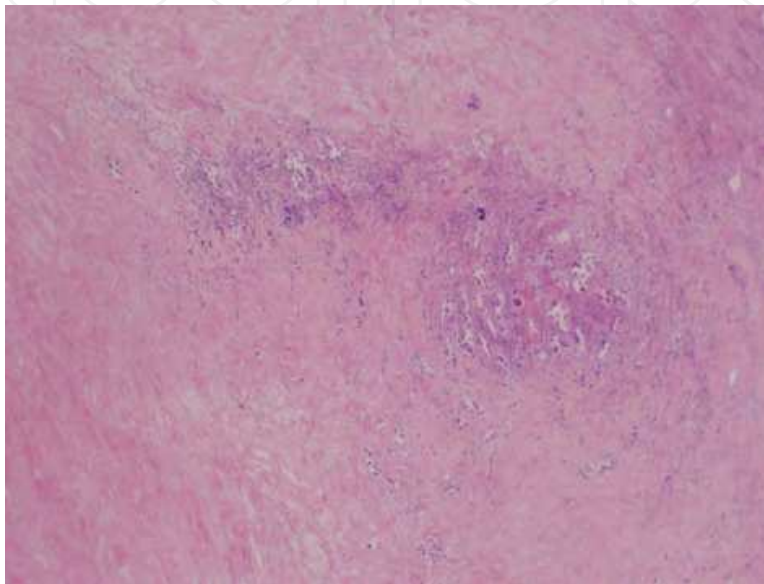


Fig. 8.a. Ovarian carcinoma after neoadjuvant therapy: The tumor presents extensive areas of fibrosis with few areas of remaining viable tumor cells.

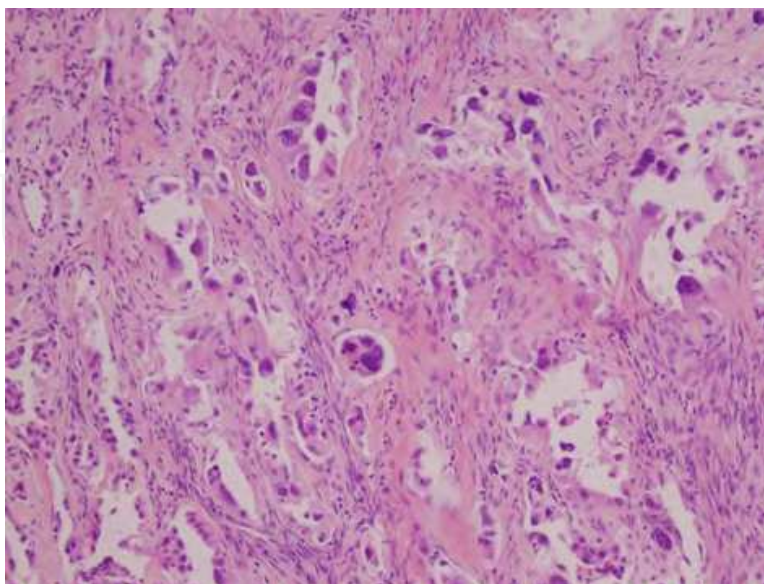


Fig. 8.b. Ovarian carcinoma after neoadjuvant therapy The nuclear changes seen including nuclear enlargement, hyperchromasia, irregular nuclear outlines and chromatin smudging.

The immunohistochemistry profile is similar to that of native untreated tumors. Ck7, CA125, WT1, ER, p53 and p16 may be of value in identifying residual tumor cells [Miller K et al., 2008].

9. Conclusion

Ovarian tumors are often complex and heterogenous in nature. In this book chapter we limited our discussion to the most common ovarian tumors in adult women. This is a concise histological description of these tumors that clinicians will find useful in their daily practice.

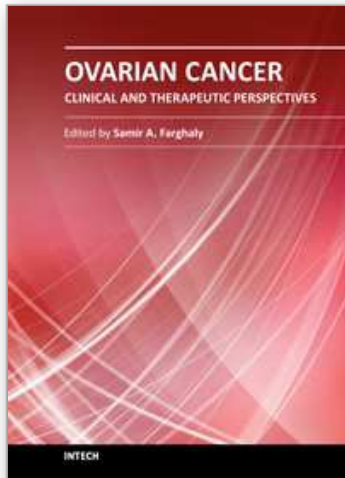
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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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