Surface Epithelial Neoplasms of the Ovary

Paulette Mhawech-Fauceglia

Abstract

Surface epithelial tumors are the most frequent neoplasms of the ovary, occurring in both reproductive and menopausal aged women. They are classified as benign, borderline (low potential malignancy/LMP), and malignant. They are classified in different histologic subtypes, such as serous, endometrioid, mucinous, clear cell, and transitional cell. However, 2014 was a year that brought significant changes to the classification of ovarian tumors. This chapter reviews the latest histologic subtyping of surface epithelial tumors based on the new World Health Organization (WHO) classification and revised grading systems as well as the new International Federation of Gynecology and Obstetrics (FIGO) staging system.

Keywords

Immunohistochemistry • Principles • Gynecologic malignancies • Differential diagnosis • Prognostic diagnosis

Contents

1 Introduction

The Surveillance, Epidemiology and End Results (SEER) cancer statistics estimated 21.290 new ovarian cases in 2015 claiming almost 14.180 lives (SEER 2015). Surface epithelial tumors accounts for almost two-third of all ovarian tumors, and they are by far the most frequent ovarian cancer types in the western world. Their origin is likely the epithelium lining of the ovarian surface, invaginations of this lining into the superficial cortex of the ovary, and/or fallopian tube tissue. Surface epithelial tumor rates are highest in women aged 55–64 years with a median age of 6.3 years. Numerous changes concerning tumor staging and histologic subtypes were introduced

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in 2014. Based on the new data regarding molecular alterations in ovarian carcinogenesis, the revised WHO classification eliminated transitional cell carcinoma subtype and reclassified them into high-grade serous and high-grade endometrioid carcinoma (Kurman et al. 2014). Second, a seromucinous category was newly introduced. There were also changes made in the 2014 FIGO staging (FIGO Committee on Gynecologic Oncology 2014) that are discussed below.

2 Benign Ovarian Cysts

The most common benign ovarian lesions are the corpus luteal cyst and solitary follicular cyst.

2.1 Corpus Luteal Cyst

Corpus luteal cysts usually occur in women in the reproductive age. They are unilocular cysts. Grossly, the cyst is lined by a convoluted golden brown rim. These cysts can become cystic, and large, filled with chocolate brown fluid (Fig. 1). Histologically, the cysts are lined by large luteinized granulosa cells and an outer layer of smaller luteinized theca interna cells.

Fig. 1 The ovary is cystically dilated. The cyst is filled with *brown* chocolate fluid with blood clot

2.2 Solitary Follicular Cyst

Solitary follicular cysts occur in women of reproductive age [although they can occur even in postmenopausal women]. They are unilocular cyst with a size ranging from 3 to 8 cm. The cyst lining is composed of an inner layer of granulosa cells and an outer layer of theca interna cells. The evidence of the two layers are seen on reticulin stain where it is negative in former and positive in the later (Fig. 2).

3 WHO Classification of Epithelial Tumors

Serous Tumors

Benign

- Serous cystadenoma
- Serous adenofibroma
- Serous surface papilloma

Borderline

- Serous borderline tumor/low malignant potential/atypical proliferative serous tumor
- Serous borderline tumor micropapillary variant/noninvasive low-grade serous carcinoma

Malignant

- Low-grade serous carcinoma
- High-grade serous carcinoma

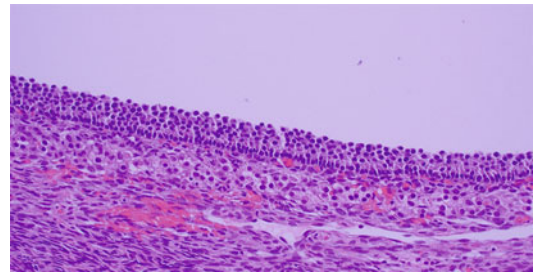

Fig. 2 Solitary follicular cyst where the cyst is lined by inner layer of granulosa cells and an outer layer of theca cells

Mucinous Tumors

Benign

- Mucinous cystadenoma
- Mucinous adenofibroma

Borderline

- Mucinous borderline tumor/low malignant potential/atypical proliferative mucinous tumor

Malignant

- Mucinous carcinoma

Endometrioid Tumors

Benign

- Endometriotic cyst
- Endometrioid cystadenoma
- Endometrioid adenofibroma

Borderline

- Endometrioid borderline tumor/low malignant potential/atypical proliferative endometrioid tumor

Malignant

- Endometrioid carcinoma

Clear Cell Tumors

Benign

- Clear cell cystadenoma
- Clear cell adenofibroma

Borderline

- Clear cell borderline tumor/low malignant potential/atypical proliferative clear cell tumor

Malignant

- Clear cell carcinoma

Brenner Tumors

Benign

- Brenner tumor

Borderline

- Borderline Brenner tumor/low malignant potential/atypical proliferative Brenner tumor

Malignant

- Malignant Brenner tumor

Seromucinous Tumors

Benign

- Seromucinous cystadenoma
- Seromucinous adenofibroma

Borderline

- Borderline seromucinous tumor/low malignant potential/atypical proliferative seromucinous tumor

Malignant

- Seromucinous carcinoma

Undifferentiated Carcinoma

3.1 Serous Tumors

3.1.1 Serous Cystadenoma and Adenofibroma

Serous cystadenoma and adenofibroma are common tumors accounting for 25% of all benign ovarian neoplasms. It occurs at any age with peak incidence during the fourth and fifth decades [highest at age 40.]. Bilaterality rate is variable and is around 20–30% of cases. Grossly, the cyst is filled with clear serous fluid. The inner layer of the cystadenoma is smooth, while the adenofibroma has focal excrescences. These excrescences are very different than those seen in borderline tumor as they are soft in the later and chalky white and very hard on touch in the former. Microscopically, serous cystadenomas are cysts lined by single cell layer which can be cuboidal or flattened due to the fluid pressure in the cyst content. The stroma may appear as normal ovarian parenchyma or it can be fibrotic. In adenofibroma, the excrescences seen grossly are large broad clefts of fibrous tissue lined by simple single layer of epithelial cells. Some cases have a focal area of pseudostratified epithelium with mild atypia. The tumor is classified as borderline if the pseudostratified epithelium with atypia is present in 10% or more of the tumor. Since this is a very arbitrary cutoff, it has been suggested to classify this finding as a serous cystadenoma with focal epithelial proliferation with a comment explaining the presence of focal areas of borderline tumor which constitute $\geq$10% of overall histological material" (Longacre et al. 2005).

3.1.2 Serous Borderline Tumor/Low Malignant Potential/Atypical Proliferative Serous Tumor

Serous borderline tumors (SBTs) represent 25–30% of nonbenign 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). Grossly, the ovarian mass is typically unilocular although it can present as a multilocular cyst, usually measuring >5 cm. The outer surface of the cyst may appear smooth, but it is important to do a close gross examination to note any surface projections/involvement as it changes the tumor FIGO staging as discussed below. The cyst is usually filled with serous fluid and the cyst lining usually exhibits very soft, friable white projections (Fig. 3). Microscopically, the cyst lining shows papillary projections lined by stratified cuboidal cells. In places, these cells are marked by hobnail features reflected by eosinophilic cytoplasm, mild to moderate atypia, and high nuclear/cytoplasmic ratio. The critical finding of a borderline tumor is the lack of invasion of the ovarian stroma (Fig. 4).

Serous borderline tumor may be associated with omental implants. Peritoneal implants are classified as noninvasive epithelial implants, invasive epithelial implants, or desmoplastic implants. Since implants are a heterogeneous group and various types may coexist, it is important that multiple biopsies of numerous foci of suspicious lesions are done at the time of surgery and that extensive tumor sampling by the pathologist is done to accurately exclude an invasive implant.

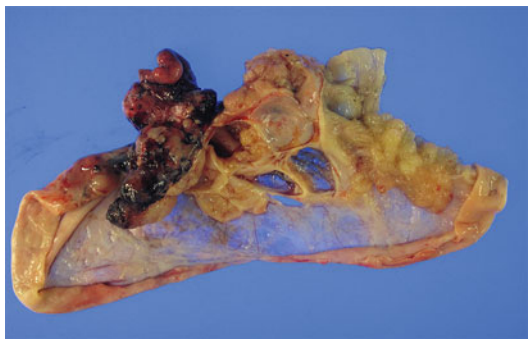

Fig. 3 The ovarian cyst is multilocular. The inner surface is smooth, but some areas of very soft friable vegetations

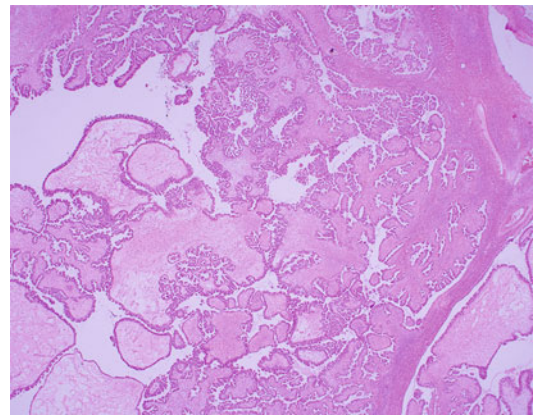

Fig. 4 The cut surface of these projections show papillary structure lined by stratified cuboidal cells. These cells exhibit mild to moderate atypia and few mitotic figures are also present. There is no stromal invasion

The diagnosis of peritoneal implants is very challenging and very difficult. It is therefore recommended of the opinion that the final diagnosis is cleared by an expert gynecologic pathologist, especially in cases where the diagnosis may change a patient's treatment options and management.

3.1.3 Serous Borderline Tumor (SBT) Micropapillary Variant (MSBT)

Serous borderline tumors account for 5–10% of all SBTs. Microscopically, MSBT 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. 5). 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 have urged that this lesion be labeled as a "micropapillary serous carcinoma." Others prefer the terminology of MSBT, avoiding the use of the term of "carcinoma," to minimize the possibility of overtreating patients (Chang et al. 2008). The general agreement on the significance of micropapillary architecture in SBTs is that they are related to significant increases in the incidence of invasive peritoneal implants. Molecular studies show that MSBTs

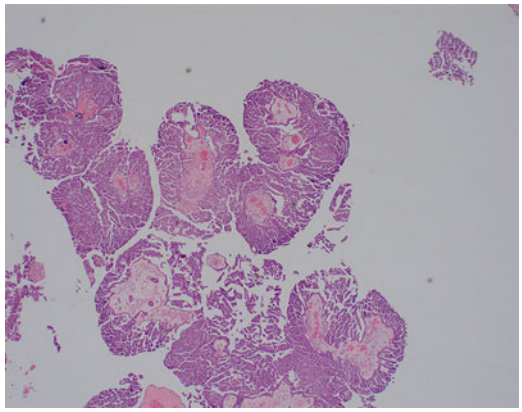

Fig. 5 Serous borderline, micropapillary variant where there is highly complex micropapillary growth in a filigree pattern looking like "medusa head." These micropapillae are long and wide

have a similar gene expression profile to low-grade serous carcinomas (LG-serous carcinoma) that are distinct from typical SBT (May et al. 2002). 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*. MSBT is the only surface epithelial-stromal tumor with a well-defined adenoma-carcinoma sequence, whereas LG-serous tumors are thought to arise in a stepwise fashion from a benign cystadenoma (through BST to an invasive LG-serous carcinoma) (Shih and Kurman 2005). Since micropapillary foci of less than 5 mm have no bearing on clinical outcome, these tumors with low levels of micropapillary foci and atypia can be classified as SBT with focal micropapillary features (Slomovitz et al. 2002).

3.1.4 Low-Grade and High-Grade Serous Carcinoma

The majority of epithelial ovarian carcinomas are of serous histology. The new WHO classification of ovarian serous carcinomas places them into two distinct categories: high grade and low grade. The two types are distinct in terms of site of origin, molecular pathways, and treatment response. Low-grade serous carcinomas (LG-SC) are type I tumors that are relatively rare. They are genetically very stable, and they frequently harbor alterations in the mitogen-activated protein kinase (MAPK) signaling pathway. Recent pathologic evidence showed that there are three possible origins for LG-SC: ovarian surface epithelium, fallopian tube origin, and endometrial cells ectopically located in the ovary by retrograde menstruation. They are cytologically very low grade with mild atypia and low mitotic rate. LG-SC are usually cisplatin resistant leading to new clinical trials with tyrosine kinase inhibitors in several cancer centers (Kurman et al. 2014).

High-grade serous carcinomas (HG-SC) are the most common histotype (70%) of the epithelial ovarian cancer. They are considered type II ovarian cancers. They occur 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 (stages III and IV) at first presentation. They are characterized by multiple gene abnormalities such as *TP 53* mutation in almost 97%, and BRCA1/BRCA2 loss is frequent (30–45%, including germline and somatic alterations). Many of these tumors are thought to originate from the fallopian tube (serous tubal intraepithelial carcinoma/STIC). Grossly, the tumor varies considerably in size from a few cm to 30 cm (Fig. 6). They can be multicystic or solid. When these tumors are diagnosed at advanced stage frequently, the omentum is replaced by tumor creating what is called "omental caking." Cytologically the tumor exhibits moderate to severe atypia

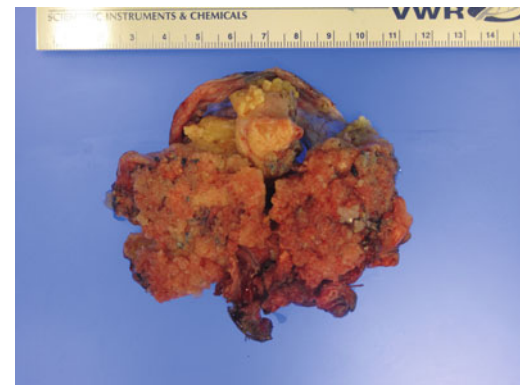

Fig. 6 Ovarian mass with serous carcinoma. The cut surface is partially cystic and partially solid, soft, and friable

with a high mitotic rate (Mhawech-Fauceglia and Pejovic 2015).

3.2 Mucinous Tumors

3.2.1 Mucinous Cystadenoma

Mucinous cystadenomas are the most common type (75%) of mucinous tumors. They can be very large (up to 20 cm) and can be unilocular or multilocular. They are filled with mucoid fluid and in 95% of cases they are unilateral. The cyst is lined by one layer of cells that have small bland looking nuclei with ample mucin-filled cytoplasm creating what is called "picket fence" appearance.

3.2.2 Mucinous Borderline Tumor/ Mucinous Tumor of Low Malignant Potential

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 those seen in their benign counterparts but without evidence of stromal invasion. MBT can be of intestinal type or endocervical-like type. Mucinous borderline tumors account for 10% of mucinous tumors. They can be multilocular and are bilateral in 40% of the cases. MBT are cystic tumors with a visible solid vegetating mass protruding from the cystic wall. Careful gross examination of the cyst wall to identify these lesions is crucial. Histologically, the lining of the cyst is composed of stratified epithelial cells having high N/C ratio and prominent nucleoli. Goblet cells and Paneth cells are present in the intestinal type. No stromal invasion is seen. Borderline tumors remain a controversial issue concerning their pathogenesis, progression, and treatment (Fischerova et al. 2012).

3.2.3 Mucinous Adenocarcinoma

Mucinous adenocarcinoma (MAC) accounts for 15% of mucinous tumors and 2–4% of all ovarian surface epithelial tumors. They are rare and unilateral in 95% of cases. Therefore, when they are bilateral, metastatic tumors especially from the gastrointestinal tract, namely, the colon, should be in question. They can be very large masses reaching more than 10 cm in the vast majority of the cases. They can be multicyctic/partially cystic and partially solid or solid tumors (Fig. 7). They have two patterns of invasion, the first and most common, pushing or expansile pattern where there are complex glands with back to back architecture and no intervening stroma. The glands are evidently malignant exhibiting mild to moderate cytologic atypia, high nuclear/cytoplasmic ratio, and lack of mucin. The second pattern is infiltrative pattern where single or groups of malignant cells are seen to invade the ovarian stroma with desmoplastic reaction. The origin of MAC is very elusive but some cases have been associated with endometriosis. They harbor Ras pathway alterations, and like LG-SC they may contain a spectrum of mucinous cystadenoma to borderline tumor to MAC in the same tumor (Brown and Frumovitz 2014).

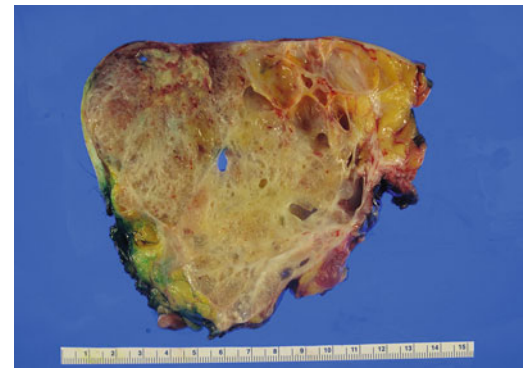

Fig. 7 Cut surface of mucinous adenocarcinoma where it is spongy with numerous tiny cystic spaces. These cysts were filled with mucin

3.2.4 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 as either a low-grade variety "diffuse peritoneal adenomucinosis" (DPAM) or a high-grade variety "peritoneal mucinous carcinomatosis" (PMCA). The classification of the tumor is

prognostically significant with 5-year survival rates of 84% for DPAM and 6.7% for PMCA (Ronnett et al. 2001). PP may originate from an ovarian primary or from an appendiceal primary. Cytoreductive surgery involves removal of the peritoneum and it is common to remove the ovaries, fallopian tubes, uterus, and parts of the large intestine, including the appendix. Whether the primary origin of this tumor is from an ovarian mucinous tumor or from an appendiceal primary or has synchronous origins is still a subject of great debate.

3.2.5 Mucinous Tumors with Mural Nodule

Mucinous tumors of the ovary, whether benign, borderline, or malignant, may contain one or more mural nodules. These nodules are more frequent in borderline and malignant tumors. Grossly, mural nodules are different than the overlying mucinous neoplasm. Grossly, nodules are yellow and pink with areas of hemorrhage and necrosis. Morphologically, they are classified as benign (sarcoma-like) or malignant anaplastic carcinoma and sarcoma. It is important to distinguish between benign and malignant mural nodules, because benign mural nodules are of no prognostic significance (Mhawech-Fauceglia et al. 2015). Whether malignant mural nodules represent a form of dedifferentiation or a collision of two divergent tumor types is still unsolved mystery.

3.3 Clear Cell Tumor

3.3.1 Borderline Clear Cell Tumor

Borderline clear cell tumors are extremely rare. The gross appearance is nonspecific as it can range from solid to spongy. Microscopic findings include a proliferation of small glands with or without cystic dilatation that are lined by flat and hobnail atypical cells. No stromal invasion is present.

3.3.2 Clear Cell Carcinoma

Clear cell carcinomas (CCC) represent 6–10% of surface epithelial tumors. They occur in postmenopausal women, with a mean age of 57 years. CCC of the ovary have a few notable characteristics. (1) They are almost always unilateral (Fig. 8), and when they are bilateral, a metastatic renal cell carcinoma should be excluded. (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 and express HNF1B. CCC are generally chemoresistant. They have numerous histological patterns including tubulocystic, papillary, solid, or a mixture of any of those patterns. Typically, the cysts are lined by atypical hobnail cells with clear cytoplasm and numerous intracytoplasmic hyaline globules (Fig. 9) (Okamoto et al. 2014).

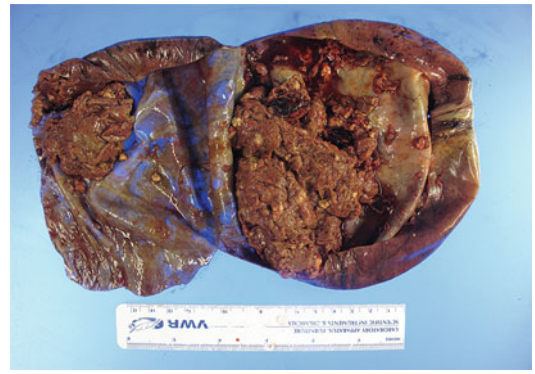

Fig. 8 Cut surface of a clear cell carcinoma. It is unusually cystic. The surface is hemorrhagic and friable

3.4 Endometrioid Tumors

3.4.1 Endometriotic Cyst

Endometriotic cyst or endometriomas are simply endometriosis cells that have undergone a cystic dilation. They are among the most common ovarian cystic lesions in the fourth and fifth decade. Grossly, they consist of a large simple cyst. The content is characteristic of chocolate brown fluid. Microscopically, they are a simple cyst lined by cuboidal endometrial cells with hemorrhage, hemosiderin deposits, and macrophages present in the cyst wall.

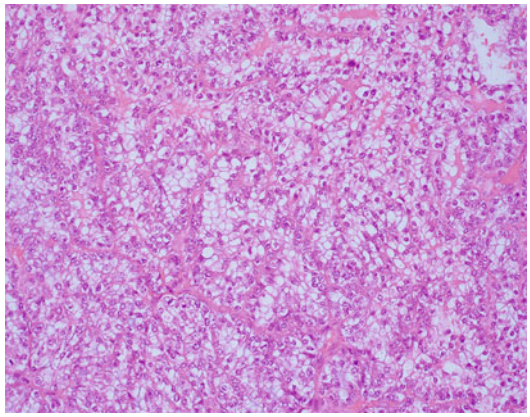

Fig. 9 Microscopic section shows diffuse sheets of tumor cells. These cells have clear cytoplasm. The nuclei are round with prominent nucleoli

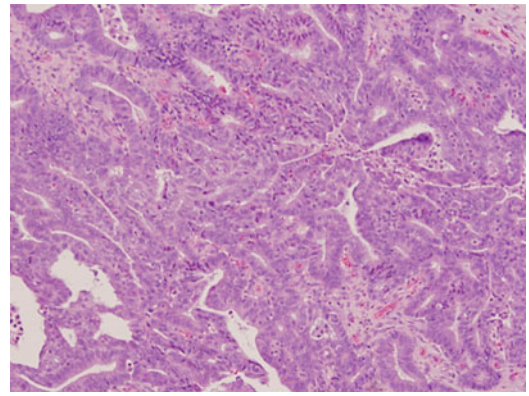

Fig. 10 Endometrioid adenocarcinoma characterized by glands back to back with no intervening stroma

3.4.2 Borderline Endometriotic Tumor

Borderline endometriotic tumors are such rare tumors that some gynecologic pathologists doubt their existence. Morphologically, they are very similar to endometrial hyperplasia occurring in the endometrium. There are composed of crowded glands that are embedded in very fibrotic stroma. The glands exhibit mild atypia and focal squamous morules.

3.4.3 Endometrioid Adenocarcinoma

Endometrioid adenocarcinoma (EAC) accounts for 10–20% of ovarian carcinomas. They occur in postmenopausal women in the fifth and sixth decade, with an average age of 56 years. They are associated with endometriosis in the same ovary or pelvis, and they can coexist with endometrioid adenocarcinoma of the endometrium in 15–20% of cases. PTEN, CTNNB1, PIK3CA, and ARID1A are commonly mutated in EAC and tumors frequently express estrogen/progesterone receptors and TFF3 by immunohistochemistry (Kobel et al. 2013). They are bilateral in 20% of cases. About half of EAC cases present as low-grade/well-differentiated tumors and with early stage disease (stages I and II). Grossly, the ovary may be cystic or solid with friable cut surface. EAC is microscopically very similar to those occurring in the endometrium, where there is back to back glandular architecture, with no intervening stroma and squamous differentiation in the form of squamous morules and keratin pearls (Fig. 10). However, EAC is the most chameleon ovarian cancer in existence as it can have numerous histologic variants such as tubular/tubulovillous, spindle shape, mucin-rich, eosinophilic, secretory, ciliated, and resembling sex-cord stromal tumors. In these cases, immunohistochemistry is necessary for accurate diagnosis.

3.5 Brenner Tumors

3.5.1 Benign Brenner Tumor

Benign Brenner tumors account for 5% of benign ovarian epithelial tumors. They occur at a wide range group age, between 30- and 60-year-old women. They are usually asymptomatic and can be totally accidental finding. In 20–30% of cases, Brenner tumors develop synchronously with other neoplasms including mucinous neoplasm, dermoid cyst, or mature cystic teratoma. They are small generally less than 2 cm in size. They are unilateral in 95% of cases. Grossly, they are a sharply delineated mass seen in a normal ovary with a whitish firm cut surface. Microscopically, benign Brenner tumors appear as islands of transitional cells with nuclear grooving embedded in a fibrotic stroma. Sometimes, cystic dilation lined by transitional or mucinous epithelium can be seen. No atypia, mitotic figures, and necrosis are seen.

3.5.2 Malignant Brenner Tumor

Malignant Brenner tumors are the least common of the surface epithelial tumors of the ovary. They occur in women over 50 years of age. They are usually large and they might be cystic or solid. Histologically, they resemble urothelial/transitional carcinoma of the urinary tract. They are composed of sheets of transitional-like epithelium exhibiting moderate atypia and fair numbers of mitotic figures. Cystic areas can be present. With extensive sampling, islands of benign Brenner tumor are seen in the background. However, if no benign Brenner tumor cells are seen after extensive sampling, a high-grade serous or endometrioid adenocarcinoma should be suspected.

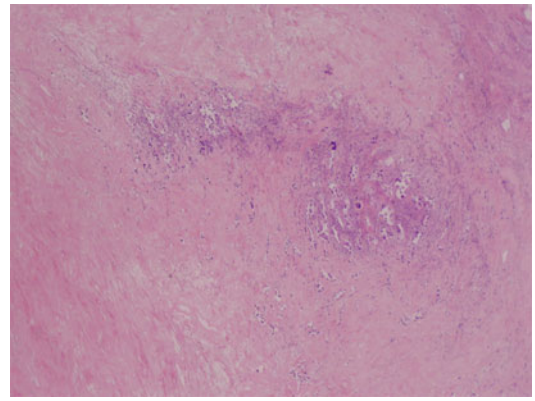

Fig. 11 Residual serous adenocarcinoma post neoadjuvant chemotherapy. Tumor cells are in single files or clusters with abundant fibrous stroma

3.6 Seromucinous Tumors

Seromucinous tumors is a new entity that was introduced in the 2014 WHO classification. It has three categories: benign, borderline, and malignant (carcinoma). They are rare neoplasms. They are composed of a variable admixture of serous and mucinous (endocervical) epithelial lining. They are likely derived from endometriosis cells but this is still subject to speculation.

3.7 Undifferentiated Carcinoma

By the WHO definition "undifferentiated tumor is a malignant tumor showing no differentiation of any specific Mullerian cell type." Undifferentiated carcinomas usually present at the late stage. They are characterized by proliferation of high-grade tumor cells with high mitotic rate in a diffuse pattern with areas of necrosis.

3.8 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. 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. 11). 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). The stroma may have pronounced fibrosis, inflammation, foamy histiocytic infiltrates, hemosiderin deposits, necrosis, calcification, and numerous free psammoma bodies (McCluggage et al. 2002; Miller et al. 2008). Fortunately, tumor cells seem to keep their antigens and therefore express antibodies similar to those seen in pretreatment including CK7+, WT1+, and p53+ (Chew et al. 2009).

3.9 Ovarian Grading Systems

Ovarian cancer is a very challenging task and it is still performed haphazardly with several systems and nonsystems 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 =>50% solid growth. In the **WHO** system, the grade is assessed by both the architectural and cytologic features, without any quantitative evaluation. The Gynecologic Oncology (GOG) system is the most commonly used system in the United States (Bendaj and Zaino 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 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 2000). Figure 12 and 13 is an example of grade 1 and grade 3 serous carcinomas. This grading system was confirmed to be reproducible in subsequent studies (Ishioka et al. 2003).

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 et al. 2004). The tumor is graded into low grade (Fig. 12) and high grade (Fig. 13). A few years after its introduction, the authors confirmed its reproducibility and urged its use to facilitate the clinical trials and protocols (Malpica et al. 2007). This grading system has gained huge popularity and even it was adopted by the 2014 WHO classification. However, this grading could be applied to only serous carcinomas.

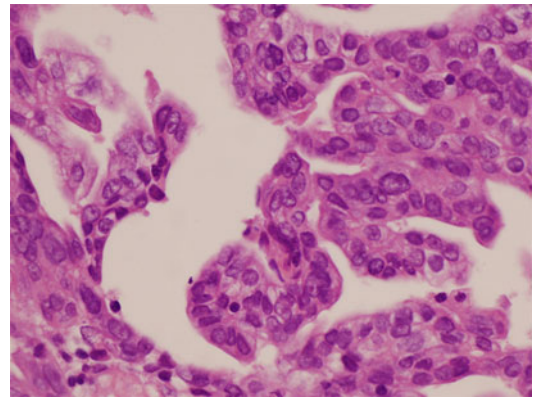

Fig. 12 Low-grade serous carcinoma defined by mild atypia and few mitotic figures

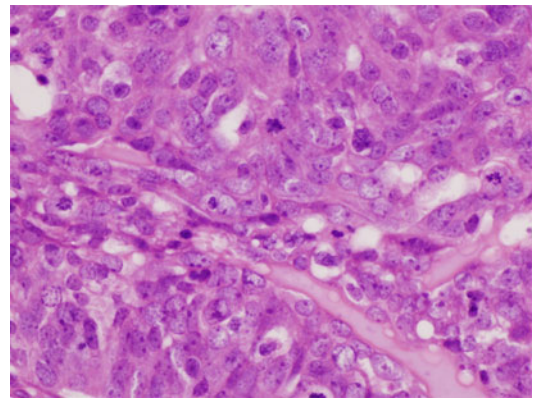

Fig. 13 High-grade serous carcinoma defined by moderate to severe atypia and high mitotic figures

3.10 Ovarian Staging FIGO 2014

The International Federation of Gynecology and Obstetrics (FIGO) staging has revised the staging

for ovarian cancer, and the approved and new ovarian cancer staging went into effect on 1 January 2014. There were some major differences between the old FIGO and new FIGO staging system.

Stage I: IC (ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites) was subdivided in IC1 (surgical spill), IC2 (capsule rupture before surgery or tumor on surface ovarian surface), and IC3 (malignant cells in the ascites or peritoneal washings).

Stage II: IIC in the old system (IIA or IIB with positive washings/ascites) was canceled. So in the new system is only stage IIA and IIB.

Stage III: IIIA was modified and subclassified into IIIA1 (positive retroperitoneal lymph nodes only) and IIIA2 (microscopic, extrapelvic peritoneal involvement ± positive retroperitoneal lymph nodes).

4 Conclusion

Epithelial ovarian tumors are very interesting and fascinating tumors. They still are a subject of debate regarding their pathogenesis, molecular pathways, diagnosis, and treatment. However, the discovery of new genetic mutations and pathways had revolutionized our understanding of ovarian cancer and has provided us with a fresh outlook based on their molecular fingerprints. In the past, histologic classification of surface epithelial tumor had poor interobserver agreement (60%), but because of the advancement of the molecular testing, the immunohistochemistry agreement has risen to 80–90% (Kobel et al. 2010). Due to these advancements in reclassification, it will not be a surprise if 10 years from now, ovarian tumors will be reclassified using not just morphology alone but will heavily incorporate the molecular findings. All the gynecologic oncologic communities are excited about these developments. Targeted therapy and personalized medicine are very promising venues for patients' care.

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