

Precursors of Low-Grade Serous Adenocarcinoma of the Ovary: Pathology and Molecular Pathways

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Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death due to gynecologic malignancy in women in the United States, with 22,240 new cases and 14,030 women estimated to have died of ovarian cancer in 2013 [1]. The majority of EOCs are of serous histology, and it is now widely accepted that ovarian serous carcinomas fall into two distinct categories: high grade and low grade. High-grade serous ovarian carcinomas (HGSCs) are the most common subtype of EOC, whereas low-grade serous carcinomas (LGSCs) are less common and represent approximately 3 % of all ovarian surface epithelial carcinomas. The two types are distinct in terms of pathogenesis, molecular pathways, treatment response, and patient prognosis. HGSCs are classified as Type II carcinomas in the Shih and Kurman dualistic model of ovarian cancer development [2]. Type II carcinomas exhibit distinct genetic hallmarks including high levels of genetic

instability and *TP53* mutations. HGSCs are de novo carcinomas and it is thought that a large proportion originate from the fallopian tube fimbriae [3, 4]. LGSCs are Type I tumors, which are more genetically stable and frequently harbor alterations in the mitogen-activated protein kinase (MAPK) signaling pathway. Unlike HGSC, they follow a stepwise progression from inclusion cyst to serous cystadenoma, serous borderline tumor, serous borderline tumor with micropapillary pattern, and finally to invasive low-grade serous carcinoma. However, the pathogenesis of this subtype is not fully understood and the cellular origins are a recent topic of debate. In this chapter we will be discuss the histology, grading, pathogenesis, and molecular characteristics of low-grade serous carcinomas.

Histology

Serous borderline tumors (SBTs)/serous tumor of low malignant potential (LMP) represents 25–30 % of non-benign serous tumors and occurs in women 30–50 years of age. In the majority of cases they are unilateral and usually present at an early stage (stage I) [5]. 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” [6].

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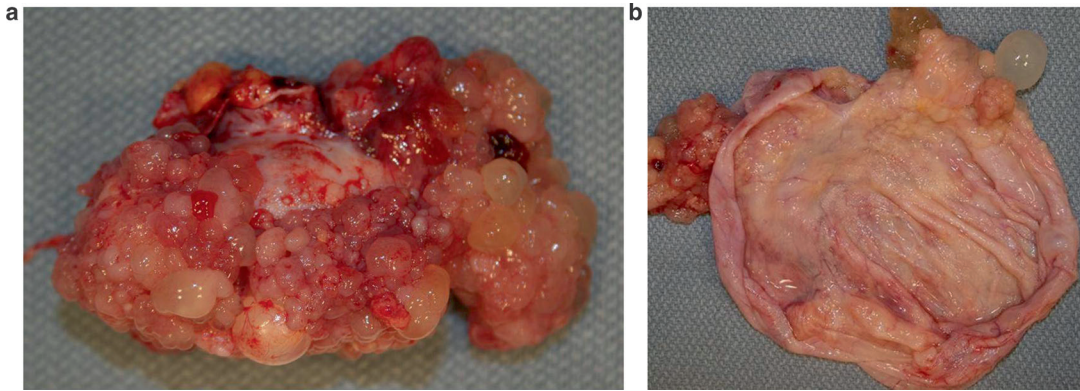


Fig. 2.1 (a) Ovarian cyst with surface involvement by friable papillary excrescences. They appear to cover most of the ovarian cyst surface. (b) The inner lining of the

same ovarian cystic mass is mainly smooth. However, there are areas showing irregular friable vegetating masses

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. 2.1a, b). The papillary structures are yellow in color, soft, and friable. SBT can be readily differentiated from the hard, stocky, white excrescences that are usually characteristic of serous cystadenofibroma. SBTs can be subgrouped into tumors with typical and tumors with micropapillary patterns.

Typical SBT

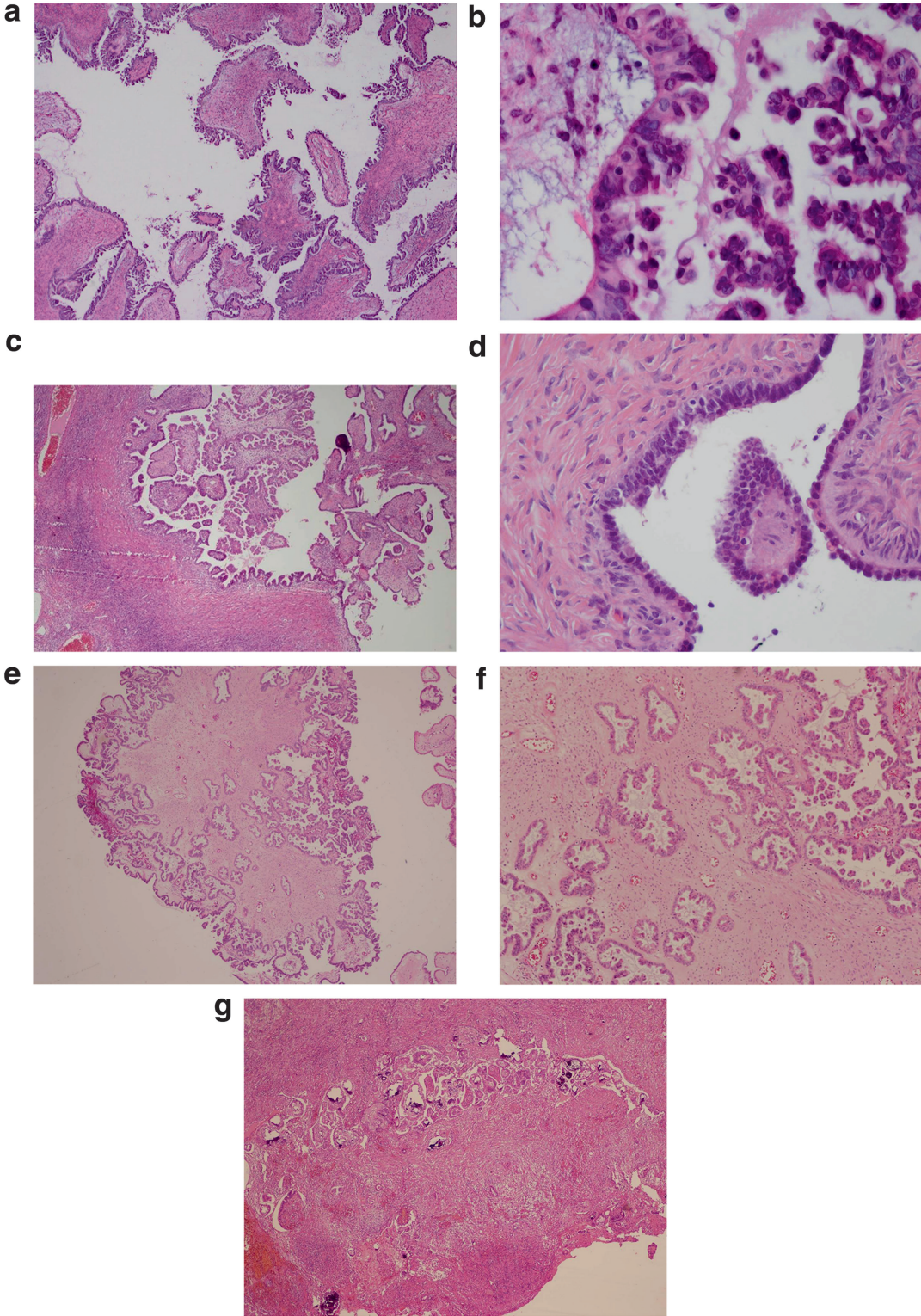
Typical SBT makes up the majority of SBT or (90 %). A diagnosis of SBT/LMP is based on three main characteristics: (1) epithelial stratification and cellular budding where the tumor cells become detached from the papillae and appear to

float in the cystic lumen with no fibrovascular core. (2) The tumor cells have mild to moderate cytologic atypia. (3) There is lack of stromal invasion. 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-to-cytoplasmic ratio (N/C), and the nuclei are hyperchromatic with prominent nucleoli. Mitotic figures are frequently present (Fig. 2.2a–c). While the histologic criteria may suggest that a diagnosis of serous LMP is straightforward, sometimes the diagnosis of serous LMP can be challenging as these diagnoses are subject to numerous pitfalls, including the following:

Serous LMP May Have Variants Some SBTs present with intracystic mucin and can mimic mucinous adenocarcinoma. The key to make the

Fig. 2.2 (a) Cut section of these vegetating masses reveals papillary structure with fibrovascular stalks. These structures are lined by stratified cuboidal to columnar epithelial cells. (b) There is stratification of tumor cells which they start getting detached and float in the lumen. These cells exhibit moderate cellular atypia with high nuclear/cytoplasmic ratio. (c) The main characteristic feature of ovarian serous borderline tumor is the absence of ovarian stromal invasion. (d) Cut surface of benign serous cystadenoma. The cyst is lined by cuboidal epithelium. There are few areas where the cells appear to be stratified. However, due to the lack of cytologic atypia, this mass is

considered as benign and this pseudo-stratification is due to tangential section. (e) Lower magnification showed tumor cells that seem to infiltrate fibrous stroma. (f) Higher magnification, these cells seemed to invade the stalk of the papillae and not the ovarian stroma which can be a major pitfall. (g) Microscopic features of autoimplantations are very similar to the features of desmoplastic noninvasive implant. They are defined by clusters of tumor cells in a background of extensive hemorrhage, fibrosis, and acute chronic inflammation. Frequent psammoma bodies are seen. These autoimplantations are usually seen on the surface of the ovary



diagnosis is that the mucin is intracyclic, not intracytoplasmic, as usually seen in mucinous tumors. The second variant is that the tumor can have a cribriform pattern and can mimic endometrioid tumor. While these variants do not carry any significance on prognosis, they can create a diagnostic challenge for pathologists.

Tangential Cut 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 (Fig. 2.2d).

Stromal Invasion By definition, SBT lacks stromal invasion. This is a major criterion to differentiate SBT from serous adenocarcinoma. Therefore, invasion of the stalk of the papillae should not be considered as ovarian stromal invasion as illustrated in Fig. 2.2e, f.

Autoimplantation Another pitfall is the failure to differentiate between stromal invasion and autoimplantation, which is the invagination of the tumor on itself creating the illusion of a stromal invasion, as shown in Fig. 2.2g. Grossly, serous LMP tumors exist as well-demarcated plaques on the surface of the ovary. It is essential to mention that autoimplantations are localized superficially on the surface of the ovary and are morphologically similar to desmoplastic noninvasive implants with disorganized groups of tumor cells embedded in dense stroma with hemorrhage, chronic inflammation, mesothelial proliferation, and massive necrosis.

Micropapillary SBT

Micropapillary SBT (MSBT) accounts for 5–10 % of all SBTs. The significance of this subtype is debated among pathologists. Some authors have found a close association between MSBT and invasive implants and urged to call this entity as “micropapillary serous carcinoma” [7, 8]. Others preferentially use the term MSBT, avoiding the use of the term of “carcinoma,” to minimize the

possibility of over-treating patients [7, 8]. The general agreement on the significance of micropapillary architecture in SBTs is that there is a significant increase in incidence of invasive peritoneal implants [9]. Molecular studies show that MSBT has a similar gene expression profile as low-grade serous carcinoma and distinct from typical SBT [10]. MSBT is the only surface epithelial stromal tumor with a well-defined adenoma-carcinoma sequence, where LGSC is thought to arise in a stepwise fashion from a benign cystadenoma through BST to an invasive low-grade serous carcinoma [11]. Microscopically, MSBTs show highly complex micropapillary growth in a filigree pattern, growing in a nonhierarchical fashion from stalk which has been aptly described as a “Medusa head”-like appearance. Micropapillae are at least five times as long as they are wide [12] (Fig. 2.3a–c). 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 [12].

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 or not exceeding 3 mm or 5 mm. SBT with microinvasion appears to have no significance on disease outcome, with 10-year survival rate of 86 % [12].

Peritoneal Implants

Peritoneal implants are classified into epithelial invasive and noninvasive implants and desmoplastic noninvasive implants. Implants are a heterogeneous group of lesions 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 are essential for the accurate evaluation of peritoneal implants. Differentiating invasive and noninvasive implants can be challenging, but given the increased probability of tumor

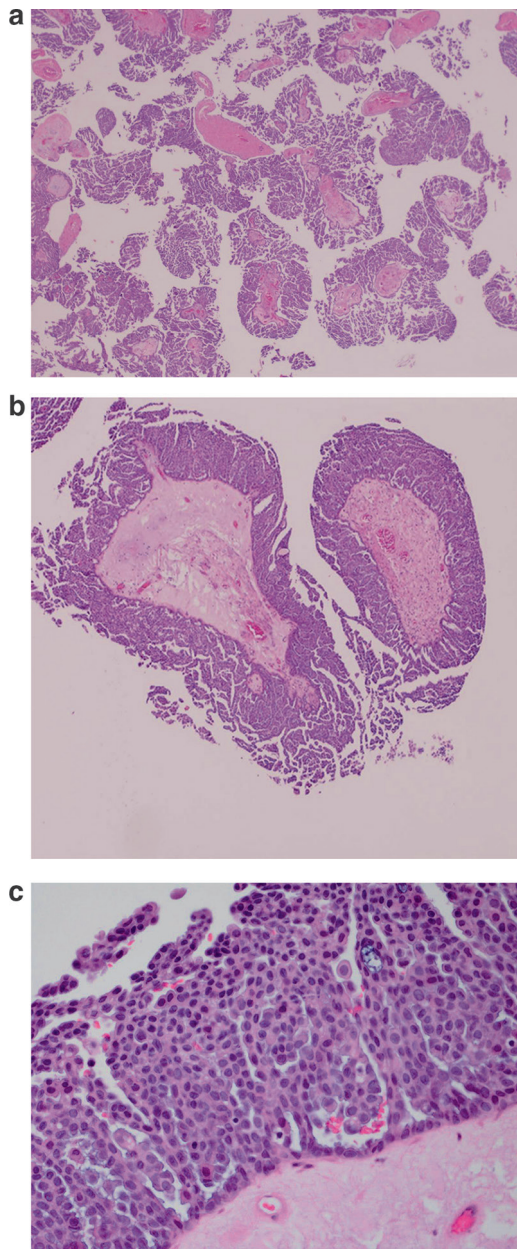


Fig. 2.3 (a) There is highly complex micropapillary growth in a filigree pattern, growing in a nonhierarchical fashion from stalk. These are described as a “Medusa head”-like appearance. (b) Micropapillae should be at least five times as long as they are wide. (c) Cytologically, tumor cells are somewhat bland looking exhibiting mild atypia and very infrequent mitotic figures

recurrence for invasive implants, accurate diagnoses have a significant impact on patient prognosis and clinical management of the case.

Epithelial noninvasive implants are characterized by the presence of papillae within cystic spaces exhibiting mild cytologic atypia. There are frequent psammoma bodies and no stromal reaction or destruction with mild degree of inflammatory cells (Fig. 2.4a, b). SBTs with noninvasive implants are considered indolent, with 5-year survival rates of 95 % and recurrence rates are typically low, ranging from 8 % to 32 % [13].

Epithelial invasive implants are characterized by haphazardly distributed glands and clusters of branching papillae infiltrating the adipose tissue and stroma. The epithelial cells have moderate to marked cytologic atypia. Psammoma bodies are sparsely distributed throughout the tumor, and the associated stroma is composed of dense fibrous tissue with mild degree of inflammation (Fig. 2.4c). Patients with SBT with invasive implants have higher chances of developing low-grade carcinomas many years after initial diagnosis [14].

Desmoplastic noninvasive implants are defined by clusters of irregular glands tumor cells exhibiting mild cytologic atypia. Frequent psammoma bodies are seen (Fig. 2.4d, e). There is no stromal reaction; on the contrary, the stroma is loose and may have granulation tissue-like features with neutrophilic infiltrates and hemorrhage.

Ovarian Grading Systems and Low-Grade Ovarian Serous Carcinoma

Before we discuss the molecular characteristics of low-grade ovarian serous carcinoma (LGSC), it is worth discussing the grading system for epithelial ovarian cancer. There are at least five grading systems that are in use by pathologists worldwide. The most commonly used around the world are from the International Federation of Gynecology Oncology (FIGO) and the World Health Organization (WHO). The FIGO grading system [15] is based on the ratio of glandular or papillary pattern to solid growth of the tumor: grade 1 tumors when <5 % is solid growth, grade II when 5–50 % is solid growth, and grade 3

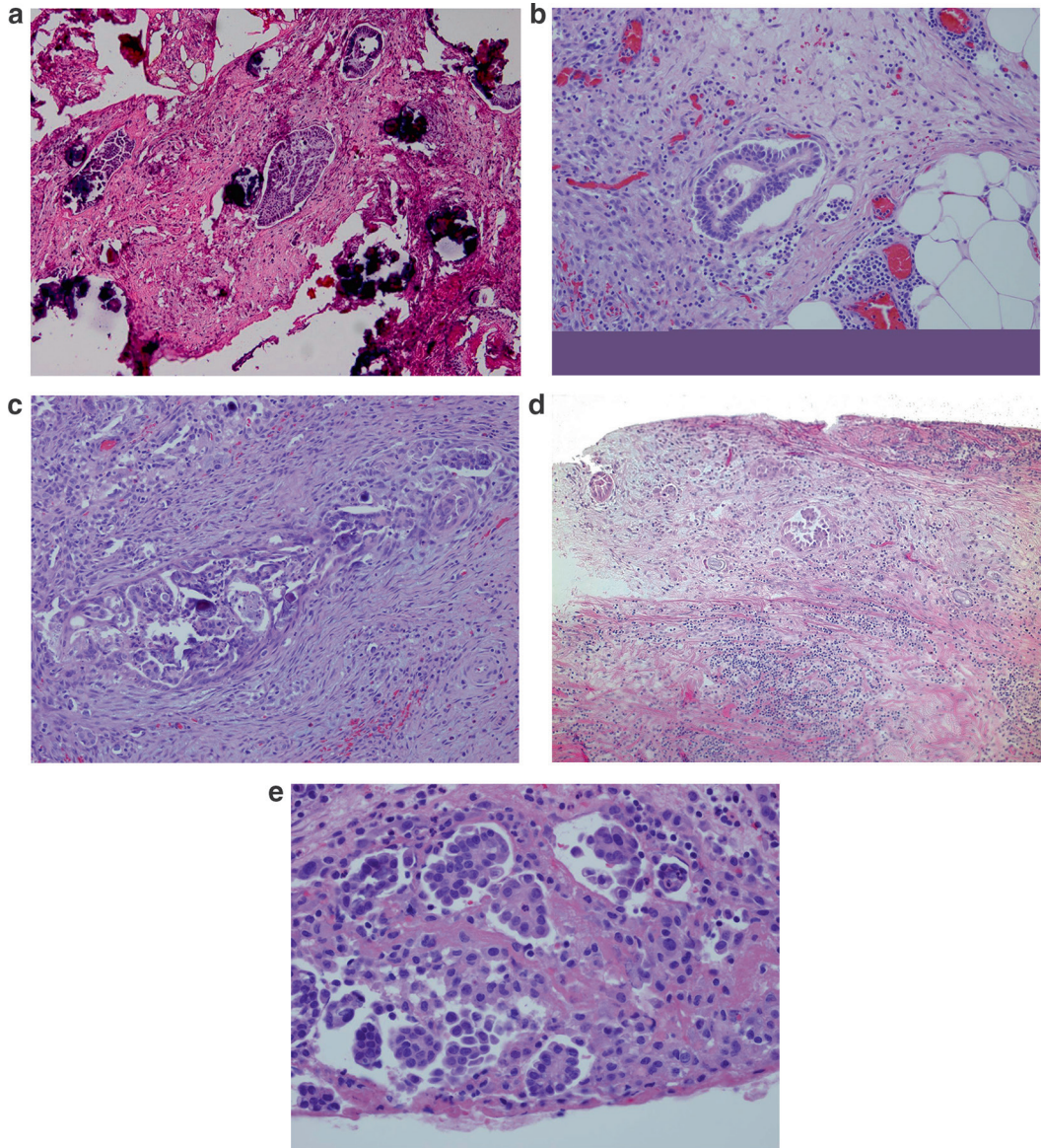


Fig. 2.4 (a) Noninvasive implants are characterized by cluster of tumor cells embedded in a fibrous tissue with no desmoplastic reaction. Psammoma bodies are frequently present. (b) Empty spaces are seen surrounding these clusters. (c) Invasive implants are characterized by complex papillae structures that seemed to infiltrate the stroma. There is extensive desmoplastic reaction with

proliferation of fibrous tissue and chronic inflammation. Psammoma bodies are usually infrequent. (d) Desmoplastic noninvasive implants are defined by clusters of papillae usually seen on the surface. These papillae are seen in a background of fibrotic stroma with extensive chronic inflammation. (e) Closer magnification shows very bland-looking cells surrounded by empty spaces

tumors when >50 % is solid growth. The WHO system is more subjective, as it depends on the impression of the pathologist assessing the tumor architecture and cytologic features. It is considered an intuitive method where there are no actual objective criteria for grading. The other system used

commonly in the United States is the Gynecologic Oncology Group (GOG) grading system [16]. Basically, the GOG system borrows the grading system from cancer occurring in other sites, depending on the histologic type; for example, the FIGO system for grading endometrial cancer

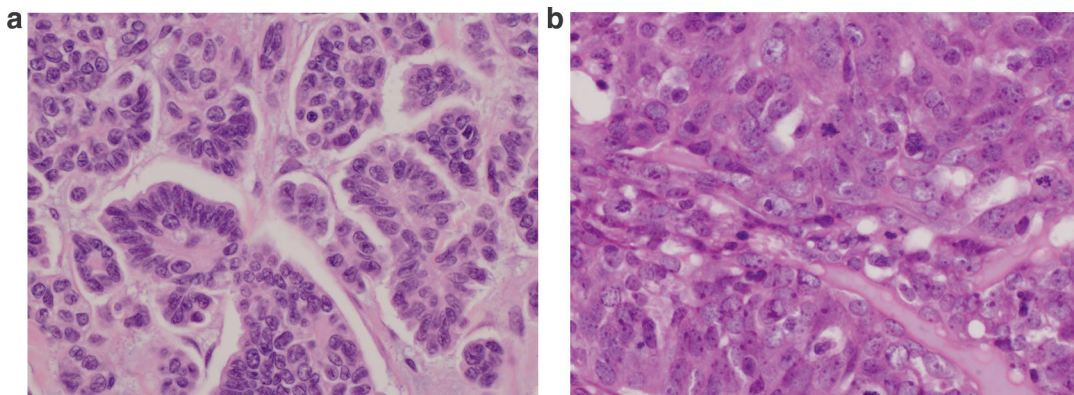


Fig. 2.5 (a) Low-grade serous carcinoma shows tumor cells with mild atypia and very few mitotic. (b) High-grade serous carcinoma is defined by tumor cells with moderate to severe atypia and high mitotic rate

will be used when the tumor is endometrioid type, and when the tumor is transitional cell type, the same grading system as for transitional cell carcinoma of the bladder is used. Clear cell carcinoma is not graded at all.

Of particular importance for basic and clinical research is the lack of reproducibility of the three grading systems and the frequent disparities between diagnoses by different pathologists using the same grading system [17, 18]. As a result, the significance of tumor grade to prognosis varies in the literature. It is clear that classification of EOC histological subtype and grading based on molecular markers would significantly improve reproducibility of diagnoses and enable more accurate clinical studies to be performed.

An additional grading system that is commonly used is Silverberg's grading system [19]. Silverberg and his colleagues tried to create a grading system using the Nottingham grading system of the breast, which is based on architecture, cytologic atypia, and mitotic counts. Each is given a number and then they added to a score. As the criteria for this system are very defined and very objective, it is not surprising that this system shows a high degree of reproducibility among pathologists. In addition, using this grading system, tumor grade was shown to be a predictive factor for survival, with lower tumor grade associated with a more favorable outcome [20]. Lastly, the MD Anderson two-tier grading system grades each tumor as low grade or high

grade [21]. Low-grade tumors are defined as tumors with mild atypia and a low frequency of mitotic figures (<12 mitoses/10 high-power fields), whereas high-grade tumors are tumors with moderate to severe atypia and high mitotic rates (Fig. 2.5a, b). This final grading system is only applied to serous carcinoma and again shows good intra-observer reproducibility [22]. Moreover, the two-tier system reveals prognostic associations that are consistent with those seen when using the Silverberg's grading system [22].

Accurate grading of serous carcinomas as low-grade or high-grade is crucial for multiple reasons: (1) LGSCs and HGSCs are associated with markedly different prognoses, (2) LGSCs are usually cisplatin resistant and so may often not receive standard chemotherapy, and (3) LGSCs may benefit from novel therapeutics designed to interrupt signaling pathways activated in this tumor type specifically.

Cellular Origins

Ovarian LGSCs are relatively rare tumors, which makes investigating the origins challenging. LGSCs can arise *de novo* but others clearly evolve in a stepwise manner beginning with a benign serous cystadenoma which progresses to a serous borderline tumor (SBT) which then develops into an invasive LGSC, as described above [23]. Not all borderline tumors will develop

into invasive cancer but the proportion that do tend to have invasive implants upon presentation. LGSCs are a distinct entity to high-grade serous counterparts and are associated with distinct somatic alterations, clinical characteristics, and epidemiological risk factors. Although some case reports identified low-grade and high-grade components within the same tumor, this appears to be a rare occurrence and the distinct somatic profiles of LGSC and HGSC most strongly support the hypothesis that the two entities are different diseases and LGSC is not a precursor of HGSC [23]. The majority of HGSCs appear to originate from secretory cells in the fimbrial portion of the fallopian tube [4, 24–26]. Although recent pathological evidence has suggested a fallopian origin for at least a subset of LGSCs, classically it has been thought that LGSCs originate from ovarian surface epithelial cells (OSECs). A third model for LGSC origins is the endometrial model. Each of these three cell-of-origin models is discussed in more detail below.

Ovarian Epithelial Cells

Historically it was thought that the majority of LGSCs arise from ovarian epithelial cells, a layer of simple, cuboidal, mesothelial-type epithelial cells covering the surface of the ovary. OSEC-type cells can also line simple cysts within the ovarian cortex, termed cortical inclusion cysts (CICs). CICs arise from invaginations of the ovarian surface that occur following ovulation. Invaginations that fuse at the top create OSEC cysts, where OSECs are in close proximity to the mitogenic environment of the ovarian stroma. Interestingly, there is a relationship between body mass index (BMI) and number of CICs [27]. BMI is associated with borderline and low-grade serous cancer risk, but not HGSC risk [28], consistent with an ovarian origin for the former histological subgroup, but not for the latter.

In this model the microenvironment of the ovarian stroma plays a key role in the early genesis of LGSC by promoting Müllerian differentiation of OSECs. Evidence shows OSECs exhibit marked phenotypic plasticity, which some argue

enables the cells to differentiate into the histologically diverse subtypes of EOC during cancer development [29]. However, theories supporting OSECs as cells of origin for serous ovarian cancer have recently come under scrutiny and have been heavily criticized. The lack of expression of EOC markers in OSECs, the divergent embryological origins of OSECs and Müllerian-type epithelium, and the scant evidence of early-OSEC-derived neoplastic lesions have all been used to question the validity of the OSEC as a precursor cell for serous EOCs.

Fallopian Epithelial Cells

Recent pathological evidence, as well as data from *in vitro* and *in vivo* models, has demonstrated that a significant proportion of high-grade serous ovarian cancers (HGSCs) originate from secretory epithelial cells located in the epithelium of the fallopian tube fimbriae [4, 24–26, 30]. This has led researchers to look more closely into whether LGSCs could also have a tubal origin. A key observation is the morphological similarity of LGSCs to the fallopian tube: LGSCs can contain both secretory and ciliated epithelia that closely resemble the morphology and immunohistochemical staining profile of normal tubal epithelium. The ratio of ciliated to secretory cells in fallopian-type inclusion cysts and serous cystadenomas is similar, with an increase in the proportion of secretory cells in borderline tumors progressing to a near absence of ciliated cells in LGSC [31]. Extensive sectioning and examination of fallopian tubes from patients with LGSC has identified regions of papillary tubal hyperplasia occurring more commonly in women with atypical proliferative serous tumors than in unaffected women [32]. Moreover, chronic salpingitis has been identified in association with ovarian serous borderline tumors, and secretory cell outgrowths (considered to be a precursor lesion) are more common in fallopian tubes from women with serous borderline tumors compared to controls [33]. Finally, mutational analyses have identified identical mutations in the *KRAS* proto-oncogene in serous borderline tumors and endosalpingiosis,

suggesting co-occurrence of the two represent different stages of the disease continuum [34].

So how do tubal epithelial cells become re-located to the ovary? This process is not fully understood, but it is known that two types of CIC exist within the ovary—PAX8 negative, calretinin positive cysts, thought to be derived from OSECs, and PAX8 positive, calretinin negative cysts, proposed to be tubal in origin [31]. However, it is worth noting that this conclusion is based on the assumption that PAX8 is never expressed by OSECs, which in our own unpublished data we find to be incorrect (in a large series of 27 normal ovaries, nearly half express PAX8). Moreover, detailed examinations of ovaries find transitions of OSEC-type to cuboidal (tubal)-type epithelial cells within the same cyst, suggesting OSECs can undergo a metaplasia and acquire tubal characteristics [35]. Nonetheless, a benign process termed endosalpingiosis does bring tubal epithelium into the ovary, which is a likely source of tubal type epithelium within CICs.

Endometriosis Epithelial Cells

An alternative hypothesis is that LGSCs may arise from other types of Müllerian epithelial cells, particularly from endometrial epithelial cells ectopically located to the ovary via the common process of retrograde menstruation. In around 10 % of women, the endometrial epithelial cells engraft and form functional glands within the ovary and at other sites, a condition termed endometriosis. While there is currently little pathological or experimental evidence to support this theory, epidemiological studies find that endometriosis is

associated with an increased risk of LGSC (with an odds ratio of 2.11, 95 % confidence interval 1.39–3.20) [36], and it is clear that this association warrants further investigation.

The Microenvironment of the Ovary

While the cellular origins of LGSC are not yet clear, one unifying theme in the above three models is the vital role played by the specific microenvironment of the ovary, as it appears that cystic structures within the ovary are hotspots for neoplastic transformation. Markers of oncogenic stress are upregulated in CICs relative to the surface epithelium [37], likely due to the effects of mitogenic molecules such as estrogen or the genotoxic and pro-inflammatory effects of follicular fluid [38]. Elucidating the pathways involved in stromal-epithelial cross talk during the development of LGSC will likely be essential for our understanding of the earliest stages of these tumors.

Somatic Genetic Characteristics of LGSC

In contrast to high-grade serous ovarian cancers, which nearly always contain *TP53* mutations [39] and which display widespread copy number aberrations and chromosomal rearrangements, *TP53* mutations are rare in LGSCs, and LGSCs typically do not contain significant amounts of chromosomal disruption. LGSCs are characterized by mutations in *KRAS*, *BRAF*, and *ERBB2* (Table 2.1). Collectively, *KRAS* and *BRAF* muta-

Table 2.1 Mutations commonly found in low-grade serous ovarian carcinoma

Pathway	Gene	Frequency of alteration (%)	Reference	Common mutations	Effect on pathway
MAPK	<i>KRAS</i>	18–30	[40, 42]	G12V, G12D	Activating
MAPK	<i>NRAS</i>	9 ^a	[43]	Q61R, Q61K	Activating
MAPK	<i>BRAF</i>	35–48	[40, 42, 44]	V600E	Activating
MAPK	<i>ERBB2</i>	6	[44]	c.2325dupTACGTGATGGCT, c.2322dupGCATACGTGATG, c.2324dupATACGTGATGGC	Activating

^aOf all invasive cases with adjacent borderline malignancies

tions are found in about two-thirds of all LGSCs and in 61 % of serous borderline tumors, in a mutually exclusive fashion [40]. Mutations in these genes result in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway. *KRAS* is a GTPase that transduces extracellular mitogenic signals into the cell, via the MAPK and also phosphoinositide 3-kinase (PI3K) pathways. In ovarian LGSCs *KRAS* is commonly mutated at codon 12, which renders the protein constitutively active in the absence of upstream mitogenic signals. Matching *KRAS* mutations can be detected in ovarian serous borderline tumors that recur as LGSC, strongly suggesting that LGSC develops from SBTs harboring activating *KRAS* mutations [41]. In LGSCs, *BRAF* is commonly mutated at position 600, where a valine to glutamate substitution renders the kinase constitutively active in the absence of activating stimuli. *BRAF* mutations are associated with better patient prognoses than *KRAS* mutations, because the most aggressive and recurrent LGSCs tend not to harbor *BRAF* alterations [42]. *BRAF* mutations are also associated with early tumor stage, which may suggest that *BRAF* alterations are early events in the genesis of ovarian LGSC. *RAS* molecules, such as *KRAS*, are major upstream regulators of *BRAF*, which is thought to explain the mutual exclusive manner in which *KRAS* and *BRAF* mutations are found in LGSC [42] and other solid tumors. Activation of the MAPK pathway can also occur via activation of *ERBB2* or *NRAS* also occur, although these alterations occur at a lower frequency than perturbations in *KRAS* or *BRAF* [43, 44]. Other key molecular alterations in BST/LGSC include p16(*INK4A*) [45] and maintained expression of p21(*WAF*) [46, 47], which could relate to the lower proliferative indices of these tumors relative to high-grade counterparts.

Conclusion

While the origins of high-grade serous ovarian cancer have been hotly debated, the cellular origins of low-grade serous ovarian cancer have been somewhat overlooked. It is, however, not

yet clear whether LGSCs arise from ovarian or fallopian epithelial cells or from Müllerian-type epithelial cells within the uterus. The Cancer Genome Atlas project has generated a comprehensive catalogue of the somatic alterations in HGSC, profiling copy number alterations, mutations, as well as the transcriptome and methylome and yielding novel candidate therapeutic targets [39]. However LGSCs were not included in this project, and similar analyses of somatic genetic alterations that occur early during the development of SBTs and LGSCs remain somewhat lacking. Although it is likely that activation of the MAPK pathway is an early event, more detailed analyses of the somatic events that lead to the genesis of LGSC will likely reveal novel opportunities for early detection and therapeutics.

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