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Review

Pathobiology of ovarian carcinomas

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Abstract

Ovarian tumors comprise a heterogeneous group of lesions, displaying distinct tumor pathology and oncogenic potentiel. These tumors are subdivided into three main categories: epithelial, germ cell, and sex-cord stromal tumors. We report herein the newly described molecular abnormalities in epithelial ovarian cancers (carcinomas). Immunohistochemistry and molecular testing help pathologists to decipher the significant heterogeneity of this disease. Our better understanding of the molecular basis of ovarian carcinomas represents the first step in the development of targeted therapies in the near future.

Key words Ovarian tumors, classification, molecular abnormalities

According to the 2014 World Health Organization (WHO) classification and tumor morphology, primary ovarian tumors are subdivided into three categories: epithelial (60%), germ cell (30%), and sex-cord stromal tumors (8%)[1]. However, the vast majority of malignant ovarian tumors (80%-85%) are classified as epithelial tumors (carcinomas). Malignant germ cell and sex-cord stromal tumors comprise approximately 10% of all malignant ovarian tumors. Ovarian tumors account for a considerable proportion of clinically relevant neoplasms in females, exhibiting a wide range of age at presentation (from infant to elderly patients). Approximately two-thirds of ovarian tumors occur in women during reproductive age, whereas less than 5% occur in children. Approximately 75%–80% of ovarian tumors are benign, occurring in patients under 40 years of age. In contrast, 80%–90% of ovarian carcinomas are detected after the age of 40, and 40% of these tumors are detected after the age of 65. The age-specific incidence of ovarian epithelial cancer rises from the age of 20 to 80 and subsequently declines[2].

Ovarian Epithelial Tumors

Ovarian epithelial tumors are subclassified into several categories based on two criteria: 1) the degree of epithelial proliferation and invasion and 2) the histotype of the epithelium composing the tumor.

Benign epithelial tumors (adenoma and cystadenoma) are characterized by the absence of cell proliferation and invasion. These tumors represent 60% of all epithelial tumors. They can occur at any age but are most often observed in adults; 60% of these tumors occur in females under the age of 40.

Borderline tumors are characterized by cell proliferation and a minor degree of nuclear atypia without stromal invasion. These tumors represent 10% of all epithelial tumors. They occur at a slightly younger age than carcinomas (median age, 45 years).

Carcinomas are characterized by cell proliferation, nuclear atypia, and stromal invasion. They represent 30% of all epithelial tumors and 80%-85% of all ovarian cancers. These tumors are primarily found in elderly patients with a median age of 60 years.

Ovarian carcinomas are characterized by a Müllerian morphology although the ovaries do not originate from the Müllerian ducts. The presence of Müllerian lesions beyond the direct derivatives of the Müllerian ducts, primarily in the ovary and pelvic peritoneum, is ascribed to the existence of a "secondary Müllerian system"[3]. It is hypothesized that the epithelium covering the ovarian surface and the peritoneum retains the potential for Müllerian differentiation given the proximity to the coelomic epithelium from which the Müllerian ducts are derived. Epithelial neoplasms of the ovary are thought to arise either directly or indirectly from the ovarian surface epithelium according to incessant ovulation theory[4]. Indeed, it has been postulated that the possible mechanisms by which repetitive ovulation could influence the development of ovarian carcinomas include an increased formation of inclusion cysts, repeated bathing of the surface epithelium by an estrogen-rich follicular fluid, excessive production of growth factors or cytokines, and an aberration of the repetitive repair process that follows the trauma to the surface epithelium as a consequence of ovulation.

However, as explained below, recent morphologic findings and molecular analyses have demonstrated that each morphologic subtype of ovarian carcinoma might be derived from a Müllerian-type epithelium.

Serous carcinomas are thought to be derived from the fallopian tubes through foci of endosalpingiosis, which are inclusion cysts from the tubal epithelium at the ovarian and peritoneal surface. In contrast,

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clear cell, endometrioid, and sero-mucinous carcinomas appear to develop from endometriosis; mucinous and Brenner malignant tumors potentially develop from the Walthard nests. All these precursors of ovarian carcinomas are Müllerian-derived structures, which explains the occurrence of Müllerian-type carcinomas in an organ (the ovary) that is not derived directly from the Müllerian ducts.

Ovarian carcinomas represent a heterogeneous group exhibiting differences in morphology, molecular biology, pathogenesis, and behavior. Their classification was initially based on the morphology of the type of epithelium found in the tumor. However, new genetic findings resulted in a phenotypic-genotypic classification of these tumors, which is represented by five distinct diseases[5] (**Table 1**).

Serous carcinomas

Serous carcinomas represent the vast majority of primary malignant ovarian tumors (75%–80%) and are composed of columnar cells with cilia. These tumors are subdivided into high-grade and low-grade serous carcinomas[6].

High-grade serous carcinoma (HGSC)

HGSC accounts for 85%–90% of serous carcinomas and 70% of ovarian surface epithelial carcinomas. This ovarian carcinoma subtype accounts for the majority of the deaths due to ovarian cancer. HGSC is a disease of elderly patients with a median age of 64 years. This carcinoma is bilateral in 60% of patients and is detected at an advanced stage in more than 80% of patients. HGSC often presents as a very large cystic and solid tumor with frequent areas of hemorrhage and necrosis. Morphologically, the cells form papillae, solid masses, or slit-like spaces with high-grade nuclear atypia and more than 12 mitoses per 10 high-power fields (**Figure 1A**). Immunohistochemical findings demonstrate CK7-, PAX8-, and WT1-positive staining and CK20-negative staining. Tumor protein 53 (*TP53*) mutations are noted in more than 96% of HGSC cases[7] with protein overexpression detected by immunohistochemical analyses.

Transitional cell carcinoma is a rare variant of ovarian HGSC (3%), exhibiting the typical papillary pattern observed in urothelial carcinomas. Most tumors exhibit an admixture of HGSC. These tumors exhibit the same immune profile as HGSC; thus, the new WHO classification system considers this type of carcinoma to be a variant of HGSC[1].

HGSCs are genomically instable and aneuploid. Approximately 10% of patients with HGSC have a germ-line *BRCA1* or *BRCA2* mutation. Moreover, sporadic tumors exhibit a BRCAness phenotype with *BRCA* loss by somatic mutation (3%) or promoter hypermethylation (11%) of *BRCA* genes[7]. HGSCs are derived from the surface epithelium without a known precursor according to the "incessant ovulation theory." However, pathologic studies on prophylactic bilateral salpingo-oophorectomies in patients with germ-line *BRCA* mutations have demonstrated occult intraepithelial serous carcinomas in 17% of patients, primarily located in the fimbriated end of the fallopian tube[8]. This serous tubal intraepithelial carcinoma (STIC) exhibited the same *TP53* mutation profile of invasive ovarian carcinomas in patients with *BRCA* mutation, indicating that STIC potentially represents a precursor of ovarian serous carcinomas. STIC was also detected in 60% of sporadic ovarian and peritoneal carcinomas with the same *TP53* mutational profile, supporting a direct relationship between a non-invasive lesion in the fallopian tube and an invasive carcinoma in the ovary or the peritoneum[9].

Low-grade serous carcinoma (LGSC)

LGSC is less common, representing 10%–15% of serous carcinomas and < 5% of all ovarian carcinomas. This carcinoma is associated with a serous borderline tumor or represents the recurrent lesion observed after a diagnosis of borderline serous tumor. This tumor is composed of non-hierarchical papillae or micropapillae without nuclear atypia and with less than 12 mitoses per 10 high-power fields (**Figure 1B**). Patients with these slow growing tumors exhibit a 10-year survival rate of 50% (median overall survival, 82 months) and a relative insensitivity to chemotherapy. The immunoprofile of LGSCs is comparable to that of HGSCs. No *TP53* mutations are observed in these tumors, so P53 overexpression is

Table 1. Phenotypic-genotypic classification of ovarian carcinomas: 5 distinct diseases according to Prat[5]

Classification	Incidence	Median age (years)	Risk factor(s)	Precursor lesions	Molecular abnormalities	Pattern of spread	Chemosensitivity	Prognosis
High-grade serous	70%	64	BRCA1/2	STIC	*P53/BRCA*	Very early transcoelomic	High	Poor
Low-grade serous	<5%	43	NA	Borderline	*BRAF, KRAS*	Transcoelomic	Intermediate	Intermediate
Mucinous	3%	45–50	NA	Borderline	*KRAS, HER2*	Typically confined to the ovary	Low	Favorable
Endometrioid	10%	40–50	Lynch syndrome	Endometriosis	*PTEN, ARID1A*	Typically confined to the pelvis	High	Favorable
Clear cell	5%–10%	55	Lynch syndrome +/–	Endometriosis	*HNF1b, ARID1A, PIK3CA, MET*	Typically confined to the pelvis	Low	Intermediate

STIC, serous tubal intraepithelial carcinoma; NA, not available.

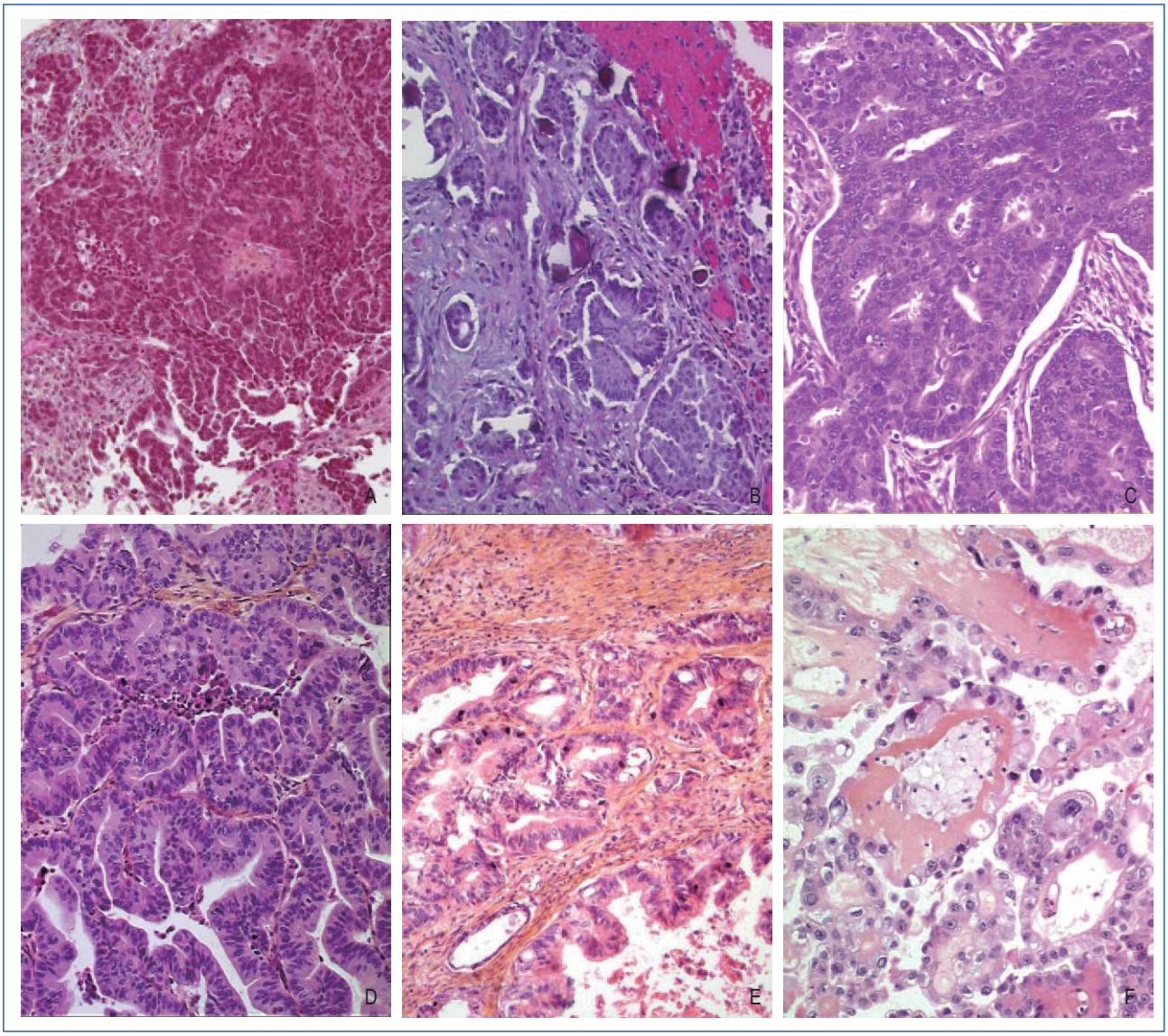

Figure 1. **Histopathology of ovarian epithelial tumors. A, high-grade serous carcinoma is composed of a solid mass of cells with slit-like spaces. Nuclei are large, hyperchromatic, and pleomorphic with high mitotic activity (>12 mitoses per 10 high-power fields) (HES ×100). B, low-grade serous carcinoma is composed of micro- or macropapillae lined by uniform small cells with limited nuclear pleomorphisms and low mitotic activity (<12 mitoses per 10 high-power fields), associated with psammoma bodies (HES ×100). C, endometrioid carcinoma is arranged in a cribriform pattern lined by cuboidal cells with eosinophilic cytoplasm and moderate nuclear atypia (HES ×200). D, the expansile pattern of mucinous carcinoma shows proliferation of complex glands arranged back to back with limited intervening stroma, exhibiting moderate cytologic atypia (HES ×200). E, destructive pattern of mucinous carcinoma shows proliferation of irregular glands, nests, and cells with malignant cytology, infiltrating ovarian stroma (HES ×200). F, clear cell carcinoma shows papillae lined by cuboidal, hobnail cells with clear or eosinophilic cytoplasm and atypical nuclei. The papillae are round and small with a dense hyaline basement membrane material forming the core of the papillary stalk (HES ×200).**

not evident by immunohistochemistry. LGSCs are genetically stable and diploid tumors[10]. They harbor *KRAS* (mutation at exon 12 or 13 in 19% of cases), *BRAF* V600E (5%–38% of cases), or *ERBB2* mutations (6% of cases) that are mutually exclusive[11]. However, *BRAF* mutation (V600E) is more frequently observed in serous borderline tumors (28%–48%) than in LGSCs (5%–38%)[12].

Endometrioid carcinomas

Endometrioid carcinomas account for 10% of all ovarian carcinomas and are generally unilateral solid masses with a smooth outer surface. These tumors are composed of glands resembling endometrial epithelium (**Figure 1C**) and may be associated (23%–42%) with ovarian or pelvic endometriosis. These tumors

exhibit CK7-, PAX8-, and hormone (estrogen and progesterone) receptor-positive as well as WT1- and CK20-negative staining; these classifications aid in the distinction from serous and colonic carcinomas, respectively. These tumors are graded into three grades according to the International Federation of Gynecology and Obstetrics (FIGO) system, which is based on the presence of solid areas and the degree of nuclear atypia. Grade 3 tumors tend to harbor *TP53* mutations and may be difficult to distinguish from HGSCs. Genomically, endometrioid carcinomas exhibit the following molecular abnormalities observed in their endometrial counterparts: *CTNNB-1* (48%), *PIK3CA* (20%), *PTEN* (20%), and *ARID1A* (30%) mutations. This ovarian carcinoma subtype is most often observed in patients with Lynch syndrome. A number of sporadic cases also exhibit microsatellite instabilities (hypermethylation of *MLH1* promoter)[13]. The same mutations (*PTEN* and *ARID1A*) have been detected in the carcinoma and in the immediately adjacent regions of endometriosis, indicating that endometriosis potentially serves as their precursor.

Mucinous carcinomas

Primary mucinous carcinomas are classified as intestinal tumors (containing goblet cells) and comprise only 2%–3% of ovarian carcinomas. These tumors are unilateral, stage I (75%–80%), large (18–22 cm), and multicystic tumors filled with mucus. They often contain solid areas. Histologically, they are composed of cysts and glands of variable size, with a confluent pattern and back-to-back glands. Complex papillary architecture is also observed. The cells are tall, columnar, and stratified with basophilic cytoplasm containing mucin. Invasive mucinous carcinomas are subclassified as expansile and infiltrative pattern types.

Expansile type mucinous carcinomas (**Figure 1D**) are classified as stage I disease. These tumors exhibit a very good prognosis and are composed of confluent glands with little or no interposed stroma; they are primarily observed in young patients.

Infiltrative type mucinous carcinomas (**Figure 1E**) exhibit a destructive invasion pattern with desmoplastic stromal reactions and are more likely to display extraovarian spread[14,15]. Mucinous adenocarcinomas may be graded according to their nuclear features[16]. By immunohistochemistry, ovarian mucinous carcinomas exhibit diffuse CK7-positive staining, whereas CK20-positive staining is generally less diffuse. Hormone (estrogen and progesterone) receptors and WT1 are usually negative and PAX8 is positive in less than 50% of cases. Mucinous carcinomas almost always arise from a mucinous borderline tumor; thus, mucinous ovarian tumors often display a heterogeneous pattern with coexisting areas of mucinous cystadenoma, mucinous borderline tumor, and mucinous adenocarcinoma. Their diagnosis requires a thorough sampling of 2 blocks per cm of tumor.

The major difficulty in the diagnosis of mucinous ovarian tumor involves the distinction from a gastrointestinal or pancreatobiliar tract tumor metastasis. Bilateral involvement, a multinodular pattern in the ovary, a small size (usually less than 10 cm), ovarian surface involvement, and a massive disorganized pattern of invasion are clues that suggest a primary gastrointestinal tumor associated with ovarian metastases. Appendectomy and a clinical assessment of the gastrointestinal tract are therefore useful in case of a mucinous carcinoma in the ovary.

The molecular biology of mucinous ovarian carcinoma reveals KRAS mutations in codons 12 and/or 13 in 68%–86% of cases. Identical mutational profiles were observed in different areas from benign to borderline and malignant components of the same tumors in 12 of 15 cases, thereby supporting the morphologic continuum of tumor progression in mucinous ovarian tumors[17]. *HER2* gene amplification has been described in 18% of carcinomas and 6% of borderline tumors. *HER2* amplification and *KRAS* mutations are mutually exclusive. Recent data suggest that *HER2* amplification or *KRAS* mutations may be associated with an improved prognosis compared with double negative tumors (*HER2* non-amplified and *KRAS* wild-type account for 34% of mucinous ovarian tumors)[18].

Sero-mucinous carcinomas

This variant has been added to the new 2014 WHO classification system[1], whereas it was previously categorized as the endocervical subtype of mucinous ovarian carcinoma in the 2003 WHO classification system. Morphologically, this rare variant of ovarian carcinoma is composed of a mixture of serous and endocervical mucinous cells with foci of endometrioid and squamous differentiation. The median age at diagnosis is 45 years, and this tumor is seldom observed in elderly patients. This tumor is often associated with endometriosis, which may serve as its precursor. Stage I tumors exhibit a good prognosis, whereas half of patients presenting with advanced disease will die of progressive disease[19].

Clear cell carcinomas

Clear cell carcinomas (CCCs) represent 6% of all ovarian carcinomas in Western countries and 15%-25% of carcinomas in Japan. These tumors are most often diagnosed at stage I/II (49% of CCCs vs. 17% of HGSCs). When exclusively considering stage I disease, the prognosis is similar to HGSCs at the same stage. CCCs are minimally responsive to platinum/taxane therapy, with response rates ranging from 11% to 45%[20].

The majority (99%) of ovarian clear cell tumors are carcinomas or clear cell adenofibromas; borderline tumors are rarely observed (<1%). The tumor is predominantly solid and unilateral with a yellow cut surface. It is typically composed of papillae with a hyalinized core; however, solid, tubulocystic and glandular growth patterns are also common (**Figure 1F**). The cells are large with abundant clear or eosinophilic cytoplasm. The nuclei are pleomorphic, irregular, and hyperchromatic; however, the mitotic index might be lower than what could be expected from the nuclear atypia.

The immunohistochemical study reveals diffuse CK7-positive staining as well as CK20-, hormone (estrogen and progesterone) receptor-, and WT1-negative staining. Hepatocyte nuclear factor 1β (HNF1β)-positive staining is observed in 93% of ovarian CCCs versus 2% of non-CCCs[21]. Napsin A also appears to be a good marker

for the diagnosis of ovarian CCCs[22]. CCCs do not harbor *TP53* mutations; they are associated with ovarian or pelvic endometriosis in 21%–54% of cases. Sequencing studies on a small number of CCCs have demonstrated frequent mutations in the *AR1D1A*, *PIK3CA*, *KRAS*, and *PPP2R1A* genes[23].

Somatic truncating or missense mutations in *ARID1A* gene encoding BAF250 protein (a key component of the SWI-SNF chromatin remodeling complex) were identified in 46% of CCCs, 30% of endometrioid carcinomas, and none of the analyzed HGSCs. The same mutation was also observed in the endometrial lining immediately adjacent to the tumor, indicating that endometriosis might serve as the precursor of ovarian CCCs[24]. Activating mutations in exon 20 (in the kinase domain) of the *PIK3CA* gene is observed in 33%–43% of CCCs and 90% of associated endometriotic cysts. Overexpression (complete membrane staining with moderate to strong intensity in >10% cells) and amplification ($\geqslant$ 4 copies in $\geqslant$ 40 cells) of the *MET* gene are reported in 22% and 24% of CCCs, respectively, whereas the percentages drop to 0 and 3%, respectively, in non-CCCs. Moreover, *MET* overexpression has been identified as an independent unfavorable prognostic factor with a 5-year survival rate of 33% for MET-overexpressed patients versus 76% for MET-negative patients.

Malignant Brenner tumors

This is a rare variant of low-grade ovarian carcinomas (<5% of all ovarian Brenner tumors) that displays an admixture of benign or borderline Brenner tumor and malignant urothelial-type cell carcinomas. These tumors occur in women over 50 years of age. *PIK3CA* mutations (exon 9) have been identified. However, in contrast to transitional cell carcinomas, these tumors do not harbor *TP53* mutations. Most tumors are stage I, and patients exhibit an excellent prognosis with a 5-year survival rate of 88%. When extra-ovarian, the prognosis is similar to other ovarian carcinomas.

Undifferentiated carcinomas

This type of carcinoma accounts for less than 1% of cases[1]. It is a high-grade tumor with sheets of small or large cells with pleomorphic nuclei and a high mitotic index. The positivity of epithelial markers (pancytokeratin, CK7, CK18, and EMA), although weakly expressed, aids in the ability to distinguish these tumors from lymphomas, melanomas, or sarcomas. Undifferentiated carcinomas observed in elderly patients should not be confused with the hypercalcemic type of small cell carcinomas that are typically observed in young patients and exhibit typical follicle-like spaces.

Malignant mixed mesodermal tumors (carcinosarcoma) (MMMT)

MMMTs account for less than 1% of ovarian cancers. These tumors are primarily reported in elderly patients with a median age of 65 years. Three-quarters of these tumors are observed in females between 60 and 80 years old. These tumors are large, cystic, and solid masses with massive areas of hemorrhage and necrosis. These tumors are often diagnosed at an advanced stage with peritoneal spread (75%). They are composed of a mixture of a high-grade epithelial component (with grade 3 endometrioid, clear cell, and high-grade serous carcinomas) and a high-grade stromal component (typically with hyperchromatic, round, or spindle cells, exhibiting numerous mitoses). Heterogonous elements in the form of rhabdomyosarcomatous, osteosarcomatous, chondrosarcomatous, or liposarcomatous elements may be observed. MMMT patients have a very poor prognosis with a 5-year overall survival rate of < 30%[25].

Genetic and molecular studies have confirmed the clonal origin of most gynecologic carcinosarcomas and have demonstrated that these tumors are genetically related to high-grade non-endometrioid carcinomas that frequently exhibit *TP53* mutations. Additionally, the process by which malignant epithelial component transdifferentiates to a malignant mesenchymal component might be related to the epithelial-mesenchymal transition (EMT) phenomenon. Indeed, embryonic transcription factors implicated in EMT have been demonstrated in MMMTs[26].

Conclusions

Each histological subtype of ovarian carcinoma exhibits a specific histogenesis and molecular abnormalities. Ovarian carcinomas are a heterogeneous group of lesions with specific morphology, biology, response to treatment, and behavior. The correct diagnosis is based on histopathologic examination of the specimen. In inoperable tumors, a percutaneous, ultrasound- or computerized tomography-guided peritoneal fine needle biopsy may serve as an alternative to obtain tissue material for correct morphologic and biological analyses for personalized medicine in the near future.

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