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Review article

Molecular insights and diagnostic challenges in epithelial ovarian cancer: A review of key histological markers

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Abstract

Background: Epithelial ovarian carcinomas represent a diverse category of neoplasms, including clear cell, endometrioid, serous, and mucinous subtypes. Often diagnosed at advanced stages, these carcinomas exhibit distinct biological characteristics and varying responses to treatment. Histologic diagnosis of these subtypes can be challenging due to overlapping morphological features.

Methods: This review synthesizes current literature on the use of specific markers for the detection and differentiation of epithelial ovarian cancer subtypes. The focus is on insights gained from histological and histopathological analyses.

Results: The review highlights the importance of antigen-antibody reaction-based techniques in identifying epithelial ovarian carcinomas. Key markers, including SATB2, CK67, HNF1B, PAX8, P53, P16, ER, and PR, play crucial roles in tumor detection, differential diagnosis, and understanding pathogenesis. These markers form a panel for the effective diagnosis and characterization of epithelial ovarian cancer.

Conclusion: Immunohistochemistry (IHC) significantly enhances the histological diagnosis of gynecological diseases. The molecular revolution has improved the understanding of gynecological cancers, with immunohistochemistry techniques advancing the identification and characterization of epithelial ovarian carcinomas. This progress includes insights into tumor aggressiveness and the potential efficacy of targeted therapies.

Keywords: Antigen-antibody reaction, epithelial ovarian carcinomas, Histological markers, Immunohistochemistry (IHC), Tumor differentiation

Introduction

Ovarian cancer is one of the most common gynecologic cancers, ranking third after uterine and cervical cancer. In 2018, ovarian cancer caused 184,799 deaths, accounting for approximately 4.4% of total female mortality. Although the prevalence of ovarian cancer is higher in countries with a high Human Development Index, the mortality rate shows a reversed pattern, being higher in countries with lower Human Development Index (1).

India has the highest mortality rate for ovarian cancer in Asia. However, in recent years, this rate has declined in Europe and North America, particularly among younger women (2). Although ovarian cancer has a lower incidence compared to breast cancer, it is three times more lethal. The mortality rate for ovarian cancer is projected to increase dramatically by 2040 (3,1). Carcinomas are characterized by cell proliferation, nuclear atypia, and stromal destruction. They account for 30% of all epithelial tumors and 80% to 85% of all ovarian cancers. These tumors are predominantly

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observed in older individuals, with an average age of sixty years (4).

The relationship among epigenetic, genetic, environmental, social, and psychological factors is important in understanding the prevalence of ovarian cancer. Several risk factors for epithelial ovarian cancer have been assessed in numerous epidemiological studies (5,6). There are well-documented differences in ovarian cancer incidence based on age at diagnosis, as well as variations in pathological and clinical characteristics such as stage, histology, clinical complications, and mortality among different racial and ethnic groups (7).

Risk factors of ovarian cancer

-Early menarche: Early menarche is a known risk factor for ovarian cancer. However, while it has a limited influence on the overall prevalence of ovarian cancer, it appears to play a stronger role in premenopausal women (8, 9).

-Family history: The paramount predisposing factor for ovarian cancer is a familial lineage characterized by a notable history of breast cancer. A heightened occurrence of ovarian cancer demonstrates a significant association with an individual's personal medical background encompassing breast cancer (10).

-Ovulation: The process of ovulation frequently exhibits a pronounced correlation with the incidence of ovarian malignancies. Research findings have further demonstrated a positive relationship between the frequency of ovulatory cycles in females and their susceptibility to ovarian cancer, indicating that a higher frequency of ovulation is associated with an increased risk of developing this disease (11). This phenomenon could potentially be attributed to the proinflammatory reaction elicited in the distal fallopian tubes upon ovulation, thereby promoting predisposition towards ovarian neoplasms (12).

-Hormonal Therapy: Estrogen is biosynthesized through the aromatization process of androgens within the ovary, particularly within the granulosa cells and surface epithelial cells. Its significant role in follicular development underscores its crucial contribution to this physiological process (13). Numerous in vivo and in vitro studies suggest that heightened estrogen therapy may play a pivotal role in the advancement of ovarian cancer (14).

-Chronic inflammation: The genetic susceptibility to ovarian cancer has been augmented by the presence of endometriosis and pelvic inflammatory disease (15, 16).

-Socioeconomic status: Socioeconomic status constitutes a primary predictor for both the incidence and survival rates associated with ovarian cancer (17). The relationship between socioeconomic status and ovarian cancer is substantiated by factors such as access to healthcare services, patient awareness regarding symptoms of ovarian cancer, lifestyle choices, and the appropriateness of responses to symptoms (18). Case-control studies have established an inverse relationship between educational attainment and the incidence of ovarian cancer (19).

Epithelial ovarian cancer

Epithelial ovarian cancer constitutes over 95% of all ovarian malignancies. The remaining less than 5% comprise primarily germ cell tumors, sex-cord stromal tumors, alongside rare occurrences of ovarian sarcomas and small cell carcinomas (20). Epithelial ovarian cancer represents a heterogeneous condition characterized by tumors exhibiting diverse histological forms, grades, and molecular and micro-environmental characteristics. Histological investigations classify epithelial ovarian cancer into numerous subtypes, each displaying unique patterns of presentation, clinical outcomes, and responses to therapy. This heterogeneity underpins distinct tumor behaviors, which in turn influence the prognostic significance and overall outcome of the disease (21). A considerable proportion of ovarian carcinomas arise spontaneously, while approximately 10% are hereditary in nature. Among the hereditary cases, nearly 90% are associated with mutations in the BRCA1 and BRCA2 genes (22).

Histological Changes

Histological changes including: 1) Pleomorphic entails alterations in the size and structural characteristics of both cells and nuclei. 2) Abnormal nuclear morphology is typified by nuclei exhibiting abundant chromatin content and a hyperchromatic appearance. These nuclei are disproportionately enlarged relative to the cell size, often displaying a 1:1 ratio rather than the normal 1:4 or 1:6 nuclear-cytoplasmic ratios. 3) Undifferentiated tumors typically manifest elevated mitotic activity compared to benign tumors and certain well-differentiated malignant neoplasms, indicating heightened proliferative tendencies among

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parenchymal cells. 4) Alongside cytological aberrations, anaplastic cells display markedly irregular orientations, characterized by anarchic, disorganized arrangements forming sheets or large masses of tumor cells within the growth (23).

Immunohistochemistry Technique

Immunohistochemistry occupies a pivotal role in diagnostic histopathology, serving as a highly informative technique for tumor detection and the treatment of oncology patients. Originating in the 1940s, this technique, largely pioneered by Coons et al., facilitates the determination of the histogenetic lineage of tumors, essential for accurate tumor identification by detecting specific cellular antigens present on tissue sections derived from frozen or formalin-fixed paraffin-embedded tissue blocks, as well as cytological specimens. Furthermore, immunohistochemistry represents a promising strategy for identifying residual tumor cells in various anatomical sites, including surgical margins, lymphoid tissues, and bone marrow, crucial for tumor staging and guiding treatment decisions. (24). Moreover, immunohistochemistry (IHC) has emerged as an integral component in the understanding of most solid tumors and has progressively become indispensable in guiding anticancer therapy (25). Numerous markers are utilized for the discernment of various subtypes of epithelial cancers, including:

The Wilms Tumor 1 (WT1) marker denotes a gene responsible for encoding a transcription factor characterized by zinc finger domains and RNA-binding properties. This transcription factor governs the transcriptional activity of a multitude of target genes, thereby exhibiting both oncogenic and tumor-suppressive actions (26). Several contemporary investigations have explored the association between WT1 and its putative role in the pathogenesis of ovarian cancer. WT1 has been implicated in promoting tumorigenesis through diverse pathways and is recognized for its significant involvement in tumor invasion and metastasis (27).

a. The PAX8 marker, a transcription factor belonging to the paired box (PAX) family, has been extensively studied in relation to renal cell tumors. It exhibits widespread expression in Müllerian glandular epithelia, renal tubules, and the upper urinary system. PAX-8 serves as a defining marker for tumors originating from Müllerian-derived tissues, including those of the uterine, endocervical, and ovarian origins. (24).

b. The hepatocyte nuclear factor 1-beta (HNF1B) marker represents a homologous protein pivotal in orchestrating differentiation and developmental processes, particularly in the liver where it governs the specific expression of numerous genes. Additionally, HNF1B exhibits expression in epithelial cells of various tissues including the urogenital tract, gastrointestinal tract, kidney, and endometrium (28)(29). Recent evidence indicates that HNF-1β is commonly observed to be upregulated in specific types of ovarian cancer (30).

c. The SATB2 marker is a protein known for its DNA-binding capability and involvement in chromatin remodeling, thereby regulating gene expression as a nuclear transcription factor. Typically absent in natural ovarian epithelium, SATB2 expression may occasionally occur in ovarian tumors. (31)

d. The protein Ki-67 (pKi-67) marker serves as a crucial indicator linked to the highly proliferative nature and unfavorable prognosis of cancerous cells. This protein, a nuclear DNA binding protein, is ubiquitously expressed across vertebrates and is commonly utilized as a proliferation marker for tumor grading. Its increased expression has been observed in certain studies involving ovarian cancer (32,33).

e. The estrogen receptor (ER) marker represents a member of the steroid hormone receptor family, functioning as a transcription factor. It exists in two isoforms, namely alpha (ER-α) and beta (ER-β), encoded by distinct genes, each with multiple splice variants. ER activation serves as a robust indicator, particularly distinguishing breast carcinomas from tumors originating in the uterus and ovaries. The expression of ER-α holds considerable importance as an indicator of response to anti-hormone therapy (24).

f. Progesterone receptor marker is a good indicator in breast cancer, ovarian cancer and endometrial cancer. The level PR expression is dependent to tumor heterogeneity (24).

g. The P16 marker denotes a tumor suppressor protein encoded by the p16INK4a gene, also recognized as INK4a or cyclin-dependent kinase inhibitor. P16 functions by inhibiting cyclin-dependent kinases 1 and 2, which play pivotal roles in regulating cell cycle progression and development (24). Aberrations in P16

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have been identified as pivotal contributors to the pathogenesis of almost all assessed human malignancies (34).

h. The Tumor protein 53 (p53) marker, encoded by the TP53 gene located on chromosome 17p13, produces various isoforms of the p53 protein. P53 functions as a tumor suppressor, inducing the synthesis of the p21 protein, which in turn regulates genomic stability and interacts with cyclin-dependent kinase 2 (cdk2), a protein pivotal in cell cycle progression. The formation of the p21-cdk2 complex inhibits cells from proceeding to the subsequent phase of the cell division cycle, and can activate apoptosis by transcribing multiple pro-apoptotic genes. Mutations in TP53 result in the overexpression and accumulation of the mutated p53 protein, which fails to stimulate p21 synthesis and halt cell cycle progression, consequently leading to uncontrolled cellular proliferation (24).

Types of Ovarian Epithelial Cancer

Ovarian epithelial cells exhibit multipotentiality and possess the capability to differentiate into various distinct epithelial forms during the progression of cancer. However, based on findings from biopsy, immunohistochemistry, and molecular genetics, epithelial ovarian cancer (EOC) is recognized as comprising at least five distinct disorders: low-grade serous carcinoma, high-grade serous carcinoma, clear cell carcinoma, endometrioid carcinoma, and mucinous carcinoma (35, 14).

High-grade Serous Carcinoma: High-grade serous ovarian cancer represents the predominant and severe subtype of epithelial ovarian cancer, characterized by significant tumor heterogeneity and unpredictable clinical prognoses. (36). Seventy percent of mortality in ovarian cancer cases is ascribed to high-grade serous ovarian cancer, despite 60 percent of these instances being diagnosed at an advanced stage (37,38,,39). High-grade serous ovarian carcinomas (HGS) typically originate within the epithelial lining of the fallopian tube fimbria and later manifest as tumors seemingly localized to the ovaries upon implantation (40).

The microscopic architecture of high-grade serous ovarian carcinomas is characterized by papillary, glandular, cribriform, and micropapillary patterns. Diagnosis of high-grade serous ovarian carcinomas is typically straightforward, especially when accompanied by a predominant papillary pattern and the presence of psammoma bodies. However, in certain instances, the solid pattern may pose challenges in distinguishing high-grade serous ovarian carcinomas from endometrioid carcinoma. Nevertheless, morphological features such as slit-like glandular formations rather than smooth or round structures, along with prominent cell budding and nuclei displaying aberrant morphology, are indicative of serous carcinoma (41). High-grade serous ovarian carcinomas are distinguished by significant nuclear pleomorphism, wherein nuclei display a size typically three times larger than the norm, along with increased mitotic activity, manifesting as the presence of more than 12 mitotic figures within 10 high-power fields (42).

Across multiple investigations, immunohistochemical examinations have consistently demonstrated positive staining for K67, PAX8, and WT1 in a considerable percentage of high-grade serous ovarian carcinomas (HGSC) cases. Additionally, mutations affecting TP53 and p16 have been documented in approximately 96% of HGSC cases (43). Pathogenic alterations, including pathogenic somatic variants or epigenetic silencing, can lead to the impairment of BRCA1 or BRCA2 function (37)(44). Various methods are employed for diagnosing dysfunction in BRCA1 and BRCA2. Laboratory techniques geared towards diagnosing, prognosticating, and identifying dysfunctional proteins primarily center around immunohistochemistry (25).

Low grade serous Cancer: Low-grade serous cancer is a significant neoplasm characterized by infiltrative invasion, mild to moderate cytological atypia, and a moderately low proliferative capacity (45). Under microscopic examination, low-grade serous cancer typically exhibits an amphophilic or moderately eosinophilic cytoplasm, characterized by a uniform arrangement of cuboidal, low columnar, and occasionally flattened cells. While the degree of cytological atypia ranges from mild to moderate, occasional cells with enlarged nuclei may be observed, although significant nuclear atypia is uncommon. A low mitotic index, typically around 12 mitoses in 10 high-power fields, is frequently encountered. Careful histological evaluation is warranted when numerous mitotic figures are present, as this may indicate a rare association with a high-grade serous carcinoma (HGSC) component. The presence of disruptive invasion in low-grade serous cancer is identified by the infiltration of neoplastic cells into the ovarian stroma,

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either within an area measuring approximately 3.0 mm in linear dimension or displaying desmoplasia (45,46). Distinct characteristics can serve to identify and differentiate between low-grade and high-grade serous carcinomas (47).

In low-grade serous cancer, there is commonly observed positive immunoreactivity for the WT-1 antibody (47) along with positive expression of estrogen receptors in the majority of cases, and progesterone receptors in a minority of cases. (48). The Ki-67 index is generally observed to be below 10%; however, in specific scenarios, it may exhibit a higher Ki-67 index expression (47)(48). According to research findings, p16 exhibits irregular immune expression in approximately 18.5% of total cases (49). Additionally, O'Neill et al. noted that intense staining for p53 was detected in 18% of low-grade serous cancer cases, in contrast to 64% observed in high-grade serous ovarian carcinomas (47).

Clear Cell Carcinoma: Following high-grade serous ovarian cancer, clear cell carcinomas represent the next most prevalent subtype of epithelial ovarian cancer, constituting approximately 10 to 15% of all ovarian carcinomas (50). The World Health Organization formally recognized clear cell carcinomas as a distinct subtype of epithelial ovarian cancer in 1973. Prior to this official classification, numerous studies had suggested that clear cell carcinomas constitute a unique pathological subtype separate from other epithelial ovarian cancer subtypes. Clear cell carcinomas are associated with several distinct clinical manifestations, including a notably higher incidence of stage I disease, expansive pelvic masses, involvement of endometriosis, thromboembolic vascular complications, hyperkalemia, and an increased likelihood of lymphovascular invasion (51).

Microscopic examination reveals that cells in clear cell carcinoma exhibit glycogen-rich, transparent, hobnail, or oxyphilic characteristics, with occasional tubulocystic or papillary architectural patterns and rarely solid formations. The distinctive glycogen-rich nature of clear cell carcinoma is evident in its morphological features, which exhibit a greater abundance of glycogen metabolism genes compared to high-grade serous ovarian cancer. Additionally, stromal components may display excessive basement material along with varying degrees of nuclear atypia and minimal mitotic activity (52).

Various authors have employed specific morphologic and immunohistochemical markers to enhance the accuracy of pathologic classification. These markers include estrogen receptor, progesterone receptor, hepatocyte nuclear factor 1-beta (HNF1B), Wilms tumor 1, and tumor protein 53 (p53). Ovarian clear cell carcinomas typically exhibit negative staining for progesterone receptor, WT1, and p53, while staining positive for HNF1B and estrogen reseptor. (53)(54)(55). These marker panels can offer valuable assistance in cases of diagnostic uncertainty, particularly in distinguishing between clear cell carcinoma and high-grade serous carcinoma histology in high-grade serous carcinomas (53).

Endometrioid cancer: Endometrioid carcinomas comprise 10% of all ovarian carcinomas and are more prevalent among women of perimenopausal age, with a majority diagnosed at an early stage. Approximately 28% of these ovarian cancers exhibit bilateral involvement, and 15-20% are associated with endometrial carcinoma. Typically, these tumors present as solid masses with a irregular outer surface. Histologically, they consist of endometrial epithelium-like glands and are frequently associated with ovarian or pelvic endometriosis, with an incidence ranging from 23% to 42%. Immunohistochemically, endometrioid carcinomas demonstrate positive staining for WT1, PAX8, estrogen receptor, and progesterone receptor, while showing negative staining for WT1 and CK. (56, 57).

In the majority of cases, both sides of the tumors exhibit endometrioid characteristics. Evidence of bilateral ovarian or pelvic endometriosis is present in up to 42% of cases. Squamous differentiation within the tumor is observed in 50% of cases. Somatic mutations in CTNNB1 (β-catenin) and phosphatase and tension homolog (PTEN) genes are the most prevalent genetic alterations identified in endometrioid carcinomas, with CTNNB1 mutations being associated with a favorable disease outcome. PTEN mutations are detected in 20% of cases, and their inactivation leads to the loss of inhibition of the PI3K-AKT signaling pathway, resulting in decreased apoptosis and increased proliferation (57).

Mucinous tumors: Mucinous tumors represent approximately 3% of all cases of epithelial ovarian cancer. These tumors exhibit cellular characteristics akin to stomach pylorus cells or intestinal cells, often

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displaying gastrointestinal differentiation. Primary ovarian mucinous carcinomas typically manifest as large, unilateral masses confined to the ovaries, devoid of ovarian surface involvement or pseudomyxoma peritonei. In contrast, mucinous ovarian metastases are generally smaller than 10 cm in diameter and tend to be bilateral (57). Histologically, mucinous tumors consist of cysts and glands of varying sizes, often demonstrating a confluence pattern and back-to-back arrangement of glands. Additionally, variable papillary structures may be observed. The cells typically exhibit large, columnar morphology with mucin-containing basophilic cytoplasm. Invasive mucinous adenocarcinomas can be further subcategorized based on their pattern styles, which include expansive and infiltrative patterns (43).

Immunohistochemical analysis of ovarian mucinous carcinomas typically reveals positive staining for PAX8 in fewer than 50% of cases. Conversely, staining for CK67, WT1, and hormone receptors (estrogen and progesterone) is typically negative. In the diagnostic process, mucinous carcinomas often necessitate the sampling of at least 2 blocks per centimeter of tumor due to the potential development of borderline tumors and mucinous adenocarcinomas under certain conditions (43).

SATB2, a Special AT-rich sequence-binding protein, has been recently identified as a marker for the comprehensive assessment of mucinous ovarian neoplasms. Immunohistochemistry plays a crucial role in distinguishing primary from secondary ovarian tumors. The relatively recent emergence of SATB2 as an immunomarker, initially discovered through exploration of the Human Protein Atlas expression database, has demonstrated considerable utility in identifying potential gastrointestinal metastases. While its expression is exceptionally rare among ovarian primary tumors, it is commonly observed in mucinous metastases (58).

Conclusion

In conclusion, ovarian cancer stands as a prominent cause of gynecologic cancer-related mortality worldwide, often presenting challenges in timely diagnosis due to its late detection and the presence of various subtypes with distinct biological features. Histological diagnosis can be particularly challenging, given the difficulty in distinguishing morphological features from other histologic types. However, the employment of immunohistochemistry techniques has significantly enhanced our ability to identify and characterize ovarian cancer, providing valuable insights into tumor aggressiveness and the potential efficacy of targeted therapies. Key markers such as SATB2, CK67, HNF1B, PAX8, P53, P16, ER, and PR play pivotal roles in tumor detection, differential diagnosis, and understanding pathogenesis. These markers collectively form a panel for effective diagnosis and characterization of epithelial ovarian cancer. The molecular revolution in gynecological oncology, facilitated by advancements in immunohistochemistry techniques, has greatly contributed to our understanding and management of ovarian carcinomas, highlighting the crucial role of antigen-antibody reaction-based techniques in improving patient outcomes and informing treatment strategies.

Conflicts of Interest

Not required.

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