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PREDICTIVE VALUE OF IMMUNOHISTOCHEMICAL BIOMARKERS IN THE DIFFERENTIAL DIAGNOSIS OF BENIGN, BORDERLINE, AND MALIGNANT OVARIAN CYSTIC TUMORS

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Abstract

Background. Differential diagnosis of ovarian cystic tumors remains an important problem in gynecologic oncology. Although histopathological examination is the basis of definitive diagnosis, some benign, borderline, and malignant ovarian tumors demonstrate overlapping morphological features. Immunohistochemical biomarkers may provide additional information regarding cellular proliferation, tumor differentiation, molecular alterations, and biological aggressiveness.

Objective. To evaluate the diagnostic and potential prognostic significance of selected immunohistochemical biomarkers in differentiating benign, borderline, and malignant ovarian cystic tumors.

Materials and Methods. The study analyzed contemporary evidence concerning the expression of p53, Ki-67, WT1, PAX8, p16, estrogen receptor (ER), progesterone receptor (PR), Napsin A, and mismatch-repair proteins in epithelial ovarian tumors. Particular attention was paid to differences in immunohistochemical profiles among benign cystadenomas, borderline tumors, and invasive ovarian carcinomas and to the relationship between biomarker expression and histological subtype.

Results. Increasing proliferative activity assessed by Ki-67 is generally associated with progression from benign lesions toward malignant tumors, although considerable variation exists among histological subtypes. Abnormal p53 expression is strongly associated with high-grade serous carcinoma. WT1 and PAX8 are useful in confirming Müllerian and serous differentiation. Napsin A may support clear-cell differentiation, while ER and PR contribute to the characterization of serous and endometrioid tumors. Assessment of mismatch-repair proteins may identify a subgroup of tumors with potential hereditary and therapeutic significance. The greatest diagnostic value is achieved when immunohistochemical findings are interpreted in combination with tumor morphology rather than as isolated markers.

Conclusion. Immunohistochemical profiling represents a valuable complementary method for differential diagnosis of ovarian cystic tumors. A combined panel incorporating proliferative, tumor-suppressor, differentiation, and molecular-surrogate markers may improve discrimination among benign, borderline, and malignant lesions and facilitate individualized oncological management.

Keywords: ovarian cystic tumors, ovarian cancer, borderline ovarian tumor, immunohistochemistry, Ki-67, p53, WT1, PAX8, malignant potential.

Introduction

Ovarian tumors constitute a heterogeneous group of neoplasms characterized by considerable differences in histogenesis, morphology, molecular biology, clinical course, and prognosis. Ovarian cystic lesions are particularly common in gynecological practice and range from benign cystadenomas to borderline tumors and invasive carcinomas[1,8].

Accurate characterization of an ovarian mass is essential because therapeutic strategies differ substantially depending on the biological nature of the lesion. Benign tumors generally require conservative surgical management, whereas invasive malignancies may require comprehensive staging or cytoreductive surgery followed by systemic treatment. Borderline ovarian tumors occupy an intermediate position and frequently affect younger women, making accurate diagnosis particularly important when fertility-preserving treatment is considered[7].

Routine histopathological examination remains the gold standard for diagnosis. Nevertheless, certain lesions demonstrate overlapping architectural and cytological characteristics. In such cases, immunohistochemistry can complement conventional morphology and provide information about cellular origin, differentiation, proliferative activity, and molecular abnormalities[9].

The development of rational immunohistochemical panels may therefore improve diagnostic accuracy and provide additional information regarding the biological potential of ovarian tumors[10].

Aim

The aim of the study was to evaluate the significance of immunohistochemical biomarkers in the differential diagnosis of benign, borderline, and malignant ovarian cystic tumors and to determine their potential role in assessing malignant potential.

Materials and Methods

An analytical assessment of morphological and immunohistochemical characteristics of epithelial ovarian cystic tumors was performed.

The lesions were conceptually classified into three principal categories:

Group I — benign ovarian cystic tumors;

Group II — borderline ovarian tumors;

Group III — malignant epithelial ovarian tumors.

Histopathological evaluation included assessment of epithelial proliferation, nuclear atypia, architectural complexity, mitotic activity, papillary structures, solid components, necrosis, and stromal invasion.

The immunohistochemical panel included:

Ki-67 — assessment of proliferative activity;

p53 — evaluation of abnormal TP53-associated expression patterns;

WT1 — identification of serous differentiation;

PAX8 — confirmation of Müllerian origin;

p16 — assessment of cell-cycle dysregulation;

ER and PR — evaluation of hormone receptor expression;

Napsin A — additional characterization of clear-cell differentiation;

MLH1, PMS2, MSH2 and MSH6 — assessment of mismatch-repair protein expression.

The diagnostic value of individual biomarkers and combined immunohistochemical profiles was evaluated in relation to morphological characteristics and histological tumor type.

Results and Discussion

Morphological Spectrum of Ovarian Cystic Tumors

Benign ovarian epithelial tumors are generally characterized by preserved epithelial organization, relatively uniform nuclei, minimal atypia, low mitotic activity, and absence of stromal invasion.

Borderline tumors demonstrate greater architectural complexity. Epithelial stratification, papillary proliferation, nuclear atypia, and increased mitotic activity may be present. However, destructive stromal invasion is absent.

Malignant tumors demonstrate substantially greater cellular and architectural abnormalities. These include marked nuclear pleomorphism, increased nuclear-to-cytoplasmic ratio, loss of polarity, atypical mitoses, complex papillary or solid architecture, necrosis, and invasive stromal growth.

The transition from benign to borderline and malignant morphology is therefore associated with progressively increasing structural and cellular abnormalities.

Ki-67 as a Marker of Proliferative Activity

Ki-67 is one of the most frequently used markers for evaluating cellular proliferation.

In benign ovarian tumors, Ki-67 expression is generally limited because the majority of epithelial cells demonstrate relatively low proliferative activity.

Borderline tumors may show an intermediate proliferative pattern. Increased Ki-67 expression reflects enhanced epithelial proliferation but does not independently establish a diagnosis of malignancy.

Malignant ovarian tumors, particularly high-grade carcinomas, frequently demonstrate substantially greater proliferative activity.

Therefore, Ki-67 may contribute to the assessment of biological aggressiveness, particularly when interpreted together with tumor architecture, nuclear atypia, and histological subtype.

p53 Expression

The tumor-suppressor protein p53 is one of the most important biomarkers in contemporary ovarian pathology.

Abnormal p53 immunohistochemical patterns are strongly associated with TP53 alterations, particularly in high-grade serous carcinoma.

Two characteristic abnormal staining patterns may be observed: diffuse strong nuclear staining in a high proportion of tumor cells and a complete absence of staining, depending on the underlying TP53 alteration.

In contrast, a heterogeneous wild-type staining pattern is more typical of tumors without TP53-driven pathogenesis.

The combination of high-grade morphology, increased Ki-67 activity, and abnormal p53 expression strongly supports the diagnosis of a biologically aggressive serous carcinoma in an appropriate morphological context.

WT1

WT1 is particularly useful in the diagnosis of serous ovarian tumors.

Strong nuclear WT1 expression is frequently observed in serous carcinomas and may help distinguish them from certain other ovarian epithelial tumor types.

However, WT1 expression should always be interpreted together with morphological findings and other immunohistochemical markers.

PAX8

PAX8 is an important marker of Müllerian differentiation.

Positive nuclear PAX8 staining is observed in many primary ovarian epithelial malignancies and is particularly useful when differentiating a primary ovarian carcinoma from selected metastatic tumors involving the ovary.

Consequently, PAX8 plays an important role not only in tumor classification but also in determining the probable primary origin of metastatic disease.

p16

p16 is involved in cell-cycle regulation and may demonstrate altered expression in malignant ovarian tumors.

Diffuse p16 expression may occur in high-grade serous carcinoma and, in combination with abnormal p53 expression and high proliferative activity, can support the diagnosis.

However, because p16 expression is not specific to a single ovarian tumor type, it should be incorporated into a multiparametric immunohistochemical panel.

Estrogen and Progesterone Receptors

ER and PR expression varies considerably according to histological subtype.

Hormone receptor evaluation may contribute to the characterization of serous and endometrioid ovarian tumors and may also provide information regarding tumor differentiation.

The potential prognostic and therapeutic implications of hormone receptor expression continue to be investigated, particularly in selected low-grade tumors.

Napsin A

Napsin A is a useful marker in the differential diagnosis of ovarian clear-cell carcinoma.

Its expression, particularly when combined with characteristic clear-cell morphology and an appropriate immunohistochemical profile, may support the diagnosis of clear-cell differentiation.

As with other markers, Napsin A should not be used in isolation.

Mismatch-Repair Proteins

Immunohistochemical evaluation of MLH1, PMS2, MSH2, and MSH6 can identify loss of mismatch-repair protein expression.

Mismatch-repair deficiency is particularly relevant in selected endometrioid ovarian carcinomas and may indicate the need for further molecular investigation and hereditary cancer assessment.

Moreover, identification of mismatch-repair deficiency may have therapeutic implications because molecular characteristics increasingly influence the selection of systemic anticancer therapy.

Combined Immunohistochemical Model

The biological behavior of ovarian cystic tumors cannot be reliably determined using a single biomarker.

A more rational diagnostic model is based on combined assessment:

Morphological characteristics + Ki-67 + p53 + WT1 + PAX8 + subtype-specific markers.

For diagnostically difficult tumors, additional markers can be selected according to morphology and the differential diagnosis.

A simplified conceptual pattern can be presented as follows:

Benign lesion: preserved architecture + minimal atypia + low proliferative activity + absence of destructive invasion.

Borderline lesion: epithelial proliferation + increased architectural complexity + variable Ki-67 activity + absence of destructive stromal invasion.

Malignant lesion: pronounced atypia + complex/solid architecture + increased proliferative activity + subtype-associated abnormal immunophenotype + destructive stromal invasion.

This integrated approach is more informative than attempting to establish malignancy on the basis of a single immunohistochemical result.

Clinical Significance

The introduction of immunohistochemical panels into routine assessment of ovarian tumors has several important advantages.

First, immunohistochemistry can improve diagnostic confidence in morphologically difficult cases.

Second, it facilitates accurate histological classification, which is increasingly important because different ovarian carcinoma subtypes demonstrate distinct molecular profiles and clinical behavior.

Third, immunohistochemical findings may identify patients who require additional molecular testing.

Fourth, improved discrimination between borderline and invasive tumors may help avoid both insufficient treatment of malignant disease and excessive radical treatment of tumors with low malignant potential.

Finally, integration of morphological and immunohistochemical characteristics creates a foundation for developing predictive models of ovarian cystic lesion malignancy.

Conclusion

Differential diagnosis of ovarian cystic tumors requires an integrated approach combining conventional histopathology with immunohistochemical assessment.

The progression from benign to borderline and malignant ovarian tumors is associated with increasing architectural complexity, cytological atypia, proliferative activity, and ultimately destructive stromal invasion.

Among immunohistochemical biomarkers, Ki-67 provides information regarding cellular proliferation, while p53 is particularly valuable in the identification of TP53-associated high-grade serous carcinoma. WT1 and PAX8 contribute to determination of tumor differentiation and origin, whereas p16, ER, PR, Napsin A, and mismatch-repair proteins provide additional subtype-specific diagnostic information.

The highest diagnostic value is achieved not by individual biomarkers but by combined interpretation of morphological and immunohistochemical parameters. Development of integrated predictive models based on these characteristics may improve early identification of ovarian tumors with high malignant potential and support personalized decision-making in gynecologic oncology.

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