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Original Article

Expression of HIF-1α, Ki67, SMA and E-Cadherin in Endometriosis, Endometrial and Ovarian Carcinoma

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Abstract

Introduction: Endometriosis is a benign gynecological condition that shares many characteristics with cancer cells, including immune evasion, survival, adhesion, invasion, and angiogenesis. The simultaneous investigation of tissue hypoxia, EMT, and proliferative index in endometriosis, endometrial, and ovarian carcinomas may provide new insight into the evolution and progression of gynecological neoplasms.

Aim: The aim of our study was to follow the immunohistochemical expression in endometriosis, endometrial and ovarian carcinoma in relation to tissue hypoxia and necrosis, EMT, proliferative index, and fibrosis.

Materials and methods: The present study used biopsy samples from 50 patients with endometriosis, endometrial carcinoma, and ovarian carcinoma in search for a correlation between HIF-1α, Ki67, SMA, and E-cadherin expression and various clinicopathological features.

Results: We observed heterogeneity and different intensity of immunohistochemical expression in different groups of patients. Immunohistochemical expression was compared with the degree of tumor cell differentiation. Cells of poorly differentiated adenocarcinomas showed a higher proliferative index with Ki67, presence of epithelial-mesenchymal transition with reduced expression of E-cadherin with stronger expression of HIF-1α. Regarding SMA in pelvic and ovarian endometriosis foci, we reported strong diffuse expression in stromal cells with marked fibrosis.

Conclusion: Understanding the mechanisms of carcinogenesis and progression of gynecological tumors and endometriosis is important for prognosis, response to therapy, and possibly better treatment of patients.

Keywords

INTRODUCTION

Of women of reproductive age, 5% to 15% have endometriosis, which is defined as the presence of endometrial glands and stroma outside the uterus.[1] Ovarian cancer has been shown to develop in 0.5%–1% of cases of ovarian endometriosis.[2] Clear cell carcinoma (CCC) is most commonly associated with ovarian endometriosis.

Endometrial carcinoma is the most common gynecological malignancy. Pathologically, it is classified into two groups, type I (endometrioid endometrial carcinoma) which accounts for 70%-80% of cases, and type II (non-endometrioid), including serous ones, and clear cell carcinoma.[3] Understanding the molecular alterations underlying the endometrial carcinogenesis and progression may be helpful in identifying new molecular therapeutic targets. The current study sought to investigate the relationship between immunohistochemical expression of HIF-1α, epithelial, mesenchymal, and proliferative markers and clinicopathological parameters in endometriosis, endometrial, and ovarian carcinomas.

Hypoxia-inducible factor-1 (HIF-1) expression can be a marker of tissue hypoxia in solid tumors and can be used for therapeutic purposes due to its role in the progression of gynecological neoplasms.[4] In the literature, the results for HIF-1α in gynecological cancers are not always consistent.

HIF-1α is the master regulator of cellular adaptation to hypoxia. It is a heterodimeric transcription factor composed of the HIF-1α and HIF-1β subunits.[5] Elevated levels of HIF-1α are observed in a number of human malignancies and are associated with metastatic potential and poor prognosis.

Decreased expression of E-cadherin is associated with positive EMT in tumor tissue and with proliferation, progression and metastasis, respectively, and a worse prognosis. In such cases, the tumors usually also have a high proliferative index.

AIM

The present study was conducted to investigate the correlation between HIF-1α expression in endometriosis and endometrial carcinomas by immunohistochemical technique. The expression of HIF-1α, Ki67, SMA and E-cadherin was studied and a comparative analysis of their expression was made in the three studied groups.

MATERIALS AND METHODS

Fifty patients were included in the current study and were evaluated both prospectively and retrospectively. All of them are from the biopsy array of the Department of Clinical Pathology of Pulmed University Hospital in Plovdiv for a period of five years (2019-2023). DAKO antibodies were used.

All patients were operated on and diagnosed in the Clinic of Obstetrics and Gynecology of Pulmed University Hospital of Plovdiv. The biopsy materials were reviewed by two independent pathologists to diagnose, the morphological type and stage the tumor according to FIGO. The histological and immunohistochemical investigation of the biopsy materials was performed in the laboratory of the Morphological Center of the Department of General and Clinical Pathology of the Medical University of Plovdiv.

Immunohistochemical analysis

The tissue was treated with standard histopathological technique according to standard protocols, and semi-quantitative analysis of the results was performed. 4-µm thick paraffin sections were dewaxed and rehydrated through descending alcohols. Hematoxylin-eosin staining was performed according to standard methods. The immunohistochemical study was performed according to standard protocols. Immunohistochemistry was performed for the protein markers HIF-1α, Ki67, SMA and E-cadherin.

An automatic immunostainer (Bond, DAKO) was used following the manufacturer's protocols.

Antibodies produced by Dako, Denmark and Abcam, USA were used:

– rabbit monoclonal antibody against human HIF-1α, 1:100 dilution

We reported nuclear staining.

– mouse monoclonal antibody against human E-cadherin

We reported cytoplasmic and membranous staining.

– mouse monoclonal antibody against human Ki67

We reported nuclear staining.

– mouse monoclonal antibody against human SMA

Cytoplasmic and membranous staining were described. DAB was used as the chromogen. An automated coloring platform was used.

Expression estimation system

A semi-quantitative method was used to assess the immunohistochemical expression: 1%–10%=1; 10%–50%=2; >50%=3.

Intensity of immunohistochemical expression: 0=missing; 1(+)=weak; 2(+)=moderate; 3(+)=strong.

We reported diffuse, focal, and heterogeneous expression patterns.

Statistical analysis

Descriptive and inferential statistics were performed. The non-normally distributed data were expressed as median and percentiles (25th; 75th). Comparisons between more than two independent groups were carried out using the nonparametric Kruskal-Wallis test (H). Multiple-comparison post hoc test was used if significant differences were found. Categorical variables were presented as absolute/relative frequencies (counts/%) and z-test was applied to test for difference of relative parts/shares between the groups. Statistical analysis of the data was performed using SPSS v. 26 for Windows (IBM Corp. Released 2019. Armonk, NY: IBM Corp). For all tests, p-value <0.05 indicated statistical significance.

RESULTS

A retrospective analysis was conducted on a total of 296 cases from 2019 to 2023. Among these cases, a subset of 50

was chosen for immunohistochemistry testing. The present study examined a cohort of women, whose median age was 64.5 years (54; 71 years), who were categorized into three distinct groups: 16 individuals (32.0%) diagnosed with endometriosis, 17 individuals (34.0%) diagnosed with endometrial carcinoma, and 17 individuals (34.0%) diagnosed with ovarian carcinoma. A distribution was generated to represent the number and proportion of patients in the three groups within the designated time frame. A statistically significant difference was seen in the age distribution of the patients under examination across different groups (H=16.44, p=0.000). Following a post hoc analysis, it was seen that patients diagnosed with endometriosis with a median age of 51 years exhibited a statistically significant difference in age when compared to patients diagnosed with endometrial cancer, who had a median age of 68 years (p=0.002). Furthermore, patients with endometriosis were also shown to be statistically substantially younger than those diagnosed with ovarian carcinoma, with a median age of 71 years (p=0.001). There was no difference between the median ages of individuals diagnosed with endometrial and ovarian carcinomas.

The proportion of the heterogeneous E-cadherin staining pattern in ovarian cancer (52.9%) was statistically significantly higher compared to the other two groups, namely endometriosis focus (6.3%) and endometrial carcinoma (11.8%) (z-test, p<0.05). Additionally, the prevalence of diffuse staining E-cadherin pattern was found to be substantially greater in cases of endometriosis (93.8%) and endometrial carcinoma (88.2%) as compared to ovarian carcinoma (47.1%) (z-test, p<0.05).

The results are shown in **Table 1** and **Fig. 1A**.

In cases with reduced expression of E-cadherin, we reported a positive EMT status, in case of preserved expression – a negative EMT status.

The proportion of negative epithelial-mesenchymal transition (EMT) in endometriosis (87.5%) was shown to statistically significantly higher compared to ovarian cancer (23.5%) (z-test, p<0.05). Furthermore, the statistical analysis revealed a statistically significantly higher occurrence of positive epithelial-mesenchymal transition (EMT) in ovarian cancer (76.5%) compared to endometriosis (12.5%) (z-test, p<0.05) **(Table 2)**.

HIF-1α, which serves as the principal functional protein within the HIF-1 complex, had a high level of HIF-1α expression in instances of endometrial carcinoma cases, at the invasive tumor front, and in proximity to areas exhibiting necrotic tissue.

In cases involving endometriosis, there was a notable increase in HIF-1α expression within adenomyosis and endometriosis foci as compared to the expression detected in normal endometrium, as shown in **Fig. 1B**.

We observed increased expression at the tumor-invasive front. HIF-1α expression was found to be associated with tumor grade, indicating a progressive increase in strength.

A statistically significantly higher proportion of HIF-1α positive cells between 25% and 50% was found in endometrial carcinoma (58.8%) compared to ovarian carcinoma (11.8%) (z-test, p<0.05) **(Fig 1C, D)**. In cases with high HIF-1α expression (more than 75%) is observed statistically significant difference between ovarian carcinoma (41.2%) compared to endometrial carcinoma (5.9%) (z-test, p<0.05).

The relative share of the diffuse pattern of staining for HIF-1α in endometriotic focus (62.5%) compared to endometrial carcinoma was statistically significantly higher (11.8%) (z-test, p<0.05) (**Table 3**).

Table 1. Relative proportions of E-cadherin expression categories by staining pattern by group

N	Endometriosis	Endometrial cancer	Ovarian cancer
Heterogeneous pattern	1 (6.3%)	2 (11.8%)	9 (52.9%)
Diffuse pattern	15 (93.8%)	15 (88.2%)	8 (47.1%)
Total	16 (100%)	17 (100%)	17 (100%)

Table 2. Relative proportions of the categories of E-cadherin expression along the epithelial-mesenchymal transition in the three studied groups

N	Endometriosis	Endometrial cancer	Ovarian cancer
Negative EMT status (preserved expression of E-cadherin)	14 (87.5%)	10 (58.8%)	4 (23.5%)
Positive EMT status (reduced to missing E-cadherin expression)	2 (12.5%)	7 (41.2%)	13 (76.5%)
Total	16 (100%)	17 (100%)	17 (100%)

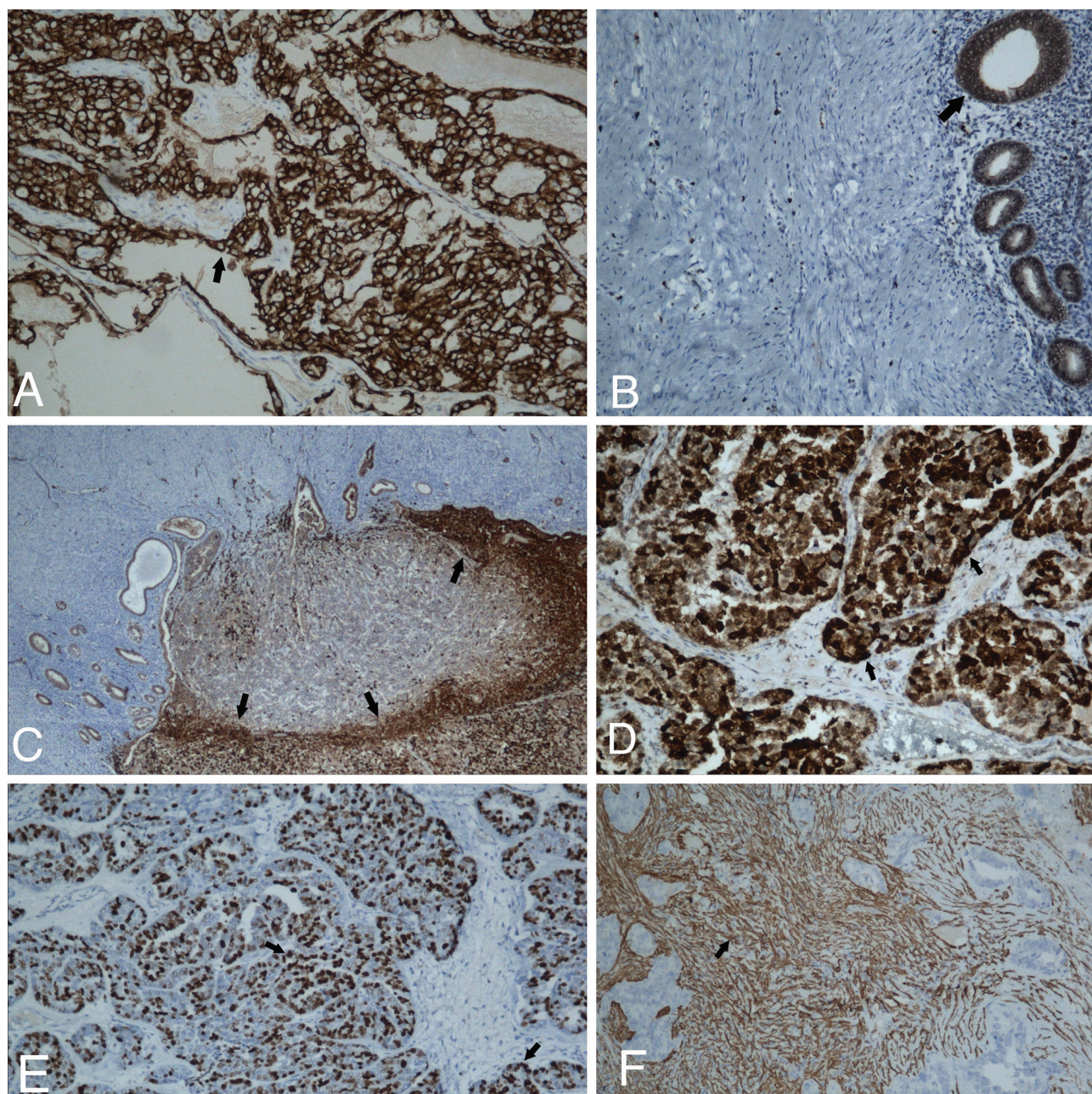**Table 3.** Relative proportions of anti HIF-1α expression categories according to the staining pattern by group

N	Endometriosis	Endometrial cancer	Ovarian cancer
Perinecrotic	0 (0.0%)	4 (23.5%)	4 (23.5%)
Diffuse	10 (62.5%)	2 (11.8%)	6 (35.3%)
Mixed	3 (18.8%)	2 (11.8%)	4 (23.5%)
Heterogeneous	3 (18.8%)	9 (52.9%)	3 (17.6%)
Total	16 (100%)	17 (100%)	17 (100%)

There is a statistically significant difference in the proportion of positive Ki67 cells, ranging from 1% to 10%, in endometriosis focus (87.5%) compared to the two other groups, endometrial carcinoma (29.4%) and ovarian cancer (11.8%) (z-test, $p<0.05$). Moreover, there was a statistically significant increase in the proportion of Ki67-positive cells ranging from 10% to 50% in endometrial cancer (58.8%) compared to endometriosis (12.5%) (z-test, $p<0.05$) (**Fig. 1E**). In ovarian cancer, the maximum relative

percentage of Ki67 positive cells exceeds 50% (41.2%). In the other two groups, namely endometrial carcinoma and endometriotic focus, the relative proportions of Ki67 positive cells are observed to be 11.8% and 0%, respectively.

No statistically significant difference was observed between the relative proportions of the SMA expression categories in the three groups (z-test, $p \geq 0.05$). A moderate type of expression predominated in all three groups, as did a diffuse staining pattern (**Fig. 1F**).

Figure 1. **A**. E-cadherin, IHC, diffuse expression pattern, low grade endometrial carcinoma, ×100; **B**. Nuclear and cytoplasmic expression of HIF-1α in an endometriosis focus, ×100; **C**. Strong nuclear expression of HIF-1α in high grade endometrioid carcinoma, combined with endometriosis, strong perinecrotic expression in the tumor and weak diffuse expression in the endometriosis focus, ×40; **D**. Heterogeneous expression pattern of HIF-1α in clear cell variant ovarian carcinoma in the nucleus and cytoplasm of tumor cells, ×100; **E**. IHC expression of Ki67 - 75% proliferative index in moderately differentiated endometrial carcinoma, ×100; **F**. Cytoplasmic and membrane expression of SMA in endometrioid variant ovarian carcinoma, ×100.

DISCUSSION

Hypoxia is a common change in the tumor microenvironment of solid malignancies due to an imbalance between the rapid growth of tumors and their blood supply. In addition, hypoxia has been shown to induce resistance to chemotherapy and radiotherapy. We show that diffuse expression of HIF-1α predominates in cases with endometriosis and endometrial carcinoma, and a heterogeneous expression pattern is also observed in ovarian carcinomas. In type 1 endometrial carcinoma, HIF-1α expression correlates with tumor grading and FIGO stage, which has also been reported by other authors.[6]

In type 2 endometrial carcinoma, stronger and diffuse expression, including perinecrotic expression of HIF-1α was observed in all examined patients, regardless of the depth of myometrial invasion, vascular invasion, and TNM stage of the tumor. This dependence is well expressed in high-grade carcinomas.

Immunohistochemical expression of HIF-1α was greater in high-grade endometrial carcinomas compared with low-grade carcinomas, but this difference was not statistically significant. We hypothesize that the lack of statistical significance is due to the small number of cases in the sample. It is interesting that around areas with necrosis, we simultaneously observed positive EMT and perinecrotic strong expression of HIF-1α. Hypoxia is likely to underlie the mechanisms in both processes.

The association between endometriosis and endometrioid and clear cell carcinoma of the ovary is well known.[7] A threefold higher risk of developing endometriosis-associated ovarian carcinoma has been found in the presence of ovarian endometriosis.[8] However, the relationship between endometriosis and endometrial carcinoma has not been well studied.[9]

Endometriosis and endometrial carcinoma share common etiologic factors, including estrogen stimulation and chronic inflammation. Atypical endometriosis is a precursor lesion associated with malignant transformation and with increased the risk of endometrial carcinoma.[10] Endometriosis was found in 30% of cases of synchronous endometrioid carcinomas of the endometrium and the ovary.[11] In our study, in 11 cases of combination between endometriosis and endometrial carcinoma, we reported a more advanced FIGO stage. We hypothesize that endometriosis paves the way for tumor cells among the uterine myometrium in adenomyosis.

Endometrioid ovarian carcinoma histologically resembles the endometrium, and recent studies have shown an association of endometriosis with endometrioid, clear cell, and low-grade serous ovarian carcinoma[12], as well as in the cases described by us. Adenomyosis is a condition in which endometrial glands and stroma are present in the myometrium of the uterus.[13] In cases with endometrioid carcinoma and adenomyosis, we observed deep myometrial invasion.

Loss of E-cadherin activates the Wnt-signaling pathway and leads to EMT.[14] E-cadherin-mediated cell adhesion is inactivated by different mechanisms in cancers. Suppression of the E-cadherin/β-catenin complex as well as upregulation of SMA are known to be key processes in EMT. An important aspect of EMT is the aberrant localization of β-catenin expression.[15] Tumor hypoxia decreases E-cadherin expression, leads to EMT, and helps tumor cells to avoid programmed cell death and adapt to unfavorable conditions.[16]

Studies on the immunohistochemistry expression of E-cadherin in relation to endometriosis have yielded inconsistent findings. In our study, E-cadherin expression in peritoneal and ovarian endometriosis cases was weaker compared to the adenomyosis expression. Around areas of necrosis, we observed reduced expression of E-cadherin in tumor cells in ovarian and endometrial cancers.

Ki67 protein is a cell proliferation marker. The number of Ki67-positive tumor cells often correlates with the clinical course.[17] The Ki67 index is higher in advanced stage tumors; a higher Ki67 index indicates more aggressive tumor behavior and worse clinical outcomes.[18] The same trend is observed with the proliferative index in low- and high-grade endometrial carcinomas. In Ki67 positive cases, positive EMT status predominated by frequency.

Although we did not find a statistical relationship between EMT status and proliferative index in each of the studied groups of working material, we performed a comparative analysis of the same tumor areas in cases with EMT positive status with a heterogeneous pattern and high Ki67 expression (50-100%). In areas of reduced E-cadherin expression, we observed increased expression with Ki67. And the inverse was valid.

Endometriosis is not a neoplastic disease, but it involves certain processes showing hallmarks of malignancy and carcinogenesis.[19] There is increasing interest in the role of the Ki67 monoclonal antibody in the development of endometriosis. Ki67 is a nuclear protein associated with cell proliferation.[20] Although little is known about the specific roles of Ki67, it is present in all active phases of the cell cycle but is absent in resting (G0) cells.[20]

Endometrial cell proliferation in patients with endometriosis was higher than that in patients without endometriosis, as determined by the proliferation index Ki67.[21] A higher level of Ki67 is associated with malignant tumors and metastasis.[22] Whether Ki67 is associated with endometriosis recurrence is not yet known. HIF-1α and Ki67 may be useful in identifying endometriosis patients who are at risk and need more specialized care.

An important histological feature of endometriosis is the presence of dense fibrous tissue in and around the lesions[23], especially in deep infiltrating endometriosis (DIE)[24]. Fibrosis can lead to subsequent adhesions, anatomic deformity, and pelvic pain, and because fibrosis in many organs is generally difficult to treat, much less cure[25], fibrosis in endometriotic lesions is very likely to be responsible for resistance to therapy, especially in DIE[25].

Another feature of endometriosis is the universal presence of smooth muscle in or around endometriotic lesions,

often referred to as smooth muscle metaplasia (SMM). SMM is common in peritoneal[26], deep[27], ovarian[28] endometriosis, as well as in adenomyosis[29]. The most pronounced fibrosis was observed in cases with peritoneal endometriosis. The possibility of stromal cells differentiated into smooth muscle cells (SMCs) undergoing physiological SMM in the uterine connective tissue is not yet sufficiently evidenced.[30]

Some authors associate the expression of SMA in endometriosis and endometrial carcinomas with EMT, other authors suggest that the strong expression of SMA in the stroma of endometrial lesions is the result of smooth muscle metaplasia of the stromal cells in the endometriotic focus. The observed strong diffuse expression of SMA in endometriosis lesions support the second hypothesis.

CONCLUSIONS

The immunohistochemical profile of the different morphologic lesions of the endometrium and ovaries can be used to analyze the progression of endometriosis in tumor tissue, as well as to assess the progression of ovarian and endometrial carcinomas. Selected immunohistochemical markers are relevant in the assessment of proliferative activity, invasion and tumor progression and may serve as prognostic factors and for future therapy.

Endometriosis should be considered as a disease with the potential for malignancy. Morphological and immunohistochemical evaluation of endometriotic tissue can increase the clinicians' awareness of the potential of an endometriotic lesion. Decreased expression of E-cadherin in endometriosis and a proliferative index greater than 10% are grounds for a follow-up and more of an increased disease recurrence.

Morphologic features such as intratumoral hypoxia and areas of necrosis in ovarian and endometrial carcinomas are poor prognostic markers, as is a high proliferative index.

Acknowledgements

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Экспрессия HIF-1α, Ki67, SMA и Е-кадгерина при эндометриозе, раке эндометрия и яичников

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Резюме

Введение: Эндометриоз – доброкачественное гинекологическое заболевание, которое имеет много общих характеристик с раковыми клетками, включая уклонение от иммунитета, выживаемость, адгезию, инвазию и ангиогенез. Одновременное исследование тканевой гипоксии, ЭМП и пролиферативного индекса при эндометриозе, карциномах эндометрия и яичников может дать новое представление об эволюции и прогрессировании гинекологических новообразований.

Цель: Целью нашего исследования было проследить иммуногистохимическую экспрессию при эндометриозе, карциноме эндометрия и яичников в связи с тканевой гипоксией и некрозом, ЭМП, пролиферативным индексом и фиброзом.

Материалы и методы: В настоящем исследовании использовались образцы биопсии 50 пациенток с эндометриозом, карциномой эндометрия и карциномой яичников с целью поиска корреляции между экспрессией HIF-1α, Ki67, SMA и Е-кадгерина и различными клинико-патологическими особенностями.

Результаты: Мы наблюдали гетерогенность и различную интенсивность иммуногистохимической экспрессии у разных групп пациентов. Иммуногистохимическую экспрессию сравнивали со степенью дифференцировки опухолевых клеток. Клетки низкодифференцированных аденокарцином показали более высокий пролиферативный индекс Ki67, наличие эпителиально-мезенхимального перехода со сниженной экспрессией Е-кадгерина при более сильной экспрессии HIF-1α. Что касается SMA(гладкомышечный актин) в очагах эндометриоза органов малого таза и яичников, мы сообщили о сильной диффузной экспрессии в стромальных клетках с выраженным фиброзом.

Заключение: Понимание механизмов канцерогенеза и прогрессирования гинекологических опухолей и эндометриоза важно для прогноза, ответа на терапию и, возможно, лучшего лечения пациенток.

Ключевые слова

эндометриоз, карцинома эндометрия, гипоксия, иммуногистохимия, рак яичников

Folia Medica