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ASPECTOS CLÍNICO-MORFOLÓGICOS E IMUNOHISTOQUÍMICOS DA PATOGENIA DO POLIPO ENDOMETRIAL NA PÓS-MENOPAUSA

CLINICO-MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL ASPECTS OF ENDOMETRIAL POLYP PATHOGENESIS IN POSTMENOPAUSE

КЛИНИКО-МОРФО-ИММУНОГИСТОХИМИЧЕСКИЕ АСПЕКТЫ ПАТОГЕНЕЗА ПЭ В ПОСТМЕНОПАУЗЕ

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RESUMO

Estudar a expressão do fator de transcrição HIF-1α induzida por hipóxia em pólipos endometriais (PE), considerando suas características clínico-morfológicas e imunológicas durante a pós-menopausa. Exames clínicos e laboratoriais complexos em 120 pacientes na pós-menopausa foram realizados. 90 deles desenvolveram PE, enquanto 30 tinham endométrio morfologicamente inalterado. O teste imuno-histoquímico (ICH) foi utilizado para avaliar a expressão do HIF-1α em células epiteliais e estromais de pólipos no endométrio adjacente e controle. Um conjunto dos fatores de risco mais significativos na gênese do PE, como alta taxa de distúrbios inflamatórios dos órgãos genitais (IDGO), distúrbios extragenitais, metabólicos e endócrinos e contracepção intra-uterina (IUC) foram encontrados. Alta expressão de HIF-1α nas células epiteliais e na área de infiltrado inflamatório do estroma PE fibroso glandular foi estabelecida em comparação com o endométrio controle. A expressão de HIF-1α em células epiteliais e na área de infiltrado inflamatório de estroma fibroso glandular PE contra o pano de fundo de alterações inflamatórias, metabólicas e endócrinas, imunológicas e processos involucionais relacionados à idade indicaram hipóxia local. Alterações epigenéticas podem se desenvolver nos processos de proliferação e apoptose e nos processos que controlam a transformação neoplásica. Os dados obtidos podem fornecer bases para a terapia de EP adaptada ao paciente em pacientes na pós-menopausa.

Palavras-chave: *endométrio, pólipo, pós-menopausa, fator transcricional, teste imuno-histoquímico*.

ABSTRACT

To study hypoxia-inducible transcription factor HIF-1α expression in endometrial polyps (EP) considering their clinical-morphological and immunological features during postmenopause. A complex clinical and laboratory examination of 120 postmenopausal patients was carried out. 90 of them developed EP, whereas 30 had morphologically unchanged endometrium. Immune histochemical (ICH) testing was used to evaluate HIF-1α expression in epithelial and stromal cells of polyps in adjacent and control endometrium. A complex of the most significant risk factors in EP genesis such as high rate of inflammatory disorders of genital organs (IDGO), extragenital, metabolic and endocrine disorders and intrauterine contraception (IUC) was found. High expression of HIF-1α in epithelial cells and in the area of inflammatory infiltrate of glandular fibrous EP stroma was established as compared with control endometrium. HIF-1α expression in epithelial cells and in the area of inflammatory infiltrate of EP glandular fibrous stroma against the background of inflammatory, metabolic and endocrine, immunological changes and age-related involutional processes indicated local hypoxia. Epigenetic changes can develop in the processes of proliferation and apoptosis and in the processes that control neoplastic transformation. The obtained data can provide grounds for patient-tailored EP therapy in postmenopausal patients.

Keywords: *endometrium, polyp, postmenopause, transcriptional factor, immune histochemical test.*

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АННОТАЦИЯ

Изучить экспрессию гипоксией индуцированного транскрипционного фактора HIF-1α в ткани полипов эндометрия (ПЭ) с учетом клинико-морфо-иммунологических особенностей их формирования в постменопаузе. Проведено комплексное клинико-лабораторное обследование 120 пациенток в постменопаузе, из которых 90 с ПЭ, а 30 с морфологическим неизмененным эндометрием. Методом иммуногистохимии (ИГХ) оценивали экспрессию HIF-1α в эпителиальных и в стромальных клетках полипов, окружающего его и контрольного эндометрия. Выявлена совокупность наиболее значимых факторов риска в генезе ПЭ: высокие уровни ВЗПО, экстрагенитальной, обменно-эндокринной патологии и внутриматочной контрацепции (ВМК). Установлена высокая экспрессия HIF-1α в эпителиальных клетках и в зоне воспалительного инфильтрата стромы железисто-фиброзных ПЭ в сравнении с контрольным эндометрием. Экспрессия HIF-1α в эпителиальных клетках и в зоне воспалительного инфильтрата стромы железисто-фиброзных ПЭ на фоне воспалительных, обменно-эндокринных, иммунологических изменений и возрастных инволютивных процессов свидетельствует о локальной гипоксии и может представлять риск эпигенетических изменений в процессах пролиферации и апоптоза в процессах, контролирующих неопластическую трансформацию. Полученные данные могут обосновать индивидуальный подход к определению тактики лечения ПЭ в постменопаузе.

Ключевые слова: *эндометрий, полип, постменопауза, транскрипционный фактор, HIF-1α, иммуногистохимия, воспаление, строма, инфильтрат, эпителий.*

1. INTRODUCTION

Endometrial polyps (EP), detected with 16 to 54% incidence rate, belong to one of the most common etiologies for abnormal uterine bleeding (AUB) in postmenopausal women (Kulhan *et al.,* 2017; Wong *et al.,* 2017). In some cases, they can be asymptomatic and detected during ultrasound screening. The EP detection rate in postmenopausal women varies from 39.28% to 69.3%. It increases when the postmenopausal period is prolonged (Voitashevsky, 2005; Chernukha *et al*., 2018). In 0.18-2.1% of cases, polyps are malignant. The transformation is more frequent in adenomatous polyps that are associated with endometrial hyperplasia (Adamyan *et al*., 2015; Savelyeva *et al*., 2015; Diwakar, 2015; Ferrazzi *et al*., 2009). However, some data show that EP cancer in postmenopausal women can develop against the background of atrophic endometrial processes (Khitrykh, 2009). High recurrence rate, which accounts for 13.3-21.5% during two years is typical of EP (Paradisi *et al.,* 2014; Yang *et al.,* 2015).

Modern ideas of EP pathogenesis are not limited to the traditional concept of hyperestrogenism. This mostly concerns the postmenopausal period when the level of systemic steroids is not high. According to the latest research, EP is a polycausal disorder; genetic, hormonal, infectious, immunological and metabolic factors can launch the proliferative endometrial activity (Sattarov *et al*., 2013; Sukhikh *et al*., 2005).

Hypoxia that activates the transcriptional factor (hypoxia-inducible 1α (HIF-1α) factor) can be the trigger of tumor growth (Potente *et al.,* 2011; Al-Sharaky *et al.,* 2016). According to Doppler velocimetry, atrophic endometrium is hypoxic due to decreased blood flow.

Endometrial cells serve as ‘primary sensors’ of hypoxic stress. They provide neovascularization due to modulation of genes, growth factors, proteins promoting cellular proliferation, extracellular matrix remodeling and reduction of apoptosis (Levina *et al*., 2009; Economopoulou *et al.,* 2009; Martorell *et al.,* 2009; Haase, 2006; Smith *et al.,* 2008). Since HIF-1α is significant in cancer and endometrial pathogenesis, it is important to study the protein expression to comprehend the mechanism of neoplastic transformation development associated with low estrogen levels in postmenopausal women.

The purpose of the study was to examine HIF-1α expression in EP tissues considering clinical-morphological and immunohistochemical features of their formation during postmenopause.

2. MATERIALS AND METHODS

A complex comparative study of interrelation among clinical, immunological, bacterial, morphological, and immunohistochemical aspects of EP development in 120 postmenopausal women was

conducted. All patients were distributed into 2 groups. Group I included 90 patients with EP (treatment group), whereas Group II included 30 postmenopausal women with morphologically altered endometrium (control group).

Study entry criteria: patients with endometrial and recurrent, not malignant polyps, patients who had no EP but who the postmenopausal endometrium could be examined in (intrauterine fluid collection, uterine synechias associated with age-related atrophy, artifact in ultrasound: lack of polyp), and submucous myoma during hysteroscopy.

Study exclusion criteria: a history of or present oncological and borderline diseases with any organ involved.

All included patients gave their consent to participate in the study that was approved by the ethics committee in both groups.

Complaints were collected and analyzed, premorbid background including gynecological and extragenital disorders, features of menstrual, genital, and reproductive functions were studied. General clinical and laboratory examination, specific gynecological examination, and extended cytological smear assay were performed.

Microbiocenosis of the vagina and cervical canal was evaluated using bacterioscopic research, and DNA-diagnostics of anaerobic and aerobic microflora of the cervical canal and uterine cavity using polymerase chain reactions (PCR) –with Bio-Rad sets (USA). Quantitative and qualitative assays were done on selective media.

Immunologic testing included detection of immunoglobulin M, A, G, secretory IgA (sIgA) and free secretory component (sc) in the uterine cavity. Immunoglobulin concentrations were measured using a modified radial immunodiffusion assay method, according to Mancini.

During an immunologic assay, the uterine lavage was done as follows: 3-5 ml of rheopolyglucin solution was flushed into the uterine cavity, left for 5-10 minutes, then the entire fluid was aspirated from the uterine cavity. The obtained secretion was mixed thoroughly and placed in Eppendorf tubes.

To detect HIF-1α, 27 patients underwent immunohistochemistry testing of the endometrial specimen. The authors used 4 μm slices mounted on positively charged glass slides. HIF-1α monoclonal antibodies were utilized as primary antibodies at a dilution of 1:100 (Abbiotec, USA 1:100). Diluent: Dako Antibody Diluent S0809. Retrieval buffer (HIER): BOND Epitope Retrieval Solution 2 - 20 min.

Bond Polymer Refine Detection system fixed in immunostainer was used to label secondary antibodies. Immunostainer: BOND III. The testing was done in the laboratory of morbid anatomy department of Moscow Municipal Oncological Hospital No. 62 (Head Physician: D. Yu. Kanner, Head of the department: N. A. Savelov).

The data were processed using a standard statistical package - Statistica 7.0. Descriptive statistics were presented for continuous variables calculating mean values and standard error of the mean. χ^2-Pearson's test was used to determine statistical significance among the values within the studied sampling.

Relative risk (RR), odds ratio (OR), sensitivity (Se) and specificity (Sp) were also calculated at 95% CI if $p<0.05$, differences between the compared values were considered statistically significant.

All women with EP underwent polypectomy, hysteroscopically controlled separate diagnostic curettage of the cervical canal and uterine cavity. All scrapings were morphologically tested.

Patients from the control group were treated at the gynecological departments for a disease not associated with endometrial pathology.

3. RESULTS AND DISCUSSION

Indication for hospital admission of the examined patients was as follows: vaginal discharge during postmenopause in 37 women (41.0%) occurring as bleeding and ultrasound-based variation between the measurements of endometrial thickness during a preventive examination. Age of women in both groups did not differ significantly ($\chi^2>0.05$) with the mean age being 60 ± 1.5 years.

Certain features were found during comparative analysis of clinical and anamnestic data obtained from postmenopausal women with EP. A high rate of endocrine chronic extragenital disorders such as exertional angina (18.9% vs. 3.3%) and impaired fat metabolism (28.9% vs. 10.0%) was registered during the analysis of somatic pathology. They could lead to hypoxia in general and endometrial pathology as a consequence.

It is shown that EP risk occurrence in women with co-existing endocrine disorders is significantly higher (RR=2.78; OR=5; 95% CI 1.33-5.82) with a sensitivity of 89% and specificity of 38%.

Obstetric-gynecological anamnesis was

analyzed to show that women from the treatment group used IUD more frequently (21 (23.4%) as compared with controls (3 (10.0%) ($p<0.05$). 8 of them developed such complications as IUD expulsion, pregnancy with an IUD in situ and bleeding, resulting in IUD removal and uterine curettage.

A lower number of pregnancies and deliveries (38%) but a high rate of artificial and spontaneous abortions (42.6%) were noted in women with EP as compared with group II (75.4% and 13.2%, respectively).

Patients from the treatment group with 223 pregnancies had 85 deliveries (38.1%) and 95 (42.6%) abortions, whereas women from the control group had more deliveries and fewer abortions - 86 (75.4%) and 15 (13.2%), respectively.

18 (20.0%) women with EP had a history of spontaneous abortions, 15 (16.7%) women had non-developing pregnancies. Extra-uterine pregnancies were registered in 10 (11.1%) observations.

When analyzing the structure of reproductive organ diseases, a significantly higher rate (60.0% vs. 26.7%) of inflammatory disorders (colpitis, adnexitis, endometritis) and surgeries (intrauterine manipulations) was found in the treatment group as compared with the control group ($p<0.05$).

Patients with the history of EP had separate diagnostic uterine curettage that is four times that of the control group - 51(56.7%) vs. 4 (13.3%), respectively ($p<0.01$). It was shown that the risk of EP is significantly higher for women with IDGO (RR=2.25; OR=4.13; 95% CI 1.21-4.17), with a sensitivity of 87% and specificity of 38%. The presence of inflammatory process was confirmed as indirect signs of chronic endometrium such as lymphoplasmacytic leucocyte infiltration in the stroma of newly found and recurrent glandular-fibrous polyp, which was found in 90.5% of observations (Melnikova, 2015).

In contrast to the control group, 30 (33.3%) patients with EP also developed a pronounced inflammatory uterine process. Since the uterine cervix forms the first barrier for the ascending infection, the analyzed results of separate cervical canal and uterine cavity bacteriological study showed a higher incidence rate of genital tract infection in patients with EP (group 1) with no significant difference between the urogenital infectious agents found in the cervical canal and uterine cavity. Gardnerella *vaginalis*, U. *parvum*, and U. *urealyticum* (22-38%) were found in most cases ($p<0.05$). The incidence rate of other types of Ureaplasma and Mycoplasma did not exceed 5-10%, whereas HPV 16, 33, 35 and 45, Cytomegalovirus and Candida fungi were revealed in 2-4% of the examined patients. 2-3-component associations were formed.

Humoral immunity values were examined locally (uterine cavity). Patients with EP had the greatest increase in basic immunoglobulin titers (IgA 0.15 mg/ml, sIgA 0.09 mg/ml, IgG 0.41 mg/ml, IgM 0.mg/ml, sc 0.25 mg/ml). Lower immunoglobulin concentrations were found in the control group (IgA 0.05 mg/ml, sIgA 0.06 mg/ml, IgG 0.12 mg/ml, IgM 0.03 mg/ml, sc 0.04 mg/ml).

In patients with EP, mean concentrations of immunoglobulins in the uterine aspirate were 2-6 times higher as compared to the control group (p 0.02 to <0.001). This is probably associated with a higher infectious load in EP patients that initiates the activation of local humoral immunity.

The persistent inflammatory process activates local immune mechanisms such as an increase in CD56+, CD^{16+} killer cells, decrease in T-suppressors (CD^{8+}), dysbalance between proinflammatory (L-1, LL-6, IFN-y) and regulatory (LL-4, IL-10) cytokines and increase in $HLA\text{-}DR^{+}$.

According to O. V. Lysenko, dysfunction of the local immune system was found during the evaluation of Il-4 and TNF-1α levels, and a decrease in Fas-dependent apoptosis in the uterine aspirate in the presence of hyperplastic endometrium and EP (Lysenko and Zanko, 2011).

Morphological study of remote polyps showed that all polyps (90) in the treatment group were fibro-glandular, 56 of them were fibrous-glandular, 11 – indifferent, 12 – mixed (retrogressive and indifferent) and 11 – basal (hyperplastic).

These polyps have a typical histological feature such as the prevalence of the stromal component over the glandular one.

20 patients (without EP) had atrophic postmenopausal endometrium with rare simple tubular glands lined with cylindrical epithelium. Endometrioid stroma was found among glands (Figure 1). No immunopositive reaction was observed in atrophic endometrial tissue element (neither stroma nor glandular epithelium) when performing immunohistochemical analysis with HIF-1α monoclonal antibodies (Figure 2).

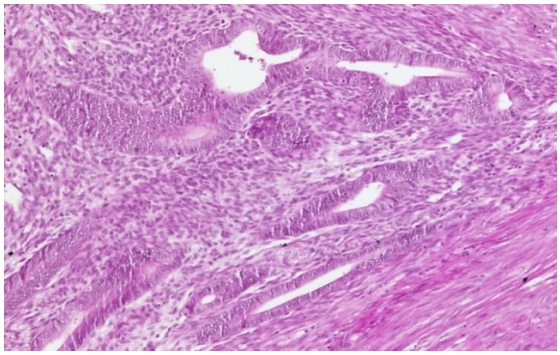

Figure 1. *Atrophic endometrium. Hematoxylin and Eosin (H&E) staining at X 40 magnification*

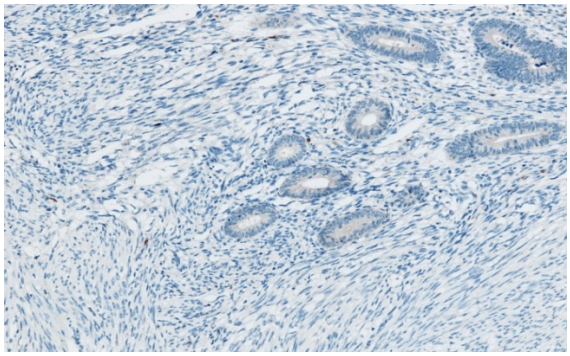

Figure 2. *Immune staining of atrophic endometrium at X 400 magnification*

The figures below (fig. 3, 4, 5) show the results of the morphological and immunohistochemical study with HIF-1α antibody located in polyps. Endometrial fibrous-glandular polyp is depicted in fig. 3. The glands are lined with epithelial cells. The endometrioid stroma is replaced with fibrous tissue containing inflammatory infiltrate, which is mainly represented by lymphoid cells with small lymphocyte morphology. Stromal inflammatory infiltration in polyps is rather diffuse than perivascular.

A fragment of fibrous-glandular endometrial polyp stained with HIF-1α antibodies is presented in fig. 4. The immunohistochemical assay of fibrous-glandular polyps shows a great immunopositive reaction mainly in glandular epithelium cells (both in nuclei and cytoplasms).

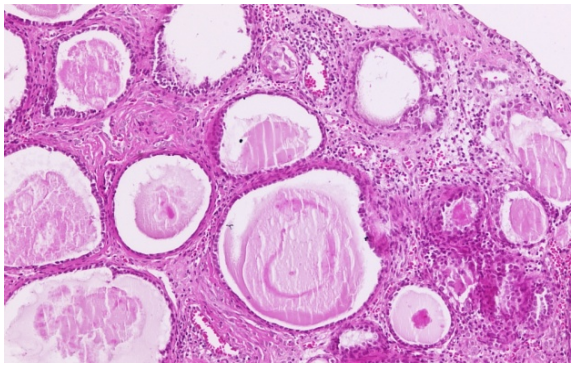

Figure 3. *Fragment of the endometrial fibrous and glandular polyp. H&E staining at X 40 magnification*

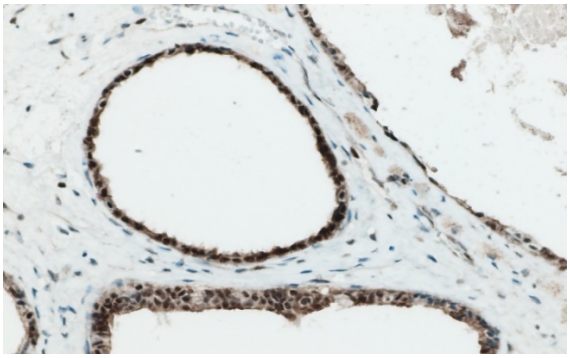

Figure 4. *Immunopositive stainings of polypoid fibrous and glandular fragments of the endometrium (HIF-1α) X 400*

The fragment of the fibrous-glandular polyp with diffuse inflammatory stromal infiltration (58.8%) in fig. 5 demonstrated a high-grade immunopositive reaction in histiocytes with nucleocytoplasmic localization.

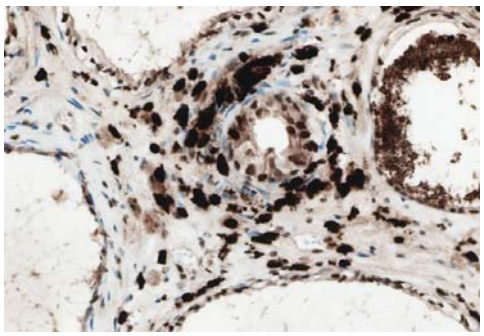

Figure 5. *Polypoid fragment of the fibrous-glandular polyp with the immunopositive reaction of glandular epithelium polyp stromal infiltrate*

Results of qualitative immunohistochemistry comparative analysis indicate HIF-1α expression in glandular epithelium and EP stroma inflammatory infiltration area in postmenopausal women. This indicates

the preserved local biological activity in cells of fibrous-glandular polyps associated with atrophic endometrium. Being a marker of local tissue hypoxia and transcription factor, HIF-1α can, to a certain extent, lead to EP formation. This opinion is confirmed by the high detected expression of receptors to estrogens and progesterone in epithelial cells and stroma and fibrous-glandular polyps during menopause (Kogan *et al*., 2014).

According to Sant Ara de Almedia *et al.*, this fact suggests a higher sensitivity of these structures to steroid hormones enabling autonomous clone proliferation of polyps associated with low estrogen level in surrounding atrophic endometrium (Sant'Ana de Almeida *et al*., 2004; Khuzhokova, 2001).

Increased expression in EP gestagenic membrane receptors (m PR) during postmenopause that are involved in apoptosis inhibition can result in excessive proliferation (Horsburgh *et al.,* 2015).

Interactive sclerosing processes, found in chronic endometritis and accompanied by accumulated products of extracellular matrix and hypoxia, form an optimal condition for the epigenetic changes in the processes regulating proliferation and apoptosis that control endometrial tumor transformation (Thomas, 2008).

Local expression of HIF-1α factor in the area of inflammatory infiltration and glandular epithelium shows that there is a causal relationship between EP and IDGO. Detection of highly expressed Cox-2 associated both with filling up and cancerogenesis in malignant polyps supports the opinion (Giordano *et al.,* 2007). According to N. A. Sheshukova (2012), the risk of EP increases by 10-11 times when chronic endometritis is present.

4. CONCLUSION

The conducted studies show that an aggregate of clinical and anamnestic, metabolic and endocrine inflammatory, immunological changes serving as the background for local hypoxia in epithelial and stromal endometrial cells is present in EP pathogenesis.

It is difficult to exclude that local tissue hypoxia due to long-term influence of unfavorable inflammatory, metabolic-endocrine, and cardiovascular factors in uterine tissues, associated with age-related involutive processes found in this study, can pose a risk of neoplastic transformation.

On the one hand, the activation of HIF-1*a* expression caused by tissue oxygen deficiency is a hypoxic marker; on the other hand, it is one of the basic mechanisms of cancerogenesis. Thus, patients with EP have a high risk of benign lesion transformation into endometrial cancer. Postmenopausal patients with EP must be treated surgically. In our opinion, expectant management is not acceptable.

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