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The proliferation markers in patients with different forms of hyperplastic endometrial processes

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Abstract

Introduction: Endometrial hyperplastic processes (EHP) are characterized by recurrent course, high risk of malignancy, difficulties in diagnosing and predicting the course, which determines their great medical and social significance

Objective: To evaluate the levels of proliferation markers Ki-67 and APRIL in serum of women with various forms of endometrial hyperplastic processes (EHP) and their correlation with clinical and anamnestic features.

Materials and Methods: The study examined 95 women with endometrial hyperplasia and endometrial adenocarcinoma who underwent treatment in the gynecology department "City Clinical Hospital №7» in Zaporizhzhya and "Zaporozhye Regional Clinical Oncology Center". The first group consisted of 32 women with simple endometrial hyperplasia. The second group included 43 patients with complex endometrial hyperplasia. The third group consisted of 22 women with endometrial adenocarcinoma.

Results: The analysis of Ki-67 level revealed an increasing in the patients with simple hyperplasia ($p < 0.05$) and complex hyperplasia of endometrium ($p < 0.05$) compare with control group. The level of the APRIL in serum is increased in group of complex hyperplasia compared with the control group ($p < 0,05$) and simple hyperplasia ($p < 0,05$).

Conclusions: Level of APRIL in serum increased in patients with complex endometrial hyperplasia and endometrial adenocarcinoma. Level of Ki-67 in serum was highest in patients with complex endometrial hyperplasia. We found a significant positive association between Ki-67 levels in serum and thickness of M-echo in endometrium, duration of hyperplastic

endometrial processes anamnesis, between APRIL in serum and age of patients, duration of hyperplastic endometrial processes anamnesis.

Keywords: endometrial hyperplastic processes; biomarkers; proliferation; non-atypical endometrial hyperplasia; atypical endometrial hyperplasia

INTRODUCTION

Endometrial hyperplastic processes (EHP) are characterized by recurrent course, high risk of malignancy, difficulties in diagnosing and predicting the course, which determines their great medical and social significance [1]. To date, many issues of pathogenesis, early diagnosis, treatment and malignant transformation of this pathology remain unresolved, despite the large number of studies in this regard [2]. The structure of EHP in gynecological pathology takes from 20 to 45% [1].

The etiopathogenetic mechanisms of this pathology are insufficiently studied, despite numerous studies on this issue [3, 4]. It is known that in EHP there is intense growth and increased proliferative activity of the glands, against which there is an imbalance between the cells of the stroma and epithelium. It is established that complex mechanisms associated with increased angiogenesis, immunosuppression and high proliferation index play an important role in the pathogenesis of EHP [1]. Given the large number of pathogenetic factors, it is of interest to search for early predictors of EHP malignancy.

The role of endometrial proliferation and increased mitotic activity in the formation of malignant neoplasms has been proven. The expression of the proliferation marker Ki-67 is increased in EHP compared with the normal endometrium, which reflects their precancerous nature [5]. At the same time, in other studies, the proliferative activity and expression of Ki-67 decreased in simple hyperplasia compared with the proliferating endometrium [5, 6]. Therefore, the role of proliferation in the development of EHP and their further malignancy remains debatable [5].

One of the modern perspective biomarkers is ligand inducing proliferation (APRIL). It is the type of membrane protein 2 (N-facing end of the cell), which is expressed by T cells, dendritic cells, monocytes, macrophages. Expression of APRIL is growing in malignant tumors of different localization [7]. According to the Burley Y.D. research was shown the increasing of this marker in the row of normal endometrium, simple hyperplasia, complex hyperplasia [8]. At the same time, the role of APRIL on the proliferation induction at EHP needs further research.

Thus, the determination of levels of Ki-67 and APRIL for diagnosis and prediction of recurrence of EHP is actuality problem.

OBJECTIVE

To evaluate the levels of proliferation markers Ki-67 and APRIL in serum of women with various forms of endometrial hyperplastic processes (EHP) and their correlation with clinical and anamnestic features.

MATERIALS AND METHODS

The study examined 95 women with endometrial hyperplasia and endometrial adenocarcinoma who underwent treatment in the gynecology department "City Clinical Hospital №7» in Zaporizhzhya and "Zaporozhye Regional Clinical Oncology Center". Patients were divided into groups depending on the particular form of endometrial hyperplasia. The first group consisted of 32 women with simple endometrial hyperplasia (SEH) (mean age 37,7 ± 1,42 years). The second group included 43 patients with complex endometrial hyperplasia (CEH) (mean age 39,8 ± 1,39 years). The third group consisted of 22 women with endometrial adenocarcinoma (EA) (mean age 44,3 ± 1,49 years). The control group consisted of 20 women without pathology of the reproductive system. All groups were not significantly differences by age. All patients involved in the study, were investigated by ultrasound on the "MyLab50" ("Esaote", Italy) and videohysteroscopy («Karl Storz», Germany). Levels of Ki-67 and APRIL in serum were determined by ELISA using reagents Elabscience (USA).

Statistical data processing was performed using the statistical software package "Statistica 6.0 for Windows" (StatSoft Inc., № AXXR712D833214FAN5). Differences between indicators considered reliable on condition $p < 0.05$. The indicators are presented as M±m (average mean ± error of the mean) or Me (25-75 ‰) (median, 25 and 75 percentil) depending on the type of distribution. To assess the reliability of the differences between using double t-criterion of Student for independent samples. For groups of uneven distribution of expected non-parametric Mann-Whitney and Wilcoxon. Correlations between parameters were calculated by Pearson and Spearman analysis.

RESEARCH RESULTS

The analysis of Ki-67 level (Table 1) revealed an increasing in the patients with simple hyperplasia ($p < 0.05$) and complex hyperplasia of endometrium ($p < 0.05$) compare with control group. Women with endometrial adenocarcinoma also had significantly higher levels of Ki-67 compared with health women ($p < 0.05$) and patients with simple hyperplasia ($p < 0.05$). There were no significant differences between the groups of complex hyperplasia and adenocarcinoma.

The level of the APRIL in serum (Table. 1) is increased in group of complex hyperplasia compared with the control group ($p < 0,05$) and simple hyperplasia ($p < 0,05$). Women with endometrial adenocarcinoma had significantly higher APRIL levels compared with the control group and patients with both types of endometrial hyperplasia ($p < 0,05$). Significant differences of the APRIL level between the control group and the simple hyperplasia group were not found.

Table 1

Levels of proliferation markers Ki-67 and APRIL in patients with different forms of endometrial hyperplasia

Parameters	Control (n = 20)	Simple hyperplasia (n = 32)	Complex hyperplasia (n = 43)	Endometrial adenocarcinoma (n = 22)
APRIL, pg/ml	36,12 (4,75; 49,23)	38,14 (16,21; 47,65)	63,81* (24,37; 68,24)	89,21# (27,82; 98,34)
Ki-67, ng/ml	32,58 (21,21; 49,68)	62,82○ (27,24; 74,42)	84,08* (43,89, 121,16)	69,25○ (24,16; 82,36)

Note:

* - significant differences with the control group and the group of simple hyperplasia ($p < 0,05$);

- significant differences with all groups ($p < 0,05$);

○ - significant differences with the control group ($p < 0,05$).

A correlation analysis of proliferation markers and morpho-functional parameters (*table 2*) in women with hyperplastic endometrial processes revealed a significant positive association between Ki-67 levels and thickness of M-echo in endometrium (+0,54; $p<0,05$). Level of APRIL in serum showed a tendency to positive association with M-echo in endometrium (+0, 22; $p<0,05$), but this correlation is not significant.

Correlation analyses of proliferation markers and clinical-anamnestic parameters showed positive correlation between level of Ki-67 in serum and duration of hyperplastic endometrial processes anamnesis (+0,39; $p<0,05$). Level of APRIL in serum had a significant positive correlation with age of patients (+0,47; $p<0,05$) and duration of hyperplastic endometrial processes anamnesis (+0,43; $p<0,05$)

Table 2

Correlation of Ki-67 and APRIL levels with clinical-anamnestic and morpho-functional parameters

Parameter	Ki-67, ng/ml	APRIL, pg/ml
	r	r
M-echo, mm	+0,54*	+0,22
Age, years	0,16	+0,47*
Duration of hyperplastic endometrial processes anamnesis, years	+0,39*	+0,43*

Note: * - significant correlations between parameters ($p < 0,05$).

DISCUSSION OF RESULTS

Our study showed, that Ki-67 level in serum is the highest in complex hyperplasia group. The level of Ki-67 in this group is higher than in healthy women and simple hyperplasia. The increasing the Ki-67 level in serum in patients with endometrial hyperplasia compared with healthy women can be explained by greater proliferative activity in hyperplastic endometrial processes [5]. Increased expression of Ki-67 in complex hyperplasia compared with simple in our study indicates the important role of proliferation in the formation and progression the hyperplastic endometrial processes. On the other hand, the absence of differences in the level of Ki-67 in the group of patients with complex hyperplasia and adenocarcinoma shows an ambiguous role of proliferation in the process of further malignancy.

In our study was found the increasing the increasing the APRIL levels in a row simple hyperplasia, complex hyperplasia and endometrial adenocarcinoma. But there are no significant differences by APRIL levels in serum between healthy women and simple hyperplasia patients. Therefore, marker APRIL is informative for non-invasive diagnostic of complex endometrial hyperplasia and adenocarcinoma, as well as to differentiate these pathological conditions. The APRIL role in malignancy of hyperplastic endometrial processes was shown in researches of other authors. But in our study it was not very informative to identification patients with simple endometrial hyperplasia.

CONCLUSIONS

1. Level of APRIL in serum increased in patients with complex endometrial hyperplasia and endometrial adenocarcinoma.
2. Level of Ki-67 in serum was highest in patients with complex endometrial hyperplasia.

3. We found a significant positive association between Ki-67 levels in serum and thickness of M-echo in endometrium, duration of hyperplastic endometrial processes anamnesis.

4. We found a significant positive correlation between APRIL in serum and age of patients, duration of hyperplastic endometrial processes anamnesis.

References

1. Trimble C.L. Management of endometrial precancers. Obstet. Gynecol. 2012; 120 (5): 1160-1175. DOI: http://10.1097/AOG.0b013e31826bb121.

2. Korniyenko SM. Optymizatsiya likuvannya hiperplastychnykh protsesiv endometriya v pizn'omu reproduktyvnomMu periodi za dopomohoyu histeroskopichnoyi tekhniky «kholodnoyi petli». Gynecology. 2017; 6 (14): 44-49. DOI: http://dx.doi.org/10.18370/2309-4117.2017.35.44-49. Ukrainian.

3. Vovk IB., Gorban NE., Borisyuk OY. Giperplaziya endometriya (Clinical lecture). Woman's health. 2016; 5: 10-18. Ukrainian.

4. Korniyenko SM. Hiperplastychni protsesy endometriya u zhinok v pizn'omu reproduktyvnomu i premenopauzal'nomu periodi: shcho vplyvaye na retsydyvy. Bulletin of the Social Hygiene and Health Organization of Ukraine. 2017; 2: 39-47. Ukrainian.

5. Arjunan Dr. A., Nilavu Dr.J., Thiriveni Balajji Dr. GS. et al. Expression of Bcl-2 and Ki-67 in Cyclical Endometrium and in Endometrial Hyperplasia - An Analysis. Journal of Dental and Medical Sciences. 2016; 15: 43-49. DOI: 10.9790 / 0853-1504084349.

6. Abike F., Tapisiz OL., Zergeroglu S. et al. PCNA and KI-67 in endometrial hyperplasias and evaluation of the potential of malignancy. Eur. J. Gynaecol. Oncol. 2011; 32. No. 1: 77-80.

7. Daud S., Jalil SS, Griffin M. et al. Endometrial hyperplasia - the dilemma of management remains: a retrospective observational study of 280 women. Eur. J. Obstet. Gynecol. Reprod. Biol. 2011; 159: 172-175. DOI: 10.1016 / j.ejogrb.2011.06.023.

8. Dubrovina SO., Berlim YD. Markery proliferativnoy aktivnosti i angiogeneza u bol'nykh s giperplasticheskimi protsessami endometriya. Reproduction Issues. 2012; (3): 22-27.

Conflict of interest is absent

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