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Features of the Hysteroscopic Picture of the Endometrium in Postmenopausal Women

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Abstract The article studied the hysteroscopic picture and immunohistochemistry in postmenopausal patients with uterine bleeding. All patients underwent therapeutic and diagnostic curettage of the uterine cavity with diagnostic hysteroscopy for the purpose of hemostasis.

Keywords Hysteroscopic, Endometrium, Postmenopausal women, Atypical endometrial hyperplasia

1. Introduction

Uterine bleeding is one of the most common reasons for visiting a gynecologist and performing intrauterine interventions [6]. Uterine bleeding is mostly based on hyperplastic processes of the endometrium [8]. As is known, endometrial hyperplasia and uterine bleeding account for 5 to 25% in gynecological pathology, and it is a medical and social problem due to the high incidence of relapses and the possibility of malignancy [1,2,3]. Despite the improvement of treatment methods, in recent years there has been an increase in the incidence of endometrial hyperplastic diseases, which is associated with an increase in the number of women suffering from metabolic disorders, an increase in the number of chronic somatic pathology, a decrease in immunity, as well as an unfavorable environment, and an increase in life expectancy.

If at a reproductive age the doctor makes efforts to preserve the uterus in patients even with atypical endometrial hyperplasia, then, as you know, radical treatment is preferable in old age. However, due to the presence of a number of contraindications to surgical treatment, usually available at this age, a properly selected conservative therapy is a treatment option.

However, most authors report that the use of hormone therapy is ineffective in about every fifth patient, a partial response was recorded from 8% to 20%, disease progression was recorded up to 3%, relapse was recorded up to 33% of cases [4,5,7,8].

Until now the question of the risk of malignant transformation of hyperplastic endometrium remains open. According to studies, the degree of risk of malignancy of various types of endometrial hyperplasia is determined by the morphological state of the endometrium. Thus, the frequency of malignancy of simple endometrial hyperplasia, according to different authors, is only 2-5% [10]. The risk of progression of complex atypical hyperplasia to invasive cancer is 47% [9].

It is traditionally believed that the leading role in the development of endometrial hyperplasia belongs to unbalanced estrogen stimulation. However, research data on the possibility of developing endometrial hyperplasia in the absence of hormonal disorders testify in favor of the presence of other mechanisms for the formation of endometrial hyperplasia associated with local dysregulation of cell proliferation [11].

The ambiguity of individual pathogenetic mechanisms, the presence of contraindications for hormonal therapy, the recurrent course of the disease, the often negative attitude of patients to hormonal therapy and radical surgical methods of treatment, as well as the organ-preserving direction in modern medicine necessitates an in-depth study of the pathogenesis of uterine bleeding in any age period of a woman's life [10].

In turn, the proliferative activity of the endometrium is assigned a leading role in the mechanism of malignant transformation [4]. In this regard, the study of markers of proliferative activity is of certain scientific and practical interest, which will allow predicting possible malignancy, as well as choosing a rational method of treating postmenopausal patients with uterine bleeding (UB).

Purpose of the study. To study the hysteroscopic picture and immunohistochemistry in postmenopausal patients with uterine bleeding.

2. Materials and Methods

We studied the clinical and laboratory data of 53 patients admitted to the gynecological department of Republican

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Specialized Scientific and Practical Medical Center for Obstetrics and Gynecology in the years between 2019 and 2021, with complaints of uterine bleeding in the postmenopausal period of life. The average age of the patients was 66.5±8.2 years, the duration of menopause ranged from 5 to 10 years, on average 7.2±3.3 years.

All patients underwent therapeutic and diagnostic curettage of the uterine cavity with diagnostic hysteroscopy for the purpose of hemostasis. Currently the leading method for diagnosing intrauterine pathology is hysteroscopy. Taking into account the literature data and our own results, curettage of the uterine cavity was performed against the background of antibiotic therapy, as well as with the addition of anti-inflammatory, desensitizing, and antianemic treatment to the therapy.

The hysteroscopic picture of the endometrium varied depending on the nature and volume of uterine bleeding. The endometrium was thickened, in the form of folds of various heights of a pale pink color. The endometrium is represented by numerous folds of the mucosal surface with a wide base with uneven edges in the form of ridges 10 to 15 mm high. A pronounced vascular pattern was determined. The hue of the folds was determined from pale pink to bright red. Changes in the flow and pressure of the injected fluid changed the rate of movement of the mucous membrane. Focal lesions of the mucosa were registered; the orifices of the fallopian tubes were visualized.

Thickening and swelling of the mucous membrane of a pale pink color in the form of numerous folds of various heights, in the form of polypoid growths, the presence of a large number of gland ducts, the undulating movement of the endometrium with a change in the rate of fluid flow into the uterine cavity - the phenomenon of "underwater plants" was detected a little less than in most patients - 41 (77.4%). In some patients, these pictures were found to have endometrial polyps in combination with fragments of endometrium that did not slough off - 18 (22.6%). In 10 (18.9%) patients, the hysteroscopic picture was characterized by the presence of a thin pale endometrium with small hemorrhages in separate areas, the presence of individual fringed patches of pale pink mucosa mainly in the area of the uterine fundus and tubal angles. This hysteroscopic picture occurred among patients with mainly prolonged uterine bleeding.

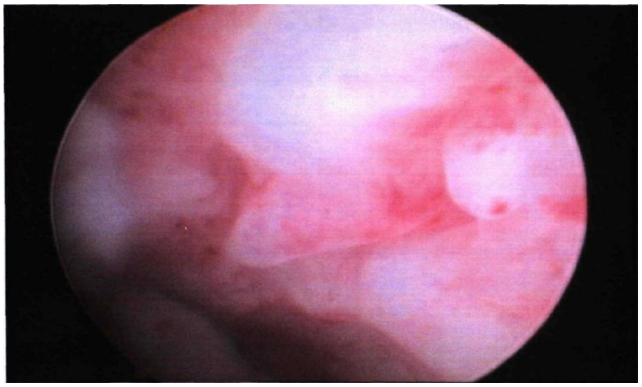

Figure 1. Hysteroscopic picture of endometrial hypertrophy

3. Results of the Study

The study of the morphology of scrapings of the uterine cavity showed the following distribution according to histological diagnoses:

1. simple endometrial hyperplasia, n=23 (43.4%);
2. atypical endometrial hyperplasia, n = 18 (34%);
3. endometrioid carcinoma, n=12 (22.6%).

In 23 patients, simple endometrial hyperplasia was histologically verified. In the study medications, there was an absence of separation of the endometrium into compact and spongy layers (Fig. 2). Also, there was no regularity in the distribution of glands in the stroma. Numerous glands of various shapes and sizes are unevenly distributed in the stroma, in separate areas with weakly expressed folds in the direction of the lumen of the glands. There were cystic enlarged glands and unevenly distributed in the stroma, some glands were cystically distended.

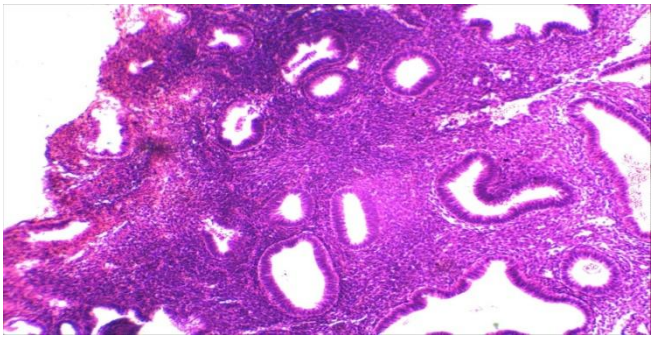

Figure 2. Simple endometrial hyperplasia. The epithelium of the glands is prismatic, falsely multinucleated due to the location of the nuclei at different levels in endometrial hyperplasia. Stained with hematoxylin-eosin. 10 x 40

The epithelium of the glands is prismatic, the apical edge is even, falsely multinucleated due to the location of the nuclei at different levels, there are many mitoses.

The result of long-term exposure to a small amount of estrogen is manifested by the development of glandular cystic hyperplasia with a large number of dilated tubular glands formed by cuboidal and prismatic epithelium. Chronic endometritis was histologically verified in 80.0% of the examined patients.

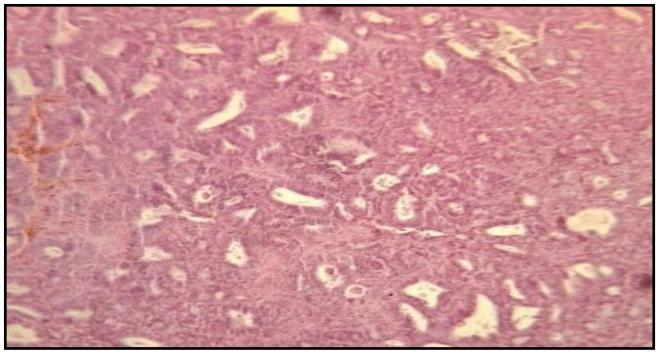

Figure 3. Histological examination. Atypical endometrial hyperplasia. Staining: Hematoxylin eosin 10x10

For atypical endometrial hyperplasia (AEH), in our

study, 18 patients with AEH were diagnosed with a predominance of the glandular component over the stromal component, with a more pronounced and intense proliferation of the glandular epithelium with signs of atypia (Figure 3).

The endometrial glands are in large numbers, located close to each other, i.e. compact, the latter of a bizarre and branched appearance.

The basal membrane of the endometrial glands is preserved, they have a narrow layer of connective tissue with fibroblast-like cells, despite their close location "back to back". Some endometrial glands have finger-shaped intussusceptions protruding into their lumen of the glands.

The epithelium of the glands is single-row, sometimes it is multi-row in nature with signs of polarity disturbance, i.e. radial arrangement of cells in relation to the basement membrane.

Endometrium in adenocarcinoma (EC), in our study, 12 patients with EC were verified, has a different degree of structural rearrangement of the endometrium, consists of numerous glandular structures of variable shape, including glandular, tubular, papillary structures, depending on the degree of differentiation of the tumor process (Figure 4).

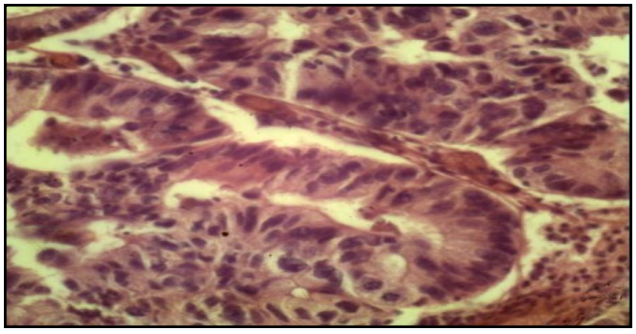

Figure 4. Histological examination. endometrioid carcinoma. Staining: Hemotaxillin eosin 10x10

Differentiation of the malignant tumor process of the endometrium depends on the degree of tissue and cellular atypism.

Tissue atypism depends on the ratio of glandular and solid structures of the endometrium in the tumor tissue, cellular atypism depends on the severity of atypical mitotic activity in the glandular epithelium and distinguish between high-, moderate- and low-differentiated endometrial adenocarcinoma.

The presented tumor tissue of the endometrium consists of numerous endometrial glands among a small content of solid areas.

The endometrial glands are expelled by atypical single- and multi-row glandular epithelium, with a moderately pronounced atypical proliferative activity, nuclear hyperchromia, an increase in the nuclear-cytoplasmic ratio, and also with the presence of atypical nuclear mitoses.

These morphological changes in the tumor tissue of the endometrium testify in favor of a moderately differentiated endometrial adenocarcinoma, while in a highly differentiated endometrial adenocarcinoma, areas of a solid structure are rarely observed, atypia of the nuclei of the glandular epithelium is weakly pronounced.

With poorly differentiated endometrial adenocarcinoma, the tumor tissue mainly consists of solid areas with severe atypia of the nuclei of tumor cells.

Along with the histological parameters of the endometrium, we also studied the immunohistochemical changes in patients with uterine bleeding and endometrial hyperplasia in postmenopausal patients. The following markers of endometrial proliferative activity were studied: p53, Ki67, as well as an inflammation marker - CD138.

In the majority of patients with AEH 14 (77.8±9.8%), the p53 marker was verified with low expression compared to the group with endometrial hyperplasia EH, $p<0.001$.

Table 1. Comparative characteristics of p53 indicators in postmenopausal patients with uterine bleeding

Histology of scrapes	Negative expression	Low expression	Medium expression	High expression
EH, **n=23**	-	5(21.7±8.6)	10(43.5±5.5) **	8(34.8%±9,9)
AEH, **n =18**	-	14(77,8±9.8) ***	4(22.2±9.8)	-
EC, **n=12**	-	4(33.3±13.6)	8(66.7±13.6)	-

*Note: ***- p<0.001-significance of differences between the group with EH and AEH;*
*** - p<0.005 - significance of differences between the group with EH and AEH;*

Table 2. Comparative characteristics of Ki67 indicators in postmenopausal patients with uterine bleeding

Histology of scrapes	Negative expression	Low expression	Medium expression	High expression
EH **n=23**	8(1.8.4±81%)	-	15(65.2±9.9%)	-
AEH **n =18**	-	4(22.2±9.8%)	5(27.8±12.9%)*	9(50.0±11.8%)
EC **n=12**	-	1(8.3±7.96%)	1(8.3±7.96%)	10(83.4±10.7%) ^

*Note: *-p<0.05 - significance of differences between the group with EH and AEH;*
^-p<0.05 - significance of differences between the group with AEH and EC.

Table 3. Comparative characteristics of CD138 indicators in postmenopausal patients with uterine bleeding

Histology of scrapes	Negative expression	Low expression	Medium expression	High expression
EH, **n=23**	4(17.4 ±7,9%)	4(17.4±7.9%)	-	15(65.2±9.8%)
AEH, **n=18**	-	6(33.3±11.1%)	4(22.2±9.8%)	8(44.5±14.2%)
EC, **n=12**	-	5(47.1±14.4%)	7(58.3±14.2%)*	-

*Note: *-p<0.05, **-p<0.005 - significance of differences between the group of AEH and EC*

Comparative analysis of p53 protein expression revealed that high levels of apoptosis protein expression were diagnosed in every third patient with simple endometrial hyperplasia - 8(34.8±9.9%) (Table 1). In addition, approximately 2 times more EH patients had mean p53 expression values compared to the AEH group, p<0.005.

High levels of this marker were absent in AEH and EC.

Thus, from the IHC (Immunohistochemistry) study of scrapings from the uterine cavity of patients with uterine bleeding, it follows that significantly high Ki67 values are observed in endometrioid carcinoma (Table 2).

When comparing the indicators of the Ki67 marker with high expression in patients with atypical endometrial hyperplasia 9 (50.0 ± 11.8%)– and endometrioid carcinoma - 10 (83.4 ± 10.7%), a significant difference was revealed, p <0.05 (Table 3).

In simple hyperplasia, cells containing Ki67 with an average expression were absent in all examined patients. While every 5th patient - 4 (20%) was verified negative for Ki67, none of the patients with atypical hyperplasia and endometrioid carcinoma was found to be negative for Ki67.

Whereas in endometrioid carcinoma, the CD138 marker of high expression was not verified immunohistochemically in any of the patients. This is due to the fact that almost all cells in this group of patients are affected by a malignant process.

4. Conclusions

The study of correlations between the studied indicators of the proliferative activity of endometrial cell populations in postmenopausal women with uterine bleeding in relation to each of the diagnosed endometrial pathologies showed the following.

In the group of patients with simple endometrial hyperplasia, a significant positive correlation was found between the indices of CD138, an inflammatory marker, with this pathology of the endometrium (r = 0.73; p<0.05).

The results of the study also showed a correlation between CD138, an inflammatory marker, and the presence of endometrioid carcinoma (r=0.87; p<0.05). Also, a positive correlation was noted between p53 and simple endometrial hyperplasia r=0.76 and endometrioid carcinoma r=0.75.

A significant positive correlation of the proliferation marker Ki 67 - r=0.86 is observed in endometrioid carcinoma, as well as in simple endometrial hyperplasia - r=0.62. As for endometrial hyperplasia with atypia, all three markers showed the absence of any correlation – r=0.0; r=0.13; r=-0.12.

The results of this section of the study indicate a rather high sensitivity of both CD138 - 78% and Ki67 - 83% in the diagnosis of endometrial pathology in postmenopausal women [RI 91.17-97.95].

The study of these markers of the proliferative activity of endometrial cell populations enables to use them with a high degree of probability in the diagnosis and choice of tactics for the treatment of uterine bleeding in the postmenopausal period.

All patients with atypical hyperplasia and endometrioid carcinoma were sent for a consultation with an oncogynecologist for surgical treatment.

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