MORPHOLOGICAL FEATURES OF EPITHELIAL-STROMAL RELATIONSHIPS IN ENDOMETRIAL GLANDULAR HYPERPLASIA

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Abstract. Alterations in the epithelial-stromal relationships in the uterine mucosa contribute to the development of various types of endometrial hyperplasia and endometrial intraepithelial neoplasia. The pathological processes studied differ from each other in the ratio between the endometrial parenchyma and stroma. Simple endometrial hyperplasia (EH) and complex endometrial hyperplasia (EH) are characterized by a predominance of the stromal component of the endometrium over the parenchymal component.

Keywords: morphology, hyperplasia, endometrium, neoplasia.

Relevance. Endometrial hyperplasia (EH) is a pathological change in the structure and function of the uterine mucosa caused by an imbalance between proliferation and apoptosis in the epithelial and stromal components of the endometrium. There are four histological types of endometrial hyperplasia: simple endometrial hyperplasia (SEH), complex (complex, adenomatous) endometrial hyperplasia (CGE), simple atypical endometrial hyperplasia (SAGE), and complex (complex) atypical endometrial hyperplasia (CAGE) (1,3,5,7). In the structure of gynecological pathology, EH accounts for 10 to 50%, and the incidence is steadily increasing (). EH is most often detected in women aged 45-55 years (2,4,6,8). EH is characterized by a tendency to a long-term recurrent course, against which malignant lesions of the uterine mucosa may develop, especially in the absence of treatment. It has been proven that endometrioid adenocarcinoma (EA) develops in 80% of patients with endometrial hyperplasia. The frequency of malignancy varies from 3% with SEH to 29% with CAGE; Malignancy occurs more frequently in postmenopause (1,9,10).

Diagnosing various histological variants of endometrial hyperplasia presents certain difficulties due to the lack of objective morphological criteria for verifying its various forms (). Some argue that the WHO classification does not fully reflect current understanding of the clinical and morphological features of precancerous lesions and endometrial cancer (2,11). The authors concluded that it is necessary to introduce a

simplified histological classification of endometrial hyperplasia compared to the WHO classification. The essence of the changes lies in combining simple endometrial hyperplasia and complex endometrial hyperplasia into a single group called "endometrial hyperplasia," and simple and complex atypical endometrial hyperplasia into a group designated as endometrial and intraepithelial neoplasia (EIN). For objective diagnosis, the authors propose using quantitative criteria obtained using computer morphometry (CM) methods. The primary diagnostic criterion was a change in the parenchymal-stromal ratio in the endometrium. In their study, the authors demonstrated that the morphometric parameters (MPs) of the parenchymal-stromal ratio they established, characteristic of endometrial insufficiency, have significant prognostic value in addition to diagnostic ones (3,12,13).

It should be noted that studies devoted to the study of endometrial hyperplasia (EH) specifically examine parenchymal-stromal relationships (1,14). However, it is known that the parenchymal component of the endometrium is represented by the uterine gland, consisting of the epithelium and lumen of the gland, and that one of the determining factors for the normal functioning of the endometrium is the epithelial-stromal relationship in the uterine mucosa. These relationships influence the metabolism and innervation of the endometrium, its capacity for physiological repair in the form of restitution, and the formation of the receptor apparatus of the glandular epithelium (). Therefore, it is obvious that any changes in these structural and functional relationships can lead to various abnormalities, including endometrial hyperplasia (EH). In some cases, these changes may not carry the potential for tumor transformation, while in others, the progression of pathological changes is the basis for malignant growth. However, the subtle mechanisms of these processes remain poorly understood. Currently, researchers attribute significant significance to regulators of proliferation and apoptosis in the pathogenesis of endometrial hyperplasia, particularly to the tumor suppressor gene PTEN, as the protein product of the PTEN gene is known to be involved in the regulation of the cell cycle and apoptosis. It signals the cell to cease division and promotes its entry into apoptosis. Thus, the PTEN gene protein appears to exert a suppressive function on cell proliferation. Inactivation of this function can lead to uncontrolled cell growth and tumor development. However, research opinions on the relationship between changes in PTEN gene activity in endometrial hyperplasia and the activity of important proteins regulating proliferation, particularly K1-67, are controversial. Some studies have shown that as the severity of the pathological process in the endometrium increases, the frequency of mutations in the tumor growth suppressor gene (PTEN) increases (2). Other researchers have noted

no significant differences in this indicator between endometrial hyperplasia without glandular epithelial atypia and atypical endometrial hyperplasia (15). Along with reports of increased endometrial proliferative activity in atypical endometrial hyperplasia (1), many researchers have noted a decrease in proliferation in the uterine mucosa, as in typical endometrial hyperplasia (2).

It is becoming clear that only a comprehensive study of various aspects of endometrial hyperplasia, including both traditional histological techniques and extensive morphometric and statistical methods, will provide an understanding of the underlying processes of endometrial hyperplasia development.

Objective of the study. To study the morphological features of epithelial-stromal relationships in various histological variants of endometrial hyperplasia.

Materials and methods. The study was performed using endometrial scrapings (60 patients) and uterine cysts (41) from 101 women aged 27 to 72 years with verified diagnoses of simple endometrial hyperplasia and complex endometrial hyperplasia. Exclusion criteria included previous hormonal therapy and type P endometrial carcinomas. Scrapings from women without endometrial pathology in the late proliferative phase, who were undergoing examination prior to intrauterine device (IUD) insertion, served as a comparison group. The groups were divided according to the morphological characteristics of the histological material according to the Classification of Tumors of the Body and Cervical Uterus (WHO, Lyon, 2003). The diagnosis of endometrial insufficiency (EIN) was established based on the morphological characteristics developed by G. Mutter, Endometrial Collaborative Group. Axio Images As software was used to obtain morphometric data. The endometrial structural unit (ESU) defined by N.I. Kondrikov was used as the object of morphometric analysis of structural changes in the endometrium. The areas of the ESU components were calculated: epithelium, gland lumen, the area of the entire gland, and the area of the connective tissue stroma surrounding the endometrial gland. The epithelial-stromal index (ESI), reflecting the expression ratio of these markers in the endometrial epithelium and stroma, was used to assess epithelial-stromal relationships. The degree of structural changes in the parenchymal and stromal components in the endometrium was measured by the ratio of the relative areas of the endometrial glands and surrounding stroma—the glandular-stromal ratio (GSR), the ratio between the glandular epithelium and stroma—the epithelial-stromal ratio (ESS), and the ratio of the lumen of the glands to the stroma (RSR). Results and discussion. The morphometric study revealed that in the normal endometrium during the proliferative phase, the

stroma predominates over the parenchyma: the relative stromal area is 68.98±3.5%, the endometrial gland area is 31.02±1.6%, and the gland-to-stromal ratio (GSR) is 0.45 ($p<0.05$). The parenchymal component of the endometrium is known to be the uterine gland, consisting of the epithelium and the lumen of the gland. Normally, the relative epithelial area is 23.29±1.2%, which is significantly greater than the relative lumen area of the glands, which is 7.73±0.4%. The ratio between the epithelial and stromal components in normal endometrium at the late proliferative stage (epithelial-stromal ratio, ESS) is 0.34, while the lumen-stromal ratio (LSR) is 0.11.

Immunohistochemical analysis reliably ($p < 0.05$) established that glandular epithelial proliferation is significantly higher than stromal cell proliferation. This is evidenced by the high expression level of the proliferation marker K1-67 in the epithelium of endometrial glands at the late proliferative stage, which is 68.75 ± 3.5%; in the stroma of normal endometrium, K1-67 expression is 10.25 ± 0.5%. The epithelial-stromal proliferation index for the K1-67 marker (ESI K1-67) is normally 6.71.

The epithelium of the glands of a normal endometrium consists of PTEN-positive cells. This is evidenced by 100% expression of the tumor marker PTEN in the epithelium of the endometrial glands during the late proliferative phase of the uterine menstrual cycle. In the stroma of a normal endometrium, the content of PTEN-positive cells is lower, at 65±3.3% ($p<0.05$).

The ESI value of PTEN in the endometrium during the late proliferative phase is 1.54.

Unlike the norm, histological variants of HE without epithelial atypia are characterized by changes in the endometrial architecture. While the glands of normal endometrium in the late proliferative stage are relatively monomorphic, convoluted, and sometimes corkscrew-shaped, with the longitudinal axis oriented from the myometrium to the endometrial surface, simple endometrial hyperplasia is characterized by numerous, unevenly distributed glands of varying shape and size, including cystic dilated ones. In some areas of the glands, faint folds are visible in the direction of the glandular lumen.

The glandular epithelium differs little structurally from the epithelium of endometrial glands in the proliferative stage. The cells of the glandular epithelium have oval, dark-stained nuclei, basophilic cytoplasm, and are usually free of secretions, with occasional mitoses. Along with individual cells of the uterine epithelium of indifferent and proliferative types, tubal epithelial cells, clear, pin-shaped, and extrusive cells, are also present. In cystic-dilated glands, the epithelium is predominantly single-row, cylindrical or flattened, and mitoses are absent.

Morphological evaluation of histological specimens with simple HE suggests a predominance of glands over stroma. However, our morphometric results indicate the opposite: the relative area of endometrial parenchyma in simple HE is 26.28±1.3%, while that of stroma is 73.72±3.7% ($p<0.05$). The gland-to-stromal ratio (GSR), as normal, is below unity and equals 0.45.

Complex HE differs from simple HE and normal endometrium not only by a clear increase in the number of endometrial glands and a decrease in stroma, but also by a structural reorganization of the glandular component: among numerous glands of varying shapes and sizes, "branching" glands predominate, with folding toward the gland lumen, and a tendency toward a compact arrangement of glands.

The glandular epithelium in complex HE differs little from that in simple HE. Morphometric parameters of complex endometrial hyperplasia (HE) indicate a less significant, but still predominant, stromal component over parenchymal tissue: the relative area of endometrial parenchyma in complex HE is 42.01±2.1%, while that of stroma is 57.99±2.9% ($p<0.05$). The glandular-stromal ratio is also below unity, equal to 0.71.

These changes are underpinned by an increase in the proliferative activity of glandular epithelium in the same sequence, as confirmed by our immunomorphological study, which reliably demonstrated ($p<0.05$) a gradual increase in K1-67 marker expression in epithelium during HE: in simple HE, marker expression is 13.36±0.7%, while in complex HE it is 14.25±0.7%.

Conclusions. A positive correlation exists between changes in the epithelial-stromal ratio in the endometrium and K1-67 expression in the epithelium and stroma of the uterine mucosa in different histological variants of hyperplasia, endometrial intraepithelial neoplasia, and endometrioid adenocarcinoma. Simple hyperplasia is characterized by minimal K1-67 ESI values and reflects an excess of stromal expression over epithelial expression. A progressive increase in the K1-67 ESI value from simple hyperplasia to complex hyperplasia and complex atypical hyperplasia is accompanied by a gradual increase in the epithelial component, with the maximum index value and the greatest increase in the glandular epithelial component observed in endometrial carcinomas.

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