HISTOPATHOLOGICAL DIAGNOSIS CRITERIA IN ENDOMETRIAL HYPERPLASIA

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HISTOPATHOLOGICAL DIAGNOSIS CRITERIA IN ENDOMETRIAL HYPERPLASIA (Abstract**):** Endometrial hyperplasia is a condition of the abnormal proliferative lesions of the endometrium. **Aim**: To highlight the value of histopathological examinations with assessment of the ways to obtain endometrial biopsies and the appreciation of the contribution of different histopathological techniques that can be used to establish a correct and complete diagnosis. **Material and methods:** The study was conducted in a group of 50 patients diagnosed with endometrial hyperplasia. In all cases the bioptic curettage was performed using a curette to obtain more abundant material for the histopathological examination. **Results**: Histopathological diagnosis guides the therapeutic attitude and has an important prognostic value. The study group was characterized by histoarchitectonic heterogeneity, presented even in the same case. Histoarchitectonic and cytological changes differentiate endometrial hyperplasia from physiological proliferative endometrium. **Conclusions**: The diagnosis of certainty between the four types of endometrial proliferation established by the WHO can only be done through the histopathological examination. **Keywords:** HISTOPATHOLOGICAL EXAMINATION, ENDOMETRIUM, HYPERPLASIA.

In the female genital apparatus, the endometrium undergoes cyclic proliferation, differentiation, degeneration and regeneration, processes regulated by the hypothalamic-pituitary-ovarian axis. The disruption of this cyclical development leads to the occurrence of dysfunctional uterine bleeding, which often has endometrial hyperplasia as morphological substrate.

The endometrial cycle undergoes physiological changes with age. Perimenopause and post menopause affects the endometrial cycle, female gonads and have a systemic impact. Hormonal imbalances also lead to morphological and functional changes in secondary sexual characteristics (1). In this context, the "aging face" phenomenon is accelerated due to the faster loss of subcutaneous supportive adipose layer and a decrease in quality of fibrous connective structures.

Endometrial hyperplasia represents abnormal proliferative lesions of the endometrium, leading to increased mucosal thickness, alterations in glandular architecture and changes in the gland-to-stroma ratio

(2). The lesion is hormone-dependent, and as a result it is reversible, but can progress to an invasive carcinoma in the presence of genetic changes that cause a monoclonal glandular proliferation (3). A category of patients with endometrial proliferation consists of those with a congenital malformation of the uterus. This type of malformation correlates with the concomitant existence of one or more malformations at other levels.

There are two types of hyperplasia, an atypical one, closely related to adenocarcinoma and a nonatypical one, which is little linked with the carcinomatous lesion (4). The notion of simple endometrial hyperplasia refers to nonatypical hyperplasia without glandular architectural abnormalities, whereas complex glandular hyperplasia defines nonatypical hyperplasia with abnormalities of glandular architecture (5). The presence of cytological atypia is the most important factor related to progression to cancer, especially in postmenopausal women (6).

The high degree of morphological variability of endometrial proliferation, even within the same tissue sample, is responsible for the difficulty in defining and establishing clinical and morphological diagnostic criteria. All forms of hyperplasia present certain morphological features showing an increase in gland-to-stroma ratio, irregularities in the shape and the size of the gland.

The macroscopic examination usually reveals an enlarged uterus and, on the hysterectomy specimens the endometrium is pale, diffuse thickened or polyploid, with a smooth, velvety or granular surface (7).

The microscopic examination highlights architectural alterations, characterized by glandular complexity and the amount of stroma that separates the glands, distinguishing simple and complex forms of hyperplasia, regardless of the presence of atypia.

Hyperplasia without atypia represents excessive proliferative response to uncompensated estrogen stimulation. The endometrium responds in a diffuse way with a balanced increase of both glands and stroma (10). *Simple hyperplasia* usually involves the entire endometrium with a diffuse thickening of the endometrium. Microscopically appears glandular proliferation with irregular shapes and sizes, separated by abundant stroma. *Complex hyperplasia* presents a disordered glandular proliferation, to the detriment of the stroma. The endometrial glands are agglomerated with an increase in architectural complexity separated by a relatively reduced stroma, the gland-to-stroma-ratio is 3/1 (8).

Atypical hyperplasia is distinguished from the precedent by cytological atypia of the glandular epithelium, represented by the loss of axial polarity, nuclear pleomorphism that often has irregular contours, prominent nuclei and distinct or dense chromatin. Atypia appears almost always focal.

MATERIAL AND METHODS

The study was conducted in a group of 50 patients aged 24 to 70 years, diagnosed with endometrial hyperplasia admitted to the Iasi "Cuza-Voda" Hospital. All patients underwent comprehensive clinical and laboratory investigations, and the certainty diagnosis was based on the histopathological examination of bioptic curettage or surgical specimens.

The routine general physical examination has been supplemented in many cases with specialized examinations (gastrointes-

tinal, cardiovascular, renal, etc.). In all cases the bioptic curettage was performed with the curette to obtain more abundant material, the practice demonstrating that the aspiration method is a less favorable opinion. The specimens were embedded in paraffin, then special stains were made: hemalums-eosin, tri-color van Gieson, periodic acid-Schiff (PAS) coloring.

RESULTS

The histopathological examination of the collected fragments aims to identify the nuclear changes occurring at the cytological level and to assess the degree of their diffusion.

Approximately 2/3 of the studied cases were identified with simple endometrial hyperplasia. Young women, up to 40 years of age, had heterogeneous histopathological aspects with simple hyperplasia zones with average glandular density; the glands retain their regular contour and circular lumens. In the same cases, it appeared on sections glands with irregularly contoured, even with a corrugated lumen (fig. 1).

Cases which has a high-density gland have an uneven and narrow lumen (fig. 2).

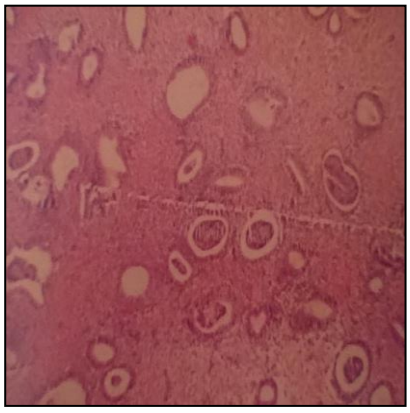

Fig. 1. Simple hyperplasia, regular contour glands and medium frequency; HE 20x

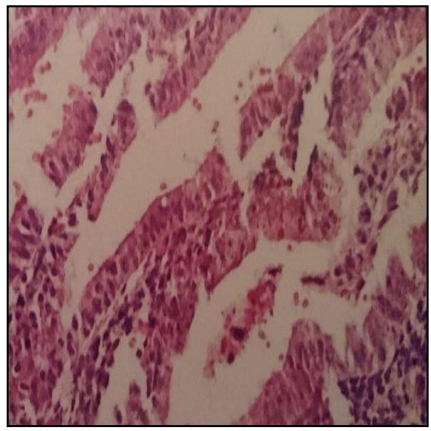

Fig. 2. Endometrium with simple hyperplasia; HE 40x

The endometrial epithelium appears simple, prismatic, tall, with fusiform nuclei perpendicular to the basal membrane (fig. 3). These glands may have endoluminal papillary proliferations.

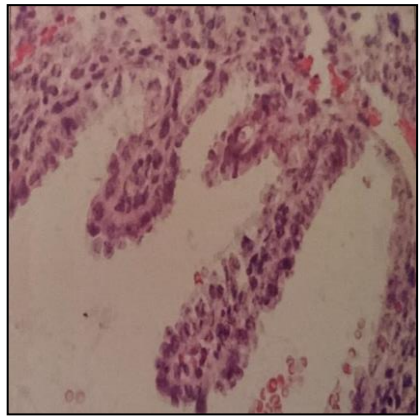

Fig. 3. Endometrium with dilated gland and papillary proliferation; HE 40x

The surface epithelium presents a decrease in height inversely proportional to age. The epithelia of older people have a homogeneous appearance, starting from glands with irregular shape and wide lumen in the premenopausal and going to areas

with regular appearance and narrow lumen in older people. In this situation, intraluminal proliferation persists.

One third of the studied cases had complex hyperplasia. This type of hyperplasia has a characteristic appearance of the glands, arranged back to back and separated by a minimal thickness stroma. Their lumens are extremely irregular due to the significant endoluminal papillary proliferation (fig. 4).

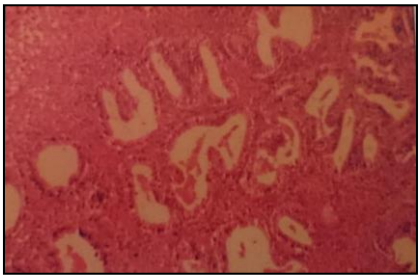

Fig. 4. Complex endometrial hypertrophy, with rare intraluminal proliferation; HE 40x

The glands also exhibit many cystic dilations that give the appearance of heterogeneity. Characteristic of this type of endometrial proliferation is the existence of glandular branches and even intergranular communication.

In both forms of hyperplasia, there is a degree of stromal fibrosis directly proportional to the age of the patient.

DISCUSSION

The importance of this study is revealed by the fact that it is unanimously accepted (9) that simple endometrial hyperplasia may progress to atypical endometrial hyperplasia, the latter being considered precancerous status. In the classic diagnosis of endometrial hyperplasia, the gland-to-stroma ratio is used.

Histopathological diagnosis guides the therapeutic attitude and has an important prognostic value. The study group is characterized by a histoarchitectonic heterogeneity. Characteristic from this point of view are the variety of shapes and glandular diameters and the intraglandular ramifications. The diagnosis of certainty of simple endometrial hyperplasia by the gland-to-stroma ratio should ideally be made between days 10-14 of the physiological endometrial cycle.

Another histopathological criterion of differentiation of the two types of hyperplasia is related to the structure of the gland, which in simple hyperplasia must be tubular, right and without branches. Variations in contour and lumen diameter occur in both types of hyperplasia.

Complex endometrial hyperplasia is histopathological diagnosed, primarily by the loss of individuality of the flanders, with the appearance of intergranular branches and communications. The type of atypical complex proliferation is marked by the existence of papillary proliferations of the glandular epithelium. Also, the epithelium appears arranged in a pseudo-stratified or even stratified form. Complex hyperplasia may present elongated cells with “cane-like” nuclei arranged in narrow bundles. Between stromal cells may be present clear cells, these being lipid-containing macrophages (10).

The presence of nuclear atypia by increase in nuclear volume and change in the nuclear/cytoplasmic ratio with budding of the core, thickening of its membrane, and the coagulation of chromatin are criteria of proliferative atypia. The nucleus migrates to the geometric center of the cell, and the cytoplasm acquires a basophilic appearance. These are malignant or premalignant changes and call into question the differen-

tial diagnosis between endometrial carcinoma and well-differentiated epidermoid carcinoma (11, 12, 13, 14). The histopathological differentiation criteria of the two possible diagnoses refer to the fact that in endometrial carcinoma papillary proliferations are extremely pronounced, with atypical cells and mitosis, and the glands get a cribriform aspect

In neither of these two situations a secretory glandular epithelium was found, no matter the age of the patient.

Another important aspect we watched was the perilesional vascularization. As in other neighboring neoplasms, such as rectal cancer, peritumoral vascular branches acquire characteristic, proliferative aspects of paraneoplastic neovasculogenic (15). These aspects have been noticed by using the PAS reaction to reveal the basal glandular membrane.

CONCLUSIONS

Endometrial hyperplasia is a non-invasive, non-physiological, estrogen-dependent endometrial proliferation. In our study results that histoarchitectonic and cytological changes differentiate endometrial hyperplasia from the physiological proliferative endometrium. The diagnosis of certainty between the four types of endometrial proliferation established by the WHO can only be done through the histopathological examination.

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NEWS

HYPERCHOLESTEROLEMIA – GENETIC DISEASE

Hypercholesterolemia is a common disorder which was reported in 39% of the worlds' adult population in 2008. Most of the patients with familial hypercholesterolemia (FH) have a mutation in the LDLR gene which is dominantly inherited. Mutations in the APOB and PCSK9 genes accounts for a smaller percentage of autosomal dominant FH. This review explored the recent evidence of association of the genetic variants with hypercholesterolemia and the 3 lipid traits: total cholesterol (TC), HDL cholesterol (HDL-C) and LDL-C and the biological effects of these genes in lipid homeostasis. The focus is mainly on the genes with a recognized or a potential role in lipid metabolism for which the association with the serum lipid traits; TC, LDL-C and HDL-C was observed in candidate gene association studies, genome-wide association studies (GWAS), genetic linkage studies and other studies with a case–control design. These include the genes encoding apolipoproteins, lipoprotein receptors and receptor related proteins, lipid transporters and lipid transfer proteins, the enzymes and proteins with a regulatory role in lipoprotein metabolism as well as the proteins that regulate the expression of those genes. The function of these genes in lipid metabolism and the association of single nucleotide variants (SNVs) in these loci with serum lipid traits, are not yet clearly identified. In summary, GWAS and meta-analyses have identified over 190 SNVs associated with serum TC, LDL-C and HDL-C levels in about 60 genes. Fourteen non-synonymous coding variants were identified in 10 genes that accounts for 7% of the variants in lipid related genes described in GWAS. Significant challenges remain. The known genes account for only a proportion of the cases and a substantial amount of missing heritability still exists (Paththinige CS, Sirisena ND, Dissanayake VHW. Genetic determinants of inherited susceptibility to hypercholesterolemia – a comprehensive literature review. *Lipids in Health and Disease* (2017); 16:103).

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