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Histological landmarks for choosing a therapeutic route in patients with overlap syndrome of genital endometriosis and benign breast disease

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Abstract. ***Background.*** *Genital endometriosis (GE) remains a very common disease, occurring in 0.5–5 % of fertile women and in 25–40 % of infertile women. Benign breast diseases (BBD) are common throughout life, from early reproductive age to the postmenopausal period, making them a potential health problem for a large number of women. The histological characteristics of endometrial and breast tissues in patients suffering from the overlap syndrome of GE and BBD are of interest, since this condition carries an increased risk of endometrial, ovarian and breast cancer. The purpose was to study and identify the most characteristic features of endometrioid tissue and ductal hyperplasia tissue of the breast in women with overlap syndrome of GE and BBD using light microscopy.* ***Materials and methods.*** *Histological preparations of endometrioid foci and breast hyperplasia tissues of 148 women with overlap syndrome of GE and BBD were studied. The material was obtained by the method of fine-needle aspiration puncture biopsy, which was performed under ultrasound control. Cytological analysis and microphotography were performed using an Olympus CX23 microscope with different magnifications (×40, ×100 (immersion)).* ***Results.*** *The study showed that in the selected cohort of patients with overlap syndrome of GE and BBD, most histological samples showed proliferative activity of mesothelial cells. At the same time, morphological signs of atypia of cellular elements of atypical ductal hyperplasia were observed in 47.3 % of histological samples of breast tissue. Cells with signs of malignant transformation were not found in any of the provided breast tissue samples. It is important to note that in 15 % of patients, histological signs of malignancy were found in endometrial samples, which led to their immediate referral to a gynecological oncologist for surgical intervention and the necessary adjuvant therapy.* ***Conclusions.*** *In the prognosis of the clinical course of GE and BBD overlap syndrome, histological confirmation of the diagnosis and detection of signs of atypia in biopsy samples play a key role. The finding of atypical cells requires clinical consultation with the participation of a gynecologist, a mammologist and a gynecological oncologist, during which a decision is made regarding surgical intervention and the necessary pharmacotherapy.*

Keywords: *endometriosis; benign breast disease; atypical ductal hyperplasia; overlap syndrome; endometrioid carcinoma; breast cancer; metabolic syndrome; bone metastases*

Introduction

The complex mechanisms of initiation and development of endometrioid foci outside the normally located endometrial tissue continue to be studied by scientists and clinicians in many research institutions and university clinics in different countries [1–4].

Endometriosis is a benign growth of tissue that is morphologically and functionally similar to the endometrium but occurs outside the normally located endometrium [5, 6]. Genital endometriosis (GE) remains a very common disease, occurring in 0.5–5 % of fertile women and in 25–40 % of infertile women [7–9]. In the structure of gynecological

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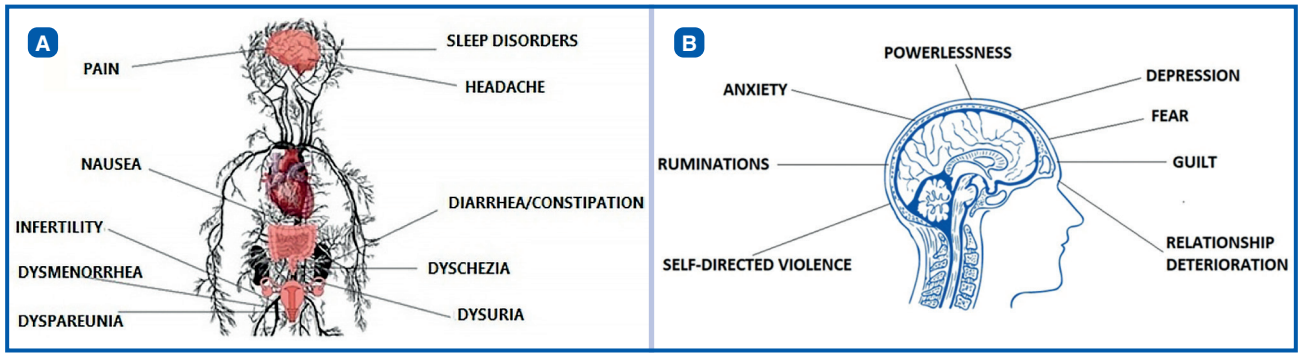

Figure 1. Physical symptoms of endometriosis (A) and mental states which may occur in women who suffer from endometriosis (B) [11]

morbidity, GE firmly occupies the third place after inflammatory diseases and uterine fibroids, leading to significant reproductive disorders, persistent pain syndrome, infertility, dysfunction of adjacent organs and disability in severe cases [10, 11] (Fig. 1).

Benign breast diseases (BBD) are common throughout a woman's life, from early reproductive age to the postmenopausal period, making them a potential health problem for a large number of women [12, 13]. It is well known that hormonal factors, in particular internal reproductive factors, the use of hormonal drugs, as well as lifestyle factors, influence the risk of breast cancer in women, but there are only a limited number of studies with relevant results on the influence of the above-mentioned factors on BBD [14, 15]. It should also be noted that BBD with or without atypia increases the risk of breast cancer (BC) by approximately 4- and 2-fold, respectively [14, 16]. Since BC is the most common oncological disease in women [17], which in 20 % of patients is characterized by the appearance of distant metastases, especially to the bone system [18], oncological vigilance in the management of patients with BBD is clinically justified.

Atypical ductal hyperplasia (ADH) is essentially a preneoplastic lesion of the breast ducts. ADH is most often diagnosed on mammography, which reveals microcalcifications. The incidence of ADH has remained stable since the introduction of population-based screening mammography, accounting for 2–14 % of diagnoses [14, 15, 20]. Histologically, ADH consists of intraductal neoplastic epithelial proliferations that include terminal ductal lobular units with small, round, monomorphic cells with well-defined margins [19, 25]. It is important to hold a consultation of gynecologists and mammologists and decide that patients with ADH with atypia should undergo surgical resection [21–24], as there is a large body of evidence in the literature supporting the feasibility of this scenario [12, 13, 16, 20].

Endometrial lesions, particularly adenomyosis, have been reported to have endometrial glands that extend beyond the uterine mucosa and may be embedded in the myometrial structure surrounded by stromal cells [26]. In cases associated with hyperplasia with or without atypia, stratified glandular epithelium, marked local inflammation, and changes in the nuclear/cytoplasmic ratio may be present [26, 27]. Based on the criteria for atypical endometriosis originally developed by Chernobilsky and Morris (eosinophilic cytoplasm, cell crowding and stratification, large hyperchromatic or pale nuclei with moderate to severe pleomorphism), LaGrenade and Silverberg proposed a new term: reactive atypia or mild atypia with stromal inflammation and epithelial cell regeneration [27, 28].

It is worth noting that mild atypia associated with inflammatory infiltration is the most common; however, severe atypia is relatively rare and corresponds to atypical endometriosis, which is considered as precancerous condition [27, 28]. In atypical endometriosis, secondary inflammatory manifestations or various degenerative changes of cells are observed, which can develop into endometrioid carcinoma [27, 29, 30]. Therefore, taking into account the above, at the current stage in the practice of gynecologists and gynecological oncologists, the histological characteristics of endometrial and breast tissues in patients suffering from the overlap syndrome of GE and BBD are of interest, since this condition carries an increased risk of endometrial cancer [31], ovarian cancer [32] and breast cancer [33].

The purpose was to study and identify the most characteristic features of endometrioid tissue and ductal hyperplasia tissue of the breast in women with overlap syndrome of GE and BBD using light microscopy.

Materials and methods

Histological preparations of endometrioid foci and breast hyperplasia tissues of 148 women with overlap syndrome of GE and BBD were studied. The material for the study was obtained by the method of fine-needle aspiration puncture biopsy (FAPB), which was performed under ultrasound control. Aspirates were applied to glass slides, air-dried and fixed.

To visualize cellular structures, the preparations were stained using the standard May-Grünwald-Giemsa (MGG) method. Cytological analysis and microphotography were performed using an Olympus CX23 microscope with different magnifications (×40, ×100 (immersion)).

The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association "Ethical principles for medical research involving human subjects" (2000).

Results

When studying histological preparations of breast hyperplasia tissues, it was found that in 66 (44.6 %) samples, high cellularity of the sample was observed due to the presence of a significant number of dense fragments of the ductal epithe-

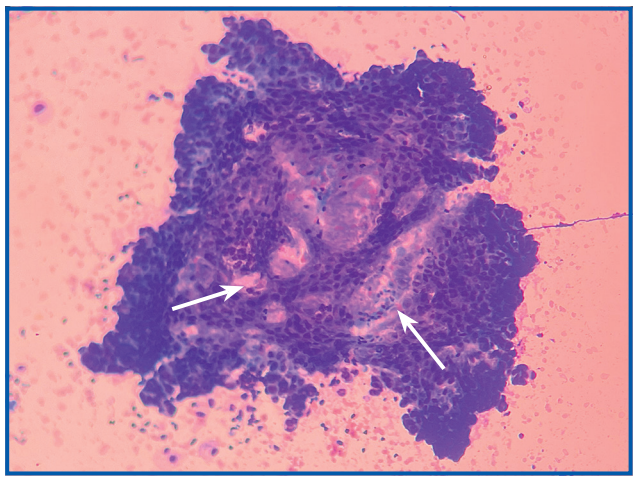

Figure 2. Patient M., age 34. Atypical benign ductal hyperplasia of the breast. High cellularity of the sample. A significant number of dense fragments of the ductal epithelium of cribrous structure, which are characterized by the presence of "stamped" enlightenments (white arrows) and a small number of cells with mild signs of atypia. According to the Yokohama classification, C3 — atypical, probably benign (atypia, probably benign). Staining with MGG, ×20

lium of cribrous structure, which were characterized by the presence of "stamped" enlightenments and a small number of cells with mild signs of atypia (Fig. 2).

The most characteristic histological signs of atypical benign ductal hyperplasia, which were recorded in 89 (59.5 %) samples, were recognized as papillary and pseudopapillary structures, in which the cellular elements are represented by ductal epithelium with signs of hyperplasia (Fig. 3). It should be noted that there were signs of fibrocystic changes, lining epithelium of fibrocystic disease with signs of apocrinization, proliferation and pseudopapillary structure. At the same time, in 70 samples, i.e. almost half (47.3 %) of histological preparations, morphological signs of atypia of cellular elements of atypical ductal hyperplasia were observed: loss of polarity and orderliness of nuclei, leading to their accumulation, dyskaryosis (increase in the size of the nucleus without changing the size of the cytoplasm); micronuclei were also present, indicating increased RNA replication activity. Cells with signs of malignant transformation were not found in any of the breast tissue samples provided.

When studying samples of endometrioid foci in 106 (71.6 %) patients, that is, in the vast majority, the presence of mesothelial cells with signs of proliferation was established,

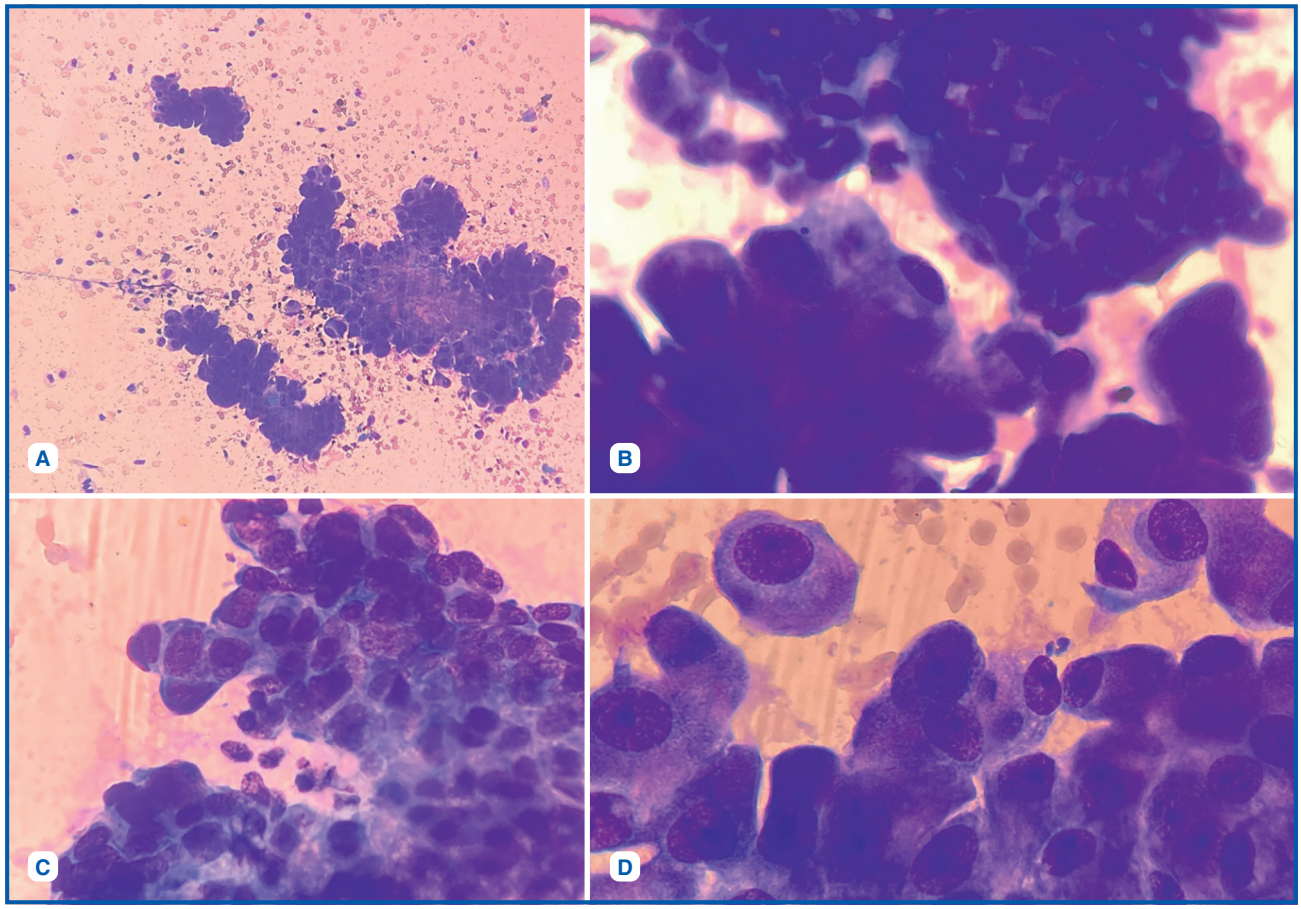

Figure 3. Patient M., age 34. Atypical benign ductal hyperplasia of the breast. Papillary (pseudopapillary) structures are present (A), cellular elements are represented by ductal epithelium with signs of hyperplasia (TAB, MGG staining, ×20). Signs of fibrocystic changes are present (B), lining epithelium of fibrocystic disease with signs of apocrinization, proliferation and pseudopapillary structure (FAPB, MGG staining, ×100). Morphological signs of atypia of cellular elements of atypical ductal hyperplasia are observed: loss of polarity and orderliness of nuclei, which leads to their accumulation (C), dyskaryosis (increase in the size of the nucleus without changing the size of the cytoplasm), micronuclei are present (D), which indicates increased activity of RNA replication (FAPB, MGG staining, ×100)

in histological preparations cells of endometrial origin of cubic shape with eccentrically located hyperchromic nuclei were determined — a characteristic sample is presented in Fig. 4. It is worth noting that in 22 (14.9 %) patients in endometrial samples histological signs of endometrioid carcinoma were found: groups of polymorphic endometrial cells forming papillary and papillary structures, as well as pleomorphic large-sized nuclei of cells with uneven contours of the nuclear membrane, eccentrically located with granular, sometimes vacuolated cytoplasm. It was also possible to clearly see atypical nucleoli against the background of uneven chromatin structure (Fig. 5). The presence of these signs of endometrial tissue malignancy necessitated the immediate referral of patients to a gynecologist-oncologist to determine a further treatment strategy using surgical intervention and conventional pharmacotherapy.

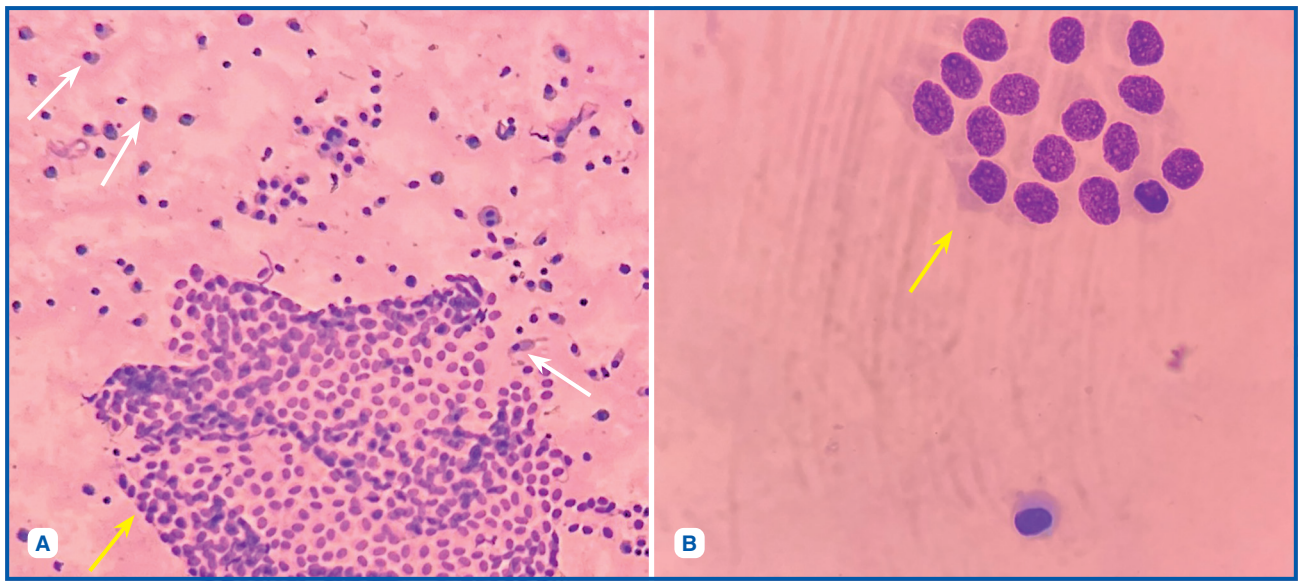

Figure 4. Patient T., age 37. Peritoneal infiltrative endometriosis. In the preparation, against the background of amorphous substance and a layer of mesothelial cells with signs of proliferation (yellow arrow), cubic cells with eccentrically located hyperchromic nuclei, which may be of endometrial origin (white arrows), are identified; A — ascitic fluid, staining with MGG (Diff-Quik), ×20; B — ascitic fluid, staining with MGG (Diff-Quik), ×100

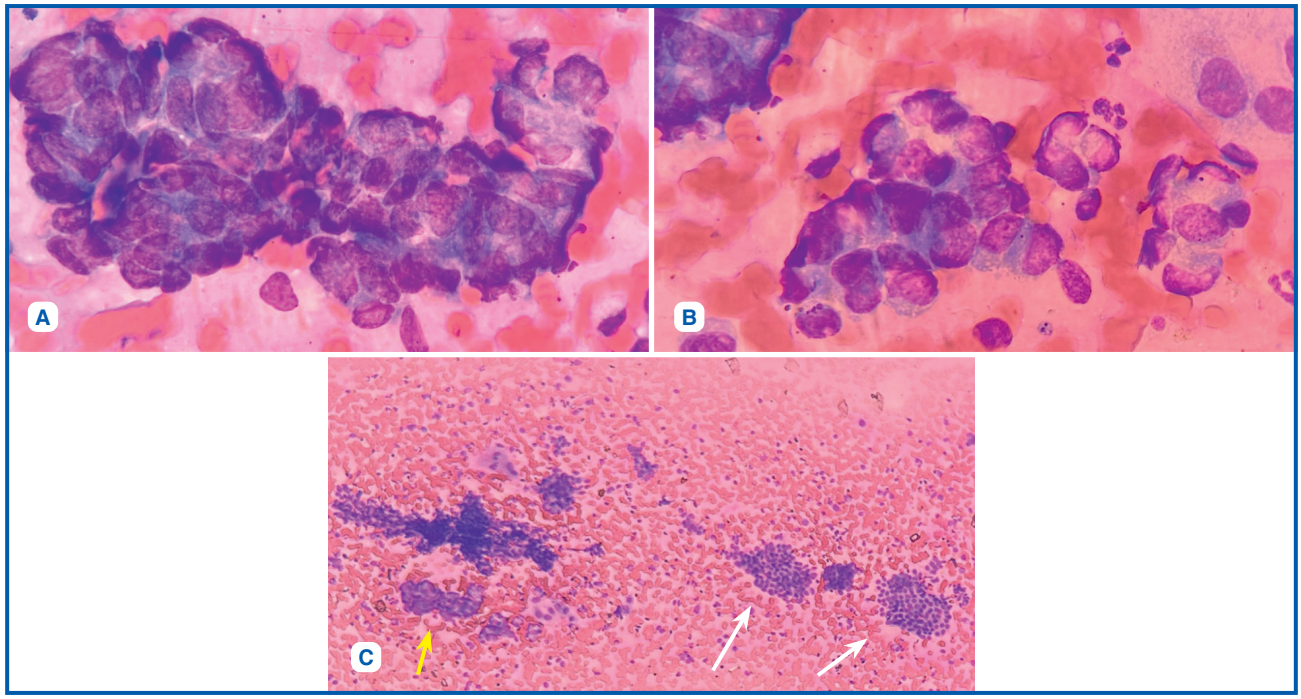

Figure 5. Patient K., age 49. Endometrioid carcinoma of the uterus. The fragment contains groups of polymorphic endometrial cells that form papillary and papillary structures. Pleomorphic large nuclei with uneven contours of the nuclear membrane are eccentrically located with granular, sometimes vacuolated cytoplasm. Atypical nucleoli are clearly visible against the background of uneven chromatin structure; A, B — aspirate from the uterine cavity, MGG staining, ×100. Against the background of atypical endometrial hyperplasia (white arrows), areas of malignant tissue transformation are visualized (yellow arrow); C — aspirate from the uterine cavity, MGG staining, ×20

Discussion

Clinical observations confirm that even after surgical removal of endometriomas, women may persist in chronic pelvic pain, which can be considered as a prognostic factor for possible relapses [12–14, 16]. The question of what the doctor should pay attention to first of all remains debatable: the priority removal of ectopic foci or the reduction of the intensity of endometriosis symptoms in the context of improving the quality of life [13–15, 17].

In the prognosis of the clinical course of both endometriosis and benign hyperplasia of the MH separately, and in the combination of these pathological conditions, histological confirmation of the diagnosis is of crucial importance, and most importantly, the detection of signs of atypia in biopsy samples [16, 21, 40, 41]. After all, the finding of atypical cells requires a clinical consultation with the participation of a gynecologist, a mammologist and a gynecological oncologist, during which a decision is made regarding surgical intervention and the necessary pharmacotherapy [27, 28, 42–44].

It is also important to note that when choosing a therapeutic route for patients, it is necessary to take into account the possible presence of comorbid conditions in them, in particular pathologies of the cardiovascular system, gastrointestinal tract, liver, and also endocrine disorders [45, 46]. For example, the results of studies indicate that the presence of metabolic syndrome and diabetes in patients may worsen the clinical course and the overall prognosis of the disease [47, 48].

Our study showed that in the selected cohort of patients with overlap syndrome of GE and BBD, the vast majority of histological samples showed proliferative activity of mesothelial cells. At the same time, morphological signs of atypia of cellular elements of atypical ductal hyperplasia were observed in 47.3 % of histological samples of breast tissue. Cells with signs of malignant transformation were not found in any of the provided breast tissue samples.

It is important to note that in 15 % of patients, histological signs of malignancy were found in endometrial samples, which led to their immediate referral to a gynecological oncologist for surgical intervention and the necessary adjuvant therapy.

Thus, histological verification of the diagnosis in patients with overlap syndrome of GE and BBD not only provides confidence to the gynecologist, mammologist, and gynecological oncologist in the correctness of the decisions made regarding the treatment strategy, but also provides the opportunity to make an individual prognosis of the clinical course of the disease, in particular, taking into account comorbid conditions and individual characteristics of each patient.

Conclusions

In the prognosis of the clinical course of GE and BBD overlap syndrome, histological confirmation of the diagnosis and detection of signs of atypia in biopsy samples play a key role.

In the vast majority of histological samples of patients with GE and BBD overlap syndrome, proliferative activity of mesothelial cells was present, while morphological signs of atypia were observed in 47.3 % of breast tissue preparations.

Histological signs of malignancy of endometrial tissues were found in 15 % of patients, who were immediately referred to a gynecological oncologist for surgical intervention and the necessary adjuvant therapy.

Prospects for further research. At the next stages of studying the chosen direction, it would be advisable to reveal the topic of different comorbidities in patients with endometriosis and benign breast disease.

Ethical compliance. The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association "Ethical principles for medical research involving human subjects" (2000). All patients gave written informed consent for the collection and processing of clinical material. Participants had the right to withdraw from participation at any time without giving reasons. The data were entered into a database for further analysis in an anonymized form.

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Гістологічні орієнтири для вибору терапевтичного маршруту в пацієнток із перехресним синдромом генітального ендометріозу та доброякісного захворювання молочної залози

Резюме. ***Актуальність.*** Генітальний ендометріоз (ГЕ) залишається дуже поширеним захворюванням, яке зустрічається в 0,5–5 % фертильних та 25–40 % безплідних жінок. Доброякісні захворювання молочної залози (ДЗМЗ) поширені протягом усього життя, від раннього репродуктивного віку до постменопаузального періоду, що робить їх потенційною проблемою для здоров'я великої кількості жінок. Гістологічні характеристики тканин ендометрію та молочної залози в пацієнток, які страждають на перехресний синдром ГЕ та ДЗМЗ, становлять інтерес, оскільки ця патологія несе підвищений ризик раку ендометрія, яєчників і молочної залози. ***Мета:*** вивчити та виявити найбільш характерні особливості ендометріоїдної тканини й тканини гіперплазії проток молочної залози в жінок із перехресним синдромом ГЕ та ДЗМЗ за допомогою світлової мікроскопії. ***Матеріали та методи.*** Досліджено гістологічні препарати ендометріоїдних вогнищ і тканин гіперплазії молочної залози 148 жінок із перехресним синдромом ГЕ та ДЗМЗ. Матеріал був отриманий методом тонкоголкової аспіраційної пункційної біопсії, яку проводили під ультразвуковим контролем. Цитологічний аналіз та мікрофотографування виконували за допомогою мікроскопа Olympus CX23 із різним збільшенням (×40, ×100 (занурення)). ***Результати.*** Дослідження показало, що у відібраній когорті пацієнток із перехресним синдромом ГЕ та ДЗМЗ переважна більшість гістологічних зразків демонстрували проліферативну активність мезотеліальних клітин. Водночас морфологічні ознаки атипії клітинних елементів атипової гіперплазії проток спостерігалися в 47,3 % випадків. Клітини з ознаками злоякісного переродження не були виявлені в жодному з наданих зразків тканини молочної залози. Важливо зазначити, що в 15 % пацієнток у зразках ендометрія діагностовано гістологічні ознаки злоякісного новоутворення, що призвело до їхнього негайного направлення до гінеколога-онколога для хірургічного втручання та необхідної ад'ювантної терапії. ***Висновки.*** У прогнозі клінічного перебігу перехресного синдрому ГЕ та ДЗМЗ ключову роль відіграють гістологічне підтвердження діагнозу та ознаки атипії у зразках біопсії. Виявлення атипових клітин вимагає клінічної консультації за участю гінеколога, мамолога та гінеколога-онколога, під час якої приймається рішення щодо хірургічного втручання та необхідної фармакотерапії.

Ключові слова: ендометріоз; доброякісне захворювання молочної залози; атипова гіперплазія проток; перехресний синдром; ендометріоїдна карцинома; рак молочної залози; метаболічний синдром; кісткові метастази