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IMPORTANCE OF ELECTRON MICROSCOPIC EXAMINATION IN THE DIAGNOSTICS OF ENDOMETRIAL CANCER

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Electron microscopy is crucial in diagnosing proliferative changes in endometrial cancer. Identifying atypical cells in cytology is challenging, and electron microscopy aids in overcoming this issue. This study involves patients with endometrial proliferation, including endometrial cancer, who were referred to the Oncology Clinic of AMU and observed from 1999 to 2004. Surgical samples were analyzed via light and electron microscopy. The patients were divided into three groups: highly differentiated variant (G1, n=53), moderately differentiated variant (G2, n=40), and poorly differentiated variant (G3, n=39). In highly differentiated adenocarcinomas, Findings revealed atypical glandular hyperplasia and structural deformities in desmosomes, such as reduced desmosome count in G2 tumors and complete disorganization in G3 tumors. Poorly differentiated tumors exhibited severe nuclear polymorphism, over 50 % desmosome degradation, and mitochondrial swelling, while well-differentiated adenocarcinomas showed mild nuclear deformation and less than 20 % desmosome degradation. These results offer valuable insight into the expected progression of proliferative processes in endometrial cancer, providing crucial information for understanding disease dynamics.

Key words: endometrial cancer, electron microscopy, atypical cells, desmosomes, nuclear polymorphism, mitochondrial swelling, tumor differentiation.

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ЗНАЧЕННЯ ЕЛЕКТРОННО-МІКРОСКОПІЧНОГО ДОСЛІДЖЕННЯ В ДІАГНОСТИЦІ РАКУ ЕНДОМЕТРІЮ

Електронна мікроскопія має вирішальне значення для діагностики проліферативних змін при раку ендометрію. Визначення атипових клітин на цитології представляє складне завдання, і електронна мікроскопія допомагає подолати це. У дослідженні взяли участь пацієнти з проліферативними змінами ендометрію, включаючи рак ендометрію, які були направлені до онкологічної клініки АМУ та спостерігалися з 1999 по 2004 рік. Зразки тканин були проаналізовані за допомогою світлової та електронної мікроскопії. Хворі були поділені на три групи: високодиференційований варіант (G1, n=53), помірно диференційований варіант (G2, n=40) та низькодиференційований варіант (G3, n=39). Виявлено атипову залізисту гіперплазію та структурні деформації десмосом, такі як зменшення числа десмосом у пухлинах G2 та повна дезорганізація у пухлинах G3. Слабко диференційовані пухлини виявили виражений ядерний поліморфізм, більше 50 % деградації десмосом та набряк мітохондрій, тоді як у добре диференційованих аденокарциномах спостерігалися слабка деформація ядер та менше 20 % деградації десмосом. Ці результати є цінними даними для прогнозування розвитку проліферативних процесів раку ендометрію і дають важливу інформацію для розуміння динаміки захворювання.

Ключові слова: рак ендометрію, електронна мікроскопія, атипові клітини, десмосоми, ядерний поліморфізм, набряк мітохондрій, диференціація пухлини.

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Endometrial cancer (EC) is the second dangerous cancer consisting of 7.1 % of other cancers after breast cancer among the cancers that occur in women. Each year new disease cases up to 200.000 and death cases up to 50.000 are registered in the world [2, 8,]. Despite the undeniable successes of modern medicine, the urgent problems of oncology and, in particular, oncogynecology are still unresolved [14]. Considering that complaints in patients with uterine cancer appear before the menopausal period, the most important and key factor for successful detection and treatment is the correct diagnosis and timely correct approach to patients with proliferative and malignant changes in the body of the uterus. Long-term intravesical obstruction leads to progressive destructive changes in the smooth muscle cells of the endometrium [1, 3]. One of the main tasks of modern oncology is to study various aspects of the pathogenesis of benign and malignant proliferative processes in the endometrium. Hyperplastic processes of the endometrium are sometimes considered one of the first signs of neoplastic cell transformation and the development of adenocarcinomas. The incidence of transition from endometrium atypical hyperplasia to cancer varies from 23 % to 57 % [11, 15].

Proliferative endometrial changes, including hyperplasia and atypical hyperplasia, are linked to atrophic processes, glandular degradation, and nuclear complex destruction, ultimately forming poorly differentiated neoplasms [10, 11]. Early EC detection enables better treatment selection, with minimally invasive techniques, such as uterine smear tests and pathohistological examination, playing a leading role in diagnosis [12]. Cytological studies using electron microscopy are especially valuable for identifying

atypical cells [9]. EC prognosis and recurrence risk are influenced by clinicopathologic factors, including age, stage, histologic subtype, and tumor grade, which is essential for assessing tumor aggressiveness [13]. Studying EC's morphological changes can aid in differentiating tumor grades.

The purpose of the study was to evaluate the importance of electron microscopic examination in the diagnosis of proliferative changes in endometrial cancer.

Materials and methods. This study involves patients with endometrial proliferation, including endometrial cancer, who were referred to the Oncology Clinic of AMU and observed from 1999 to 2004. The research was conducted at the electron-microscopic laboratory of the Research Center, and the Department of Histology, Cytology, and Embryology of AMU. The study utilized operation and archive data of patients diagnosed with endometrial adenocarcinoma. The outpatient cards and medical histories of these patients were reviewed. The research was conducted both retrospectively and prospectively. Patients with non-resectable tumors, those receiving neoadjuvant chemotherapy or radiation therapy, patients with distant metastasis, those who first presented with relapse, and patients with cancers of the ovaries, vulva, or other genital organs, as well as those with joint extragenital tumors, were excluded from the study. Before taking part in interviews and research, participants gave written informed consent through signatures. Ethical approval for the study was obtained from the Ethics Council of Azerbaijan Medical University (05.04. 2016, protocol No. N11). A total of 132 patients (main group) diagnosed with endometrial adenocarcinoma were included in the research. The age of the patients ranged from 39 to 76 years, with an average age of 49.6 ± 2.7 years.

The well-differentiated variant (G1) was found in 53 patients (40.2 %), the moderately differentiated variant (G2) in 40 patients (30.3%), and the poorly differentiated variant (G3) in 39 patients (29.5%) ($p<0.05$). Anamnesthetic data of patients were studied in detail, clinical, laboratory and instrumental investigations (examination, vaginal and ultrasound scan, swab test of the uterus) were performed. The results of the clinical, ultrasound, morphological and electron-microscopic examinations were systematized and analyzed.

Of the 132 patients diagnosed with cancer, 35 (26.5 %) had a tumorin the upper part of the uterine body, 27 (20.4 %) inthe lower 1/3 of the uterine body, and 31 (23.5 %) in the central part of the uterus; In 18 (13.6 %) patients, the uterine cavity was completely filled and in 21 (15.9 %) patients, cervical damage was detected. In addition to the US examination, 87 patients with endometrial cancer were examined by MRI, 74 of whom were diagnosed with myometrial invasion, and 13 patients with cervical invasion. According to the MRI examination, the rate of metastatic damage to regional lymph nodes was 9 (10.3 %). Samples from operation materials obtained from patients with uterine corpus cancer for the purpose of studying light and electron microscopic examination (1.5-cm-sized tissue pieces consisting of all layers of uterus, taken from pathological derivative of uterine corpus, surround derivative and taken from the unchanged areas) were submitted to the electron microscopy laboratory by fixing in 2.5 % paraformaldehyde, 4 % sucrose, 0.1 % picric acid solution prepared in 1.0 M phosphate buffer (pH = 7.4). Semithin (1mkm) sections were prepared using Leica EM UC7 ultramicrotome by separating fully prepared blocks from molds.

Ultrathin sections were investigated on a JEM - 1400 transmission electron microscope (JOEL-Japan) under 80 – 120 KW voltage and electronograms were recorded via lower and side chambers (Veleta).

The analysis of morphometric parameters (length, diameter, surface area, form factor, etc.) of the tissues and cells was performed by the computer program (The TEM imaging platform) developed by the German company "Olympus Soft Imaging Solution Gmbh"using microphotos and electrograms obtained in TIF format by the semi-automatic method.

The number of indicators obtained during the research were implemented by applying methods of variation (U-Mann-Whitney), discriminant (Pearson Chi-Square) and regression (Kaplan-Meier criteria with Log Rank (Mantel-Cox) model). All calculations were made in the electron table EXCEL-2016 and in the package program SPSS-22.

Results of the study and their discussion. The clinical and structural features of three variants of endometrial adenocarcinoma (well-differentiated, moderately differentiated, and poorly differentiated) based on histological studies were reviewed. The distribution of patients by clinical stage shows that the vast majority of patients were in stage I, accounting for 73.5 %. According to our results, stage IA occurred in 85 patients (64.4%), stage IB in 28 patients (21.2 %), stage II in 9 patients (6.8 %), stage IIIA in 6 patients (4.6 %), and stage IIIC in 4 patients (3.0%) [6].

When examining the disease stage with age, it becomes clear that stage I prevails in all age groups, but as age increases, the rate of II and III phases also increase. Thus, in women of reproductive age, stage II and III occur in 7.1 % of cases and 30.9 % of cases in patients over 50 years, $p<0.05$. Cytochorectomy of the endometrium during the electron-microscopic examination, changes in the shape, size and structure

of gllandulocytes, number and structure of organelles, intercellular contacts, also the modifications of active secretory cells that provide hemostasis of the inner layer of the uterine wall during the malignant process were investigated and systematized. Structural changes described by us include adenocarcinomas of the endometrium.

In order to make a comparative assessment of cell and tissue structure disorders at the electron-microscopic level, some indicators have been based, and changes in atypical and neoplastic processes have been identified. This includes plasma membrane, dark and light cells, intercellular contacts, cell nuclei, mitochondria, Golgi complex, as well as quantitative and neovascularization properties of secretory cells in the endometrium.

Well differentiated adenocarcinomas of the endometrium was met in patients of 40.2 %, the 5-year survival rate was 84.9 %. The granular endoplasmic reticulum is in the shape of enlarged figures, with thin fibrous structures in the center. Largely fragmented crystal mitochondria are found. The nuclei differ with their diversity, their outlines are inaccurate, are characterized by deep invaginations of the nuclear membrane, and the area of around nuclear is enlarged (fig.1).

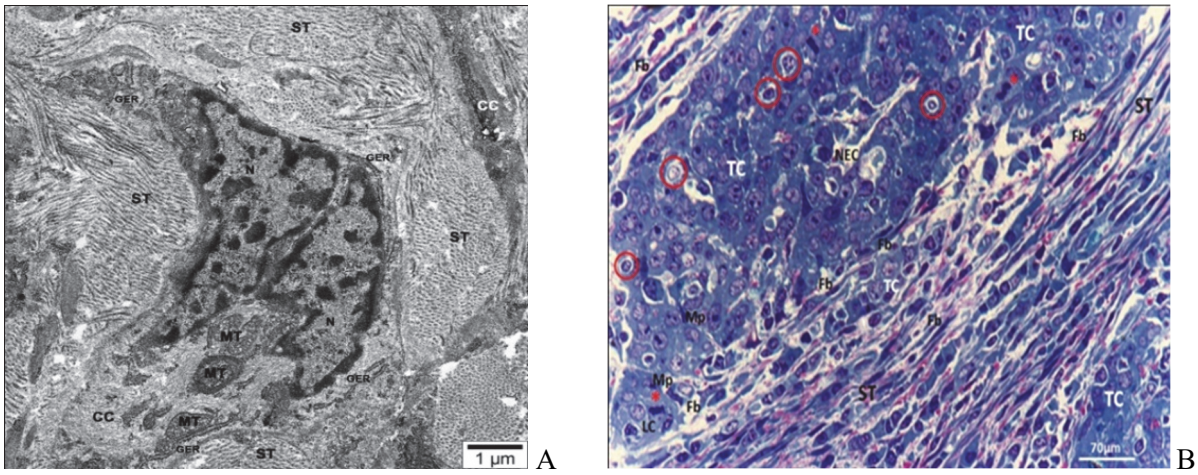


Fig. 1. A – poorly differentiat edendometrial adenocarcinoma. Dye: uranyl-citrate and lead citrate. Zoom – 1: 5000; B – most of the cells are lysed. Dye: hematoxylin-eosin, Zoom: Objective 12.5x, 40x.

Table 1

In endometrial adenocarcinoma electron microscopy function set algorithm

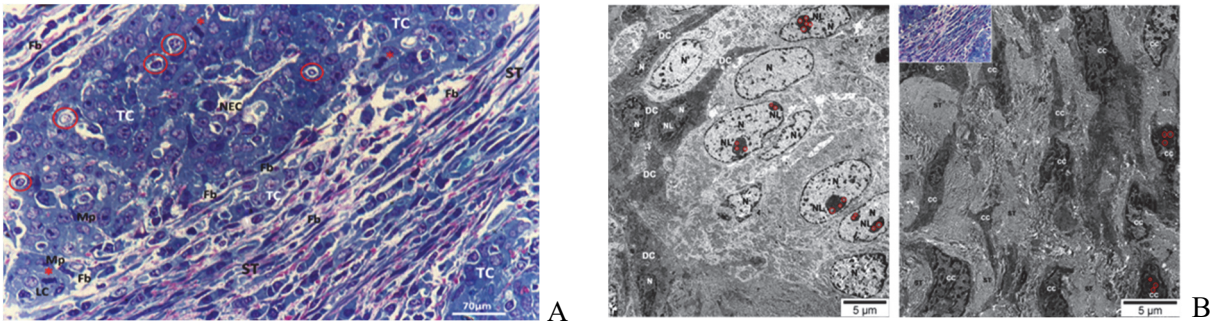
Indices of Electron Microscopy	Well-Differentiated Adenocarcinomas	Moderately Differentiated Adenocarcinomas	Poorly Differentiated Adenocarcinoma	F	p
Plasma Membrane	Twists (15 %)	Invaginations (30 %)	Invaginations (35 %)	5.922	0.003
Desmosomes	Structural disorders (20 %)	Structural disorders (50 %)	Completely destroyed (50 %)	14.850	<0.001
Nucleus	Size increased, sharp coiling in intranuclear channels (30 %)	Size increased, increased coiling, fragmentation in most channels (50 %)	Size increased, dramatic fragmentation, disassembly in intranuclear channels (80 %)	38.128	<0.001
Nuclear Membrane	Thickened (20 %)	Thickened, invaginations in some parts (30 %)	Deep and numerous invaginations (40 %)	5.034	0.007
Nucleolus	No change (0 %)	Hypertrophied (30 %)	Numerous, complex fibrillar center, hypertrophied (50 %)	56.430	<0.001
Endoplasmic Reticulum	Vesiculation (10 %)	Cysts and vesicles (20 %)	Multivesicles, corpuscles (30 %)	6.750	0.001
Mitochondria	Edema, swelling (20 %)	Partial fragmentation (40 %)	Complete fragmentation (60 %)	21.214	<0.001
Mitochondrial Crystals	Edema, swelling (20 %)	Partial destruction (40 %)	Complete destruction (60 %)	21.214	<0.001
Golgi Complex	Hypertrophic (20 %)	Hypertrophic (20 %)	Fragmented (40 %)	7.425	<0.001
Lipid Granules	Few (10 %)	Many (40 %)	Multiple (50 %)	26.088	<0.001
Lysosomes	Many (30 %)	Many (40 %)	Many (50 %)	4.368	0.014
Light Cell	20 %	30 %	40 %	5.034	0.007
Dark Cell	50 %	60 %	85 %	17.471	<0.001

Despite the basal membrane is fragmented, complete destruction is not detected. Although the mitochondria have a dense matrix, the crystals are swollen, edematous, and the collapse of some of the crystals is visualized. Numerous dense osmiophilic bodies are revealed between the inner and outer membranes of mitochondria. The number of lysosomes and lysosomal-like elements in the pathological fire-setting has increased dramatically. Desmosomes and covering plates providing intracellular contacts are found, but in some areas, structural disorders of the desmosomes are revealed.

Moderately differentiated adenocarcinomas of the endometrium have been found in 30.3 % of patients, the 5-year survival rate is 85 %. Small mitochondria with the dense matrix are found between the membranes of the Ergocytoplasm. Mitochondrial matrix contains osmiophilic granules and few crystals. The nuclei are characterized by a rough, jagged surface. Mitochondria are located close to the plasma membrane of cells (Table 1).

The color change of the matrix characterizes the anastomosis of the crystals, which are located in numerous perpendiculars. On the contact surface of cells, interdegradations and complex contacts are selected. The number of desmosomes and covering plates has been reduced, with the weakening of intercellular contacts seen as the detection of tumor cells between the stromal elements in areas around the pathological fire-setting. The basal areas of cancer cells have been undergone fragmentation. Endoplasmatic network has been undergone degranulation. Thus, ultrastructural change in the moderately differentiated adenocarcinoma is characterized by a disorder of intracellular metabolism. This case manifests itself by the structural variability of organoids that cause metabolic disorders.

Poorly differentiated adenocarcinomas of endometrium have been found in 29.5 % of patients, the 5-year survival rate is 64.1 %. Electron microscopic studies have revealed that the most notable process in the cytoplasm of atypical cells is multivesicular bodies, consisting of endoplasmic reticulum elements. (Fig. 2).



A B

Fig. 2. Poorly Differentiated Adenocarcinoma. A – light microscope view: Tumor cells (TC), fibroblasts (FB), dark cells (DC), and light cells (LC) are observed. Connective tissue (CT) and fibroblasts (FB) show cell polymorphism and areas of necrosis (NEC) within tumor cells (TC). Numerous macrophages and intraepithelial lymphocytes (marked with a red circle) are seen, along with multivesicular bodies. Dye: Hematoxylin-eosin. Zoom: 7x, Objective: 20x. B – electron microscope view: Metastatic chain development of dark tumor cells extending from collagen fibers, with invasion into the connective tissue stroma (ST) due to the proliferation of dark cells. Cancer cells (CC) show distorted nuclear outlines, with visible cell and nuclear polymorphism compared to light cells. Large fibrillar centers are marked with a red circle. Dye: Uranyl-citrate and lead citrate. Zoom: 1:5000.

The cytoplasms of the cells are seen in the light areas. The endoplasmic network is fragmented, partially vacuumed. The rapid growth of nuclear dimensions, abnormal shape, abrupt changes in nuclear form due to numerous deep invaginations of the membrane is seen.

In some areas that have been destructed, intercellular interaction is disrupted, and epithelial cells are more noticeable in flat forms. The Golgi complex is about 65–70 % fragmented in observations. Mitochondria have been fully decomplexationed, crystals have been fragmented. Intercellular interactions have been disrupted more than 50 %.

Thus, the data obtained indicate that electron microscopic research is important not only in the differential diagnosis of endometrial adenocarcinomas but even in the assessment of prognosis. In addition to complementing the existing histological, histochemical and other methods, these indicators are fundamentally a new approach that allows studying the metastatic potential of tumor cells by studying intracellular structures. As a result of the research, we have found that with increased levels of malignancy there is a sharp decline in intracellular contacts. As a result of the research, we have found that with increased levels of malignancy there is a sharp decline in intracellular contacts. Firstly, it concerns desmosomes. Thus, if the structure of the desmosome is maintained during atypical glandular hyperplasia, deformation of the structure of desmosome in some of the cells in well differentiated adenocarcinoma, decrease in the number of desmosomes in the G2 tumors, and the complete disintegration of the small number of desmosomes in G3 are observed. One of the important points here is that these symptoms

coincide with histological research and clinical indications. In the low gradient endometrial adenocarcinomas, the distribution of large numbers of tumor cells in the stroma is determined, the loss of intracellular contacts in this type of tumor is, in our opinion, an indication of growth rate of cancer and high metastatic potential. The number and structure of desmosomes are of great prognostic significance.

The second major point is the structure of the nuclear and mini nuclear. Nuclear size growth, generating deep and sharply expressed invaginations of nuclear layer, a large form of the nuclear, in short, sharply expressed nuclear polymorphism are indicators of the malignancy. Thus, in our study, this symptom was clearly expressed in G3 gradient tumors, with mini nuclei underwent hypertrophy, forming large fibrillary centers with complex configuration. On the other hand, we have observed high mitotic activity in tumors that sharply expresses nuclear polymorphism, which is one of the ultrastructural parameters of cancer progression.

A third important electron-microscopic finding is related to the structure of mitochondria. We did not observe any significant structural changes in mitochondria during AGH. However, as the degree of differentiation in the adenocarcinomas diminishes, these organelles become more swollen, and the crystals are destructed starting from partial fragmentation. These changes can be attributed to increased hypoxia during tumor progression and cells' rapid undergoing aerobic glycolysis.

As a result of electron microscopic research, another interesting fact is the prognostic criteria. This factor is very important in our opinion. A number of scientists have found secretory cells in the uterus and endometrium of these cells is stable and hemostasis is protected. We studied the number and secretory activity of these cells in the endometrium. The number of these cells increases in poorly differentiated tumors, and secretory activity increases dramatically at the ultrastructural level. The latter shows itself with a severe development of cisterns of endoplasmic reticulum network and intracellular tubules, an increase in number of secretory granules.

Another image revealed at the ultrastructural level is dark cells with the cytoplasm. We think that the number of these cells is closely related to malignancy; mentioned elements are rarely found in ultrathin cuts when atypical glandular hyperplasia occurs, their number increases in well differentiated tumors, and they are revealed more than 50 % of area in poorly differentiated tumors. Even in G3 tumors, separate layers of these cells are found. In our view, dark cells have important differential diagnostic value. In addition, when investigating the features of stromal invasion, it was found that dark cells are one of the main components of the infection in poorly differentiated adenocarcinomas. We think that the number of these cells can be taken as prognostic factors.

As a result of electron-microscopic research on the endometrial adenocarcinomas, we have found that there are specific ultrastructural changes inherent to various differentiated tumors and that their modification can be used in differential diagnostics of cancer and assessment of prognosis. In addition to morphological, histochemical data, these indicators visualize reorganization in the cell at the structural and substructural levels [4, 5].

In general, the study investigated the properties of metastasis of various types of differentiated adenocarcinomas, some of the ultrastructural transformational indicators obtained are associated with the gradient of the malignancy, allowing us to advance an idea on the clinical course and potential for the tumor spread. They are of prognostic and diagnostic significance.

During the electron-microscopic examination, the cytoarchitectonics of the endometrium, the shape, size and structural changes of gllandulocytes, the number and structure of organelles, intercellular contacts, as well as the modifications of secretory active cells that provide hemostasis of the inner layer of the uterus during the malignancy were studied and systematized [4, 7].

Conclusion

The presence of secretory and dark cells in the endometrium, as well as the observed disruptions in intercellular contacts (such as desmosomes), are significant prognostic markers for endometrial adenocarcinomas. Notably, poorly differentiated adenocarcinomas that show pronounced alterations in these cellular structures are associated with a less favorable prognosis compared to other histological types. The insights gained from this study provide a deeper understanding of the cellular changes that accompany different stages and types of adenocarcinoma, thus contributing to improved accuracy in predicting the progression of these tumors in patients. These findings emphasize the importance of incorporating ultrastructural and histopathological evaluations into routine diagnostics to facilitate early detection and tailor treatment plans more effectively. By refining diagnostic criteria and enhancing predictive assessments, we can aim to reduce both the progression of endometrial adenocarcinoma and the number of patients presenting with advanced stages of the disease. Ultimately, the application of these insights will

support clinicians in selecting optimal therapeutic approaches, minimizing invasive treatments, and potentially improving patient survival rates and quality of life.

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