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Some Morphological and Immunohistochemical Features of Different Histotypes of Uterine Cancer

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A B S T R A C T

Morphological and immunohistochemical analyses revealed characteristics of endometrial squamous cell carcinoma and endometrioid adenocarcinoma with squamous cell metaplasia, compared to endometrioid adenocarcinoma. These characteristics allow us to assess the aggressiveness and higher tumor potential of tumors with a squamous cell component. These results will help further individualize the treatment approach for patients with specific histotypes.

Introduction

Endometrial cancer (EC) ranks sixth in the world (1, 6) and third in Uzbekistan (2, 8, 10) in terms of incidence among the female population. Over the past 30 years, the incidence rate in Uzbekistan has increased by 132% (60) and no downward trend is expected in the near future (3, 11, 12), reflecting the increasing prevalence of risk factors such as obesity and the ongoing aging of the population (4, 5). According to United Nations projections, the proportion of people aged 65 and older in the world population will increase from 10% in 2022 to 16% in 2050 (1, 7). It is important to note that in most countries, including Uzbekistan, women constitute the majority of the elderly population (2, 8). Given the emerging socio-demographic trend, an increase in the number of EC patients over 70 years of age is expected in the coming years. In 2020, the incidence of newly diagnosed endometrial malignancies in the global population aged 70 years and older was 25.6% (107,001 people). By 2040, this figure is expected to increase to 33.5%, or approximately 204,000 people (3, 9). In Uzbekistan, the same figure in 2021 was 6,732 (26.4%) patients in the age group ≥ 70 years (5).

Uterine cancer (UC) is a malignant tumor originating from the mucous membrane of the uterus (endometrium). UC is currently the most common malignant neoplasm of the female reproductive organs and ranks second in frequency after cervical cancer globally (1, 2). The

increase in the incidence of endometrial cancer is primarily due to the increase in life expectancy and the rise in the incidence of "diseases of civilization" (infertility, endometriosis, uterine fibroids) (3). Uterine cancer is a morphologically heterogeneous tumor and is predominantly (more than 80%) represented by endometrioid adenocarcinoma, which is characterized by a favorable course with a 5-year survival rate after treatment reaching 90%. In contrast, there are rare endometrial tumors, accounting for 15–20% of all forms of endometrial cancer, which are characterized by a poor prognosis, which is determined by a high recurrence rate (50%) and a 5-year survival rate of patients not exceeding 40% (4). Similar histotypes of endometrial cancer include endometrioid adenocarcinoma with squamous cell differentiation and squamous cell carcinoma of the endometrium. Both of the aforementioned morphological variants of endometrioid adenocarcinoma, according to the 2020 WHO International Histological Classification, are combined into a variant of adenocarcinoma with squamous cell metaplasia. The classification also lists 13 histotypes of epithelial tumors, of which 3 (mucinous, serous, and clear cell) subtypes occur with a frequency of 1 to 10% (5). Squamous cell carcinoma of the endometrium is also recorded within 1%; however, this tumor is not distinguished as a separate morphotype in any of the existing classifications. Nevertheless, interest in this histotype of endometrioid adenocarcinoma has been growing in recent years and is attracting increasing attention from both foreign and domestic researchers due to its aggressiveness and high tumor potential (6, 8). The leading factor in the mechanism of malignant transformation of cells in the biological behavior of existing tumors is proliferative activity. This is one of the most important characteristics of the tumor phenotype, largely determining the rate of tumor growth, the risk of metastasis and relapse, and the potential response to treatment. The Ki-67 antigen, which is expressed in virtually all phases of the mitotic cycle (G1, S, G2, and M phases), except for the G0 period, and reflects the size of the proliferative pool, is widely used to identify the proliferation patterns of human malignant tumor cells (2, 17). The p16 (p16INK4a) and pRb proteins are also involved in cell cycle regulation. An increase in the p16INK4a protein level is associated with impaired cell division: its concentration increases to inhibit active cell proliferation (3, 18). Functional inactivation of the pRb protein by the HPV E7 protein leads to overexpression of p16 INK4a, which ultimately leads to uncontrolled cell proliferation and the formation of a tumor cell clone (6). Recently, the above-described markers have been studied in various locations, but their significance in endometrial cancer remains insufficiently studied.

The aim of the present study was to compare the morphological and immunohistochemical characteristics of endometrioid adenocarcinoma, adenocarcinoma with squamous cell metaplasia, and endometrial squamous cell carcinoma in order to identify the more aggressive histological subtype. The study further sought to evaluate the diagnostic and prognostic significance of these pathological features for improved characterization and clinical management of endometrial malignancies.

Materials and Methods

The study utilized clinical and laboratory data from 91 patients with endometrial cancer treated at the Kharezm National Medical Research Center of Oncology. The diagnosis of endometrial carcinoma was confirmed in all cases at the outpatient stage; the tumor histotype was clarified postoperatively in accordance with the international histological classification of RTM (World Health Organization (WHO) classification, 2020). No treatment was administered prior to surgery. The study group included 41 patients with endometrioid adenocarcinoma, 31 patients with endometrioid adenocarcinoma with squamous cell metaplasia, and 19 patients with endometrial squamous cell carcinoma. In all groups, patients with stages I and II of the disease predominated, patients with stage III were noted only in the group with endometrial squamous cell carcinoma. The study included patients aged 32 to 89 years (Me = 62.5; 36–81). All patients underwent surgery using a standard technique, according to clinical guidelines from 2022. For fixation of the material, a solution of 10% neutral buffered formalin was used, followed by automatic processing in a Sakura Tissue-Tek xpress x 120 device. Next, sections of 3–5 μm thickness were prepared. Histological preparations were stained with hematoxylin and eosin. Immunohistochemical (IHC) analysis was performed on sections from paraffin blocks of tumors intended for standard morphological analysis. Deparaffinization and rehydration of paraffin sections were performed in xylene and alcohols of different concentrations. Antigen retrieval was performed in a PT-Link Thermo. The IHC analysis followed a previously published protocol (12). Polyclonal antibodies to Ki-67 (Diagnostic BioSystems, diluted 1:200), p16 (Ventana, RTU), and monoclonal mouse antibodies to pRB (clone BF0614) from Affinity Biosciences diluted 1:100 were

used. The analysis was performed on a Thermo scientific 480S autostainer using the Reveal Polyvalent HRP-DAB Detection System. The percentage of stained tumor cells was assessed by counting 100 tumor cells in several fields of view. The immunohistochemical reaction results were assessed and histological studies were performed using an AxioLab.A1 light microscope (Germany) with an objective magnification of 20x and 40x. The obtained data were processed using the Statistica 13.0 software package (StatSoftInc., USA). The studied data were tested for compliance with normal distribution using the Shapiro-Wilk test. Since the primary data did not follow the normal distribution law, group comparisons were performed using the nonparametric Mann-Whitney test (U-test).

Results and Discussion

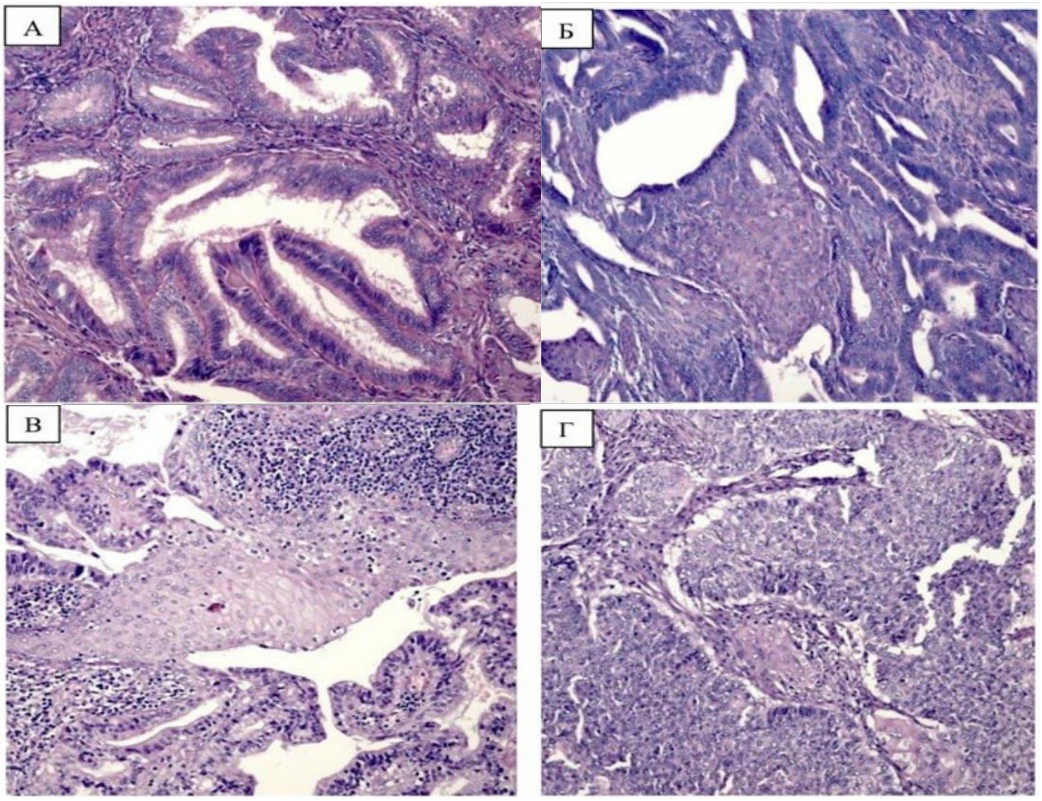
Histological examination revealed that endometrioid adenocarcinoma consisted of glandular or villous-glandular structures of complex structure with tubular foci. The glands were lined with columnar epithelium. The cytoplasm was eosinophilic with varying degrees of atypia. Tumors most often developed against a background of hyperplastic endometrium and uterine myomatosis (Fig. 1A). Morphologically, endometrioid adenocarcinoma exhibited typical adenocarcinoma structures with a few "rounded" formations of squamous epithelium, referred to in the literature as morulae. The morulae consisted of rounded, uniform cells with oval, centrally located nuclei and small, solitary nucleoli; they filled the glandular lumens and were sometimes located around the glands. Occasionally, foci of necrosis could be seen in the morulae (Fig. 1B).

Endometrioid adenocarcinoma with squamous cell metaplasia presented as extensive fields or scattered foci of squamous differentiation, occupying 20–50% of the area, represented by diffuse foci of varying size and shape. In some cases, pearl-shaped keratinization was detected in the foci of squamous cell differentiation in carcinomas. Foci of squamous cell metaplasia were observed in the middle sections of the epithelial tumor layer, occupying no more than 20–40% of the area (Fig. 1B). Squamous epithelial cells in the tumor were not fully differentiated, with eosinophilic cytoplasm. The nuclei were uniform, and nucleoli were not visualized. Mitoses were rare. Intercellular bridges were present in the squamous epithelium. In some tumors with diffuse squamous cell differentiation, glands were absent. Tumors with cytological features of squamous cell differentiation occupied up to 50% of the area and consisted of nests of spindle-shaped cells that obscured the glandular lumens. Atypia and isolated mitoses were noted. The tumors developed against a background of hyperplastic or mixed endometrium with myomatous and adenomyotic lesions. Squamous cell carcinoma was represented by typical structures (Fig. 1G), often with foci of keratinization, meeting all the criteria of squamous cell carcinoma and differing from adenocarcinoma with squamous cell metaplasia by the extension of the lesion to the entire uterine cavity, deep invasion of the myometrium against a background of diffuse adenomyosis. The tumor developed against a background of atrophic endometrium; the absence of glands, the presence of intercellular bridges and keratinization, the development of stratified squamous keratinizing or nonkeratinizing epithelium were observed. Many tumors were characterized by angular, irregularly shaped infiltrating nests with nuclear pleomorphism and a high number of abnormal mitoses. Anastomosing bands were also identified, with inflammatory or desmoplastic stroma located between them. Lymphatic vascular invasion was observed in many tumors.

Immunohistochemical analysis included analysis of Ki-67, p16, and pRb markers. Median Ki-67 expression in endometrioid carcinoma and endometrioid adenocarcinoma with squamous cell metaplasia cells was low, whereas in squamous cell carcinoma, an increased number of stained cells with a predominance of this marker expression was observed. Thus, a statistically significant predominance of Ki-67 expression values was found in squamous cell carcinoma cells, 2.7 times higher than in endometrioid carcinoma ($p=0.046$) and 3.3 times higher than in endometrioid adenocarcinoma with squamous cell metaplasia ($p=0.002$).

Median p16 expression values in cells tended to increase from endometrioid carcinoma to squamous cell carcinoma. Expression of this marker increased with the appearance of squamous cell metaplasia by 1.7 times ($p=0.059$) and statistically significantly by 2.3 times ($p=0.020$) in squamous cell carcinoma itself. The differences between endometrioid carcinoma with squamous cell metaplasia and squamous cell carcinoma were small (1.3 times) and therefore not statistically significant ($p\geq0.05$). In the endometrioid adenocarcinoma groups, the median pRb marker values showed virtually no differences.

Fig.1 The studied histotypes of endometrial cancer. Stained with hematoxylin and eosin. Magnification x200. A – Endometrioid adenocarcinoma with tubular foci. B – Endometrioid adenocarcinoma with foci of necrosis in the morulae. C – Endometrioid adenocarcinoma with foci of squamous cell metaplasia with areas of keratinization. D – Non-keratinizing squamous cell endometrial carcinoma with foci of keratinization.



However, in the squamous cell carcinoma group, a sharp decrease in the expression of this protein was observed. Statistically significant differences in pRb expression in the tumor were found between patients with endometrioid adenocarcinoma and squamous cell carcinoma (2.2-fold, p=0.046), and between patients with endometrioid adenocarcinoma with squamous cell metaplasia and squamous cell carcinoma (2.3-fold, p=0.047). Analysis of the obtained results revealed a sharp decrease in pRb expression in the squamous cell carcinoma group, indicating a more aggressive development of this tumor compared to endometrioid adenocarcinoma with a squamous cell component.

Thus, the obtained results demonstrate the differences between endometrioid adenocarcinoma, endometrioid adenocarcinoma with squamous cell metaplasia, and endometrial squamous cell carcinoma. Squamous cell carcinoma of the endometrium differed from adenocarcinoma with squamous cell metaplasia by the absence of glands, the presence of keratinization and intercellular bridges, the development of stratified squamous epithelium, and lymphovascular invasion. This type was distinguished by a higher Ki-67 (35%) and p16 (67.5%) index with simultaneous pRb inhibition of up to 19% compared to endometrioid adenocarcinoma (Ki-67 - 13%, p16 - 30%, pRb - 41.5%), thereby demonstrating aggressiveness and high tumor potential with an unfavorable prognosis requiring significant correction of adjuvant treatment methods. Our data are consistent with the results of studies in the foreign literature, for example, with the data presented in the article by L. Song *et al.,* (13). Endometrioid carcinoma with squamous cell metaplasia was characterized by individual foci of keratinization (from 20 to 50%); cells with clear boundaries, eosinophilic cytoplasm and a low nuclear-cytoplasmic ratio, the appearance of foci of squamous epithelium. A sufficiently high index of p16 (50%) and pRb (43.5%) with a small Ki-67 coefficient (10.5%) increases the risk of recurrence in case of

squamous cell differentiation. The obtained data are also consistent with the results of studies by reputable clinicians. Thus, in the publication of B. Ocak *et al.,* (14) they report the observation of the prognosis of endometrial carcinoma with squamous cell metaplasia and hyperexpression of the Ki-67 antigen in treated patients. Vaginal recurrences occurred in 47.0% of patients within the first two years, and lung metastases occurred in 23.5% of cases. A study by D.A.P. Andrade (15) provides evidence that squamous cell metaplasia in endometrial cancer has a 5.6-fold increased risk of recurrence within the first two years of follow-up.

In conclusion, among all patients, endometrioid adenocarcinoma with a high and moderate degree of differentiation is the most common histological type. It was found that the higher the age, the higher the frequency of unfavorable histological types of endometrial cancer. It is important to note that age-related characteristics of the endometrium, where carcinomas develop, were identified. In the majority of cases, hyperplastic endometrium and atypical hyperplasia are the background for the development of uterine cancer in reproductive patients, while in patients aged 45 years and over, the frequency of endometrial transformation of the atrophic and mixed type increases.

Author Contributions

M. T. Khamdamova: Investigation, formal analysis, writing—original draft. G. K. Kuryazova: Validation, methodology, writing—reviewing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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