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Modern aspects of morphology of endometrial cancer and neuroendocrine tumors (to the 100th anniversary of the birth of O.K. Khmelnitsky)

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Abstract

November 4, 2020, marks the 100th anniversary of the birth of Oleg Konstantinovich Khmelnitskiy, an outstanding Russian pathologist, Corresponding Member of the Russian Academy of Medical Sciences (04.11.1920–08.02.2004). The creative legacy of O.K. Khmelnitskiy has a large number of works devoted to endometrial cancer and neuroendocrine tumors. Modern concepts of these tumors take a lot from the scientist's ideas. The development of the classification of endometrioid carcinomas is determined by new data in molecular genetic research. The most common genetic changes in endometrioid adenocarcinomas involve mutations in the PTEN, KRAS, CTNNB1, PIK3CA, and MS1 genes. Serous carcinomas are characterized by TP53 mutations and HER2-neu gene amplification. The immunohistochemical panel allows differentiation of endometrioid and serous carcinomas. There is evidence of the role of the POLE gene mutation. Various advantages of the introduction of molecular genetic classification are presented, which allow changing approaches to the treatment of endometrial cancer depending on the risk of its development. The 2019 neuroendocrine tumors (NETs) classification allows interpreting morphological characteristics of these tumors in a new way.

Keywords: O.K. Khmelnitskiy, endometrial cancer, neuroendocrine tumors.

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November 4, 2020, marked the 100th anniversary of the birth of a wonderful person, a scientist, a philosopher, a writer, a historian, an amateur and a construct of music, a corresponding member of the Russian Academy of Medical Sciences, Do ctor of Medical Sciences, Professor, Honored Science Worker Oleg Konstantinovich Khmelnitsky (Fig. 1).

O.K. Khmelnitsky mainly developed the pathomorphology of mycoses and questioned the functional morphology of the endocrine system in various aspects (ecological and ontogenetic) in cardiovascular diseases, obesity, and stress-adaptive states. Two monographs are devoted to the pathology of thyroid diseases: "Cytological and histological diagnosis of thyroid diseases" (2002) and "Thyroid gland of St. Petersburg residents in health and disease" (2003).

O.K. Khmelnitsky and his collaborators discovered the mechanisms of action of immunomodulators on the immune system and published this in the monograph "Morphology of the immunocompetent system under the influence of immunomodulators" (1992).

Fig. 1. Corresponding Member of the Russian Academy of Medical Sciences, Professor Oleg Konstantinovich Khmelnitsky

With his investigation of oncomorphological problems, O.K. Khmelnitsky was the first Russian researcher to describe a malignant variant of a glomus tumor (1957). As an expert of the World

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Health Organization (WHO), he took part in the creation of a histological classification of tumors of the endocrine system (1980).

His great works are devoted to the methodology and philosophical problems of medicine. He wrote two monographs jointly with A.I. Strukov and V.P. Petlenko: "Determinism and the theory of causality in pathology" (1978) and "Morphological equivalent of function" (1983).

Together with A.V. Smolyannikov and V.P. Petlenko, they wrote the monograph "Theoretical Foundations of Morphological Diagnosis" (1995).

For 50 years, O.K. Khmelnitsky headed the department of the pathological anatomy of the Leningrad State Institute for Advanced Medical Studies, which was later named the St. Petersburg Medical Academy of Postgraduate Education.

O.K. Khmelnitsky was an honorary member of the society J. Purkinje and an honorary member of the Association of Polish Pathologists. In 1999, he was elected as a member of the International Academy of Informatization. He was awarded the Rudolf Virchow Medal of the European Academy of Natural Sciences for special merit and research in the development of pathology. His extensive scientific research was not confined to the same type of morphological specialization. He devoted his works to the study of endometrial cancer and neuroendocrine tumors, which turned out to be relevant and in demand today and, to a certain extent, justified his prediction of changes in the morphological structure of some tumors.

Currently, emerging publications have indicated the relationship of the morphological transformation of endometrial carcinoma into a tumor with squamous cell differentiation under the influence of viral agents. At this stage, there have been changes in the morphological treatment of endometrial cancer. According to the literature, observations of endometrioid adenocarcinoma with partial or complete squamous cell differentiation have been increasing. The clinical aspect is characterized by a worse prognosis, since these tumors are classified as low-grade adenocarcinomas. In addition, these tumors require molecular genetic testing.

One of the forms of endometrial cancer is adenocarcinoma with squamous cell differentiation (WHO Classification of Tumors of the Female Genital Tract, 2014) [1]. Previously, this histotype was designated glandular squamous cell carcinoma (also called adenoacanthoma, mucoepidermoid carcinoma, and adenoacanthocarcinoma). This histotype occupies a distinct place among malignant endometrial tumors, including squamous epithelium [2]. Several authors distinguished two types in the general group of these neoplasms, each of which claims to have oncological independence, namely, adenoacanthoma proper and glandular squamous cell cancer.

1. Squamous cell structures found in hyperplastic processes and cancerous growths in the endometrium are caused by the direct metaplastic transformation of the glandular epithelium into a flat epithelium, carried out through several intermediate stages, often microscopically detected during intraglandular localization of squamous cell proliferates.

2. Another hypothesis, the authors of which consider the endometrial adenoacanthoma as a kind of combined malignant tumor, is represented by glandular and squamous cell cancerous structures, developing independently of each other from independent cell populations. In other words, they suggest the existence of an independent source of squamous cell proliferation in the endometrium. However, this theory has few supporters.

3. Authors also mentioned the possibility of rare true combined types of cancer, which are multiple primary cancers of the cervix and uterine body with fusion and, in advanced cases, into one tumor conglomerate of squamous cell carcinoma foci of the vaginal part of the cervix or cervical canal and endometrial carcinoma. These rare tumors are collisional cancers of anatomically adjacent areas and require a separate category.

4. Some authors explain the appearance of adenoacanthotic structures in the tumors by considering the pathological proliferation of the catabiotically altered prismatic epithelium, which forms solid or simulating squamous epithelial structures. This view has the least number of supporters.

Controversies exist not only in the terminology and histogenesis of endometrial adenoacanthomas. There is no consensus on the biological nature of squamous cell proliferates.

O.K. Khmelnitsky believed that both components — glandular and squamous — have comparable biological cancerous or, respectively, precancerous properties.

Meanwhile, in much rarer cases, the morphological features of the squamous component of adenoacanthoma do not raise doubts about its cancerous nature, showing pronounced atypia and anaplasia of multiple cell layers, pronounced nuclear and cellular polymorphism, and signs of invasive growth. Such malignant formations in both components are designated in glandular squamous (adenosquamous) or mucoepidermoid cancers.

To date, the existing terminological discord barely elucidated the issue, and each group of researchers remains unconvinced. The WHO histo-

logical classification of tumors of the female genital tract (2014) recommends calling bimorphic adenocarcinomas as endometrioid adenocarcinomas with squamous cell differentiation. The development of the classification of endometrioid carcinomas is attributed to new data found in molecular genetic studies [3].

The most common genetic changes that occur in endometrioid adenocarcinomas (Bochmann type I) are mutations in *PTEN*, *KRAS*, *CTNNB1*, *PIK3CA*, and *MSI* genes. Bochmann type 2 endometrioid carcinomas, which are mainly serous carcinomas, are characterized by *TP53* mutations and *HER2/neu* amplification.

A panel of immune markers, including p53, estrogen receptor (ER), progesterone receptor (PR), and *PTEN*, differentiates endometrioid from serous carcinomas. Wild-type p53 (focal weak nuclear positivity), strong ER and PR expression, and PTEN loss are indicative of endometrioid carcinoma. Aberrant expression of p53 (strong diffuse nuclear staining or no staining at all), weak or absent expression of ER and PR, and expression of PTEN are characteristic of serous carcinoma.

S.V. Vtorushin and R.D. Malykh (2017) [4] present a literature review with an analysis of endometrial cancer studies based on molecular genetic data. The need for the latter is attributed to clinical observations that the genetic profile of tumors does not always correspond to their morphological structure. The latter circumstance changes the strategies of treating patients. The concept of the four new subgroups of endometrial malignant neoplasms is proposed: ultramutated, hypermutated, copy-number low, copy-number high (serous-like). The results of molecular genetic studies typical for each group are presented. Much attention is necessary to the role of *POLE* mutation in tumors of the ultramutated subgroup. Different theories of a favorable prognosis in this category of patients are discussed. Various advantages of the introduction of molecular genetic classification are presented, which allow changing approaches to the treatment of endometrial cancer, depending on the degree of risk of its development and prognosis.

All the data presented expands the understanding of endometrioid carcinomas of the uterine body and confirms the fundamental research in this area, as laid down by O.K. Khmelnitsky.

According to the National Medical Research Center of Oncology (Rostov-on-Don), for over 5 years (2016–2020), 1281 patients have been treated in the Department of Oncogynecology for cancer of the uterine body. Moreover, endometrioid adenocarcinoma was detected in 995 (77.7%) patients and serous, clear cell, and undifferentiated carcinomas in 75 (5.9%) women. Endometrioid adenocarcinoma with squamous cell differentiation was found in 181 (14.1%) patients, and squamous cell carcinoma of the endometrium was found in 30 (2.3%) patients. Clinically, bimorphic endometrioid adenocarcinoma proceeds as an unfavorable variant.

Neuroendocrine tumors are one of the most important oncomorphology focus of O.K. Khmelnitsky.

In the 70s–80s, few works were devoted to the neuroendocrine system. The publication of a collection of articles "Endocrine granulocytomas (apudomas)" [5], which was edited by D.I. Golovin and O.K. Khmelnitsky, showed great importance for the Russian pathological anatomy.

These works showed that several endocrine tumors secreted biogenic amines and peptide hormones. The term "endocrine granulocytomas" was proposed as a general name for these neoplasms, partly known as apudomas. The book deals with the issues of histogenesis, histological structure, classification, and diagnosis, which are encountered by pathologists. The greatest attention was given to the histological variants of the structure of endocrine granulocytes of various localizations and to the issues of their differential morphological diagnoses. The proposed replacement of the term "apudomas" with "incretor granulocytomas" was substantiated. Particular attention was paid to the histological classification of the WHO and difficulties with terminology. The latter circumstance remains. The terminological debate does not end, and each time, new terms appear, which will be discussed below.

In the book by O.K. Khmelnitsky and A.A. Cheremnykh, the issues of differential diagnosis of endocrine granulocytes were based mainly on their morphological features detected by light microscopy using staining methods available to practical pathologists. The book also emphasized the need to determine the functional characteristics of tumors.

The characteristic morphological features of neuroendocrine tumors are combinations of alveolar, trabecular, or solid structures with a well-developed network of sinusoidal vessels. Possible cellular, pseudo-iron nests of small prismatic dark or light cells sometimes form "palisades" along the periphery of the cell nests.

In endocrine cell cancers, identifying secretory granules determined by silvering is important, but primary importance was given to the cytological features of tumor tissue. However, morphological criteria for malignancy are often scarce and uncertain, and absolute clinical and morphological signs of malignancy are persistent relapses and metastases.

In the conclusion of the monograph, D.I. Golovin and O.K. Khmelnitsky, instead of the next Anglicism (science-like term "apudoma"), justified the introduced term "endocrine granulocytomas," which simplified and reflected the morphological principle of tumor elements.

All further history of the study of neuroendocrine tumors shows that the terms are temporary definitions that can change with new knowledge and research methods. However, the morphological portrait of these tumors, described in the book "Endocrine granulocytomas," has not lost its relevance. Thus, at present, we pay a deep tribute to the authors of this guide, and the term "apudoma," according to the figurative expression of O.K. Khmelnytsky "foreign-branded," still has historical significance today.

Currently, advances in the development of research on neuroendocrine tumors have become extremely important because new diagnostic methods are used. Successes of the immunodiagnostic method allowed the development of new classifications and creation of targeted therapy drugs, which leads to the implementation of an individualized treatment of patients with neuroendocrine tumors.

The increase in the number of diagnosed neuroendocrine tumors worldwide is largely associated with the increased attention on this pathology. In addition to the usual routine research methods, molecular genetic methods are used to explain the etiology of these tumors from based on gene and chromosome disorders.

The classification of neuroendocrine neoplasms that can be localized in different organs was one of the most important changes in the 5th edition of the WHO classification of gastrointestinal tract tumors (2019) [6]. Common features that determine the classification of all neuroendocrine neoplasms are presented in a separate introduction.

According to the 2017 consensus agreement, experts proposed to distinguish highly differentiated neuroendocrine tumors from poorly differentiated neuroendocrine carcinomas in all areas where these neoplasms arise.

The use of genomic data led to a change in the classification of mixed neuroendocrine neoplasms. They are grouped under the conceptual category "mixed neuroendocrine-non-neuroendocrine carcinomas," similar to changes in adenocarcinomas, or neuroendocrine carcinomas rather than neuroendocrine tumors, and are likely to reflect clonal evolution within tumors, which garnered the growing interest of researchers. The study of these mixed carcinomas may lead to a clearer understanding of other aspects of tumor clonality, in particular tumors of the digestive system, as well as other tumors of organs and tissues.

This topic is widely developed within the walls of our institution, including the multidisciplinary approach by O.K. Khmelnitsky. The life path of an outstanding Russian pathologist is highlighted in the article by Khmelnitskaya et al. (2020) [7]. O.K. Khmelnitsky was an unusually talented and creative person. Undoubtedly, Oleg Konstantinovich belongs to the elite individuals who bring good knowledge and art.

Conclusion. The cited research results at a new methodological level show modern achievements that make it possible to reveal pathomorphological processes described above. Based only on previous knowledge, it is possible to interpret the results obtained in a new way and apply them in the treatment of patients.

In celebration of the 100th anniversary of his birth, O.K. Khmelnitsky — a talented scientist who made an invaluable contribution to the development and improvement of pathological anatomy — everyone who had the opportunity to communicate with him remembers him with gratitude.

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