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Rare forms of skin cancer

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ABSTRACT

In recent decades, there has been a steady increase in the incidence of skin cancer worldwide. Annual growth is from 3 to 10%. In the structure of the oncological morbidity of the population of the Russian Federation in 2016, malignant skin neoplasms (MSN), with the exception of melanoma, took the second ranking place, making up 11.7% (74 551 patients) among cancer patients. 81.3% of patients were diagnosed with the I stage of MSN, 15.8% — with stage II, in 1.9% — with stage III, 0.5% — with stage IV. Mortality in the first year since diagnosis was 0.6% in Russia and 1.6% in Moscow. Over the past decade, an increase in the incidence of skin cancer in Russia amounted to 26% (2007—2017).

The risk group includes people with a light skin phenotype. In addition, skin cancer is more common in people who spend most of the time outdoors in direct sunlight.

Despite the high prevalence of skin cancer and low mortality from it, there are conditions that are much more aggressive in the clinical course and are less treatable with standard methods — so-called rare (orphan) skin tumors. This article discusses these forms, describes the classification, etiology, risk factors, diagnostic and treatment methods for the possibility of rational prognosis and modern treatment of patients.

Keywords: skin cancer, squamous cell carcinoma, Merkel cell carcinoma, vulvar cancer, penile skin cancer, metatypical skin cancer, skin appendages tumor, TNM-classification.

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To date, rare forms of skin cancer remain understudied. Nevertheless, according to many foreign sources, these diseases are the most aggressive malignant tumors, as they have a high tendency to regional and distant metastasis. The difficulty in diagnosing rare forms of skin cancer lies in their similarity with common forms of malignant skin tumors. This review highlights current work in this area and outlines the main aspects of diagnosis and treatment.

Merkel-cell carcinoma

Merkel-cell carcinoma (MCC) is a rare malignant skin epithelial tumor with neuroendocrine differentiation that does not have a dysplastic precursor. Despite the rarity, MCC is one of the most aggressive malignant tumors with high metastatic potential. Accroding to the research from Paulson K.G., 2000–2013, the number of reported cases of MCC in the world increased by 95%. In 2013 in the USA the incidence rate of MCC was 0.7 cases per 100.000 people, which corresponds to 2488 cases per year and is expected to exceed 3000 cases per year by 2025 [1]. There is currently no precise determination of the origin of this type of skin cancer. MCC cells have immunophenotypic and ultrastructural similarities with normal Merkel cells However, Merkel cells are rarely found in this carcinoma. Currently, there is no fundamental evidence regarding a MCC host cell. Nevertheless, Erovic I., Erovic B. believe that MCC originates from pluripotent stem cells of the skin, and this is confirmed by the fact that the Bmi-1 marker is positive in 100% MCC samples [2]. According to Zur Hausen, carcinoma originates from pro / pre— and pre-B cells; there is also an opinion that MCC originates from dermal fibroblasts [3,4]. The main causes of CM are the clonal integration of Merkel cell polyomavirus (MCPyV) and chronic exposure to ultraviolet radiation. Thus, there are virus-positive (VP-MCC) and virus-negative (VN-MCC) MCCs: Research by Feng H. et al. showed that MCPyV was detected in 8 out of 10 cases (80%) of MCC [5,6]. According to research by James A. DeCaprio, MCPyV causes a lifelong but relatively harmless infection, and is one of 14 different types of human poliomaviruses. Poliomaviruses usually do not cause disease in healthy people and mainly affect immunocompromised patients [7]. Poliomavirus triggers a cascade of carcinogenesis, initiating the production of cancer proteins: LT (large tumor antigen) and ST (small tumor antigen), which in turn are expressed by MCC cells, as well as MCPyV activates genes encoding 57-kT antigenic transcripton [8]. In addition, there is a correlation between MCC and cell DNA damage mediated by ultraviolet radiation, which leads to a high mutational load on the

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tumor and inactivation of tumor suppressor genes, including RB1 and TP53 [9, 10]. The second most important risk factor for the development of MCC is the effect of ultraviolet radiation (UVI): according to Heath, James, MCC in 81% of cases was registered in people living in regions with increased insolation, and 98% of them had fair skin [11]. The incidence of MCC is directly related to gender, age, and phototype. In the United States, most patients are elderly. Studies of Albores-Saavedra J. showed that the incidence is higher in men (2380 cases, or 61.5%) than in women (1490 cases, or 38.5%) of 3870 cases recorded. Moreover, most patients were fair-skinned (94.9%) aged 60 to 85 years. MCC was a very rare tumor in blacks. The ten-year relative survival was higher in women than in men (64.8 versus 50.5%, p <0.001). Fifty to sixty-seven years old patients had the highest 10-year relative survival (59.6%). The stage of the disease was the best predictor of survival [12]. In addition, a study by Lanoy E. showed that MCC is more common in individuals with immunosuppression: there is an increase in the risk of CM in individuals with immunodeficiency, patients after organ transplantation, with lymphoproliferative malignant tumors (chronic lymphocytic leukemia [CLL] or HIV-associated leukemia). Several researchers reported that the prognosis in individuals with immunosuppression with MCC is poor, but no other relationship was found in other studies [13]. MCC is a dense, painless, fast-growing, red-violet knot with a smooth surface. The most commonly affected areas are head and neck (50%), trunk (30%), upper and lower extremities (10%), but MCC may occur on any part of the body, including on the mucous membranes [14]. MCC occurs in the dermis and only occasionally presents with epidermal lesions [11]. Given the absence of characteristic clinical features, in most cases, MCC in is diagnosed on the basis of the morphological studies. Diagnosis of MCC with light microscopy is often difficult due to the similarity of symptoms with other low-grade small-squamous tumors. The trabecular type, the intermediate type (80%) and the small cell type (10%) are distinguished. Differential diagnosis with melanoma, lymphoma and small cell lung cancershould be carried out. An accurate diagnosis of MCC is possible only by immunohistochemical analysis using a wide range of antibodies characteristic of microscopically similar tumors (**Table 1**) [15,16].

Platelet-derived growth factor receptor (PDGF), C-kit (CD117) and phosphoinositide-3-kinase (PI3K) are often expressed in tumors, and this overexpression may be associated with a worse prognosis for patients with MCC. Although analysis of samples with PI3K mutations suggests a more aggressive tumor, a relationship between the status of PI3K mutation and patient survival has not been established [17]. Several other biomarkers, including PD-L1, p63, vascular endothelial growth factor receptor (VEGFR), Ki-67, CD34, Ep-CAM, and nuclear factor B, t have been suggested for the prediction of treatment outcomes for patients with MCC. According to the results of the Focky E. study, computed tomography as a method of early staged imaging in patients with MCC leads to fewer follow-up studies and the rapid completion of tumor diagnosis [18]. The choice of treatment depends on several characteristics of the disease, including the stage (especially in relation to the location of the tumor), the level of invasion, concomitant diseases and the patient's condition. Since CM is a rare tumor, established treatment

Table 1. **Marker-specific antibodies [15]**

Specific antibodies for the markers of	MCC	B-cell carcinoma	Melanoma	Small-cell lung cancer
Cytokeratin 20 (CK20)	+	–	–	–
Vimentin	–	+	+	–
Neurofilaments	+	–	–	–
Chromogranin A (ChrA)	+/–	–	–	–
Neuron-specific enolase	+	–	–	+/–
S100	–	–	+	–
Leukocyte common antigen	–	+	–	–
Thyroid transcription factor	–	–	–	+

Table 2. **Merkel cell carcinoma treatment algorithm [17]**

Stage	Treatment algorythm	Notes
Stage I	Surgical treatment	Adjuvant chemotherapy not recommended
Stage II	Surgical treatment + radiation therapy (postoperative scar and regional areas)	
Stage III	Surgical treatment +/— radiation therapy when indicated	• Routine adjuvant chemotherapy is not recommended, but may be used in some cases • Cisplatin +/— etoposide • Carboplatin +/— etoposide
Stage IV	Drug treatment: Chemotherapy, immuno-oncologic therapy Radiation therapy Clinical trials participation	• Cisplatin +/— etoposide • Carboplatin +/— etoposide • Topotecan • Cyclophosphamide, doxorubicin and vincristine • Pembrolizumab

methods are often based on retrospective rather than prospective randomized trials **(Table 2)**.

Surgical treatment. Primary method of treatment for the early stages of MCC is tumor excision. The recommended indent within normal tissue is 1–2 cm (according to the recommendations of the National Comprehensive Cancer Network). However, half of patients with MCC have a relapse of the disease (usually within 2 years after diagnosis) [19]. In patients without clinical signs of regional lymph node damage (N0), a sentinel lymph node biopsy is recommended, if possible. In case of a metastatic lesion of the regional lymph nodes, lymphadenectomy is performed. Cytotoxic chemotherapy is usually used to treat patients with metastatic MCC, but not as adjuvant therapy. Although MCC is often sensitive to chemotherapy in first-line conditions, the responses are rarely long-term, and most patients subsequently relapse with the development of metastases. Treatment with metastatic MCC with PD-1 / PD-L1 immune checkpoint inhibitors (avelumab, pembrolizumab, nivolumab) and anti-CTLA-4 agents led to a significant improvement in treatment, immunotherapy (characterized by good tolerance) led to a quick, long-term response [20, 21].

In March 2017, the monoclonal antibody PD-L1, avelumab, was the first approved treatment for MCC [22]. According to Green MD, radiation therapy (RT) is most often used as adjuvant therapy to improve local control in patients with MCC. Nevertheless, this method can be used as monotherapy for patients who refuse surgical treatment, as well as palliative treatment in patients with terminal stage of the disease [23].

Metatypical basal cell carcinoma

Metatypical basal cell carcinoma (MBCC) is a rare aggressive epithelial malignant tumor, an intermediate form between basal cell (BCC) and squamous cell carcinoma (SCC), which is reflected in the histological picture of the tumor. This is of great prognostic value, since MBCC of the skin is characterized by infiltrative growth with the spread and destruction of the underlying tissues, pain and bleeding, the formation of distant metastases and frequent local recurrence, but at the same time it simulates both BCC and SCC both clinically and morphologically. Thus, the main and most accurate diagnostic criterion can only be a histological examination [24]. MBCC was first described by MacCormas in 1910 as a histological version in a series of ulcers in rodents in which basal cell and squamous tumors were present "side by side", without a transition zone, as a result of the fusion of two autonomous tumors: basal cell and squamous cell tumors. MBCC is considered a particularly aggressive form of basal cell carcinoma, with an increased risk of metastases and a pronounced tendency to relapse [25,26]. Based on data from Sune Frankild, Albert Pallejà, Kalliopi Tsafou, Lars Juhl Jensen, hand-selected database annotations, oncological mutation data, and studies of entire genome associations, the following genetic mutations were identified for metatypical basal cell carcinoma **(Table 3)**.

During histological examination, cell clusters with a mesh configuration, consisting of an incomplete outer layer of dark staining basal cells and an inner layer, which actually represents most of the tumor, with larger and brighter stained cells are noted. There are two primary subtypes: mixed one, incidence of which is 32%, and an intermediate one — 68% [27]. MBCC may occur primarily on normal skin or as a relapse of basal cell carcinoma. Cases of MBCC development after radiation, cytostatic therapy, and cryodestruction have been described. Usually, MBCC is described as a single ulcerative lesion, however Snarskaya E.S. described three foci of MCC in one patient on the skin of the face [28]. In 1996-2006 a retrospective study (n = 240) was conducted at the Department of Plastic Surgery of the University of Rome "LaSapienza" The study included 90 women and 150 men aged 27 to 95 years. The average age of patients with metatypical basal cell carcinoma was 70.5 years. Moreover, it was found that this type of tumor affects men (62.5%) more often than women (37.5%) [29].

In 2011 Tarallo M. conducted a retrospective study of MBCC (n = 327; 213 men, or 65%; 114 women, or 35%). Most often, MBCC was localized in the cervical-facial region — in 220 (67.3%) patients, on the torso — in 33 (10.1%), in other areas — in 29 (8.86%), on the extremities— in 32 (9.8%), on the scalp — in 13 (4%), which confirms the data of earlier studies **(Table 4)** [30]. Incidence of MBCC is 4.5% of all BCC and 8.5% among its ulcerous species. The average duration of an oncological history from the time of the initial diagnosis of BCC to the diagnosis of MBCC is 7.7 years. According to Snarskaya E.S. and Molochkov V.A., most often, MBCC is localized on the face, especially in the nose and auricles, somewhat less often in the temples, forehead, scalp, neck, back, localization on the extremities is possible, which is not typical for basal cell carcinomas, as well as on the tongue, larynx, pharynx [31]. More often it metastasizes to the re-

Table 3. **Association between genes and MTSC [26]**

Gene	Score	Accuracy
SLC12A2	5,4	***
AGGF1	3,4	**
IDO1	3,3	**

Notes. The confidence of each association is indicated by asterisks, where *** is the highest confidence, and * is the lowest.

Table 4. **Incidence of MTSC depending on localization [30]**

Localization	%
Cervical-facial region	71,7
Torso	10
Extremities	9,6
Scalp	3,7
Other regions	5

Note. Relapse occurred in 24 cases (10%), mainly in the head and neck.

Table 5. **Comparative pathomorphological characteristics of metatypical cancer, basal cell carcinoma and squamous cell carcinoma [33]**

Patomorphologic signs of tumor	Patomorphologic signs of tumor		
	MBCC	Basalioma	Squamous cell carcinoma
Cords type	Elongated, irregular basaloid cords	Basaloid cords of various forms and sizes	Elongated, peculiarly-shaped cords from atypical prickle cells
Signs of structure orderliness	Destruction of the "palisade" on some of the peripheral areas of the cords,	Pronounced "Palisade" structure or radical cord periphery orientation of the cells.	No
Differentiation	Basaloid cells towards the prickle elements	Elements of skin appendages	No
Growth type	Infiltrative active	Infiltrative	Active infiltrative and destructive

gional lymph nodes, more rarely, by the hematogenous route, in addition, tumor cells can spread along the neural spaces or to neighboring organs with invasion of vessels and neural spaces (**Table 5**) [32].

Surgical treatment is the promary method of treatment of the MBCCs; cytostatics, photodynamic therapy, and other methods used to treat skin basalomas are also used [33]. According to Snarskaya E.S., Plieva L.R., Maksimova I.S., a complex pathogenetic method for the treatment of MBCC has been developed and patented, including interstitial administration of recombinant interferon-α2 β (intron A, reaferon) in combination with a course of prospidine (patent No. 2229306 dated 05/27/2004). This method allows makes it possible to influence the pathogenesis of the tumor process, does not have a damaging, aggressive effect on the tissues surrounding the tumor, and is also easy to use, including in outpatient treatment of patients, has a great advantage compared to other treatment methods [34].

Skin Appendages Carcinoma

Skin appendages carcinoma (SAC) is a heterogeneous group of extremely rare malignant epithelial tumors, characterized by a diverse histological structure with a tendency to regional and distant metastasis. Usually, skin appendage carcinomas are less common than benign neoplasms, and are more common in Western countries with a Caucasian population. Depending on the alleged origin, tumors from the appendages of the skin include tumors of eccrine, apocrine glands and hair follicle. Most of these types of tumors show similarities with benign neoplasms [35]. From January 1, 1990 to August 31, 2012, a retrospective review of patients treated at the Roswell Park Cancer Institute was conducted under the supervision of Tolutope Oyasiji . The study included adult patients aged 18 years and older with a histologically confirmed SAC diagnosis. Patients with a concomitant diagnosis of BCC, SCC and melanoma were excluded. The incidence rate among men is statistically significantly higher than among women (6.3 versus 4.2, respectively; the incidence rate of men and women is 1.51; p <0.001). Among the patients there were 28 (56%) men; the average age for this series was 59.5 and 62.4 years, respectively. It should be noted that over the past 30 years, the incidence rate of these tumors has increased by 150% [36]. According to Martinez S.R.,, a 5-year survival rate for patients with malignant tumors of the appendages of the skin is 54%. Adverse factors for the development of SAC are old age, male gender, the presence of distant metastases, stage IV tumors [37].

The etiology of the development of skin appendages carcinoma is unclear. In some cases, the cause is considered an autosomal dominant mutation in the tumor suppressor gene. Risk factors are UV exposure and immunosuppression. There is currently no consensus on treatment. In the absence of metastases, the standard of treatment is surgical removal (possibly using the Mohs' micrographic surgery method). If metastases are present or if surgical complete removal is not possible, chemotherapy and / or radiation therapy may be suggested. Careful monitoring is indicated [38]. In the presence of distant metastases, the tumor is usually resistant to standard chemotherapy. It is reported that the targeted drug sunitinib (an oral tyrosine kinase inhibitor) is also effective in treating SAC. Battistella M., Mateus C described the effective use of the drug sunitinib: in the first patient, the tumor was stabilized for 8 months by sunitinib before it recurred; the second patient (with a hair follicle tumor) achieved partial remission with sunitinib, and the stabilization of the disease occurred after 10 months. It is worth noting that a dynamic ultrasound study with contrast enhancement, performed to evaluate tumor vascularization during treatment, showed a sharp and early decrease in tumor vascularization [39].

Conclusion

Thus, rare forms of skin cancer are highly malignant tumors. Since these diseases are rare, large-scale clinical trials are difficult to conduct. Therefore, it is logical that many sources often describe clinical cases, retrospective analyzes of databases, or the results of small clinical trials.

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