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EPIDEMIOLOGY, PATHOGENESIS, CLINICAL COURSE AND TREATMENT METHODS OF MELANOMA

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Abstract: Melanoma is a highly aggressive malignant tumour that develops from skin melanocytes and, despite being relatively rare among skin cancers, accounts for a significant proportion of deaths. According to global data, about 330 thousand new cases of melanoma and more than 58 thousand deaths are registered annually. The main risk factor is ultraviolet (UV) radiation, including sunlight and solar cells, which, along with hereditary factors, skin phototype, the number of nevi, and immune status, play an important role in the development of the disease. This article covers the epidemiological indicators, pathogenesis, main molecular mechanisms, clinical classification, diagnostic approaches, and modern treatment methods of melanoma.

Input

Melanoma is a malignant tumor originating from melanocytes, most commonly found in the skin (cutaneous melanoma), but may also develop in the retina, mucous membranes, and other areas. Although melanoma accounts for a small percentage of all skin cancers, it is one of the leading causes of death from skin cancer.

With late diagnosis, metastases develop rapidly and the prognosis deteriorates sharply, therefore, early screening, risk assessment, and strengthening of preventive measures are relevant.

Epidemiology

According to global data:

The annual number of new cases of melanoma according to the GLOBOCAN database for 2022 is approximately 331,700.

On a global scale, melanoma ranks approximately 17th among all types of cancer.

Over the past decades, morbidity rates have been steadily increasing, especially in the light skin population.

Many epidemiological studies show a significant increase in the incidence of melanoma in areas with high doses of UV radiation, as well as in populations that "accumulate" in the sun and actively use solar cells.

Risk factors

The following factors have proven importance in the development of melanoma:

Ultraviolet radiation

UV radiation (solar and artificial solar cells) is the main, modifiable risk factor.

Repeated sunburns in childhood and adolescence significantly increase the risk of developing melanoma in the future.

Due to the fact that regular use of solar beds significantly increases the incidence of melanoma, the issue of their restriction or prohibition is being discussed in a number of countries.

Skin phototype and phenotypic features

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Individuals with phototypes I-II (very pale skin, blue or green eyes, yellowish hair) have a higher risk of melanoma.
The presence of multiple banal nevi (>50) and dysplastic nevi increases the risk.

Hereditary factors and family history

About 5-10% of cases of melanoma are familial forms; Syndromes associated with mutations in tumor suppressor genes, such as CDKN2A (e.g., FAMMM), have been described.

Immunity status

Patients with immunosuppression (organ transplantation, AIDS, etc.) have an increased risk of melanoma and skin cancer in general.

Pathogenesis and molecular mechanisms

In the pathogenesis of melanoma, damage to DNA caused by UV radiation and a lack of mechanisms for its restoration occupy a central place. UV rays cause mutations in melanocytes, which leads to disruption of the signaling pathways controlling cell proliferation, apoptosis, and differentiation.

4.1. MAPK pathway and main driving mutations

The most important molecular changes in melanoma are:
BRAF mutations (most often V600E) - occur sharply in most cutaneous melanoma and constantly activate the MAPK (RAS-RAF-MEK-ERK) pathway.
NRAS (in most cases in the Q61 codon) - enhance proliferation similarly to the BRAF mutation.
KIT, NF1 and other genes are especially important in acral and mucous melanoma types.
These mutations enhance the ability of tumor cells to grow, survive, and evade the immune system and serve as targets for targeted therapy.

Clinical presentation and classification

Clinical types

The main clinical and histological types of melanoma are:
Superficial spreading melanoma
Nodular melanoma
Acral lentiginous melanoma (under palms, feet, and nails)
Lentigo maligna melanoma (often elderly, facial area)
Melanoma of mucous membranes
Clinically, melanoma most often manifests as a nevus or as a newly formed pigmented tumor. The ABCDE criterion (Asymmetry, Unevenness of the boundary, Variation of color, Diameter >6 mm, Evolution - change over time) is widely used in practice.

AJCC 8th Edition Staging

In the staging of melanoma, the AJCC system (8th edition) is based on clinical and pathological indicators of T, N, M:
T (tumor) - thickness (in mm), presence or absence of ulcer
N (nodus) - regional lymph node involvement
M (metastasis) - presence of distant metastases and their localization
The 8th edition of AJCC is currently the most accepted system for early staging of melanoma.

6. Diagnosis

The diagnosis of melanoma consists of several stages:

Clinical examination

The patient's entire skin is carefully examined, and the number, shape, and variation of nevi are assessed.
Dermatoscopy helps to assess thick pigmented tumors.

Biopsy

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- Complete excision biopsy of the tumor (along with its width) - "gold standard."
Histological examination reveals prognostic indicators such as Breslow thickness, mitotic activity, ulceration, and lymphatic invasion.

Sentinel lymph node biopsy

- Used at certain stages to detect micrometastases in regional lymph nodes.

Depiction methods

CT, MRI, PET/CT - for detecting metastases to the lungs, liver, brain, bones, and other organs.

Molecular tests

- Detection of mutations in BRAF, NRAS, KIT, and other genes is necessary when choosing targeted therapy.

Treatment

Treatment tactics depend on the stage, molecular profile, and the patient's general condition. The individual treatment plan is formed by a multidisciplinary team, including an oncologist, dermatologist, surgeon, and other specialists.

Surgical treatment

In the early and middle stages, the main method is extensive excision, which is performed at a predetermined distance from the surrounding healthy tissue.
If the sentinel lymph node is positive, in some cases, additional lymphadenectomy is considered.

Immunotherapy

In recent decades, immune checkpoint inhibitors have revolutionized the treatment of melanoma:
Anti-PD-1 (nivolumab, pembrolizumab, etc.)
Anti-CTLA-4 (ipilimumab) or combinations
In metastatic and high-risk post-resection (adjuvant) melanoma, these drugs have become the current standard, significantly improving overall survival.

Targeted therapy

Based on the molecular profile:
BRAF-mutant melanoma - BRAF inhibitors (dabrafenib, vemurafenib, etc.) + combination of MEK inhibitors (trametinib, etc.).
KIT-mutant acral or mucous melanoma - Tyrosine kinase inhibitors (e.g., imatinib) may be effective in some cases.
However, there is a problem of drug resistance and side effects, and research on combination strategies continues.

Chemotherapy and radiotherapy

In modern conditions, chemotherapy (dacarbazine, etc.) is mainly used in cases where immuno- and targeted therapy is ineffective or absent.
Radiotherapy is used for palliative purposes or for symptomatic control in cases of brain and bone metastases.

Prevention and early detection

Melanoma, especially cutaneous forms associated with UV radiation, is considered to be a **preventative** disease to a large extent. Main directions:

Sun protection

- Avoid direct sun exposure during peak hours of UV radiation
- Closed clothing, wide-brimmed headwear, glasses
- Daily use of broad-spectrum sunscreen with SPF ≥30

Rejection of Solarium

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- Due to the fact that the use of sunbeds significantly increases melanoma, discussions about their restriction and prohibition have intensified in many countries.

Self-examination and early medical consultation

- Regular observation of all nevi and newly appeared pigmented spots
- If there are changes corresponding to the ABCDE criterion, see a dermatologist immediately.

Screening of high-risk groups

- Regular dermatoscopy and follow-up examinations are recommended for patients with pale skin, multiple nevi, family history of melanoma.

Conclusion

Melanoma is the most aggressive and high-mortality skin cancer, placing a significant burden on the global health system. UV radiation, in particular burns in childhood and adolescence, use of solaria, pale skin phototype, multiple nevi, and hereditary syndromes are the main risk factors.

Hyperactivation of the MAPK pathway, associated with UV-induced DNA damage and mutations in genes such as BRAF, NRAS, KIT, NF1, plays a leading role in pathogenesis. Staging according to the 8th edition of the modern AJCC, biopsy of the sentinel lymph node, and molecular tests allow determining the prognosis and treatment strategy.

Immunocontrol point inhibitors and targeted therapy significantly increased the survival time in metastatic melanoma, however, the problem of resistance and side effects has not been fully resolved. At the same time, it is possible to significantly reduce the incidence of melanoma and mortality by limiting UV radiation, protecting against the sun, avoiding solaria, and strengthening early diagnostic measures.

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