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What should every doctor know about ocular melanoma? - review of literature

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Purpose

The aim of this study is to present the current state of knowledge on ocular melanoma.

Review methods

The PubMed and Google Scholar databases were used for the literature review. The following phrases were searched for in English: “ocular melanoma”, “uveal melanoma”, “iris melanoma”, “ciliary body melanoma”, “choroidal melanoma”.

Key words: melanoma malignum, ocular melanoma, uveal melanoma, iris melanoma, ciliary body melanoma, choroidal melanoma

Abstract

The following paper aims to discuss melanoma located in the eye. Melanoma is a malignant tumor arising from melanocytes, in which a mutation has occurred in the DNA and pathological cells have developed. In most cases, this tumor is located on the skin exposed to sunlight, but it is also rarely located in the structures of the eye, especially in the part called uvea. It consists of the anterior and posterior parts, and in each of them the process of carcinogenesis can occur. The disease can cause very non-specific symptoms, mainly pain, visual disturbances, floaters and photopsia, or exophthalmos, but almost half of the cases are asymptomatic. Treatment is complicated and depends on many factors, radiation therapy, laser therapy, local resection and enucleation are used. Most patients are diagnosed when the changes are already extensive, or metastases occur. In the case of liver metastases, the prognosis is unfavorable. For this reason, we want every doctor to pay attention to the eye symptoms reported by the patient in order to be able to recognize this disease as soon as possible and treat it effectively.

Introduction

Melanocytes are cells derived from neuroectoderm, which are responsible for maintaining cutaneous homeostasis.[1] They are mainly located in the epidermis and hair follicles and have the ability to produce melanin pigment.[2] When mutations occur in their DNA, pathological cells are formed, the further changes of which lead to carcinogenesis and the development of melanoma.[3,4] The main risk factors for the development of these changes are ultraviolet (UV) light and deficiency of the p16ink4a gene.[3,4,5] Mutations that

overactivate BRAF and NRAS are also known.[6,7] Diagnosis is based on histopathological examination of a sample of the lesion.[8] There are four basic histopathological types of melanoma, which is superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma.[9,8] It can be distinguished from other skin cancers by immunohistochemical staining methods: S100, Melan-A, and human melanoma black-45 (HMB-45).[8] The Breslow thickness scale is used as a survival prognosis, while the second known Clark scale should not be used as a prognostic indicator for survival.[10, 11] The main locations of melanoma are sun-exposed areas, mostly facial areas and upper back.[12] Approximately 17.9% of lesions are located in the head, but this varies depending on age and gender - in older people, lesions are more common on the head and neck, while in young people they are more common on the limbs, in women the lesions are more common on the lower limbs, and in men on the torso.[13, 14] Diagnosed in the early stages, it has a 94% survival rate, but when metastases occur, this rate drops significantly.[15, 16] 15% of patients with melanoma have metastases at diagnosis or develop them during the course of the disease.[17] Characteristics of a lesion that does not tend to metastasize include a size of < 1 mm in vertical dimensions.[18] A well-known prognostic factor is the status of the sentinel lymph node.[8, 19] Determining the stage of the disease determines the possible methods of treatment, which include surgery, radiotherapy and chemotherapy.[20] Recently, there has been significant progress in melanoma therapy thanks to the introduction of immunotherapy.[21] It should be remembered that melanoma increases the risk of developing multiple primary melanomas, which is why it is important to remain under oncological supervision.[22]

Less common locations of melanoma are the areas and structures of the eye, i.e. the uvea, conjunctiva, eyelid and eye socket.[23] There are two types of melanin in the eye - eumelanin, referred to as photoprotective, and pheomelanin, phototoxic.[24] Uveal melanomas are the most common intraocular malignancy in adults.[25] Among ocular melanomas, about 83% arise from the uvea, 5% from the conjunctiva, and 10% from other sites.[23] The uvea is divided into two parts - the anterior part which is the iris and the ciliary body, and the posterior part which is the choroid - in each of these parts melanoma can develop.[26] The symptoms reported by the patient are nonspecific, patients most often complain of floaters and photopsia, change in eye pigmentation, pain, proptosis, loss of field of vision and vision loss, rarely vitreous hemorrhage, however in about 40% there are no symptoms and the change is detected accidentally.[27] Diagnosis is based on the use of slit-lamp evaluation, high-frequency ultrasound, fluorescein angiography, anterior and posterior segment optical coherence

tomography, computed tomography, and magnetic resonance imaging.[28, 27] The basic methods of treatment are radiation therapy, laser therapy, local resection and enucleation.[29] Most cases of the disease are detected when the neoplastic changes are extensive with features of infiltration of the iris or choroid.[30] The most common distant metastases are located in the liver and are associated with an unfavorable prognosis.[31] Approximately half of patients will develop metastases within 10 years of diagnosis.[32]

Epidemiology

The occurrence of melanoma varies depending on geographical latitude. In Europe, the incidence of uveal melanoma increases directly in proportion to geographical latitude, with a minimum of 2 per million per year in Spain and southern Italy, to a maximum of 8 per million per year in Norway and Denmark.[33] This is related to the dark pigmentation of both the irises and skin of residents in southern European countries. The incidence of uveal melanoma is low in Africa and Asia, with an incidence rate of 0.2 – 0.3 cases per million per year.[34] Uveal melanoma mainly affects older generations. There is an increasing trend up to the age of 75, after which a plateau effect is observed. The average age of diagnosis of this cancer in European countries and the United States, where the dominant population is Caucasian, is between 59 and 62 years. In Asian countries, the median age of onset is slightly earlier, typically between 45 and 55 years.[35] Studies have shown a higher prevalence of uveal melanoma among men. In an analysis of SEER data, the age-adjusted incidence of uveal melanoma was 5.8 per million in males compared to 4.4 per million in females.[36] Risk factors predisposing to the development of ocular melanoma include fair skin, light-colored irises, blonde hair, and susceptibility to sunburn after sun exposure.[35, 37] A connection has also been found between the presence of skin moles, including atypical ones, and freckles, and the development of choroidal melanoma. Studies have documented a 4.36 to 10.4 times higher risk of developing choroidal malignancies compared to individuals without these skin changes. Increased risk of developing uveal melanoma is also associated with mutations in the BAP1 gene (BRCA1-associated protein 1), which is a tumor suppressor gene. Its mutation, whether somatic or germline, has been identified as a factor in the development of hereditary cancer syndrome.[35]

Clinical features

The clinical presentation of uveal melanoma and its diagnosis slightly vary depending on the anatomical location of the lesions. Therefore, we can distinguish melanoma in the:

- anterior part of the uvea: iris, ciliary body,

- posterior part of the uvea: choroid.

Iris

The iris is a structure located in the anterior part of the uvea. It is made up of connective and muscular tissue. It is about 12 mm in diameter and in the middle is an oval opening called the pupil.[38] In embryonic development, its cells differentiate from the optic cup and the periocular mesenchyme. Its structure consists of the iris pigmented epithelium, then the iridial muscles- sphincter pupillae and the dilator pupillae and the iris stroma, describing from the back which is the closest to the lens.[39] The iris itself is a continuation of the ciliary body and it separates compartments of anterior and posterior chambers of the eye.[40] Its primary function is to control the amount of light falling on the retina, possible thanks to the aforementioned muscles.[38] Iris also regulates the amount of aqueous humor, which contributes to the regulation of intraocular pressure.[39] An individual's eye color is dependent on the amount and distribution of melanin in iris.[40] The main diseases related to this structure are angle closure diseases.[41]

Iris melanoma, due to changes in the color of the iris and distortion of the pupils, is usually detected 10-20 years earlier than melanomas of other ocular locations, without the need for additional diagnostic tests. Unfortunately, it accounts for a minority of diagnoses. It is classified into two forms: circumscribed (90%) or diffuse. It typically localizes in the lower quadrant. The main symptoms include, most common corectopia and then secondary glaucoma, angle seeding, ectropion uveae, hyphema and extraocular extension.[35] Secondary glaucoma may develop due to pressure on the angle of the anterior chamber of the eye.

The diagnosis of the diffuse form is more challenging due to its infiltrative, flat, and poorly defined growth pattern, with confluent or multifocal iris involvement.[42]

The American Joint Committee on Cancer (AJCC) classifies iris melanoma based on tumor location, tumor size in clock hours, tumor extension to the ciliary body and/or choroid, and associated features such as secondary glaucoma and extraocular extension. The tumors are divided into 4 groups (T1-T4).

In order to make a diagnosis of iris melanoma, slit-lamp examination is usually sufficient. Gonioscopy can be helpful to assess the drainage angle, its width, and thereby evaluate the risk of glaucoma development. For small-sized lesions, Optical Coherence Tomography (OCT) is essential for a detailed assessment of the anterior segment of the eye in high resolution. This examination, along with ultrasound biometry (B-scan ultrasound), is also

used to assess the extent of the lesions and potential infiltration into the posterior segment of the eye, including the posterior chamber. In some cases, fine-needle biopsy is used to confirm the histopathological diagnosis, particularly for small melanomas, to differentiate them from non-cancerous lesions before applying radical treatment methods.[43]

Ciliary body

The ciliary body is a structure of the uvea placed behind the iris. During development, it is formed from the optic vesicle and mesenchymal cells.[44] It is a continuation of the retina and choroid.[45] It consists of three main structures. The ciliary muscle, which is located in the stroma, participates in shaping the lens, controls the size of the pupil, cooperating with the iris muscles. The ciliary processes are attached to the lens by the fibrous zonular fibers thanks to which they participate in the accommodation reflex. Finally the ciliary epithelium, which is a structure composed of two parts. Pigmented part contains cuboid cells rich in melanin and nonpigmented part involved in the production of aqueous humor.[44, 45, 46, 47, 48] The ciliary body plays an important role in the ciliary processes: it is responsible for the aqueous humor production and the regulation of its output through the uveoscleral pathway.[44, 47] Another important role is the nutrition of the cornea, lens, and vitreous.[44]

Ciliary body melanomas are very rare, accounting for 0.3% of all uveal melanomas.[49] Due to their location, they are often detected late, when the melanoma is in a more advanced stage and the lesion is large. The most common symptoms reported by patients are vision deterioration—issues with sharpness—as well as signs of astigmatism, or painless loss of part of the visual field due to displacement of the visual axis. When intraocular pressure increases, the patient may experience pain and worsening of vision quality.[50]

Due to the unfavorable location of the melanoma, it is not visible during a slit-lamp examination or other instruments used in routine ophthalmic checks. Most lesions are detected when they invade the iris or choroid. Gonioscopy allows the detection of changes in the corneal-iris angle, typically with its narrowing. For small lesions, below 4 mm, special attention should be given to Ultrasound Biomicroscopy (UBM), which, due to its higher frequencies, penetrates tissues more deeply and allows for imaging of the ciliary body.[35]

Choroid

The choroid is a structure of the eye located between the sclera and the retina. It is approximately 200 μm thick in newborns and this dimension decreases with the aging of the organism.[51] It is most often composed of five layers: the acellular Bruch membrane, the

choriocapillaris, the Sattler small and medium vessels, the Haller large vessels and the suprachoroidal layer.[52] Its structure has been identified thanks to the use of indocyanine green angiography, laser Doppler flowmetry and ultrasonography.[53] As a vascular structure, its main task is to supply the outer retina. Other functions include: light absorption, thermoregulation, modulation of intraocular pressure and drainage of the aqueous humor from the anterior chamber.[54] Blood flow in the choroid is regulated by parasympathetic, sympathetic and trigeminal sensory nerve fibers.[55] With age, it undergoes atrophy, which is a risk factor for the development of glaucoma.[51, 56]

Melanomas are one of many diseases that develop in the choroid of the human eye. They constitute 80% of all cases of uveal melanomas.[57] They are mostly pigmented and should be suspected when there is orange pigmentation upon fundus examination, tumour thickness is more than 2 mm and on its largest basal diameter is more than 5 mm or there is a fluid in subretinal location. Vision loss is also an important sign.[58] More than half are located within 3 millimeters of the optic disc or fovea.[57] They extend from the vascular choroid and then push the retina towards the vitreous humor. They are nourished by underlying choroidal vasculature.[59] Choroidal nevus, choroidal metastasis, choroidal hemangioma should be taken into account in the differential diagnosis as they can imitate melanoma.[57, 60] There are two types of tumor: diffuse tumor and non-diffuse tumor melanoma. The diffuse type accounts for approximately 3-17% of choroid melanoma cases and is associated with a poorer prognosis.[32, 61] Treatment consists of several lines, depending on the stage of the tumor, the first line option is brachytherapy, the second treatment option is external beam radiotherapy and the third treatment option is stereotactic radiotherapy.[57] Metastases are a very important issue, because they largely determine the prognosis of the disease. As one of the three parts of the uveal tract in which melanoma can develop, choroidal melanoma is in the middle in terms of the frequency of metastases.[32] The risk of metastases depends on the size of the tumor and the mutation present in the tumor and increases with each additional millimeter of thickness and poorly defined margins of the tumor.[62, 63] Distant metastases are more common in the case of monosomy of chromosome 3, gain of chromosome 8q and somatic mutation in tumor suppressor gene BAP1.[57, 64] Patients who underwent local resection had significantly better 5-year overall survival than patients who underwent enucleation.[58]

Treatment of uveal melanoma

Treatment of uveal melanoma includes radiotherapy, laser therapy and surgery. Prior to treatment, patients undergo clinical assessment and investigations such as ocular ultrasonography, fundus examination, visual field assessment and optical coherence tomography. For small tumours <3 mm in thickness and <10 mm in diameter in the absence of risk factors, observation of the lesions described may be considered. If the lesions are larger or risk factors such as light eye colour, fair complexion, excessive tanning have been identified, the therapeutic options listed above should be decided upon.[65] The surgical treatment of ocular melanoma is classified as sparing including exo- and endoresection and radical treatment, which includes enucleation and exenteration. Historically, enucleation involving removal of the eyeball along with part of the optic nerve was considered the gold standard treatment for uveal melanoma. Today, enucleation is only applicable if the tumour size is large, if there is extensive tumour growth outside the eyeball and if there is a low likelihood of preserving vision after surgery. Modern ophthalmic methods aim to preserve the eyeball and save vision and therefore several forms of radiotherapy have been developed to maximise radiation doses while reducing side effects. The technique of choice for the treatment of uveal melanoma remains brachytherapy, using applicators with Ru-106 and I-125 isotopes, which emit gamma and beta radiation.[66] Brachytherapy involves suturing an applicator containing a radioactive source to the area of the sclera adjacent to the tumour and removing it after an appropriate dose of radiation. Iodine plates emit gamma radiation characterised by a greater range than the beta radiation emitted by Ru-106 applicators and are therefore used for tumours ≥10 mm thick.[67] During radioactive therapy, the radiation passes successively through the sclera, tumour, retina and vitreous body and is absorbed by them as it exits the eye. The use of intravitreal anti-VEGF after brachytherapy has been shown to reduce or delay the occurrence of macular oedema, moderate visual loss and visual acuity deterioration.[68] Previously, brachytherapy was often combined with another technique-transarterial thermotherapy (TTP). TTP involves superheating a tumour mass with a diode laser beam. Nowadays, both transepithelial thermotherapy and photocoagulation are methods used primarily for residual disease or less frequently as part of adjuvant therapy.[69, 70] A method that is also not currently used as a primary treatment is photodynamic therapy. Photodynamic therapy uses the intravenous administration of a photosensitive substance that is captured in newly formed blood vessels and then irradiates selected vessels leading to their damage.[71]

Another type of radiotherapy used in ocular melanoma is proton beam therapy. In this method, the proton beams are a source of ionising radiation. The advantage of this technique is

a very high degree of precision, due to the beam being aimed directly at the tumour lesion, which limits the damage to neighbouring tissues, and the possibility of using several daily fractions, which maximises the therapeutic index. The disadvantage, on the other hand, is the low availability of equipment in treatment centres.[71] After treatment with uveal melanoma radiotherapy, patients should be closely monitored for both local recurrence and distant disease. Patients should have an ultrasound of the eye every 3-4 months for the first 2 years, every 6 months for the next 2-3 years, and then once a year.[65] Radiotherapy can lead to numerous complications such as dry eye, scarring, skin discolouration, loss of eyelashes, keratitis, inflammation and scarring of the ducts and tear ducts. Late complications of radiotherapy include radiation retinopathy, cataracts and secondary glaucoma, of which retinopathy is one of the more common complications seen after eye irradiation. It involves damage to the endothelium of the retinal vessels, which manifests as retinal haemorrhages, cotton wool spots, exudation and microangiopathy. Diabetic patients with developed vascular lesions have been found to have a significantly higher risk of developing radiation retinopathy.[72] Scleral complications after radiotherapy are rare, which is due to the vascular-free and cell-poor structure of the sclera. Secondary glaucoma and secondary cataracts developing after radiotherapy depend primarily on the radiation dose and tumour size. The above-mentioned complications result in deterioration of visual acuity. Studies have shown that 43% to 49% of patients treated with brachytherapy developed significant visual loss within 3 years of treatment.[73]

For cutaneous melanoma, molecularly targeted drugs and immunotherapies are used in therapy. Unfortunately, attempts to use the aforementioned methods in uveal melanoma have not yielded promising results. Compared to other cancers, uveal melanoma is characterised by a low mutation burden and a small number of potential neoepitopes for effective antitumour immunity.[74] Other prospective studies have shown that conventional cytotoxic chemotherapy is also ineffective for both primary and metastatic ocular melanoma.[75] Despite attempts to introduce the aforementioned therapies, sustained clinical responses in patients have rarely been achieved. New perspectives in the treatment of uveal melanoma using light-activated particles of the pharmaceutical agent AU-011 synthetically produced from HPV-derived viral particles appear promising at this time. The drug is administered to the eye by injection into the vitreous body and then activated with a diode laser to destroy tumour cells.[76] Despite treatment of the primary eye tumour, studies have shown that around half of patients will develop metastases, with the liver being the first site of metastasis in more than 90% of cases. Metastases are most

often multiple and localised in both lobes. Systemic therapy for metastatic uveal melanoma using, for example, dacarbazine or combination therapy including a BOLD regimen has not yielded satisfactory results.[77] Modern systemic therapy includes the use of a fusion protein called tebentafusp - composed of a T-cell receptor fused to an antibody fragment that binds to CD3. As metastases mainly involve the liver, therapies targeting the liver directly are used in addition to tebentafusp to reduce the toxicity of systemic therapy. Examples of methods used include embolisation, ablation, surgical excision and transarterial chemoembolisation.[78] Transarterial chemoembolisation with cisplatin and carboplatin and selective internal radiotherapy in studies showed a partial response in patients analysed.

Summary

The above work is a review of knowledge about malignant melanoma located in the eyeball. We distinguish melanoma of the iris, ciliary body and choroid, which is the most common form of intraocular melanoma. Predisposing factors for the development of changes are fair skin, light iris color, freckles, exposure to UV light and age, with the average age of onset between 59-62 years. Symptoms reported by patients are usually non-specific, including pain or deterioration of vision. Diagnostics should begin with imaging the lesion using a slit lamp available in every ophthalmologist's office, and then extend it with high-frequency ultrasound, optical coherence tomography, and imaging techniques such as CT and MRI according to indications and suspected location of melanoma. Treatment methods include radiation therapy, laser therapy and surgical options. The liver is the most common site for distant metastases. They correlate with a poor prognosis - half of patients develop metastases within 10 years. Due to the location of the lesions and sparse symptoms, diagnosis is often made late, when the cancer is already in an advanced stage. In order to prevent the presented disease, it is necessary to remember about appropriate protection of the eye organ. It seems reasonable to use sunglasses with UV protection and regular eye check-ups, especially in people with risk factors for the development of eye melanoma.

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