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Comprehensive insights into uveal melanoma – risk factors, pathophysiology, prognosis, and diagnostic approaches

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Abstract

Introduction and purpose

Uveal melanoma is the most common primary intraocular neoplasm in adults, which originates from melanocytes and arises from the choroid, ciliary body, or iris. The range of symptoms is wide but there are also asymptomatic cases. Metastases mainly concern the liver, and their occurrence significantly worsens the prognosis. Therefore, early detection is so crucial. This article summarizes significant information regarding epidemiology, pathophysiological processes, and genetic abnormalities underlying the disease. Moreover, we highlight possible clinical manifestations and discuss currently applied diagnostic methods.

Description of the state of knowledge

The average annual incidence worldwide is 6 cases per million. Risk stratification takes into account mutations, chromosomal abnormalities, tumor size, or invasion of adjacent tissues. In clinical practice, several diagnostic modalities are available, such as gonioscopy, indirect ophthalmoscopy, fundus photography, ultrasound biomicroscopy, ocular ultrasonography, optical coherence tomography, angiography, computed tomography, magnetic resonance, and positron emission tomography.

Conclusions

The publications analyzed in this article have shown that uveal melanoma is quite a medical challenge. Understanding the disease pathogenesis and underlying genetic abnormalities that may be the target of drugs, could be of great importance for patients and may constitute a step towards a personalized approach. However, further research is necessary to recognize cancer mechanisms more precisely, expand diagnostic options, and consequently register targeted drugs and develop comprehensive management guidelines, especially for metastatic disease to achieve improved survival outcomes.

Keywords: uveal melanoma; pathophysiology; genetics; metastasis; diagnosis;

Introduction and objective

Uveal melanoma (UM) represents the most significant primary intraocular neoplasm in adults. It derives from modified melanocytes. The alternative terms for the tumor are choroidal or ocular melanoma [1]. The frequency of UM origin is as follows: 83% from uvea, 5% from conjunctiva, and 10% from other localizations [2]. Among uveal melanomas 90% develop in the choroid, 7% in the ciliary body, and 3% in the iris [3]. The neoplasmatic process involves the anterior uveal tract - containing the iris, or posterior - containing the choroid and ciliary body [4]. Posterior tract tumors characterize later diagnosis, increased frequency of metastases, and generally more malignant properties. Clinical presentation of the tumor reveals on average at the age of 60 years old. Among young patients before 20 years old, the more frequent is iris melanoma [5]. Because uveal melanoma is a rare cancer, knowledge about this disease may be scarce and not widespread. Therefore, this paper aims to change the current status. The intention of this article is to summarize significant information regarding epidemiology, pathophysiological processes and genetic abnormalities underlying the disease. Moreover, we highlight possible clinical manifestations and discuss currently applied diagnostic methods.

Material and methods

The literature referenced in this paper includes the manuscripts published in PubMed and Google Scholar scientific databases in 2010-2024 years regarding uveal melanoma, risk factors, pathophysiology, genetics, prognosis, and diagnosis.

The current state of knowledge

Epidemiology

The incidence of disease is the same in both sexes. Men belong to the more symptomatic group than women but the tumor dimension at diagnosis is wider among women [6]. Male gender is associated with a more severe course and the frequency of metastases within the first decade of the disease is higher in men than in women [7]. The average incidence worldwide is approximately 6 cases per million annually and this value is constant over the years [8].

Risk and prognostic factors

The disease is sporadic, but the pathogenesis may be related to dysplastic naevus syndrome and ocular melanocytosis [8]. Risk factors predisposing to initiation and occurrence of the neoplastic process include Caucasian ethnicity, light eye color – green or blue, fair skin, and welding [9]. The germline predisposing mutations include BAP1 (BRCA1-associated protein 1), MLH1 (mutL homolog1), and PALB2 (Partner and Localizer of BRCA2). Patients with atypical and common cutaneous naevi and cutaneous freckles belong to the risk group. Moreover, the exposition to blue light constitutes a risk factor but exposure to ultraviolet radiation is an ambiguous risk factor [10]. The age of clinical presentation of the tumor has prognostic significance and the course of disease is more convenient in children compared to adults. Kaliki et al. have concluded the younger the age at diagnosis of UM, the lower rate of metastasis [11].

However, the tumor size remains the most important prognostic factor. An uveal melanoma size determines the possibility of using therapeutic methods and each additional millimeter of thickness increases the risk of metastasis within 5 years by approximately 5% [12]. Among the histopathological poor prognosis factors, should be mentioned: domination of epithelioid cells with high mitotic activity, higher microvascular density, lymphocytic and macrophage infiltration, presence of fibrovascular loops, and large diameter of ten largest nucleoli (MLN) [13]. There are also several biomarkers whose expression correlates with increased risk of metastatic death, such molecules include IGF1R (insulin growth factor 1 receptor) and HLA (human leukocyte antigen) [14].

Metastasis

The metastatic disease affects up to 50% and even 30% of uveal melanoma patients within 10 years after local treatment. The estimated time of survival in disseminated disease is 3-16 months and a mortality rate is about 92% within two years.

Choroid is characterized by rich vascularization which is convenient for the nourishment of the ocular tissues but it facilitates the spread of neoplasm cells through the bloodstream. Because the lymphatic system of the eye is limited, metastases through this route, and regional spreading is extremely rare [15].

There are several predictors of spread such as older age, larger tumor size, ciliary body involvement, extraocular spread, epithelioid cytomorphology, chromosome 3 loss, chromosome 8q gain, class 2 gene expression profile, loss of BRCA1-associated protein (BAP1), presence of inflammation. The most common site of metastasis is the liver – about 90%. The other locations include lung, bone, skin, and lymph nodes [16]. It is considered possible that micro metastases may occur at the time of diagnosis, which due to limitations and diagnostic accuracy, are not visualized but may be responsible for relapses [17].

Symptoms and signs

Clinical manifestations of uveal melanoma may be various. The tumor could be detected accidentally due to an asymptomatic course. However, there are also some suggestive signs such as painless loss of vision or distortion of vision – metamorphopsia, blurred vision, photopsia –flashing or flickering lights, floaters, or pain. Discoloration of the iris and heterochromia, chronic conjunctivitis, or persistent episcleral injection may occur if an anterior segment of the eye is affected. Although it is rare, the disease may manifest as cataract or blindness. Moreover, it is possible the presentation of astigmatism, subretinal fluid accumulation in the case of larger tumor size, retinal detachment, pupil deformation, and secondary glaucoma. [18, 19].

Genetic abnormalities

The genetic disorders involved in UM development may include structural chromosome changes and gene mutations. Understanding the genetic background of the disease is significant because it creates new diagnostic possibilities, allows for the assessment of patient risk, and develops future personalized therapies. Among chromosome aberrations, there are monosomy 3, loss of 1p, 6q, 8p, and gain of 6p and 8q. The monosomy of the 3rd chromosome is the most common and is associated with an unfavorable course of disease, larger diameter of the tumor, high mitotic index, location in the ciliary body, epithelioid cell type, and tendency to infiltrate adjacent tissues. Both 3 monosomy, 1p loss, and 8q gain could increase the risk of metastasis [20]. The best-known mutations with pathogenetic significance for the tumor include GNAQ, GNA11, PLCB4, CYSLTR2, MAPKAPK5, and also BAP1, SF3B1, SRSF2, EIF1AX. These mutations bring different effects depending on what protein the mutated gene encodes. Some of them are exclusive mutations such as GNAQ – subunit alpha of guanine nucleotide-binding protein G(q) and GNA11 – subunit 11 of guanine nucleotide-binding protein. Mentioned mutations contribute to GTP-ase inhibition and continuous activation of G-protein which promotes cell proliferation with participation of pathways: MAPK, YAP, and PI3K/Akt [21]. The other abnormalities concern suppressor protein – BAP, splicing factor – SF3B1, translation initiation factor – EIF1AX, telomerase reverse transcriptase – TERT, cellular receptor – CYSLTR2 or phospholipase – PLCB4 [22].

The specific gene expression profile provides an opportunity to categorize patients into two classes according to the risk of metastasis: low-risk – class 1, and high-risk – class 2, with an average survival of 95% within 7 years among the first group and 30% among the second group [23]. Some authors emphasize the role of miRNAs (microRNA) in oncogenesis. MicroRNAs are non-coding particles involved in the regulation of gene expression.

Disorders resulting in its abnormal methylation, amplification, or deletion may contribute to pathological cell proliferation [24]. Epigenetics and incorrect methylation patterns could influence uveal melanoma pathogenesis. Bakhoum et al. report the particular importance of BAP1 hypermethylation in uveal melanoma development and found a high degree of methylation worsens the prognosis and constitutes the marker of distant metastasis [25].

Diagnosis

An inconvenient prognosis and often an advanced stage of disease at diagnosis create a necessity to detect the lesion as early as possible in the aim to implement the treatment. Taking into account the symptoms, patients may consult an ophthalmologist, neurologist, or family doctor.

At the beginning of the diagnostic process, a clinical examination is conducted to evaluate both segments of the eye [26]. The anterior one is assessed with slit lamp biomicroscopy and the posterior with indirect ophthalmoscopy. The last-mentioned test provides relevant information regarding the tumor such as size, location, and anatomical relation to the optic disc and foveola, ciliary body involvement, pigmentation, extrascleral extension, or retinal detachment. If visualization of a tumor is doubtful or impossible, the above-mentioned diagnostic tools allow for the detection of secondary features resulting from the presence of the neoplasm like cataract, subretinal fluid, orange pigment on the tumor, and episcleral sentinel vessels [27].

If any lesion in the posterior segment of the eye is suspected, a dilated fundus examination is necessary to be performed. Fundus photography (FP) after dilating the pupil significantly increases the range of tissues that can be observed and offers wide-field imaging which means greater than 50º field of view, some wide-field cameras can capture up to 200º [28]. Photographic documentation can be useful with very small dimensions of the lesion when the basal diameter is lower than 3mm and can be applied in the follow-up process. The manifestation of choroidal melanoma in FP is a brown flat, dome mass. The pathognomonic features remain mushroom or collar button shape which results from Bruch's membrane disruption. When the retina is damaged by neoplasm, this may result in vitreous bleeding [29].

If the anterior segment is involved, the most advantageous methods are gonioscopy, ultrasound biomicroscopy (UBM), and anterior segment optical coherence tomography (AS-OCT). In gonioscopy, the existence of abnormalities in the anterior chamber angle can be checked using special lenses and mirrors. It is significant in iris and ciliary body melanoma. Proliferating neoplastic cells may gradually obstruct the outflow of aqueous humor in the eye and, in extreme cases, lead to complete closure of the angle which manifests similarly to a glaucoma attack [30]. Transillumination makes it possible to confirm or exclude the involvement of the ciliary body in the disease process. This method is based on the assessment of the ocular structures with bright light and observing how the light penetrates [31].

Ocular ultrasonography (US) remains one of the most widespread diagnostic methods of UM which enables the detection of the tumor mass, its progression, and follow-up patients submitted conservative treatment. In ophthalmology high frequency transducers are implemented - 8 or 10 MHz. Higher wave frequencies do not reach deep into the tissues, but the resolution increases, and the obtained image is accurate and precise [31]. The A-scanning mode aims to perform biometric measurements and assess the mobility of the structures. The result is presented as an echogram with spikes on the isoelectric baseline.

The characteristic presentation of choroidal melanoma on A-scan is a positive angle kappa sign which means the spikes are high initially and decrease toward the sclera. The B-scanning mode is designed to obtain two-dimensional images of ocular structures in real-time which the examiner sees as grayscale views based on reflected waves. A typical presentation of uveal melanoma on B-mode comprises homogenous, low-acoustic mass, acoustic hollowing, excavation of choroid, and orbital shadowing. [32]. In general, the US provides crucial information regarding tumor apical height, internal reflectivity, shape, location, and retinal detachment. It is considered US to be a dedicated method for the detection of extraocular extension and is even more sensitive than MRI and CT. Due to the fact the waves penetrate the eye better than light, the US gains an advantage over OCT in imaging pigmented lesions. In turn, compared to MRI, the results obtained using the US overestimate the tumor size by 1mm [33]. Despite the repeatability of the exam, a significant limitation of this imaging technique is dependence on the examiner's interpretation.

Ultrasound biomicroscopy (UBM) is a B modality that adapts increased frequencies of ultrasound waves which further improves the resolution of the method. The dependencies are as follows wavelength ≈150 μm at 10 MHz and 30 μm at 50 MHz. Due to the absorption phenomenon, the validity of UBM use is limited to the anterior segment of the eye. An undoubted advantage is the penetration of opaque tumors, visualization of posterior tumor margin, and assessment of adjacent tissue invasion. UBM allows us to answer the question about the tumor extent, invasion of adjacent tissues, and whether the ciliary body is affected in the case of iris melanoma [34]. This modality is useful in detecting choroidal lesions with dimensions less than 4 mm and can be implemented in patients' follow-ups. Comparing UBM and AS-OCT in the anterior segment examination reveals biomicroscopy is more advantageous in posterior margin visualization and tumor configuration compared to OCT [35].

In fluorescein angiography (FA), after intravenous administration of fluorescein dye, retinal, choroidal vascularization, retinal pigment epithelium (RPE), and integrity of blood-retina barrier are examined. Abnormalities observed in FA of uveal melanoma include double circulation pattern, hot spots, and leakage from tumoral vasculature. The double circulation is caused by abnormal tumor vascularization and develops usually in medium and large tumors. Lack of impairment of epithelial RPE integrity results in leaks and is responsible for the occurrence of hot spots. Generally, the use of angiography is limited to the differentiation of other ocular lesions presenting vascular disorders such as choroidal hemangioma and might be a control tool in post-radiation maculo- and retinopathy [36].

Indocyanine green angiography (ICGA) is analogous to FA, but the dye – indocyanine green presents slightly different properties which ensures penetration of retinal layers and melanin, macular pigment so the structures beneath RPE could be visible.

This method allows to evaluation of various-sized vessels, including choriocapillaris and the vascular pattern of the tumor. The degree of fluorescence depends on the extent of tumor pigmentation, small uveal melanomas are hypocyanescent and large ones are hypercyanescent [37]. Another imaging method is autofluorescence which focuses on searching for lipofuscin accumulating in retinal cells which is visible in indirect ophthalmoscopy as orange pigment. Small choroidal melanomas present hyper-autofluorescence, in contrast to benign lesions – choroidal nevi which perform iso- or hypo-autofluorescence. Blue-light autofluorescence may be used to check the proper position of radioactive plaque [38].

Optical coherence tomography (OCT) is based on a light interferometry phenomenon and remains a relevant non-invasive ocular imaging tool. The obtained cross-sectional images and high resolution of the method facilitate the tumor assessment which makes it widely used in diagnostics, selecting the appropriate treatment, and controlling the treatment response. The structures such as vitreoretinal interface, retina, and RPE are particularly well visible with OCT. The usefulness of this modality results from the ability to detect small lesions, less than 3mm in thickness [39]. The choroidal melanoma may contribute to atrophy of RPE overlying the tumor, compression of choriocapillaries, and loss of photoreceptors, but the most indicative symptoms include shaggy photoreceptors and subretinal fluid [36].

Initially, the scope of examination was limited to the posterior segment, but over time anterior segment OCT (AS-OCT) was introduced. It assesses the cornea, sclera, anterior chamber angle, iris, and lens but the posterior structures are poorly presented due to shadows caused by pigmented lesions. In that method, the light is retained by opaque tissues and it is difficult to penetrate deeper layers and detect the posterior tumor margin, therefore taking any measurements is impossible [40].

Optical coherence tomography angiography (OCTA) shows the vascularization of the retina primarily and to a lesser extent the choroid. The image analysis may be difficult when tumor thickness is more than 3,5 mm. Microvascular retinal blood flow, which is disrupted in many ocular diseases, can be measured. The eyes with choroidal melanoma present increased central macular thickness, enlarged foveal avascular zone, and reduced capillary vascular density. The mentioned abnormalities do not occur in the healthy eye or choroidal naevus, therefore the role of OCTA in differentiation is significant. The other usefulness of this imaging tool comes from detecting posttreatment radiation retinopathy [41].

The utility of computed tomography (CT) and magnetic resonance imaging (MRI) is quite limited. The advisability of using these techniques manifests when the clinical examination and other methods do not provide a clear assessment and raise diagnostic doubts. It is particularly important when a lens is opaque in cataract, it occurs subretinal effusion or vitreous hemorrhage. In CT uveal melanoma presents as a hyperdense mass with slight to moderate enhancement. The minimal detection thickness is 2 mm [42]. Cross-sectional images primarily can provide information regarding the location of the lesion and its anatomical relations to adjacent tissues which is important in the surgical and local treatment planning process. The advantage of this method is revealed in large tumors, bony orbital expansion suspected, and when MRI is unavailable [43]. Nevertheless, the relatively rare use of CT in the uveal melanoma diagnosis is due to its limitations and advantages over other available imaging methods.

US is more adequate compared to CT in the evaluation of extrascleral extension and is more precise in the measurement of tumor dimension. The difficulties in unequivocal assessment of ocular lesions usually result from image signal attenuation by the choroid. Then, MRI is estimated as more sufficient. Taking into account these restrictions and the issue of radiation exposure, CT significance is limited especially to evaluation at the stage of metastatic disease [44].

MRI is a radiation-free technique that utilizes electromagnetic waves and allows three-dimensional imaging with a resolution of less than 1mm [45]. A tissue contrast ensures particularly effective visualization of soft tissues compared to US or CT.

Therefore, it is possible to evaluate the location of the tumor, measure its dimension, and assess tissue involvement [46]. Unlike vitreous, which is hypointense on T1-weighted (T1w) images and hyperintense on T2-weighted (T2w), UM is hyperintense on T1w and hypointense on T2w with diffuse moderate enhancement after contrast administration, but this characteristic is not specific. The other conditions that mimic UM include vitreous hemorrhage, choroidal hemangioma, amelanotic melanoma, and choroidal metastases. MRI should not be applied in detecting the tumor, but rather in the aim to evaluate extraocular extension. Parameters obtained from MR scans are used to establish anatomical relationships and planning processes of brachytherapy, proton beam therapy, and stereotactic radiotherapy procedures. In addition to primary tumor visualization, MR imaging can be implemented for the identification of metastases, especially to the liver [47].

Positron emission tomography (PET) is based on the property of cancer cells to increase glucose uptake. The glucose labeling facilitates determining the tumor localization and eventual metastases and controls the treatment response and recurrences. However, this method is characterized by relatively low specificity and gives false-positive results in inflammation or trauma. To reduce the number of false signals and obtain additional information about anatomical context, PET and CT modalities are combined. Their utility is restricted to medium-sized and large tumors. Distant metastases can be recognized with PET/CT even if would be missed on conventional imaging [48].

Due to the unusual location of UM, the diagnostic process is relatively complicated and several methods usually need to be used to visualize intraocular lesions. In general, the gold diagnostic standard in neoplasm constitutes a biopsy with histopathological examination. The analysis of cytological, histological changes and gene abnormalities can provide valuable information of prognostic importance. Nevertheless, in ocular tumors, fine-needle aspiration biopsy (FNAB) could contribute to the spread of cancer cells. Biopsy may be non-diagnostic because of tumor heterogenicity and brings the risk of iatrogenic ocular damage. Due to the dynamic development of non-invasive techniques, biopsy is dedicated primarily to doubtful cases and requires experienced, high-class specialists' involvement [49].

Conclusions

This review aims to summarize the most important and current information regarding uveal melanoma. The knowledge of risk factors and understanding of the pathogenetic processes facilitates the division of patients into groups that differ in metastatic potential.

Implementation of various available tests and combining different modalities in the diagnostic process increases the effectiveness of detection and determines the time of initiation of therapy. An unfavorable UM prognosis poses a significant medical challenge for both primary and disseminated disease.

Disclosure

Author's Contribution Statement

Conceptualization, Natalia Paduszyńska, Anna Dąbrowska, and Marta Justyna Gonciarz; methodology, Dominika Zaliwska; software, Magdalena Czach; check, Agnieszka Aleksandra Strojny, Dominika Karolina Adamiec and Adrianna Kraszkiewicz; formal analysis, Monika Anna Kamińska and Monika Kienanh Do; investigation, Dominika Karolina Adamiec, and Adrianna Kraszkiewicz; resources, Natalia Paduszyńska; data curation, Monika Anna Kamińska, and Monika Kienanh Do; writing - rough preparation, Natalia Paduszyńska; writing - review and editing, Anna Dąbrowska, and Magdalena Czach; visualization, Dominika Zaliwska; supervision, Marta Justyna Gonciarz; project administration, Agnieszka Aleksandra Strojny

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