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UVEAL MEALNOMA: CLINICAL FEATURES AND DIAGNOSTIC PROCEDURES

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Summary

Uveal melanoma is the most common primary intraocular malignancy in adults and the eye is the second most common site for primary melanoma after the skin. Early recognition is important in protecting visual acuity, saving the eye and preventing metastasis. Signs for early detection of uveal melanoma when it simulates a nevus include thickness >2 mm, presence of subretinal fluid, symptoms, orange pigment, margin of the tumour near the optic disc, acoustic hollowness, surrounding halo, and the absence of drusen. This is essential considering that each millimetre increase in melanoma thickness imparts a 5% increased risk for metastatic disease. Delays or inability to make an accurate and early diagnosis may have grave consequences. Methods of diagnosis have substantially improved, although clinical diagnosis remains the standard method in the eyes with clear media. In eyes with opaque media ultrasound is the most useful ancillary diagnostic technique. Newer imaging modalities such as optical coherence tomography and fundus autoflouroscence facilitate in detection of subretinal fluid and orange pigment. Additional molecular biomarkers and cytological features which can predict the clinical behaviour of a small melanocytic lesion have been identified. Although the role of a good clinical evaluation cannot be underestimated, it is advisable to assess the various radiological, molecular and cytological features in order to enhance the accuracy of early diagnosis and improvement in the patients' prognosis.

KEY WORDS: *uveal melanoma, pathogenesis, clinical features, diagnostic procedures*

MEALNOM SREDNJE OČNE OVOJNICE: KLINIČKE OSOBITOSTI I DIJAGNOSTIČKE METODE

Sažetak

Melanom srednje očne ovojnice najčešća je primarna zloćudna bolest oka u osoba odrasle dobi, a oko je drugo po učestalosti najčešće sijelo primarnog melanoma nakon kože. Kasna ili pogrešno postavljena dijagnoza može imati ozbiljne posljedice. Rano otkrivanje melanoma srednje očne ovojnice ključno je u prevenciji gubitka vidne oštrine, spašavanju oka i sprečavanju razvoja metastaza. Čimbenici koji omogućuju rano otkrivanje malih melanoma srednje očne ovojnice koji se mogu zamijeniti s nevusom su debljina tumora > 2 mm, prisutnost subretinalne tekućine, nazočnost simptoma, narančasti pigment, rub tumora u blizini optičkog diska, određene ultrazvučne karakteristike tumora te odsutnost druza. Rano otkrivanje tumora je vrlo važno obzirom da povećanje debljine melanoma za 1 mm povećava rizik metastatske bolest za 5%. Dijagnostičke metode posljednjih su godina znatno unaprijeđene, no klinička dijagnoza i dalje ostaje standardna metoda kod očiju s prozirnim optičkim medijima. Ultrazvuk predstavlja najkorisniju pomoćnu dijagnostičku metodu, osobito u slučaju zamućenja optičkih medija oka. Novije dijagnostičke metode poput optičke koherentne tomografije i autoflou-

roscencije fundusa olakšavaju otkrivanje subretinalne tekućine i narančastog pigmenta. Također postoje određeni molekularni biomarkeri i citološke značajke tumorskih stanica koje mogu pomoći u predviđanju kliničkog ponašanja male melanocitne lezije. Iako je uloga dobre kliničke procjene važna i ne smije se podcijeniti, preporuča se i primjena dodatnih dijagnostičkih metoda, te određivanje molekularnih i citoloških značajki tumorskih stanica kako bi se omogućila točna rana dijagnoza i time poboljšala prognoza bolesnika.

KLJUČNE RIJEČI: *melanom srednje očne ovojnice, patogeneza, kliničke osobitosti i dijagnostičke metode*

INTRODUCTION

Melanoma is a malignant tumour arising from melanocytes. It may originate from the skin, mucous membrane, ocular region including uvea, conjunctiva, eyelid, orbit and rarely from an unknown primary site. Although both cutaneous and uveal melanomas share the melanocyte as their common origin, their clinical behaviour and underlying molecular mechanisms are significantly different (1-3).

The eye is the second most common site for primary melanoma after the skin accounting for 5% of all melanoma cases (1,4). Uveal melanoma is the most frequent site of origin ocular melanomas and the most common primary intraocular malignancy in adults occurring in all parts of the uvea: choroid (90%), ciliary body (7%) and iris (2%) (5). The incidence of uveal melanoma has remained relatively constant, between five and six cases per million people in the United States and Europe (1,2) and is slightly more common among men. The incidence of uveal melanoma in Europe was found to vary in different countries with higher incidences associated with higher geographic latitude (2 per million in Spain and southern Italy; 4–5 per million in France, the Netherlands, Switzerland and Germany; and > 6 per million in the United Kingdom) (6). Predisposition for uveal melanoma is ethnicity, with a white to black incidence ratio of 196:1 (7), age with the mean age at initial diagnosis being 60 years (6,7), light eye colour, fair skin and the inability to tan. Other predisposing factors are cutaneous, iris and choroidal nevus, ocular or oculodermal melanocytosis and familial uveal melanoma (2,4) which is presumed to be related to somatic or germline BAP1 (BRCA1 - breast cancer -associated protein 1) mutations (2,8,9).

Molecular pathogenesis

The molecular pathogenesis of uveal melanoma differs from cutaneous melanoma whilst both types appear to activate the mitogen-activated protein kinase (MAPK) pathway; however via different mechanisms. While the majority of cutaneous melanomas are associated with activation of the MAPK pathway, causing mutations in *BRAF* (approx. 50% of cases) or *RAS* (10% to 25% of cases) or loss of function mutations in *NF1* (14% of cases) (10,11). Uveal melanoma is characterized by point mutations in the G protein α-subunits *GNAQ* and *GNA1* with mutations in *GNAQ* and *GNA11*being in about 80% of patients and are mutually exclusive (8,11,12).

Increased risk of metastasis of uveal melanoma has been associated with specific genetic alterations. Monosomy 3 occurs in approximately half of uveal melanomas indicating high risk melanoma and metastasis related death. (3,11-14) Harbour and colleagues (9) reported that 84% metastasizing uveal melanomas contained BAP1 mutations. BAP1 is located on chromosome 3 and biallelic inactivation of this gene explains the association between monosomy 3 and metastasis risk. A more favourable prognosis is correlated with *SF3B1* and *EIF1AX* mutations (8,13,15).

Clinical characteristic and diagnosis

Common symptoms of uveal melanoma include blurred vision, photopsia (flashing lights), visual field defects, visible tumour, irritation and pain whilst metamorphopsia, floaters, redness and pressure can also occur. Visual impairment is usually caused by tumour involvement of the macula or by exudative retinal detachments whilst almost 30% of patients are asymptomatic at diagnosis (2,3,16-18).

Approximately 2% of all uveal melanomas arise in the iris most frequently in the inferior quadrant (45%) (1,5). Iris melanomas can induce secondary glaucoma, corectopia, ectropion uveae, hyphaema, causing pain and blurred vision yet rarely metastasize. They tend to have a more benign course than other subsets of uveal melano-

mas however it is still uncertain whether it is due to the fact that they are biologically different or simply the result of early detection. The overall mortality associated with iris melanomas is less than 5% due to early diagnosis, given the visible location and the relatively low rate of metastasis. Only 5% of small iris tumours will demonstrate growth over a 5-year interval enabling follow up by serial photographs, measurements and ophthalmic examinations (16,18,19).

One of the most difficult areas of the uveal tract to visually detect is ciliary body, where 7% of uveal melanomas arise (Figure 1) (5). At presentation these tumours are often large, due to delayed diagnosis and they often remain undetected until the development of visual disturbance or pain (18). *Sentinel vessels* (very enlarged blood vessels feeding the tumour) in the episclera as well as episcleral nodules indicate the presence of a tumour. Ciliary body melanoma growth may present with rapidly progressive lateral cataract due to pressure or inflammation and may cause secondary glaucoma. The overall mortality from ciliary body melanoma is approximately 40% (8,3,17).

Ninety percent of uveal melanoma arise in the choroid (5) (Figure 2). There are basically two clinical subtypes of choroidal melanoma: diffuse and nodular. The diffuse form is an uncommon variant that accounts for 4 to 5 % of posterior melanomas. Nodular choroidal melanomas present as a dome or mushroom shaped subretinal mass and colour may vary from typically brown pigmented to amelanotic (Figure 3) (1,16,18).They may cause serious secondary sensory retinal detachment adjacent to the tumour. This detachment can be responsible for visual loss, even though the tumour does not directly involve the submacular choroid. The retina overlying the tumour may show degenerative changes, occasionally to the point of complete attenuation with the tumour perforation into the vitreous. The majority of choroidal melanomas are discovered during routine fundoscopic examination (2-4,7). Posterior uveal melanomas are generally graded based on tumour size (Table 1) (2,17). It has been established that the risk of metastasis increases 5% with each 1 mm increase in tumour thickness as measured by ultrasonography (USG) (20,21). Furthermore other grading systems include classification on the basis of clinical, pathologic and genetic factors (2-4,16).

Table 1.

COLLABORATIVE OCULAR MELANOMA STUDY CLASSIFICATION OF CHOROIDAL MELANOMA ACCORDING TO SIZE

Classification	Thickness (mm)	Largest basal diameter (mm)
Small	1.0 to 2.5	5.0 to 16.0
Medium	2.5 to 10.0	≤ 16.0
Large	≥2.0	>16.0
Large	>10.0	Any

mm: millimetres

Table 2.

CLINICAL CHARACTERISTICS AND LOCALISATION OF UVEAL MELANOMA

Localisation	Frequency	Signs and symptoms
Iris	2%	Well circumscribed, pigmented masses, corectopia, darkening of one iris, unilateral glaucoma, blurred vision, pain, loss of corneal clarity, hyphaema
Ciliary body	7%	Invasion into the base of iris, sentinel vessels, unilateral glaucoma, cataract, visual disturbances, pain, asymmetric astigmatism
Choroid	90%	Solid tumour beneath the retina, retinal detachment, vitreous haemorrhage, decrease of visual acuity, visual field defects, pain

The diagnosis of uveal melanoma is based primarily on clinical examination by biomicroscopy, indirect ophthalmoscopy and in some cases gonioscopy. Clinical diagnosis is the most accurate means of detecting a choroidal melanoma in patients with clear media (Table 2). Ancillary tests including colour fundus photography, ultrasonography (USG), fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), fundus autofluorescence (FAF) and ultrasound biomicroscopy (UBM). Computed tomography (CT) and magnetic resonance imaging (MRI) can also be used in order to confirm diagnosis. Fine-needle aspiration biopsy (FNAB), of the tumour can be performed when the clinical diagnosis is unclear (2-4,8,17,18).

The most useful ancillary diagnostic and monitoring tool in uveal melanoma is **ultrasonography (USG).** It is particularly useful in diagnosis of melanoma in eyes where the posterior pole can-

not be seen directly and should be done routinely in all eyes with opaque media (2-4). The A scan is accurate in helping to estimate the height of the tumour which aids in distinguishing thin melanomas from nevi and in assessing its growth over time. B-scan USG is useful for characterising the tumour and for obtaining tumour dimensions. Typical findings in larger melanomas include choroidal excavation and orbital shadowing with the tumour showing low to medium internal echogenicity.USG is also useful in the evaluation of extraocular extension; areas of hyporeflectivity compared to normal orbital tissue are considered as orbital extensions of the tumour (22,23).

High-resolution **ultrasound biomicroscopy (UBM)** allows excellent visualization of iris and ciliary body tumours, which are generally difficult to evaluate during clinical examination.UBM identifies hyporeflective plaques on the tumour surface, tumour-specific vasculature, internal reflectivity and if present, extraocular extension (2,24).

Optical coherence tomography (OCT) is particularly useful in the diagnosis of small choroidal melanomas less than 3 mm in thickness which can be misdiagnosed during routine examination. It is useful in differentiating choroidal nevus from small choroidal melanoma and the detection of the presence of subretinal fluid, which is considered one of the high-risk features predicting transformation into melanoma. However it has limited use in tumours larger than 3 mm (2,16,24,25).

Anterior segment OCT (AS-OCT) is a newer technique used in the imaging of iris and ciliary body melanoma, however is not successful as USG owing to its lack of ability to penetrate deeper tissues (24). In the absence of AS-OCT, substitutional diagnostic methods which allows the visualisation of the tumour may be transillumination, gonioscopy and biomicroscopy (22).

Flourescein angiography (FFA) is another valuable technique in diagnosis of melanoma. A frequent finding is *double-circulation*, the pattern that refers to the filling of the retinal vessels overlying the tumour, superimposed on dilated vessels within the tumour itself. The retinal pigment epithelium overlaying choroidal melanomas is frequently altered, and focal defects are seen as *hot spots* as they leak fluorescein. Other typical fluorescein patterns include areas of capillary nonperfusion and blockage of larger retinal vessels. (2,16,18,26). FFA is also used in the detection and follow-up of complications arising after brachytherapy such as radiation retinopathy and radiation maculopathy (2,16).

Indocyanine green (ICG) angiography is an alternative technique for imaging choroidal vasculature which shows details of choroidal circulation more effectively than fluorescein. It can be combined with scanning laser conofocal microscopy to study the vasculature at a particular level (16,18,26).

On **fundus autofluorescence imaging (FAF)**, pigmented tumours exhibit moderate hypoautofluorescence, whilst nonpigmented (amelanotic) tumours show moderate hyperautofluorescence. These regions of hyperautofluorescence are visible owing to the presence of orange pigment, drusen and subretinal fluid overlying the tumour. FAF may also reveal hypoautofluorescent retinal pigment epithelium defects, such as hyperplasia, atrophy and fibrous metaplasia or hyperautofluorescent drusen, which may suggest chronic stable nevus (27).

Computed tomography (CT) and **magnetic resonance imaging (MRI**) can be utilized when tumours cannot be visualised by clinical examination in patients with opaque media (cataract, vitreous haemorrhage or retinal detachment) and if a differential diagnosis is still not possible after USG. These imaging methods also have an important role in the evaluation of extraocular extension (2,18,22).

Fine-needle aspiration biopsy (FNAB) is a technique that may be useful in the differential diagnosis in selected cases and may be warranted for diagnostic dilemmas, particularly if it alters subsequent management. Anterior segment tumours can be evaluated by aqueous humour sampling, incisional or excisional biopsy. Transscleral, transvitreal or transcameral FNAB, vitrectomy biopsy, incisional or excisional biopsy can be done in order to evaluate posterior segment intraocular tumours. Needless to say the result obtained with FNAB for the sampled area may not be representative of the entire tumour (3,18,28).

Differential diagnosis

A number of lesions can stimulate melanoma, especially those with clinically dark appearance. The most common differential diagnosis is melanocytic nevi which is difficult to distinguish

from small melanomas. Metastatic tumours can stimulate amelanotic melanomas however they tend to be bilateral and multifocal and the patients usually have a known primary tumour. Subretinal blood can appear as dark rounded lesions simulating melanoma. With time this blood will disappear or be replaced by fibrous scar. Diseases such as age-related macular degeneration or disciform scars can also be mistaken for melanoma. Retinal pigment epithelial proliferation occurs in response to many stimuli including ocular trauma, intraocular infection or inflammation and retinal detachment. In some cases FNAB has proven useful. Furthermore choroidal hemangioma and choroidal osteoma can simulate melanoma. Hemangiomas are orange-red in appearance; nearly the same colour as the fundus and usually do not change size appreciably. USG shows more internal reflectivity than is typical for melanoma. Choroidal osteomas are amelanotic lesions with minimal elevation and can be diagnosed by their characteristic USG or CT appearance (2-4,17,18).

Risk factors for metastasis

Even though the lesion is ophthalmoscopically visible it can be considerably difficult to differentiate a nevus from a small choroidal melanoma. Shields et al. (29) proposed the mnemonic *to find small ocular melanoma using helpful hints daily* namely T-thickness greater than 2 mm, F-subretinal fluid, S-symptoms, O-presence of orange pigment, M-margin within 3 mm of the optic disc, H-ultrasound hollowness, H- absence of surrounding halo and D- absence of drusen. The further management of the melanocitic lesion is important due to the prognostic implications and psychological impact of the disease (Table 3). With advancement in molecular biology and cytogenetics, several biological and cytological markers have been identified which can predict the prognosis of the tumour and aid with decision making (29,30).

Clinical risk factors

Tumour size has been a substantial predictor of prognosis of the disease. Large tumours are associated with poor prognosis and higher metastatic rates. Shields et al. reported that each millimetre increase of melanoma thickness causes a 5% increased risk for metastatic disease (20). Other clinical features found to be predictive of metastasis in their analysis were increasing age, ciliary body location, more pigmented tumour and the presence of subretinal fluid, intraocular haemorrhage or extraocular extension. Additionally, the greatest basal diameter of the tumour also has an impact on patient prognosis. Diffuse melanoma which has been defined as a tumour with thickness < 20% of the tumour base had a greater risk of metastasis and death. A 5 mm increase in basal diameter of the tumour increases the risk of metastasis by 5.6 times. Melanocytosis is also a risk factor for uveal melanoma development and metastatic spread (30).

Table 3.

MANAGEMENT GUIDELINES OF MELANOCYTIC LESION OF UVEAL TRACT ACCORDING TO THE RISK FACTORS (SHIELDS ET AL., 2009.)

Number of risk factors	Hazard ratio	Management
1-2	3	Monitoring every 4-6 months
3-4	5	Refer to an experienced centre for ocular oncology evaluation
5-6	9	Refer to ocular oncology centre for further management
≥ 7	21	Urgent referral to ocular oncology centre

Risk factors: tumour thickness > 2 mm, subretinal fluid, symptoms, the orange pigment, tumour margin near to the optic disc, ultrasound hollowness, absence of surrounding halo, absence of drusen

Histopathological risk factors

Histopathological features are the bases for diagnosing ocular melanoma and differentiating it from a nevus. McLean et al. at the Armed Forces Institute of Pathology (AFIP) proposed histopathological classification of uveal melanoma: spindle cell nevus, spindle cell malignant melanoma, mixed cell melanoma and epithelioid cell melanoma (31). According to this classification, spindle cell tumours are linked with the best prognosis and epithelioid cell tumours with the less favourable. Juxtapapillary placed and ciliary body tumours are in most cases epitheloid cell tumours and are also more likely to metastasize and progress (32). A diffuse growth pattern has been shown to be related to a higher incidence of extraocular extensions and greater metastatic ability (32). Presence of mitotic figures is connected with ma-

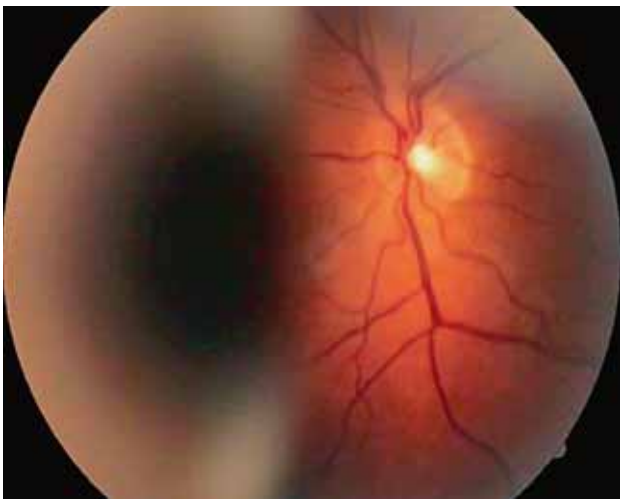

Figure 1. Ciliary body melanoma

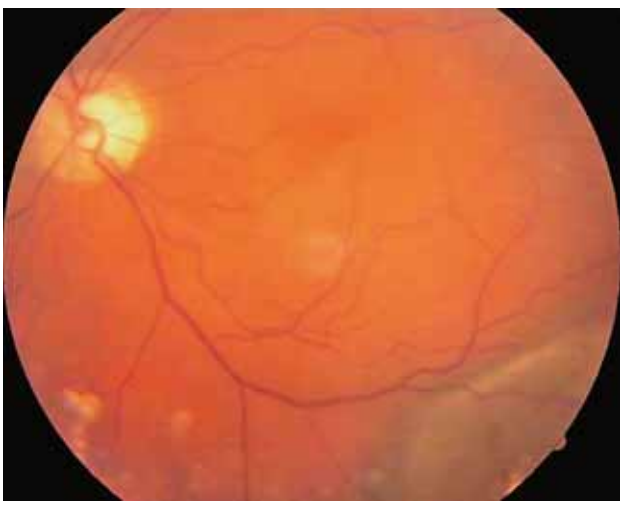

Figure 2. Choroidal melanoma

lignancy and is a well-known risk factor for metastasis (32). Increased pigmentation of the tumour is associated with epithelioid cell type with necrosis and the presence of macrophages, which indicate an increased risk of malignancy (30,32).

Molecular risk factors

It is well known that micro-metastasis of uveal melanoma may occur prior to primary treatment and such metastasis can in fact remain undeveloped for a prolonged period of time (30,33). Identification of high-risk patients is of greater importance in treatment planning. Uveal melanoma cells disseminate hematogenouslly and thus hematological markers may be useful for the detection of distant metastases. The potential molecular markers for the early detection of disseminated tumour cells includes increased serum tyrosinase m-RNA levels, hepatocyte growth factor and its receptor c-Met levels, over expression of vascular endothelial growth factor (VEGF) and decreased insulin-like growth factor-1 (IGF-1). Regardless of the potential benefit of serum molecular markers in determining metastatic disease at a subclinical level their use in monitoring is limited owing to a wide variety in the normal range of values within the population (30).

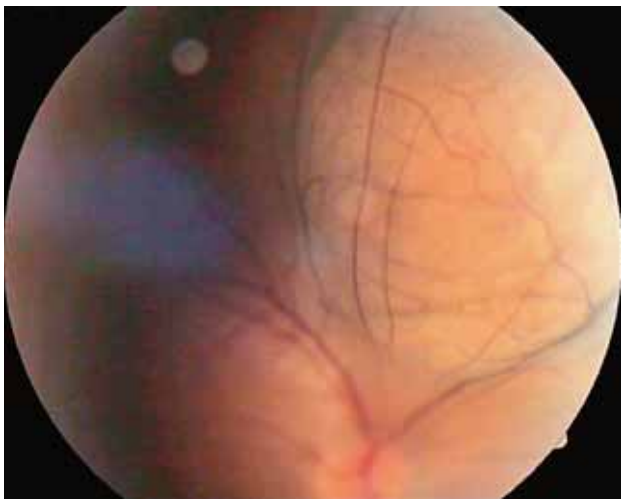

Figure 3. Amelanotic choroidal melanoma

Cytological risk factors

With advancements in treatment of choroidal melanoma the importance of obtaining a sample for evaluation of prognostic markers is growing. In fact FNAB could prove to be a reliable tool for genetic testing of uveal melanoma (2,10,14,30).

Chromosomal alterations

The major chromosome alterations characteristic for uveal melanoma correlated with the clinical high-risk factors for metastasis have been found in chromosomes 3, 6, 8, and 11. Monosomy of chromosome 3 is associated with a 5-year survival rate of approximately 50%, whilst disomy of chromosome 3 reports a 100% survival rate. Using gene expression profiling, melanomas have been categorized into two groups. Class I indicates tumours with two copies of chromosome 3 (disomy 3) and other beneficial chromosome changes such

as gain in chromosome 6p. Class II includes tumours with only one copy of chromosome 3 (monosomy 3) and other detrimental chromosome changes including gain of chromosome 8p and/or isochromosome 8p (30,34).

Gene alterations

Mutations in genes *GNAQ* and *GNA11* have been associated with the development of uveal melanoma (11,30). Both genes up-regulate the MAPK pathway in melanocytes when active simultaneously. In fact nearly 83.0% of uveal melanomas have constitutively active mutation in either *GNAQ* or *GNA11* (30,35).

CONCLUSION

Uveal melanoma is a rare yet fatal disease whose biological behaviour is notably different from other forms of melanoma requiring distinct treatment strategies. Improvement in local treatment has not provided an increase in survival and new treatment options in patients with metastatic disease are needed. Even though no standardized treatment for metastatic uveal melanoma exists, considerable progress has been made to improve our understanding of the biology of this type of melanoma, leading to novel targeted therapy and immunotherapy approaches. Therefore early detection and proper management of malignancy is crucial in preventing metastasis and thereby patient survival.

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