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Review Article

Ocular melanoma: an overview of the current status

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Abstract: Ocular melanoma is the second most common type of melanoma after cutaneous and the most common primary intraocular malignant tumor in adults. Large majority of ocular melanomas originate from uvea, while conjunctival melanomas are far less frequent. Incidence of uveal melanoma has remained stable over last three decades. Diagnosis is in most cases established by clinical examination with great accuracy. Local treatment of uveal melanoma has improved, with increased use of conservative methods and preservation of the eye, but survival rates have remained unchanged. Recent advances in cytogenetics and genetics enhanced prognostication and enabled to determine tumors with high metastatic potential. However, due to lack of effective systemic therapy, prognosis of patients with metastasis remains poor and metastatic disease remains the leading cause of death among patients with uveal melanoma. Conjunctival melanoma is rare, but its incidence is increasing. It mostly occurs among white adults. In majority of cases it originates from preceding primary acquired melanosis. Current standard treatment for conjunctival melanoma is wide local excision with adjuvant therapy, including brachytherapy, cryotherapy and topical application of chemotherapeutic agent. Rarity of this tumor limits conduction of controlled trials to define the best treatment modality. As well as for uveal melanoma, prognosis of patients with metastasis is poor because there is no effective systemic therapy. Better understanding of underlying genetic and molecular abnormalities implicated in development and progression of ocular melanomas provides a great opportunity for development of targeted therapy, which will hopefully improve prognosis of patients with metastatic disease.

Keywords: Melanoma, ocular, uveal, conjunctival

Introduction

Ocular melanoma is the second most common type of melanoma after cutaneous. It arises from melanocytes situated in conjunctival membrane and uveal tract of the eye. Although rarely, it can also arise from melanocytes located in the orbit. Uvea is the most frequent site of origin of ocular melanomas and comprises 82.5% of all of them, while conjunctival melanoma is far less common [1]. Great majority of ocular melanomas are primary however, metastatic melanoma from primary cutaneous site can also occur in the ocular region, and it accounts for less than 5% of all metastases to the eye and orbit [2].

In this article, we presented a brief overview of the current status of uveal and conjunctival melanoma, with emphasize on prognostic factors, recently discovered molecular changes and comparison between cutaneous and ocular melanoma subtypes.

Epidemiology of ocular melanoma

Although it is the second most common type of melanoma, ocular melanoma is still rare, and accounts for 3.7% of all melanoma cases [1]. In the US incidence of ocular melanoma is 6 per million, compared with 153.5 for cutaneous melanoma [1]. It is more common among men, with incidence of 6.8 per million, compared with 5.3 per million in women (male to female rate ratio 1.29) [1]. In Australia ocular melanoma shows higher rates, with incidence of 8 per million in men, and 6.1 per million in women [3].

Incidences of uveal and conjunctival melanomas in the US are 4.9 and 0.4 per million, respectively [1]. In Europe uveal melanoma incidence shows the north-to-south gradient,

decreasing from over 8 per million in northern to less than 2 per million in southern countries [4]. In the US ocular melanoma rates were found to be lower in southern states than in northern states mainly because of lower rates of choroidal melanoma [1]. In contrast, iris and ciliary body melanoma were more common in southern and costal states than in northern and non-costal states, which is also characteristic of cutaneous melanoma [1].

Ocular melanoma rates are 8-10 times higher among whites compared with blacks, but although obvious this difference is less pronounced compared to cutaneous melanoma which shows 16 times higher rates among whites [1]. In contrast to other ocular melanomas conjunctival melanoma rates are 2.6 times higher in whites than in blacks, which is similar with that of mucosal melanomas [5].

Incidence of ocular melanoma is increasing with age, with a peak in seventh and eighth decade of life [1, 3]. In contrast to uveal melanoma which incidence has remained stable over last three decades [6], conjunctival melanoma has shown an increase in incidence, especially among white men and older than 60 years [7]. In Australian population higher incidence of ocular melanoma was found among men older than 65 years and among residents of rural areas [3].

Uveal melanoma

Uveal melanoma is the most common primary intraocular malignant tumor in adults. It can affect any part of the uveal tract, but choroidal melanoma is predominant (86.3%), while iris and ciliary body melanomas are far less frequent [1]. Choroidal and ciliary body melanoma are together named posterior uveal melanoma and have some different features compared to iris or anterior uveal melanoma. Iris melanoma is the least common uveal melanoma, but has more benign clinical course compared with posterior uveal melanoma. Most patients with uveal melanoma are age between 50 and 80 years, with peak in seventies [1], and mean age at diagnosis 58 years [8]. Iris melanoma is more common among young patients (<20 years) and represent 21% of all uveal melanomas among them, compared to 4 and 2% in age groups 20-60 and >60, respectively [9].

Risk factors

Several host factors have been associated with increased risk for uveal melanoma. Congenital ocular and oculodermal melanocytosis (nevus of Ota) and uveal nevus are predisposing factors for uveal melanoma. Lifetime risk to develop uveal melanoma from oculo (dermal) melanocytosis is 1 in 400 individuals [10]. Choroidal nevi are quite frequent in white individuals, with an estimated prevalence between 5% and 8%, but they are estimated to show low rate of malignant transformation, only 1 in 8845 [11]. However, giant choroidal nevi (10 mm or more in diameter) were estimated to transform into melanoma in 18% over 10 years [12]. Meta-analysis of Weis and colleagues has shown the association between other host susceptibility factors such as light eye color, fair skin color, and inability to tan and increased risk for uveal melanoma [13]. Atypical cutaneous nevi, common cutaneous nevi, cutaneous freckles, and iris nevi are also associated with higher risk for development of uveal melanoma [14].

Exposure to solar UV radiation is well known risk factor for development of cutaneous melanoma however, evidences on its role in development of uveal melanoma are still inconclusive. In a population-based case-control study in Australia, Vajdic and colleagues [15] found that sun exposure is an independent risk factor for choroidal and ciliary body melanoma, but they did not find firm evidences for an association between sun exposure and iris or conjunctival melanomas (although the number of these tumors were low). However, in a meta-analysis of Shah and colleagues [16] outdoor leisure was found to be nonsignificant, and occupational sunlight exposure to be a borderline nonsignificant risk factor for development of uveal melanoma. Schwartz and colleagues [17] compared location of choroidal melanoma and dose distribution of UV light to the eye, using a method of geographic tumor mapping. They concluded that “it is very unlikely” that UV radiation exposure is responsible for choroidal melanoma and that only a small percentage of the UV rays reach the posterior and inferior part of the retina (but not anterior and superior) because UVC and UVB do not reach the choroid, and UVA is mainly filtered by the cornea and the lens. Li and colleagues [18] evaluated tumor location in relation to retinal topography

and a light dose distribution on the retinal sphere, and concluded that tumor initiation was not uniformly distributed, with rates of occurrence concentrated in the macular area and decreasing monotonically with distance from the macula to the ciliary body. That correlated positively with the dose distribution of solar light on the retinal sphere, supporting the hypothesis that solar exposure plays a role in the induction of uveal melanoma. Considering conflicting data obtained from previous studies further investigations are necessary to elucidate the role of solar UV radiation in the pathogenesis of uveal melanoma.

Artificial UV radiation from welding and use of sunlamps increases risk for choroidal and ciliary body melanoma [19]. Occupational cooking was also suggested as a factor that carries increased risk for uveal melanoma [20]. Use of mobile phone and occupational pesticide exposure were not proven as risk factors for uveal melanoma [21, 22].

Symptoms and clinical features

Presentation of uveal melanoma mainly depends on size and location of the tumor and can vary from asymptomatic, detected incidentally on eye examination, over various visual disturbances to visual loss in the affected eye. At the time of diagnosis majority of patients with uveal melanoma are symptomatic, but still up to 30% could be asymptomatic [23, 24]. The most common symptoms are blurred vision, visual field defect, photopsia, irritation and pain, but symptoms as metamorphopsia, floaters, redness and pressure can also occur [23]. Choroidal melanoma usually presents as dome or mushroom shaped subretinal mass, or less common it shows diffuse growth configuration [25]. Tumor growth can cause secondary retinal detachment with consequent visual loss or rupture Bruch's membrane acquiring mushroom shape. Color can vary from typically brown pigmented to amelanotic [26]. Ciliary body melanoma can cause lens displacement with consequent refractive and accommodation disturbances, localized cataract or increased intraocular pressure. Before it becomes clinically manifest, it can be asymptomatic for a long period. Feeder vessels can be seen on the overlaying sclera, or pigmentation in the cases of extrascleral extension. Ciliary body melanoma can be seen with wide dilated pupil, and presents as dome shaped or sessile lesion. Iris melanoma is usually asymptomatic, and manifests as growth of previously noted iris lesion, or as new pigmented spot on iris which patients notice themselves or is discovered on routine eye examination. It can cause distortion of pupil, localized cataract, hyphema, or secondary glaucoma due to obstruction of aqueous outflow from the eye. Iris melanoma mostly shows circumscribed growth and in approximately 80% of cases arises in inferior half of iris [27]. Diffuse iris melanoma is rare variant which presents with unilateral hyperchromic heterochromia and glaucoma due to angle invasion [28]. Ring iris melanoma grows around circumference of anterior chamber angle, and presents with unilateral increased intraocular pressure [29]. Tapioca iris melanoma is rare variant characterized by multiple nodules [30].

Iris melanoma is most likely to be discovered as small tumor because of its visible location, unlike ciliary body melanoma which is, because of its hidden location, usually large in size when diagnosed. Mean tumor thickness for iris, ciliary body and choroidal melanoma is 2.7 mm, 6.6 mm and 5.5 mm, respectively, and mean basal diameter 6.5 mm, 11.7 mm, and 11.3 mm, respectively [8].

Diagnosis of uveal melanoma is mostly established by ophthalmic examination including slit lamp biomicroscopy, indirect ophthalmoscopy, and ancillary diagnostic testing such as ultrasonography, fluorescein angiography and optical coherence tomography. Accuracy of diagnosis established by clinical examination is nowadays very high, over 99% [31]. However, results of one study showed that tumor was initially missed or misdiagnosed in 23% of patients, which resulted in more advanced tumor and higher rate of primary enucleation among those patients [24].

Management of uveal melanoma

Management of uveal melanoma varies from observation to orbital exenteration depending on the particular case, and mostly depending on the site, size of tumor and local extension.

Most patients with posterior uveal melanoma are currently treated with plaque radiation therapy or enucleation. Other available options include particle beam radiotherapy, transpupil-

lary thermotherapy, laser photocoagulation, gamma knife stereotactic radiosurgery and local surgical resection. Iris melanoma is in most cases treated by surgical resection. Larger non-resectable tumors can be treated by plaque radiotherapy or enucleation [32, 33]. Method of treatment of iris melanoma did not show an impact on the occurrence of metastases [32]. Small and medium-sized choroidal tumors are mostly treated by radiation therapy, while large tumors, especially if locally advanced, are still mostly treated by enucleation or orbital exenteration. COMS trial for medium-sized tumors did not show a difference in mortality rates between patients managed by brachytherapy compared to those managed by enucleation [34, 35]. For large-sized tumors preceded external radiation did not show advantage compared to enucleation alone [36].

Although in the past observation was advocated for small choroidal melanomas, nowadays there is a trend toward earlier treatment of small tumors [37, 38]. It was found that of small choroidal melanomas initially managed by observation, 21% demonstrated growth by 2 years and 31% by 5 years [39]. Factors predictive for growth of small choroidal lesions should be considered when making decision for treatment [39, 40].

Local treatment of uveal melanoma has improved a lot with increased use of conservative treatment and preservation of the eye. However, improvement in local treatment did not provide significant increase in survival rates [6, 41], and metastatic disease is remaining a leading cause of death among the patients with uveal melanoma [42, 43].

Metastases and survival

At the time of diagnosis, less than 4% of patients with uveal melanoma have detectable metastatic disease [44]. However in further course about half of patients will develop metastases, and when metastatic disease appears it unavoidably leads to death because of lack of effective systemic treatment.

Uveal melanoma disseminates hematogenously, with a high propensity for liver, which is typical and most common (93%) site of metastasizing, followed by lung (24%) and bones (16%) [45]. It can also metastasize in brain and skin, or any other site in the body. Majority of patients with metastatic disease have metastases in multiple sites [45]. Patients without liver metastases or with liver being not the first site of metastases have better survival [46]. Patients with iris melanoma have better prognosis. Among them at 5 and 10 years of follow up metastases were found in 4.1%, and 6.9%, respectively, compared to 15% and 25%, respectively, for choroidal melanomas [8]. On the other hand, ciliary body melanoma carries worse prognosis with metastases found at 5 and 10 years follow up in 19% and 33%, respectively [8].

Due to lack of lymphatic drainage in uvea uveal melanoma does not spread to regional lymph nodes, except in rare cases of direct invasion of conjunctiva and then through conjunctival lymphatics to regional lymph nodes [47]. Five-year survival rates for uveal melanoma ranges from 69% to 81.6% [6, 42, 43, 48] and ten-year survival rates from 57% to 62% [42, 43]. After detection of metastases 80% of patients die within 1 year, and 92% within 2 years [49]. Long term survivals are rare, and mean survival is only few months [45, 46, 50].

Prognostication

Numerous clinical and histopathological features have been investigated in order to predict prognosis of uveal melanoma. Size of tumor is one of the most important clinical features for predicting prognosis of uveal melanoma. Increasing tumor thickness, as well as increasing largest basal tumor diameter carries increased risk for metastases [8]. Shields and colleagues showed that risk for metastases is gradually increasing with tumor thickness, and each millimeter increase in tumor thickness showed a 1.06 hazard ratio [8]. With increasing tumor thickness risk for metastases at 10 years showed increase from 6% for tumors 0-1.0 mm in thickness up to 51% for tumors over 10.0 mm in thickness [8]. Among small choroidal melanomas (≤3 mm thickness) those with diffuse growth configuration (thickness/base ≤20%) carry higher risk for metastases than small non-diffuse tumors (thickness/base >20%) [51]. Factors predictive of metastasis from diffuse melanoma include larger tumor basal dimension and plateau/flat tumor configuration [51]. Ciliary body location, extraocular extension, increasing patient age, presence of

subretinal fluid or intraocular hemorrhage and presence of brown tumor are also associated with increased risk for metastases [8].

Histopathological features such as epithelioid cell type, mitotic activity, increased HLA expression, tumor infiltration by proangiogenic M2-macrophages and lymphocytes, microvascular loops and networks, and extracellular matrix patterns are also predictors of poorer prognosis [52-55]. However, all these parameters are not precise and reliable enough in detecting patients in high risk for metastases.

Cytogenetic studies of uveal melanoma have significantly improved prognostication in uveal melanoma. It was revealed that abnormalities on chromosomes 3, 6, 8 and 1 are common in uveal melanoma, and that the presence of certain types of abnormalities on these chromosomes is a good predictor of tumor behavior [56-58]. Monosomy of chromosome 3 is the most frequent chromosomal aberration in uveal melanoma observed in approximately 50% of tumors [59-61]. Loss of chromosome 3 is detected in more than 70% of metastasizing, and in approximately 20% of non-metastasizing uveal melanomas [58]. Monosomy of chromosome 3 strongly correlates with metastases and decreased survival [56, 57, 60]. Losses of 1p were detected only in metastasizing tumors and metastases [58], and loss of chromosome arm 1p with concomitant monosomy 3 is strongly predictive of decreased survival [62]. Chromosome 6q loss mostly occurs in metastasizing tumors and metastases, while 6p gain is common in non-metastasizing tumors, and is associated with low risk of metastasizing [58, 63]. Chromosome 8q gains are mostly present in metastasizing uveal melanoma and their metastases [58]. It is commonly present together with monosomy 3 [58] and associated with poor prognosis [56, 57, 60]. Loss of chromosome 8p is linked to more rapid metastasizing [64]. Based on the fact that monosomy 3, associated with high risk for metastases, and 6p gain, associated with low risk for metastases, are almost mutually exclusive in uveal melanoma, a bifurcated tumor progression pathway was proposed [65]. Monosomy 3 and 6p gain, which are both shown to be early events in uveal melanoma genesis, are proposed to be two alternative starting points of two different karyotypic pathways [63, 65].

So far the best prediction of metastatic potential of uveal melanoma was provided by gene expression profiling. Difference in gene expression profile between tumors with and without monosomy of chromosome 3 was observed, and based on gene expression profiles two different classes of tumors, which correlate with metastatic risk, were identified [66, 67]. According to that, uveal melanoma was classified into two classes: class 1 or low grade tumors with low metastatic risk, and class 2 or high grade tumors with high metastatic risk [67]. Molecular classes have shown a correlation with other known risk factors - patient age, cell type and chromosome abnormalities [67]. Molecular signature strongly predicts survival, with 92 months survival probability of 95% for class 1, and 31% for class 2 tumors [67]. Later, it has been shown that class 2 tumors are associated with higher level of aneuploidy [68], and higher proliferation rate [69] than class 1 tumors. Gene expression profiling based molecular classification of uveal melanoma has shown to be superior for predicting metastasis compared to monosomy 3, and clinical and histopathological prognostic factors [70, 71]. Molecular classification can be assayed on small tissue samples obtained by fine-needle aspiration biopsy [72] in patients treated with conservative methods.

Cytogenetics and gene expression profiling based molecular classification significantly enhanced prognostication of patients with uveal melanoma, allowing detection of patients at high risk for metastases and stratification of patients for entry into clinical trials of emerging adjuvant therapy.

Conjunctival melanoma

Conjunctival melanomas arise from melanocytes located in the basal layer of the epithelium of the conjunctival membrane. Unlike the other mucous membranes, bulbar part of the conjunctiva is directly exposed to sun radiation. Conjunctival melanoma is very rare and comprises about 5% of all melanomas in the ocular region [73]. Conjunctival melanoma almost exclusively occurs in whites, and only less than 1% are African-American patients [74]. It does not show a predilection for either gender [1, 75]. Incidence of conjunctival melanoma is increasing with age; more than half patients are age over 60 years (54%), while it is extremely rare in younger than 20 years (1%) [75].

Risk factors

Conjunctival melanomas can arise de novo and from preexisting primary acquired melanosis (PAM) or conjunctival nevus. About 60% of conjunctival melanomas arise from PAM [76, 77]. Primary acquired melanosis with severe atypia undergoes transformation to melanoma in approximately 13%, with greater extent of PAM carrying a greater risk for malignant transformation [78]. Primary acquired melanosis without atypia or with mild atypia are not likely to show progression in melanoma. Conjunctival nevi very rarely progress to melanoma. In a large series of 410 patients with conjunctival nevus, only 3 patients (<1%) developed melanoma from preexisting nevus during a mean period of 7 years [79].

In the United States, significant increase in incidence of conjunctival melanoma was observed in the age group over 60 years and among white men [7]. In white men, the incidence rate increased 295% within the 27 years. Similar increase in incidence of conjunctival melanoma, comparable to that of cutaneous melanoma, was also observed in Finland and Sweden [76, 80]. This coincidence between increasing in cutaneous and conjunctival melanoma and the similar pattern of increasing suggests a possible link to a sunlight exposure and its role in the etiology of conjunctival melanomas [7, 81].

Symptoms and clinical features

Conjunctival melanoma usually presents as raised pigmented lesion often surrounded with prominent feeder blood vessels or areas of PAM. Most common symptoms noticed by patients are pigmented spot or lump, while irritation and pain are rare [75]. Although it can appear on any part of conjunctiva, it is most common on bulbar conjunctiva (92%), in the temporal quadrant (63%) and very often touches the limbus (61%) [75]. Other locations including palpebral and forniceal conjunctiva, plica semilunaris and caruncula, are less common but associated with less favorable prognosis. Multifocal lesions are present in almost one third of patients [82]. Local recurrence after primary treatment is common, 26% at 5 years, and 51% at 10 years [75], and could be multiple. Recurrence is more common in non-epibulbar tumors [77].

In most cases, diagnosis of conjunctival melanoma could be established by careful clinical examination with a slit lamp. Incisional biopsy is not recommended in order to minimize the risk of seeding the tumor cells, and since it was found to be associated with higher risk for recurrence [75]. However, although excisional biopsy is preferred, in the cases of extensive lesions when it is not possible, incisional biopsy may be performed. Conjunctival melanoma and PAM can also appear as unpigmented lesions which delays diagnosis and makes it possible only after histopathological examination [83].

Management of conjunctival melanoma

Current standard treatment for conjunctival melanoma is wide local excision with adjuvant therapy, including brachytherapy, cryotherapy and topical application of chemotherapeutic agent (Mytomicin C). Effective treatment of conjunctival melanoma is complicated by a high rate of local recurrence. In order to provide better local control and eradication of tumor cells surgical excision is usually combined with adjuvant therapy, but adjuvant treatment of choice still remains to be defined. Missotten and colleagues [77] found that the probability of recurrence of the primary tumor was lower when treatment was excision with brachytherapy compared with other treatment modalities (excision with cryotherapy or excision alone), but still there was not significant difference in survival between different treatment modalities. Shields and colleagues [75] recommended excisional biopsy using the “no-touch technique” combined with alcohol corneal epitheliectomy and cryotherapy since they found that patients treated with this method had a better prognosis, regarding recurrence, metastasis and death, than those treated with excisional biopsy alone. Topical application of Mitomycin C is not recommended as primary treatment for patients with nodular melanoma because of high rate of local recurrence, but should be considered as an alternative primary treatment for PAM with atypia and an adjuvant therapy for nodular disease [84]. Orbital exenteration as the primary therapy is nowadays used only for advanced conjunctival melanoma since early exenteration did not show advantage for survival [85]. However, during the course of disease because of multiple recurrences or locally advanced tumor exenteration is required in about one third of patients [77].

The role of sentinel lymph node biopsy in order to detect micrometastases in regional lymph nodes is being evaluated in patients with conjunctival melanoma [86, 87]. Current indications for sentinel lymph node biopsy are histologic thickness of conjunctival melanomas ≥2 mm and/or histologic ulceration [87].

Metastases and survival

Metastases in conjunctival melanoma occur through lymphatic and hematogenous spread. It usually firstly metastasize in lymph nodes, predominantly in the parotid and preauricular, and also in submandibular and cervical, but distant metastases can occur without prior regional disease [77, 88]. Owing to that not all patients with conjunctival melanoma may benefit from sentinel lymph node biopsy. Temporal conjunctival melanomas show a tendency to metastasize to preauricular lymph nodes, while nasal conjunctival melanoma shows a tendency to metastasize to submandibular lymph nodes [89]. Metastases occur in approximately 16% at 5 years, and 26% at 10 years [75]. Frequent sites of distant metastases are lungs, liver, skin and brain [75, 77, 88]. It can also spread directly toward eyeball and orbit, nasolacrimal system and sinuses [90, 91]. In a nationwide study of conjunctival melanoma, Missotten and colleagues [77] found five-year survival rate of 86.3% and ten-year survival rate of 71.2%. Paridaens and colleagues [85] estimated five and ten-year survival rate at 82.9% and 69.3%, respectively, which is similar to results of previous study.

Prognostication

Location is one of the most important prognostic factors for conjunctival melanoma. Unfavorable locations include palpebral conjunctiva, fornices, plica, carunculae and lid margins, and they are associated with higher mortality compared with epibulbar location [75, 77, 82, 85, 92]. Non-epibulbar location is also associated with higher risk for local recurrence [76, 77]. On the other hand, epibulbar tumors show a lower rate of local recurrence and distant metastases [77]. The presence of one or more recurrence is associated with an increased incidence of distant metastases [93].

Histopathological findings of mixed cell is associated with three times higher mortality compared with pure spindle cell tumors, and lymphatic invasion by tumor cells is associated with four times higher mortality [85]. Tumor-associated lymphangiogenesis carries increased risk for local recurrence, lymphatic spread, distant metastases and melanoma-related death [94]. Positive margins on histopathology also predict higher risk for local recurrence and distant metastases [75]. Unilocular lesions were found to be associated with better survival [77]. However, Paridaens and colleagues [85] found that only multifocal tumors in favorable (epibulbar) location were associated with increased mortality (fivefold) while on unfavorable locations (non-epibulbar) multifocality was not predictive. Nodular growth pattern of the tumors carries a higher risk for metastases and mortality [82, 92]. Increasing tumor thickness and diameter are also predictors of poorer prognosis, and they are predictive of lymphatic spread, distant metastases and melanoma-related death [94]. Regional and distant metastases are more common in tumors more than 2 mm in thickness [76, 77]. Melanoma arising de novo is associated with a higher risk of metastases and death compared with those arising from nevus and PAM [92]. In one large retrospective series of 382 conjunctival melanomas, at 10 years metastatic disease occurred in 49% of de novo conjunctival melanomas, compared with 25% and 26% for those arising from PAM and conjunctival nevus, respectively [92]. In the same study, melanoma-related death at 10 years was 35% in patients with tumors arising de novo, compared with 9% for those arising from PAM and nevus [92].

Genetic mutations in ocular melanomas

Genetic mutations in cutaneous melanoma are much more studied compared to melanomas originating in other extracutaneous sites. However, in recent years the knowledge about genetic mutations underlying ocular melanomas has started growing.

Cutaneous melanomas and nevi frequent carry oncogenic mutations in BRAF and NRAS which are leading to constitutive activation of MAPK (mitogen-activated protein kinase) pathway [95, 96] which plays an important role in development of melanoma [97]. Activation of the MAPK pathway also exists in uveal melanoma [98, 99], but in contrast to cutaneous melano-

ma it does not occur through mutations of BRAF and NRAS [98-101].

It has been recently revealed that uveal melanomas in more than 80% carry activating mutations in either GNAQ or GNA11 genes [102, 103]. These genes encode a heterotrimeric GTP-binding protein α-subunit ($G\alpha_q$ and $G\alpha_{11}$) that couples G-protein-coupled receptor signaling to the MAPK pathway. Mutations in GNAQ or GNA11 result in constitutive activation of MAPK pathway [102, 103].

Somatic mutations in GNAQ have been found in approximately 50% of uveal melanomas [102, 104-106] and 55-83% of blue nevi, including 6-10% of nevus of Ota [102, 103] which is a form of blue nevus, and predisposing factor for uveal melanoma.

Iris melanoma less often carries GNAQ mutations since they have been found in 22% of tumors in this location [104]. However, BRAF mutations were detected in almost half of examined iris melanomas (9 of 19) [107], suggesting that besides clinical, there also exist genetic differences between the iris and posterior uveal melanoma.

Mutations in GNA11 have been detected in 32% of uveal melanomas, 6.5% of blue nevi (5% of nevus of Ota) and in 57% of uveal melanoma metastases, in contrast to GNAQ which were present in 22% of metastatic tumors [103]. GNA11 mutations were significantly more common in uveal melanoma metastases, and less common in blue nevi, which are benign neoplasm, suggesting the possibility that effects of GNA11 mutations on melanocytes may be more potent compared to GNAQ mutations [103]. GNAQ mutation is believed to be an early oncogenic event in development of uveal melanoma because it was present in tumors at all stages of malignant progression, and did not show a correlation with indicators of advanced tumor progression [104] or with disease-free survival [105].

In conjunctival melanoma mutations of BRAF gene were detected in 22.7% (5/22) [108], but GNAQ gene mutations were absent [102, 106]. In the study of Beadling and colleagues [109] mutation of KIT gene (receptor tyrosine kinase) was found in 1 of 13 (7.7%) conjunctival melanomas but not in any of 60 uveal melanomas. Mutations of KIT gene are more commonly present in mucosal melanomas [109].

Recently, inactivating somatic mutations in the tumor suppressor gene BAP1 (BRCA1 associated protein-1), located on chromosome 3p21.1, have been detected in 84% of class 2 uveal melanomas [110]. In contrast, it has been found in only 1 of 26 tumors in class 1. Depletion of BAP1 in cultured class 1 cells resulted in the shift toward class 2 gene expression signature, suggesting that BAP1 loss is linked to metastatic phenotype [110]. In the same study, one germline mutation in BAP1 was detected, suggesting that BAP1 germline mutation can predispose to uveal melanoma. More recently, BAP1 germline mutations were associated with predisposition not only for uveal but also for cutaneous melanoma, and several other cancers [111, 112]. Unlike GNAQ mutations, which occur early in UM, and do not correlate with prognosis, BAP1 mutations strongly correlate with metastatic behavior of uveal melanoma [110].

Decreased or complete loss of PTEN (phosphatase and tensin homolog) expression has been found in high percent (58.7%) of uveal melanomas and was associated with shortened disease-free survival [113]. PTEN is a tumor suppressor gene, located on chromosome 10q23, which acts as a negative regulator of AKT in prosurvival PI3K-AKT pathway. Thus, loss of PTEN function results in AKT overexpression, aberrant activation of PI3K-AKT pathway, and block of apoptosis. The expression of phosphorylated AKT has been detected in over a half of uveal melanomas and was associated with negative prognostic indicators [114]. The most important mechanism of loss of PTEN expression in uveal melanoma seems to be by submicroscopic deletions, while mutations in the coding region of PTEN are present less frequently [113]. Down-regulation of PTEN has also been found to be associated with increased aneuploidy, suggesting it to be late event in tumor progression [68].

Better understanding of underlying genetic and molecular abnormalities implicated in development and progression of ocular melanomas provides a great opportunity for development of targeted therapy. Many potential target therapeutic agents are currently being explored [115, 116]. Hopefully, in near future emerging

Table 1. Comparison of cutaneous and ocular melanoma characteristics

	Cutaneous melanoma	Ocular melanoma
Origin	Melanocytes located in the basal layer of the epidermis of the skin	Uveal - melanocytes situated in the stroma of the uveal layer of the eye Conjunctival - melanocytes situated in the basal layer of the conjunctiva
Rate per million [1]	153.5	6 all ocular melanomas 4.9 uveal melanoma 0.4 conjuctival melanoma
Male vs. female rate per million [1]	193.7 vs. 125.2	6.8 vs. 5.3 for all ocular melanomas 5.7 vs. 4.4 for uveal melanomas 0.4 both genders for conjunctival melanoma
Trends in incidence	Rising [81, 117]	Uveal melanoma - stable [6] Conjunctival melanoma - rising [7, 76, 80]
Role of a UV light as risk factor	Well supported [118]	Still uncertain
Mean age	55.3 years [119]	Uveal melanoma - 58 years [8] Conjunctival melanoma - 57.4 years [77]
White:black ratio	16:1 [1]	8-10:1 for all ocular melanomas [1] 2.6:1 for conjunctival melanoma [5]
Metastasizing	Lymphogenous and hematogenous	Uveal - hematogenous Conjunctival - lymphogenous and hematogenous
Most common sites of metastases	skin (13–38%) distant lymph nodes (5–34%) distant subcutaneous tissues (32%) lung (18–36%) liver (14–20%) CNS (2–20%) bone (4–17%) [120]	Uveal Liver (93%) Lung (24%) Bones (16%) [45] Conjunctival Lymph nodes (cervical, preauricular, parotid and submandibular) Lungs, liver, skin and brain [75, 77, 88]
Five-year survival	80.8% [119]	81.6% - uveal melanoma [6] 86.3% - conjunctival melanoma [77]
Treatment	91.5% surgery only [119]	Uveal - 28.3% surgery only 62.5% radiotherapy only [6] Conjunctival - nowadays mostly surgical excision combined with adjuvant therapy
Common genetic mutations	BRAF CDKN2A NRAS [121]	GNAQ and GNA11 - uveal melanoma [102, 103] BAP1 - metastasizing uveal melanoma [110] BRAF - iris and conjunctival melanoma [107, 108]

knowledge of molecular pathogenesis of ocular melanomas will translate into a novel and more effective systemic therapeutic agents which will improve, currently poor, prognosis of patients with metastatic disease.

Comparison of cutaneous and ocular melanomas

As well as melanocytes situated in the skin, melanocytes that reside within the uvea and conjunctiva originate from neural crest. Despite shared cellular origin cutaneous and ocular melanomas show noticeable differences regarding incidence rate, pattern of metastasizing, treatment modality and underlying genetic mutations. Role of solar UV radiation which is well supported as risk factor for cutaneous melanoma is still uncertain for ocular melanoma. Comparison of cutaneous and ocular melanoma is presented in **Table 1**.

Conclusions

Ocular melanoma is rare, but still responsible for death of a significant proportion of affected patients. Improvement in local treatment did not provide increased survival, and new treat-

ment options to improve survival in patients with metastatic disease are needed. Emerging knowledge of molecular changes underlying uveal and conjunctival melanoma promises new perspectives for development of novel targeted therapeutic agents. This will hopefully lead to improvement in systemic treatment of patients with metastatic disease or prevent metastatic disease in those known to have tumor with high metastatic potential.

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