Identity

Other names: Ocular melanoma

Classification

Note: Uveal melanoma is a tumor of the adult age, which derives from the pigmented uveal tract of the eye, comprising iris, ciliary body and choroid. The most common site of origin is the choroid (80-90% of cases), while tumors arising from the ciliary body (5-12%) and iris (3-8%) are extremely rare. Choroid melanomas are the commonest type (60-70%), while iris melanomas are particularly rare (5-8%).

Clinics and pathology

Embryonic origin

Neuroectodermal cell lineage.

Etiology

Despite a large amount of epidemiological and molecular studies, the etiology of uveal melanoma remains largely obscure. Unlike cutaneous melanoma, which shows familial aggregation in at least 10% of cases and for which two major responsible genes have been identified to date, uveal melanoma is rarely caused by inherited mutations. In fact, less than 2% of uveal melanoma are associated to germline mutations in BRCA2 and CDKN2A genes. Moreover, the influence of environmental factors, especially exposure to sunlight, is still debated. However, it is well known that uveal melanomas are more common in older patients, particularly if of Caucasian ancestry and with blue/grey eyes. Therefore, to date, a potential role of sunlight exposure in the pathogenesis of uveal melanoma could not be excluded.

Epidemiology

Uveal melanoma is the most common human intraocular tumor in adult patients, although it represents only 3% of all melanomas. Overall annual incidence is 5-7 cases per million/year. In particular, the mean age-adjusted incidence of uveal melanoma is 4.3 per million/year in the United States, where this value remained stable in a 25-year period. Conversely, in Sweden, the incidence of uveal melanoma declined from 11.7 to 8.4 per million males/year and from 10.3 to 8.7 per million females/year over a 4-decade period. There is no evidence of sex predominance. Likely cutaneous melanoma, the incidence is higher amongst fair skinned pale eyed individuals.

Clinics

Obscured vision symptoms of a retinal detachment. Uveal melanoma is a tumor of the adult age. The mean age at diagnosis is about 55 years. The early progression of uveal melanoma is usually asymptomatic. In fact, nearly half of the patients are free of symptoms at the time of the diagnosis. The most common reported abnormalities are blurred vision, photopsia and visual field loss. Additional features are inflamed and painful eye, cataract and glaucoma. Occasionally, uveal melanoma may be externally visible and mimick iris cysts. The diagnosis is established by the ophthalmologist. Binocular indirect ophthalmoscopy and documentation by colour and digital photography greatly enhanced the diagnosis of uveal melanoma. Indocyanine green angiography represents a diagnostic support in defining tumor
margins. Ocular ultrasonography is useful for measuring tumor dimensions when planning treatment.

**Pathology**

Uveal melanoma may develop from melanocytoma, ocular melanocytosis or choroidal nevus. Histologically, six different types of uveal melanoma can be identified:
(i) spindle A,
(ii) spindle B,
(iii) fascicular,
(iv) mixed spindle and epithelioid,
(v) necrotic, and
(vi) epithelioid.

The mixed (spindle and epithelioid) type is largely the most common variant among the choroidal melanomas. Spindle cell melanoma has the best prognosis. Epithelioid is most likely to spread, whilst mixed cell melanomas have an intermediate behaviour. Of note, the size and position of the tumour also affects the prognosis of individual melanomas. Uveal melanomas can invade locally within the eye, and form deposits in other organs, but most commonly the liver.

**Treatment**

Local resection, enucleation, photocoagulation, external beam irradiation, brachytherapy, and laser therapy (these techniques are all included in the following sentences but with a different sequence). The major aims of the actual therapeutic protocols for uveal melanoma are:

(i) to prevent metastatic disease,
(ii) to reduce disfiguring consequences, and
(iii) to preserve ocular function.

Conservative therapeutic procedures include brachytherapy, proton beam radiotherapy, stereotactic radiotherapy, transpupillary thermotherapy, trans-scleral local resection, transretinal resection and diode laser therapy. However, local resection and enucleation is still required in a significant proportion of patients.

**Evolution**

Metastasis occurs, mainly to the liver, with approximately half of patients treated with enucleation dying within ten to fifteen years; the highest rates of metastasis occur in the first five years, but have been recorded over forty years after the primary tumour was detected.

**Prognosis**

Despite recent progress in local therapy, the prognosis of patients with uveal melanoma have remained stable. 15-30% of treated patients died within 5 years following the diagnosis and initial therapy due to metastases, particularly in the liver. Disseminated disease is usually fatal within 1 year after the diagnosis. Spindle cell tumours, and those less than 10 mm in diameter have the best outcome. Ciliary body melanomas and those with extravascular matrix patterns and where there is scleral invasion have a worse prognosis. Other prognostic modifiers are emerging from cytogenetic and molecular studies (see below).

**Cytogenetics**

**Cytogenetics morphological**

Most analysis have been performed on ciliary body and choroid melanomas, usually revealing relatively simple chromosome alterations, often with diploid karyotypes. The most common abnormality is loss of all or part of chromosome 3. Chromosome 3 monosomy is the major genetic factor of poor prognosis, as it is associated with a 70% rate of mortality within 4 years following tumor enucleation. This cytogenetic anomaly is also associated with other clinical and histological poor prognostic factors and, therefore, seems to represent a distinct pathologic entity.

A significant proportion of uveal melanomas show gross abnormalities of one of the 2 copies of chromosome 6 (either duplication of 6p, or deletion of 6q). Trisomy of 6p appears to be mutually exclusive with chromosome 3 monosomy and links with a better prognosis. Conversely, 6q deletion occurs more commonly in metastasizing tumors.

A further poor prognostic factor, strongly associated with metastatic death, is 8q trisomy (also in form of 8q isochromosome), which usually appears later in the natural history of uveal melanoma.

Other less frequent chromosome abnormalities reported in uveal melanoma include 1p and 13q monosomy, as well as chromosome 21 trisomy.

**Cytogenetics molecular**

Comparative genomic hybridization and spectral karyotyping studies mainly confirmed cytogenetic data and identified other minor chromosome abnormalities, such as alterations on 7q and 9p, which at the moment do not show a clear relationship with tumor formation, progression and prognosis. Loss of heterozygosity (LOH) analysis by microsatellite genotyping significantly increased the rate of detected chromosome imbalances, especially of chromosome 3, 6 and 8. This finding is explained by the fact that LOH studies detect not only monosomy/trisomy but also isodisomy. The actual rate of the major chromosome abnormalities in uveal melanoma, resulting from an integrated approach of standard cytogenetics, comparative genomic hybridization, spectral karyotyping and LOH studies by microsatellite analysis is: 50-60% for chromosome 3 monosomy, 40% for 8q trisomy, 25% for 6p trisomy, 25% for 6q monosomy, 17% for 1p monosomy and 15% for 13q monosomy.

Fluorescent in-situ hybridization techniques are used to detect single gene or small chromosome region amplification (see below). Recently, an MLPA kit has been developed in order to...
quickly identify the more common chromosome abnormalities in uveal melanoma.

**Genes involved and Proteins**

**TGFBR2** *(Transforming growth factor-beta receptor, type 2)*

**Location:** 3p22

**Note:** LOH of the 3p22 chromosome region, in which maps TGFBR2, has been identified in 6 out of 19 uveal melanomas, and 61% of these tumors demonstrated perturbed TGFbeta pathway. At the moment, no mutation in genes encoding components of these pathways has been demonstrated in uveal melanoma. TGFbeta seems to upregulate levels of MMP-2 and, in particular, to increase adhesion of non-invasive uveal melanoma cell to hepatic ones. Therefore, it may contribute to the preferential targeting of the liver by uveal melanoma.

**MDM2** *(HDM2, Mouse double minute 2 homolog)*

**Location:** 12q14.3-q15

**Note:** More than 90% of the analyzed uveal melanomas show HDM2 overexpression. HDM2 is an inhibitor of p53. Thus, overexpression of HDM2 may partially inhibit p53 pathway in uveal melanoma and is associated to poor outcome.

**CCND1** *(Cyclin D1)*

**Location:** 11q13

**Note:** Cyclin D1 is overexpressed in nearly 40% of uveal melanoma. This protein activates CDK4, which is the Rb kinase. Therefore, overexpression of Cyclin D1 blocks the active repressor function of Rb on the cell cycle. Also Cyclin D1 overexpression seems to link to poor prognosis.

**CDKN2A** *(Cyclin-dependent kinase inhibitor 2A)*

**Location:** 9p21

**Note:** Although CDKN2A mutations are extremely rare in uveal melanoma, LOH at the CDKN2A locus and CDKN2A promoter methylation occur in 24% and 6% of the analyzed tumors, respectively. A further study demonstrated that CDKN2A promoter methylation is more frequent and may occur up to 32% of the cases.

**C-MYC**

**Location:** 8q24

**Note:** C-MYC is a protooncogene regulating cell proliferation, apoptosis and differentiation. Seventy to 90% uveal melanoma display overexpression of C-MYC. This finding associates to larger tumor size and improved survival. There are emerging evidences that C-MYC overexpression could be related to interfenon resistance of the tumor. Recently, over expression of two other genes, namely DDFE1 and NBS1, mapping to 8q24 and 8q21, respectively, has been documented in uveal melanomas as a potential relevant consequence of 8q amplification.

**BCL2** *(B cell CLL/lymphoma 2)*

**Location:** 18q21.3

**Note:** The vast majority of uveal melanoma shows overexpression of BCL-2. This gene seems to be required for tumor cell survival and proliferation, as its inhibition leads to cell apoptosis.

**To be noted**

The molecular basis of tumor progression is recently emerging. It is hypothesized that the earliest event may be the underactivity of the Rb pathway, for example due to overexpression of Cyclin D or underexpression of CDKN2A. These features could determine the formation of a choroidal nevus. The switch to melanoma could be determined by the inhibition of the p53 pathway. Monosomy of the chromosome 3 determines the transformation in a more aggressive type of uveal melanoma with features of neoangiogenesis and local infiltration. Finally, 8q trillication, with the consequent overexpression of several protooncogenes, among others C-MYC, NBS1 and DDEF1, lead to metastasis formation.

**References**


This article should be referenced as such: Castori M, Grammatico P. Head and neck: Posterior uveal melanoma. Atlas Genet Cytogenet Oncol Haematol.2007;11(4):357-360.