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9

Uveal Melanoma

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1. Introduction

The eye's uveal tract consists of the iris, ciliary body, and choroid. It contains a population of melanocytes. Uveal melanomas develop from melanocytes that reside within the stroma of the choroid, ciliary body or iris.
The choroid is the vascular part of the human eye between retina and sclera. Though accurate measurements of the choroidal blood flow is difficult, it is known that choroid is one of the most vascular tissues in the body and its blood flow is one of highest (1). It is a feared condition because it is potentially lethal and the treatment of metastatic melanoma is ineffective.

2. Epidemiology

Uveal melanomas are found in 3% of cases in the iris, in 5–10% of cases in the ciliary body and in 90% of cases in the choroid in about 40% of cases within 3 mm of optic disc and/or fovea.
Metastatic tumors of the choroid are the most common intraocular malignancy but they are only slightly more common than choroidal melanoma. Choroidal melanoma is the most common primary intraocular malignancy in adults. It has an estimated annual incidence in the United states of 6 cases permillion people (2). Before the age 50 it has an incidence of 3 per million people and after the age 50 it reaches to 21 per million people (3). Sixty five percent of patients are above the age 50 (4). There is no sex predominance. Choroidal melanoma is typically unilateral and unifocal (1). Whites are eight times more likely to have melanoma than African-Americans and three times more likely than Asians. Most melanomas arise from pre-existing, benign choroidal nevi. The prevalence of nevi is 1-2% and the incidence of malignant degeneration into melanoma is less than 1% (5). Exposure to sunlight has been implicated in the development of iris melanomas but there is no convincing evidence to show that sunlight causes choroidal melanomas. Pregnancy accelerates the growth of existing melanoma perhaps through endocrine factors such as excess melanocyte-stimulating hormone (6). Exposure to UV light or other agents is not a risk factor for choroidal melanoma (7).
The most common predisposing factor for choroidal melanoma is ocular melanositosis. Still in congenital ocular melanocytosis the incidence of choroidal melanoma does not exceed %5 (8). In the white population a lifetime risk of developing uveal melanoma increases from 1 in 13000 to 1 in 400 when there is an underlying congenital melanocytosis (9).

3. Diagnosis

Mostly the patients are asymptomatic and the tumor is discovered on ophthalmic examination. On ophthalmoscopy choroidal melanoma usually present as dome shaped tumor with variable pigmentation and sometimes with serous detachment. Tumors are generally pigmented but one fourth are relatively non-pigmented or amelanotic (Figure 1). Symptomatic patients have may have distorted and/or reduced vision when the tumor develops next to or in the macula. Vision field defects may occur due to exudative detachment or corresponding to the tumor. Exudative retinal detachments are usually seen with tumors more that 4 mm thick. Flashes floaters or photosias may occur due to retinal pathology. Pain is rare but occur when there is angle closure or neovascular glaucoma.

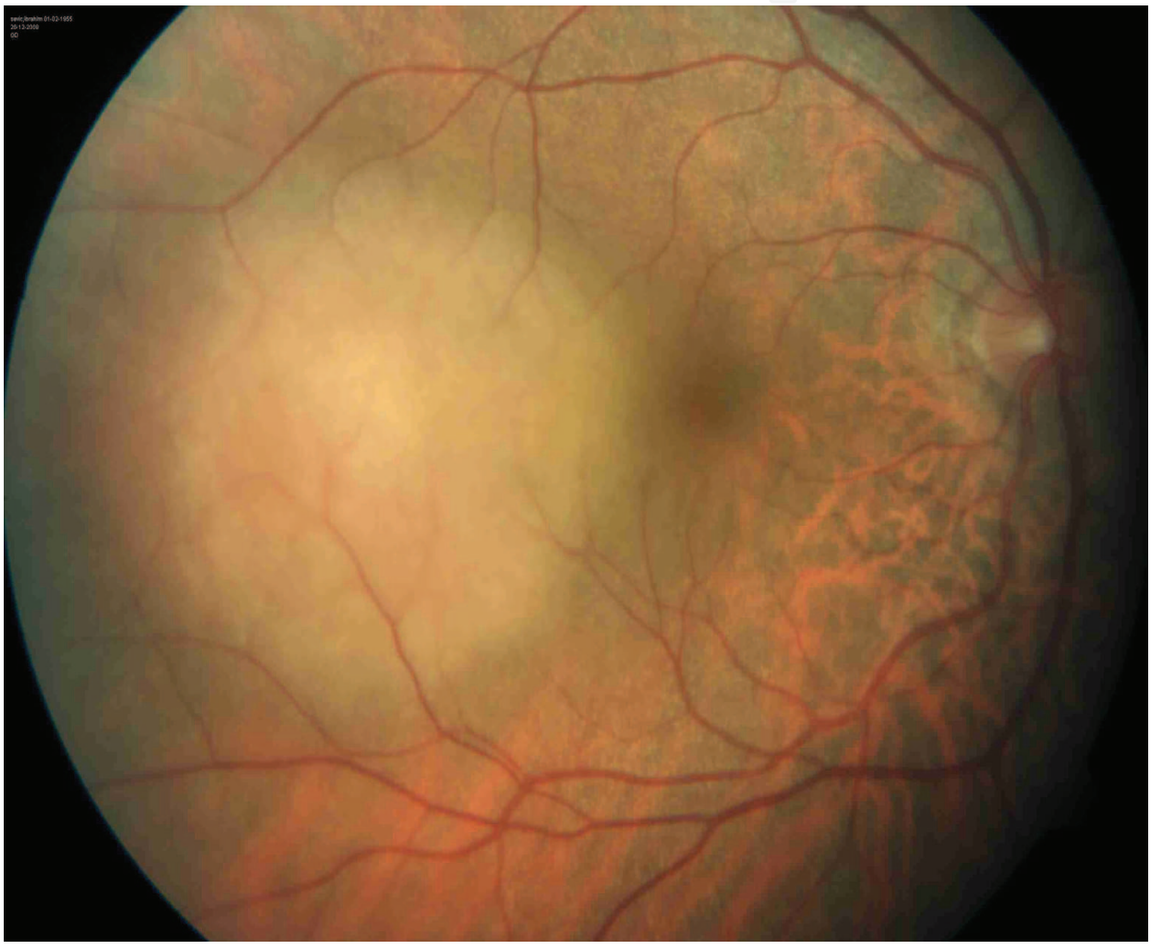

Fig. 1. An amelonocytic choroidal melanoma of the posterior pole

An examination consisting of indirect ophthalmoscopy, fluorescein angiography, scleral transillumination, b-scan ultrasonography has a diagnostic accuracy rate of 99.7% as reported by the Collaborative Ocular Melanoma Study (COMS) (10). In the same study an examination with indirect ophthalmoscopy, revealing a choroidal tumor with orange pigment on its surface and subretinal fluid is correctly diagnosed as choroidal melanoma in 99.6% of cases (10).

Flourescein angiography is reported to have a diagnostic accuracy rate of %36.6 (11). Early hypofluorescence is seen in pigmented melanomas and late hyperfluorescent areas can be seen depending on the interaction of the tumor with the retina pigment epithelium. With changes in RPE early dot-like areas of hyperfluorescence become prominent and they increase in intensity in late phases. Fluorescein angiography may also reveal a typical double circulation seen in choroidal melanomas, a characteristic image caused by simultaneusly retinal and tumor circulation.

For tumors greater than 3 mm thick a combined A-mode and B-mode ultrasonography is more than 95% accurate in diagnosing choroidal melanoma. B-mode ultrasonography might reveal a typical acoustically silent zone within the melanoma, choroidal excavation and acoustic shadowing of the orbit. With A-mode medium to low internal reflectivity might be seen.

Fine needle biopsy is usually not suggested for seeding of the needle tract is reported (12, 13).

4. Prognosis

Long-term follow-up reveals that eventually more than 50% of patients die of disseminated disease (14). About 30-50% of patients with choroidal melanoma will die within 10 years from diagnosis and treatment. As found in the Collaborative Ocular Melanoma Study, for large melanomas the 10-year rates of death secondary to metastasis are 45% in pre-enucleation radiation and 40% and in the enucleation alone treatment groups (10).

It is usually secondary to distant metastases, and the risk is greatest in larger tumors. Though at presentation only 1-3 % of patients have detectable metastases. Overt metastases are fatal and if untreated median survival time is 2-6 months (15, 16). If treated survival time prolongs only up to 12-15 months (17).

Study	Small Size	Medium Size	Large Size
Meta-analysis 1966-1988 [a]	<3mm height <10mm diameter	10-15 mm diameter	>15 mm diameter
	<10 mm diameter	10-15 mm diameter	>15 mm diameter or >5 mm height
	<11 mm diameter	11-15 mm diameter	
	< 300mm^2	<15 mm diameter	
COMS	1,5-2,4 mm height	2,5-10 mm height[b]	>10 apical height
	5-16 mm diameter	<16 mm diameter	>16 mm diameter

[a] Included 8 studies with overlapping size criteria
[b] Changed November 1990 3,1 to 8,0 mm.

Table 1. Definition of size in choroidal melanomas*

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Commonly accepted clinical risk factors are larger size of the tumor, anterior location, proximity to the foveal avascular zone, advanced patient age and histopathology (Table 1). Especially the character of specific vascular abnormalities such as vascular networks, closed loops, and parallel-with-cross-linking microcirculation-related patterns appear to predict tumors more likely to metastasize (18).

	Small Size Melanoma Mortality	Medium Size Melanoma Mortality	Large Size Melanoma Mortality
Meta analysis	16%	32%	53%
5-year all cause (COMS)	16 %	19% [a] 18% [b]	43% [a] 38% [b]
5-year tumor related (COMS)	1%	11% [a] 9% [b]	28% [a] 26% [b]
(Helsinky Study) [a]		All sizes	
4 year tumor related mortality		31%	
15 year tumor related mortality		45%	
25 year tumor related mortality		49%	
35 year tumor related mortality		52%	

[a] enucleation alone
[b] enucleation with preoperative radiation

Table 2. Mortality rates of choroidal melanoma*

5. Treatment

Treatment modalities for choroidal melanoma are brachytherapy,The Collaborative Ocular Melanoma Study (COMS) is a multicenter investigation designed to evaluate therapeutic interventions for patients who have choroidal melanoma. This study aimed to find out which one of the treatment modalities would prolong the remaining lifetime and which of them would have better prognosis for vision overall. There are several treatment modalities:

a) Observation

If the diagnosis is not definite, the lesion should be followed with fundus photography and ultrasound. Factors that differentiate a choroidal melanoma from choroidal nevi are

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thickness (>2mm), subretinal fluid, symptoms, orange pigment and a lesion margin that is touching to optic disc.

Observation as a management choice is a situation where:

1. The ophthalmologist has detected a presumably melanocytic choroidal tumor that is either a relatively large but benign choroidal nevus or a small but malignant choroidal melanoma,
2. That he or she has informed the patient of the findings and differential diagnosis,
3. That he or she has recommended comprehensive reevaluation of the suspicious tumor on a periodic basis (at intervals to be determined on a case-by-case basis by the ophthalmologist, depending on his or her level of concern about the lesion's "prior probability" of being a true malignant melanoma), and
4. That he or she had indicated to the patient that some form of intervention is likely to be recommended when a particular threshold of change in the lesion has been identified (19).

b) Transpupillary Thermotherapy

In the mid-1990s the initial observations of Transpupillary Thermotherapy (TTT) for small choroidal melanoma reported successful with minimal side effects (20), but its popularity later waned following documented recurrences (21, 22).

In TTT light in the infrared range (810 nm) is delivered trough a modified slit-lamp. The long wavelenght passes through ocular tissues and it is absorbed by melanin which is found in high concentration in choroidal melanomas. The tumor is heated up to 60°C and causes tissue necrosis. It is preferred when the lesion is under 2 mm thick but a growth in size is documented. It has also been used for tumors up to 4 mm in thickness (23-25), preferably coupled with brachytherapy treating the tumor base. In 1998 Shields et al. reported the results of the largest published case series of TTT for choroidal melanoma with 100 patients. After a mean of three treatment sessions and 14 months of follow-up, tumor control was successful in 94 of 100 eyes. The remaining 6 eyes were classified as treatment failures. Four of these eyes showed partial or no response to thermotherapy, thus requiring plaque radiotherapy or enucleation and two eyes showed recurrence, but subsequently controlled with additional thermotherapy. The most frequent ocular side-effects in that series included vascular obstruction in 23% and retinal traction in 20% of patients, which occurred within a mean time interval of 4–5 months after TTT.

TTT offers great advantages over enucleation or radiation. Because light can be focused easyly, TTT causes minimal callateral damage and therefore it does not cause cataract, optic neuropathy or retinopathy and visual outcome following TTT may be outstanding.

c) Charged particle Irradiation and Plaque Brachytherapy

Radiotherapy may be a vision-sparing alternative to enucleation for patients with choroidal melanoma. The most commonly used forms of radiotherapy are ophthalmic plaque brachytherapy and charged-particle (external beam) radiotherapy.

External beam irradiation of melanomas with charged particles, protons or helium nuclei, has been performed since 1975.

Plaque radiotherapy or charged-particle radiation is particularly recommended for medium or small sized uveal melanoma which are not suitable to TTT. In CMOS study eyes of patients with tumors from 2.5 mm to 10 mm in apical height and basal diameter of 16 mm or less are treated with a radioactive plaque if randomized to radiation.

The tumor control rate after plaque or charged-particle radiotherapy appears to be similar but charged-particle irradiation may produce worse anterior-segment complications than plaque radiotherapy (26, 27). Currently ^{125}I radiation therapy is considered excellent for intraocular tumors because since it lacks alpha or beta rays, its penetrance allows the treatment of large tumors and the seeds are commercially available and can be reused. Only 125I is used in CMOS study.

The local recurrence rate of melanomas treated with ^{125}I plaques is 4% (28). After all forms of radiotherapy many patients experience sight-limiting side effects due to optic neuritis and an average of 16.3% of patients treated with radiotherapy subsequently require enucleation because of tumor regrowth or uncontrollable neovascular glaucoma.

d) Enucleation

Until the 1980's, the standard treatment of choroidal melanoma was the removal of the eye by enucleation (29). Enucleation is still performed for large uveal melanoma when there is no hope of regaining useful vision but based on the published literature, it seems that enucleation carries the same survival prognosis as each of the conservative treatment modalities. According to CMOS study mortality rates following ^{125}I brachytherapy does not differ from those following enucleation through 12 years follow-up time.

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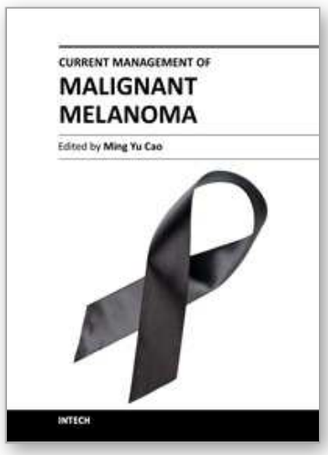

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Management of melanoma is challenging, especially for the late stage of the disease. Development of new therapies and optimizing current treatments are being pursued in attempt to further improve the survival rate. The book provides up-to-date knowledge and experience in early diagnosis, prevention and treatment of melanoma as well as current ongoing clinical studies on melanoma. The book also provides the most recent perspectives of research on the molecular basis of melanoma, such as melanoma associated genes and a possible link between stress and melanoma.

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