

Choroidal melanoma

This article reviews the current literature on choroidal melanoma and discusses its presentation, simulating lesions and current management. Choroidal melanoma is a major ocular problem that could threaten the patient's life and requires early diagnosis and treatment.

Uveal melanoma is the commonest primary malignant intraocular tumour in adults. Nevertheless, it is an uncommon cancer in humans, with an approximate incidence of 5–7 cases per million per year (Jensen, 1963; Keller, 1973; Scotto et al, 1976). About 80% of uveal tract melanomas arise in the choroid, 12% in the ciliary body and 8% in the iris. With recent advances in treatment more than 80% of eyes with choroidal melanoma can now be conserved.

Epidemiology and risk factors

Choroidal melanoma affects mainly adults in their 6th decade. Occasionally, young adults can be affected and, rarely, young children. Exceptionally, a congenital form of uveal melanoma has been encountered (Palazzi et al, 2005). Melanomas are almost always unilateral but bilateral disease may be seen, usually sequentially and only very rarely simultaneously. Melanomas generally occur as sporadic tumours but familial cases have been reported. The tumour has a predilection for white Caucasians especially those of northern European ancestry, and is extremely rare among people of Afro-Caribbean ancestry.

Few risk factors have been identified for uveal melanoma although oculodermal melanocytosis and the familial atypical mole syndrome may be predisposing factors in a few sufferers. The origin of the tumour is controversial with opinion divided between de novo and in a pre-existing benign choroidal naevus. The rate of transformation of uveal naevus to melanoma has been found to be less than 0.0001 (Singh et al, 2005).

Light eye colour and skin pigmentation are constitutional associations with choroidal and ciliary body melanoma (Stang et al, 2003), and may indicate that melanin confers a protective role against melanoma.

Genetic studies show that uveal melanoma may arise as a result of alteration in the tumour suppressor gene and apoptosis mechanisms. Loss of one copy of chromosome 3 is found in nearly half of the uveal melanomas and is particularly associated with the ability of the tumour to metastasize (Scholes et al, 2003).

Pathology

Primary choroidal melanoma arises from melanocytes within the choroid. Two distinct cell types are seen in uveal melanoma: spindle and epithelioid. Tumours composed mainly of epithelioid cells are more aggressive and associated with poor survival prognosis.

Ocular manifestations

Uveal melanoma can present with a variety of symptoms depending on the size and the location of the uveal melanoma. Up to 40% of cases of choroidal melanoma could be asymptomatic at the time of diagnosis (Servodidio and Abramson, 1992) especially in the case of small and anteriorly located tumours. Some patients may present with photopsia (a sensation of flashing lights) or a visual field defect caused by the mass itself or an associated exudative retinal detachment. Metamorphopsia (distortion of vision) and reduction in visual acuity can be seen in cases of posteriorly located tumours affecting the fovea, and also because of macular exudation. Diminution of vision may also be seen with tumour obstructing the visual axis or as a result of cataract development with ciliary body tumours. Pain is not characteristic of uveal melanoma but may be occasionally experienced in cases of elevated intraocular pressure.

Choroidal melanoma is typically a discrete solid elevated subretinal mass. Rarely, a thin, diffuse melanoma may affect more than half of the choroid. Multifocal melanomas are exceptional. The colour of the mass is usually brown but the degree varies from dark brown to white (amelanotic) (Figure 1). Clinically, it may be difficult to distinguish a small melanoma from a large naevus. The presence of orange lipofuscin pigment on the surface of the tumour or accumulation of subretinal fluid around the base of the tumour suggests malignancy whereas the absence of these features and the presence of retinal pigment epithelium changes with white hyaline thickenings of Bruch's inner limiting membrane of the choroid called drusen are more suggestive of a benign tumour. In about 20% of cases, melanoma may pass through Bruch's membrane and become mushroom-shaped as it extends into the subretinal space. This configuration is characteristic of malignant melanoma of the choroid and is only rarely seen in other choroidal tumours.

Diagnosis and work up

Detailed history taking is important before proceeding with examination. Questions about previous systemic cancers are vital to exclude metastatic tumour to the choroid. It is also important to ask about family history

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Figure 1. Choroidal melanomas with variable degrees of pigmentation.

of ocular neoplasms as, although melanomas generally occur as sporadic tumours, familial cases of uveal melanoma have been documented.

Indirect ophthalmoscopy through a dilated pupil is the most important clinical method for assessment of the tumour. It provides a wide, three-dimensional view of the fundus and enables the clinician to establish the diagnosis and document the basal dimension as well as the apical height of the lesion. Ophthalmoscopic examination of peripheral lesions is usually made easier with scleral indentation. Slit lamp biomicroscopy enables fundus examination with high magnification and is needed for observation of subtle features like minimal subretinal fluid and lipofuscin.

Trans-pupillary transillumination is still a useful test in evaluation of the basal dimensions of pigmented ciliary body and anterior choroid melanomas. As light from a fiberoptic probe is reflected from the retina and through the sclera, the tumour casts a shadow.

Ultrasound is the most important investigative modality for evaluation of any fundus mass. It is especially needed in eyes with opaque media that preclude ophthalmoscopic examination and can help establish the diagnosis, assess the size of the lesion and detect extraocular extension (*Figure 2*). Echographically, choroidal melanomas characteristically exhibit low internal reflectivity, best seen on A-scan, and choroidal excavation visible only on B-scan. Serial ultrasound is also useful to monitor growth of suspicious naevi and regression of melanomas after treatment.

Figure 2. Ultrasound of a choroidal melanoma depicting a dome-shaped lesion with central lucency.



Although fundus fluorescein angiography (FFA) defines the vascularity and level of the lesion, it is not routinely used in the diagnosis in melanoma. There is no distinct angiographic pattern for melanoma with FFA but most melanomas show some degree of late hyperfluorescence. Sometimes intrinsic tumour vessels can be seen with FFA, and are suggestive of the diagnosis.

Computed tomography and magnetic resonance imaging are less reliable for the detection of extraocular extension than ultrasonography and are not recommended as routine tests.

In specialist centres, fine needle aspiration biopsy and cytology or transcleral biopsy and histology may be used occasionally to establish the diagnosis in atypical cases. Interpretation of results is difficult and is more reliable after biopsy than aspiration. As the techniques are invasive, they carry a potential risk of extrascleral spread and so should be used only when clinical diagnosis is not possible.

At diagnosis, systemic evaluation is advised to exclude first the presence of systemic metastases from uveal melanoma which might contraindicate futile radical treatment by enucleation and, second, particularly in amelanotic tumours, any possibility that the ocular lesion is a metastasis rather than a primary choroidal melanoma. Routine tests usually include liver function tests (particularly the serum gamma-glutamyl transferase level), chest X-ray and abdominal ultrasound. Other tests may be needed if any one of these tests proves abnormal or in patients suspected of harbouring a metastatic uveal lesion.

Differential diagnosis

Several fundus lesions can simulate choroidal melanoma. Figures from the Collaborative Ocular Melanoma Study show that the incidence of eyes enucleated for lesions mistakenly thought to be melanoma was as low as 0.33% (Albert, 1997). This high accuracy of diagnosing uveal melanoma is probably attributed to increased awareness of clinicians about the simulating lesions, improved diagnostic modalities and increased referrals to ocular oncology centres (Rennie, 2002).

Choroidal naevus, a benign tumour of the uveal melanocytes, is much more common than melanoma with an incidence up to 8.5% in the white population (Sumich et al, 1998). A typical choroidal naevus is usually 1–5 mm in diameter, flat or minimally elevated, with an ill-defined

margin. The tumour is usually slate grey in colour although the degree of pigmentation may vary. The surface of the lesion may be associated with drusen (*Figure 3*). As naevi are common, follow up of typical cases can be done by the optician with fundus photography documentation. Benign melanocytic tumours are almost always asymptomatic but visual loss can rarely result from a sub-foveal location or the development of a choroidal neovascular membrane.

A diagnostic dilemma may arise because of overlapping clinical features between small choroidal melanoma and benign choroidal nevus. As early detection and treatment of small melanoma before it starts growing may decrease the risk of developing metastases, several studies have tried to identify features predictive of tumour growth. In 1995, Shields and associates identified five features that they included in the mnemonic 'TFSOM' (to find small ocular melanoma), where T = thickness >2 mm, F = subretinal fluid, S = presence of symptoms as photopsia and metamorphopsia, O = orange pigment on the tumour, M = margin of the tumour touching or within 3 mm of the optic disc. According to their results, tumours with no risk factors had 3% risk of growth in 5 years and probably represented benign naevi. Lesions with one risk factor had 38% risk of growth and more than half of those with two or more risk factors showed evidence of growth. The authors concluded that melanocytic lesions with two or more risk factors are presumably small melanomas and advocated treatment (*Figure 4*).

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is another benign condition that can simulate a naevus or choroidal melanoma. CHRPE is usually asymptomatic and appears as a discrete, flat, well-delineated, subretinal lesion. It is usually black or dark grey in colour with areas of depigmentation (*Figure 5a*). Congenital grouped pigmentation of the retina is a variant of CHRPE that appears as a multiple, grouped sectorial lesions, usually in the mid periphery of the retina that have the appearance of 'bear tracks' (*Figure 5b*). CHRPE has no malignant potential but similar grouped lesions have been reported to be associated with familial polyposis of the colon, a disease that invariably undergoes transformation to colonic carcinoma. These lesions differ from the grouped subset of CHRPE in being bilateral, haphazardly scattered in the fundus, and have peculiar fish tail-shaped hypopigmentation.

Subretinal blood from age-related macular degeneration can appear as a dark lesion simulating a melanoma. Marked subretinal haemorrhage is very uncommon in melanomas with an apical height less than 5 mm. Bleeding in macular degeneration will usually disappear and the lesion flattens after a few months' observation whereas a melanoma will grow.

Several pale choroidal lesions including circumscribed haemangioma, osteoma and secondary carcinoma may simulate amelanotic melanoma.

Choroidal haemangiomas are usually orange-red and blend with the colour of the normal fundus (*Figure 6*)

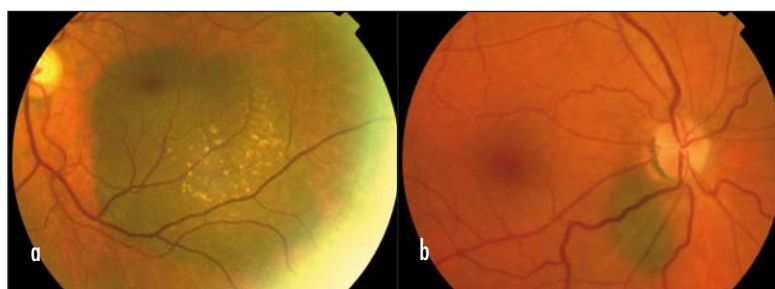


Figure 3. Choroidal naevus (a) at the macula and (b) inferior to the disc. Note the presence of surface drusen in (a).

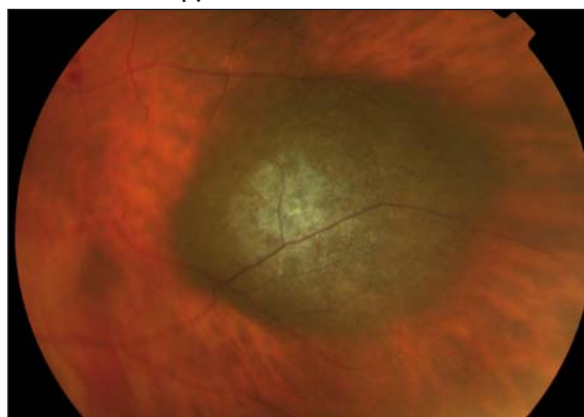


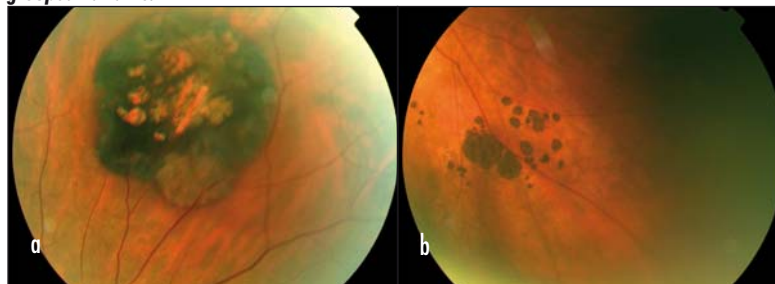
Figure 4. Melanotic choroidal mass suspicious of a small melanoma.

whereas amelanotic melanoma tends to be white. Haemangiomas may leak subretinal fluid and may exhibit early hyperfluorescence with FFA. The high internal reflectivity of haemangioma on ultrasound distinguishes it from the melanoma with characteristic low internal reflectivity.

Choroidal osteoma is a rare, benign, commonly bilateral hamartoma in which bone tissue develops in the choroid. It occurs most commonly in middle-aged females, with a predilection for the posterior pole of the eye. It is yellow to orange in colour, minimally elevated and characterized by pseudopodium-like edges, and brown mottling of the retinal pigment epithelium. The bony lesion produces an intense acoustic shadow on ultrasound and can be seen as a high intensity mass on computed tomography making these two imaging techniques the diagnostic tests of choice.

Choroidal metastases are thought to be the commonest intraocular malignancy overall. A history of malignancy

Figure 5. Congenital hypertrophy of the retinal pigment epithelium, (a) solitary and (b) grouped variants.



nancy is noted in nearly two thirds of the cases, mostly lung carcinoma in men or breast carcinoma in women. Although the presence of bilateral and/or multifocal lesions is suggestive, choroidal metastasis tends to be unilateral and discrete in nearly 65% of cases. Tumours originating from lung and breast appear as minimally elevated, placoid, creamy or pale yellow lesions with ill-defined edges and subretinal fluid around the tumour (Figure 7). Ultrasonography and FFA are not usually helpful in the distinguishing metastasis from primary. Fine needle aspiration cytology or biopsy may be considered in cases presenting as discrete amelanotic lesion with no history of systemic tumour.

Metastases and mortality

Despite treatment, up to 50% of patients with choroidal melanoma will die from metastases within 10 years of diagnosis. There is no effective treatment and the prognosis for patients who develop metastatic melanoma remains poor.

The liver is the most common site of involvement by metastatic melanoma, but other organs such as skin, lungs and bone may be affected. Only up to 2% of patients have clinical metastases when their primary uveal melanoma is diagnosed (Pach and Robertson, 1986). Results from

studies of tumour doubling times of choroidal melanoma and metastases suggest that most uveal melanomas have micrometastases many years before the diagnosis and that the size of metastasizing melanoma could be as small as 3 mm in basal diameter and 1.5 mm in height (Eskelin et al, 2000). This highlights the importance for early detection and treatment of small melanomas.

Although it was once speculated that enucleation may be associated with a higher mortality as a result of dissemination of tumour cells (Zimmerman et al, 1978), unpublished retrospective data from Moorfields Eye Hospital in 1985 (Hungerford, 2003) and later Collaborative Ocular Melanoma Study group (2001), proved that there is no statistical significant difference in survival after enucleation or plaque radiotherapy. However, data from the latter study showed that in general, mortality tends to be highest 2–3 years after treatment and then slowly declines.

Treatment

The primary goal of uveal melanoma treatment is to prevent metastases. Other objectives are to preserve a comfortable, cosmetically satisfactory eye with as much vision as possible (Damato, 2006). The potential for micrometastases many years before the diagnosis means that the most effective way of improving survival rates will be to maximize early detection and treatment of small melanomas. Patients are warned that metastases can develop after local treatment to the eye even when systemic staging is negative for dissemination.

At present, plaque radiotherapy (brachytherapy) is the mainstay of treatment for both small and medium-sized melanoma. The application of a radioactive plaque to the sclera overlying the uveal melanoma relies on the effect of attenuation of radiation in accord with the inverse square law to spare adjacent ocular structures in a way that cannot be achieved with conventional external beam radiotherapy. Although several different isotopes have been used for treatment, ruthenium-106 and iodine-125 are the two most commonly used radioactive sources now. In Europe, the preferred source is ruthenium-106. Data from London prove that using bigger plaques and titrating the depth dose according to the thickness of the tumour could achieve a rate of tumour control very comparable to that of iodine plaques (about 95%) and at the same time, maintain the ability of the beta-emitting ruthenium applicators to preserve better vision than iodine plaques using X-rays (Hungerford, 2003).

Most of the complications of brachytherapy are of late onset and include radiation retinopathy and optic neuropathy. They tend to be more severe in tumours near the fovea and the optic nerve head. Cataract was common following iodine plaque brachytherapy but does not occur with ruthenium plaques.

High local tumour control rates have been reported using charged particle radiotherapy with protons or helium ions. Charged particles can be directed in a pencil

Figure 6. Choroidal haemangioma.

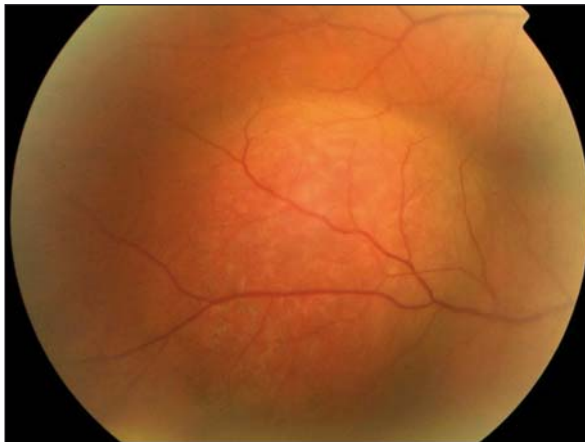


Figure 7. Choroidal metastasis. Note the presence of a pale mass (black arrows) and subretinal fluid (white arrow heads).



beam in which the dose falls rapidly at the edge and, because of the effect of the Bragg peak, beyond the target. Reduced entry dose is another potential benefit of the Bragg peak but unfortunately modulation of the beam to encompass the whole tumour depth substantially reduces this effect. Consequently, particularly when it is used to treat large or anteriorly located melanomas, charged particle radiotherapy delivers a high dose to the lids and anterior segment structures, limiting its application mainly to small posterior tumours. Most of the radiation complications of charged particles therefore affect the anterior segment (Finger, 1997) and include lid keratinization and loss of lashes. Neovascular glaucoma commonly follows charged particle therapy of large melanomas with persistent ischaemic retinal detachment (Foss et al, 1997). It is not a direct side effect of the irradiation. In London, the use of charged particles is now limited to proton beam radiotherapy of peripapillary tumours extending more than 180° around the optic nerve head that cannot be managed safely with plaques. Patients treated with local radiation techniques require close serial assessment because of the potential risks of tumour recurrence. Nevertheless, with careful patient selection, more than 90% of eyes with a choroidal melanoma can be retained (Wilson and Hungerford, 1999).

Enucleation is still needed for large tumours with thickness more than 8–10 mm and basal diameter more than 16 mm that cannot be safely treated with irradiation.

Evolving new treatment methods include transpupillary thermotherapy and local resection techniques. Transpupillary thermotherapy involves the application of diode laser to the surface of the tumour at a low energy setting. The aim is to induce hyperthermia of the tumour that results in tumour destruction. Although this modality is claimed to be successful in small tumours, the rate of local recurrence is relatively high (Shields et al, 2002). Transpupillary thermotherapy may be a reasonable treatment option in managing cases with edge recurrence following plaque radiotherapy. Eye wall resection is selectively considered in some centres for cases of uveal melanoma that are unlikely to be controlled with radiotherapy because of tumour thickness and the patient is highly motivated to keep the eye. Concerns about this procedure include difficulty of the technique as well as the potential risk of extraocular dissemination and systemic metastases (Damato, 2006).

Conclusions

Uveal melanoma is a major intraocular problem that could threaten the patient's life. Current treatments are able locally to eradicate the tumour without the need for removing the eye in most cases. All efforts should be directed towards early diagnosis and management of small melanomas before the development of subclinical metastases. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Up to 40% of cases of choroidal melanoma could be asymptomatic at the time of diagnosis, hence the importance of routine fundus examination by opticians.
- The accuracy of diagnosing uveal melanoma exceeds 99.5%.
- At present treatment modalities are able to conserve the eye in about 80% of cases.
- The 10-year mortality rate in uveal melanoma is still high, between 30 and 50%.
- The only way to increase survival rate in uveal melanoma is through early detection and treatment of small melanoma before they develop micrometastases.
- The presence of systemic metastases at the time of diagnosis contraindicates all but palliative local treatment to the eye.