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Uveal melanoma: Current diagnosis and treatment

Uveal melanoma (UM) is a rare but lethal form of melanoma that arises from melanocytes in the uvea, with an incidence of 7.6 cases per million per year in Australia.[1] UM can arise in any part of the uveal tract, including the iris and ciliary body; however, 90% occur in the choroid. The incidence of UM varies with age and race, typically occurring in middle-aged Caucasian patients, with a much lower incidence in black and Asian populations.

Diagnosis of uveal melanoma

Optometrists play an important role in detecting and referring patients with choroidal tumours.[2] Initial detection of UM commonly occurs following routine screening visits to optometrists or ophthalmologists. Patients with UM are frequently asymptomatic; however, symptoms suggestive of retinal or choroidal pathology, including flashing sensations or visual field loss, require a dilated fundus examination. The increasing availability in optometry practices of wide-angle fundus imaging systems, for example, Optos is likely to lead to earlier detection and referral of patients at risk and potentially to lives saved through earlier treatment. Formal diagnosis of UM is made by clinical examination by an ophthalmologist with experience in ocular tumours (ocular oncologist). Features such as subretinal fluid, orange pigment and documented growth, combined with multimodal imaging techniques such as optical coherence tomography (OCT), autofluorescence and ultrasound, are needed to accurately diagnose UM.[3] Differentiation between a choroidal naevus and a small choroidal melanoma may be challenging even for an experienced ocular oncologist, and an observation period may be recommended. Documented growth of a pigmented choroidal tumour usually indicates a diagnosis of melanoma; however, up to 31% of choroidal naevi show slight enlargement without clinical evidence of transformation into melanoma.[4]

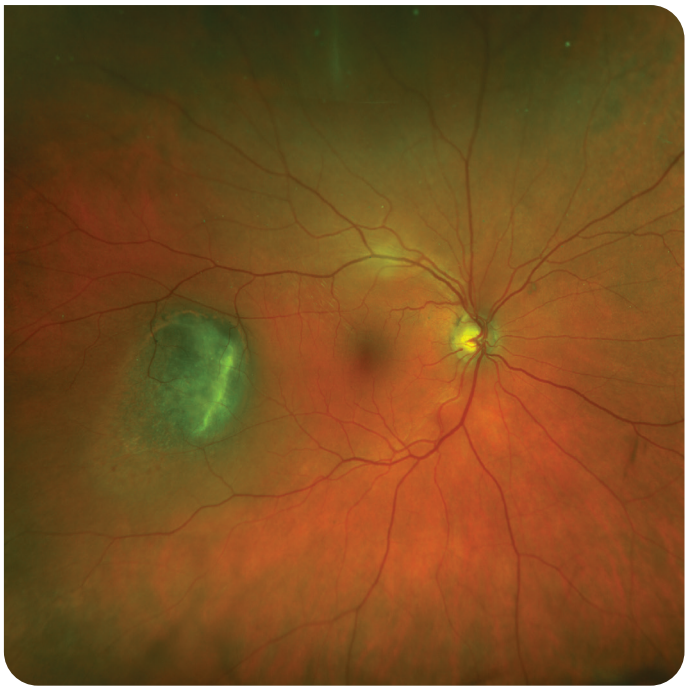

Figure 1. Elevated pigmented choroidal mass in the temporal mid-periphery.

Case presentation

A 70-year-old man attended his optometrist complaining of flashing sensations in the peripheral field of his right eye for one month. His optometrist performed a dilated fundus examination and noted a pigmented choroidal lesion in the temporal mid-periphery of his right eye. The patient was referred to an ocular oncologist for further evaluation. At presentation, corrected visual acuities were R and L 6/6. Fundus examination for the right eye showed an elevated pigmented choroidal mass in the temporal mid-periphery (**Figure 1**). There was some overlying subretinal fluid (**Figures 2. a & b**) but no orange pigment. In the following months, a clear increase in the size of the mass was noted (**Figure 3**).

Apical height increased from 1.9 to 3.7 mm, and there was pigment proliferation on the surface with orange lipofuscin at the temporal margin and subretinal fluid now encroaching the temporal macula (**Figure 4. a & b**). The mass was diagnosed as choroidal melanoma, and the patient underwent radiation treatment with Ruthenium (Ru) plaque brachytherapy. Postoperatively, the patient has remained well with no evidence to date of metastatic disease. The tumour shows atrophy and regression, indicating adequate treatment (**Figure 5**). Following treatment, the patient developed signs of radiation maculopathy (**Figure 6**), which responded well to treatment with a course of anti-vascular endothelial growth factor (VEGF) injections (**Figure 7**).

Current treatment of uveal melanoma

Current management options for patients with UM depend upon the size and location of the tumour, the visual potential of the eye and the presence or absence of metastatic disease. Iris melanoma is usually treated with radiation, preferably proton beam irradiation, though this is currently unavailable in Australia. Most patients with posterior UM arising from the choroid or ciliary body are treated with radiation, usually via plaque brachytherapy and less commonly with external beam radiation. In the case of the largest tumours, brachytherapy cannot be performed, and enucleation is the only possible option. →

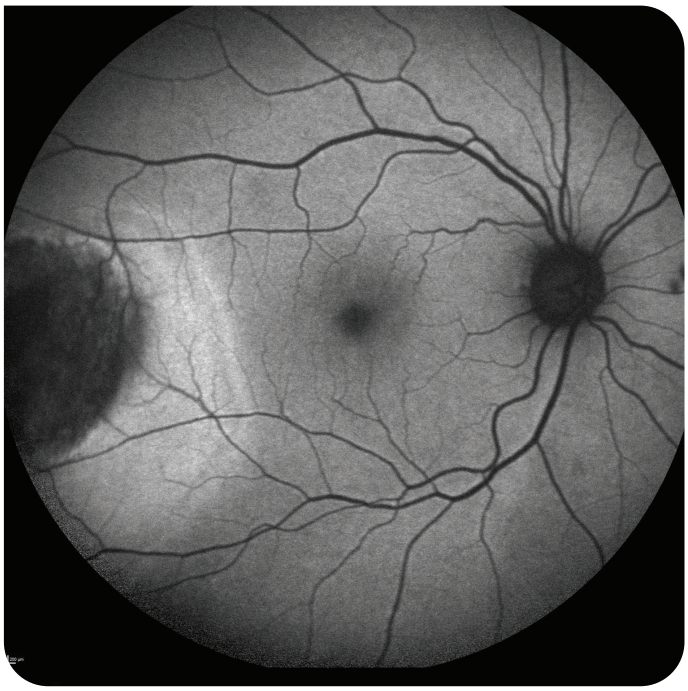

Figure 2. a) Autofluorescence showing overlying subretinal fluid of the choroidal mass.

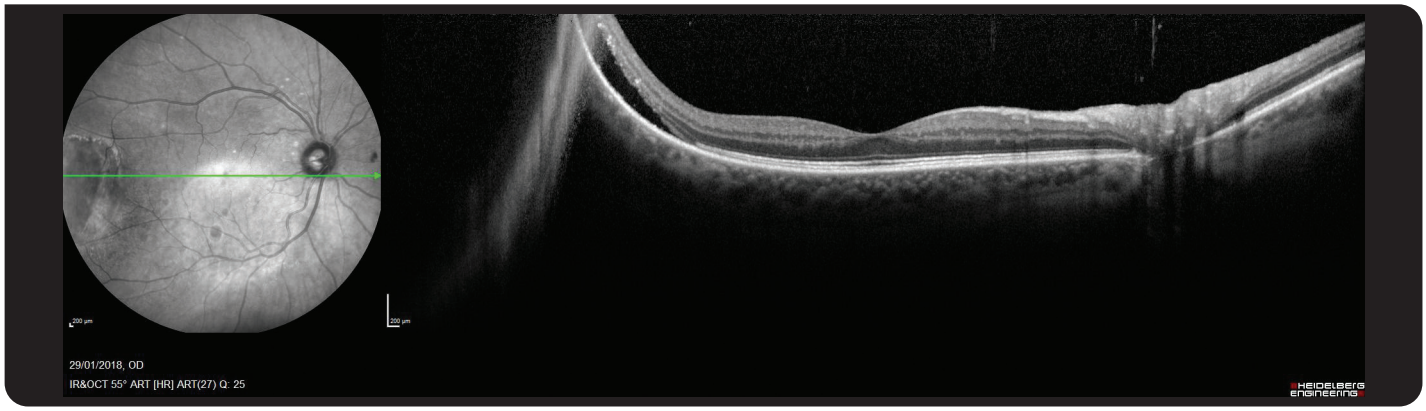

Figure 2. b) OCT highlighting overlying subretinal fluid.

Genetic biomarkers in uveal melanoma

Accurate characterisation of the metastatic risk of individual patients is now possible through genetic profiling of UM tumours. This can only be achieved by a melanoma biopsy, typically performed via vitrectomy and trans-retinal biopsy during plaque surgery. Molecular analysis of the tumour allows the identification of changes relevant to prognosis, such as somatic copy number alterations (SCNAs), gene expression profiling or specific gene mutations. As early as 1990, chromosomal abnormalities were noted in UM cells, with loss of one copy of chromosome 3 (monosomy 3) found in approximately 50% of tumours.[5] The presence of monosomy 3 within UM cells increases the risk of metastatic spread.[6] Subsequent studies have revealed that mRNA-based gene expression profiling can differentiate 2 distinct molecular forms of UM cells. Class 1 UMs have a low risk of metastasis, with gene expression similar to normal uveal melanocytes, while class 2 UMs harbour a high risk of metastases, with a more primitive stem cell-like gene expression profile.[7] Determination of metastatic risk following biopsy may help guide follow-up of these patients and the frequency of metastatic screening thereafter.

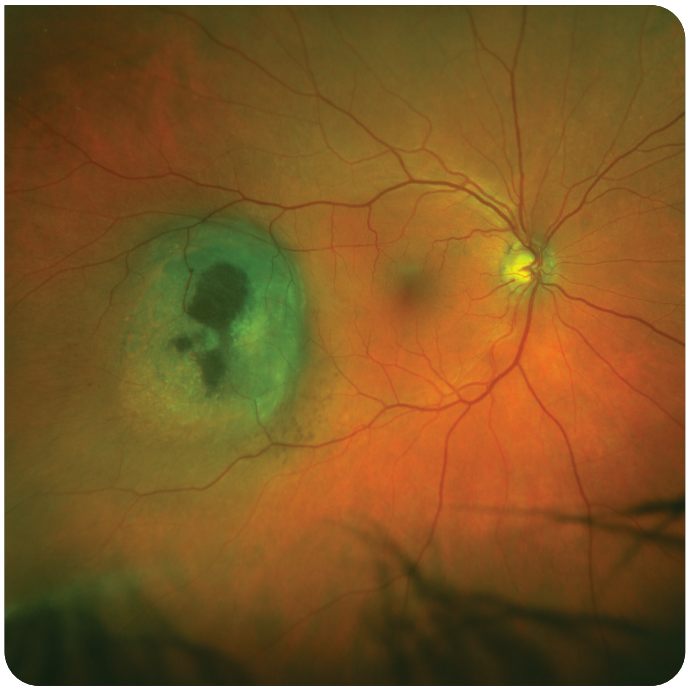

Figure 3. Increase in size of choroidal mass.

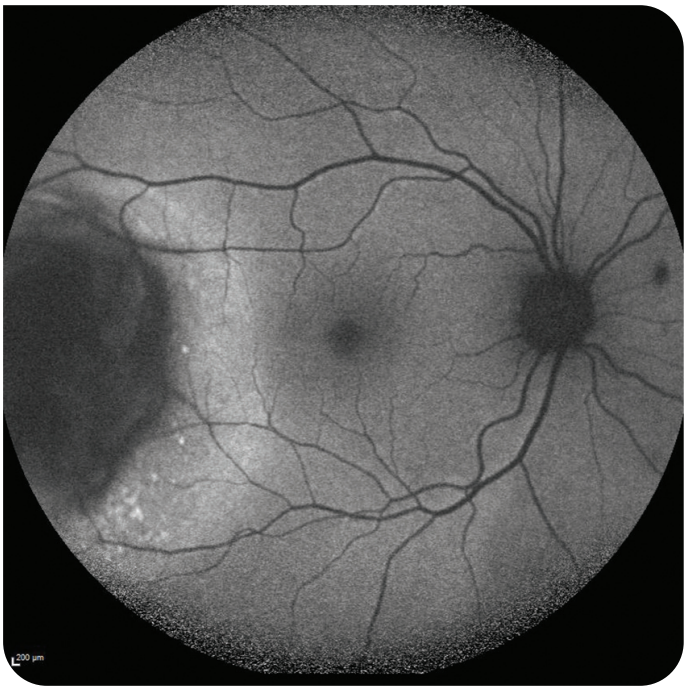

Figure 4. a) Hyper-autofluorescence indicating subretinal fluid encroaching temporal macula.

Figure 4. b) OCT showing subretinal fluid encroaching temporal macula.

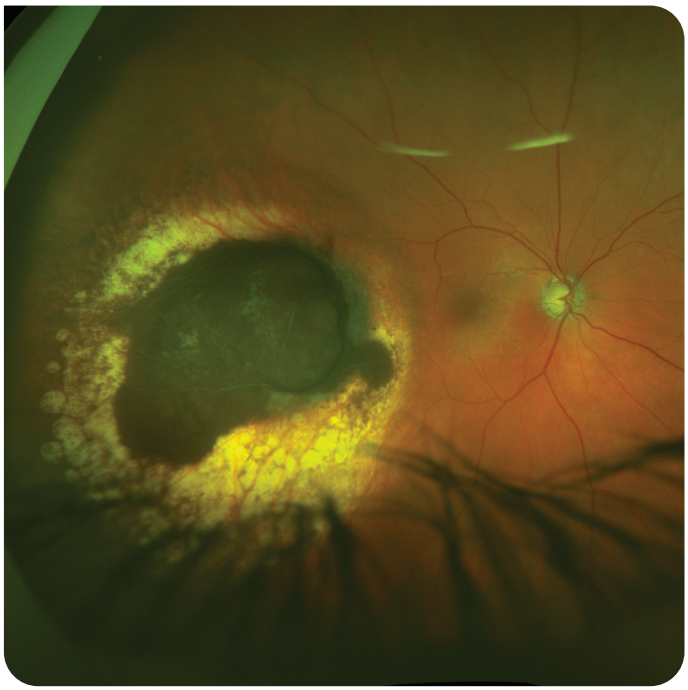

Figure 5. Atrophy and regression of the tumour following treatment.

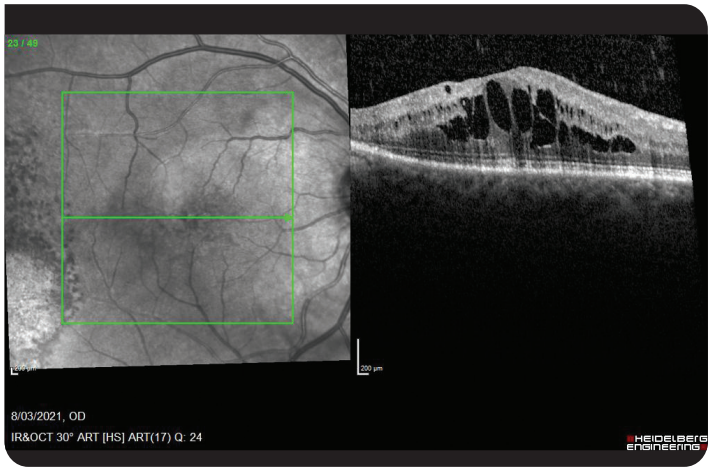

Figure 6. Radiation maculopathy after treatment.

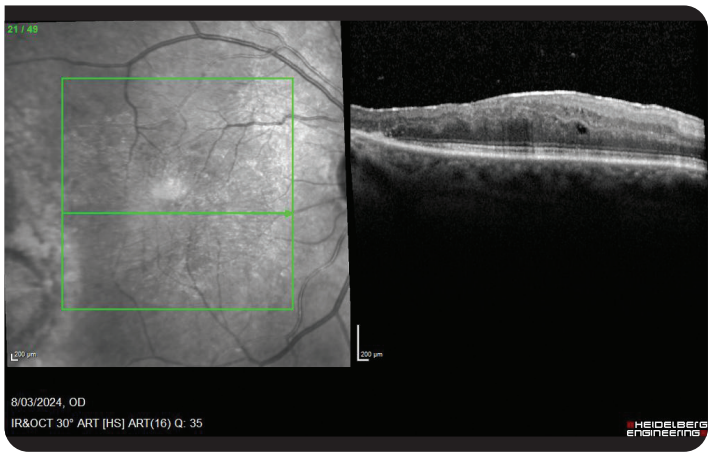

Figure 7. Appearance of macula after anti-VEGF injections.

Metastatic uveal melanoma

UM has a propensity to metastasise to the liver, and following diagnosis with UM, patients undergo screening examination with either liver ultrasound, magnetic resonance imaging (MRI) or positron emission tomography–computed tomography (PET-CT). Fewer than 4% of patients have detectable metastatic disease at the time of primary diagnosis.[8] Unfortunately, approximately 50% of patients will develop metastases[9] after a median interval of 3.1 years following diagnosis of the primary.[10] Metastatic UM is usually fatal, with reported survival rates of just 20% at 1 year and 8% at 2 years following diagnosis with metastases.[11] Until 2022, no systemic therapy had received regulatory approval for patients with metastatic UM; however, a series of recent studies of the biology of these tumours has driven the development of novel therapies, including tebentafusp, the first systemic therapy to achieve regulatory approval for this disease.[12] These developments and preliminary results from ongoing clinical trials of adjuvant therapies with agents such as darovasertib, offer the hope of improved future survival of patients diagnosed with UM.[13]

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Australasian Ocular Melanoma Alliance Virtual Summit

The 2024 Australasian Ocular Melanoma Alliance (AOMA) Virtual Summit on Saturday, 15 June, is the premier cross-disciplinary meeting for healthcare professionals, researchers and consumers interested in UM. This free virtual event will feature international and Australian experts, along with consumers and will cover the latest in clinical trials, therapies, advances in ophthalmology, new research and more. Optometrists are encouraged to attend the virtual summit or register to access the videos at their convenience. For more information and to register, visit the AOMA Summit webpage: **www.masc.org.au/aoma-summit/**

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