Multifocal Intraretinal Tumour Deposits following Treatment of an Ipsilateral Choroidal Melanoma

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Established Facts

- Retinoinvasive melanoma is characterised by transvitreal melanoma invasion of the retina at a site non-contiguous with the uveal tumour.
- Retinoinvasive melanoma typically arises in cases of iris or ciliary body melanoma, and usually presents with raised intraocular pressure/secondary glaucoma and exhibits optic nerve invasion.

Novel Insights

- Although rare, retinoinvasive melanoma may arise from choroidal tumours, in the absence of both optic nerve invasion and raised intraocular pressure.

Keywords

Retinoinvasive melanoma · Uveal melanoma · Choroidal melanoma · Metastasis · Recurrence · Retinal melanoma

Abstract

Background/Aims: The aim of this study was to report a patient who, following plaque brachytherapy for a choroidal melanoma, developed two separate retinal foci of malignant melanoma in the same eye, and suggest possible mechanisms that might explain such an occurrence. **Methods:** We conducted a retrospective case report. **Results:** A 79-year-old Caucasian male developed a left inferotemporal choroidal melanoma in 2016 and subsequently underwent ruthenium-106 plaque brachytherapy under the care of the Scot-

tish Ocular Oncology Service. Serial B-scan ultrasonography demonstrated a post-treatment reduction in tumour height to <2 mm. In 2018, 27 months after the treatment, the patient complained of a “black spot” in the centre of his left eye vision. His visual acuity had reduced to counting fingers from 6/24 (corrected Snellen visual acuity). Several new areas of pigmentation and elevation were observed, and uveal melanoma recurrence was initially suspected. Given the multifocal nature of the presentation, the multi-disciplinary team recommended enucleation. Histological examination of the enucleated eye revealed three discrete foci of malignant melanoma – the previously treated choroidal malignant melanoma, and two solitary deposits of malignant melanoma within the retina. **Conclusion:** Retinoinvasive melanoma is a rare subtype of uveal melanoma, characterised by trans-

vitreal melanoma invasion of the retina at a site non-contiguous with the uveal tumour, which may explain the clinical and pathological findings of the reported case.

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Introduction

Uveal melanomas (UM) are the most common form of primary intraocular malignancy and usually present as a pigmented mass of the choroid, ciliary body, or iris. UM spreads haematogenously, and in 93% of the cases this involves the liver [1]. Death due to hepatic metastasis is variably reported to occur, irrespective of treatment, in 23.3–50% of cases within 15 years of diagnosis [2, 3]. Other common sites of metastasis include the lungs (24%) and bone (16%), although it has also been reported to occur in the brain, skin, adrenal glands, gastrointestinal tract, spleen, heart, and even the contralateral choroid or orbit [4].

We report an interesting patient who, following plaque brachytherapy for a choroidal melanoma, developed two separate retinal foci of malignant melanoma in the same eye, and suggest possible mechanisms that might explain such an occurrence.

Case Report

A 79-year-old Caucasian male was referred to the Scottish Ocular Oncology Service (SOOS) in June 2016 and diagnosed with an AJCC (American Joint Committee on Cancer) stage IIB inferotemporal choroidal melanoma of the left eye associated with a small adjacent retinal detachment (Fig. 1). Basal tumour dimensions of 16.3 × 13.8 mm and a height of 4.0 mm were confirmed by B-scan ultrasonography. The patient had bilateral primary open angle glaucoma, managed with topical bimatoprost. His past medical history included atrial fibrillation, for which he took warfarin and had been fitted with a cardiac pacemaker. Abdominal ultrasonography and chest radiography confirmed the absence of hepatic and lung metastases, respectively. Tumour biopsy was not undertaken. The patient underwent ruthenium-106 (¹⁰⁶Ru) plaque brachytherapy in August 2016.

The patient was followed up by the SOOS, and serial B-scan ultrasonography demonstrated a reduction in tumour height to <2 mm. In March 2017, the patient developed radiation-induced cystoid macular oedema. In March 2018, he was noted to have multifocal macular, peri-papillary, and nasal periphery pigmentary changes, associated with some subretinal haemorrhages (Fig. 2). The treated choroidal melanoma remained clinically and radiologically stable, with a height of 1.57 mm. The nature of these changes was not clear, and so close observation was planned.

Unfortunately, the patient's next appointment was delayed till November 2018, 27 months after treatment, when the patient returned to the clinic complaining of a "black spot" in the centre of

Fig. 1. Colour fundus photo of the left eye demonstrating an isolated inferotemporal choroidal melanoma prior to treatment.

Fig. 2. The inferotemporal choroidal melanoma remains stable with surrounding atrophic retinal changes. Pigmented lesions are noted in the macular, peripapillary and nasal peripheral regions, and are associated with retinal haemorrhage.

his left eye vision. His visual acuity had reduced to counting fingers from 6/24 (corrected Snellen visual acuity) recorded seven months previously. Significant growth and elevation were observed in each of the areas of pigmentation noted in March 2018 (Fig. 3). Intraocular pressure was well controlled (15 mm Hg), as it had been throughout his previous appointments. UM recurrence was suspected. Given the multi-focal nature of the presentation, the multi-disciplinary team recommended enucleation.

Histological examination of the enucleated eye revealed three discrete foci of malignant melanoma (Fig. 4).

1. The previously treated choroidal malignant melanoma, found in the inferotemporal aspect, which was composed of mostly pleomorphic epithelioid melanocytes with mild lymphocytic infiltrate. This tumour was confined to the choroid within an adjacent area of atrophic retina, in keeping with previous plaque brachytherapy. Maximum basal dimension = 12.5 mm, height = 1.3 mm.

Fig. 3. Further growth of the pigmented lesions is noted on colour fundus photography, particularly within the macula and in the nasal periphery. The three main foci of disease are later defined, on histological examination, as tumour 1 (the treated choroidal melanoma), tumour 2, and tumour 3. B-scan ultrasonography (below) demonstrates, from right-to-left, transverse images of the inferotemporal treated choroidal melanoma (right, tumour 1), longitudinal images of the macular tumour (centre, tumour 2), and longitudinal images of the nasal tumour (left, tumour 3).

2. A solitary peripapillary deposit of malignant melanoma within the retina, composed of spindle cell-type melanocytes and invading focally through the internal limiting membrane. Maximum basal dimension = 13.0 mm, height = 5.0 mm.
3. A further deposit of malignant melanoma within the nasal retina, also composed of spindle cell-type melanocytes. Maximum basal dimension = 2.7 mm, height = 1.6 mm.

Further histological examination confirmed the absence of ciliary body involvement, vortex vein involvement, optic nerve in-

volvement, or extra-scleral invasion. GFAP staining of tumours 2 and 3 showed intermittent staining of the retina and negative staining of the tumour, consistent with a tumour within the retina. All three tumours demonstrated the absence of *BAP1* on immunohistochemical staining, and the presence of both monosomy 3 and chromosome 8q gain on cytogenetic analysis. Gene mutation analysis identified no *BRAF*, *NRAS* or *KIT* mutations, no *GNAQ* mutations, but a *GNA11* mutation [c.626A>T (p.Gln209Leu)] in all three tumours.

Fig. 4. Histological examination (macroscopic and microscopic photos) reveals three discrete foci of malignant melanoma. Tumour 1 is the previously treated choroidal melanoma, found in the inferotemporal aspect (a). It is confined to the choroid within an adjacent area of atrophic retina (b), in keeping with previous plaque brachytherapy, and is composed of predominantly pleo-

morphic epithelioid melanocytes (c). Tumour 2 is a solitary peripapillary deposit of malignant melanoma within the retina (d). It is composed of spindle cell-type melanocytes (e) and is invading focally through the internal limiting membrane (f). Tumour 3 is a further deposit of malignant melanoma (g) within the nasal retina (h), and is also composed of spindle cell-type melanocytes (i).

Since undergoing enucleation, the patient has remained well, with no evidence of local orbital UM recurrence. Due to the tumour's unfavourable cytogenetic profile, he was offered 6-monthly triple arterial phase computed tomography imaging surveillance to detect hepatic metastasis. Magnetic resonance imaging was contraindicated by the patient's cardiac pacemaker. The most recent scan in June 2019 did not show any evidence of hepatic metastasis.

Discussion

We present a patient who, following plaque brachytherapy for a choroidal melanoma, developed two separate retinal foci of malignant melanoma in the same eye. The authors suggest possible mechanisms that might explain the presence of retinal malignant melanoma in the

presence of a known choroidal melanoma in the same eye.

UM may recur following treatment, and this is the first possibility to be considered. UM tumour recurrences have previously been categorised into marginal recurrences (i.e., growth on the lesion margin with an initially flat extension), global recurrence (i.e., growth in all dimensions), distant recurrences (i.e., a new uveal tumour location within the eye, with a free choroidal interval from the irradiated area), and finally, extra-scleral recurrences [5]. UM recurrences have been reported to occur in 3.3% at seven years following ^{106}Ru plaque brachytherapy, while the COMS IV trial reported a 10.3% rate of local tumour recurrence at five years following iodine-125 (^{125}I) plaque brachytherapy [6, 7]. However, recurrence (in contrast to metastasis) suggests the occurrence of new tumour material within the same anatomical structure, and the new lesions described here were located within the retina in the context of a pre-existing choroidal lesion. The original lesion also remained stable both clinically and radiologically. Given these features, UM recurrence as a mechanism for this presentation is unlikely.

Secondly, all three tumours may represent metastases from an unknown primary cutaneous melanoma. Such a scenario is not likely in this patient given the absence of a *BRAF* or *NRAS* mutation, and the simultaneous presence of monosomy 3 and chromosome 8q gain. Metastatic melanomas to the eye are rare, and according to Zografos et al. [8] generally only occur in patients with disseminated metastases during the terminal stages of disease. The vast majority of such intraocular melanoma metastases involve the choroid (88%), followed by the iris (9%), ciliary body (2%), and optic disc [9]. Retinal metastases have been demonstrated to comprise <1% of all intraocular metastases, and while retinal metastases of malignant melanoma have been described previously, they generally present with vitreous involvement, uveitis, and/or neovascular glaucoma [10–12]. Finally, this patient underwent thorough examination, which did not detect any primary cutaneous lesions.

Thirdly, the two retinal lesions may represent haematogenous metastatic spread from the “primary” choroidal melanoma in the same eye, although this has not been previously reported. Local metastatic spread would share similarities with the in transit and satellite metastases seen in the context of cutaneous melanoma, although these are believed to occur via lymphatic spread (and are therefore unlikely within the eye) [13]. Furthermore, the presence of *GNA11* mutations in all three tumours sup-

ports the hypothesis that all three tumours are choroidal in origin, if not location.

Finally, these lesions may suggest the presence of a retinoinvasive melanoma. This is a rare subtype of uveal melanoma, which was described by Kivelä and Summanen [14] in 1997, and has been further reported in a small number of limited case series [15, 16]. It is characterised by transvitreal melanoma invasion of the retina at a site non-contiguous with the uveal tumour. Our case meets this description, although retinoinvasive tumours typically arise in iris or ciliary body melanomas, and rarely from choroidal tumours. Additionally, retinoinvasive melanomas usually exhibit optic nerve invasion, and usually present with raised intraocular pressure due to secondary angle closure, which redirects neoplastic cells posteriorly, and potentially predisposes the optic nerve to invasion due to subsequent ischaemia and oedema. The enucleated specimen was examined for evidence of tumour 1 breaching Bruch’s membrane, which would support the possibility of retinoinvasive melanoma, but this was not seen.

Interestingly, the two new retinal tumours were comprised of spindle cells, whilst the previously treated choroidal tumour was comprised predominantly of pleomorphic epithelioid cells. Normal transformation of cell type has been described in uveal melanoma, and this may explain tumours of spindle cell-type arising from an epithelioid cell-type tumour [17]. Alternatively, the authors postulate that, prior to ^{106}Ru plaque brachytherapy, the original untreated choroidal melanoma was composed of predominantly spindle cell-type melanocytes, which had already resulted in undetectable secondary retinal metastasis or seeding. The subsequent radiation exposure preferentially destroyed the radiosensitive spindle cell melanocytes leaving a treated choroidal tumour now composed predominantly of epithelioid melanocytes. As the secondary foci are not within the area covered by the ^{106}Ru plaque, the spindle cell component has not been affected by the treatment. Whether due to transvitreal invasion of a retinoinvasive melanoma or retinal metastasis from the treated tumour, this hypothesis may explain why the new foci of malignant melanoma could be of predominantly spindle cell-type in the context of a treated tumour containing predominantly epithelioid melanocytes.

Consideration of the underlying pathophysiology is important as it may offer the patient some prognostic insights. Local recurrence of UM has been associated with a significantly increased risk of metastatic disease (with a hazard ratio of 6.28), while intraocular metastasis of a cu-

taneous melanoma is seen in the terminal stages of disseminated disease [8, 18]. There are too few reported cases of retinoinvasive melanoma to offer any reliable prognostic data, while retinal metastasis from an ipsilateral choroidal melanoma has not previously been described, and the prognostic impact of such an event is not known.

Statement of Ethics

This patient has given his written informed consent to publish his case, including the publication of images. This study adhered to the tenets of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.