Choroidal malignant melanoma in an albino

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SUMMARY This is the first report of an amelanotic melanoma arising in the unpigmented choroid of a tyrosinase-positive oculocutaneous albino (TPOCA). Melanosomes within the tumour showed a maturation arrest in the unpigmented type II (premelanosome) phase. Other neural crest derived melanocytes in iris and choroid showed similar limited melanogenesis. The neuroectodermally derived melanocytes of the iris, ciliary body, and retinal pigment epithelium (RPE) contained mature melanosomes, though clinically the RPE was pale. The significance of this tumour arising in an albinotic eye is discussed.

Although cutaneous malignant melanomas are described in albinos,¹ ocular melanomas have not been reported. Oculocutaneous albinism has an incidence of 1 in 10 000 in the UK,² and the incidence of tyrosinase-negative and tyrosinase-positive albinism is roughly equal.³ Tyrosinase-positive oculocutaneous albinism (TPOCA) therefore probably has an incidence of 1 in 20 000. The incidence of choroidal melanoma is 2–6 per 10 000.⁴ The cumulative risk, if the two conditions are unrelated, should be at most 3 per 100 000 000, but may be as little as 1 per 100 000 000.

Case report

A 22-year-old Caucasian woman presented with a one-month history of painless loss of vision in her left eye. She was a tyrosinase-positive oculocutaneous albino and was born with white hair but had subsequently developed some pigmentation and was a light blond. Her best visual acuity had previously been 6/24 in each eye. She was in excellent health with no systemic symptoms on direct questioning. Both her sisters were albinos, and there was no other relevant family history.

On examination she had light blond hair with skin that did not tan in the sun. The irides were blue but translucent on retroillumination. The corrected

visual acuity was 6/24 in the right eye but hand movements in the left. Pendular nystagmus affecting both eyes had a rotatory element and was typical of that found in albinos. The fundi appeared non-pigmented, with an absent foveal reflex at the right posterior pole. At the posterior pole of her left eye a pale oval choroidal mass was situated beneath the macula (Fig. 1A). The tumour extended to, and obscured, the optic disc. It was globular and measured approximately 4 disc diameters at its longest axis. There were no drusen or orange pigment deposits on its surface. When the patient was upright, there was evidence of shifting fluid, with the retina detached inferiorly. No retinal holes were seen on examination of the retinal periphery.

Ultrasonography showed a solid mass which was sharply elevated, and though a collar stud appearance was not seen the configuration suggested a choroidal malignant melanoma that had burst through Bruch's membrane.

Fundus fluorescein angiography showed tumour vessels during dye transit (Fig. 1B) and hyperfluorescence of the mass in the later stages (Fig. 1C).

The patient was fully investigated for a primary neoplasm elsewhere in the body.

The clinical appearance was more suggestive of an amelanotic melanoma than a choroidal metastasis or haemangioma, and this was the consensus of several ophthalmologists. During the two weeks following presentation the retina became totally detached, and the eye was enucleated. It was immediately placed in paraformaldehyde fixative for electron microscopy.

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Fig. 1A

Fig. 1B

Fig. 1 A: Choroidal malignant melanoma at the posterior pole of the left eye. B: With tumour vessels demonstrated during fluorescein transit. C: Hyperfluorescence of the tumour in the late stages of the study.

Fig. 1C

The indications for radical approach were the juxta-papillary situation of the tumour and the presence of total serous retinal detachment. To improve her cosmetic appearance the extraocular muscles were sutured to an implant. This resulted in nystagmoid movements being transferred to her prosthesis.

PATHOLOGY

The eye had a pale blue-grey iris, and when it was

opened pigmentation of the posterior iris pigment epithelium (IPE) and ciliary body was seen. The retinal pigment epithelium (RPE) was very lightly pigmented macroscopically, but the choroid and the cut surface of the iris stroma were white, showing no evidence of melanisation. This was confirmed microscopically where the iris stromal and anterior border cells border and the choroid were unpigmented. Samples were taken from the iris stroma and

Fig. 2 Gross specimen with an amelanotic choroidal mass at the posterior pole.

epithelium, RPE, and choroid for electron microscopy.

There was a pale tumour, 6.5 mm in diameter (Fig. 2), with a rounded outline, arising in the superotemporal posterior fundus, overlapping the optic disc, associated with a large, almost complete serous detachment of the neural retina. The tumour was sampled for light and electron microscopy, and whole-eye sections were also prepared.

On microscopy the solid choroidal tumour had prolapsed over part of the optic disc and had focally ruptured Bruch's membrane (an event which would have eventually led to a collar stud configuration had the tumour continued to grow). No extrascleral or scleral extension of the tumour was seen. The spindle cells of the tumour were arranged in fascicles and in some areas were arranged in a pseudoadenomatous pattern. The appearances were not, however, those of a metastatic adenocarcinoma or carcinoid tumour, as had been suggested in the clinical differential diagnosis, nor was there any palisading of nuclei or foci of myxoid degeneration typical of a schwannoma, which might be included in the differential diagnosis of a spindle cell tumour of the choroid.

The appearances were those of an amelanotic melanoma, with a predominance of spindle B cells with plump nuclei and prominent red nucleoli (Fig. 3). More compressed spindle A cells with

elongated nuclei were seen at the periphery, pressed against the sclera. Reticulin was found on special staining, but there was no evidence of an epithelioid cell population. In view of the lack of clinical,

Fig. 3 Fasciculated pattern of spindle cells in amelanotic malignant melanoma. ($\times 350$).

Fig. 4. Stage II premelanosomes in tumour cell cytoplasm (arrow). ($\times 29\,000$).

macroscopic, and microscopic pigmentation the failure to demonstrate melanin with conventional stains such as Schmorl and bleach, and Masson-Fontana was perhaps not surprising. Electron microscopy clinched the diagnosis by demonstrating immature and atypical melanosomes typical of amelanotic melanomas.⁵ A few type II⁶ melanosomes (premelanosomes) were visible, as well as more abortive vesicular organelles. These immature melanosomes were demonstrable in both types of spindle cells, but more atypical forms were commoner in the spindle B cells. No maturation to type III and IV melanosomes was visible in the tumour and most melanosomes were rather poorly formed (Fig. 4). No dense core vesicles (consistent with carcinoid tumours) or Luse type bodies, more typical of schwannomas, were present. Immunohistochemical studies were subsequently performed, though fixation in paraformaldehyde was not optimal. S100 protein was demonstrable in the tumour, especially at the periphery, in the choroid in dendritic cells, and in the cellular iris stroma. These findings were consistent with a neural crest origin. S100 protein was also found within perivascular glia

of the nerve fibre layer in the detached retina. Similarly the Warthin-Starry-DOPA reaction⁷ was also performed and showed a small amount of silver staining only just demonstrable at light level but more certainly at electron microscopic level, where an argyrophil reaction highlights the DOPA-reactive immature melanosomes.

Since reports of albinotic eyes are still rare,^{8,9} electron microscopy was performed on other parts of this enucleated eye. Despite the clinical translucence of the iris and the pallor of the fundus, some pigmentation had developed in the epithelia of the iris (IPE) (Fig. 5) and ciliary body and to a less extent in the RPE. This pigment was visible macroscopically and with the light microscope, and it stained as melanin with the traditional techniques (Schmorl and Masson Fontana). On electron microscopy type III and some type IV melanosomes were seen in these melanocytes. Type IV melanosomes were demonstrable in the RPE, albeit in fewer numbers than in some fundi, especially at the apices of the cells, and an osmication—non-osmication technique confirmed that these electron dense organelles were not all lipofuscin, generated after phagocytosis of rod outer

Fig. 5 Normal type IV melanosomes in iris pigment epithelium. ($\times 8400$).

segments. Such a potential confusion of organelles is less likely to occur in IPE (Fig. 5) and ciliary body, and again maturation of melanogenesis had occurred, with type IV melanosomes present.

Immature melanogenesis, to the same stage (type II) as the tumour, had occurred in the iris stromal and anterior border melanocytes and in the choroidal melanocytes. No type III or type IV organelles were seen.

Discussion

If the incidence of choroidal melanoma is 2-6 per 10 000 and the theoretical incidence in tyrosinase-positive albinos is 3 per 100 000 at most, then it is unlikely with a confirmed incidence of 1-3 per 100 000 000 that the two conditions will be reported together, especially as there is underdiagnosis of TPOCA in the Caucasian population, with a high incidence of blonds. Foveal hypoplastic abnormalities,¹⁰ indicative of abnormal decussation of the optic pathways, coupled with nystagmus are the most selective diagnostic criteria.

Choroidal melanomas are said to be commoner in people with pale irides and the increased incidence may be associated with exposure, especially intermittent exposure, to ultraviolet irradiation.¹¹ Pale irides are less able to block sunlight than dark ones, and circumstantial evidence, such as the higher incidence of inferior pole melanomas, where the greatest incidence of unblocked light might impinge, and the relative paucity of melanomas in brown eyed people would seem to support this hypothesis. Therefore one might expect albinos with iris translucence to have a higher incidence of melanomas than blonds with blue or grey irises.

TPOCA patients do slowly develop darker irides than they are born with, as there is selective melanogenesis in the neural crest derived melanocytes of hair, skin, and iris stroma.⁹ However, most albinos are photophobic and many wear eye protection, a factor previously examined and associated with less frequent use among cases of melanoma than controls.¹¹ Most of the damage from incident UV light is thought to occur through the immature (non-adult) lens, which does not screen it out.¹² Albino children are probably less

likely to be sun worshippers than their more pigmented peers.

It is interesting to note that this girl had no evidence of maturing melanisation in her iris stroma or choroid (and did not tan) and that a similar phase of maturation arrest was apparent in her tumour, also derived from neural crest melanocytes. She had more mature pigmentation in the pigment epithelia, where melanogenesis is usually complete at birth after starting at five weeks' gestation in normal people. Her neuroectodermally derived melanocytes had developed along normal lines, despite there appearing to be more type III melanosomes than usual and fewer type IV, though both were present in all three epithelia. The development of a weak positive argyrophilic response when the 'double labelled' Warthin-Starry-DOPA technique was used indicates that in this TPOCA patient the tumour could precipitate silver even though it was amelanotic. This is analogous to the positive hair-bulb incubation test technique where tryosine is utilised if presented to the melanocytes in TPOCA patients' hairs, and darkening occurs.

This paper illustrates what may be a chance occurrence of two relatively uncommon conditions occurring together, but further reports should be expected if there is a non-random association.

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