Ring melanoma—a rare cause of refractory glaucoma

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Abstract

***Background*—Ring melanoma of the ciliary body and iris is extremely rare and often has adverse histology. This tumour may cause raised intraocular pressure.**

***Methods*—A review of four cases of ring melanomas with insidious presentations seen in the ocular oncology service over a 12 month period.**

***Results*—All four patients presented with unilateral anterior segment abnormalities and refractory glaucoma. The misdiagnoses of the causes of the glaucoma included angle recession from previous blunt trauma (patient 1); iridocorneal endothelial (ICE) syndrome supported by endothelial specular microscopy (patients 2 and 3); and melanocytoma on ciliary body biopsy (patient 4). Two patients were treated by several cyclodiode ciliary body ablation treatments and the other two underwent trabeculectomies and Molteno tubes. Two of the four patients have since died from their disease.**

***Conclusion*—The ophthalmologist should re-evaluate the diagnosis in patients with anterior segment abnormalities and refractory ipsilateral glaucoma. Endothelial specular microscopy and biopsy of the suspicious lesion may give misleading reassurance. The potential presence of an anterior uveal melanoma must always be considered.**

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Ring melanoma of the ciliary body and iris was first described by the Russian ophthalmologist Ewetsky in 1898[1] who called it a ring sarcoma. It is a rare variant of the "diffuse melanoma" which is defined as a primary uveal tumour that involves more than a quarter of the uveal tract.[2] In practice, ring melanomas seldom infiltrate the uveal tract as extensively, but the ciliary body is the main site of involvement.[3] The ring may arise from coalescence of tumours arising from multiple sites.[4]

Materials and methods

We reviewed four cases of ring melanomas causing unilateral refractory glaucoma which were seen in the ocular oncology clinic over a 12 month period.

Results

CASE 1

A 23 year old white man was admitted via the accident and emergency in department of a district general hospital with a history of vomiting and malaise. A computed tomograph (CT) scan of the abdomen was performed and showed multiple liver lesions which were biopsied, and which showed poorly differentiated round cell tumour of uncertain origin.

He was commenced on chemotherapy for extraosseus Ewing's sarcoma. At admission the right pupil was noted to be distorted and a pigmented cystic lesion was noted on the conjunctiva of the right eye. An ophthalmological opinion was sought.

Further questioning revealed that the patient had sustained blunt trauma to the right eye from a tennis ball at the age of 10, and 2 years before admission had been diagnosed with glaucoma secondary to angle recession at another eye unit. Iris heterochromia had also been noted. The glaucoma was refractory to conservative treatment and he had undergone two episodes of cyclodiode ciliary body ablation 6 months earlier. The vision had deteriorated over the past year and the eye had become painful.

On examination visual acuity was no perception of light (NPL) in the affected right eye and 6/5 in the left eye. In the right eye, there was a temporal bulbar conjunctival mass and nasal scleral pigmentation with associated iris stromal depigmentation. There was a mild degree of lenticular nuclear sclerosis with posterior subcapsular opacity and pigment cells in the anterior vitreous with total optic disc cupping and pallor. Transillumination revealed a circumcorneal dark shadow of a ring melanoma (Figs 1 and 2). HBM45 and S100 immunohistochemical staining performed on the liver biopsy specimen was positive. The patient was then changed onto the chemotherapy regimen for metastatic melanoma.

Meanwhile staging with CT scan confirmed disseminated metastases. Three months from initial systemic presentation, the patient was

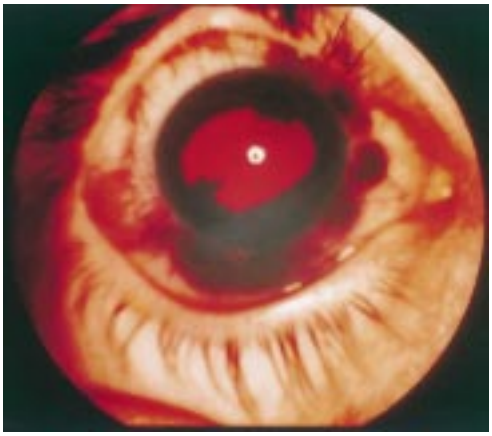

Figure 1 Circumcorneal dark shadow of ring melanoma.

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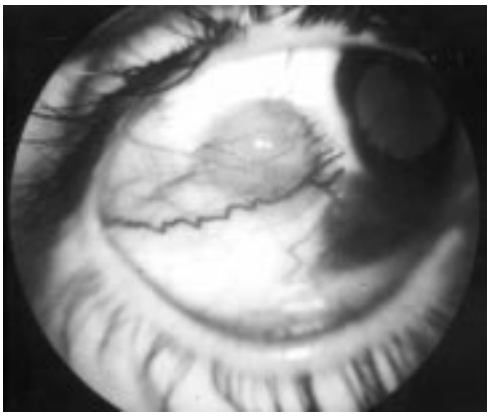

Figure 2 Conjunctival nodule of extrascleral extension of ring melanoma.

urgently admitted with brain stem infarction and disseminated intravascular coagulopathy. He deteriorated rapidly and died.

CASE 2

A 63 year old white woman noticed a change in iris colour and presented to an ophthalmologist who diagnosed glaucoma for which she underwent a trabeculectomy. A year later she noticed further visual loss and the intraocular pressure remained uncontrolled. On examination there was uveal prolapse through the lamellar sclerostomy and ectropion uveae with dilated blood vessels and marked distortion of the normal anatomy with an area of angle closure in the inferonasal quadrant. A clinical diagnosis of iridocorneal endothelial (ICE) syndrome was confirmed by specular microscopy showing the presence of ICE cells on the corneal endothelium. The intraocular pressure was resistant to conservative treatment. A Molteno tube drainage was performed. Three months postoperatively, a Tenon's cyst developed around the Molteno plate which was thought to cause the uncontrolled intraocular pressure rise. Inferior 180 degree cyclocryotherapy was performed with deroofing of the Tenon's cyst. One month after cyclocryotherapy, the iris appearance changed dramatically with the development of amelanotic vascularised masses on the iris. B scan ultrasound did not show any large intraocular mass. An iris biopsy demonstrated histology suggestive of an iris melanoma. Enucleation followed and microscopic examination of the specimen showed a large partly pigmented mass expanding the iris and ciliary body around the circumference of the eye (Fig 3). The tumour was composed of spindle B and epithelioid cells with considerable nuclear pleomorphism and prominent nucleoli. The tumour had an exophytic growth pattern within the anterior chamber and tumour cells were also present along the lateral border of the lens and the anterior surface of the vitreous. The vitreous itself did not seem to be involved. Tumour cells were present within the trabecular meshwork and the canal of Schlemm. Mitoses were frequent at 2.6 per mm^2. There was no extrascleral extension. There was pronounced cupping of the optic nerve consistent with long standing glaucoma. The characteristics of ICE were not seen.

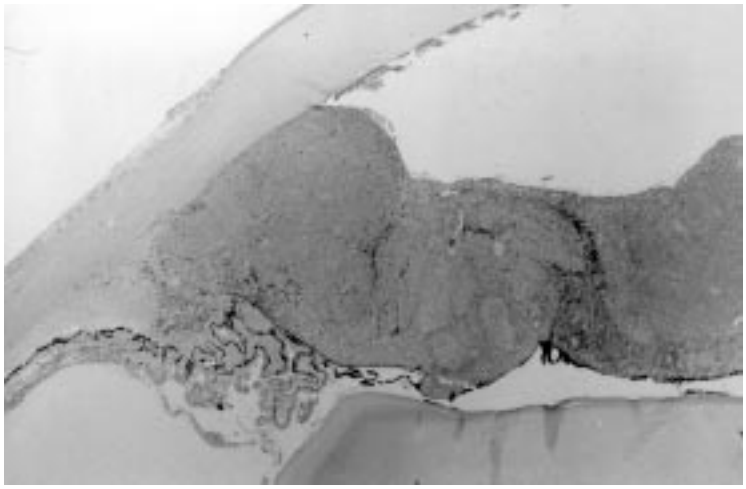

Figure 3 Low power view of the iris in the enucleation specimen showing an extensive melanocytic lesion filling the angle, invading the trabecular meshwork, and replacing the iris. (Haematoxylin and eosin, original magnification, ×20).

CASE 3

A 45 year old man first attended the glaucoma clinic at a district general hospital with unilateral raised intraocular pressure in left eye. There was a melanotic lesion noted on the left iris in the 6 o' clock position and gonioscopy revealed the left angle to be deeply pigmented. There was no previous history of trauma in the left eye. The patient underwent a trabeculectomy, which controlled his pressure to a satisfactory level. The following year, the intraocular pressure was noted to be raised at 42 mm Hg. There were extensive anterior synechiae and pigment dispersion was noted on the cornea. After failing to respond to conservative treatment another unaugmented trabeculectomy was performed with fluctuating intraocular pressure control. Three months postoperatively, the intraocular pressure was once again raised consistently above 30 mm Hg despite maximal topical and oral antiglaucoma treatment and he was referred to the glaucoma unit. A diagnosis of left ICE syndrome was made and a double plate Molteno tube was inserted. Three months after Molteno tube insertion the patient presented acutely to the eye casualty department with

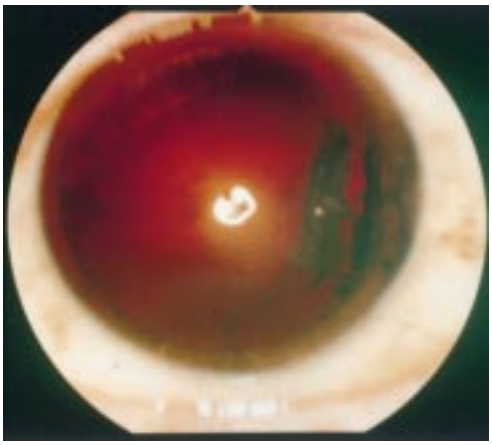

Figure 4 Focal lens opacity.

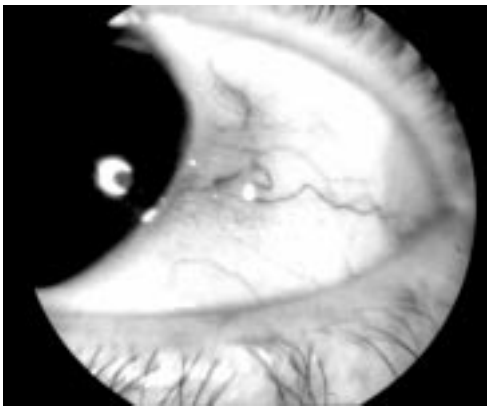

Figure 5 Sentinel vessel over pigmented iridociliary lesion.

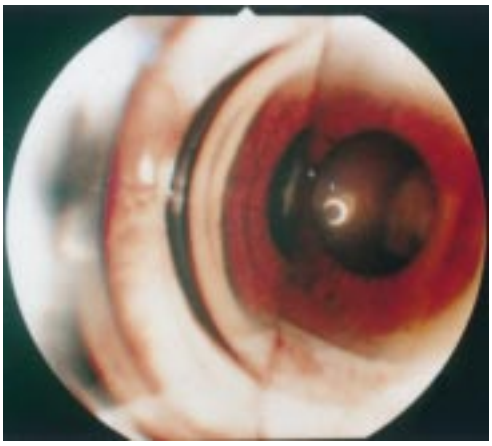

Figure 6 Darkly pigmented angle on gonioscopy.

abrupt visual deterioration from 6/18 to hand movements. Tenon's cyst formation around the bleb was thought to cause an intraocular pressure spike leading to central retinal artery occlusion. A paracentesis was performed, which lowered the intraocular pressure with no improvement in vision. The Tenon's cyst was subsequently needled with supplementary subconjunctival 5-fluorouracil given in the region of the bleb. Eight months after the Molteno tube drainage surgery, the patient presented again acutely to the eye casualty department.

Figure 7 Obliteration of the ciliary processes by cyclodiode therapy adjacent to an area of infiltration of the root of the iris and trabecular meshwork by densely pigmented cells (periodic acid Schiff, original magnification, ×100).

He had a moderate hyphaema filling two thirds of the anterior chamber. Multiple new pale vascular iris masses were noted. The intraocular pressure was 20 mm Hg. The patient was sent home for bed rest. When he was reviewed 1 week later the hyphaema filled four fifths of the anterior chamber. He suffered recurrent hyphaemas over the subsequent 2 weeks. The patient underwent instillation of tissue plasminogen activator, anterior chamber washout, and iris biopsy. The biopsy specimen showed histology consistent with iris melanoma. Meanwhile, the intraocular pressure had risen again. The blind and painful eye was finally enucleated. Histopathological examination of the enucleated eye showed multiple foci of tumour at different sites from the iris and ciliary body with microscopic episcleral extension. Epithelioid cells were present. A small focus of tumour was noted in the vitreous. Focal HMB4 immunoreactivity was demonstrated in the main component of the tumour. Glaucomatous changes were noted in the retina and the optic nerve and there was endothelial cell loss. The characteristics of ICE were not seen. The patient has since died from metastatic disease.

CASE 4

A 73 year old woman of Mediterranean descent first presented to the ocular oncology service with a pigmented iridociliary lesion and uncontrolled glaucoma in her left eye. There were prominent episcleral vessels over the tumour sector. The lesion had features that suggested chronicity. The lens was notched and there was focal lens opacification (Fig 4). There was pigment dispersion noted in the anterior chamber and angle (Figs 5 and 6). The patient underwent a ciliary body biopsy. Histological examination showed no evidence of malignancy. A diagnosis of melanocytoma was made. The procedure resulted in a small anterior staphyloma over the biopsy site. This was an expected surgical complication in an eye with raised intraocular pressure. Despite maximum antiglaucoma medication postoperatively the patient required three cyclodiode ciliary body ablation treatments to control the intraocular pressure satisfactorily. Three months after the last cyclodiode application the patient developed a small perforation over the area of the anterior staphyloma. The perforation sealed spontaneously. The vision had by then deteriorated to counting fingers with a dense cataract. At this stage, 1 year from first referral, a decision was made to enucleate the eye as the diagnosis of a ring melanoma could not be excluded. Macroscopic examination of the enucleated specimen showed no distinct tumour mass but histological examination showed several large foci of epithelioid cells in the parenchyma of the ciliary body consistent with a ring melanoma. No mitoses were seen. There was no evidence of extrascleral extension. The most significant histological finding was focal destruction of melanoma cells in the areas where the cyclodiode had been applied (Fig 7).

Discussion

Ring melanoma is a rare, distinct entity among anterior uveal tumours with a tendency to annular infiltrative spread around the anterior segment. Classically, it should involve the uveal tissues in a complete ring but in current usage applies to any melanoma involving 6 or more clock hours of the uvea circumferentially.[5] Patients rarely present with visual symptoms because of the absence of a space occupying mass causing retinal detachment or lens subluxation. It is often impossible to identify the site of primary growth which may be the ciliary body, the base of iris, or the iridociliary junction. It is notoriously difficult to detect the presence of a ring melanoma using indirect ophthalmoscopy or conventional B scan ultrasonography because of its diffuse nature and anterior location. Ultrasound biomicroscopy may offer superior imaging of this location.[6]

Anterior uveal malignant melanomas have been shown to affect the intraocular pressure variably. Yanoff[7] observed that they are generally associated with an increase in intraocular pressure but Foos and coworkers[8] found that at early diagnosis these eyes are often hypotonic.

The syndrome of ipsilateral raised intraocular pressure and heterochromia has been reported as the cardinal sign in the diagnosis of anterior uveal melanoma in many reported cases.[3 5 9] Shields and coworkers[10] found raised intraocular pressure in 17% of patients with ciliary body melanoma. The mechanism of secondary glaucoma included pigment dispersion, tumour invasion of the angle, angle closure, and iris and angle neovascularisation.

All our patients underwent multiple surgical glaucoma procedures. Cases 1 and 4 had multiple cyclodiode ciliary ablations. Cases 2 and 3 underwent trabeculectomies and Molteno tube drainage surgery. There has been no study comparing survival rates of patients who have or have not undergone intraocular surgery with untreated uveal melanoma. Singer *et al* [11] suggested a higher mortality after filtration surgery. It is not known whether an externally applied treatment such as cyclodiode or cyclocryotherapy ciliary body ablation has any adverse effect on the eventual mortality from metastatic death. The histological findings in patient 4 suggests that cyclodiode ciliary ablation may delay the diagnosis further by focally destroying melanoma cells (as diode laser is a well known therapeutic option for treating small choroidal melanomas) and therefore maintaining the intraocular pressure at an acceptable level obscuring the true diagnosis.

All our patients presented with unilateral refractory glaucoma and abnormal iris and gonioscopic appearances. Case 1 is unusual because of the young age of the patient, the presentation to a medical team with metastatic disease, and the misdiagnosis of post-traumatic/heterochromic cyclitic glaucoma. The misleading history of trauma is not uncommon as reported by Barr *et al* [12] in a large survey of paediatric and adolescent patients with uveal melanoma. Cases 2 and 3 had the clinical diagnosis of ICE syndrome with secondary glaucoma. Again this is an entirely plausible diagnosis in a middle aged patient with unilateral glaucoma.[13] These diagnoses were supported by endothelial specular microscopy (ESP). This method had previously been advocated as providing a definitive diagnosis of ICE syndrome,[13] but at present ICE has been shown to have pleomorphic manifestations on ESP.[14] It may be that ring melanoma deposits on the corneal endothelium mimic the in vivo ESP appearance of ICE cells during one of its transitional stages.

The adverse prognosis in ring melanomas may be due to a higher than expected rate proportion of epithelioid cells than circumscribed melanomas of equal thickness.[15] Shields and Klintworth[16] described six cases of ring melanomas containing epithelioid cells, three of whom eventually died after a follow up of 2 years. They suggested that the penetration of melanoma cells into Schlemm's canal provides a potential route of haematogenous spread through the episcleral veins.

Some ring melanomas, especially the diffuse variety, tend to grow slowly with a low mitotic rate and cases have been reported where the tumour has been present for many years.[17] Case 4 appears to illustrate this finding. No tumour mass was identified macroscopically in the enucleated specimen and the diagnosis was only established by microscopy. This case has similarities to the diffuse malignant melanomas reported by Brown *et al* [18] and Spaulding *et al*.[19] Ring tumours with unusual histology, including T cell lymphoma[20] and borderline spindle cell naevus,[21] have also been described.

In the past the correct diagnosis was often reached when the underlying pathology was re-evaluated after the small repertoire of antiglaucoma treatment was exhausted. As the armoury of antihypertensive agents and procedures is constantly expanding, the ophthalmologist must refrain from only focusing on the goal of target intraocular pressure control without re-evaluating the primary diagnosis. Endothelial specular microscopy does not rule out the presence of intraocular malignancy and may give a misleading diagnosis of ICE. Biopsy of the suspicious area may, but not invariably, provide the diagnosis. Any patient, regardless of age, presenting with unilateral refractory glaucoma associated with suspicious anterior segment findings such as prominent episcleral vessels in one sector, iris heterochromia, iris mass, variation in anterior chamber depth,[8] or unilateral pigment dispersion[22] should alert the clinician to the potential presence of an anterior uveal melanoma.

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1 Ewetzky T. Weitre Studien uber intraoculare Sarkome. *Graefes Arch Ophthalmol* 1898;**45**:563–612.
2 Font RL, Spaulding AG, Zimmerman LE. Diffuse malignant melanoma of the uveal tract: a clinicopathological report of 54 cases. *Trans Am Acad Ophthalmol Otolaryngol* 1968;**72**:877–95.
3 Omulecki W, Pruszczynski M, Borowski J. Ring melanoma of the iris and ciliary body. *Br J Ophthalmol* 1988;**69**:514–18.
4 Kurz GH. Malignant melanoma of the ciliary body and iris manifested in two locations. *Am J Ophthalmol* 1965;**59**: 917–21.
5 Fitzpatrick M, Augsburger JJ, Koreischi FM, *et al.* Complete ring melanoma of the choroid. *Retina* 1996;**16**:228–31.

6 Ausburger JJ, Affel LL, Benarosh DA. Ultrasound biomicroscopy of cystic lesions of the iris and ciliary body. *Trans Am Ophthalmol* 1996;**94**:259–71.
7 Yanoff M. Glaucoma mechanisms in ocular malignant melanomas. *Am J Ophthalmol* 1970;**70**:898–904.
8 Foos RY, Hull SN, Straatsma BR. Early diagnosis of ciliary body melanomas. *Arch Ophthalmol* 1969;**81**:336–44.
9 Rones B, Zimmerman LE. The production of heterochromia and glaucoma by diffuse malignant melanoma of the iris. *Trans Am Acad Ophthalmol Otolaryngol* 1957;**61**:447–63.
10 Shields CL, Shields JA, Shields MB, *et al.* Prevalence and mechanisms of secondary intraocular pressure elevation in eyes with intraocular tumors. *Ophthalmology* 1987;**94**:839–46.
11 Singer PR, Krupin T, Morton ES, *et al.* Recurrent orbital and metastatic melanoma in patient undergoing previous glaucoma surgery. *Am J Ophthalmol* 1979;**87**:766–8.
12 Barr CC, McClean IW, Zimmerman LE. Uveal melanoma in children and adolescents. *Arch Ophthalmol* 1981;**99**: 2133–6.
13 Frangoulis MA, Sherrard ES, Kerr Muir MG, *et al.* Clinical features of the irido-corneal endothelial syndrome. *Trans Ophthalmol Soc UK* 1985;**104**:775–81.
14 Levy SG, Kirkness CM, Moss J, *et al.* On the pathology of the iridocorneal endothelial syndrome: the ultrastructural appearances of "subtotal ICE". *Eye* 1995;**9**:318–23.
15 Reese AB, Howard GM. Flat uveal melanomas. *Am J Ophthalmol* 1967;**64**:1021–8.
16 Shields MB, Klintworth GK. Anterior uveal melanomas and intraocular pressure. *Ophthalmology* 1980;**87**:503–17.
17 Duke-Elder WS. *Textbook of ophthalmology*. St Louis; CV Mosby, 1945;**3**:2491.
18 Brown D, Boniuk M, Font R. Diffuse malignant melanoma of the iris with metastases. *Surv Ophthalmol* 1990;**34**:357–64.
19 Spaulding AG, Green WR, Font RL. Ring shaped limbal tumour. *Arch Ophthalmol* 1967;**77**:76–80.
20 Jensen OA, Johansen S, Kiss K. Intraocular T-cell lymphoma mimicking a ring melanoma. *Graefes Arch Clin Exp Ophthalmol* 1994;**232**:148–52.
21 Kremer I, Ben-Sira I. Borderline spindle cell nevus of the ciliary body as a second primary melanoma—a clinicopathologic case. *Ann Ophthalmol* 1989;**21**:217–21.
22 Chaudury IM, Moster MR, Ausburger JJ. Iris ring melanoma masquerading as pigmentary glaucoma. *Arch Ophthalmol* 1997;**115**:1480–1.