Bilateral ovarian carcinoma with bilateral uveal melanoma

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SUMMARY A case of bilateral uveal melanoma in a 60-year-old woman in association with primary bilateral ovarian carcinoma is described. This is the first case in which ultrastructural studies have been performed on the ocular tumours. Seven previously described cases are summarised, and the extreme rarity of such reports would suggest that this may indeed be a new syndrome.

The coincidence of diffuse bilateral uveal melanocytic infiltrations with a dissociated visceral malignancy has only recently begun to be reported.¹⁻⁴ Barr *et al.*¹ collated 4 cases which were available to the Armed Forces Institute of Pathology in Washington and added 2 of their own, believing that this unusual occurrence represented a new syndrome. Table 1 summarises the reports to date. It is the purpose of the present paper to contribute an eighth such case.

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Case report

A 60-year-old woman first attended on 10 March 1982 complaining of pain and blurring of vision in both eyes for the previous 6 months. The patient had had oophorectomy for bilateral ovarian papillary adenocarcinoma (Fig. 1) with calcospherites (Dr J. O'Driscoll) in August 1981, which was followed by radiotherapy. At this time her visual acuity was 6/9 in both eyes and the fundi were recorded as being normal. She had deep vein thrombosis in September 1981, for which she was taking anticoagulants. The patient was also on chlorambucil, prednisolone, and

Table 1 Summary of cases reported to date

Reference	Age (years)	Sex	Case data
Machemer ² (FDR)	57	F	1960 decreased VA and redness both eyes. Four months later (1961) pancreatic mass found. Both eyes had cataracts, iridic nodules, and retinal detachment, and were irradiated. Eyes enucleated May 1961. Died November 1961. No necropsy
Curtin, reported at meeting 1974 (USA)	68	M	1971 laparotomy. Suspected primary in pancreas. Retroperitoneal lymph nodes, noted at laparotomy. Abdominal irradiation. Cataracts extracted 6 and 9 months later. Vision deteriorated. Died 1974. No necropsy
Font, reported at meeting 1976 (USA)	78	F	1973 cataract extraction, left. 1976 failing vision, left retinal detachment, metastatic carcinoma suspected. Died 1977. Necropsy: bowel adenocarcinoma
Ryll <i>et al.</i> ³ (USA)	64	M	1977 progressive visual loss. Bilateral cataracts. Mediastinal lymph node biopsy showed undifferentiated lung carcinoma. Fundal choroidal pigmented lesions. Bilateral cataract extractions 2 months later. Died 1978. Necropsy performed
Barr <i>et al.</i> ¹ (USA)	77	F	Case 1. 1976 bilateral decrease in VA with cataracts and macular degeneration. 1976 left cataract extraction. 1976 retinal detachments. Died 1978. Necropsy showed adenocarcinoma left ovary
	61	M	Case 2. 1976 bilateral loss of vision. Found to have retinal detachment. One month later died. Necropsy showed bronchial squamous cell carcinoma. Left eye only available for study
de Wolff-Rouendaal ⁴ (Netherlands)	54	F	Gall bladder carcinoma presented with cholelithiasis. One year later vision (both eyes) deteriorated. Funduscopy showed multiple flat, slightly pigmented tumours. Eyes irradiated. Cataracts developed 8 months later. R lens extraction. Death 23 months after first seen. No necropsy

Fig. 1 Ovarian carcinoma with focal calcification (arrow). (Haematoxylin and eosin, $\times 43$).

spironolactone. Family and social histories were unremarkable.

On examination the visual acuity was 6/24 RE and 6/36 LE. The right cornea and iris were normal, but there were numerous small round scars in the sub-epithelial region of the left cornea suggestive of a previous viral keratitis. There was an area of about 2 mm in diameter of thickening of the left iris stroma, with a few overlying vessels at the 5 o'clock position. The lenses were clear, but bilateral phakodonesis was present. Intraocular pressures were normal, 17 mmHg in the right eye and 15 mmHg in the left eye (applanation). The right vitreous was clear and the right disc and blood vessels were normal, but the macula appeared to be slightly elevated due to either oedema or a subretinal mass, and there was what appeared to be a small choroidal naevus in the upper nasal quadrant of the right fundus measuring about 3 mm in diameter. The left vitreous, disc, and blood vessels were also normal, but the left macula had a thickened oedematous appearance similar to that of the right macula. There were 2 pigmented slightly raised lesions measuring about 4–6 mm in diameter, one in the lower nasal periphery and one in the upper temporal equatorial region of the left fundus. The lower one-third of the left retina was detached, but no retinal tear was seen.

The patient was seen again on 28 April 1982, and the only significant change was a subtotal retinal

detachment in the left eye with a drop in visual acuity to hand movements. Chest x-ray and brain scan were normal, but bone scan suggested metastatic disease involving the bones of the spine. Left ocular ultra-

Fig. 2 Fluorescein angiography: widespread, blotchy dye leakage from the choriocapillaris and around the posterior pole in both fundi (right fundus shown above).

sound confirmed the presence of retinal detachment but did not reveal any choroidal masses. The left electroretinogram was extinguished. Fluorescein angiography (Fig. 2) revealed a widespread blotchy pattern of dye leakage throughout both fundi, in particular around the posterior poles of both eyes. The appearance was suggestive of a generalised choroidal inflammation. The patient was admitted to hospital on 16 June 1982, when vision had dropped to

hand movements in the right eye and no perception of light in the left eye, due to lower-half retinal detachment in the right eye and total detachment of the left retina. There were now dense lens opacities in both eyes, and ultrasonography showed the presence of a lower-half retinal detachment in the right eye and a total detachment in the left eye. A course of oral prednisolone 120 mg daily was started on 22 June 1983 without any improvement in the clinical condition. All blood investigations were normal, and general physical examination was unremarkable apart from an abdominal scar.

The cataracts rapidly matured, and bilateral lens extractions with sector iridectomies were carried out on 1 July 1982. Bilateral hyphaemata were noted at first dressing. Within 24 hours the patient developed severe abdominal pain, and she died the following day. No permission was granted for necropsy, but the eyes were removed for pathological examination.

OCULAR PATHOLOGY

Macroscopic examination (Fig. 2) of both eyes, which measured $24.5 \times 24 \times 23$ mm, showed extensive retinal detachment and solid masses about 3 mm thick at the ciliary body, spreading to fill the choroid as far as the optic disc (Figs. 3A, B). In the left eye an elevated (3 mm) black tumour lay in the choroid behind the nasal equator.

Microscopic examination showed mild autolytic changes in the cornea, with occasional infiltration by polymorphonuclear leucocytes. There was a linear limbal scar, with neighbouring sutures without a cellular reaction. Haemorrhage was confined to the anterior chamber, and there was surgical aphakia. Much of the iris was filled by neoplastic tissue at different levels, and this process continued to cause widespread panuvea thickening to the optic disc (Figs. 4A, B). The cells were mixed polyhedral and spindle (Figs. 5A, B). Melanin pigment was irregularly and coarsely dispersed with fine intracytoplasmic pigment granules. The architecture varied with occasional fasciculi and in some areas an alveolar pattern, the cells either lining these arrangements or lying free in the lumen. There was some variation in nuclear size and chromatin arrangement. A search of approximately 200 sections showed rare mitotic activity of abnormal form. Three small heavily pigmented foci lay in the outer choroidal layers of the nasal ciliary body and peripapillary regions. A bleach preparation showed fairly uniform spindle and polyhedral cells. The large melanin nodule in the nasal posterior uvea consisted of polyhedral and spindle cells of varying size and nuclear content. There was extension along the posterior ciliary nerve into the sclera by the lesion at some levels. Drusen with focal calcification, hyperplasia of retinal pigment epithelial

Fig. 3A

Fig. 3B

Fig. 3 Calottes of (A) right and (B) left eye with panuvea thickening and retinal detachments.

Fig. 4A

Fig. 4B

Fig. 4 Left (A) and right (B) eyes with panuveal tumours. (Haematoxylin and eosin, $\times 0.65$).

cells, and lipofuscin accumulations were widespread. The choriocapillaris was only focally obliterated by the neoplastic tissue. There were schisis and microcystoid changes in the periphery of the retina and extensive general retinal detachment with subretinal fluid accumulation and haemosiderin-laden macrophages. The optic nerve was not remarkable.

ELECTRON MICROSCOPY

The tissue was fixed in glutaraldehyde, postfixed in osmium tetroxide, stained with uranyl acetate/lead citrate, and examined in a Jeol 100CX electron microscope.

The cytoplasm of the tumour cells (located behind the ciliary body) contained numerous compound melanosomes. Solitary melanosomes were found in a small group of cells only after a prolonged search. These were well developed, ellipsoid in shape, and showed characteristic cross-banded internal structure (Fig. 6). The nuclei of the cells were irregular with some infoldings. Nucleoli were not prominent. In some areas of close apposition of tumour cells desmosome-like structures were present, but no true desmosomes were seen. In many areas the tumour cells were separated from each other by collagen.

Other cells present showed the features of myofibroblasts with cytoplasmic filaments. Basal lamina material was present around many of these cells. Examination of sections from the equatorial region of the choroidal mass showed similar features. Compound melanosomes were more scattered and only an occasional ellipsoidal melanosome was seen but without cross-banded internal structure.

Discussion

The clinical appearance of the fundi was very suggestive of secondary deposits from the ovarian carcinoma, though the choroidal lesions were quite dark. Fluorescein angiography showed a widespread blotchy dye leakage throughout both fundi, which was suggestive of some choroidal vascular abnormality leading to leakage from choroidal vessels, but the angiogram did not help in outlining the 3 small choroidal masses. The elevation of both maculae was more suggestive of oedema than of tumour deposits. Ophthalmologically the patient's condition deteriorated rapidly, and her lenses, which had been noted to be clear but tremulous on 10 March 1982 had progressed to a state of mature cataract bilaterally by

Fig. 5A Choroidal tumour pattern (right eye). (Haematoxylin and eosin, $\times 80$).

Fig. 5B Atypical melanoma cells (choroid left eye). (Haematoxylin and eosin, $\times 200$).

Fig. 6 Electron micrograph of a melanoma cell showing electron dense melanin pigment, numerous compound melanosomes, and occasional melanosome (inset) with cross-banded internal structure. ($\times 9900$; inset $\times 64\,000$).

the end of June 1982. As retinal detachment had been observed in both eyes prior to the maturation of the cataracts, it was decided to perform cataract extraction with a view to possible retinal detachment surgery at a later date. The failure of ultrasound to outline any choroidal tumours might be accounted for by the diffuse rather than the elevated nature of the choroidal masses histologically. The rapid progression of the lens opacities to maturity has been noted by other authors, and this rendered ophthalmic examination very difficult in the later stages of the disease.

The bilateral uveal tumours in the patient now reported behaved clinically as rapidly proliferating lesions. This was evidenced by the progressive deterioration in vision and the development of cataracts and bilateral retinal detachments. Histologically the tumours showed varying stages of cell dedifferentiation, and, while mitoses were few, they were present but atypical, and there was also evidence of early extension along the ciliary nerves into the sclera.

The ultrastructural finding of solitary melanosomes with characteristic internal periodicity supports the

melanocytic nature of the tumour cells. Previously the histogenesis has been based on light microscopic appearances. This is the first case studied by electron microscopy. Although solitary (as opposed to compound) melanosomes have been described in a number of other tumours, including Schwannomas,⁵ the light and electron microscopic appearances in the present case indicate a melanocytic origin.

The cells were well differentiated and the melanosomes were relatively normal. While some workers have claimed that this supports the view that it is a benign naevus or at most a lentigo maligna in the skin,⁶ others have shown that this is not a reliable criterion.⁷ Electron microscopy confirms the true melanocytic origin of these tumours but does not assist in determining their behaviour.

Machemer² suggested that the diffuse uveal masses which he described represented proliferation of the Schwann cell system like that seen in the phakomatoses. Bilateral uveal malignant melanoma is extremely rare, with only 18 reports in the literature,¹ and unilateral diffuse malignant melanoma is also uncommon, being found only in 5% of uveal melanomas.^{8,9}

It has been suggested¹ that these cases are an oncogenic response to the same stimulus that caused the lethal carcinomas, but these writers state: 'it is our impression that these tumours essentially are benign and unlikely to metastasise,' despite the presence of scleral extension in each case and malignant-looking epithelioid cells in 4 of their cases, and they draw a parallel between hamartomatous lesions and neoplasia such as is seen in Cowden's disease.

The role of radiotherapy with possible immunosuppression in the total of 8 cases reported to date cannot be evaluated. Three patients had no irradiation—Barr *et al.*'s cases 1, 2, and 4.¹ There was

abdominal radiotherapy in 2 patients (case 3 of Barr *et al.*¹ and in the present case), and irradiation to the eyes was given in 3 patients, those of Barr and associates' case 3,¹ de Wolff Rouendaal,⁴ and Machemer.²

We believe that the ocular tumours which we describe in our patient are malignant melanomata and that they appeared in association with visceral carcinoma. The explanation for this concurrence remains undetermined.

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