Clinicopathological findings in a growing optic nerve melanocytoma

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SUMMARY We present an unusual case of a melanocytoma of the optic disc that showed documented progressive growth over a period of six years. It reached the largest size of any reported optic nerve melanocytoma and the eye was enucleated because of the possibility of malignant degeneration. Optic nerve melanocytomas are locally invasive but are not known to undergo transformation into malignant melanoma. Follow-up should remain the primary approach in the management of patients with optic nerve melanocytomas, as previously advocated by Zimmerman.

The management of melanocytomas of the optic disc has changed over the past two decades from enucleation to simple serial observation. Before the pioneering work of Zimmerman,1–4 deeply pigmented lesions of the optic nerve were considered to be primary malignant melanomas of the optic disc.5 Loewenstein suggested that such lesions may represent malignant transformation in a naevus of the optic nerve.6 DeVeer reviewed the literature related to malignant melanoma of the optic nerve and doubted the existence of a primary malignant melanoma of the disc, as most of the reported lesions showed a peripapillary origin.7 Seven years later DeVeer examined an eye enucleated for a so-called malignant melanoma of the optic nerve. The cells did not appear to be anaplastic, and he concluded that this lesion is benign despite its infiltration into the retina and the optic nerve.8

As a result of a large clinical and histopathological study of such lesions with long-term follow-up Zimmerman established the entity of 'melanocytomas', choosing this term in part to indicate the benign behaviour of the darkly pigmented tumour of the optic disc.1–4 Subsequently Cogan coined the term 'magnocellular nevus'9 and Reese the term 'benign melanoma' to describe the same lesion.10 Melanocytomas are now thought to be predominantly stable lesions with no malignant potential.11

We present the first clinicopathological study of an optic nerve melanocytoma with prominent growth that led to enucleation of the eye because of suspected malignant transformation. This case along with a review of the literature helps to establish the point that there is no documented case of malignant change in optic nerve melanocytomas, and that growth in these tumours reflects simply their locally invasive behaviour.

Case report

The patient was a 42-year-old fair-complexioned Caucasian man who presented for routine physical examination in February 1968. The physical examination gave essentially negative results except for mild systemic hypertension and a pigmented right optic disc. In April 1968 he presented to his local ophthalmologist with the complaint of sensitivity to light in the right eye. An eye examination revealed 20/20 vision bilaterally, enlarged right blind spot, and a pigmented lesion over the right optic disc. An examination in May 1968 gave unchanged results, but
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Fig. 1  Serial funduscopic findings showing the gradual growth of the optic nerve melanocytoma over a total period of 64 months. Dates are serially as follows: June 1968, June 1970, June 1971, June 1972, August 1972, and September 1973.

it was the impression of the ophthalmologist that the lesion grew in size in June 1968 (Fig. 1-1).

In August 1968 the patient was referred to the Walter Reed Army Medical Center for examination. The lesion was jet black in colour, with feathery edges, covering half the disc and extending inferiorly and nasally over the peripapillary retina. Two senior consultants agreed on the diagnosis of optic disc melanocytoma and recommended periodic observation. At follow-up in June of 1970 there was enlargement of both the pigmented lesion and the visual field defect (Fig. 1-2). Vision was 20/20 − 1 in the right eye. During subsequent visits in June 1971 (Fig. 1-3) and June 1972 (Fig. 1-4) further enlargement of the lesion, progressive obscuration of the disc, and scattering of pigment clumps into the adjacent retinal nerve fibre layer were noted. In August 1972 (Fig. 1-5) a nerve fibre layer haemorrhage was observed adjacent to the tumour temporally. This cleared over the following two months. In December 1972 the patient complained of ‘foggy vision’. His vision remained 20/20 in the right eye. An enlarging field defect was approaching fixation. The pigmented lesion was noted to be enlarged inferiorly, with a surrounding new nerve fibre layer haemorrhage inferiorly. In January 1973 the patient was referred to the Edward S Harkness Eye Institute for a B scan ultrasonogram. The report stated ‘optic tumor at the posterior pole of the right eye, not typical of a melanoma of the choroid, and consistent with melanocytoma.’ The dimensions of the lesion as determined by ultrasonography were 1.5 mm in elevation, 6 mm in diameter, and with evidence of extension of the tumour posterior to the cribiform plate.

In February 1973 the vision was 20/20 − 2, with the optic disc becoming almost totally obscured by the pigmented lesion. Fluorescein angiography revealed blockage of fluorescence of both the choroidal and retinal vasculatures by the mass, with absence of leakage around the mass. In September 1973 (Fig. 1-6) the patient presented with decreased vision and floaters in the right eye. Vision in the right eye was 20/40+2. There was a mild afferent pupillary defect.
Histological sections through the optic nerve and macula. A: Cross section of the posterior pole reveals small groups of pigmented cells extending to the level of the lamina cribrosa and behind the lamina nasally. The nasal juxtapapillary choroid is similarly involved. The peripapillary retina is diffusely thickened especially temporally from tumour infiltration. Haematoxylin and eosin, ×7. The tumour is formed of small spindle cells (upper inset, haematoxylin and eosin, bleached preparation, ×600), large polyhedral heavily pigmented cells (lower inset, haematoxylin and eosin, bleached preparation, ×600), and pigment laden macrophages. B: Section through the fovea reveals a detachment of the retina by proteinaceous exudate. There is diffuse infiltration of the retina by pigmented cells with involvement of the retinal surface and formation of an epiretinal membrane. Large cystoid spaces in the outer plexiform layer are filled with proteinaceous material and pigment laden macrophages. Haematoxylin and eosin, ×60.

Dispersed brown and black pigments were noted in the vitreous cavity, with layering along the inferior surface of the posterior lens capsule. The tumour had increased in its anteroposterior thickness. There was further encroachment of the field defect on fixation. In April 1974 the patient reported a drastic decrease in vision. Vision was 20/100–1, and the enlarging scotoma had covered fixation by visual field testing. The lesion had enlarged, and exudates were observed in the macula. No dye leakage was noted on fluorescein angiography. Because of the possibility of a malignant melanoma arising in a melanocytoma, enucleation was advised. A P-32 test with readings taken at the time of enucleation was negative. The patient remained healthy on his last medical visit in March 1986.

HISTOPATHOLOGICAL DESCRIPTION
On gross examination the specimen was seen to consist of a right eyeball with 13 mm segment of attached optic nerve. Transillumination of the eye and optic nerve revealed no definite shadow. The external examination of the eye revealed no abnormality. A cross section of the optic nerve 1 mm from
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Fig. 2B

the sclera revealed no evidence of pigmentation.

The globe was opened horizontally through the optic nerve, revealing a heavily pigmented tumour covering the optic disc and measuring 7 mm in greatest horizontal dimension. The tumour was raised by a coagulated subretinal exudate. Yellowish intraretinal exudates were present along the temporal edge of the tumour. Pigmented deposits were present in the subretinal space at the temporal edge of the optic disc. Very little tumour was seen deep in the optic nerve head except for a small patch of intense pigmentation behind the lamina cribrosa nasally. The vitreous was detached posteriorly and contained large pigmentary deposits. Moderate pigmentation and thickening of the nasal peripapillary choroid was noted. The pigmented tumour had spread into the bulging juxtapapillary retina inferiorly and superiorly. Two patches of superficial retinal haemorrhages were noted superiorly.

On microscopic examination (Figs. 2A, B) the anterior segment was unremarkable except for the presence of several foci of free pigment granules adherent to the posterior lens capsule, zonular fibres, and anterior hyaloid surface. Moderately heavy pigmentation of the uveal tract was most pronounced posteriorly. Within the optic nerve and extending into the peripapillary area was a very heavily pigmented tumour. The tumour lay superficially in the optic nerve, though small groups of pigmented cells extended to the level of the lamina cribrosa and a short distance behind the lamina nasally. The nasal juxtapapillary choroid showed only a small amount of tumour. The tumour involved the juxtapapillary retina more extensively in the temporal side, where it replaced most of the nasal half of the macula.

The fovea was detached by a large accumulation of proteinaceous subretinal exudate containing heavily pigmented macrophages. There was a large accumulation of serous exudate and foamy histiocytes in the outer plexiform layer of the foveal region. Between
the disc and the fovea the retina was severely thickened, measuring 1.5 mm in thickness as the result of the massive infiltration by the pigmented cells. These cells included a mixture of heavily pigmented polyhedral melanocytes with round, ovoid, and even chromatic nuclei like those found in melanocytomas, large rounded melanophages, and smaller pigmented spindle cells with irregular, vesicular, and hyperchromatic nuclei resembling the spindle A melanoma cells of the iris. The spindle cells were the predominant cells at the junction between the tumour and normal retina nasally.

The internal limiting membrane was infiltrated in the temporal peripapillary area by the pigmented cells to form a thin placoid pigmented layer along the inner retinal surface. Tumour cells infiltrated along the retinal vessels in the peripapillary area and the major vessels in the optic nerve head. No tumour was noted in the cross sections of the optic nerve, meninges, or orbital tissues. Special stains revealed dropout of axons and foci of demyelinisation, especially on the temporal side of the optic nerve.

Transmission electron microscopic findings have been reported previously.12

The final pathological diagnosis was melanocytoma of the optic nerve head.

Discussion

Several features in our case are typical of an optic nerve melanocytoma. They include the jet black colouration, the feathery edges, the origin from the optic disc as noted on initial presentation, the relatively well preserved vision and visual fields for a long period of follow-up, and the findings on ultrasonography and fluorescein angiography. Unusual features include the relatively very large size of the mass, its growth pattern, infiltration of the macular region, the presence of retinal haemorrhages, and the formation of a preretal pigmented plaque.

Melanocytomas of the optic nerve have been characterised as stable or slowly growing lesions.11 A total of 38 cases followed up for five years or more showed no evidence of growth11-15 and no evidence of metastasis following enucleation.1 Joffe et al.11 followed up 27 cases for more than one year and found no change in size in 22 eyes. Mild enlargement of the melanocytoma has been recorded in a total of 11 cases,1,10,11,16 usually after several years of follow-up. The average size of the lesion was calculated from the series of 40 cases reported by Joffe et al. to be around 40% of the optic disc size.11 Complete obscuration of the optic disc was found in nine cases.1,10,11,18 The three largest reported tumours were around 2 disc diameters in diameter.1,11,18

The pattern of growth in the occasionally expanding melanocytomas is not known. In one case the tumour grew progressively over a period of seven years and became stationary over the next eight years of follow-up.2 In another case the tumour seemed to grow over a period of one week.3 Malignant melanoma arising in a melanocytoma of the uveal tract had been encountered in several of the cases seen at the Ophthalmic Registry of the Armed Forces of Pathology, and in several case reports.19,20 However, there is still no documented case of a malignant melanoma arising from an optic nerve melanocytoma. Apple et al.21 described the first case of malignant transformation of an optic nerve melanocytoma. However, the initial grey mass at the superior aspect of the disc was not recorded and seemed atypical in location and discoloration for a primary optic nerve melanocytoma favouring a peripapillary choroidal origin. Moreover it was not clear if the melanoma arose originally from the choroidal or the optic nerve part of the naevus. It has been estimated that there is one in 5000 chance for a choroidal naevus to develop into a malignant melanoma.22 If this is applied to the optic nerve melanocytoma, an uncommon form of naevus, malignant transformation would be extremely rare. Growth in melanocytomas reflects their known locally invasive behaviour.3

The causes of visual loss in melanocytomas of the optic disc are multiple. There have been seven cases of decreased vision from 20/50 or less2,3,8,11,23 up to hand motion1 and to no light perception,16 with two of these cases having a sudden loss of vision.3,16 Papilloedema followed by occlusion of the central retinal artery was the initial manifestation of a deeply seated optic nerve melanocytoma.14 Similarly, ocular pain was the presenting sign of a partially necrotic optic nerve melanocytoma that showed vasocoocclusive disease of the optic nerve, ischaemic necrosis of the tumour, hypoxic retinopathy, and neovascular glaucoma.24 Zimmerman1 described one case showing ischaemic necrosis of an optic nerve melanocytoma that invaded deeply into the nerve and was related to an occlusion of an anomalous vascular supply to the tumour and temporal retina. Loss of vision with subsequent progressive partial recovery was described in one case of optic nerve melanocytoma, though the mechanisms of recovery were not clear.15 Disciform scarring over a choroidal melanocytoma may lead to decrease in vision and simulate a choroidal melanoma.25 No disciform lesion has been seen overlying an optic disc melanocytoma.

Despite these isolated reports, the major cause of decreased vision is attributed to the swelling of axons from compression of the nerve fibres and their vascular supply by the tumour.28 This explains why
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deeply seated optic nerve melanocytomas, despite their small apparent size, may result in visual loss.\textsuperscript{24} Computed tomography and ultrasonography can help in delineating the posterior extension of melanocytomas, and such investigations should be carried out if the visual symptoms are not commensurate with the fundus picture. Sectorial optic nerve atrophy in such lesions has been demonstrated histopathologically.\textsuperscript{27} Direct infiltration of the nerve fibre layer by the mass, along with pressure atrophy of the nerve axons, can explain the not infrequent occurrence of nasal steps, arcuate nerve fibre layer visual defects, and the Marcus Gunn pupillary sign in optic nerve melanocytomas. Our case is unique in that the nasal macula was infiltrated by the tumour and the temporal macula was elevated by a serous subretinal fluid. Moreover the surface of the macula was covered by a pigmented layer and pigment dispersion from the melanocytoma was found in the anterior aspect of the posterior segment. This dispersion of pigment granules and pigmented cells should not be taken as a sign of active tumour growth, as previously noted by Reese.\textsuperscript{10}

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