Uveal malignant melanoma and optic nerve glioma in von Recklinghausen's neurofibromatosis

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Abstract

A case of uveal malignant melanoma and contralateral optic nerve glioma is described in a 53-year-old Caucasian male with multiple uveal melanocytic hamartomas and neurofibromatosis. The eye was enucleated, and histologically the melanoma was found to consist of 70% epithelioid cells, with many bizarre, multinucleated forms. CT scan demonstrated a non-enhancing, fusiform enlargement of the contralateral optic nerve with enlargement of the optic canal and intracranial extension. This combination of tumours has not previously been reported in a patient with neurofibromatosis and serves to emphasise the common neuroectodermal origin of tumours in this autosomal dominant condition.

Optic nerve glioma^{1,2} and uveal malignant melanoma³⁻¹³ have both been reported in von Recklinghausen's neurofibromatosis (NF). While the incidence of optic nerve glioma varies from 10 to 70%,² only 11 cases of uveal malignant melanoma in NF are reported.³⁻¹³ In NF uveal malignant melanoma has been reported with acoustic schwannoma³ and with orbital neuroma.⁵ We describe the previously unreported association of uveal malignant melanoma and contralateral optic nerve glioma in a patient with multiple uveal melanocytic hamartomas and neurofibromatosis.

Case report

A 53-year-old Caucasian man with multiple cutaneous neurofibromata, café-au-lait spots, and a family history of NF presented with a four-day history of spots and blurring in the left eye rapidly progressing to total grey-out of vision.

The visual acuities were 20/20-3 in the right eye and 20/400 in the left, with a left afferent pupillary defect. The interpupillary fissures, results of exophthalmometry, and IOP measurements were normal and symmetrical. Neither globe showed displacement. Multiple Lisch nodules and iris naevi were seen, particularly in the left eye, which also had a large inferior sentinal vessel and a cataract. There was a large ciliochoroidal tumour between 4 and 8 o'clock, with 9-10 mm of elevation, a total retinal detachment, and anterior iris displacement between 4 and 6 o'clock.

Ultrasonography showed a solid, horseshoe shaped mass in the choroid extending from inferotemporal to inferonasal quadrants.

Computed tomography showed a normal left orbit and a left globe of normal size with an enhancing lobulated uveal mass in its inferior half extending bilaterally to the ora (Fig 1)

Figure 1 Axial CT scan showing fusiform enlargement of the optic nerve with intracranial extension (right) and lobulated uveal mass (left).

without extrascleral extension. On the right the optic nerve had a non enhancing, fusiform enlargement, with expansion of the optic canal and intracranial extension. No cerebellopontine angle or internal auditory canal abnormality was seen.

Malignant melanoma was suspected, and it was confirmed on intraoperative fine needle aspiration biopsy, which showed numerous malignant epithelioid melanocytes with large vesicular nuclei and prominent nucleoli. The biopsy was followed by a cryonucleation. The globe was 24-25 mm in diameter with corneal measurements of 13×11.5 mm. Oblique sectioning exposed a black tumour with a 17 mm base and a height of 7 mm. The overlying retina was detached.

Figure 2 Low power view of globe showing lobulated tumour arising from the uveal tract and associated retinal detachment. (Haematoxylin and eosin, ×2.7.)

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Figure 3 Uveal malignant melanoma with epithelioid cells showing granular cytoplasmic S100 positivity (arrows). (Bleached preparation; immunoperoxidase staining for S100 antigen; $\times 800$.)

Histologically a poorly differentiated malignant melanoma arose from the uvea, abutted the lens, occupied the pars plana, and extended three-quarters of the way to the posterior pole (Fig 2). The densely pigmented tumour cells were 70% epithelioid and 30% spindle, with many bizarre, multinucleated forms (Fig 3). The tumour stained moderately for S100 protein and strongly with the monoclonal antibody HMB45. Large sinusoidal spaces and focal areas of haemorrhage and necrosis were identified. There was no paraemissarial extension. The detached retina was degenerated.

In the neovascularised iris spindle to polygonal shaped cells, many with intranuclear inclusions, formed numerous S100-positive melanocytic hamartomas (Fig 4). In the choroid multiple diffuse hamartomatous aggregations of melanocytes, some extending round the emissaria posteriorly, were present and stained strongly positive for S100 protein and occasionally with HMB45 (Fig 5).

The patient presented three months later with diffuse metastatic disease and died 13 months after enucleation.

Discussion

Neurofibromatosis, first described by von Recklinghausen in 1882,¹⁴ is a common autosomal dominant disorder with a prevalence of 1 in 3000.^{15 16} It has one of the highest mutation rates in humans.¹⁷ Though it was previously considered to be a heterogeneous disorder with variable expression, linkage analysis in NF families has recently identified a consistent mutation at a single locus on chromosome 17.¹⁸

Melanocytic and glial lesions of NF are derived from the neural crest. The association of optic nerve glioma and NF is established,^{1 2} and an increased incidence of uveal malignant melanoma is also noted¹⁹ despite the small number of cases (11) reported.³⁻¹³ Uveal naevi are also found more frequently.^{11 15} Concurrent malignant melanoma and optic nerve glioma

Figure 4 Melanocytic hamartoma of the iris. (Haematoxylin and eosin, $\times 80$.)

have not previously been reported, but the conjunction illustrates the pathogenesis of NF as a 'complex neurocristopathy' as initially defined by Bolande.²⁰ This concept envisages NF as a defect in development and regulation in which tissues derived from the neural crest show an increased incidence of benign tumours such as neurofibromas, schwannomas, neuromas, gliomas, meningiomas, café-au-lait spots, other cutaneous naevi, uveal naevi,^{1 2 16 21-23} and malignant tumours such as malignant schwannoma,^{24 25} pheochromocytoma,^{26 27} cutaneous malignant melanoma,^{24 28-30} and uveal malignant melanoma.³⁻¹³ A predisposition to uveal malignant melanoma may also exist because of the increased incidence of choroidal naevi in NF³¹ and the supposition that malignant melanoma arises from these naevi.³²

Other features of NF cannot be attributed directly to maldeveloped neural crest but may arise secondarily to interactions with other developing tissues, leading to additional anomalies¹⁵ such as malignant tumours (rhabdomyosarcoma, nephroblastoma, and myelogenous leukaemia),³³⁻³⁷ mesodermal defects (macrocephaly, pseudoarthrosis, kyphoscoliosis, short stature, sphenoid wing dysplasia), diminished intellect, speech defects, and pruritus.¹⁶

The commonest ocular feature of NF is the Lisch nodule, present in over 90% of adult patients.^{22 23} Additional neural crest derived ocular features include neurofibromas of eyelid, conjunctiva, and orbit, café-au-lait spots, prominent corneal nerves, uveal naevi, choroidal glial hamartomas, optic nerve gliomas, intraocular schwannomas, sphenoid wing dysplasia,^{17 22 23 38} and uveal malignant melanoma.³⁻¹³

The average age of patients with NF-related

Figure 5 Melanocytic hamartoma of the choroid. (Immunoperoxidase staining for S100 antigen, $\times 160$.)

uveal malignant melanomas is reported as 47, and our patient was 55. Two-thirds of enucleations for uveal malignant melanoma in the general population occur after age 50.³⁹ Despite the lack of sex predilection in NF alone, nine of the 11 previously reported patients in whom it was associated with uveal malignant melanoma were female, a distribution not seen in other series of uveal malignant melanoma. Seven tumours were reported as spindle cell, three as mixed cell, and one as epithelioid cell. The tumour in our case did not. The malignant cell type of our tumour and the large size suggested a poor outcome, with a five-year survival less than 40%.⁴⁰

- 1 Rush JA, Young BR, Campbell RJ, MacCarthy CS. Optic glioma. Long term follow-up of 85 histopathologically verified cases. *Ophthalmology* 1982; 89: 1213-9.
- 2 Lewis RA, Gerson LP, Axelson KA, Riccardi VM, Whitford RP. von Recklinghausen neurofibromatosis. II. Incidence of optic glioma. *Ophthalmology* 1984; 91: 929-35.
- 3 Bair HL, Love JG. Acoustic neurofibroma associated with melanoepithelioma of the choroid: successful removal of both tumors. *Mayo Clin Proc* 1937; 12: 481-5.
- 4 Gartner S. Malignant melanoma of the choroid and von Recklinghausen's disease. *Am J Ophthalmol* 1940; 23: 73-8.
- 5 Strachov VP. Recklinghausen's disease, neurinoma of the right orbit and neoplasm of the left choroid. *Vestn Oftalmol* 1941; 18: 12-16 (in Russian).
- 6 Szekler R. Ein Uvealsarkom bei einem Mitglied einer Familie mit Recklinghausenscher Krankheit. *Ophthalmologica* 1954; 126: 248-51.
- 7 Nordmann J. Cancer de la choroïde et maladie de Recklinghausen. *Bull Soc Ophthalmol Fr* 1961; 5: 322-5.

- 8 Nordmann J, Brini A, Ruolt J. Tumeur mélanique de la choroïde et neurinomes chez un même sujet. *Bull Soc Ophthalmol Fr* 1963; 7: 551-3.
- 9 Yanoff M, Zimmerman LE. Histogenesis of malignant melanomas of the uvea: III. The relationship of congenital ocular melanocytosis and neurofibromatosis to uveal melanomas. *Arch Ophthalmol* 1967; 77: 331-6.
- 10 Cernea P, Dobrescu G. Mélanome malin uvéal, manifestation de la maladie de Recklinghausen. *Ophthalmologica* 1973; 166: 161-71.
- 11 Wiznia RA, Freedman JK, Mancini AD, Shields JA. Malignant melanoma of the choroid in neurofibromatosis. *Am J Ophthalmol* 1978; 86: 864-87.
- 12 Croxatto JO, Charles DE, Malbran ES. Neurofibromatosis associated with nevus of Ota and choroidal melanoma. *Am J Ophthalmol* 1981; 92: 578-80.
- 13 Specht CS, Smith TW. Uveal malignant melanoma and von Recklinghausen's neurofibromatosis. *Cancer* 1988; 62: 812-7.
- 14 Crump T. Translation of case reports in Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen bei F.v. Recklinghausen. *Adv Neurol* 1981; 29: 259-76.
- 15 To KW, Rabinowitz SM, Friedman AH, Merker C, Cavanaugh CP. Neurofibromatosis and neural crest neoplasms: primary acquired melanosis and malignant melanoma of the choroid. *Surv Ophthalmol* 1989; 33: 373-9.
- 16 Riccardi VM. von Recklinghausen neurofibromatosis. *N Engl J Med* 1981; 305: 1617-27.
- 17 Sergeyev AS. On the mutation rate of neurofibromatosis. *Hum Genet* 1975; 28: 129-38.
- 18 Barker D, Wright E, Nguyen K, et al. Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science* 1987; 236: 1100-2.
- 19 Font RL, Ferry AP. The phakomatosis. *Int Ophthalmol Clin* 1972; 12: 31-42.
- 20 Bolande RP. The neurocristopathies: a unifying concept of disease arising in neural crest maldevelopment. *Hum Pathol* 1974; 5: 409-29.
- 21 Huson S, Jones D, Beck L. Ophthalmic manifestations of neurofibromatosis. *Br J Ophthalmol* 1987; 71: 235-8.
- 22 Lewis RA, Riccardi VM. von Recklinghausen neurofibromatosis. Incidence of iris hamartoma. *Ophthalmology* 1981; 88: 348-54.
- 23 Ilgren EB, Kinnier-Wilson LM, Stiller CA. Gliomas in neurofibromatosis: a series of 89 cases with evidence for enhanced malignancy in associated cerebellar astrocytomas. *Pathol Annu* 1985; 1: 331-58.
- 24 Brasfield RD, Das Gupta TK. von Recklinghausen's disease: a clinico-pathologic study. *Ann Surg* 1972; 175: 86-104.
- 25 Sayed AK, Bernhardt B, Perez-Atayde AR, et al. Malignant schwannoma in siblings with neurofibromatosis. *Cancer* 1987; 59: 829-35.
- 26 Healy FH, Mekelatos CJ. Pheochromocytoma and neurofibromatosis. *N Engl J Med* 1958; 258: 540-3.
- 27 Modlin IM, Fardon JR, Shephard A, et al. Pheochromocytoma in 72 patients: clinical and diagnostic feature, treatment and long term results. *Br J Surg* 1979; 66: 456-65.
- 28 Riccardi VM, Eichner JE. *Neurofibromatosis: phenotype, natural history and pathogenesis*. Baltimore: Johns Hopkins University Press, 1986: 162-8.
- 29 Silverman JF, Blahove M, Collins JL, Norris HT. Cutaneous malignant melanoma in a black patient with neurofibromatosis. *Am J Dermatopathol* 1988; 10: 536-40.
- 30 Mastrangelo MJ, Goepp CE, Patel YA, Clark WH. Cutaneous melanoma in a patient with neurofibromatosis. *Arch Dermatol* 1979; 115: 864-5.
- 31 Hope DG, Mulvihill JJ. Malignancy in neurofibromatosis. *Adv Neurol* 1981; 29: 33-56.
- 32 Yanoff M, Zimmerman LE. Histogenesis of malignant melanoma of the uvea. *Arch Ophthalmol* 1967; 77: 331-6.
- 33 Bader JL, Miller RW. Neurofibromatosis and childhood leukemia. *J Pediatr* 1978; 92: 925-9.
- 34 Bestak M, Miller DR, Mouradian JS. Juvenile chronic myelogenous leukemia and dermal histiocytosis. *Am J Dis Child* 1979; 133: 831-3.
- 35 McKeen EA, Bodurtha J, Meadows AT, et al. Rhabdomyosarcoma complicating multiple neurofibromatosis. *J Pediatr* 1978; 93: 992-3.
- 36 Stay EJ, Vawter G. The relationship between nephroblastoma and neurofibromatosis. *Cancer* 1977; 39: 2550-5.
- 37 Walden PAM, Johnson AG, Bagshawe KD. Wilms's tumour and neurofibromatosis. *Br Med J* 1977; i: 813.
- 38 Freedman SF, Elner VM, Donev ID, Gupta G, Albert DM. Intraocular neurilemmoma arising from the posterior ciliary nerve in neurofibromatosis. *Ophthalmology* 1988; 95: 1559-64.
- 39 Zimmerman LE. Malignant melanoma of the uvea. In: Spencer WH, ed. *Ophthalmic pathology*. Philadelphia: Saunders, 1986: 2072-136.
- 40 McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type and enucleation as risk factors in metastasis. *Hum Pathol* 1982; 13: 123-32.