CASE REPORT

Orbital recurrence of iris melanoma 21 years after enucleation

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SUMMARY

We present the case of a 56-year-old man who developed a neoplasm of epithelioid histology in his anophthalmic left orbit 21 years after he underwent enucleation for a spindle cell iris melanoma. The recurrent tumour was managed by orbital exenteration. Neither further recurrence nor metastasis was diagnosed over a 5-year follow-up period. This case, along with five other similar cases in the literature,^{1–3} emphasises the importance of long-term follow-up after treatment of iris melanoma.

BACKGROUND

Despite being the most common primary intraocular malignancy in adults, uveal melanoma only accounts for 5% of all melanomas.⁴ Although it can arise anywhere within the uveal tract, uveal melanoma occurs far more frequently in the choroid (90%) than in the ciliary body (6%) and the iris (4%).⁵ Among all uveal melanomas, those which originate from the iris manifest the less aggressive behaviour.⁶ Nonetheless, they must be recognised and treated early since they can progress to invade adjacent structures and lead to metastatic disease.⁷ Differentiation from other benign iris lesions, such as nevi and cysts, relies mainly on clinical grounds: documented substantial growth over time remains the main predictive feature of malignancy.⁸ Iris melanoma is usually managed by radiotherapy (proton beam or plaque radiotherapy) or surgical resection (local resection or enucleation),⁶ both approaches sharing similar prognosis in terms of local recurrence after treatment (range: 0%–8%) and development of metastases (range: 0%–14%).⁶ However, late recurrences of iris melanoma occurring decades after primary management have seldom been reported in the literature.^{1–3}

CASE PRESENTATION

A 35-year-old man, with a history of type 1 diabetes, was first referred to our ocular oncology clinic in 1991 for evaluation of a left-sided iris lesion, which had progressed significantly over 3 years (figure 1). Slit-lamp examination revealed an elevated pigmented lesion with well-defined feathery margins. It emerged from the iris root and occupied both inferior quadrants (between four and nine clock hours). Despite involvement of the iridocorneal angle, there was no secondary glaucoma. Ectropion uveae, hyphema and angle seeding were not observed. Clinical examination was not

suggestive of ciliary body invasion. Assessment of the lesion with ultrasound biomicroscopy to rule out further extension was not performed, as this device was not in clinical use in 1991.⁹ Indirect ophthalmoscopy showed no posterior extension.

A diagnosis of iris melanoma was suspected. Systemic investigation that includes liver function tests, chest radiography as well as liver and bone scintigraphy excluded metastatic disease. Therapy options were discussed with the patient. He opted for tumour resection instead of enucleation because the neoplasm appeared to be limited to the iris on initial examination and because his diabetes could eventually impair the visual function of his other eye. It should be noted that plaque radiotherapy was not employed in the management of iris melanoma in 1991.¹⁰

Partial iridocyclectomy was performed. The pathology report confirmed the diagnosis of spindle cell melanoma, but showed positive resection margins. The patient thus underwent enucleation. Subsequent histopathological examination revealed residual spindle cells in the iris root and ciliary body, but ruled out extrascleral extension of the tumour (TNM (tumour, node, metastases) staging T2N0M0).¹¹ No further treatment was recommended in light of presumed complete excision. The patient was monitored biannually using ophthalmological examination and liver function tests until he was lost to follow-up in 1998. Over this 7-year period, there was no sign of local recurrence or evidence of metastatic disease.

In 2012, twenty-one years after he underwent enucleation, the patient was again referred to our oncology clinic by his ocularist for evaluation of a mass interfering with the implant-prosthetic interface. Ophthalmological examination revealed a painless, non-pigmented mass located in the antero-nasal region of the left orbit. There was no regional lymphadenopathy. The presumptive diagnosis was orbital recurrence of iris melanoma.

INVESTIGATIONS

A CT scan of the orbits showed a 35 mm×28 mm×27 mm mass displacing the spherical implant posteriorly and invading all rectus muscles (figure 2A). Immunohistochemical analyses were conducted on a biopsy and revealed focal expression of melanocytic markers, thus supporting the diagnosis of orbital recurrence of iris melanoma (figure 2B). The BRAF^{V600E} mutation status was determined by Sanger sequencing,¹² and no mutation was found. Screening for metastasis

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Figure 1 Progression of pigmented and feathery iris lesion observed in inferonasal and inferotemporal quadrants of the left eye. Slit-lamp photographs of the iris taken on February (A) 1988, (B) 1990 and (C) 1991.

with liver function tests, hepatic ultrasonography, thoracoabdominal CT, MRI of the brain and bone scintigraphy was negative.

TREATMENT

A palliative orbital exenteration was discussed but deferred, since the patient was asymptomatic and still able to wear his prosthesis comfortably at the time of the diagnosis. However, the mass progressed significantly over the following months, causing pain and prosthesis instability; an orbital exenteration was performed 6 months later. The recurrent tumour was classified as epithelioid, with more than 85% of epithelioid cells (figure 2C). Surgical margins were clear; therefore, no adjuvant radiotherapy was recommended. Later, the orbital cavity was fitted with a bone-anchored epithesis.

Figure 2 Orbital recurrence of iris melanoma. (A) CT scan of the orbits that demonstrates a 35 mm×28 mm×27 mm solid mass (white arrow) located between the prosthesis and the implant in the anterior subconjunctival surface of the left socket and invading the superior, inferior, medial and lateral rectus muscles. (B) Immunohistological analyses of a biopsy of the recurrent tumour showing positive staining (dark brown; 3,3'-Diaminobenzidine (DAB) chromogen) for melanocytic markers HMB45, MART1 and S100. Nuclei were counterstained with haematoxylin (blue). Scale bars, 50 µm. (C) Histopathological examination of the exenterated tumour with H&E showing a high content of epithelioid cells. Scale bar, 50 µm.

OUTCOME AND FOLLOW-UP

Biannual follow-up using ophthalmological examination, liver function tests and hepatic ultrasonography has not shown any evidence of local recurrence or metastasis to present.

DISCUSSION

Several risk factors for local recurrence of iris melanoma have been identified. A key element is the clinical stage of the disease. The American Joint Committee on Cancer (seventh edition) proposed a classification system in which iris melanoma is graded according to three important clinical criteria: size and extent of the primary tumour (T), lymph node involvement (N) and presence of distant metastasis (M).¹¹ A multicentre, international study of 131 patients with biopsy-proven iris melanomas demonstrated that increasing T category was consistent with a more aggressive behaviour, as shown by a significantly greater occurrence of metastasis.¹³ Another important prognostic feature is the histopathological grade of the tumour. Among all histological subtypes (spindle, epithelioid and mixed cell types), spindle cell melanoma carries the best prognosis, whereas epithelioid cell melanoma carries the poorest, with regard to both local recurrence after treatment and metastatic development.^{4 7 13} A third risk factor is the presence of the *BRAF*^{V600E} mutation. The *BRAF*^{V600E} point mutation is more frequent in sun-exposed melanomas such as those of the conjunctiva¹⁴ and the iris,¹² and is predominantly present in recurrent iris melanomas.¹² However, other studies did not report this mutation in any of their iris melanoma cases, so the *BRAF* mutational frequency in anterior uveal melanoma is still under debate.^{3 15} In the case described here, the patient had a T2N0M0 spindle cell iris melanoma that recurred 21 years later. The recurrence was classified as epithelioid, suggesting that the iris tumour arose as a spindle cell neoplasm and evolved over 21 years into an epithelioid melanoma. Sanger sequencing showed that the recurrent tumour was *BRAF* wild type. The T2 stage of the primary tumour and the epithelioid histology of the recurrent lesion being predictors of a more aggressive behaviour^{13 16} may have played a role in the recurrence, but do not explain why it occurred decades later.

Both proton beam and plaque radiotherapy, as well as surgical interventions such as local resection or enucleation, have proven effective in the primary treatment of iris melanoma.^{4 6 17 18} Rates of local recurrence (range: 0%–8%) and progression towards metastatic disease (range: 0%–14%) remain similar, whichever method is chosen.^{6 18 19} However, because invasive intraocular procedures carry the risk of malignant cell dissemination, not all iris melanomas should be managed with iridectomy: tumours

selected for resection should be small (<5 clock hours) and cohesive, without angle seeding nor secondary glaucoma.^{6 19} In our case, however, decision making regarding the treatment of our patient was limited since the use of plaque radiotherapy in the management of iris melanoma had not yet been studied in 1991.¹⁰ Moreover, because of his concomitant diagnosis of type 1 diabetes and its potential future visual morbidity, our patient expressed a strong preference for eye-sparing treatments. Therefore, he first underwent iridocyclectomy, but since the margins of the resected material were unclear, he subsequently underwent enucleation.

Regarding the mechanism underlying the development of late orbital recurrence of iris melanoma, we hypothesise that subclinical melanoma cells were implanted in the orbit during surgical removal of the tumour. Another possible explanation is migration of melanoma cells and formation of orbital micrometastases before the patient underwent enucleation. However, the relevance of this article is related to the fact that the tumorous cells remained dormant for two decades before causing clinically significant recurrent disease. Only five other cases of late recurrences of iris melanomas have been reported in the literature.^{1–3} Such behaviour has also been observed in the liver with metastasis occurring many years after excision of the primary ocular tumour.^{17 18} In fact, despite developments in diagnostic and therapeutic methods, survival rates among patients with uveal melanoma have remained the same over the past 30 years.^{4 7 20} Studies on tumour doubling times suggest that micrometastases occur several years before diagnosis²¹; consequently, even successful local treatment achieving complete tumour control may have a limited impact on the life expectancy of these patients.^{4 7 20} Further research will need to address the factors that allow iris melanoma cells to enter and exit dormancy in both recurrent and metastatic disease.

Learning points

- Iris melanoma can recur decades after primary management.
- Long-term follow-up after treatment of iris melanoma is indicated.
- Factors that stimulate dormant malignant cells in recurrent iris melanoma are yet to be established.

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