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Case report

Iris melanoma relapsing sixteen years after proton-beam therapy: The importance of lifelong follow-up

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ABSTRACT

Purpose: To report a case of locally recurrent spindle-cell iris amelanotic melanoma 16 years after proton-beam therapy.

Observations: In 2001, a 45-year-old man presented with an amelanotic iris melanoma, extending from the 5 to 10 o'clock positions on his left eye. High-frequency ultrasonography showed extension of melanoma into the ciliary body. He was initially managed with proton-beam therapy (60 Gy delivered in four fractions over four consecutive days) and underwent ocular and systemic examination at regular intervals over the following years. Local tumor control was achieved, and the patient did not develop metastasis during sixteen consecutive years. In 2017, 16 years after he received proton-beam therapy, the patient developed a focal amelanotic lesion strongly suggestive of a local recurrence of iris melanoma, although it extended from the 1 to 6 o'clock positions. He also presented with treatment-resistant glaucoma with an intraocular pressure (IOP) of 37 mmHg, despite maximal topical IOP-lowering therapy. Since a second irradiation of the anterior segment was contraindicated, the eye was enucleated. Pathological analysis confirmed the diagnosis of iris melanoma and demonstrated iridocorneal angle invasion extending from the initial site to the recurrent tumor location.

Conclusions and importance: Regular ophthalmological surveillance for life with gonioscopy and high-frequency ultrasonography is recommended in patients with iris melanoma, due to the possibility of delayed local recurrence more than a decade after the initial treatment.

1. Introduction

Iris melanoma accounts for 4% of all uveal melanoma. The most frequent location is the choroid (90%) followed by lesions involving the ciliary body (6%).[1] The diagnosis of circumscribed iris melanoma is clinical: iris melanoma are pigmented, and more rarely amelanotic lesions showing unequivocal evidence of growth. Other clinical features suggesting the diagnosis are large tumor size, development of feeder vessels with spontaneous hyphema, ectropion uveae, focal or complete cataract formation, corneal edema due to endothelial contact, tumor cells seeding in the iridocorneal angle away from the tumor, often inferiorly,[2] treatment-resistant glaucoma, diffuse involvement of the iris or feathery margins. The diagnosis of diffuse iris melanoma is challenging, and should be considered in eyes presenting progressive acquired heterochromia and unilateral glaucoma.[2]

Usually, fair-skinned Caucasian individuals and those with light irides have a higher propensity for iris melanomas.[3,4] Males and females appear to be affected in nearly equal proportions.[2] Iris melanomas can be melanotic (~80%), amelanotic (~20%) or mixed (< 1%).[5] Imaging with ultrasound biomicroscopy is required to assess tumor dimensions and extension to structures posterior to the iris, such as the ciliary body.[6,7] It also identifies features suggestive of malignancy such as irregular internal reflectivity of the tumor, extension through the iris pigmented epithelium, and presence of intralesional cystic areas[8]

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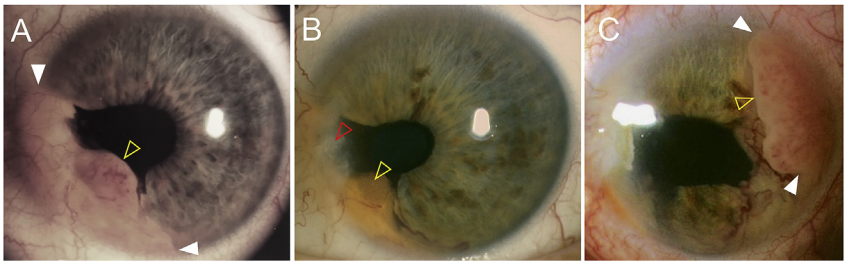

Fig. 1. Biomicroscopy of an iris amelanotic melanoma diagnosed in a 45-year-old man. A. At diagnosis, the lesion (yellow arrow) extended from the 5 to 10 o'clock positions (white arrows). Intrinsic tumor vessels were visible. B. Four years after treatment by proton-beam irradiation, the tumor had become atrophic (yellow arrow) and band keratopathy had developed at the level of the lesion (red arrow). C. Sixteen years after irradiation, biomicroscopy showed a recurrent iris amelanotic iris mass in the temporal sector (yellow arrow), extending from the 1 to 4 o'clock positions (white arrows). Gonioscopy revealed wider margins extending inferiorly along the iridocorneal angle to the 6-o'clock position, overlapping the initial tumor site. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

corresponding to the histopathological findings.[9] Systemic monitoring for metastases is performed by iterative liver ultrasonography. According to literature reports,[5,10] the estimated rate of metastases is ~3–5% and ~5–10% at 5-year and 10-year, respectively. Mortality related to iris melanoma is estimated at ~3% and ~4%, 5 and 10 years after diagnosis, respectively.

1.1. Case report

A 45-year-old man was referred to the ophthalmology department of our institution in November 2001 after reporting the growth of an iris nevus in his left eye over the last 2 years. The lesion had been present since his childhood. He also experienced recent spontaneous episodes of hyphema. The patient did not report any other ocular symptoms. At presentation, visual acuity was 20/25 and intraocular pressure (IOP) was normal. On slit-lamp examination, his iris presented an amelanotic, elevated lesion, located between the 5 and 10 o'clock positions, with visible intratumoral vascularization (Fig. 1A). Gonioscopy revealed iridocorneal angle invasion extending from the 5 to 11 o'clock positions, with the tumor adherent to the corneal endothelium, without pigment seeding in the iridocorneal angle away from the tumor. Fundus examination was normal. High-frequency ultrasonography confirmed the presence of an iris lesion with 6.8-mm maximal diameter and 2.1-mm thickness, with ciliary body extension (Fig. 2). Based on these findings, the diagnosis of amelanotic iris melanoma was made. Liver ultrasonography was normal. After

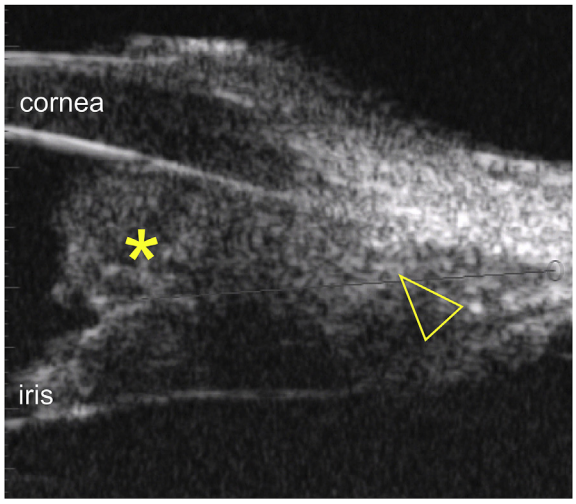

Fig. 2. High-frequency 50-MHz ultrasonography of the anterior segment acquired in 2001 showing the iris melanoma at diagnosis (yellow star), extending to the ciliary body, with iridocorneal angle invasion (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

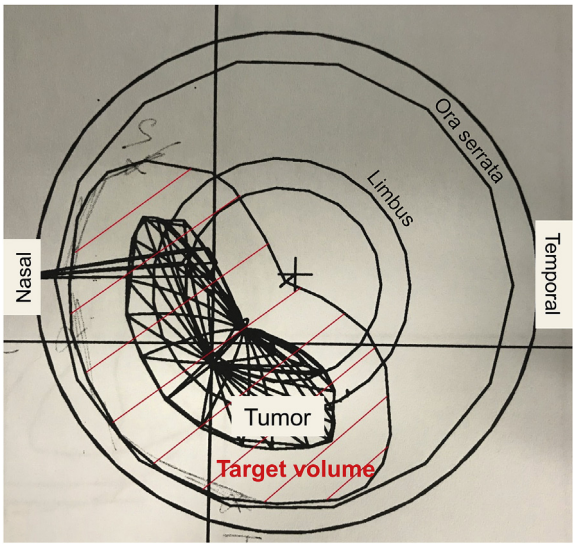

Fig. 3. Treatment plan for the proton-beam therapy performed in 2001. The target volume comprised the tumor expanded by 2.5-mm margins (red hatch marks). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

multidisciplinary evaluation, proton-beam irradiation was indicated. Sixty Gray were delivered over four sessions on the tumor volume expanded by a 2.5-mm safety margin (Fig. 3).

Over the next 10 years, the patient was evaluated every 3 months, alternatively by the ocular oncologist and the referring ophthalmologist. Ocular high-frequency ultrasonography was performed every 6 months for 2 years, and annually thereafter. Systemic follow-up by hepatic ultrasonography every 6 months was also conducted. A progressive decrease in tumor volume was observed over the post-treatment visits. The lesion became atrophic and avascular. Band keratopathy developed (Fig. 1B, red arrow), as a consequence of corneal compression by the tumor. Over the next years, no objective changes were noted on biomicropscopy, gonioscopy or high-frequency ultrasonography. Liver ultrasonography did not detect any lesion. Ten years after treatment, the follow-up was simplified and consisted in a yearly visit with the referring ophthalmologist.

In 2017 (16 years after the initial management), the patient was referred for suspected local recurrence. He presented a painful left eye, with elevated IOP of 37 mmHg despite maximal topical IOP-lowering treatment. Visual acuity was 20/20. On biomicroscopy, his iris presented a new amelanotic, elevated and vascularized lesion, between the 1 and 4 o'clock positions (Fig. 1C). Gonioscopy showed tumor extension along the iridocorneal angle from 1 to 6 o'clock. The diagnosis of recurrent amelanotic iris melanoma was made. Abdominal ultrasonography was normal. Enucleation was indicated due to the contraindication of a second anterior segment proton-beam irradiation, and

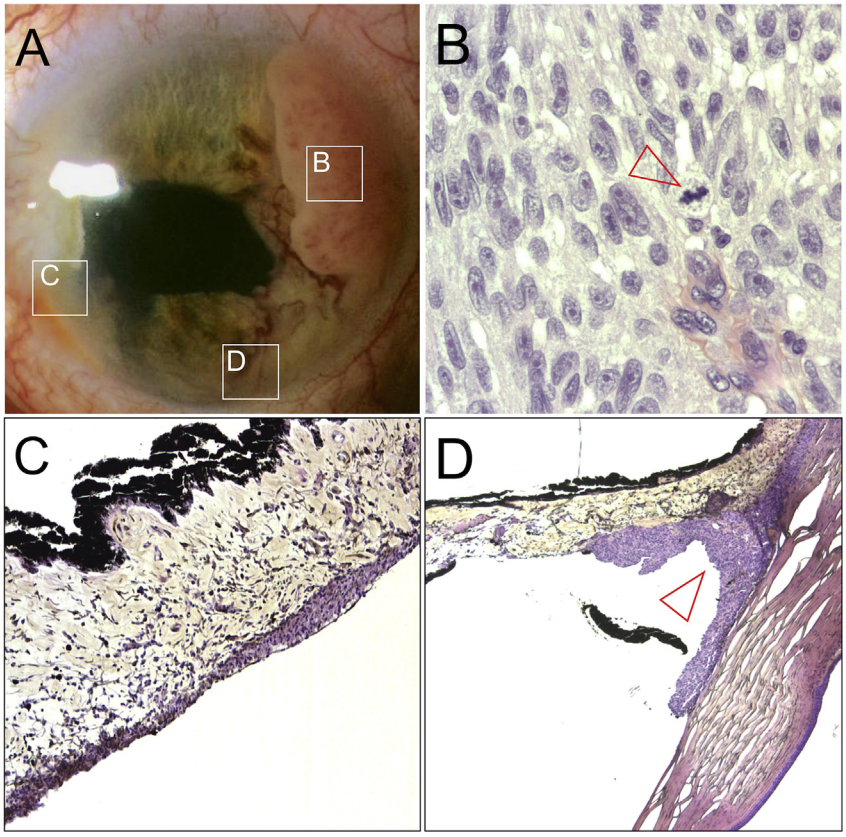

Fig. 4. Clinical and histopathological characteristics of distant relapsing iris melanoma. A. Inlets localizing the histopathological sections after enucleation for suspected recurrence of iris amelanotic iris melanoma in the temporal sector, sixteen years after the initial management by proton-beam therapy. B. Temporally, the histopathological evaluation confirmed the diagnosis of relapsing iris melanoma, with spindle cells, moderate cytonuclear atypia, enlarged nucleoli and mitoses (red arrow) (HES x400). C. Nasally, the histopathological examination revealed a scar corresponding to the initial tumor treated by proton beam therapy, showing residual melanocytes without atypia, fibrous histiocytic thickening of the underlying iris, and melanophages (HES x100). D. Along the iridocorneal angle there was an infiltration by melanocytic non-pigmented tumor cells (red arrow), extending from the post-radiation fibrotic scar at the 9 o'clock position and in continuity with the large iris mass located from 1 to 6 o'clock positions (HES x 50). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

because of the absence of local tumor control after the initial irradiation.

Histopathological analysis confirmed the diagnosis of amelanotic iris melanoma with predominant spindle-cell type (Fig. 4B). The recurrent lesion extended into the anterior chamber, iridocorneal angle and ciliary body from 1 to 6 o'clock positions, and its maximal thickness was 3.5 mm. In this active tumor, melanocytes presented cytonuclear atypia, prominent nucleoli and numerous mitotic figures. The mitotic rate was 9 mitoses per 10 high-power fields (HPF). Noticeably, a 0.1–0.2 mm thick infiltration of the iridocorneal angle by active tumor extended from this lesion to the 9 o'clock position (Fig. 4D). A fibrous thickening of the iris was found from the 6 to 11 o'clock positions corresponding to the post-irradiation scar (Fig. 4C). Molecular genetic analysis (array comparative genomic hybridization) of the tumor showed a partial loss of chromosome 3 which included the *BAP1* gene. Immunohistochemistry with BAP1 labelling showed preserved nuclear expression of BAP1 in tumor cells (Supplementary Fig. 1).

2. Discussion

This case report illustrates the possibility of late relapse of iris melanoma after irradiation, and the need for prolonged follow-up after treatment. The patient presented an apparent distant relapse of iris melanoma, that likely resulted from microscopic infiltration along the iridocorneal angle connecting the site of the initial tumor with the relapse, as evidenced by the histopathological analysis. This infiltration had not been detected during ocular examination for 16 years, and its exact progression pattern is not known. It may have recurred from outside the margins of the irradiated target volume, or from the initial ciliary body involvement, in a pattern similar to ring melanoma. High-frequency ultrasonography could possibly have detected early signs of relapse not visible on biomicroscopy, such as infiltration of the ciliary body but unfortunately this imaging follow-up was discontinued 10 years after the initial diagnosis.

The long duration from proton therapy to recurrence suggests that a very low number of malignant cells had survived irradiation. Moreover, the slow development of the recurrent tumor is consistent with the preserved nuclear expression of BAP1, as recently reported by van Poppelen and colleagues.[11] These authors observed preserved nuclear BAP1 expression in 21 out of 30 iris melanoma cases (70%), and a longer disease-free survival in those patients, although the difference failed to reach statistical significance due to the limited size of the study population.

Proton-beam therapy for iris melanoma provides excellent local tumor control and ocular preservation. Several reports indicate that recurrence after proton therapy is uncommon.[12–15] No prospective study estimating the recurrence rate of iris melanoma has been reported to date. In particular, iris melanoma was an exclusion criteria in the prospective Collaborative Ocular Melanoma Study assessing the long-term outcomes of uveal melanoma.[16] Several retrospective series have analyzed the incidence of local recurrence after iris melanoma.[4,5,10,13,17–20] Findings from the three most recent studies are detailed below. Noticeably, the reported low rate of local relapse may be underestimated in the literature because studies do not typically span between 15 and 20 years after the initial treatment.

Shields et al. studied 432 cases of iris melanomas with a median follow-up of 4.4 years and classified them according to the 8th edition of the American Joint Committee on Cancer Classification (T1, limited to the iris; T2, confluent or extending to the ciliary body, choroid of both; T3, scleral extension and T4 extrascleral extension).[5] The overall risk of local relapse was 16.8% at 10-year. This risk was 15.0% for T1 tumors and 20.4% for T2 tumors, whereas T3 and T4 categories were not evaluable due to small cohorts. Using multivariate analysis, the sole predictor of local recurrence was T4 category, and predictors of secondary enucleation included diffuse tumor configuration, tumor involving the entire iris, secondary glaucoma and local recurrence.

Recently, Thariat et al. identified 5 local relapses among 107 patients with iris melanoma treated by proton therapy (5-year cumulative

incidence: 7.9%).[20] All relapsing patients presented trabecular involvement at diagnosis. Relapses occurred outside the treatment field in 4 patients and involved the iridocorneal angle in 1 patient. This finding suggests that microscopic extension might have been underestimated, as observed in the present case. Interestingly, all recurrences occurred within a median of 36 months (range, 13–60 months), with a median follow-up of 49 months. The histological subtype did not influence the risk of recurrence, but diffuse forms and trabecular involvement at diagnosis were associated with a higher risk of recurrence.

In a subset analysis of 160 patients with iris melanoma, the Ocular Oncology Task Force identified 5 local recurrences (constituting a recurrence rate of 3.1%), over a median follow-up of 3.7 years.[19] However, risk factors for local relapses were not investigated.

In a 66-months-median-follow-up study of 150 patients treated for iris melanoma with proton-beam therapy, Sandinha et al. observed 8 cases of local recurrences.[17] According to authors, most recurrences developed because the extent of diffuse tumors had been underestimated at initial treatment. Seven relapses were marginal and one occurred within the irradiated field. As a result, authors indicate that their irradiation protocol was updated to include wider safety margins. Moreover, whole anterior segment irradiation was indicated for diffuse iris melanomas, as previously reported.[15] Whole anterior segment irradiation of diffuse forms allows to achieve successful local tumor control, despite the high rate of complications, including visual acuity loss, cataract, angle-closure glaucoma, tear-film instability and stem-cell failure.[14,15] In the present case, whole anterior segment irradiation could possibly have prevented this late relapse since exact tumor margins are difficult to identify especially in the iridocorneal angle and ciliary body. However, such therapy would have placed the patient at risk for severe post-irradiation complications.

In summary, local recurrences of iris melanoma are uncommon but may develop more than a decade after initial management, as illustrated by this report. Lifelong clinical follow-up with biomicroscopy, gonioscopy and high-frequency ultrasonography should be maintained, to detect relapses at early stages.

Patient consent

The patient consented to publication of the case in writing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2018.12.007.

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