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Late Solitary Extraocular Recurrence from Previously Resected Iris Melanoma

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Short title: Late extraocular relapse of previously excised iris melanoma

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ABSTRACT

Purpose

To report on cases of late extraocular relapse of previously resected iris melanoma, without concurrent intraocular recurrence.

Design

Retrospective case series.

Methods

A retrospective chart review of 4 patients diagnosed with late subconjunctival relapse of previously resected iris melanoma.

Results

Three females and one male underwent iris tumour resection and presented to our service with suspicious conjunctival lesions at a median of 22 years later (mean: 21). None showed intraocular relapse. Treatment of the conjunctival tumours included excisional biopsy (n=4) followed by cryotherapy (n=3) and/or brachytherapy (n=3). In all cases, histopathology confirmed malignant melanoma, with no intraepithelial component or associated melanosis. Genetic sequencing (n=3) showed wildtype *BRAF* and *NRAS* in all. *GNA11* mutation was found in 1 case. On array CGH (n=3), gain of 6p was found in 2 cases and gain of 8 in 2. Overall, findings were strongly suggestive of a diagnosis of late extraocular relapse from previously resected iris melanoma. In a median of 2.5 years (mean: 7.7) from the subconjunctival relapse, no further episodes of intra/extraocular recurrence were recorded, and all patients were free from distant metastasis.

Conclusions

Patients undergoing iris melanoma resection are at risk of developing late solitary extraocular relapse even over 30 years after surgery. In the absence of an intraocular component, diagnosis may be challenging, as tumours mimic a primary conjunctival lesion. Management by excisional biopsy followed by adjuvant therapy was successful, and histopathology and genetic analysis supported a diagnosis of extraocular uveal tumour spread rather than a primary conjunctival tumour.

INTRODUCTION

Uveal melanoma is a rare malignancy and iris melanoma is the rarest variant, accounting for 2-3% of cases.[1,2] Compared to choroidal and ciliary body melanoma, iris melanoma is associated with better prognosis, with 5% of patients estimated to develop metastasis within 10 years.[1] Traditionally, the majority of iris melanoma cases were treated by tumour resection or enucleation.[3–5] However, enucleation was generally abandoned as a primary modality for this indication, reserved only for cases associated with a circumferential drainage angle component ("ring melanoma") or extraocular extension, and tumour resection, which was a common therapeutic approach in the second half of the 20th century, was largely replaced at the turn of the century with conservative radiotherapy.[6–12] Over 80% of such cases are now treated by plaque brachytherapy or proton beam radiotherapy,[13] especially as iris melanoma resection requires management of long-term postoperative complications.[14,15]

It is estimated that 15% of uveal melanoma patients develop extraocular tumour extension,[16] also, though in lower rates, from iris melanoma.[1,17] When extraocular extension of untreated iris melanoma occurs it is usually continuous with the intraocular iris mass. In resected cases, the recurrence most often occurs at the edge of the surgical margin. Herein we report the diagnosis and management of a series of 4 cases of late solitary extraocular iris melanoma recurrence following resection up to several decades previously.

Summary of Cases

The study was approved by the Moorfields Eye Hospital institutional review board (reference number: 16/036) in accordance with the tenets of the Declaration of Helsinki. The cohort included 3 females and 1 male patient. The median age at which the original iris tumour was treated (elsewhere in 3 cases) by means of resection was 28 years old (mean: 36, range: 26-60; **Table 1**). The median interval from iris tumour resection to presentation to our service with a suspicious conjunctival lesion was 22 years (mean: 21, range: 3-36).

Presentation

Of the 4 patients, 2 presented to our service with a suspicious conjunctival lesion and history of a previously excised iris tumour of unknown nature. No supporting medical documents were available in these 2 cases. Of the remaining 2, one patient initially presented to our service with an iris tumour, underwent surgical resection and the diagnosis was iris melanoma. Three years after initial diagnosis and treatment the patient presented with a suspicious conjunctival lesion. The final patient first presented to our service with an intraocular iris melanoma relapse following resection elsewhere for which she was treated with ruthenium plaque brachytherapy. Two years after plaque brachytherapy the patient presented with a suspicious conjunctival lesion with no intraocular component.

Clinical findings and management

At our evaluation, best-corrected visual acuity of the involved eye at presentation with the suspicious conjunctival lesion was 20/20 in 2 cases, 20/30 in another and light perception (LP) in a fourth case, and median intraocular pressure (IOP) was 14mmHg (mean: 13, range: 12-14). Examination of the suspicious conjunctival lesions revealed a single small (<5mm in diameter) red lesion in one case, large single multilobed pink lesion in another, and several small pigmented lesions in 2 cases. Lesions in all cases were located on the bulbar conjunctiva on the side of the resected iris in the same quadrant as the iris melanoma. A concurrent intraocular tumour relapse was not present in any of the cases. Surgical management of the suspicious conjunctival lesions included excisional biopsy followed by cryotherapy in 3 cases (2014-2016), and excisional biopsy only in one case (1991).

Histopathology and genetic studies

Histopathology of the conjunctival specimens revealed all cases to be invasive malignant melanoma, with no intraepithelial component and no associated melanosis with atypia. Three cases were reported to be incompletely excised at the deep margin. In one case (1991), margin involvement was not indicated (further histopathologic evaluation was not possible). Of the 4 cases, samples from 3 were available for genetic mutation analysis (**Table 2** and **Supplemental Digital Table 1**), including *GNAQ* and *GNA11*,[18,19] and *BRAF* and *NRAS*.[20] The latter were found to be wildtype in all cases evaluated, whereas a mutation in *GNA11*

Q209 was found in a single case. Further array CGH analysis[21,22] was performed on the 3 cases (via whole genome amplification in 2 cases): in 1 case changes were not detected, in the other 2, altered chromosomes included 6p+ in both, 8p in 1 and 8p and 8q in 1. Further genetic analysis findings are shown in **Table 2**.

Adjuvant therapy and outcome

Three patients were treated with adjuvant strontium radiotherapy, one declined. In a median follow-up of 2.5 years (mean: 7.7, range: 0.8-25.0) from presentation with the extraocular relapse, no cases of intra- or extraocular relapse were recorded. Systemic surveillance was performed by an expert medical oncologist, radiographically by means of abdominal ultrasound every 6 months, and all were found to be free from distant metastatic spread.

Case 1

A 43-year-old white female was referred to our service in March 2011 due to spontaneous hyphaema in the left eye associated with elevated IOP and history of left iris melanoma resection, performed elsewhere 15 years earlier. Supporting documents confirmed the primary diagnosis and treatment, indicating there was no postoperative residual mass. On our examination, BCVA was 20/30 in each eye. The right eye was normal. In the left eye there was evidence of sector iridectomy temporally. Inferonasally was an intraocular tan-coloured elevated iris mass lesion that encompassed 2 clock hours (**Fig. 1**). No hyphaema was present and IOP was 17mmHg. Gonioscopy revealed the mass was reaching the iris root but was not spreading circumferentially into the angle, and showed no seeding into the angle. Transpupillary transillumination failed to demonstrate a ciliary body component, and fundus examination was normal. The patient underwent ruthenium plaque radiotherapy (total of 80Gy) for the intraocular relapse and on follow-up examinations, the tumour had regressed, no iris neovascularization developed and IOP remained within normal limits. Two years after brachytherapy, the patient presented with a red 4x4mm lesion in the supero-temporal aspect of the left bulbar conjunctiva with an associated feeder vessel. BCVA was 20/30, IOP 14mmHg and there were no signs of intraocular tumour relapse (ruled out by means of gonioscopy, B-scan ultrasonography (US) and ultrasound biomicroscopy (UBM)). Topical maxitrol drops did not resolve the lesion, so an excisional biopsy was undertaken. On histopathology, a nodule of malignant melanoma comprising epithelioid cells with moderate pleomorphism was identified. The tumour was present in the stroma, without involvement of the overlying epithelium and was incompletely excised at the deep margin. There was no evidence of melanosis with atypia. Immunohistochemistry was positive for Melan A and HMB45 and failed to demonstrate an intraepithelial component. Genetic sequencing performed on DNA extracted from the extraocular sample found *BRAF* and *NRAS* to be wildtype. *GNAQ* and *GNA11* were also found to be wildtype. On array CGH

analysis, trisomy 6p and 8p were found. The diagnosis was a late extraocular relapse, with no intraocular component, of a previously resected iris melanoma, and the patient was treated with adjuvant strontium radiotherapy (total of 50Gy). During follow-up, no intra- or extraocular relapses were recorded. At the last visit, 40 months after treatment of the extraocular recurrence, the eye was tumour-free, BCVA was counting fingers, IOP 26mmHg under Cosopt BID, and brunescent cataract was present. Systemically, she remains free from distant metastatic spread.

Case 2

An 87-year-old white male patient was referred to our service in November 2014 due to a large pink conjunctival mass in the left eye, that he first noticed 8 months earlier. His medical history was positive for a basal cell carcinoma, previously excised from his forehead, and, per patient anamnesis, a left iris tumour previously excised elsewhere 27 years earlier. No supporting medical documents were available. On examination, BCVA were 20/60 in the right eye and LP in the left. Anterior and posterior segments of the right eye were unremarkable, but nuclear sclerosis cataract. The left eye had a multilobed, vascularized, non-pigmented conjunctival mass lesion at the infero-nasal limbus, encroaching over 4 clock hours **(Fig. 2)**. IOP was 14 mmHg, there was a large inferonasal iris defect and advanced cataract, precluding fundus view. Gonioscopy, US, UBM and anterior chamber optical coherence tomography (AC-OCT) ruled out the presence of an intraocular tumour, and computed tomography failed to demonstrate an orbital mass. The patient refused excisional biopsy, hence was given interferon α-2b eye drops, offered as a conservative alternative. Two months after initial topical therapy the conjunctival tumour increased in size. Excisional biopsy, alcohol epitheliectomy, cryotherapy and placement of an amniotic membrane graft were performed. On histopathology, a large nodule of malignant melanoma was found, located within the subepithelial stroma, with no junctional component. Morphology was predominantly spindle cell, with minimal melanin pigmentation. The tumour was shown to be incompletely excised at the deep surgical margin, and there was no evidence for melanosis with atypia. Immunohistochemistry was strongly and diffusely positive for both Melan A and HMB45, and AE1/AE3 confirmed there was no junctional component. On genetic sequencing, a mutation in *GNA11*, exon 5, codon 209 was found. All others were wildtype. On array CGH analysis, gain of 6p, and trisomy 8 were detected. Given the patient's history and laboratory findings, the diagnosis was of an extraocular relapse of an iris melanoma excised many years earlier. The patient declined further adjuvant ocular treatments and on last follow-up visit, 18 months after initial presentation to our service, BCVA was LP, IOP 21mmHg, the conjunctiva healed, without intra- or extraocular relapse. Systemically the patient was clear of metastasis.

Case 3

A 64-year-old white female noticed new conjunctival lesions in her right eye and was referred in April 2016 to our service for evaluation and management. History was positive for an iris tumour resection in the same eye, performed elsewhere 36 years earlier. She had no supporting medical documents, and was not aware of the precise original tissue diagnosis, but stated that it was a cancer excised from the iris during pregnancy, and that she has been clear since. General medical history was positive only for sleep apnoea. On examination, BCVA was 20/20 in each eye. The left eye was structurally normal. In the right eye there was an inferior broad iridectomy. On the conjunctiva there were 3 discrete pigmented spots adjacent to the original area of corneal incision **(Fig. 3)**. Two of these were mobile and one appeared to be deeper. IOP was 12mmHg, gonioscopy showed normal ciliary processes with no other ciliary body lesion, and US and AC-OCT failed to demonstrate an intraocular lesion. The lesions were excised with adjuvant cryotherapy and on histopathology, all specimens showed similar features – fairly well-demarcated spindle cell malignant melanoma with modest melanin pigmentation. Excision was incomplete at the deep margin in all 3 specimens and, in all; the conjunctival surface epithelium was not involved. There was no evidence of melanosis with atypia and immunohistochemistry was strongly positive for Melan A, with modest positivity for HMB45. Additional immunohistochemistry staining for CD34 delineated an apparent structure surrounding the lesions, raising the possibility that the tumour was within lymphatic channels. Further staining however with D2-40 was negative. Genetic sequencing performed on DNA extracted from the extraocular sample found *BRAF* and *NRAS* to be wildtype. *GNAQ* and *GNA11* were also wildtype. On array CGH analysis, no changes were detected, likely due to technical difficulties associated with the small size of the lesion. Taken together, the diagnosis was of a late extraocular relapse of a previously resected iris melanoma and the patient was further treated with adjuvant therapy strontium radiotherapy (total of 50Gy). On last follow-up visit, 10 months after presentation, BCVA was 20/20, IOP 13mmHg and no intra- or extraocular relapse was noticed. Systemically, the patient remains clear.

Case 4

A 28-year-old white woman patient was referred in January 1988 with an iris mass in the right eye. BCVA was 20/20 in both eyes and examination of the left eye was unremarkable. Examination of the right eye revealed a pigmented iris tumour, occupying the inferonasal quadrant, extending from the angle to the mid-pupillary zone and anteriorly to the cornea endothelium, and measuring 5x5 mm **(Fig. 4)**. IOP was 16 mmHg and fundoscopy was normal. The patient underwent iridocyclectomy, and histopathology indicated that the tumour was a malignant spindle cell melanoma. On follow-up visit in January 1991, the patient presented with new sub-conjunctival pigmented lesions on the nasal aspect of the

bulbar conjunctiva, but with no intraocular component (ruled out by means of gonioscopy and US). She underwent a biopsy, which showed spindle melanoma cells arranged in solid coves within lymphatic vessels. The working diagnosis was late extraocular relapse of a previously excised iris melanoma and the patient was treated with adjuvant strontium radiotherapy (total of 50Gy). She was further followed-up for 25 years, last seen in August 2016, at which visit BCVA was 20/30, IOP 17mmHg, eye tumour-free, and systemically she was free from metastasis.

DISCUSSION

Melanoma of the iris is a relatively rare diagnosis that has a better local and systemic prognosis compared to ocular melanoma at other sites. Treatments used have included surgical resection and radiotherapy with plaque applicators or proton beam. Local relapse is encountered infrequently, and if it occurs tends to involve the margin of the original tumour. In the current study, we report the previously undocumented finding that patients who previously underwent iris melanoma resection are at risk of developing late extraocular tumour relapse with no concurrent intraocular component.

This form of extraocular recurrence may mimic a primary conjunctival tumour and surprisingly the onset can be decades after the primary iris tumour resection. Surgical resection has largely been replaced by radiotherapy,[13] but there are many patients under long-term follow up after iridectomy or iridocyclectomy for melanoma, so recognition of late subconjunctival relapse is of the utmost importance for the general ophthalmologist, ocular oncologist and pathologist.

In the literature, there are several publications on surgical resection of iris tumours, but none have reported the phenomenon of late conjunctival relapse in the absence of intraocular disease. Vail reviewed 244 cases of iridocyclectomy for iris and ciliary body tumours, presumably most were uveal melanomas, and did not report on any case of extraocular tumour relapse.[23] Similarly, Reese and Cleasby in their study on 63 iris melanoma cases that underwent iridectomy, did not encounter this complication.[3] Rones and Zimmerman reported on 125 iris melanoma cases that underwent iridectomy.[4] In their series they described 3 cases that developed extraocular relapse, but which also had a concurrent intraocular component. Daubner et al. monitored 20 iris melanoma cases for a mean time of 16.4 years after performing iridocyclectomy and found that 2 relapsed, but only intraocularly,[14] and no case of extraocular relapse was reported in a review by Müller on 70 resected iris malignant tumours (presumably most were uveal melanoma).[24] Shields et al. reported on 169 iris melanoma patients, 102 of which were treated by local resection.[1] Patients were followed-up for a mean of nearly 10 years, at which time no case of extraocular extension was found. Popovic et al. recently reviewed the literature,[13] comparing iris melanoma management outcomes after conservative radiotherapy versus surgical resection. The recurrence pattern described in the present study was not reported in their review, which included relatively recent studies (2001 and on). Altogether, we could not find in the literature any description of the complication herein reported of late extraocular subconjunctival recurrence from previously resected iris melanoma.

From a diagnostic perspective, the cases shown in this study were challenging, first at presentation, when only clinical data was at hand, and differential diagnosis included late relapse of a previously excised presumed iris melanoma versus a primary conjunctival lesion, and second, after histopathology assessment indicated the lesions were invasive

melanoma, to differentiate pathologically between the aetiology of an iris (late extraocular spread) or conjunctival (new primary) tumour. The long period between iris surgery and presentation with an ocular surface lesion, the presence of an ocular surface lesion in the absence of an active intraocular recurrence, and the lack of reports in the literature on this clinical entity, have led us in 2 of the cases (#1 and #2) to consider other possible ocular surface pathologies as the initial working diagnosis. Of note, in 2 cases, lesions were amelanotic, in case #1, in contrast to a previously pigmented intraocular relapse. However, all subconjunctival recurrences occurred in the same quadrant as the resected iris melanoma.

The alternative diagnosis of a primary iris and distinct primary conjunctival melanoma, has been described but is rare.[25] In this regard, histopathology and immunohistochemistry were found to be useful diagnostic tools, ruling out the presence of melanosis with atypia, a common predisposing condition for the development of primary conjunctival melanoma, and in showing there was no junctional component,[26] suggesting that tumour origin was from a previously excised iris melanoma.

To further characterize the lesions and strengthen our hypothesis regarding the origin of the melanomas, we undertook genetic testing using sequencing and array CGH analyses techniques. Interestingly, *BRAF* and *NRAS*, both mutations known to be associated with conjunctival melanoma,[27,28] were found to be wildtype, likely excluding this diagnosis. In addition, of the 3 cases tested for common uveal melanoma mutations,[18,19,22] *GNA11* was found in 1 case as well as partial trisomy 6p and 8q. In another case partial trisomy 6p was found. A third case was wildtype for all tested genes and the array profile was flat, most likely as a result of contaminating normal tissue and the small size of the lesion. Taken together, genetic analysis results support a uveal melanoma origin and overall a diagnosis of late extraocular relapse of a previously resected iris melanoma.

In terms of the mechanism of developing late extraocular spread with no concurrent intraocular component, one possibility is implantation of melanoma cells into the conjunctiva during surgical removal. Another is circulating melanoma cells in the anterior chamber that after tumour removal have lodged into the surgical site and grown over time. A third possibility is post-surgery tumour cell migration via lymphatic vessels. Only little is known regarding intraocular lymphatics, but accumulating evidence suggests the presence of lymphatic structures in the eye.[29] However, in case #3, despite positive staining for CD34, negative staining for D2-40 likely ruled out this option,[30] and in case #4, further tissue sample for immunostaining was not available, precluding a definite diagnosis. Whilst the Zimmerman hypothesis[31] for enucleation surgery for intraocular melanomas has been abandoned,[32] it is possible that resection surgery for iris melanoma plays a role in extraocular (subconjunctival) recurrence.

The interval from iris tumour resection to presentation with an extraocular relapse ranged widely, 3-36 years, with a mean time of 21 years (median: 22 years). Of note, 3 out of 4 of the extraocular tumours comprised spindle cell melanoma, which are less aggressive and grow in slower rate compared to epithelioid cells.[33] Interestingly, a single case of epithelioid cell melanoma relapsed 17 years after iris tumour resection, whereas a case of spindle cell melanoma relapsed 3 years after primary resection. In comparison, intraocular recurrence after iris tumour resection, an infrequent event, occurred in 4 (8%) cases as reported by Conway et al., in a mean time of 3.25 years (range: 1-7) from initial surgery.[34] Distant metastasis from iris melanoma, also an uncommon event, occurred in 9 (5%) cases according to Shields et al., at a mean interval of 5 years (median<4 years).[1] We have no explanation to the significantly longer time span to develop late subconjunctival relapse in the present case series as compared to the time to develop intraocular relapse or distant metastasis in the abovementioned studies.

Management of extraocular recurrence by excisional biopsy followed by adjuvant therapy (cryotherapy (n=3) and strontium radiotherapy (n=3)) was an efficient approach in these cases. After an average of nearly 8 years, all patients were tumour, extraocular and distant metastasis free. Extraocular spread of uveal melanoma was found to correlate with increased mortality from metastasis.[16] However, in the present study it did not predispose patients to develop distant systemic spread, findings that coincide with the known low iris melanoma metastasis rate.[1]

Limitations of the study include its retrospective design and small cohort size. In terms of ruling out an intraocular tumour component at time of extraocular presentation, investigations were tailored to the clinical features. Supportive tests such as ultrasound and UBM were completed in the majority of cases to reasonably rule out the possibility of a contiguous intraocular recurrence.

In summary, patients that underwent previous iris melanoma resection are at risk of developing solitary extraocular (subconjunctival) recurrence even over 30 years after primary surgery. In the absence of a concurrent active intraocular component, initial diagnosis can be challenging, as lesions mimic a primary conjunctival tumour. General ophthalmologists and ocular oncologists should be aware of this mode of presentation. Management by excisional biopsy followed by adjuvant therapy was found to be useful in reaching tumour control and histopathology, immunohistochemistry and genetic analysis were required to complete the diagnosis, and rule out a new primary conjunctival melanoma. This report highlights the need for long-term follow-up for patients that previously underwent iris melanoma resection.

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REFERENCES

1. Shields CL, Shields JA, Materin M, Gershenbaum E, Singh AD, Smith A. Iris melanoma: Risk factors for metastasis in 169 consecutive patients. *Ophthalmology*. 2001;108(1):172-178.

2. Jensen OA. Malignant melanomas of the human uvea: 25-year follow-up of cases in Denmark, 1943--1952. *Acta Ophthalmol*. 1982;60(2):161-182.

3. Reese AB, Cleasby GW. The treatment of iris melanoma. *Am J Ophthalmol*. 1959;47(5 Pt 2):118-125.

4. RONES B, ZIMMERMAN LE. The prognosis of primary tumors of the iris treated by iridectomy. *AMA Arch Ophthalmol*. 1958;60(2):193-205.

5. STALLARD HB. Surgery of malignant melanoma of the iris. *Br J Ophthalmol*. 1951;35(12):774-783.

6. Damato B, Kacperek A, Chopra M, Sheen MA, Campbell IR, Errington RD. Proton beam radiotherapy of iris melanoma. *Int J Radiat Oncol Biol Phys*. 2005;63(1):109-115.

7. Fernandes BF, Krema H, Fulda E, et al. Management of Iris Melanomas With 125 Iodine Plaque Radiotherapy. *Am J Ophthalmol*. 2010;149(1):70-76.

8. Finger PT. Plaque radiation therapy for malignant melanoma of the iris and ciliary body. *Am J Ophthalmol*. 2001;132(3):328-335.

9. Lumbroso-Le Rouic L, Delacroix S, Dendale R, et al. Proton beam therapy for iris melanomas. *Eye*. 2006;20(11):1300-1305.

10. Razzaq L, Keunen JEE, Schalij-Delfos NE, Creutzberg CL, Ketelaars M, De Keizer RJW. Ruthenium plaque radiation therapy for iris and iridociliary melanomas. *Acta Ophthalmol*. 2012;90(3):291-296.

11. Shields CL, Shields JA, De Potter P, Singh AD, Hernandez C, Brady LW. Treatment of non-resectable malignant iris tumours with custom designed plaque radiotherapy. *Br J Ophthalmol*. 1995;79(4):306-312.

12. Tsimpida M, Hungerford J, Arora A, Cohen V. Plaque radiotherapy treatment with ruthenium-106 for iris malignant melanoma. *Eye (Lond)*. 2011;25(12):1607-1611.

13. Popovic M, Ahmed IIK, DiGiovanni J, Shields CL. Radiotherapeutic and Surgical Management of Iris Melanoma: A Review. *Surv Ophthalmol*. 2017;62(3):302-311.

14. Daubner D, Prokosch V, Busse H, Stupp T. [Long-term results of iridocyclectomy for iris tumours]. *Klin Monbl Augenheilkd*. 2008;225(12):1045-1050.

15. Rospond-Kubiak I, Damato B. The surgical approach to the management of anterior uveal melanomas. *Eye (Lond)*. 2014;28(6):741-747.

16. Coupland SE, Campbell I, Damato B. Routes of Extraocular Extension of Uveal Melanoma. Risk Factors and Influence on Survival Probability. *Ophthalmology*. 2008;115(10):1778-1785.

17. Shields CL, Kaliki S, Shah SU, Luo W, Furuta M, Shields JA. Iris melanoma: Features and prognosis in 317 children and adults. *J AAPOS*. 2012;16(1):10-16.

18. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA 11in uveal melanoma. *N Engl J Med*. 2010;363(23):2191-2199.

19. Onken MD, Worley LA, Long MD, et al. Oncogenic mutations in GNAQ occur early in uveal melanoma. *Investig Ophthalmol Vis Sci*. 2008;49(12):5230-5234.

20. Edwards RH, Ward MR, Wu H, et al. Absence of BRAF mutations in UV-protected mucosal melanomas. *J Med Genet*. 2004;41(4):270-272.

21. Salawu A, Ul-Hassan A, Hammond D, Fernando M, Reed M, Sisley K. High Quality Genomic Copy Number Data from Archival Formalin-Fixed Paraffin-Embedded Leiomyosarcoma: Optimisation of Universal Linkage System Labelling. Shipley J, ed. *PLoS One*. 2012;7(11):e50415.

22. Hammond DW, Al-Shammari NSD, Danson S, Jacques R, Rennie IG, Sisley K. High-resolution array CGH analysis identifies regional deletions and amplifications of chromosome 8 in uveal melanoma. *Investig Ophthalmol Vis Sci*. 2015;56(6):3460-3466.

23. Vail DT. Iridocyclectomy. A review. Gleanings from the literature. *Am J Ophthalmol*. 1971;71(1 Pt 2):161-168.

24. Müller HK. [Partial excision of the iris and ciliary body]. *Doc Ophthalmol*. 1969;26:679-697.

25. Fabian ID, Thaung C, Cohen VML. A conjunctival and choroidal melanoma in the same eye: report of two cases. *Graefes Arch Clin Exp Ophthalmol*. 2017;255:841-842.

26. Shields CL, Markowitz JS, Belinsky I, et al. Conjunctival Melanoma: Outcomes based on tumor origin in 382 consecutive Cases. *Ophthalmology*. 2011;118(2):389-395.

27. Spendlove HE, Damato BE, Humphreys J, Barker KT, Hiscott PS, Houlston RS. BRAF mutations are detectable in conjunctival but not uveal melanomas. *Melanoma Res*. 2004;14(6):449-452.

28. Griewank KG, Westekemper H, Murali R, et al. Conjunctival melanomas harbor BRAF and NRAS mutations and copy number changes similar to cutaneous and mucosal melanomas. *Clin Cancer Res*. 2013;19(12):3143-3152. doi:10.1158/1078-0432.CCR-13-0163.

29. Karpinich NO, Caron KM. Schlemm's canal: More than meets the eye, lymphatics in disguise. *J Clin Invest*. 2014;124(9):3701-3703.

30. Vermeulen, Harris AL, Dirix LY, Vermeulen PB. First international consensus on the methodology of lymphangiogenesis quantification in solid human tumours. *Br J Cancer*. 2006;95(12):1611-1625.

31. Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells. *Br J Ophthalmol*. 1978;62(6):420-425.

32. Singh AD, Rennie IG, Kivela T, Seregard S, Grossniklaus H. The Zimmerman-McLean-Foster hypothesis: 25 years later. *Br J Ophthalmol*. 2004;88(7):962-967.

33. Gass J, Donald M. Comparison of uveal melanoma growth rates with mitotic index and mortality. *Arch Ophthalmol*. 1985;103(7):924-931.

34. Conway RM, Chua WC, Qureshi C, Billson FA, Conway RM. Primary iris melanoma : diagnostic features and outcome of conservative surgical treatment. *Br J Ophthalmol*. 2001;85:848-854.

FIGURE LEGEND

Figure 1. Case 1. A 43-year-old female with an iris melanoma relapse (arrow) 15 years after primary iridectomy (**Top left**), shown on gonioscopy not to involve the iridocorneal angle (**Top center left**). Nine months following ruthenium plaque brachytherapy the intraocular melanoma completely regressed (**Top center right**). Two years after brachytherapy and 17 years after iridectomy, a red lesion was noticed on the temporal bulbar conjunctiva, distant from the intraocular relapse site (**Top right**). Following excisional biopsy, histopathology showed the lesion was invasive melanoma without involvement of the overlying epithelium (**Bottom left**; H&E), and immunohistochemistry was found to be positive for Melan A (**Bottom center left**) and HMB45 (**Bottom center right**). Following adjuvant strontium radiotherapy, after 40 months, the patient was tumour-free (**Bottom right**).

Figure 2. Case 2. An 87-year-old male with a pink conjunctival mass in the left eye, 27 years after left iris tumour resection (**Top left**). Two months following treatment with interferon α-2b eye drops the tumour has increased in size (**Top center**). Following excisional biopsy, histopathology showed the tumour was invasive melanoma without involvement of the overlying epithelium (**Top right**; H&E), and immunohistochemistry was found to be positive for Melan A (**Bottom left**), HMB45 (**Bottom center left**), and AE1/AE3 (**Bottom center right**). The patient refused adjuvant therapy; however 18 months after initial presentation to our service, no intra-or extraocular relapses were recorded (**Bottom right**).

Figure 3. Case 3. A 64-year-old female with pigmented conjunctival lesions in her right eye, 36 years following right iris tumour resection (**Top left** and **center**). Following excisional biopsy, histopathology showed the tumour was invasive melanoma without involvement of the overlying epithelium (**Top right**; H&E), and immunohistochemistry was found to be positive for Melan A (**Bottom left**), HMB45 (**Bottom center left**), and CD34 (**Bottom center right**). Following adjuvant strontium radiotherapy, after 10 months, the patient was tumour-free (**Bottom right**).

Figure 4. Case 4. A 28-year-old female presented in January 1988 with an iris tumour in the right eye (**Top left** and **center**; original illustrations from patient's medical chart). Following iridectomy, histopathology indicated the tumour was an iris melanoma (**Top right**; H&E). Three years later, the patient presented with new sub-conjunctival pigmented lesions (**Bottom left**; original illustration from patient's medical chart) and underwent tissue biopsy. Histopathology showed the tumour was invasive melanoma without involvement of the overlying epithelium (**Bottom center**; H&E). On last visit, 25 years after the extraocular relapse, the patient was tumour-free (**Bottom right**).