



Oral isotretinoin and topical retinoid use in a series of young patients with ocular melanoma

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ABSTRACT

Purpose: To describe the first series of six young uveal melanoma (UM) patients with oral isotretinoin and/or topical retinoid therapy prior to diagnosis.

Observations: The case series is based on clinical observations at our UM quaternary referral center. Six UM patient cases are reported, ages 16–44 years old. All had been using either oral (isotretinoin) and/or topical (tretinoin or tazarotene) retinoid treatment (3 months–10 years) prior to or at the time of diagnosis (3 of 6 cases). All patients had ocular complaints on presentation, and the onset of certain symptoms corresponded with the course of retinoids. Other potential risk factors or relevant history included Caucasian background, cone-rod dystrophy and active smoker status (Case 2), family history of UM and pregnancy at time of diagnosis (Case 3), past smoking and possible secondary Chernobyl exposure as a baby (Case 5). All patients were treated with proton beam radiotherapy and currently have no sign of recurrent or metastatic disease.

Conclusions and importance: Retinoid therapy has been linked to various benign and/or reversible effects on the anterior and posterior eye, though pathophysiology remains not well understood. Uveal melanoma (UM) is a rare cancer diagnosis in young adults. We report here the first case series of young UM patients with a history of retinoid use and ocular complaints. No causal link is claimed and further systematic epidemiologic and biologic study of retinoid therapy and ocular impact may provide additional relevant data, particularly in young ocular melanoma patients.

1. Introduction

Uveal melanoma (UM), a malignant eye tumor, is especially rare in young adults.^{1,2} Risk factors, particularly for young patients, are challenging to delineate, controversial, and may include genetic factors as well as other factors such as skin/eye color, family history, sun/snow burn history, artificial UV light or other unusual solar event exposure, tanning bed use, and arc welding exposure.^{2–5} UM is generally treated with radiation therapy with excellent local control overall. However, if metastatic disease develops the patient life expectancy is poor. There is significant interest in further research on genetic and environmental risk factors in this rare disease entity.

Isotretinoin, an oral retinoid commonly used for acne and other dermatologic conditions, has been linked to multiple adverse effects (AEs), including ocular risks.^{6–9} A comprehensive review of the National Registry of Drug-Induced Ocular Side Effects, FDA and WHO databases showed 2449 ocular AEs for patients on isotretinoin within days to up to a few years of therapy.^{6,7} 38 different isotretinoin-related ocular AEs were categorized (see Table 1), including: a) “certain”, i.e. abnormal meibomian gland secretion and atrophy, decreased dark adaptation, decreased vision, ocular discomfort, ocular sicca, photophobia, and teratogenic ocular abnormalities; and b) “probable”, i.e. decreased color vision (reversible), and permanent loss of dark adaptation. There were 25 reports of various retinal/choroidal pigment disturbances.

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Table 1
Reported Adverse Ocular Effects in Patients on Isotretinoin categorized by World Health organization definitions for certain, probable/likely, possible, and conditional/unclassifiable drug-related events.^{6,7}

“Certain” Isotretinoin-related adverse event		
Abnormal meibomian gland secretion	Decreased vision	Ocular discomfort
Blepharoconjunctivitis	Increased tear osmolarity	Ocular sicca
Corneal opacities	Keratitis	Photophobia
Decreased dark adaptation	Meibomian gland atrophy	Teratogenic ocular abnormalities
Decreased tolerance for contact lens wear	Myopia	
“Probable/Likely”		
Decreased color vision (reversible)	Loss of dark adaptation (permanent)	
“Possible”		
Corneal ulcers	Idiopathic intracranial hypertension with optic disc edema	Permanent sicca-like syndrome
Diplopia	Optic neuritis	Subconjunctival hemorrhage
Eyelid edema		
“Conditional/unclassifiable”		
Cataracts	Iritis	Retinal findings
Cortical blindness	Peripheral field loss	Scleritis
Decreased accommodation		

Specifically, reports have described anterior as well as posterior ocular effects with retinoid therapy including pigment disturbances,^{6,7} teratogenic eye anomalies,^{10–12} altered rod/cone function,^{13–16} and peripapillary changes.¹⁷ A recent study using optical coherent tomography (OCT) showed a significant increase in peripapillary choroidal thickness after patients received oral isotretinoin.¹⁷ Oral isotretinoin and topical tazarotene are contraindicated in pregnancy (class X) based on significant animal studies and teratogenic case reports, including ocular effects.^{9–12,18,19} Oral retinoids may have a potentially differential adverse effect in smokers versus nonsmokers.^{20,21} Topical retinoid and retinoid-antibiotic combinations have variable local/systemic absorption with a possible link to ocular side effects.²²

We describe the first case series of six young UM patients with reported retinoid use prior to diagnosis. Three of the six patients used oral isotretinoin therapy and three patients used topical only facial retinoid treatment (one with topical tazarotene and two with tretinoin).

Table 2
Patient/tumor characteristics and retinoid use details in young-aged uveal melanoma cases.

Case	Age/Gender	Tumor/Patient history/Baseline visual acuity	Ocular/facial symptoms and history	Type of Retinoid use ^a	Duration of Retinoid use	Using retinoid at dx
1	16 F	Ciliochoroidal melanoma, T3bN0M0 right ^b 20/25 OD, 20/20 OS	Blurry vision, ocular headache	Topical	10 mos	Yes
2	35 M	Ciliochoroidal melanoma, T3bN0M0 left, class 1B History of cone-rod dystrophy, active smoker 20/200 OU	Persistent light sensitivity, floaters, visual disturbance	Oral	3 mos	No
3	31 F	Choroidal macular-peripapillary melanoma, T1aN0M0 right ^b Family history OM; pregnant at time of diagnosis 20/30 OD, 20/20 OS	Visual disturbance, wavy lines, central vision changes Facial rash on retinoid	Topical	6 years	Yes
4	27 F	Choroidal melanoma, T2aN0M0 left, class 1A 20/20 OD, 20/25 OS	Tingling sensation in eyes Facial skin sensitivity on retinoid	Topical - tazarotene	10 years	Yes
5	32 M	Choroidal melanoma, T1aN0M0 left, multigene panel low risk Possible secondary Chernobyl exposure; past smoker 20/20 OU	Persistent dryness of eyes Temporary lip dryness on retinoid	Oral	6–12 mos	No
6	44 M	Ciliary body melanoma, T2bN0M0 left, class 1A, PRAME negative OD 20/25, 20/30 OS	Ocular nevus other eye Facial patches, dry lips on retinoid	Oral + Topical	3 years	No

^a Retinoid use was isotretinoin (oral) and tretinoin (topical) unless otherwise noted.

^b Pt chose to forgo biopsy.

2. Findings

The cases below were all seen and treated at the University of California San Francisco, a major quaternary referral center for UM patients for over four decades. Briefly, a total of 2731 UM patients have been treated, with approximately 14% aged 45 and younger. Over the past five years, the median age of diagnosis was 64 (range 16–90) and 53 patients were aged ≤ 45 (median 35, range 16–45 years old). For the overall group, 82% had posterior choroidal tumors and 14.5% had tumors involving the ciliary body; for the 45 and younger group, this was similar at 83% and 11%, respectively. The case observations below were noted recently during routine clinical work and a follow-up study is underway to analyze all young patient histories over the past five years. Consent was attained for all patients in this series.

The young UM patients below each had a history of retinoid therapy use, were aged 16 to 44 at diagnosis, three were male and three female, with tumors AJCC T stage T1 to T3b, and three tumors involving the ciliary body (see Table 2). Fig. 1 shows the fundus photographs.

2.1. Case 1

A 16-year old female presented with a large right superonasal ciliochoroidal melanoma. Initially at age 12, she had sudden onset of right eye floaters and noted headaches. She presented to her local emergency department and was noted to have a linear object in her right eye vitreous. On subsequent ophthalmology follow-up she was thought to have a normal exam and symptoms were attributed to ocular migraine.

The patient continued to have headaches intermittently and persistent floaters in the right eye. At age 15 she began retinoid-based acne medication, clinda-tretinoin 1.2–0.025% topical gel daily, for facial acne around her hairline in particular. She took a few weeks break intermittently, otherwise was on the medication daily for 10 months prior to UM diagnosis. During this period, she noted right eye blurry vision and daily headaches.

The patient had no history of ocular melanocytosis and no family history of BAP1 associated cancer or other cancers. The biological father was African-American, and the mother Caucasian/Native American. The patient had hazel eyes, had not had any significant sunburns/ski burns/unusual solar exposure, was not pregnant, and had no welding exposure.

Ophthalmology evaluation revealed pigmented cells in the vitreous and a large ciliochoroidal melanoma, measuring 12.7 mm × 10.7 mm x

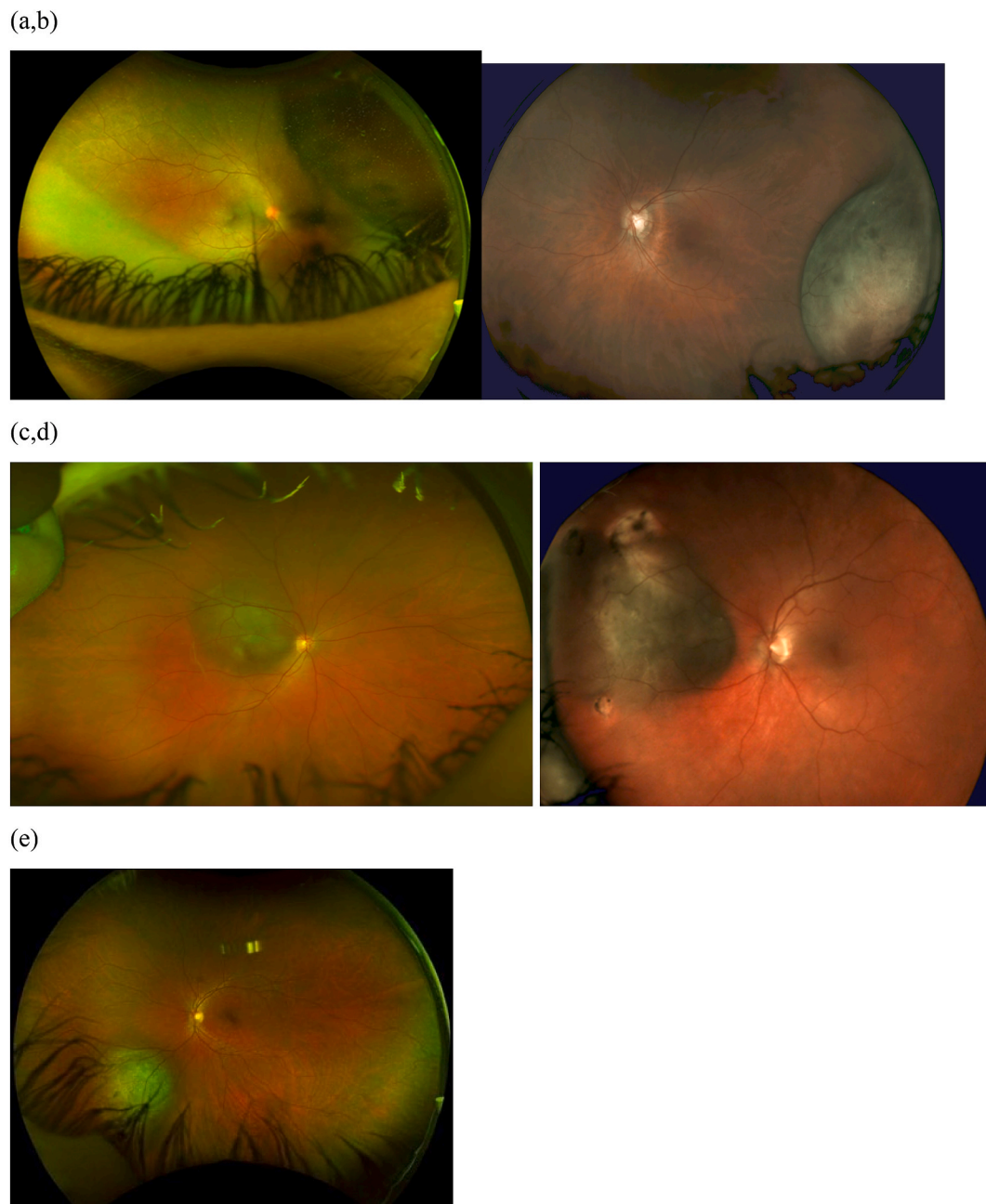


Fig. 1. Fundus photographs for (a) Case #1 - 16-year old (yo) female with a large right eye superonasal ciliochoroidal melanoma; (b) Case #2-35 yo male with a left ciliochoroidal melanoma (c) Case #3-31 yo female with a right peripapillary melanoma; (d) Case #4-27 yo female with a left eye choroidal melanoma; (e) Case #5-32 yo male with a left eye choroidal melanoma. Of note, Case #6 was a 44 yo male with a left anterior ciliary body melanoma, not seen on fundus photograph.

9.4 mm. Ultrasonography revealed that the mass had low internal reflectivity consistent with ocular melanoma; systemic evaluation was negative for metastatic disease. The family chose to forgo tumor biopsy. The patient underwent tantalum ring placement and completed proton beam radiation (PBRT).

2.2. Case 2

A 35-year old Caucasian male presented with a left ciliochoroidal melanoma in the setting of bilateral retinal cone-rod dystrophy since age 5.

About 2.5 years prior to UM diagnosis, he started to use daily oral isotretinoin for acne. About one month after starting, he began to experience light sensitivity and visual decline especially in bright light.

He also developed headaches and ocular tearing. After three months of oral isotretinoin, his light sensitivity increased and he discontinued the medication. Unfortunately, significant light sensitivity persisted despite discontinuation. He also described having had floaters in both eyes, left more than right for a few years and a wavy light in the left eye for about a month prior to diagnosis. He had blue eyes, no family history of cancer or other potential known risk factors. He was an active smoker, with a history of 1.5 packs/day for 20 years. His maternal grandfather was presumed to have cone-rod dystrophy type vision problems.

At diagnosis, a ciliochoroidal lesion was seen, measuring 12.5 mm × 12 mm x 8.5 mm, extending from ~2 to 4 o'clock. Metastatic work-up was negative. Tumor biopsy showed mixed cell type melanoma and class IB gene profile. At 5-year follow-up post-PBRT, his tumor had responded well and there was no sign of recurrent/metastatic disease.

2.3. Case 3

A 31-year old Caucasian female, with a family history of UM, presented with a right eye peripapillary melanoma.

She initially complained of visual disturbance with wavy lines and central vision changes in her right eye. Her MGF had UM diagnosed in his 60s, underwent enucleation, and died shortly thereafter due to metastatic liver disease. The patient was using topical 0.025% tretinoin cream a few times weekly and had started six years prior (age 25) for facial cystic acne. She did not take an oral retinoid. She sometimes got a rash with the topical retinoid cream. She had also used tanning beds since age 16 without eye protection to avoid lines around the eye. She had blue eyes.

On examination, a pigmented lesion was noted involving the macula and optic disc from ~7:30 to 11:30 o'clock, measuring 8.6 mm × 8.1 mm × 2.4 mm thick, with associated subretinal fluid (SRF). Metastatic work-up was negative and the patient chose to forgo biopsy. The patient was 6 weeks pregnant when first diagnosed, however during the work-up process lost her pregnancy by spontaneous miscarriage. At 5 years follow-up post-PBRT, she had no sign of local progressive or metastatic disease.

2.4. Case 4

A 27-year old Caucasian female presented with a left choroidal melanoma, class IA.

Initially she was followed for years with an asymptomatic nevus in the left mid equator periphery. She reported having hazel colored eyes "years ago" which gradually became more blue in color. She used a topical retinoid cream extensively, every night or twice daily since age 17. For many years she described using a stronger concentration and was on tazarotene (a topical retinoid) until recently when she moved to another regimen with a lighter topical retinoid. She had used antibiotics for acne as well. While on topical facial only retinoid, she had general skin thinning, sensitivity and more pronounced skin reactions in facial and even in non-facial areas with no direct topical retinoid contact. In addition, she stated using light therapy for acne in her dermatologist office and an at-home blue/red wavelength LED light and described feeling tingling in her eyes at times during use. She had no other known potential risk factors or relevant history.

At her most recent visit, the lesion showed signs of malignant transformation with extension anteriorly as well as posteriorly towards the disc and presence of macular edema. The tumor was 2.5 mm from the disc and measured 12.5 mm × 10.5 mm × 2.1 mm. She was treated with PBRT.

2.5. Case 5

A 32-year old male presented with a left choroidal melanoma.

The patient was of European/Greek descent, with hazel eyes, and smoked 0.5 packs/day for 6 years and quit ~10 years prior to diagnosis. His father had esophageal cancer, maternal grandmother had metastatic cancer to the liver (unknown primary). He worked as a post-doctoral student in a chemistry laboratory and recalled no significant chemical eye or facial exposures or temporary blindness. He was a baby when the Chernobyl explosion occurred and was living in Sweden and the family recalled a cloud of dark airborne material in their region attributed to the explosion. He reported using oral isotretinoin daily for ~12 months at age 17/18 years for back acne. His acne resolved, however he noted dryness of his lips and bilateral eyes during the course. Once off the oral medication, his lips dryness improved, however his eyes remained dry bilaterally to date.

On routine eye examination, he had an inferonasal pigmented choroidal mass with orange pigment and SRF. The lesion was 2.5 mm from the disc, and 9.1 mm × 10.7 mm × 2.5 mm in height. Tumor biopsy confirmed overall low metastatic risk melanoma. The UCSF500 Cancer

Gene Test panel showed pathogenic mutations of GNA11 and EIF1AX and no detectable chromosomal aberrations. Specifically, GNA11 p. Q209L and EIF1AX p. P2S mutations had mutant allele frequencies of 36% and 67%, respectively. While GNA11 mutations are associated with more aggressive tumors, the overall constellation with lack of BAP1 inactivation and copy number changes appeared consistent with improved prognosis. There was no evidence of microsatellite instability. No pathogenic alterations were identified in the normal tissue sample. The patient was treated with PBRT.

2.6. Case 6

A 44-year old male with a known history of a right ocular nevus, was noted to have a left eye ciliary body melanoma.

The patient was of Scottish/Irish/Slavic descent, with brown eyes, with no history of ocular trauma, not a pilot, no welding, no unusual solar exposure/sunburns/snow burns, no tanning booth use, worked in an IT business. He had no family history of ocular melanoma, PGF with stomach cancer, and MGM with throat cancer. As a teenager he used oral isotretinoin and topical tretinoin daily for about three years, from age 15 to 17. He noted that it cleared his acne. He used the daily topical retinoid on his face and back, and he noted significant lip dryness/chapping and patchy burns on his face during therapy. He had severe depression with suicidal thoughts during these years which went away after discontinuing retinoid therapy.

On routine ophthalmic examination, in the right eye, there was a stable choroidal nevus 3 mm nasal to the right optic nerve, 3.5 × 2.5 × 1.7 mm with overlying drusen. In the left eye, there was a nasal periphery thick ciliary body melanoma, 8:30 to 10 o'clock measuring 8 mm × 6 mm × 6.1 mm. Sentinel vessels were present in the left eye nasally. There was invasion of the iris root in the middle of the lesion without any drop deposits or neovascularization. Biopsy confirmed melanoma as class IA, PRAME negative (preferentially expressed antigen in melanoma) and he was treated with PBRT.

3. Discussion

Uveal melanoma, a potentially lethal and rare disease, is particularly rare in young adults and the potential synergy of genetic and environmental risk factors in contributing to pathogenesis is not well understood. We present the first case series of six young UM patients with a history of oral isotretinoin and/or topical retinoid therapy (tretinoin or tazarotene) prior to diagnosis. All had used 3 months to ~10 years of retinoid treatment prior to UM diagnosis and in half the cases continued at the time of diagnosis. All had some ocular complaint at presentation. The onset of certain patient visual complaints corresponded with their time course of oral and/or topical facial retinoid treatment. For Cases 1, 2, and 5, these ocular symptoms persisted at the time of diagnosis.

The patients were aged 16 to 44 at diagnosis, and three of six tumors involved the ciliary body. Each patient noted ocular complaints, including blurry vision, ocular headache, light sensitivity, floaters, visual disturbance, wavy lines, tingling sensation, ocular fatigue, dryness in the eyes, and history of ocular nevus. Potential risk factors or other relevant history for patients included at least partial Caucasian background for all cases; cone-rod dystrophy and active smoker (Case 2); family history of UM and pregnancy at time of diagnosis (Case 3), past smoking and possible secondary Chernobyl exposure as a baby (Case 5). All patients were offered biopsy, two chose to forgo it, and none of the other four had high risk disease on biopsy (Cases 2,4,5,6). All patients were treated with PBRT and currently have no sign of recurrent or metastatic disease.

Retinoid therapy has been linked to various benign and/or reversible anterior and posterior eye side effects, though the pathophysiology is unclear. An extensive review^{6,7} of ocular AEs with oral isotretinoin therapy revealed of note (a) 243 cases with ocular sicca, 16 of which were irreversible at last follow-up; (b) 140 reports of decreased dark

adaptation, including 11 patients with probable permanent night blindness [10 days to 4 months after drug exposure]; (c) 79 reports of retinal changes, of which notably 25 had various retinal/choroidal pigment disturbances; (d) 16 cases of decreased color vision, of which 11 returned to normal upon drug discontinuation.

Another large cohort study reported on 14,682 adolescents and young adults who were new users of isotretinoin for acne.⁸ The study demonstrated a strong association between isotretinoin therapy and inflammatory and structural ocular AEs, with a peak risk at 4 months after use. Follow-up was limited to one year and no ocular malignancy has been reported in these studies.

Pathophysiology of eye changes associated with retinoid treatments remain unclear. While anterior segment changes to the ocular surface and adnexa could lead to surface irritation, blurry vision, pain, and possibly light sensitivity, posterior segment changes have been noted as well, including retinal/choroidal pigment disturbances and other abnormalities.^{6–8,17} One recent study of 94 eyes analyzed changes in peripapillary choroidal thickness after oral isotretinoin treatment.¹⁷ OCT results showed that between baseline measurements and those taken at the third month of oral acne treatment, a significant increase in the peripapillary choroidal thickness could be seen in the temporal and superotemporal quadrants. Whether the observed choroidal thickness changes are linked with development of posterior segment eye abnormalities is unknown but possible, and requires further study.

Abnormal vision associated with rod/cone dysfunction and electroretinogram abnormalities has been described among individuals on retinoid therapy.^{13–16} Some have speculated that synthetic retinoids may interfere with vitamin A binding sites or with its storage/delivery at target tissues, affecting the visual cycle of retinal photoreceptors.¹³

Of note, the effect of low-dose, oral isotretinoin is being studied to lower the risk of proliferative vitreoretinopathy (PVR) following rhegmatogenous retinal detachment (RRD) repair.²³ It is hypothesized that isotretinoin may in fact benefit by affecting retinal pigment epithelium (RPE) cell migration, proliferation, and/or transdifferentiation and may inhibit overgrowth of confluent RPE cells associated with PVR. The relationship of isotretinoin and the various parts of the eye is complex and the physiologic interactions remain to be fully elucidated.

Effects of topical tretinoin and topical retinoid-antibiotic combinations have been controversial, with some literature showing potentially variable ocular and systemic absorption and effects.^{22,24–30} A prospective study of 43 patients starting daily topical retinoid-erythromycin for facial acne vulgaris found significant development of ocular surface disease and dry eye after one month of use.⁹ The authors hypothesized that acne vulgaris patients may have altered local systemic absorption due to diseased skin and/or facial topical retinoid may be present in facial sweat running into the eyelids and possibly contaminate the eye.

Systemic retinoids and related compounds have shown a potential increased morbidity and mortality effect in smokers.^{20,21} In our case series, Cases 2 and 5 had a smoking history. Also, oral isotretinoin as well as topical tazarotene (applied in Case 4) is contraindicated in pregnancy (Class X) due to potential teratogenic side effects, including ocular abnormalities such as microphthalmia, hypertelorism, corneal opacities, retinal and optic nerve abnormalities.^{9–12,18,19}

This observational case series notes six young UM patients who used retinoid therapy and had ocular symptoms, some of which were irreversible despite cessation of treatment. Importantly, a much larger systematic study is required to look at young UM patients and their various environmental history and cytogenetics/gene expression profiles. Dermatologic medications, particularly topical and acne medicine, often did not appear in records and must be retrieved by comprehensive medical history-taking and database evaluation of current as well as prior/discontinued medications. Retinoid use is wide spread and it is possible that some of the young patients represent a lead time bias with early diagnosis due to closer patient or physician observation with ocular side effects associated with the retinoid therapy. The common use of retinoids and ocular symptoms in these cases may be coincidental. No

causal link should be assumed. Continued study is required to determine the complex nature of the relationship between retinoid therapy and the eye.

4. Conclusions

This is the first-reported case series of oral isotretinoin and topical retinoid use in young UM patients. First, there is a need to systematically study young UM patients in particular, as they are a very rare group and genetic/environmental risk factors are not well understood. Second, no causal link is claimed, and reported here is a series of cases describing retinoid use as a common finding for certain young UM patients. Further study is necessary with systematic long-term follow-up in large scale databases due to (a) the rarity of the disease and (b) the challenges in drug toxicity reporting given lack of resources, the voluntary nature of reporting, and limited data. Third, benign and mainly reversible ocular adverse effects and retinoid treatment have been described, including pigment disturbances, changes in choroidal thickness and altered physiology. Given the significant use of retinoids across patients, continued epidemiologic and translational studies will allow for better delineation of potentially long-term, significant, or irreversible ocular side effects and mechanisms of action.

Patient consent

All patients have been consented.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None.

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None.

CRediT authorship contribution statement

Kavita K. Mishra: Conceptualization, Methodology, Writing - original draft. **Jessica E. Scholey:** Writing - review & editing. **Inder K. Daftari:** Writing - review & editing, Data curation. **Armin Afshar:** Writing - review & editing. **Tony Tsai:** Writing - review & editing. **Susanna Park:** Writing - review & editing. **Jeanne M. Quivey:** Writing - review & editing, Supervision. **Devron H. Char:** Writing - review & editing, Supervision.

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