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Recurrent melanoma arising from sclera

Hillary C. Stiefel *, Audra Miller, David J. Wilson, Daniel M. Albert

Oregon Health & Science University, Department of Ophthalmology (Casey Eye Institute), 3375 SW Terwilliger Blvd, Portland, OR, 97239, USA

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ABSTRACT

Purpose: To report a case of recurrent malignant melanoma suspected to have arisen from intrascleral melanocytic cells.

Observations: En bloc removal of melanoma was performed with iridocyclectomy in a 46-year-old Caucasian male. Histopathologic examination confirmed a diagnosis of malignant melanoma in the subconjunctival space, which was presumed to have arisen from the sclera and extended both intraocularly and subconjunctivally. 15 years later, a pigmented limbal lesion near the site of the previous iridocyclectomy was excised by lamellar sclerectomy. Histopathology showed a proliferation of pigment-containing cells with atypical nuclei consistent with recurrent melanoma.

Conclusions and Importance: We report a case of recurrent melanoma that we suspect arose from intrascleral melanocytes, extended both intraocularly and subconjunctivally, and recurred 15 years following initial excision.

1. Introduction

The differential diagnosis of pigmented scleral lesions includes ocular melanocytosis, scleral extension of conjunctival or uveal melanoma, metastatic melanoma, ochronosis, argyrosis, scleral calcification, nevus, and Axenfeld nerve loop. Malignant melanocytic tumors typically involve the sclera only as a result of direct extension from intraocular or conjunctival sites, with primary scleral melanoma being very rare. We present a case of melanoma presumed to have arisen from the sclera, with extension both intraocularly and subconjunctivally as well as delayed tumor recurrence.

2. Case Report

In February 2001, a 46 year old man was seen with a complaint of a "brown spot on his left eye that was enlarging in size." Examination revealed a darkly pigmented, sub-conjunctival tumor present in the inferonasal quadrant of the left eye (Fig. 1a and b). Slit lamp biomicroscopy and gonioscopy revealed that the tumor had infiltrated the anterior chamber angle (Fig. 1c). Ultrasound biomicroscopy demonstrated an echolucent channel communicating between the pars plana internally and the subconjunctival mass externally (Fig. 1d). A subsequent en bloc removal of the tumor with iridocyclectomy was performed, followed by a corneoscleral patch graft (Fig. 1e). The tumor was inspected under the operating microscope and appeared to be roughly 5 mm in anterior-posterior dimension and 7 mm along the cornea and limbus. On gross description, the specimen consisted of a 9.5 × 7.5 mm piece of tissue including sclera, ciliary body, and iris. Microscopic examination revealed atypical melanocytic cells in the substantia propria, with no involvement of the conjunctival epithelium (Fig. 2a and b). Atypical plump, spindle-shaped and epithelioid melanocytes were observed within the anterior chamber and trabecular meshwork, and were noted to extend into the anterior aspect of the ciliary body (Fig. 2a–c, e). These cells stained positively with Melan-A (Fig. 2d). No atypical melanocytes were present in the iris. No cutaneous source of melanoma was identified, and imaging of the liver and chest did not reveal metastatic disease. The final pathologic diagnosis was malignant melanoma believed to have arisen from intrascleral melanocytic cells. Atypical melanocytes were noted within a prominent scleral emissary and within associated nerves and blood vessels (Fig. 2a–b, f-g), with these findings believed to account for the connection between the extraocular and intraocular tumors. Following the en bloc tumor excision, no additional treatment was performed.

The patient developed a cataract in the left eye over the next year as well as a macular hole. In July 2002, the patient underwent a pars plana vitrectomy and lensectomy in the left eye with an internal limiting membrane peel and a sewn-in intraocular lens. The patient was followed at an outside clinic, where reports indicate his vision remained largely stable. When the patient was re-examined at Casey Eye Institute in March 2009, vision in the left eye was 20/100, and an inferior elevation

* Corresponding author. Casey Eye Institute Oregon Health & Science University, 3375 SW Terwilliger Blvd, Portland, OR, 97239, USA.
E-mail address: Stiefel@ohsu.edu (H.C. Stiefel).

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suggestive of schisis was noted. Both gonioscopy and high-frequency ultrasound showed no evidence of tumor recurrence. When next seen at Casey Eye Institute in 2016, a small focus of flat pigmentation was observed above the sclera at the level of the pars plicata and pars plana (Fig. 3a and b). It was recommended that this area be resected and examined for recurrence of the melanoma. A partial sclerectomy was performed on the left eye to resect the pigmented limbal lesion, followed by an alcohol epitheliectomy and amniotic membrane transplant. On gross description, the specimen was noted to be rubbery, dark brown, and measured 6 × 5 × 1 mm. The surrounding nasal, temporal, and inferior margins were submitted as separate specimens, measuring approximately 4 × 1 × 1 mm each, noted to be rubbery and tan in color. Microscopic examination of the main specimen showed non-keratinized squamous epithelium with goblet cells consistent with conjunctival tissue. The epithelium appeared normal without evidence of dysplasia or atypia. Within the substantia propria was a proliferation of pigment-containing cells with atypical nuclei and pigment granules (Fig. 3c and d). These cells stained positive with Melan-A, consistent with a diagnosis of recurrent malignant melanoma (Fig. 3e). Increased vascularity and a mild inflammatory infiltrate consisting primarily of lymphocytes and plasma cells was also noted. The specimen included corneal epithelium and underlying stroma which was unremarkable. No tumor cells were seen in the surgical margin specimens.

3. Discussion

Ocular melanoma typically arises from the uveal tract or the conjunctiva. Uveal melanomas are derived from uveal melanocytes or uveal nevi, including melanocytomas. Conjunctival melanomas can originate either from primary acquired melanosis (PAM), nevi, or de novo from melanocytes in the conjunctiva. With this report, we contribute a case of ocular melanoma which is interesting for three reasons: 1) the tumor appears to have arisen from intrascleral melanocytes given a lack of involvement of the conjunctival epithelium or iris, with only minimal, secondary involvement of the ciliary body; 2) the tumor demonstrated both intraocular and subconjunctival extension; and 3) the tumor recurred 15 years after original resection.

Primary scleral melanoma is extremely rare, with only two other reported cases found upon review of the literature.[1,2] In one of these reports, an episcleral melanoma arose in an otherwise healthy 36 year old male with no known predisposing risk factors.[1] In the other, a primary episcleral melanoma was found in a 62 year old male with pre-existing ocular melanocytosis.[2] In both of these cases, the tumors were removed via lamellar scleroconjunctivectomy with subsequent cryotherapy, and there was no report of tumor recurrence.

The 46-year-old Caucasian male patient in our report had no evidence of pre-existing ocular melanocytosis or other risk factors for the development of intraocular melanoma. The original tumor was present in the subconjunctival tissue, without evidence of involvement of the conjunctival epithelium, supporting the presumed scleral origin of the tumor. The possibility that the tumor arose from a subconjunctival primary melanocytic nevus, such as a blue nevus, is highly unlikely given the lack of suggestive histologic features as well as the extreme rarity of blue nevi of the conjunctiva and even more rare phenomenon of

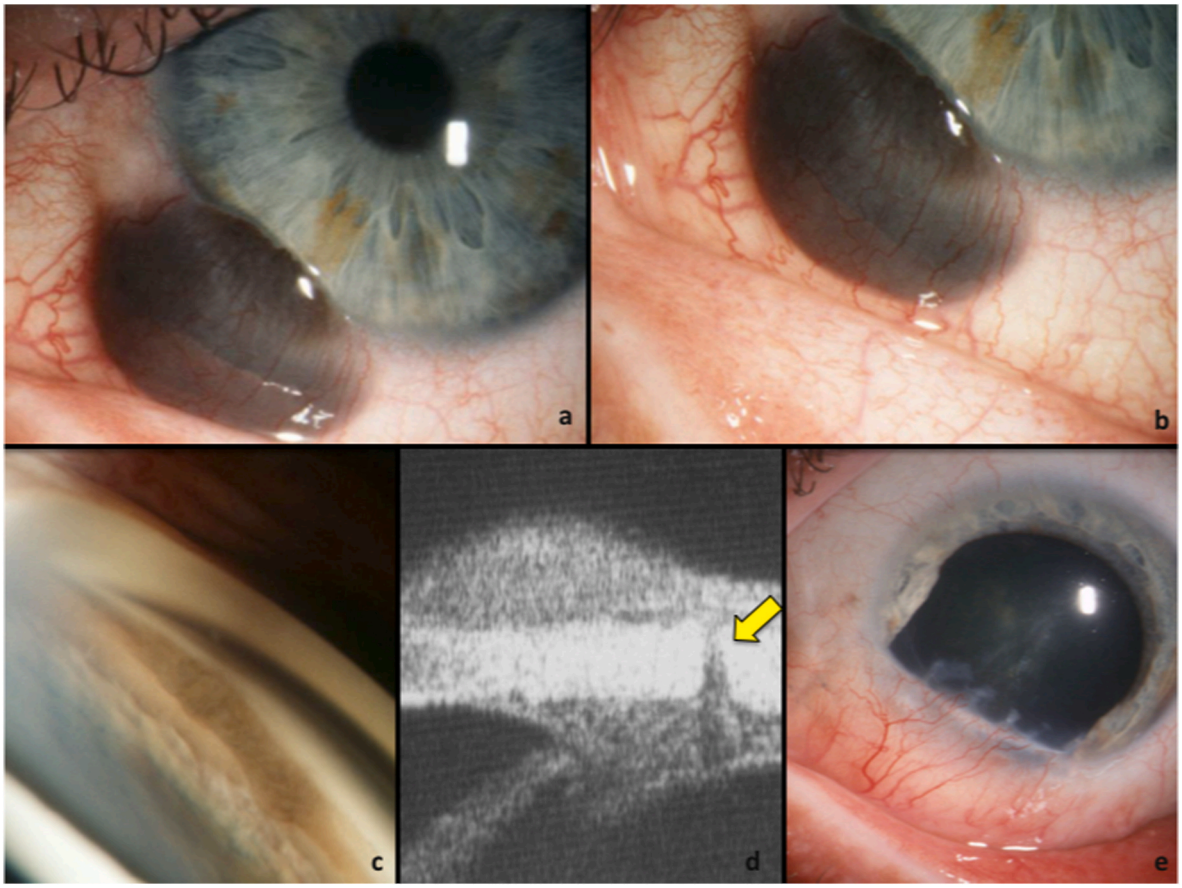

Fig. 1. a and **b** Slit lamp photographs taken in 2001 demonstrating a darkly pigmented tumor in the inferonasal quadrant of the left eye. Visualization of the overlying conjunctival vessels highlights the subconjunctival location of the tumor. **c** Gonioscopic photograph demonstrating tumor presence in the anterior chamber angle. **d** Ultrasound biomicroscopy demonstrating an echolucent channel (yellow arrow) communicating between the ciliary body internally and the subconjunctival mass externally. **e** Slit lamp photograph taken after the patient underwent en bloc removal of the tumor with iridocyclectomy with a corneoscleral patch graft. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

malignant transformation of these lesions.[3] The possibility of malignant transformation of a blue nevus of the sclera cannot be entirely excluded, although the histologic features of the tumor are not suggestive of such origin. The lesion in our case invaded the anterior chamber, angle, and anterior aspect of the ciliary body, with no atypical melanocytes found in the iris. There was no clinical or ultrasonic evidence of choroidal involvement beyond the area of direct invasion of the ciliary body adjacent to the intrascleral origin of the tumor.

A prominent scleral emissary was observed which is believed to account for the connection between the intraocular and extraocular tumors. The notion of extension of melanoma from the intraocular to extraocular space is well established. In one study of 847 globes enucleated as the primary therapy for intraocular melanomas of all uveal sites, 124 (14.6%) had evidence of extraocular extension, which occurred most frequently via the aqueous channels and then via the ciliary arteries.[4] To our knowledge, no other reports of primary scleral melanoma with intraocular extension exist in the current literature, making this report unique in this regard.

As noted, our patient's original tumor was treated in 2001 with en bloc iridocyclectomy, and was noted to recur in the conjunctiva 15 years later. The rarity of scleral melanoma precludes generalization about the success of particular treatment protocols, but for the more common entity of uveal melanoma, transscleral local resection has been regarded as an acceptable treatment option for patients with ciliochoroidal tumors who are poor candidates for radiotherapy but wish to avoid enucleation.[5–9] In a 1995 study of local tumor control following transscleral local resection of uveal melanoma, a recurrence rate of 6–57% at 4 years was found, corresponding to patients with zero to two or more risk factors for recurrence, respectively.[10] These risk factors included epithelioid cell type, posterior tumor extension near the optic disc or fovea, basal tumor diameter >16 mm, and lack of adjunctive plaque radiotherapy. In this study, residual tumor was found in 24 out of 310 patients, with nearly all the recurrent tumors located within or at the margin of the surgical coloboma, which was also seen in our case.[10] Recurrent tumor from microscopic deposits had an overall incidence of 32% at 7 years, but no cases occurred more than 7 years postoperatively. The recurrence in our case 15 years after original resection is noteworthy but not unparalleled. In the literature, there is a report of a local recurrence of uveal melanoma 26 years following successful *trans*-scleral local resection, as well as a recurrent ciliary body melanoma noted 18 years following resection.[11,12] A very late recurrence of iris melanoma was reported 45 years following surgical resection.[13]

In a separate chart review of 494 patients who underwent transscleral local resection for uveal melanoma, Kim et al. identified 9 cases of noncontiguous tumor recurrence, which they noted to be related to intraocular dissemination from the primary tumor, either through the natural course of the disease or secondary to surgical manipulation.[14] It is both interesting and fortunate that while our case demonstrated

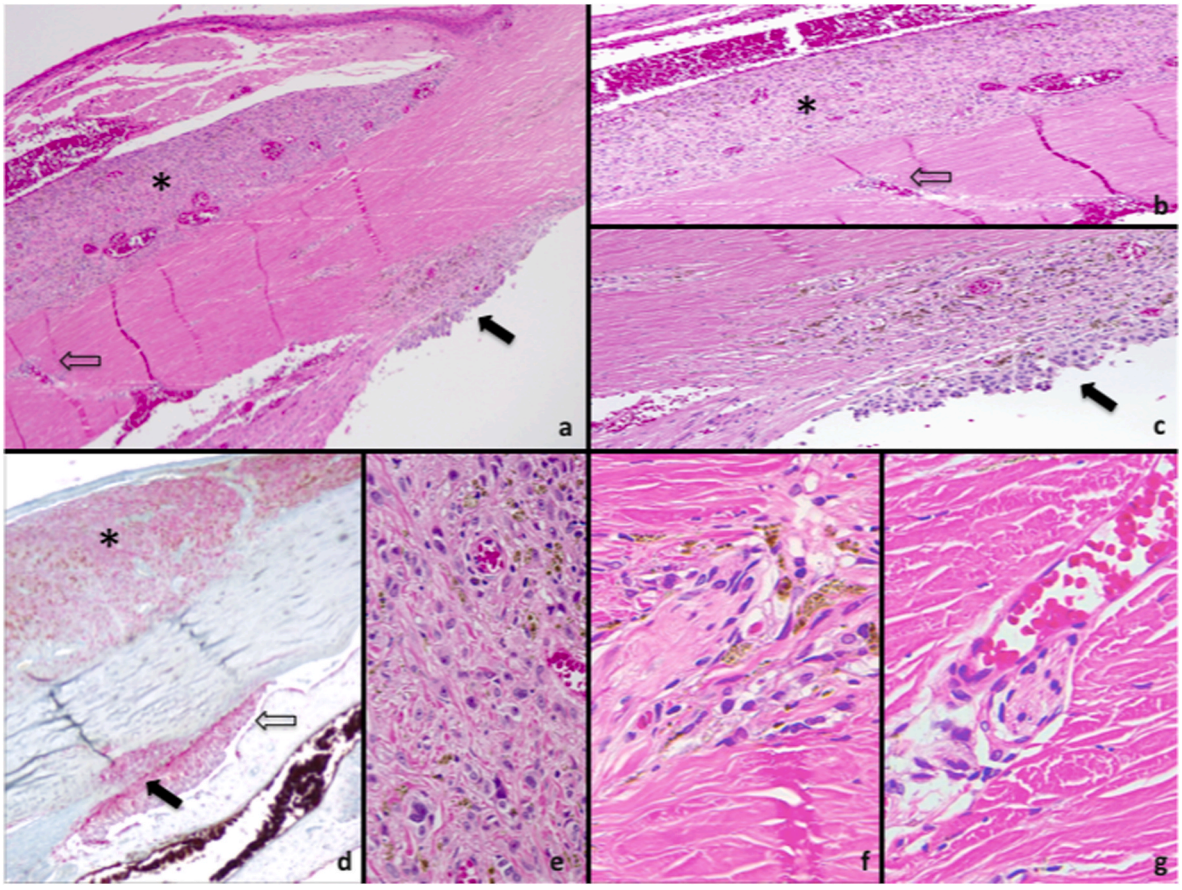

Fig. 2. a Image of the resected specimen showing a large collection of atypical melanocytic cells in the subconjunctival space (asterisk), involving the episclera and sclera. There is no involvement of the overlying conjunctival epithelium. A scleral emissary canal (open arrow) containing atypical melanocytes is present, and atypical melanocytes can be seen within the trabecular meshwork, the adjacent anterior chamber, and extending along the anterior aspect of the ciliary body (solid arrow). **b-c** Higher magnification images of the tumor features highlighted in **a**. **d** The distribution of melanocytes in the episclera and sclera (asterisk), trabecular meshwork, anterior chamber (open arrow), and anterior ciliary body (solid arrow) is highlighted on Melan A stain with a red chromogen. **e** Higher magnification view of the atypical epithelioid and spindle-shaped melanocytes comprising the subconjunctival mass. **f** and **g** Nerves and a prominent blood vessel within the sclera containing melanocytes and believed to account for the clinically suspected connection between the extraocular and intraocular tumors.[**a-c, e-g** Hematoxylin and eosin: X5 **(a),** X10 **(b),** X20 **(c)**, X40 **(e**–**g); d** Melan A: X5]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

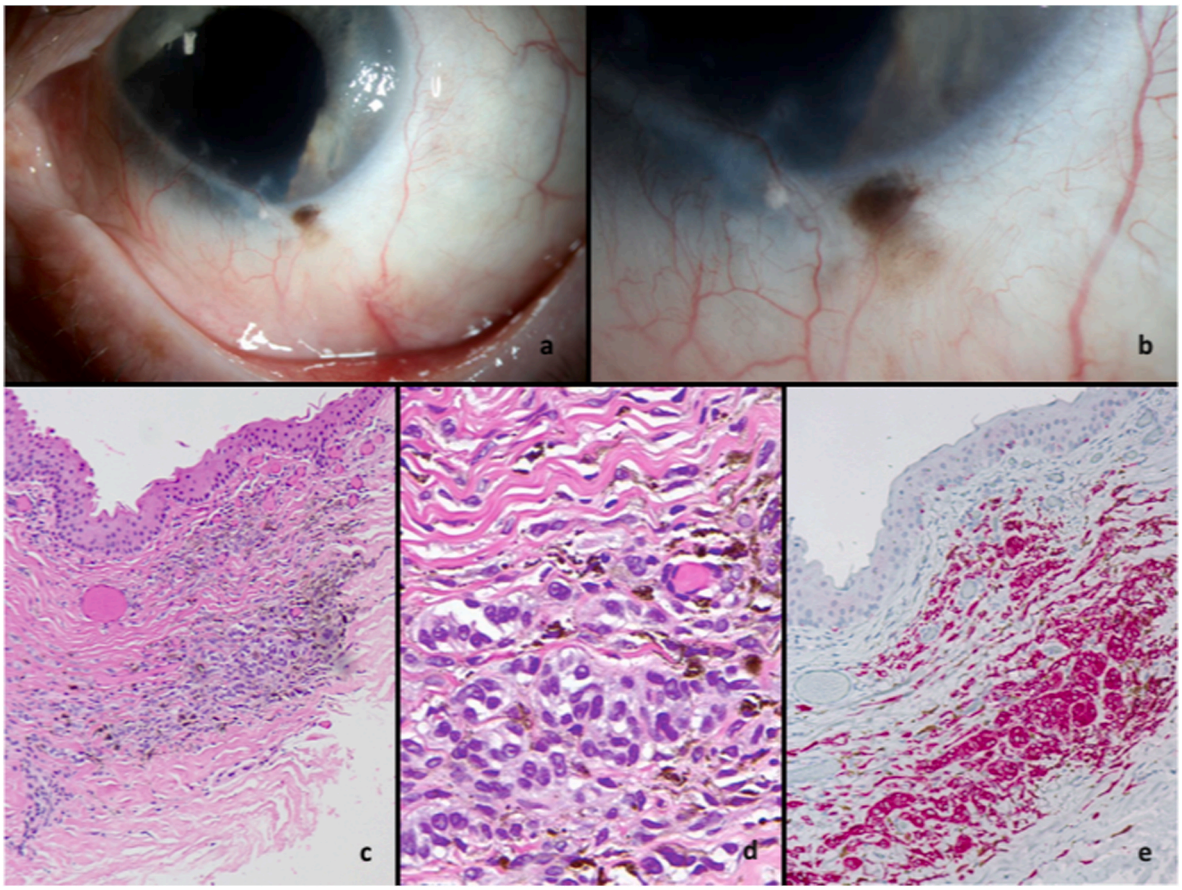

Fig. 3. a and **b** Slit lamp photographs taken in 2016 demonstrating a small, darkly pigmented lesion inferiorly in the left eye, concerning for recurrent melanoma. An excisional biopsy with sclerectomy was performed, followed by an alcohol epitheliectomy and amniotic membrane transplant. **c-d** Histologic images of the resected specimen showing a proliferation of pigment-containing cells with atypical nuclei and pigment granules in the substantia propria, with no involvement of the overlying conjunctival epithelium. These findings were consistent with a diagnosis of recurrent malignant melanoma. Increased vascularity and a mild inflammatory infiltrate consisting primarily of lymphocytes and plasma cells was also noted within the substantia propria. **e** The distribution of the melanocytes can be seen on Melan-A stain with a red chromogen.[**c-d** Hematoxylin and eosin: X10 **(c)**, X40 **(d)**; **e** Melan A: 20X]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

intraocular extension at the time of primary tumor diagnosis, the recurrence was localized to the substantia propria at the margin of the original surgical coloboma, without noncontiguous or intraocular recurrence. An alternate explanation for the development of the second tumor in this case, such as a second primary melanoma not related to the first tumor, was entertained but considered highly unlikely.

In the uveal melanoma literature, very late tumor recurrence has been associated with the presence of spindle cells with low malignant potential on histology.[10] In our case, the original tumor showed a similar percentage of spindle and epithelioid cells. Very late recurrence in uveal melanoma has also been postulated to result from tumor dormancy, where malignant cells are maintained in a quiescent state but are later triggered to proliferate.[15]

Review of the literature suggests that 12–32% of eyes with a history of transscleral local resection for uveal melanoma are ultimately enucleated, most commonly for local tumor recurrence, with recurrence of tumor at or adjacent to the original surgical margins reported in 3–18% of cases.[5,6,8,10,16] Fortunately, our patient was able to undergo additional resection at the isolated site of tumor recurrence, and has not required enucleation. Despite the apparent success of our patient's surgical treatment thus far, it is important to note that local tumor recurrence significantly increases the risk of metastatic disease.[17]

This case reminds clinicians that primary melanoma of the sclera, while exceedingly rare, can occur. Given the potential for both intraocular and subconjunctival extension and a risk of late recurrence following original resection, these patients require long term monitoring for tumor recurrence as well as for metastatic disease.

Patient Consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the ICMJE Criteria for Authorship.

Declaration of competing interest

The authors declare no conflicts of interest or financial interests.

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None.

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