RUSH

Case study

Conjunctival melanoma

Author: Jacob Fondriest, MD
RUSH University Medical Center, Department of Ophthalmology

Background

The goal of treating most ophthalmic diseases is to optimize vision. However, in ocular disease with potentially fatal consequences, the goal of preserving vision comes secondary to the goal of preserving life. Sometimes dangerous conditions can initially be subtle. In this article, we present a case of a conjunctival melanoma that was missed by two experienced ophthalmologists. We review the clinical care for our patient, and summarize the presentation, treatment and prognosis for this disease.

Patient Case

Our patient is a 71-year-old Hispanic female with a history of multiple myeloma, hypertension and dyslipidemia who presented to the RUSH Eye Center as an urgent visit for one day of itchiness of the left periorbital skin. She noted that when she rubbed her eye, there was a small amount of blood produced. Three months earlier, she had been evaluated by a cataract surgeon for blurry vision and was noted to have cataracts in both eyes. She was subsequently scheduled for bilateral sequential cataract surgery starting with the right eye.

She was evaluated by a retinal specialist, who noted an epiretinal membrane in the right eye, but was cleared for cataract surgery. The exam from these evaluations noted pigmentation of the temporal bulbar conjunctiva without further comment. When evaluated in our clinic, the visual acuity, intraocular pressures, cataract grade, and retinal findings were stable from previously reported evaluations. Initial gross examination showed a subtle lesion of the left temporal conjunctiva (Figure 1). Closer examination revealed that the pigmentation was extensive (Figure 2). The patient was not aware of the extent of this lesion at the time of diagnosis.

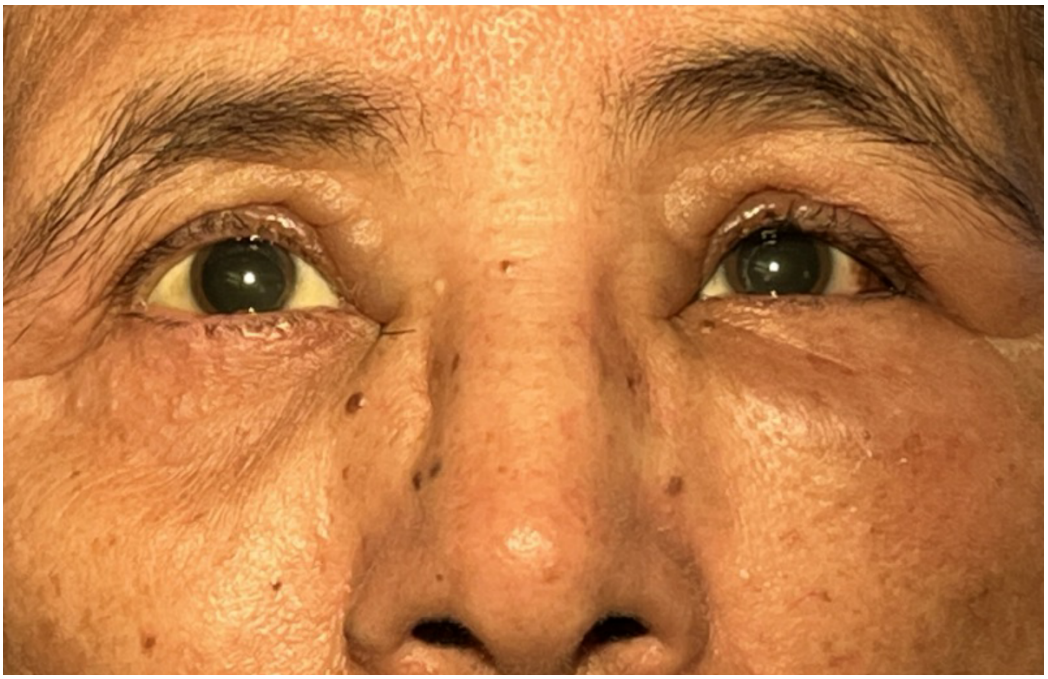

Figure 1: External photograph of our patient upon presentation to the RUSH Eye Center. In primary gaze, there is a small patch of pigment on the temporal bulbar conjunctiva. The left periocular skin appears fuller than the right.

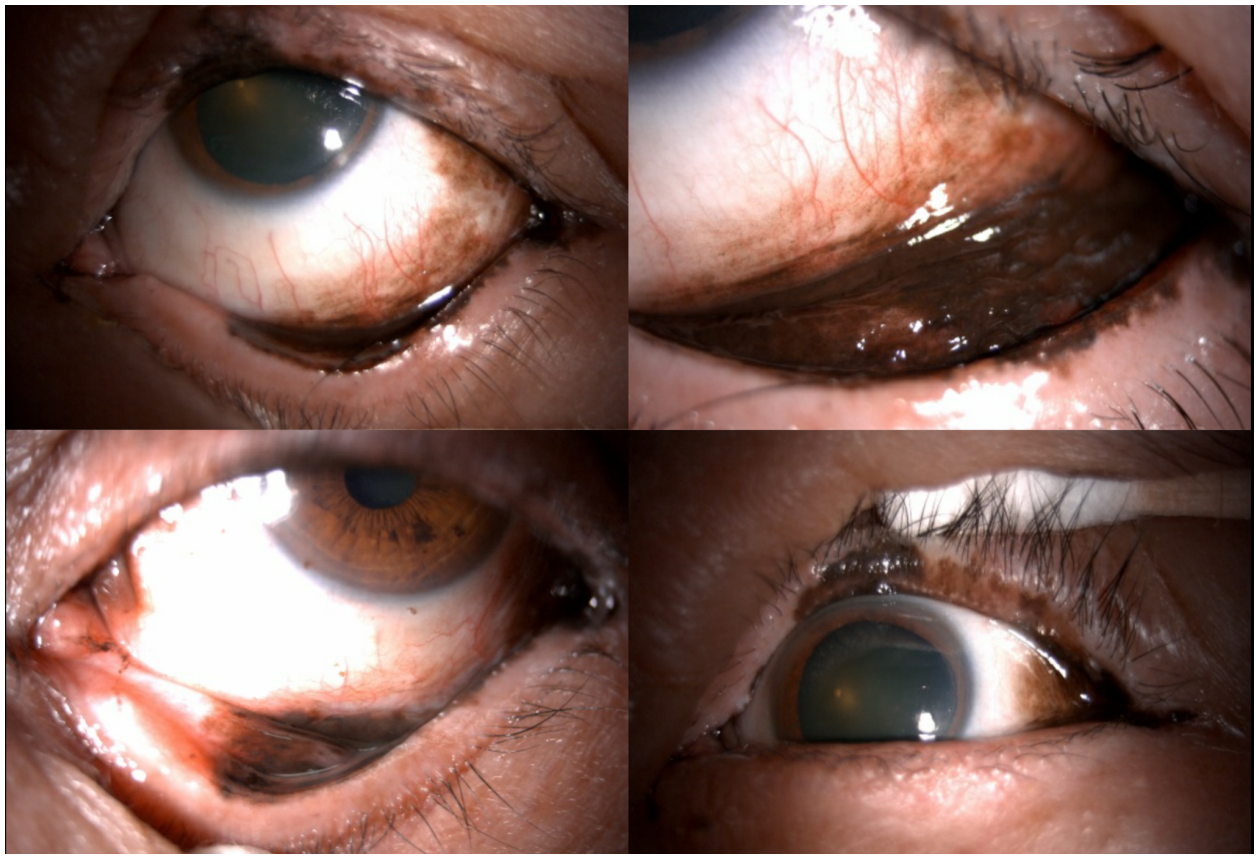

Figure 2. Conjunctival melanoma of the left eye. There is involvement of the plica semilunaris, as well as the superior and inferior bulbar conjunctiva, palpebral conjunctiva, fornices, and external eyelid margins. The cornea and limbus are spared.

An MRI of the brain and orbits with and without contrast was obtained which was unremarkable. A conjunctival map biopsy was performed under MAC anesthesia. Due to the extensive nature of the lesion, a “no touch technique” was not possible and cryotherapy was not performed due to concern for excessive morbidity. The pathology results revealed full-thickness melanoma in situ with adnexal involvement (Figure 3). Given local extension onto the external eyelid, this cancer was categorized as locally invasive disease (Figures 4 & 5). The patient was given punctal plugs, and started on topical Mitomycin C drops 0.04%, four times daily in the left eye, alternating two weeks on, and two weeks off. Prednisolone acetate and artificial tears were also started four times daily in the left eye.

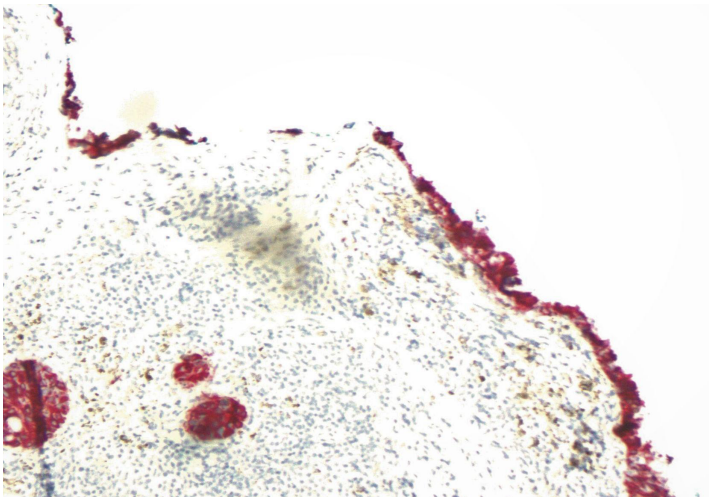

Figure 3: Melan A pathology slide from biopsy of the superior fornix and plica semilunaris. There is full thickness conjunctival involvement with adnexal glandular involvement.

TABLE 1. American Joint Committee on Cancer (AJCC) classification of conjunctival melanoma

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T(is)	Malignant melanoma confined to conjunctival epithelium
T1	Malignant melanoma of the bulbar conjunctiva
T1a	<1 quadrant
T1b	>1 but <2 quadrants
T1c	>2 but <3 quadrants
T1d	>3 quadrants
T2	Malignant melanoma of palpebral conjunctiva, forniceal conjunctiva, and/or caruncle
T2a	<1 quadrant but not involving caruncle
T2b	>1 quadrant but not involving caruncle
T2c	<1 quadrant and involving caruncle
T2d	>1 quadrant and involving caruncle
T3	Malignant melanoma with local invasion
T3a	Globe
T3b	Eyelid
T3c	Orbit
T3d	Paranasal sinus
T4	Malignant melanoma with intracranial invasion

Figure 4: American Joint Committee on Cancer Staging System for Conjunctival Melanoma[1].

Cumulative proportion with event ± SE [# failed / # Left]

	1 yr.	3 yr.	5 yr.	10 yr.	15 yr.	20 yr.
T1	0% [0/119]	3.1% ± 1.8 [3/72]	4.8% ± 2.5 [4/51]	13.6% ± 4.8 [8/24]	13.6% ± 4.8 [811]	13.6% ± 4.8 [8/3]
T2	0.9% ± 0.9 [1/68]	10.3% ± 4.1 [6/38]	19.6% ± 6.3 [9/19]	19.6% ± 6.3 [9/8]	19.6% ± 6.3 [9/3]	19.6% ± 6.3 [9/1]
T3	0% [0/20]	14.3% ± 9.4 [2/11]	22.9% ± 11.7 [3/5]	-	-	-

T1 vs. T2, p =0.0655; T1 vs. T3, p=0.0526; T2 vs. T3, p=0.8581; Log-rank test

Figure 5: Metastasis related death due to conjunctival melanoma. There are higher rates of metastasis-related death in T2 and T3 stage tumors compared to T1.[1]

Expert opinion was sought from Carol Shields, MD, of Wills Eye Hospital, who agreed with the assessment of locally invasive disease, with a moderate risk of metastasis. She recommended aggressive local therapy with consideration for additional biopsy for BRAF and PD1 biomarkers. She also suggested consideration for plaque radiotherapy, or surgical exenteration. The patient's case was discussed in a multidisciplinary tumor board at Rush with consideration paid to her diagnosis of multiple myeloma and overall health status. She had been in clinical remission for multiple myeloma but experienced biochemical relapse only months prior to the diagnosis of conjunctival melanoma. A PET/CT scan at that time failed to show any metastases, and her oncologists felt her disease was under good control. She was deemed overall in good health. We repeated another PET/CT, which did not show any clear evidence of metastatic disease. The patient was offered an exenteration of the affected orbit combined with a sentinel lymph node biopsy. The patient accepted this. At the time of this writing, she has completed two rounds of topical MMC therapy and has experienced significant irritation and an epithelial defect, which was managed with a bandage contact lens and topical antibiotics. She is currently scheduled for a total orbital exenteration.

Discussion

Conjunctival melanoma is a rare and potentially fatal cause of conjunctival pigmentation. It can arise from three sources: primary acquired melanosis (PAM), from a pre-existing conjunctival nevus, and de novo. One study of 382 cases noted 53% arise from PAM, 37% de novo, and 4% from a conjunctival nevus.[2] In patients with PAM, smaller lesions (less than 1 clock hour) tend not to progress to melanoma. Of those lesions which are biopsied, those with no atypia or with mild atypia carry minimal risk for transformation to melanoma. PAM with severe atypia can progress to melanoma in 13% of cases.[3] For tumors less than three clock hours, periodic observation every 6-12 months with photography or excisional biopsy may be pursued. In this latter approach, the "no touch technique" should be employed, to avoid seeding of the malignant cells into the conjunctiva, and the surgical field should remain dry until the end of the case for the same reason. Adjuvant cryotherapy with a double freeze-thaw technique is also recommended to the scleral base and surrounding conjunctiva. Lesions occupying greater than three clock hours, may be managed with a map biopsy of all affected quadrants with double freeze-thaw cryotherapy to the affected sites.[4] Corneal epitheliectomy with alcohol is indicated

for corneal involvement.[5] Adjuvant topical mitomycin C 0.04% eye drops can be used for residual disease. A summary of the evidence on the efficacy of this modality is summarized below (Figure 6).[6-8]

Efficacy of topical Mitomycin C

Source	Tx (MMC 0.04% QID)	Response Rate	Recurrence
Conjunctival Melanoma			
Russel et. al (2010)	3 on, 3 off, 3 on Steroid gtt QID x9 wk Artificial tears	1/21 none 4/21 partial 16/21 complete	25% recurrence Mean time: 14 months
Kuri and Finger (2005)	7 days + Excision/Cryo	3/6 controlled locally 3/6 not controlled locally	50% recurrence Mean time: 43 months
Ditta et. al (2011)	3 on/1 off (x3) Steroid gtt during off week	15/15 partial response (All PAM on f/u bx)	33% recurrence Mean time: 19.3 months
PAM			
Russel et. al (2010)	3 on, 3 off, 3 on Steroid gtt QID x9 wk Artificial tears	2/17 none 13/17 partial 2/17 complete	20% recurrence Mean time: 16 months
Kuri and Finger (2005)	2 on, 2 off, 2 on	2/8 partial 6/8 complete	38% recurrence Mean time: 40 months

Figure 6: Summary of evidence of efficacy of topical mitomycin C 0.04% eye drops. Recurrence of these pigmented lesions is common.

Topical mitomycin C is toxic to the ocular surface. Transient adverse effects include punctal stenosis, keratoconjunctivitis, and irritation, and tearing. Long-term sequelae include limbal stem cell deficiency, corneal haze, and cataract.8 For locally invasive or metastatic disease, management should be coordinated through an interdisciplinary team including oncology. Management can include full body PET/CT scan, sentinel lymph node biopsy, biomarker testing for BRAf and PD1 mutations, plaque radiotherapy and possible orbital exenteration.

Conclusion

Although rare, conjunctival melanoma is a potentially fatal condition. Early diagnosis and treatment are crucial for maximizing the chance for a favorable outcome.

References

1. Shields, Carol L., et al. "American Joint Committee on Cancer (AJCC) clinical classification predicts conjunctival melanoma outcomes." Ophthalmic Plastic & Reconstructive Surgery 28.5 (2012): 313-323.
2. Shields, Carol L., et al. "Conjunctival melanoma: outcomes based on tumor origin in 382 consecutive cases." Ophthalmology 118.2 (2011): 389-395.
3. Shields, Jerry A., et al. "Primary acquired melanosis of the conjunctiva: experience with 311 eyes." Transactions of the American Ophthalmological Society 105 (2007): 61.
4. Vora, Gargi K., et al. "Advances in the management of conjunctival melanoma." Survey of ophthalmology 62.1 (2017): 26-42.
5. Shields, Carol L., et al. "Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients." Archives of Ophthalmology 118.11 (2000): 1497-1507.
6. Russell, Heather C., et al. "Topical mitomycin C chemotherapy in the management of ocular surface neoplasia: a 10-year review of treatment outcomes and complications." British journal of ophthalmology 94.10 (2010): 1316-1321.
7. Kurli, Madhavi, and Paul T. Finger. "Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: 12 years' experience." Graefe's Archive for Clinical and Experimental Ophthalmology 243.11 (2005): 1108-1114.
8. Ditta, Lauren C., Yevgeniy Shildkrot, and Matthew W. Wilson. "Outcomes in 15 patients with conjunctival melanoma treated with adjuvant topical mitomycin C: complications and recurrences." Ophthalmology 118.9 (2011): 1754-1759.