Separate Primary Melanomas of the Bulbar Conjunctiva and Eyelid Skin: Clinical Implications of Multiple Primary Melanomas

Frances A. Jacinto^a George H. Fisher^a Edgar M. Espana^a Ilya M. Leyngold^a
Curtis E. Margo^{a, b}

Departments of ^aOphthalmology and ^bPathology and Cell Biology, Morsani College of Medicine, University of South Florida, Tampa, Fla., USA

Key Words

Conjunctival melanoma · Melanoma · Eyelid

Abstract

Purpose: We report a patient with previous in situ melanoma of the forehead skin who was referred for treatment of a bulbar conjunctival melanoma and a separate superficially invasive melanoma of the eyelid skin, and we offer a review of the biological and clinical implications of patients who have multiple primary melanomas. **Methods:** This article offers a clinicopathological correlation with a review of the relevant literature. **Results:** An 80-year-old white man was referred for evaluation of a suspicious conjunctival tumor and a lower-eyelid lesion. Excisional biopsies revealed that both were primary melanomas arising within in situ disease. Over the span of 25 years, the patient had three separate foci of in situ melanoma, two of which spawned invasive melanoma. **Conclusion:** Separate melanomas arising from the bulbar conjunctiva and eyelid skin have rarely been reported. Multiple primary melanomas of the skin, however, are not uncommon. Based on studies of persons with multiple cutaneous melanomas, the prognosis is best predicted by the tumor with the greatest depth of invasion. Patients with multiple

melanomas should be examined for dysplastic nevi, additional cutaneous melanomas, and screened periodically for future lesions. Ongoing studies enrolling patients with multiple primary melanomas are attempting to generate insights into low-penetrance susceptibility genes.

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Introduction

Conjunctival melanoma is an uncommon malignancy with roughly 3 cases occurring for every 2 million persons over the age of 65 years [1]. The incidence of conjunctival melanoma is roughly 1/500th that of cutaneous melanoma [2]. The majority of conjunctival melanomas arise from melanocytic intraepithelial neoplasia (or primary acquired melanosis with atypia; 75%) with the remainder being associated with nevi or arising de novo [2, 3]. Conjunctival melanoma occurring simultaneously with a separate cutaneous melanoma of the eyelid has rarely been reported [4–6]. We report a patient with a history of in situ melanoma of the facial skin who was referred for management of two separate melanomas of the conjunctiva and ipsilateral eyelid skin.

Case Report

An 80-year-old white man was referred for evaluation and management of pigmented lesions of the right conjunctiva and of the right lower eyelid. The conjunctival mass had been present for 3 years; the duration of the eyelid lesion was at least 6 months. The relevant past medical history was significant for a previous primary cutaneous melanoma in situ of the right temple treated by local excision 25 years ago and a basal cell carcinoma on the tip of the nose 6 years ago. There was no family history of melanoma and no history of dysplastic nevi. Although he had annual skin examinations searching for new melanomas, his eyes were not included in those exams.

On exam, corrected visual acuity was OD 20/50 and OS 20/30 due to cataracts with intraocular pressures of 15 and 14 mm Hg of each eye, respectively. Slit-lamp examination showed a mottled brown plaque of 4×1.8 mm in the middle of the right lower eyelid with loss of lashes (fig. 1). There was no visible pigment on the adjacent tarsal conjunctiva or inferior cul-de-sac. A 5-mm dark brown nodule was present at the superior temporal limbus, where it was fixed to deeper tissue. Speckled coffee-colored conjunctiva surrounded the mass, extending clockwise from 6 to 3 o'clock (fig. 1). Pigment extended on the contiguous cornea. The remainder of the eye exam was noncontributory. No adenopathy was palpable. Magnetic resonance and PET imaging showed no evidence of metastatic disease.

The conjunctival lesion and melanosis were excised with a 'no-touch' surgical approach. A lamellar dissection of the limbus was performed to obtain a clear surgical margin. Double freeze-thaw cryotherapy was applied to the remaining conjunctival borders. An amniotic membrane was placed over the exposed sclera and secured with a fibrin sealant. Three weeks later, the pigmented tumor of the right lower eyelid was excised with a full-thickness pentagonal resection. A lateral canthotomy, inferior cantholysis, and myocutaneous flap were used to close the surgical defect.

Histologic evaluation of the conjunctival specimen showed a melanoma arising within widespread intraepithelial melanocytic neoplasia (fig. 2). Multiple sections failed to reveal lymphatic involvement or spread along perivascular spaces. The melanoma was 1 mm thick and extended to the deep limbal margin. After the margins of the full-thickness lid resection were removed for histological examination, the central portion of the pentagonal resec-

tion was embedded and cut vertically. A superficially invasive melanoma (Breslow depth 0.15 mm) arose within melanoma in situ (fig. 3). Neoplastic melanocytes extended focally into follicular and ductal structures (fig. 3). The tumor expressed MART-1, which was used to identify the extent of in situ spread. Intraepithelial melanocytic neoplasia spread anteriorly to the lashes and posteriorly to the superior edge of the tarsus (fig. 4). Abnormal melanocytes were not found on the tarsal conjunctiva. The surgical margins were uninvolved.

The patient was referred to a dermatologist who found no other primary melanomas. He has been followed for 2 years without any new skin lesions. A single focus of conjunctival melanocytic intraepithelial neoplasia was detected in the inferior cul-de-sac 1 year after surgery. It was excised, and the margins were frozen. This was followed by a regimen of topical mitomycin C.

Fig. 1. Few lashes remain in a tan 4×1.8 mm plaque on the right lower lid margin. A deep brown nodule of the bulbar conjunctiva fixed to underlying tissue wraps around the limbus from 8 to 12 o'clock. It is surrounded by diffuse hyperpigmentation of the bulbar conjunctiva and cornea.

Fig. 2. The conjunctival nodule consists of sheets of malignant cells filling the substantia propria (HE; bar = $275 \mu\text{m}$). **Inset** Higher magnification showing atypical melanocytes in the epithelium and similar cells replacing the substantia propria (HE; bar = $150 \mu\text{m}$).

Fig. 3. The epithelial surface of the lid margin is partially replaced by atypical melanocytes that have spread into a duct which is dilated distally (*). Neoplastic melanocytes lining the duct have expanded into the surrounding dermis (HE; bar = 75 μ m).

Fig. 4. MART-1 stain of the posterior lid margin shows atypical melanocytes lining a follicle on the right. Neoplastic melanocytes spread no further posteriorly than the epithelium above the tarsus on the left (bar = 75 μ m). There was no involvement of the palpebral conjunctiva.

Discussion

The differential diagnosis in this setting includes separate primary melanomas and regional metastasis, also referred to as in-transit spread. The histologic hallmark of in-transit spread is lymphatic involvement or spread

along perivascular conduits, neither of which was found in this case. In situ metastases would also be highly unusual, as both melanomas arose within intraepithelial neoplasia. As we are unaware of any previous report describing in-transit spread of a conjunctival melanoma giving rise to a cutaneous eyelid melanoma with in situ disease, the diagnosis of separate primaries was thus favored.

Separate primary melanomas of the conjunctiva and eyelid are rare. We found 3 cases reported in the English literature [3–6]. One of these cases occurred in a patient with neurofibromatosis type 1, which may have represented a unique inherited predisposition [6]. Multiple primary cutaneous melanomas, however, are not uncommon, ranging from 0.2 to 8.6% of primary melanomas [7–13]. The observed numbers in most studies are well beyond those expected by chance alone [7–10, 12, 13]. In one large study of 2,470 patients with melanoma, roughly 0.8% developed three or more primaries during a mean follow-up of 12 years [7]. The cumulative 5-year risk of second skin melanoma is about 11%, with about half developing within the first year of initial diagnosis [12]. Patients with two melanomas have a greater than anticipated risk of developing a third and even fourth melanoma [7–9, 12, 13]. The relative rarity of primary conjunctiva and eyelid skin melanomas compared to multiple skin melanomas may simply reflect the relatively smaller surface areas of the conjunctiva and eyelid compared to the total skin area. Solitary cutaneous melanomas of the eyelid skin are uncommon [14–16]. In general, they tend to have a better prognosis than comparable melanomas of the skin located elsewhere [14].

The second melanoma in patients with two primaries tends to be thinner, on average, than the initial tumor [7–13]. In persons with multiple primary melanomas, Breslow thickness is the main determinant of prognosis [7–13]. Other independent risk factors include mitotic index, ulceration, and location on the scalp [11]. Family histories of melanoma and dysplastic nevi have been associated with multiple primary melanomas [12]. Importantly, second primary melanomas do not convey any added risk of mortality [7–13].

Patients with multiple cutaneous melanomas tend to be older than those with single primaries, but few other consistent features have been reported [7]. The genetic basis for melanoma susceptibility is being actively investigated using a variety of techniques including genome-wide analysis of low-penetrance susceptibility loci [17]. The Genes, Environment, and Melanoma (GEM) study is a case-control study with over 1,200 incident cases of

multiple primary melanomas and nearly 2,500 first primary melanomas. Future results hope to shed light on the genetic regions that convey vulnerability to melanoma.

In summary, simultaneously diagnosed primary melanomas of the conjunctiva and eyelid skin are rare. Persons with two or more primary skin melanomas are older than patients with single melanoma. They are also at continued risk of developing additional melanomas [7–9, 12, 13]. The Breslow depth of invasion of the thickest melanoma tends to best determine overall prognosis.

Patients with a cutaneous melanoma require periodic monitoring for new skin melanomas for life. Although population-based evidence is lacking, it seems biologically feasible that this same risk might apply to melanomas of the conjunctiva and eyelid. Given the potential benefit

of early detection of melanoma and few downsides of screening examinations, periodic inspections should include the conjunctiva and eyelids.

Statement of Ethics

Written informed consent was obtained from the patient for the purpose of this publication.

Disclosure Statement

The authors have no conflicts of interest to declare with no financial interest in any materials or methods presented in this paper.

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