Melanocytoma of the Conjunctiva: Clinicopathologic Features of Three Cases

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Keywords

Conjunctiva · Melanocytoma · Magnocellular nevus · Tumor · Histopathology

Abstract

Background: Melanocytoma (magnocellular nevus) is a jet-black benign lesion histologically composed of polygonal tumor cells with small, inconspicuous nuclei and abundant cytoplasm. Melanocytomas in general are rare. Most cases occur in the optic nerve head. Conjunctival melanocytoma (magnocellular nevus) is extremely rare, and only 3 lesions of the ocular surface have been reported. **Objectives:** To describe the clinical and histological spectrum of conjunctival melanocytoma and discuss differential diagnoses of this rare lesion. **Method:** Four heavily pigmented conjunctival lesions were excised for slight tumor growth and histologically processed. The specimens were routinely stained with hematoxylin and eosin and periodic acid-Schiff. Sections were bleached and immunohistochemical stains were performed for CD68, HMB-45, S100, melanin, and Ki-67. **Results:** Histological examination revealed findings of a conjunctival melanocytoma in 3 cases. The fourth case was diagnosed histologically as a combined melanocytic lesion with a compound nevus and an inverted type A nevus.

None of the lesions exhibited transition towards malignancy. The differential diagnoses included conjunctival melanoma, granular cell nevus, compound nevus with reactive changes, and blue nevus. **Conclusions:** Conjunctival melanocytic lesions suspicious for melanocytoma should be bleached to evaluate their cytologic features. CD68 can be helpful in identifying heavily pigmented melanomacrophages which may mimic a melanocytoma. As conjunctival melanocytomas are extremely rare, their pathogenesis may be different from that of other conjunctival nevi.

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Introduction

Melanocytoma in general is a rare, heavily pigmented lesion that is characterized by its benign nature and typical histological features. The most frequent location for a melanocytoma is the optic nerve head. Zimmerman and Gar-

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ron [1] coined the term “melanocytoma” in 1962, emphasizing its benign behavior, since the tumor had previously been considered to be a primary malignant melanoma of the optic disc. The synonymous term “magnocellular nevus” was coined by Cogan [2] in 1964. The first conjunctival melanocytoma was reported by Verdaguer et al. [3] in 1974. They described a congenital, multifocal, slowly progressive, and pigmented lesion in a Caucasian girl which was classified by light and electron microscopy as a melanocytoma surrounded by ectopic gland tissue. Folberg et al. [4] interpreted this case as a “most exceptional congenital, multifocal, slowly progressive blue nevus.” They also described an episcleral/scleral melanocytoma in epibulbar tissue rather than in the substantia propria of the conjunctiva.

Histologically, melanocytoma cells exhibit characteristic cellular features that become apparent – due to their intense pigmentation – only after bleaching with, for instance, potassium permanganate. The cells are round or slightly polyhedral with small, uniform, centrally placed nuclei and inconspicuous nucleoli; the abundant cytoplasm is filled with mature giant melanosomes, and these cells have been referred to as type I cells. Type II cells are less common and are described as spindle-shaped and sparingly pigmented. They reveal a high nuclear-to-cytoplasmic ratio and partly conspicuous nucleoli, are interpreted to be metabolically active, and are therefore considered responsible for the growth potential of melanocytomas [5]. In general, mitotic figures are uncommon. Scattered melanomacrophages have been observed.

Herein, we (1) report the clinical and pathologic features of 3 cases of conjunctival melanocytoma, (2) compare our cases to the previously described conjunctival melanocytomas, and (3) provide hints and pitfalls regarding this histopathologic diagnosis.

Materials and Methods

Materials

In the period from 1989 to 2010, 2 cases of conjunctival melanocytoma were identified from the cases on file in the L.F. Montgomery Laboratory, Emory Eye Center, Atlanta, GA, USA. Another case was contributed by Ramon L. Font (Ophthalmic Pathology Laboratory, Cullen Eye Institute, Baylor College of Medicine, Houston, TX, USA). The fourth case, which clinically and histologically mimics a melanocytoma, was identified at the Ophthalmic Pathology laboratory, University of Bonn, Bonn, Germany.

The medical records of the corresponding patients were retrospectively reviewed. The histological specimens were analyzed for size, cell type, cytologic features, and immunohistochemical findings. The excisional biopsies were independently reviewed by at least two ophthalmic pathologists (H.E.G., M.C.H.-C., Ramon L. Font, and K.U.L.).

Methods

The formalin-fixed specimens were grossly examined for size and color. They were routinely processed for light microscopic examination and stained with hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS). H&E stains were bleached with 0.25% potassium permanganate for 30 min followed by rinsing with 5% oxalic acid.

One specimen (case 1) was further immunohistochemically characterized by CD68 (DAKO, Carpinteria, CA, USA; 1:2,560), melanin (Masson-Fontana Silver Method), HMB-45 (DAKO; 1:60), S100 (DAKO; 1:3,200), and Ki-67 (DAKO; 1:160). Case 4 was also further analyzed immunohistochemically by CD68 (DAKO; 1:50), melan A (DAKO; 1:200), HMB-45 (DAKO; 1:50), S100 (DAKO; 1:10,000), and Ki-67 (DAKO; 1:500).

Results

Case 1

A 14-year-old Caucasian girl presented with a dark-brown lesion in the nasal bulbar conjunctiva of her right eye suspicious for a conjunctival nevus. According to the patient, the lesion had first been noticed after a basketball game (2 or 3 years before) and slow growth was noted over several months. The patient’s ocular history was otherwise unremarkable. An excisional biopsy was performed at the patient’s request. The patient was lost to follow-up.

Histological examination revealed a pigmented lesion (measuring $2 \times 1 \times 1$ mm) in the substantia propria of the conjunctiva without epithelial involvement mostly composed of plump polyhedral cells with bland nuclei and abundant granular cytoplasm (Fig. 1a). Mitotic figures were absent. Although only moderately pigmented, bleached H&E stains exhibited typical melanocytoma cells. The lesion was PAS negative. A Masson-Fontana stain (indicating melanin) was strongly positive in the magnocellular nevus cells, as was a stain for HMB-45. CD68 was sparsely expressed, highlighting scattered macrophages (Fig. 1b). Immunohistochemical stains were weakly positive for S100 and negative for Ki-67. There were epithelial inclusion cysts surrounded by sporadic nests of nevocellular nevus cells associated with the lesion. The lesion was completely excised. In summary, this lesion showed histopathological characteristics of a melanocytoma.

Case 2

A 52-year-old African-American woman underwent excisional biopsy of a jet-black lesion of the bulbar conjunctiva in the right eye. Within 5 years’ growth, an increased vascularity (feeder vessels) had been observed

Fig. 1. Case 1: conjunctival melanocytoma. Histology showed a moderately pigmented lesion (**a**, **inset**; H&E stain). Bleached stains revealed plump polyhedral cells with an unsuspicious nucleus and abundant “granular” cytoplasm (**a**; bleached H&E stain). Only scattered macrophages (**b**; CD68 immunostain; arrows) were observed.

Fig. 2. Case 2: conjunctival melanocytoma. The clinical picture showed a jet-black lesion of the bulbar conjunctiva (**a**). Histology of this primary lesion revealed a heavily pigmented tumor (**b**; H&E stain) with polyhedral tumor cells and still many pigment-containing cells after bleaching (**c**; higher magnification; H&E stain).

(Fig. 2a) while the patient had administered latanoprost (50 µg/mL) eye drops once a day. The tumor was clinically suspicious for malignant melanoma, but the diagnosis was changed to melanocytoma after histological examination. Another nevoid lesion – diagnosed histopathologically as blue nevus – was present at the palpe-

bral conjunctiva. There was no intervening pigmentation between the lesion of the bulbar conjunctiva and the lesion of the tarsal conjunctiva. No recurrence of either pigmented lesion was observed within 8 years.

Histologically, the lesion was composed of heavily pigmented melanocytes in the substantia propria (with-

Fig. 3. Case 3: conjunctival melanocytoma. Histology (unbleached stains) showed a heavily pigmented lesion underneath the conjunctival epithelium (**a**; H&E stain) with conjunctival inclusion cysts (asterisk). The tumor consisted of polyhedral nevus cells with melanin granules in their cytoplasm (**b**; H&E stain).

out epithelial involvement) of the conjunctiva. After bleaching, sheets of polygonal cells with round-to-oval nuclei (and a few prominent nuclei) were uncovered (Fig. 2b, c). Many of these cells still contained visible melanin pigment in their cytoplasm. Mitotic figures were absent. There were also scattered chronic inflammatory cells present in the lesion. The lesion was completely excised with tumor-free margins. These findings led to the diagnosis of a conjunctival melanocytoma.

Case 3

A 49-year-old Hispanic woman underwent excisional biopsy for a conjunctival tumor of her right eye.

Histologically, the conjunctival stroma was interspersed with heavily pigmented polygonal cells with round-to-oval nuclei and inconspicuous nucleoli (Fig. 3). Mitotic figures were absent. There were conjunctival inclusion cysts – which are typical for conjunctival nevi – present in the substantia propria. The lesion was diagnosed as conjunctival melanocytoma.

None of the lesions was associated with primary acquired melanosis or showed features of transition towards a melanoma.

A summary of the clinical and histopathological findings on our 3 cases, as well as on 3 cases of ocular surface melanocytomas which have been reported in the literature, is shown in Table 1.

Case 4 (Combined Melanocytic Nevus with Compound Nevus and Inverted Type A Nevus Histologically Mimicking Conjunctival Melanocytoma)

A 7-year-old boy presented with a jet-black lesion suspicious for a nevus on the medial conjunctiva of the right eye (Fig. 4a). The slowly growing lesion was excised to rule out a malignant process.

Histopathological analysis revealed a nevus of the conjunctiva with nevus cell nests within the epithelium and the underlying conjunctival stroma. There were epithelial inclusion cysts present. Some areas of the nevus were pigmented (Fig. 4b). Adjacent to the classic nevus cell nests were larger heavily pigmented cells with a polygonal appearance and round-to-oval nuclei suspicious for melanocytoma (Fig. 4c, d). Within this area were small “clonal” nests of brighter cells present which shared the polygonal appearance with the heav-

Fig. 4. Case 4: combined melanocytic nevus with a compound nevus and an inverted type A nevus histologically mimicking conjunctival melanocytoma. There was a dark-brown lesion on the bulbar conjunctiva (**a**). Histology showed a compound nevus which was composed of nests of nevus cells. Adjacent to the nevus was a heavily pigmented lesion with small “clonal” nests of brighter (arrows) cells sharing the polygonal appearance with the heavily pigmented cells (**b**; H&E stain). Polyhedral cells with incon-

spicuous nuclei were visible after bleaching (**c**; bleached H&E stain). Higher magnification showed the polyhedral cells which contained many melanin granules and small clonal nests (**d**; H&E stain; arrows). The nevus cells were highlighted by a melan A stain (**e**; melan A immunostain). The heavily pigmented cells were CD68 positive, identifying them as melanomacrophages (**f**; CD68 immunostain).

spicuously pigmented cells. The nevus cell nests were positive for melan A (Fig. 4e), HMB-45, and S100, and so were the “clonal” cells. Ki-67 was positive in less than 2% of the nevus cell nests. The heavily pigmented polygonal cells were CD68 positive (but melan A, HMB-45, and S100 negative), allowing for a characterization as mela-

nomacrophages (i.e., macrophages which have incorporated melanin pigment) (Fig. 4f). Based on these findings, the diagnosis of a combined conjunctival melanocytic nevus with a compound nevus and an inverted type A nevus surrounded by melanomacrophages was made.

Discussion and Conclusion

We have presented 3 cases of conjunctival melanocytoma. The lesions were located in the bulbar conjunctiva. However, the race and age of the 3 female patients differed. Two lesions (cases 2 and 3) and the nonmelanocytomatous lesion (case 4) had a typical jet-black color. Analyzing the demographic characteristics of all reported patients with melanocytomas of the anterior segment ($n = 6$; Table 1) [3, 4, 6], the lesions seem to occur in African-Americans, Hispanics, and Caucasians at all ages. However, there may be a preponderance of females. A closer look at the cases showed only sparse similarities that were restricted to the histopathological features. Some cases displayed specific findings adjacent to the melanocytoma, such as an additional compound nevus (case 1) or ectopic lacrimal gland tissue [3]. This indicates that a melanocytoma of the conjunctiva is not only a rare lesion but also an entity that displays variable features.

All cases revealed unexpected findings that required further consideration. The first case consisted of typical melanocytoma cells, although the lesion was not as heavily pigmented as expected. Next to the magnocellular nevus cells, nest-building nevocellular nevus cells were also observed in the superficial conjunctiva. This indicates that a melanocytoma of the conjunctiva can – similar to a blue nevus [4] – arise beside a nevocellular nevus. Granular cell nevus has to be included in the differential diagnoses in this case, as there are some histopathological characteristics overlapping with those of melanocytoma. However, granular cell nevi exhibit less intense pigmentation than melanocytomas and are usually strongly positive for S100, while only a weak immunoreaction was observed in this case [7, 8]. The magnocellular nevus cells did not reveal PAS-positive granules in the cytoplasm (which would be characteristic of a granular cell nevus [8]), which, together with the strongly positive Masson-Fontana stain (highlighting melanin), strengthens the diagnosis of melanocytoma.

The second case showed a deeply pigmented tumor with slight growth over 5 years and the development of feeder vessels. The lesion exhibited characteristic features of a melanocytoma. In addition, a blue nevus was present at the palpebral conjunctiva. This is of interest, as Folberg et al. [4] reclassified the pigmented conjunctival lesion representing the first case of a conjunctival melanocytoma reported by Verdaguer et al. [3] as blue nevus. This dispute is representative of the difficulty with classifying melanocytic lesions of the conjunctiva. Further investiga-

tion of this case by electron microscopy may be helpful in detecting ultrastructural features to ensure the diagnosis.

The third case represents a melanocytoma with typical histological findings. However, inclusion cysts were present, which are usually observed in nevi with a junctional component, dragging epithelial cells downwards during their migration into the substantia propria. The first case also showed inclusion cysts. However, they were associated with nests of “regular” nevus cells. As the melanocytoma cells were only detected subepithelially without junctional activity, the presence of inclusion cysts in case 3 is surprising.

Differential Diagnoses

The differential diagnoses include conjunctival melanoma, granular cell nevus, compound nevocellular nevus with reactive changes, blue nevus (particularly epithelioid blue nevus), and conjunctival foreign body. When pigmented conjunctival lesions exhibit growth, a malignant melanoma of the conjunctiva and extraocular growth of an intraocular uveal melanoma need to be ruled out histologically. However, none of our cases showed evidence of a malignant lesion or a transition towards it. The immunohistochemical granular cell nevus characteristics that are different from our melanocytomas have been mentioned above [7, 8]. A combined melanocytic nevus with a “regular” nevocellular compound nevus and an inverted type A nevus, with the clonal population being surrounded by CD68+ melanomacrophages (case 4), can mimic cytologic features of magnocellular nevus cells and has to be carefully distinguished from a genuine melanocytoma by immunohistochemistry [4]. An inverted type A nevus (or clonal nevus) of the conjunctiva is extremely rare, and only a few cases have been described so far [8–10]. Blue nevi that also exhibit heavily pigmented nevus cells reveal characteristic spindle-shaped cells that may share some cellular characteristics with type II melanocytoma cells. Also, deeply pigmented foreign bodies can mimic a melanocytoma clinically [11].

Pigmented Epithelioid Melanocytoma

In contrast to ocular melanocytoma, skin lesions termed “pigmented epithelioid melanocytoma” comprise a group of lesions including cases previously diagnosed as animal-type melanoma and epithelioid blue nevus, and they are best considered as borderline melanocytic neoplasms or low-grade melanomas [12, 13]. Their clinical behavior, as well as their histological appearance, differs from that of genuine melanocytomas of the nervous system, and the term pigmented epithelioid melanocytoma is rather misleading.

Origin of Melanocytic Lesions

As only 1 (equivocal) case of a conjunctival melanocytoma has been previously described [3], its origin is unclear and must be reconsidered in relation to other melanocytic lesions. A literature search (PubMed search for “melanocytoma” in July 2018; 573 entries) revealed that melanocytomas were predominantly reported in the nervous system including the eye. Rarely, lesions were described in the orbit. An association of melanocytoma with oculodermal melanocytosis has also been described and was interpreted as different clinical expressions of the same congenital pigmentary abnormality, although both lesions are considered to represent different entities [14, 15]. Conjunctival melanocytomas have more frequently been reported in dogs [16]. However, the reason for this observation is still unknown (Jan U. Prause, pers. commun., 2010).

The preponderance of melanocytomas of the nervous system distinguishes them from other melanocytic lesions. Ocular melanocytomas, which usually arise in the optic nerve head (and the uveal tract), derive from proliferating melanocytes of the optic nerve and the lamina cribrosa as well as the uveal tract. It is well known that intraocular melanocytes differ from melanocytes of the conjunctival and skin epithelium. These findings may help to explain the rare occurrence of melanocytomas in the conjunctiva: melanocytes derive from the neural crest [17], followed by migration (and differentiation) of these cells to either the epithelium of the conjunctiva/epidermis or the connective tissues of, for instance, the uvea [4]. The connective tissue melanocytes in the uvea and optic nerve from which melanocytomas usually arise may be scattered during the embryonic/fetal development of the eye, finally leading to extraocular melanocytomas in the orbit and conjunctiva/(epi)sclera. Alternatively, melanocytoma cells may represent neural crest-derived cells which have never reached the surface epithelium and usually disappear by the end of gestation [18]. The latter theory better fits the blue (cellular) nevi [4, 18], as blue nevi – named after their blue appearance (in contrast to their dark appearance in the conjunctiva [8]) – predominantly occur in the dermis and are also only rarely found in the conjunctiva. In contrast, common congenital nevus cell nevi (junctional nevus, subepithelial nevus, and compound nevus) arise from intraepithelial melanocytes [4].

From a genetic point of view, (benign and malignant) melanocytic lesions of the conjunctiva share more similarities with skin melanocytic lesions than with uveal nevi and melanomas [19]. Melanocytic lesions of the central nervous system show genetic similarities to uveal mel-

anocytic neoplasms [20]. For instance, genetic similarities to uveal melanoma have been reported in a case of a leptomeningeal melanocytoma [21]. Melanocytomas of the optic nerve have been reported to show a class 1A genetic signature [22]. However, blue nevi – in contrast to other skin and conjunctival melanocytic lesions arising from epithelial melanocytes (typical nevus and melanoma) – have GNAQ mutations which are similar to those found in uveal melanoma [19, 23]. Unfortunately, due to the lack of a sufficient amount of remaining material, we are unable to provide a genetic analysis of the reported cases, which would be helpful for further characterization. Future studies with a focus on genetic alterations may result in a better understanding of conjunctival melanocytic lesions.

In summary, conjunctival melanocytoma is a rare entity and has to be carefully distinguished from other melanocytic lesions with which they share clinical similarities. Bleaching is required for heavily pigmented tumors of the conjunctiva to uncover cytologic features that allow a profound diagnosis. Additional immunohistochemical evaluation is recommended in equivocal cases. As malignant transformation and infiltrative growth were described for melanocytomas of the optic disc and uvea [24], and only a few cases of melanocytoma of the ocular surface have been described, follow-up examinations are suggested – although we have no evidence for recurrence in our 3 cases (based on follow-up [$n = 1$] or submission of further excisional biopsies [$n = 2$]).

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Statement of Ethics

Institutional review board/ethics committee approval was obtained. Our research adhered to the tenets of the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors made significant contributions to the manuscript (see below). All authors approved the final manuscript and agree to be accountable for the accuracy and integrity of the work. M.C.H.-C.: conception, analysis, interpretation, and writing; K.U.L.: case acquisition, interpretation, and revision; H.E.G.: conception, case acquisition, interpretation, and revision.

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