Balloon Cell Nevi of the Conjunctiva: Clinicopathologic Correlation and Literature Review.

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Abstract:

Balloon cell nevi are rare, benign melanocytic tumors that may involve the conjunctiva, choroid, and skin. In the ocular adnexa they typically present as raised and mobile hyperpigmented masses. Histologically balloon cell nevi consist of large cells forming nests that usually lack melanin pigment. The balloon cells have a clear or vacuolated cytoplasm with centrally located nuclei. The vacuolated cytoplasm may be the result of defective melanin synthesis, with the accumulation of melanin precursors in premelanosomes. Balloon cells can resemble xanthoma cells, adipocytes, macrophages, sebaceous adenomas, melanoma with balloon cell changes, and metastatic renal cell carcinoma. Differentiating between these various entities via morphology and immunohistochemistry thus remains clinically significant. We report three cases of conjunctival balloon cell nevi and review the literature.

Keywords: Balloon cells, nevi, nevocellular, melanocytic, balloon cell nevi

Introduction:

Melanocytic nevi of the conjunctiva are common benign tumors. The nevocellular nevus is the most common type of conjunctival melanocytic tumor and frequently arises within the bulbar conjunctiva, plica semilunaris, or caruncle during the first two decades of life.^{21,31} Balloon cell nevi are uncommon melanocytic tumors that are characterized histologically by their large size, lack of melanin pigment, and vacuolated cytoplasm. Although balloon cell nevi in the conjunctiva are rarely documented in the literature, they have been reported in up to 2% of cutaneous and 4% of choroidal nevi.^{4,20} The histologic appearance of balloon cells may mimic other pathologic entities, and thus immunohistochemistry and morphologic characteristics are used to differentiate between them. We report the clinicopathologic features of three new cases of balloon cell nevi of the conjunctiva and summarize the previously reported cases.

Report of Cases:

Case 1. A 12-year-old Hispanic male presented with a pigmented caruncular mass that was present since birth with fluctuation in size and noted to be slowly growing over the past four years. Prior to presentation he had been treated intermittently with anti-inflammatory eye drops. Examination revealed visual acuity of 20/15 in both eyes. Intraocular pressures were 15 mm Hg OD and 16 mm Hg OS. The lid skin was clear. A raised, hyperpigmented caruncular mass OD was painless and mobile (Figure 1A). The caruncular mass was excised.

Microscopic examination disclosed caruncular tissue that contained nests of nevus cells located within both the epithelium as well as the substantia propria (Figure 1D). In the substantia propria many of the nevus cells had clear cytoplasm with centrally located nuclei. There was no evidence of cellular atypia. Immunohistochemical staining revealed the cells to be weakly PAS positive (Figure 2A), melan-A positive (Figure 2B), S-100 positive (not shown), HMB-45 negative, CD68 negative, CD45 negative, and colloidal iron positive, Alcian blue negative, and Lysozyme negative. The immunohistochemical and morphological features were consistent with a compound nevocellular nevus with balloon cell features (balloon cell nevus).

Case 2. A 14-year old Afro-Caribbean female presented with a pigmented conjunctival mass. The lesion was first noticed when she was one year old and grew over the next few years. Visual acuity was 20/20 OU. A 4.5 mm x 5.0 mm pale, brown, gelatinous mass was present on the temporal bulbar conjunctiva (Figure 1B). The lesion was raised, mobile, and painless. This was excised.

Microscopic examination disclosed conjunctiva that contained nests of nevus cells located within the epithelium and substantia propria (Figure 1E). The cells in the substantia propria contained vacuolated cytoplasm, centrally located nuclei, and no evidence of cellular atypia. A moderate amount of extracellular pigment was observed within the substantia propria; however, the nevus cells in the substantia propria largely lacked melanin pigment. Immunohistochemical staining revealed the cells to be positive for melan-A and S-100 and negative for HMB-45, consistent with a balloon cell nevus.

Case 3. A 29-year-old Caucasian male presented with a cystic conjunctival lesion OS. He reported that the lesion was red and painless, had been present for several years, and had not grown. Visual acuity was 20/20 OU with intraocular pressures of 12 mm Hg OD and 13 mm Hg OS. A 6.5 mm pink, fleshy cystic mass was identified in the plica semilunaris OS (Figure 1C). This was excised.

Histopathologic examination revealed mucosal epithelium that contained nests of nevus cells located within the epithelium and substantia propria (Figure 1F). Clear cells were seen in the substantia propria with no mitotic activity or cellular atypia. The melan-A stain was positive within the nevus cells as well as the within the clear cells located in the substantia propria, consistent with a compound nevus with balloon cell features.

Discussion:

Balloon cell nevi are benign melanocytic tumors typically found in the choroid and skin and rarely in the conjunctiva. They represent histologic variants of the more common nevocellular nevi. Proliferation of such nevus cells in the epithelium normally starts within the first decade of life, after which the cells may migrate into the substantia propria.⁸ The nevi are thought to become more noticeable around puberty as the result of hormonally-induced hyperpigmentation and focal inflammation.^{17,23} Cutaneous balloon cell nevi were first described by Judalewitsch in 1901, and Miescher reported the first well-documented case in 1935.^{13,19} These benign tumors were more extensively described by Schrader and Helwig in 1967 when they reviewed cases from the Armed Forces Institute of Pathology.²⁸ Pfaffenbach *et al* reported the first case of a conjunctival balloon cell nevus in 1972.²⁴ Subsequently, there have been a total of 13 documented cases of conjunctival balloon cell nevi, with only one being located in the caruncle (Table 1).^{2,8-9,11-12,17,23-24,27,33}

Balloon cell nevi typically present as raised, hyperpigmented, mobile lesions. The age at presentation ranges from 7 to 44 years; however, several of these lesions had been noticed for many years before coming to medical attention. Approximately 37.5% were in the nasal bulbar conjunctiva, 37.5% in the temporal bulbar conjunctiva, and 12.5% in the caruncle (Table 1). One was in the nasal palpebral conjunctiva at the lid margin, and one was in the plica semilunaris. Ten out of 15 were in females. Of note, however, there does not appear to be a gender predilection in cutaneous balloon cell nevi.¹⁸ Because of the rarity of conjunctival balloon cell nevi, and given that excision was the treatment for all cases, their natural history remains unknown. The rate of recurrence after excision is also unclear as only three reports comment on recurrence, with one case having multiple recurrences²⁴ and two cases without recurrence after 4 and 6 months.^{11,33} Table 1 summarizes the characteristics of the cases of conjunctival balloon cell nevi reported to date.

Balloon cell nevi are characterized histologically by nests of large cells that lack melanin pigment and have a clear or vacuolated cytoplasm with centrally located nuclei. The vacuolated cytoplasm may be the result of several different processes, including being filled with fat or undergoing lipomatous transformation.^{16,19} The prevailing hypothesis is that the balloon cells are merely altered nevus cells with a defect in melanin synthesis. This results in the buildup of melanin precursors in premelanosomes and

gives rise to the vacuolated appearance of the cells.^{7,28} Electron microscopy studies have subsequently demonstrated the abnormal remnants of premelanosomes.² For comparison, the histopathologic features of other benign conjunctival nevi are illustrated in Table 2.

The presence of balloon cells does not in itself indicate benignity as they have been found in malignant melanomas of the skin and in 10% of uveal melanomas.²⁴⁻²⁵ Kao *et al* reviewed cases of balloon cell malignant melanomas of the skin from the Armed Forces Institute of Pathology and found that the presence of balloon cells did not affect metastatic potential, and the prognosis was similar to other types of cutaneous melanomas.¹⁵ Additionally, balloon cells in malignant melanoma simply represent a morphologic feature, not a specific subtype of melanoma. The morphologic features of malignant balloon cells (i.e. nuclear pleomorphism, prominent nucleoli, hyperchromatic nuclei, mitotic figures) can aid in differentiating between benign and malignant melanocytic disease; however, several other histologic entities may contain similar appearing cells.

In addition to balloon cell nevi the histologic differential diagnosis of clear cells in the ocular adnexa includes xanthoma cells, adipocytes, macrophages, sebaceous adenomas, clear cell hidradenomas, balloon cell melanomas, and metastatic renal cell carcinomas.^{9,11} As previously mentioned, the morphologic characteristics of the cells, including mitotic activity and prominence of nucleoli, is helpful in distinguishing benign and malignant disease. Furthermore, immunohistochemical staining is a useful adjunct to narrow the differential. Balloon cell nevi are derived from the neural crest and thus stain positively for S-100. The melan-A immunostain is also positive and identifies the cells as melanocytes. The balloon cells are weakly periodic acid-Schiff (PAS) and colloidal iron positive and negative for HMB-45, CD45 (leukocytes), Alcian blue, CD68 and lysozyme (histiocytes).²¹ Jakobiec *et al* further elaborate on the adjunctive utility of the Ki-67 and HMB-45 immunostains in conjunction with morphology in differentiating benign conjunctival nevi from malignant melanoma.¹⁰ Adipophilin (lipid) has also been reported to be negative in cutaneous balloon cell nevi.²²

Conclusion:

We add three additional cases of conjunctival balloon cell nevi, one of which is only the second reported case of a balloon cell nevus in the caruncle and the first with clinicopathologic correlation. Our third case is the first report of a balloon cell nevus in the plica semilunaris. The clinical presentation as a hyperpigmented, mobile caruncular or conjunctival lesion is consistent with previously reported cases. As our cases show, on rare occasion these lesions may be amelanotic and present as red, cystic masses. The immunohistochemistry revealed that the cells stained positively for S-100 and melan-A. The HMB-45, Ki-67, CD68, CD45, lysozyme and Alcian blue stains were negative. The bulbar conjunctiva is the most common location for balloon cell nevi, followed by the caruncle and palpebral conjunctiva. There also appears to be a female predilection. Although balloon cell nevi of the conjunctiva are uncommon, clinicians and ophthalmic pathologists should be aware of these benign lesions and remain vigilant in ruling out other histopathologic entities, including malignancies, with similar appearing morphologies and clinical presentations.

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Method of Literature Search:

The terms used for our literature search included “balloon cells”, “balloon cell nevi”, “balloon cell melanoma” and “balloon cell nevus AND conjunctiva”. Articles pertaining to “balloon cell nevi and conjunctiva” were included, whereas articles concerning balloon cell nevi at sites other than the eye and ocular adnexa were excluded. Methods used to search the international scientific literature were MEDLINE/PubMed and the University of Miami Library. The German articles included were translated into English to obtain pertinent case information.

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Figure Legend:

Figure 1. Clinical photographs with corresponding histopathologic microphotographs from cases 1 (A and D), 2 (B and E) and 3 (C and F). Microscopic examination reveals nests of large nevus cells with vacuolated cytoplasm and centrally positioned nuclei located within the epithelium and substantia propria (Figures D through F). The balloon cells lack melanin pigment and display no mitotic activity (D—F, hematoxylin-eosin, original magnification X200).

Figure 2. Microphotographs of PAS (A) and melan-A (B) stains from case 1. Histopathologic examination reveals that the balloon cells are faintly positive for PAS and notably positive with the melan-A immunostain, which highlights the melanocytic balloon cells (A, PAS, original magnification X200; B, melan-A, original magnification X200).

Location (Conjunctiva)		Author	Presentation	History	Age	Sex
Bulbar	Temporal (limbus)	Folberg <i>et al</i> ⁸	Pigmented lesion	-	16	-
Bulbar	Temporal	Lyall <i>et al</i> ¹⁷	Darkly pigmented lesion	Present for 3 months, increasing in size over the next 12 months	7	F
Caruncle	-	Pecorella <i>et al</i> ²³	Brown cystic lesion	-	16	F
Palpebral	Nasal (lid margin)	Pfaffenbach <i>et al</i> ²⁴	Pigmented cystic lesion	Recurrent lesion since age 25	39	F
Bulbar	Nasal	Haleman <i>et al</i> ⁹	Tan-yellow mobile nodule with deep brown area	Present for 3 weeks	11	F
Bulbar	Nasal	Jao <i>et al</i> ¹²	Pigmented papule	-	44	F
Bulbar	Nasal	Budde <i>et al</i> ²	Pigmented lesion	Present for 6 years	19	F
Bulbar	Nasal	Budde <i>et al</i> ²	Brown, well-circumscribed lesion	Present for 3 months	19	M
Bulbar	Nasal	Jakobiec <i>et al</i> ¹¹	Elevated, mobile, oval brown lesion with foci of darker speckling	-	44	F
Bulbar	Nasal	Schlageter <i>et al</i> ²⁷	Brown-black nodule	Present for 4 years	26	F
Bulbar	Temporal	Schlageter <i>et al</i> ²⁷	Pigmented lesion	-	17	M
Bulbar	Temporal (limbus)	Schlageter <i>et al</i> ²⁷	Partially pigmented nodule	Present since age 3	24	F
Bulbar	Temporal	Vijay Shankar <i>et al</i> ³³	Elevated, brown, mobile plaque	Present since birth	6	M
Bulbar	Temporal	Thompson <i>et al</i>	Raised, pigmented mass	Present since age 1	14	F
Caruncle	-	Thompson <i>et al</i>	Hyperpigmented mass	Present since birth	12	M
Plica Semilunaris	-	Thompson <i>et al</i>	Red, cystic mass	Present for several years	29	M

Table 1. Summary of the location, clinical features and demographic information of all of the documented cases of balloon cell nevi of the conjunctiva to date.

Nevus	Histopathologic Features
Nevocellular <ul style="list-style-type: none"> Compound Junctional Subepithelial 	Nesting pattern of nevus cells located in the: <ul style="list-style-type: none"> Epithelium and substantia propria Junction of the epithelium and substantia propria Substantia propria
Common Blue	Darkly pigmented dendritic cells located in the substantia propria. ¹
Cellular Blue	Blue nevus cells with cellular nodules composed of epithelioid cells. ³⁴
Combined	Combination of blue nevus cells and nevocellular nevus cells. ³
Balloon	Nests of clear cells with vacuolated cytoplasm and central nuclei. ²⁴
Spitz	Pigmented spindle and/or epithelioid cells, perpendicular or parallel to the epithelium. ^{6,14}
Spindle cell*	Pigmented spindle cells organized perpendicular to the epithelium. ²⁹
Magnocellular**	Large, oval or round cells with densely pigmented cytoplasm; low nuclear to cytoplasmic ratio. ^{30,32}
Nevus of Ota [†]	Pigmented dendritic cells similar to blue nevi that involve the deep stroma and epibulbar tissue. ⁵

Table 2. Histopathologic characteristics of different subtypes of conjunctival nevi.

*Cutaneous pigmented spindle cell nevi are considered to be variants of Spitz nevi.²⁶

**Also known as melanocytomas and two types of cells can be recognized, including spindle cells and the typical round cells.³⁰

[†]Also termed congenital oculodermal melanocytosis.⁵

Figure 1

Figure 2