Villous Sebaceous Adenoma Arising from the Caruncular Surface Squamous Epithelium

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Established Facts

- Benign and malignant sebaceous cell tumors are both known to originate in the caruncle.
- These tumors typically grow in nests and lobules in the caruncular stroma.
- Sebaceous tumors arising from the surface non-keratinizing squamous epithelium of the epibulbar and tarsal regions have been reported.

Novel Insights

- A caruncular sebaceous adenoma originated from the surface squamous epithelium which displayed focal sebaceous cell differentiation.
- The pattern of growth was most unusual and consisted of multiple invaginated crypts with intervening finger-like villi.
- Lateral lobular sebaceous lobules originated as outgrowths from the crypts and were mostly responsible for the widening of the stroma between the crypts.
- p16 nuclear and cytoplasmic positivity indicated a possible causative role for high-risk human papilloma virus, while immunohistochemical results for intact mismatch nuclear repair proteins ruled out an association with the Muir-Torre syndrome.

Keywords

Caruncle · Sebaceous adenoma · Villous feature · Cytokeratins · Adipophilin · DNA mismatch repair protein · p16 · High-risk human papilloma viruses · Muir-Torre syndrome

Abstract

A 68-year-old woman developed an asymptomatic left caruncular multilobular lesion over one year. Excision of the lesion displayed a benign sebaceous neoplasm taking origin from the surface squamous epithelium which invaginated into the stroma to create crypts resembling the conjunctival pseudoglands of Henle or the glands of Lieberkuhn of the

small intestine. Scattered sebaceous cells were also discovered in the surface squamous epithelium. The cryptal walls spawned lateral sebaceous gland lobules that were adipophilin positive. p16 was positive in the surface epithelium, the cryptal walls, and in the basal cells of the sebaceous lobules. No defects in nuclear mismatch repair protein expression were identified, which together with the absence of a familial cancer history, rendered unlikely an association with the Muir-Torre syndrome.

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Introduction

The overwhelming majority of sebaceous tumors, mostly malignant but occasionally benign, arise from subepithelial, preexistent sebaceous glands [1, 2]. Clinically these lesions can appear as nodular or diffuse. The Meibomian glands of the tarsi, the Zeis glands associated with the eyelid marginal cilia, the sebaceous glands associated with the strong hairs of the brow, and the sebaceous glands associated with the delicate vellus hairs of the caruncle are the usual primary sites of origin for periocular sebaceous neoplasms [3, 4].

A subset of various sebaceous tumors, however, may arise from the epibulbar and tarsal conjunctival surface epithelium in areas lacking sebaceous glands on a normal anatomic basis [5–14]. The vast majority of sebaceous lesions are hyperplasias, adenomas, sebaceomas, and carcinomas [1, 2, 14–16]. These lesions must be distinguished from clear cell squamous carcinoma [17]. The caruncular lesion described in this report developed from the surface epithelium and displayed an unusual villous (non-papillary) growth pattern that has not been previously documented in periocular sebaceous neoplasms. The lesion was evaluated immunohistochemically with a range of biomarkers, including p16 for indirectly detecting a role for high-risk human papilloma virus (HPV) infection. Further studies focused on the detection of a DNA mismatch repair (MMR) nuclear protein expression defect that might point to the Muir-Torre syndrome.

Clinical History

A 68-year-old white woman developed a right caruncular mass over a 1-year period (Fig. 1a). She had experienced excessive sun exposure as a child. She denied any personal history of skin cancer or moles, nor was there a family history of cancer proneness. A screening colonoscopic examination 3 years prior showed some polyps that were found to be benign. There was a family history of

diabetes mellitus in a brother and tonsillar cancer in her father who died at age 56.

The caruncular mass did not cause a foreign body sensation, redness, or dryness. On physical examination, vision was 20/20 in both eyes. She had full extraocular movements and symmetric 2-mm pupils that were equally reactive to light without an afferent pupillary defect. The intraocular pressures were within normal limits and the fundus examination was unremarkable. A firm, white to yellow lesion composed of “knobby” subunits larger than papillae was seen replacing the plica and caruncle (Fig. 1b). There was no ulceration nor associated lymphadenopathy.

Due to the localization of the mass, interferon drops four times a day were administered to reduce to the tumor’s size prior to surgery. After 2 months of use, the patient noticed a significant decrease in the size of the mass. Surgery was performed 7 months after the initial consultative encounter with adjunctive cryotherapy applied to the base and surrounding margins. Reconstruction of the surgical site was performed with an amniotic membrane and Tisseel. The surgical zone healed well over several weeks with an excellent cosmetic result and no limitations in ocular motility. No recurrence was noted 3 years after surgery and no signs of a visceral malignancy had emerged.

Histopathologic Findings

The excised specimen consisted of two fragments of soft, tan-brown tissue measuring $1.0 \times 0.7 \times 0.5$ cm and $1.0 \times 0.3 \times 0.1$ cm. The first was labelled as the main lesion and the other as adjacent conjunctiva. The two pieces of tissue were submitted in total for microscopic evaluation.

Low-power microscopy disclosed a cup-like structure with a thin lamina of collagen at its base. The surface epithelium extended downward as clefts forming cryptal lumens that were separated from each other by finger-like villous proliferations (Fig. 1c). The villous units separated by the clefts were repeated throughout the lesion. The lumens of the crypts contained eosinophilic material in their depths consistent with holocrine secretions (Fig. 1d). Large lymphoid aggregates, some with germinal centers, were distributed throughout the tumor (Fig. 1c, d).

On closer inspection, the invaginated surface epithelium retained a non-keratinizing squamous character with focal sebaceous cells. The lateral lobular extensions extending into the stroma constituted the basis for the repeating villous/adenomatous units (Fig. 1e). At the opening of the crypts, there were some lobules of pale sebaceous cells deriving from the surface epithelium (Fig. 1f). All of the vacuolated cells were periodic acid-Schiff, Alcian blue, and mucicarmine negative, which thus established that these cells were not a goblet cell variant.

In areas away from the cryptal orifices, the surface epithelium focally displayed involvement by small groups of vacuolated sebaceous cells (Fig. 2a). All of the lobules originated from either the surface epithelium or the invaginated cryptal epithelium. The vacuolated cells comprising the centers of the lobules were embraced by an outer basaloid cell layer devoid of cytoplasmic vacuoles. The tumor cells’ vacuolated cytoplasm surrounded a central, round, vesicular, non-hyperchromatic nucleus with a small nucleolus (Fig. 2b). Mitotic figures were not observed. The second piece of excised tissue was a portion of conjunctiva that was negative for tumor.

Fig. 1. Clinical and histopathologic features of the caruncular tumor. **a** A tumor completely replaces the right normal caruncle of a 48-year-old woman who developed the lesion over several months. **b** Higher-power clinical photograph of a knobby tumor with many crevices between the units. **c** Excised specimen reveals several thick finger-like villous units (V) separated by invaginations of surface epithelium to create crypts (C) in a cup-like fashion of inverted growth. The crypts contain eosinophilic holocrine secretions and generate nearby lobules. The arrow indicates a lymphoid aggregate. **d** Another field with more villous units (V) separated

by crypts (C), some of which are obliquely sectioned and only partially delineated. There are lymphocytic collections adjacent to the lobules (arrows). **e** On both sides of a crypt (C) and along its entire length are lateral outpouchings of lobules with pale cells. The **inset** depicts a portion of the cryptal wall with a focal collection of amorphous eosinophilic material and degenerating cells and holocrine secretion. **f** Apical pore region of a crypt (C) is present next to lobules (L) of tumor originating in this area from the surface epithelium rather than from a cryptal wall. **b–f** Hematoxylin and eosin; **c, d** $\times 2$; **e** $\times 4$; **inset** $\times 40$; **f** $\times 10$.

Immunohistochemical Findings

Cytokeratin (CK) 14 stained the surface epithelium and the full thickness of all of the cryptal and lobular elements of the lesion (Fig. 2c). CK7 revealed a similar staining pattern except that the centers of the lobules were more weakly staining (Fig. 2d). Cam 5.2 stained only the surface epithelium and the basaloid cells in the lobules. Nuclear androgen receptors were identified in the vacuolated cells (Fig. 1e). While CD163 was negative, adipophilin staining confirmed that the vacuolated lobular, cryptal, and surface epithelial clear or vacuolated cells were sebaceous in nature (sebocytes)

by virtue of exhibiting vesicular positivity for the presence of endogenously synthesized lipid (Fig. 1f). p16 was strongly positive in the nuclei and cytoplasm of the surface epithelium, the cryptal structures, and portions of the sebaceous lobules (Fig. 3a, b), suggesting an association of the tumor with high-risk HPV. p53 was negative in all cells. Ki-67 was positive in 20–40% of the basaloid cells depending on the size of the lobule, but predominantly negative in the centers of the lobules (Fig. 2f, inset). Testing for DNA MMR protein expression was intact for MLH1, MSH2, PMS2, and MSH6 (Fig. 3c–f, respectively), thereby failing to implicate a possible association with the Muir-Torre syndrome.

Fig. 2. Additional histopathologic features and results of immuno-histochemical stains. **a** Clear cells involve the conjunctival epithelium (arrow), which also forms lobules (L). **b** Highly vacuolated cells with central vesicular nuclei in the absence of mitoses represent sebaceous cells (sebocytes). **c** Cytokeratin (CK) 14 uniformly stains the surface conjunctival epithelium (arrows), the sebaceous lobules (L), and the lining of the crypts (C). P, surface pore at opening of crypt. **d** CK7 immunostains the crypts (C) and perimeters of the lobules with weaker staining of the center of the lobules (L).

e Androgen receptor positivity is identified in the tumor cell nuclei, a usual finding in sebaceous cells. **f** Adipophilin stains the vacuoles in the sebaceous tumor cells. The staining has a vesicular form with central clearance, a characteristic of endogenously synthesized cytoplasmic lipid. The **inset** shows Ki-67 nuclear positivity mostly seen among the basal cells, while the central lobular cells are only rarely positive. **a, b** Hematoxylin and eosin; **a** $\times 20$; **b** $\times 40$. **c–f** Immunoperoxidase with diaminobenzidine and hematoxylin counterstain; **c** $\times 4$; **d** $\times 10$; **e** $\times 20$; **inset** $\times 40$; **f** $\times 40$.

Discussion

The dominant histopathologic feature of the current lesion was its villous or finger-like architectural subunits containing sebaceous lobules, a pattern which has never been clearly delineated among ocular adnexal sebaceous neoplasms. This pattern is referred to in general pathologic terms as inverted or downwardly “acanthotic.” The lesion’s villous organization was the consequence of invaginations of the surface epithelium (endophytic growth pattern) with

lateral projections, perpendicular to the vertical crypts of numerous sebaceous lobules. These lobules were composed of central vacuolated sebocytes and a single layer of outer germinal basaloid cells. Scattered sebocytes were also discovered in the surface epithelium and in the walls of the invaginated crypts. By expanding the caruncular stroma, these lobules produced the lesion’s “knobby” and creviced (cryptal) surface appearance observed clinically.

When non-neoplastic, lumenized invaginations of the surface epithelium are encountered in the tarsal and for-

Fig. 3. Immunohistochemical staining for the detection of high-risk human papilloma virus and DNA mismatch repair protein expression. **a, b** Two different fields immunostained for high-risk human papilloma virus demonstrated indirectly with p16 positivity of both the nuclei and cytoplasm of the surface epithelium and sebaceous cells in the lobules. **b–f** DNA mismatch repair nuclear protein expression is intact for MLH1, MSH2, MSH6, and PMS2, respectively. These findings render unlikely an association of the tumor with the Muir-Torre syndrome. **a–f** Immunoperoxidase with diaminobenzidine and hematoxylin counterstain; **a–f** $\times 20$.

niceal regions of the conjunctival sac, they are called pseudoglands of Henle [3, 4, 18, 19]. These structures are apt to be seen in the forniceal and tarsal conjunctiva with varying depths of the invaginations into the stroma; on the other hand, the epibulbar and caruncular epithelium tends to be spared from the formation of these pseudoglands. In the present caruncular lesion, the unusual tubular downgrowths of surface epithelium imitated more closely the appearance of the crypts of Lieberkuhn of the bowel [20] in that the crypts alternated with thickened or widened villi. This pattern is different from that of an exophytic papilloma, which features thin or delicate, outwardly projecting fibrovascular fronds. However, rare inverted conjunctival squamous papillomas have been encountered [21–23]. In addition to the neoplastic sebaceous lobules, the present wide villi were the consequence of prominent stromal aggregates of lymphocytes sometimes

evinced follicular organization, as well as pools of eosinophilic holocrine secretions that expanded the dead-end luminal bases of the crypts. The current lesion should be distinguished from inverted squamous papilloma and dacryoadenoma [21–24].

The ability of mature, fully differentiated conjunctival epithelium to spawn benign and malignant sebaceous tumors is consistent with its embryologic role in providing sebaceous glands and vellus hairs for the caruncle. A latent capacity to undergo sebaceous differentiation obviously must persist into adulthood, as exemplified by the current lesion and previous reports of “ectopic” epibulbar and tarsal sebaceous tumors [5–14]. The multipotentiality of the conjunctival epithelium is also exemplified by an epibulbar dacryoadenoma [24]. Again, one should recall that the major and accessory lacrimal glands are also outgrowths of the embryonic conjunctival epithelium [25].

Immunohistochemical staining with CK7 and CK14 highlighted the architecture of lobular sebaceous units and their direct attachment to the invaginated surface epithelium that became the tubular crypts. Nuclear androgen receptors were detected, a feature of benign and malignant sebaceous cells [26]. Adipophilin staining disclosed that the suprabasal cells in the lobules possessed abundant positive cytoplasmic lipidic granules in the specific form of membranous vesicles with empty centers (signifying endogenous synthesis), as opposed to nonspecific granular positivity that can be seen in many cells especially in areas displaying necrosis (wherein there can be phagocytosis of lipid-rich cellular detritus) [27–29]. Negative p53 immunostaining of the tumor cells favored a benign diagnosis of adenoma [28, 30]. The single layer of outer basal germinal cells displayed a Ki-67 proliferation index with a range of 20–40% depending on the size of the lobules, while the suprabasal cells were non-staining and there was no evidence of nuclear atypia. An important immunohistochemical finding was the p16 nuclear and cytoplasmic positivity, indirect evidence of high-risk HPV infection. HPV has already been implicated as a promotor of the development of both benign and malignant sebaceous tumors [31, 32]. Squamous dysplasia of the conjunctiva and the lacrimal sac has also been shown to be associated with HPV [33, 34]. DNA MMR nuclear protein expression was intact in the tumor cells for MSH6, MSH2, MLH1, and PMS2, thereby failing to implicate the Muir-Torre syndrome [35–39]. Furthermore, there was no personal or family history of cancer proneness.

References

- Boniuk M, Zimmerman LE. Sebaceous carcinoma of the eyelid, eyebrow, caruncle and orbit. *Int Ophthalmol Clin*. 1972;12(1):225–57.
- Straatsma BR. Meibomian gland tumors. *AMA Arch Ophthalmol*. 1956 Jul;56(1):71–93.
- Jakobiec FA, Iwamoto T. The ocular adnexa: Lids, conjunctiva and orbit. In: Fine BS, Yanoff M, editors. *Ocular Histology: A Text and Atlas*. 2nd edition ed. Maryland: Harper and Row, Hagerstown; 1979. p. 289–342.
- Bron AJ, Tripathi RC, Tripathi BJ. The ocular appendages: Eyelids, conjunctiva and lacrimal apparatus. *Wolff's Anatomy of the Eye and Orbit*. 8th ed. London: Chapman and Hall Medical; 1997. pp. 30–49.
- Jakobiec FA, Zimmerman LE, La Piana F, Hornblass A, Breffeilh RA, Lackey JK. Unusual eyelid tumors with sebaceous differentiation in the Muir-Torre syndrome. Rapid clinical regrowth and frank squamous transformation after biopsy. *Ophthalmology*. 1988 Nov;95(11):1543–8.
- Meier-Gibbons F, Messmer E. Sebaceous gland adenoma of the palpebral conjunctiva in a patient with Muir-Torre-syndrome: a case report. *Graefes Arch Clin Exp Ophthalmol*. 1994 Dec;232(12):734–6.
- Margo CE, Grossniklaus HE. Intraepithelial sebaceous neoplasia without underlying invasive carcinoma. *Surv Ophthalmol*. 1995 Jan-Feb;39(4):293–301.
- Honavar SG, Shields CL, Maus M, Shields JA, Demirci H, Eagle RC Jr. Primary intraepithelial sebaceous gland carcinoma of the palpebral conjunctiva. *Arch Ophthalmol*. 2001 May;119(5):764–7.
- Rishi K, Font RL. Sebaceous gland tumors of the eyelids and conjunctiva in the Muir-Torre syndrome: a clinicopathologic study of five cases and literature review. *Ophthalm Plast Reconstr Surg*. 2004 Jan;20(1):31–6.
- Font RL, Rishi K. Sebaceous gland adenoma of the tarsal conjunctiva in a patient with Muir-Torre syndrome. *Ophthalmology*. 2003 Sep;110(9):1833–6.
- Kiratli H, Poyraz C, Gököz A. Sebaceous adenoma of the bulbar conjunctiva in association with glioblastoma multiforme and chronic lymphocytic leukemia. *Cornea*. 2007 Oct;26(9):1136–7.
- Tok L, Tok OY, Argun M, Ciris IM, Baspinar S, Gunes A. Corneal limbal sebaceous adenoma. *Cornea*. 2014 Apr;33(4):425–7.
- Ilhan HD, Turkoglu EB, Bilgin AB, Bassorgun I, Dogan ME, Unal M. A unique case of isolated sebaceous adenoma of the bulbar conjunctiva. *Arq Bras Oftalmol*. 2016 Jul-Aug;79(4):253–4.
- Spraul CW, Jakobczyk-Zmija MJ, Lang GK. [Sebaceous hyperplasia of the lower eyelid]. *Klin Monatsbl Augenheilkd*. 1999 Nov;215(5):319–20.
- Jakobiec FA. Sebaceous adenoma of the eyelid and visceral malignancy. *Am J Ophthalmol*. 1974 Dec;78(6):952–60.
- Yonekawa Y, Jakobiec FA, Zakka FR, Fay A. Sebaceoma of the eyelid. *Ophthalmology*. 2012 Dec;119(12):2645.e1–4.

Statement of Ethics

This study complies with the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act regulations. The clinical photographs have been cropped to protect the patient's identity. Nonetheless, all surgical consent forms signed by the patient at our institution contain an approval for the clinical photographs to be used in any future publications.

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Author Contributions

Frederick A. Jakobiec: main author; responsible for supervision, conceptual guidance and writing of the manuscript. Paula Cortes Barrantes: responsible for data summary, preparation, library search, references, and illustrations. Tatyana Milman: responsible for additional MMR immunohistochemical staining and interpretation of the results; consultant of the genetic and molecular concepts and interpretations.

- 17 Rashid A, Jakobiec FA, Mandeville JT. Squamous cell carcinoma with clear-cell features of the palpebral conjunctiva. *JAMA Ophthalmol*. 2014 Aug;132(8):1019–21.
- 18 Jakobiec FA, Rashid A, Massoud V, Fay A. Pseudoadenomatous hyperplasia of the inferior forniceal conjunctiva due to prosthetic irritation in an anophthalmic socket. *Ophthalm Plast Reconstr Surg*. 2016 Mar-Apr;32(2):e32–4.
- 19 Margo CE, Grossniklaus HE. Pseudoadenomatous hyperplasia of the conjunctiva. *Ophthalmology*. 2001 Jan;108(1):135–8.
- 20 Ross M, Pawlina W. *Histology: A Text and Atlas*. Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins; 2011. pp. 586–92.
- 21 Streeten BW, Carrillo R, Jamison R, Brownstein S, Font RL, Zimmerman LE. Inverted papilloma of the conjunctiva. *Am J Ophthalmol*. 1979 Dec;88(6):1062–6.
- 22 Jakobiec FA, Harrison W, Aronian D. Inverted mucoepidermoid papillomas of the epibulbar conjunctiva. *Ophthalmology*. 1987 Mar;94(3):283–7.
- 23 Stagner AM, Jakobiec FA, Chi A, Bradshaw SH, Mendoza SD. Conjunctival inverted squamous papilloma: a case report with immunohistochemical analysis and review of the literature. *Surv Ophthalmol*. 2015 May-Jun;60(3):263–8.
- 24 Jakobiec FA, Perry HD, Harrison W, Krebs W. Dacryoadenoma. A unique tumor of the conjunctival epithelium. *Ophthalmology*. 1989 Jul;96(7):1014–20.
- 25 Mann I. *The Development of the Human Eye*. New York: Grune and Strtton; 1964. pp. 268–9.
- 26 Jakobiec FA, Werdich X. Androgen receptor identification in the diagnosis of eyelid sebaceous carcinomas. *Am J Ophthalmol*. 2014 Mar;157(3):687–96.e1–2.
- 27 Ostler DA, Prieto VG, Reed JA, Deavers MT, Lazar AJ, Ivan D. Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases. *Mod Pathol*. 2010 Apr;23(4):567–73.
- 28 Jakobiec FA, Mendoza PR. Eyelid sebaceous carcinoma: clinicopathologic and multiparametric immunohistochemical analysis that includes adipophilin. *Am J Ophthalmol*. 2014 Jan;157(1):186–208.e2.
- 29 Milman T, Schear MJ, Eagle RC Jr. Diagnostic utility of adipophilin immunostain in periocular carcinomas. *Ophthalmology*. 2014 Apr;121(4):964–71.
- 30 Kiyosaki K, Nakada C, Hijiya N, Tsukamoto Y, Matsuura K, Nakatsuka K, et al. Analysis of p53 mutations and the expression of p53 and p21WAF1/CIP1 protein in 15 cases of sebaceous carcinoma of the eyelid. *Invest Ophthalmol Vis Sci*. 2010 Jan;51(1):7–11.
- 31 Miura-Karasawa M, Toshida H, Ohta T, Murakami A. Papilloma and sebaceous gland hyperplasia of the lacrimal caruncle: a case report. *Int Med Case Rep J*. 2018 Apr;11:91–5.
- 32 Tetzlaff MT, Curry JL, Ning J, Sagiv O, Kandl TL, Peng B, et al. Distinct biological types of ocular adnexal sebaceous carcinoma: HPV-driven and virus-negative tumors arise through nonoverlapping molecular-genetic alterations. *Clin Cancer Res*. 2019 Feb 15;25(4):1280–90.
- 33 Afrogheh AH, Jakobiec FA, Hammon R, Grossniklaus HE, Rocco J, Lindeman NI, et al. Evaluation for high-risk HPV in squamous cell carcinomas and precursor lesions arising in the conjunctiva and lacrimal sac. *Am J Surg Pathol*. 2016 Apr;40(4):519–28.
- 34 Hanbazazh M, Gyure KA. Ocular human papillomavirus infections. *Arch Pathol Lab Med*. 2018 Jun;142(6):706–10.
- 35 Schwartz RA, Torre DP. The Muir-Torre syndrome: a 25-year retrospect. *J Am Acad Dermatol*. 1995 Jul;33(1):90–104.
- 36 Orta L, Klimstra DS, Qin J, Mecca P, Tang LH, Busam KJ, et al. Towards identification of hereditary DNA mismatch repair deficiency: sebaceous neoplasm warrants routine immunohistochemical screening regardless of patient's age or other clinical characteristics. *Am J Surg Pathol*. 2009 Jun;33(6):934–44.
- 37 Milman T, McCormick SA. The molecular genetics of eyelid tumors: recent advances and future directions. *Graefes Arch Clin Exp Ophthalmol*. 2013 Feb;251(2):419–33.
- 38 Mensenkamp AR, Vogelaar IP, van Zelst-Stams WA, Goossens M, Ouchene H, Hendriks-Cornelissen SJ, et al. Somatic mutations in MLH1 and MSH2 are a frequent cause of mismatch-repair deficiency in Lynch syndrome-like tumors. *Gastroenterology*. 2014 Mar;146(3):643–646.e8.
- 39 Mahalingam M. MSH6, past and present and Muir-Torre syndrome – connecting the dots. *Am J Dermatopathol*. 2017 Apr;39(4):239–49.