Primary Myoepithelial Carcinoma of the Conjunctiva

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Established Facts

- Myoepithelial tumours occur in the lacrimal gland, orbit, and eyelids, with no cases recorded in the conjunctiva.
- Myoepithelial tumours are usually positive for cytokeratins alongside other immunohistochemical markers.

Novel Insights

- We describe the first case of a primary myoepithelial carcinoma of the conjunctiva.
- The tumour did not express cytokeratin, which is unusual, but expressed the alternative epithelial marker beta-catenin.

Keywords

Conjunctiva · Myoepithelial carcinoma

Abstract

A 38-year-old female, otherwise fit and well, presented with a mass on her left medial bulbar conjunctiva that had been enlarging for several months. Examinations showed a fixed pinkish tumour, 9 mm in maximum extent, spanning from the plica to the medial limbus. The tumour was removed in toto. Histology revealed it to be a biphasic tumour composed of lobules and infiltrative cords within a sclerotic matrix. The cells were spindle-shaped to epithelioid, with nuclear atypia and occasional mitotic figures. The tumour was

positive for smooth muscle actin, beta-catenin, and vimentin. All other markers of myoepithelial differentiation and cytokeratins were negative. Genetic analysis showed no evidence of *EWSR1* or *PLAG1* rearrangements. The light microscopic features and immunohistochemistry strongly supported a tumour with myoepithelial differentiation. The cellular atypia, mitotic activity, and infiltrative edges all pointed to myoepithelial carcinoma. Body imaging/screening showed no evidence of tumour elsewhere, supporting that the tumour was a primary of the conjunctiva. This is the first report of a myoepithelial tumour of the conjunctiva. The patient remains recurrence-free after 3 years of follow-up.

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Introduction

Myoepithelial tumours comprise a spectrum of lesions ranging from benign myoepithelioma at the one end to myoepithelial carcinoma at the other [1, 2]. There are many other tumours in which myoepithelial cells are a component, of which the example par excellence is pleomorphic adenoma of the salivary and lacrimal glands. While a handful of case reports have documented primary myoepithelial tumour or myoepithelial-rich components in other tumours in the orbit, lacrimal gland, and eyelid [3–9], there have been no published cases of primary myoepithelial tumours arising in the conjunctiva. We document an unusual conjunctival primary myoepithelial carcinoma of the bulbar conjunctiva in a 38-year-old woman.

Case Report

A 38-year-old woman with no prior medical or ophthalmic history presented to the eye clinic with an enlarging lump on her left medial bulbar conjunctiva that had been present for several months. On examination, the nodule measured 9 mm horizontally by 6 mm vertically, extending from the edge of the limbus to the edge of the plica, present over the nasal bulbar conjunctiva. It was cream to pink in colour with prominent surface vascular markings (Fig. 1). It was present under the conjunctival epithelium, fixed in location, and the epithelium could not be moved over it. The rest of the ophthalmic examination was unremarkable. No regional lymphadenopathy was present. An excision was performed and the specimen fixed in standard buffered formalin and submitted to the ophthalmic pathology laboratory.

Histology showed conjunctival tissue containing a neoplasm in the substantia propria, with a biphasic appearance. There was a solid component comprising lobules of variable size and coalescence, made up of epithelioid cells with indistinct cell boundaries. The nuclei exhibited pleomorphism, were vacuolated, and contained basophilic nucleoli. The cytoplasm was lightly basophilic and vacuolated. Mitotic figures were observed in the tumour cells. These tumour lobules were embedded in a predominantly fibrous matrix with some myxoid foci. The other tumour component comprised more angulated and hyperchromatic tumour cells, arranged as infiltrative cords and in a reticular pattern, coursing through dense, keloid-like stromal collagen and infiltrating the surrounding tissue (Fig. 2a–e).

Immunohistochemistry showed positivity for antibodies to alpha-smooth muscle actin, beta-catenin, and vimentin only (Fig. 2f–i). The smooth muscle actin immunopositivity was accentuated at the edges of the cytoplasm in the tumour cells. The tumour was negative for MNF116, AE1/AE3, CK7, CK20, CK5/6, CAM 5.2 (all cytokeratins except for CK20 strongly stained the conjunctival epithelium overlying the tumour and acted as an internal control), EMA (the conjunctival epithelium overlying the tumour was positive), S100, Melan A, CA-125, RCC, CD68, CD45, CD34, HMB45, GCDFP15, GFAP, caldesmon, calponin, desmin, TTF-1, alpha-inhibin, WT1, ER, PR, neurofilament, CD138,

Fig. 1. In vivo view of the lesion.

CD31, CD56, MUM1, BerEP4, calretinin, mesothelin, MyoD1, p63, E-cadherin, collagen IV, and smooth muscle myosin. Ki-67 showed a proliferation fraction of around 20% (Fig. 2j), and p53 (against mutated protein) stained around 30% of the tumour population nuclei (not shown).

Transmission electron microscopy of tissue removed from the paraffin wax block showed every cell containing a peripheral band of filamentous actin (Fig. 3). No desmosomes or cytokeratin filaments were identified. No basement membrane elaboration was seen. No fibronexus junctions (as seen in myofibroblastic cells) were identified.

The light microscopic, immunohistochemical, and ultrastructural features all pointed to a tumour with myoepithelial differentiation. Given the infiltrative growth pattern at the edges, the nuclear atypia, the Ki-67 proliferation fraction, and the p53 positivity in a significant proportion of the tumour cells, the interpretation was that of a myoepithelial carcinoma. There was no evidence of ectopic or accessory lacrimal gland tissue within the lesion. The surgical margins were free of tumour. To exclude the possibility of a metastasis to the conjunctiva, body imaging was carried out and showed no evidence of tumour elsewhere, supporting the interpretation that the tumour was a primary at this site. As a proportion of myoepithelial tumours are known to harbour genetic changes, FISH analysis with probes to *EWSR1* and *PLAG1* showed no rearrangements.

The patient remains tumour-free after 3 years of follow-up.

Fig. 2. **a** Scanning power haematoxylin and eosin (H&E)-stained section of the tumour showing a lobular architecture (arrow). **b** H&E showing another part of the tumour with a fibrotic stroma. **c** H&E showing the tumour cells at higher power. **d** H&E. The arrow points to a tumour mitotic profile. **e** H&E. The edge of the tumour shows an infiltrative front. **f** Immunohistochemical positivity for smooth muscle actin with membranous accentuation (arrow). **g** Immunohistochemistry for beta-catenin showing the positive conjunctival epithelium membranous staining (internal control) and positive tumour below the epithelium. **h** Higher power of the tumour in **g** showing the beta-catenin positivity. **i** Immunohistochemistry for vimentin showing strong positivity in the cytoplasm of the tumour cells. **j** Immunohistochemistry for Ki-67. Around 20% of the nuclei are stained.

Discussion

This report documents a rather unusual primary myoepithelial tumour of the bulbar conjunctiva. Its infil-

trative interface with the surrounding conjunctiva, presence of nuclear atypia, and mitotic figures indicated a diagnosis of myoepithelial carcinoma. The tumour showed morphological features that have been well doc-

Fig. 3. Transmission electron microscopy showing submembranous actin filaments (arrow).

umented in previous reports of myoepithelial carcinomas in the head and neck region. These include a heterogeneous architecture, featuring lobules and infiltrative cords of cells and heterogeneous cytology with epithelioid, spindle, and angulated cells [2]. An immunohistochemical panel that includes a cytokeratin, EMA, S100, and GFAP is said to identify myoepithelial differentiation in most cases [2]. Other markers that are identified on myoepithelial cells include caldesmon and calponin, p63, smooth muscle actin, and cytokeratin 14. These latter markers are expressed to a variable degree from case to case [2]. In our case the tumour was only positive for vimentin, smooth muscle actin, and the epithelial marker beta-catenin and negative for cytokeratin, which is unusual. However, by analogy, it is known that cutaneous syncytial myoepithelioma is negative for cytokeratin too, and therefore the absence of cytokeratin does not exclude myoepithelial differentiation [10]. We had to resort to transmission electron microscopy to identify the presence of actin filaments, concentrated below the cell membrane, to seek additional evidence for myoepithelial differentiation.

The key question is the origin of the tumour. It is known from a handful of ophthalmic case reports that primary myoepithelial tumours (myoepitheliomas and myoepithelial carcinomas) can arise from the eyelid skin, lacrimal gland, and orbit [3–9]. In dogs the third eyelid can give rise to lesions that resemble myoepithelial tumours [11, 12]. In our case, the tumour may have arisen *de novo*, originating from the minor lacrimal gland tissue, or represented a metastasis to the conjunctiva. Me-

tastases to the conjunctiva tend to present with rapidly expanding masses comparable to the one in this case [13] and often possess aggressive cytology. Overall, the features supported a primary tumour, and it is speculative whether it arose *de novo*, from minor lacrimal gland tissue, or indeed from a benign tumour arising from the minor lacrimal glands (e.g., pleomorphic adenoma). The tumour did not reveal any normal or benign tumour precursors although numerous histological sections were examined.

The histological differential diagnosis based on haematoxylin and eosin staining would include primary leiomyosarcoma, mucoepidermoid carcinoma, spindle cell/metaplastic carcinoma, squamous cell carcinoma, plasmacytoma, and melanoma. Metastatic tumours would include melanoma, lymphoma, and breast carcinoma. In this case, a systemic workup was negative. The biphasic morphology of the tumour with multiple nodules of epithelioid- and plasmacytoid-type cells with a trabeculated and single file morphology is quite characteristic of myoepithelial carcinomas [1, 2], and coupled with negativity to a broad range of immunohistochemical markers would exclude most of these differential diagnoses. The tumour in question was slowly enlarging, which is a clinical feature much more in keeping with a primary tumour rather than a metastasis to the conjunctiva, which would grow rapidly [13]. Also, metastatic tumours do not tend to adopt the morphology that was observed, except for lobular breast carcinoma. However, the systemic survey was negative and the tumour was negative for oestrogen receptor. In the context of the histological morphology, the immunohistochemical differential diagnosis (vimentin, beta-catenin, and smooth muscle actin positivity) includes myofibroma, myofibrosarcoma, fibromatosis, nodular fasciitis, and leiomyosarcoma. Myofibroma has biphasic peripheral and central zones with distinct vasculature. Myofibrosarcoma occurs mostly in bone. Fibromatosis comprises sweeping fascicles of uniform, non-atypical, slender spindle cells, whereas the tumour here showed biphasic cytology with nuclear atypia, without sweeping fascicles. Nodular fasciitis has a zoned appearance of mitotically active plump non-atypical spindle cells, with a tissue culture arrangement, with S- or C-shaped fascicles, with extravasated red cells, inflammatory cells, and occasional giant cells. Leiomyosarcoma has pink spindled cytoplasm with blunt-ended elongated nuclei. None of the distinctive features of these tumours were seen in this case.

A proportion of myoepithelial tumours can harbour specific genetic changes. These include *EWSR1* and *PLAG1* rearrangements. *EWSR1* is usually identified in primary skin, soft tissue, and bone myoepithelial tumours [14–17]. *PLAG1* is rearranged in a high number of salivary gland neoplasms (pleomorphic adenoma) and carcinoma ex pleomorphic adenoma [18, 19]. In this case, none of these genetic changes were identified.

In summary, this case illustrates a unique location for a primary myoepithelial carcinoma treated by surgical excision with no recurrence after 2 years. In such circumstances, we recommend that a metastatic myoepithelial carcinoma from other sites be excluded before regarding the lesion as a primary.

Statement of Ethics

The patient gave written consent for publication of this case report. The study was conducted in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors declare that there are no financial or other conflicts of interest.

Author Contributions

All authors were involved in the final approval of the submitted manuscript.

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