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A Rare Conjunctival/Caruncular Tumor, Squamous Cell Carcinoma with Mucinous Differentiation: A Case Report and Review of the Literature

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Abstract

Mucoepidermoid Carcinoma (MEC) is a very rare tumor for the conjunctiva defined in 1976 for this extraordinary localization. The term 'MEC' was revised as Adenosquamous Carcinoma (ASC) in the latest WHO classification of tumors of eye in 2018. Nevertheless, neither MEC nor ASC correctly reflected the histopathological features found in the vast majority of these conjunctival tumors. Therefore Squamous Cell Carcinoma (SCC) with mucinous differentiation was suggested as an alternative term for such tumors. Our case located in the caruncle had characteristic histopathological features completely representing SCC with mucinous differentiation. The caruncular localization is extremely rare for this type of conjunctival malignant tumor with only two case reports up to now. Furthermore, our case is also the first report in the literature presented as a polypoid benign-looking mass of which the main bulk was comprised of a ductal cyst and malignant tumor (SCC with mucinous differentiation) was coincidentally found very close, but completely unassociated with this ductal cyst.

Keywords: Carcinoma; Mucoepidermoid carcinoma; Caruncular tumor; Mucinous

Abbrevations: MEC: Mucoepidermoid Carcinoma; WHO: World Health Organization; ASC: Adenosquamous Carcinoma; SCC: Squamous Cell Carcinoma; CK: Cytokeratin; CIN: Conjunctival Intraepithelial Neoplasia; HPV: Human Papillomavirus; EBER: Epstein-Barr Encoding Region; CISH: Chromogenic *In-Situ* Hybridization; NEC: Necrotizing Enterocolitis

Introduction

Mucoepidermoid Carcinoma (MEC) of the conjunctiva was first defined in 1976 by Rao and Font as a new entity for conjunctiva [1]. This entity has been published as a single case report [2-14] and one series with only 3 cases [15]. Reviewing all these publications and noticing that their histopathologic findings were not fully consistent with the diagnostic criteria defined for MEC [16,17], the World Health Organization (WHO) classification of tumours of the eye suggested the term ASC in 2018 [18]. Afterwards in 2020 Mudhar et al., published a series with 14 cases drawing attention that the terminology of ASC is not suitable to explain this type of tumors and further suggested the term 'SCC with mucinous differentiation' [19].

Because this type of malignant conjunctival tumor is so scarce in routine practice and its histopathologic findings greatly vary from one case to another, we wanted to publish this special tumor to present its diagnostic histopathological criteria, special localization and unique features. It is the first reported case that was presented as a benign-looking polypoid mass in which malignant tumor component was coincidentally found next to ductal cyst.

Case Presentation

A 68-year-old woman visited the ophthalmology clinic complaining of a conjunctival mucosal polypoid mass that had been enlarging over the past few months. The clinical diagnosis was of the benign cystic lesion and was excised totally with free surgical margins (Figure 1).

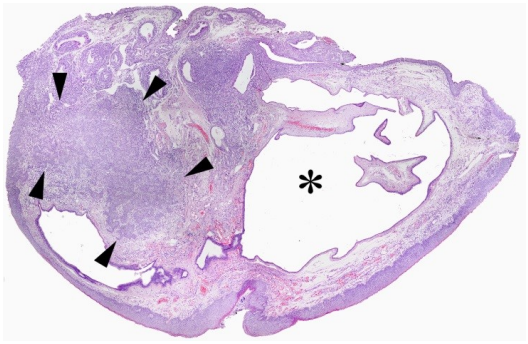

Figure 1: Overall polypoid mass was encircled by conjunctival epithelium which undergoes squamous metaplasia and dysplastic changes in various grades (conjunctival intraepithelial neoplasia with scattered mucinous cells). Endophytic solid squamous proliferation (between black arrowheads) starts directly from the dysplastic surface epithelium and infiltrates as solid irregular islands into the inflammatory polypoid stroma. Nevertheless, the main bulk of the whole polypoid mass is occupied by a benign ductal cyst (asterisk) which is very close but completely unassociated with neoplastic squamous proliferation (Hematoxylin and Eosin (H and E)), original magnification Histopathology (x40) and software supported panorama).

Preliminary pathological examination was of 1 cm polypoid mucosal mass containing a main cystic lesion and additional atypical epithelial proliferation next to it. The pathology specimen was sent to our laboratory for consultation of this atypical focus and further immunohistochemical analysis.

In our histopathological examination, this polypoid mass had an edematous inflammatory stroma and the main cystic cavity lined by benign pseudostratified columnar epithelium without mitosis and atypia, occupying more than half of the caruncular mass (Figures 1 and 2). The epithelium lining the cyst, which appeared flattened in some areas, was stained diffusely either with Cytokeratin 5/6 (CK5/6) or CK7 and further, there were some basal cells stained partially with Tumor Protein 63 (p63) (Figure 2).

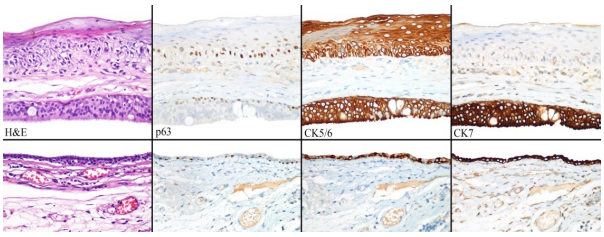

Figure 2: In the upper figures, the epithelium seen in the top is the conjunctival metaplastic keratinized squamous epithelium and lying just beneath this conjunctival epithelium is the cystic cavity lined by benign pseudostratified or bilayered to multilayered columnar-cuboidal epithelium with a few goblet cells. In the bottom figures, the epithelium of the cystic cavity appears flattened due to pressure atrophy. Both in the top and the bottom figures, cyst epithelium are diffusely stained either with CK5/6 or CK7; but, in contrast only the basal layer is stained with p63 (magnification of all sections x200).

The polypoid mass was encircled externally by conjunctival epithelium focally undergoing squamous metaplasia. In addition to metaplasia and hyperplasia, dysplasia; Conjunctival Intraepithelial Neoplasia (CIN) with mucinous cells was seen in different degrees up to high grade (Figure 3a). In continuation with this dysplastic epithelium, there was an endophytic proliferation of atypical nonkeratinized squamous epithelium in which a few benign mucinous epithelial cells of goblet cell type were dispersed singly or as clusters (Figure 3a and 3b). Squamoid cells forming irregular tumor islands showed positive staining with p63 (Figure 3c) and CK7 (Figure 3f). Goblet-like mucinous cells were stained intracytoplasmic with mucicarmine (Figure 3e). This atypical endophytic proliferation was infiltrating as irregular solid complex islands in an edematous inflammatory stroma close to the cyst. There was cellular pleomorphism, nuclear atypia, loss of polarity, and a few mitoses in the squamous cell component of endophytic proliferation (Figure 3b). Kiel 67 (Ki67) index was increased significantly (Figure 3d). Immunohistochemically p16, Human Papillomavirus (HPV) high-risk and Epstein-Barr Encoding Region (EBER) with Chromogenic *In-Situ* Hybridization (CISH) analysis all revealed negative results.

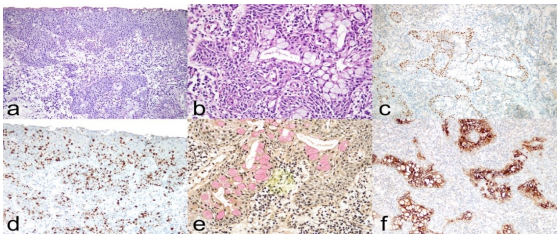

Figure 3: The tumor grows as irregular solid islands which start just directly from the surface epithelium within a chronically inflamed stroma: a) These solid tumoral islands are populated by two different cell types: nonkeratinised atypical squamous epithelium and benign mucinous cells of goblet cell type (H and E, original magnification x100); b) Irregular and infiltrative proliferation of atypical squamous cells accompanied by mucinous cells of goblet type (H and E, original magnification x100); c) A typical neoplastic squamous component mainly occupies the periphery of solid tumoral islands stained with p63 immunohistochemically (p63, x100); d) Dysplastic surface epithelium and tumoral invasions towards the stroma show remarkably increased Ki67 proliferation rate (Ki67, x100); e) Central parts of these solid islands are partly inhabited by benign looking mucinous cells stained positively with mucicarmine (Mucicarmine, x400); f) The main population of the invasive solid tumoral islands is diffusely stained with CK7 which is consistent with MEC (CK7, x100).

Results and Discussion

Our case really did not show an apparent high grade invasive tumor histomorphology so that we considered the inverted mucoepidermoid papilloma in the differential diagnosis. Inverted mucoepidermoid papilloma was described as a variant of conjunctival squamous papilloma with an inverted and papillary growth pattern and accompanied by mucinous differentiation [20-22]. This entity was benign with bland histomorphology, without any mitotic activity, cytologic atypia, nuclear pleomorphism, and increased Ki67 proliferation index [23]. In contrast, our case showed infiltrative pattern, remarkable cytological atypia, pleomorphism, mitosis and high Ki67 proliferative index.

Even in the first series, 2 of 5 cases of conjunctival MEC were really ASC, but not MEC. Since then, there were only a handful of cases reported in conjunctiva as either MEC or ASC [23-24]. Furthermore, the caruncle is an extraordinarily rare localization for this type of conjunctival tumor. Only the one case report each found as either MEC or ASC up to now in the literature. Our case is the third one among all the case reports of caruncular MEC or ASC cases up to now.

The latest WHO classification of tumours of eye in 2018 preferred to use the term ASC instead of Necrotizing Enterocolitis (NEC) because none of these conjunctival tumors had fulfilled the criteria originally defined for MEC [14,15]. In contrast to histopathological characteristics of MEC, many of the reported cases took the origin from the surface epithelium accompanied by either *in-situ* squamous carcinoma or conjunctival intraepithelial dysplasia with or without scattered mucous cells [18,19]. Some of them had an overt keratinization, but none of them had intermediate/clear cells as expected from the MEC. These are all the features shared by our case completely. In addition, just like our case none of them showed MAML2 chromosomal translocation as expected usually from most of MECs.

The term ‘ASC’ itself also does not reflect all the histopathological features reported in conjunctiva for this type of tumor [18,23,24]. Because many such cases do not harbor two different components: glandular and squamous components within a single tumor. For example, in the largest series of conjunctival malignant tumor cases published in 2020 by Mudhar et al., [19], only 3 out of 11 cases had the histomorphology of ASC. In contrast, 6 out of 11 cases had the histomorphology of SCC with mucinous differentiation. There was not any dual pattern of two different adeno-and squamous cell carcinoma components in our case either. Consistent with the majority of the cases reported in the literature, this finding also supports the argument that ASC is not exactly the proper term for the majority of such conjunctival tumors.

There was only one case reported in the literature of conjunctival MEC or ASC that contained a cystic component [4]. The cystic part of this case was due to the degeneration of the high-grade malignant squamous component usually seen in many of conventional SCCs. In contrast, our case is unique and is the first report in the literature because of its presentation as a polypoid mass in which the vast majority of its volume was comprised of a benign ductal cyst unassociated with the malignant tumor.

Conclusion

The histopathological features of our case support the argument that 'SCC with mucinous differentiation' can be used instead of ASC for

conjunctival tumors of this type. One should be alert to screen conjunctival benign polypoid or cystic masses very carefully not to miss any malignant tumor incidentally found close to a benign ductal cyst. In addition, one should also be very stringent on the histopathological criteria for diagnosing 'SCC with mucinous differentiation', because such conjunctival tumors may easily be underdiagnosed due to their bland histomorphological features.

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