·Letter to the Editor·

Apocrine adenocarcinoma of the eyelid

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Dear Sir,

Sweat gland neoplasms of the ocular region are rare [1]. Traditionally, these lesions are classified as either of eccrine or apocrine origin. The cardinal feature of apocrine tumors includes having apical decapitation secretions from the cells rather than forming simple secretory units with tubules, such as the case with their eccrine counterpart [2-4]. Apocrine lesions can be both benign and malignant. There are only 22 cases of apocrine adenocarcinoma (AC) involving the eyelid in the English literature [2,5]. In the present series, we show two primary AC of the eyelid with a broad morphological spectrum and with extensive immunohistochemical analysis.

Case 1 A 59-year-old female presented with a left lower lid lesion that has recurred for over 2y. The lesion was diagnosed clinically a chalazion and has been excised twice since it first appeared at another hospital without further histopathological evaluation; however, it progressed clinically to become red and nodular with projections and was associated with madarosis (Figure 1). On clinical examination, no lymph node enlargement was noticed. An incisional biopsy was then obtained and microscopic analysis of the tumor revealed a dermal tumor composed of epithelial cells forming tubules and papillary structures with no attachments to the overlying epidermis. At higher magnification, the cells were columnar to cuboidal with eosinophilic cytoplasm showing apical decapitation. The nuclei were mildly polymorphic with small nucleoli. The infiltrative tumor border reached the margins of the biopsy and vascular invasion was observed. A diagnosis of AC of the eyelid was made. The lesion was then excised and the surgical margins were assessed intra-operatively with frozen sections. Microscopic examination of this specimen showed an epithelial tumor infiltrating up to the skeletal muscle composed of tubules and pseudopapillary structures showing similar cytological characteristics as the incisional biopsy. The margins were free of neoplastic involvement (Figure 2). An immunohistochemical panel was performed on formalin-fixed paraffin-embedded (FFPE) tissue and showed positivity for gross cystic disease fluid protein (GCDFP) -15, cytokeratin (CK)-7, both supporting the sweat gland nature of the lesion, and carcinoembryonic antigen (CEA), supporting the malignant nature of the cells. CK 20, CDX2, and thyroid transcription factor-1 (TTF-1), markers for colon and lung primaries, respectively, were negative, ruling out colon and lung metastasis. The expression of human epidermal growth factor receptor 2 (HER2) was negative; however, there was a focal expression of adipophilin. No recurrence of the lesion has been documented after 6mo follow up.

Case 2 An 81-year-old male had a left upper lid tumor. The lesion was excised and sent as a consultation case to our institution. Histopathological slides of the eyelid specimen showed a nodular tumor attached to the overlying epidermis with well-demarcated borders. The tumor was composed of glandular and tubular structures with apocrine differentiation. On higher magnification, the tubular structures were formed by epithelial cells with high nuclear to cytoplasmic ratio and nuclei with irregular borders and clump chromatic pattern with overlapping of the nuclei. The cytoplasm is eosinophilic with decapitation of the apical border. The tumor has loose stroma intimately associated with tumor islands with dense infiltration of lymphocytes and plasma cells. Several atypical mitotic figures were seen [more than 10/high power fields (HPFs)]. Immunohistochemical studies were performed on FFPE tissue and showed positivity for CK-7 and GCDFP-15, both supporting a sweat gland origin, and positivity for CEA, supporting the malignant nature of this apocrine lesion. CK20, CDX2, TTF-1 and prostate specific antigen (PSA) were all negative, ruling out metastatic colon, lung, and prostatic carcinomas, respectively. Estrogen receptor (ER), progesterone receptor (PR), HER2 and adipophilin were all negative (Figure 3). A diagnosis of AC was made.

Interestingly, the two AC in this series showed histopathological differences. For example, in case 2 at low magnification, a well-demarcated tumor with multiple

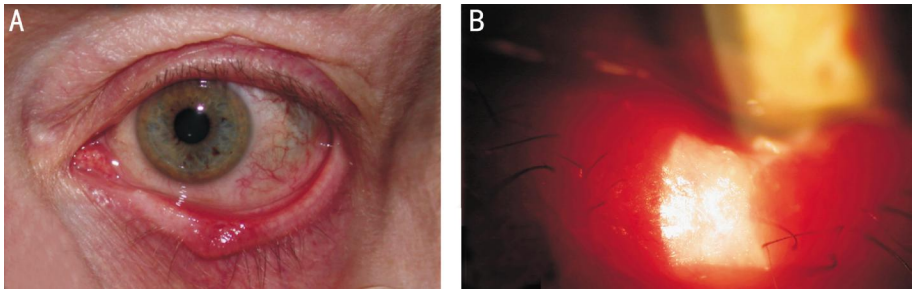

Figure 1 Slit-lamp examination of the left eye for case 1 A: A notched, red, papillated, chalazion-like lesion; B: The lesion was associated with madarosis.

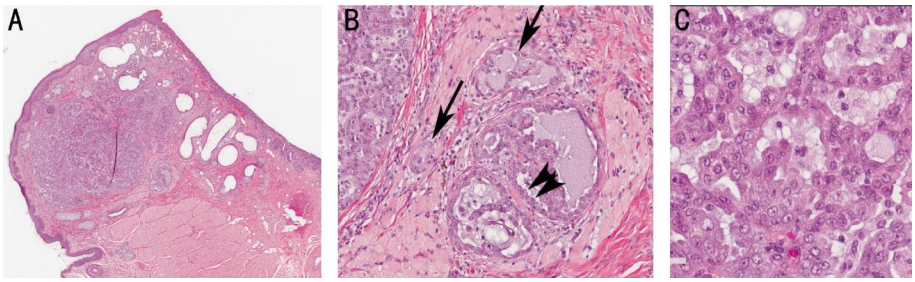

Figure 2 Histopathological findings of case 1 A: On a low power view, a tubule forming tumor located in the skin surface of the free margin of the eyelid and infiltrating up to the skeletal muscle is seen. Note the lack of connection between the tumor and the epidermis (2.8×, H&E); B: High power view reveals that tubules are lined by large cells with irregular nuclei and prominent nucleoli; the cytoplasm is eosinophilic (arrows). Note the presence of apical decapitation in the luminal border of the cells (arrow heads), which is characteristic of apocrine differentiation (20.4×, H&E); C: Higher power view showing multiple mitotic figures and eosinophilic cytoplasm with decapitation secretions indicating the apocrine differentiation (40×, H&E).

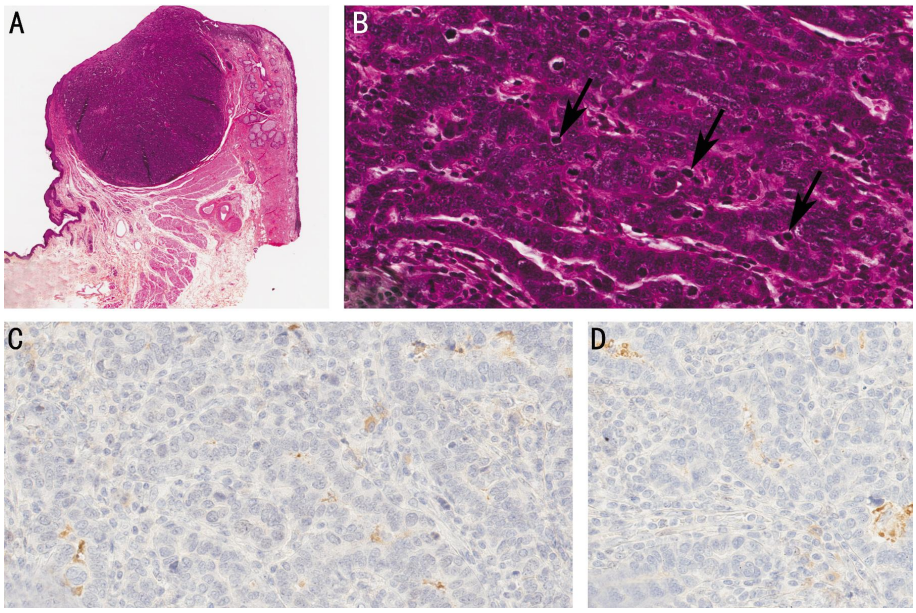

Figure 3 Histopathological findings of case 2 A: On a low power view, a well-demarcated tumor forming tubules is seen. The tumor is connected to the epidermis (1.1×, H&E); B: On higher magnification, tubules are formed by cells with highly pleomorphic, irregular and overlapped nuclei. Several mitotic figures are seen (arrows) (40×, H&E); C: The neoplastic cells were negative for ER (40×); D: PR (40×).

attachments to the overlying epidermis can be seen; however, an infiltrative pattern with ill-defined borders is noticed at low magnification in case 1. Moreover, marked nuclear pleomorphism and numerous mitotic figures are recognized at higher magnification in case 2. Conversely in case 1, the nuclei are mildly hyperchromatic, the nuclear/cytoplasm ratio is less striking, and there are fewer nuclear abnormalities. These features have also been reported previously, showing a wide spectrum of histopathological presentation ranging from infiltrative to well-circumscribed borders and low cellular atypia to anaplastic features; therefore, in order to make the correct diagnosis, the infiltrative pattern or malignant cellular atypia must be demonstrated [2,4-6]. However, the delicate and limited ocular and peri-ocular areas impose difficulties when it comes to obtaining adequate biopsies. Therefore, this will also make diagnosis of apocrine carcinomas of the eyelid more challenging.

Apocrine neoplasms express GCDFP-15, which is a marker

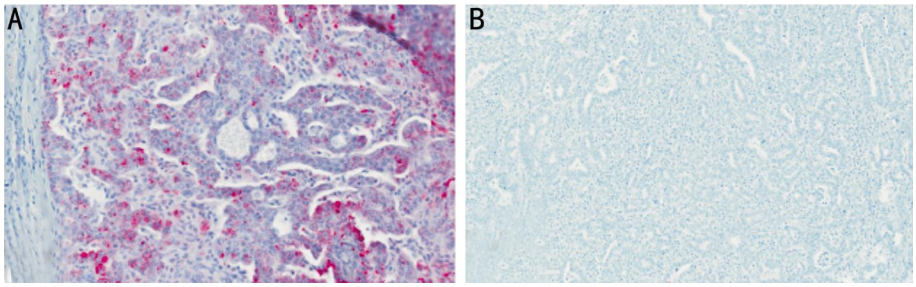

Figure 4 Adipophilin expression in both our cases Adipophilin was focally expressed in case 1 (A) (24×); however, it was negative in case 2 (B) (12×).

for adnexal tumors, including breast [7]. Because they share common histological features and immunohistochemical profiles, the diagnosis of primary cutaneous apocrine carcinoma (PCAC) of the eyelid versus metastatic apocrine tumor of the breast (MATB) to the eyelid is very difficult. However, differentiation is very important as treatment plans may differ [7-8]. Immunohistochemicaly, both PCAC and MATB show strong androgen receptor positivity [6-7,9]. Moreover, Piris *et al* [7] reported 36% of PCAC staining positive for adipophilin versus 88% for MATB. On the other hand, PCAC is more likely to express ER and PR than cases of MATB (50% versus 12%, 29% versus 4%, respectively)[7,10]. They also reported that MATB more likely will have a strong and diffuse adipophilin staining (>50% of the cells). HER2 positivity is exclusively seen in cases of MATB with HER2 genomic expression [7,10]. Thus, there is no single marker available to differentiate between the two entities; however, a panel of the aforementioned markers can be helpful though non-diagnostic. Both our cases showed negativity for HER2; however, only one showed focal positivity for adipophilin (Figure 4). Moreover, ER and PR were negative in the second case where it was available.

Although AC usually arise *de novo*, they can also arise from a pre-existing benign lesion, as in the case of adenocarcinoma derived from an apocrine cyst [2,11]. Furthermore, the majority of apocrine carcinomas present clinically as a recurrent eyelid lesion that is misdiagnosed as a chalazion[5,12-15]. Our group has proposed previously the careful histopathological assessment of all cases diagnosed clinically as chalazion, because a number of different benign, premalignant, and malignant conditions may clinically masquerade as chalazion[16].

In conclusion, AC of the eyelid can clinically and histopathologically mimic other lesions of the same site. This adds to the difficulty in diagnosing such lesions. Immunohistochemistry serves as a valuable tool for diagnosing lesions with apocrine differentiation. Differentiating eyelid apocrine carcinoma from breast metastatic carcinoma is a challenge and the clinico-pathologic correlation is mandatory.

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