Endocrine mucin-producing sweat gland carcinoma of the eyelid: A clinical and histological conundrum

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A 60-year-old male presented with a 6-month-old history of a left upper lid mass. The mass was excised, and histopathological evaluation showed a well-circumscribed, multinodular, intradermal tumor consisting of round-to-oval cells with round nuclei and mucin filled cysts. On immunohistochemical analysis, the tumor cells stained positively for cytokeratin (CK)-7, CK-8, estrogen receptor (ER), progesterone receptor (PR), mucicarmine, synaptophysin, gross cystic disease fluid protein-15 (GCDFP-15), and neuron-specific enolase (NSE). A diagnosis of endocrine mucin-producing sweat gland carcinoma (EMPSGC) of the eyelid was made and at 6-month follow-up, no recurrence was noted. In this communication, we discuss the pathology and treatment options of EMPSGC of the eyelid. Although an uncommon entity, EMPSGC may be considered as a differential when encountered with a suspicious, potentially malignant eyelid mass.

Key words: Endocrine mucin-producing sweat gland carcinoma, eyelid, mucin, sebaceous gland carcinoma, tumor, Tenzel

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is an under-recognized low-grade sweat gland carcinoma.[1] In itself, it remains a rare entity with less than fifty cases of EMPSGC of the eyelid being reported in English literature. However, over three-fourth of the cases in literature have been published in the past 3 years (2015–2018). This trend reflects a possible increase in diagnosis and reporting, rather than a true increase in incidence – confirming that although uncommon, EMPSGC has largely been an under-reported entity until recently. In this communication, we present the first documented case of EMPSGC from the Indian subcontinent.

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Case Report

A 60-year-old male presented with complaints of a slow-growing, painless mass on his left upper eyelid [Fig. 1a]. He had initially noticed the mass 6 months before this visit, following which the lesion had slowly grown to assume its current size. On examination, the mass was at the edge of the center of the eyelid and measured 6 mm × 6 mm × 4 mm. The mass had a bluish hue, and at the tip, a scab was noted suggestive of recent ulceration along with localized loss of lashes. No rounding of the lid margin or surrounding telangiectasia was noted, and on eversion, the tarsal surface appeared healthy. Visual acuity, intraocular pressure, and dilated fundus examination were normal. There was no local/regional lymphadenopathy. The patient was a smoker with 35 pack-years and a hypertensive on treatment with no other significant systemic history. The differential diagnoses considered were Merkel cell carcinoma and sebaceous gland carcinoma. A pentagon excision was planned with 3-mm margin clearance. The mass was excised, and the eyelid defect was amenable to direct closure with a Tenzel's semicircular flap.

The histopathological examination showed a well-circumscribed, multinodular, intradermal tumor consisting of round-to-oval cells with round nuclei [Fig. 1b and c]. The

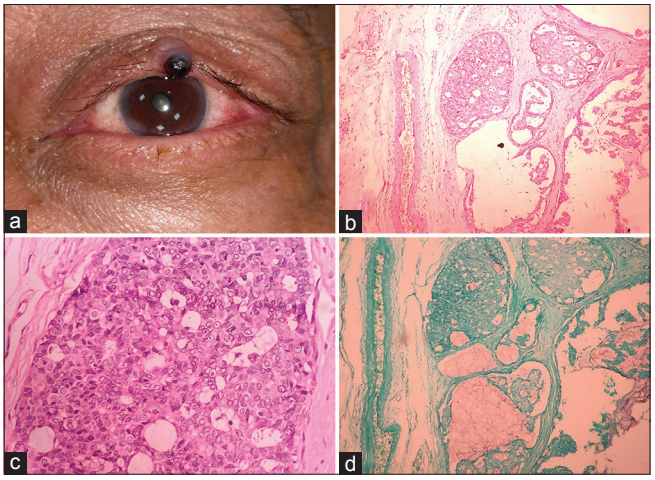

Figure 1: (a) An external clinical photograph of the eyelid mass. (b) Tumor nests showing cystic, mucin-filled areas, and solid areas showing cribriform and papillary growth patterns (H and E, ×100). (c) A cribriform tumor nest at high magnification. Small, round to polygonal tumor cells displaying moderate amounts of granular, eosinophilic cytoplasm, and anisomorphic nuclei with bland chromatin and inconspicuous nucleoli (H and E, ×400). (d) Intra-tumoral mucin pools stained red with Mucicarmine stain (×100)

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cytoplasm was abundant and lightly eosinophilic. There were mucinous microcysts within the tumor, and although moderate pleomorphism was noted, mitotic figures were infrequent [Fig. 1d]. The surgical margins were uninvolved. A broad immunohistochemistry panel was used, and the results were as follows cytokeratin (CK)-7+, CK-8+, ER +, PR +, mucicarmine +, synaptophysin +, GCDFP-15 +, NSE +. Therefore, based on the tumor architecture, the abundant mucin production, and immunohistochemical features [Figs. 2 and 3], a final diagnosis of EMPSGC of the eyelid was made (T2b N0 M0). The recovery was uneventful, and at his 6-monthly follow-up, he was asymptomatic with no recurrence.

Discussion

Given the rarity of EMPSGC, our case presented a challenge both clinically and histopathologically. EMPSCG was not on our list of probable differentials during evaluation and planning. This stems from the fact that there have been no reports of EMPSGC from the Indian subcontinent; and most of the cases in literature being Caucasian patients. This geographical variation could indicate that this tumor may have a racial predilection - much like how sebaceous gland carcinoma is the most common malignant eyelid tumor in the subcontinent as opposed to basal cell carcinoma in the rest of the world.[2]

EMPSGC is a rare, low-grade cutaneous adnexal carcinoma with neuroendocrine differentiation and may be a precursor lesion of mucinous carcinoma of the skin.[3] The tumor is morphologically considered to be analogous to endocrine ductal carcinoma *in situ*/solid papillary carcinoma of the breast.[1,4] Immunohistochemically, EMPSGC cells typically express at least one or more neuroendocrine markers.[1] Owing to common embryological origin of sweat glands, breast, and salivary glands; tumors developing from these sites exhibit similar morphological features. The immunohistochemical profile of strong positivity for estrogen/progesterone receptors and cytokeratin 7 along with the histological resemblance to breast carcinoma makes it crucial to rule out the possibility of cutaneous metastases in all cases of EMPSGC.[5] However, our patient did not clinically show any mass lesion in the breast, retraction, discharge from the nipple or pain; all of which are the most common presenting signs in male breast cancer.

Zembovicz *et al*. in their landmark paper reported the clinical and pathological characteristics of 12 cases of EMPSGC. In their cohort, the lesions occurred in both sexes but were twice more common in females than males. The mean age at presentation was 70 years. The tumor was also more frequently encountered in the lower lid.[1] Usually, in cases of eyelid malignancies, clinical suspicion based on age and growth characteristics drives the appropriate management of surgical resection. Our case, surprisingly, did not classify as a "typical" case of EMPSGC, based on the demographics and location. Furthermore, the diagnosis of EMPSGC on the basis of clinical characteristics alone is difficult, as this tumor has the appearance of being a benign lesion on the eyelid. The differentials discussed in other reports in literature include metastasis and primary adnexal neoplasms such as hidradenoma, hidradenocarcinoma, apocrine adenoma, and dermal duct tumor.[6]

Histologically, EMPSGC typically has solid nodules of cells which may demonstrate a papillary or cribriform architecture, prominent cystic spaces, and intracellular and extracellular mucin.[1,7,8] In the series presented by Zembovicz *et al*., half the cases of EMPSGC were associated with invasive mucinous carcinoma, which in their opinion provided evidence for the possibility of multistage progression of noninvasive sweat gland neuroendocrine carcinoma to EMPSGC and then to mucinous carcinoma of the eyelid. Whether EMPSGC represents an *in situ* or an invasive carcinoma depends on the presence or absence of a peripheral rim of myoepithelial cells.[5] The presence of the rim of myoepithelial cells around the tumor cells should be confirmed using smooth muscle actin (SMA). However, SMA reactivity should be interpreted with caution because staining of stromal myofibroblasts around tumor nodules may result in an erroneous impression of an intact layer of myoepithelial cells.[1,5] Therefore, as Zembowicz *et al*. have mentioned, in most cases EMPSGC is best regarded as an invasive malignant tumor.[1]

With regards to the management, reports of recurrence and local invasion are rare, but owing to its histological similarity with carcinoma of the breast, it is believed that complete surgical excision is curative. Mohs micrographic surgery has also been used with success in the management of EMPSGC.[7,8]

This report is the first one documenting an EMPSGC from the Indian subcontinent. EMPSGC is a rare tumor and like other sweat gland carcinomas tend to grow slowly; tumors of the American Joint Committee on Cancer category T2b or less are reported associated with better outcomes.[9] In the Indian scenario, even though extremely uncommon, it should be considered as a differential when encountered with a suspicious eyelid mass.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

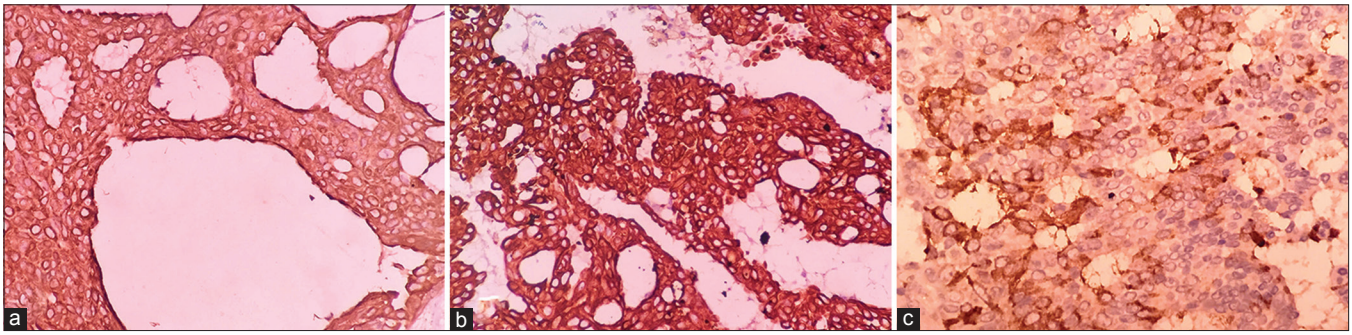

Figure 2: The tumor cells strongly expressed CK-8 (a), CK-7 (b), and synaptophysin (c)

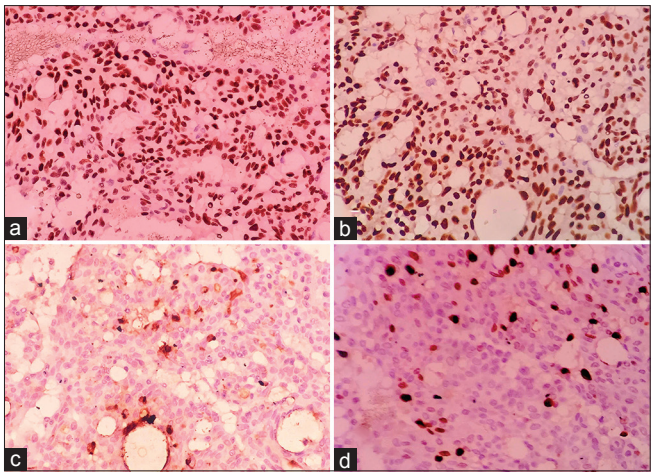

Figure 3: The tumor cells stained positively for ER (a), PR (b), and GCDFP-15 (c). The Ki-67 index was considered low at 6% (d)

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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