Endocrine mucin-producing sweat gland carcinoma (EMPSGC) of the eyelid: Clinicopathologic features, immunohistochemical findings and review of literature

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Sweat gland neoplasms are rare adnexal tumors that pose a diagnostic challenge for both, ophthalmologists and pathologists. Endocrine, mucin producing sweat gland carcinoma (EMPSGC), considered to be analogous to the solid papillary mammary carcinoma is one such tumor. It usually affects elderly, is more frequent in women and has a predilection for skin of the eyelid. Although it has an indolent clinical course, EMPSGC is believed to be a precursor of the invasive mucinous carcinoma and has a potential for local recurrence. We report a series of 10 biopsy-proven EMPSGCs with their immunohistochemical features and review the literature.

Key words: Carcinoma, endocrine, eyelid, mucin, sweat gland

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is a rare tumor of sweat gland origin with predilection for periocular skin of elderly women. Histpathologically, it is analogous to the mammary solid-papillary carcinoma and considered as being a precursor of cutaneous mucinous carcinoma.[1,2] It has an indolent clinical course and favorable prognosis. We describe 10 such cases with their clinicopathological and immunohistochemical features and review the existing literature on EMPSGC.

Case Reports

Ten cases of EMPSGC were diagnosed between 2013 and 2018. Patient folders were assessed for basic demographic data, clinical findings, and outcomes. Hematoxylin and eosin stained sections were reviewed to confirm or refute the original diagnosis. Immunohistochemical staining was performed in all patients.

The clinicopathological and immunohistochemical features of our patients are shown in Table 1.

Demographic and clinical features

Average age at presentation was 68.7 years (range, 55–82); majority were females (male: female ratio 3:7). The upper eyelid (6/10) was slightly more affected than the lower eyelid. All patients presented with a gradually progressive, painless mass that was, firm and nodular to solid to cystic [Fig. 1] and less than 2 cm in size (range, 7-20 mm). The average duration of symptoms was 9.7 months (range, 5–24 months). Systemic examination was normal in all patients.

Histopathological features

The tumor was dermal, multi-nodular and solid to cystic [Fig. 2a and b]. Cribriform [Fig. 2c] and papillary patterns [Fig. 2d] were also noted. Alcian blue-positive material was present in the lumina [Fig. 2f]. Individual tumor cells were round with pale, eosinophilic cytoplasm and bland, vesicular nuclei. Mitoses were rare. An invasive component comprising of nests of tumor cells floating in mucin lakes [Fig. 2e] was present in all; 2 patients lacked an *in-situ* component.

Immunohistochemical features

All tumors showed diffuse positivity for estrogen receptor, progesterone receptor, pan-cytokeratin, epithelial membrane antigen and gross cystic disease fluid protein-15 [Fig. 3]. Focal immunoreactivity for chromogranin A [Fig. 3] and neurone specific enolase was seen in all. In 1 patient, focal, weak positivity for AR was observed. Tumor cells were negative for CK20, CDX2, and TTF1. Myoepithelial cells in the *in-situ* component were positive for SMA [Fig. 3h].

Treatment and outcomes

All patients were treated by surgical excision alone. Average follow-up duration was 15 months (range, 6–36). While complete excision was curative in 9 patients, recurrence was observed in 1 patient after 7 months; the recurrent tumor was surgically excised with adequate margin clearance. None developed metastases.

Discussion

Diagnosis of cutaneous adnexal tumors can be a challenge, especially the sweat gland tumors given their rarity, lack of consensus regarding their nomenclature and classification and, multiplicity of terminologies. Sweat glands may be eccrine or apocrine. The glands of Moll and the mammary gland, considered to be modified apocrine glands, are affected by

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Table 1: Clinicopathological and immunohistochemical features of patients with endocrine, mucin-producing sweat gland carcinoma of the eyelid

Total cases	10
Gender distribution	
Males	3 (30%)
Females	7 (70%)
Age distribution	
Range (years)	55-82 (average, 68.7)
Laterality	
Right	5 (50%)
Left	5 (50%)
Location	
Upper eyelid	6 (60%)
Lower eyelid	4 (40%)
Size	
Range (milimeter)	7-20 (average, 11)
Presenting symptoms	
Gradually progressive mass	10 (100%)
Duration of symptoms	
Range (months)	5-24 (average, 9.7)
Tumor features	
Telangectasia	8 (80%)
Rounding of posterior eyelid margin	0
Madarosis	1 (10%)
Tarsal plate fixity	10 (100%)
Skin fixity	0
Light microscopic features	
Multinodular pattern	10/10 (100%)
Cribriform pattern	10/10 (100%)
Solid and cystic foci	10/10 (100%)
Papillary pattern	4/10 (40%)
Extra-cellular mucin	10/10 (100%)
In-situ component	8/10 (80%)
Invasive component	10/10 (100%)
Cytoplasm	Pale eosinophilic
Nucleus	Vesicular
Nucleoli	Inconspicuous
Nuclear atypia	None to minimal
Mitoses	Rare
Lymphovascular invasion	0/10
Perineural tumor spread	0/10
Immunohistochemical features	
Pan-cytokeratin	10/10 (100%), diffuse
Epithelial membrane antigen (EMA)	10/10 (100%), focal/diffuse
Estrogen receptor (ER)	10/10 (100%), diffuse
Progesterone receptor (PR)	10/10 (100%), diffuse
Neurone-specific enolase (NSE)	10/10 (100%), focal
Gross cystic disease fluid protein (GCDFP)-15	10/10 (100%), diffuse
Cytokeratin 7 (CK 7)	10/10 (100%), diffuse
Chromogranin A (CGA)	10/10 (100%), focal
Cytokeratin 20 (CK 20)	0
Primary treatment	
Surgical excision	10/10 (100%)
Clinical outcome	
Complete remission	9/10 (90%)
Recurrence	1/10 (10%)

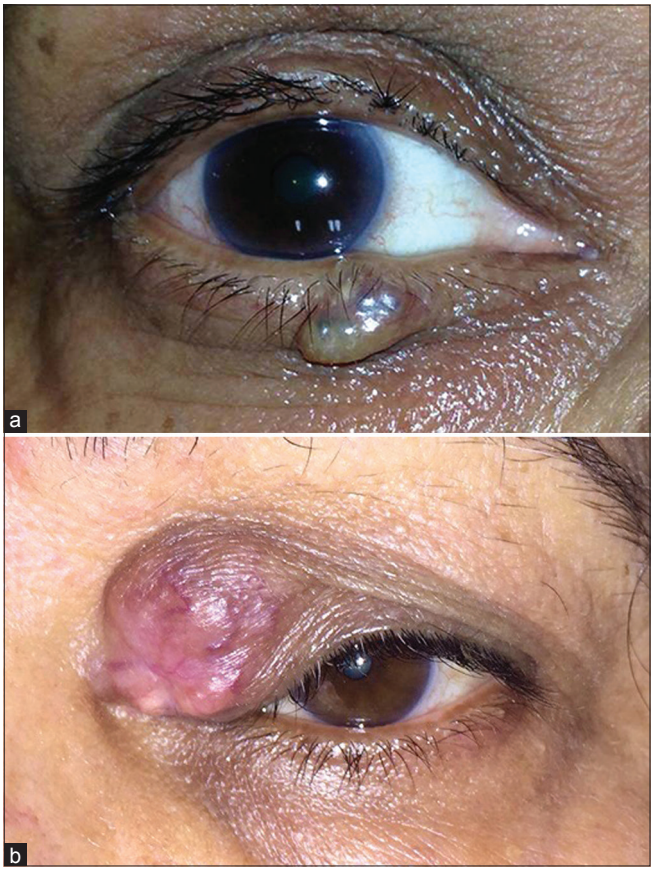

Figure 1: Clinical presentations of endocrine mucin producing sweat gland carcinoma (EMPSGC): (a) Solid and cystic nodule on the lower eyelid with associated indentation of the eyelid margin. (b) Nodular mass involving the medial half of the upper eyelid extending up to the inner canthus

many neoplasms with similar histomorphologies. EMPSGC is one such neoplasm.

First described in 1997, EMPSGC is rare and usually affects periocular skin of females in their 6th or 7th decades.[1-4] Rare cases affecting the cheeks, scalp, and extrafacial sites have been described.[4-6] Zembowicz *et al*. describe the lower eyelid to be more frequently involved as compared to the upper; Hoguet *et al*. report otherwise.[4,7] The upper eyelid was slightly more involved in our series. Clinically, EMPSGC are slow-growing, nodular, or pedunculated, vascular, occasionally cystic, non-ulcerated growths at the eyelid margin. Histologically, they are circumscribed, multi-nodular having cystic and solid components. Papillary and cribriform patterns are often seen. Individual cells have pale eosinophilic and relatively bland nuclei displaying minimal atypia. Mitoses are scanty.[1-5]

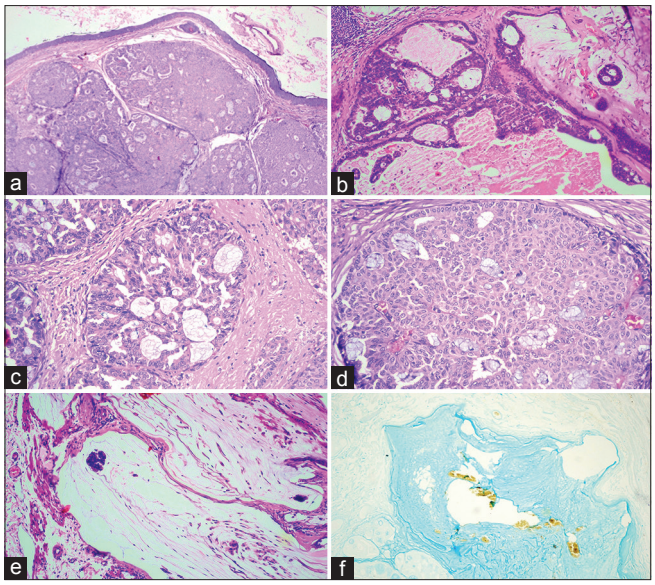

Figure 2: Light microscopic features of EMPSGC: (a) Multinodular appearance (Hematoxylin and eosin, ×40). (b) Solid and cystic dermal nodule with papillary fronds and central luminal mucin (Hematoxylin and eosin, ×40). (c) Cribriform pattern with bluish, mucinous material in the lumina (Hematoxylin and eosin, ×100). (d) Papillae with fibrovascular cores within solid nodules (Hematoxylin and eosin, ×100). (e) Nest of tumor cells floating in mucin lakes in the invasive component (Hematoxylin and eosin, ×100). (f) Mucin lakes stains positive with Alcian blue (Alcian blue, ×100)

EMPSGC may have in-situ and/or invasive patterns.[1,4] Invasive foci lack discernible myoepithelial cells, but these can be easily demonstrated around tumor nodules in the in-situ lesions and stain positive for p63, calponin and SMA. The 2 patterns may co-exist indicating a progression of the in-situ component to an invasive tumor where nests of tumor cells float in pools of mucin. Multiple serial sections are hence essential to exclude an invasive component.

EMPSGC co-expresses estrogen and progesterone receptors.[1-7] Variable immunoreactivity for at least 1 neuroendocrine marker is consistent in these tumors. The tumor cells express CK 5/6, CK7, CK8, CK18, CAM5.2, and EMA and are negative for CK20.[1,3-7] Similarity of the IHC staining patterns in non-invasive and invasive components has further strengthened the belief on the multi-stage progression of a non-invasive endocrine carcinoma to a EMPSGC and then to an invasive mucinous carcinoma.[4,7] Given that light microscopic and immunohistochemical features of EMPSGC overlap with those of solid, papillary breast carcinoma, it is essential that pathologists and clinicians exclude a breast primary. A thorough radiological and physical examination of the breast thus becomes necessary. None of our patients had a breast neoplasm.

EMPSGC is considered to be indolent in nature; though recurrences may occur, metastases have not been reported so far.[1-10] One of our patients had a recurrence. The recurrent disease was treated with complete excision and the patient continues to be disease-free at 6-month follow-up. Complete surgical excision with eyelid reconstruction is usually advocated in these tumors. Although Mohs' micrographic surgery is considered appropriate, a traditional surgical excision with adequate margin clearance performed under frozen section control also yields successful results.[2,3,10]

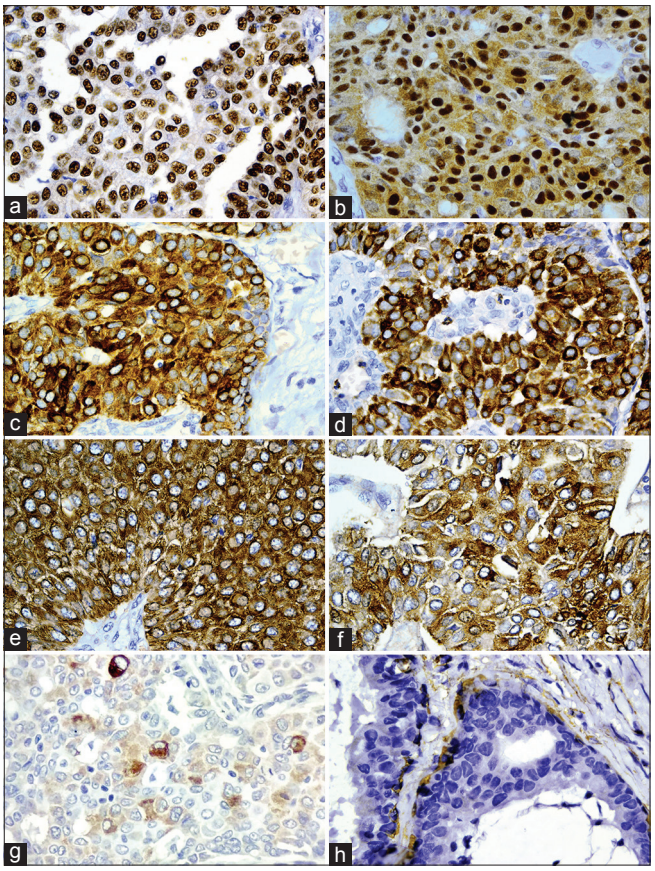

Figure 3: Immunohistochemistry of EMPSGC. Positive staining for (a) Estrogen receptor (ER). (b) Progesterone receptor. (c) Pan-cytokeratin. (d) Cytokeratin 7. (e) Epithelial membrane antigen (EMA) and, (f) Gross cystic disease fluid protein 15 (GCDFP 15). (g) Chromogranin (CGA) and (h) Alpha-smooth muscle actin (SMA) in myoepithelial cells (×400)

In conclusion, we describe clinicopathologic and immunohistochemical features in patients with EMPSGC of the eyelids, a rare and low-grade sweat gland neoplasm. Given its close association with invasive mucinous carcinoma and potential for local recurrence, complete surgical excision with a close follow-up is essential in managing such patients.

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Conflicts of interest

There are no conflicts of interest.

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