Case Reports in Dermatology

Case Rep Dermatol 2020;12:255–261

DOI: 10.1159/000509516
Published online: November 23, 2020

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Case and Review

A Case of Endocrine Mucin-Producing Sweat Gland Carcinoma: Is it Still an Under-Recognized Entity?

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Keywords
Endocrine mucin-producing sweat gland carcinoma · Mucinous carcinoma · Eyelid · Molecular analysis

Abstract
Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is a rare low-grade sweat gland carcinoma characterized by immunoexpression of neuroendocrine markers and mucin production. It occurs most frequently at the head and neck region with strong predilection to the eyelids. Up to 2013, only few cases have been reported. However, in the following years, the number of cases reported has increased significantly, which indicates an upsurge in awareness and increased recognition of this neoplasm. Herein, we describe another case of EMPSGC in a 78-year-old man who presented with a 6-mm skin lesion at the lower eyelid. We discuss the clinical, histopathologic and immunophenotypic features of the tumor with particular emphasis on molecular features and prognosis.

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Introduction

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is a rare low-grade sweat gland carcinoma that had been first described by Flieder et al. [1] in 1997. The tumor has

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predilection for the eyelids and usually occurs in females in the 7th decade [1–4]. Some cases have been found to co-exist with invasive mucinous carcinoma and believed to be related to the same lesional spectrum [1–3, 5, 6]. The tumor has a risk of local recurrence; however, distant metastasis has not been reported [1–3, 7, 8].

In the past, this neoplasm has been underrecognized. However, the number of cases reported in the last five years has increased significantly, indicating that dermatopathologists are becoming more familiar with this entity. The immunohistochemical features of this neoplasm are thoroughly analyzed, but information regarding its molecular profile is limited. Herein, we present another case of EMPSGC and discuss the recent updates in the literature.

Case Presentation

A 78-year-old man presented with a lesion at the right lower eyelid that was slowly increasing in size over the last 2 years. Clinical examination revealed a 6-mm skin colored lesion with superficial vascularization. The lesion was not adherent to the tarus. Excisional biopsy was performed. Histopathologic examination showed a dermal tumor composed of solid nodules with focal solid papillary architecture (Fig. 1a, b). The tumor is not connected to the epidermis. It is composed of cells having eosinophilic cytoplasm with mild to moderate nuclear pleomorphism. The nuclei are ovoid in shape with stippled chromatin and inconspicuous nucleoli (Fig. 1c). Few mitotic figures are present; however, no necrosis or atypical mitoses are identified. There is no evidence of lymphovascular or perineural invasion. Alcian blue/periodic acid Schiff (PAS) stain revealed intracytoplasmic and luminal mucin (Fig. 1d).

Immunohistochemical stains demonstrated that the tumor cells are reactive for cytokeratin 7 (CK7), cytokeratin 8 (CK8), cytokeratin 18 (CK18), synaptophysin, estrogen receptor (ER), progesterone receptor (PR) and gross cystic disease fluid protein-15 (GCDFP-15) (Fig. 2a–g). Epithelial membrane antigen (EMA) is positive at the luminal aspect of the ducts. Smooth muscle actin (SMA) and p63 highlight scattered myoepithelial cells at the periphery of the solid nests (Fig. 2h, i). The tumor cells are negative for other neuroendocrine markers including chromogranin A and CD56. They are also negative for cytokeratin 20 (CK20), TTF-1 and CD117. Based on the morphological and immunohistochemical findings, the diagnosis of EMPSGC was rendered.

Next-generation sequencing (NGS) was performed on genomic DNA of tumor extracted from formalin-fixed paraffin-embedded (FFPE) tissue. The panel targeted frequently mutated 59 genes (including *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *HRAS*, *NRAS*, *NTRK, AKT1*, *PIK3CA*, *KIT* and *PDGFRA*). However, no gene mutations or fusions were found.

The tumor was extending to the resection margin; therefore, a re-excision was performed, and histologic examination showed stromal scarring only with no evidence of residual tumor. The patient was followed up for 2 years; during that period, no local recurrence or distant metastases were reported.

Discussion/Conclusion

EMPSGC is a rare low-grade sweat gland carcinoma. This entity had been first described by Flieder et al. [1] in 1997, who reported two cases with histomorphological features analogous to solid papillary carcinoma of the breast. The tumor usually occurs around the eye, most

commonly at the lower eyelid [1–4]. Less frequently, it can involve the upper eyelid, cheeks, supra-auricular, retroauricular and occipital regions [9]. It occurs most commonly in elderly females with a mean age of 66 years. However, cases occurring in males have also been reported, including our case [2, 4, 9].

Clinically, the lesion has no specific features. It usually presents as a slowly growing skin-colored nodule. The lesion can be cystic, multiple, or pigmented. Therefore, the clinical differential diagnosis is wide including hidradenoma, chalazion, dermatofibroma or even basal cell carcinoma [2, 4, 9].

The morphological appearances resemble those of endocrine ductal carcinoma in situ (DCIS) and solid papillary carcinoma of the breast [1, 2]. Histologically, EMPSGC is a dermal tumor characterized by having multinodular growth pattern with solid and cystic areas. The solid areas may show cribriform growth pattern or pseudorosettes. The cystic spaces are sometimes filled with mucin. The tumor cells are columnar in shape with moderate amount of eosinophilic cytoplasm along with intracytoplasmic and extracellular mucin. The nuclei are ovoid with stippled chromatin and inconspicuous nucleoli. By immunoperoxidase stains, the tumor cells show reactivity for at least one neuroendocrine marker. Synaptophysin has been found to be more sensitive than chromogranin A. Most of the cases reported showed consistent reactivity for CK7, EMA, ER and PR, but were negative for CK20. In our case, the immunohistochemical findings are congruent with the literature [2, 9–11].

The histopathologic differential diagnosis includes primary skin neoplasms or cutaneous metastasis [8, 9, 11]. Primary skin neoplasms mainly include nodular hidradenoma, apocrine adenoma and high-grade adenocarcinoma. Nodular hidradenoma is characterized by having duct-like structures with areas of squamoid differentiation and stromal hyalinization. The cells in apocrine adenoma are different and characterized by having abundant eosinophilic cytoplasm, prominent nucleoli with lack of intracytoplasmic mucin. In adenocarcinoma, the cells are markedly pleomorphic with frequent mitotic activity and tumor necrosis. Cutaneous metastasis from breast or colorectal origin should be considered. The presence of a myoepithelial layer, as highlighted by SMA and p63 antibodies, favors a primary cutaneous origin over metastasis. The tumor cells in EMPSGC are usually negative for CK20 antibody, which makes metastatic colorectal carcinoma highly unlikely.

Invasive mucinous carcinoma is a deeply infiltrative tumor into the dermis with clusters of tumor cells floating in pools of mucin. Several studies have found a strong relationship between EMPSGC and invasive mucinous carcinoma [2, 3, 5, 6]. Both tumors can occur synchronously, and it is hypothesized that EMPSGC could represent a precursor lesion. In a study of 12 cases of EMPSGC reported by Zembowicz et al. [2], 6 cases were associated with invasive mucinous carcinoma. However, Quin et al. found only 1 case out of 11 cases of EMPSGC with an invasive mucinous carcinoma component [4]. Chang et al. and Charles et al. also reported cases of EMPSGC co-existing with mucinous carcinoma [5, 6]. In our case, no invasive mucinous carcinoma component was identified.

Information regarding the molecular profile of EMPSGC is limited. However, some efforts have been made in this regard. Cornejo et al. performed NGS with a targeted panel of 50 frequently mutated genes on two cases of EMPSGC [12]. In that study, mutations were not detected in any of the genes that are commonly involved in mucinous neoplasms including *EGFR*, *KRAS* and *GNAS*. No mutations were also detected in *AKT1* and *PIK3CA* genes, which are frequently mutated in papillary carcinomas of the breast. Qin et al. [4] performed array comparative genomic hybridization (aCGH) on two cases of EMPSGC, which demonstrated 6p11.2 to 6q16.1 deletion in one of the cases. $BRAF^{V600E}$ pyrosequencing performed in that study was

negative. In our case, NGS with a panel targeting 59 frequently mutated genes was performed. The panel included most of the genes examined in previous studies including *EGFR*, *KRAS*, *BRAF*, *AKT1* and *PIK3CA*. No gene mutations or fusions were detected in our case.

Recently, Held et al. [9] have stained 10 cases of EMPSGC with MYB antibody, they found that all cases showed strong nuclear MYB expression, but was negative in primary mucinous cutaneous carcinomas and mucin-rich basal cell carcinomas. They concluded that MYB could be a useful surrogate marker, especially in mucin-poor EMPSGC cases. However, all cases in that study were negative for translocation or amplification of *MYB* gene by fluorescent in situ hybridization (FISH). We were not able to examine MYB in our case.

EMPSGC has indolent behavior. Local recurrence can occur; however, distant metastasis has not been reported. In the study of twelve cases performed by Zembowicz et al. [2], none of the patients reported recurrence or metastases during a follow-up period that ranged from 1 to 4 years. In a study of two cases reported by Dhaliwal et al. [8], both patients were free from local recurrence or clinical signs of distant metastases at the end of the follow-up period spanning from 7 to 18 months. Emanuel et al. [7] described a case of EMPSGC in a 65-year-old woman in which the tumor recurred 3 years after excision. For this reason, complete surgical excision and clinical follow-up for a period of at least 24 months have been suggested [3, 4, 7].

In summary, EMPSGC should always be considered in the differential diagnosis of skin lesions at the head and neck region, particularly the eyelid, in order not to make an erroneous diagnosis of more aggressive neoplasms. Complete excision and clinical follow-up are recommended as the tumor has risk of local recurrence and progression to invasive mucinous carcinoma. The increase in number of reported cases in the last 5 years is reassuring and indicates that dermatopathologists are becoming more familiar and aware of this particular neoplasm. Finally, the genetic profile of the tumor is still obscure and needs further investigations and studies.

Acknowledgements

We would like to express our thanks to the Ophthalmology Department at Hamad Medical Corporation Qatar, for providing the clinical information for the patient.

Statement of Ethics

The Institutional Review Board of the Medical Research Council, Hamad Medical Corporation, Qatar reviewed the protocol and approved it under this reference number: MRC-04–20–208. Written informed consent was taken from the patient for publication.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The publication of this article was funded by the Qatar National Library (QNL).

Author Contributions

K.A.M. conceived and designed the idea, performed literature review, wrote the manuscript, and overall organized the case report. M.B.G reviewed the manuscript and supervised the project.

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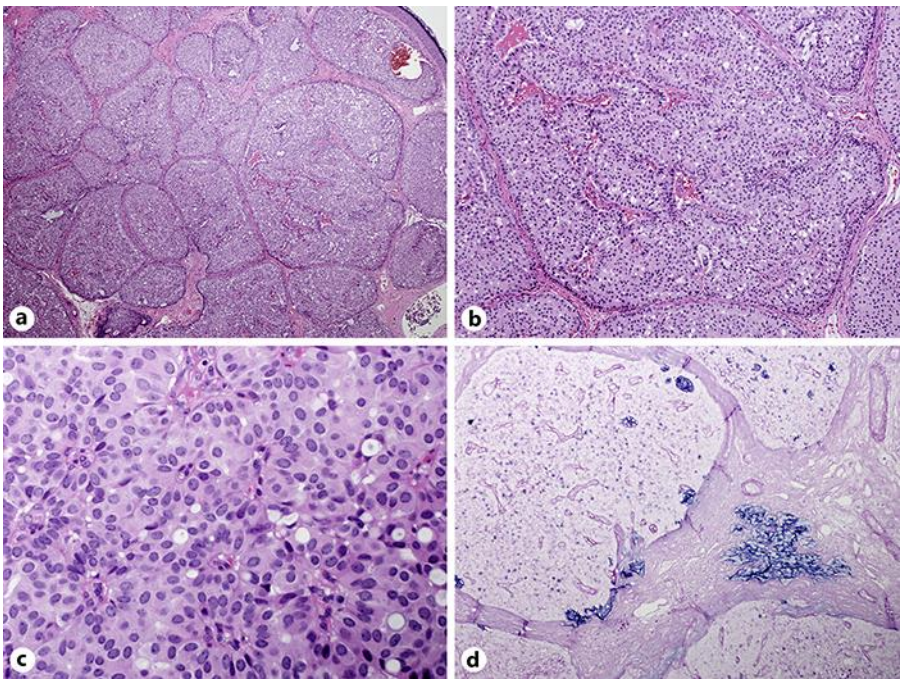

Fig. 1. Microscopic features of EMPSGC. **a** Photomicrograph shows multinodular solid tumor occupying the dermis. **b** A lobule of tumor cells exhibits pseudoglandular and solid papillary growth pattern with focal cystic changes. **c** The tumor cells are columnar in shape with mild nuclear pleomorphism and have abundant eosinophilic cytoplasm. **d** Alcian blue/PAS stain highlights intracytoplasmic and intracystic mucin deposition.

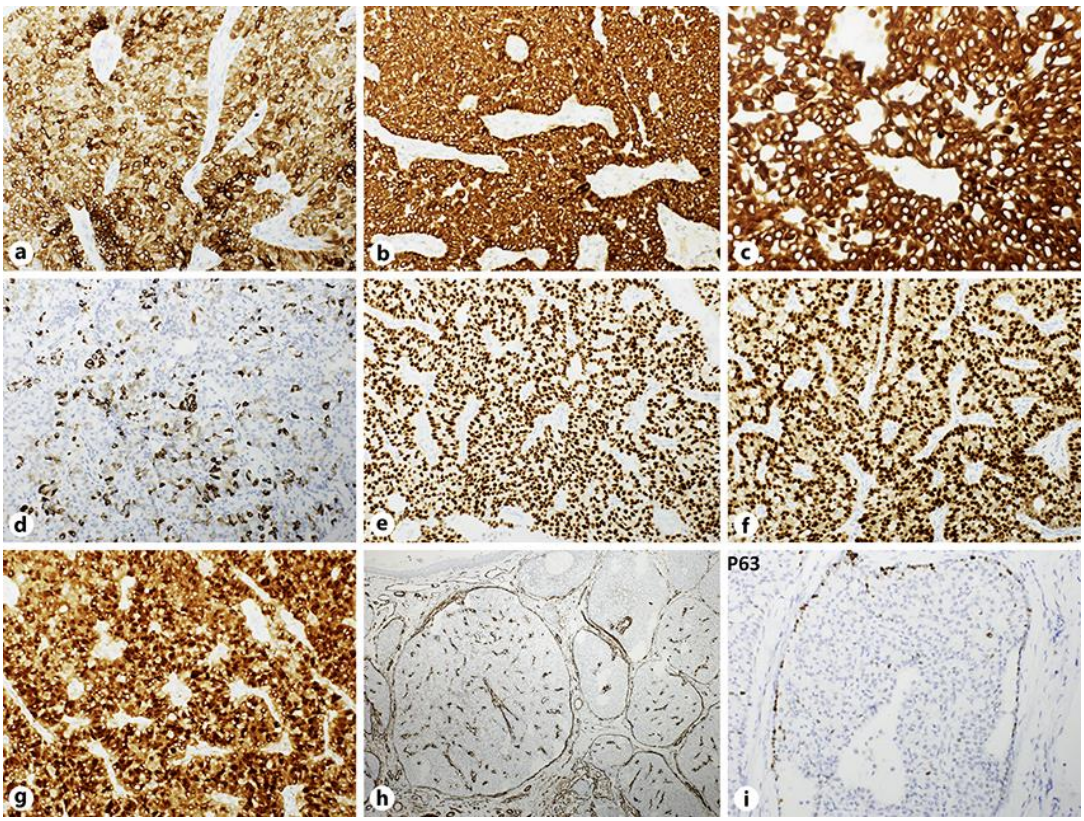

Fig. 2. Immunohistochemical features of EMPSGC. **a** The tumor cells demonstrate positive staining for cytokeratin 7. **b** Cytokeratin 8. **c** Cytokeratin 18. **d** Patchy staining for synaptophysin. **e**, **f** Strong nuclear staining for ER and PR. **g** Positive staining for GCDFP15. **h** SMA highlights rim of myoepithelial cells at the periphery of the tumor nodules. **i** p63 is also positive in the cells at the periphery of tumor lobules.