ISSN: 2977-0033

Review Article

Journal of Clinical Research and Case Studies

Endocrine Mucin-Producing Sweat Gland Carcinoma of the Eyelid: A Comprehensive Review of a Rare Entity

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Received: August 19, 2025; **Accepted:** August 29, 2025; **Published:** September 08, 2025

ABSTRACT

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) of the eyelid is a rare, low-grade adnexal neoplasm with neuroendocrine differentiation, primarily affecting the periocular skin of elderly individuals [1,2]. This review provides an in-depth analysis of the histopathological features, immunohistochemical profile, clinical presentation, and differential diagnosis of EMPSGC, with a comparative perspective against solid papillary carcinoma (SPC) of the breast. The aim is to equip pathologists with the knowledge necessary for accurate diagnosis and to highlight the importance of recognizing this entity in the context of other eyelid and breast lesions.

Introduction

EMPSGC is a distinctive cutaneous malignancy recognized as a homologue of endocrine ductal carcinoma in situ (eDCIS) or SPC of the breast [3,4]. First described in 1997, EMPSGC is characterized by its unique histomorphological and immunohistochemical features, often presenting diagnostic challenges [3-5].The tumor's predilection for the eyelid region and its association with mucinous carcinoma warrant a detailed understanding for accurate diagnosis and appropriate management [6].

Epidemiology and Clinical Presentation

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is a rare tumor predominantly affecting elderly individuals, with a notable prevalence in women, particularly in their sixties and seventies. The median age at presentation is typically around 70 years, but cases have also been documented in patients as young as 36 and as old as 84 [1-3]. This variability indicates that while EMPSGC is more common among older adults, it is not exclusive to this demographic.

Epidemiological studies reveal that EMPSGC primarily occurs in the periocular region, especially on the eyelids. However, there have been reports of lesions in other locations, including the cheeks, temples, scalp, and even the chest and scrotum [2-4]. This broad range of potential sites underscores the need for heightened awareness among clinicians, as these tumors may be misdiagnosed as benign conditions such as chalazia or cysts.

Clinically, EMPSGC typically presents as a slow-growing, painless nodule. Patients often notice a skin-colored or slightly pigmented mass that can remain asymptomatic for months or years before prompting medical evaluation [1]. Upon examination, these nodules are usually well-circumscribed and may exhibit features such as a bluish hue or surface keratinization, particularly if ulceration occurs (Figure 1 A-C).

While most cases of EMPSGC are localized and exhibit a favorable prognosis, local recurrences have been documented following surgical excision. The risk of recurrence is particularly relevant for tumors with an invasive component, which highlights the importance of ensuring clear surgical margins during initial treatment [6]. Furthermore, although metastasis is rare, recent reports have indicated instances where the carcinoma has spread to regional lymph nodes and distant sites, such as the parotid gland, after a significant interval post-excision [7], [8].

Citation: Maryam Hammad. Endocrine Mucin-Producing Sweat Gland Carcinoma of the Eyelid: A Comprehensive Review of a Rare Entity . J Clin Res Case Stud. 2025. 3(4): 1-4. DOI: doi.org/10.61440/JCRCS.2025.v3.81

This possibility necessitates ongoing surveillance for patients diagnosed with EMPSGC, as the tumor's behavior may not always align with its initial indolent nature.

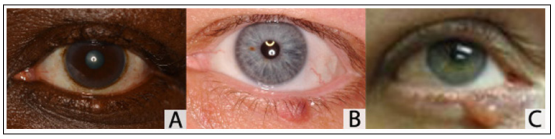

Figure 1: Clinical appearance of EMPSGC and neuroendocrine-type mucinous sweat gland carcinoma. A, Skin-colored, nodular, erythematous, and cystic lesion at the left lower eyelid margin. B, Skin-colored, smooth, nodular, pearlescent, and firm lesion at the left lower eyelid margin. C, Pedunculated, cystic lesion at the right lower eyelid margin [1].

Histopathological Features

General Architecture

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is characterized by well-circumscribed, multinodular tumor masses within the dermis, often exhibiting both solid and cystic areas (Figure 2A-C), (Figure 3 A-F) [1-7]. The tumor typically resides intradermally, situated beneath an intact epidermis [7]. This architectural arrangement allows for clear differentiation from other cutaneous tumors, making histological evaluation critical for accurate diagnosis.

Cellular Morphology

At higher magnification, EMPSGC is composed of uniform, round-to-oval cells with abundant pale eosinophilic cytoplasm [7]. The nuclei are round and feature finely stippled chromatin, which is indicative of neuroendocrine differentiation [7]. Mitotic activity within these tumors is generally low, which aligns with their classification as low-grade malignancies [7]. A key histological feature is the presence of extracellular mucin, which may be abundant and create cystic spaces within the tumor [2], [7]. Additionally, areas transitioning into mucinous carcinoma may be observed, where tumor islands appear to "float" in pools of mucin [7] (figure 3 A-F).

Growth Patterns

The tumor cells are arranged in solid nests, trabeculae, and papillary or cribriform patterns [6], [8]. The papillary structures consist of neoplastic cells supported by fibrovascular cores [6], [7]. In some instances, EMPSGC may coexist with mucinous adenocarcinoma, highlighting a potential progression from EMPSGC to invasive mucinous carcinoma [7]. This coexistence suggests that careful examination of histological samples is essential to identify all components of the tumor (figure 3 E, F).

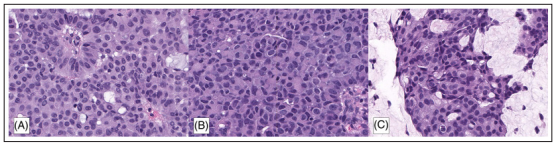

Figure 2: Endocrine mucin-producing sweat gland carcinoma is composed of columnar secretory epithelial cells with abundant amphophilic cytoplasm, pools of mucin between cells, and bland, monotonous round-to-ovoid nuclei with inconspicuous nucleoli (A). One tumor had slightly angulated nuclei with stippled chromatin and occasional mitotic figures (B). The cytomorphologic features of endocrine mucin-producing sweat gland carcinoma are identical to those of primary cutaneous mucinous carcinoma (C) (A-C H&E, ×400)

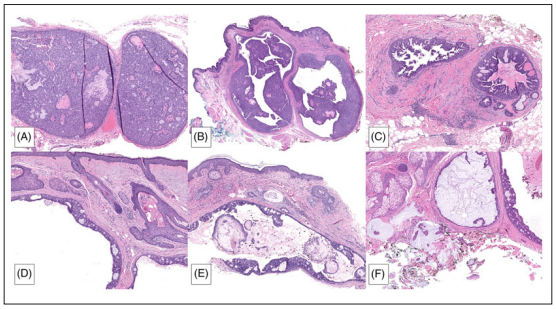

Figure 3: Endocrine mucin-producing sweat gland carcinoma can exhibit a range of architectures including predominantly solid growth (A), solid and cystic growth with intraluminal papillary projections (B), solid and cystic growth with intraluminal micropapillary projections that anastomose in a Roman bridge pattern (C), solid and cribriform growth along the perimeter of a cystically dilated space reminiscent of hidrocystoma and hidrocystadenoma (D and E), and in association with primary cutaneous mucinous carcinoma, which is composed of epithelial islands suspended in colloidal pools of mucin (F) (A-F H&E, ×40)

Immunohistochemical Profile

Immunohistochemistry (IHC) plays a crucial role in confirming the diagnosis of endocrine mucin-producing sweat gland carcinoma (EMPSGC) and differentiating it from other eyelid tumors. Key markers are routinely assessed to provide clarity in diagnosis and treatment options.

One of the primary findings in EMPSGC is the positive staining for cytokeratins, particularly CK7 and CK8/18. These markers are commonly expressed, indicating the epithelial nature of the tumor [2], [4]. The presence of these proteins supports the diagnosis and helps distinguish EMPSGC from other neoplasms that may present similarly.

In addition to cytokeratins, neuroendocrine markers such as synaptophysin, chromogranin A, and neuron-specific enolase (NSE) are typically positive in EMPSGC. The expression of these markers confirms the neuroendocrine differentiation characteristic of the tumor [1-4]. This aspect is essential as it aligns EMPSGC with other neuroendocrine tumors and reinforces the need for a comprehensive immunohistochemical analysis (Figure 4 A-F). Recently, the marker Insulinoma-associated protein 1 (INSM1) has gained attention in the characterization of EMPSGC. Studies have shown that INSM1 is a highly sensitive and specific marker for neuroendocrine differentiation, demonstrating stronger and more diffuse expression compared to traditional markers like synaptophysin and chromogranin A [7](Figure 4 A, B, C). This finding suggests that INSM1 could be a valuable addition to the immunohistochemical panel for diagnosing EMPSGC.

Hormone receptors also play a significant role in the immunohistochemical profile of EMPSGC. The majority of cases demonstrate strong positivity for estrogen receptors (ER) and progesterone receptors (PR), reflecting the tumor's endocrine characteristics [4,7]. This hormonal sensitivity can

influence treatment decisions, particularly in cases where surgical excision is not feasible.

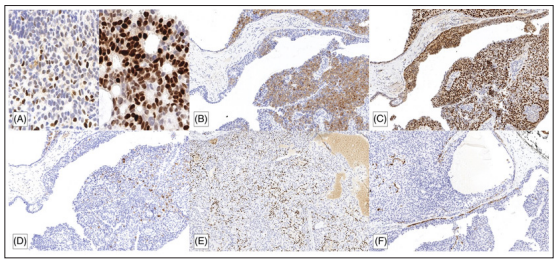

Figure 4: Endocrine mucin-producing sweat gland carcinoma showed moderate (2+) to strong (3+) intensity staining for INSM1 (A, left and right side respectively, ×400). In many cases, the percent of cells staining, the intensity, and the pattern of expression were comparable to that of synaptophysin cytoplasmic expression (B); however, the crisp nuclear expression of INSM1 (C) and relative absence of non-specific background staining provided for a greater ease of interpretation. In contrast, chromogranin highlighted fewer cells in all cases (D). Another example of INSM1 shows staining in only 25% of cells; however, the 3+ intensity permits for rapid interpretation (E). All cases had evidence of a partially intact myoepithelial layer at the periphery of the lesion as illustrated here with calponin (F) (B-F: ×100).

Hormone receptors also play a significant role in the immunohistochemical profile of EMPSGC. The majority of cases demonstrate strong positivity for estrogen receptors (ER) and progesterone receptors (PR), reflecting the tumor's endocrine characteristics (4, 7). This hormonal sensitivity can influence treatment decisions, particularly in cases where surgical excision is not feasible.

Other relevant markers include epithelial membrane antigen (EMA) and gross cystic disease fluid protein-15 (GCDFP-15), which may also show positivity in EMPSGC (4). These markers contribute further to the understanding of the tumor's nature and behavior.

Finally, the proliferation marker Ki-67 typically shows a low proliferation index, usually ranging between 3% to 5% (7, 9). This low index is consistent with the tumor's classification as a low-grade malignancy and suggests a more indolent clinical course compared to more aggressive cancers.

The collective findings from these immunohistochemical analyses are vital for distinguishing EMPSGC from other similar tumors and ensuring accurate diagnosis and optimal patient management.

Differential Diagnosis

The differential diagnosis of endocrine mucin-producing sweat gland carcinoma (EMPSGC) encompasses several eyelid lesions and cutaneous adnexal tumors. Among these, basal cell carcinoma is the most prevalent skin cancer [5]. However, EMPSGC can be distinguished by its unique neuroendocrine differentiation and mucin production, which set it apart from more common lesions [6,7].

Another important consideration is sebaceous carcinoma, characterized by sebaceous differentiation [6]. Unlike EMPSGC, sebaceous carcinoma notably lacks neuroendocrine markers, making it a distinct entity in the differential diagnosis. This differentiation is crucial for appropriate clinical management and treatment planning.

Additionally, EMPSGC may coexist with or progress to mucinous carcinoma [8]. This latter type is characterized by abundant extracellular mucin and typically demonstrates minimal neuroendocrine differentiation. Understanding this relationship is essential, as it can influence therapeutic approaches and prognostic assessments.

Lastly, Merkel cell carcinoma, known for its aggressive nature, exhibits strong neuroendocrine marker expression; however, it is devoid of mucin production [7]. Recognizing these differences is vital in ensuring accurate diagnosis and treatment strategies for patients presenting with eyelid tumors. This nuanced understanding of differential diagnoses ultimately enhances patient outcomes by facilitating timely and effective interventions.

Comparison with Solid Papillary Carcinoma of the Breast

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) and solid papillary carcinoma (SPC) of the breast exhibit several notable similarities, highlighting their analogous nature. Both tumors are characterized by solid, well-circumscribed nodules supported by fibrovascular cores [9]. In SPC, there is often the presence of perivascular pseudorosette formation, which further emphasizes the histological resemblance between these two entities [10].

Both EMPSGC and SPC display neuroendocrine differentiation, as evidenced by positivity for markers such as synaptophysin and chromogranin A [11]. This shared feature underscores their common pathophysiological characteristics. Furthermore, both tumors show expression of hormone receptors, including estrogen receptor (ER) and progesterone receptor (PR), which may have implications for therapeutic approaches [12].

Both EMPSGC and SPC are considered potential precursors to mucinous carcinomas in their respective anatomical locations [13]. Their similarities extend to genetic profiles, suggesting a shared molecular background that warrants further investigation [14].

Despite these similarities, there are important differences between the two. One significant distinction is the myoepithelial layer; SPC of the breast typically lacks this layer, which can be assessed using specific markers like p63 [15]. This feature is not commonly evaluated in EMPSGC. Additionally, the clinical presentation varies: SPC often manifests with nipple discharge or a palpable mass, while EMPSGC usually presents as a slow-growing nodule on the eyelid [15]. These differences are crucial for accurate diagnosis and management of these tumors.

Management and Prognosis

The primary treatment for endocrine mucin-producing sweat gland carcinoma (EMPSGC) is complete surgical excision

with clear margins [6-8]. Mohs micrographic surgery may be considered to ensure complete tumor removal while preserving eyelid function [12]. Adjuvant radiation therapy may be used in cases with positive margins or aggressive features [8].

The prognosis for EMPSGC is generally favorable, with low rates of recurrence and metastasis (4, 1). However, long-term follow-up is essential to monitor for local recurrence or the development of mucinous carcinoma [8].

Conclusion

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) of the eyelid is a rare and distinct entity with unique histopathological and immunohistochemical characteristics. Accurate recognition and differentiation of this tumor from other eyelid lesions are essential for effective diagnosis and management. Its similarities to solid papillary carcinoma (SPC) of the breast highlight the shared traits of adnexal neoplasms exhibiting neuroendocrine differentiation.

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