UPDATE IN MALIGNANT SWEAT GLAND TUMOURS
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MALIGNANT SWEAT GLAND TUMORS

CRITERIA FOR THE DIAGNOSIS OF MALIGNANCY

- Infiltrative growth pattern
- Cytological atypia (this can be focally seen in many benign sweat gland tumors)
- Mitotic count (mitotic figures can often be found in benign sweat gland tumors)
- Necrosis
- Vascular invasion
- Perineural invasion
MALIGNANT SWEAT GLAND TUMORS

- Some benign tumors have potential for local recurrence (mixed tumor)
- Many distinctive subtypes are recognised by the presence of a residual benign component (spiradenoma, mixed tumor)
- A small percentage of malignant cutaneous glandular tumors do not have a benign counterpart (microcystic adnexal carcinoma, digital papillary adenocarcinoma) and in some, distinction from a metastasis from elsewhere is often very difficult (mucinous carcinoma)
MALIGNANT SWEAT GLAND TUMORS

- Microcystic adnexal carcinoma (eccrine epithelioma, syringoid eccrine carcinoma)
- Mucinous carcinoma
- Neuroendocrine mucin-producing sweat gland carcinoma
- Cutaneous adenoid cystic carcinoma
- Extramammary Paget disease
- Apocrine carcinoma
- Porocarcinoma
- Ductal eccrine carcinoma
- Digital papillary adenocarcinoma
- Malignant eccrine spiradenoma
- Malignant cylindroma
- Malignant mixed tumor
- Hidradenocarcinoma (malignant acrspiroma)
- Cutaneous mucoepidermoid carcinoma
- Lymphoepithelioma-like carcinoma
### Malignant Sweat Gland Tumours: Classification

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<th>Malignant Counterpart</th>
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<td>Porocarcinoma</td>
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<tr>
<td>Nodular hidradenoma</td>
<td>Hidradenocarcinoma</td>
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<tr>
<td>Cylindroma</td>
<td>Malignant cylindroma</td>
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<tr>
<td>Spiradenoma</td>
<td>Spiradenocarcinoma</td>
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<tr>
<td>Chondroid syringoma</td>
<td>Malignant chondroid syringoma</td>
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### No Benign Counterpart

- Paget and extra-mammary Paget disease
- Microcystic adnexal carcinoma
- Neuroendocrine mucin producing sweat gland carcinoma
- Mucinous carcinoma
- Mucoepidermoid (low-grade adenosquamous) carcinoma
- Adenoid cystic carcinoma
- Digital papillary adenocarcinoma
- Squamoid ductal eccrine carcinoma
- Secretory carcinoma
Hidradenoma: Definition &

Synonyms: Nodular hidradenoma, solid cystic hidradenoma, clear cell hidradenoma. Acrospiroma

Definition: Benign dermal tumour with areas of solid nodular growth, lumina and frequent cystic change.

Clinical: Usually solitary, occasionally painful, skin coloured or red nodule. Widespread anatomic locations.
Hidradenoma

Dermal circumscribed nodular proliferation. May be predominantly solid or mixed solid and cystic

Circumscribed dermal nodule predominantly solid

Cystic areas
Hidradenoma

Dermal circumscribed nodular proliferation. May be predominantly solid or mixed solid and cystic

Circumscribed dermal nodule: solid cystic

Large Cystic areas
Hidradenoma

Poroid, larger squamoid cuticular cells, clear cells

Lumina small intracytoplasmic to large and cystic.

Lumina are lined by squamoid cuticular and cuboidal or flattened cells
Hidradenoma

Clear Cell

Clear cells
Hidradenoma

Mixed poroid and larger squamoid cuticular cells

Multiple small punched out lumina lined by cuticular cells and containing bright eosinophilic secretions
Hidradenom

- Clear cells
- Peripheral poroid cells
Hidradenoma

- Thin walled capillary vessels
- Cystic space lined by flattened squamoid cuticular cells
- Characteristic hyaline stroma
Atypical and malignant hidradenomas: a histological and immunohistochemical study

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The histological features of atypical hidradenoma are worrisome for increased risk of recurrence and possible malignant potential; however, earlier studies with immunohistochemistry or patient follow-up have not been reported. In addition, immunohistochemical analysis of hidradenocarcinoma exists in the literature mainly as case reports and as a single series of six cases. We compare the histological features and Ki-67, phosphorylated histone H3, epidermal growth factor receptor, and Her2/neu expression profiles of 15 atypical and 15 malignant hidradenomas with those of benign hidradenoma and metastasizing adnexal carcinomas. Infiltrative growth pattern, deep extension, necrosis, nuclear pleomorphism, and ≥ 4 mitoses per 10 high-power fields are specific features of hidradenocarcinomas. Significant difference in mean Ki-67% was observed between benign and malignant hidradenomas (P<0.001), benign and metastasizing adnexal carcinomas (0.002), atypical and malignant hidradenomas (P<0.001), and between atypical hidradenomas and metastasizing adnexal carcinomas (0.002). Significant difference in mean phosphorylated histone H3% was observed between benign and malignant hidradenomas (P<0.001), benign and metastasizing adnexal carcinomas (0.003), atypical and malignant hidradenomas (P<0.001), and between atypical hidradenomas and metastasizing adnexal carcinomas (P<0.001). Mean epidermal growth factor receptor total score was significantly different in benign and atypical hidradenoma when compared with that in metastasizing adnexal carcinoma (P=0.014 and 0.019, respectively). Equivocal or 2+ Her2/neu positivity was observed in one hidradenocarcinoma and in two metastasizing adnexal carcinomas. Receiver operating characteristic curve analysis for Ki-67 and phosphorylated histone H3% positivity reveals statistically significant criterion values of > 11.425 and > 0.7, respectively, for distinguishing malignant hidradenomas from atypical hidradenomas. Despite the presence of some worrisome histological features, the significantly different immunoprofile from the malignant counterpart suggests that atypical hidradenomas are likely to recur but are unlikely to metastasize. A tumor with Ki-67>11% and/or phosphorylated histone H3>0.7% would likely be a malignant rather than an atypical hidradenoma. The infrequent Her2/neu overexpression in hidradenocarcinoma suggests its limited therapeutic role.

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“ATYPICAL” HIDRADENOMA

- Poorly circumscribed
- Focally infiltrative
- Cytological atypia (nuclear)
- Focal necrosis
Μετάστασις = changing location
Clear Cell Nodular Hidradenoma Involving the Lymphatic System

A Tumor of Uncertain Malignant Potential or a Novel Example of “Metastasizing” Benign Tumor?

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CLINICAL HISTORY

- 30-year old female
- One-year history of enlarging nodule, left thigh
- Incidental discovery of a palpable LN left inguinal region at the time of surgery
- Both lesions were excised
CUTANEOUS LESION
<table>
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<th>DIAGNOSIS</th>
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<tr>
<td>CUTANEOUS LESION</td>
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<tr>
<td>Clear Cell Nodular</td>
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<tr>
<td>Hidradenoma</td>
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<tr>
<td>LYMPH NODE</td>
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<tr>
<td>“Benign” Metastasis</td>
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<tr>
<td>of Clear Cell Nodular</td>
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<td>Hidradenoma</td>
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</tbody>
</table>
CASE 2

Male, 58. Lesion on scalp. Partially removed, recurrence after 2 years
RECURRENCE
CASE 3

Male, 48. Lump on the lateral aspect of fifth metatarsal head
CASE 4
Female, 67. Lesion on left middle finger
HIDRADENOCARCINOMA (MALIGNANT HIDRADENOMA)

- Infiltrative growth pattern (loss of circumscription) with deep involvement
- Cytological atypia
- Mitotic activity (more than 4 per 10HPF)
- Necrosis
- Perineural/lymphovascular invasion
Hidradenocarcinoma
Clinical Features

- M=F
- No age predilection
- Face & extremities> scalp, lip, neck, chest wall, leg, toe & vulva
- No distinctive clinical features presenting as a dermal solid or cystic nodule
HIDRADENOCARCINOMA
HISTOLOGICAL FEATURES 1

- Solid or cystic
- No epidermal origin
- Lobular or diffuse growth pattern
- Infiltrating border
- Ductal differentiation
- Areas of necrosis & haemorrhage
HIDRADENOCARCINOMA
HISTOLOGICAL FEATURES 2

- Nuclear pleomorphism
- Mitotic activity
- Atypical mitoses
- Lymphovascular and perineural infiltration
- Clear cell variant common
- Diagnosis can be difficult unless pre-existing benign tumour found
HIDRADENOCARCINOMA
PROGNOSIS

- Recurrences: 50-75%
- Metastases 30-40%
- Mortality probably high
  (most documented cases represent single reports)
Primary Cutaneous Adenoid Cystic Carcinoma
A Clinicopathologic and Immunohistochemical Study of 27 Cases

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and Eduardo Calonje, MD, Dip RCPath*  

Aims: This study examines clinical and pathologic features of primary cutaneous adenoid cystic carcinoma (ACC), with emphasis on biological behavior of these tumors. A total of 27 cases of primary cutaneous ACC with detailed follow-up information were evaluated. Clinically, these were solitary, slow-growing lesions, half of which were in the head and neck area. The median age was 62 years with a male predilection. Surgical excision was the treatment of choice. Histologically, the lesions were similar to those seen in the salivary glands. Tumors were classified as grade 1 (17), grade 2 (3), and grade 3 (7). The mitotic count was generally low (mean = 1.9/mm²), except in 2 high-grade tumors (> 10 mitotic figures/mm²). Sixteen cases showed perineural invasion. Immunohistochemically, cytokeratin positivity was noted in 13/13 cases, and CD117 was observed in 10/10 cases, with luminal/cytoplasmic staining for epithelial membrane antigen (14/16) and at least focal luminal expression for carcinoembryonic antigen (11/16), smooth muscle actin (10/13), and S100 staining (9/13). Eighteen cases had follow-up data (median 54 mo, 9 of which had local recurrences (50%). Three cases showed metastatic disease. No statistical difference was noted between tumor grade and local recurrence.

Key Words: adnexal tumors, cutaneous adenoid cystic carcinoma, sweat duct carcinoma, Bartholin gland tumor


Adenoid cystic carcinoma (ACC) is a rare, slowly growing neoplasm. The most common site of involvement for this malignant neoplasm is the minor salivary glands; however, less frequently it is also observed in the major bronchi, breast, uterine cervix, external auditory canal and lacrimal glands1–7; it rarely presents in the skin. Primary cutaneous ACC has been the subject of many case reports; however, it has only been documented in 1 major series, published in 1987.8 To date, < 50 primary cutaneous ACC cases have been reported in the English literature; herein, we describe a further 27 cases, reviewing both clinical and pathologic features and comparing the biological behavior of such lesions with ACCs from other sites.
Primary cutaneous adenoid cystic carcinoma in the United States: Incidence, survival, and associated cancers, 1976 to 2005

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Background: Primary cutaneous adenoid cystic carcinoma (PCACC) is a rare appendageal tumor of uncertain origin. Details on epidemiologic features of PCACC are sparse and largely based on clinical reports.

Objective: We sought to develop an understanding of PCACC incidence, survival, and associated cancers using population-based data.

Methods: We used the Surveillance, Epidemiology, and End Results program to calculate age-adjusted incidence rates (IRs), IR ratios, 95% confidence intervals, standardized incidence ratios (SIRs), and 5-year relative survival of PCACC diagnosed during 1976 to 2005.

Results: In a population of 723,174,580 person-years, the overall PCACC IR was 0.23 per 1 million person-years (n = 152), with similar IRs among male and female patients (IR = 0.24). Most cases of PCACC presented at a localized stage and arose on the face/head/neck. Among 122 of the 2-month survivors of PCACC and more than 2.4 million 2-month cancer survivors, risk of associated cancers overall was not significantly increased (SIR = 1.17 [n = 24] and SIR = 1.43 [n = 16], respectively). However, PCACC was associated with significantly increased risks of subsequent lymphohematopoietic (n = 6; SIR = 3.70) and thyroid (n = 2; SIR = 15.25) cancers, whereas the converse associations were not observed. Five-year relative survival was excellent (96.1%; n = 122) with more favorable survival noted for PCACC involving the face/head/neck than the trunk.

Limitations: A pathologic review of reported cases was not undertaken.

Conclusion: PCACC is a rare appendageal tumor that affects male and female individuals equally, primarily presents at localized stage, predominates in the face/head/neck, and is associated with favorable survival. Immunosuppression does not appear to contribute to the development of PCACC, and the observed associated cancer patterns will need to be confirmed in larger studies. (J Am Acad Dermatol 2010;63:71-8.)

Key words: adenoid cystic carcinoma; epidemiology; incidence; second primary cancers; skin cancer; survival.
CUTANEOUS ADENOID CYSTIC CARCINOMA
CLINICAL FEATURES

- Rare (0.23/1 million)
- Solitary/slowly growing
- Asymptomatic/ulceration rare
- M > F
- Wide age range (middle-aged to elderly, median 2 years)
- Scalp>face>neck>>back>>>flexures
- It has been suggested that patients with CACC have higher risk of developing hematolymphoid malignancies
CUTANEOUS ADENOID CYSTIC CARCINOMA
HISTOLOGICAL FEATURES

- Dermal and subcutaneous
- Most cutaneous tumors are grade 1
- Infiltrative
- Cribiform pattern
- More solid areas without a cribiform pattern often found
- Hyaline intercellular basement membrane material
- Low-mitotic activity
- Perineural invasion ++ (60%)
73-year-old female. Lump on the left arm
Adenoid cyst carcinoma (solid variant)
Most rounded spaces contain stromal type acidic mucin (Inset: Alcian blue) and are stromal pseudo-glands.
CUTANEOUS ADENOID CYSTIC CARCINOMA
IMMUNOHISTOCHEMISTRY

- Cytokeratins
- CD117 ++
- Luminal and cytoplasmic staining for EMA
- Luminal staining for CEA in true glands
- S100 (80%)
- Focal positivity for BerEP4
- SMA and p63 positive in myoepithelial cells
- Basement membrane material + for collagen type IV and laminin
CUTANEOUS ADENOID CYSTIC CARCINOMA
DIFFERENTIAL DIAGNOSIS

- Salivary adenoid cystic carcinoma (tumors at both sites are identical)
- Adenoid basal cell carcinoma
Adenoid Cystic Carcinoma

Inconspicuous true glands highlighted with BerEP4, CEA or EMA or mucin stains

Bland cytological features
CUTANEOUS ADENOID CYSTIC CARCINOMA

PROGNOSIS

- Very good prognosis
- Local recurrence in about 33% of patients
- Five year survival 96%
- Metastatic spread very rare, tends to occur late and seems more common in vulval tumors
Endocrine Mucin-Producing Sweat Gland Carcinoma: A Cutaneous Neoplasm Analogous to Solid Papillary Carcinoma of Breast

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**Abstract**

We describe two cases of a distinctive in situ and invasive cutaneous adnexal neoplasm occurring in the eyelid. Mucinous carcinoma represented the invasive portion of the tumor in one case, whereas the other infiltrated in small solid nests. The in situ component is identical to the recently described solid papillary carcinoma of the breast (endocrine ductal carcinoma in situ). Both tumors produced intra- and extracellular mucin, exhibited endocrine differentiation by immunohistochemistry and ultrastructural analysis, and were positive for estrogen and progesterone receptors.

Carcinomas of the sweat gland constitute a heterogenous group of neoplasms. Some of these lesions are considered the malignant counterpart of well-recognized benign tumors of similar derivation, others have unique distinguishing features, and yet others are morphologically analogous to carcinomas occurring more frequently in the embryologically related mammary and salivary glands. The carcinomas we report here fall into this latter category and display all of the histologic and immunohistochemical features of a mammary lesion described as solid papillary carcinoma by two of the authors (F.C.K., H.M.M.) (3), and as endocrine ductal carcinoma in situ by Tsang and Chang (10). Like their counterparts in the mammary gland, these cutaneous tumors are characterized by their bland histologic appearance, neuroendocrine differentiation, and mucin production.
Endocrine Mucin-Producing Sweat Gland Carcinoma

Twelve New Cases Suggest That It Is a Precursor of Some Invasive Mucinous Carcinomas

Artur Zembowicz, MD, PhD,*† Christine F. Garcia, MD,* Zeiba S. Bannous, MD,‡ Martin C. Mihm, MD,* Frederick Koerner, MD,* and Ben Z. Pilch, MD*†

Abstract: Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is an underrecognized low-grade carcinoma with predilection for the eyelid. Only four cases of EMPSGC have been described in the literature. Here, we describe 12 cases of EMPSGC. The lesions were twice as frequent in females than males with an average age of 70 years (range, 45-84 years). Clinically, they presented as slowly growing cyst or nodule. The most common site of occurrence was the lower eyelid (8 cases). Two lesions occurred on the upper eyelid and 2 on the cheek. Histologically, they were well-differentiated, typically multilobulated tumors with solid or partially cystic nodules, frequently showing areas of papillary architecture. Punctate epithelial arrangements were also present. The nodules were formed by uniform small to medium-sized oval to polygonal epithelial cells with lightly eosinophilic in nuclei cysts. The nuclei were bland with finely stippled chromatin and intranuclear vacuoles. Heteropolyploidy and extracellular mucin was usually present. Mitotic activity was present but not brisk. All tumors maintained immunohistochemically expressed at least one neuroendocrine marker, synaptophysin or chromogranin. CD107 and neuron-specific enolase, secondary markers of neuroendocrine differentiation, were expressed in most cases. All tumors tested expressed estrogen and progesterone receptors, synaptophysin, low molecular cytokeratins 5, 10, and epithelial mucin markers 20 and 5-100 and vimentin. Calponin, smooth muscle actin, and p63 immunohistochemical stains did not displace epithelial cells around larger tumor masses in most cases, supporting the notion that EMPSGC is an in situ carcinoma in 10 cases, synaptophysin by benign epithelial indistinguishable from eccrine ducts were present. In some cases, the benign ductal epithelium was undermined by carcinoma in situ with similar cytologic features to solid or papillary areas of EMPSGC. Mucous cells were preserved in the area of its carcinoma. In 6 cases, EMPSGC was associated with invasive mucinous carcinoma. In situ carcinoma and mucinous carcinoma also expressed neuroendocrine markers. Clinical follow-up showed no recurrence or metastasis, consistent with low-grade carcinomas.

METHODS

We collected the cases prospectively in the course of routine diagnostic activities (2 cases) and second opinion
ENDOCRINE MUCIN-PRODUCING SWEAT GLAND CARCINOMA
CLINICAL FEATURES

- Slowly growing cyst /swelling/nodule
- Variable clinical diagnosis: cyst/BCC/ chalazion
- Location: 21 cases eyelid (Lower >Upper )
  2 cases cheek
- Age 48-84
- Females>Males
- 4 cases recurred  (2 with uncertain margin status)
- No follow-up for 5 cases
ENDOCRINE MUCIN-PRODUCING SWEAT GLAND CARCINOMA
HISTOLOGICAL FEATURES

- Well-circumscribed
- Typically multinodular
- Solid or partially cystic nodules
- Areas of papillary and/or cribriform architecture
- Uniform cells with some degree of cytological atypia
- Eosinophilic cytoplasm
- Intracytoplasmic and extracellular mucin
- Mitotic activity variable (tends to be low)
ENDOCRINE MUCIN-PRODUCING SWEAT GLAND CARCINOMA IMMUNOHISTOCHEMISTRY

- At least one neuroendocrine marker
  - Synaptophysin-Chromogranin (most useful)
  - NSE
  - CD57
  - CD56
- Estrogen and progesterone receptors
- Cytokeratin 7
- Low molecular cytokeratin Cam5.2
- Epithelial membrane antigen
- GCDFP15
SYNAPTOPHYSIN
ENDOCRINE MUCIN-PRODUCING SWEAT GLAND CARCINOMA
DIFFERENTIAL DIAGNOSIS

❖ Carcinoid tumor (primary or metastatic)
✓ Eccrine sweat gland tumour of clear cell origin
✓ Adenocarcinoma of eccrine sweat glands
✓ Primary mucinous sweat gland carcinoma
✓ Primary infiltrating signet-ring cell carcinoma
✓ Primary histiocytoid carcinoma of the eyelid
✓ Monocle tumour
PRIMARY HISTIOCYTOID CARCINOMA

- Rare (less than 40 cases reported)
- Slowly-growing
- Locally aggressive
- Elderly men
- Eyelid or, rarely, axilla
- Mimics an inflammatory process such as blepharitis or chalazion, orbital cellulitis, fat herniation
Gradual swelling/thickening/firmness of the eyelid

Gradually progress to involve the other eyelid – ‘monocle-like’ appearance

Extend beyond the clinically visible area

Tx: surgery and radiotherapy +/- adjunctive chemotherapy
PRIMARY HISTIOCYTOID CARCINOMA OF THE EYELID

HISTOLOGY

- Usually dermis and subcutis, but epidermis spared (only rarely pagetoid – axillary cases)

- Single cells and small strands or solid aggregations, infiltrating between the collagen bundles

- Neoplastic cells with large, hyperchromatic nuclei and ample cytoplasm, signet-ring appearance

- Intermingled sparse inflammatory cells

DDx: metastasis from

- breast cancer (primarily lobular)
- prostatic adenocarcinoma
- signet-ring cell carcinoma of GIT
# IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
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<tr>
<td>CK7</td>
<td>S100</td>
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<tr>
<td>CEA</td>
<td>PSA</td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>TTF1</td>
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<tr>
<td>AE1/AE3</td>
<td>CK20</td>
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<tr>
<td>EMA</td>
<td>CDX2</td>
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