Review Article

Sweat Gland Tumors – A Systematic Review on the Histopathology and Immunohistochemistry

Sana Khan[1], Khalid Mahmood Uddin[2], Shamail Zia*[,3], Cynthia Chizoba Esimoleze[4], Sarah Khalid[5], Farozaan Shamail[6], Fazail Zia[3], Syed Jawwad Ali[7], Muhammad Ali Khan[3]

[1]*Department of Medicine, Islamic International Medical College, Rawalpindi, Pakistan.*
[2]*Department of Neurology, Henry Ford Hospital, Detroit, USA.*
[3]*Department of Pathology, Jinnah Sindh Medical University, Karachi, Pakistan.*
[4]*Department of Medicine, Faculty of Medicine and Health Sciences, Abia State University Uturu, Nigeria.*
[5]*Department of Dermatology, Baqai Medical University, Karachi, Pakistan.*
[6]*Department of Pathology, Ziauddin Medical University, Karachi, Pakistan.*
[7]*Department of Pathology, Dow University of Health Sciences, Karachi, Pakistan.*

Abstract: Objective: The categorization of sweat gland tumors has been inconsistent over time. These tumors, having varying potential for malignancy, may behave as indolent neoplasms while others can be highly metastatic. The characteristics of most of these tumors are overlapping and the information of distinctive findings about these neoplasms is imperative. Traditionally, sweat gland tumors were classified as eccrine and apocrine only but recently, this has been found that several sweat gland tumors may exhibit eccrine and apocrine types both. Some tumors exhibit further complex features due to the existence of other differential appearances. This can be in the instance of apocrine neoplasms because of the close embryological link between apocrine glands, hair follicles and sebaceous glands and they can be classified as follicular and/or sebaceous tumors. Cutaneous adnexal neoplasms are a diagnostic challenge, especially for tumors with sweat gland differentiation, due to a huge number of uncommon entities, designation of different terms to the identical tumor following to disagreement about the taxonomy and nomenclature of such tumors. This review article provides updated information about various cancerous sweat gland neoplasms with emphasis on recent conclusions for the diagnosis and generalized therapy of such neoplasms.

Keywords: Malignancy, Sweat gland, Cancerous neoplasm, Skin diseases, Eccrine gland, Apocrine gland.

INTRODUCTION

Sweat gland cancers are heterogeneous cancerous neoplasms with apocrine and eccrine differentiation, that are alienated in further 17 categories as per 4th edition of the WHO taxonomy of skin neoplasms [1]. In recent years, the taxonomy of adnexal tumors has been is regarded as one of the more perplexing features of dermatopathology [2-4]. A number of entities that were formerly regarded to be of eccrine glands origin due to their position in non-apocrine body sites, are now considered to be of apocrine source [5]. Some eccrine tumors exhibit heterogeneous characteristics hence they challenge the existent classification systems. This article reviews sweat gland carcinomas focusing their important clinical and histopathological aspects [6]. Sweat gland neoplasms constitute a heterogeneous group of rare cancerous tumors [7, 8] having diverse biological actions. Certain neoplasms have a benign complement like porocarcinoma and hidradenocarcinoma, whereas other neoplasms are mainly cancerous deprived of a benign correspondent i.e., primary cutaneous mucinous cancer and aggressive kind of digital papillary adenocarcinoma [5].

REVIEW

Methods

The literature was surveyed in PubMed using systematic keywords. Articles from 2012 – 2022 are included without setting any exclusion criteria and can be seen in Table **1**. The search was limited to articles written in English and providing general information on the sweat gland tumors mainly histopathology and immunohistochemistry. Whereas, articles comprised of clinical studies, observational studies, case reports, randomized or controlled clinical trials were not included.

RESULTS

By regular search in PubMed, total 6,065 articles were found with the keyword Sweat gland tumors out of which, 1,752 articles were found in from 2012 to 2022. Articles were finally sought after hand-searching of relevant review articles, as well as analyzing the references of key articles. From these, 92 articles were included in this review.

*Address correspondence to this author at the Department of Pathology, Jinnah Sindh Medical University, Karachi, Pakistan.
Email: drshamailzia@gmail.com

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Table 1. Literature Survey of Systematic Keywords.

Regular Keywords	Results	Number of results after applying inclusion criteria	MeSH Keywords	Results after application of inclusion criteria
Sweat gland tumors	5,499	1,677	Sweat gland neoplasms/diagnosis	406
Malignant sweat gland tumors	5,771	1,544	Sweat gland neoplasms/therapy	1,068
Sweat gland carcinoma	2,519	792	Sweat gland tumor/ Immunohistochemistry	221
Sweat gland tumors classification	150	33	Sweat gland tumor/ etiology	143

DISCUSSION

Taxonomy of Sweat Gland Neoplasms

Cancerous sweat gland neoplasms are usually categorized as: (a) those with cancer probability of low-grade with damaging local growth and local relapse risk and (b) those with high-grade cancer potential with metastasis risk and disease-related death [9, 10]. Some sweat gland neoplasms may display substantial morphologic inconsistency. In at least certain neoplasms, morphology can be a predictor of disease consequence in some tumors i.e. low contrasted with high level spiradenocarcinoma, whereas for others, the course of illness is exclusively unconstrained of morphology i.e. digital papillary spiradenocarcinoma [10, 11].

Cribriform Cancer

It is a sweat gland neoplasm which is distinctive and rare [12]. It is an indolent carcinoma with a tendency for the extremities. The neoplasms exist measuring 1–3 cm protuberances with a high tendency for the extremities of persons of middle age [13-15]. Women are more often affected than men with this disease [14]. These tumours are infrequently associated with superficial subcutaneous adipose tissue and are located in the mid to deep dermis without encapsulation. These tumours are composed of basaloid epithelioid to ovoid cells that are arranged in nests and groups with concrete anastomoses, exhibit opulent duct differentiation, and transform into cribriform low-power forms [16]. There can be presence of focal cystic cosmoses, micropapillary appearances, and apocrine differentiation with beheading discharge. The cells of tumor encompass modest volumes of cytoplasm and different nuclei with tiny nucleoli. There is insignificant nuclear pleomorphism with meager mitotic activity and mild cytologic atypia. Tumors are devoid of second myoepithelial cell layer with irregular edges and actual infiltrative growth array is absent. Intratumoral desmoplastic stroma are scanty [11]. According to immune-histochemistry, tumour cells exhibit the cytokeratins MNF116, CK7, AE1/3 and CK5/6. Additionally, they are in favour of CD117, CEA, EMA, S100, and BerEP4. SMA, CK20, P63, calponin, androgen receptor, progesterone and oestrogen receptors, GATA3 and GCDFP15 staining are all negative [14, 15, 17].

So far, cribriform carcinoma is an indolent cancer ensuing total excision without local relapse, metastasis, or disease-related death. The neoplasms may be mistaken as primary or metastatic to the skin, for adenoid cystic cancer. As compared to cribriform cancer, adenoid cystic cancer is not well demarcated, disjointed by intervening stroma and settled into the tumors of erratic shapes and sizes. Besides, mucinous pseudocysts are characteristic of adenoid cystic carcinomas which are not found in cribriform cancer. Tube-shaped adenomas, inclusive of papillary eccrine adenoma and apocrine tube-shaped adenoma, demonstrate coinciding aspects with a protruding development in dermis. The chief differentiating characteristic is the development of discrete tubules disjointed by plentiful overriding fibrous stroma and existence of a myoepithelial cell sheet [11].

Endocrine Mucin Creating Sweat Gland Malignancy

This is a distinguishing carcinoma morphologically having neuroendocrine differentiation, similar to concrete papillary or endocrine ductal malignancy of the mammary glands [18]. It is an indolent disease which exhibits a constricted anatomic dissemination with a resilient tendency for the eyelids and cheek. It may be an originator as subset of mucinous carcinoma at the least. Elderly women are more affected by these neoplasms. The tumors emerge as gradually expanding sole nodular and cystic wounds [19-21]. The lower eyelid is most often affected and extra-facial appearance is remarkable [11]. These neoplasms display a multinodular and well-regulated development within dermal skin layer with infrequent further association of superficial subcutaneous adipose tissue. They are peculiar of having a blend of firm, cribriform, cystic, and papillary development. Intracellular mucin may be existent with mild, dispersed cytologic atypia and scanty mitoses. The malignant cells display a firm and sheet-like appearance with added regions of mucinous pseudocyst development, resulting

in a cribriform formation. Focal papillary development and apocrine differentiation can be present and duct differentiation and cystic components are additional outcomes. A focal in situ illness is there involving pre-prevailing sweat ducts and regions with extracellular mucin pools are an alarm for mucinous cancer development. Immunohistochemistry has shown that tumour cells express BerEP4, Cam5.2, CK7, GATA3, EMA, PR, MYB, WT1 and ER but they consistently test negative for CK20 [22-24]. They demonstrate expression of minimum one marker of neuroendocrine differentiation. The tumors may reappear locally; metastases or disease-linked death has been unknown. The suggested treatment is complete excision [11].

On the eyelid, sebaceous cancer and basal cell cancer are essential to consider and these malignancies don't differentiate into ducts or cysts and grow more solid tumors with noticeable cytologic atypia. The neoplasms are ill defined with a diffusely infiltrative development very often. Histological identification of sebaceous differentiation can be helpful in identification. Basal cell cancer may display neoplasm development that is multinodular with mucinous and cribriform regions. The basal cell cancer and sebaceous cancer both strongly and diffusely express P40 and P63 as compared to EMPSGC yet neuroendocrine markers expression is particularly uncommon. Hidradenoma is another drawback in identification as it also exhibits duct or cyst differentiation and multinodular development. The cells of neoplasm display obvious cell modification or poroid cytologic characteristics and absence of mucinous pseudocysts. Adenoid cystic cancer comprises of minor islands in a diffused infiltrative growth [11, 25].

Secretory Skin Cancer

This cancer influences the skin rarely with middle age to elderly female predominance. It demonstrates morphologic and immune-histochemical outcomes identical to secretory cancer at further areas, mainly the mammary and salivary glands [26-29]. The neoplasms are sole nodules of about 1 cm with the axilla as the maximum frequently influenced body part. These protruding neoplasms are not encapsulated but well confined and they exist in the dermis with likely oriented towards superficial subcutis. Ornate microcystic differentiation with abundant colloid shaped intraluminal eosinophilic discharges is present; firm and tubular formations can be there too. There is limited cytologic atypia with low mitotic rate and absence of necrosis or infiltrative development [11]. Staining can be observed by use of anti-pan-NTRK antibody. The neoplasms display a recurring t(12;15) translocation ensuing ETV6-NTRK3 fusion gene. A NFIX-PKN1 fusion gene was observed in a sole neoplasm [26, 27]. This type of skin carcinoma demonstrates similar characteristics to salivary or mammary tumors and medical association is essential to eliminate cutaneous metastasis from a visceral primary. A thyroid primary cancer metastasis may be omitted by lack of staining of TTF-1 [11].

Microcystic Adnexal Cancers

Microcystic adnexal neoplasms are characteristic with follicular and ductal differentiation [30]. They seem weak on morphological analysis and can be wrongly diagnosed as benign adnexal skin neoplasms, ensuing damaging tumor development due to late diagnosis and management. The tumors exist with induration with gradually expanding plaques. The tumor size is misjudged clinically every so often and is up to many centimeters. Among middle-aged to older adults, there may be a propensity for the head, particularly the periorbital and nasolabial folds areas; the outside skin of the head and neck regions is just infrequently affected. Specific gender propensity is unimportant [31-33].

Follicular and ductal differentiation in variable ranges and insipid cytologic aspects are characteristic of microcystic adnexal cancers. There is mild cytologic atypia with rare mitotic elements. Keratocyst creation and dystrophic calcifications are displayed by these tumors in the superficial characteristics particularly. There is occasional observation of focal link with the epidermis or a hair follicle. Furthermore, the neoplasm illustrates regions of duct differentiation with well-shaped ducts comprising a solo layer of bland looking ductal cells. Obvious cell modification and a further solid growth form are other probable consequences. Sebaceous differentiation can too be present and perineural infiltration is common. The cancerous cells display expression of cytokeratin AE1/3, and EMA by immunohistochemistry or CEA staining spots the luminal differentiation. There is a inconstant expression of BerEP4 and immunohistochemistry has insignificant part overall in the finding. A primary cutaneous neoplasm is supported by diffuse P63 staining in this situation and contends contrary to a cutaneous metastasis [11].

Microcystic adnexal cancer may result in destructive development and relapse locally, if not excised completely; metastases and disease-linked death are notable. To avoid local aggressive activities and relapse, it is crucial to have prompt identification and extensive local excision or Mohs micrographic surgical procedure [32, 34].

Syringoma has ductal appearance displaying short epithelial strands without follicular differentiation with keratocysts. Desmoplastic trichoepithelioma and trichoadenoma closely imitate microcystic adnexal cancer. They are very restricted to superficial and mid dermis, lacking duct differentiation. Superficial biopsy does not provide a reliable separation and to eliminate the likelihood of microcystic adnexal carcinoma, a replicate biopsy or excision completely for inclusion of whole dermis and superficial subcutis is desirable. Microcystic adnexal cancer is resembled with infiltrative and morpheic basal cell cancer in some aspects; there is a diffusely infiltra-

tive array with more prominent cytologic atypia and lacking of duct differentiation in the infiltrative and morpheic basal cell cancer. Its performance and management are akin to microcystic adnexal cancer [11, 35].

Squamoid Eccrine Ductal Cancer

It is a biphasic cancer of low-level of the sweat glands, with superficial features resembling well-to-discreetly differentiated squamous cell cancer and deeper portions resembling eccrine ductal cancer [36]. Hence with superficial biopsies, the neoplasms are mistaken for squamous cell cancer. These neoplasms have also been documented as adenosquamous skin carcinoma [37]. The neoplasms frequently exist as ulcerated protrusions or plaques, with a tendency for the head and neck parts of ageing persons, measuring around 1 cm; the median age reported as 80 years[38]. There is a male prominence for this cancer [39].

The tumors are dermal and exhibit link with the superimposing generally ulcerated epidermis. They are characteristic of diffusely infiltrative growth, and have a common incursion of subcutaneous tissues. In the superficial side the neoplasms comprise of uncharacteristic keratinocytes set in islands and nests of different dimensions, similar to well- to discreetly differentiated squamous cell cancer. A history of actinic keratosis or in situ squamous cell carcinoma may also present. In-depth examinations of the tumour show the establishment of tiny nests of pleomorphic ductal cells with luminal or duct differentiation that are diffusely infiltrative. Approximately 30% neoplasms commonly exhibit perineural infiltration while only about 7% display lymphovascular invasion. Though immunohistochemistry is insignificant to diagnose these tumors yet EMA and CEA staining may be helpful in identifying the ductal differentiation [11, 40].

Due to the infiltrative tumor growth and the perineural infiltration, local relapse exists in 25% patients. Lymph node metastases and disease-linked death is uncommon. Wide local excision or Mohs micrographic surgical procedure are best treatment choices [11, 39]. The tumors are easily mistaken mainly in superficial biopsies for squamous cell cancer in which ductal element is excluded. Porocarcinoma can demonstrate focal squamous differentiation. There is absence of zonation which is characteristic of squamoid eccrine ductal cancer. Microcystic adnexal cancer is defined by follicular and ductal differentiation. Cytologic atypia is negligible as compared to squamoid eccrine ductal cancer [11].

Adenoid Cystic Skin Cancer

Primary cutaneous adenoid cystic cancer is uncommon neoplasm displaying same genetic, immunohistochemical and histologic, and characteristics to its visceral corresponding parts, usually of lacrimal or salivary glands or respiratory tract basis [41]. Cutaneous adenoid cystic cancer is solitary which is in form of gradually developing nodules and plaques, having 3 cm diameter approximately. The neoplasms influence middle-aged to ageing persons without gender prominence; the median age being 62 years. The scalp in particular, the head and neck are most commonly influenced followed by the trunk and the extremities [42, 43].

The neoplasms are defined by diffusely infiltrative development within dermal skin layer with incursion of subcutaneous tissues frequently. These are set in cases and islands of different forms and dimensions comprising of small or medium sizes of basaloid cells; the cytoplasm is inadequate and hyperchromatic to vesicular nuclei contain inconsistently noticeable and infrequent numerous nucleoli. The cancerous cells have concrete or cribriform appearance and characteristic pseudocysts filled with mucin. Moreover, the cancerous islands may have hyaline basement membrane protein [44]. Proper duct differentiation is a focal observation and regions of a tube-shaped development might be valuable. There is limited nuclear pleomorphism with low mitotic activity. As per Batsakis grading scheme most neoplasms are grade 1 [11, 45].

The cancerous cells express cytokeratins as per immunohistochemistry; S100, SOX10, and SMA expression is noticed in a subdivision of cells. There is overexpression of MYB and CD117 is diffusely expressed all through the neoplasm. EMA and CEA stains duct differentiation and collagen IV pigments basement membrane substance. Similar to adenoid cystic cancer of visceral areas, most of the cutaneous neoplasms illustrate MYB gene reorganizations together with t(6;9) translocation ensuing MYB-NFIB gene fusion [46]. The fusion gene taking on MYBL is rarely spotted [47]. Cutaneous adenoid cystic cancer illustrates great predilection in around 50% cases for local relapse. Generally, metastases and disease-related death is less, particularly in contrast to the neoplasms at visceral regions. The frequent metastatic sites are lymph nodes, lung, and liver. Vulvular tumors can exhibit more destructive actions. There are reports of 96% overall 5-year survival rate [48].

Adenoid basal cell cancers do not have proper duct differentiation and they display a peripheral picket and stromal cleft appearance. Sometimes, spiradenoma may look like adenoid cystic cancer sharing the overexpression of MYB on immunohistochemical basis. It is defined by a double cell populace and is deficient in mitotic activity, cytologic atypia and perineurial infiltration [5, 11].

Cancerous Tumors Originating from Spiradenoma, Cylindroma, and Spiradenocylindroma

Certain cancerous neoplasms are very related having identical histological aspects and behavior that develop from previously present benign spiradenoma, cylindroma, or the spiradenoma-cylindroma hybrid neoplasms [49]; the identification of the precursor of benign spiradenoma, cylindroma, or spirade-

nocylindroma is essential to diagnose these neoplasms and most of them originate in relation to spiradenoma. The neoplasms are self-contained protrusions with a size of several centimeters and a median of 2.7 cm. There can be an old account with new development. The patients are middle aged to ageing persons with no sex preponderance. Several anatomic regions are influenced that include the trunk, limbs, and head and neck [50-52].

An extensive morphologic range is observed for the malignant tumors. These neoplasms are often occurring with numerous nodules having pushing margins instead of diffusely infiltrative ones. A sudden changeover from the benign precursor to the cancerous form is frequent; this changeover is gradual infrequently. According to the cancerous forms, the neoplasms are morphologically categorized as high grade, low grade, and sarcomatoid, though a combination may exist in a sole neoplasm. Prominent cytologic atypia is characteristic of morphologically high-grade neoplasms and nuclear pleomorphism is not then specified, which resembles carcinoma or adenocarcinoma. There is an abrupt mitotic activity inclusive of atypical forms with presence of tumor necrosis. The presence of lymphovascular invasion and perineural infiltration is also reporetd. A gradual changeover from the benign precursor is often demonstrated by morphologically low-grade neoplasms. The general appearance of spiradenoma seems reserved at least on low-power investigation in the cancerous regions. Closer examination of low-grade cancerous regions exhibit loss of dual cell populace which is typical of spiradenoma. Furthermore, squamoid differentiation and regions of obvious cell modification can be seen. There are chancers of tumor ulceration, necrosis and perineural infiltration. Sarcomatoid differentiation exists mostly as undifferentiated sarcoma. Heterologous chondro-, osteo-, or rhabdosarcomatous components can also be observed. Spiradenoma, cylindroma, and the hybrid tumors display overexpression of MYB by immunohistochemistry. The cancerous regions display loss of MYB staining and can be employed for diagnostically challenging low-grade tumors as another marker of cancer. The cancerous regions exhibit elevation of mib1-proliferative index with probable overexpression of P53. However, these findings lack sensitivity and are inconsistent [11, 53].

Patients suffering from the Brooke–Spiegler syndrome have germline mutations in the CYLD gene and CYLD mutations are steady findings for sporadic cylindromas; mutations of CYLD are uncommon in spiradenomas and their cancerous complements, which generally display ALPK1 gene mutations with CYLD in a jointly selective manner [54]. The behavior and morphology of these tumors correlate well. Morphologically low-grade tumors act in a sluggish way with 20% danger for relapse locally and there is absence of metastasis and disease-related death. On the contrary, morphologically high-grade neoplasms demonstrate substantial potential up to 50% for distant metastasis and disease-linked death. Sarcomatous (metaplastic) neoplasms are at least slightly little destructive than their complements that are of high-grade morphologically [49, 50, 52].

Low-grade neoplasms bear a very close resemblance to their benign precursors morphologically. Higher-power inspection provides correct diagnosis with identification of the dual cell element, level of cytologic atypia, and enlarged mitotic activity. An additional supportive finding by immunohistochemistry is absence of MYB expression. High level or sarcomatoid neoplasms can be wrongly taken for metastatic cancer or adenocarcinoma or undifferentiated sarcoma morphologically. Sample selection and identification of a former benign spiradenoma, cylindroma, or hybrid neoplasm are essential for accurate identification [11, 55].

Digital Papillary Adenocarcinoma

They are typical but difficult neoplasms diagnostically which are restricted to the distal extremities of limbs with a tendency for the distal areas of the fingers mostly and toes. These neoplasms have an extensive morphologic range with bland morphological characteristics to high-grade instances morphologically; however morphology is not a extrapolative of conduct [56]. The neoplasms exist as median 2 cm nodules. People of all ages can be affected [57-62].

These are multinodular neoplasms showing a firm and cystic development in dermal skin layer and/or superficial subcutis. The neoplasms are often well-confined with typical papillary differentiation and rare infiltrative growth. A broad morphologic range is there from bland forms to high-grade histologic topographies, inclusive of noticeable nuclear pleomorphism, abrupt and uncharacteristic mitotic activity and tumor necrosis. Atypical mitoses and tumor necrosis may be seen with variable mitotic activity. Typical observation includes duct differentiation and a tubular growth. Other outcomes are obvious focal cell modification, spindle cell differentiation, and squamoid differentiation. A layer of ductal cell population lines the cystic spaces displaying related cytologic structures to the solid regions of tumour. A second outer myoepithelial cell layer is present too. The papillary elements are both micro- and micropapillary with fibrovascular cores originating from the cyst lining and projecting into the cystic cosmoses [11, 57]. The tumor cells have diffused and strong cytokeratins expression by immunohistochemistry. EMA has multifocal expression highlighting ductal lumina too. A subdivision of the cancerous cells display expressesion of S100 and the outer myoepithelial cell lining is featured by expression of P40, calponin, P63 and SMA. There is limited availability of data and there is no identification yet for recurrent genetic abnormalities [63]. Overexpression of FGFR2 is displayed by transcriptome analysis [56].

Digital papillary adenocarcinoma has a strong potential for

metastasis. J Cutan Pathol 2018; 45: 348-51. DOI: 10.1111/cup.13124

[18] Flieder A, Koerner FC, Pilch BZ, Maluf HM. Endocrine mucin-producing sweat gland carcinoma: A cutaneous neoplasm analogous to solid papillary carcinoma of breast. Am J Surg Pathol 1997; 21: 1501-6. DOI: 10.1097/00000478-199712000-00014

[19] Zembowicz A, Garcia CF, Tannous ZS, Mihm MC, Koerner F, Pilch BZ. Endocrine mucin-producing sweat gland carcinoma: Twelve new cases suggest that it is a precursor of some invasive mucinous carcinomas. Am J Surg Pathol 2005; 29: 1330-9. DOI: 10.1097/01.pas.0000170348.40057.60

[20] Shon W, Salomão DR. WT 1 expression in endocrine mucin-producing sweat gland carcinoma: a study of 13 cases. Int J Dermatol 2014; 53: 1228-34. DOI: 10.1111/ijd.12470

[21] Qin H, Moore RF, Ho CY, Eshleman J, Eberhart CG, Cuda J. Endocrine mucin-producing sweat gland carcinoma: a study of 11 cases with molecular analysis. J Cutan Pathol 2018; 45: 681-7. DOI: 10.1111/cup.13308

[22] Abdulkader M, Kuhar M, Hattab E, Linos K. GATA3 positivity in endocrine mucin-producing sweat gland carcinoma and invasive mucinous carcinoma of the eyelid: Report of 2 cases. Am J Dermatopathol 2016; 38: 789-91. DOI: 10.1097/-DAD.0000000000000561

[23] Chou Y-H, Chang Y-C, Huang Y-L, Wu C-T. Endocrine mucin-producing sweat gland carcinoma with GATA3 expression: Report of two cases. Pathology 2017; 49: 805-8. DOI: 10.1016/j.pathol.2017.08.018

[24] Held L, Ruetten A, Kutzner H, Palmedo G, John R, Mentzel T. Endocrine mucin-producing sweat gland carcinoma: Clinicopathologic, immunohistochemical, and molecular analysis of 11 cases with emphasis on MYB immunoexpression. J Cutan Pathol 2018; 45: 674-80. DOI: 10.1111/cup.13290

[25] Agni M, Raven ML, Bowen RC, *et al*. An update on endocrine mucin-producing sweat gland carcinoma: Clinicopathologic study of 63 cases and comparative analysis. Am J Surg Pathol 2020; 44: 1005-6. DOI: 10.1097/PAS.0000000000001462

[26] Kastnerova L, Luzar B, Goto K, *et al*. Secretory carcinoma of the skin. Am J Surg Pathol 2019; 43: 1092-8. DOI: 10.1097/PAS.0000000000001261

[27] Bishop JA, Taube JM, Su A, *et al*. Secretory carcinoma of the skin harboring ETV6 gene fusions: A cutaneous analogue to secretory carcinomas of the breast and salivary glands. Am J Surg Pathol 2017; 41: 62-6. DOI: 10.1097/PAS.0000000000000734

[28] Kazakov DV, Hantschke M, Vanecek T, Kacerovska D, Michal M. Mammary-type secretory carcinoma of the skin. Am J Surg Pathol 2010; 34: 1226-7. DOI: 10.1097/PAS.0b013e3181e4f49d

[29] Brandt SM, Swistel AJ, Rosen PP. Secretory carcinoma in the axilla: probable origin from axillary skin appendage glands in a young girl. Am J Surg Pathol 2009; 33: 950-3. DOI: 10.1097/PAS.0b013e31819c2628

[30] Goldstein DJ, Barr RJ, Cruz DJS. Microcystic adnexal carcinoma: A distinct clinicopathologic entity. Cancer 1982; 50: 566-72. DOI:10.1002/1097-0142(19820801)50:3<566::AID-CN-CR2820500330>3.0.CO;2-Q

[31] James BY, Blitzblau RC, Patel SC, Decker RH, Wilson LD. Surveillance, Epidemiology, and End Results (SEER) database analysis of microcystic adnexal carcinoma (sclerosing sweat duct carcinoma) of the skin. Am J Clin Oncol 2010; 33: 125-7. DOI: 10.1097/COC.0b013e31819791eb

[32] Chiller K, Passaro D, Scheuller M, Singer M, McCalmont T, Grekin RC. Microcystic adnexal carcinoma: Forty-eight cases, their treatment, and their outcome. Arch Dermatol 2000; 136: 1355-9. DOI: 10.1001/archderm.136.11.1355

[33] LeBoit PE, Sexton M. Microcystic adnexal carcinoma of the skin: A reappraisal of the differentiation and differential diagnosis of an under recognized neoplasm. J Am Acad Dermatol 1993; 29: 609-18. DOI: 10.1016/0190-9622(93)70228-L

[34] Friedman PM, Friedman RH, Jiang SB, Nouri K, Amonette R, Robins P. Microcystic adnexal carcinoma: Collaborative series review and update. J Am Acad Dermatol 1999; 41: 225-31. DOI: 10.1016/S0190-9622(99)70053-8

[35] Macagno N, Sohier P, Kervarrec T, *et al*. Recent advances on immunohistochemistry and molecular biology for the diagnosis of adnexal sweat gland tumors. Cancers 2022; 14: 476. DOI: 10.3390/cancers14030476

[36] Wong TY, Suster S, Mihm M. Squamoid eccrine ductal carcinoma. Histopathology 1997; 30: 288-93. DOI: 10.1046/j.1365-2559.1997.d01-593.x

[37] Fu JM, McCalmont T, Siegrid SY. Adenosquamous carcinoma of the skin: A case series. Arch Dermatol 2009; 145: 1152-8. DOI: 10.1001/archdermatol.2009.218

[38] Salih AM, Kakamad F, Baba HO, *et al*. Porocarcinoma; presentation and management, a meta-analysis of 453 cases. Ann Med Surg 2017; 20: 74-9. DOI: 10.1016/j.amsu.2017.06.027

[39] van der Horst MP, Garcia-Herrera A, Markiewicz D, Martin B, Calonje E, Brenn T. Squamoid eccrine ductal carcinoma. Am J Surg Pathol 2016; 40: 755-60. DOI: 10.1097/PAS.0000000000000599

[40] Kaseb H, Babiker HM. Eccrine Carcinoma. Treasure Island (FL): StatPearls Publishing 2022.

[41] Boggio R. Adenoid cystic carcinoma of scalp. Arch Dermatol

1975; 111: 793-4. DOI: 10.1001/archderm.1975.01630180121024

[42] Ramakrishnan R, Chaudhry IH, Ramdial P, *et al*. Primary cutaneous adenoid cystic carcinoma: A clinicopathologic and immunohistochemical study of 27 cases. Am J Surg Pathol 2013; 37: 1603-11. DOI: 10.1097/PAS.0b013e318299fcac

[43] Seab JA, Graham JH. Primary cutaneous adenoid cystic carcinoma. J Am Acad Dermatol1987; 17: 113-8. DOI: 10.1016/S0190-9622(87)70182-0

[44] Van der Kwast TH, Vuzevski V, Ramaekers F, Bousema M, Van Joost T. Primary cutaneous adenoid cystic carcinoma: Case report, immunohistochemistry, and review of the literature. Br J Dermatol 1988; 118: 567-78. DOI: 10.1111/j.1365-2133.1988.tb02469.x

[45] Batsakis JG, Luna MA, El-Naggar A. Histopathologic grading of salivary gland neoplasms: III. Adenoid cystic carcinomas. Ann Otol Rhinol Laryngol 1990; 99: 1007-9. DOI: 10.1177/000348949009901215

[46] North JP, McCalmont TH, Fehr A, van Zante A, Stenman G, LeBoit PE. Detection of MYB alterations and other immunohistochemical markers in primary cutaneous adenoid cystic carcinoma. Am J Surg Pathol 2015; 39: 1347-56. DOI: 10.1097/PAS.0000000000000463

[47] Kyrpychova L, Vanecek T, Grossmann P, *et al*. Small subset of adenoid cystic carcinoma of the skin is associated with alterations of the MYBL1 gene similar to their extracutaneous counterparts. Am J Dermatopathol 2018; 40: 721-6. DOI: 10.1097/DAD.0000000000001091

[48] Dores GM, Huycke MM, Devesa SS, Garcia CA. Primary cutaneous adenoid cystic carcinoma in the United States: Incidence, survival, and associated cancers, 1976 to 2005. J Am Acad Dermatol 2010; 63: 71-8. DOI: 10.1016/j.jaad.2009.07.027

[49] Kazakov DV, Zelger B, Rütten A, *et al*. Morphologic diversity of malignant neoplasms arising in preexisting spiradenoma, cylindroma, and spiradenocylindroma based on the study of 24 cases, sporadic or occurring in the setting of Brooke-Spiegler syndrome. Am J Surg Pathol 2009; 33: 705-19. DOI: 10.1097/PAS.0b013e3181966762

[50] Granter SR, Seeger K, Calonje E, Busam K, McKee PH. Malignant eccrine spiradenoma (spiradenocarcinoma): a clinicopathologic study of 12 cases. Am J Dermatopathol 2000; 22: 97-103. DOI: 10.1097/00000372-200004000-00002

[51] Dai B, Kong YY, Cai X, Shen XX, Kong JC. Spiradenocarcinoma, cylindrocarcinoma and spiradenocylindrocarcinoma: A clinicopathological study of nine cases. Histopathology 2014; 65: 658-66. DOI: 10.1111/his.12448

[52] Van Der Horst MP, Marusic Z, Hornick JL, Luzar B, Brenn T. Morphologically low-grade spiradenocarcinoma: A clinicopathologic study of 19 cases with emphasis on outcome and MYB expression. Modern Pathol 2015; 28: 944-53. DOI: 10.1038/modpathol.2015.48

[53] Mirza I, Kloss R, Sieber SC. Malignant eccrine spiradenoma. Arch Pathol Lab Med 2002; 126: 591-4. DOI: 10.5858/2002-126-0591-MES

[54] Rashid M, van der Horst M, Mentzel T, *et al*. ALPK1 hotspot mutation as a driver of human spiradenoma and spiradenocarcinoma. Nat Commun 2019; 10(1): 2213. DOI: 10.1038/s41467-019-09979-0

[55] Bansal C, Batra M, Lal N, Srivastava A. Solitary cylindroma with malignant transformation. Indian J Dermatol 2012; 57: 141. DOI: 10.4103/0019-5154.94289

[56] Surowy H, Giesen A, Otte J, *et al*. Gene expression profiling in aggressive digital papillary adenocarcinoma sheds light on the architecture of a rare sweat gland carcinoma. Br J Dermatol 2019; 180: 1150-60. DOI: 10.1111/bjd.17446

[57] Kao G, Helwig E, Graham J. Aggressive digital papillary adenoma and adenocarcinoma. A clinicopathological study of 57 patients, with histochemical, immunopathological, and ultrastructural observations. J Cutan Pathol 1987; 14: 129-46. DOI: 10.1111/j.1600-0560.1987.tb00488.x

[58] Duke WH, Sherrod TT, Lupton GP. Aggressive digital papillary adenocarcinoma: (aggressive digital papillary adenoma and adenocarcinoma revisited). Am J Surg Pathol 2000; 24: 775-84. DOI: 10.1097/00000478-200006000-00002

[59] Suchak R, Wang W-L, Prieto VG, *et al*. Cutaneous digital papillary adenocarcinoma: A clinicopathologic study of 31 cases of a rare neoplasm with new observations. Am J Surg Pathol 2012; 36: 1883-91. DOI: 10.1097/PAS.0b013e31826320ec

[60] Scolyer RA, Karim RZ, Thompson JF, Stretch JR, McCarthy SW, Murali R. Digital papillary adenocarcinoma: A tumour that should be considered in the differential diagnosis of neoplasms involving the digits. Pathology 2013; 45: 55-61. DOI: 10.1097/PAT.0b013e32835af778

[61] Molina-Ruiz A-M, Llamas-Velasco M, Rütten A, Cerroni L, Requena L. "Apocrine Hidrocystoma and Cystadenoma"-like tumor of the digits or toes: A potential diagnostic pitfall of digital papillary adenocarcinoma. Am J Surg Pathol 2016; 40: 410-8. DOI: 10.1097/PAS.0000000000000547

[62] Weingertner N, Gressel A, Battistella M, Cribier B. Aggressive digital papillary adenocarcinoma: A clinicopathological study of 19 cases. J Am Acad Dermatol 2017; 77: 549-58. DOI: 10.1016/j.jaad.2017.02.028

[63] Bell D, Aung PP, Prieto VG, Ivan D. Next-generation sequencing reveals rare genomic alterations in aggressive digital papillary adenocarcinoma. Ann Diagn Pathol 2015; 19: 381-4. DOI: 10.1016/j.anndiagpath.2015.08.002

[64] Heiwig E. Eccrine acrospiroma. J Cutan Pathol 1984; 11: 415-20. DOI: 10.1111/j.1600-0560.1984.tb00398.x

[65] Geethamani V, Shetty A, Chiwdappa V. Aggressive digital papillary adenocarcinoma-a rare entity posing a diagnostic challenge. Malays J Med Sci 2014; 21: 54. DOI: 10.1007/s12593-010-0028-1

[66] Gole GN, Tati SY, Deshpande AK, Gole SG. Aggressive digital papillary adenocarcinoma in a young female - a rare presentation. J Hand Microsurg 2011; 3: 31-3. DOI: 10.1097/DSS.0000000000001483

[67] Rismiller K, Knackstedt TJ. Aggressive digital papillary adenocarcinoma: Population-based analysis of incidence, demographics, treatment, and outcomes. Dermatol Surg 2018; 44: 911-7.

[68] Frey J, Shimek C, Woodmansee C, *et al*. Aggressive digital papillary adenocarcinoma: A report of two diseases and review of the literature. J Am Acad Dermatol 2009; 60: 331-9. DOI: 10.1016/j.jaad.2008.07.038

[69] Hsu HC, Ho CY, Chen CH, Yang CH, Hong HS, Chuang YH. Aggressive digital papillary adenocarcinoma: A review. Clin Exp Dermatol 2010; 35: 113-9. DOI: 10.1111/j.1365-2230.2009.03490.x

[70] Lee JJ, Mochel MC, Piris A, Boussahmain C, Mahalingam M, Hoang MP. p40 exhibits better specificity than p63 in distinguishing primary skin adnexal carcinomas from cutaneous metastases. Hum Pathol 2014; 45: 1078-83. DOI: 10.1016/j.humpath.2014.01.006

[71] Criscitiello C, Morganti S, Curigliano G. Antibody-drug conjugates in solid tumors: a look into novel targets. J Hematol Oncol 2021; 14: 1-18. DOI: 10.1186/s13045-021-01035-z

[72] Ito T, Hashimoto H, Tanaka Y, *et al*. TROP2 Expression in sebaceous and sweat gland carcinoma. J Clin Med 2022; 11: 607. DOI: 10.3390/jcm11030607

[73] Ohmachi T, Tanaka F, Mimori K, Inoue H, Yanaga K, Mori M. Clinical significance of TROP2 expression in colorectal cancer. Clin Cancer Res 2006; 12: 3057-63. DOI: 10.1158/1078-0432.CCR-05-1961

[74] Shen M, Liu S, Stoyanova T. The role of Trop2 in prostate cancer: An oncogene, biomarker, and therapeutic target. Am J Clin Exp Urol 2021; 9: 73-87.

[75] Hsu E-C, Rice MA, Bermudez A, *et al*. Trop2 is a driver of metastatic prostate cancer with neuroendocrine phenotype via PARP1. Proc Natl Acad Sci 2020; 117: 2032-42. DOI: 10.1073/pnas.1905384117

[76] Trerotola M, Jernigan DL, Liu Q, Siddiqui J, Fatatis A, Languino LR. Trop-2 promotes prostate cancer metastasis by modulating β1 integrin functions. Cancer Res 2013; 73: 3155-67. DOI: 10.1158/0008-5472.CAN-12-3266

[77] Mori Y, Akita K, Ojima K, *et al*. Trophoblast cell surface antigen 2 (Trop-2) phosphorylation by protein kinase C α/δ (PKCα/δ) enhances cell motility. J Biol Chem 2019; 294: 11513-24. DOI: 10.1074/jbc.RA119.008084

[78] Cubas R, Zhang S, Li M, Chen C, Yao Q. Trop2 expression contributes to tumor pathogenesis by activating the ERK MAPK pathway. Mol Cancer 2010; 9: 1-13. DOI: 10.1186/1476-4598-9-253

[79] Trerotola M, Cantanelli P, Guerra E, *et al*. Upregulation of Trop-2 quantitatively stimulates human cancer growth. Oncogene 2013; 32: 222-33. DOI: 10.1038/onc.2012.36

[80] Guerra E, Trerotola M, Aloisi A, *et al*. The Trop-2 signalling network in cancer growth. Oncogene 2013; 32: 1594-600. DOI: 10.1038/onc.2012.151

[81] Zhao W, Kuai X, Zhou X, *et al*. Trop2 is a potential biomarker for the promotion of EMT in human breast cancer. Oncol Rep 2018; 40: 759-66. DOI: 10.3892/or.2018.6496

[82] Li Z, Jiang X, Zhang W. TROP2 overexpression promotes proliferation and invasion of lung adenocarcinoma cells. Biochem Biophys Res Commun 2016; 470: 197-204. DOI: 10.1016/j.bbrc.2016.01.032

[83] Gray JE, Heist RS, Starodub AN, *et al*. Therapy of small cell lung cancer (SCLC) with a topoisomerase-i-inhibiting antibody-drug conjugate (ADC) targeting trop-2, sacituzumab govitecan. Clin Cancer Res 2017; 23: 5711-9. DOI: 10.1158/1078-0432.CCR-17-0933

[84] Heist RS, Guarino MJ, Masters G, *et al*. Therapy of advanced non-small-cell lung cancer with an SN-38-anti-trop-2 drug conjugate, sacituzumab govitecan. J Clin Oncol 2017; 35: 2790-7. DOI: 10.1200/JCO.2016.72.1894

[85] Faltas B, Goldenberg DM, Ocean AJ, *et al*. Sacituzumab govitecan, a novel antibody-drug conjugate, in patients with metastatic platinum-resistant urothelial carcinoma. Clin Genitourin Cancer 2016; 14: 75-9. DOI: 10.1016/j.clgc.2015.10.002

[86] Bardia A, Hurvitz SA, Tolaney SM, *et al*. Sacituzumab govitecan in metastatic triple-negative breast cancer. New Engl J Med 2021; 384: 1529-41. DOI: 10.1056/NEJMoa2028485

[87] Bardia A, Messersmith W, Kio E, *et al*. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: Final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. Ann Oncol 2021; 32: 746-56. DOI: 10.1016/j.annonc.2021.03.005

[88] Kibbi N, Worley B, Owen JL, *et al*. Sebaceous carcinoma: Controversies and their evidence for clinical practice. Arch Dermatol Res 2020; 312: 25-31. DOI: 10.1007/s00403-019-01971-4

[89] Owen JL, Kibbi N, Worley B, *et al*. Sebaceous carcinoma. Evidence-based clinical practice guidelines. Lancet Oncol

2019; 20: 699-714. DOI: 10.1016/S1470-2045(19)30673-4

[90] Le NS, Janik S, Liu DT, *et al*. Eccrine porocarcinoma of the head and neck: Meta-analysis of 120 cases. Head Neck 2020; 42: 2644-59. DOI: 10.1002/hed.26178

[91] Chaudhari SP, Mortazie MB, Blattner CM, *et al*. Treatments for microcystic adnexal carcinoma-a review. J Dermatol Treat 2016; 27: 278-84. DOI: 10.3109/09546634.2015.1089351

[92] Au RTM, Bundele MM. Endocrine mucin-producing sweat gland carcinoma and associated primary cutaneous mucinous carcinoma: Review of the literature. J Cutan Pathol 2021; 48: 1156-65. DOI: 10.1111/cup.13983

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