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Skin adnexal neoplasms - part 2: An approach to tumours of cutaneous sweat glands

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ABSTRACT

Tumours of cutaneous sweat glands are uncommon with wide histological spectrum; complex classification and many different terms often used to describe the same tumour. Furthermore, many eccrine/apocrine lesions co-exist within hamartomas or within lesions with composite/mixed differentiation. In addition to the eccrine and apocrine glands, two other skin sweat glands have been recently described: the apoeccrine and the mammary-like glands of the anogenital area. In this review (the second of two articles on skin adnexal neoplasms), we will describe common as well as important benign and malignant lesions of cutaneous sweat glands, as well as outlining a summary for differentiating primary adnexal neoplasms from metastatic carcinoma, striving to maintain a common and acceptable terminology in this complex subject. We will also briefly discuss composite/mixed adnexal tumours.

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1. Many sweat gland tumours have both eccrine and apocrine origins.

2. A malignant counterpart of most benign lesions has been described. Features that suggest malignancy include asymmetry of the lesion, jagged/infiltrative borders, irregular arrangement of neoplastic cells, cytonuclear atypia, and significantly increased mitotic activity.

3. Apocrine lesions are usually immunoreactant for androgen receptors and gross cystic disease fluid protein-15 , and negative for oestrogen and progesterone receptors, and bcl-2.

4. Differentiating primary cutaneous sweat gland carcinomas from metastatic carcinoma is often difficult. Clinical history, other histomorphological features as well as immunohistochemical stains are all very important.

5. Composite/mixed adnexal tumours display a varied composition with a mixture of eccrine, apocrine, sebaceous, and pilar differentiation.

INTRODUCTION

The classification of cutaneous sweat gland lesions is very complex (Table 1), as these lesions have a wide histological spectrum, and the pathogenesis and exact origin of many lesions is still under investigation and not clear. [1,2] Many different terms are often used to describe the same tumour (Table 2), making this subject more difficult for the pathologist to reach a uniform way for the diagnosis of these lesions. Furthermore, the issue is complicated by the co-existence of eccrine and/or apocrine lesions within cutaneous hamartomas or within adnexal lesions with composite/mixed differentiation, which also includes those with follicular and sebaceous differentiation. A detailed practical approach to different skin adnexal lesions has been illustrated in the first review article of this series [3], which the reader is referred to. Nonetheless, some important general features of sweat glands are reviewed here.

Table 1. Classification of cutaneous sweat gland adnexal lesions according to the current thinking of the predominant 'accepted' origin.

Origin	*Benign*	*Malignant*
Eccrine and apocrine (mixed origin)	Hidrocystoma Apocrine/eccrine nevus Tubulopapillary hidradenoma (including papillary eccrine adenoma, tubular apocrine adenoma) Chondroid syringoma	Malignant mixed tumour of the skin (has eccrine/apocrine and mesenchymal components)
Eccrine	Poroma Hidradenoma Spiradenoma Cylindroma Syringometaplasia Syringoma Syringofibroadenoma	Porocarcinoma Hidradenocarcinoma Spiradenocarcinoma Malignant cylindroma Syringoid carcinoma Microcystic adnexal carcinoma Mucinous carcinoma Adenoid cystic carcinoma Aggressive digital papillary adenocarcinoma
Apocrine	Syringocystadenoma papilliferum Hidradenoma papilliferum	Syringocystadenocarcinoma Apocrine carcinoma Extramammary Paget's disease
Composite/mixed cutaneous adnexal tumours		

Table 2. Cutaneous sweat gland lesions and their synonyms

Lesion	*Synonyms*
Hidrocystoma	Apocrine/eccrine hidrocystoma, cystadenoma
Syringofibroadenoma	Acrosyringeal adenomatosis, acrosyringeal nevus
Poroma	Hidroacanthoma simplex (intraepidermal poroma), eccrine poroma, and dermal duct tumour
Hidradenoma	Nodular hidradenoma, solid-cystic hidradenoma, clear cell hidradenoma, clear cell acrospiroma, eccrine acrospiroma
Cylindroma (multiple)	Turban tumour
Tubulopapillary hidradenoma	Papillary eccrine adenoma, tubular apocrine adenoma, papillary apocrine fibroadenoma
Syringocystadenoma papilliferum	Papillary syringadenoma
Hidradenoma papilliferum	Papillary hidradenoma
Chondroid syringoma	Mixed tumour of the skin
Digital papillary adenocarcinoma	Aggressive digital papillary tumour, aggressive digital papillary adenoma/carcinoma, aggressive digital papillary adenoma
Sweat gland ductal carcinoma	Syringoid eccrine carcinoma, eccrine ductal carcinoma
Porocarcinoma	Malignant 'eccrine' poroma
Microcystic adnexal carcinoma	Sclerosing sweat duct carcinoma
Hidradenocarcinoma	Malignant nodular/clear cell hidradenoma, Malignant acrospiroma, malignant clear cell acrospiroma, clear cell eccrine carcinoma, primary mucoepidermoid cutaneous carcinoma.
Apocrine carcinoma	Tubular apocrine carcinoma, malignant hidradenoma papilliferum

Eccrine sweat glands are widely distributed almost everywhere in the skin. The cells in the excretory coil express positivity for low molecular weight keratin (LMWK), epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA), as well as S-100 protein in the basal layer only. The myoepithelial cell layer may be highlighted by smooth muscle actin (SMA), p63 and calponin. Acrosyringeal cells (intraepidermal portion) stain for high molecular weight keratin (HMWK) and cytokeratin (CK) 14. A sub-population of cells also expresses positivity to bcl-2. Skin tumours with eccrine differentiation often also express positive immunohistochemical staining for oestrogen and progesterone receptors (ER and PR, respectively). [4] The positivity of some eccrine carcinomas to ER has important clinical implications, as affected patients may be partially treated with hormonal therapy. [5] Unfortunately, positivity for ER and PR does not distinguish cutaneous eccrine tumours from cutaneous metastases of breast carcinoma [6], in which case clinical and radiological correlation is critical.

Apocrine lesions of the skin are rare and found mainly in body folds including the axillary, groin and anogenital regions where apocrine glands are most concentrated, as well as in the umbilicus, eyelid (Moll's

glands), areola, and in external auditory meatus. They also occur as heterotopic lesions elsewhere in the body, exemplified by tubular apocrine adenoma and within hamartomatous adnexal lesions such as in nevus sebaceous of Jadassohn (NSJ) in the scalp. In lesions of apocrine origin, the cells have abundant eosinophilic cytoplasm and eccentric, basally located nuclei. In addition, there is usually evidence of decapitation secretion in the luminal cells, and the tumour cells contain Periodic Acid-Schiff (PAS) positive diastase-resistant granules, and iron pigment (best illustrated with Prussian blue stain). The luminal cells are immunoreactive to CEA and EMA. The secretory cells are positive for LMWK, and the glandular epithelium often also expresses gross cystic disease fluid protein 15 (GCDFP-15) and androgen receptors (AR), which may be useful in the assessment of lesions suspicious of apocrine carcinoma. However, ER/PR/bcl-2 negativity is more consistent and considered more helpful to confirm the diagnosis of apocrine carcinoma than GCDFP-15/AR positivity. [7]

Apoeccrine glands are mostly found in the axillary region, and within lesions of nevus sebaceous of Jadassohn. [8] Their presence helps to explain the existence of some adnexal lesions that have both eccrine as well as apocrine components, including syringocystadenoma papilliferum (SCAP) [1] and Fox-Fordyce disease. [9] Some authors [10] believe that these glands are synonymous with cutaneous mammary-like glands (MLG), which are now recognised to be a normal component of the skin in the anogenital region, including the perianal skin. [11] MLG are unique in having features of apocrine, eccrine and mammary glands. The previous assumption that these glands represent ectopic/accessory breast tissue lying along the milk line (mammary ridge) is now believed to be incorrect. [12] Many adnexal lesions of the anogenital area are now recognized to be of MLG origin, including “apocrine” adenoma/fibroadenoma, hidrocystoma, hidradenoma papilliferum, extramammary Paget’s disease, and adenocarcinoma. [11-14] These lesions often have papillary/cribriform growth pattern and a fibrous stroma reminiscent of fibroepithelial lesions of the breast. A helpful feature in attributing MLG origin to an adnexal tumour is the presence of normal MLG in the deep dermis and subcutaneous fatty tissue, in the vicinity of the lesion of interest [13], with a transition zone between benign and lesional areas. [12]

Tumours of pure apocrine origin appear to be much less common than those of eccrine origin, by virtue of the localisation of apocrine glands in the body. However, it is important to mention at the outset of this review that many of the sweat gland tumours traditionally assumed to have an eccrine origin are now recognised to have apocrine counterparts as well, as evidence of apocrine differentiation has been elucidated in many of them. These tumours include hidrocystoma, poroma, cylindroma, spiradenoma, and chondroid syringoma. In addition, many sweat gland lesions have both eccrine and apocrine differentiation (as well as pilosebaceous occasionally) within the same tumour. Examples of this are the many composite/mixed adnexal tumours and hamartomas that continually appear in the literature. Therefore, it was felt necessary in this review to drop the prefix “eccrine” from many of these terms.

This review will concentrate on common and/or important benign as well as malignant tumours of cutaneous sweat glands (Tables 3 and 4, respectively), with emphasis on diagnostic approach. Many benign sweat gland tumours have malignant counterparts, which are discussed under the same subheading. Some entities are only referred to in the tables, but not considered within the text. After reading this review, the practicing pathologist will be able to diagnose most of the entities considered herein. However, when a tumour is difficult to be classified, it is more important to differentiate between benign and malignant lesions, and in that setting it may be sufficient to describe the tumour as a benign or malignant cutaneous sweat gland tumour, with predominant eccrine or apocrine differentiation. Furthermore, complete excision of all skin adnexal lesions is always advisable. The differentiation of sweat gland tumours from metastatic carcinomas is discussed where appropriate.

Table 3. Morphologic approach to benign cutaneous sweat gland lesions

Predominant morphology	*Lesion*	*General features*
Solid tumours with prominent basaloid component	Poroma, hidroacanthoma simplex and dermal duct tumour	Large nodules of monomorphic small 'poroid' cells connected to epidermis
	Nodular hidradenoma	Large dermal nodules
	Cylindroma	Jigsaw-puzzle appearance Thickened basement membrane
	Spiradenoma	Basaloid cells with 2 cell types
Cystic lesions	Hidrocystoma	Simple cyst lined by two rows of cells Lining may have eccrine or apocrine epithelial features Papillary projections or solid buds of secretory cells may be seen
Solid-cystic tumours	Nodular hidradenoma	Solid lobules with cystic changes May have spindle or squamous differentiation Eosinophilic or clear cell change may be prominent
	Mixed tumour of the skin	Tubular or anastomosing ductal/glandular proliferation Chondromyxoid stroma Eccrine more common than apocrine May also have 'hamartomatous' components
Glandular tumours with eccrine differentiation	Syringoma	"Tadpole" or "comma shaped" small ducts with two rows of cells
	Tubulopapillary hidradenoma with eccrine differentiation (papillary eccrine adenoma)	Dermal/subcutaneous tubular structures Intraluminal papillary projections
	Syringofibroadenoma (Acrosyringeal adenomatosis)	Diffuse proliferation of anastomosing acrosyringeal epithelium in epidermis and dermis
Glandular tumours with apocrine differentiation	Hidradenoma papilliferum	Vulvar/ perianal Mostly in females Prominent papillary fronds Fibrous stroma
	Tubulopapillary hidradenoma with apocrine differentiation (Tubular apocrine adenoma and fibroadenoma)	Dermal/subcutaneous tubular apocrine structures Lobular pattern of with epidermal connection Intraluminal papillary projections
	Syringocystadenoma papilliferum	Mostly over scalp in young Elaborate epithelial papillary infolding. Open to epidermis Plasma cell rich stroma Apocrine differentiation is not always apparent
Tumours demonstrating clear cell change	Nodular hidradenoma Syringoma Poroma Spiradenoma	This may occur in many sweat gland tumours Should be considered in conjunction with other features Follicular lesions with trichilemmal differentiation are also in the differential
Miscellaneous/ hamartomatous/ hyperplastic lesions	Apocrine/ eccrine nevus	Localised proliferation of apocrine/ eccrine glandular/ductal structures within deep dermis

	Syringometaplasia	Mostly reaction to damaged eccrine ductal epithelium induced by different stimuli; especially chemotherapeutic drugs Metaplasia of eccrine duct epithelium into squamous cells with intercellular bridges similar to the stratum spinosum Keratinisation and focal necrosis. [110]
	Apocrine hyperplasia	Axillae and groin
	Nipple adenomatosis	Nipple Papillated ducts open to surface. Apocrine differentiation
Composite/ mixed skin adnexal tumours		Have two or more lines of differentiation towards eccrine, apocrine, sebaceous or pilar structures

Table 4. Malignant cutaneous sweat gland tumours that have relatively constant identifiable features (discussed in text)

Eccrine	*Apocrine*
Porocarcinoma	Apocrine carcinoma
Hidradenocarcinoma	Extramammary Paget's disease
Spiradenocarcinoma	
Malignant cylindroma	
Syringoid carcinoma	
Malignant chondroid syringoma	
Aggressive digital papillary adenocarcinoma	
Microcystic adnexal carcinoma	
Adenoid cystic carcinoma	
Mucinous carcinoma	

POROMAS

Most of these tumours originate from the outer cells of the intraepidermal (acrosyringeal) excretory ducts of eccrine sweat gland. They usually occur in adult with predilection to palms and soles, and less frequently the head and neck, and trunk regions. Clinically they can be solitary or multiple, and present as superficial plaques or dermal nodules, with tendency to ulceration and bleeding. Histologically, three main benign tumours are recognised and distinguished according to their location in relation to the epidermis [15,16] 1. poroma (fig.1A), involves both epidermis and dermis. 2. hidroacanthoma simplex, also known as intraepidermal poroma, confined within the epidermis, and 3. dermal duct tumour, limited to dermis with no epidermal attachment. These tumours consist of solid sheets and nodules of basaloid poroid cells with pushing borders that emanate from the epidermis. The neoplastic cells are small, monomorphous, and polyhedral cuboidal with well-defined cell membrane. They have small, centrally located bland nuclei, and variable amount of cytoplasm that ranges from scant to ample, eosinophilic to clear glycogenated PAS positive and diastase sensitive. Variable number of mitotic figures can be identified. The tumour cells are sharply delineated from adjacent keratinocytes. Foci of squamous differentiation and clear cell change are commonly seen. The intervening stroma is characteristically very vascular. Inconspicuous to prominent CEA positive small ducts lined by cuboidal cells, and PAS-positive eosinophilic cuticle material, are present in most tumours. Poroma cells are also reactive for CK17. [17] More recently, there have been reports of poromas with sebaceous, follicular, and apocrine differentiation, suggesting a possible apocrine origin. These cases have been labelled as 'apocrine' poromas. [18]

Porocarcinomas (malignant eccrine poromas) (fig. 1B) are usually found on the lower extremities. They usually arise in pre-existing benign poroid tumours, and are histologically characterised by asymmetrical, solid, nodular growth pattern with infiltrative or pushing borders. The neoplastic cells in porocarcinoma may have basaloid features, resembling those of poroma, but demonstrate varying degrees of cytonuclear atypia, hyperchromatic nuclei, and prominent nucleoli. Large polyhedral cells with abundant clear cytoplasm can be present. Foci of squamous and spindle cell differentiation are common. Evidence of eccrine differentiation in the form of CEA-positive ductal formation is present in most of the cases. Brisk mitotic activity, necrosis, and desmoplastic stromal reaction can be prominent (fig. 1C). Continuity with a benign pre-existing poroma, and prominent intraepidermal component, occasionally displaying severe cellular pleomorphism and resembling Paget's disease, can be present (fig. 1D). [19,20]. A purely "porocarcinoma in situ" adjacent to a benign poroma may also occur. Porocarcinomas are aggressive tumours with potential for local recurrence, and nodal and distant metastases. [21] It has been suggested that more than 14 mitoses per high power field, tumour depth more than 7 mm, and presence of lymphovascular invasion are associated with more aggressive clinical course. [20] The main differential diagnosis of porocarcinoma is squamous cell carcinoma, which lacks intracytoplasmic lumina and ductal formation. The differential diagnosis of "porocarcinoma in situ" includes clonal seborrheic keratosis, clonal squamous cell carcinoma in situ (Bowen's disease), melanoma in situ, and Paget's disease. [22] The presence of an adjacent benign poroid component is a helpful feature in establishing the diagnosis. In clonal Bowen's disease the tumour cells are more atypical and there is more severe architectural abnormality. Clonal seborrheic keratosis and Bowen's disease are negative for CEA, CK7 and S100, which are often positive in porocarcinoma. [16] Negativity for melan-A and HMB45 helps rule out melanoma in situ. In Paget's disease, the cells are large with clear PAS-positive cytoplasm.

HIDRADENOMA AND HIDRADENOCARCINOMA

Hidradenoma is a benign tumour, usually presents as solitary, skin-coloured lesion, and it occurs more commonly in females. [16] Hidradenoma may have variable histomorphological patterns (fig. 2A-C), reflected by the various terms used to describe this entity: nodular hidradenoma, eccrine acrospiroma, solid-cystic hidradenoma, clear cell hidradenoma, and clear cell acrospiroma. It shows variably sized nests and nodules of neoplastic epithelial cells, with small ductular lumens, confined within the upper dermis. The tumour cells are small, monomorphous and polyhedral, resembling those of poroma cells. In fact, some tumours have epidermal attachment, and occasionally may also have features overlapping with those of typical poromas. [23] Clear cell change and/or squamous metaplasia may be prominent. However, squamoid change does not seem to denote worse prognosis. Occasionally, focal apocrine components may also be present. The lesion is also characterised by its pushy, but well-circumscribed, peripheral border. Nodular hidradenoma should be fully excised, as malignant transformation may be present in other areas of the lesion. Furthermore, hidradenoma has a recurrence rate of approximately 12% if not fully excised [24], especially in lesions with irregular peripheral margins. [23]

Although most cases of hidradenocarcinoma arise de novo, the tumour may also arise in pre-existing hidradenoma. [23] Hidradenocarcinoma is also often referred to as malignant nodular/clear cell hidradenoma, malignant clear cell acrospiroma, clear cell eccrine carcinoma, or primary mucoepidermoid cutaneous carcinoma. Histologically (fig. 2D), it is a multinodular solid malignant neoplasm, showing ductal structures and intracytoplasmic tubular vacuoles, with areas of tumour necrosis. The tumour cells have similar morphology to those of nodular hidradenoma, but may also show cytonuclear atypia and increased mitotic activity. Apocrine differentiation is frequently seen. Evidence of nodular hidradenoma remnants may be present. An infiltrative growth pattern is not universally seen, and the carcinoma is distinguished from benign hidradenoma by the presence of brisk mitotic activity, and cellular pleomorphism. The tumour cells stain positively for LMWK, and the ductal structures/luminal surfaces are highlighted by EMA and CEA. Although these rare tumours do not always behave aggressively, they may have an aggressive course with metastasis and/or local recurrence. The primary treatment is wide local excision with or without lymph node dissection. [25,26]

Interestingly, clear cell hidradenoma and hidradenocarcinoma may occasionally mimic metastatic clear cell carcinomas including thyroid, lung, or renal cell carcinomas. However, the first two are usually

distinguished by their positivity to thyroid transcription factor-1 (TTF-1), and the later by its prominent vascularity, and the presence of haemorrhage and focal granular necrosis within the lesion. [22] Renal cell carcinoma also expresses both EMA and CD10.

SYRINGOMA AND SYRINGOID ECCRINE CARCINOMA

Syringomas constitute a spectrum of benign sporadic tumours that arise from the straight segment of the intradermal eccrine sweat duct. They predominantly affect middle-aged women, and most commonly involve the head and neck region, with a predilection for the eyelids. Uncommon variant is eruptive syringoma, a clinical condition characterised by multiple yellow-brown-coloured, firm papules, with no specific site predilection in young adults. [27] The pathogenesis of eruptive syringoma is controversial and it has been suggested that it represents a reactive eccrine gland ductal proliferation following cutaneous inflammatory conditions. [28] There is also an increased incidence of eruptive syringoma in patients with Down syndrome, and rarely, syringomas can occur in familial form. [29]

Histologically, syringomas are symmetrical, well circumscribed, confined to the upper dermis, and usually have no connection with the overlying epidermis. The tumours consist of proliferation of epithelial cells, arranged in nests, cords, or tubules, in which some display a “comma” or “tadpole” shape (fig. 3A). The tubules are lined by single or double layers of bland, monomorphous, cuboidal epithelial cells with small normochromic nuclei, and small to moderate amount of pale eosinophilic cytoplasm. In some tumours, the neoplastic cells predominantly exhibit abundant clear cytoplasm [30] (clear cell syringoma) (fig. 3B). A PAS-positive eosinophilic material is often present within the tubular lumina. Syringoma should be distinguished from the extremely rare malignant counterparts, syringoid eccrine carcinoma and microcystic adnexal carcinoma. In contrast to benign syringomas, syringoid eccrine carcinoma (fig. 3C) exhibits cytonuclear atypia, mitotic activity, lymphovascular and perineural invasion, and infiltrative growth pattern with tumour extension into the deep dermis and subcutaneous tissue, and potential for local recurrence and distant metastases. [31,32] In superficial skin biopsies, microcystic adnexal carcinoma may be misdiagnosed as syringoma (see below). Therefore, re-evaluation of these tumours and especially their base after complete excision is important.

Chondroid syringoma (mixed tumour of the skin) and malignant chondroid syringoma

This uncommon tumour presents as a slowly growing, painless, firm nodule, generally occurring in the head and neck region, but most commonly affecting the nose, cheek, and upper lip. [1,33] Less frequently, the extremities, trunk or back may also be affected. Histologically, chondroid syringoma is similar to the benign mixed tumour of the salivary glands, having both epithelial and mesenchymal stromal components. The tumour shows a circumscribed nodule, consisting of bland epithelial cells, arranged in cords, ducts (fig. 4A), or tubules (fig. 4B). The stromal component is most often myxoid-cartilaginous (chondromyxoid), but may also be hyalinised/fibrous, fatty, osteoid or may even be minimal or absent. [16] The stromal cells display myoepithelial differentiation, illustrated by positivity to S-100, vimentin and neurone-specific enolase, and less commonly by glial fibrillary acid protein, SMA, calponin, or p63. Desmin is usually negative. [1,33] Chondroid syringoma is classified into apocrine and eccrine types, based on the histopathological appearance of the sweat gland lumina within the tumour. In the apocrine type, lesions incorporating areas with pilar and sebaceous differentiation have been repeatedly described [34], suggesting that some tumours are best viewed as hamartomatous lesions of the pilosebaceous-apocrine unit. Chondroid syringoma is best completely excised because of the possibility of local recurrence and malignant transformation.

Malignant chondroid syringoma is very rare, and may arise de novo or from a pre-existing chondroid syringoma, which has undergone malignant transformation. [35,36] Histologically, there is cellular atypia, increased mitotic activity, infiltrative margins, satellite tumour nodules, and tumour necrosis. [1] Haematogenous and lymphatic spread to lymph nodes, lungs, and bone may occur. The term “Atypical chondroid syringoma” is used to describe tumours with histological features of malignancy as well as recurrence, local invasion and satellite tumour nodules, but without proven metastases. [37]

SYRINGOFIBROADENOMA (ACROSYRINGEAL ADENOMATOSIS)

This is a rare benign eccrine tumour of acrosyringeal origin, with variable clinical presentation. Histologically, there are reticulated and irregularly anastomosing epithelial cords and strands extending from the epidermis into the superficial dermis (fig. 5), usually embedded in a fibrovascular stroma. The cells are basophilic and monomorphous, and they are smaller than adjacent epidermal keratinocytes. They are positive for HMWK and CK14. Occasional ductal structures may be identified, and enhanced with CEA or EMA. Areas of clear cell change may also occur. This lesion has indeterminate pathogenesis, variously being labelled as a neoplasm, hamartoma, nevus, or reactive hyperplasia; therefore it probably represents a group of heterogeneous disorders. [38,39]

SPIRADENOMA AND SPIRADENOCARCINOMA

Spiradenomas are commonly encountered benign tumours, originating from the straight intradermal eccrine duct. They usually present as solitary, painful, nodular lesion in young adult with a predilection to the trunk and upper extremities. Rarely, spiradenomas can be associated with Brooke-Spiegler syndrome, a rare autosomal dominant inherited disorder, characterised by the development of multiple skin adnexal tumours. [40] Microscopically, there is a well-circumscribed nodular tumour in the dermis and subcutaneous tissue, encapsulated by a well-defined fibrous capsule, and lack connection with the epidermis. The neoplastic nodules are solid, variable in size, and characteristically formed of two epithelial cell types (fig. 6A and B): 1. large cells with round vesicular nuclei, prominent nucleoli, and abundant pale cytoplasm, located in the centre of the neoplastic nodules. 2. small cells with hyperchromatic nuclei and scant cytoplasm rimming the periphery of the neoplastic nodules. Mitotic figures can be present. The cells can be arranged in cords, or exhibit tubular and alveolar differentiation. Globules of dense eosinophilic PAS-positive basement membrane material are present within the tumour lobules. Richly vascular stroma with occasional thrombi, foci of squamous differentiation, fibrosis, and cystic degenerative changes are commonly seen. Apocrine differentiation has also been reported in spiradenomas, leading some authors to suggest that not all spiradenomas are of eccrine origin. [41]

Spiradenocarcinoma (fig. 6C) is a very rare malignant neoplasm, arises from a pre-existing spiradenoma, and histologically characterised by loss of nodular growth pattern, infiltrative borders, cytonuclear pleomorphism, increased mitotic activity, and tumour necrosis. [42]. The presence, at least in focal parts within the lesion, of dual population (central basaloid cells and larger peripheral cells) is required for the diagnosis of spiradenocarcinoma, which has a high recurrence rate, and occasionally can metastasize to lymph nodes and distant organs.

CYLINDROMA

Cylindromas are benign neoplasms; usually affect adult females, with 90% occurring in the head and neck region, particularly the scalp and face. They can be sporadic and present as a solitary lesion, or less commonly as a variably sized, multiple coalescing tumours causing marked disfiguring of the scalp and face (turban tumour). Rarely, multiple cylindromas can be associated with familial cylindromatosis; an autosomal dominant disorder, and Brook-Spiegler syndrome, in which case there are multiple tumours that may also involve trunk and extremities in children or young adults. Mutations in the cylindromatosis tumour suppressor gene (CYLD1) on chromosome 16q12-13 play an essential role in the pathogenesis of hereditary and sporadic cylindromas. [43] This mutation is also associated with developing spiradenoma, trichoepithelioma, milia or membranous variant of salivary gland basal cell adenoma. The histogenesis of cylindroma is controversial; while accumulated evidences favour an eccrine origin from the coiled part of intradermal duct [44], others suggest an apocrine differentiation. [45]. Histologically, these tumours are readily recognised and characterised by numerous well defined, non-encapsulated variably sized islands and nodules of epithelial cells, lined by thick PAS-positive basement membrane-like, hyalinized material, and arranged in characteristic “jigsaw puzzle” pattern (fig. 7). Two populations of cells are usually identified within the tumour epithelial islands: 1. large cells with pale-staining nuclei and moderate amount of amphophilic cytoplasm, located at the central zone, and 2. peripherally-located, small, basaloid cells with

dark-staining nuclei and scant cytoplasm that exhibit palisading pattern. Ductulotubular structures, lined by cuboidal or columnar cells and contain intraluminal eosinophilic material, are usually present. PAS-positive hyaline globules are also found in the tumour islands. Some tumours, termed spiradenocylindromas, have features of both cylindromas and eccrine spiradenomas [46]; the existence of which may suggest that both entities represent a continuous morphological spectrum of a single entity, or a transitional or maturing phase from one lesion to the other. [32]. In addition to the morphological similarity between cylindroma and spiradenoma, both entities express immunopositivity for S-100 protein within the tubular and large, pale-staining cells, human milk fat globulin (HMFG) and lysosome in tubular cells, SMA in small basaloid cells, and CK 7, 8, and 18. [47]

Malignant cylindroma is a rare tumour, arises from pre-existing benign cylindroma, both in solitary sporadic, and in autosomal dominant multiple forms. Malignant cylindroma is clinically characterised by rapid growth, long-standing ulceration or bleeding, and aggressive clinical behaviour with local recurrence and potential for distant metastases. [48,49] Histologically, there is an infiltrative growth pattern with cytonuclear pleomorphism, increased mitotic activity, and loss of jigsaw appearance, hyaline sheath and peripheral palisading.

SYRINGOCYSTADENOMA PAPILLIFERUM AND SYRINGOCYSTADENOCARCINOMA PAPILLIFERUM

Syringocystadenoma papilliferum (SCAP) is a benign hamartomatous tumour usually affecting the young adults, and occurs as a solitary or less commonly multiple lesions, most commonly in the face and scalp. They can arise within a pre-existing NSJ [50], and rarely they are associated with papillary eccrine adenoma [51], tubular apocrine adenoma [52], and hidradenoma papilliferum. [13] Mutations in tumour suppressor gene p16 may contribute to the pathogenesis of SCAP. [53] The tumour is variably denoted to be derived from eccrine, apocrine or apoeccrine origins. [1,2] Histologically, SCAP is a verrucous tumour that displays multiple epithelial invaginations extending down from the epidermis, and contains numerous papillae (fig. 8A and B). These papillary structures consist of a dermal fibrovascular core, lined by two layers of epithelial cells; luminal columnar cells with decapitation secretion and outer cuboidal cells. Characteristically marked plasmacytic inflammatory cell infiltrate is present within the fibrous cores. [54] Apocrine sweat glands are often identified at the deep part of the tumour. Immunohistochemically, the luminal columnar cells express GCDFP-15, CEA, and CK7 and CK19, while the basal cuboidal cells express CK 5, 7, 8, and 14. [55] Syringocystadenocarcinoma papilliferum (fig. 8C and 8D) is very rare, and characterised histologically by disorderly arrangement of papillary projections, cytological atypia, and loss of double-layered epithelium. [56]

HIDRADENOMA PAPILLIFERUM

Hidradenoma papilliferum (HP) is a benign tumour, occurs almost exclusively in females with predilection to the vulva and perianal region. Rare cases of HP have been reported in males [57], and in extra-anogenital locations, particularly in the head and neck. [58] The tumours are solitary, and usually small and asymptomatic. Occasionally, the tumours can be large and elevated, forming reddish-brown mass with ulcerated and bleeding surface. [59] Human papilloma virus may have a potential role in the pathogenesis of HP [60], an observation that needs to be confirmed by further study. Histologically (fig. 9), HP is a well-circumscribed solid or cystic dermal nodular lesion, not connected to the epidermis. It is formed of frond-like papillae or tubulopapillary structures that are lined by two-cell layer: luminal cuboidal or low columnar epithelial cells with apical secretions, resting on an outer myoepithelial cell layer. The epithelial cells typically have histochemical characteristics in keeping with an apocrine origin. HP lacks cytonuclear atypia, mitotic activity, or tumour necrosis. Morphological features analogous to benign breast diseases can be frequently encountered, and include oxyphilic (apocrine) metaplasia, sclerosing adenosis-like changes, atypical apocrine adenosis-like changes, ductal epithelial hyperplasia, clear cell change of the myoepithelium, foamy histiocyte reaction, and stromal fibrosis. [60] Rare malignant transformation in HP (apocrine adenocarcinoma) is characterised by cytological pleomorphism, mitoses, and necrosis with or

without epidermal pagetoid spread of the malignant cells. [61] Immunohistochemically, the tumour cells often express CEA [62], GCDFP-15 [63], lysosome, and CD-15 (Leu M1) [64] Furthermore, ER, PR, and AR are commonly expressed in HP [65]. This and the presence of histomorphological features analogous to benign breast diseases, lends further evidence to a possible origin of HP from MLG.

TUBLOPAPILLARY HIDRADENOMA WITH ECCRINE/APOCRINE DIFFERENTIATION (INCLUDING PAPILLARY ECCRINE ADENOMA, TUBULAR APOCRINE ADENOMA, AND PAPILLARY APOCRINE FIBROADENOMA)

Papillary eccrine adenoma (PEA) and tubular apocrine adenoma (TAA) occur most commonly on the scalp, but rare variants of TAA have been also described in the vulva [66] as well as in the perianal skin. [67] In the anogenital skin, apocrine adenoma is believed to arise from MLG. [11,68] As TAA may be histologically indistinguishable from PEA (fig.10), the term 'tubulopapillary hidradenoma' was recently introduced to describe benign sweat gland tumours characterised by combining ductal as well as apocrine and eccrine glandular differentiation, incorporating features of TAA and/or PEA, with a predominance of eccrine or apocrine differentiation. [45,69] This incorporates entities previously designated as PEA, TAA, and other related lesions. Clinically, these lesions appear as well-circumscribed superficially located solitary dermal/subcutaneous nodules. Microscopically, the tumour is composed of dilated tubular/ductular structures of varying size, lined by a double layer of epithelial cells and a peripheral myoepithelial cell layer. Delicate intraluminal papillary projections are commonly seen. Immunohistochemical evidence of both eccrine and apocrine differentiation may be found [45], raising the possibility that such lesions have dual origin or arise from apoeccrine glands [70] or MLG (in lesions of the anogenital area). [45,69] The lumina are usually filled by eosinophilic amorphous material. In lesions of tubulopapillary hidradenoma with apocrine differentiation, irregularly shaped tubular structures lined by two layers of epithelial cells, with decapitation secretion evident in the lumina are evident in many areas. [69] Immunohistochemically, the tumour is reactive to S-100 protein, CEA, and EMA. [71] The coexistence of SCAP with TAA [72] and with PEA [51] has been reported, suggesting that TAA, PEA, and SCAP may represent a spectrum of inter-related tumours. Hidradenoma papilliferum is distinguished from these tumours by its more closely arranged tumour cells and glands [13], and by its almost consistent presence in the female anogenital area.

MICROCYSTIC ADNEXAL CARCINOMA

Microcystic adnexal carcinomas (MAC) (sclerosing sweat duct carcinomas) are uncommon malignant neoplasms. They are widely believed to be of eccrine origin. However, the issue is complicated by the presence of keratinous cysts and the description of apocrine and sebaceous differentiation in many cases. [73] This may suggest that the tumour has a mixed adnexal lineage with eccrine, apocrine, and pilosebaceous features. Microcystic adnexal carcinoma occurs as a solitary lesion in middle-aged adults, commonly in the face with predilection to the upper and lower lip. [32] Risk factors include previous radiation therapy and immunosuppression. [74] Histologically (fig. 11), microcystic adnexal carcinoma consists of poorly circumscribed proliferation of deceptively bland epithelial neoplastic cells infiltrating the dermis and subcutaneous tissue, and exhibits prominent perineural and intraneural invasion. The neoplastic cells are small, uniform and basaloid, or less commonly clear, and have no or minimal cytological atypia and mitotic activity. Keratin-filled microcysts are often present in superficial dermis. Tubular and ductal structures lined by a single layer of neoplastic cells dominate the deeper parts of the lesion. Small, solid clusters and single tumour cells often infiltrate the subcutaneous and skeletal muscle tissues, as well as into perichondrium and periosteum. The tumour stroma is characteristically sclerotic. The ductal elements are usually positive for EMA and CEA. Recently, CD5 was found to stain the epithelial component in most cases. [75] MAC is locally aggressive with propensity to invade nerves and cause local tissue destruction, and it has a high recurrence rate. Occasionally, nodal and distant metastases also occur. [76] The differential diagnosis of microcystic adnexal carcinoma includes syringoma, desmoplastic trichoepithelioma, sclerosing/ morpheic basal cell carcinoma, and papillary eccrine adenoma (Table 5). [22,77] In all cases, the

base of the lesion must be observed to rule out this tumour. If a syringoma-like lesion infiltrates deeply into underlying tissues with/without perineural involvement, it is highly suspicious for MAC.

Table 5. Histological features of microcystic adnexal carcinoma and its differential diagnoses

Microcystic adnexal carcinoma	The epidermis is usually not involved Poorly circumscribed Deep invasion into deep dermis and underlying tissues Depth greater than width Keratinous microcysts in superficial part Deeper areas with glandular and ductal differentiation Sclerotic stroma Cells are not pleomorphic Mitoses are rare to absent Perineural/ intraneural involvement CEA and EMA highlight ductal structures
Syringoma	Well circumscribed strands of basaloid cells Confined to upper to mid dermis Well differentiated ductal/glandular structures "tadpole" or "comma" shape Small horn cysts Width greater than depth Desmoplastic stroma No perineural involvement
Desmoplastic trichoepithelioma	Superficial Numerous small keratin cysts Foreign body reaction Calcification Lacks eccrine duct formation No perineural involvement
Sclerosing/ morpheic basal cell carcinoma	Infiltrative basaloid cells Prominent sclerotic stroma
Papillary eccrine adenoma	Fairly well circumscribed Epithelial islands Glandular differentiation Luminal micropapillary projections Tumour stroma is fibrotic and frequently hyalinized

PRIMARY CUTANEOUS MUCINOUS CARCINOMA

Primary cutaneous mucinous carcinoma (PCMC) is a rare low-grade malignancy tumour that affects older adults, and occurs most frequently in the head and neck, and axillary regions, with a predilection to the eyelids. Histologically, the tumour has a morphologic spectrum comparable to its mammary counterpart [22,78], and usually appears as well demarcated, lobular dermal lesion, with frequent extension into the subcutaneous tissue and no connection with the overlying epidermis. It consists of PAS-positive, diastase resistant multilocular pools of mucin, in which nests of bland, monotonous, polygonal epithelial cells are embedded (fig. 12). The tumour cells posses round, hyperchromatic nuclei, inconspicuous nucleoli, moderate amount of pale eosinophilic to clear cytoplasm, and well-defined cell membrane. Secretory snouts may be present. Mitotic figures are rare. Solid sheets of tumour cells, and single neoplastic cells

arranged in an Indian-file pattern can be seen. [79] Immunohistochemically, the tumour cells are often immunoreactant to EMA, LMWK, and CEA [19], as well as GCDFP-15, CK7, ER and PR. [80] PCMC should be differentiated from metastasising mucinous carcinoma originating in extracutaneous organs, therefore, an extensive clinical workup to exclude metastasis from breast or visceral mucinous carcinoma is essential. Histologically, in situ component in the form of epithelial islands bounded by a myoepithelial layer, and highlighted by CK5/6, p53, calponin, and smooth muscle actin is frequently present in PCMC in comparison to metastatic mucinous carcinoma. [78] In comparison, breast mucinous carcinoma metastatic to the skin mostly presents with lesions on chest wall, breast, and axillae, and these locations can serve as clue to the breast origin. In addition these metastatic lesions lack an 'in situ' component histologically. PCMC is typically an indolent tumour with tendency for local recurrence; however distant metastasis is rare. [22]

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma (ACC) is a very rare malignant tumour, affecting older adults with female predominance. It can occur in different anatomic sites, most commonly in the scalp. [81] The tumour has a 50% local recurrence rate [81], but metastasis to regional lymph nodes and distant organs is exceedingly rare. [82] Histologically, ACC is indistinguishable from its salivary gland counterpart, usually presenting as a dermal tumour that consists of bland, monomorphous basaloid cells with round or angulated hyperchromatic nuclei, indistinct nucleoli, and inconspicuous cytoplasm, arranged in cribriform, solid or trabecular growth patterns (fig. 13). A basement membrane-like PAS-positive, diastase- resistant eosinophilic material is often present within the microcystic spaces. The tumour cells are immunoreactant to LMWK and pankeratin (AE1/AE3). EMA and CEA are frequently expressed in the luminal cells. [83] Inconstant expression of actin was described, possibly an indication of the presence of a myoepithelial cell population. [81] Before diagnosing primary cutaneous ACC, it is essential to clinically rule out the presence of salivary gland ACC, and exclude other cutaneous basaloid tumours, especially adenoid BCC. The lack of epidermal connection and absence of peripheral palisading of neoplastic cells, and the presence of PAS-positive material and perineural space invasion favour the diagnosis of adenoid cystic carcinoma over adenoid BCC. [19] In addition, CEA and CD117 (c-kit protein) are seen in adenoid cystic carcinoma but not in BCC. [84] Adenoid cystic carcinoma may have squamous metaplasia, in which case it must also be distinguished from squamous cell carcinoma with adenoid (pseudoglandular) features. The positivity for CEA and S-100 protein, and negativity for p63 favour the diagnosis of ACC.

DIGITAL PAPILLARY ADENOCARCINOMA (AGGRESSIVE DIGITAL PAPILLARY TUMOUR, AGGRESSIVE DIGITAL PAPILLARY ADENOMA/CARCINOMA, AGGRESSIVE DIGITAL PAPILLARY ADENOMA)

These are rare sweat gland neoplasms, largely accepted to be of eccrine origin, that occur in middle-aged adults (with male predominance) and have a mostly digital location (most frequently on fingers, but also on toes, palms, and soles). [85] They typically have clinically aggressive growth behaviour. Histologically (fig. 14), the tumour shows intradermal multinodular solid and cystic growth pattern, composed of cuboidal/low columnar epithelial cells, with back-to-back/cribriform glands. Multiple cystic spaces, containing eosinophilic material, with luminal papillary projections are characteristically present. Not uncommonly, there may be cytonuclear atypia, increased mitotic activity, or tumour necrosis. Rarely, decapitation secretion (traditionally attributed to apocrine glands) may be seen in parts of the lesion. Areas of squamous, clear cell, or spindle cell change are less frequently observed. There is no connection to the overlying epidermis. The tumour expresses CEA within the luminal cells and S-100 protein within other tumour cells. The presence of poor glandular differentiation, necrosis, cytological atypia, increased mitotic rate, and invasion of soft tissue, bone, and blood vessels was deemed important in labelling these tumours as adenocarcinomas. However, the distinction between adenoma and carcinoma on histological grounds alone does not seem to predict the clinical progression of these tumours [86], which often have a high rate of local recurrence and potential for metastasis. [87] Therefore, all these tumours are best considered malignant, and they should be completely excised with or without amputation of the affected digit, as they may recur in 50% of cases, with 14% risk for metastasis. Sentinel lymph node biopsy has also been suggested in the staging of these tumours. [88] All patients should be followed up for potential local recurrence/metastatic

disease, even after apparent complete excision, in which case the risk of local recurrence is estimated at 5%.

The differential diagnosis of this tumour includes spiradenocarcinoma, which should have at least foci of two-cell population, and hidradenocarcinoma, which is usually less circumscribed and lacks the papillary pattern and back-to-back glandular differentiation. [86] Papillary eccrine adenoma is well circumscribed and lacks the back-to-back glandular differentiation and the cystic component of digital papillary adenocarcinoma. This tumour may also resemble breast carcinoma; however, it is unusual for an invasive papillary breast carcinoma to metastasize.

APOCRINE CARCINOMA

Apocrine carcinoma is a rare and highly aggressive cutaneous adenocarcinoma, more commonly seen in middle-aged women, and mostly occurs in areas rich in apocrine glands, especially the axilla. [89,90] Other possible sites include eyelid (in Moll's glands), ear, and scalp. [91] These tumours have also been described in NSJ. [92] Histologically (fig. 15), the tumour shows an asymmetric poorly demarcated malignant tumour, composed of conspicuous tubular and ductal structures. Papillary projections within the lumina may be present. The tumour has infiltrative margins, occupies the dermis and may extend to the subcutis. Cytonuclear pleomorphism, increased mitotic activity and areas of tumour necrosis are also noted. Decapitation secretion, as a sign of apocrine differentiation, is often present. PAS positive diastase-resistant material is identified in the cells or lumen. The tumour cells are positive for LMWK, and the luminal cells are reactive for CEA, EMA and GCDFP-15. S-100 protein is also occasionally positive. [91]Although positivity to AR and GCDFP-15 are considered helpful, it is more relevant from a practical point of view that these tumours are negative for ER and PR. The use of calponin and SMA as markers for the peripheral myoepithelial is helpful in delineating invasion. [1]

Of interest, is the possible association between apocrine carcinoma and benign apocrine lesions (apocrine hyperplasia and apocrine adenoma), which is reported in the axillary region in 5 elderly male Japanese patients [90], and a single case in the perianal region reported from this institution. [93]. Another case we encountered, in a perianal skin tag, the lesion was present within an apocrine tubulopapillary hidradenoma and showed features reminiscent of breast lesions, specifically ductal carcinoma in situ, with no break up of the peripheral myoepithelial layer, possibly arising in MLG. [94] Helpful features in distinguishing tubular apocrine carcinoma from metastatic visceral carcinoma are the presence of decapitation secretion and attachment of the lesion to neighbouring follicular epithelium or the presence of benign apocrine component within the lesion.

EXTRAMAMMARY PAGET'S DISEASE

Extramammary Paget's disease (EMPD) is an uncommon cutaneous malignant neoplasm that arises in areas rich in apocrine glands, most commonly in vulvar and perianal region of middle-aged females. It has also been described in the axillae, eyelids, external auditory canal, penis, and scrotum. Apocrine gland origin or apocrine differentiation of cells in EMPD has been generally accepted. However, some authors believe that EMPD arises from intraepidermal stem cell of sweat ducts. [23] An alternative origin from Toker cells, with possible association to MLG, has been also suggested. [14] Lesions usually present with erythematous eczematoid plaques and erosive ulceration. Histologically, there is proliferation in a Pagetoid pattern within the epidermis of single and small clusters of large malignant cells (fig. 16), which have less defined intercellular bridges and exhibit glandular differentiation [22], occasionally showing intracytoplasmic luminal and ductal formation. The tumour cells contain alcian blue, mucicarmine and PAS-positive mucin in the majority of cases. AE1/AE3, LMWK, and CK7 are typically positive [95], with variable positivity seen for EMA and CEA. GCDFP-15, AR and Her2/neu are also commonly expressed in EMPD, whereas ER and PR are not. [96,97]

In contrast to mammary Paget's disease, EMPD is most commonly a primary intraepidermal lesion, with only 20% of cases demonstrating a dermal invasive element. [12] When the invasive component is less than

1.0 mm in depth, this is considered minimally invasive disease, and complete excision is usually curative. [98] EMPD may also be associated with an underlying cutaneous adnexal carcinoma, usually an apocrine adenocarcinoma. [23] In up to 30% of cases, it represents metastatic spread from a regional visceral malignancy, such as cervical [99] rectal [100], prostate [101] or transitional cell carcinoma [102], in which case the tumour cells are positive to CK7 and possibly GCDFP-15 [98], but they also demonstrate immunohistochemical profile similar to the original carcinoma, including positivity to CK20 or CA19.9 in genitourinary or gastrointestinal carcinomas [23], or prostate-specific antigen (PSA) in prostate cancer. [101] An underlying regional visceral malignancy or cutaneous adnexal carcinoma is more commonly seen in perianal EMPD compared to the vulvar variant. Primary intraepidermal EMPD typically has a CK7+/ GCDFP15+/CK20-/PSA- immunohistochemical profile.

Anaplastic cases of Paget's disease have also been described, in which there is full-thickness epidermal atypia, loss of nuclear polarity, marked cytologic anaplasia and inconspicuous glandular differentiation. [22,103] It is distinguished from Bowen's disease by sparing the basal cell layer and the presence of mucin-containing cells. Furthermore, the lesion in Bowen's disease is positive for HMWK but not CK7. In contrast, EMPD expresses positivity to CEA, CK7, GCDFP-15, AR and CD5. [22] In addition to Bowen's disease and metastatic visceral malignancy, the differential diagnosis of EMPD also includes other lesions that exhibit Pagetoid spread. In melanoma, the tumour cells usually have melanin granules in their cytoplasm, and they are positive for melan-A and HMB45 immunostains.

OTHER SWEAT GLAND CARCINOMA

Apart from the well-defined entities aforementioned, there are many malignant adnexal tumours that have prominent eccrine component /differentiation. These tumours have no characteristic clinical picture, and they are usually very difficult to differentiate from metastatic carcinomas, as they usually lack an epidermal connection and they simulate carcinomas from other parts of the body, including thyroid, breast, salivary glands, and renal cell carcinomas. This group includes eccrine ductal carcinoma, basaloid eccrine carcinoma, clear cell eccrine carcinoma, and other non-specified sweat gland carcinomas.

Eccrine ductal carcinoma (fig. 17A) resembles breast ductal carcinomas, with different growth patterns possibly seen in isolation or in combination, including solid, papillary, tubular and cribriform. In most occasions, only a clinical history may help differentiate these tumours from their mammary counterparts. In eccrine carcinomas with basaloid morphology, the tumour cells are small, with scanty cytoplasm, and prominent nuclei. Apoptotic cells, geographic necrosis, and desmoplastic stroma are usually seen. The differential diagnosis of basaloid eccrine carcinoma is wide, and includes Merkel cell carcinoma, Ewing's sarcoma, metastatic carcinoma, as well as small cell melanoma and squamous cell carcinoma. Immunohistochemically, the eccrine carcinomas are positive for AE1/AE3 and CEA and occasionally for S-100 protein. Typically, chromogranin, melan-A, HMB45, and CD45 are negative. [16] On occasions, eccrine carcinomas may exhibit squamous differentiation, and in some of them CK14 is positive, suggesting that such cases originate from the acrosyringium (acrosyringeal eccrine carcinoma) (fig. 17B). Prominent clear cell change may be seen in benign as well as malignant sweat gland tumours, including poroma/porocarcinoma, hidradenoma/hidradenocarcinoma, syringoma, spiradenoma, microcystic adnexal carcinoma, and other eccrine carcinomas (fig. 17C). Furthermore, clear cell change may also be present in metastatic carcinomas, including thyroid, lung, urogenital and renal cell carcinomas. Differentiating these entities from each other is very important, but not always possible. Clinical history, other histomorphological features as well as immunohistochemical stains are very important in this regard. CK 5/6 is expressed by most skin adnexal carcinomas, but only in 33% of metastatic adenocarcinomas. [104] CA-125 may be helpful in identifying urogenital carcinomas, and positivity for TTF-1 may be seen in thyroid and lung carcinomas.

COMPOSITE/MIXED ADNEXAL TUMOURS

Cutaneous adnexal tumours may display a varied composition with a mixture of eccrine, apocrine, sebaceous, and pilar differentiation. [105-108] The diagnosis of these mixed lesions relies on histological evaluation, and they are usually classified according to the predominant morphological component. If no component is predominant, different terminology is used to describe these lesions, including "combined adnexal tumours of the skin" [105] “benign adnexal tumour with multi-directional differentiation” [108], “benign adnexal tumour of mixed lineage” [2,16], and “composite adnexal tumours of the skin”. [109]. Clinically, these tumours are located in the head and neck and the extremities, and rarely elsewhere in the body, as a case we diagnosed recently from the ventral aspect of the penis (fig. 18A). [109] They present as slowly enlarging solitary dermal/subcutaneous nodules. [2,108] Histologically, they are characterized by well-circumscribed, non-encapsulated nodules composed of a lobular proliferation of epithelial cells displaying a spectrum of eccrine, apocrine, sebaceous, and follicular differentiation. Another example of these lesions is illustrated in fig. 18B.

The occurrence of these different elements together in one lesion may be explained by the common embryologic origin of these structures in the primary epithelial germ of the superficial ectoderm. [1] The existence of these cases highlight the difficulties encountered in the classification of some benign skin adnexal neoplasms, where more than one cell lineage is encountered. In our opinion, the term “composite adnexal tumours of the skin” better reflects the common embryologic origin of these lesions, and the potential variable combination of eccrine, apocrine, sebaceous, and pilar differentiation.

FIGURE LEGENDS

Figure 1. (A) Poroma: multiple epidermal attachments with downgrowth into the dermis. (B) Porocarcinoma, with clear cell change. (C) Higher power of porocarcinoma demonstrating cellular atypia, tumour necrosis, infiltration and budding into adjacent desmoplastic stroma. (D) In situ component adjacent to the invasive porocarcinoma depicted in fig 1B and 1C.

Figure 2. (A) Hidradenoma - solid-cystic variant. (B) Hidradenoma - solid variant. (C) Hidradenoma: Tubular/ductal differentiation and clear cell change (clear cell hidradenoma). (D) Hidradenocarcinoma, with cellular atypia and tumour necrosis (arrow).

Figure 3. (A) Syringoma: Typical eccrine ducts with comma-shape and intraductal eosinophilic material. (B) Clear cell syringoma. (C) Syringoid eccrine carcinoma: hyperchromatic nuclei, ductular/tubular structures (arrows), infiltrating into a desmoplastic stroma are illustrated.

Figure 4. (A) Chondroid syringoma: proliferating ductulo-glandular eccrine epithelium in chondromyxoid stroma. (B) Chondroid syringoma with prominent tubular proliferation in chondroid stroma.

Figure 5. Syringofibroadenoma reticulated and irregularly anastomosing epithelial cords with areas of ductal differentiation (arrow).

Figure 6. (A) Spiradenoma: A lobulated mass composed of multiple nests of small basophilic cells, admixed with squamoid cells and clear cells, with hyalinized basement membrane. (B) Spiradenoma, high power: focal ductal differentiation is evident (arrow). (C) Spiradenocarcinoma, with cellular atypia and increased mitotic activity. The lesion is seen adjacent to benign spiradenoma.

Figure 7. Cylindroma: Jigsaw puzzle appearance and eosinophilic peripheral basement membrane.

Figure 8. (A) Syringocystadenoma papilliferum: Papillary epithelial projections with opening into the surface. (B) Decapitation secretion and prominent plasma cell stromal component in syringocystadenoma papilliferum. (C) Syringocystadenocarcinoma papilliferum. (D) Syringocystadenocarcinoma papilliferum: Cellular atypia, tumour necrosis and mitoses.

Figure 9. Hidradenoma papilliferum: A cystic and papillary dermal neoplasm demonstrating decapitation secretion characteristic of apocrine differentiation.

Figure10. (A) Tubulopapillary hidradenoma. (B) Tubulopapillary hidradenoma with eccrine differentiation (papillary eccrine adenoma). (C) Tubulopapillary hidradenoma with apocrine differentiation (tubular apocrine adenoma).

Figure 11. Microcystic adnexal carcinoma: Deceptively benign-looking epithelial proliferation reaching the subcutis.

Figure 12. Primary cutaneous mucinous carcinoma in pools of mucinous stroma.

Figure 13. Adenoid cystic carcinoma, with perineural invasion (inset).

Figure 14. Digital papillary adenocarcinoma. Tumour necrosis is more evident in inset.

Figure 15. Apocrine carcinoma, with infiltrative growth and tumour necrosis (left side), and cellular atypia, prominent nucleoli and mitotic activity (right side).

Figure 16. Extramammary Paget's disease: Single units and small clusters of atypical cells scattered throughout epidermal layers.

Figure 17. (A) Eccrine ductal carcinoma. (B) Eccrine ductal carcinoma with cellular atypia, brisk mitotic activity, and squamous differentiation, probably arising from the syringeum (acrosyringeal carcinoma). (C) Eccrine carcinoma with clear cell change.

Figure 18. (A) Composite adnexal tumour on penis, combining features of syringocystadenoma, trichilemmoma, and benign eccrine ductal proliferation. (B) Composite adnexal tumour showing a mixed follicular cyst with infundibular and papillary apocrine components (insets).

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