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REVIEW

Molecular pathology of skin adnexal tumours

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Aims: Tumours of the cutaneous adnexa arise from, or differentiate towards, structures in normal skin such as hair follicles, sweat ducts/glands, sebaceous glands or a combination of these elements. This class of neoplasms includes benign tumours and highly aggressive carcinomas. Adnexal tumours often present as solitary sporadic lesions, but can herald the presence of an inherited tumour syndrome such as Muir–Torre syndrome, Cowden syndrome or CYLD cutaneous syndrome. In contrast to squamous cell carcinoma and basal cell carcinoma, molecular changes in adnexal neoplasia have been poorly characterised and there are few published reviews on the current state of knowledge.

Methods and results: We reviewed findings in peer-reviewed literature on molecular investigations of cutaneous adnexal tumours published to June 2021.

Conclusions: Recent discoveries have revealed diverse oncogenic drivers and tumour suppressor alterations in this class of tumours, implicating pathways including Ras/MAPK, PI3K, YAP/TAZ, beta-catenin and nuclear factor kappa B (NF-κB). These observations have identified novel markers, such as NUT for poroma and porocarcinoma and PLAG1 for mixed tumours. Here, we provide a comprehensive overview and update of the molecular findings associated with adnexal tumours of the skin.

Keywords: cutaneous adnexal, hair follicle, molecular pathology, mutation, sebaceous, sweat gland, tumor syndrome

Introduction

Tumours of the cutaneous adnexa are lesions that arise from, or differentiate towards, structures in normal skin such as regions of hair follicles, sweat ducts/glands, sebaceous glands, or a combination of these elements.[1–3] This class of neoplasms includes benign tumours and highly aggressive carcinomas. Adnexal tumours often present as solitary sporadic lesions, but in some cases can herald the presence of an inherited tumour syndrome.[1–4] In contrast to cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), molecular changes in adnexal neoplasia have been poorly characterised. However, recent discoveries have revealed diverse oncogenic drivers and tumour suppressor alterations in this class of tumours.[3] Here, we provide a comprehensive overview and update of the molecular genetics and genomics associated with adnexal tumours of the skin.

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Tumours with sebaceous differentiation

GENERAL FEATURES

Sebaceous neoplasia exists on a spectrum from benign (sebaceous adenoma, sebaceoma) to malignant [sebaceous carcinoma (SC)]. These lesions present as a painless nodule with a predilection for the periocular region. SC has potential for recurrence and metastasis.[2,4,5]

HISTOPATHOLOGY

Sebaceous differentiation is characterised by multiple clear cytoplasmic vacuoles lending a microvesicular appearance and scalloping of the nucleus. Sebaceous adenoma is well-circumscribed, with abnormal architecture but retained polarisation (central sebocytes surrounded by unusually prominent peripheral basaloid germinative cells) (Figure 1A). Sebaceoma is circumscribed, with loss of polarisation (mingling of sebocytes and basaloid cells) and >50% basaloid cells (Figure 1B). In SC, malignant findings can include atypia, infiltrative growth and pagetoid scatter within the overlying epidermis; sebaceous differentiation may be extensive or focal and subtle (Figure 1C).[1,2,5]

MOLECULAR FEATURES

Sebaceous tumours can be sporadic or syndromic. Muir–Torre Syndrome (MTS) is a subtype of Lynch syndrome/hereditary non-polyposis colon cancer associated with germline mutation of MMR genes including *MLH1*, *MSH2* and *MSH6*, manifested by sebaceous tumours and internal carcinomas (Tables 1 and 2).[5] Immunohistochemistry is highly sensitive for detecting loss of MMR protein expression related to MTS (Figure 1D), although this approach can display limited specificity for distinguishing sporadic from syndromic tumours (as low as 48%) when risk factors for MTS are not considered in case selection.[6] MUTYH-associated polyposis syndrome, associated with germline mutation of the DNA damage repair gene *MUTYH* (previously known as *MYH*), can also be associated with sebaceous neoplasms.[5,7]

Sporadic cutaneous (extraocular) SC can be divided into three molecular categories: MMR-deficient, ultraviolet (UV)-damaged and pauci-mutational (Table 2).[8] Highly recurrent mutations vary by subtype. *TP53* mutations are a frequent finding in MMR and UV-damaged tumours.[8,9] Of note, ocular SC has similarities to extraocular SC but also displays distinct drivers in some tumours, including human papillomavirus (HPV) or loss of *ZNF750*.[5,10,11]

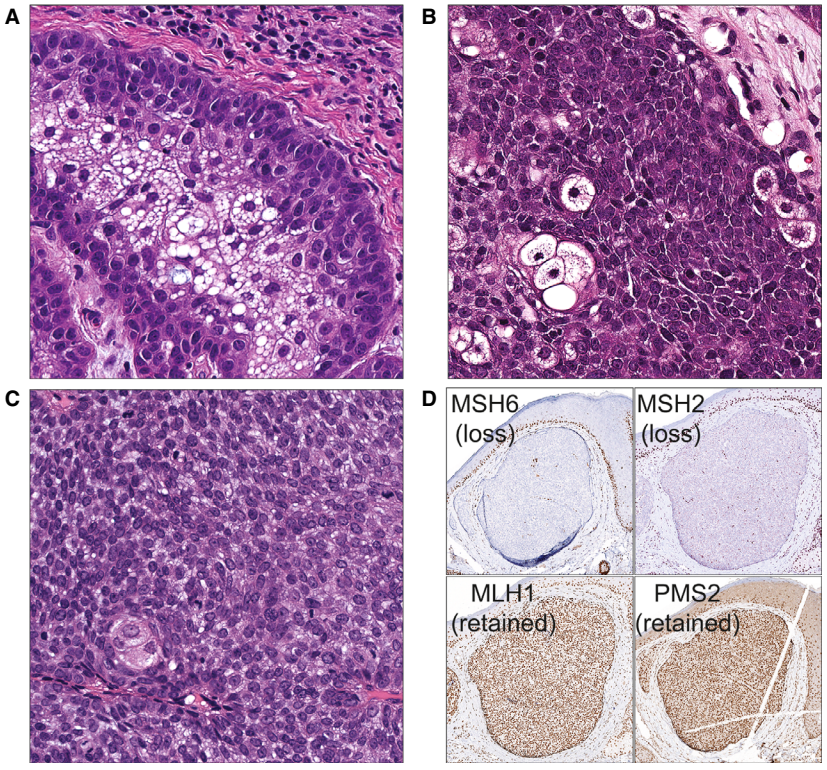

Figure 1. Sebaceous tumours. **A,** Sebaceous adenoma, displaying normal polarisation with prominent basaloid germinative layer. **B,** Sebaceoma, with predominance of basaloid cells. **C,** Sebaceous carcinoma, with mitotically active atypical cells and subtle sebaceous differentiation. **D,** Example of mismatch repair gene immunohistochemistry, demonstrating the most common pattern (loss of MSH2 and MSH6). **A–C,** Haematoxylin and eosin. **D,** Immunohistochemistry with diaminobenzidine (DAB) brown chromogen detection.

Table 1. Syndromic associations with cutaneous adnexal tumors

Syndrome	Gene function	Cutaneous tumors	Extracutaneous neoplasms	Other findings	Estimated prevalence
Bazex–Dupré–Christol (*ACTRT1*)	Ciliary function	BCC, less frequently trichoepitheliomas	N/A	Follicular atrophoderma, hypotrichosis, hypohidrosis, milia, facial hyperpigmentation, hair shaft anomalies	<1/1 000 000
Birt-Hogg-Dube (*FLCN*)	Inhibition of mTOR pathway	Fibrofolliculoma/ trichodiscoma, acrochordon	Pulmonary cysts, renal tumors (most commonly oncocytoma or renal cell carcinoma)	Spontaneous pneumothorax	Unknown
CYLD cutaneous syndrome/Brooke-Spiegler (*CYLD*)	Deubiquitinase (NF-κB inhibition)	Trichoepithelioma, spiradenoma, cylindroma, spiradenocylindroma with rare malignant transformation	Membranous basal cell adenoma (salivary gland)	N/A	<1/100 000
Clouston (*GJB6, GJB2*)	Connexins	Syringofibroadenoma	N/A	Palmoplantar keratoderma, hypotrichosis, nail dystrophy	Unknown
Cowden (PTEN)	Inhibition of PI3K signaling	Trichilemmoma, multiple hamartomatous lesions	High risk for breast, thyroid, and endometrial carcinoma	Acral keratoses, oral papillomas	1/200 000
Familial Pilomatricoma (*PLCD1*)	Phospholipase C (Protein kinase C, MAPK)	Multiple pilomatricomas	N/A	N/A	Unknown
FAP (*APC*)	Inhibition of Wnt/ β-catenin signaling	Multiple pilomatricomas, epidermoid cysts, cutaneous fibromas, lipoomas	Osteomas, colorectal adenomas, desmoid tumors, adrenal adenomas, nasopharyngeal angiofibroma Increased risk for colon, thyroid, hepatobiliary, and CNS malignancies	N/A	(~1/8000)
Generalized basaloid follicular hamartoma syndrome (*PTCH1*)	Hedgehog signaling (less prominent activation than NBCCS)	Basaloid follicular hamartomas; less frequently acrochordons, steatocystomas	N/A	Palmoplantar pitting, hypohidrosis, hypotrichosis, alopecia	
Happle-Tinschert Syndrome (unknown)	Unknown	Unilateral segmental basaloid follicular hamartoma	N/A	Cerebral, osseous, dental abnormalities	Unknown

Table 1. (*Continued*)

Syndrome	Gene function	Cutaneous tumors	Extracutaneous neoplasms	Other findings	Estimated prevalence
Muir-Torre (MMR genes: *MLH1, MSH2,* and *MSH6*)	DNA mismatch repair	Sebaceous adenoma, sebaceoma, sebaceous carcinoma, keratoacanthoma	Colonic adenocarcinoma (most common), genitourinary, breast, and hematologic malignancies	N/A	1/300
Malta syndrome/ Nicolau-Balus (*MYH9*, possible)	Myosin heavy chain	Syringoma, microcystic adnexal carcinoma-like lesions	N/A	Atrophoderma vermiculata, milia	Unknown
NBCCS (*PTCH1*)	Inhibition of Hedgehog signaling	Numerous BCCs; basaloid follicular hamartomas (infrequent)	Odontogenic keratocysts, CNS tumors, ovarian cysts	Palmoplantar pits, skeletal anomalies, coarse facial features, hypertelorism, macrocephaly	~1/31000
Schimmelpenning–Feuerstein–Mims (postzygotic *HRAS/KRAS*)	RAS-MAPK signaling	Nevus sebaceus	CNS, ocular, and skeletal anomalies	N/A	Unknown
Schöpf-Schulz-P assarge (*WNT10A*)	Wnt/β-catenin signaling	Syringofibroadenoma, eyelid apocrine hidrocystoma	N/A	Palmoplantar keratoderma, telangiectasia, dental anomalies, onychodystrophy, hypotrichosis	<1/1 000 000
Steatocystoma multiplex (*KRT17*)	Keratin	Steatocystomas, eruptive vellus hair cysts	N/A	Pachyonychia congenita	Unknown

BCC, basal cell carcinoma; FAP, familial adenomatous polyposis; MMR, mismatch repair; NBCCS, nevoid basal cell carcinoma syndrome.

Sporadic sebaceous adenomas and sebaceomas are less well characterised, but show similar aberrations to SC, including mutations of MMR genes, *HRAS/KRAS* and/or *TP53* (Table 2).[9,12]

Tumours with follicular differentiation

FIBROFOLLICULOMA/TRICHODISCOMA

General features

Fibrofolliculoma/trichodiscoma displays hair follicle and stromal differentiation. The tumour classically presents on the nose and can be associated with Birt–Hogg–Dube syndrome.[1,4]

Histopathology

Tumours are characterised by a stromal nodule with collagenous, mucinous and fibroblastic elements. In fibrofolliculoma this is accompanied by a central distorted follicular infundibulum. Trichodiscoma consists predominantly of loose edematous stroma, often with an epidermal collarette or distorted sebaceous units at the periphery.[1]

Molecular features

Fibrofolliculoma/trichodiscoma can be sporadic, or associated with Birt–Hogg–Dube syndrome linked to germline mutation in the folliculin (*FLCN)* gene that regulates the mammalian target of rapamycin complex 1 (mTORC1) signalling cascade (Tables 1 and 3).[1]

The spindle cell-predominant variant of trichodiscoma (SCPT) lacks association with Birt–Hogg–Dube syndrome, and can bear close resemblance to spindle cell lipoma.[13] Evaluation for *RB1* deletion (present in spindle cell lipoma, absent in SCPT) is helpful in this distinction.[14]

Table 2. Molecular findings in cutaneous sebaceous tumors

Tumor	Molecular Findings	Diagnostic Correlations
Sebaceous carcinoma	Sporadic—3 subtypes: 1) MMR (mismatch repair genes, *HRAS/KRAS, TP53, RB1, RREB1, NOTCH1/2, FAT3, KMT2D)* 2) UV (*TP53, RREB1, NOTCH1/2, FAT3, KMT2D*) 3) Paucimutational (*HRAS, NOTCH1*) Syndromes-2: Mismatch repair genes (*MSH2* > *MLH1, MSH6*): Muir-Torre Syndrome *MUTYH*: MUTYH-Associated Polyposis	UV signature correlates with poor differentiation, infiltrative growth, squamous differentiation MMR immunohistochemistry may show expression loss in syndromic or sporadic MMR-deficient tumors
Sebaceous adenoma, sebaceoma	Sporadic (subtypes not established) *MSH2, HRAS/KRAS, TP53, CDKN2A, EGFR, CTNNB1* Syndromes—2: Mismatch repair genes (*MSH2* > *MLH1, MSH6*): Muir-Torre Syndrome *MUTYH*: MUTYH-Associated Polyposis	MMR immunohistochemistry may show expression loss in syndromic or sporadic MMR-deficient tumors

Table 3. Molecular findings in cutaneous tumors with hair follicle differentiation

Tumor	Molecular Findings	Diagnostic Correlations
Basaloid follicular hamartoma	Sporadic: unknown Syndrome: *PTCH1* (NBCCS, GBFHS)	
Fibrofolliculoma/trichodiscoma	Sporadic: unknown Syndrome: *FLCN* (Birt-Hogg-Dube Syndrome)	No *RB1* deletion (unlike spindle cell lipoma)
Pilomatricoma, pilomatrical carcinoma	Sporadic: *CTNNB1* activating mutation Syndromes/Inherited: *APC* (Familial Adenomatous Polyposis/Gardner) *PLCD1* (familial pilomatricoma) *CTNNB1* somatic mutation superimposed on germline mutation in other gene (MMR syndromes, myotonic dystrophy)	IHC: Beta-catenin (nuclear and cytoplasmic), LEF1, CDX2 expression
Trichoblastoma (TB), other than trichoepithelioma	Sporadic: *HRAS* (subset)	
Trichoblastic carcinoma	Sporadic: *TP53, CDKN2A, TERT* promoter, *CTNNB1*	
Trichoepithelioma (TB subtype)	Sporadic: *PTCH1, CTNNB1* Syndromes—2: *CYLD* (CYLD Cutaneous Syndrome) *ACTRT1* (Bazex–Dupré–Christol Syndrome) *MYH9* (possible) (Rombo Syndrome)	
Trichilemmoma	Sporadic: *HRAS* Syndrome: *PTEN* (Cowden Syndrome)	PTEN protein loss is specific to syndromic tumors
Trichilemmal carcinoma	Sporadic: *TP53*, variable mutations and oncogenic fusions	.
Trichilemmal cyst	Sporadic: unknown Inherited: *PLCD1* (familial)	
Trichilemmal tumor (benign, malignant)	Sporadic: Aneuploidy, (1 malignant case) *PIK3CA* and *ALPK1* mutations	

GBFHS, generalized basaloid follicular hamartoma syndrome; NBCCS, nevoid basal cell carcinoma syndrome.

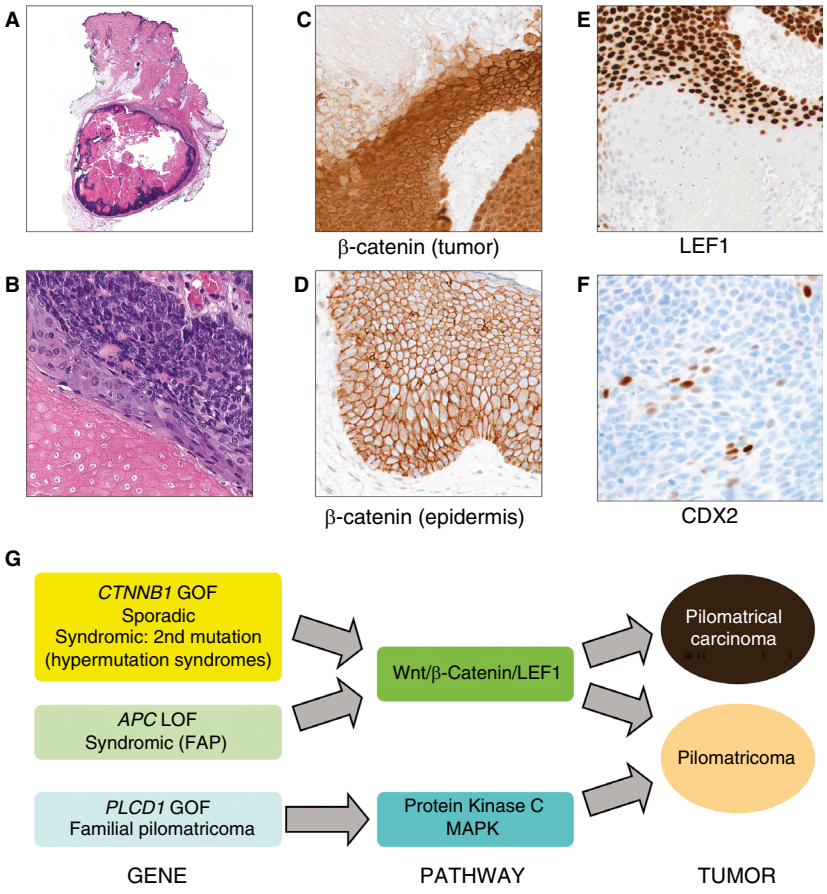

Figure 2. Pilomatricoma. **A,** Circumscribed tumour in dermis or subcutis. **B,** Cell types include ghost cells (bottom left), basophilic cells (top right) and transitional cells. **C,** Beta-catenin expression in pilomatricomas, with nuclear and cytoplasmic staining of peripheral basaloid cells. **D,** Beta-catenin staining in background epidermis, demonstrating membranous staining of keratinocytes. **E,** Lymphoid enhancer–binding factor 1 (LEF1) nuclear expression consistent with activated beta-catenin signalling in basaloid cells of pilomatricoma. **F,** CDX2 expression in pilomatricomas may be downstream of Wnt/beta-catenin signalling. **G,** Gene alterations in pilomatricomas implicate Wnt/beta-catenin and protein kinase C pathways. **A,B,** Haematoxylin and eosin; **C–F,** immunohistochemistry with diaminobenzidine (DAB) brown chromogen. FAP, familial adenomatous polyposis; GOF, gain-of-function variant/mutation; LOF, loss of function.

PILOMATRICOMA AND PILOMATRICAL CARCINOMA

General features

Pilomatricoma and pilomatrical carcinoma differentiate towards the hair matrix.[1] Tumours are typically found as large nodules on the head and neck (Figure 2A). Pilomatricoma is a relatively common tumour that usually arises on younger adults, whereas pilomatrical carcinoma is rare and tends to present after middle age. Multiple pilomatricomas may be associated with inherited tumour syndromes, as discussed below. Pilomatrical carcinoma can be associated with recurrence, metastasis and death, although the risk of aggressive disease is unclear.[1–3]

Histopathology

Pilomatricoma is a well-circumscribed dermal tumour lesion composed of peripheral basophilic cells that transition into centrally located shadow cells, accompanied by frequent calcification and rupture reaction (Figure 2A,B). The 'proliferating pilomatricoma' subtype can display cytological atypia and high mitotic rate, but lacks infiltrative growth or significant tumour necrosis. Pilomatrical carcinoma displays asymmetric, infiltrative growth, tumour necrosis and a predominance of basophilic cells.[1–3]

Molecular features

Pilomatricoma and pilomatrical carcinomas harbour *CTNNB1* mutations resulting in constitutive activation

of the Wnt/beta-catenin pathway, with associated immunophenotypical findings (Table 3, Figure 2C–G).[15–17] Subclonal trisomy 18 (including the anti-apoptotic gene *BCL2*) has also been demonstrated.[18]

Familial multiple pilomatricoma can be associated with a germline gain-of-function missense variant of *PLCD1* that stimulates the protein kinase C pathway.[19] Multiple pilomatricomas may also arise in association with germline *APC* variants.[20] In mismatch repair deficiency or myotonic dystrophy, hypermutation phenotypes lead to secondary somatic mutations of *CTNNB1* that result in formation of multiple pilomatricomas (Table 3, Figure 2G).[21,22]

Pilomatrical carcinomas usually arise *de novo*, rather than from a pre-existing pilomatricoma, and genetic events that might trigger progression of pilomatricoma to pilomatrical carcinoma have not been identified. Pilomatrical carcinosarcoma can show clonal similarity between epithelial and mesenchymal components.[23]

TRICHOBLASTOMA (INCLUDING TRICHOEPITHELIOMA) AND TRICHOBLASTIC CARCINOMA/CARCINOSARCOMA

General features

Trichoblastoma recapitulates primitive hair follicle (hair germ) and follicular mesenchyme and typically presents as a solitary nodule on the head and neck, or in association with naevus sebaceous. Malignant forms are rare, and include trichoblastic carcinoma and carcinosarcoma.[1,3,4]

Histopathology

Trichoblastoma is a circumscribed tumour in the deep dermis and/or subcutis, consisting of uniform basaloid cells arranged in retiform or racemiform patterns, accompanied by fine fibroblastic stroma (follicular mesenchyme). There is no significant tumour retraction or atypia, unlike BCC. Variant morphologies include lymphadenoma, trichoepithelioma and desmoplastic trichoepithelioma. By immunohistochemistry, cells are positive for BerEp4 with scattered CK20-positive Merkel cells in most cases.[1,3]

Trichoblastic carcinoma displays diagnostic features of trichoblastoma accompanied by epithelial atypia, including pleomorphism with hyperchromasia, mitotic figures and crowding. Carcinosarcoma demonstrates malignant atypia of both epithelial and stromal components.[1,2]

Molecular features

Activating mutations in *HRAS* have been described in a subset (11%) of trichoblastomas (Table 3).[24] No classical *PTCH1* mutations have been found in conventional trichoblastoma, unlike in BCC.[3,25]

The trichoepithelioma subtype can occur sporadically or in the setting of *CYLD* cutaneous syndrome and related entities (Brooke–Spiegler syndrome, familial cylindromatosis and multiple familial trichoepithelioma), associated with germline variants in *CYLD* on chromosome 16q12-q13 (Tables 1 and 3).[26–29] The product of *CYLD* is a deubiquitinase, the loss of which results in aberrant activation of the NF-κB signalling pathway.[30] Other syndromic associations include Rombo syndrome (possibly associated with *MYH9* germline variants) and Bazex–Dupré–Christol syndrome (*ACTRT1* germline variants).[31,32] The dominant driver of sporadic trichoepithelioma remains unknown; occasional cases display somatic mutations in *PTCH1* or *CTNNB1* (Table 3).[33,34]

Molecular findings in two cases of trichoblastic carcinosarcoma implicated inactivating tumour suppressor mutations (*TP53*, *CDKN2A*) and oncogene activation (*TERT* promoter mutation and subclonal *CTNNB1* mutation) (Table 3).[35,36]

TRICHILEMMOMA AND TRICHILEMMAL CARCINOMA

General features

Trichilemmoma differentiates towards the hair follicle outer root sheath, and presents as a solitary lesion (most commonly on the central face) or within naevus sebaceous. Multiple trichilemmomas occur in Cowden syndrome (Table 1).[1,3,4]

Trichilemmal carcinomas tend to develop as solitary nodules on sun-exposed skin. Small studies suggest a favorable prognosis, with potential for rare metastasis.[37] The existence of trichilemmal carcinoma as a distinct entity from SCC has been debated.[1]

Histopathology

Trichilemmomas are lobular tumours connected to the epidermis, composed of monomorphic clear cells and squamous cells, bordered by peripheral palisading and well-defined hyaline basement membrane material. Trichilemmal carcinoma displays cytological and architectural similarity to trichilemmoma, with additional findings including infiltrative growth, cytological atypia, prominent nucleoli and frequent mitoses.[3]

Molecular features

Multiple trichilemmomas are included in the diagnostic criteria for Cowden syndrome, which is part of the *PTEN* hamartoma tumour syndrome associated with *PTEN* loss (10q23.31) resulting in disinhibition of the PI3-kinase pathway (Table 1).[3,4] Trichilemmomas arising sporadically or within naevus sebaceous can

harbour *HRAS* mutations and lack alteration of *PTEN* (Table 3).[38,39] Thus, PTEN protein expression can distinguish sporadic from syndromic cases.[39]

NGS profiling of four trichilemmal carcinomas revealed frequent *TP53* mutation, with variable additional alterations (Table 3).[40] With the exception of *TP53* mutation, these mutations were substantially different from recurrent changes previously described for SCC.[41]

OTHER FOLLICULAR TUMOURS

Molecular findings in additional follicular tumours, including basaloid follicular hamartoma and trichilemmal cysts and tumours, are shown in Tables 1 and 3.[3,4,42–47] Of note, one case of malignant proliferating trichilemmal tumour displayed an *ALPK1* hot-spot mutation identical to those described for spiradenomas (see below).[43,48] As of this writing, the molecular genetics of many follicular tumours (such as trichofolliculoma, pilar sheath acanthoma, melanocytic matricoma and tumour of the follicular infundibulum) remain undescribed.

SWEAT GLAND TUMOURS

Eccrine sweat glands are distributed throughout the body, and consist of a deep secretory coil that secretes sweat through a long duct onto the epidermal surface. In contrast, apocrine sweat glands are confined to specific body sites (including axilla, perineum and eyelids) and are associated with hair follicles. Of note, adnexal tumours with mixed follicular and glandular differentiation have been historically designated as apocrine, even in the absence of specific apocrine morphology.[1,3]

CYLINDROMA, SPIRADENOMA, SPIRADENOCYLINDROMA AND THE MALIGNANCIES ARISING FROM THESE ENTITIES

General features

Cylindromas, spiradenomas and spiradenocylindromas are solitary when sporadic, but can be multiple when associated with CYLD cutaneous syndrome.[4] Malignant forms are typically several centimetres in size and can grow rapidly from existing benign lesions. The prognosis of malignant lesions has been correlated with histological grade, with low-grade tumours metastasising less frequently than high-grade tumours.[2,3,49]

Histopathology

Spiradenomas are characterised by well-circumscribed round dermal nodules consisting of two cell populations (small monomorphous basaloid cells and larger clear cells), prominent infiltrating lymphocytes and intratumoral basement membrane material and lumen formation (Figure 3A). Cylindromas have numerous basaloid nests interconnecting in a 'jigsaw puzzle' pattern, with basement membrane material surrounding individual nests (Figure 3B). Many lesions have hybrid features (spiradenocylindromas).[1,3]

Diagnosis of malignant counterparts (cylindrocarcinoma, spiradenocarcinoma) relies upon identification of a benign precursor (Figure 3C). Diagnostic features include cytological atypia (which may be low- or high-grade), mitotic figures and (for spiradenocarcinoma) loss of lymphocytes within the tumour (Figure 3D). Ki67 is typically elevated in malignant lesions, and Myb expression may be lost.[1–3,49]

Molecular features

Cylindromas are associated with CYLD cutaneous syndrome and related syndromes (familial cylindromatosis, Brooke–Spiegler syndrome), characterised by germline mutation of the *CYLD* gene resulting in aberrant activation of the NF-κB pathway (Table 1, Figure 3E-G).[29,30,50] Sporadic cylindromas can also harbour *CYLD* mutations (Table 4).[29,48] Alternatively, *MYB::NFIB* fusions have been reported in cylindromas (Table 4, Figure 3F),[51] although the incidence is unclear as this finding was not further demonstrated in a subsequent genomic study.[48] *c-MYB (MYB)* is a transcription factor associated with regulation of cell cycle, cell survival and differentiation.[52] Interestingly, Myb expression occurs in *CYLD*-mutant cylindromas lacking the MYB fusion,[48,53] suggesting that Myb may act downstream of NF-kB in such tumours (Figure 3G).[54] Additional mutations have been described in the epigenetic modifiers *BCOR* and *DNMT3A*, which are more traditionally associated with haematological malignancy.[48,55]

Spiradenomas and spiradenocarcinomas are also associated with loss-of-function mutations in *CYLD,* or gain-of-function mutations in *ALPK1*, resulting in NF-κB activation (Figure 3G).[48] *TP53* mutations are restricted to malignant tumours (spiradenocarcinoma/cylindrocarcinoma), supporting a role in progression from benign precursors (Table 4, Figure 3G).[48,56–58]

DIGITAL PAPILLARY ADENOCARCINOMA

General features

Digital papillary adenocarcinoma (DPA) is an adnexal neoplasm presenting as a slow-growing nodule in acral locations, with high rates of recurrence (up to 21%) and metastasis to lungs or lymph nodes (26–50% of cases).[1–3,59]

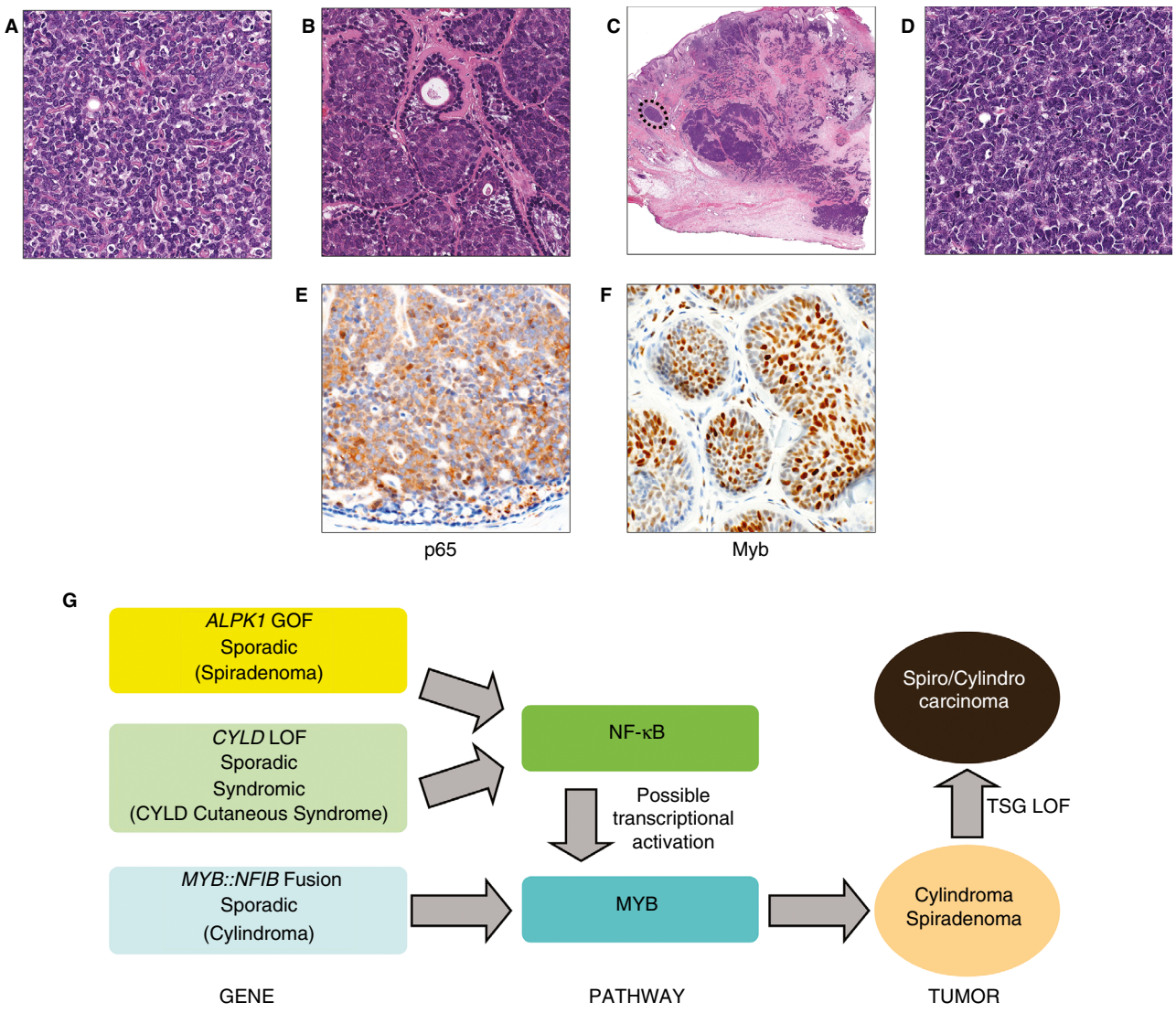

Figure 3. Spiradenoma and cylindroma. **A,** Spiradenoma displaying small monomorphous cells with duct formation and intermingled lymphocytes. **B,** Cylindroma. Interlocking 'jigsaw puzzle' formation with prominent basement membrane. **C,** Spiradenocarcinoma. Scanning magnification of large infiltrative tumour. Dashed circle denotes precursor spiradenoma. **D,** Spiradenocarcinoma, displaying poorly differentiated tumour cells. **E,** Nuclear and cytoplasmic p65 expression in spiradenoma (reproduced from Ref. [48]), correlating with nuclear factor kappa B (NF-κB) pathway activation. **F,** Myb expression in cylindroma. **G,** Molecular drivers for spiradenomas and cylindromas implicate NF-κB and Myb, with tumour suppressor loss-of-function events (TSG LOF) associated with malignant progression. **A–D,** Haematoxylin and eosin. **E,F.** Immunohistochemistry with diaminobenzidine (DAB) brown chromogen. GOF, gain-of-function variant/mutation; LOF, loss of function variant/mutation.

Histopathology

DPA is composed of multiple dermal nodules of mild-to-moderately atypical cuboidal cells lining cystic spaces with papillary invaginations. Cribriform or solid growth may also be present.[1,3]

Molecular features

Driving mutations in DPA remain poorly understood. Somatic mutations in *BRAF* V600E[60,61] and *TP53*[56,62] occur in a minority of cases (Table 4).

ENDOCRINE MUCIN-PRODUCING SWEAT GLAND CARCINOMA

General features

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is a low-grade neuroendocrine tumour,

Table 4. Molecular findings in sweat gland tumors

Tumor	Molecular Findings	Diagnostic Correlations
Cylindroma	Sporadic: *CYLD* mutation, *MYB::NFIB* fusion Syndrome: *CYLD* (CYLD Cutaneous Syndrome)	Myb expression (not specific)
Spiradenoma	Sporadic: *CYLD* mutation, *ALPK1* mutation Syndrome: *CYLD* (CYLD Cutaneous Syndrome)	Myb expression (not specific)
Carcinoma ex spiradenoma, cylindroma (spiradenocarcinoma, cylindrocarcinoma)	Sporadic or syndromic: *TP53* (secondary mutation in addition to molecular driver of precursor benign tumor)	Loss of Myb expression may correlate with malignancy
Adenoid cystic carcinoma	Sporadic: *MYB::NFIB* fusion, *MYBL1::NFIB* fusion	Myb expression (not specific)
Apocrine carcinoma	Sporadic: *ERBB2* (HER2-neu) gene amplification (1 case)	
Digital papillary adenocarcinoma	Sporadic: *BRAF* V600E (minority), *TP53* (minority)	
Endocrine mucin-producing sweat gland carcinoma	Sporadic: heterogeneous mutations affecting DNA damage response/repair (*BRD4, PPP4R2, RTEL1*) and tumor-suppressor pathway (*BRD4, TP53, TSC1, LATS2*)	MUC2 expression suggestive of conjunctival origin
Hidradenoma	Sporadic: *CRTC1::MAML2* fusion (rarely *CRTC3::MAML2*), *EWSR1::POU5F1* fusion	
Hidradenoma papilliferum	Sporadic: *PIK3CA*, other PI3K pathway mutations	
Hidradenocarcinoma	Sporadic: *CRTC1::MAML2* fusion, *ERBB2* amplification, *TP53* mutation (minority)	
Hidrocystoma	Sporadic: unknown Syndrome: *WNT10A* (Schöpf-Schulz-Passarge Syndrome)	
Mammary analog secretory carcinoma	Sporadic: *ETV6* fusions including *ETV6::NTRK3;* (rare) *NFIX::FKN1* fusion	
Microcystic adnexal carcinoma	Sporadic: *TP53, JAK1,* paucimutational	Phospho-STAT3 and/or altered p53 expression (majority)—unlike syringoma
Mucoepidermoid carcinoma	Sporadic: *CRTC1* rearrangements (non-*MAML2*)	
Papillary eccrine adenoma (tubular adenoma)	Sporadic: *BRAF* V600E, *KRAS*	
Poroma	Sporadic: *YAP1::MAML2, YAP1::NUTM1,* or (rarely) *WWTR1::NUTM1* fusions	NUT expression (minority)
Poroid hidradenoma	Sporadic: *YAP1::NUTM1* (majority)	NUT expression (majority)
Porocarcinoma	Sporadic: *YAP1::MAML2, YAP1::NUTM1* fusions; *TP53, RB1, CDKN2A, HRAS* mutation	NUT expression (majority) Aberrations of p53, Rb, and/or p16 expression
Syringocystadenoma papilliferum	Sporadic: *BRAF* V600E, *HRAS*	
Signet-ring cell/histiocytoid carcinoma	Sporadic: *PIK3CA* (2 cases), *CDH1* (1 case)	
Syringofibroadenoma	Sporadic: HPV (1 of 2 cases with SCC) Syndromes—2: *WNT10A* (Schöpf-Schulz-Passarge Syndrome) *GJB6*, *GJB2 (*Clouston syndrome)	

Table 4. (*Continued*)

Tumor	Molecular Findings	Diagnostic Correlations
Syringoma	Sporadic: unknown Syndromes/Inherited: Chr 16q22 (multiple syringomas) Trisomy 21 (Downs Syndrome) *MYH9* (possible) (Nicolau-Balus Syndrome)	
Tubular apocrine adenoma (tubular adenoma)	Sporadic: *BRAF* V600E, *KRAS*	

analogous to solid papillary carcinoma of the breast. EMPSGC presents as a slow-growing nodule that may clinically mimic a cyst. Metastasis has not been reported; however, there can be local recurrence with incomplete excision.[2,63,64]

Histopathology

Tumours are composed of nodules of low-grade neuroendocrine cells displaying varying architectures, including solid, cystic, papillary or cribriform patterning. There may be associated mucinous carcinoma. Immunohistochemically, the tumour is positive for markers including cytokeratins, horomone receptors (AR, ER and PR), neuroendocrine markers and MUC2.[1,64,65]

Molecular features

A recent next-generation sequencing study analysed three cases of EMPSGC and identified heterogeneous mutations affecting DNA damage response/repair (e.g. *BRD4*, *PPP4R2* and *RTEL1*) and tumour-suppressor pathway (e.g. *BRD4*, *TP53*, *TSC1* and *LATS2*) (Table 4).[65] A separate case–series described deletion on chromosome 6.[66] Other limited molecular studies have been negative for driver alterations.[67,68]

HIDRADENOMA AND HIDRADENOCARCINOMA

General features

Hidradenoma and hidradenocarcinoma are tumours with sweat duct secretory features. The typical presentation is as a solitary nodule.[4] Malignant transformation is rare. Metastasis has been reported for both low- and high-grade hidradenocarcinomas.[1–3]

Histopathology

Hidradenoma is a dermal tumour with solid and cystic configuration, composed of variable proportions of clear, polygonal, oncocytic, epidermoid, squamoid and mucinous cells. There is ductal formation and associated hyalinised stroma. When significant atypia, infiltration and mitoses are present, the lesion is best characterised as hidradenocarcinoma.[1,3]

Molecular features

Approximately half of hidradenomas harbour the $t_{(11;19)}$ translocation resulting in the fusion of *CRTC1* (previously known as *TORC1* or *MECT1*) and *MAML2* (Table 4).[69,70] *CRTC1::MAML2* fusions activate the cAMP response element binding protein (CREB) pathway to promote tumorigenesis. Fusions of *CRTC3::MAML2* or *EWSR1::POU5F1* have also been described.[71,72] The poroid variant of hidradenoma displays genetic features of poroma (discussed below).

Hidradenocarcinomas can also display *CRTC1*::*MAML2* fusions.[73] In addition, *AKT1* mutation, *PIK3CA* mutation and *ERBB2* [human epidermal growth factor receptor 2 (HER2)/*neu*] amplification have been described in single cases.[56,73] *TP53* mutations occur, although these are not universal (Table 4).[56,58,62,73,74]

MICROCYSTIC ADNEXAL CARCINOMA (MAC)

General features

Microcystic adnexal carcinoma (MAC) is a malignant sweat duct neoplasm usually presenting as a firm plaque. Tumours are locally aggressive with frequent recurrence after excision, but rarely metastasise. Although multiple tumours can occur, a syndromic association has not been demonstrated.[1–4]

Histopathology

MAC is an infiltrative carcinoma with superficial keratinising cysts, deeper infiltrative bilayered strands with sweat duct differentiation, minimal cytological atypia and fibrotic to hyalinised stroma.[1–3]

Molecular features

In a study of 18 tumours, approximately 39% of MACs harboured mutually exclusive alterations including either inactivation in *TP53* (22%) or

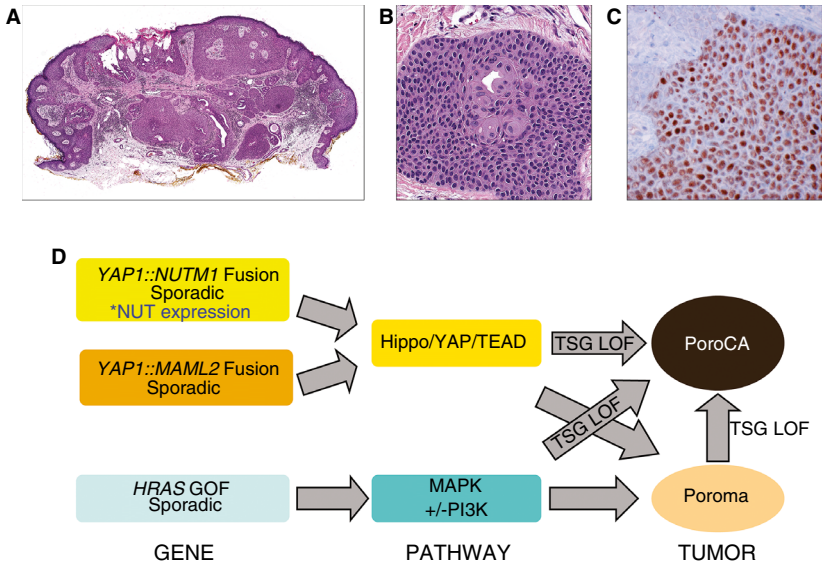

Figure 4. Poroma. **A,** Nodular tumour with glandular differentiation and broad connection to epidermis. **B,** Tumours consist of small poroid cells and larger cuticular cells, with lumen formation. **C,** When *NUTM1* is present as a fusion partner, NUT protein expression is a specific finding for poroma and related tumours. **D,** Molecular drivers of poroma implicate HIPPO/Yes-associated protein (Hippo/YAP) and mitogen-activated protein kinase (MAPK) pathways, with tumour suppressor loss-of-function (TSG LOF) potentially related to malignant progression.

insertions affecting *JAK1* (17%) associated with increased phospho-signal transducer and activator of transcription (STAT3) expression by immunohistochemistry.[75] Case reports have also described alterations of genes including *TP53*, *CDKN2A* and *CDKN2B*[74,76] and deletion of 6q (Table 4).[77] There is no known syndromic association for multiple MACs; however, benign proliferations similar to MAC have been linked to elastin abnormalities and germline *MYH9* variants.[31,78]

POROMA AND POROCARCINOMA

General features

Poromas display dermal sweat duct differentiation. Clinically, poromas are solitary papules with a sessile, pedunculated or papillomatous appearance.[4] Porocarcinomas are often ulcerated nodules, that present *de novo* or as transformation of an existing poroma. Porocarcinomas carry significant risk of local recurrence/regional metastasis (up to 20%) and distant metastasis (up to 12%).[1–3,79,80]

Histopathology

Poromas are nodular tumours with broad connection to the epidermis, composed of two cell types: poroid and cuticular cells (Figure 4A,B). Poroid cells are small, monomorphous, round cells with uniform ovoid nuclei and little cytoplasm. Cuticular cells have a centrally placed nucleus with abundant eosinophilic cytoplasm. Ductal differentiation manifests as small vacuoles or true ducts. Variants include purely dermal tumours (dermal duct tumour), intra-epidermal lesions (hidroacanthoma simplex) or those with hybrid features with hidradenoma (poroid hidradenoma). Porocarcinomas demonstrate similar morphology, accompanied by infiltration and cytological atypia.[1–3]

Molecular features

Poromas and porocarcinomas harbour activating mutations in *HRAS*[81,82] or fusions of YAP/TAZ, including *YAP1::MAML2*, *YAP1::NUTM1* or (rarely) *WWTR1::NUTM1* fusions (Table 4).[83–85] *YAP* is a key transcriptional regulator controlling essential functions such as proliferation and apoptosis that is negatively regulated by the Hippo pathway.[86,87] Notably, immunohistochemical expression of the fusion partner NUT represents a highly specific marker for poromas and porocarcinomas, although sensitivity is limited for classic poromas (approximately 17–20%), with higher sensitivity in poroid hidradenomas (93%) and porocarcinomas (50–58%) (Figure 4C).[83–85,88,89]

Porocarcinomas have also been reported to harbour other oncogene mutations (including *EGFR*, *ERBB2*, *FGFR3*, *KRAS*, *NRAS* or *PIK3CA*) or *EWSR1* rearrangement (Table 4).[74,81–83,90] Mutations in tumour suppressor genes (*TP53*, *RB1*, *CDKN2A*) may be restricted to porocarcinomas rather than poromas

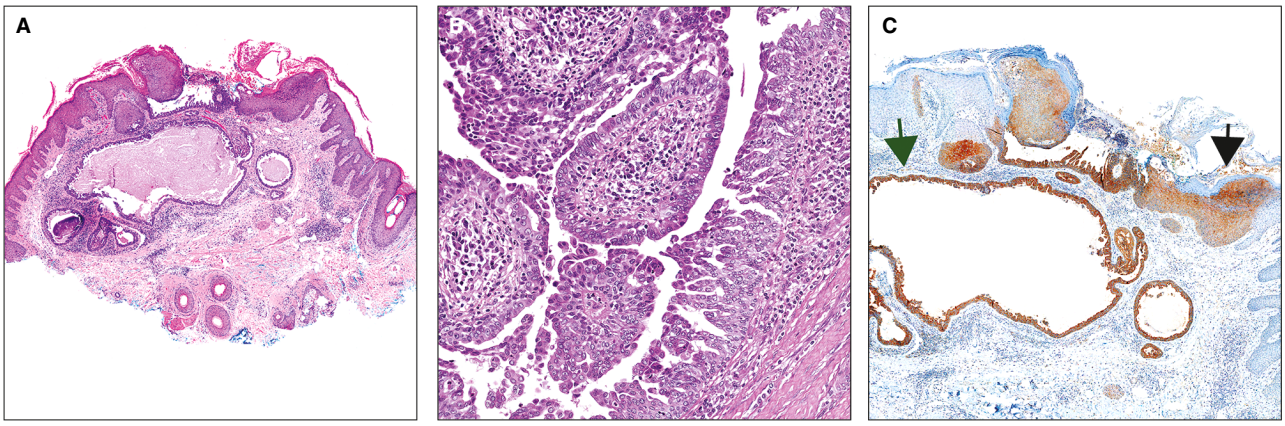

Figure 5. Syringocystadenoma papilliferum. **A,** Cystic glandular proliferation with associated epidermal hyperplasia. **B,** Papillary growth with plasma cell-rich stroma. **C,** In the subset of tumours with *BRAF* V600E mutations, immunohistochemistry for BRAF–V600E can demonstrate presence of mutation in glandular (green arrow) and epidermal (black arrow) components.

(Table 4, Figure 4D), although reports have been mixed.[81–83] Aberrant immunohistochemical expression of p53, Rb and p16 is a sensitive and specific finding for porocarcinoma relative to poroma.[91]

SYRINGOCYSTADENOMA PAPILLIFERUM AND SYRINGOCYSTADENOCARCINOMA PAPILLIFERUM

General features

Syringocystadenoma papilliferum (SCAP) may occur in isolation or in association with naevus sebaceous (discussed below). Clinically, SCAPs are solitary papules, predominantly on the head and neck.[4] Malignant lesions (syringocystadenocarcinoma papilliferum, or verrucous carcinoma arising in SCAP) are rare. Complete surgical excision of carcinomas is typically curative.[1,3]

Histopathology

Syringocystadenoma papilliferum (SCAP) is a benign apocrine neoplasm associated with the epidermis or hair follicle, composed of papillary and cystic structures formed by a double layer of columnar luminal cells and ovoid basal cells (Figure 5A). The surrounding stroma is rich in plasma cells (Figure 5B). There may be overlying verrucous epidermal hyperplasia.[1,3]

Syringocystadenocarcinoma papilliferum are similar to SCAP, with overtly malignant cytologic features including atypia, mitoses, loss of polarity and areas of infiltrative growth.[1,3]

Molecular features

Mutations of *BRAF V600E* (approximately 52%)[24,92] and *HRAS* (approximately 26%)[24,93,94] are the most commonly identified drivers associated with SCAP (Table 4). *BRAF* V600E mutation is detectable in both the glandular and verrucous (keratinocytic) components of the tumour (Figure 5C).[95] A SCAP arising within naevus sebaceous was found to harbour a *PIK3CA* mutation not present in the precursor lesion.[93]

Table 5. Molecular findings in cutaneous tumors with multilineage differentiation

Tumor	Molecular Findings	Diagnostic Correlations
Nevus sebaceus	Sporadic: *HRAS, KRAS* postzygotic mutation Additional mutations in secondary tumors (trichoblastoma, SCAP, etc.) Syndrome: Mosaic *HRAS, KRAS, NRAS* (Schimmelpenning–Feuerstein–Mims Syndrome) *HRAS* (Costello Syndrome) *KRAS* (Noonan Syndrome) *FGFR2* (various craniosynostosis syndromes)	
Mixed tumor, benign (chondroid syringoma)	Sporadic: *PLAG1* fusions (partners include *NDRG1*, *TRPS1*)	PLAG1 is sensitive and specific marker
Mixed tumor, malignant	Sporadic: *PLAG1* rearrangement, (single case) *PFH1::TFE3* fusion	

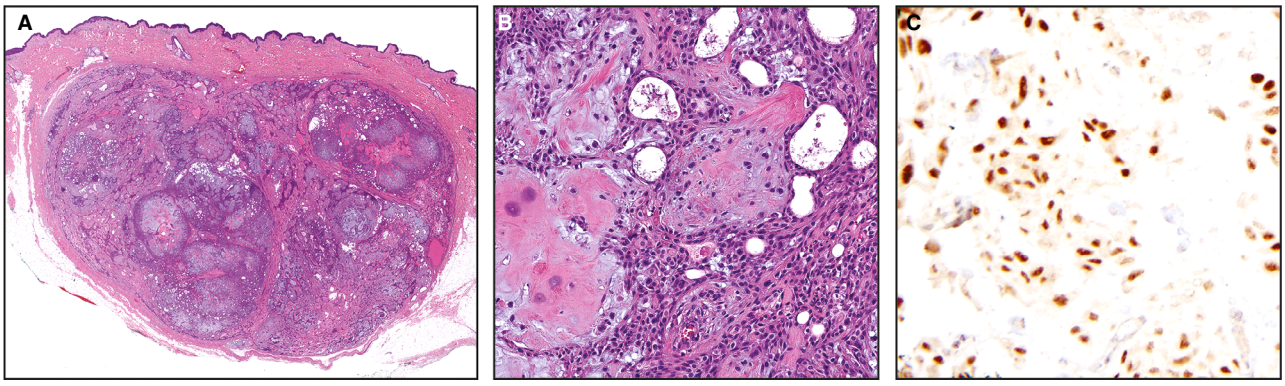

Figure 6. Benign mixed tumour. **A,** Circumscribed dermal nodule with glandular structures in chondromyxoid stroma (haematoxylin and eosin). **B,** Glandular structures in myxoid stroma (haematoxylin and eosin). **C,** PLAG1 immunohistochemical expression in mixed tumour [diaminobenzidine (DAB) chromogen].

Genomic events in malignant tumours are poorly understood. Verrucous carcinomas arising in SCAP demonstrate corresponding *BRAF* mutations.[96] One metastatic tumour classified as syringocystadenocarcina papilliferum demonstrated multiple mutations including *TP53* and *PIK3CA* E453K (Table 4),[97] although *TP53* mutation may not be consistently present in these tumours.[58]

OTHER SWEAT GLAND TUMOURS

Molecular findings in additional sweat gland tumours are listed in Table 4, including adenoid cystic carcinoma, apocrine carcinoma, hidradenoma papilliferum, hidrocystoma, mammary analog secretory carcinoma, mucoepidermoid carcinoma, tubular adenoma, signet-ring/histiocytoid carcinoma, syringoma and syringofibroadenoma.[1–4,98–102] At the time of this writing, there are no well-characterised genomic aberrations in many sweat gland neoplasms, including mucinous carcinoma, cribriform carcinoma or squamoid eccrine ductal carcinoma.

Tumours with mixed differentiation

Although many adnexal tumours can display mixed differentiation in a subset of cases, multilineage differentiation is a consistent feature of mixed tumour and naevus sebaceus (Table 5).

MIXED TUMOUR (CHONDROID SYRINGOMA) AND MALIGNANT MIXED TUMOUR

General features

Mixed tumour (chondroid syringoma) is a benign neoplasm analogous to pleomorphic adenoma of the salivary gland. The tumour presents as a large solitary nodule, with no predilection for anatomical location. Benign mixed tumour has an uneventful course. Malignant mixed tumours are rare, arise from benign mixed tumours and have metastatic potential.[1,3,4]

Histopathology

Apocrine mixed tumours have a prominent glandular component arranged as tubules and cysts with two cell layers, as well as myoepithelial and mesenchymal (chondromyxoid) components (Figure 6A,B). Major subtypes are eccrine mixed tumour (EMT) and apocrine mixed tumour (AMT). EMTs have simple ductal structures in a chondromyxoid stroma, whereas glands are larger and more extensive in AMT. Malignant mixed tumour arises from a pre-existing benign mixed tumour, and can resemble adenocarcinoma, myoepithelial carcinoma, sarcomatoid carcinoma or not otherwise specified (NOS).[1,3]

Molecular features

Benign and malignant cutaneous mixed tumours harbour *PLAG1* rearrangements (Table 5),[103] with potentially different fusion partners (*NDRG1* and *TRPS1*)[104] from *PLAG1* fusions in pleomorphic adenomas in the salivary gland.[105] PLAG1 immunohistochemistry can thus be useful for identifying mixed tumours in cases with partial sampling or poor differentiation (Figure 6C),[103,105] although this marker may be less sensitive for the eccrine subtype.[106] *PHF1::TFE3* fusion was reported in one case of malignant mixed tumour (Table 5), a fusion also associated with ossifying fibromyxoid tumours.[107]

Conclusion

Our understanding of the molecular alterations in cutaneous adnexal neoplasms has advanced greatly

in recent years. However, the rarity and diversity of these tumours has made large-scale definitive studies challenging; for many tumour types, molecular data is based only on case reports or small series. Further, there is little understanding of germline and somatic events related to adnexal tumorigenesis in populations of non-European descent. Finally, additional investigations of tumour progression and functional characterisation of potential driver genes are necessary to place genomic findings in a biological context. Together with the many recent advances described in this review, such studies will significantly improve diagnosis, prognostication and management of these challenging tumours.

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Conflict of interest

The authors declare no relevant conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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