Advances in the clinicopathological and molecular classification of cutaneous mesenchymal neoplasms

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In recent years, there have been several important refinements in the classification of cutaneous mesenchymal neoplasms, including the description of new tumour types, along with the identification of novel and recurrent molecular genetic findings. In addition to providing new insights into tumour biology, many of these advances have had significant clinical consequences with regard to diagnostics, management, and prognostication. Newly described entities include pseudomyogenic haemangioendothelioma, haemosiderotic fibrolipomatous tumour, and fibroblastic connective tissue naevus, which are reviewed in the context of the principal differential diagnoses and significant clinical implications. Genetic characterization of several soft tissue tumour types that occur in the skin has resulted in the identification of diagnostically useful markers: ALK gene rearrangement with corresponding ALK protein expression by immunohistochemistry in epithelioid fibrous histiocytoma; the WWTR1–CAMTA1 fusion gene with CAMTA1 protein expression in epithelioid haemangioendothelioma; MYC amplification and overexpression in radiation-associated angiosarcoma; and EWSR1 gene rearrangement in cutaneous myoepithelial tumours. Finally, the classification of intradermal smooth muscle tumours and unclassified/pleomorphic dermal sarcoma has been refined, resulting in both improved classification and improved prognostication. Many of the tumour types listed above are encountered not only by specialist dermatopathologists, but also by practising general surgical pathologists, and this review should therefore provide a widely applicable update on the histological and molecular classification of cutaneous mesenchymal neoplasms, along with the appropriate use of ancillary diagnostic tests, in particular immunohistochemistry, in the evaluation of such lesions and their histological mimics.

Keywords: cutaneous neoplasm, immunohistochemistry, sarcoma, soft tissue tumour, tumour classification

Introduction

Recent refinements in tumour classification, the description of new tumour types and advances in the molecular understanding of many cutaneous mesenchymal neoplasms have resulted in important changes to diagnostic criteria and broadened the spectrum of available ancillary tests for the surgical pathologist.

Newly described entities include pseudomyogenic haemangioendothelioma (PHE), haemosiderotic fibrolipomatous tumour (HFLT), and fibroblastic connective tissue naevus (FCTN) (summarized in Table 1), with the former two entities having important clinical implications with regard to management and prognosis. Genetic characterization of several soft tissue tumours has offered insights into disease pathogenesis and resulted in the identification of
diagnostic markers (summarized in Table 2); the long-running debate regarding the biology of benign fibrous histiocytoma (FH) (dermatofibroma) has finally ended with the discovery of recurrent PKC gene fusions in this tumour type, confirming a neoplastic, rather than reactive, origin. Epithelioid FH, which was previously thought to represent a morphological variant of benign FH, has been found to harbour anaplastic lymphoma kinase (ALK) gene rearrangements with corresponding ALK protein expression in the majority of tumours. Genetic characterization of other cutaneous mesenchymal tumours, in particular vascular neoplasms, has resulted in the identification of diagnostically useful immunohistochemical markers—epithelioid haemangiendothelioma (EHE) has been found to be a translocation-associated tumour (WWTR1–CAMTA1 fusion being the most common recurrent genetic change) and immunohistochemistry (IHC) for CAMTA1 protein expression a sensitive and specific marker to distinguish histological mimics. In addition, MYC amplification and MYC overexpression by IHC has become an extremely useful tool for distinguishing secondary radiation-associated angiosarcoma (AS) from florid atypical post-radiation vascular lesions. Finally, the classification of several soft tissue tumours has been refined in recent years by large studies evaluating (or re-evaluating) histological features and outcome data, resulting in improved prognostication (summarized in Table 3). Atypical intradermal smooth muscle neoplasms were formerly classified as cutaneous leiomyosarcomas; however, large studies have shown that when these tumours are confined to the dermis they have almost no risk of metastasis, making the designation of sarcoma for these patients inappropriate. Many of the tumour types listed above are encountered not only by specialist dermatopathologists, but also by practising general surgical pathologists, and this review should therefore provide a broadly applicable update on the histological and molecular classification of cutaneous mesenchymal neoplasms, important clinical implications, and the appropriate use of ancillary diagnostic tests, in particular IHC, in the evaluation of such lesions and their histological mimics.

Newly described cutaneous mesenchymal neoplasms

**PSEUDOMYOVENIC HAEMANGIOENDOTHELIOMA**

Pseudomyogenic haemangiendothelioma, which has also been referred to as epithelioid sarcoma-like haemangiendothelioma, is a rare soft tissue tumour of intermediate biological potential. Originally described
as a ‘fibroma-like’ variant of epithelioid sarcoma more than 20 years ago,\(^1\) this lesion has only recently been fully characterized in large series of cases and recognized as an endothelial neoplasm.\(^2\)\(^3\) This clinically and histologically distinctive tumour typically arises in young adults, with a peak incidence at

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### Table 2. Key features of recently genetically characterized cutaneous mesenchymal neoplasms

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<thead>
<tr>
<th>Tumour type</th>
<th>Clinicopathological features</th>
<th>Immunohistochemistry</th>
<th>Genetics</th>
<th>Clinical behaviour</th>
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| Epithelioid fibrous histiocytoma | Extremities of young to middle-aged people  
Well-circumscribed, epidermal collarette  
Prominent epithelioid morphology, frequent binucleate forms | Positive: ALK (>90%), EMA (64%)  
Negative: SMA, desmin | **ALK** rearrangement | Benign; local recurrence is uncommon |
| Syncytial myoepithelioma     | Well-circumscribed, solid proliferation of bland spindle/histiocytoid cells  
Pale syncytial eosinophilic cytoplasm         | Positive: S100, EMA; variable GFAP  
Negative: keratin | **EWSR1** rearrangements in 82% | Benign; low recurrence rate; no metastasis reported in this subset |
| Epithelioid haemangioendothelioma | Multifocal lesions due to metastasis  
‘Aggressive/malignant’ subset shows a solid growth pattern and higher-grade cytomorphology | Positive: CD31, CD34, ERG  
CAMTA1 in 90%  
TFE3 in <10% (CAMTA1-negative group) | **WWTR1**–**CAMTA1** fusion gene in 90%  
**YAP1**–**TFE3** fusion gene in 5% | Malignant; metastastic rate ~30% |
| Radiation-associated angiosarcoma | Most commonly occurs on the chest wall after radiation for breast cancer  
Should be distinguished from atypical post-radiation vascular lesions | Positive: CD31, ERG  
MYC overexpression distinguishes it from atypical post-radiation vascular lesions | **MYC** amplification  
(absent in atypical post-radiation vascular lesions) | Malignant; frequent local recurrences and early metastasis |
| Epithelioid haemangioma       | Variety of anatomical locations  
Morphological variants: angiolymphoid hyperplasia with eosinophils, atypical, cellular/solid, intravascular | Positive: CD31, CD34, ERG | **FOS** rearrangements  
**ZFP36**–**FOSB** fusion gene in ‘atypical’ variant | Benign; low recurrence rate |

**ALK**, anaplastic lymphoma kinase; **EMA**, epithelial membrane antigen; **GFAP**, glial fibrillary acidic protein; **SMA**, α-smooth muscle actin.

### Table 3. Key features of classification refinements of cutaneous mesenchymal neoplasms

<table>
<thead>
<tr>
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| Atypical intradermal smooth muscle neoplasm | Slow-growing mass on trunk/lower limbs—male predilection (~4:1)  
Poorly circumscribed fascicles of myoid spindle cells with mild to moderate atypia and mitotic activity  
Confined to the dermis or, at most, only minimal extension into the subcutis allowed | Positive: SMA, desmin, h-caldesmon, keratin (focal in 50%) | –                          | 20% recurrence rate; essentially no risk of metastasis |
| Pleomorphic dermal sarcoma    | Rapidly growing mass on sun-damaged skin of the elderly  
Pleomorphic spindled and epithelioid cells with marked nuclear atypia and atypical mitotic figures, extension into subcutis  
Must exclude spindle cell squamous cell carcinoma and melanoma | Positive: SMA (70%), CD10  
Negative: cytokeratins, p63, S100, SOX10 | **TP53** mutations  
and **TERT** promoter mutations with UV signature | Local recurrence in 20%; distant metastasis in 10–20% |

**SMA**, α-smooth muscle actin; **UV**, ultraviolet.
age 30 years and a marked (4:1) male predilection. Patients usually present with dermal or subcutaneous nodules on the extremities, most commonly the lower limbs, and 66% of patients have multifocal disease at presentation, often involving multiple tissue planes and deep soft tissue, skeletal muscle, or bone; the vast majority of lesions measure <30 mm. Tumours are \[^{18}\text{F}]fluorodeoxyglucose-avid on positron emission tomography scan, which helps to delineate the extent and multifocality of disease.

Pseudomyogenic haemangioendothelioma is considered to be a tumour of intermediate biological potential in terms of clinical behaviour, given its propensity for local recurrence and the frequent (and characteristic) development of additional nodules in the same region, which occur in almost 50% of patients; however, metastasis is very rare. The time interval between excision and local recurrence is short, usually 1–2 years. Conservative management is therefore the mainstay of treatment, often in the form of complete but narrow excision or curettage of bone lesions, avoiding large disfiguring surgeries. Although the majority of PHEs pursue a relatively indolent clinical course, several cases of PHE with aggressive clinical behaviour resulting in distant metastasis and death have been reported.

Microscopically, tumours have infiltrative edges and are composed of sheets and loose fascicles of spindled cells with abundant brightly eosinophilic cytoplasm, vesicular nuclei, and small nucleoli (Figure 1). Tumour cells are cytologically relatively bland, showing only mild atypia and low mitotic activity. Focal areas with epithelioid cytomorphology may be present, and ~50% of cases have a prominent neutrophilic infiltrate. Some tumour cells have a rhabdomyoblast-like appearance.

Figure 1. Pseudomyogenic haemangioendothelioma presenting as an infiltrative dermal lesion (A). The tumour cells grow in fascicles (B) or, less often, sheets, and are spindled with abundant eosinophilic cytoplasm, imparting a myoid appearance (C). Tumour cells express cytokeratin AE1/AE3 (D), and show nuclear positivity for the endothelial marker ERG (D, inset).
Although PHE shares some clinicopathological features and expression of broad-spectrum keratins (AE1/AE3) with its closest histological mimic, epithelioid sarcoma, the immunophenotype of PHE otherwise differs quite significantly. PHE shows consistent nuclear expression of ERG and FLI1 (Figure 1), consistent with endothelial differentiation, and variable expression of CD31, α-smooth muscle actin (SMA), CAM5.2, and (weak) epithelial membrane antigen (EMA), and is negative for CD34, S100, and desmin.² INI1 (SMARCB1) expression is retained in PHE, which is also helpful in the distinction from epithelioid sarcoma, which shows loss of INI1 expression in the vast majority of cases.²,⁸ Other histological differential diagnoses for PHE depend on the location of tumour, with superficial mimics including spindle cell squamous cell carcinoma, cellular benign FH, and smooth muscle neoplasms, and deep-seated lesions potentially mimicking other epithelioid vascular neoplasms and other fascicular spindle cell neoplasms. Recognition of the classic histological features, in conjunction with the distinctive immunoprofile, should distinguish PHE from the above tumour types. The distinction of PHE from EHE may be more difficult, owing to very similar immunohistochemical profiles; however, PHE lacks intracytoplasmic vacuoles and, in general, does not grow in the corded or nested pattern of EHE. The presence of CAMTA1 expression in the vast majority of EHEs can also help to resolve this differential diagnosis.⁹

Interestingly, the recognition of this histologically distinct group of tumours allowed for the identification of the recurrent balanced translocation t(7;19)(q22;q13) in these tumours, which results in fusion of SERPINE1 and FOSB. To date, this translocation has not been identified in any other tumour of bone or soft tissue.¹⁰,¹¹ As the SERPINE1–FOSB fusion gene appears to be pathognomonic for PHE, its detection offers a potential additional diagnostic tool with which to separate this entity from histological mimics.

**HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR**

Haemosiderotic fibrolipomatous tumour is an uncommon, locally aggressive neoplasm of uncertain lineage that arises almost invariably as a slow-growing mass in the ankle or foot region of women during the fifth and sixth decades.¹²,¹³ Tumours can become quite large, with an average size of 77 mm,¹² and the gross appearance is predominantly fatty or yellow-brown, with occasional areas of haemorrhage and ill-defined edges. Microscopically, tumours are rich in haemosiderin pigment and composed of bland, spindled fibroblasts with vesicular nuclei and indistinct nucleoli admixed with a variable amount of mature adipose tissue (Figure 2). Scattered inflammatory cells are usually present, and osteoclast-like giant cells may also be seen. Mitoses and necrosis are rare.¹⁴ The immunohistochemical profile of HFLT is non-specific, and IHC plays a limited, if any, role in diagnosis; the spindle cell component is positive for CD34 and negative for SMA, desmin, and S100.

Recent attention has focused on the relationship between HFLT and myxoinflammatory fibroblastic sarcoma (MIFS). MIFS is a relatively hypocellular neoplasm that shows a prominent inflammatory cell infiltrate, myxoid stroma, and admixed atypical cells with ‘virocyte-like’ or ‘Reed–Sternberg-like’ nuclei.
and also typically occurs in the distal extremities of older adults. Prominent myxoid areas, similar to MIFS, can be seen in HFLT, and 'hybrid' tumours showing features of both HFLT and MIFS have been described; recently, the same chromosomal translocation t(1;10)(p22;q24) and fusion gene, \( TGFBR3-MGEA5 \), have been identified in both neoplasms.\(^{15-17} \) The same fusion gene has also been identified in pleomorphic hyalinizing angiectatic tumour (PHAT),\(^{18} \) a rare, locally aggressive mesenchymal tumour that may show striking histological overlap with HFLT and MIFS but which contains distinctive vessels with hyalinization and fibrinoid change within their walls and an abundance of pleomorphic cells without discernible mitotic activity, suggesting that HFLT is potentially related to both MIFS and PHAT, and that these tumours may represent morphological variants of the same genetic entity, with only MIFS having the capacity to metastasize.\(^{18} \)

Haemosiderotic fibrolipomatous tumour is best considered a tumour of intermediate biological potential, owing to its tendency for local recurrence in 30–50% of cases,\(^{13} \) often as a result of incomplete excision because of poorly demarcated borders. Complete excision is generally curative, but occasional cases with associated MIFS have progressed to high-grade myxoid sarcoma, with resultant metastatic spread.\(^{19} \)

The differential diagnosis of HFLT includes plexiform fibrohistiocytic tumour (PFHT), dermatofibrosarcoma protuberans (DFSP), and reactive non-neoplastic processes. PFHT is composed of a more polymorphous cellular population, comprising frequent giant cells, spindled fibroblast cells and histiocytoid cells within small, distinct nodules. The adipocytic component is less prominent than in HFLT, and, unlike in HFLT, the tumour cells are usually positive for SMA. The honeycombing pattern of infiltration of DFSP into adipose tissue may be reminiscent of HFLT, but DFSP typically does not contain prominent haemosiderin pigment, and is more cellular than HFLT. HFLT may also mimic a reactive non-neoplastic process, such as post-traumatic change, and in some cases this differential diagnosis may be difficult. Helpful features favouring a diagnosis of HLFT include a clinical history of a long-standing, slow-growing mass, a lack of fat necrosis, and a relatively monotonous appearance of the neoplastic spindled cells.

**Fibroblastic Connective Tissue Naevus**

Connective tissue naevi are benign hamartomatous lesions of the papillary or reticular dermis that are found either in isolation or associated with syndromes such as Proteus and Cowden syndrome.\(^{20} \) FCTN is a newly described entity within the connective tissue naevus spectrum, and is distinguished by its relative hypercellularity as compared with ‘conventional’ connective tissue naevi, which consist of collagen or elastic tissue deposition in the dermis.\(^{21} \)

Fibroblastic connective tissue naevus presents as a solitary, slow-growing, painless cutaneous plaque or nodule, typically on the head and neck or trunk of young girls (average age of 10 years). The lesions are relatively small in size, ranging from 3 to 20 mm, and are ill-defined.\(^{21} \) Histologically, FCTN is composed of a proliferation of bland spindled fibroblastic or myofibroblastic cells with pale eosinophilic cytoplasm arranged in a disorderly fashion in the reticular dermis, with extension into the superficial subcutis in ~50% of cases (Figure 3). Intersecting bundles of spindled cells characteristically ramify
through the dermis and entrap appendages. Adipocytes are typically found in an abnormally superficial location in the dermis, and the overlying epidermis is often papillomatous. The most consistent immunohistochemical finding is CD34 expression, which is found in 87% of cases and typically shows a weak and multifocal staining pattern; S100 and desmin are usually negative.

The main differential diagnoses of FCTN include plaque-stage DFSP, dermatomyofibroma, pilar leiomyoma, and the fibroblastic-predominant subtype of PFHT. DFSP is the most important differential diagnosis to consider, given the propensity of DFSP to recur and potentially undergo fibrosarcomatous transformation and thereby acquire metastatic potential. Both entities present as a plaque-like CD34-positive spindle cell dermal lesion in young adults and children; however, helpful distinguishing features that support a diagnosis of DFSP include a striking storiform growth pattern with infiltration of subcutaneous fat, an absence of overlying epidermal papillomatous hyperplasia, and the typically larger size and greater cellularity seen in DFSP. CD34, although positive in both lesions, is typically expressed in a strong diffuse pattern in DFSP. Dermatomyofibroma, another benign entity, is also composed of an ill-defined proliferation of bland spindle fibroblastic/myofibroblastic cells in the reticular dermis, but, in contrast to FCTN, usually arises on the upper extremities of young adults, and shows more organized growth of tumour cells, with fascicles arranged parallel to the overlying epidermis. The cytoplasm of tumour cells of dermatomyofibroma tends to be more eosinophilic than in FCTN, and the cells are characteristically positive for SMA, with more variable CD34 expression, in contrast to FCTN.

The aetiology of FCTN is not yet fully understood, although it has been suggested, owing to the presence of superficial dermal fat and overlying papillomatous epidermal hyperplasia, that it may represent a developmental anomaly. Regardless of aetiology, FCTN is an entirely benign entity without the potential to metastasize. The likelihood of recurrence is very low, even in the setting of incomplete excision.

Recently genetically characterized cutaneous mesenchymal neoplasms

Conventional FH

Conventional FH, or dermatofibroma, is the most common cutaneous mesenchymal tumour encountered by pathologists. Since it was first described in its original form, a large number of histological variants have been recognized, including cellular, aneurysmal, atypical, lipidized and epithelioid types. Conventional or usual-type FH typically presents as a solitary reddish-brown nodule on the extremities, particularly in young to middle-aged women. These lesions are usually small, the majority measuring <10 mm. Conventional FH is generally and appropriately regarded as a benign tumour, with a low risk of local recurrence; the cellular and aneurysmal types have higher rates of local recurrence, approaching 20% in cases of incomplete excision. Exceptionally rare cases of metastasis of morphologically benign FH occur, and these cases are more likely to be histological variants of FH such as cellular, aneurysmal or atypical types, than conventional FH. They are also likely to have been preceded by multiple local recurrences.

The biology of FH has long garnered much debate, in particular as to whether it represents a neoplastic or a reactive process, such as in response to trauma or insect bite. The occurrence of metastasis (albeit extremely rare) and local recurrences have favoured a neoplastic origin, and biological evidence has now confirmed that FH is a true neoplasm. Although data supporting a clonal origin had been previously reported, until very recently no characteristic genetic aberrations had been described. In 2014, Plaszczyc et al. identified gene fusions involving a protein kinase C (PKC) gene in cases of benign FH investigated at the RNA level. However, a more recent study found that, although PKC fusions occurred in several morphological and clinical subsets of FH, these findings were present in only a minority of cases of FH. PKC isoforms PRKCB and PRKCD have been detected fused with genes encoding membrane-associated proteins (PDPN, CD163, and LAMTOR1). These gene fusions are thought to result in a chimeric protein that causes constitutive activity of PKC and promotes tumorigenesis. This discovery demonstrates that benign FH is indeed a true neoplasm, and also offers a potential method for distinguishing benign FH from other skin and soft tissue tumours.

Epithelioid FH

Epithelioid FH (EFH), also known as epithelioid cell histiocytoma, was first described in 1989 by Wilson Jones et al., as a variant of cutaneous benign FH with prominent epithelioid morphology. However, given the obvious morphological differences between EFH and conventional FH, and recent data showing a dis-
tinct immunohistochemical and genetic profile with the identification that EFH is an ALK-translocated neoplasm, the evidence suggests that EFH probably represents a distinct entity.\textsuperscript{29–31} EFH, according to the current definition, is a variant of FH with at least 50% of lesional cells having epithelioid morphology.\textsuperscript{28,32} EFH typically presents as a solitary dermal-based nodule, most commonly on the extremities of young to middle-aged adults.\textsuperscript{28,32,33}

Histologically, EFH is typically well circumscribed and exophytic with an associated epidermal collarette, features that are uncommon in conventional FH, and is composed of monotonous, plump epithelioid cells with abundant pale eosinophilic cytoplasm, vesicular nuclei, and small nucleoli (Figure 4).\textsuperscript{28,32–35} Binucleate cells are present in nearly all cases but, in contrast to conventional FH, multinucleate giant cells are less common, and lateral entrapment of collagen is usually absent. Tumours often contain prominent small to medium-sized vessels with perivascular accentuation of tumour cells.\textsuperscript{34} Mitotic activity in EFH is usually low.\textsuperscript{32,34} EFH follows a benign course in the majority of cases, with only rare reports of local recurrence associated with incomplete excision.\textsuperscript{32} A single case of lung metastasis from a morphologically benign EFH has been reported in the literature.\textsuperscript{23} Until recently, the immunohistochemical profile of EFH has been largely non-specific. Tumour cells in EFH are usually negative for SMA and desmin, in contrast to classic FH, in which variable expression of these markers is seen.\textsuperscript{34,36,37} EMA expression, which is usually absent in classic FH, has recently been reported in 64% of EFH cases,\textsuperscript{34} posing a potential
diagnostic pitfall in differentiating EFH from other EMA-positive cutaneous tumours, particularly epithelioid sarcoma; however, EFH retains expression of INI1.34

Anaplastic lymphoma kinase, first described in 1994, encodes a receptor tyrosine kinase protein that is implicated in a variety of tumour types of different cell lineages.29,38–40 ALK rearrangements resulting in the formation of VCL–ALK and SQSTM1–ALK fusions were originally described in two cases of ‘atypical’ FH with epithelioid features,30 and since then a further two cases of EFH have been shown to also harbour these rearrangements.31 A larger, more recent series of 33 epithelioid FHs showed diffuse cytoplasmic expression of ALK in 88% of cases (with moderate to strong staining in all but one case), with corresponding gene rearrangement being identified in IHC-positive cases examined by fluorescence in-situ hybridization (FISH), but not in ALK-negative tumours.29 Other tumour types examined [including other variants of FH, cutaneous syncytial myoepitheliomas, and atypical fibroxanthomas (AFXs)] were negative for ALK, and ALK staining is therefore a reliable diagnostic aid to distinguish EFH from histological mimics, with the exception of Spitz naevi, as discussed below. CD30 expression was found in 62% of cases in the same series,29 although the significance of this association (also seen in other ALK-positive tumour types41) is not fully understood. Differential diagnoses of EFH to consider include cutaneous syncytial myoepithelioma, epithelioid sarcoma, and Spitz naevi. Cutaneous syncytial myoepithelioma often causes the most diagnostic confusion, owing to shared expression of EMA and somewhat overlapping morphological features, but lacks ALK expression. Epithelioid sarcoma can have a similar clinical presentation and cytology to EFH (although it is usually found deeper and shows more cytological atypia) and shares EMA expression, but can be distinguished from EFH by immunopositivity for cytokeratins and CD34, and loss of nuclear expression of INI1.8,42 Notably, ~10% of Spitz naevi have also been shown to harbour ALK rearrangements; however, expression of S100 and melanA and absence of EMA expression in Spitz naevi44 readily distinguishes the two.

The recent discovery of ALK expression in EFH marks an important step in the evolving characterization of this entity. Not only can ALK expression now be used as a diagnostic tool, but it also further supports the argument that, morphologically and biologically, EFH is a distinct tumour type that is unrelated to other variants of FH.

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Figure 5. Cutaneous syncytial myoepithelioma is usually well circumscribed and located in the dermis (A). The cells are spindled to ovoid in shape with minimal atypia, and have variable amounts of pale eosinophilic cytoplasm with indistinct cell borders, imparting a syncytial appearance (B). The characteristic immunoprofile is that of coexpression of epithelial membrane antigen (C) and S100 (C, inset).
cutaneous myoepithelioma, and myoepithelial carcinoma. Mixed tumour, or chondroid syringoma as it is known in the skin, includes myoepithelial neoplasms that show tubuloductular differentiation and are analogous to pleomorphic adenoma of the salivary gland, both morphologically and genetically. Mixed tumours show rearrangement of the pleomorphic adenoma gene 1 (PLAG1) gene, located on chromosome 8q12. IHC for PLAG1 is useful to confirm this diagnosis. These tumours are benign, and although local recurrence may occur in up to 20% of cases, metastasis is exceptional.

Cutaneous myoepithelioma, defined by the presence of a pure myoepithelial cell population without tubuloductual differentiation, occurs in patients of all ages, with a 3:1 male predominance. Patients present with a long-standing, painless dermal-based mass, most commonly on the extremities, and with an average size of 10 mm. These neoplasms show a spectrum of morphology, with the majority having a nodular or lobulated architecture and being composed of epithelioid, plasmacytoid or spindled cells set in a myxoid or hyalinized matrix. In 2004, Hornick et al. published a series of 14 cases of cutaneous myoepithelioma, 50% of which were found to have a distinctive morphology and immunophenotype. In 2013, Jo et al. further characterized this subtype of 'cutaneous syncytial myoepithelioma' in a larger series. This distinct subset lacks any significant matrix, and instead shows a solid, well-circumscribed proliferation of ovoid, spindled or histiocytoid cells with pale eosinophilic syncytial cytoplasm, bland nuclei, and minimal mitotic activity (Figure 5).

As a group, myoepithelial tumours show a variable immunophenotype, typically coexpressing epithelial antigens (keratin and/or EMA), S100, and/or glial fibrillary acidic protein (GFAP), with variable staining for p63, SMA, and calponin. Cutaneous syncytial myoepitheliomas show characteristic coexpression of S100 and EMA with weak and multifocal expression of GFAP in 75% of cases, and, in contrast to most myoepithelial tumours, keratin expression is usually absent. Correspondingly, these lesions also appear to be genetically distinct. EWSR1 rearrangements have been detected with variable frequency (ranging from 29% to 44%) in cutaneous myoepithelial tumours to date; however, in syncytial-type cutaneous myoepitheliomas, EWSR1 rearrangements have been found in 82% of cases. A subset of myoepithelial tumours that are negative for EWSR1 rearrangement instead have alternative FUS rearrangement. EWSR1 fusion partners identified to date include POU5F1 (6p21), PBX1 (1q23), ZNF444 (19q23), ATP1 (12q13), PBX3 (9q33), and KLF17 (1p34). It is of note that an EWSR1 fusion partner has not yet been identified for the cutaneous syncytial variant.

Although it is now known that EWSR1 rearrangement is present in the vast majority of the syncytial subtype of cutaneous myoepithelioma, FISH is rarely needed to confirm this diagnosis, and the combination of characteristic morphological features and immunohistochemical profile allow for the diagnosis in almost all cases. Differential diagnoses to consider, which can usually be reliably distinguished on the basis of morphology and immunophenotype, include the following: epithelioid FH (most frequent mimic; S100-negative and ALK-positive); early-stage juvenile xanthogranuloma (expresses the histiocytic markers CD163 and CD68; absent expression of myoepithelial markers); and epithelioid sarcoma (expresses pankeratin and CD34, negative for S100 and GFAP, and shows loss of INII expression).

Cutaneous myoepithelioma pursues a benign clinical course, with local recurrence occurring in 20% of cases. Published follow-up data on the syncytial subtype suggest a very low local recurrence rate (one of 38 cases, with incomplete excision), and there are no reports of tumour metastasis. In contrast, myoepithelial carcinomas, which also contain EWSR1 rearrangements, pursue a more aggressive clinical course.

**Cutaneous Vascular Tumours**

Epithelioid haemangioendothelioma

Epithelioid haemangioendothelioma is a rare, malignant tumour that shows endothelial differentiation and can occur in a variety of anatomical sites, including soft tissue, bone, lung, liver, and skin. Although less clinically aggressive than angiosarcoma (AS) EHE is associated with metastasis in ~30% of cases, and ~15% of patients will die of disease. "The epithelioid cytomorphology of EHE may mimic carcinoma or melanoma, especially in visceral sites such as liver or lung and in small biopsy samples. Furthermore, cytokeratin expression is commonly seen in epithelioid vascular tumours, and is a diagnostic pitfall. EHE expresses the endothelial markers CD31, CD34, and ERG transcription factor, which are not present in melanoma and the vast majority of carcinomas. Nuclear expression of ERG has emerged as a highly specific and sensitive marker for endothelial differentiation, and shows greater sensitivity than CD31 and CD34 for the diagnosis of benign vascular..."
tumours and AS.61 These markers are therefore useful in distinguishing EHE from carcinoma and melanoma.

Although EHE usually shows low-grade morphology, a small subset of cases are of cytologically higher grade and may show a significant solid growth pattern mimicking AS, a so-called ‘aggressive’ or ‘malignant’ variant of EHE—this variant of EHE is typically associated with a more aggressive clinical course.57,62

To date, careful morphological evaluation has been the only way of distinguishing these two tumour types. However, recent insights into the molecular biology of EHE have resulted in the identification of more specific diagnostic markers of EHE.

Epithelioid haemangioendothelioma has recently been genetically characterized and found to be a translocation-associated sarcoma. In 2001, a t(1;3) (p36;q25) translocation was identified in two cases of EHE63; however, it was not until 2011 that the genes involved in the translocation, WWTR1 on 3q25 and CAMTA1 on 1p36, were cloned.64,65 WWTR1 is a gene involved in transcriptional factor activation and signalling in the Hippo pathway that is normally expressed in endothelial cells,66 whereas CAMTA1 belongs to a family of calmodulin-binding transcription activators, and has been implicated as a tumour suppressor gene that is frequently lost in neuroblastoma and gliomas.67,68 This WWTR1–CAMTA1 fusion gene has been identified in ~90% of EHE cases with classic morphology,64,65 and is not found in morphological mimics. Subsequently, a subset of EHEs negative for the WWTR1–CAMTA1 fusion gene were shown to harbour a YAP1–TFE3 fusion gene.69 This latter subtype was found mainly in soft tissues of young adults, and shows distinct well-formed vasoformative channels and brightly eosinophilic cytoplasm. YAP1 is also associated with the Hippo pathway, and shares significant functional and sequence homology with WWTR1.70

From a biological and clinical standpoint, not only have these findings elucidated the pathogenesis of EHE as a translocation-associated tumour, but they have also shown, through the identification of similar genetic changes in tumours at different sites, that the often multifocal nature of EHE is, in fact, due to metastasis, rather than synchronous primaries, as previously thought. From a diagnostic standpoint, the discovery of these two fusion genes in EHE has allowed for the application of immunohistochemical surrogates of these genetic changes as a diagnostic tool. Nuclear expression of CAMTA1 has very recently been shown to be a sensitive and specific surrogate marker for the fusion gene, and expression is seen in >90% of EHEs (Figure 6).9,71 Expression of CAMTA1 is not seen in epithelioid AS, other epithelioid vascular tumours or soft tissue tumours of other types. This application is particularly useful for distinguishing those EHEs with marked cytological or architectural atypia (so-called ‘malignant’ EHEs) from AS. Of those EHEs negative for CAMTA1, the vast majority will show expression of TFE3, but TFE3 is a less specific surrogate marker for the YAP1–TFE3 gene fusion—in a recent study, only positive cases with a strong, diffuse staining pattern correlated with the presence of the fusion gene.72

Epithelioid haemangioendothelioma limited to skin is rare, and typically presents as a solitary lesion with variable clinical appearances, including an erythematous nodule, papule or plaque, hyperkeratosis, or a non-healing ulcer.57,73–76 Cutaneous EHE has a significantly more favourable outcome than EHE arising at other locations. Metastatic disease is very rare,57,74,77,78 and complete excision is adequate

Figure 6. Epithelioid haemangioendothelioma of soft tissue composed of epithelioid endothelial cells with intracytoplasmic lumina and mild cytological atypia (A). Nuclear expression of CAMTA1 is present in the vast majority of epithelioid haemangioendothelioma (B).

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treatment in the majority of cases. This contrasts sharply with mortality rates of EHE in other sites, ranging from 15% in soft tissue to 31% and 43% in bone and liver, respectively.59,72,79 Histologically, cutaneous EHE usually shows classic morphological features of nests and cords of epithelioid cells embedded within a myxoid or hyalinized stroma; atypical or ‘malignant’ features are rarely seen.57,78 In 2014, Flucke et al.60 detected the WWTR1–CAMTA1 fusion gene in two cases of cutaneous EHE examined in a larger series of EHEs of various anatomical sites, one with an exon 4–exon 8 fusion transcript variant; these findings are in keeping with those seen in extracutaneous EHE. However, only small numbers of cutaneous EHE have been included in recent studies.

Radiation-associated vascular lesions
Atypical vascular proliferations and secondary AS are uncommon but well-established complications of radiation therapy. Cutaneous AS can arise de novo, usually in sun-exposed areas of the elderly with a predilection for the scalp, or secondary to chronic lymphoedema80,81 or radiation therapy, most frequently associated with the treatment of breast cancer.82 Radiation-associated AS was historically the least common subtype of cutaneous AS; however, the incidence has increased in recent years, owing to the combination of conservative excision with radiation therapy now being the standard of care in early-stage breast cancers.83,84 The development of secondary cutaneous AS typically occurs after a latency period of several years; however, shorter latency periods have been particularly associated with radiotherapy of the chest wall or breast, with some patients presenting with tumour within 3 years.85,86

Angiosarcoma arising secondary to radiation for breast cancer usually occurs within the dermis and subcutaneous tissue, in contrast to primary mammary AS, which primarily involves the breast parenchyma. Similarly to mammary AS, secondary AS of the skin is associated with an aggressive clinical course, characterized by frequent local recurrences and early metastasis. Although radiation-associated AS is relatively rare, atypical radiation-associated vascular lesions/proliferations (AVLs) occur more commonly in radiated skin. AVLs present clinically as small papules, usually <5 mm, with red to brown discoloration. AVLs tend to present earlier than cutaneous AS, and also develop after a shorter post-radiation interval.82 Histologically, AVLs consist of scattered small lymphatic-like vascular spaces in the dermis that are often dilated or irregular in shape and lined by hyperchromatic endothelial cells. In contrast to cutaneous AS, AVLs lack complex anastomosing or dissecting architecture, endothelial multilayering, marked cytological atypia, and mitotic activity. Although AVLs usually pursue a benign course, they may be associated with AS, and it is still controversial as to whether they represent a precursor lesion or a marker of increased risk.87

Some cases of AVL may be extremely difficult to distinguish from well-differentiated vasoformative AS morphologically, but recent studies have identified MYC amplification and MYC protein overexpression as a consistent finding in secondary AS (Figure 7), a finding that is not seen in AVLs, and is seen rarely in non-radiation-associated AS.88,89 IHC to identify MYC overexpression has become an extremely useful tool for distinguishing secondary/radiation-associated AS from florid AVLs.90 Expression of MYC is nuclear, and when present is usually seen in the majority of neoplastic cells. It is of note that MYC IHC should not be used to determine whether an AS is radiation-associated, as expression of MYC can be

Figure 7. Radiation-associated angiosarcoma with vasoformative features (A) can be distinguished from florid atypical post-radiation vascular lesion by nuclear expression of MYC (B).
seen in a subset of non-radiation-associated sarcomas of the skin and visceral sites.\textsuperscript{89}

Cutaneous AS typically shows aggressive biological behaviour, with a high rate of metastases and a 5-year survival of \textasciitilde 34\%.\textsuperscript{91} The reported clinical behaviour associated with radiation-associated AS is controversial, with some studies proposing a slightly more favourable outcome, with high rates of local recurrence but less frequent distant metastasis and death from disease.\textsuperscript{86,92–94} The current treatment approach for radiation-associated AS is complete excision of all skin within the affected radiation field; in the case of breast cancer-associated radiation AS, this usually necessitates a large chest wall resection to include total mastectomy. For AVLs, because of the association with AS, complete excision (when feasible) and close clinical follow-up is warranted.

Epithelioid haemangioma

Epithelioid haemangioma (EH) is a rare benign vascular neoplasm composed of prominent epithelioid endothelial cells, often with cytoplasmic vacuoles, lining well-formed vascular lumina.\textsuperscript{95–97} EH arises at a wide variety of anatomical locations, including soft tissue, bone, penis, heart, colon, eye, and lymph nodes.\textsuperscript{98} The spectrum of EH ranges from so-called ‘angiolymphoid hyperplasia with eosinophilia’ (ALHE), in which a prominent lymphocytic and eosinophilic infiltrate is present, to cellular/solid and intravascular variants.\textsuperscript{99–102} The growth pattern of these vascular tumours is typically lobulated, although destructive or multifocal growth can be seen in intraosseous locations.\textsuperscript{103} Although once thought to harbour metastatic potential, particularly bone lesions,\textsuperscript{104,105} it is now established that EH, regardless of location, is a benign entity with a low recurrence rate when treated with surgical excision.\textsuperscript{96,97} Because of its varied histological appearance, EH can pose diagnostic challenges; the cellular variant, in particular, often shows overlapping features with EHE and epithelioid AS. Cellular atypia, mitoses and necrosis have also been reported in a subset of EHs, further complicating its separation from malignant vascular tumours.\textsuperscript{106}

Following the identification of recurrent translocations in EHE and PHE, in 2014 Antonescu et al.\textsuperscript{106} reported the novel recurrent fusion gene ZFP36–FOSB in a small subset of EHs showing increased cellularity, necrosis, and atypia. Shortly thereafter, FOS rearrangements were identified in osseous EH,\textsuperscript{107} and with the identification of the FOS–LMNA fusion gene in an index case of osseous EH with typical morphology, FOS gene rearrangements were detected in an additional 57 cases of EH with typical and cellular morphology.\textsuperscript{102} FOS rearrangements were found across different anatomical locations and histological variants; however, a higher prevalence was found in cellular EH and intraosseous lesions. All cases of the ALHE variant examined lacked FOS rearrangement. The ALHE variant of EH is typically seen in the head and neck and extremities, associated with a history of trauma;\textsuperscript{108} these features, along with the absence of detectable
rearrangements in this subtype to date, suggest a different, possibly reactive, underlying pathogenesis. The discovery of recurrent FOS and FOSB rearrangements in a subset of EHs confirms its distinct pathogenesis from other epithelioid vascular neoplasms. Although it may also offer a potential diagnostic tool for distinguishing atypical cases from AS, at this time there is no well-developed clinical test available in routine clinical practice.

Refinements in classification of cutaneous mesenchymal neoplasms

INTRADERMAL SMOOTH MUSCLE TUMOURS

The diagnostic term ‘atypical intradermal smooth muscle neoplasm’ (AISMN) represents a recent refinement in the classification of tumours formerly considered to be ‘cutaneous leiomyosarcoma’, to represent those atypical smooth muscle tumours that are confined to the dermis, with at most minimal extension into subcutaneous fat.\textsuperscript{109,110} Historically, leiomyosarcomas of the dermis and subcutis were grouped together, but recent studies have shown that primary dermal ‘leiomyosarcomas’ have an excellent prognosis as compared with their subcutaneous counterparts or those tumours that show significant extension into subcutaneous tissue from the dermis, with almost no risk of metastases, making the label ‘sarcoma’ inappropriate for these patients.\textsuperscript{109–114}

AISMN arises in middle-aged to elderly adults, with a striking male predominance (male/female ratio of >4:1).\textsuperscript{109} The clinical presentation is typically a solitary, slow-growing cutaneous nodule on the trunk or

Figure 9. Pleomorphic (unclassified) dermal sarcoma shows extension into subcutaneous tissue, with pushing (A) or infiltrative (B) edges. Note the depth of tumour beyond the layer of solar elastosis in the superficial dermis (arrow). In contrast, atypical fibroxanthoma is confined to the dermis. Pleomorphic dermal sarcoma may be composed of fascicles of spindle cells (C) or have an epithelioid morphology (D), and usually shows marked cytological atypia and mitotic activity (C, D).
lower limbs, usually <20 mm, which is occasionally painful. Microscopically, AISMN is dermal-based, usually poorly circumscribed with infiltrative edges, and composed of fascicles of spindle cells with bright eosinophilic cytoplasm, well-defined cell borders and blunt-ended or ‘cigar-shaped’ nuclei—it is usually readily apparent that the tumour cells show smooth muscle differentiation, resembling normal smooth muscle (Figure 8). However, the presence of mild to moderate nuclear atypia and mitotic activity distinguishes AISMN from pilar leiomyoma. Only very limited extension into the superficial subcutis, with a tendency to infiltrate the border, is allowed for the designation of AISMN.109,110 A tumour that shows infiltration beyond the superficial subcutis is designated ‘cutaneous leiomyosarcoma’, as these tumours have a small but well-established risk of metastasis. AISMN recurs locally in ~20% of cases, but does not metastasize.109,110 Recurrent tumours are more likely to have a nodular growth pattern, severe cytological atypia, necrosis, and more frequent mitoses, and are usually associated with prior incomplete excision.110

The main differential diagnostic considerations for AISMN are pilar leiomyoma, metastatic leiomyosarcoma, and cellular benign FH. Pilar leiomyoma often presents with multiple lesions, and lacks the nuclear atypia and mitotic activity seen in AISMN. Metastatic leiomyosarcoma should be considered for any atypical intradermal or subcutaneous smooth muscle proliferation when the lesion is well circumscribed or nodular, and for such cases it is advisable to recommend clinical correlation to evaluate this possibility. The tumour cells of cellular benign FH lack the bright eosinophilic cytoplasm of AISMN, and are less reminiscent of smooth muscle; whereas tumour cells of cellular benign FH are often positive for SMA and show desmin expression in ~30% of cases,36 expression of the latter is typically focal or multifocal in distribution, and cells are negative for h-caldesmon. The vast majority of AISMNs express SMA, desmin, and h-caldesmon, consistent with smooth muscle differentiation, and focal keratin positivity is seen in ~50% of cases.109 CD34, S100 and HMB-45 are typically negative.

The clinical presentation of PDS is similar to that of AFX, with a rapidly growing, often ulcerated, exophytic tumour on sun-damaged skin, most commonly on the scalp of men in the seventh or eighth decade.115 PDS tends to be larger (median size of 25 mm) and less well circumscribed than AFX.115 Microscopically, PDS is composed of pleomorphic spindled and epithelioid cells with pale eosinophilic cytoplasm and marked nuclear atypia (Figure 9). Admixed giant cells are frequently present. Mitotic activity is often high, and includes atypical mitotic figures. Perineural invasion, lymphovascular invasion and necrosis may be seen.

Pleomorphic dermal sarcoma falls under the umbrella designation of ‘undifferentiated/unclassified sarcoma’,120 albeit with a better prognosis, and therefore not to be confused with, undifferentiated pleomorphic sarcoma of the subcutis or deep soft tissues.121 By virtue of the fact that, to date, no definite line of differentiation has been identified, PDS remains a diagnosis of exclusion, and requires evaluation with an appropriate immunohistochemical panel to exclude the possibility of melanoma, sarcomatoid squamous cell carcinoma, and, in some cases, spindle cell AS or atypical intradermal smooth muscle neoplasm/leiomyosarcoma. Application of multiple cytokeratins, such as pan-cytokeratin and cytokeratin 5, as well as p63, is advised to distinguish PDS from poorly differentiated squamous cell carcinoma, which may be otherwise morphologically indistinguishable; similarly, S100 and SOX10 help to exclude a diagnosis of melanoma.115 In a recent series, SMA was expressed in 70% of PDS cases, CD31 in 48% of cases (in both tumour cells and intratumoral histiocytes), and CD10 in 100% of cases, although the last of these markers is non-specific and of limited or no diagnostic utility.115 When S100 expression is evaluated, it is important to be aware that PDS often contains numerous intratumoral S100-positive dendritic cells, which should not be confused with positivity in tumour cells; this is important to prevent misclassification of PDS as desmoplastic or spindle cell melanoma.112

Genetically, both AFX and PDS remain incompletely characterized. TERT promoter mutations, which allow cells to continuously proliferate without...
entering apoptosis or senescence, have been identified in many types of cancer and are the most frequent mutations found in PDS to date. Recent data have shown that TERT mutations, with an associated ultraviolet (UV) signature very similar to those found in malignant melanoma, are present in 76% of PDS cases and 93% of AFX cases.\(^1\)\(^2\)\(^3\) Other mutation types often associated with a UV signature have been also been found, i.e. RAS in PDS, and TP53 in both AFX and PDS.\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)

The prognosis of PDS remains better than that of undifferentiated pleomorphic sarcomas of other body sites. Local recurrence rates, usually in the setting of incomplete excision, have been reported to be in the range of 20–28%.\(^1\)\(^2\)\(^3\)\(^4\) The incidence of metastatic disease now appears to be higher than initially suggested, with distant metastases occurring in 10% and 20% of cases in two recent studies.\(^1\)\(^2\)\(^3\)

**Conclusion**

Over recent years, refinements in tumour classification, the description of new tumour types and advances in the molecular understanding of a variety of different cutaneous mesenchymal neoplasms have had significant diagnostic, therapeutic and prognostic implications. Protein correlates of molecular alterations offer useful diagnostic adjuncts that are widely applicable in clinical practice; examples are ALK and CAMTA1 expression for the diagnosis of epithelioid FH and EHE, respectively, and MYC overexpression in radiation-associated AS. Newly described entities widen the differential diagnostic considerations in certain settings: PHE was previously considered to be a variant of epithelioid sarcoma, until it was recognized as a clinicopathologically and molecularly distinct entity with a penchant for local recurrence but not for metastasis. The refinement in the classification of PDS and atypical cutaneous smooth muscle neoplasms has significant clinical implications. Strict criteria now separate PDS from AFX, two entities that show similar clinicopathological features but striking differences in clinical behaviour. This review highlights important advances in the histological and molecular classification of a spectrum of cutaneous neoplasms that have significant clinical consequences with regard to management and prognostication, and provide insights into the biology of a diverse group of tumours.

**Conflicts of interest**

The authors have no conflicts of interest to declare.

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