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Overview

An Overview of Uncommon Cutaneous Malignancies, Including Skin Appendageal (Adnexal) Tumours and Sarcomas

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Abstract

A standardised classification of malignant skin appendageal (adnexal) tumours and sarcomas is required for improved patient management and prognosis. This has been hindered by considerable morphological variation both within and between tumour types, the use of many synonyms for the same tumour types and variation in classification between pathologists.

This update uses the improved classification in the 2018 *WHO classification of skin tumours* as the basis to discuss malignant skin appendageal tumours, sarcomas and cutaneous metastases that regularly present to skin cancer clinicians, multidisciplinary skin cancer teams and tumour boards, with current evidence for management, where appropriate.

Keywords: Appendageal; cutaneous; pathology; sarcoma; tumour; adnexal

Statement of Search Strategies Used and Sources of Information

The review is based on a search of peer-reviewed publications found using PubMed search tools and including the keywords identified above. In addition, the reference lists from other key articles were used to obtain other pertinent articles.

Textbooks searched are referenced in the manuscript. The Royal College of Pathologists dataset for cutaneous adnexal carcinomas and regional lymph nodes 2019 and the Royal College of Pathologists dataset for soft tissue sarcomas 2017 (both RCPath.org) have also been searched.

Introduction

A more robust classification of primary skin malignancies is required for improved patient care, including for treatment strategies and prognosis.

The 2018 multi-author *WHO classification of skin tumours* [1] has provided a much needed and updated classification and includes epidemiology, clinical features and pathological features of tumours, including molecular and genetic data, prognosis and predictive factors, although it does not include management strategies.

This review covers many primary cutaneous malignancies that, although relatively uncommon, do regularly present to clinicians involved in skin cancer care, including some guidance towards management where appropriate. It does not include squamous cell carcinoma and basal cell carcinoma, malignant melanoma, Merkel cell carcinoma or lymphoma. The remaining primary cutaneous malignancies can mainly be divided into two categories, namely skin appendageal (adnexal) tumours and sarcomas; metastases in the skin are also discussed.

Malignant Skin Appendageal (Adnexal) Tumours

The classification of malignant skin appendageal (adnexal) tumours is problematic as there is considerable

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morphological variation within entities and overlap between many entities [2] and incidence is low [3]. Although nomenclature is beginning to standardise, identical tumours and histological variants may still have several different names in the literature (Table 1).

Based on embryological derivation where follicular, sebaceous and apocrine units have a common origin distinct from the eccrine apparatus, skin adnexal tumours have been categorised by many into these two groups, i.e. follicular/sebaceous/apocrine or eccrine [4]. Follicular, sebaceous and apocrine tumours may indeed show more than one line of differentiation (Figure 1). It should be noted, however, that basal cell carcinomas are also follicular tumours and show differentiation towards hair follicle epithelium [5]; they were named for their similarity to the basal layer of the epidermis but more closely resemble normal follicular epithelium. Furthermore, many, if not most, squamous cell carcinomas also show follicular differentiation, probably towards more superficial portions of the hair follicle such as the isthmus, infundibulum and ostium. The bulge region of the hair follicle is the proliferative component [6] and is susceptible to ultraviolet radiation damage, which links many of these cancers and also plays an important role in wound healing. Indeed, the scalp heals much better than non-glabrous skin and carcinomas are rarely seen on non-glabrous skin such as the palms and soles.

Table 1
Malignant skin appendageal (adnexal) neoplasms included in the 2018 *WHO classification of skin tumours* [1]

Non-invasive
Primary extramammary Paget's disease*
Secondary extramammary Paget's disease†
Invasive
Miscellaneous
Adenocarcinoma, not otherwise specified
Microcystic adnexal carcinoma (synonyms include syringomatous carcinoma)
Squamoid eccrine ductal carcinoma (synonyms include adenosquamous carcinoma)
Invasive neoplasms that may arise from a benign counterpart
Porocarcinoma (synonym malignant eccrine poroma)
Hidradenocarcinoma (synonyms malignant eccrine acrospiroma, malignant hidradenoma)
Spiradenocarcinoma (synonym malignant spiradenoma)
Cylindrocarcinoma (synonym malignant cylindroma)
Invasive neoplasms analogous to those in salivary gland and other glandular sites including breast
Adenoid cystic carcinoma
Secretory carcinoma
Apocrine carcinoma
Cribriform carcinoma
Malignant mixed tumour
Malignant myoepithelioma
Invasive neoplasms with hair follicle differentiation
Trichilemmal carcinoma
Pilomatrical carcinoma (synonyms malignant pilar tumour, malignant proliferating pilar tumour)
Invasive neoplasms arising within the eyelid, periocular area or cheek
Endocrine mucin-producing sweat gland carcinoma‡
Mucinous carcinoma
Signet ring cell carcinoma (synonym histiocytoid carcinoma)

* Invasive cutaneous carcinomas may arise in primary or, very rarely, secondary extramammary Paget's disease.
† 20% of extramammary Paget's disease have an associated underlying non-cutaneous carcinoma, i.e. secondary extramammary Paget's disease.
‡ Some regard as minimally or non-invasive.

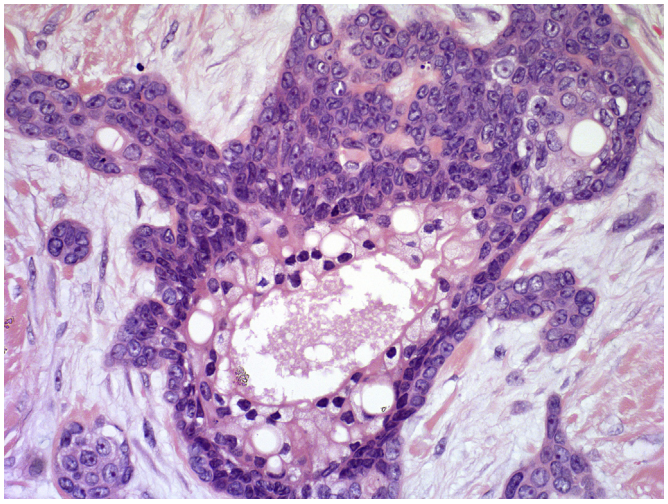

Fig 1. This adenocarcinoma, not otherwise specified, shows central sebaceous differentiation and secretions and peripheral ductal differentiation.

Using strict diagnostic criteria due to the overlapping entities, some cases of skin adnexal carcinomas may in fact best fit the diagnosis 'adnexal adenocarcinoma not otherwise specified' (Figure 2) [1], especially as patients become more elderly in their 80s and 90s when immunosenescence may alter biology and hence morphology of tumours, and management strategies may change as the balance between quality of life and desire for curative therapy changes [7].

The 2018 *WHO classification of skin tumours* [1] recommends use of either 'atypical skin adnexal tumour' or 'skin adnexal tumour of uncertain malignant potential' for neoplasms where it is difficult to categorise as benign or malignant. In such cases, a description and differential diagnosis should be included with a recommendation for complete excision with consideration of follow-up.

Unsurprisingly given the difficulties in diagnosis and their relative rarity, reliable treatment algorithms for malignant skin appendageal tumours are lacking [8].

Non-invasive Neoplasms

Extramammary Paget's Disease

Primary extramammary Paget's disease (EMPD) is an *in situ* adenocarcinoma within the skin and mucosa primarily from the anogenital region, including vulva, perianal region,

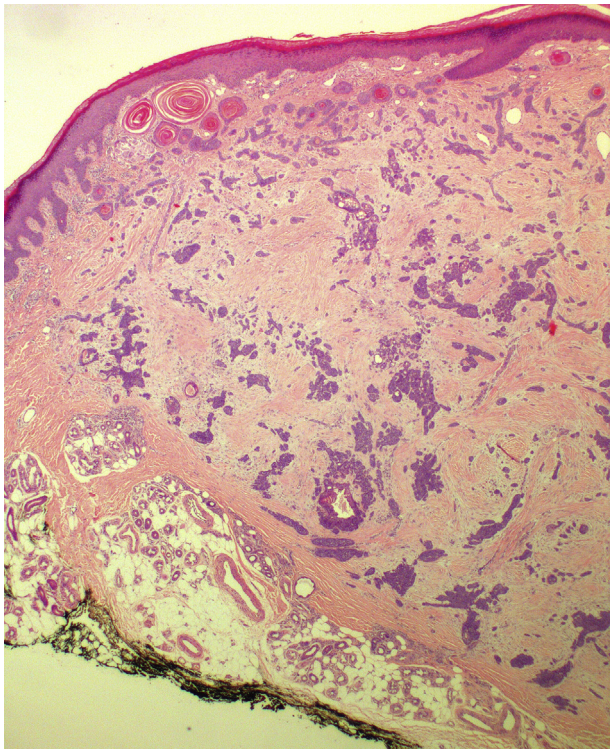

Fig 2. The same carcinoma as in Figure 1 under the 2018 *WHO classification of skin tumours* [1] can be classified as an adenocarcinoma, not otherwise specified; previously it may have been diagnosed as an adenosquamous carcinoma or even a sebaceous carcinoma.

scrotum and penis and adjacent inguinal folds and lower abdominal skin. It probably develops within glands or ducts and spreads from these into the epidermis. Vulval EMPD is the most common, with a median presentation at 70–75 years. As it often presents with ill-defined erythema it may mimic dermatoses such as eczema and therefore diagnosis may be late or delayed.

An underlying invasive carcinoma from the large intestine, urethra, bladder or cervix is found in 20% of EMPD (in contrast with mammary Paget's disease with an underlying invasive breast adenocarcinoma in more than 95% of cases) and is known as secondary EMPD. Therefore, investigations such as ultrasound scanning of regional lymph nodes, hysteroscopy, sigmoidoscopy and cystoscopy should be strongly considered to assess for an underlying invasive carcinoma. Progression to invasive adenocarcinoma is uncommon in primary EMPD but is associated with lymph node metastasis and a worse prognosis [9,10].

The recommended primary treatment is usually surgical, with various margins between 1.5 and 5 cm [11,12]; a 5 cm margin can achieve 97% 5-year disease-free survival [12]. Mohs surgery has shown a 5-year disease-free survival of 91% with further reduced recurrence using intraoperative immunostaining for cytokeratin 7 [13]. Other management strategies include mapping biopsies, radiotherapy, photodynamic therapy, topical imiquimod, conventional chemotherapy and targeted therapy [14]. Radiotherapy alone can be considered in extensive inoperable disease or medical contraindications. Adjuvant radiotherapy may be considered where there are risk factors associated with local recurrence [15].

Invasive Neoplasms

Porocarcinoma

Porocarcinoma is a form of carcinoma with ductal differentiation most commonly found on the lower limbs, although it may be seen on the trunk, head and neck and upper limbs, with a mean presentation at 62–73 years [1]. In some cases, a pre-existing benign poroma is also seen or there is also *in situ* porocarcinoma; either of these features may aid diagnosis. Conversely, more poorly differentiated tumours may be difficult to diagnose as there is an overlap with other carcinomas and, therefore, data on prognosis and management may not be entirely reliable. Local recurrence is reported in 17%, local nodal metastases in 19% and distant metastases and death in 11% [16].

Complete surgical excision is usually considered the optimum treatment and sentinel lymph node biopsy has been used by some without recurrence or other disease-related morbidity [17] together with adjuvant chemotherapy in positive cases [18]. Complete response of a metastatic porocarcinoma treated with paclitaxel, cetuximab and radiotherapy has been reported [19].

Microcystic Adnexal carcinoma (Synonyms Include Syringomatous Carcinoma) and Squamoid Eccrine Ductal Carcinoma (Synonyms Include Adenosquamous Carcinoma [1])

Microcystic adnexal carcinoma (MAC) shows follicular differentiation, whereas squamoid eccrine ductal carcinoma (SEDC) shows mixed squamous and ductal differentiation, but there is an overlap [20]. Both usually have an indolent presentation of an ill-defined plaque or nodule or area of firmness, especially in perioral and periocular sites for MAC [21] and the cheek for SEDC [20]. Although both commonly show perineural invasion and recur locally when incompletely excised in 25% [22], MAC very rarely involves regional nodes or shows distant metastases, whereas SEDC has a worse prognosis, with 13% showing lymph node metastases and 3% distant metastases [22,23]. Timely and complete wide surgical excision is the favoured treatment and Mohs surgery should be considered in both due to good outcomes in many cases; the role of radiotherapy is uncertain [21,24].

Sebaceous Carcinoma

Sebaceous carcinoma occurs most commonly on the head and neck, especially the periocular region, in middle-aged to elderly adults. Extrafacial tumours, in common with benign sebaceous tumours, are associated with Muir-Torre syndrome in up to 25% of cases [25]; however, periocular sebaceous carcinoma has little or no association. Periocular and non-periocular sebaceous carcinomas have similar local recurrence rates of 30–40%, a 20–25% risk of distant metastases and up to a 30% 5-year risk of death from disease [26].

Surgery is considered to be the optimum treatment for sebaceous carcinoma; Mohs micrographic surgery shows low

recurrence rates [27]. Advanced cases can be treated with radiation therapy, chemotherapy or combination therapy.

Trichilemmal Carcinoma

Trichilemmal carcinoma (synonym tricholemmal carcinoma) primarily occurs on sun-damaged skin of the head and neck of the elderly and shows differentiation towards hair follicle outer root sheath epithelium. It therefore histologically comprises, at least partly, clear cells. Its true incidence is unknown, as many include this under a clear cell variant of squamous cell carcinoma [28]. It is generally regarded as a relatively low-grade carcinoma, with few reports of metastases and simple excision with 1 cm margins is sufficient [29].

Digital Papillary Adenocarcinoma

This rare adenocarcinoma is almost entirely confined to the distal digits, especially the fingers and especially in middle-aged men [30], with a mean size of 1.7 cm. It mimics benign adnexal tumours histologically. Local recurrence occurs in 21%, with 26% showing metastases to lymph nodes and/or the lungs and are reduced with more radical treatment, especially amputation of the distal digit [30].

Adnexal Adenocarcinoma Not Otherwise Specified

This is a primary skin carcinoma with ductal/glandular differentiation, but which lacks other specific histological features for further classification [1]. Subsequently there is little reliable literature in this area. It may include a variety of tumours given different names in the literature, including skin adnexal carcinoma not otherwise specified, sweat duct carcinoma, sweat gland carcinoma, high-grade eccrine carcinoma and high-grade eccrine syringomatous carcinoma. Differentiation from metastases in the skin is important and may be impossible (see below).

No consensus is available for the management of such tumours, but multidisciplinary teams (tumour boards) may manage them as for porocarcinoma or as a poorly differentiated/high-risk primary cutaneous squamous cell carcinoma.

Further Rare Skin Adnexal Carcinomas

The literature regarding the following rare primary skin adnexal carcinomas is mainly confined to case series [1]. Primary cutaneous adenoid cystic carcinoma [31], malignant mixed tumour [32], malignant myoepithelioma [33], secretory carcinoma [34], apocrine carcinoma [35] and cribriform carcinoma [36] are analogous, to varying degrees by histology and molecular signatures, to those in salivary glands and other glandular sites, including the breast, and this may provide common diagnostic and therapeutic strategies.

Hidradenocarcinoma (synonyms include malignant eccrine acrospiroma) [37], which may overlap with porocarcinoma in the literature (synonym malignant hidradenoma), spiradenocarcinoma (synonym malignant spiradenoma) and cylindrocarcinoma (synonym malignant cylindroma), are malignant counterparts of the much more common benign hidradenomas, spiradenomas and cylindromas, respectively, and often arise within the benign counterpart and can be categorised into low- and high-grade variants, which significantly affects prognosis [38].

Some adnexal tumours primarily affect the eyelid, periocular area and cheeks, including endocrine mucin-producing sweat gland carcinoma [39], which may represent a multistage progression to mucinous carcinoma [40], which is also seen at these sites, and signet ring cell carcinoma (synonym histiocytoid carcinoma) [41].

Pilomatrical carcinoma (synonyms malignant pilar tumour, malignant proliferating pilar tumour) differentiates towards follicular matrix cells [42].

Cutaneous Sarcomas

The behaviour of primary cutaneous sarcomas often differs from those in deep soft tissue or within the abdominal or pleural cavities. Primary cutaneous sarcomas overall have a better prognosis, although this differs by subtype; for example, primary cutaneous angiosarcoma (cAS) is a locally aggressive cancer.

Cutaneous sarcomas can be divided into those arising within ultraviolet-damaged skin, almost exclusively of the head and neck of the elderly, and those not related to ultraviolet damage (Table 2). Occasionally, sarcomas usually seen in deeper soft tissue present in the skin and should be managed as for their deeper counterparts, including with appropriate classification [43], grading [44] and staging systems [45,46].

Atypical Fibroxanthoma and Pleomorphic Dermal Sarcoma

Atypical fibroxanthoma (AFX) is almost exclusively found in the head and neck region and rarely in other areas of chronic sun damage (Figure 3).

Table 2
Cutaneous sarcomas included in the 2018 *WHO Classification of skin tumours* [1] and categorized by their association with ultraviolet-damaged skin

Cutaneous sarcomas in ultraviolet-damaged skin (almost all head and neck)
Atypical fibroxanthoma (AFX)/pleomorphic dermal sarcoma (PDS)
Angiosarcoma
Cutaneous sarcomas not related to ultraviolet damage
Dermatofibrosarcoma protuberans
Angiosarcoma (radiation or lymphoedema associated)
Atypical smooth muscle tumour of dermis* and cutaneous leiomyosarcoma
Atypical lipomatous tumour* and liposarcoma
Kaposi sarcoma*
Rarer sarcomas usually of deeper soft tissue or extremities: myxofibrosarcoma, epithelioid sarcoma, synovial sarcoma, ossifying fibromyxoid tumour alveolar soft part sarcoma, clear cell sarcoma, acral myxoinflammatory fibroblastic sarcoma, low-grade fibromyxoid sarcoma, haemangioendotheliomas, etc.

* AFX is generally regarded as not fully malignant, whereas PDS is malignant.

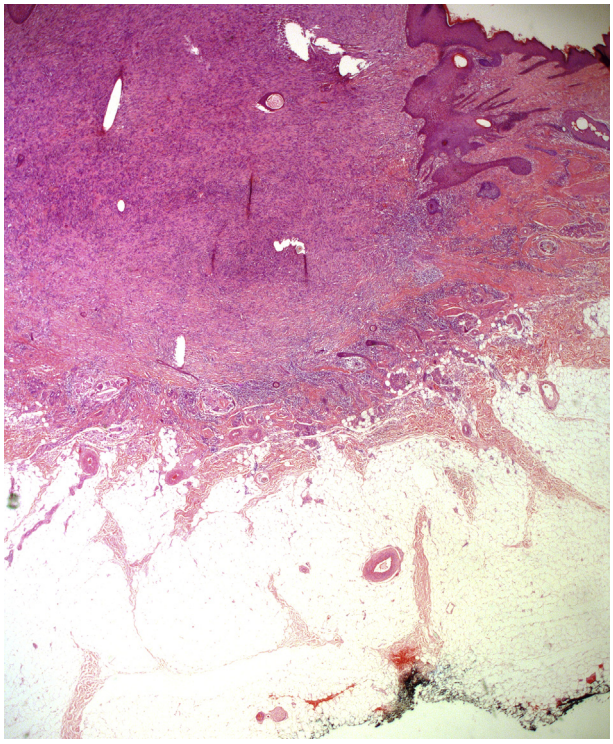

Fig 3. Atypical fibroxanthoma, occupying the entire upper left quadrant of the field, has a relatively "pushing" (cohesive and non-widely infiltrative) deep border and does not show extension into the subcutaneous fat in the bottom half of the field.

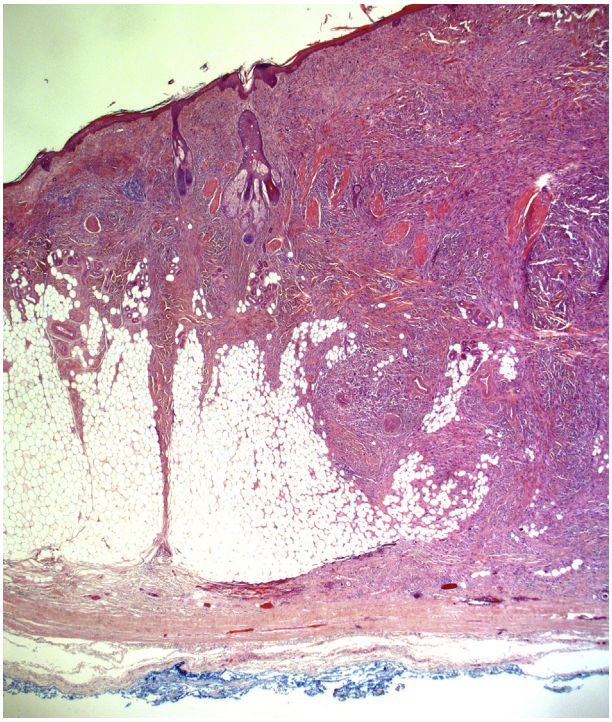

Fig 4. Pleomorphic dermal sarcoma extends into and replaces subcutaneous fat with an infiltrative growth pattern in the bottom right quadrant of the field; otherwise histological features are identical to the atypical fibroxanthoma in Figure 3.

The line of differentiation has sparked much controversy and some researchers suggest it should be regarded as a form of undifferentiated carcinoma, but more include it as a non-epithelial tumour with uncertain differentiation. Almost all immunohistochemical markers are negative; CD10 is usually positive but is not specific and can be expressed by carcinomas.

AFX has an excellent prognosis and it is debatable whether it should be considered a malignant neoplasm in most cases [47]. However, when a histologically identical tumour also shows 'significant extension into the subcutaneous fat' [48] or necrosis then it is termed a pleomorphic dermal sarcoma (PDS) and regarded as fully malignant [48] (Figure 4). PDS in the past was included under an umbrella term of 'malignant fibrous histiocytoma', some of which pre-dated most immunohistochemical and molecular analysis. However, significant extension into the subcutaneous fat is not well defined and is subjective, and biologically it may be unsatisfactory to classify otherwise histologically identical lesions based mainly on their depth of invasion; necrosis, found in some PDS, is also used as a discriminatory feature, but is relatively uncommon. The prognosis for AFX/PDS is therefore variable in the literature, as some studies separate the entities and others do not, with local recurrence and metastases ranging from 8% [49] to 20–30% [48,50], although survival with metastatic disease is accepted to be poor. Although complete excision is usual treatment for both AFX and PDS, radiotherapy may be of adjuvant benefit for those where clear surgical margins cannot be achieved [51]. More studies are required to address whether they are separate entities and to guide management.

Cutaneous Angiosarcoma

There are three main variants of primary cAS; those arising in sun-damaged skin of the head and neck, usually in elderly patients [52,53], those arising within a radiation field, usually of the chest wall several years after breast cancer treatment (average 5 years, range 1–20) [54–56] and those arising in a limb affected by chronic lymphoedema, most commonly after axillary clearance for breast cancer (after an average of 10 years) [56,57]. Outside of these three settings, cAS is very rare, although sporadic cases do occur [52], and diagnosis should be questioned, especially if not made by a specialist soft tissue or skin pathologist.

cAS of the skin of the head and neck is an aggressive neoplasm, often with a fatal course [53]. Although earlier presentations can clinically mimic an inflammatory dermatosis, bruise, vascular malformation or haemangioma, it commonly presents with more extensive disease, with solitary or multifocal erythematous or purplish patches, plaques and nodules. Histological extension beyond the clinically visible lesion is often present and clearance of the lesion by simple excision is often not achieved. Radical wide excision is potentially curative but often not achievable and, like radiotherapy, may not affect

outcome [58], although disease may be controlled by systemic therapy, including taxanes and anthracyclines [58,59].

Myc is a proto-oncogene encoding a nuclear cell cycle and cellular transformation protein. Secondary cAS after either radiation therapy or lymphoedema show MYC amplification in more than 90% of cases [60,61], whereas the primary cAS of sun-damaged skin of the head and neck rarely show this. Immunohistochemistry for c-myc can be helpful in some cases for margin assessment in these clinically ill-defined secondary cAS. They must also be distinguished from atypical vascular lesions after radiotherapy, which histologically show less atypia and lack MYC amplification or expression [60]. Radical chest wall resection and hyperfractionated accelerated radiotherapy can be safe and effective management in radiation-associated angiosarcoma of the breast [62].

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a grade 1 (low-grade) sarcoma [44] of fibroblastic differentiation seen predominantly on the trunk and proximal extremities of young to middle-aged adults. Diagnosis may be delayed due to its non-specific, sometimes apparently multinodular, presentation. Histologically it can mimic the fibrous histiocytoma group of lesions, especially atypical and cellular fibrous histiocytomas. It harbours genetic aberrations involving the PDGFB gene [63], enabling effective systemic therapy with imatinib for advanced disease [64,65]. Complete excision with 2 cm margins shows local recurrence of 1% [66] but occurs in at least 20% of cases [65], especially if incompletely excised, and Mohs surgery may have a role [67]. Postoperative radiotherapy could improve disease-free survival [68]. Transformation to a higher grade sarcoma (fibrosarcomatous transformation) occurs in up to 10% of cases and confers a worse prognosis, with death from disease in 14.7% rather than 0.8% [69]; overall, 3% of 5249 dermatofibrosarcoma protuberans cases died of disease [70].

Atypical Lipomatous Tumours and Pleomorphic Liposarcoma

Atypical lipomatous tumours are the superficial counterpart to liposarcoma of deep soft tissue and, if present in the skin, arise from underlying subcutaneous or deeper tissue. Although they harbour the same genetic aberrations, the excellent prognosis of atypical lipomatous tumours led to the change in nomenclature; simple complete excision is usually curative and recurrence is uncommon [71]. The rare pleomorphic liposarcomas of subcutaneous and dermis also have a more favourable prognosis than deeper lesions [72].

Atypical Smooth Muscle Tumour of the Dermis and Cutaneous Leiomyosarcoma

Similar to the change in nomenclature of superficial atypical adipocytic tumours, atypical smooth muscle tumours, which are probably derived from pilar smooth muscle, when confined to the dermis have been shown to have an excellent prognosis and simple complete excision may be curative [73]. Subcutaneous variants or those that significantly extend into subcutaneous fat are still designated as leiomyosarcomas and complete excision with at least 1 cm margin or Mohs surgery improves outcomes [74]. In such cases, a metastasis such as from a primary uterine leiomyosarcoma should be excluded.

Kaposi Sarcoma

Kaposi sarcoma is driven by the virus human herpes virus 8 (HHV8), synonym Kaposi sarcoma herpes virus. It presents in the skin, most commonly as solitary or multiple (and oligoclonal) lesions and is often described as a pigmented purple or red nodule with either patch, plaque or tumour stage disease. The most common site is the lower limb, followed by face and genitalia and mucosal involvement; visceral involvement without skin involvement usually occurs in AIDS. It occurs where HHV8 is endemic, including in Africa and around the Mediterranean rim, as well as most commonly in the immunocompromised, especially in those with HIV and AIDS, again in Africa. In Western countries it occurs in those with HIV/AIDS (most prevalent in men who have sex with men) and organ transplant recipients where tapering immunosuppression is the most important management [75]. Radiotherapy can be effective treatment [76]. Advanced cutaneous Kaposi sarcoma, especially when there is associated lymphoedema, can be difficult to treat. Rarely, a much more aggressive phenotype, especially in Africa, known as anaplastic Kaposi sarcoma, shows deeper invasion and behaves more like a high-grade sarcoma. In advanced-stage Kaposi sarcoma, chemotherapy with pegylated liposomal doxorubicin or paclitaxel is a common treatment, but is not usually curative [77].

Other Cutaneous Sarcomas

The most common soft tissue sarcoma to present in the skin is myxofibrosarcoma, most commonly on the limbs of the elderly, although most cases present in deeper soft tissue of the extremities. Many other soft tissue sarcoma can present in the skin, including epithelioid sarcoma on the distal extremities of young adults, synovial sarcoma, ossifying fibromyxoid tumour, especially on the head and neck, and rarer tumours, such as alveolar soft part sarcoma, clear cell sarcoma and acral myxoinflammatory fibroblastic sarcoma and haemangioendotheliomas. The *WHO classification of skin tumours* [1] and the *WHO classification of tumours of soft tissue and bone* [43] cover these entities in more detail.

Metastases in the Skin

The skin is a common site for metastases; the scalp, followed by the rest of the head and neck, is the most common site, other than the local metastases seen in chest wall skin from breast carcinoma. Unusual presentations of

cancers or difficulties in providing a diagnosis of a primary cutaneous malignancy should alert clinicians to this possibility; clearly, correlation with the patient's medical records, including imaging investigations, is vital. The incidence of different types of cutaneous metastasis is similar to the incidence of the primary lesions, such that breast, lung and colorectal cancers are common, as well as primary cutaneous malignancies, most commonly melanoma [78]; conversely, sarcoma metastases are rare. The lack of an epidermal connection, the presence of tumour necrosis and a rounded tumour profile histologically or radiologically, as well as more specific immunohistochemical phenotypes, are clues to a metastasis. Management varies depending on the tumour type, grade and degree of local and systemic spread.

Discussion

As described, there are many malignant cutaneous appendageal neoplasms and sarcomas, although none is common. As many entities show similar or overlapping pathological features, this has historically caused difficulties in diagnosis and, hence, reliable management guidelines are lacking for many of these neoplasms.

The 2018 *WHO classification of skin tumours* [1] has redefined or amalgamated some of these neoplasms while including some newer entities and this update has discussed the literature in these areas.

This improved classification, together with the increase in molecular pathology knowledge and techniques, should further enhance the diagnosis and classification of these neoplasms and enable more robust studies into their epidemiology and management.

Conflict of Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.07.019.

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