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REVIEW

WHO classification of skin tumours: key updates in the fifth edition

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WHO classification of skin tumours: key updates in the fifth edition

The 5th edition of the World Health Organization Classification of Tumours (WCT) serves as a foundation for global diagnostic standards in tumour pathology. Similar to other volumes in this series, the Skin Tumours (Skin5) edition follows a standardized approach. This edition introduces two new chapters: 'Tumours of the nail unit' and 'Metastases to skin', along with new entities across relevant chapters. This review article provides an overview of the updates in Skin5 based on currently

published evidence, with emphasis on newly introduced chapters and newly described entities that involve the skin, in particular, epidermal, melanocytic and appendageal tumours.

Keywords: appendageal tumors, hematopoetic and lymphoid tumors, keratinocytic tumors, melanocytic tumors, nail unit tumors, skin metastases, soft tissue tumors

Introduction

The 5th Edition of the WHO Classification of Tumours (WCT5) adopts Linnaean taxonomy principles, distinguishing it from the previous editions. Tumours are now classified within a hierarchy of 'Site-category-Family-Type-Subtype', moving from benign to malignant tumours across the volumes to reflect their neoplastic progression and spectrum of aggressiveness. WCT5 embraces a multidimensional approach, incorporating a range of tumour characteristics expanding beyond histopathology to include immunohistochemistry and molecular genetics, enhancing diagnostic precision.

The 5th edition benefits from the contributions of clinicians, radiologists and molecular biologists, whose input has enriched its scientific foundation and improved diagnostic reliability crucial for guiding patient treatment. Of note, the term 'variant' now exclusively refers to 'genetic variant' (no longer being used as a tumour 'subtype'), meaning an alteration in the DNA nucleotide sequence and can describe an alteration that is benign, pathogenic or of unknown clinical significance. In contrast, 'subtype' refers to a tumour that differs from the main type in at least one distinct characteristic – clinical, histologic or genetic – often suggesting a distinct treatment approach or outcome. A significant addition in WCT5 is the inclusion of 'Essential and desirable diagnostic criteria' for each entity, providing clearer guidelines for diagnosis.

As mentioned above, the 12th volume of WCT5 on Skin tumours (Skin5) has implemented the taxonomy of Site-Category-Family-Type-Subtype. As an example, 'Spitz naevus with *Alk* fusions' is organized as follows: Site: Skin; Category: melanocytic; Family: Spitz; Type: Spitz naevus; Subtype: Spitz naevus with *Alk* fusions. Skin5 introduces two new chapters: Tumours of the nail unit and Metastases to skin. Additionally, the chapter on Inherited tumour syndromes involving the skin from the previous edition has been revised and is now titled 'Genetic Tumour Syndromes associated with skin malignancies,' aligning with similar chapters across the 5th edition.

This volume also includes newly recognized entities, especially molecularly rearranged tumours, identified through the increased application of molecular techniques. A deeper understanding of the genetic landscape of melanocytic tumours has led to an expanded use of the melanocytoma terminology, which was previously applied to only a few entities.

This review of the Skin5 highlights important new diagnostic entities, changes in nomenclature and other updates from the revised 4th edition published in 2018 [1,2].

KERATINOCYTIC/EPIDERMAL TUMOURS

New information and criteria for the diagnostic distinction of keratoacanthoma (KA) from cutaneous squamous cell carcinoma (cSCC) are presented in this chapter.

Historically, KA has been considered a distinctive squamous proliferation usually of hair follicular origin, developing in response to trauma and other factors, eventually undergoing spontaneous regression [1–3]. Nonetheless, the status of KA has remained controversial because of its frequent confusion and overlap with cSCC. Because of this, KA has been

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Abbreviations: angiotropic EVMM, angiotropic extravascular migratory metastasis; AST, atypical Spitz tumour; BAP1-TPDS, BAP1 tumour predisposition syndrome; CN, congenital nevus; CNS, central nervous system; cSCC, cutaneous squamous cell carcinoma; CUP, cancer of unknown primary site; HGPs, histopathological growth patterns; IDC, indeterminate dendritic cell; IEI, inborn error of immunity; KA, keratoacanthoma; MSI/MRD, Microsatellite Instability/Mismatch Repair Deficiency; PEM, pigmented epithelioid melanocytoma; Skin5, WCT5 on Skin tumours; TMB, tumour mutational burden; WCT5, 5th Edition of the WHO Classification of Tumours.

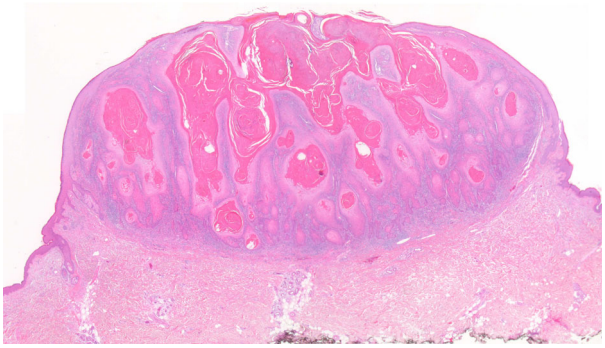

Figure 1. Squamoproliferative lesion of uncertain malignant potential. This lesion metastasized to axillary lymph node at 18 months following complete excision after a favoured diagnosis of keratoacanthoma. These architectural features are quite typical for keratoacanthoma including an exo/endophytic nodule, well-formed crater, organized multilocular infundibular-trichilemmal pattern (H&E). However, this tumour also exhibits abnormal features concerning for squamous cell carcinoma. These features include thickening of the proliferative border, cytologically increased nuclear: cytoplasmic ratios, slight hyperchromasia and, finally, loss of p16 expression with an aberrant, focally weak and cytoplasmic pattern (not shown here).

classified by many as a well-differentiated subtype of cSCC [2,4]. While the distinction between KA and SCC remains controversial, KA is likely to be considered a separate entity from SCC [5–7]. Clinical correlation, adequate biopsy sampling, histopathological and immunohistochemical criteria (by using p53, Ki67 and p16) (Figures 1 and 2) may permit distinction of KA from follicular SCC in many cases.

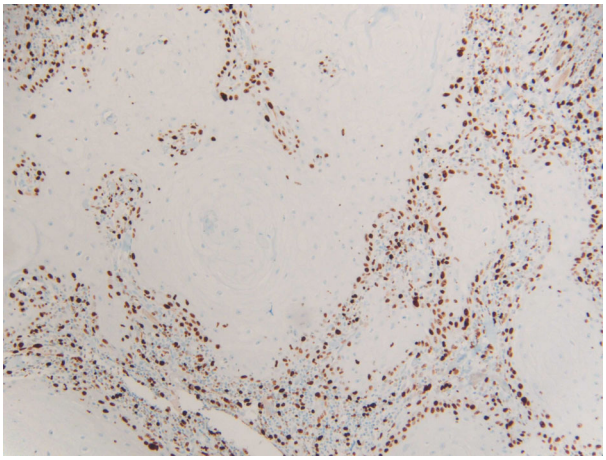

Figure 2. Keratoacanthoma. Ki67 shows a typical peripheral-only pattern of expression. Irregular Ki67 distribution beyond the peripheral cells is relatively specific for conventional squamous cell carcinoma (cSCC). A peripheral graded pattern may be seen in some well-differentiated cSCC.

However, reliable distinction of these two entities is not always possible and this uncertainty may be communicated as 'squamoproliferative tumour of uncertain malignant potential' (Figure 1).

Adenosquamous carcinoma is no longer included as a subtype of cSCC since evidence of ductal differentiation supports the classification of most of these tumours as squamoid eccrine ductal carcinoma [8,9].

Although included in the previous edition, 'Pseudovascular SCC' is no longer considered a subtype of SCC and is not a recommended term for 'Acantholytic SCC'. 'SCC with sarcomatoid differentiation' is now the only acknowledged uncommon subtype of SCC. ' Lymphoepithelioma-like SCC' is not a recommended terminology for 'lymphoepithelial carcinoma'.

MELANOCYTIC TUMOURS

The continual discovery of new genetic alterations in melanocytic lesions has provided increasing evidence for nine distinct progression pathways to melanoma [1,10–11]. This has resulted in the description of new entities, clarification of the status of particular entities and changes in nomenclature [1] in Skin5. A major focus is the detailed description of particular 'intermediate-grade melanocytic tumours' including newly emerging entities under the term 'melanocytoma' [12,13]. Consequently, a new category 'Melanocytoma' has been created within 'Melanocytic neoplasms in intermittently sun-exposed skin'. However, melanocytomas also occur in other progression pathways to melanoma, including the eye and central nervous system [1,10]. In skin and conjunctiva, 'melanocytoma' connotes morphologically distinctive dermal-based neoplasms of melanocytes that have progressed, in general, one step beyond conventional melanocytic naevi but have not yet acquired sufficient criteria for melanoma. Although formally defined by at least two pathogenic genetic alterations, for example a BRAF V600E mutation in a conventional naevus, followed by a 'second hit or hits', such as a mutation in the *BAP1* gene [12,13], melanocytoma is also recognized by morphological criteria that are often aligned with genetic criteria but not always. In brief, morphological criteria include, to varying degrees, the tumorogenic properties of increased cellularity, cytological atypia and mitotic (proliferative) activity, usually allowing separation from conventional nevi. Spitz melanocytoma (atypical Spitz tumour) and cellular blue melanocytoma (atypical cellular blue nevus) are, in general, morphological exceptions to the genetic definition of melanocytoma.

It is also emphasized that not all intermediate melanocytic lesions are melanocytomas. In particular, a large category of atypical/dysplastic naevi in the common pathway to melanoma, exhibiting higher-grade architectural and cytological atypia, is not considered to be melanocytomas [2,14]. For melanocytic neoplasms with two or more pathogenic variants that would define them as melanocytoma, the use of naevus in the diagnosis is acceptable (e.g. BAP1-inactivated naevus instead of melanocytoma), if they have entirely bland histopathological features and absence of high-risk morphological criteria.

WNT-activated deep-penetrating/plexiform melanocytoma (naevus) constitutes a change in nomenclature incorporating two closely related entities previously described as deep-penetrating naevus and plexiform spindle-cell naevus [2,12] (Figure 3). The basis for this change is the linkage of the WNT-signalling pathway to the morphologically defined pigmented spindle and epithelioid cell tumoural phenotype in these neoplasms [15,16]. These tumours are often biphasic, with a conventional naevus component commonly overlying or adjacent to the second distinctive pigmented morphological component [17]. However, monophasic tumours are also common. Of note, the term 'naevus' has been retained in this new terminology because of the indolent behaviour of the great majority of these tumours in both skin and conjunctiva [18,19]. Two subtypes are delineated: (1) the deep penetrating and (2) plexiform spindle-cell subtypes.

Pigmented epithelioid melanocytoma (PEM) is monophasic or biphasic, heavily pigmented, and usually comprised of distinctive enlarged pigmented epithelioid melanocytes, spindled or ovoid melanocytes and melanophages [20–22]. In biphasic variants, a conventional naevus remnant may be present. The genetic background/driver mutation determines the subtype of PEM. At present, these subtypes include common PEM often with a BRAF V600E driver mutation and Spitz PEM with kinase-fusion Spitz-defining alterations. Classification of *PRKC* fusion tumours is currently being reconsidered as a subtype of fusion naevus or tumour in the blue naevus family. The essential genetic alteration characterizing PEM is the *PRKAR1A* inactivation mutation. This terminology anticipates the recognition of additional PEM-defining abnormalities in *PRKAR1A* wild-type PEMs, for example Protein Kinase A-activated PEM [20].

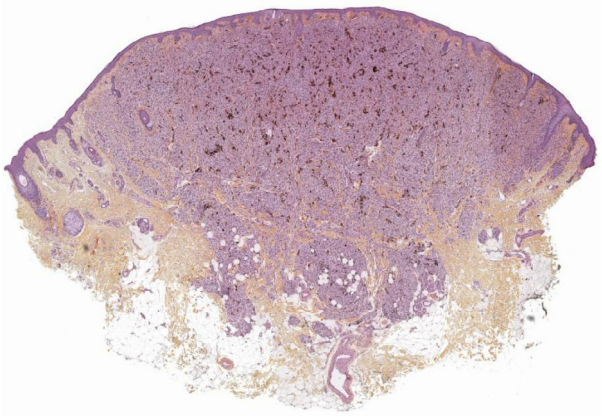

Figure 3. WNT-activated deep-penetrating/plexiform melanocytoma (naevus). Deep-penetrating subtype. Fascicles of melanocytes with scattered melanophages infiltrate the deep dermis (Haematoxylin Phloxyne Saffron stain).

BAP1 (BRCA1-associated protein-1) -inactivated melanocytoma is an epithelioid cell neoplasm occurring sporadically or in the context of the BAP1 tumour predisposition syndrome (BAP1-TPDS) [16,23]. In Skin5, this melanocytoma is distinguished from combined naevus because of its clearly defined ' two-hit' molecular and morphological phenotypes of a *BRAF* mutation supervened by BAP1 inactivation [12,24]. The term combined naevus is now reserved for melanocytic naevi with two or more morphologically distinctive populations of melanocytes that lack clear-cut genetic characterization. While neoplastic progression (or clonal evolution) may still be operative in combined naevi, insufficient tumoural tissue often confounds definitive genetic study.

Two newly described neoplasms within the MITF pathway-activated melanocytic tumours are dermal clear cell tumours with melanocytic differentiation and *ACTIN::MITF* or *MITF::CREM* translocations [25,26]. They should be distinguished from primary clear cell sarcoma and primary or metastatic melanoma.

As mentioned above, melanocytic tumours in other progression pathways to melanoma qualify as melanocytomas: Atypical Spitz tumour (AST) (melanocytoma), Cellular blue/atypical cellular blue melanocytoma and Nodule in congenital nevus (CN) (melanocytoma). The term Spitz melanocytoma has been proposed to replace AST in accordance with melanocytomas in other progression pathways [1]. Spitz melanocytoma (AST) is now recognized as intermediate in the Spitz tumour progression pathway, rather than a subtype of Spitz naevus [1,23]. Consequently, in Skin5, Spitz tumours comprise Spitz naevi, Spitz melanocytomas (AST) and Spitz melanomas.

Cellular blue/atypical cellular blue melanocytoma constitutes another change in nomenclature for

cellular blue naevus, plaque-type blue naevus and atypical subtypes (atypical cellular blue naevus) [1]. Cellular blue naevus and plaque-type blue naevus are most commonly biphasic melanocytic neoplasms with a dendritic blue naevus component and a second 'cellular' ovoid/spindle-cell component [27]. Atypical cellular blue naevi display atypical morphological features [28,29]. Sufficient high-risk morphological criteria and the presence of *BAP1* or *SF3B1* (Splicing Factor 3B Subunit 1A) mutations provide support for melanoma [1]. Atypical neoplasms (melanocytomas) falling short of melanoma criteria may be considered to have uncertain malignant potential.

Proliferative nodule in congenital naevus (CN) (melanocytoma) is another suggested change in nomenclature [1]. Such proliferative nodules in CN often show one or more atypical features representing intermediate tumoural lesions and frequently raise concern for melanoma. However, in general, such nodules usually fail to show sufficient high-risk morphological features. These proliferative nodules/melanocytomas typically have whole chromosomal gains and losses versus the structural gains and losses observed in true biological melanoma [30]. However, there are exceptions to these criteria, and biological outcome remains the gold standard for melanoma [1].

Assessment of these various melanocytomas is described in detail in Skin5. In particular, the use of high-risk morphological criteria [23] is helpful for the diagnosis. In addition, ancillary testing such as the loss of p16 expression, increased Ki67 (usually >20%), and molecular or chromosomal studies for whole or structural chromosomal alterations, various mutations or translocations, including *TERT* promoter 'hot spot' mutations, may provide additional information as to the potential presence or absence of melanoma [1].

Skin5 also includes melanocytic tumours of the central nervous system (CNS), ensuring that all types of melanocytic neoplasia are accessible in one location [1]. This is pertinent since one group of primary leptomeningeal melanocytic tumours and melanomas share the same G-αq (G protein) signalling progression pathway, as do uveal melanomas and cutaneous blue nevi and melanomas derived from blue nevi. In addition, another category of congenital melanocytic proliferations and melanomas arising in the leptomeninges that are associated with cutaneous congenital melanocytic naevi shares the *NRAS* mutations typically found in these naevi [1].

Melanoma metastatic to other organs is included as a new section in Skin5. In addition to frequent lymphatic and haematogenous spread, melanoma and other cancers may metastasize by an additional recently described mechanism: angiotropic extravascular migratory metastasis (angiotropic EVMM). Such tumour spread involves progressive migration of tumour cells along abluminal surfaces of vascular channels without entering or exiting the circulation. Angiotropic EVMM has an embryological basis since such cellular migration is common during embryogenesis [31–34]. Angiotropic tumour cell migration is observed frequently in satellite and in-transit metastases [35], and in the replacement histopathological growth patterns (HGPs) of liver metastases [36–39]. Two principal HGPs of melanoma (and other solid cancers) liver and other organ metastases are significant because of their important biological and prognostic properties [37–39]. The replacement or angiotropic infiltrating HGP connotes an aggressive and poor prognostic phenotype with resistance to therapy [36–39]. Diffuse microscopic involvement of an organ such as the liver by micrometastases of the replacement (or infiltrating) type is termed 'miliary' metastases [40]. The desmoplastic HGP represents a less aggressive inflammatory angiogenic and more favourable prognostic phenotype with formation of an expansile nodule with a surrounding collagenous desmoplastic rim [37–39].

APPENDAGEAL TUMOURS

Progress in characterizing the molecular phenotypes of a number of adnexal tumours is provided in Skin5 and these are summarized in Table 1. Cribriform carcinoma is now downgraded to cribriform tumour owing to the absence of reported recurrences and metastases. Primary cutaneous NUT (Nuclear protein in testis) carcinoma is included as a new provisional entity.

Cutaneous cribriform tumour, an indolent adnexal neoplasm with apocrine differentiation, is composed of epithelial cells with eosinophilic cytoplasm forming solid and cribriform structures and small lumina with an absence of a myoepithelial cell layer.

Primary cutaneous NUT carcinoma with rearrangements of *BRD3* or *NSD3* and a fusion partner in the NUT family is a provisional and rare entity, distinct from *NUTM1*-rearranged porocarcinoma and shares some phenotypic similarities with other NUT carcinomas in the thorax and in other organs [41,42]. Clinically, these tumours present as papules or nodules. The histopathology is that of a primitive epithelial tumour composed of monotonous cells displaying a prominent single nucleolus with frequent formation

Table 1. Molecular alterations in sporadic cutaneous adnexal neoplasms [1]

Tumour type	Mutations/fusions
Apocrine/eccrine tumours	
Adenoid cystic carcinoma	*MYB::NFIB* fusion *MYBL1::NFIB* fusion (rare)
Cutaneous mixed tumour	*PLAG1* fusions *HMGA2* fusions (rare)
Cylindroma, spiradenoma and malignant tumours evolving therein	*CYLD* inactivation ALPK1 p.V1092A mutation and *TP53* mutations (so far reported in spiradenoma and its malignant transformation)
Digital papillary adenocarcinoma	*BRAF* in a subset of cases, *TP53* mutations (rare)
Hidradenoma, hidradenocarcinoma	*CRTC1::MAML2* fusion *CRTC3::MAML2* fusion (rare)
Microcystic adnexal carcinoma	*TP53, JAK1* pathway mutations (rare)
Myoepithelioma	*EWSR1* fusion *FUS* fusion (rare)
Poroma, porocarcinoma	*YAP1* and *NUTM1* fusions *PAK1/2/3* fusions (porocarcinoma); *PAK2*-fusions (poromas) Additional *TP53, RB1, CDKN2A* mutations in porocarcinoma (rare)
NUT (adnexal) carcinoma	*BRD3 or NSD3 fusions with NUTM1 or NUTM2B*
Secretory carcinoma	*ETV6::NTRK3* fusion *NFIX::PKN1* fusion (rare)
Signet-ring cell/histiocytoid carcinoma	*PIK3CA, CDH1* mutations (rare)
Syringocystadenoma papilliferum, tubular adenoma	BRAF p.V600E mutation *HRAS*, *KRAS* mutations (rare)
Hair follicular tumours	
Adamantinoid trichoblastoma (Lymphadenoma)	*EGFR, PIK3CA, FGFR3* mutations
Trichoblastoma (including trichoepitheloma)	*CTNNB1, HRAS, PTCH1* mutations
Trichilemmoma	*HRAS* mutations
Trichogerminoma	*FOXK1::GRHL* and *GPS2::GRHL* fusions (rare)
Trichoblastic carcinoma/carcinosarcoma	*TP53, CDKN2A, TERT-p, CTNNB1* mutations (rare)
Proliferating trichilemmal tumour	*TP53, PI3KCA* mutations (rare)
Pilomatricoma and pilomatrical carcinoma	*CTNNB1* mutations *CDX2*, *LEF*-1 mutations (rare)
Sebaceous tumours	
Sebaceous carcinoma	*P53, PIK3CA, NOTCH1*, TP53, *ZNF750, RB1, FAT3, KMT2D, PCDH15* mutations
Sebaceous adenoma and sebaceoma	*HRAS, KRAS, TP53, CDKN2A, EGFR, CTNNB1* mutations (rare)
Nevus sebaceus	*HRAS, KRAS, NRAS* mutations

Note: The significance of these alterations and their role in the aetiology and prognosis should be established in future studies.

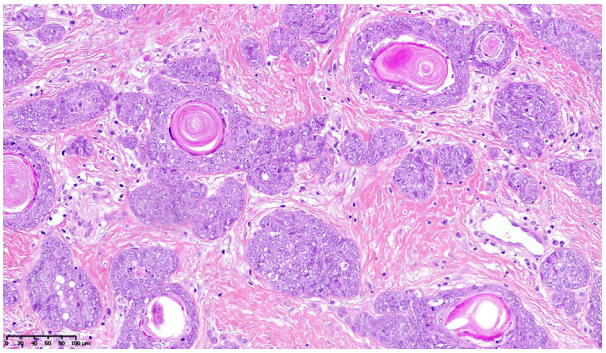

Figure 4. NUT carcinoma. Characteristic features with the presence of small round ducts and foci of abrupt keratinization in a BRD3::NUTM1 rearranged NUT adnexal carcinoma (Haematoxylin Phloxyne Saffron stain).

of ducts and keratinous cystic structures (Figure 4). They harbour *BRD3* or *NSD3* gene fusions with a partner from the NUT family (*NUTM1* or *NUTM2B*). An extracutaneous metastasis and primary *YAP1::NUTM1* rearranged poroma or porocarcinoma should be excluded (Figure 4) [41,42].

Trichodiscoma and fibrofolliculoma have been added as appendageal tumours in this volume, whereas only spindle-cell predominant trichodiscoma was covered in the previous 4th edition.

TUMOURS OF HAEMATOPOIETIC AND LYMPHOID ORIGIN

In the 5th Edition, among histiocytic and dendritic disorders, mature plasmacytoid dendritic cell proliferation associated with a myeloid neoplasm (Figure 5) and ALK-positive histiocytosis (Figure 6) are described

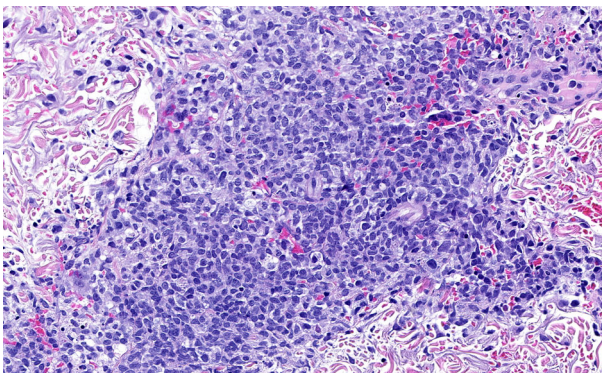

Figure 5. Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm. Aggregates of plasmacytoid dendritic cells with irregular nuclear contours, associated with some apoptotic cells (H&E).

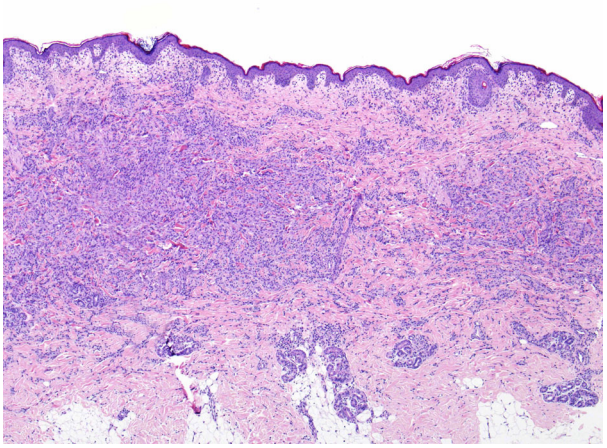

Figure 6. ALK-positive histiocytosis involving skin. A poorly circumscribed dermal infiltrate of histiocytes is observed (H&E).

for the first time. The recent correlation of disease relapse with BRAF V600E mutation in Langerhans histiocytosis provides important prognostic and potentially therapeutic information for this disorder. Another new entity mentioned is the group of inborn error of immunity (IEI)-associated T-cell lymphoproliferative disorders, which includes in particular cutaneous CD8+ T-cell rich (and histiocyte rich) infiltrates associated with inborn immunodeficiencies not linked to Epstein–Barr virus (EBV) infection. The characteristics of these new entities are summarized in Table 2. The terminology of some entities has changed in this edition. In Skin5, the term 'indeterminate dendritic cell (IDC) tumour' replaces the previous term 'IDC histiocytosis/tumour' of the 4th Edition, since it is now established as a clonal proliferation [1,43]. Reactive T- and B-cell rich lymphoid proliferations that may be triggered by various causative factors are covered in Skin5 [44]; they were previously termed 'pseudolymphoma' in the 3rd edition and not included in the 4th edition. Because of consistent indolent behaviour, primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder has now been downgraded from lymphoma status to a lymphoproliferative disorder [1,45–46].

TUMOURS OF THE NAIL UNIT

This is a new chapter dedicated to nail bed epithelial tumours, since epithelial tumours in this anatomic site were not covered in the previous edition. It includes the following entities:

Onychomatricoma is a benign matrical fibroepithelial proliferation usually arising in the nail matrix

Table 2. Tumours of haematopoietic and lymphoid origin in skin: new entities

Tumour types	Definition	Clinical features	Histopathology	Prognosis
Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm	Clonal proliferation of plasmacytoid dendritic cells with low-grade cytomorphology associated with an established myeloid neoplasm	Rash, macules, papules and, rarely, nodular lesions Predominance in male adults. Context of a defined myeloid neoplasm such as chronic myelomonocytic leukaemia or acute myeloid leukaemia [1,47]	Accumulation of mature dendritic cells with plasmacytoid morphology (Figure 6) Expression of CD123 and/or other pDC markers. May show an aberrant pDC immunophenotype and absence or low/partial expression of CD56	Correlates with adverse outcomes of the associated myeloid neoplasms
ALK-positive histiocytosis	Histiocytic neoplasm lacking high-grade cytopathologic atypia, characterized by ALK (anaplastic lymphoma kinase) immunoreactivity usually due to *ALK* gene rearrangement	Isolated skin lesions (single or multiple papules or nodules) or may be part of systemic disease. Multi-system systemic form in infancy, female predominance.	Aggregates or sheets of histiocytes, sometimes with irregular nuclear contours, lacking high-grade cytologic atypia (Figure 7), positivity for ALK by immunohistochemistry (albeit focal and weak sometimes) and two or more histiocytic markers [1,48]. *ALK* gene translocation may be present	Variable, depending on the pattern of disease involvement (isolated vs multi-system disease); skin lesions may regress spontaneously
IEI-associated T-cell lymphoproliferative disorders	CD8+ T-cell rich cutaneous infiltrates associated with inherited immunodeficiencies not associated with EBV infection	Generalized papulo-nodular indurated lesions with variable erythema, scaliness and haemorrhagic ulcero-necrotic appearance and hypogammaglobulinemia from IEI or other acquired causes [1,49]. Often in children	Granulomatous CD8+ T-cell rich dermal infiltrate with negative EBV status; Hypogammaglobulinemia from IEI or other acquired causes; exclusion of other potential infectious conditions. Genetic diagnosis of the IEI and molecular assessment for rubella virus and *TCR* gene rearrangement analysis may be performed, when available and clinically indicated	Variable, chronicity associated with limited progression

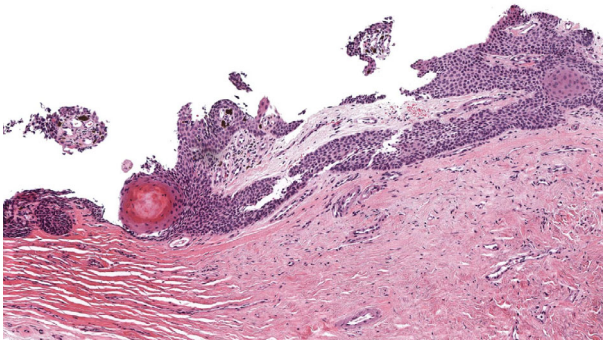

Figure 7. Onychocytic matricoma. Acanthosis of the matrical epithelium and whorls of epithelium with differentiation towards onychocytes, characterizing the acanthotic subtype (H&E).

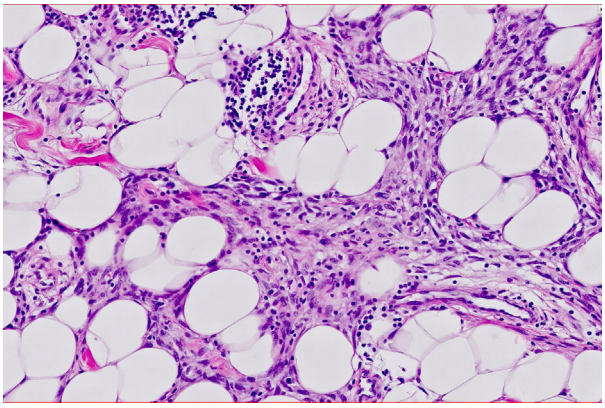

Figure 8. NTRK-rearranged spindle-cell neoplasm. Superficial tumour with *TPR::NTRK1* fusion resembling lipofibromatosis (H&E).

[50]. The nail plate may be thickened, with loculated serum and haemorrhage, and adjacent interdigitating epithelium.

Onychopapilloma, on the other hand, is a benign epithelial proliferation originating in the distal nail matrix [51] with hyperplastic nail bed and matrical metaplasia. Subungual haemorrhage and distal hyperkeratosis, with multinucleate nail bed keratinocytes, may be observed.

Ungual fibrokeratoma is a benign fibrokeratotic lesion of the nail plate occurring in the periungual areas [52]. Multiple ungual fibrokeratomas occur in tuberous sclerosis and in this clinical context are termed 'Koenen tumours'. It displays a fibrovascular core and epidermal hyperplasia, hyperkeratosis and a sausage-shaped appearance at low power view, with serum present at the distal pole of the specimen.

Onychocytic matricoma is a benign nail plate-producing tumour that usually presents as longitudinal pachymelanonychia [53] (Figure 7). For the diagnosis, the nail plate should be thickened in some area of the tumour, with hyperplasia (in some form) of the matrix epithelium and there is no dermal component. Desirable diagnostic criteria include whorls of epithelium differentiating into onychocytes, papillomatous projections of the epithelium, or an expanded keratogenous zone depending on subtype.

Subungual keratoacanthoma is a rapidly growing squamoproliferative tumour of the nail bed that may be histopathologically indistinguishable from squamous cell carcinoma without clinical information and ancillary studies (see keratoacanthoma above) [54]. Subungual tumours of incontinentia pigmenti represent a subset. They are nodular or nodulocystic lesions consisting of a lobular to cystic proliferation of eosinophilic keratinocytes, with many dyskeratotic keratinocytes present, forming clusters, with associated hyperkeratosis. Calcification of individual keratinocytes and corneocytes may be seen.

Acral naevus and melanoma are covered in the dedicated chapter for melanocytic tumours.

SOFT TISSUE TUMOURS

The Skin5 includes four new soft tissue tumour entities: *EWSR1::SMAD3* rearranged fibroblastic tumour; *NTRK*-rearranged spindle-cell neoplasm (Figure 8); superficial CD34-positive fibroblastic tumour (also known as *PRDM10*-rearranged soft tissue tumour); and *CRTC1::TRIM11* cutaneous tumour (Figure 9). Their main characteristics are summarized in Table 3. The last, specific to the skin, has not previously been described in the WCT5 of Soft Tissue and Bone tumours. With regard to changes in the terminology, 'atypical intradermal smooth muscle neoplasm' is now the preferred term to be used in place of 'cutaneous' leiomyosarcoma, now restricted to deeply located tumours. In addition, epithelioid fibrous histiocytoma has been removed from the section of fibroblastic, myofibroblastic and fibrohistiocytic tumours as in the 4th Edition and reclassified as a tumour of uncertain differentiation. The vascular tumours section has been reorganised with distinct subsections for hemangiomas, other benign vascular tumours, intermediate vascular neoplasms and malignant vascular sarcomas.

Myofibroma and myofibromatosis were covered under Fibroblastic, myofibroblastic and fibrohistiocytic tumours in the 4th edition and are included under Pericytic and perivascular tumours in Skin5. Furthermore, myxofibrosarcoma is now classified under

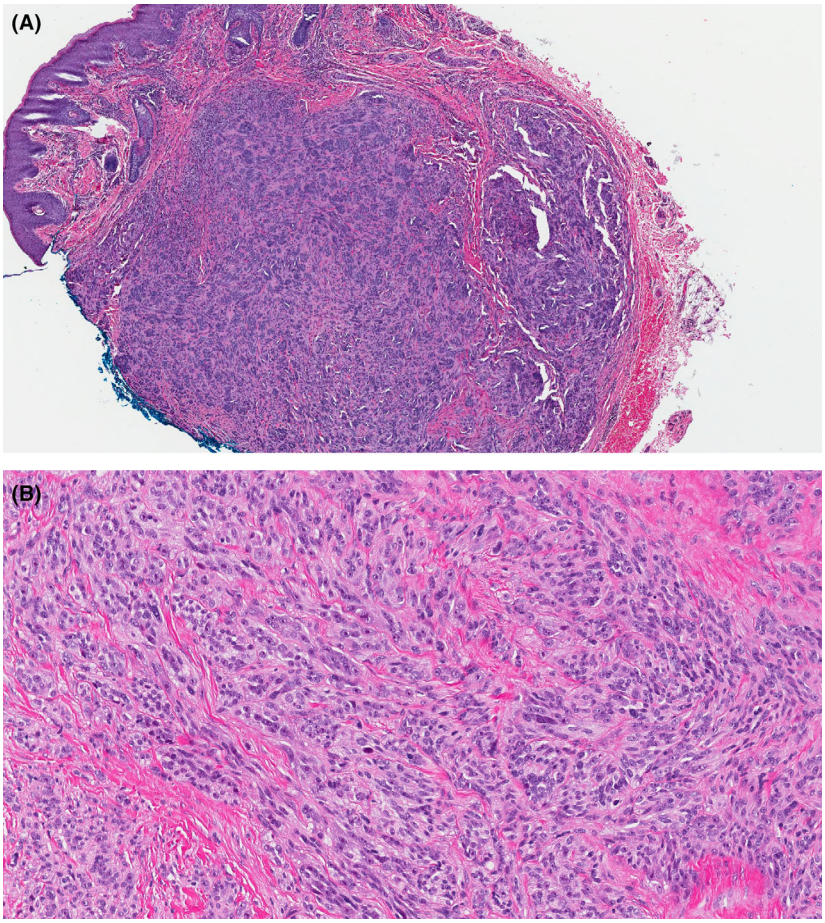

Figure 9. (**A**) *CRTC1::TRIM11* cutaneous tumour. A well-circumscribed, non-encapsulated dermal, spindle-cell tumour. (**B**) *CRTC1::TRIM11* cutaneous tumour. Cells have pale, vacuolated cytoplasm and vesicular chromatin with central, variably prominent nucleoli (H&E).

Fibroblastic, myofibroblastic and fibrohistiocytic neoplasms, in alignment with the 5th edition of the WHO Classification of Soft tissue and bone tumours [60], based on likely fibroblastic/myofibroblastic differentiation due to smooth muscle actin expression on immunohistochemical analysis. Previously, it was considered a tumour of uncertain differentiation.

METASTASES TO SKIN

This newly introduced chapter represents an alignment with the other volumes of WCT5 aiming to categorize tumours that frequently metastasize to the related organs. It comprises metastases to skin and cancer of unknown primary site (CUP).

Metastases to skin are malignancies involving mainly the dermis and the subcutaneous tissue and rarely the epidermis. They are usually epithelial, melanocytic or mesenchymal in origin. They may occur as either isolated or multiple lesions, sometimes in preferential sites (such as chest, abdomen or scalp) and may rarely be the first symptom of the malignancy. The most frequent primary cancers are breast cancer in women and melanoma in men [61]. Cutaneous metastases most often resemble their primary, and the differential diagnosis includes primary cutaneous lesions, desmoplastic lesions such as dermatofibroma, or primary cutaneous melanoma in the presence of an intraepidermal spread. Immunohistochemistry and molecular analyses may be useful to identify the origin of the tumour [62]. Recently, immunohistochemistry work-up recommendations have been published [63].

CUP may occur in the skin, although other organs are more frequently involved, such as the liver, lung, lymph nodes, brain and bones, with adenocarcinoma being the most common tumour type [64]. CUP is confirmed when a disseminated malignancy is diagnosed and a primary site is not identified despite a standardized and comprehensive diagnostic work-up.

Table 3. Soft tissue tumours in skin: new entities

Tumour types	Definition	Clinical features	Histopathology	Prognosis
EWSR1::SMAD3 rearranged fibroblastic tumour	Benign fibroblastic neoplasm with strong predilection for the hands and feet	Small painless superficial tumours in acral sites. Female predominance	Dermal and subcutaneous nodule with anastomosing hypercellular fascicles comprising bland monomorphic spindle cells lacking mitotic activity, centrally located acellular hyalinized areas. Diffusely and strongly positive for ERG, and negative for CD34 and smooth muscle Actin. *EWSR1::SMAD3* Fusion is required for the diagnosis [1,55]	Indolent but local recurrences may occur after incomplete excision
NTRK-rearranged spindle-cell neoplasm	Monomorphic spindle-cell proliferation involving the dermis and subcutaneous fat with activating NTRK or other kinase fusions [1,56]	Deep dermis and subcutis of the extremities, trunk and head and neck areas; predominance in children	Histopathologic spectrum ranging from cellular fibrous septae extending through subcutaneous adipose tissue to hypercellular tumours composed of sheets or fascicles of spindled cells; stromal or perivascular hyalinization may be prominent and a staghorn vascular pattern is common (Figure 8). Activating receptor tyrosine kinase fusion (e.g. NTRK or other) is required for determination of therapy. Pan-TRK, CD34 and S100 protein immunohistochemistry may be used for the diagnosis	Highly infiltrative, may recur after incomplete resection
CD34-positive fibroblastic tumour	Low-grade neoplasm of the skin and subcutis, characterized by proliferation of spindled cells with characteristic morphological features, diffuse expression of CD34. *PRDM10* rearrangements may be present	Slowly growing painless mass, mostly on the lower extremities, in middle-aged adults	Superficial location of prominent eosinophilic cellular infiltrates, with granular to glassy cytoplasm, marked nuclear pleomorphism, low mitotic rate, diffuse expression of CD34. *PRDM10* rearrangements are often present [1,57]. CADM3 immunohistochemistry may be used for the diagnosis	Overall excellent
CRTC1::TRIM11 cutaneous tumour	Dermal spindle and epithelioid cell tumour with partial melanocytic differentiation and *CRTC1::TRIM11* translocation [1,58–59]	Discrete, slowly growing, skin-coloured nodule without pigmentation. Ubiquitous, but more common on the limbs	Anastomosing fascicles and nests of ovoid, epithelioid and spindled cells with pale cytoplasms and vesicular nuclei (Figure 9A,B). The cells usually show diffuse positivity for SOX10, variable expression of S100 protein and focal expression of melan-A/Mart-1 and HMB45 on immunohistochemistry. The absence of *EWSR1* rearrangement is essential to exclude a clear cell sarcoma	Less aggressive than melanoma and clear cell sarcoma, with limited cases showing regional or distant metastasis

Many algorithms can be used to determine, if possible, the origin of the metastasis, utilizing testing panels of immunohistochemical markers. If available, molecular investigation may be performed, including Microsatellite Instability/Mismatch Repair Deficiency (MSI/MRD), and tumour mutational burden (TMB) analysis, to enable targeted therapy and potentially support the use of PD1 and PDL1 inhibitors in case of MSI-high/MRD and TMB-high cancers [65]. However, no superiority of 'site-specific' therapy based on gene expression profiling over standard empiric chemotherapy has been demonstrated so far [66]. In the majority of cases, CUP is associated with a poor prognosis.

GENETIC TUMOUR SYNDROMES ASSOCIATED WITH SKIN MALIGNANCIES

This chapter, previously entitled 'Inherited tumour syndromes involving the skin' in the 4th edition, has been renamed, as above, in alignment with the other volumes of the 5th edition. The subject matter is unchanged [1] with the exception of a new section on Brookle-Spiegler, an inherited autosomal dominant disease characterized by multiple cutaneous spiradenomas, cylindromas, spiradenocylindromas and trichoepitheliomas and related syndromes including multiple familial trichoepitheliomas. Malignant tumours in this setting are rare. Hence, this additional section completes the panel of the most common genetic tumour syndromes involving skin tumours.

Conclusion

Skin5 has comprehensively reviewed the latest published evidence to offer a most up-to-date understanding of cutaneous tumours. This edition expands on the previous one by encompassing a wider spectrum of entities, with advances in molecular genetics enabling the identification of new tumour types. As the integration of an ever-increasing number of molecularly defined tumours into future classifications presents ongoing challenges, WCT remains dedicated to ensuring worldwide access to essential diagnostic criteria for cancer.

Author contributions

Gabrielle Goldman-Lévy and Raymond Barnhill: these two authors contributed equally in the manuscript as first co-authors. All the other co-authors revised, edited and approved the final article.

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