

Review

The 2023 WHO updates on skin tumors: advances since the 2018 edition

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Summary

Pathology is pivotal in diagnosing skin tumors, and the precision of diagnosis is crucial to devise customized treatment plans and enhance patient care in dermatology. The latest edition of the World Health Organization's classification of skin tumors serves as a comprehensive compendium, summarizing and categorizing all recent advancements in both anatomical-pathological and molecular aspects of cutaneous neoplasms. Several relevant advances have been introduced and new entities have been described. While the fundamental structure of the classification remains unchanged, notable additions include three new sections aimed at providing a more exhaustive description of skin lesions: nail unit tumors, skin metastases, and genetic tumor syndromes associated with skin malignancies. Recent strides in molecular pathology have led to significant breakthroughs in decoding the underlying mechanisms of various skin tumors, ranging from adnexal neoplasms to hematomatoid neoplasms, soft tissue tumors, and melanocytic lesions. Of particular importance is the evolution in our understanding of melanocytic neoplasms, with the introduction of the term "melanocytoma" reserved for lesions exhibiting "intermediate" biological behavior and characterized by specific molecular mutations. The pathologic diagnosis process integrates morphological, immunohistochemical, and molecular features, playing a crucial role in clinical decision-making. The WHO classification serves as a valuable tool in promoting multidisciplinary in the management of cutaneous neoplasms with the aim of translating novel pathological discoveries into more effective treatments. This review aims to distill the major updates introduced by the new classification, providing a synthesis of the latest scientific insights.

Key words: WHO classification, skin tumors, histology, immunohistochemistry, molecular pathology

Introduction

The 5th edition of the new World Health Organization (WHO) ¹ classification of skin tumors has sparked great interest among pathologists and dermatopathologists worldwide. This eagerly awaited development represents a significant step in the field of dermatopathology, a discipline that play a crucial role in the diagnosis and management of skin tumors and constitutes roughly 30% of the histological case volume in a general pathology laboratory. The classification organization remains unchanged, with sections divided according to anatomical compartments: epithelial/keratinocytic, melanocytic, cutaneous appendages, hemolymphopoietic, and mesenchymal. Three sections have been added that allow for a more comprehensive description of skin diseases, including nail unit tumors, metastases to skin, and genetic tumor syndromes associated with skin malignancies. Recent

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advancements in molecular biology have revolutionized our understanding of tumor biology, and cutaneous neoplasms are no exception. These novelties have facilitated significant progress in elucidating the molecular underpinnings of various skin tumors, including adnexal neoplasms, where molecular studies have revealed an increasing number of mutations (some of which parallel those found in salivary gland counterparts), hematolymphoid neoplasms, soft tissue tumors, and melanocytic lesions. The multidimensional pathway classification of melanoma has been reaffirmed in this latest edition and has resulted in the identification of 9 distinct families of melanoma based on their association with solar damage, origin from specific anatomical districts, or distinct molecular pathways². An attempt has been made to simplify and unify from a taxonomic perspective the so-called “intermediate” lesions, reserving the term “melanocytoma” for some of them where specific molecular signatures are evident (such as BAP1 inactivation or WNT pathway alteration). The aim of this review is to summarize the major updates introduced by the new classification, additionally providing an illustrative iconographic section derived from the authors’ cases to visually depict the changes and additions to the classification.

KERATINOCYTIC/EPIDERMAL TUMORS

Keratinocytic/epidermal tumors describes benign, premalignant, and malignant lesions that originate from keratinocytes in the epidermis and adnexa. It encompasses benign conditions such as verrucae, acanthomas, and seborrheic keratoses, along with premalignant lesions like actinic, arsenical, and PUVA keratoses. Notably, keratinocytic malignancies, including basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), are highlighted as being more prevalent than all other cancers combined. Key insights underscore the significance of UV radiation, particularly UVB and UVA, contributing to 95% of keratinocytic tumors³. In-depth discussions on BCC emphasize histopathological diversity, presenting a classification system that recognizes subtypes with varying recurrence risks. The low-risk group includes superficial, nodular (including pigmented and keratotic subtypes), infundibulocystic (characterized by adnexal differentiation), and fibroepithelial. Typically, perineurial invasion is not present in this group, unlike the high-risk group, which includes basosquamous, BCC with sarcomatoid differentiation, micronodular, infiltrating, and sclerosing/morpheic. For the last three histotypes, unification under the term “infiltrative BCC” has been proposed for increased diagnostic reproducibility⁴. SCC, more prevalent in immuno-

suppressed populations, is characterized by several subtypes (acantholytic, clear cell, adenosquamous, lymphoepithelioma-like carcinoma, spindle cell, SCC with sarcomatoid differentiation) and differentiation grades, with UV radiation established as a significant factor. Histologically confirmed prognostic indicators for high-risk cases include tumor thickness exceeding 2 mm, invasion at Clark level IV or V, perineural invasion, primary occurrence on the ear or lip, and poor differentiation⁵. Notably, perineural invasion involving nerves with a diameter of ≥ 0.1 mm is associated with elevated disease-specific mortality rates⁶. Keratoacanthoma (KA), a low-grade squamous proliferation, is acknowledged for its distinctive clinical and histologic appearance, sparking debates about its biological potential. There are several molecular and histological overlap between KA and SCC that several studies tried to decipher. KA exhibits lower burden of genetic, epigenetic, and malignant phenotype biomarker expression abnormalities compared to SCC, suggesting that KAs are generally proliferations of low to intermittently UV-damaged skin, while SCC predominantly arises in severely UV-damaged skin⁷. Immunohistochemically, specific markers like p53 (null or diffuse) and irregular Ki-67 distribution beyond peripheral cells are relatively indicative of SCC. In contrast, concordant peripheral graded patterns for Ki-67 and p53 are typical for keratoacanthoma⁸. The role of p16 is debated, with evidence suggesting that deletion of the 9p21 region, which encodes for p16(INK4a), correlates with progression to SCC⁹⁻¹⁰. In cases where a definitive diagnosis of either KA or SCC-KA like, cannot be confidently established, the term “squamoproliferative tumor of uncertain malignant potential, keratoacanthoma-like” can be employed for challenging lesions (Fig. 1). Merkel cell carcinoma (MCC) is the primary cutaneous neuroendocrine carcinoma. From an etiopathogenic perspective, two subtypes are distinguished: polyoma virus (MCPyV)-positive¹¹ and virus-negative MCC. The latter can coexist with SCC, are characterized by mutations in the *TP53* and *RB1* genes, a UV-mutational profile with many C > T transitions, a higher total mutational burden, and a worse prognosis¹². The most sensitive immunohistochemical markers for the diagnosis of MCC include perinuclear dot-like staining for CK20 on the epithelial side and INSM1 for the neuroendocrine differentiation. Additionally, they express neurofilaments and SATB2¹³ (Fig. 2). The association with the virus can be documented through immunoreactivity with a monoclonal antibody (CM2B4 or Ab3) that recognizes the large T-antigen of MCPyV¹⁴.

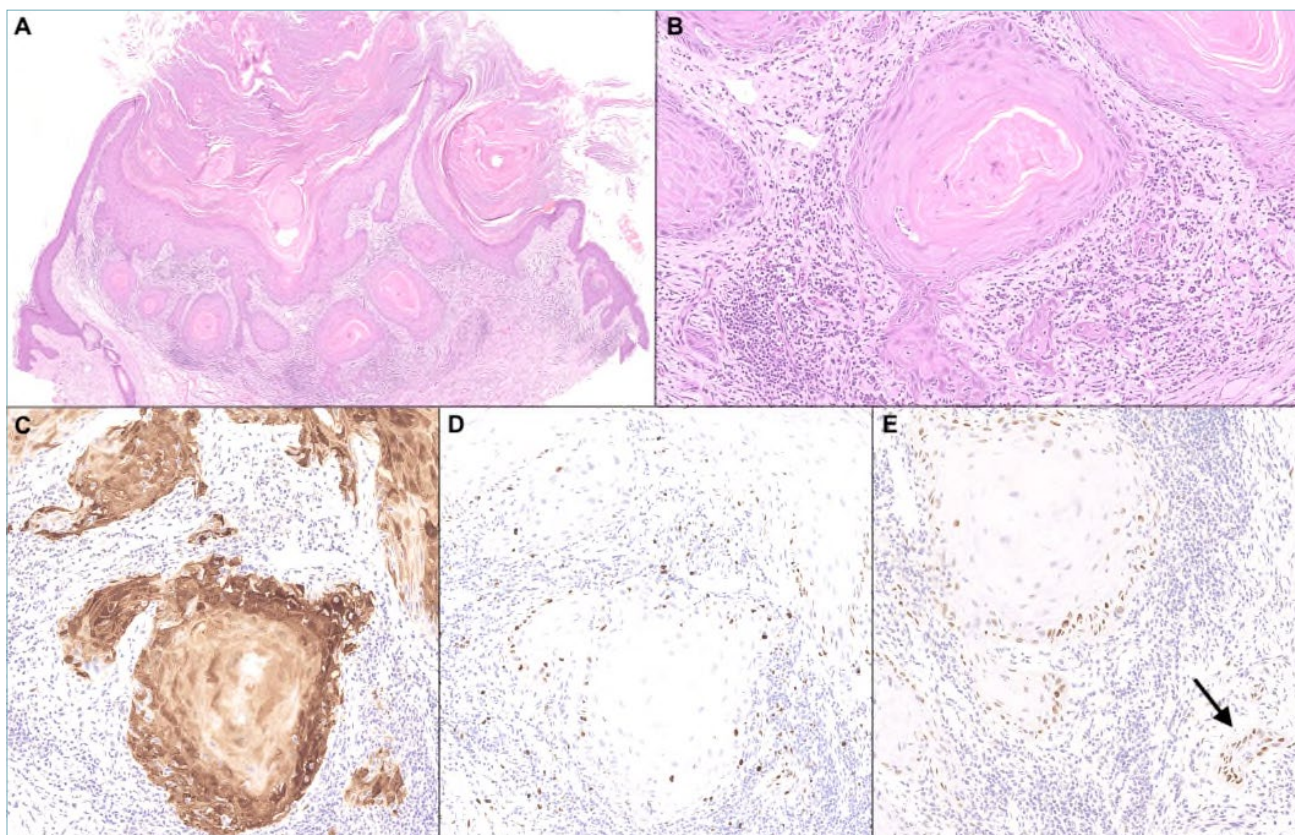


Figure 1. Squamoproliferative lesion with keratoacanthomatous features (A), characterized by intradermal nests with trichilemmal keratinization (B). Immunohistochemical staining shows positivity for p16 (C), and basal and suprabasal positivity for Ki-67 (D) and p53 (E), although the latter exhibits diffuse positivity in a small nest with infiltrative appearance (arrow). In this case, the differential diagnosis between KA and SCC may be challenging; therefore, the WHO classification proposes the terminology: “squamoproliferative tumor of uncertain malignant potential, keratoacanthoma-like”.

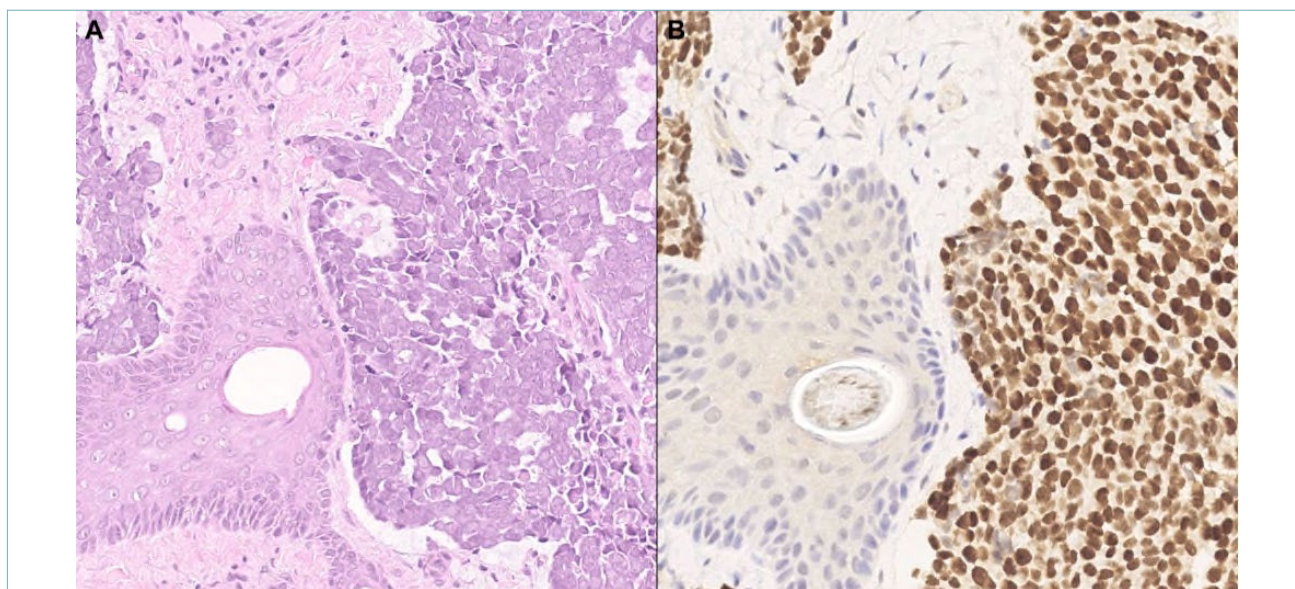


Figure 2. Merkel cell carcinoma (A) showing a diffuse positivity for SATB2 (B).

MELANOCYTIC TUMORS

Melanocytic tumors include benign, intermediate (melanocytoma) and malignant (melanoma) lesions and their classification has been further refined as new molecular signatures have been discovered integrating clinical-pathological and molecular features. The multidimensional pathway classification proposed by Bastian et al, introduced in the 4th edition, has been reaffirmed in this latest edition and has resulted in the identification of 9 distinct families of melanoma based on their association with solar damage, origin from specific anatomical districts, or distinct molecular pathways². Among melanomas occurring on sun-exposed skin, further categorization is made according to the histopathologic degree of cumulative solar damage (CSD) in the surrounding skin. This classification divides melanomas into low and high CSD subtypes, based on the extent of associated solar elastosis. Low-CSD melanomas typically include superficial spreading melanomas, while high-CSD melanomas encompass lentigo maligna and desmoplastic melanomas. Melanomas not associated with solar exposure fall into the “nonsolar” category, comprising Spitz melanoma, acral melanomas, mucosal melanoma, melanomas arising in congenital nevi, those found in blue nevi, and uveal melanomas. The first group is characterized by a UV molecular signature, which consists of a high number of point mutations, mostly cytosine to thymidine (C > T) transitions at dipyrimidine sites¹⁵. The mutation burden is a function of the amount of

solar damage. On the other hand, melanomas originating in sun-shielded skin exhibit low mutation burdens, usually lacking a UV radiation signature¹⁶ and displaying numerous copy-number changes, which often involve multiple amplifications¹⁷. The classification complexity stems from the molecular heterogeneity underlying melanoma tumorigenesis. Indeed, within each pathway, various molecular events are distinguished, including MAP-kinase (MAPK) pathway activation (such as *BRAF*^{V600E} in low-CSD types or *GNAQ*/*GNA11* in uveal melanoma), mutations in G1/S checkpoint genes (primarily *CDKN2A* loss), alterations in the p53 pathway, chromatin modifiers (such as alteration of *SWI/SNF* or *BAP1*), or telomerase activation (*TERT* promoter mutations or amplification).

Starting from the hypothesis that these events follow a hierarchical order and considering that morphologically benign naevi show a single mutation mainly in the MAPK pathway¹⁸, it has been postulated that the emergence of new mutations could lead to the formation of intermediate melanocytic neoplasms characterized by progression beyond the initial stage of tumor development but not yet reaching malignancy. These lesions display atypical histopathological features with some potential for local recurrence¹⁹. Consequently, entities previously designated as “nevi” have been renamed as “melanocytomas” and include: Wnt-activated deep penetrating/plexiform melanocytoma (naevus), pigmented epithelioid melanocytoma (PEM, also known as PRKAR1A-inactivated melano-

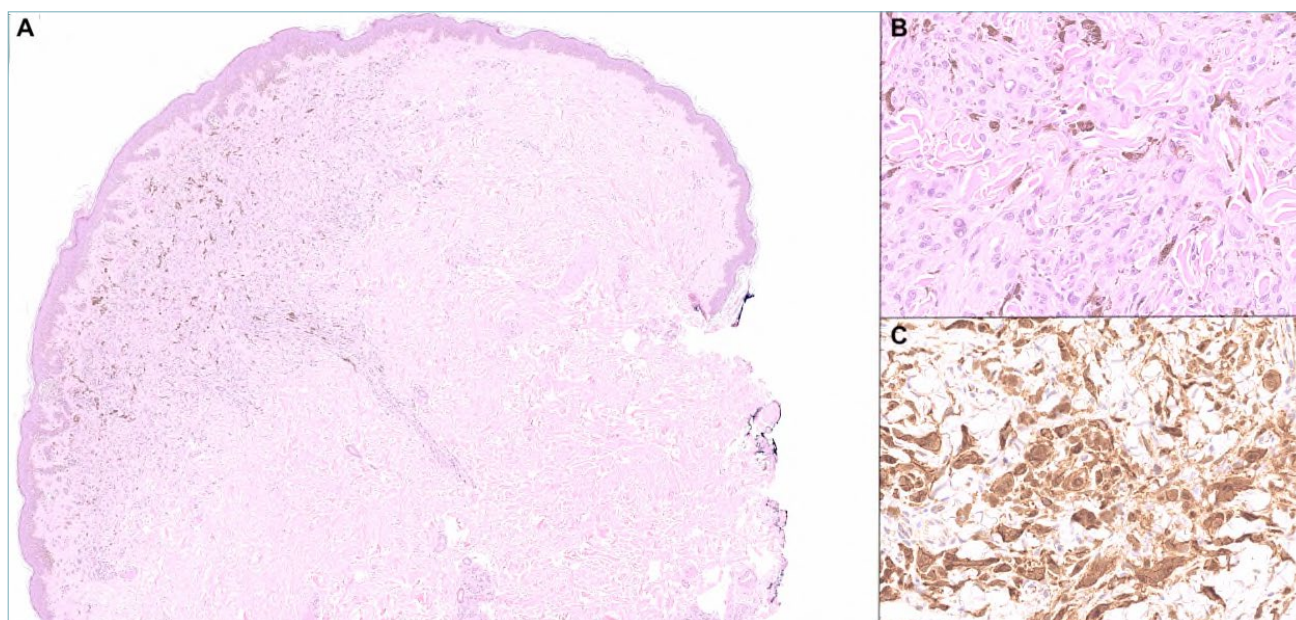


Figure 3. WNT-activated deep penetrating melanocytoma characterized by the typical cuneiform profile (A) and composed of spindled and epithelioid melanocytes and melanophages (B). The immunoreaction for beta-catenin shows nuclear positivity (C).

cytoma), BAP-1 inactivated melanocytoma, and microphthalmia-associated transcription factor (MITF) pathway-activated melanocytic tumors. Wnt-activated deep penetrating/plexiform melanocytoma (naevus) is a neoplasm constituted of spindled and/or epithelioid melanocytes and melanophages, arranged in a wedge-shaped, fascicular, or plexiform pattern that frequently extends into the deep reticular dermis. It is caused by the combined activation of the MAPK and WNT signaling pathways and can be diagnosed for the diffuse nuclear β -catenin and/or nuclear LEF1 stains by immunohistochemistry²⁰ (Fig. 3). PEM is a distinctive, melanocytic neoplasm composed of pigmented epithelioid melanocytes, characterized by *PRKAR1A* inactivation, leading to the constitutive activation of protein kinase A catalytic subunits associated with genetic changes defining other lineages of melanocytic proliferations such as activation of the MAPK pathway or presence of a kinase fusion such as *ALK*, *ROS1* and/or *NTRK*. Two-third of PEM can be immunohistochemically diagnosed highlighting the loss of cytoplasmic expression of *PRKAR1A*²¹. BAP-1 inactivated melanocytoma is characterized by epithelioid cell morphology and genetically by inactivation of the *BAP1* gene. It can occur sporadically or in association with BAP1 tumor predisposition syndrome²².

Spitz melanocytoma (previously defined as atypical Spitz tumor) is a melanocytic neoplasm characterized by one or more atypical features and it is morphologically and genetically “intermediate” between Spitz naevus and Spitz melanoma²³. All Spitz entities can harbor translocation resulting in a kinase fusion in a mutually exclusive manner (such as *ROS1*, *NTRK*, *ALK*, *BRAF*, *RET*)²⁴ (Fig. 4). MITF pathway-activated melanocytic tumors represent a novel entity of melanocytomas introduced in the WHO classification and characterized by cytoplasmic clearing and fusion genes, such as *ACTIN::MITF* (clear cell tumor with melanocytic differentiation and *ACTIN::MITF* Translocation [CCTMAM]) and *MITF::CREM* (clear cell tumor with melanocytic differentiation and *MITF::CREM* translocation [CCTMMC]) translocations, resulting in overactive MITF pathway²⁵.

A new section is dedicated to primary melanoma arising in the central nervous system. These entities affect the meninges and stem from leptomeningeal melanocytes or colonization of the meninges by melanoblasts within the context of neurocutaneous melanosis or congenital nevus syndrome. They are categorized into circumscribed and diffuse meningeal melanocytic neoplasms, including melanocytomas and melanomas. Circumscribed forms are caused by mutations in the *Gαq* pathway, similar to uveal melanomas and melanomas originating from blue nevi, suggesting that all

these entities involve melanocytes unrelated to epithelia. Diffuse forms typically occur in children within the context of congenital nevus syndrome and are more commonly associated with *NRAS* and, rarely, *BRAF* mutations²⁶. The definitions of Intraepidermal Atypical Melanocytic Proliferation of Uncertain Significance (IAMPUS), Superficial Atypical Melanocytic Proliferation of Uncertain Significance (SAMPUS), and Melanocytic Tumor of Uncertain Malignant Potential (MELTUMP) have been reaffirmed in the latest WHO classification. The first two are reserved for lesions that do not meet all the criteria for a diagnosis of melanoma in situ or in the radial growth phase, re-

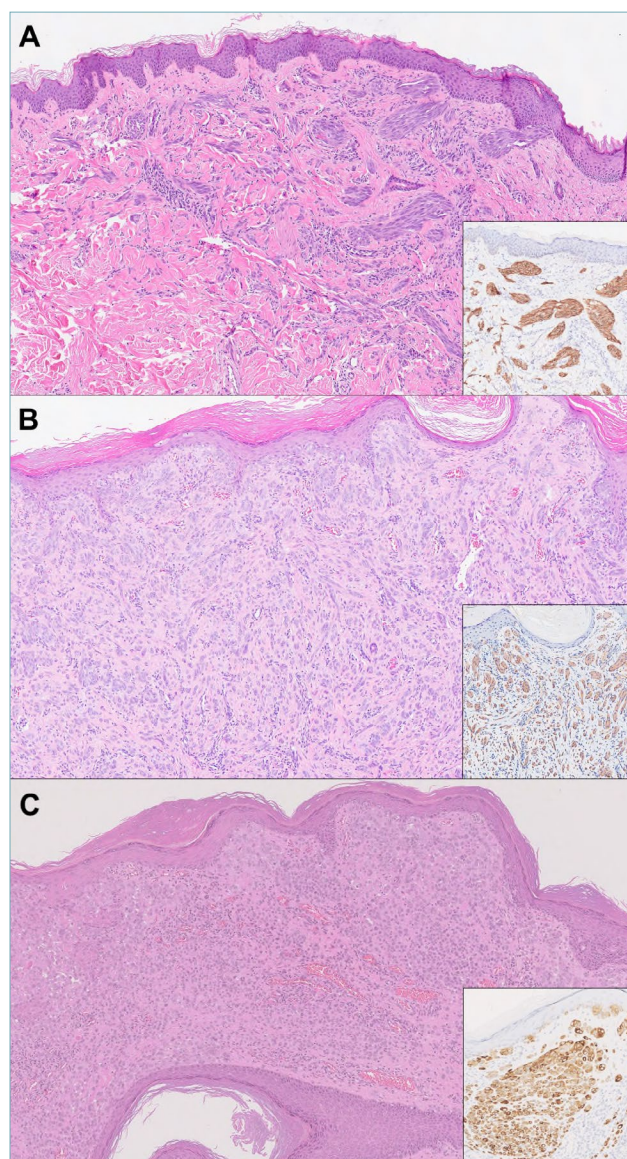


Figure 4. Spitz melanocytomas displaying immunopositivity for ALK (A), ROS1 (B) and pan-TRK (C).

spectively, and represent neoplasms with an extremely low risk of distant spread. MELTUMP is reserved for melanocytic lesions where the possibility of a vertical growth phase for melanoma cannot be ruled out.

Finally, the latest revision of the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx V2.0)²⁷ schema has been proposed, aiming to provide a classification based on the management of melanocytic lesions to facilitate dialogue between pathologists and clinicians. Specifically, four classes have been identified: Class I, with a very low risk of progression to melanoma (including common acquired and congenital nevi without atypia, dysplastic nevi with low-grade atypia, common blue nevus); Class II, with a low risk of progression warranting further evaluation (including dysplastic nevi with high-grade atypia, Spitz nevus, tumor/melanocytoma and atypical variants, cellular blue nevus/melanocytoma and atypical variants, plexiform or deep penetrating nevus/melanocytoma, lentigo maligna, melanoma in situ); Class III, encompassing melanoma AJCC stage pT1a with low risk for local and regional metastasis; and Class IV, including melanoma AJCC stage pT1b or greater, characterized by moderate to increased risk for regional and/or distant metastasis.

APPENDAGEAL TUMORS

Cutaneous adnexal tumors represent a heterogeneous group of neoplasms that exhibit differentiation towards various skin appendages. This category encompasses tumors with predominant apocrine, eccrine, follicular, sebaceous, and multilineage features. Additionally, it includes entities that are site-specific, originating from specific anatomical structures such as the glands of Moll and anogenital mammary-like glands. The Figure 5 illustrates benign entities alongside their malignant counterparts, representing groups of neoplasms with eccrine/apocrine, follicular, and sebaceous differentiations. Benign tumors are significantly more prevalent than their malignant counterparts and can manifest at any age. Some lesions include a benign component, indicating progression from pre-existing conditions. Immunohistochemistry plays a limited role in the diagnosis of adnexal tumors, but, in certain situations, it can be useful, such as in highlighting ductal differentiation via EMA/CEA²⁸, sebaceous differentiation via androgen receptor²⁹ (Fig. 5H), and pilomatrical differentiation via nuclear beta-catenin³⁰ (Fig. 5F). Adnexal neoplasms may serve as indicators of hereditary syndromes, with syndromic cases often being multiple and commonly found in the head and neck region. The key revisions in the new WHO classification pertain to the recent advancements in the molecular pathology of adnexal tumors, offering valuable insights into their

classification. Notably, a substantial portion of poromas and certain porocarcinomas has been identified to harbor gene fusions, specifically *YAP1::MAML2* or *YAP1::NUTM1*. Immunohistochemistry utilizing NUT aids in the identification of lesions with *NUTM1* rearrangements³¹. Additionally, some hidradenomas exhibit the presence of a *CRTC1::MAML2* fusion gene³². In certain spiradenomas and spiradenocarcinomas, *ALPK1* mutations have been identified, activating the NF-κB pathway, and interestingly, these mutations are mutually exclusive of *CYLD* mutations³³.

Another noteworthy discovery includes the identification of *ETV6::NTRK3* translocation and *NFIX::P-KNI* fusion in cutaneous secretory carcinoma³⁴. A novel addition to the classification is the introduction of cutaneous NUT carcinoma, which is provisionally categorized. These tumors are characterized by rare *BRD3::NUTM1* or *NSD3::NUTM1* rearrangements and present as dermal, infiltrating neoplasms arranged in islands, cords, and/or nests. They exhibit glandular and squamoid differentiation with abrupt keratinization, vesicular nuclei, prominent nucleoli, and positive NUT immunohistochemistry. Furthermore, CEA/EMA highlights ductular differentiation. Adnexal carcinomas associated with *NUT* gene alterations exhibit metastatic potential, yet their behavior is comparatively less aggressive than classic NUT carcinomas characterized by *BRD4::NUTM1* fusions³⁵. Lastly, the term “cribriform carcinoma” has been reevaluated and renamed as “cribriform tumor,” although the definite malignant potential remains unclear.

Tumors of the nail unit

The WHO classification introduces a new section on nail unit epithelial tumors that are classified as benign or malignant neoplasms derived from the epithelium of the nail bed. The classification includes onychomatricoma, onychopapilloma, ungual fibrokeratoma, onychocytic matricoma, subungual keratoacanthoma and one malignant neoplasm represented by onycholemmal carcinoma, a variant of squamous cell carcinomas arising from the nail bed. Onychomatricoma is a benign fibroepithelial proliferation of the nail matrix, including different subtypes such as pleomorphic, pigmented, myxoid and proliferative³⁶. Onychopapilloma represents a benign epithelial proliferation originating in the distal nail matrix³⁷. Ungual fibrokeratoma is a benign fibrokeratotic lesion occurring in the periungual areas and, when multiple, can be sign of tuberous sclerosis (so-called Koenen tumor)³⁸. Onychocytic matricoma is a benign nail plate-producing tumor that usually presents as longitudinal pachymelanonychia

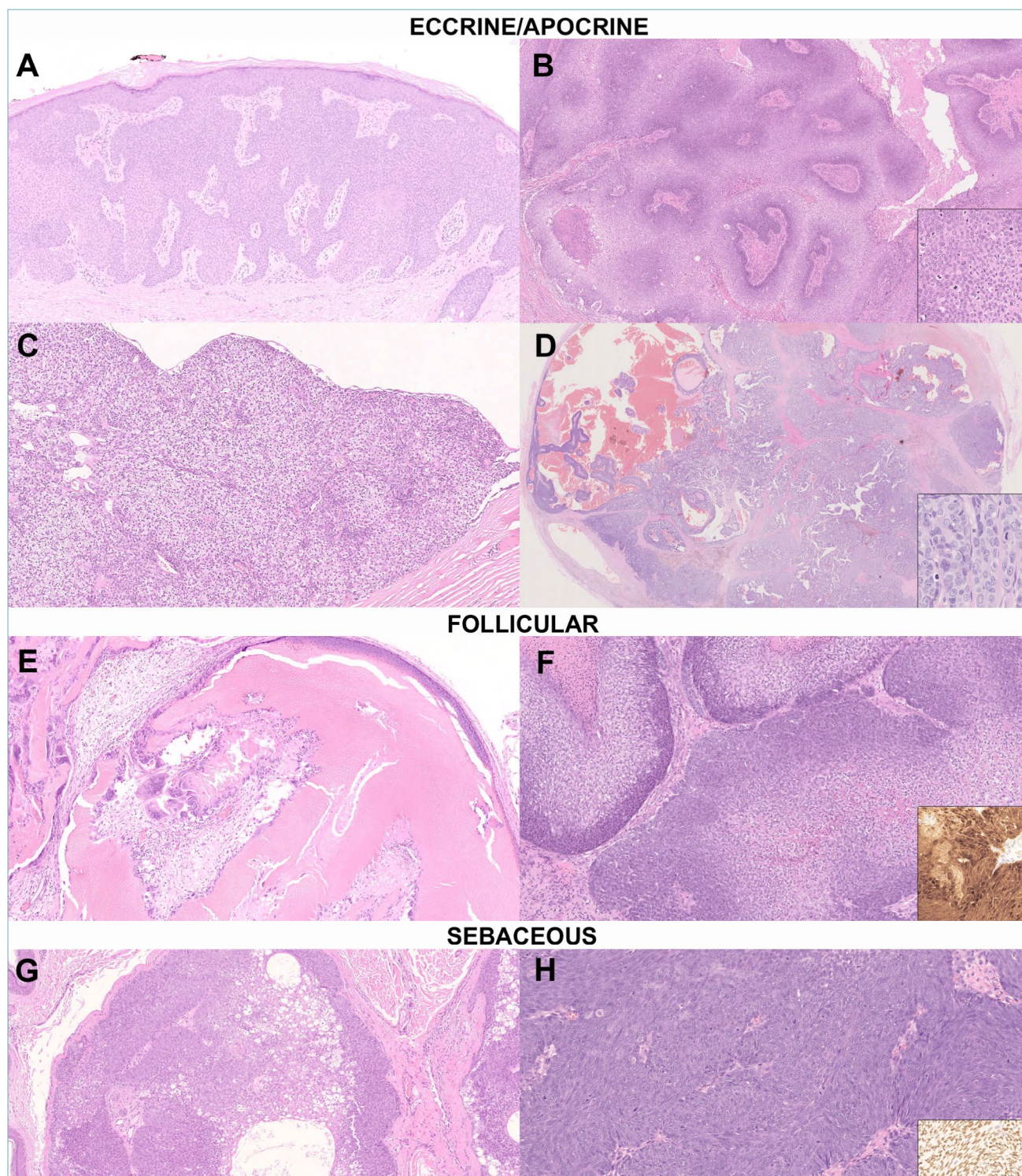


Figure 5. The panel displays several benign and malignant entities belonging to adnexal neoplasms with apocrine/eccrine, follicular, and sebaceous differentiation. Poroma (A). Porocarcinoma (B) with a high magnification detail showing brisk mitotic activity (inset of B). Clear cell hidradenoma (C). Hidradenocarcinoma (D). At high magnification, atypical cells with brisk mitotic activity are observed (inset of D). Pilomatricoma (E). Pilomatrix carcinoma (F) showing immunohistochemical expression of β -catenin (inset of F). Sebaceoma (G). Sebaceous carcinoma (H) with diffuse nuclear expression of the androgen receptor (inset of H).

and include three histotypes: acanthotic, papillomatous and keratogenous³⁹. Finally, subungual keratoacanthoma is a nail bed rapidly growing squamoproliferative tumor⁴⁰.

Tumors of hematopoietic and lymphoid origin

Regarding the chapter on tumors of hematopoietic and lymphoid origin, the most significant updates concern dendritic cell and histiocytic neoplasms, T-cell and NK-cell lymphoproliferative disorders and neoplasms. Four categories of histiocytic and dendritic cell disorders have been grouped: plasmacytoid dendritic, Langerhans cell, histiocytic, and interdigitating dendritic neoplasms. Among dendritic cell neoplasms, a new entity has been introduced known as mature plasmacytoid dendritic cell proliferation, representing a low-grade proliferation of plasmacytoid dendritic cells associated with myeloid neoplasms such as chronic myelomonocytic leukemia and acute myeloid leukaemia⁴¹. Recent evidence has highlighted that the *BRAF*^{V600E} mutation plays a role as a negative prognostic factor in Langerhans cell histiocytosis, although, on the other hand, it represents a therapeutic target⁴² (Fig. 6). A newly identified entity known as ALK-positive histiocytosis has emerged, characterized by a histiocytic neoplasm histologically resem-

bling juvenile xanthogranuloma, exhibiting ALK gene rearrangement and positive ALK immunohistochemical staining⁴³. Moreover, there has been a shift in terminology from “indeterminate dendritic cell histiocytosis” to “indeterminate dendritic cell tumor.”

Primary cutaneous lymphomas (CL) represent the second most common group of extranodal lymphomas and encompasses a diverse array of lymphoma entities. Among CL, primary cutaneous T-cell lymphomas (PCTCL) represent the majority, with mycosis fungoides (MF) and cutaneous CD30+ lymphoproliferative disorders alone accounting for 80% of all CTCL. The rare subtypes of PCTCL are now listed as individual entities, e.g. 1) subcutaneous panniculitis-like T-cell lymphoma, 2) extranodal NK/T-cell lymphoma, 3) primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, 4) primary cutaneous γ/δ T-cell lymphoma, 5) primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder and 6) primary cutaneous acral CD8-positive lymphoproliferative disorder. The WHO recommends that the category Not Otherwise Specified (NOS) should be used only for cases that do not fit in these categories. Regarding changes of classification, cutaneous CD8-positive acral T-cell lymphoma is reclassified as a lymphoproliferative disorder due to his indolent course with excellent clinical outcomes⁴⁴. A new section concerning lymphoproliferative disorders associated with inborn errors of immunity has

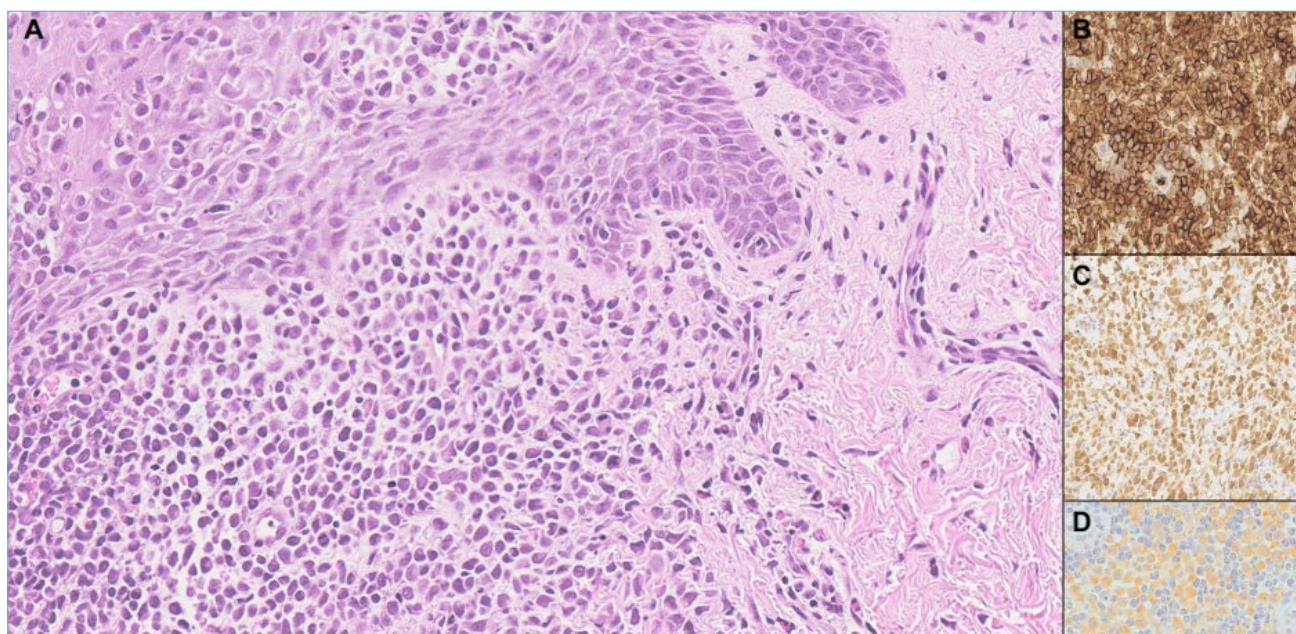


Figure 6. A cutaneous histiocytic infiltrate with the presence of eosinophilic granulocytes. The histiocytic elements are immunopositive for CD1a (A), S100 (B), and BRAF VE1 (C). These findings are conclusive for Langerhans cell histiocytosis.

been introduced. These disorders are characterized by CD8-positive T-cell-rich dermal infiltrates, sometimes associated with granulomatous inflammation, within the context of congenital immunodeficiencies. These conditions may manifest as papules, nodules, and/or ulceronecrotic lesions ⁴⁵, with EBV in-situ hybridization consistently negative.

Soft tissue tumors

The chapter dedicated to soft tissue tumors focuses on entities primarily found in the skin or those with characteristic expressions in the skin. The WHO classification recognises four tumor behavior categories: benign, locally aggressive intermediate, rarely metastasizing intermediate, and malignant. Grading, predicting clinical behavior based on histological variables, applies to some sarcomas. The widely used AJCC/UICC staging system incorporates histological grading and site of involvement ⁴⁶. Cutaneous sarcomas generally carry a lower risk of metastasis compared to deeper-seated counterparts. Prognosis is assessed based on histological grade, histological subtype, site, and tumor size. Four new entities have been added to the new classification: *CRTC1::TRIM11* cutaneous tumor, superficial CD34-positive fibroblastic tumor, *EWSR1::SMAD3* rearranged fibroblastic tumor, and *NTRK*-rearranged spindle cell neoplasm. *CRTC1::TRIM11* cutaneous tumor is a malignant neoplasm of uncertain differentiation, with partial melanocytic differentiation due to the namesake translocation ⁴⁷. Predominantly found on the extremities, this tumor is generally indolent but may exhibit local recurrence or metastasis. Histologically they resemble clear cell sarcoma, characterized by a dermal neoplasm composed of spindled/epithelioid cells featuring pale cytoplasm, arranged in nests or fascicles, and exhibiting a vaguely palisaded appearance. The tumor shows diffuse SOX10 expression with variable positivity for S100 and other melanocytic markers. Superficial CD34-positive fibroblastic tumor is an indolent neoplasm occurring in the skin and subcutis, primarily affecting the extremities, with the morphologic, immunohistochemical, and molecular features superimposable with *PRDM10*-rearranged soft tissue tumor ⁴⁸. Histologically, it is characterized by a mixture of spindled and epithelioid cells, sometimes lipidized, displaying moderate to marked pleomorphism, prominent nucleoli, nuclear pseudo-inclusions, eosinophilic cytoplasm, and low mitotic activity (Fig. 7). Immunohistochemistry consistently reveals CD34 expression, with focal immunoreactivity for keratins in close to 70% of cases. The *EWSR1::SMAD3* rearranged fibroblastic tumor is an uncommon fibroblastic neoplasm primarily found

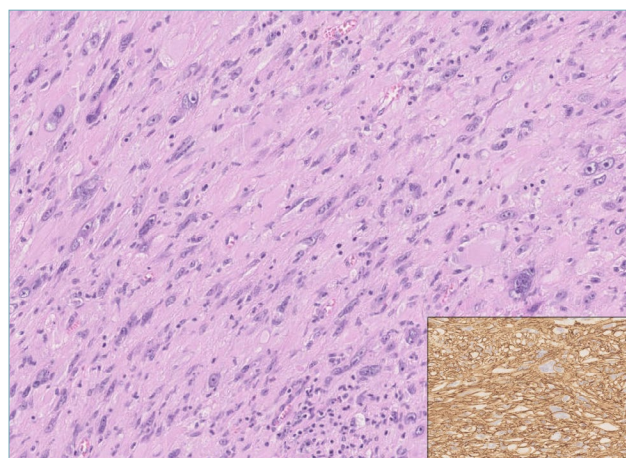


Figure 7. Superficial CD34-positive fibroblastic tumour composed of spindle and epithelioid cells with moderate to marked pleomorphism. Immunohistochemistry show strong CD34 expression (inset).

in the subcutaneous tissues of the hands and feet ⁴⁹. It presents as a well-defined superficial proliferation characterized by intersecting hypercellular fascicles composed of bland, monomorphic spindle cells with no mitotic activity. Notably, it consistently exhibits diffuse strong ERG immunopositivity, while testing negative for SMA, EMA, SOX10, CD34, and S100. Generally, the prognosis is benign, although local recurrence may occur following incomplete excision.

Lastly, the *NTRK*-rearranged spindle cell neoplasm comprises a group of spindle cell lesions frequently observed in children, involving the deep dermis and subcutis of the extremities, trunk, and head and neck. Histologically, the tumor exhibits several morphological features, ranging from lipofibromatosis-like patterns to more cellular arrangements ⁵⁰. Immunohistochemistry reveals variable co-expression of CD34, S100, and occasionally SMA. Pan-TRK is typically diffusely expressed in tumors with activating *NTRK* fusions. The tumor is highly infiltrating and may recur after incomplete resection. Moreover, there have been subtle adjustments to key terminologies. The term “atypical intradermal smooth muscle neoplasm,” initially introduced in the prior edition, is now the preferred designation for cutaneous leiomyosarcoma. The latter should be specifically reserved for tumors located deep within tissues. Additionally, epithelioid fibrous histiocytoma has been reclassified under the category of tumors with uncertain differentiation, marking its departure from the previous classification within fibrohistiocytic tumors.

Metastases to skin

The 5th edition of WHO classification include a new chapter dedicated to skin metastases that represent an adverse prognostic factor. Virtually any malignancy (epithelial, melanocytic, or mesenchymal lesion) can metastasize to the skin⁵¹. The most common origin is breast in women and melanoma in men, followed by lung, colon, head and neck, ovary, and others⁵². The histological features reflect those of the primary malig-

nancy, and immunohistochemistry proves valuable in identifying its origin⁵³.

Genetic tumor syndromes associated with skin malignancies

A newly introduced section highlights genetic tumor syndromes associated with skin malignancies. This comprehensive segment delves into various syn-

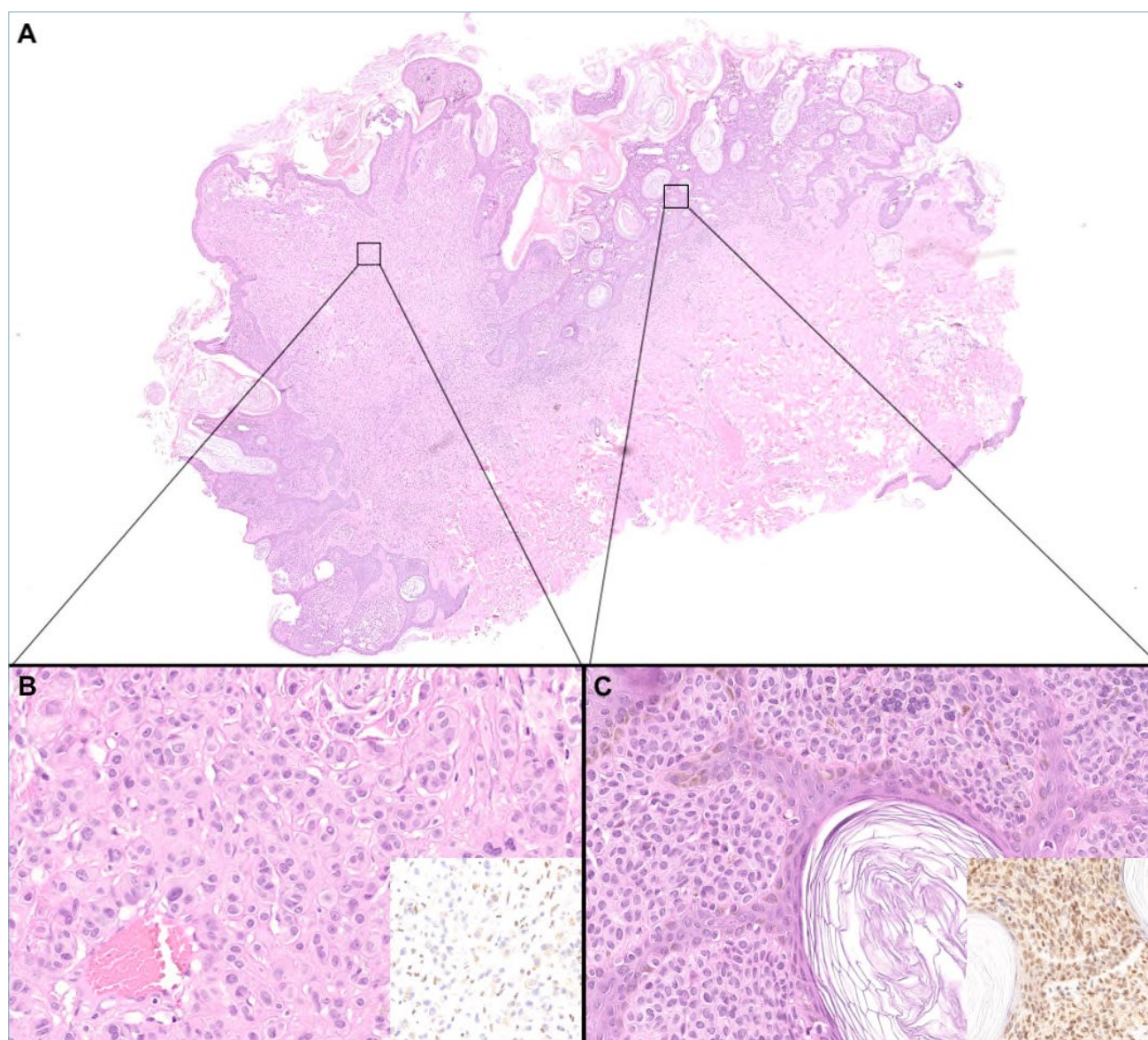


Figure 8. BAP1-inactivated melanocytoma. A low-power view lesion resembling a benign papillomatous nevus, although one papilla appears more expanded, conferring asymmetry (A). At high magnification, a dual cellular population is evident: one epithelioid characterized by well-defined cellular contours, abundant cytoplasm, prominent nucleoli (B), and loss of nuclear immunohistochemical expression of BAP1 (inset of B); and a second population consisting of non-atypical melanocytes (C) showing preserved immunohistochemical expression of BAP1 (inset of C).

dromes linked with cutaneous neoplasms, encompassing familial melanoma, BAP1 tumor predisposition syndrome, xeroderma pigmentosum, nevoid basal cell carcinoma syndrome (commonly known as Gorlin syndrome), Carney complex, Muir-Torre syndrome, and Brooke-Spiegler and related syndromes. Each syndrome represents a distinct genetic predisposition associated with the development of skin malignancies, contributing to a more nuanced understanding of the complex relationship between genetics and cutaneous tumors. Familial melanoma is characterized by the presence of either two first-degree relatives or three or more individuals with melanoma on the same side of the family (regardless of their degree of relationship) being diagnosed with melanoma⁵⁴. Commonly linked to disruptions in *CDKN2A*⁵⁵,

familial melanoma presents with an earlier onset, multiple primaries, and associations with atypical nevi. Additionally, germline variants in genes (such as *BAP1* and *POT1*) contribute to distinct phenotypes⁵⁶. *BRCA1*-associated protein-1 (BAP1) tumor predisposition syndrome is an autosomal dominant hereditary cancer syndrome arising from germline mutations in the *BAP1* gene⁵⁷. Individuals with pathogenic BAP1 variants face an elevated risk of diverse tumors, notably BAP1-inactivated melanocytic nevi/tumors, uveal melanoma, cutaneous melanoma, mesothelioma, renal cell carcinoma, and basal cell carcinoma. The syndrome typically manifests with multiple skin-colored to reddish-brown dome-shaped papules, mainly on sun-exposed skin, beginning in the second decade of life. The syndrome arises from heterozygous

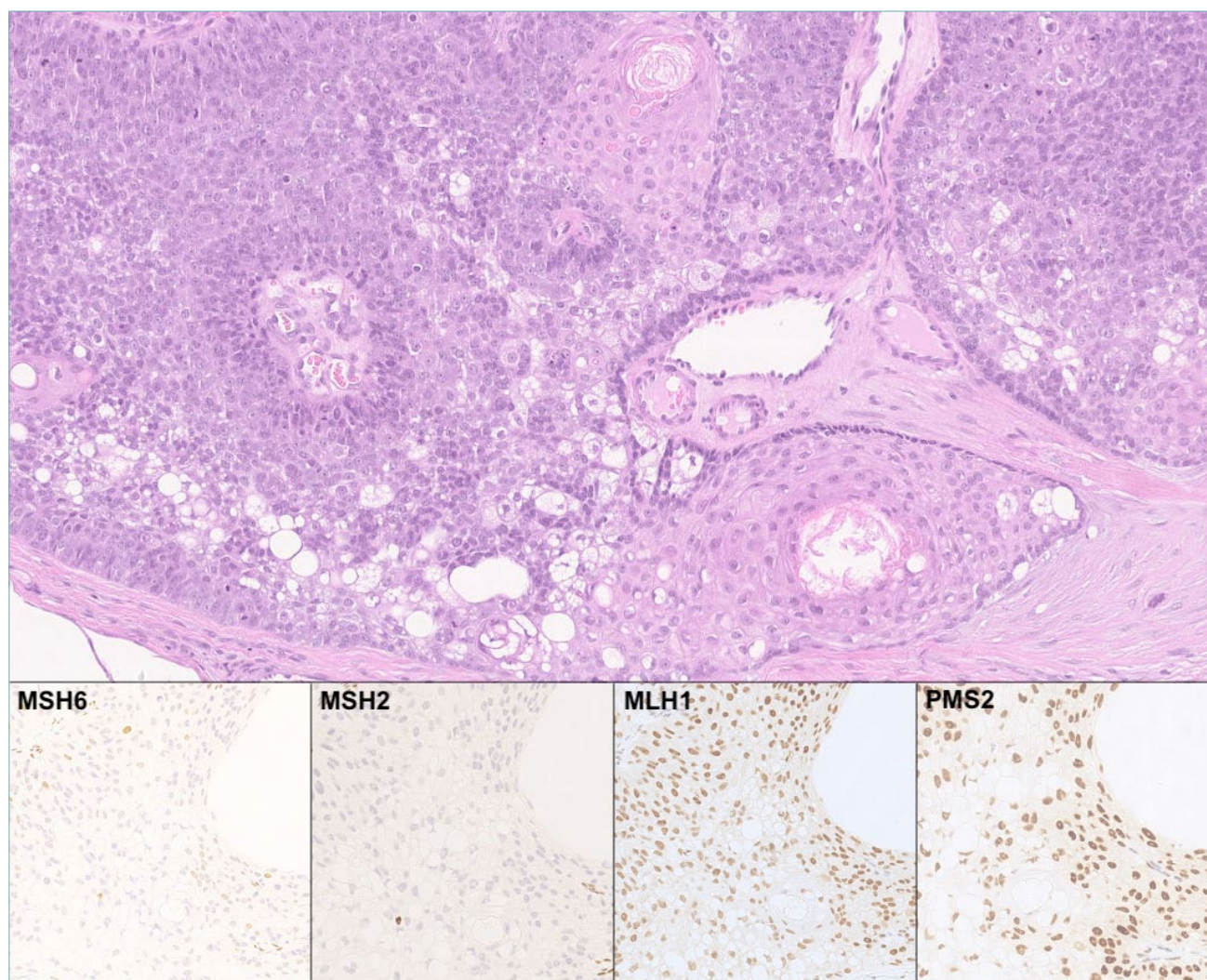


Figure 9. Sebaceoma showing loss of expression of mismatch repair proteins MSH2 and MSH6. The expression of MLH1 and PMS2 appears preserved. These findings could be associated with Muir-Torre syndrome.

mutations in the *BAP1* gene, leading to inactivation of BAP1's tumor-suppressor functions. Histologically, BAP1-inactivated melanocytic nevi/tumors exhibit a spectrum from benign lesions to potentially more aggressive melanocytomas⁵⁸ (Fig. 8). Xeroderma pigmentosum is an autosomal recessive disease characterized by deficient nucleotide excision repair of DNA damage, leading to heightened cellular sensitivity to ultraviolet (UV) radiation⁵⁹. Clinical manifestations include skin sensitivity to sunlight, ocular photophobia, and the early appearance of freckle-like skin pigmentation, often progressing to neoplastic changes in sun-exposed areas. Tumors primarily manifest on UV-exposed skin and eyes, with increased occurrence of haematological malignancies and brain tumors. Nevroid basal cell carcinoma syndrome, also known as Gorlin syndrome, is an autosomal dominant disorder linked to developmental abnormalities and a predisposition to both benign and malignant tumors⁶⁰. It is characterized by multiple manifestations, including BCCs, odontogenic keratocysts, calcification in the central nervous system, and various skeletal and skin abnormalities. The syndrome results from inactivating constitutional sequence variants in the *PTCH1* gene, *SUFU*, and, rarely, *GPR161*.

Carney Complex is an autosomal dominant tumor predisposition syndrome characterized by spotty skin pigmentation, nevi, myxomatosis, secretory endocrine tumors, and pigmented schwannomas⁶¹. *PRKAR1A* gene mutations are identified in 60% of cases. Typically diagnosed in the early 20s, the syndrome exhibits its various clinical features affecting the skin, heart, mucosa, endocrine glands, peripheral nerves, and bones.

Muir-Torre Syndrome (MTS) is an autosomal dominant tumor predisposition disorder characterized by cutaneous neoplasms, including sebaceous tumors (Fig. 9) and keratoacanthomas, along with visceral malignancies⁶². MTS has been identified in at least 9% of Lynch syndrome cases. It is linked to mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), and a similar phenotype can be observed in individuals with inherited *MUTYH* pathogenic mutations. Visceral malignancies associated with MTS involve various organs, such as the colorectum, endometrium, stomach, etc.

Brooke-Spiegler Syndrome is an autosomal dominant inherited disease characterized by multiple cutaneous spiradenomas, cylindromas, spiradenocylindromas, and trichoepitheliomas, with occasional involvement of the salivary glands⁶³. The tumors typically manifest on the head and neck, presenting as skin-colored, reddish, or blue nodules that can coalesce and increase in number with age. The germline heterozy-

gous pathogenic sequence variants in *CYLD* on chromosome 16q12-q13 are implicated in BSS. Malignant transformation, especially in cylindromas, spiradenomas, and spiradenocylindromas, may lead to rapid growth, ulceration, bleeding, and potential pulmonary metastasis.

Conclusions

The recent WHO classification has marked a significant step forward towards a more comprehensive categorization of cutaneous neoplasms, characterized by intrinsic heterogeneity due to the multitude of cellular lineages involved. This edition strives to be more comprehensive by integrating innovative sections that individually address topics that previously lacked their own autonomy. Advances in molecular biology enable increasingly detailed categorization of neoplasms and this is particularly true for melanocytic neoplasms, although further studies are needed to place lesions that cannot be categorized within one of the pathways currently codified. If the molecular pathology marks a revolution in pathological anatomy, an even more recent one is represented by the "digital era" and implementation of artificial intelligence algorithms in histological diagnostics. It is necessary to understand what the impact of this revolution will be on the diagnosis of skin tumors and whether it will play a role in future WHO classifications.

CONFLICTS OF INTEREST STATEMENT

The Authors declare no conflict of interest.

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AUTHORS' CONTRIBUTIONS

Conception and design of the study: FF. Data collection: FF, GC. Manuscript writing: FF, GC, GI. Critical revision and editing: FF, GC, GI, APDT. Approval of the final version: APDT.

References

- 1 WHO Classification of Tumours Editorial Board. Skin tumours [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2023 [cited YYYY Mmm D]. (WHO classification of tumours series, 5th ed.; vol. 12). Available from: <https://tumourclassification.iarc.who.int/chapters/64>.
- 2 Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. *Annu Rev Pathol*. 2014;9:239-271. <https://doi.org/10.1146/annurev-pathol-012513-104658>
- 3 Armstrong BK, Kricke A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B*. 2001;63(1-3):8-18. [https://doi.org/10.1016/s1011-1344\(01\)00198-1](https://doi.org/10.1016/s1011-1344(01)00198-1)

- 4 Fernández-Figueras MT, Malvehi J, Tschandl P, et al. Position paper on a simplified histopathological classification of basal cell carcinoma: results of the European Consensus Project. *J Eur Acad Dermatol Venereol*. 2022;36(3):351-359. <https://doi.org/10.1111/jdv.17849>
- 5 Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99. <https://doi.org/10.3322/caac.21388>
- 6 Ross AS, Whalen FM, Elenitsas R, Xu X, Troxel AB, Schmults CD. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. *Dermatol Surg*. 2009;35(12):1859-1866. <https://doi.org/10.1111/j.1524-4725.2009.01354.x>
- 7 Lim YH, Fisher JM, Bosenberg MW, Choate KA, Ko CJ. Keratoacanthoma Shares Driver Mutations with Cutaneous Squamous Cell Carcinoma. *J Invest Dermatol*. 2016;136(8):1737-1741. <https://doi.org/10.1016/j.jid.2016.04.002>
- 8 Carr RA, Mesiano D, Heffron C, et al. Aberrant p16, p53 and Ki-67 immunohistochemistry staining patterns can distinguish solitary keratoacanthoma from cutaneous squamous cell carcinoma. *Pathology*. 2023;55(6):772-784. <https://doi.org/10.1016/j.pathol.2023.07.001>
- 9 Mortier L, Marchetti P, Delaporte E, et al. Progression of actinic keratosis to squamous cell carcinoma of the skin correlates with deletion of the 9p21 region encoding the p16(INK4a) tumor suppressor. *Cancer Lett*. 2002;176(2):205-214. [https://doi.org/10.1016/s0304-3835\(01\)00757-1](https://doi.org/10.1016/s0304-3835(01)00757-1)
- 10 Brown VL, Harwood CA, Crook T, Cronin JG, Kelsell DP, Proby CM. p16INK4a and p14ARF tumor suppressor genes are commonly inactivated in cutaneous squamous cell carcinoma. *J Invest Dermatol*. 2004;122(5):1284-1292. <https://doi.org/10.1111/j.0022-202X.2004.22501.x>
- 11 Bhatia K, Goedert JJ, Modali R, Preiss L, Ayers LW. Merkel cell carcinoma subgroups by Merkel cell polyomavirus DNA relative abundance and oncogene expression. *Int J Cancer*. 2010;126(9):2240-2246. <https://doi.org/10.1002/ijc.24676>
- 12 Pulitzer MP, Brannon AR, Berger MF, et al. Cutaneous squamous and neuroendocrine carcinoma: genetically and immunohistochemically different from Merkel cell carcinoma. *Mod Pathol*. 2015;28(8):1023-1032. <https://doi.org/10.1038/modpathol.2015.60>
- 13 Fukuhara M, Agnarsdóttir M, Edqvist PH, Coter A, Ponten F. SATB2 is expressed in Merkel cell carcinoma. *Arch Dermatol Res*. 2016;308(6):449-454. <https://doi.org/10.1007/s00403-016-1655-6>
- 14 Rodig SJ, Cheng J, Wardzala J, et al. Improved detection suggests all Merkel cell carcinomas harbor Merkel polyomavirus. *J Clin Invest*. 2012;122(12):4645-4653. <https://doi.org/10.1172/JCI64116>
- 15 Brash DE. UV signature mutations. *Photochem Photobiol*. 2015;91(1):15-26. <https://doi.org/10.1111/php.12377>
- 16 Zhang J, Tian H, Mao L, Si L. Treatment of acral and mucosal melanoma: Current and emerging targeted therapies. *Crit Rev Oncol Hematol*. 2024;193:104221. <https://doi.org/10.1016/j.critrevonc.2023.104221>
- 17 Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med*. 2005;353(20):2135-2147. <https://doi.org/10.1056/NEJMoa050092>
- 18 Giubellino A, Torres-Cabala C. Editorial for Special Issue “Molecular Mechanisms and Signaling Pathways in Melanoma”. *Cancers (Basel)*. 2023;15(19):4675. Published 2023 Sep 22. <https://doi.org/10.3390/cancers15194675>
- 19 Yeh I. Melanocytic naevi, melanocytomas and emerging concepts. *Pathology*. 2023;55(2):178-186. <https://doi.org/10.1016/j.pathol.2022.12.341>
- 20 Castillo P, Castrejon N, Marginet M, et al. Combined WNT-activated deep-penetrating/plexiform melanocytoma: insights into clinicopathological and molecular characterization. *Clin Exp Dermatol*. 2024;49(4):356-363. <https://doi.org/10.1093/ced/llad405>
- 21 Cazzato G, Arezzo F, Colagrande A, et al. “Animal-Type Melanoma/Pigmented Epithelioid Melanocytoma”: History and Features of a Controversial Entity. *Dermatopathology (Basel)*. 2021;8(3):271-276. Published 2021 Jul 5. <https://doi.org/10.3390/dermatopathology8030033>
- 22 de la Fouchardiere A, Blokk W, van Kempen LC, et al. ESP, EORTC, and EURACAN Expert Opinion: practical recommendations for the pathological diagnosis and clinical management of intermediate melanocytic tumors and rare related melanoma variants. *Virchows Arch*. 2021;479(1):3-11. <https://doi.org/10.1007/s00428-020-03005-1>
- 23 Cheng TW, Ahern MC, Giubellino A. The Spectrum of Spitz Melanocytic Lesions: From Morphologic Diagnosis to Molecular Classification. *Front Oncol*. 2022;12:889223. Published 2022 Jun 7. <https://doi.org/10.3389/fonc.2022.889223>
- 24 Wiesner T, He J, Yelensky R, et al. Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. *Nat Commun*. 2014;5:3116. <https://doi.org/10.1038/ncomms4116>
- 25 Alexandrescu S, Imamovic-Tuco A, Janeway K, Hanna J. Clear cell tumor with melanocytic differentiation and MITF::CREM translocation. *J Cutan Pathol*. 2023;50(7):619-622. <https://doi.org/10.1111/cup.14427>
- 26 Küsters-Vandeveld HV, Küsters B, van Engen-van Grunsven AC, Groenen PJ, Wesseling P, Blokk WA. Primary melanocytic tumors of the central nervous system: a review with focus on molecular aspects. *Brain Pathol*. 2015;25(2):209-226. <https://doi.org/10.1111/bpa.12241>
- 27 Barnhill RL, Elder DE, Piepkorn MW, et al. Revision of the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Classification Schema for Melanocytic Lesions: A Consensus Statement. *JAMA Netw Open*. 2023;6(1):e2250613. Published 2023 Jan 3. <https://doi.org/10.1001/jamanetworkopen.2022.50613>
- 28 Hoang MP. Role of immunohistochemistry in diagnosing tumors of cutaneous appendages. *Am J Dermatopathol*. 2011;33(8):765-774. <https://doi.org/10.1097/DAD.0b013e31820a4837>
- 29 Bourlond F, Velter C, Cribier B. Androgen receptor expression in epidermal and adnexal tumours. *Ann Dermatol Venereol*. 2021;148(2):116-121. <https://doi.org/10.1016/j.annder.2020.08.054>
- 30 Battistella M, Carlson JA, Osio A, Langbein L, Cribier B. Skin tumors with matrical differentiation: lessons from hair keratins, beta-catenin and PHLDA-1 expression. *J Cutan Pathol*. 2014;41(5):427-436. <https://doi.org/10.1111/cup.12313>
- 31 Sekine S, Kiyono T, Ryo E, et al. Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma. *J Clin Invest*. 2019;129(9):3827-3832. Published 2019 May 30. <https://doi.org/10.1172/JCI126185>
- 32 Russell-Goldman E, Hanna J. MAML2 Gene Rearrangement Occurs in Nearly All Hidradenomas: A Reappraisal in a Series of 20 Cases. *Am J Dermatopathol*. 2022;44(11):806-811. <https://doi.org/10.1097/DAD.0000000000002276>
- 33 Rashid M, van der Horst M, Mentzel T, et al. ALPK1 hotspot mutation as a driver of human spiradenoma and spiradenocarcinoma. *Nat Commun*. 2019;10(1):2213. Published 2019 May 17. <https://doi.org/10.1038/s41467-019-09979-0>
- 34 Bishop JA, Taube JM, Su A, et al. Secretory Carcinoma of the Skin Harboring ETV6 Gene Fusions: A Cutaneous Analogue to Secretory Carcinomas of the Breast and Salivary Glands. *Am J Surg Pathol*. 2017;41(1):62-66. <https://doi.org/10.1097/PAS.0000000000000734>

- 35 Chau NG, Ma C, Danga K, et al. An Anatomical Site and Genetic-Based Prognostic Model for Patients With Nuclear Protein in Testis (NUT) Midline Carcinoma: Analysis of 124 Patients. *JNCI Cancer Spectr.* 2019;4(2):pkz094. Published 2019 Nov 6. <https://doi.org/10.1093/jncics/pkz094>
- 36 Joo HJ, Kim MR, Cho BK, Yoo G, Park HJ. Onychomatricoma: A Rare Tumor of Nail Matrix. *Ann Dermatol.* 2016;28(2):237-241. <https://doi.org/10.5021/ad.2016.28.2.237>
- 37 Kim TR, Bae KN, Son JH, et al. Onychopapilloma: its clinical, dermoscopic and pathologic features. *J Eur Acad Dermatol Venereol.* 2022;36(11):2235-2240. <https://doi.org/10.1111/jdv.18461>
- 38 Ballan A, Zeinaty P, Tomb R, et al. Acquired ungual fibrokeratoma: a systematic review of the literature. *Int J Dermatol.* 2021;60(5):533-539. <https://doi.org/10.1111/ijd.15278>
- 39 dAlmeida LFV, Jeunon T, Leverone AP, Nakamura R. Onychocytic matricoma. *An Bras Dermatol.* 2019;94(2):214-216. <https://doi.org/10.1590/abd1806-4841.20197865>
- 40 Miguel-Gomez L, Turrión-Merino L, Reguero-Calleja ME, Muñoz-Zato E. Subungual Keratoacanthoma. *Indian J Dermatol.* 2015;60(6):623-624. <https://doi.org/10.4103/0019-5154.169148>
- 41 Facchetti F, Cigognetti M, Fisogni S, Rossi G, Lonardi S, Vermi W. Neoplasms derived from plasmacytoid dendritic cells. *Mod Pathol.* 2016;29(2):98-111. <https://doi.org/10.1038/modpathol.2015.145>
- 42 Abila O, Rollins B, Ladisch S. Langerhans cell histiocytosis: progress and controversies. *Br J Haematol.* 2019;187(5):559-562. <https://doi.org/10.1111/bjh.16099>
- 43 Kempf PG, Picarsic J, Durham BH, et al. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition. *Blood.* 2022;139(2):256-280. <https://doi.org/10.1182/blood.2022017205>
- 44 Alberti-Violetti S, Fanoni D, Provasi M, Corti L, Venegoni L, Berti E. Primary cutaneous acral CD8 positive T-cell lymphoma with extra-cutaneous involvement: A long-standing case with an unexpected progression. *J Cutan Pathol.* 2017;44(11):964-968. <https://doi.org/10.1111/cup.13020>
- 45 Charli-Joseph YV, Gatica-Torres M, Pincus LB. Approach to Cutaneous Lymphoid Infiltrates: When to Consider Lymphoma?. *Indian J Dermatol.* 2016;61(4):351-374. <https://doi.org/10.4103/0019-5154.185698>
- 46 Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67(2):93-99. <https://doi.org/10.3322/caac.21388>
- 47 Hanna J, Ko JS, Billings SD, et al. Cutaneous Melanocytic Tumor With CRTC1::TRIM11 Translocation : An Emerging Entity Analyzed in a Series of 41 Cases. *Am J Surg Pathol.* 2022;46(11):1457-1466. <https://doi.org/10.1097/PAS.0000000000001952>
- 48 Puls F, Carter JM, Pillay N, et al. Overlapping morphological, immunohistochemical and genetic features of superficial CD34-positive fibroblastic tumor and PRDM10-rearranged soft tissue tumor. *Mod Pathol.* 2022;35(6):767-776. <https://doi.org/10.1038/s41379-021-00991-8>
- 49 Kao YC, Flucke U, Eijkelenboom A, et al. Novel EWSR1-SMAD3 Gene Fusions in a Group of Acral Fibroblastic Spindle Cell Neoplasms. *Am J Surg Pathol.* 2018;42(4):522-528. <https://doi.org/10.1097/PAS.0000000000001002>
- 50 Agaram NP, Zhang L, Sung YS, et al. Recurrent NTRK1 Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors. *Am J Surg Pathol.* 2016;40(10):1407-1416. <https://doi.org/10.1097/PAS.0000000000000675>
- 51 Komurcugil I, Arslan Z, Bal ZI, Aydoğan M, Ciman Y. Cutaneous metastases different clinical presentations: case series and review of the literature. *Dermatol Reports.* 2022;15(1):9553. Published 2022 Aug 2. <https://doi.org/10.4081/dr.2022.9553>
- 52 Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Acad Dermatol.* 1993;29(2 Pt 1):228-236. [https://doi.org/10.1016/0190-9622\(93\)70173-q](https://doi.org/10.1016/0190-9622(93)70173-q)
- 53 Ivan D, Nash JW, Prieto VG, et al. Use of p63 expression in distinguishing primary and metastatic cutaneous adnexal neoplasms from metastatic adenocarcinoma to skin. *J Cutan Pathol.* 2007;34(6):474-480. <https://doi.org/10.1111/j.1600-0560.2006.00644.x>
- 54 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer.* 2005;41(14):2040-2059. <https://doi.org/10.1016/j.ejca.2005.03.034>
- 55 Aoude LG, Wadt KA, Pritchard AL, Hayward NK. Genetics of familial melanoma: 20 years after CDKN2A. *Pigment Cell Melanoma Res.* 2015;28(2):148-160. <https://doi.org/10.1111/pcmr.12333>
- 56 Rossi M, Pellegrini C, Cardelli L, Ciciarelli V, Di Nardo L, Fagnoli MC. Familial Melanoma: Diagnostic and Management Implications. *Dermatol Pract Concept.* 2019;9(1):10-16. Published 2019 Jan 31. <https://doi.org/10.5826/dpc.0901a03>
- 57 Rai K, Pilarski R, Cebulla CM, Abdel-Rahman MH. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. *Clin Genet.* 2016;89(3):285-294. <https://doi.org/10.1111/cge.12630>
- 58 de la Fouchardiere A, Blokx W, van Kempen LC, et al. ESP, EORTC, and EURACAN Expert Opinion: practical recommendations for the pathological diagnosis and clinical management of intermediate melanocytic tumors and rare related melanoma variants. *Virchows Arch.* 2021;479(1):3-11. <https://doi.org/10.1007/s00428-020-03005-1>
- 59 Black JO. Xeroderma Pigmentosum. *Head Neck Pathol.* 2016;10(2):139-144. <https://doi.org/10.1007/s12105-016-0707-8>
- 60 Bresler SC, Padwa BL, Granter SR. Nevroid Basal Cell Carcinoma Syndrome (Gorlin Syndrome). *Head Neck Pathol.* 2016;10(2):119-124. <https://doi.org/10.1007/s12105-016-0706-9>
- 61 Bosco Schamun MB, Correa R, Graffigna P, de Miguel V, Fainstein Day P. Carney complex review: Genetic features. Revisión del complejo de Carney: Aspectos genéticos. *Endocrinol Diabetes Nutr (Engl Ed).* 2018;65(1):52-59. <https://doi.org/10.1016/j.endinu.2017.09.006>
- 62 Bhaijee F, Brown AS. Muir-Torre syndrome. *Arch Pathol Lab Med.* 2014;138(12):1685-1689. <https://doi.org/10.5858/arpa.2013-0301-RS>
- 63 Kazakov DV. Brooke-Spiegler Syndrome and Phenotypic Variants: An Update. *Head Neck Pathol.* 2016;10(2):125-130. <https://doi.org/10.1007/s12105-016-0705-x>