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# Dermatopathology 101. Part 2 – Skin tumors

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## Summary

The present CME article highlights fundamental aspects with respect to the histopathology of the most common skin tumors (epidermal, adnexal, melanocytic, and mesenchymal), their laboratory workup, as well as the importance of supplementary immunohistochemical and molecular studies. The information provided is meant to assist experienced clinicians in choosing the correct biopsy technique and in interpreting dermatopathology reports, and to provide dermatology residents with a better understanding of dermatopathology. Similar to inflammatory dermatoses, the diagnosis of skin tumors, too, requires the close cooperation between clinicians and dermatopathologists. The diagnostic quality and the resultant therapeutic approach can be significantly improved if this collaboration is based on the same dermatological understanding.

## Introduction

Following the previously published first part of "Dermatopathology 101 – Inflammatory skin diseases" [1], the second part focuses on skin tumors. This second article is aimed at dermatology residents as well as board-certified specialists who would like to refresh their basic dermatopathology knowledge. Following the description of standard methods of sample processing including potential pitfalls, the "special part" of this article will highlight examples of individual tumor entities, their most important differential diagnoses, and their relevance for the diagnosis of various tumor-associated syndromes. Due to space limitations, this article can only provide an exemplary presentation of epithelial, melanocytic, mesenchymal, and adnexal tumors. With respect to non-solid neoplasms, for example, mastocytosis, histiocytosis, lymphoma, and cutaneous metastases, the reader is referred to previously published reviews [2–6].

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Tumors result from faulty regulation of tissue structures, subsequently leading to benign or malignant proliferations. The term tumor merely denotes a swelling; it does not imply any information about its biological behavior. The present article exclusively addresses cutaneous neoplasms (uncoordinated – usually irreversible – benign or malignant proliferation of cells). Hamartomas, choristomas, malformations, and hyperplastic lesions are not included.

## Methods

### Biopsy

Biopsies that are too superficial do not allow for dermal and subcutaneous processes to be adequately assessed, if at all.

In order to be able to take a representative biopsy that includes the anatomical structure in question, it is essential that clinicians have the requisite knowledge of the potential biological behavior and growth of a tumor. In particular, biopsies

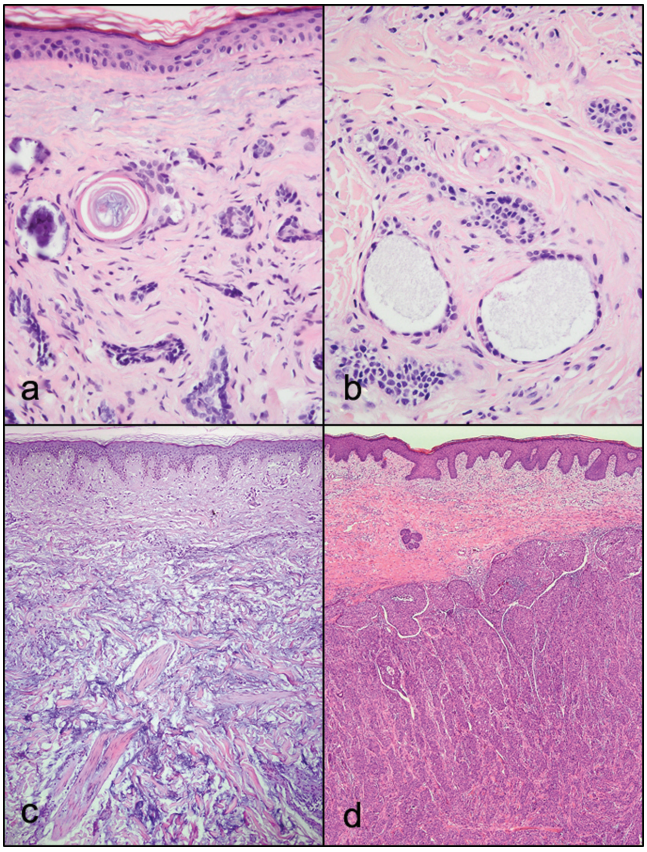


**Figure 1** The clinician's influence on the quality of the histological assessment. Suspected clinical diagnosis: basal cell carcinoma. Histology: subepidermal proliferation of tadpole-like basaloid cells with follicular differentiation, small keratin pearls, and nodular calcifications surrounded by a desmoplastic stroma (hematoxylin-eosin stain [H&E|, original magnification x 400). Given the incomplete architecture, complete excision was recommended (a). Close-up of the subsequent complete excision (including the entire dermis and parts of the subcutis). Now, the deep reticular dermis also revealed a proliferation of tumor cells with ductal differentiation that extended downwards along the small nerves. Given the aforementioned findings, the diagnosis of microcystic adnexal carcinoma was made (H&E, x 400) (b). Biopsy without clinical information: pronounced mucin deposition in the upper and mid-dermis. Suspected histological diagnosis: some form of mucinosis (H&E, x 100) (c). Complete excision: nodular tumor cell proliferation in the dermis with large mucin deposits due to metastatic bronchial carcinoma (H&E, x 40) (d).

that are too superficial do not allow for dermal and subcutaneous processes to be adequately assessed, if at all (Figure 1).

The taking and processing of tissue samples requires utmost care as crushing artifacts and electrocaustic changes can severely compromise the histopathological assessment.

To avoid unnecessary re-excisions, it is recommended to perform the excision with surgical margins of at least 1 mm, given that the microscopic control of excisional margins requires a minimum of tumor-free tissue. If the diagnosis has already been established by a previous biopsy or excision, surgical margins as recommended by guidelines can be factored in during preoperative planning. In case

 

of infiltrating tumors, for example, sclerosing basal cell carcinoma, sufficiently wide surgical margins should be observed, too, in particular with regard to the depth of the excision, as this facilitates proper tissue processing.

Micrographic control of excisional margins requires one or two suture markings – if possible cranially and caudally to the biopsy site – to enable exact identification of the excisional margins. (Alternatively, marking by small incisions has also proven useful; however, in doing so, it is essential not to damage the tumor.) Lateral markings harbor a greater risk of confusing sides. While dye markings are also possible, the dye may come off during shipment and fixation.

In order to allow for the exact identification of samples, it is imperative that each vial contain only one sample.

In order to allow for the exact identification of samples, it is imperative that each vial contain only one sample. The histopathology request form should contain precise information concerning the patient, the suspected clinical diagnosis, and the biopsy site (Figure 1). In case of inhomogeneous lesions or if several lesions are present in one biopsy, it is recommended to provide a drawing or a clinical photo to allow for precise cutting through all parts of the biopsy to be analyzed.

## Fixation

Regardless of its possible oncogenic potential, fixation with aqueous formaldehyde (approximately 4 %) is still considered the best fixation method for routine histology. To prevent underfixation, the volume of the formaldehyde solution should be 10–25 times greater than that of the excised tissue [7].

The time required for fixation depends on sample size (at least 6–24 hours) [8]. In case of extreme subzero outdoor temperatures, prefixation at room temperature for six hours is recommended to avoid subsequent freezing artifacts [8]. Rapid fixation and embedding may be associated with impaired cell morphology and DNA alterations [8]. Especially in case of melanocytic lesions and lymphomas, the fixation time should be sufficiently long (at least 24 hours) to achieve optimal tissue quality. Fixation results in tissue shrinkage (depending on the tissue structure up to a maximum of 30–50 %). This affects the interpretation of surgical margins as measured under the microscope, and explains why – in soft tissue tumors – such measurement should always be done in vivo prior to excision.

Fixation results in tissue shrinkage.

## Cutting/sectioning

With respect to tissue cutting/sectioning, a distinction is made between techniques performed by the surgeon during surgery or soon after tissue collection (for example, "Tübinger Torte" [9], classic Mohs surgery), and those techniques that are performed at the laboratory after formalin fixation. Given the softness of the tissue, intraoperative cutting is often challenging [10] and is inferior to the sectioning of formalin-fixed tissue at the histopathology laboratory, which is less prone to artifacts.

Sectioning of formalin-fixed tissue at the histopathology laboratory is associated with fewer artifacts than intraoperative cutting.

The most common cutting techniques used at histopathology laboratories in German-speaking countries are:

- The "bread loaf" technique (lamination of the entire tissue using numerous parallel sections) (Figure 2a, b, c),
- Micrographically controlled surgery (syn.: 3D histology) based on Mohs surgery. Here, the entire tumor is excised, marked with sutures or dye, and subsequently processed either directly using cryostat sections or by formalin fixation and paraffin embedding. If the size of the specimen allows, a cross-section is made as well as sections at the margins and, if necessary, at the bottom of the specimen (Figure 2d–f).

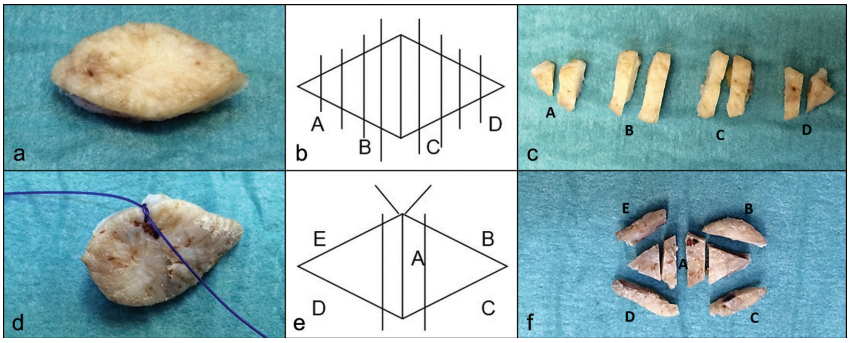


**Figure 2** Cutting/sectioning techniques at the histological laboratory. The bread loaf technique is used for small tissue samples with or without suture marking; example of a suitable specimen (a). Schematic illustration of sectional planes (A–D) (b). Lamination of tissue (A–D) (c). Three-dimensional histology requires a sufficiently large specimen with suture marking; example of the initial specimen (d). Schematic illustration of 3D histology: A) central cross-section, B–E) marginal sections (e). Real-life 3D histology: A) central cross-section, B–E) marginal sections (f).

## Tissue processing

Paraffin embedding allows for the conservation and proper sectioning of specimens. Following sectioning and mounting on slides, the sections (approximately 3 µm thick) are deparaffinized through a series of graded ethanol baths (followed by xylene clearing) for routine hematoxylin and eosin staining (H&E). In addition, special stains used in the diagnosis of tumors also include elastica-van Gieson stain (EvG) and periodic acid-Schiff stain (PAS). EvG staining facilitates the visualization of invasive growth by the displacement of elastic fibers. PAS staining is used to visualize glycogen-rich tumors and basement membranes.

If a lesion cannot be conclusively classified on H&E sections, supplementary immunohistochemical or molecular pathology studies may be helpful.

If a lesion cannot be conclusively classified on H&E sections, for example, in case of dedifferentiated squamous cell carcinomas, spindle-cell mesenchymal tumors, ambiguous melanocytic lesions, collision tumors, or cutaneous metastases, supplementary immunohistochemical or molecular pathology studies may be helpful. These methods can also be used to more precisely classify tumors or to detect receptors in the context of specific therapies.

## Immunohistochemistry

Tissue formalin fixation alters the epitopes on target antigens. This alteration may be reversed by mild proteolysis. Today, there is a wide range of monoclonal antibodies that can be subsequently used on paraffin-embedded tissue. There are various methods of visualizing specific antigen-antibody reactions in tissue sections. Currently, one of the most commonly employed techniques involves the use of enzyme-labeled antibodies; here, bound antibodies are microscopically visualized by a color reaction. Depending on the target structure, this method not only allows for the detection of cell membranes, cytoplasm, nuclei, and extracellular matrix but also specific mutations or translocations. The most important antibodies are listed in the "special part", along with respective tumor entities.

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## Molecular pathology

Molecular pathology studies are required to detect clonality, genetic aberrations, and specific mutations.

Molecular pathology studies are required to detect clonality, genetic aberrations, and specific mutations. The latter is becoming increasingly important for the use of mutation-specific therapeutic approaches, for example, targeted therapy for BRAF-mutated melanoma. On principal, almost all molecular pathology tests can be performed on formalin-fixed tissue.

*Polymerase chain reaction (PCR)* detects specific mutations or allows for the sequencing of a small number of genes. *Next-generation sequencing* has revolutionized molecular pathology. It enables genomic analysis in a cost- and time-efficient manner, as several patient samples can be analyzed at the same time Finally, *fluorescence in situ hybridization (FISH)* allows for the detection of structural and numerical chromosomal aberrations.

## Histopathological assessment

Following evaluation of the type of tissue differentiation, diagnostic criteria – presented in Table 1 in a simplified manner – are used to microscopically assess whether the lesion at hand is benign or malignant; that assessment involves using various magnifications. If necessary, supplementary immunohistochemical or molecular pathology studies are performed.

## Dermatopathology report

Apart from the clinical information previously provided, the dermatopathology report includes a description of the histological characteristics as well as a diagnosis that is as precise as possible and also indicates whether the tumor is benign or malignant.

For malignant tumors, the report should include the following details:

- Staging with information on the staging classification used, including the year of publication (e. g. UICC classification [Union internationale contre le cancer] [11], AJCC classification [American Joint Committee on Cancer] [12]),
- Differentiation (grading),
- Growth pattern (in situ or invasive),
- Tumor thickness,

**Table 1** Simplified overview of histological criteria for the differentiation between benign and malignant tumors.

| Criterion | Rather benign | Rather malignant |
|---|---|---|
| Architecture | – Well-demarcated<br>– Symmetric lesion | – Ill-defined<br>– Asymmetric lesion |
| Growth pattern | – Expansive growth | – Infiltration and invasion (connective tissue, nerves, vessels) |
| Cytology | – High degree of differentiation<br>– Monomorphic nuclei | – Loss of differentiation<br>– Pleomorphic nuclei<br>– Mitoses<br>– Cell necrosis<br>– Densely packed nuclei |


 

**Table 2** Overview of the most important benign and malignant epidermal tumors.

| Benign | In situ changes | Malignant |
|---|---|---|
| – Seborrheic keratosis | – Actinic keratosis | – Squamous cell carcinoma |
| – Clear cell acanthoma | – Bowen's disease | – Bowen's carcinoma |

- Presence of ulceration or an area of regression,
- Information on whether the tumor was completely removed, if necessary by measuring the minimum width of tumor-free (lateral) margins,
- Information on whether the assessment was somehow hampered, for example, due to electrocaustic alterations or too superficial a biopsy.

## "Special Part": Tumors

Below, the most important epithelial, melanocytic, and mesenchymal tumors, including Merkel cell carcinoma, are presented in a simplified manner.

## 1 Epithelial tumors

Based on the tissue of origin, epithelial tumors can be divided into epidermal and adnexal tumors (follicular, sebaceous, eccrine/apocrine [sweat gland] tumors).

### 1.1 Epidermal tumors

The most important benign and malignant epidermal neoplasms are summarized in Table 2.

Characterized by a heterogeneous histological appearance, seborrheic keratosis is one of the most common examples of a benign epidermal neoplasm. Histologically, several variants are distinguished, including hyperkeratotic, acanthotic, adenoid/reticular, clonal as well as inverted types. Common features of all variants include a regular, acanthotic and papillomatous epidermis with hyperkeratosis and intraepidermal proliferation of monomorphic basaloid cells as well as horn cysts and pseudohorn cysts (Figure 3).

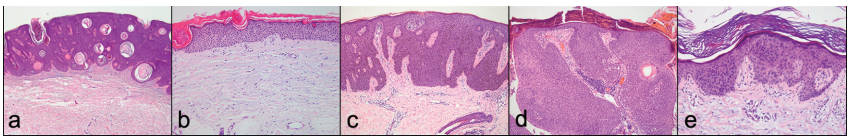


**Figure 3** Histological variants of seborrheic keratosis (SK). Acanthotic SK: hyperkeratosis, acanthosis of basal keratinocytes, pseudohorn cysts, epidermis with regular maturation (H&E, x 40) (a). Flat SK: acanthosis yet significantly flatter, hyperparakeratosis, and pseudohorn cysts (H&E, x 200) (b). Pigmented SK: same pattern as in (a); in addition, hyperpigmentation of all epidermal layers (H&E, x 100) (c). Irritated SK: similar to (a); in addition, para- and orthohyperkeratosis with serum and neutrophils, mild squamous metaplasia, exocytosis of lymphocytes, and a mixed inflammatory infiltrate in the upper dermis (H&E, x 100) (d). Clonal SK: regular epidermis with circumscribed acanthosis; relatively sharply demarcated intraepidermal nests of large pale keratinocytes (H&E, x 200) (e).

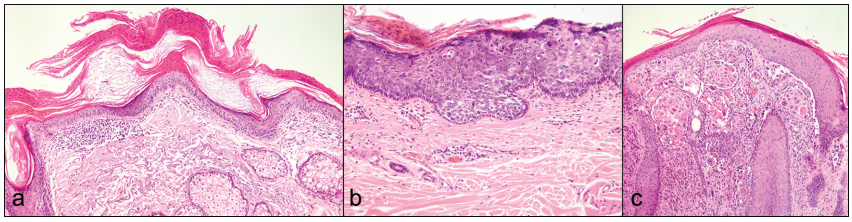


**Figure 4** Precancerous lesions and malignant epidermal tumors. Actinic keratosis: flattened epidermis with disorderly maturation of basal keratinocytes as well as single dyskeratotic cells, alternating para- and orthohyperkeratosis, and actinic elastosis in the upper dermis (H&E, x 100) (a). Bowen's disease: acanthotic epidermis with complete loss of regular maturation; focal hyperparakeratosis, dyskeratosis, and numerous mitoses (H&E, x 200) (b). Squamous cell carcinoma: proliferation of eosinophilic atypical keratinocytes arising from the basal epidermal layers; numerous dyskeratotic cells and mitoses as well as nuclear pleomorphism (H&E, x 100) (c).

Histologically, seborrheic keratoses are characterized by a regular, acanthotic and papillomatous epidermis with hyperkeratosis and intraepidermal proliferation of monomorphic basaloid cells as well as horn cysts and pseudohorn cysts.

Actinic keratoses are characterized by loss of regular maturation in the basal layers of the epidermis as well as dyskeratosis and isolated mitotic figures.

Bowen's disease is characterized by numerous mitotic figures, dyskeratotic cells, and nuclear pleomorphism throughout all epidermal layers.

Squamous cell carcinoma is characterized by focal proliferations of dyskeratotic eosinophilic keratinocytes with large nuclei, prominent nucleoli, and mitotic figures.

With respect to the differential diagnosis, it may be difficult to distinguish an irritated or inflamed seborrheic keratosis from Bowen's disease or well-differentiated squamous cell carcinoma, in particular if the specimen was obtained by shave biopsy.

The term actinic keratosis refers to an incipient squamous cell carcinoma in situ. The basal epidermal layers show loss of regular maturation as well as dyskeratosis and isolated mitotic figures (Figure 4a). In most cases, there is also evidence of alternating areas of ortho- and hyperparakeratosis (pink and blue) as well as actinic elastosis in the superficial dermis. Histologically, various types of actinic keratosis (hypertrophic, bowenoid, pigmented, lichenoid, and acantholytic) can be distinguished.

Bowen's disease is a squamous cell carcinoma in situ. Histologically, the regular architecture of all epidermal layers, including the epithelium of the follicular ostia, is lost. Other features include numerous mitotic figures, dyskeratotic cells, and nuclear pleomorphism (Figure 4b). An important histological variant is clonal (pagetoid) Bowen's disease, which should be distinguished from extramammary Paget's disease (positive for Cam5.2 and CK7) and melanoma in situ (positive for S100, Melan-A and HMB-45) by immunohistochemical studies.

Squamous cell carcinoma is a malignant epidermal tumor. Besides the loss of regular epidermal maturation, there is a variable degree of cellular and nuclear atypia. Originating from the basal cell layers, there are focal proliferations of more or less dyskeratotic eosinophilic keratinocytes with large nuclei, prominent nucleoli, and mitotic figures. These proliferations form digitate or broad-based extensions into the dermis. A mixed inflammatory infiltrate frequently surrounds the tumor cell aggregates (Figure 4c).

The differential diagnosis encompasses other malignant tumors, such as Bowen's carcinoma, porocarcinoma, basal cell carcinoma, and cutaneous metastases of squamous cell carcinomas (not just of epidermal origin). Keratin pearls and dyskeratotic cells are suggestive of squamous cell carcinoma. A connection to the epidermis is considered an important indication of primary cutaneous squamous cell carcinoma. Immunohistochemical studies using cytokeratin markers (CK5/6) may be useful for the diagnosis of dedifferentiated squamous cell carcinomas as well as for the precise assessment of their infiltrating growth pattern.

**Table 3** Overview of the most important tumors with predominant follicular differentiation and their presumed histological origin.

| Tumor entity | Presumed histological origin |
|---|---|
| Basal cell carcinoma | Follicular germinative cell differentiation |
| Trichoblastoma | Biphasic epithelial-mesenchymal differentiation |
| Pilomatrixoma | Matrix differentiation |
| Trichoadenoma | Infundibulum |
| Trichofolliculoma | Panfollicular differentiation |
| Trichilemmal cyst | Follicular cyst |

Adnexal tumors include follicular, seba-ceous, and sweat gland tumors.

## 1.2 Adnexal tumors

Adnexal tumors include follicular, seba-ceous, and sweat gland tumors.

### 1.2.1 Follicular tumors

The hair follicle consists of a matrix, an inner and an outer hair root sheath made up of clear cells. Both the ducts of sebaceous glands and those of apocrine glands open into the hair follicle. The hair follicle is characterized by a special mesenchyme that includes the follicular papilla and the perifollicular hair sheath.

Table 3 provides an overview of the most important tumors with predominant follicular differentiation and their presumed histological origin; the exact classification of basal cell carcinoma (epidermal vs. follicular origin) is subject to controversial debate in the literature [13].

Trichoblastoma is a well-circumscribed, dermal tumor. Its nodular components consist of epithelial cell aggregates with follicular differentiation embedded in a typical follicular stroma.

In everyday dermatopathology practice, the diagnostic differentiation between benign follicular tumors and basal cell carcinoma is of crucial importance. Using trichoblastoma as an example, we would like to address this conundrum in more detail. Trichoblastoma is a benign follicular tumor, clinically characterized by a well-circumscribed, dermal lesion. Its nodular components consist of epithelial cell aggregates with follicular differentiation embedded in a typical follicular stroma (Figure 5a). Unlike basal cell carcinoma, there is no peritumoral clefting.

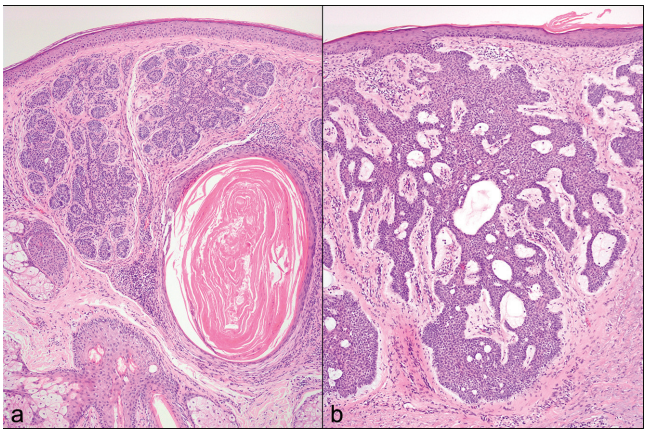


**Figure 5** Trichoblastoma vs. basal cell carcinoma (BCC). Trichoblastoma: well- circumscribed dermal tumor with basaloid tumor cells, partly with peripheral nuclear palisading and distinct follicular differentiation. The lesion is embedded in a fibrotic stroma with cleft formation solely between tumor cell nests (a). Nodular BCC: nodular proliferation of basaloid tumor cells with mucin deposits, peripheral nuclear palisading, and peritumoral clefting (H&E, x 100) (b).

 

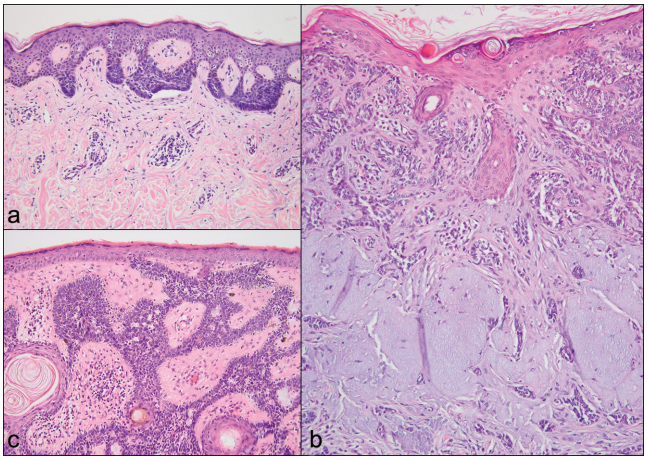


**Figure 6** Types of basal cell carcinoma (BCC). Superficial BCC: subepidermal proliferation of basaloid tumor cells with peripheral palisading and peritumoral clefting (H&E, x 200) (a). Sclerosing BCC: infiltration of small strands of basaloid tumor cell aggregates, made up of only few cell layers; there is also pronounced actinic elastosis (HE, x 200) (b). Pigmented BCC: nodular proliferation of basaloid tumor cells similar to Figure 5b; in addition, there are pigment deposits within the basaloid tumor cell nests (H&E, x 200) (c).

Histologically, nodular basal cell carcinoma is characterized by nodular basaloid tumor cell proliferations with peripheral palisading and typical peritumoral clefting.

Basal cell carcinoma also exhibits characteristics of a tumor with follicular differentiation. Several types are distinguished: nodular basal cell carcinoma (solid, adenoid, cystic, micronodular), superficial (multifocal) basal cell carcinoma, infiltrating basal cell carcinoma (non-sclerosing, sclerosing, desmoplastic, morphea-like) as well as special forms (fibroepithelial basal cell carcinoma, also referred to as Pinkus tumor) and a pigmented variant (Figure 6). Histologically, nodular basal cell carcinoma is characterized by nodular basaloid tumor cell proliferations with peripheral palisading and typical peritumoral clefting (Figure 5b). The cause of clefting in basal cell carcinoma is subject to controversial debate in the literature. The interested reader is referred to the article published Ríos-Martín et al. [14]. Detailed morphological descriptions of the individual subtypes are presented in a review by Liersch and Schaller [15].

Besides trichoblastoma, other benign follicular tumors such as trichofolliculoma, but also sebaceous gland tumors must be distinguished from basal cell carcinoma in the differential diagnosis. In this context, immunohistochemical studies, for example, using anti-Ber-Ep4 antibodies are not diagnostically useful, though, as germinative cells of follicular structures are predominantly labeled; these can be found both in basal cell carcinoma and trichoblastoma.

Occasionally, it may be challenging to differentiate sclerosing basal cell carcinoma from microcystic adnexal carcinoma. In this case, however, immunohistochemical staining with anti-Ber-Ep4 antibodies is useful as the latter shows only focal staining or none at all.

For additional information on adnexal tumors with follicular differentiation, we refer to the review by Mentzel and Rütten [13].

### 1.2.2 Sebaceous gland tumors

With the exception of the palmoplantar region, sebaceous glands are ubiquitous in the skin. They are particularly abundant in the face and on the upper back. While

Table 4 Overview of the most important benign and malignant sebaceous tumors.

| Non-neoplastic/hamartoma | Benign | Malignant |
|---|---|---|
| – Nevus sebaceus | – Sebaceous adenoma | –Sebaceous carcinoma |
| – Sebaceous hyperplasia | – Sebaceous epithelioma | |
| – Ectopic sebaceous glands | | |

sebaceous glands usually open into the hair follicles, they may also occur in a non-follicular variant as ectopic sebaceous glands in the buccal and areolar region as well as on the glans and the labia minora. The sebaceous gland consists of several lobules, which in turn consist of an outer layer with immature, basophilic, round to cuboidal sebocytes, and an inner layer with polygonal, fully differentiated sebocytes with vacuolated cytoplasm. These lipid-filled cytoplasmic vacuoles cause characteristic nuclear indentations. As a result of holocrine secretion, the excretory duct frequently contains an eosinophilic material. The detection of fully differentiated sebocytes or sebaceous ductal structures are a sine qua non for the diagnosis of tumors with sebaceous differentiation.

Sebaceous neoplasms exhibit various characteristic patterns: a rippled pattern that resembles Verocay bodies observed in Schwannomas, a labyrinthine/sinusoidal pattern, a carcinoid-like pattern (trabeculae, ribbons, rosettes, pseudorosettes), and a petaloid pattern (flower-like).

Sebaceous adenoma consists of an outer layer of small, monomorphic, basophilic germinative cells and an inner layer of mature sebocytes without cellular atypia.

Based on characteristic patterns, sebaceous neoplasms are usually diagnosed and classified on H&E-stained sections. These include a rippled pattern that resembles Verocay bodies observed in Schwannomas, a labyrinthine/sinusoidal pattern, a carcinoid-like pattern (trabeculae, ribbons, rosettes, pseudorosettes), and a petaloid pattern (flower-like) [5, 16]. A combination of patterns is also possible. Immunohistochemical studies are only of limited use, given that only anti-adipophilin antibodies allow for lesions to be generally classified as sebaceous tumors. The most important sebaceous tumors are summarized in Table 4.

Sebaceous adenoma is an example of a benign sebaceous tumor that imitates the structure of normal sebaceous glands and has a connection to the overlying epidermis. The outer layer consists of small, monomorphic, basophilic germinative sebocytes and the inner layer of central mature sebocytes without cellular atypia (Figure 7a).

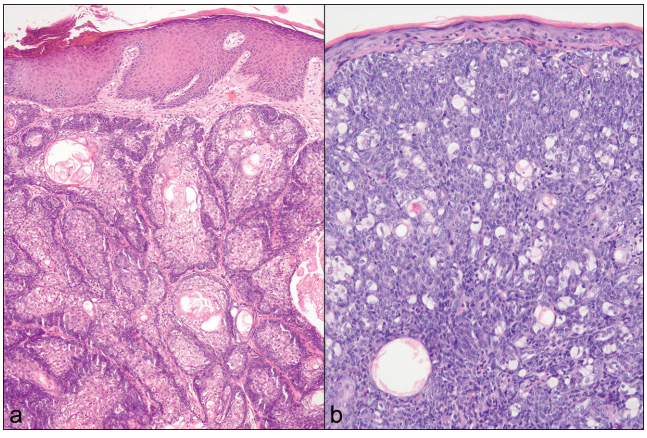


Figure 7 Sebaceous adenoma vs. sebaceous carcinoma. Sebaceous adenoma in a patient with Muir-Torre syndrome: epidermal hyperplasia, multilobular, well-circumscribed tumor with an outer layer of small basaloid tumor cells; at the center, there are mature sebocytes without cellular atypia (H&E, x 100) (a). Sebaceous carcinoma: asymmetric tumor with sebaceous differentiation made up of basaloid cells with intracytoplasmic vacuoles; pronounced nuclear pleomorphism with numerous prominent nucleoli and mitoses (H&E, x 100) (b).

Infiltrating tumor growth, cytological atypia, mitotic figures, and necrotic areas as well as the formation of spindle cells are suggestive of malignancy.

With respect to sebaceous carcinoma, a distinction is made between an ocular and an extraocular variant. Histology reveals aggregates of atypical, basaloid epithelial cells with variable sebaceous differentiation. In addition, there are structures resembling sebaceous ducts. Infiltrative tumor growth, cytological atypia, mitotic figures, and necrotic areas as well as the formation of spindle cells are suggestive of malignancy (Figure 7b). A summary can be found in the review by Böer-Auer [17].

### 1.2.3 Sweat gland tumors

Sweat gland tumors are divided into lesions with apocrine and eccrine differentiation.

Sweat gland tumors are divided into lesions with apocrine and eccrine differentiation. Eccrine sweat glands are abundant in the palmoplantar area, whereas apocrine sweat glands are predominantly found in the axillae and the anogenital region. Both apocrine and eccrine glands consist of a secretory and a ductal portion. The apocrine secretory portion has a large oval or round lumen that sometimes contains a pale eosinophilic material. The cells are marked by a round nucleus at the base and granular cytoplasm. Apically, cytoplasmic structures are pinched off. This type of secretion is referred to as "decapitation secretion". The myoepithelial cells are surrounded by a basement membrane.

Eccrine glands have a flat, secretory epithelium surrounded by a myoepithelial layer. Morphologically, secretion is not visible. It is impossible to distinguish apocrine and eccrine glands immunohistochemically.

Apocrine and eccrine ducts are morphologically indistinguishable. They consist of small cuboidal, eosinophilic cells with a round nucleus and cuticular cells that line the duct lumen.

An overview of the most important sweat gland tumors is given in Table 5. A more comprehensive review of malignant sweat gland tumors can be found in the article by Rütten and Requena [18].

Based on location and morphology the following types of poroma are distinguished: hidroacanthoma simplex (intraepithelial poroma), nodular poroma, poroid hidradenoma, and dermal duct tumor.

Poroma is an example of a benign glandular tumor of eccrine lineage. While it typically occurs in acral areas, other sites, such as the trunk, are also possible. Based on location and morphology, the following types are distinguished: hidroacanthoma simplex (intraepithelial poroma), nodular poroma, poroid hidradenoma, and dermal duct tumor [16].

Histologically, poroma presents as a well-circumscribed tumor with two different cell types: on the one hand, small monomorphic, cuboidal, basophilic cells; on the other, larger eosinophilic, squamoid cells as well as focal intracytoplasmic vacuoles, which are interpreted as rudimentary ductal differentiation (Figure 8a). Large areas of necrosis (necrosis en masse) are a typical feature of poroma.

**Table 5** Overview of the most important benign and malignant sweat gland tumors.

| Benign, primarily eccrine differentiation | Benign, primarily apocrine differentiation | Malignant |
|---|---|---|
| – Hidrocystoma<br>– Syringoma<br>– Eccrine mixed tumor<br>– Poroma (hidroacanthoma simplex, nodular poroma, poroid hidradenoma, dermal duct tumor) | – Spiradenoma<br>– Cylindroma | – Porocarcinoma<br>– Spiradenocarcinoma<br>– Cylindrocarcinoma<br>– Extramammary Paget's disease<br>– Microcystic adnexal carcinoma<br>– Digital papillary adenocarcinoma |

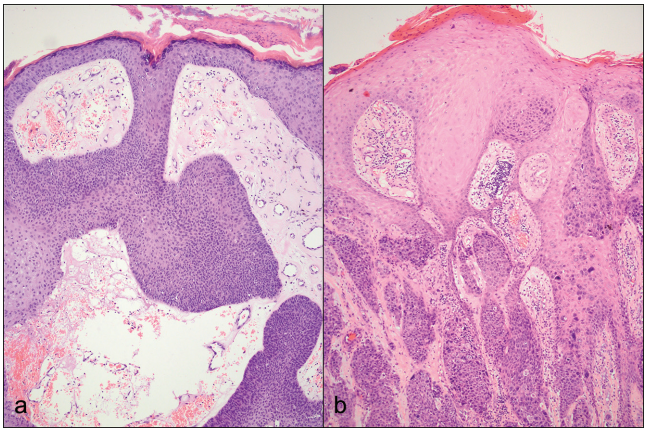


**Figure 8** Poroma vs. porocarcinoma. Poroma: well-circumscribed tumor with a regular, dome-shaped, acanthotic epidermis. Monomorphic, cuboidal, and basophilic cells (focally showing intracytoplasmic vacuoles) arise from the acrosyringium in a cord-like, sometimes nodular arrangement (H&E, x 100) (a). Porocarcinoma: similar epidermis; however, there are intraepidermal nests and invasive cords of pleomorphic cuboidal cells with nuclear pleomorphism and numerous mitoses (H&E, x 100) (b).

Unlike poroma, porocarcinoma presents with epithelial atypia with numerous mitotic figures and an infiltrating growth pattern.

Unlike poroma, porocarcinoma presents with epithelial atypia with numerous mitotic figures and an infiltrating growth pattern (Figure 8b). Intralymphatic metastasis is typical and frequently observed.

*Syndromes associated with multiple adnexal tumors*

Multiple benign or malignant adnexal tumors are indicator lesions for the syndromes presented in Table 6 [16]. A comprehensive review of this subject can be found in the article by Böer-Auer [19].

## 2 Merkel cell carcinoma

UV exposure, immunosuppression, and the detection of Merkel cell polyomavirus seem to play a key role in the tumor's pathogenesis.

While the exact histogenesis of Merkel cell carcinoma has not yet been elucidated, it has been proposed that it derives from epidermal or dermal neuroendocrine stem cells [20]. UV exposure, immunosuppression, and the detection of Merkel cell polyomavirus seem to play a key role in the tumor's pathogenesis [21].

Histologically, Merkel cell carcinoma is characterized by small to medium-sized, hyperchromatic, basophilic, round cells with large nuclei with coarse chromatin and abundant mitotic figures (Figure 9a).

The following histological types are distinguished: small-cell, trabecular, and intermediate; overlapping features may occur. The trabecular growth pattern corresponds to conventional Merkel cell carcinoma.

Immunohistochemically, Merkel cell carcinoma typically shows punctate or annular perinuclear staining using antibodies directed against various low-weight cytokeratins, especially CK20.

Immunohistochemical investigations should be performed to differentiate Merkel cell carcinoma from other tumors with small hyperchromatic, basophilic round cells [21]. Here, Merkel cell carcinoma typically shows punctate or annular perinuclear staining using antibodies directed against various low-weight cytokeratins, especially CK20 (Figure 9b) as well as neuroendocrine markers, including chromogranin A, synaptophysin, neurofilament, and CD56. By contrast, CD7 staining is not always positive [21].

 

**Table 6** Overview of adnexal tumor-associated syndromes with extracutaneous manifestation (modified after Kazakov D et al.) [16].

| Classification | Cutaneous manifestations | Extracutaneous manifestations | Inheritance pattern/ locus/gene |
|---|---|---|---|
| Bird-Hogg-Dubé syndrome | Fibrofolliculomas | Renal tumors, pulmonary cysts | AD, 17p11, BHD(FLCN) |
| Brooke-Spiegler syndrome | Cylindromas, multiple trichoepitheliomas of the face | Salivary gland tumors, basal cell adenoma | AD, 16q12-13(9p21), CYLD |
| Cowden syndrome | Numerous hamartomas, e. g. trichilemmomas of the face, mucous membrane papilloma, palmoplantar keratoses | Breast, endometrial, and thyroid cancer, Lhermitte-Duclos syndrome | AD, 10q23, PTEN |
| Gardner syndrome and familial adenomatous polyposis | Infundibular cysts, fibromas, desmoid fibromatosis | Colorectal adenomas with progression to carcinomas, abdominal desmoid fibromatosis, cerebellar medulloblastomas, congenital hypertrophy of the retinal pigment epithelium, osteomas, odontomas, abnormal dental status, cribiform-morula variant of thyroid cancer | AD, 5q21-22, APC |
| Gorlin-Goltz syndrome | Multiple basal cell carcinomas, palmoplantar pits, cutaneous cysts | Skeletal abnormalities, calcification of the falx cerebri, keratocystic odontogenic tumor, ovarial fibroma | AD, 9q22-31, PTCH |
| Muir-Torre and Lynch syndrome | Multiple benign and malignant sebaceous tumors, keratoacanthomas | Carcinomas of the gastrointestinal and urogenital tracts | AD, 2p22-21, MSH2, 3p23-21, MLH1, 2p16-15, MSH6, 2q31-33, PMS2 |

AD: autosomal dominant.

## 3 Melanocytic tumors

Melanocytic neoplasms are characterized by the proliferation of melanocytes. Table 7 provides an overview of benign and malignant melanocytic tumors.

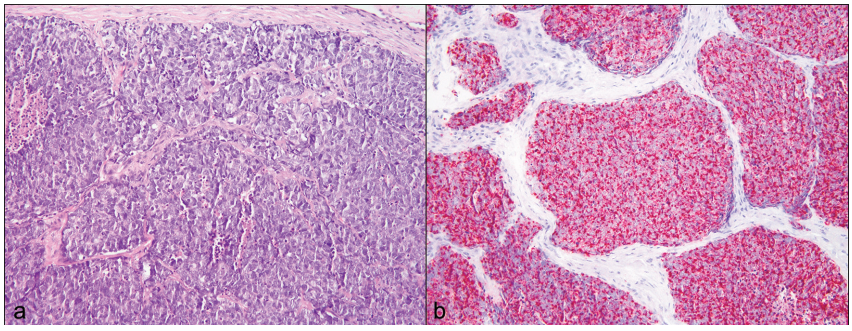


**Figure 9** Merkel cell carcinoma. Nodular, sometimes cord-like proliferation of small to medium-sized, hyperchromatic, densely packed, basophilic round cells with coarse chromatin and numerous mitotic figures. Some areas show central necrosis (HE, x 200) (a). Typical immunohistochemistry of Merkel cell carcinoma: partly punctate, partly annular perinuclear staining using antibodies directed against CK20 (CK20 × 200) (b).

**Table 7** Overview of important melanocytic tumors.

| Benign | Malignant in-situ | Malignant invasive |
|---|---|---|
| – Congenital melanocytic nevus | – Melanoma in situ | – Superficial spreading melanoma |
| – Acquired melanocytic nevus | – Lentigo maligna | – Nodular melanoma |
| – junctional nevus | | – Lentigo maligna melanoma |
| – compound nevus | | – Acral lentiginous melanoma |
| – dermal nevus | | – Desmoplastic melanoma |
| – Blue nevus | | |
| – Spitz nevus | | |

Nevi occurring at certain sites, including the acral, genital, and umbilical region as well as around the nipple and on the ear, exhibit distinctive histological features and are referred to as *special site nevi*.

Nevi occurring at certain sites, including the acral, genital, and umbilical region as well as around the nipple and on the ear, exhibit distinctive histological features and are referred to as *special site nevi*. For the correct histological classification of melanocytic tumors, it is therefore crucial to provide the dermatopathologist with clinical details, possibly supplemented by a sketch or a clinical photo, and the location of the lesion.

Histologically, melanocytic nevi are divided into junctional and dermal lesions or a combination of the two (compound nevus) (Figure 10). In general, a distinction

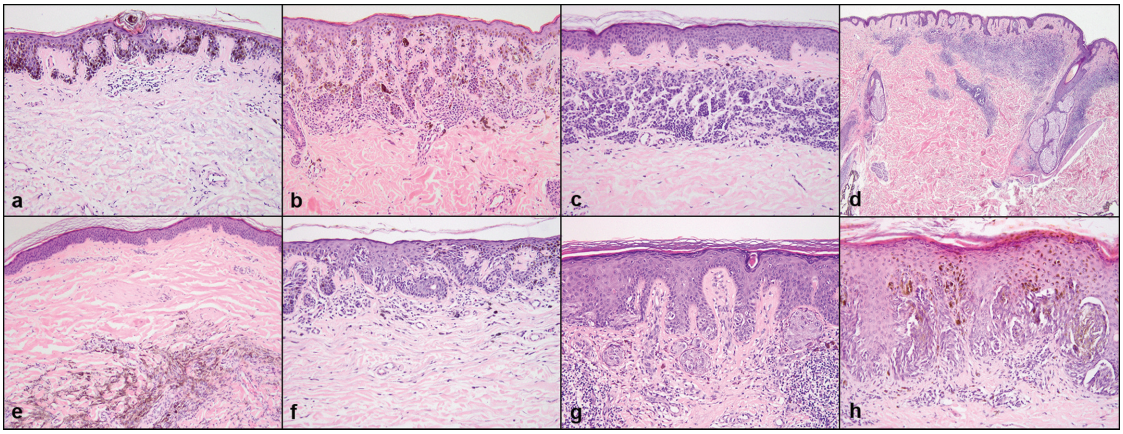


**Figure 10** Melanocytic nevi. Junctional nevus: symmetrical nests of monomorphic pigmented melanocytes with small round nuclei along the dermoepidermal junction (H&E, x 200) (a). Compound nevus: nests of monomorphic melanocytes with regular nuclei along the dermoepidermal junction and in the upper dermis, showing complete maturation with progressive descent (H&E, x 200) (b). Dermal nevus: exclusively dermal nests of monomorphic melanocytes without nuclear atypia; there is complete maturation. The dermoepidermal junction is not involved (H&E, x 200) (c). Congenital nevus: band-like, periadnexal distribution of monomorphic melanocytic nests with small inconspicuous nuclei and complete maturation (H&E, x 40) (d). Blue nevus: predominantly dermal proliferation of dendritic melanocytes arranged in fascicles between collagen fibers; abundant fine granular pigment intracellularly and extracellularly; predominantly spindle-shaped and monomorphic nuclei (H&E, x 100) (e). Dysplastic compound nevus: junctional aggregates of spindle-shaped melanocytes with partly spindle-shaped yet monomorphic nuclei; the cells are arranged as single cells or in irregular nests; the latter show confluence. Ascent of single melanocytes into upper epidermal layers; complete maturation with progressive descent (H&E, x 200) (f). Spitz-nevus: hyperkeratosis and acanthosis. Junctional aggregates of monomorphic epithelioid melanocytes with large oval nuclei and broad cytoplasm, disposed as single cells or in nests; there is maturation with progressive descent. Lymphocytic infiltrate in the dermis; junctional melanocytic mitoses (H&E, x 200) (g). Pigmented spindle cell nevus: similar epidermal pattern as in Spitz nevus. There are, however, strongly pigmented spindle-shaped, vertically arranged melanocytes. These are arranged as single cells or in large monomorphic nests along the dermoepidermal junction and in the upper dermis. The nuclei are spindle-shaped and monomorphic; there are few junctional mitoses (H&E, x 200) (h).

 

must be made between congenital and acquired nevi. Melanocytes originate from the neuroectoderm. In congenital lesions, melanocytes ascend into the dermis (Figure 10), whereas – according to a hypothesis by Unna – they "drop off" from the epidermis into the dermis in acquired lesions.

Examples of various types of melanoma are given in Figure 11. The most important histological criteria as regards malignancy are summarized in Table 8. Weighting these criteria is difficult and requires a lot of experience in the histological assessment of melanocytic lesions. In case of an incomplete biopsy, essential criteria with respect to the assessment of malignancy may be missing. Thus, establishing a definitive diagnosis ultimately requires the entire lesion to be excised, especially in case of atypical melanocytic tumors.

In case of an incomplete biopsy, essential criteria with respect to the assessment of malignancy may be missing. Thus, establishing a definitive diagnosis ultimately requires the entire lesion to be excised, especially in case of atypical melanocytic tumors.

Immunohistochemical staining (S100, Melan-A, HMB45, SOX-10, MITF) is only of limited value in the differentiation of benign and malignant melanocytic lesions, given that there is as yet no melanoma-specific marker. Such stains may, however, be useful for a more precise visualization of the tumor's silhouette, its growth pattern, or mitotic figures (staining with anti-phospho-histone).

Immunohistochemical staining (S100, Melan-A, HMB45, SOX-10, MITF) is only of limited value in the differentiation of benign and malignant melanocytic lesions, given that there is as yet no melanoma-specific marker.

Apart from the exact diagnosis, the melanoma dermatopathology report should include information on the vertical depth of invasion, the presence of ulceration, regression, neurotropism, or vascular infiltration as well as the T stage based on the most recent classification [11]. The 2017 classification no longer

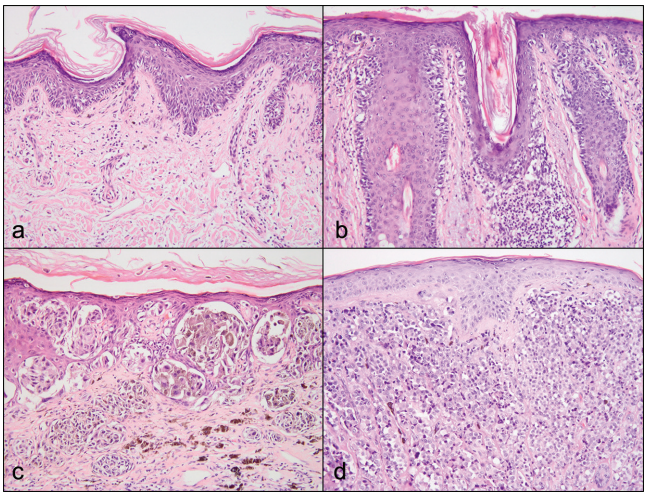


**Figure 11** Melanoma types. Melanoma in situ (MIS): proliferation of atypical melanocytes in all epidermal layers with pagetoid infiltration of the entire epidermis. No dermal melanocytic proliferation (H&E, x 200) (a). Lentigo maligna (variant of MIS in actinically damaged skin): proliferation of atypical melanocytes and nests in actinically damaged skin, predominantly in the basal and suprabasal layers. Some areas show involvement of the entire epidermis in a buckshot-like pattern, as well as involvement of the hair follicle epithelium (H&E, x 200) (b). Superficial spreading melanoma: atypical pleomorphic melanocytes are found in irregular nests – but also arranged as single cells – in all layers of the epidermis and the upper dermis. No maturation with progressive descent. The nuclei exhibit marked pleomorphism; mitoses are found throughout the entire melanocytic proliferation (H&E, x 200) (c). Nodular melanoma: regular epidermis without proliferation of melanocytes. Immediately below, there is a nodular proliferation of atypical melanocytes with cellular and nuclear pleomorphism. No maturation with progressive descent. Mitotic figures can be observed throughout the lesion (H&E, x 200) (d).

**Table 8** Overview of important criteria for the differentiation between melanocytic nevi and melanoma.

| | Rather benign | Rather malignant |
|---|---|---|
| Silhouette | Symmetry of the entire lesion | Asymmetry of the entire lesion |
| | Sharp demarcation of lateral nests | Ill-defined demarcation of lateral nests |
| | Nests are more common than single melanocytes | Numerous single melanocytes; melanocytic proliferation along adnexal structures |
| | Epidermal nests at the tip of the rete ridges | Intraepidermal nests |
| | Nests do not differ in size, shape, distance to each other, and pigmentation | Nests differ in size, shape, distance to each other, and pigmentation; nests tend to coalesce |
| | Melanocytes in basal layers | Melanocytes ascend into the epidermis |
| | In the dermis, melanocytes and nests become smaller with progressive descent (maturation) | Lack of maturation |
| | Regular dermis | Actinic elastosis is replaced by cell nests; fibrosis with melanophages; pronounced inflammatory response |
| Cytomorphology | No or rare mitoses | Numerous mitoses |
| | Monomorphic melanocytes | Pleomorphic melanocytes; angular, large nuclei, pagetoid |

includes information on mitoses; based on tumor thickness, a distinction is now made between stage T1a and T1b.

Both benign and malignant melanocytic tumors are marked by an exceptionally wide clinical variety. For a detailed discussion on the subject, the reader is referred to the reviews by Hauschild et al. and Brenn [22, 23].

Lesions designated as dysplastic nevi are a special variant whose biological significance is subject to controversial debate among dermatopathologists. In particular, it is still unclear whether this nevus represents an acquired nevus or a precursor lesion of melanoma. Histologically, two variants are distinguished. Junctional dysplastic nevi present with melanocytes disposed as single cells or in nests (not equidistant from each other) along the dermoepidermal junction or suprabasally, often with "bridging" of the nests. The morphology of the melanocytes can be spindle-shaped or epithelioid. Some cells exhibit signs of atypia with irregular, hyperchromatic nuclei. Compound dysplastic nevi also show dermal melanocytes marked by maturation with progressive descent. There is characteristic lamellar fibroplasia around the rete ridges as well as lymphocytic infiltrates with melanophages [5] (Figure 10).

## 4 Mesenchymal tumors

Based on their origin, mesenchymal tumors are generally divided into lipogenic, fibrohistiocytic, myogenic, neurogenic, and vascular tumors as well as tumors of uncertain differentiation. An overview of the most important mesenchymal tumors is presented in Table 9. Given the limited space, only some tumor entities of each subclass will be addressed below. For more comprehensive reviews, the reader is referred to publications by Lindberg [24], Costigan [25], and Kohlmeyer [26].

In general, it can be challenging to distinguish mesenchymal tumors from each other. In addition, the spectrum of differential diagnoses also includes melanocytic tumors and dedifferentiated carcinomas. Supplementary immunohistochemical

**Table 9** Overview of the most important benign and malignant mesenchymal tumors.

| Classification | Benign | Malignant |
|---|---|---|
| Lipogenic | – Lipoma<br>– Angiolipoma<br>– Spindle cell lipoma | – Liposarcoma |
| Fibrohistiocytic | – Acrochordon<br>– Angiofibroma<br>– Dermatofibroma (fibrous histiocytoma) | – Dermatofibrosarcoma protuberans<br>– Pleomorphic dermal sarcoma |
| Myogenic | – Leiomyoma, angioleiomyoma<br>– Rhabdomyoma | – Leiomyosarcoma<br>– Rhabdomyosarcoma |
| Neurogenic | – Neuroma<br>– Schwannoma<br>– Neurofibroma<br>– Granular cell tumor | – Malignant peripheral nerve sheath tumor<br>– Malignant schwannoma |
| Vascular | – Pyogenic granuloma<br>– Hemangioma<br>– Angiokeratoma<br>– Lymphangioma<br>– Glomus tumor | – Angiosarcoma<br>– Kaposi's sarcoma<br>– Epithelioid hemangioendothelioma |
| Uncertain differentiation | | – Clear cell sarcoma<br>– Atypical fibroxanthoma<br>– Epithelioid sarcoma |

In order to determine whether a given mesenchymal tumor is malignant or not, histological criteria are of crucial importance, including growth pattern, cytology, accompanying inflammatory infiltrate, presence of giant cells, nuclear morphology, stromal reaction, vascular pattern, and tumor deposits.

and molecular pathology studies are highly relevant for the differential diagnosis and the choice of treatment, in particular for less common mesenchymal tumors.

Given that, unlike other skin tumors, tumor size is included in the histological evaluation, precise staging requires information on the tumor size in vivo and a sufficiently wide excision. In order to determine whether a given mesenchymal tumor is malignant or not, histological criteria are of crucial importance, including growth pattern, cytology, accompanying inflammatory infiltrate, presence of giant cells, nuclear morphology, stromal reaction, vascular pattern, and tumor deposits [24].

### 4.1 Lipogenic tumors

Lipomas are common benign tumors of adulthood that are frequently removed for cosmetic reasons. Histologically, lipomas consist of mature adipocytes with cell-poor connective tissue septa (Figure 12). Important histological differential diagnoses include atypical lipomatous tumor and the lipomatous variant of liposarcoma, which frequently shows multivacuolated lipoblasts. Cutaneous pleomorphic liposarcoma is rare; it can easily be identified as sarcoma based on its high cell density with numerous mitotic figures, its pleomorphism, and the large hyperchromatic nuclei.

### 4.2 Fibrohistiocytic tumors

Dermatofibroma (fibrous histiocytoma) is the prototype of a benign fibrohistiocytic cutaneous lesion.

Dermatofibroma (fibrous histiocytoma) is the prototype of a benign fibrohistiocytic cutaneous lesion. Many variants can be distinguished histologically [27]. The most common is presented in Figure 13.

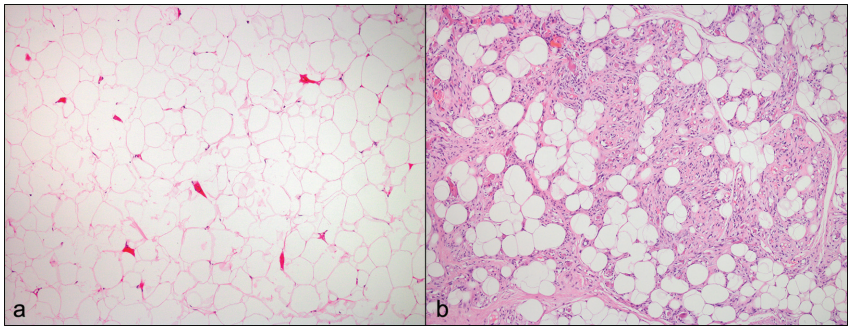


**Figure 12** Lipogenic soft tissue tumors. Lipoma: nodular aggregates of mature adipocytes with connective tissue septa (H&E, x 100) (a). Angiolipoma: nodular aggregates of mature adipocytes with cell-rich and highly vascular adipose tissue septa (H&E, x 100) (b).

The differential diagnosis includes dermatofibrosarcoma protuberans (DFSP). Although DFSP is rare, it is one of the most common cutaneous sarcomas. Histologically, DFSP is characterized by diffuse infiltration of spindle cells into the dermis and, along the septa, into the subcutis. Arranged in a storiform pattern, these

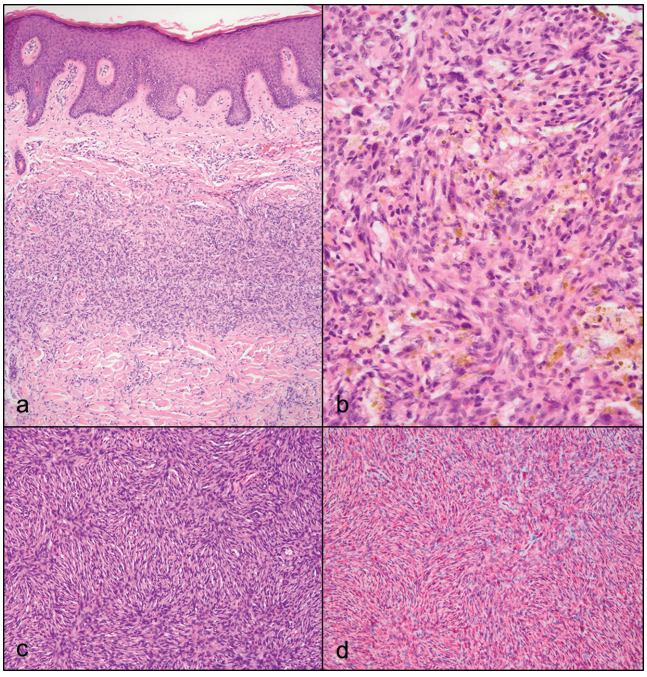


**Figure 13** Fibrohistiocytic soft tissue tumors. Fibrous histiocytoma: acanthotic epidermis with basal hyperpigmentation. The upper and lower dermis shows interstitial proliferation of monomorphic spindle cells with spindle-shaped nuclei without marked atypia. The thickened collagen fibers are partly surrounded by spindle cells (collagen pockets) (H&E, x 100) (a). Hemosiderotic histiocytoma with iron deposits in the deep dermis: light-brown, finely granular pigment is found intracellularly and extracellularly (H&E, x 400) (b). Dermatofibrosarcoma protuberans (DFSP): proliferation of spindle cells arranged in a storiform pattern without marked nuclear pleomorphism and without significant increase in mitotic figures (H&E, x 200) (c). Immunohistochemistry: DFSP is typically CD34-positive (CD34 × 200) (d).

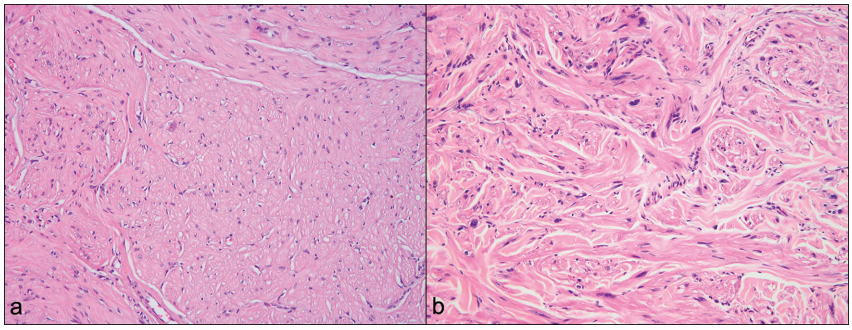


**Figure 14** Myogenic soft tissue tumors. Leiomyoma: longitudinal and cross-sections of cords and nests of smooth muscle cells with eosinophilic cytoplasm and cigar-shaped nuclei (H&E, x 200) (a). Leiomyosarcoma: similar growth pattern as in (a). There is, however, a highly cellular dermal proliferation of spindle cells with an eosinophilic cytoplasm and cigar-shaped, pleomorphic nuclei; few mitotic figures (H&E, x 200) (b).

cells show no distinctive morphological features and no increased mitotic activity. Immunohistochemically, they are marked by CD34 expression (Figure 13). Potentially relevant with respect to treatment, COL1A1-PDGFB fusion can be identified using FISH.

Immunohistochemically, DFSP cells express CD34.

## 4.3 Myogenic tumors

Histologically, cutaneous leiomyomas consist of bands and nests of smooth muscle cells with eosinophilic cytoplasm and cigar-shaped nuclei.

Cutaneous leiomyomas are relatively common myogenic tumors. Histologically, they consist of bands and nests of smooth muscle cells with eosinophilic cytoplasm and cigar-shaped nuclei (Figure 14a).

Histological variants include sclerosing, granular-cell, myxoid, or epithelioid leiomyoma. In case of multiple leiomyomas, differential diagnostic considerations have to encompass cutaneous and uterine leiomyomatosis as well as hereditary leiomyomatosis with renal cell carcinoma syndrome [28]. Given that the differentiation from malignant pilar tumors of the skin (leiomyosarcoma) can be challenging in case of incomplete removal, leiomyomas should be excised completely, if possible.

Important diagnostic criteria for leiomyosarcoma include nuclear atypia and increased mitotic activity with atypical mitotic figures.

Leiomyosarcomas are frequently larger and exhibit greater cell density than common leiomyomas. Important diagnostic criteria for leiomyosarcoma include nuclear atypia and increased mitotic activity with atypical mitotic figures (Figure 14b). Depth of tumor invasion is an important prognostic factor. Tumors confined to the corium virtually never metastasize; however, the prognosis of lesions with deeper invasion is less favorable [29].

## 4.4 Neurogenic tumors

Neurofibromas are the most common benign neurogenic tumors. They consist of Schwann cells, perineural cells, and fibroblasts.

Neurofibromas are the most common benign neurogenic tumors. They consist of Schwann cells, perineural cells, and fibroblasts. They may occur as solitary lesions or, in the context of type 1 or – less frequently – type 2 neurofibromatosis. Neurofibromas are made up of small, spindle-shaped, sometimes comma-shaped cells that may also form fascicles or show an onion skin-like arrangement (Figure 15).

The spindle cells are S100-positive (Schwann cells), while the perineurium is EMA-positive.

The spindle cells are S100-positive (Schwann cells), while the perineurium is EMA-positive. In addition, there is a variable number of CD34-positive fibroblasts, which may present a pitfall in the differentiation from DFSP. Numerous variants have been described: localized, diffuse, plexiform, ancient, myxoid,

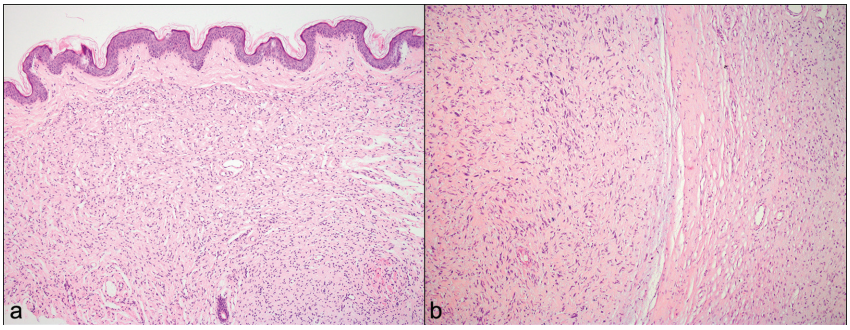


**Figure 15** Neurogenic soft tissue tumors. Neurofibroma: nodular proliferation of small monomorphic spindle cells in fascicular arrangement surrounded by loose connective tissue. No nuclear atypia (H&E, x 100) (a). Malignant peripheral nerve sheath tumor arising in a neurofibroma. Right side: typical spindle cells as in (a). Left side: well-demarcated dense proliferation of pleomorphic spindle cells with nuclear pleomorphism and mitoses (H&E, x 100).

granular-cell, pigmented, epithelioid, and lipomatous neurofibroma [24]. Among others, the differential diagnosis has to include malignant peripheral nerve sheath tumor (MPNST). MPNSTs are tumors derived from a peripheral nerve or nerve sheath. They are frequently associated with a nerve or a preexisting neurofibroma. Histology shows spindle-shaped neoplastic cells arranged in a fishbone pattern, sometimes in a storiform-fascicular pattern. Some tumor cells have a wavy and comma-shaped appearance. Hyperchromatic nuclei and mitotic figures are common (Figure 15b). Focal loss of S100 is characteristic [30].

MPNST is characterized by focal loss of S100.

### 4.5 Vascular tumors

Overlapping features between vascular proliferations and malformations or dilatations pose a challenge with respect to consistently classifying benign vascular tumors.

Characterized by rapid exophytic growth, pyogenic granuloma is an example of a benign vascular tumor that frequently develops after trauma. Histology usually reveals a superficial ulceration with neutrophil-rich granulation tissue. Embedded therein are lobular capillary proliferations in the dermis. While there may be an increase in mitotic activity, there is no significant nuclear atypia (Figure 16a). Almost all benign vascular tumors are characterized by a regular, well-circumscribed lobular architecture, whereas malignant vascular tumors tend to show a nodular, multinodular, diffuse, or interstitial growth pattern (Figure 16).

Almost all benign vascular tumors are characterized by a regular, well-circumscribed lobular architecture, whereas malignant vascular tumors tend to show a nodular, multinodular, diffuse, or interstitial growth pattern.

Angiosarcomas represent approximately 1–2 % of all soft tissue sarcomas. They occur either idiopathically, in the context of chronic lymphedema (Stewart-Treves syndrome), in photodamaged skin, or as a result of radiation. The histological picture is marked by atypical vascular proliferations throughout the entire dermis, including the subcutis. Said proliferations show endothelial nuclear atypia, mitoses, endothelial papillae, and endothelial multilayering (Figure 16).

The vascular proliferations exhibit various growth patterns. Dissecting and infiltrating patterns are the most common. The histological findings are markedly varied, including highly differentiated, spindle-cell, epithelioid as well as anaplastic changes, which may simultaneously occur in different areas of the tumor (Figure 16).

The histology of angiosarcoma includes highly differentiated, spindle-cell, epithelioid as well as anaplastic changes, which may simultaneously occur in different areas of the tumor.

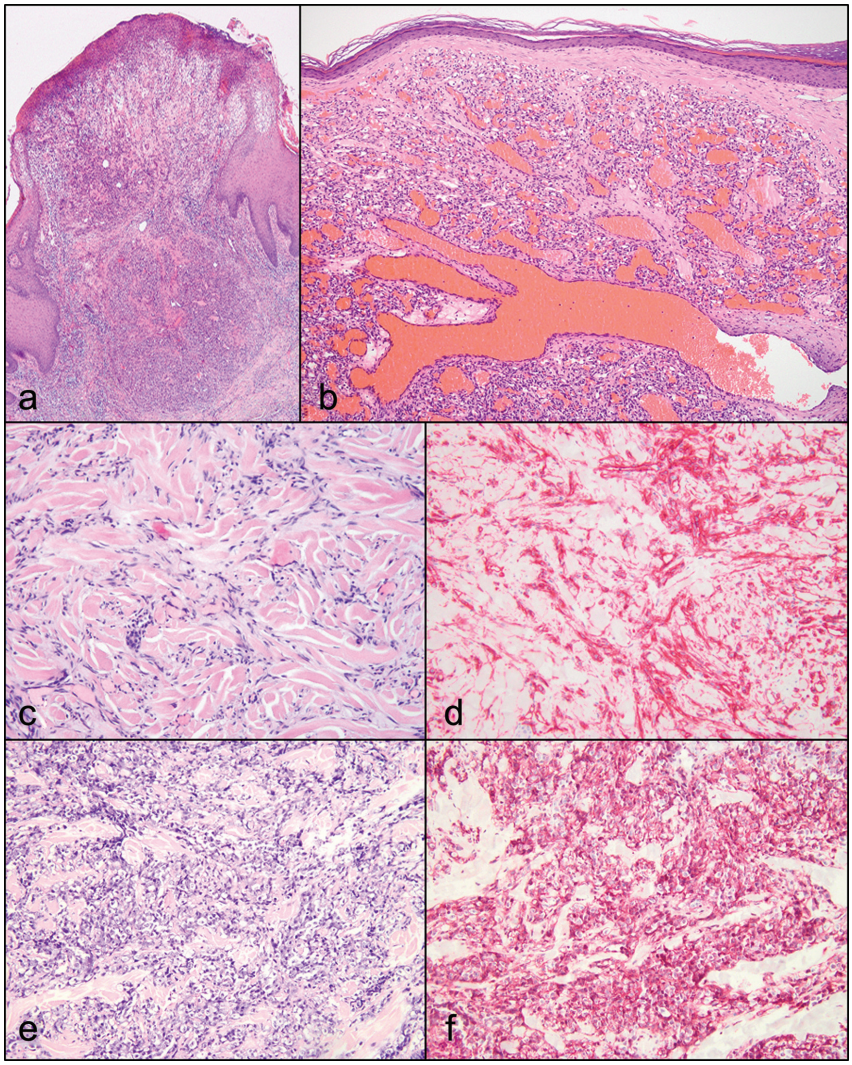


**Figure 16** Vascular soft tissue tumors. Pyogenic granuloma: exophytic tumor with superficial ulceration flanked on both sides by a regular, acanthotic epidermis. Neutrophil-rich granulation tissue at the base of the ulcer. Circumscribed lobular capillary proliferations arising from a central conglomerate (H&E, x 40) (a). Lobular hemangioma: circumscribed lobular proliferation of regular capillaries with a single-layer endothelium without nuclear atypia. Some capillaries are filled with erythrocytes (H&E, x 100) (b). Spindle-cell angiosarcoma: interstitial proliferation of partly atypical spindle cells between thickened collagen fibers; only few mitoses. There is no clear evidence of vascular proliferations or the endothelial origin of the spindle cells (H&E, x 200) (c). Immunohistochemical staining with antibodies directed against podoplanin: the spindle cells show complete positivity for this vascular marker, which is a diagnostic clue to angiosarcoma (podoplanin, x 200) (d). Epithelioid angiosarcoma: dense – partly nodular, partly interstitial – infiltrates of atypical epithelioid cells. Focal vascular formations with endothelial nuclear atypia, endothelial papillae, and endothelial multilayering (H&E, x 200). Remarkably, both biopsies are from the same tumor. This is a good example of all types of angiosarcoma differentiation occurring in the same tumor (e). Immunohistochemical staining with antibodies directed against podoplanin: here, too, there is complete positivity of the atypical epithelioid cells (podoplanin x 200) (f).

Immunohistochemically, angiosarcomas show variable positivity for various vascular and endothelial markers (actin, CD31, CD34, podoplanin, and others). The majority of angiosarcomas reveals MYC expression. Additive expression of cytokeratins makes angiosarcoma an immunohistochemically "unpredictable" tumor, which should always be assessed in correlation with its morphology. Ultimately, the spectrum of differential diagnoses includes all vascular tumors and their imitators. Given the particularly aggressive biological behavior of angiosarcomas, swift and precise histological diagnosis is of crucial importance.

### 4.6 Tumors of uncertain differentiation

Histologically, AFX presents as a well-circumscribed dermal lesion with a pleomorphic cellular pattern consisting of histiocytic cells, spindle cells as well as bizarre multinucleated giant cells with numerous atypical mitotic figures and nuclear pleomorphism.

Today, most authors consider atypical fibroxanthoma (AFX) a superficial variant of pleomorphic dermal sarcoma (PDS). Histologically, it presents as a well-circumscribed dermal lesion with a pleomorphic cellular pattern consisting of histiocytic cells, spindle cells as well as bizarre multinucleated giant cells with numerous atypical mitotic figures and nuclear pleomorphism. With respect to the differentiation of AFX from PDS as well as the immunohistochemical workup to rule out important differential diagnoses, the reader is referred to the recent review by Kohlmeyer et al. [26].

## Summary

The objective of the present article is to highlight fundamental aspects with respect to the histopathology of the most common skin tumors (epidermal, adnexal, melanocytic, and mesenchymal origin), their laboratory workup as well as the importance of supplementary immunohistochemical and molecular studies. These fundamentals are supposed to assist the clinician in choosing the correct biopsy technique and in interpreting dermatopathology reports. Overall, due to the enormous diversity of skin tumors, the article does not claim to be all-encompassing. Nevertheless, it is meant to contribute to avoiding misdiagnoses, which may be the result of an inadequate specimen, lack of additional information, or erroneous processing at the laboratory. Another goal of this article is to raise awareness among clinical dermatologists for the problems associated with the histopathological workup. Similar to inflammatory dermatoses, the diagnosis of skin tumors, too, requires the close cooperation between clinicians and dermatopathologists. The diagnostic quality and the resultant therapeutic approach can be significantly improved if this collaboration is based on the same dermatological understanding.

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# Fragen zur Zertifizierung durch die DDA

**1. Das Ergebnis einer unkoordinierten benignen oder malignen Proliferation von Zellen, die in der Regel irreversibel ist, bezeichnet man als ...?**

a) Hamartom
b) Choristom
c) Malformation
d) Hyperplasie
e) Neoplasie

**2. Welches Verfahren eignet sich für die kosten- und zeiteffiziente Analyse des Genoms, wobei auch mehrerer Patientenproben gleichzeitig untersucht werden können?**

a) PCR (Polymerase-Kettenreaktion) mit Sanger-Sequenzierung
b) Next-Generation-Sequencing
c) Fluoreszenz-in-situ-Hybridisierung (FISH)
d) PCR (Polymerase-Kettenreaktion)
e) Immunhistochemie

**3. Welche histologischen Muster weisen auf eine Talgdrüsendifferenzierung hin?**

1 wellenartiges Muster (rippled pattern)
2 sandartiges Muster (sand pattern)
3 labyrinthartiges/sinusoidales Muster
4 karzinoidartiges Muster (Trabekel, Schleifen, Rosetten, Pseudorosetten)
5 petaloides Muster (Kronblatt, Blumen-ähnlich).

a) 1–3 sind richtig.
b) 1, 2 und 4 sind richtig.
c) 1, 2 und 3 sind richtig.
d) 1, 3, 4 und 5 sind richtig.
e) Alle sind richtig.

**4. Welches Syndrom geht mit multiplen Trichoepitheliomen und Zylindromen einher?**

a) Gorlin-Goltz-Syndrom
b) Gardner-Syndrom
c) Brooke-Spiegler-Syndrom
d) Cowden-Syndrom
e) Bird-Hogg-Dubé-Syndrom

**5. Mit welchem Marker färbt das Merkelzellkarzinom gewöhnlicherweise?**

a) CK20
b) TTF1
c) Melan A
d) CK7
e) CD45

**6. Welche Lokalisation von Naevi wird **nicht** als *special site* angesehen?**

a) genital
b) Oberarm
c) perimamillär
d) Ohr
e) Nabel

**7. Was ist ein Malignitätskriterium einer melanozytären Läsion?**

a) Scharfe Begrenzung der lateralen intraepidermalen melanozytären Komponente.
b) Überwiegen von Melanozytennestern im Vergleich zu einzeln liegenden Melanozyten.
c) Keine Varianz der Melanozytennester in der Epidermis und Dermis.
d) Melanozyten in allen Epidermisschichten nachweisbar.
e) Im Korium werden Melanozyten sowie Nester zur Tiefe hin kleiner (Ausreifung).

**8. In welche Gruppe von mesenchymalen Tumoren wird das Dermatofibrom eingeordnet?**

a) lipogene Tumoren
b) fibrohistiozytäre Tumoren
c) myogene Tumoren
d) neurogene Tumoren
e) vaskuläre Tumoren

**9. Mit welchen Markern können neurogene Tumoren färben?**

1) CK 20
2) S100
3) Melan A
4) CK7
5) EMA

a) 1–3 sind richtig.
b) Nur 5 ist richtig.
c) Nur 3 ist richtig.
d) 2 und 5 sind richtig.
e) 1–5 sind richtig.

**10. Wem obliegt die Endkontrolle, ob Histopathologie und klinischer Befund stimmig sind?**

1 dem Patienten
2 dem Histopathologen
3 dem klinisch tätigen Dermatologen

a) 1–3 sind richtig.
b) Nur 2 ist richtig.
c) Nur 3 ist richtig.
d) 2 und 3 sind richtig.
e) Eine Endkontrolle ist nicht nötig, da der histologische Befund ausschlaggebend ist.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 27. Oktober 2017. Die richtige Lösung zum Thema „Kutane Sarkome“ in Heft 6 (Juni 2017): (1b, 2c, 3d, 4a, 5e, 6d, 7a, 8d, 9d, 10b).

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