Received: 16 October 2022 | Accepted: 4 December 2022

DOI: 10.1111/ddg.14984

CME ARTICLE

Seborrheic keratosis

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Finanzielle Interessen: Ja
Erklßrung zu nicht-finanziellen Interessen: DDG

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Finanzielle Interessen: Nein
Erklßrung zu nicht-finanziellen Interessen: Keine

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Erklßrung zu nicht-finanziellen Interessen: DDG, AGDV

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Erklßrung zu nicht-finanziellen Interessen: Keine

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Erklßrung zu nicht-finanziellen Interessen: Keine

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Erklßrung zu nicht-finanziellen Interessen: Keine

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Finanzielle Interessen: Nein
Erklßrung zu nicht-finanziellen Interessen: DDG, DDCG, BDC, DGPRÄC, DGCH, ICW

Summary
Seborrheic keratosis (SK) is the most common benign epidermal tumor in clinical dermatological practice. This review summarizes current knowledge about the clinical and histological appearance, epidemiology, pathogenesis, and treatment of SK. There are different subtypes of SK based on clinical presentation and histologic findings. Several factors, including age, genetic predisposition, and possibly also exposure to ultraviolet radiation, are thought to contribute to the development of SK. The lesions can occur on all areas of the body except for the palms and soles, but the most common sites are the face and upper trunk. The diagnosis is usually made clinically, and in some cases by dermatoscopy or histology. Many patients prefer to have the lesions removed for cosmetic reasons although there is no medical indication. Treatment options include surgical therapy, laser therapy, electrocautery, cryotherapy, and topical drug therapy, which is currently in development. Treatment should be individualized depending on the clinical picture and patient preference.

DEFINITION AND CLINICAL FEATURES

Seborrheic keratosis (SK), also referred to in the literature as senile wart, seborrheic wart, verruca senilis, verruca seborrheica, basal cell acanthoma, basal cell papilloma or benign acanthokeratoma, is a common benign lesion of the epidermis. Seborrheic keratoses can occur in many variations (Figure 1). They are usually roundish or oval in shape, but

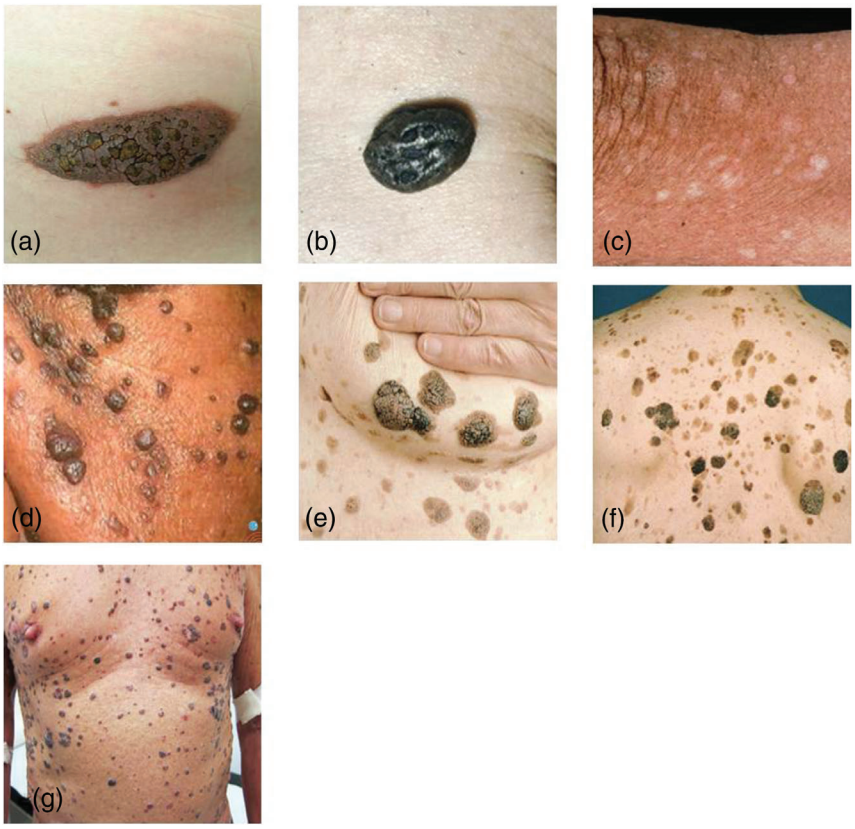

FIGURE 1 Clinical forms of SK. (a) "Typical" SK. (b) Melanoacanthoma. (c) Stucco keratosis. (d) Dermatosis papulosa nigra. (e-g) Multiple SK.

irregular lesions also occur. The degree of pigmentation can vary, from skin-colored or yellowish to light brown and even black. The size can also vary, ranging from a few millimeters to several centimeters. The exophytic growth and sharp demarcation from the surrounding skin lend it its characteristic "stuck-on" appearance. The verrucous surface is usually fissured and forms pore-like keratin (pseudo-) cysts. They can appear greasy and shiny, which explains the misleading name. The term "seborrheic" implies increased sebum production, but this has no association with SK. Unlike raised lesions, flat seborrheic keratosis tends to have a smoother and velvety surface structure. In intertriginous skin areas such as the axilla or groin, the lesion can appear pedunculated.[1] Typically, the lesions grow rapidly initially and then remain largely constant in size for years. However, they can also increase in both size and thickness with time, and their color may change over the years due to increased melanin production. SK rarely regresses spontaneously.[2] Histological examination is warranted when the nature is unclear, the lesion continues to grow, there are defects in the epidermis, and the clinical or dermatoscopic appearance is atypical.

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The exophytic growth and sharp demarcation from the surrounding skin lend it its characteristic "stuck-on" appearance. The verrucous surface is usually fissured and forms pore-like keratin (pseudo-) cysts.

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EPIDEMIOLOGY

Seborrheic keratoses are by far the most common human tumors. Both the prevalence and the median number of lesions increases steadily with increasing age, and there can be up to hundreds of lesions in advanced age. Men and women are affected equally. Seborrheic keratoses are found in all population groups and with a similar incidence; a familial predisposition is often observed, though there is surprisingly little epidemiological data in this regard.[1] According to an American survey, SK is found in roughly 30% of all Americans.[3] In an Australian study, SK were found in as many as 100% of patients over 50 years, with an average number of 69 SK in patients over 75 years. Among 15–25-year-old subjects, the prevalence was 12%, with a median number of six SK per subject.[4] In another study with 170 subjects aged from 15 to 30 years, SK was found in 15.7% of 15–19-year-olds and in 32.3% of 25–30-year-olds. These results show that seb-

orrheic warts also occur in younger patients and that the prevalence in this age group is possibly underestimated. In the US, each dermatologist diagnoses SK in 155 patients monthly, and 33% of them have more than 15 lesions.[5]

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SK can occur on all hair-bearing areas of the body. Sites of predilection are the chest, the back, the head, especially the temples, and the neck. The palms and soles [4] and mucous membranes are not affected though there are isolated reports of SK on the conjunctiva.[6,7] When there is a large number of lesions, a special distribution pattern on the trunk can sometimes be observed. This is called a *Christmas tree pattern* when the tumors are arranged on the back along the Langer lines.[1] Another striking pattern described in the literature is the *raindrop and stream pattern*, in which the lesions are seen in a vertical raindrop-like distribution on the back.[8,9] In dark-skinned persons, SK can appear in extensive aggregates mainly on the face. In the Anglo-American literature, this is also referred to as dermatosis papulosa nigra.

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SK is normally asymptomatic. If the tumor is located at sites where mechanical irritation occurs, for example due to abrasive clothing, pruritus, pain, and erythema are possible, and even bleeding with subsequent crusting or superinfection.[1] Removal of the lesion can be recommended in this case.

SK is normally asymptomatic.

SPECIAL FORMS OF SK

There are different clinical variants of SK, which differ from the usual SK described above (Figure 1).

Melanoacanthoma

Melanoacanthoma denotes a highly pigmented acanthotic SK. The pronounced pigmentation is explained by numerous pigment-rich melanocytes in the epidermis and subepidermal melanophages. Melanoacanthoma must be distinguished clinically and if necessary, histologically from malignant melanoma.[10]

Melanoacanthoma denotes a highly pigmented acanthotic SK.

Stucco keratosis (keratosis alba)

Stucco keratosis is described as a special type of hyperkeratotic SK because of its histologically visible orthohyperkeratosis. Unlike the latter, however, no keratin cysts are found in stucco keratosis. They often appear as whitish papules, only a few millimeters in size, that can be easily scraped off the skin. Preferred sites are the extensor surface of the forearms and dorsum of the hands, the extensor surfaces of the shins and the dorsum of the feet, where the benign lesions accumulate more often, especially in elderly patients.

Stucco keratosis is described as a special form of hyperkeratotic SK.

Dermatosis papulosa nigra

Dermatosis papulosa nigra is a variant of acanthotic SK, first described by Castellani in 1925. The flat, raised, brown-black papules occur predominantly on the face and neck. It is diagnosed mainly in the African and Asian population, and women are affected twice as often as men. Increased familial incidence is not unusual because of the genetic pathogenesis.[11]

Lichen planus-like seborrheic keratosis

This lesion, also termed benign lichenoid keratosis or lichen planus-like lichenoid keratosis, is probably an inflammatory change in different precursor lesions, including SK, and should therefore be avoided as a diagnosis. The sites of predilection of the reddish-violet and sometimes brown papules or plaques are the upper trunk, forearms, and dorsum of the hands. This dermatosis, which usually appears as a single lesion, shows scaling of the surface in some cases.[12]

Inflamed verruca seborrheica

SK can develop into an inflamed verruca seborrheica due to trauma, for instance due to scratching, or other irritation. Erythema and pain are typical symptoms.

Leser-trélat sign (leser-trélat syndrome)

The Leser-Trélat sign, the existence of which is much disputed, is characterized by the sudden appearance of multiple seborrheic keratoses, usually diffusely on the trunk. It is often accompanied by pruritus, and by acanthosis nigricans in about 30% of cases. Since an association with malignant tumors at an advanced stage has been described with

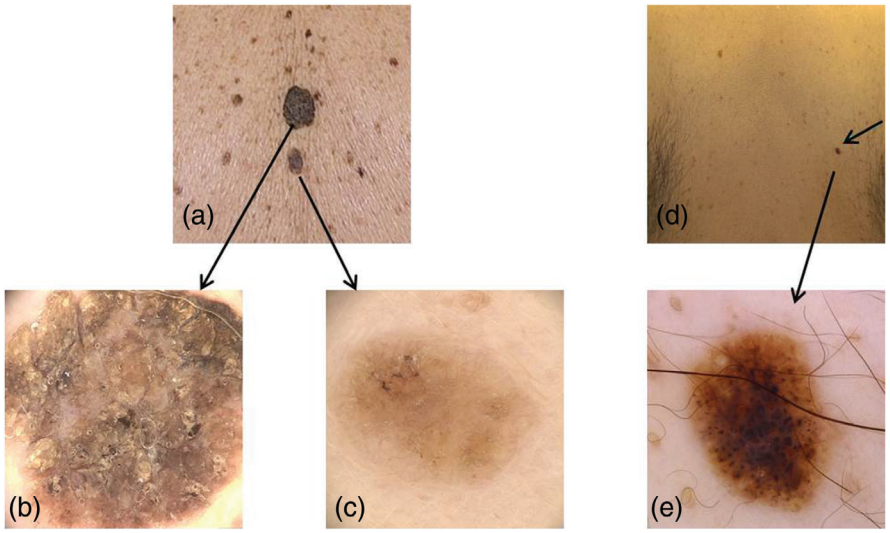

FIGURE 2 Dermatoscopy. (a) Patient with multiple SK on the back. (b) Dermatoscopy of large pigmented SK. (c) Dermatoscopy of classical SK. (d) Patient with pigmented lesion on the back. (e) Dermatoscopy of melanoacanthoma.

this very rare disease, it is often termed a paraneoplastic syndrome. Adenocarcinomas of the gastrointestinal tract in particular are among the causes of the syndrome; it occurs more rarely in association with breast cancer, lung cancer, lymphoma or leukemia. The diagnosis of Leser-Trélat syndrome has been associated with a poor prognosis. The mean/median survival following diagnosis is eleven months. Different authors report remission of the warts as a result of treatment of the causative disease and further appearance of the lesions if the tumor recurs.[1]

The Leser-Trélat sign, the existence of which is much disputed, is characterized by the sudden appearance of multiple seborrheic keratoses, usually diffusely on the trunk.

In most cases of eruptive SK, however, no underlying malignancy is diagnosed so this should be described as a facultative and not obligatory paraneoplastic condition.[13] Because of these differences in findings, clear assignment of the syndrome to the paraneoplastic syndromes is not possible. The fact that the incidence of SK is increased at advanced age and that elderly patients develop cancer more than younger persons raises more doubts about a causal association. For this reason, it is doubtful whether a wide-ranging search for a tumor is really indicated with the eruption of multiple SKs.

DERMATOSCOPY

SK can be diagnosed clinically in most cases because of the characteristic appearance of SK, its often greasy and shiny, warty, fissured, or keratotic surface and other distinguishing features. In case of doubt, dermatoscopy is used to aid diagnosis as different benign or malignant diseases should be considered in differential diagnosis due to the morphological variety. It is usually easy to differentiate it from melanocytic neoplasms (Figure 2).

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The most important dermatoscopic features of SK are milia-like cysts, comedo-like openings and a honeycomb-like or cerebriform sulcus and gyrus pattern.[14,15] The tumors usually appear non-transparent and grey-brown in color, but colorless variants also occur.[1] Pseudocysts filled with keratin material opening towards the surface correspond to the comedo-like openings on the surface of the lesion seen by dermatoscopy. Milia-like cysts appear in addition, which are seen as small, whitish-yellow nodules in the lesion. These are intraepidermal keratin cysts. The papillomatous growth of the epidermis is seen on dermatoscopy as a cerebriform sulcus and gyrus pattern with fissures and ridges. Hairpin-shaped vascular structures with a white halo are often visible on the ridges. Dermatoscopic diagnosis can be difficult when the SK is highly pigmented. Due to the increased number of melanocytes, typical findings that assist diagnosis can remain hidden, thereby making it more difficult to distinguish from malignant melanoma.[16–19] The irritated subtype of SK is a special case in dermatoscopy. Instead of the typical dermatoscopic findings of SK described above, small round structures are seen, pink in color on a whitish background. These structures are explained histopathologically by dilated vessels in the dermal papillae, surrounded by acanthotic cells of the epidermis.[20]

In a study in which 203 pigmented seborrheic keratoses were examined by dermatoscopy, other morphological

dermatoscopic features were found in addition to the main characteristics described above. These include, for example, sharp demarcation, which was found in 183 of the 203 cases, or a "moth-eaten" margin, found in 94 of the 203 lesions. Through these additional criteria it is usually possible to identify SK clearly and reduce misdiagnosis.[14] Nevertheless, in some cases a clear diagnosis is not possible. The lesion should then be removed and clarity provided by histological examination.[1]

In some cases, nevertheless, a clear diagnosis is not possible. The lesion should then be removed and clarity provided by histological examination.

OTHER DIAGNOSTIC METHODS

Other diagnostic methods include confocal laser scan microscopy (CLSM) and optical coherence tomography (OCT). These methods image the depth of the lesion, providing a three-dimensional impression to give further diagnostic certainty to the two-dimensional dermatoscopy. The methods do not compete with dermatoscopy, but rather supplement it. CLSM can show the cellular structure of the skin to a depth of about 250–300 μm. This method is well established in the diagnosis of SK. A disadvantage is the relatively small field that can be imaged, causing some difficulty, especially for larger structures. The structures that can be detected by dermatoscopy find their correlates in CLSM. The milia-like cysts correspond to keratin pseudocysts in expanded papillary spaces on the suprabasal plane. The comedo-like openings can be seen as superficial epidermal invaginations filled with keratin.[21] Not every subtype of SK can be reliably diagnosed by CLSM, in particular due to the small penetration depth of the method.[22]

Other diagnostic methods include confocal laser scan microscopy (CLSM) and optical coherence tomography (OCT).

OCT can demonstrate structures three-dimensionally to a depth of 1–2 mm but at a lower resolution than with CLSM. Optical coherence tomography has to date played a lesser role in the diagnosis of SK, and not many studies are available. A diagnostic advantage may be the differentiation of various subtypes of SK.[23]

Both methods are suitable especially for small lesions that cannot be clearly classified clinically and therefore may assist decision-making in early diagnosis with regard to the further treatment strategy. In addition, they may offer a prospect of monitoring treatment with the use of newly developed topical drugs.

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HISTOLOGY

Seborrheic keratosis is an intraepidermal proliferation of squamous epithelial or basaloid cells. The histological diagnostic criteria of SK are acanthosis, papillomatosis, (ortho-) hyperkeratosis, keratin cysts and keratin pseudocysts. Keratin cysts are keratin pearls formed intraepidermally which are discharged transepidermally, while keratin pseudocysts are keratin invaginations of the overlying stratum corneum. Nuclear or cellular atypia is not usually found. Melanocytes and melanin are present to a variable degree depending on pigmentation. SK can demonstrate great variability, not only clinically but also histologically, and distinguishing it from other neoplasms such as keratoacanthoma and clear cell acanthoma is not always easy.[24–26] Six basic histological types can be distinguished, however. Mixed types, for example of acanthotic and adenoid type, are possible, with one type usually dominating in each lesion (Figure 3).[1,2,10,12,27]

Seborrheic keratosis is an intraepidermal proliferation of squamous epithelial or basaloid cells. The histological diagnostic criteria of SK are acanthosis, papillomatosis, (ortho-) hyperkeratosis, keratin cysts and keratin pseudocysts.

Six basic histological types of SK can be distinguished.

Acanthotic type

The acanthotic type is the most common histological variant of SK. The epidermis shows marked acanthosis of monomorphous basaloid cells. Papillomatosis and hyperkeratosis are less pronounced, and keratin and keratin pseudocysts are found in abundance. Not infrequently there can be a subepidermal inflammatory lymphocytic infiltrate. Roughly one third of acanthotic SK is hyperpigmented basally (melanoacanthoma).[1,17]

The acanthotic type is the most common histological variant of SK.

Hyperkeratotic type

Unlike the acanthotic type, hyperkeratosis and marked papillomatosis predominate in the hyperkeratotic type, with only slight acanthosis. The epidermis shows a saw-toothed appearance that can sometimes be reminiscent of church spires. Keratin cysts and keratin pseudocysts are uncommon, as is hyperpigmentation.[1,28]

Adenoid or reticular type

Double-row cords of basaloid cells extend from the epidermis into the dermis and anastomose to form reticular patterns. Hyperpigmentation is found regularly but keratin

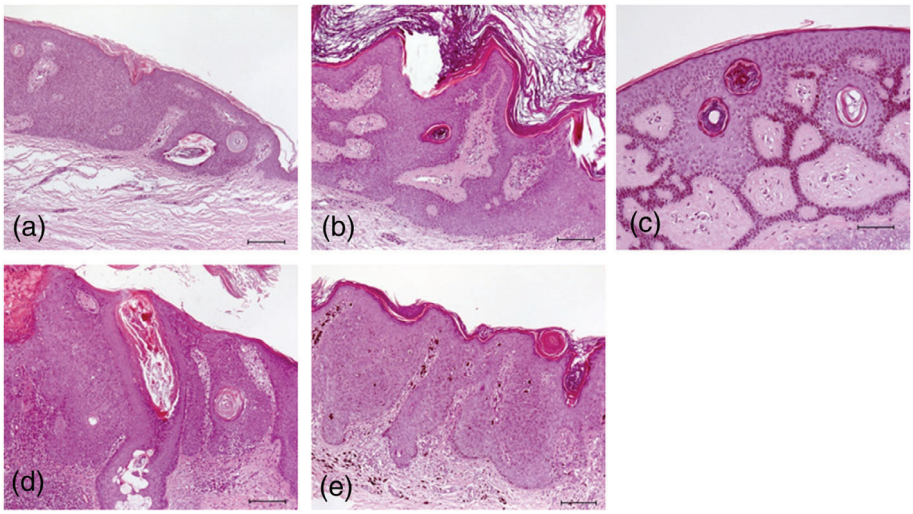

FIGURE 3 Histological forms of SK. (a) Acanthotic. (b) Hyperkeratotic. (c) Adenoid. (d) Bowenoid. (e) Melanoacanthoma.

pearls are rarer. Because of the increased incidence in light-exposed areas, some authors suspect that reticular SK could arise from solar lentigines by sprouting basaloid cords.[1,17,29]

Clonal type

Intraepidermal cell nests of basaloid cells with a small basophilic nucleus or larger pale cells with intercellular bridges are characteristic of SK of the clonal type. The coexistence of cell nests of different form is called the Borst-Jadassohn phenomenon. It is typical but not specific for SK of the clonal type and can also be observed with hidroacanthoma simplex, intraepidermal malignant poroma and Bowen's disease.[10]

The coexistence of cell nests of different forms is called the Borst-Jadassohn phenomenon. It is typical but not specific for SK of the clonal type.

Irritated or inverted follicular type

Squamous eddies are the most striking histopathological feature of irritated SK. These are whorled intraepidermal collections of eosinophilic squamous epithelial cells resembling an onion skin. Basaloid cells are rarely found in this subtype. Acantholysis, dyskeratosis and spongiosis can be observed in the vicinity of the squamous eddies. Irritated SK and inverted follicular SK are probably identical.[1,10]

Bowenoid type

In the bowenoid type, bowenoid transformation of the SK occurs. This type is found mainly in UV-exposed areas of the body. Histology shows intraepidermal cell atypia with markedly disturbed layers and subepidermal round cell infiltration along with the typical histological features of SK. The degree of bowenoid transformation may vary and can include intraepidermal carcinoma.[10]

PATHOGENESIS

Risk factors

Despite being so common, the etiology and pathogenesis of SK remain largely unknown. As described above, age is the most important risk factor for SK. Genetic predisposition is certainly another risk factor for SK. As early as 1952, Reiches identified an autosomal-dominant inheritance pattern of SK in several families in which the lesions occurred over three generations.[30] Other clinical case reports noted families in which there was an increased incidence of SK over several generations, also at an unusually young age.[1,31,32] Despite the clear association between genetics and the pathogenesis of SK, the precise mode of inheritance has not been conclusively determined.

Despite being so common, the etiology and pathogenesis of SK remain largely unknown. As described above, age is the most important risk factor for SK. Genetic predisposition is certainly another risk factor for SK.

Besides age and genetic predisposition, UV exposure and viral genesis have also been considered risk factors for SK.

Besides age and genetic predisposition, UV exposure and viral genesis have also been considered risk factors for SK.[33–35] Reports on an increased incidence of SK in sun-exposed regions of the body and markedly higher percentage case numbers in Australia compared to the UK can be regarded as evidence for an association between the occurrence of SK and cumulative UV exposure.[1,4,36]

Research from a national health and nutrition survey in the US likewise showed an association between UV exposure and the incidence of SK.[37] A Korean study with 303 male subjects showed that most SK occurred on UV-exposed body sites, that lesions on UV-exposed sites increased in size with advancing age and increased sun exposure, and that patients with a lifetime sun exposure of more than six hours per day had 2.28 times greater prevalence of SK than patients with less than three hours of sun exposure per day.[38] By contrast, a study from the Netherlands with 966 subjects reported that while painful sunburn and lifelong sun exposure are important risk factors for developing squamous cell carcinoma, basal cell carcinoma and malignant melanoma, they do not increase the risk for developing SK.[39] Thus, the association between UV radiation and the incidence of SK has not been clearly explained and is controversial in the literature.

Moreover, whether human papilloma viruses must be considered as risk factors for SK has also been discussed.[40–42] In 1989, Zhao et al. found human papilloma viruses in SK in only four of 89 subjects,[33] and more recent studies by Lee et al. and Kambiz et al. could not find a positive association between HP viruses and the development of SK.[43,44]

MOLECULAR PATHOGENESIS

Although SK is clearly benign, it shows oncogenic mutations surprisingly often. In particular, mutations in the AKT signaling pathway and in fibroblast growth factor receptor 3 (FGFR3) in the epidermis appear to play an important role in the pathogenesis of SK.[45]

The molecular pathogenesis of SK is as yet poorly understood.

In particular, mutations in the AKT signaling pathway and in fibroblast growth factor receptor 3 (FGFR3) in the epidermis appear to play an important role in the pathogenesis of SK.

FGFR3 is a cellular receptor that is activated by binding soluble FGF (fibroblast growth factors). It is a transmembrane receptor from the receptor tyrosine kinase family; these are autophosphorylated after extracellular binding of a ligand, thereby inducing intracellular signaling pathways that control proliferation, cell differentiation, cell migration and apoptosis of the cell. Germline mutations in the *FGFR3* gene may be responsible for skeletal dysplasia in humans. Somatic *FGFR3* mutations have in turn been identified in various neoplasms, including multiple myeloma, and in epithelial malignancies, such as bladder and cervical cancer, with bladder tumors having the highest prevalence of *FGFR3* mutations. In noninvasive papillary bladder tumors, which have uncertain malignant potential and match SK in some features, these often occur in combination with *PIK3CA* mutations.[46] To investigate the significance of FGFR3 in the skin, an activated mutant of FGFR3 was introduced into basal mouse epidermis cells. These animals develop benign epidermal tumors with acanthosis, papillomatosis, and hyperkeratosis, which showed similarities to SK or acanthosis nigricans.[45] *FGFR3* mutations, which also occur in other epithelial neoplasms, also accelerate the proliferation of keratinocytes *in vitro* and reduce their apoptosis and adhesion to matrix proteins.[47]

Studies in humans showed that 24 (39%) of 62 SK of hyperkeratotic and acanthotic subtype examined by molecular genetics had an *FGFR3* mutation. The mutations found in the SK were identical with the *FGFR* mutation already identified in epithelial tumors and skeletal dysplasia.[45] In the congenital dysplasia syndromes with *FGFR3* mutation, the degree of activation of the FGFR3 receptor by the different mutations was found to correlate with the severity of the disease. A similar association was not seen, however, with the somatic mutations in SK. In the benign lesions, mutations with a high degree of receptor activation were mainly found, permitting the conclusion that only highly activating *FGFR3* mutations predispose to SK.[48] Compared with the benign skin lesions, no *FGFR3* mutations were found in studies of other epidermal neoplasms,[45] with the exception of solar lentigines, which sometimes show *FGFR3* or *PIK3CA* mutations but no $BRAF^{V600}$ mutations, which are common in melanocytic neoplasms.[49] This possibly points to a joint pathogenesis of solar lentigines and SK.

FGFR3, *PIK3CA* and *RAS* mutations were also found in special forms of SK (benign lichenoid keratosis, stucco keratosis, dermatitis papulosa nigra).[50,51] A study by Hafner et al., who examined a series of 27 SK of adenoid subtype, showed similar results. They found that in this histological subtype as many as 85% of SK had an *FGFR3* mutation and that the mutation ranges of different SK were very similar. This included the substitutions R248C, S249C, G372C, S373C, Y375C, A393E, K652M and K652E.[52] In a follow-up study Hafner et al. analyzed 175 SK by molecular genetic means with a focus on the FGFR3-RAS-MAPK and phosphoinositide-3-kinase (PI3K)-AKT signal cascades. It was found that SK had mutations in the oncogenes *KRAS* (20%), *HRAS* (3%) and *EGFR* (5%) as well as mutations in *FGFR3* (71%) and *PIK3CA* (50%).[53,54] Heidenreich et al. also found mutations in the *Tert* and *DPH3* promoter in a quarter of the SK examined.[55] Thus, oncogenic mutations in the afore-mentioned signal cascades are important not only in malignant disease but also in the development of benign epidermal lesions.

Whether mutations in the FGFR3 locus can act as a target structure for treatment is currently being investigated. Different FGFR inhibitors are currently under clinical investigation for the treatment of malignant tumors but whether these might also be effective in the (topical) treatment of SK is as yet unknown.

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Another important element in the pathophysiology of SK is increased activity of AKT kinase (protein kinase B), which appears to be crucially important for the development of SK.[56] AKT is recruited to the cell membrane by substrates of PI3K, where it is phosphorylated at amino acids serine-473 and threonine-308 by the phosphoinositide-dependent protein kinase-1 (PDK1) and activated. It then in turn phosphorylates a number of proteases involved in the regulation of apoptosis and the cell cycle, such as Bcl-2 or the forkhead transcription factors FOXO1, FOXO3 and FOXO4. In this manner the AKT signaling pathway, which is inhibited by the tumor suppressor PTEN, controls the cell cycle and apoptosis. It is particularly significant that AKT inhibitors, which can also be applied topically, are potent inhibitors *in vitro* of the growth of SK cells.[56] New therapeutic agents based on this mechanism are currently in clinical development.[57]

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Despite the known oncogenic mutations that have been found in SK, the tumors do not have any malignant potential.

Despite the known oncogenic mutations that have been found in SK, the tumors do not have any malignant potential even though the proliferation marker Ki-67 is overexpressed in the suprabasal cell layer of the SK. There must therefore be mechanisms in SK that suppress tumor progression. Thus Hafner et al. hypothesized that activation of a senescence program occurs in SK that does not prevent the development of neoplasia but does prevent malignant degeneration.[54] This could be due to FOXN1 activation caused by overexpression of FGFR3, which induces cell differentiation and growth arrest.[58] Moreover, SK is genetically stable and does not exhibit *p53* mutation, and AKT activation causes a certain resistance to cellular stress caused by reactive oxygen. The inherent terminal differentiation of keratinocytes, which represents a form of programmed cell death and is associated with caspase activation and transition of keratinocytes to corneocytes,[59,60] could therefore play an important part in suppressing malignant degeneration of SK.

TREATMENT

Due to the benign nature of SK, treatment is generally not necessary. Treatment may nonetheless be desired or contemplated, mostly for cosmetic reasons, so the risk of complications and the post-treatment cosmetic appearance should be particularly relevant when deciding on treatment options.

Due to the benign nature of SK, treatment is generally not necessary.

Locally destructive methods

Very large, highly pigmented lesions and those located on exposed areas are perceived by patients as particularly troublesome aesthetically and are removed if desired. Patients with very many SK often prefer to have them removed. The current method is curettage using a sharp or ring curette. Patients must be informed about potential scarring and the risk of recurrence if removal is incomplete, and also that lesions can recur persistently. Alternatively, the lesions can be removed by shave excision with a scalpel, though recurrence must be expected in this case as well. Treatment is more rarely indicated for medical reasons. In the case of persistent mechanical irritation, for example, due to clothing because of their location (belt or bra area), the lesion should be removed as the irritation can lead to repeated inflammation, bleeding, and increased pruritus. If the SK interferes functionally, for example if located on the eyelid or in the ear, it should be treated. When the diagnosis is unclear, the lesion should be removed for diagnosis, with histopathological examination to rule out malignancy.[1,29]

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Other possible treatment methods besides curetting and shave excision are cryotherapy and electrodesiccation.

Removal of the lesion by ablative laser treatment with an erbium:YAG (Er:YAG) or CO_2 laser is another possible method of treating SK.

Other possible treatment methods besides curetting and shave excision are cryotherapy and electrodesiccation. Among 25 subjects of an American study, the majority preferred cryotherapy compared to curetting, which was attributable to the need for less wound care. However, recurrence, both short- and long-term, occurred more often with freezing than with removal by a sharp curette.[61] Removal of the lesion by ablative laser treatment with an erbium:YAG (Er:YAG) or CO_2 laser is another possible method of treating SK. In a comparative study, SK of the same size and location were treated differently in 42 subjects: by cryotherapy in one half and by Er:YAG laser in the other half. The results showed a 100% success rate among the lesions treated by laser with markedly less hyperpigmentation, while the cryotherapy success rate was only 68%.[62] Zaresharifi et al. also compared the success rates of the different treatment methods in their study published in 2021. They compared treatment by means of Er:YAG laser, CO_2 laser, electrodesiccation, and cryotherapy. The focus of the evaluation, besides patient satisfaction, was on the pigmentation and texture of the skin site and on healing. Eight weeks after removal, both laser treatments and electrodesiccation achieved better results than cryotherapy

with regard to overall healing. The same results were also recorded in terms of patient satisfaction. No significant difference was found between the different groups regarding pigmentation and texture.[63] In another study, Culbertson et al. treated over 1500 SK with a 532-nm diode laser. The results showed complete resolution of the lesion in 93% of cases, while a second laser treatment was necessary in 7% to achieve complete clinical remission. Hypopigmentation developed in 6% of the laser-treated SK, whereas hyperpigmentation or hypertrophic scarring was not observed.[64]

A major disadvantage of these ablative treatment methods is that pathological examination of the tissue is not possible, so they should on no account be used if the diagnosis is in doubt, where mechanical removal and histological confirmation of the diagnosis is the method of choice.

Topical treatments

Because of the frequency of SK and substantial patient interest in non-invasive treatments, several attempts at treating the lesions topically with drugs have been made, but there is not yet a reliable method that is consistently used. There are case reports of successful treatment of SK with 3% diclofenac gel.[65] By contrast, the conclusion arrived at in another study was that once-daily topical use of tazarotene, calcipotriol and imiquimod was not a promising treatment option. There was a visible improvement in the skin lesion in seven of 15 subjects only with twice daily application of tazarotene cream, after initial irritation and erythema of the area.[66] Once to twice-daily topical treatment of SK with a vitamin D3 ointment for more than three months yielded remission in only 30.2% of the 116 subjects.[67] However, other new agents that were investigated in different studies for the treatment of SK showed good efficacy. Most notably, this included treatment with 40% hydrogen peroxide solution, which was investigated in two major placebo-controlled clinical studies with nearly 1000 patients in total and was marketed in America under the trade name Eskata®. Two applications three weeks apart led to healing of at least three of four treated SK in about 30% of the patients.[68–70] As further possible alternatives, a combined preparation of alpha- and beta-hydroxy acids, urea and thuja showed a success rate of 99% in a study with 20 subjects,[71] and topical use of 5% calcium dobesilate cream[72] and a combination of trichloroacetic acid and formic acid[73] also proved effective, although studies on larger groups of patients are lacking to date. Thus, these methods cannot yet be regarded as established treatments of SK. In an *in vitro* study by Neel et al., explanted SK were completely dissolved by incubation with an AKT inhibitor (A-443654).[56] Another AKT inhibitor, SM-020, is currently being tested for topical use for SK (NCT05136144), which might be particularly promising due to the relevance of the AKT signaling pathway for the development of SK.

In Germany, no approved topical treatment options are available for SK.

Another AKT inhibitor, SM-020, is currently being tested for topical use for SK, which might be particularly promising due to the relevance of the AKT signaling pathway for the development of SK.

Oral treatments

As an alternative to topical drug treatment, oral administration of 1,25-dihydroxyvitamin D3 to 51 patients was tested in a case study. Here, it was reported that in 15 patients treated with a high dose of the drug (0.5 μg/day), the SK changed within a short time from brown-black papules to brownish papules with erythema and further to atrophic scars or pigmented macules. In 36 patients treated with a low dose (0.25 μg/day), the SK faded almost completely and shrank without any erythema, leading the authors to conclude that oral 1,25-dihydroxyvitamin D3 might be a good treatment option especially for small SK.[74] However, these results have remained unconfirmed to date, and data from larger groups of patients are completely lacking, so the reported efficacy of vitamin D3 therapy for SK appears questionable.

In summary, advances in novel, non-invasive treatment methods represent an enrichment of the treatment options for SK, both for patients and for dermatologists. Further research is urgently needed in this area.

ACKNOWLEDGEMENT

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

None.

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How to cite this article: Barthelmann S, Butsch F, Lang BM, et al. Seborrheic keratosis. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2023;21:265–277. https://doi.org/10.1111/ddg.14984

[CME Questions / Lernerfolgskontrolle]

1. Welches sind häufige histologische Subtypen der SK?
   a. Hyperkeratotische SK, klonale SK und verruköse SK
   b. Akanthotische SK, hyperkeratotische SK und adenoide SK
   c. Akanthotische SK, hyperkeratotische SK und maligne SK
   d. Klonale SK, papulomatöse SK und bowenoide SK
   e. Adenoide SK, papulomatöse SK und klonale SK

2. Welche der folgenden Veränderungen in intrazellulären Signalwegen werden bei SK häufig gefunden?
   1. BRAF-V600E-Mutation
   2. FGFR3-Mutationen
   3. PIK3CA-Mutationen
   4. NRAS-Mutationen
   a. 1–4 sind richtig.
   b. Nur 1–3 sind richtig.
   c. Nur 2 und 3 sind richtig.
   d. Nur 2–4 sind richtig.
   e. Nur 3 und 4 sind richtig.

3. Welches ist kein Synonym der SK?
   a. Senile Warze
   b. Basalzellakanthom
   c. Basalzellpapillom
   d. Verruca vulgaris
   e. Gutartiges Akanthokeratom

4. Welche Aussage trifft zu?
   a. Pigmentierte SK gelten aufgrund der gesteigerten Melaninproduktion als Vorstufe eines malignen Melanoms.
   b. Ihren Namen „seborrhoische Keratose“ verdankt die Läsion ihrer gesteigerten Talgproduktion.
   c. SK können grundsätzlich am gesamten Körper auftreten. Prädilektionsstellen sind Fußsohlen und Handinnenflächen.
   d. SK können sowohl solitär als auch multipel auftreten. Multiple SK sind ein obligates Zeichen einer internen Neoplasie.
   e. Der Nachweis von Hornperlen in der Dermatoskopie ist für SK.

5. Welche Aussage trifft **nicht** zu?
   a. Die Dermatosis papulosa nigra ist eine überwiegend bei der afrikanischen und asiatischen Bevölkerung auftretende Sonderform der SK.
   b. Eine eher seltene Sonderform der SK stellt das Leser-Trélat-Syndrom dar. Bei diesem Syndrom liegt dem plötzlichen Auftreten multipler SK manchmal eine bösartige Erkrankung der inneren Organe, wie zum Beispiel ein Adenokarzinom des Gastrointestinaltraktes, zugrunde.
   c. Histologisch weisen SK nur selten Kern- oder Zellatypien auf.
   d. Die Stukkokeratose, auch Keratosis alba genannt, ist eine Sonderform der hyperkeratotischen SK. Charakteristisch sind weißliche Papeln vorwiegend an den Extremitäten, die sich leicht von der Haut abkratzen lassen.
   e. SK bilden sich häufig spontan zurück.

6. Welche dieser Krankheiten gehört nicht zu den typischen Differenzialdiagnosen?
   a. Malignes Melanom
   b. Fibroepitheliale Polypen
   c. Viruspapillome
   d. Pigmentierte Basalzellkarzinome
   e. Psoriasis

7. Welche Aussage trifft **nicht** zu?
   a. Ein höheres Lebensalter stellt einen unabhängigen Risikofaktor für senile Warzen dar. Weitere Risikofaktoren sind eine erhöhte UV-Exposition sowie eine genetische Prädisposition.
   b. SK treten deutlich häufiger bei Frauen als bei Männern auf.
   c. In der Literatur wird kontrovers diskutiert, ob humane Papillomviren als Triggerfaktor für das Auftreten der SK in Betracht gezogen werden können.
   d. Die Diagnose der SK erfolgt aufgrund ihres charakteristischen Aussehens meist klinisch, im Zweifelsfall kann ein Dermatoskop oder eine Biopsie bei der Diagnosestellung helfen.
   e. Zu den wichtigsten dermatoskopischen Erkennungszeichen zählen Pseudohornzysten sowie pseudofollikuläre Öffnungen. Weitere dermatoskopische Merkmale sind eine scharfe Begrenzung und eine wabenartige, gyrierte Textur.

8. Welche ist kein typisches histologisches Kriterium der SK?
   a. Kern- oder Zellatypien
   b. Akanthose
   c. Papillomatose
   d. (Ortho-) Hyperkeratose
   e. Pseudohornzysten

9. Welche Aussage trifft zu?
   a. Sonnenexposition in der Kindheit spielt eine entscheidende Rolle in der Pathogenese der SK.
   b. Patienten mit vielen SK haben ein erhöhtes Risiko, ein Melanom zu entwickeln.
   c. Patienten mit Psoriasis haben ein erhöhtes Risiko, multiple SK zu entwickeln.
   d. Patienten mit Hauttyp V/VI nach Fitzpatrick entwickeln nur sehr selten SK.
   e. Multiple SK können familiär gehäuft auftreten.

10. Welche ist keine typische Therapieform der SK?
   a. Topische Cortisontherapie
   b. Kürettage mittels scharfen Löffels
   c. Keine Therapie aufgrund der Gutartigkeit der Läsion
   d. Shave-Exzision mit Skalpell
   e. Ablative Laserbehandlung

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 31.Mai 2023. Die richtige Lösung zum Thema „Pharmakologie der Januskinase—Inhibitoren Teil 2: Pharmakodynamik“ in Heft 12 (Dezember 2022) ist: 1a, 2c, 3e, 4b, 5a, 6d, 7d, 8e, 9e, 10d

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