DOI: 10.1111/j.1610-0387.2008.06788.x

CME

Seborrheic keratosis

Christian Hafner, Thomas Vogt
Clinic and Polyclinic for Dermatology, University of Regensburg, Germany

JDDG; 2008 · 8:664–677 Submitted: 1. 4. 2008 | Accepted: 15. 04. 2008

Section Editor
Prof. Dr. Jan C. Simon,
Leipzig

Keywords
- seborrheic keratosis
- verruca seborrhoica
- stucco keratosis
- dermatosis papulosa nigra
- sign of Leser-Trelat
- FGFR3
- PIK3CA

Summary
Seborrheic keratosis is one of the most common skin tumors. Because this tumor is benign, treatment is not mandatory. However, the lesions are often removed especially for cosmetic reasons. Despite its frequency, many aspects of seborrheic keratosis remain elusive. In the last years new molecular genetic insights into seborrheic keratoses have been gained. The current knowledge about seborrheic keratosis with respect to epidemiology, pathogenesis, diagnosis and therapy is summarized.

Introduction
Seborrheic keratosis is one of the most common skin tumors seen by dermatologists.

Seborrheic keratosis is one of most common skin tumors seen by dermatologists in everyday practice. Older patients in particular often have large numbers of these benign tumors. Seborrheic keratoses are often an incidental finding. Given their benign nature, treatment is not mandatory. Yet many patients wish to have them removed for cosmetic reasons, especially if multiple lesions are present. Seborrheic keratoses must sometimes be distinguished from other skin tumors which may be benign or malignant. Deeply pigmented seborrheic keratoses, for instance, can resemble malignant melanoma, and these may be confused by laymen or by non-dermatologist physicians. Seborrheic keratosis is therefore an important skin tumor for dermatologists to be familiar with for differential diagnosis as well as therapy. That such knowledge is also cost-effective has been demonstrated by at least one study in the United States. This study examined records of confirmed seborrheic keratoses to determine the methods used in collection of histological material. The results showed that considerably less expensive methods (e.g., biopsy or shave excision) were used by dermatologists than non-dermatologists, who tended to favor more expensive methods such as complete excision (sometimes with reconstruction) [1].

Dermatologists should be familiar with the differential diagnosis and therapy of seborrheic keratoses.

The limited number of publications on seborrheic keratosis is surprising considering its frequency. Much is still unknown, particularly with regard to epidemiology and pathogenesis. At the same time, our understanding of the pathogenesis of this disorder has been aided in recent years by findings made in molecular genetics. The following presents an overview of the current state of knowledge on seborrheic keratosis.

Definition and clinical presentation
Seborrheic keratosis is also known by various synonyms: verruca senilis, senile wart, verruca seborrhoica, seborrheic wart, basal cell acanthoma, benign acanthokeratoma, and basal cell papilloma.

Seborrheic keratosis is also known by various synonyms: verruca senilis, senile wart, verruca seborrhoica, seborrheic wart, basal cell acanthoma, benign acanthokeratoma, and basal cell papilloma. The present paper uses the internationally prevalent term "seborrheic keratosis" to describe this highly common, benign epithelial skin tumor.

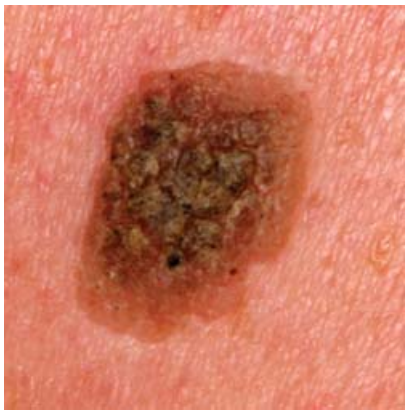

Figure 1: Clinical picture of a typical seborrheic keratosis.

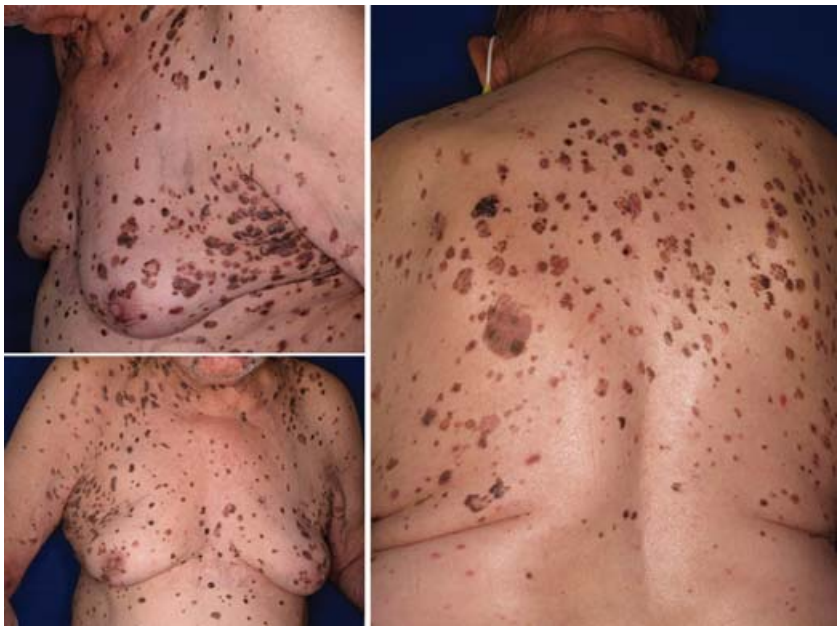

Figure 2: Seborrheic keratoses may appear in large numbers. This male patient displays a large number of darkly pigmented seborrheic keratoses showing a striking morphological variety with some lesions revealing an unusual rosette-like pattern. The patient reported that his father revealed also multiple seborrheic keratoses. An increased cumulative sun-exposure or multiple sunburns were denied.

Lesions are sharply demarcated, round or oval-shaped, usually elevated and stuck on the skin with a verrucous, uneven, dull, or punched-out surface (Figure 1). Flat seborrheic keratoses often have a smooth, velvety surface and are barely elevated above the surface of the skin. Whether these flat forms are merely initial seborrheic keratoses, which grow thicker over time, or whether they are a sub-type is still unclear. Some seborrheic keratoses have a surface which appears rather oily and shiny, hence the misnomer "seborrheic" (i.e., greasy) keratosis. Seborrheic keratoses typically appear as if stuck on the skin. Lesions range in size from a few millimeters to several centimeters, with a typical diameter of 0.5–1 cm. Lesions vary in color and may be skin-color/yellowish, gray-brown, or black. Pediculated forms have also been observed in intertriginous areas. Seborrheic keratoses are often penetrated by invaginations of keratotic plugs and horn cysts (filled with concentrically attached keratin). On dermatoscopy these appear as "pseudofollicular openings" and "horn pseudocysts" with light, sharply bordered, round plugs. Inflammation around the margin of the lesion can occasionally occur (Meyerson phenomenon).

Lesions are sharply demarcated, round or oval-shaped, usually elevated and stuck on the skin with a verrucous, uneven, dull, or punched-out surface

Seborrheic keratoses can appear anywhere on the body with the exception of the palms or soles. The mucus membranes are also generally spared. The most commonly affected sites are the chest, back, head (near the temples), and neck. Involvement of the conjunctiva has also been reported. Lesions may be solitary, but more often they are disseminated in large numbers, especially in older patients (Figure 2). Some patients may have a hundred or more lesions. A "Christmas tree pattern" may be seen on the trunk in which lesions are distributed along skin folds (Figure 3). Seborrheic keratoses are generally asymptomatic, but occasionally irritation or trauma may occur with itching, pain, or bleeding and redness and crusting of the keratosis. In rare instances, large tumors located about the eyelids or around the external auditory canal can cause impaired hearing or vision.

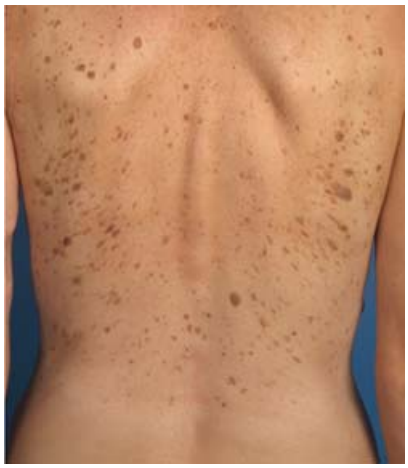

Figure 3: This woman has multiple brownish seborrheic keratoses which show a striking arrangement reminiscent of a "Christmas tree pattern."

Epidemiology

Despite the frequency of seborrheic keratosis, little is known about the epidemiology of the disorder. It is believed to be more prevalent among Caucasians and to affect roughly equal numbers of men and women. It is also generally acknowledged that its prevalence increases with advancing age. One Australian study reported a 100 % prevalence of seborrheic keratoses among people over age 50. On average, 69 seborrheic keratoses were found per patient in those over age 75. A British study reported

The prevalence of seborrheic keratoses increases with advancing age.

slightly lower prevalences. One or more lesions were found in 82 % of men and 62 % of women over age 70. Another European case control study, which was conducted in the Netherlands, examined 966 skin cancer patients (basal cell carcinoma, squamous cell carcinoma, and melanoma) for seborrheic keratoses [2]. (The pre-selection of this group of patients may influence the reported prevalence of seborrheic keratosis.) 72 % of patients in the study had seborrheic keratoses (76 % of men and 68 % of women). There was also a clear correlation with age: prevalence among 24–49-year-olds was 38 %, while among 50–59-year-olds it was 69 %, among 60–69-year-olds 86 %, and among 70–79-year-olds 90 %. Another Australian study reported at least one seborrheic keratosis in 83 % of non-dermatology patients aged 35–76 years, with 60 % having more than 5 lesions. A Korean study with 303 men aged 40 to 70 years reported the prevalence of seborrheic keratosis at 88 %, with an increase from 79 % among 40-year-olds to 99 % among those over age 60 [3]. The 60-year-olds had an average of 13 seborrheic keratoses. Seborrheic keratoses are rare among blacks and Native Americans, although dermatosis papulosa nigra, a variant of seborrheic keratosis is common among dark-skinned people.

Seborrheic keratosis can also occur at relatively young ages.

Despite the positive correlation between older age and increasing prevalence, seborrheic keratoses can also appear at relatively young ages. In the aforementioned British study, for instance, 8 % of men and 17 % of women under age 40 had at least one seborrheic keratosis. Yeatman and colleagues reported that among the Australian patients in their study, the prevalence was 12 % among patients aged 15 to 25 with an average of 6 lesions per patient [4]. Another Australian study focusing on this aspect [5] investigated the prevalence of seborrheic keratoses among 170 Caucasian patients aged 15 to 30 years. This study found that 24 % of subjects had at least one seborrheic keratosis. There were no significant differences between men and women, although slightly higher numbers were reported for women (26 % vs. 21 %). Most patients had only a single lesion, most often located on the trunk. The prevalence and diameter of lesions tended to increase with age. These results suggest that the frequency of seborrheic keratoses may be underestimated in younger patients. Yet, there are no directly comparable data available for regions in our own latitudes. It is conceivable that overall prevalence in Australia is much higher. Analogous to the high incidence and prevalence of skin cancer there, a higher prevalence may be the result of a causal relationship between exposure to UV light and the development of seborrheic keratoses.

Pathogenesis

Risk factors

Along with the influence of age on the prevalence of seborrheic keratosis, exposure to UV light may also play a role in pathogenesis.

Although the etiology and pathogenesis of seborrheic keratosis are still not well understood, new insights have been gained in recent years. It is widely agreed that older age significantly increases the risk of seborrheic keratoses. The few available epidemiological studies have also indicated a possible causal role of UV light in development of seborrheic keratoses. In one Australian study, Caucasian patients had a higher prevalence than those in a British study; the authors of this study reported disproportionate occurrence of seborrheic keratoses on sun-exposed areas of the skin (i.e., head, neck, and backs of hands) [4]. The aforementioned Korean study yielded similar results. Patients with cumulative exposure of more than 6 hours a day had a 2.3 times greater risk of seborrheic keratosis than those with less than 3 hours of exposure per day [3]. Along with sun exposure, age was also found to be an independent risk factor. Yet the Dutch case control study found that neither a history of painful sunburns nor a high cumulative exposure to UV light increased the risk of having seborrheic keratoses [2]. Thus controversy continues to exist around the role of UV light in the etiology of seborrheic keratoses.

A genetic predisposition in seborrheic keratosis has been suggested.

In addition to the exogenous risk factor of exposure to UV light in seborrheic keratoses, the possibility of a genetic predisposition has also been raised, although validated data are still lacking. Indeed, patients with unusually large numbers of lesions often have a family history of seborrheic keratosis. The patient shown in Figure 2 reported that his father had had numerous seborrheic keratoses, yet he denied having any intermittent or cumulative excessive exposure to UV radiation, a claim which was supported by the absence of typical signs of actinic skin damage.

There are also isolated case reports of families with increased incidence of seborrheic keratoses, sometimes at unusually young ages. An autosomal dominant pattern of inheritance has been suggested. Detailed studies are needed to answer whether genetic predisposition is indeed a factor in developing seborrheic keratoses. Along with genetic disposition and cumulative UV radiation exposure, another factor that has been previously discussed is the possible involvement of papillomaviruses given that many patients with seborrheic keratoses have tested positive for HPV-DNA on PCR. Yet whether there is a causal relationship or whether it is coincidence (HPV-DNA may also be detected in normal skin) is still unclear. A recent study seems to support the latter. In it HPV-DNA was detected only at the surface of most seborrheic keratoses but not deeper within the lesions, suggesting that many patients have only surface contamination.

Molecular pathogenesis

Although the etiological risk factors involved in seborrheic keratoses must still be confirmed, new insights have been gained in recent years in the area of molecular pathogenesis. A clonality analysis showed that the majority of seborrheic keratoses are monoclonal tumors and thus true autonomous neoplasias rather than simple epidermal hyperplasias. Unlike other tumors, seborrheic keratoses do not have any chromosomal anomalies on comparative genomic hybridization (CGH) analysis, which suggests chromosomal stability. An accumulation of p16 has also been reported, related to an arrest of epidermal cells in the G1 phase and hence senescence.

In an important breakthrough, a French working group showed that the *FGFR3* receptor plays an important role in the development of seborrheic keratoses [6]. *FGFR3* stands for Fibroblast Growth Factor Receptor 3 and represents a membrane-bound receptor tyrosine kinase. It was already known that germ line mutations in this gene lead to skeletal dysplasias and craniosynostoses (such as achondroplasia, thanatophoric dysplasia, and Crouzon syndrome). Along severe skeletal deformities, some of these syndromes also involve skin disorders such as acanthosis nigricans. This was an initial indication that *FGFR3* might also play an important pathophysiological role in these. *FGFR3* mutations also occur somatically in bladder tumors and in multiple myeloma. The French working group achieved expression of a mutated *FGFR3* gene construct under control of the keratin 5 promoter specifically in the basal layer of the epidermis in transgenic mice. The mice developed verrucous skin changes which closely resembled human seborrheic keratoses on histology. This led the authors of the study to examine human seborrheic keratoses. In 40 % of lesions they found somatic *FGFR3* mutations. These mutations cause constitutive activation of *FGFR3* and thus constant transmission of signals to the cell, without ligand binding. Yet it is still unclear which signal pathways in the keratinocytes influence the growth of seborrheic keratoses. Other studies have confirmed the presence of *FGFR3* mutations in seborrheic keratoses, reporting a somatic *FGFR3* mutation in 40–85 % of seborrheic keratoses. Eight different *FGFR3* mutations have been described so far in seborrheic keratosis. Patients with multiple seborrheic keratoses can have various mutations. *FGFR3* mutations may already be present in relatively flat (initial) lesions. Studies have also shown that activating mutations in the *PIK3CA* gene, which codes for the catalytic p110 subunit of class 1 phosphatidylinositol 3-kinase, are involved in the pathogenesis of seborrheic keratosis [7]. These mutations also possess oncogenic properties and are found in a number of malignant tumors such as colon, breast, and bladder cancer. It is still unclear why these mutations lead to malignant tumors in certain organ systems, while inducing benign seborrheic keratoses without any malignant potential. No relationship has yet been found between the various *FGFR3* and *PIK3CA* mutations and various histological subtypes. It is thus also unclear which factors ultimately determine these subtypes. Moreover, depending on the study population, there is a varying proportion of seborrheic keratoses which have neither an *FGFR3* nor a *PIK3CA* hotspot mutation, suggesting that other genes may also be involved.

The discovery of underlying somatic mutations re-raised the possibility of UV radiation-induced mutagenesis. In a study on 65 patients with acanthotic seborrheic keratoses, *FGFR3* mutations were found to be associated with older age and a location at chronically sun-exposed areas of the head and neck region. The FGFR3 mutations do

Somatic *FGFR3* and *PIK3CA* mutations are involved in the molecular pathogenesis of seborrheic keratosis .

It is still largely unknown which functional changes are caused by these mutations in affected keratinocytes.

not represent typical "signature" mutations produced by exposure to UV radiation. This does not completely rule out the possibility of UV-induced mutagenesis, however, since indirect mechanisms may also be involved. For instance, although the BRAF hotspot mutation V600E is not a signature mutation of UV light exposure, it is characteristic for malignant melanoma in areas of the skin with intermittent UV light exposure, and sunburns are recognized as a risk factor. It is possible that polymorphisms exist in other genes which would increase the susceptibility in certain people to *FGFR3* or *PIK3CA* mutations in the skin. This would explain a genetic predisposition, similar to *MC1R* variants in melanoma. We thus studied a family in whom it appeared that seborrheic keratoses was inherited in an autosomal dominant pattern. The lesions examined showed the same *FGFR3* and *PIK3CA* mutation spectrum as seen in sporadic tumors. The detected mutations were not in the germ line, however, suggesting the presence of a still unknown hereditary susceptibility factor for somatic *FGFR3* and *PIK3CA* mutations and related seborrheic keratoses in affected families [8].

Histology

Seborrheic keratoses are well-defined epidermal tumors which may exhibit exophytic or endophytic growth. Two keratinocytic components may be distinguished: basaloid cells and monomorphous squamous epithelial cells. The latter may also form small clusters known as "squamous eddies." Proliferation of basaloid cells, in particular, leads to acanthosis, which, along with papillomatosis, is highly characteristic of the disorder. Hyperkeratosis and hyperpigmentation may also be seen to varying degrees. An estimated one-third of seborrheic keratoses are hyperpigmented. Yet epidemiological studies have shown no correlation between pigmentation and location on sun-exposed areas of the skin. Horn cysts and horn pseudocysts are also often present. Horn cysts develop intraepidermally and are expelled transepidermally, while pseudohorn cysts are formed by downgrowths of keratin from the overlaying stratum corneum and are thus connected to it. Both cysts have a round keratin-filled center with a thin granular cell layer near adjacent keratinocytes.

Seborrheic keratoses are characterized histopathologically by acanthosis, papillomatosis, hyperkeratosis, horn cysts and horn pseudocysts.

Seborrheic keratoses may be grouped into different histological subtypes (Table 1). These often overlap and no exact figures are available on their percentage distribution. The three major subtypes are acanthotic, hyperkeratotic (also verrucous), and adenoid (Figure 4). Of these, the acanthotic subtype appears to be the most common. The acanthotic subtype involves marked acanthosis with predominantly basaloid cells. The acanthosis can have a vertical diameter of 3 mm or more. Papillomatosis and hyperkeratosis tend to be moderate. Horn cysts or pseudocysts are a characteristic feature and numerous cysts may be present. Proliferation of melanocytes and hyperpigmentation are not uncommon (about 30 % of lesions). An inflammatory lichenoid or circumscribed lymphocytic accompanying infiltrate is not uncommon. Squamous eddies, as seen in irritated seborrheic keratosis, are absent. Very heavily pigmented acanthotic seborrheic keratoses with melanocytic proliferation have also been termed melanoacanthomas.

The three major histological subtypes are acanthotic, hyperkeratotic, and adenoid seborrheic keratosis.

In the hyperkeratotic form, there is marked papillomatosis. Acanthosis tends to be mild, but has an exophytic saw-tooth (verrucous) appearance with elongated projections ("church spire" pattern). There is pronounced orthohyperkeratosis. Horn cysts and pseudocysts may be present, but are less common than in the acanthotic form. Hyperpigmentation is also rather unusual in hyperkeratotic seborrheic keratosis. Adenoid seborrheic keratosis is characterized by reticular proliferation of double rows of basaloid epidermal cell tracts in the dermis. Hyperpigmentation is relatively common, while horn cysts and pseudocysts are not. It has been postulated that adenoid seborrheic keratosis can develop from solar lentigo by continued proliferation of the club-like, elongated rete ridges and ultimately reticulated fusion of individual bands. There are also a number of other subtypes. Clonal seborrheic keratosis is marked by proliferation of intraepithelial clusters (known as the Borst-Jadassohn phenomenon). Irritated seborrheic keratosis, which is presumably identical with inverted follicular seborrheic keratosis, has an inflammatory cell infiltrate with partly lichenoid aspects in the dermis and squamous eddies. These are onion-skin-like aggregations of eosinophilic squamous epithelial cells. The basal layer may contain apoptotic cells. Occasionally, acantholysis, dyskeratosis, and spongiosis are present. The bowenoid

Table 1: Histologic subtypes of seborrheic keratosis.

Acanthotic subtype	Most common variant, pronounced acanthosis with moderate papillomatosis and hyperkeratosis, especially basaloid cells, numerous horn pseudocysts, about one-third are pigmented, lymphocytic lichenoid or circumscribed accompanying infiltrate is not uncommon
Hyperkeratotic subtype	Pronounced papillomatosis and hyperkeratosis and only moderate acanthosis; the saw-tooth appearance of the epidermis resembles church spires; especially monomorphous squamous epithelial cells, fewer basaloid cells
Adenoid subtype	Reticulated proliferation of double-row basaloid epidermal cell tracts in the dermis, hyperpigmentation is relatively frequent while horn pseudocysts tend to be rare; adenoid seborrheic keratosis may arise from solar lentigo
Clonal subtype	Proliferation of sharply demarcated intraepithelial nests of basaloid or pale, larger cells (Borst-Jadassohn phenomenon)
Bowenoid subtype	Bowenoid transformation within a seborrheic keratosis, characterized by intraepidermal cell atypia, predilection for sun-exposed areas
Irritated subtype (presumably identical with inverted follicular seborrheic keratosis)	Onion-skin like aggregations of eosinophilic squamous epithelial cells (squamous eddies), inflammatory cell infiltrate with partly lichenoid appearances in the dermis (may be absent), acantholysis, dyskeratosis, spongiosis, and apoptotic basal cells are possible
Melanoacanthoma	Very heavily pigmented acanthotic seborrheic keratosis with proliferation of melanocytes

subtype refers to bowenoid transformation within a seborrheic keratosis, which is characterized by intraepidermal cell atypia. This subtype is thought to have a predilection for sun-exposed areas. Some authors also distinguish flat seborrheic keratoses with minimal acanthosis and papillomatosis which are barely elevated above the level of the surrounding epidermis.

Clinical variants

A few skin tumors and syndromes have been described as clinical variants of seborrheic keratosis (Table 2).

Stucco keratosis

Many authors view stucco keratosis or keratosis alba as a special form of seborrheic keratosis. These white or white-gray verrucous papules are usually only a few millimeters large. Stucco keratoses affect older patients. They are often present in larger numbers (100 or more) on the extensor surfaces of the forearms and lower legs, the

Stucco keratoses are usually only a few millimeters in size. These white or white-gray verrucous papules may be present in larger numbers in older patients on sun-exposed areas of the skin (extensor surfaces of the forearms and lower legs, and dorsal aspects of the hands and feet).

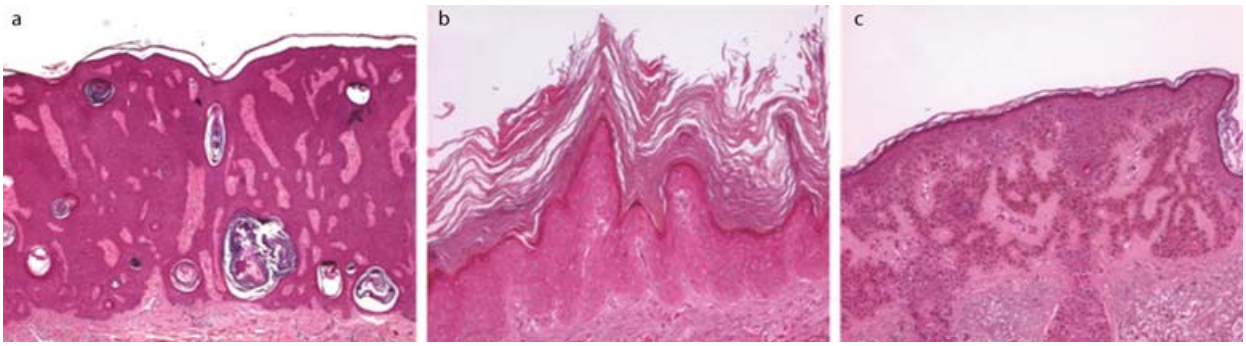

Figure 4: The three main histological subtypes of seborrheic keratoses are the acanthotic, hyperkeratotic and adenoid subtype. In many cases, the different subtypes are combined in the same lesion. (a) Acanthotic seborrheic keratosis represents the most frequent subtype and is characterized by a prominent acanthosis of predominantly basaloid cells. Horn pseudocysts are common and hyperpigmentation can often be observed. (b) The hyperkeratotic subtype shows less acanthosis, but prominent papillomatosis resembling church spires ("church-spire pattern") along with marked hyperkeratosis. Horn pseudocysts are less common than in the acanthotic subtype. (c) Adenoid seborrheic keratosis shows a reticulated pattern resulting from proliferation of epidermal strands into the dermis. This subtype is often hyperpigmented, whereas horn pseudocysts are not very common. It has been proposed that adenoid seborrheic keratoses may evolve from solar lentigines. The prominent actinic elastosis in the dermis of the shown sample would be congruent with this theory.

Table 2: Clinical variants of seborrheic keratosis..

Stucco keratosis	White or gray-white verrucous papules a few millimeters in size, often in large numbers (100 or more) on sun-exposed areas (extensor surface of forearms and lower legs, dorsal aspects of hands and feet), more common in men, relatively easily scratched off, histologically strong resemblance to hyperkeratotic seborrheic keratosis but without horn pseudocysts
Dermatosis papulosa nigra	Very common among blacks (considered a variant of seborrheic keratosis in people with dark skin), more common among women, positive family history is common, multiple 1–5 mm large black papules on the face, neck, chest, and upper back, histologically indistinguishable from acanthotic seborrheic keratosis, although horn pseudocysts are less common
Leser-Trelat syndrome	Paraneoplastic syndrome, abrupt eruption and growth of numerous seborrheic keratoses, especially on the trunk associated with internal organ malignancy (often adenocarcinoma), in one-third associated with acanthosis nigricans (often also pruritus), generally rare, considered a marker for an unfavorable prognosis; seborrheic keratoses may resolve with treatment of the underlying malignancy and reappear with its recurrence

backs of the hands, and dorsal aspects of the feet. They are believed to occur in men up to four times as often as women. The reported prevalence is 7–20 % with lesions generally appearing at age 40 and older. The disorder appears to be more common among Caucasians. No significant predisposition is presumed. The lesions appear to be stuck on the skin and may be relatively easily scraped off without any bleeding. Histologic examination shows a church spire-like epidermal papillomatosis ("saw-tooth" appearance) with orthohyperkeratosis resembling hyperkeratotic seborrheic keratosis. There are no horn cysts or pseudocysts.

The histological features of stucco keratosis strongly resemble those seen in hyperkeratotic seborrheic keratosis.

Dermatosis papulosa nigra

Dermatosis papulosa nigra is very common among black people and is considered a variant of seborrheic keratosis in people with dark skin. It has also been reported in Asians and Mexicans. According to one study, the prevalence is 77 % among dark-skinned patients with a ratio of 1 : 2 among men and women. Although the skin lesions are not usually seen in children, dermatosis papulosa nigra generally manifests at earlier ages than seborrheic keratosis. A genetic component has been discussed, since many patients report a family history of the disorder. Lesions are often found as multiple 1–5 mm large black papules on the face, neck, chest, and upper back. The number of lesions also typically increases with age. It cannot be distinguished histologically from seborrheic keratosis, although horn cysts and pseudocysts are less common.

Dermatosis papulosa nigra is very common among black people and is considered a variant of seborrheic keratosis in people with dark skin.

Lesions are often found as multiple 1–5 mm large black papules on the face, neck, chest, and upper back.

Leser-Trelat syndrome

Leser-Trelat syndrome is a paraneoplastic syndrome which is defined by the sudden eruption and growth of numerous seborrheic keratoses, especially on the trunk, in conjunction with a malignancy affecting the internal organs. It is associated with acanthosis nigricans in 35% of patients. Nearly half of patients have concomitant pruritus. Various subtypes of seborrheic keratosis are seen on histologic examination. Leser-Trelat syndrome is most often associated with adenocarcinomas of the stomach and colon, as well as breast cancer, lymphoma, and leukemia. The syndrome is considered a marker for an unfavorable prognosis, as the underlying cancer is often already in advanced stages. The average survival rate of patients with Leser-Trelat syndrome is 11 months after diagnosis. There are also isolated reports of the syndrome occurring in conjunction with benign tumors (testes, pituitary) and during pregnancy. Eruption of seborrheic keratoses has also been observed in patients with generalized eczema. There are also reports of linearly arranged seborrheic keratoses in colon cancer. In patients with breast cancer, there have been reports of multiple seborrheic keratoses appearing on the affected breast. Some authors have also reported resolution of seborrheic keratoses with treatment of the underlying malignancy and its later reappearance with recurrence of the tumor.

Nevertheless, the existence of this paraneoplastic syndrome is debated. Seborrheic keratoses are common at advanced ages and continue to increase in numbers and size. Sudden onset is often difficult to discern and trace in the patient's history. Given that cancer is also more common among older people, some authors suggest that the simultaneous appearance of these disorders is merely coincidental. Leser-Trelat syndrome has, however, also been reported in relatively young patients. It has been suggested that Leser-Trelat syndrome is triggered by growth factors (e.g., epidermal growth factor, growth hormone) which are secreted by the tumor. This would explain its onset (and that of the histologically similar acanthosis nigricans) in patients with acromegaly. New molecular genetic findings on the importance of activating mutations of the FGF receptor for the development of seborrheic keratoses further support this hypothesis. Yet one would expect that, unlike sporadic seborrheic keratosis, the seborrheic keratoses in Leser-Trelat syndrome would not be associated with any *FGFR3* or *PIK3CA* mutations, since activation of involved signal pathways would be due to an excess of ligands secreted by the cancer cells.

Leser-Trelat syndrome is a paraneoplastic syndrome which is defined by the sudden eruption and growth of numerous seborrheic keratoses, especially on the trunk, in conjunction with a malignancy affecting the internal organs.

The syndrome is considered a marker for an unfavorable prognosis, as the underlying cancer is often already in advanced stages.

Haber syndrome

Haber syndrome involves rosacea-like skin changes on the face as well as verrucous or bowenoid papules on the body, predominantly about the axillae. The lesions resemble seborrheic keratosis on histology.

Table 3: Dermatoscopic characteristics of seborrheic keratosis.

Horn cysts or pseudocysts
Pseudofollicular openings
Opaque yellow-brown or gray-brown in color
Streak-like densities are possible, but unlike melanocytic lesions they are not clearly demarcated
Gyrus sulcus pattern
Superficial serpiginous vascular structures

Given the typical morphological criteria, diagnosis can usually be made based on clinical appearance.

The primary dermatoscopic criteria for seborrheic keratosis are horn pseudocysts and pseudofollicular openings.

Diagnosis

Due to the typical morphological characteristics described above, a diagnosis of seborrheic keratosis can usually be made based on clinical appearance. Dermatoscopy can be helpful in unclear cases (Table 3, Figure 5). The primary dermatoscopic criteria for seborrheic keratosis are horn pseudocysts and pseudofollicular openings. A specific arrangement of pseudofollicular openings at the surface can produce a "gyrus sulcus pattern." Unlike melanocytic tumors, there are no pigment networks, streaks, or globules. Seborrheic keratoses typically appear as opaque yellow-brown or gray-brown with superficial serpiginous vascular structures. In pigmented seborrheic keratoses, there may also be streak-like densities which, unlike melanocytic lesions, are poorly defined. If certain diagnosis is still not possible, histological confirmation is occasionally warranted, especially to rule out malignant processes.

There are several benign and malignant skin tumors (Table 4) that should be considered in the differential diagnosis of seborrheic keratosis. Pigmented seborrheic keratoses, for instance, may be confused with malignant melanoma, a melanocytic nevus, a pigmented basal cell carcinoma, or angiokeratoma.

Differential diagnosis

There are several benign and malignant skin tumors (Table 4) that should be considered in the differential diagnosis of seborrheic keratosis. Pigmented seborrheic keratoses, for instance, may be confused with malignant melanoma, a melanocytic nevus, a pigmented basal cell carcinoma, or angiokeratoma. The rare verrucous melanoma is a particular challenge. Lightly pigmented seborrheic keratosis may resemble basal cell carcinoma or Bowen disease. Fibromas, verrucae vulgares, condylomata acuminata, acrokeratosis verruciformis of Hopf, and various adnexal tumors (e.g., eccrine poroma) must also be considered. Especially flat, slightly pigmented

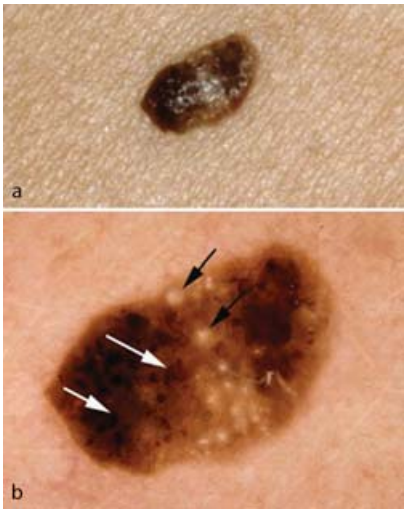

Figure 5: Dermatoscopy of seborrheic keratosis (with permission of Prof. Dr. Wilhelm Stolz). (a) Clinical picture of a seborrheic keratosis. (b) Corresponding dermatoscopy of this seborrheic keratosis shows typical horn pseudocysts (black arrows) and pseudofollicular openings (white arrows).

Table 4: Differential diagnosis of seborrheic keratosis

Seborrheic keratosis	Basal cell carcinoma, Bowen disease, fibroma, verruca vulgaris, condyloma acuminatum, diverse adnexal tumors, actinic keratosis
Pigmented seborrheic keratosis	(Verrucous) melanoma, melanocytic nevus, pigmented basal cell carcinoma, angiokeratoma
Flat (initial) seborrheic keratosis	Verruca plana juvenilis, solar lentigo
Histological differential diagnosis	Epidermal nevus, acanthosis nigricans, papillomatosis confluens et reticularis (Gougerot-Carteaud), acrokeratosis verruciformis of Hopf, solar lentigo (flat/initial seborrheic keratosis), squamous cell carcinoma (irritated seborrheic keratosis)

seborrheic keratoses may be mistaken for verrucae planae juveniles. Solar lentigo may also be clinically difficult to distinguish from very flat, pigmented seborrheic keratoses. It is possible that solar lentigo is a precursor to seborrheic keratosis. Hyperkeratotic seborrheic keratoses may be mistaken for actinic keratoses.

Histology cannot distinguish seborrheic keratoses from common epidermal nevi, both of which may exhibit acanthosis, papillomatosis, hyperkeratosis, and horn pseudocysts. The deciding factors in differential diagnosis are clinical description (solitary tumor vs. linear arrangement along the lines of Blaschko) and patient history (onset at later age vs. manifestation in early childhood). Morphological homology of both entities reflects their common molecular genetic basis (*FGFR3* and *PIK3CA* mutations). Acanthosis nigricans, acrokeratosis verruciformis of Hopf, and papillomatosis confluens reticularis (Gougerot-Carteaud syndrome) may also resemble seborrheic keratosis histologically. Irritated seborrheic keratoses exhibit squamous eddies, similar to keratin pearls in squamous cell carcinoma. Yet seborrheic keratosis has an uninterrupted row of basal cells without invasion of the dermis; and the squamous eddies are generally smaller, more numerous, and more clearly demarcated than the keratin pearls in squamous cell carcinoma.

Therapy

Operative therapy

As previously mentioned, treatment of seborrheic keratosis is not mandatory, given the benign nature of the disorder. Removal of lesions may nevertheless be warranted to exclude malignancy if clinical appearance is equivocal. Persistent mechanical irritation (e.g., from clothing, etc.) which leads to inflammation, bleeding, or itching is also an indication for removal. Yet in the majority of patients, especially those with multiple lesions, removal is for cosmetic reasons.

Seborrheic keratoses may be removed to exclude the presence of malignancy (if clinical findings are equivocal), to treat inflammation caused by irritation, or, most commonly, for cosmetic reasons.

The treatment of choice is removal of the lesion using one of various operative procedures currently available. Curettage with a sharp spoon or ring curette is a common method. The wound bed is treated afterward with antiseptic. Shave excision with a scalpel also usually produces good cosmetic results. Pediculated seborrheic keratoses may also be removed with using an electric snare. The use of cryotherapy is also commonly reported in international literature. For flat lesions, spray cooling for 5–10 seconds is recommended; for thicker tumors, the duration may be longer or a second spurt may be applied. Electrodessication has also been used. George Lundberg, Professor of Health Policy at the Harvard School of Public Health and Editor-in-Chief of Medscape General Medicine said he uses "fingernail surgery" to remove seborrheic keratoses, referring to the fact that some lesions are relatively easy to remove from the surface of the skin given that they are merely "stuck on." Yet in view of potential complications such as hemorrhage and wound infection as well as the possibility of missing a possibly malignant skin tumor, "fingernail surgery" is to be condemned and avoided.

The treatment of choice is removal of the lesion using one of various operative procedures currently available.

Another treatment option in removal of seborrheic keratoses is ablative laser such as erbium YAG or CO_2 laser. Studies have reported the successful use of a 532 nm diode laser in dermatosis papulosa nigra. This variant, which is common in dark-skinned people, is considered especially challenging given an increased risk of scar or keloid formation as well as hyper- or hypopigmentation. Cryotherapy is thus not advised in dermatosis papulosa nigra. It is important to note that ablative procedures (i.e., laser therapy and cryotherapy) preclude the potential for obtaining material for histologic analysis. Such measures are therefore only appropriate for lesions that are unequivocally diagnosed as seborrheic keratoses based on clinical presentation. If malignancy cannot be completely ruled out, a procedure must be chosen which also allows simultaneous collection of tissue for histologic analysis. Patients with a large number of seborrheic keratoses, sometimes well over 100, present a particular challenge. If the patient wishes to have them removed, multiple procedures are currently the method of choice. If Leser-Trelat syndrome is suspected, a comprehensive search to exclude underlying malignancy must be performed.

Drug therapy

There have also been reports on the effectiveness of topical vitamin D analogues in the treatment of seborrheic keratosis [9]. The presumed mechanism is the induction of apoptosis of keratinocytes. In one study with a treatment duration of 3 to 12 months

Despite some reports on topical (vitamin D analogues, tazarotene) and systemic (vitamin D analogues) drug therapy in seborrheic keratoses, such approaches have generally proven unsuccessful.

with once or twice daily application, about one-third of lesions resolved completely or nearly completely without visible inflammation, while others sowed a marked decrease in volume. However, one-fourth of lesions failed to adequately respond to topical therapy. In another study, tazarotene 0.1 % in a cream base, applied twice daily, achieved complete resolution (confirmed on histology) in 7 of 15 patients, although the drug caused considerable irritation [10]. Imiquimod was found in the same study to be ineffective.

Systemic therapy in multiple seborrheic keratoses would certainly be desirable in some patients, given limitations on performing multiple surgeries. One study on systemic administration of 1,25 dihydroxyvitamin D3 yielded noteworthy results [11]. 1,25 dihydroxyvitamin D3 was given orally to patients with multiple seborrheic keratoses in two different doses orally. The higher dose produced inflammatory changes in the lesions after only 2 weeks and ultimately led to their resolution with an atrophic scar or brown macule. Regression was visible on histology as vacuolation and degeneration of basal cells.

On the whole, however, neither topical nor systemic therapies have proven to be a viable option in the treatment of seborrheic keratosis. Treatment must usually be continued over an extended period of time and its effectiveness is generally clearly inferior to that of operative procedures. Yet in the future, the discoveries made in molecular genetics may provide a basis for developing novel topical therapies.

Prognosis

Seborrheic keratosis is a benign skin tumor without a significant tendency toward malignancy.

Seborrheic keratosis is a benign skin tumor without a significant tendency toward malignancy. After removal of lesions, local recurrence can occur. No exact figures on recurrence are available. Patients should also be made aware that given the relationship between incidence of seborrheic keratosis and increasing age, after the removal of multiple lesions the appearance of de novo tumors is also to be expected.

There have been isolated reports of an association between seborrheic keratoses and malignant skin tumors (e.g., basal cell carcinoma, squamous cell carcinoma, and malignant melanoma), although it is unclear whether this is due to a pathogenetic relationship or merely coincidence.

There are case reports in the literature of an association between seborrheic keratoses and malignant skin tumors arising within the seborrheic keratosis or related to it. The most common is an association with superficial basal cell carcinoma. In situ or invasive squamous cell carcinomas, keratoacanthomas, and malignant melanomas have also been described. It is unclear whether these tumors can develop directly from a seborrheic keratosis or whether the lesions appear coincidentally. Even if these malignant tumors arise directly from a seborrheic keratosis in individual patients, the stochastic risk would be negligible.

Summary

Seborrheic keratoses are among the most common skin tumors and as such are seen by dermatologists on a daily basis. These well-demarcated, round or oval neoplasias may be skin-colored, light brown or black, and appear stuck on the skin. Most seborrheic keratoses can be readily diagnosed based on clinical presentation. Occasionally, differentiating these lesions from others such as malignant melanoma may be difficult. Dermatoscopy is a useful aid; horn pseudocysts and pseudofollicular openings help establish a diagnosis. Histologically, seborrheic keratosis is characterized by acanthosis, papillomatosis, hyperkeratosis, and horn pseudocysts. Depending on how prominent these features are, the disorder may be grouped into different histological subtypes. The most important of these are the acanthotic, hyperkeratotic, and adenoid. The pathogenesis of the disorder remains largely unclear. It is known that the prevalence of seborrheic keratosis increases markedly with increasing age, although tumors are also found in relatively young patients. A genetic predisposition for multiple seborrheic keratoses is thought to exist. The causal role of UV light in the development of the lesions is also under discussion. Molecular genetics has shown that somatic *FGFR3* and *PIK3CA* mutations are involved in the pathogenesis of seborrheic keratosis, although the precise mechanisms and the responsible signaling pathways are still unclear. Stucco keratosis and dermatosis papulosa nigra are considered to be variants of seborrheic keratosis. Leser-Trelat syndrome is a rare paraneoplastic syndrome, which is most commonly associated with adenocarcinoma and eruption of multiple seborrheic keratoses. Although seborrheic keratosis is a benign disorder, there are various indications for the removal of lesions: exclusion of malignancy (if clinical appearance is unclear), irritation with inflammation, and especially cosmetic

concerns in patients with multiple lesions. The treatments of choice cover a range of operative procedures such as curettage, shave excision, electrodessication, cryotherapy, and ablative laser. Depending on the availability and the physician's experience with each, these methods are all relatively equally suitable. The use of topical and systemic drug therapies in the treatment of seborrheic keratosis has not yet been widely adopted. <<<

Conflict of interest
None.

Correspondence to
Priv.-Doz. Dr. med. Christian Hafner
Klinik und Poliklinik für Dermatologie
Universität Regensburg
Franz-Josef-Strauß-Allee 11
D-93053 Regensburg
Tel.: +49-941-944-9610
Fax: +49-941-944-9611
E-mail: christian.hafner@klinik.uni-regensburg.de

References
1 Duque MI, Jordan JR, Fleischer AB, Jr., Williford PM, Feldman SR, Teuschler H, Chen GJ. Frequency of seborrheic keratosis biopsies in the United States: a benchmark of skin lesion care quality and cost effectiveness. Dermatol Surg 2003; 29: 796–801; discussion 801.
2 Kennedy C, Bajdik CD, Willemze R, De Gruijl FR, Bouwes Bavinck JN. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. J Invest Dermatol 2003; 120: 1087–1093.
3 Kwon OS, Hwang EJ, Bae JH, Park HE, Lee JC, Youn JI, Chung JH. Seborrheic keratosis in the Korean males: causative role of sunlight. Photodermatol Photoimmunol Photomed 2003; 19: 73–80.
4 Yeatman JM, Kilkenny M, Marks R. The prevalence of seborrhoeic keratoses in an Australian population: does exposure to sunlight play a part in their frequency? Br J Dermatol 1997; 137: 411–414.
5 Gill D, Dorevitch A, Marks R. The prevalence of seborrheic keratoses in people aged 15 to 30 years: is the term senile keratosis redundant? Arch Dermatol 2000; 136: 759–762.
6 Logie A, Dunois-Larde C, Rosty C, Levrel O, Blanche M, Ribeiro A, Gasc JM, Jorcano J, Werner S, Sastre-Garau X, Thiery JP, Radvanyi F. Activating mutations of the tyrosine kinase receptor FGFR3 are associated with benign skin tumors in mice and humans. Hum Mol Genet 2005; 14: 1153–1160.
7 Hafner C, Lopez-Knowles E, Luis NM, Toll A, Baselga E, Fernandez-Casado A, Hernandez S, Ribe A, Mentzel T, Stoehr R, Hofstaedter F, Landthaler M, Vogt T, Pujol RM, Hartmann A, Real FX. Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. Proc Natl Acad Sci U S A 2007; 104: 13450–13454.
8 Hafner C, Vogt T, Landthaler M, Müsebeck J. Somatic FGFR3 and PIK3CA mutations are present in familial seborrhoeic keratosses. Br J Dermatol 2008; 159: 214–217.
9 Mitsuhashi Y, Kawaguchi M, Hozumi Y, Kondo S. Topical vitamin D3 is effective in treating senile warts possibly by inducing apoptosis. J Dermatol 2005; 32: 420–423.
10 Herron MD, Bowen AR, Krueger GG. Seborrheic keratoses: a study comparing the standard cryosurgery with topical calcipotriene, topical tazarotene, and topical imiquimod. Int J Dermatol 2004; 43: 300–302.
11 Asagami C, Muto M, Hirota T, Shimizu T, Hamamoto Y. Anti-tumor effects of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) in seborrheic keratosis. J Investig Dermatol Symp Proc 1996; 1: 94–96.

Fragen zur Zertifizierung durch die DDA

1. Welche Aussage zur seborrhoischen Keratose trifft **nicht** zu?
a) Sie gehört zu den häufigsten Hauttumoren des Menschen.
b) Die seborrhoische Keratose ist als benigne zu betrachten, ein signifikantes malignes Entartungsrisiko liegt nicht vor.
c) Stark pigmentierte Varianten müssen differenzialdiagnostisch vom malignen Melanom abgegrenzt werden.
d) Häufig sind die Tumoren palmoplantar lokalisiert.
e) Ihre Farbe kann von hautfarbengelblich über braun bis schwarz variieren.

2. Welche Aussagen sind richtig?
1) Die Prävalenz seborrhoischer Keratosen nimmt mit steigendem Lebensalter zu.
2) Einzelne Patienten können mehr als hundert seborrhoische Keratosen aufweisen.
3) Stukkokeratosen kommen bei der kaukasischen Bevölkerung nicht vor.
a) Nur Aussage 1 ist richtig.
b) Nur Aussagen 1 und 2 sind richtig.
c) Nur Aussagen 1 und 3 sind richtig.
d) Nur Aussagen 2 und 3 sind richtig.
e) Alle Aussagen sind richtig.

3. Was sind auflichtmikroskopische Kriterien für eine seborrhoische Keratose?
1) Pseudohornzysten
2) Pigmentnetz, Streifen und Schollen
3) opake gelb-braune Farbe
4) pseudofollikuläre Öffnungen
a) Nur Aussagen 1 und 3 sind richtig.
b) Nur Aussagen 1, 2 und 3 sind richtig.
c) Nur Aussagen 1, 3 und 4 sind richtig.
d) Nur Aussagen 2, 3 und 4 sind richtig.
e) Alle Aussagen sind richtig.

4. Welcher histologische Subtyp der seborrhoischen Keratose existiert nicht?
a) akanthotischer Subtyp
b) klonaler Subtyp
c) adenoider Subtyp
d) hyperkeratotischer Subtyp
e) sklerodermiformer Subtyp

5. Welche Aussage ist richtig?
a) Die adenoide seborrhoische Keratose stellt den häufigsten histologischen Subtyp dar.
b) Das Melanoakanthom ist eine stark pigmentierte Variante der seborrhoischen Keratose, aus der sich häufig ein malignes Melanom entwickelt.
c) Die Dermatosis papulosa nigra tritt vor allem im Bereich der unteren Extremität auf.
d) Stukkokeratosen sind nur wenige Millimeter große grauweiße Papeln im Bereich lichtexponierter Areale und können in großer Zahl vorkommen.
e) Seborrhoische Keratosen kommen nicht bei jungen Personen unter 25 Jahren vor.

6. Für welchen Rezeptor sind bei der seborrhoischen Keratose somatische Mutationen beschrieben?
a) Epidermal Growth Factor Receptor
b) Fibroblast Growth Factor Receptor
c) Fibroblast Growth Factor Receptor
d) Vascular Endothelial Growth Factor Receptor
e) Keratinocyte Growth Factor Receptor

7. Welche Aussage zum Leser-Trelat-Syndrom trifft nicht zu?
a) Es handelt sich um ein paraneoplastisches Syndrom, das durch ein abruptes Aufschießen multipler seborrhoischer Keratosen charakterisiert ist.
b) Es kann mit einer Akanthosis nigricans maligna assoziiert sein.
c) Häufig liegen als maligne Tumoren Adenokarzinome zugrunde.
d) Das Leser-Trelat-Syndrom ist in der Regel mit sehr frühen Tumorstadien assoziiert und weist deshalb auf eine für den Patienten besonders günstige Prognose hin.
e) Nach erfolgreicher Behandlung des zugrunde liegenden Tumors können sich die seborrhoischen Keratosen wieder zurückbilden.

8. Welche Methoden können zur Entfernung seborrhoischer Keratosen prinzipiell zur Anwendung kommen?
1) Kürettage
2) Kryotherapie
3) ablative Laser
a) Nur Aussage 1 ist richtig.
b) Nur Aussagen 1 und 2 sind richtig.
c) Nur Aussagen 1 und 3 sind richtig.
d) Nur Aussagen 2 und 3 sind richtig.
e) Alle Aussagen sind richtig.

9. Welche Aussage trifft nicht zu?
a) Das Leser-Trelat-Syndrom kann laborchemisch sicher diagnostiziert werden.
b) Multiple seborrhoische Keratosen stellen oft ein kosmetisches Problem dar.
c) Gestielte seborrhoische Keratosen lassen sich gut mit der elektrischen Schlinge abtragen.
d) Epidermale Nävi und seborrhoische Keratosen lassen sich rein histologisch nicht sicher voneinander unterscheiden.
e) Eine erbliche Disposition für seborrhoische Keratosen wird angenommen.

10. Welche Aussagen sind richtig?
1) Sogenannte „Kirchturmspitzen" sind ein charakteristisches histologisches Kennzeichen der adenoiden seborrhoischen Keratose.
2) Die Stukkokeratose und die hyperkeratotische seborrhoische Keratose sind sich histologisch ähnlich.
3) (Pseudo-)Hornzysten sind für die histologische Diagnose einer seborrhoischen Keratose zwingend erforderlich.

a) Nur Aussage 1 ist richtig.
b) Nur Aussage 2 ist richtig.
c) Nur Aussage 3 ist richtig.
d) Nur Aussagen 1 und 2 sind richtig.
e) Nur Aussagen 2 und 3 sind richtig.

Liebe Leserinnen und Leser,

der Einsendeschluss an die DDA für diese Ausgabe ist der 18. September 2008.
Die richtige Lösung zum Thema „Urtikaria" in Heft 4 (April 2008) ist: 1a, 2d, 3e, 4a, 5a, 6a, 7c, 8b, 9d, 10c.
Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda.de ein.